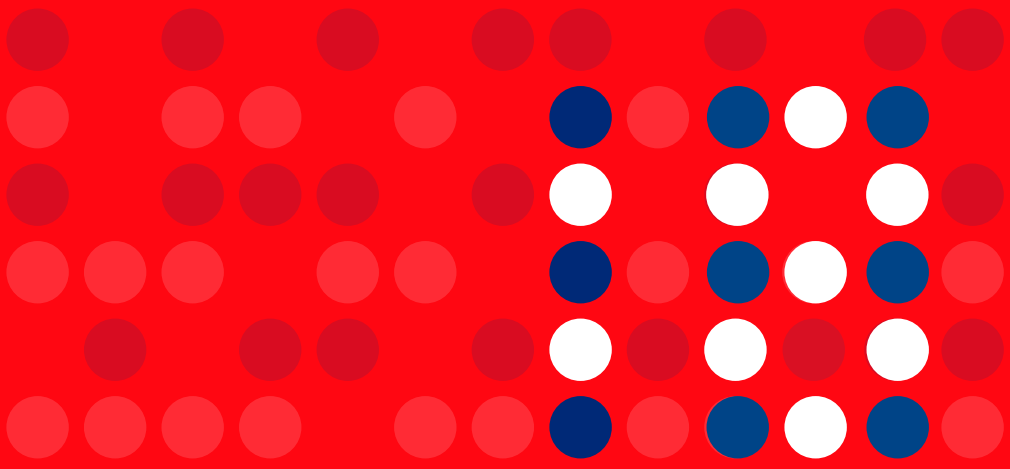
Human Immunodeficiency Virus (HIV)
infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2018



About Stichting HIV Monitoring

Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, was founded in 2001 and appointed by the Dutch minister of Health, Welfare and Sport as the executive organisation for the registration and monitoring of HIV-positive individuals in the Netherlands.

SHM comprehensively maps the HIV epidemic and HIV treatment outcomes in the Netherlands, thereby contributing to the knowledge of HIV. In collaboration with the HIV treatment centres in the Netherlands, SHM has developed a framework for systematically collecting HIV data for the long-term follow up of all registered individuals. The Netherlands is the only country in the world to have such a framework, which enables healthcare professionals to aspire to the highest standard of HIV care.

In addition to national reports, healthcare professionals are provided with treatment centre-specific reports to enable them to monitor and optimise care provided in their centres. Moreover, upon request, SHM data are also made available for use in HIV-related research, both in the Netherlands and internationally. The outcome of SHM's research and international collaborations provides tangible input into policy guidelines and further improves HIV care in the Netherlands.

Our 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.

HIV Monitoring

Monitoring Report 2018

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

Interactive PDF user guide

This PDF allows you to find information and navigate around this document more easily.

Links in this PDF

Words and numbers that are underlined are links — clicking on them will take you to further information within the document or to a web page (which opens in a new window) if they are a url (e.g http://www.cdc.gov/hiv/guidelines/).

Reference numbers

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Acknowledgements

Authors: Ard van Sighem, Sonia Boender, Ferdinand Wit, Colette Smit, Amy Matser, Peter Reiss

Co-authors: Joop Arends, Ward van Bilsen, Kees Brinkman, Ashley Duits, Suzanne Geerlings, Gonneke Hermanides, Frank Kroon, Kees van Nieuwkoop, Eline Op de Coul, Jan Prins, Maria Prins, Clemens Richter, Annemarie van Rossum, Marc van der Valk, Anne Wensing, Diederik van de Wetering, Tom Wolfs

Production and support: Catriona Ester, Mireille Koenen, Yunka de Waart

Requests for digital copies: Stichting HIV Monitoring, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands
T +31 20 5664172
E: hiv.monitoring@amc.uva.nl, www.hiv-monitoring.nl

Visiting address: Stichting HIV Monitoring, Nicolaes Tulphuis, Tafelbergweg 51, 1105 BD Amsterdam, the Netherlands

KvK#: 34160453
Correspondence to: Peter Reiss, hiv.monitoring@amc.uva.nl

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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 2018, 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 Lairesse - 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	Universitair Medisch Centrum Utrecht (UMC Utrecht)	Utrecht
26	Isala	Zwolle

**Following an administrative merger in June 2018, AMC-UvA and VUmc now work together under the collective name: Amsterdam UMC (Amsterdam University Medical Centers). However, for the purpose of this report, which mainly focuses on data collected up to December 2017, the original names AMC-UvA and VUmc will be used. In future publications these centres will be known as Amsterdam UMC (AMC site) and Amsterdam UMC (VUmc site), respectively.*

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 2018 on Human Immunodeficiency Virus (HIV) Infection in the Netherlands is the 17th in the series published by Stichting HIV Monitoring (SHM). The report provides a comprehensive review of trends over time in the HIV epidemic in the Netherlands and the effect of treatment. It also describes quality of care in HIV treatment centres, and includes special reports on HIV in Curaçao and on the Amsterdam Cohort Studies.

2018 marks the 20th anniversary of the AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort. The ATHENA cohort was originally established in 1998 to support the decision taken by the minister of health at the time, Els Borst, to rapidly make HIV-protease inhibitors available for what was then known as highly active antiretroviral therapy (HAART) and to provide evidence of the life-saving effectiveness of HAART. Following the success of the monitoring system set up to achieve this goal, the minister decided in 2001 that there was a need for a sustainable monitoring system. SHM was established to fulfil this task and has managed the ATHENA cohort ever since. Today, the cohort's very broad, nationwide coverage and the quality and extensiveness of the data collection affords us a unique insight into the HIV epidemic in the Netherlands and facilitates ongoing improvements in the quality of HIV care provided to people living with HIV.

In addition to publishing this annual Monitoring Report, SHM continues to makes centre-specific information available to individual treatment centres, enabling treating physicians to assess and improve the patient care in their own 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 form a nationwide benchmark. Moreover, following approval of a formal proposal, aggregated data from all centres are available 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, people living with HIV, government and healthcare at large.

The Monitoring Report is the culmination of a great deal of hard work by many people both within and outside SHM. I would therefore like to thank the HIV treating physicians, HIV nurse consultants, and staff of the diagnostic laboratories, along with the data collecting and monitoring staff. Without their ongoing efforts, our work would not be possible.

My thanks also go to our group of reviewers whose in-depth knowledge on relevant chapter topics has helped shape the content of this report. Their input is highly valuable and further improves the report's clinical and public health relevance.

Finally, I 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 affected communities that we can further our insight into the many facets of HIV and HIV treatment, and thereby continue to not only improve the care for people living with HIV in the Netherlands, but also provide guidance for prevention.

Professor Peter Reiss, MD

Director, Stichting HIV Monitoring

Summary & recommendations

The HIV epidemic in the Netherlands in 2017

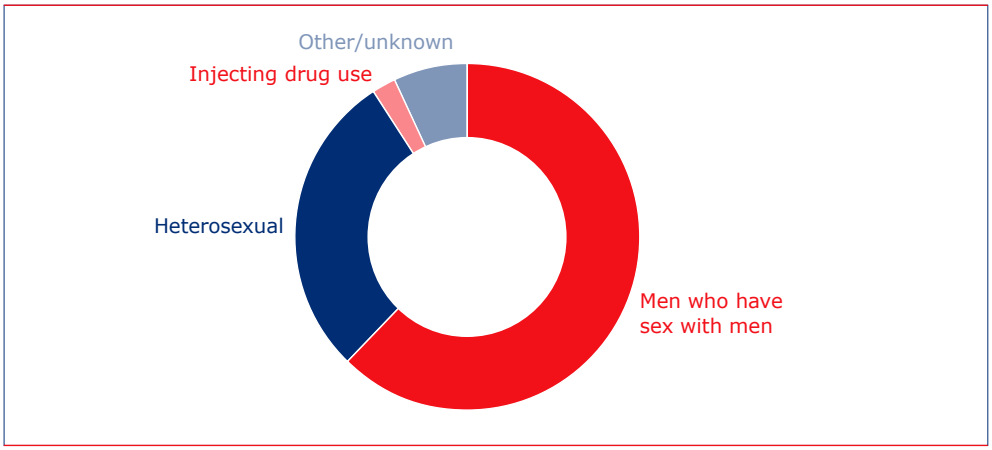
Trend of fewer new HIV diagnoses continues in 2017

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 2017. The projected number of new diagnoses for 2017 is 749, although this may change as registration of HIV diagnoses for 2017 has not yet been finalised.

Majority of new diagnoses continue to be in men who have sex with men

In 2017, the majority (69%) of newly-diagnosed infections were in men who have sex with men (MSM), while 23% were acquired through heterosexual contact and around 7% through other or unknown modes of transmission *(Figure 1)*.

Figure 1: *Most likely route of HIV transmission in people in HIV care in the Netherlands in 2017.*



People newly-diagnosed with HIV rapidly receive specialised care

Over 95% of people newly-diagnosed with HIV entered specialised HIV care within 6 weeks after diagnosis. This rate was more or less the same regardless of where the diagnosis was made (i.e., hospital, general practice, sexually transmitted infections clinic, or other test location).

HIV testing is becoming more common

The rates of testing for HIV appear to be increasing in the Netherlands. This conclusion is based on the following observations. Firstly, our data show that the proportion of individuals with a previously negative HIV test has increased (73% of MSM, 33% of other men and 49% of women diagnosed in 2017 had a reported previous negative test). In addition, the proportion of individuals who are diagnosed with HIV relatively early in their infection (including during primary HIV infection) continues to increase, particularly among MSM. This is reflected in the CD4 count at diagnosis gradually having risen over time to a median of 380 cells/mm^3 in 2017.

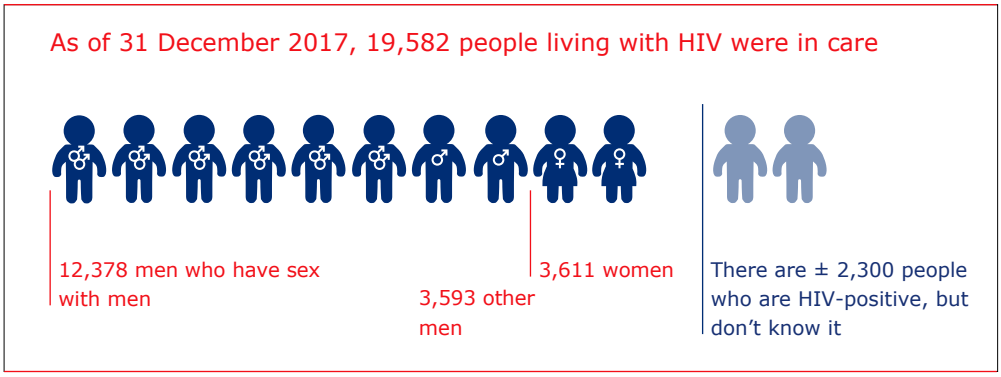
Late presentation for care remains a problem that needs attention

Despite the observed earlier diagnosis among certain groups, too many people still present late for care, i.e., with an already impaired immune system (CD4 count below 350 cells/mm^3) or even AIDS; in 2017, this was the case for 37% of MSM, 63% of other men and 52% of women.

How many people were in HIV care in 2017?

As of 31 December 2017, a total of 19,582 people living with HIV in the Netherlands (19,390 adults and 192 children and adolescents) were known to be in care in one of the 26 adult or 4 paediatric HIV treatment centres *(Figure 2)*.

Figure 2: *Number of people living with HIV and in care in the Netherlands in 2017.*



Continuum of HIV care in 2017: "90-93-95"

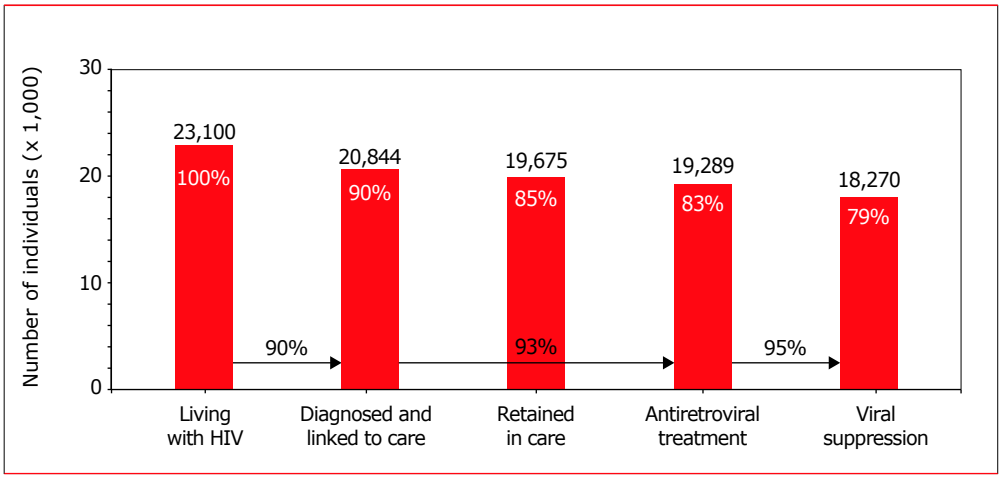
One of the goals of HIV treatment is to achieve viral suppression. The key steps that need to be achieved to reach viral suppression are illustrated in a continuum of HIV care. A continuum of care also gives a measure of progress towards achieving the UNAIDS 90-90-90 goals for HIV care by 2020.

The continuum of care in *Figure 3* shows that the Netherlands reached these goals in 2017 (90-93-95):

- By the end of 2017, 23,100 individuals were estimated to be living with HIV, of whom an estimated 2,300 were still undiagnosed.
- In total, 20,844 individuals (**90%** of the total number estimated to be living with HIV) had been diagnosed, linked to care, and registered by SHM.
- Of the individuals who had been diagnosed, linked to care, and registered by SHM, the majority (19,289; **93%**), had started antiretroviral treatment, and 18,270 of those (**95%**) had achieved viral suppression.

This means that overall, 79% of the total estimated population living with HIV and 88% of those diagnosed and linked to care had a suppressed viral load by the end of 2017.

Figure 3: Continuum of HIV care for the total estimated HIV-positive population in the Netherlands by the end of 2017, based on UNAIDS 90-90-90 goals for 2020: 90-93-95. The percentages at the bottom of the bars correspond to UNAIDS' 90-90-90 targets.



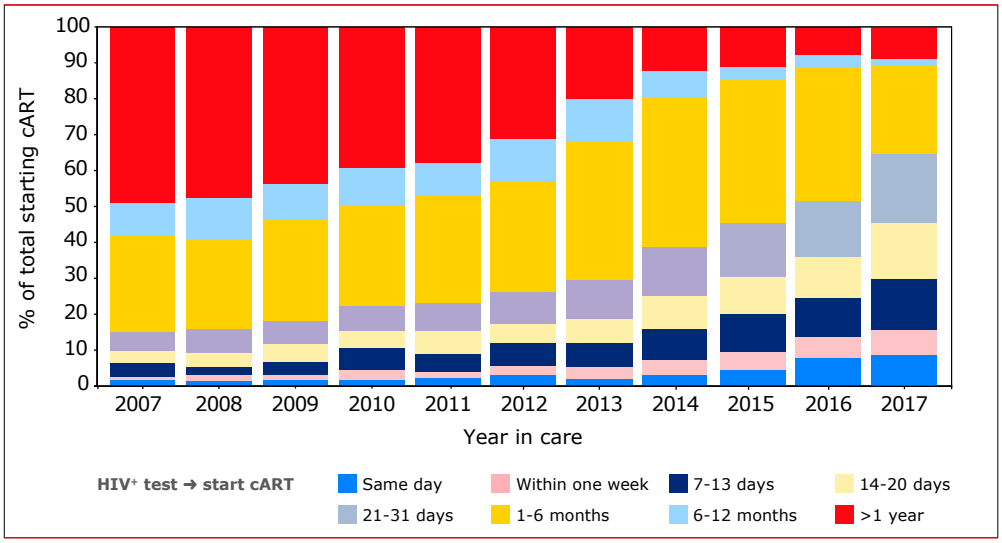
The figures for the Netherlands are impressive compared with other parts of the world. Nonetheless, in 2017 there were around 750 new diagnoses and an estimated 2,300 people who remained undiagnosed. To achieve a significant decline in these numbers, novel transdisciplinary strategies are needed to simultaneously reduce the likelihood of HIV transmission in key populations at risk, identify individuals with HIV infection early, rapidly link all people living with HIV to care, and immediately offer them the possibility of starting combination antiretroviral therapy.

Combination antiretroviral therapy in adults

In 2017, most people started HIV treatment within a month of diagnosis

People are increasingly starting cART sooner after being diagnosed with HIV. Of those starting cART in 2017 more than half did so within one month, and 90% within 6 months after diagnosis *(Figure 4)*. Importantly, this was the case irrespective of the CD4 cell count at diagnosis.

Figure 4: *Time between HIV diagnosis and starting combination antiretroviral therapy (cART) for those starting cART between 2007–2017.*



People are increasingly starting treatment with a less impaired immune system

People are increasingly starting cART at higher CD4 counts. The proportion of people who had a CD4 count of 500 cells/mm^3 or above at diagnosis and who had begun cART within 6 months of diagnosis rose from 87% in 2015 to 91% in 2017.

Most common cART regimens in 2017

Initial regimens

More than 80% of people started on an integrase inhibitor-containing regimen in 2017, with abacavir/lamivudine/dolutegravir and tenofovir alafenamide/emtricitabine/cobicistat-boosted elvitegravir being the most frequently-prescribed initial regimens in 2017.

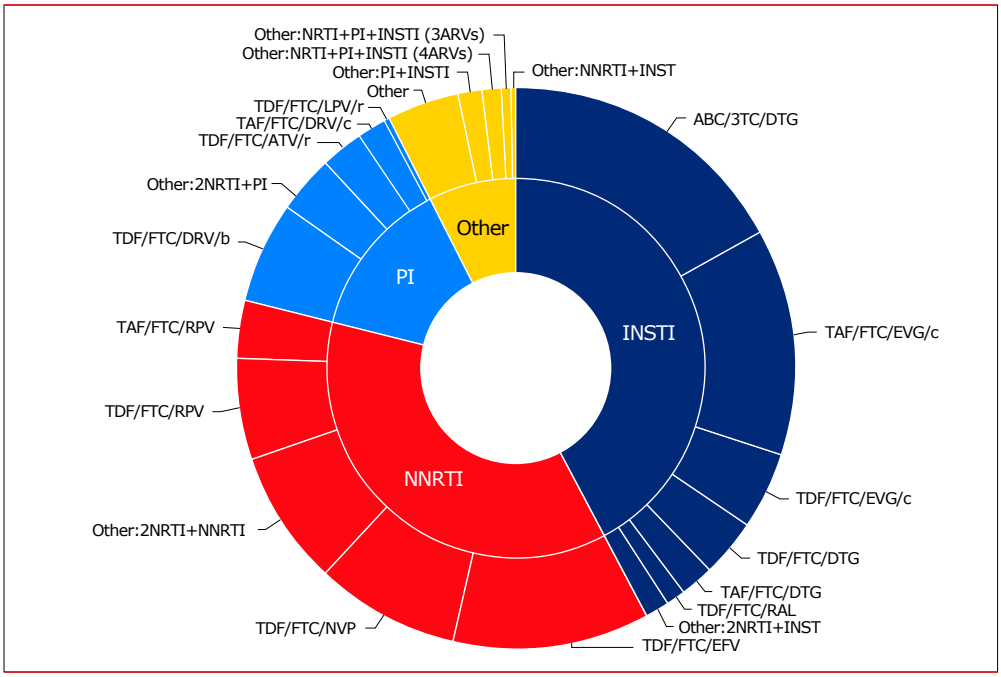
The likelihood of discontinuing or switching the initial regimen has been decreasing since 1996. As in previous years, toxicity continued to be a main reason for discontinuing or switching the initial regimen during the first year of treatment. Toxicity-related discontinuations were often due to neuropsychiatric, gastrointestinal, or renal problems, or medication-related skin rash. Other, more recent, important reasons for discontinuation or regimen switch during the first year of treatment include regimen simplification or the availability of new drugs.

Integrase inhibitor–based cART used increasingly frequently

Since its introduction a few years ago, integrase inhibitor-based cART has been implemented on a large scale in the Netherlands: in 2017, 42% of all adults in care and on cART received an integrase inhibitor, compared with 27% in 2015. Half of the population on cART in 2017 received a backbone consisting of tenofovir disoproxil fumarate/emtricitabine, although the availability of new fixed-dose combinations has led to an increase in the use of abacavir/lamivudine and tenofovir alafenamide/emtricitabine.

Among all HIV-positive individuals in care and on treatment in 2017, the majority received a cART regimen based on two nucleoside analogue reverse transcriptase inhibitors, combined with an integrase inhibitor (42%), a non-nucleoside reverse transcriptase inhibitor (36%), or a protease inhibitor (14%) (*Figure 5*). The most commonly-prescribed regimens in 2017 were abacavir/lamivudine/dolutegravir (17%), tenofovir alafenamide/emtricitabine/cobicistat-boosted elvitegravir (13%), and tenofovir disoproxil fumarate/emtricitabine combined with efavirenz (11%) or nevirapine (8%).

Figure 5: Combination antiretroviral therapy (cART) use in 2017 by all HIV-positive individuals in care.



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

Excellent virological response, including in long-term survivors

Both short-term and long-term viral suppression rates remain high and continue to improve. Of all adults in care and on cART in 2017, 97% had an undetectable viral load (<200 copies/ml). Individuals who had been diagnosed with HIV before 1990 and who remained in care and on cART in 2017 (i.e., long-term survivors) had equally high levels of viral suppression.

Changing cART landscape

Following revised HIV treatment guidelines, prompt cART initiation has continued to become more common in 2017. 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 durable.

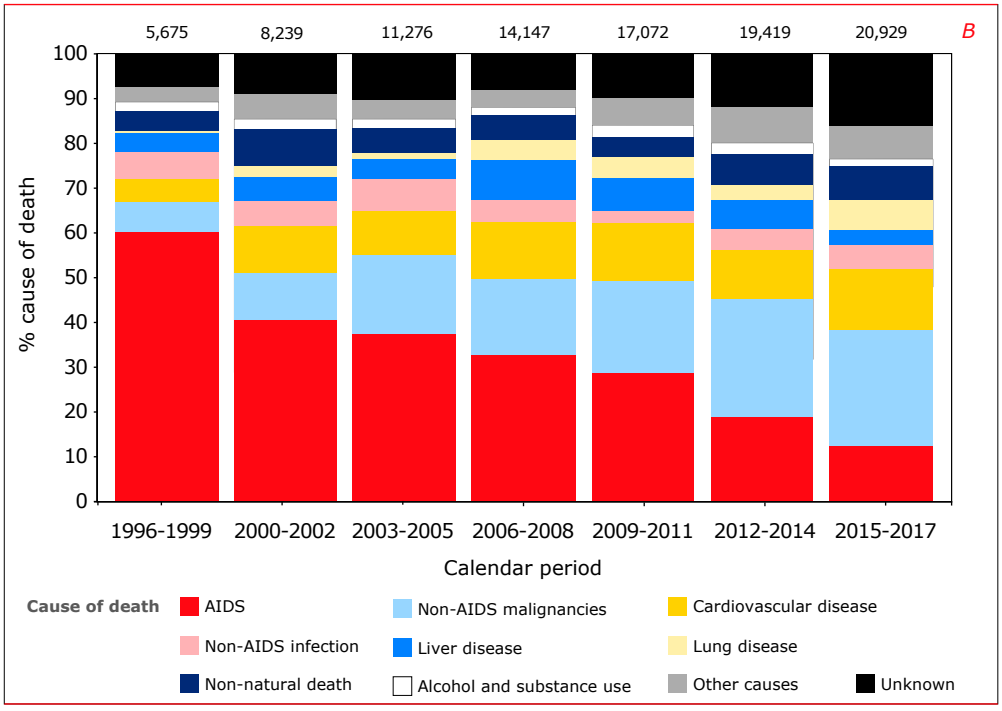
Morbidity and mortality

Sustained decline in AIDS-related death

Mortality remains low in HIV-positive individuals in care in the Netherlands. There has been a sustained decline in the risk of death from AIDS, with a shift towards death from non-AIDS comorbidities, including non-AIDS-defining malignancies (NADM), cardiovascular disease (CVD) and chronic liver disease (*Figure 6*).

Those cases of AIDS-related death that do occur 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.

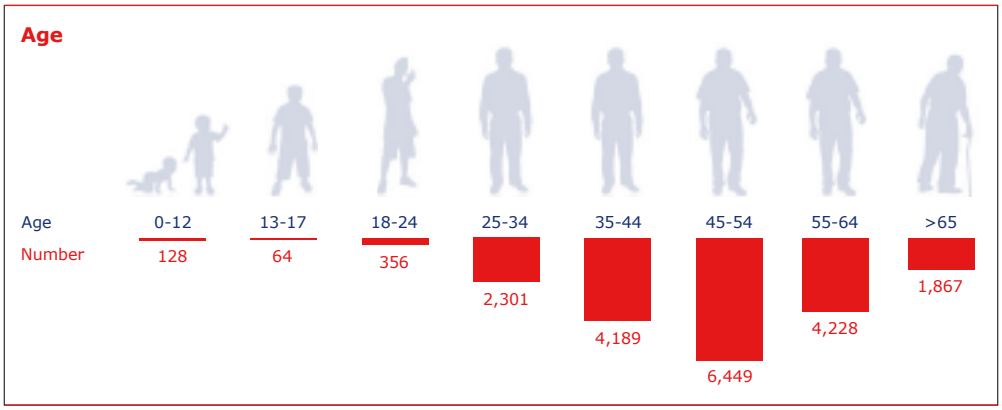
Figure 6: *Relative changes in cause of death in different calendar periods since the introduction of combination antiretroviral therapy (cART) in the Netherlands. Numbers above each bar represent the number of people at risk during that calendar period.*



Ageing and comorbidities

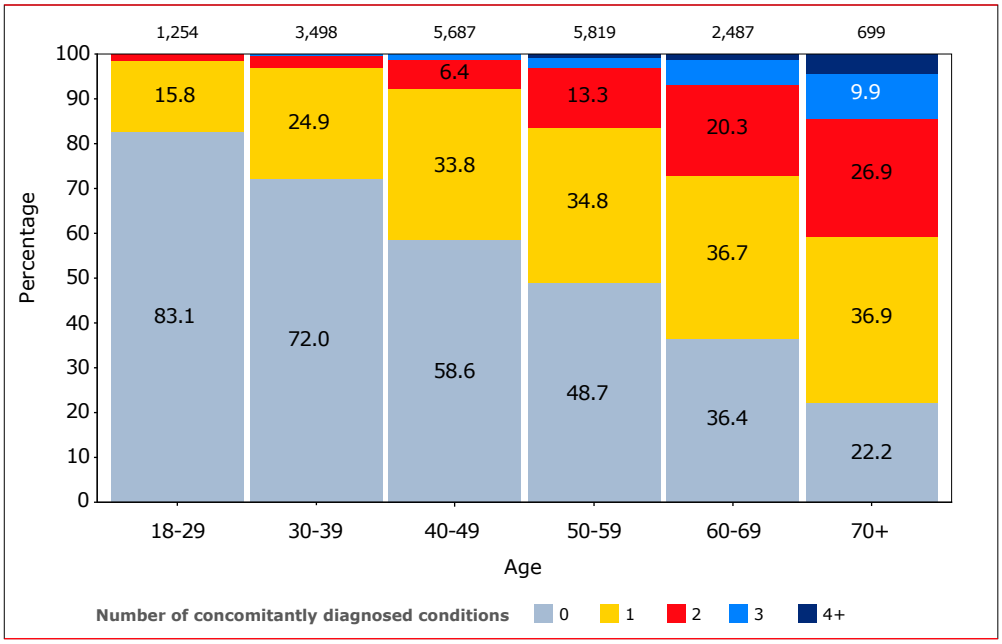
A substantial proportion of those people who were newly-diagnosed with HIV and entered HIV care in 2017 were older individuals; 27% were 50 years or older. At the same time, the overall population of people with HIV in care in the Netherlands also continues to age (*Figure 7*), with 48% currently older than 50 years compared with 39% in 2013.

***Figure 7:** Age distribution of people living with HIV and in care in the Netherlands in 2017.*



As in the general population, older age was an important risk factor for comorbidities such as cardiovascular disease and non-AIDS malignancies. Of particular concern is the increasing proportion of individuals with multiple comorbidities, the risk of which appears to be increased in those with HIV *(Figure 8)*.

Figure 8: Prevalence of non-HIV/AIDS multimorbidity in adults in HIV care in 2017. Numbers on top of the bars represent the number of individuals contributing data to that age category.



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 2000-2017. 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 limited uptake of these medications in the prevention of primary cardiovascular disease in high-risk individuals.

Non-AIDS malignancies

The most common non-AIDS malignancies are lung cancer, Hodgkin's lymphoma, anal, gastrointestinal, prostate, and head and neck cancers. Although the incidence rate of non-AIDS malignancies in the Netherlands has remained stable over time, the number of deaths due to these malignancies has increased. However, when taking the increasing age of the HIV-positive population into account, we did observe a decline in the risk of new non-AIDS malignancies in men, including anal cancer. This may be the result of a reduction in risk factors such as smoking, as well

as expanded screening and treatment for early stages of anal cancer, together with a higher proportion of individuals living with higher CD4 cell counts in more recent years.

Improved awareness of risk factors may reduce comorbidity

Resilient ageing in people living with HIV and a lower comorbidity burden can be achieved by increasing awareness of the role of modifiable and often lifestyle-related risk factors among both physicians and the people living with HIV themselves. This is particularly relevant for older individuals and those at increased risk of comorbidity, and applies not only to conditions such as cardiovascular disease and diabetes mellitus, but also to cancer, chronic kidney disease and loss of bone mineral density.

Hepatitis B and C virus co-infections

Hepatitis B and C virus screening is now universal

Hepatitis C (HCV) and hepatitis B (HBV) co-infections are far more prevalent in HIV-positive individuals than in the general population due to shared routes of transmission. Screening for HCV and HBV co-infection is part of standard HIV care in the Netherlands and the presence or absence of these co-infections is now documented for almost all HIV-positive individuals.

Hepatitis C virus co-infection

Approximately 12% of all individuals monitored by SHM had evidence of ever having been exposed to HCV, with 6% having documented evidence of chronic infection and 2% having evidence of acute HCV infection. Most individuals with HCV infection were male and from the Netherlands or other European countries.

Hepatitis B virus 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 for treatment of HIV. Six percent of individuals ever in care were found to have chronic HBV infection.

HBV vaccination remains a priority

An estimated 29% of HIV-positive individuals overall and 21% of MSM had not been exposed to HBV and had not been successfully vaccinated and therefore 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.

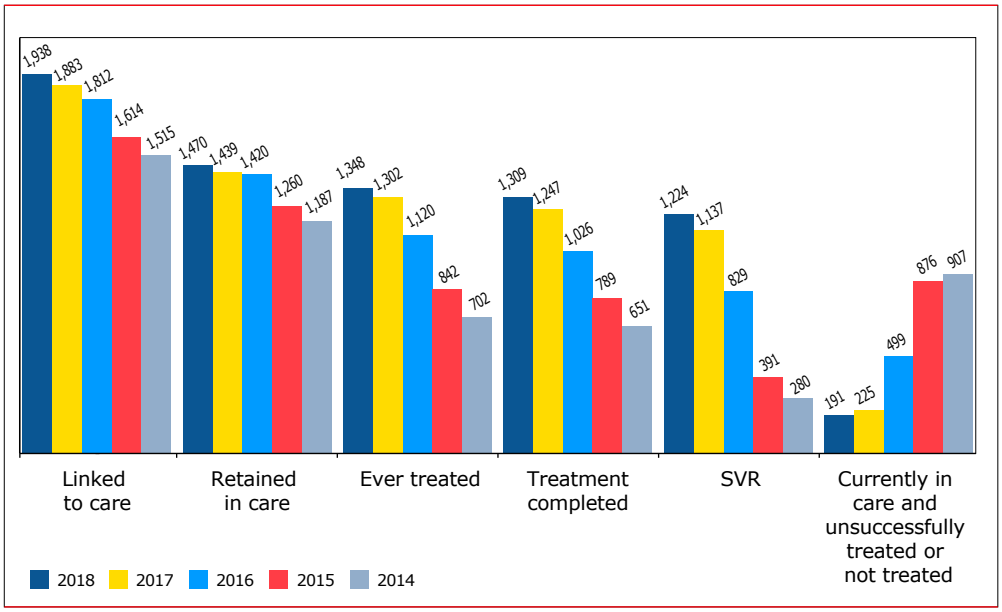
Risk of dying from HCV or HBV co-infection is decreasing

Overall, HIV-positive individuals with an active HCV or HBV co-infection remain at increased risk of liver-related morbidity and mortality. However, people diagnosed with chronic HCV or HBV after 2000 (i.e., after tenofovir was introduced), have a lower risk of liver-related death. For those with chronic HBV infection, this is likely a result of increasingly effective HBV treatment through the use of tenofovir-containing cART.

Successful HCV treatment with direct-acting antivirals has progressed further

Our data clearly show that the large majority of HIV-positive individuals with HCV co-infection have now received treatment for HCV. By 31 December 2017, over 800 individuals had received, or were receiving, treatment with novel direct-acting antiviral agents (DAAs). Of all people treated with DAAs, 97% achieved a sustained virological response and no longer had evidence of an active HCV infection. These developments have resulted in fewer HCV co-infected individuals remaining in need of treatment than in previous years *(Figure 9)*.

Figure 9: Hepatitis C virus continuum of care.



Legend: SVR=sustained virological response.

Successful HCV treatment prevents HCV transmission

Successful treatment of HCV may also prevent onward HCV transmission, as suggested by the lower number of acute HCV infections observed in the past year, together with the rapid decline in prevalence of active HCV infections. In MSM the prevalence of active HCV infections decreased to less than 1% in 2017. Although there has been a drop in the HCV re-infection rate in most recent years, re-infection following successful treatment continues to be reported, indicating that HCV transmission has not ceased completely.

Regular HCV screening among sexually-active MSM recommended

Over time, the rapidly expanding availability of DAA regimens for HCV, together with optimised screening for HCV co-infection, is expected to limit the impact of HCV co-infection on long-term liver-related morbidity and mortality; however, this effect should be monitored. To reduce new HCV infections among the key affected population of sexually-active MSM, regular screening for HCV among successfully-treated individuals is recommended for early detection of HCV re-infections, in combination with preventive behavioural interventions.

Children living with HIV

No new cases of perinatal transmission of HIV within the Netherlands since 2015

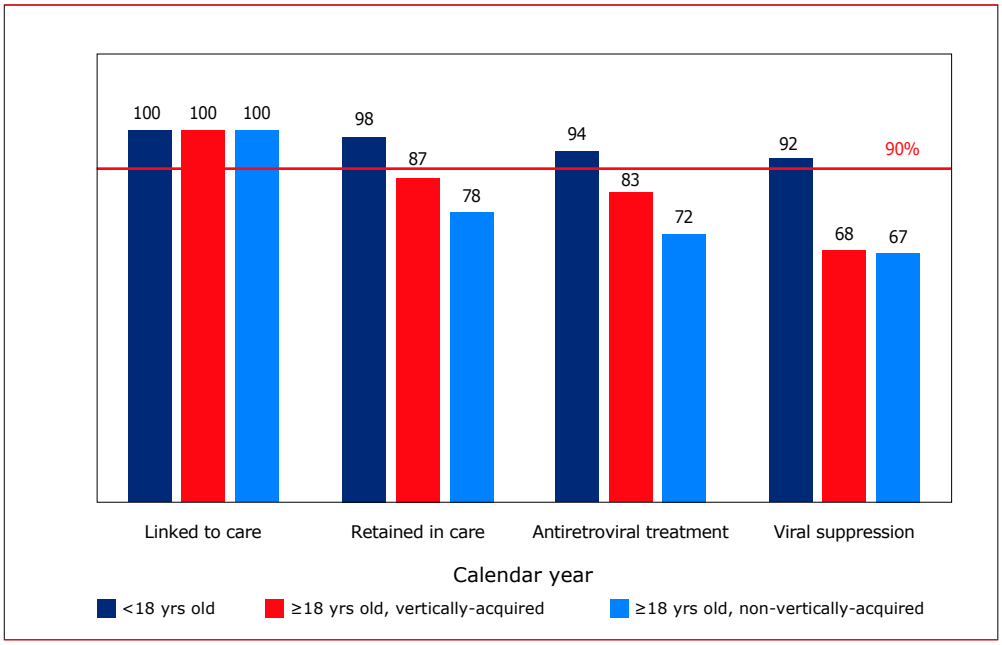
Of 603 children diagnosed with HIV before the age of 18 and ever registered by SHM, the majority (77%) remains in care. Of the children who are currently in care, 115 (25%) were born outside the Netherlands and adopted by Dutch parents.

The majority (67%) of children who acquired HIV perinatally were born outside the Netherlands, Perinatal transmission of HIV within the Netherlands has become extremely rare, with no new cases reported since 2015.

Favourable outcomes for HIV-positive children

There is a high retention-in-care rate among children currently under the age of 18. Outcomes for children who are receiving cART are generally favourable and have resulted in a low mortality rate and good long-term immunological responses *(Figure 10)*.

Figure 10: Cascade of care by age and mode of HIV acquisition, as of 31 December 2017. The numbers on top of the bars indicate the proportion of individuals.



Poorer viral suppression around transition to adult care

Of those individuals who were originally registered as a child and were still in care in 2017, 61% were older than 18 as of 31 December 2017. In the individuals who had transitioned from paediatric to adult care, 21% did not have suppressed viraemia at the time of transition, suggesting challenges for these adolescents with respect to adherence to treatment around the time of transition to adult care.

Optimisation of long-term care for young people

The relatively large proportion of adolescents who have inadequately-suppressed viraemia at the time of transitioning to adult care illustrates that long-term care for this particularly vulnerable and difficult-to-manage group of young individuals clearly needs to be further optimised.

Quality of care

High overall retention in care

The quality of care provided in Dutch adult HIV treatment centres was explored using indicators based on the national guidelines issued by the Dutch Association of HIV-Treating Physicians. Overall, retention in care was found to be high in most HIV treatment centres in the Netherlands, although it was lower for people not born in the Netherlands.

Earlier start of cART and high rates of viral suppression

In addition, across most centres, people are starting cART sooner after entering into care, confirming that most centres are following the guideline to offer cART to everyone with newly-diagnosed HIV regardless of CD4 count. However, there are some centres in which this policy could be improved further for people who enter care with CD4 cell counts above 350 cells/mm^3. Regardless of time since entering care, a median proportion of 99% of all individuals who entered care between 2012 and 2016 and who were retained in care in 2017 had initiated cART.

Viral suppression rates in the first 6 months on cART, as well as during longer term use of treatment, were high across all centres, regardless of the number of people receiving care at a particular centre.

Heterogeneity in repeat HCV screening

Greater heterogeneity was observed in repeat HCV screening in MSM. This variation is thought to be to a difference in screening policy, with centres screening partly on the basis of elevated liver enzymes. Given that HCV transmission still occurs, continued monitoring of (repeat) HCV screening rates is certainly warranted.

HIV in Curaçao

In recent years, individuals with HIV in care at the St Elisabeth Hospital in Willemstad 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, cART is being started at increasingly higher CD4 cell counts. However, although early start of treatment appears to be possible, data also suggest that long-term retention in care needs to be improved to optimise the sustained effect of treatment.

Amsterdam Cohort Studies

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS were started in 1984 a few years after the first cases of AIDS were diagnosed in the Netherlands. By enrolling men who have sex with men (MSM) in a prospective cohort study, the ACS aimed 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. A second cohort involving people who use drugs (PWUD) was initiated in 1985. Follow up of PWUD ended in 2016. In 2017, the cohorts reached 33 years of follow up.

As of 31 December 2017, 2,796 MSM had been included in the ACS, of whom 607 were HIV-positive when they entered the study and 253 seroconverted during follow up. In 2017, 701 HIV-negative and 73 HIV-positive MSM remained in active follow up at the GGD Amsterdam, with an additional 256 HIV-positive MSM being followed at the MC Jan van Goyen or the DC Klinieken Lairesse-Hiv Focus Centrum in Amsterdam. In 2017, 60 additional HIV-negative MSM were recruited. The median age in this group was 29.5 years, while that of the total group of MSM in active follow up was 42.5 years at their last visit. The majority (85.0%) of the total group were born in the Netherlands and 83.8% were residents of Amsterdam. Finally, 75.3% of the participants had a college degree or higher. In 2017, 2 MSM participating in the ACS seroconverted for HIV. The observed HIV incidence among MSM has remained relatively stable and low in recent years and was 0.5 per 100 person years in 2017.

Monitoring programme report

1. The HIV epidemic in the Netherlands

Ard van Sighem and Eline Op de Coul

Introduction

As of May 2018, 28,457 HIV-positive individuals had ever been registered by Stichting HIV Monitoring (SHM). Of those, 27,352 were followed in one of the HIV treatment centres in the Netherlands (*Figure 1.1*), while the remaining 1,105 were followed in the St. Elisabeth Hospital in Willemstad, Curaçao (see *Chapter 9*). Of the 27,352 people in the Netherlands, the majority were diagnosed with HIV-1 (25,988; 95%). A small group of people, 98 in total, were diagnosed with HIV-2, while 68 people had antibodies against both HIV-1 and HIV-2. Serological results were not available in the SHM database for 1,198 individuals, a group that mostly comprised people who were registered in the AIDS Therapy Evaluation in the Netherlands (ATHENA) study, but for whom no data were collected.

This chapter will first focus on the 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 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 2017.

Back to Chapter 2 >

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

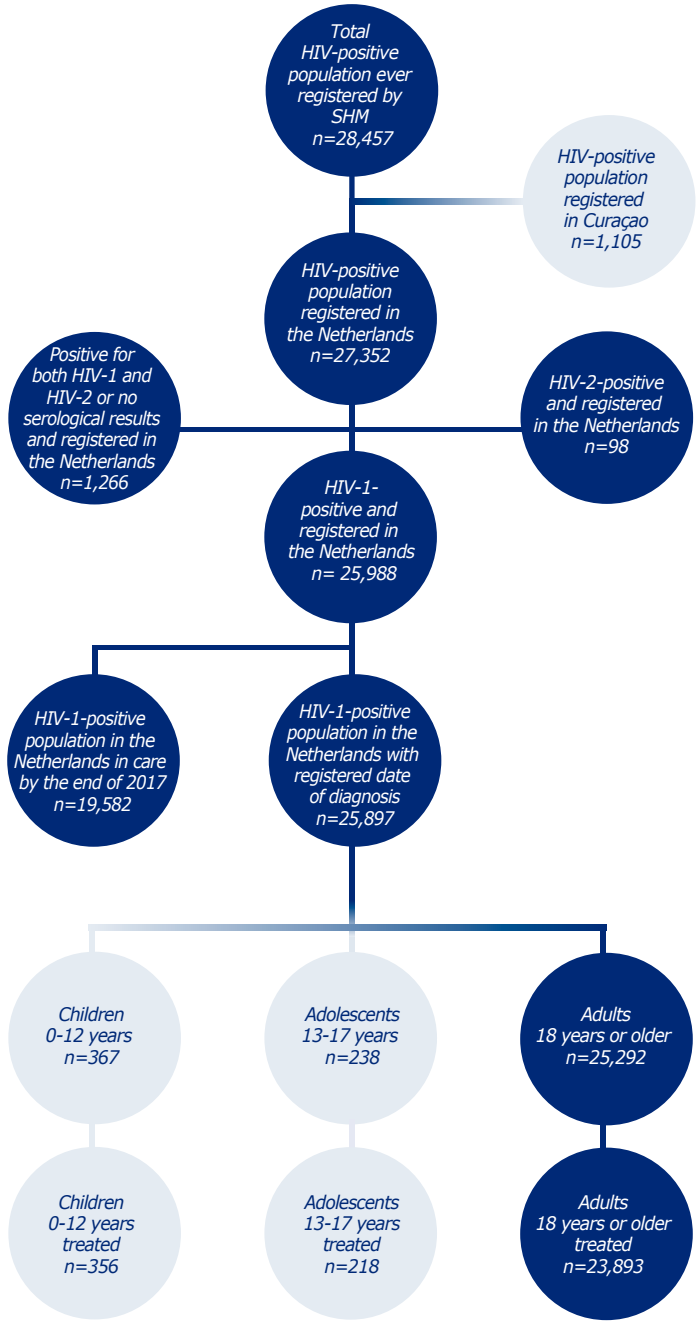
Infection	The moment an individual acquires an HIV infection. The time of infection is often unknown.
Diagnosis	The moment an individual is newly diagnosed with an HIV infection. The time of diagnosis can be weeks, months, or years after infection.
Entry into care	The moment an HIV-positive individual is first seen for care in an HIV treatment centre, which usually is within a few weeks of HIV diagnosis.
Registration	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, 25,292 individuals were ever diagnosed with HIV-1 as adults and had a recorded date of diagnosis (*Figure 1.1*). The majority of these 25,292 adults were men who have sex with men (MSM; 15,281 [60%]), while 3,441 other men (14%) and 4,139 (16%) women reportedly acquired their HIV infection via heterosexual contact (*Appendix Table 1.1*). For 767 (3%) individuals, the reported mode of transmission was injecting drug use, while for 326 (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 2017.*

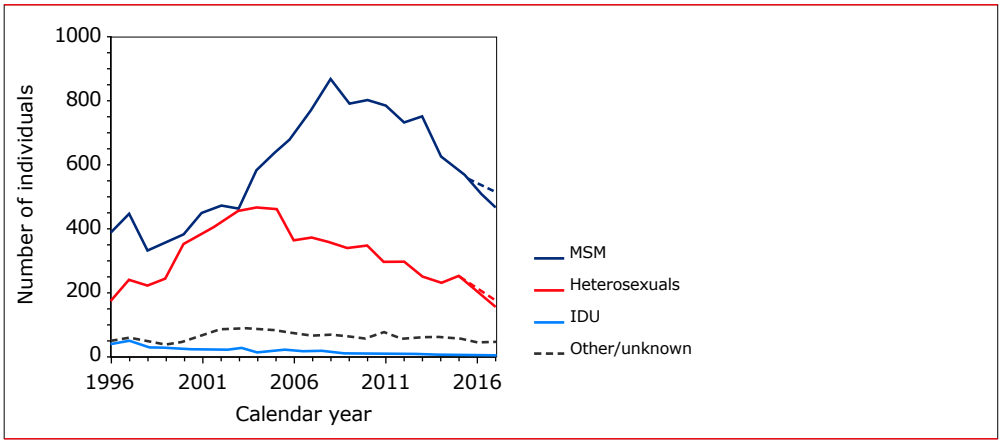


Decreasing number of diagnoses

From the 1990s until 2008, the annual number of new diagnoses in the entire population increased from approximately 650 to well above 1,300 (*Appendix Table 1.1*). From 2009 onwards, the registered number of new diagnoses has steadily declined. In 2017, the decreasing trend continued and the projected number of new HIV diagnoses, taking into account a backlog[a] in registration of HIV cases, was approximately 750.

In MSM, the annual number of diagnoses was approximately 400 in 1996 and increased to more than 850 in 2008 (*Figure 1.2*). Thereafter, the number of diagnoses decreased gradually to approximately 516 in 2017. In individuals who acquired their HIV infection via heterosexual contact, the number of new diagnoses has declined to approximately 200 cases per year in the last few years. As shown later in this chapter, this decline in the heterosexual population is largely the result of a reduced number of diagnoses in people born abroad. 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 2017, men who have sex with men (MSM) accounted for 69% of new diagnoses, infections via heterosexual contact for 23%, infections via injecting drug use 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 2016, 11% in 2017) is taken into account.*



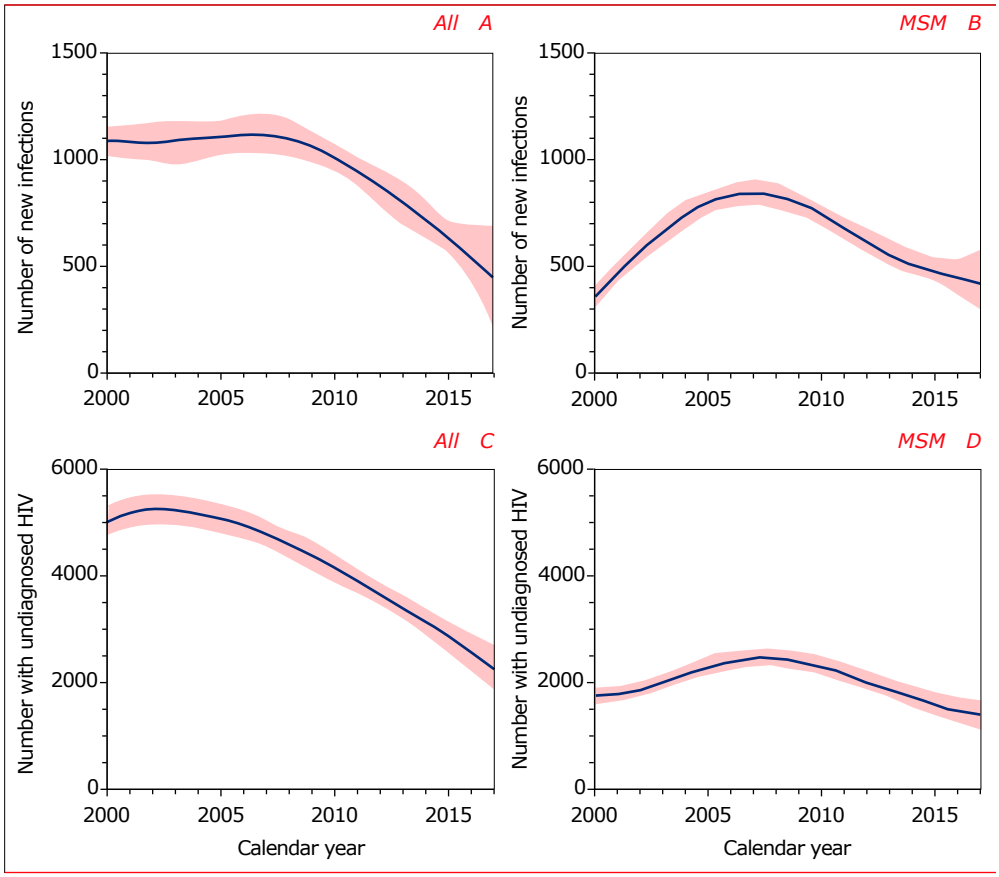
Legend: *MSM=men who have sex with men; IDU=injecting drug use.*

a 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 2016 and 11% in 2017.

Decreasing number of newly-acquired 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 newly-acquired HIV infections each year between 2000 and 2010[1]. Thereafter, the number of new infections decreased over time to 450 (95% CI, 200-650) in 2017 (*Figure 1.3A*). In MSM, the annual number of newly-acquired HIV infections reached a peak of approximately 800 around 2007 and then decreased to around 400 (95% CI, 250-550) in 2017 (*Figure 1.3B*). Since 2000, 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.*

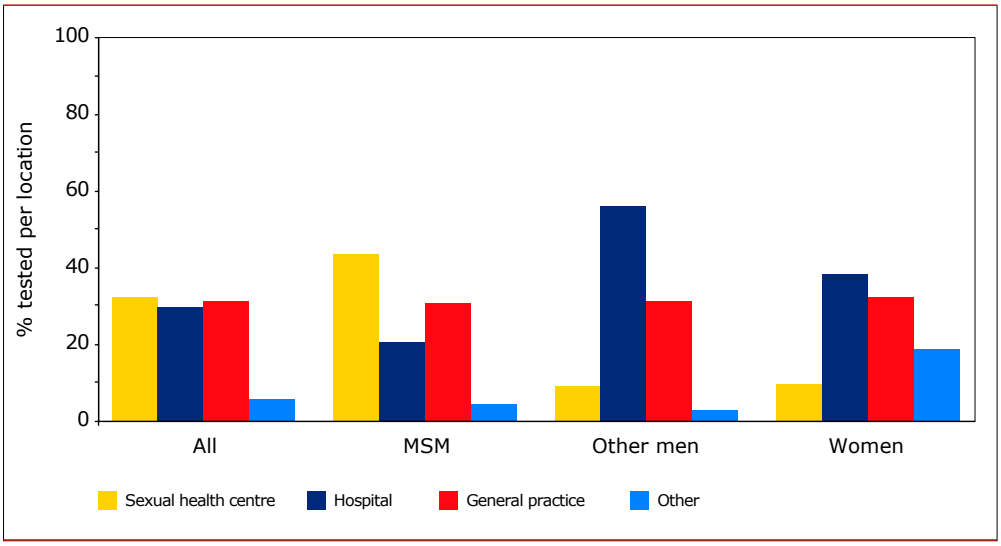


Legend: *MSM=men who have sex with men.*

Testing location

Information on the location of HIV testing was available for 90% of people diagnosed in 2015 or later. Overall, 30% of these individuals received their first HIV-positive test result at a sexual health centre, 27% at a hospital, and 28% at a general practice (*Figure 1.4*). Among those tested at sexual health centres, 90% were MSM, 6% were other men, and 4% were women. These proportions are identical to those directly reported by sexual health centres in 2017[2].

Figure 1.4: *Proportion of individuals diagnosed in 2015 or later, stratified by location of testing and transmission risk group.*



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

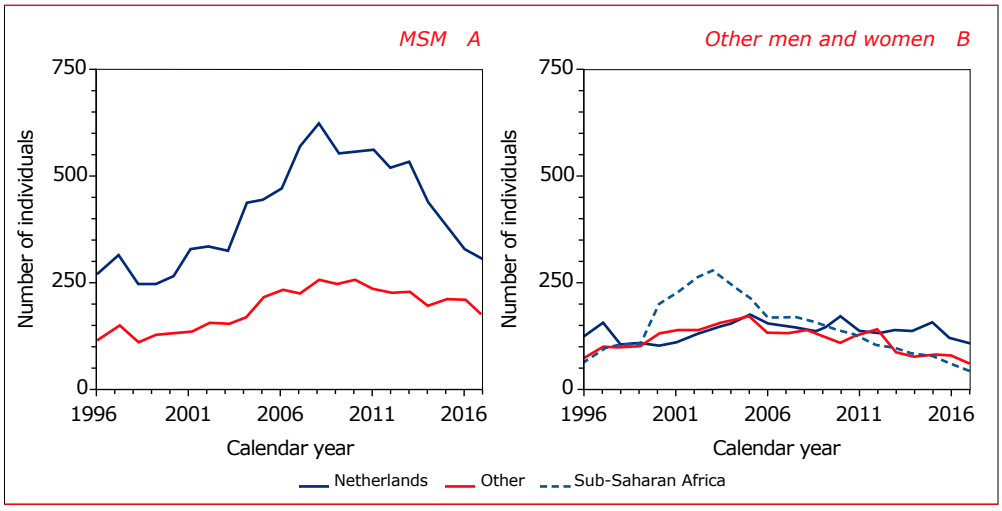
Geographical region of origin

Overall, 69% of people 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 (i.e., in those diagnosed in or after 2015), the proportion of MSM of Dutch origin was 63% (*Appendix Table 1.2*), while minor changes were observed in the proportion of MSM from western and central Europe and the Caribbean.

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 2015 onwards, 50% of the newly-diagnosed women and other men were of Dutch origin, and 23% 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 people aged 18 years or older at the time of diagnosis. Of the 15,281 MSM, 10,582 (69%) originated from the Netherlands, 1,670 (11%) from other European countries, 1,048 (7%) from South America, and 592 (4%) from the Caribbean. Among the other 10,011 people, 3,332 (33%) originated from sub-Saharan Africa, 3,701 (37%) from the Netherlands, 849 (8%) from South America, 460 (5%) from the Caribbean, and 411 (4%) from south and south-east Aisa. Note: data collection for 2016 and 2017 has not yet been finalised.*



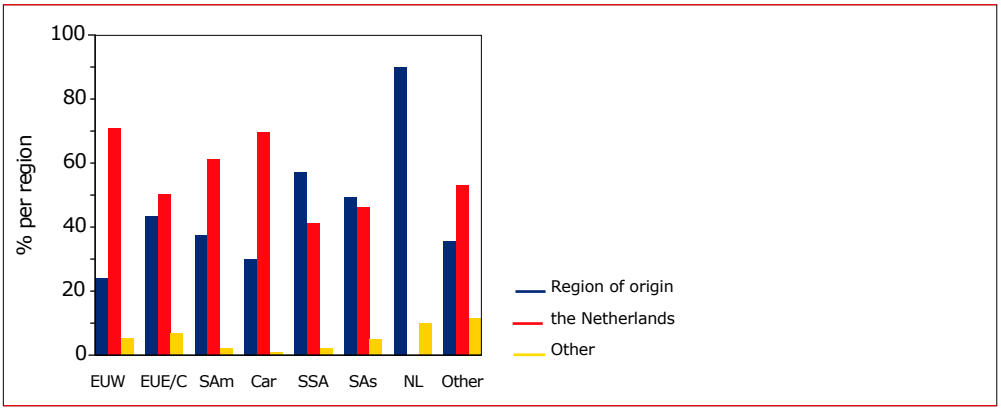
Legend: *MSM=men who have sex with men.*

Overall, 21% of the people newly diagnosed since 2015 were living in the Amsterdam public health service (PHS) region at the time of diagnosis and 14% were living in the Rotterdam-Rijnmond PHS region. These proportions were 15% and 13%, respectively, for people of Dutch origin and 29% and 16%, respectively, for people originating from other countries. Among MSM, 24% were living in Amsterdam at the time of diagnosis and 14% were living in Rotterdam, while in other groups these proportions were 14% and 15%, respectively. Other PHS regions with at least 4% of new diagnoses were Haaglanden (7%, including Den Haag), Utrecht (6%), Hart voor Brabant (5%, including Den Bosch and Tilburg), and Gelderland-Midden (4%, including Arnhem).

Geographical region of HIV acquisition

The most likely country of HIV acquisition was reported for 1,810 (75%) of the adult population diagnosed in 2015 or later (*Figure 1.6*). The majority of the people born in the Netherlands (90%) reported having acquired their HIV infection in the Netherlands. Among foreign-born individuals, the proportion who acquired their HIV infection in the Netherlands increased from 39% before 2015 to 55% in 2015 or later. This shift towards migrants being more likely to acquire their HIV infection in the Netherlands was most apparent in people born in sub-Saharan Africa. Before 2015, 81% reported probably having acquired their HIV infection in sub-Saharan African and 16% in the Netherlands, whereas these proportions were 57% and 41%, respectively, among those diagnosed in 2015 or later.

Figure 1.6: *Proportion of all HIV-1-positive adults diagnosed in 2015 or later per region of origin who reported to have acquired their HIV infection in their own region of origin, in the Netherlands, or elsewhere.*



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

The majority (82%) of MSM diagnosed in 2015 or later acquired their HIV infection in the Netherlands. Of the other people with a reported region of acquisition, 66% acquired HIV in the Netherlands, while 14% reported having acquired HIV in sub-Saharan Africa. The proportion of Dutch-born people who likely acquired HIV in the Netherlands was 91% for MSM, 84% for other men and 86% for women.

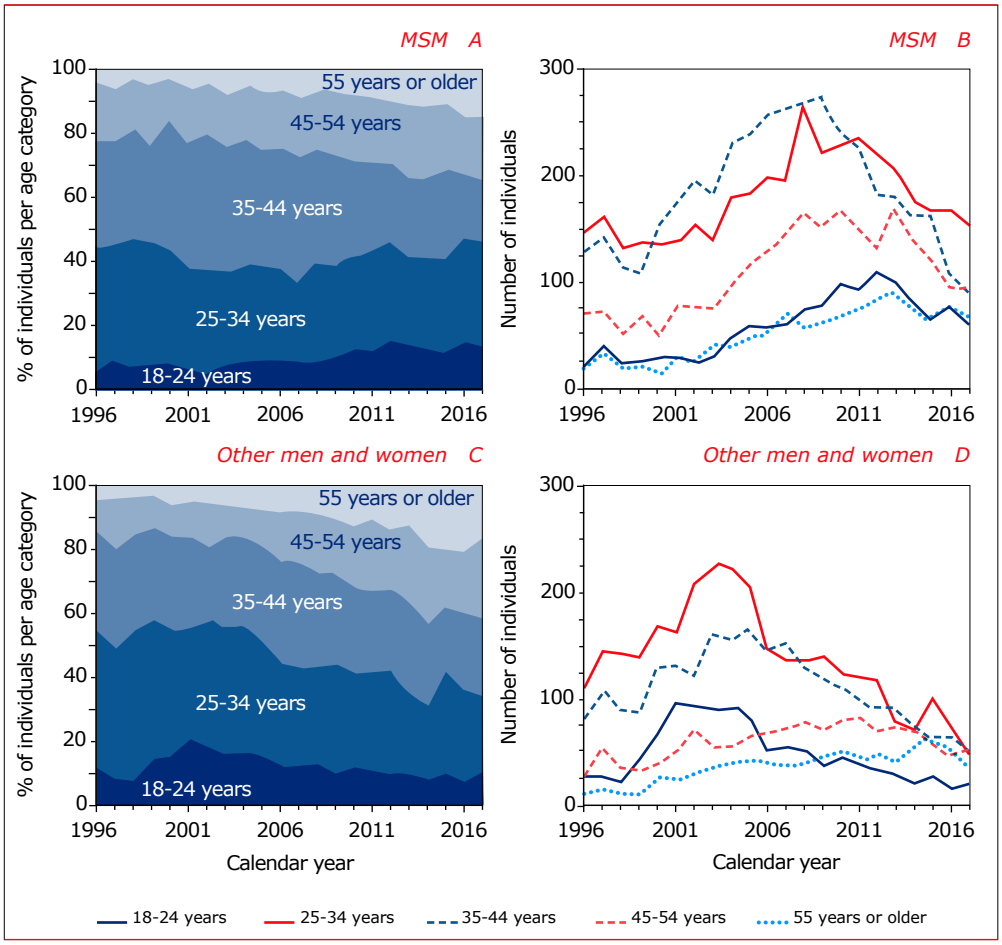
Increasingly older age at time of HIV diagnosis

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 2017, it was 38 (IQR 29-50) years. Over the entire period from 1996 through 2017, 16% of adults who received an HIV diagnosis were 50 years or older; in 2017, 25% were 50 years or older.

There were considerable age differences between MSM, other men, and women diagnosed in 2015 or later. MSM born in the Netherlands were diagnosed at a median age of 42 (31-52) years, while those of foreign origin were diagnosed at 32 (27-40) years. Among other people of Dutch origin, the median age at the time of diagnosis was 40 (30-56) years for women and 46 (32-57) years for men. Individuals born in sub-Saharan Africa (women: 37 years; men: 39 years) or elsewhere (women: 36 years; men: 38 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 people 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 2017, the proportion of MSM aged 45 years or older at the time of diagnosis increased from 24% to 35%, while these proportions were 15% and 42% for other individuals. During the same period, the proportion of individuals between 25 and 34 years of age decreased from 38% to 33% for MSM and from 43% to 23% for other individuals.*



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

Young adults

The number of diagnoses among young adults less than 25 years of age who did not acquire their HIV infection via homosexual contact was approximately 90 in the early 2000s and decreased to approximately 20 in 2017, or to 10% 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 15% (109) of the diagnoses. Thereafter, the proportion of diagnoses among young MSM remained around this level, although the absolute number has decreased.

Entry into care

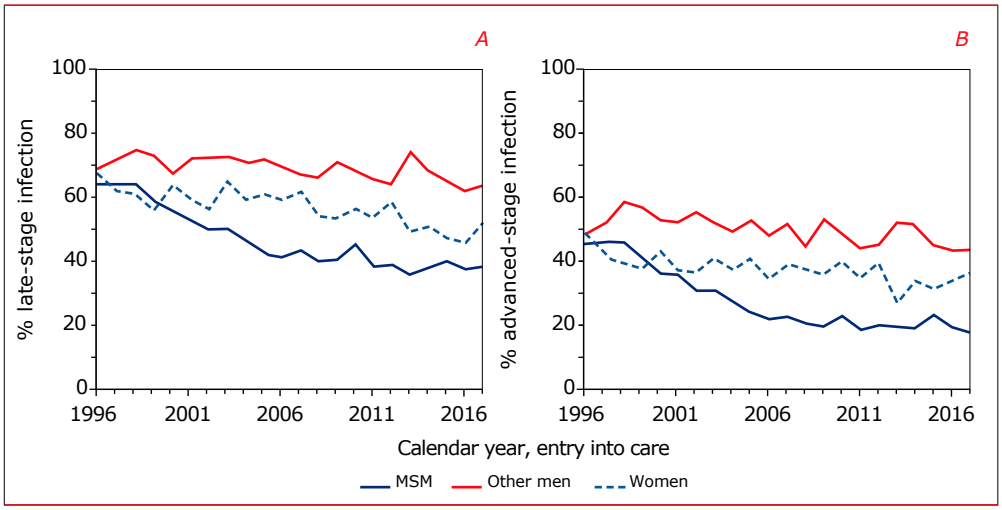
Of all individuals diagnosed with HIV in 2015 or later for whom the location of testing was known, excluding those diagnosed abroad, 92% had entered care within 4 weeks of receiving their diagnosis and 96% within 6 weeks. The proportion in care within 6 weeks was 96% for individuals who received their first HIV-positive test at a sexual health centre, and similar for those who tested HIV-positive in a hospital (97%), at a general practice (96%), or at other locations (96%). Overall, the proportion in care within 6 weeks was similar for MSM (96%), other men (96%), and women (97%), and did not differ by age at the time of diagnosis. However, the proportion in care within 6 weeks was larger among individuals born in the Netherlands (98%) than among those born abroad (94%).

Late presentation

In total, 30% of the individuals entering care from 1996 onwards had CD4 counts of 500 cells/mm^3 or higher, 20% had CD4 counts between 350 and 499 cells/mm^3, 20% had CD4 counts between 200 and 349 cells/mm^3, and 30% had CD4 counts below 200 cells/mm^3, while 17% had already been diagnosed with AIDS. For people entering clinical care in 2015 or later, these proportions had somewhat improved and were 36%, 21%, 19%, and 25%, respectively; 12% had already been diagnosed with AIDS.

Overall, 52% of the individuals were late presenters, i.e., presenting for care with either a CD4 count below 350 cells/mm^3 or an AIDS-defining event regardless of CD4 count[3]. Although the proportion of late presenters has decreased over time, in 2017, 45% 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^3 or AIDS, has likewise decreased over time and was 26% in 2017.

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 (2015) onwards, 52% (44%) presented with late-stage HIV infection: men who have sex with men (MSM) 44% (38%), other men 69% (63%), and women 57% (48%). Overall, 33% (27%) presented with advanced-stage HIV infection: MSM 26% (20%), other men 51% (45%), and women 38% (34%). Late-stage HIV infection: CD4 counts below 350 cells/mm³ or having AIDS, regardless of CD4 count. Advanced-stage HIV infection: CD4 counts below 200 cells/mm³ or having AIDS.



Legend: MSM=men who have sex with men.

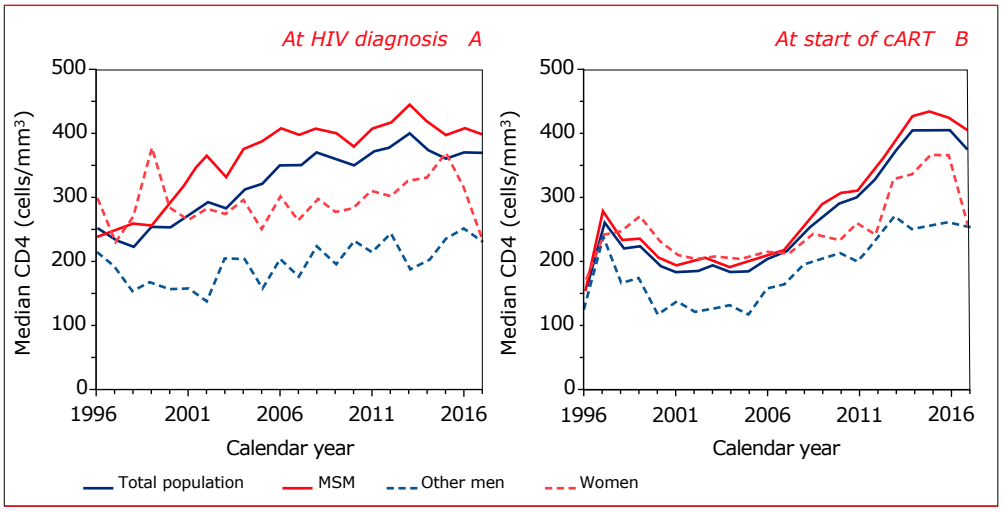
Among individuals entering clinical care in 2015 or later, 38% of MSM, 63% of other men, and 48% of women were late presenters. Late presentation was most commonly found among people originating from sub-Saharan Africa (57%) or south and south-east Asia (56%), and among people originating from the Netherlands (60%) or from South America (54%) who acquired their HIV infection via other routes than homosexual contact (*Appendix Table 1.3*).

Late presentation was also more common in individuals entering care at older ages. Late presentation was seen in 50% of MSM, 71% of other men, and 59% of women entering care in 2015 or later at 45 years of age or older, compared with 23% of MSM, 48% of other men, and 26% of women entering care at ages younger than 25 years (*Appendix Table 1.3*). 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 (75%) compared with those who were tested at a general practice (44%), a sexual health centre (26%), or another testing location (38%).

Earlier diagnosis

Between 1996 and 2017, median CD4 counts in the total adult population at the time of diagnosis increased from 250 to 380 cells/mm³ (*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). (A) Between 1996 and 2017, CD4 counts at the time of diagnosis increased from 250 (interquartile range [IQR], 80-437) to 380 (IQR 182-550) cells/mm³ in the total adult population. The increase was most apparent for men who have sex with men (MSM): 245 (IQR 80-450) cells/mm³ in 1996 and 410 (IQR 260-580) cells/mm³ in 2017. During the same period, CD4 counts in other men and in women were 220 (IQR 40-410) and 300 (IQR 130-450) cells/mm³, respectively, in 1996, and 235 (IQR 100-460) and 237 (IQR 83-480) cells/mm³ in 2017. (B) In the total adult population, CD4 counts at the start of cART rose to 260 (IQR 130-400) cells/mm³ shortly after cART became available, decreased to a plateau of approximately 180 cells/mm³ between 2000 and 2005, and increased thereafter. In 2017, CD4 counts were 380 (IQR 202-554) cells/mm³ in the total population, 410 (IQR 260-580) cells/mm³ in MSM, 254 (IQR 100-470) cells/mm³ in other men, and 256 (IQR 80-360) cells/mm³ in women. The apparent decrease in CD4 counts in women in 2017 is most likely a consequence of the relatively low number of diagnoses in this group.*



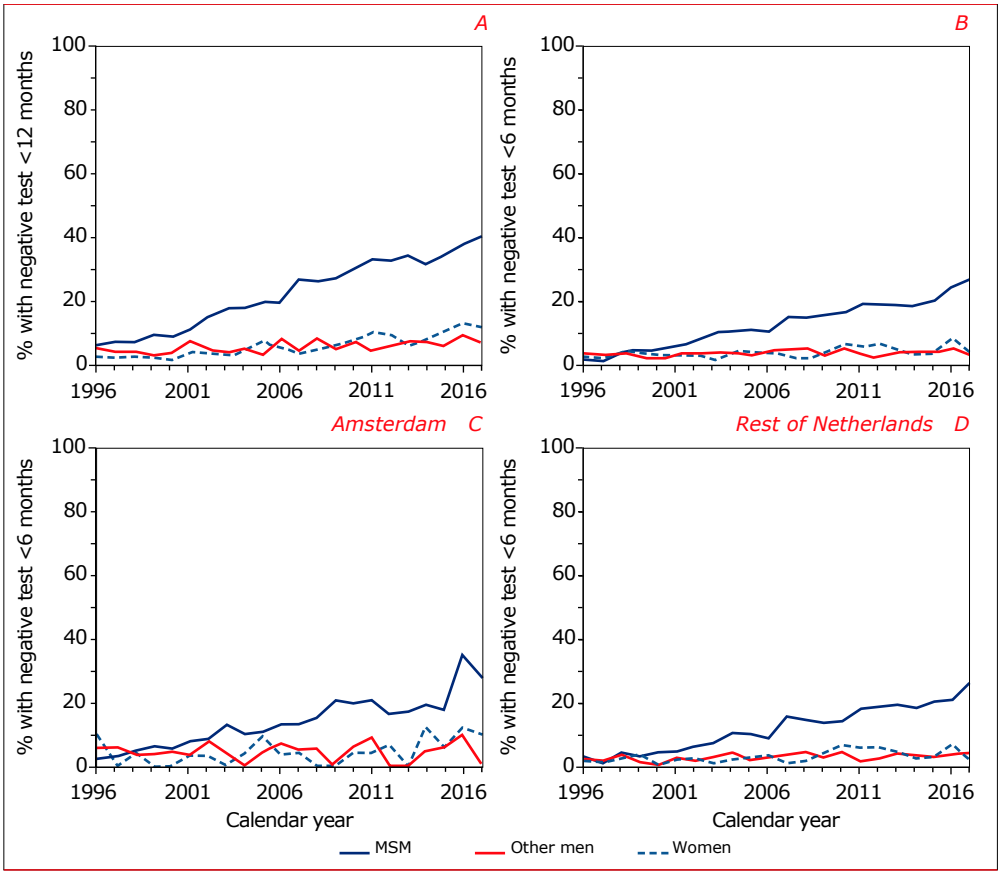
Legend: *MSM=men who have sex with men; cART=combination antiretroviral therapy.*

Recent infection

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; by 2017, these proportions had increased to 40% and 26%, respectively. For other men and for women, the proportions with a recent infection between 2010 and 2017 were considerably lower: only 7% had a negative test in the 12 months before diagnosis, while 4% had a negative test in the 6 months before diagnosis.

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. Panels C and D show the proportions with a last negative test in the preceding 6 months for (C) Amsterdam and (D) for the rest of the Netherlands. Altogether, 40% of men who have sex with men (MSM), 7% of other men, and 12% of women diagnosed in 2017 had a last negative test at most 12 months before diagnosis, whereas 26% of MSM, 3% of other men, and 2% of women had a last negative test at most 6 months before diagnosis.*



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

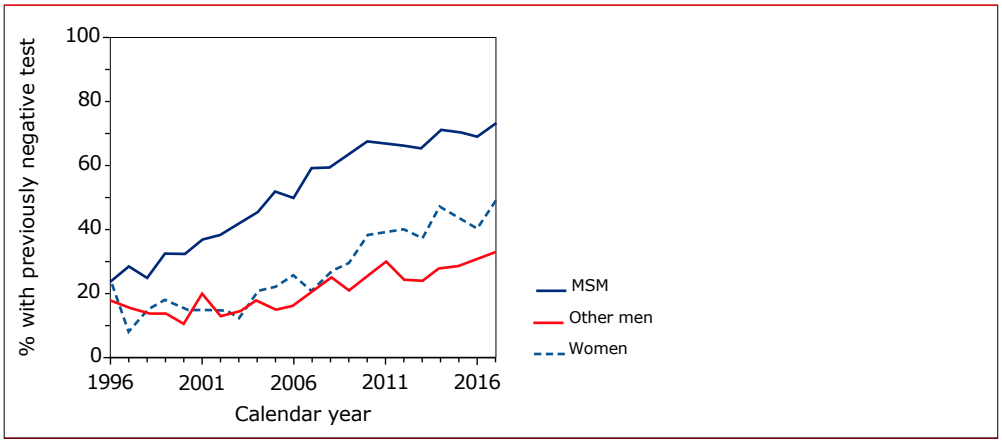
Amsterdam compared with the rest of the Netherlands

Last year, we reported an increase in the proportion of MSM in Amsterdam with a negative test in the 6 months before diagnosis - from 18% between 2010 and 2015 to 36% in 2016 - while there was a more modest increase in the rest of Netherlands[4]. In this year's monitoring report, with more data being available for 2016, the proportion was slightly lower at 34% in 2016 and 27% in 2017 (*Figure 1.10C*). In the rest of the Netherlands, the proportion with a negative test in the 6 months before diagnosis was 21% in 2016 and increased to 26% in 2017, which was not significantly different from the proportion in Amsterdam in that year (*Figure 1.10D*).

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 2017, 73% of MSM, 33% of other men, and 49% of women newly diagnosed with HIV had a known previous test with a negative result. The proportion with a known previously negative test was highest among those diagnosed at a sexual health centre (81%), compared with 40% of those diagnosed in a hospital, 61% of those diagnosed at a general practice, and 79% of those diagnosed elsewhere.

Figure 1.11: *Proportion of individuals diagnosed after a previously negative HIV test. Altogether, 73% of men who have sex with men (MSM), 33% of other men, and 49% of women diagnosed in 2017 had a previously negative HIV test.*



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

Treated population

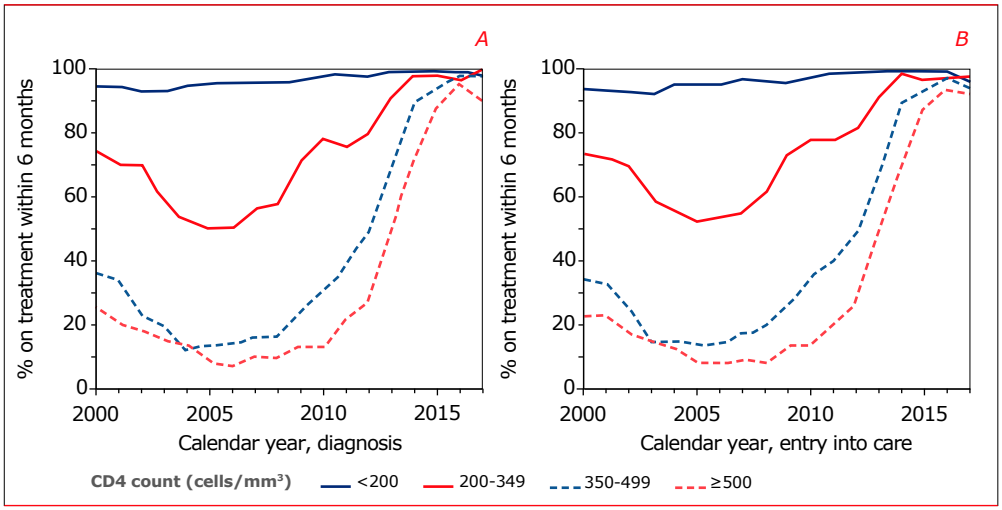
Of the 25,292 adults ever registered with an HIV-1 infection, 23,893 (94%) had started cART by May 2018. The majority of these individuals (89%) started cART while being antiretroviral therapy-naive. Treatment and treatment outcomes are described in more detail in *Chapter 2*.

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 2017, median CD4 counts at the start of treatment had increased to 380 cells/mm^3. Of those starting cART in 2017, 24% of people started treatment at CD4 counts already below 200 cells/mm^3, 21% started at CD4 counts between 200 and 349 cells/mm^3, 24% started at CD4 counts between 350 and 499 cells/mm^3, and 32% started at CD4 counts of 500 cells/mm^3 or above.

The main reason for starting treatment too late, i.e., at low CD4 counts, appears to be a late diagnosis, because most people who are able to start treatment on time now do so. Those with less than 200 CD4 cells/mm^3 at diagnosis or at the time of entry into care have always started treatment almost immediately, with nearly everyone starting cART within 6 months after diagnosis (*Figure 1.12*). On the other hand, those with higher CD4 counts used to be less likely to start treatment within 6 months of diagnosis, but this likelihood has rapidly increased in recent years, reflecting changes in treatment guidelines towards a universal start of treatment regardless of CD4 count. In 2017, 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 (*Appendix Figure 1.2*).

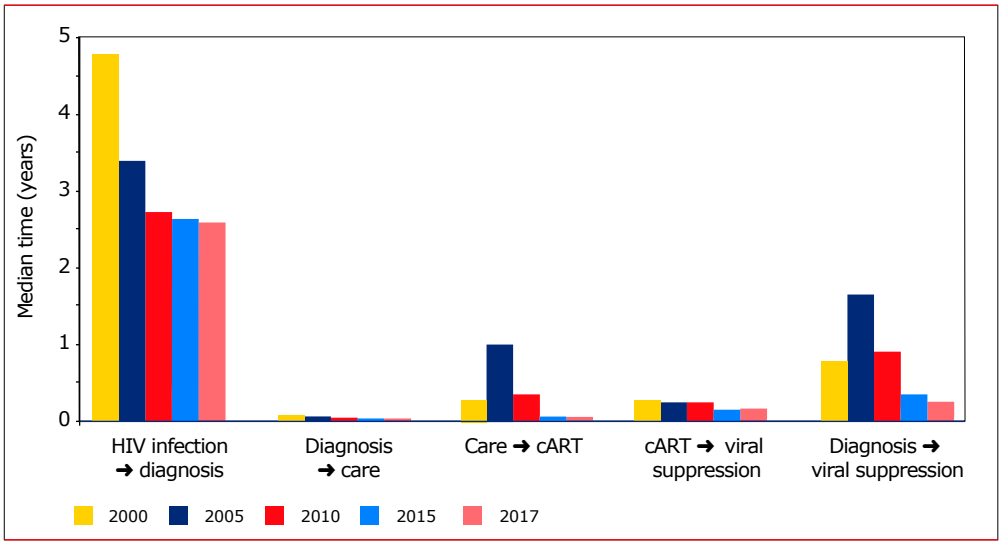
Figure 1.12: (A) Proportion of individuals who started combination antiretroviral treatment (cART) within 6 months after HIV diagnosis by CD4 count at the time of diagnosis. (B) Proportion of individuals who started cART within 6 months after entry into care, stratified by CD4 counts at the time of entry into care. 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 2015 or later, 99% of those with CD4 counts below 200 cells/mm³, 98% of those with CD4 counts between 200 and 349 cells/mm³, 96% of those with CD4 counts between 350 and 499 cells/mm³, and 91% of those with CD4 counts of 500 cells/mm³ or above had started cART within 6 months of diagnosis. In people who entered HIV care in 2015 or later, 99% of those with CD4 counts below 200 cells/mm³, 97% of those with CD4 counts between 200 and 349 cells/mm³, 95% of those with CD4 counts between 350 and 499 cells/mm³, and 91% of those with CD4 counts of 500 cells/mm³ or above had started cART within 6 months of entry.



Time between HIV infection and viral suppression

People with a suppressed viral load are highly unlikely to transmit their virus to uninfected partners[5,6]. Therefore, it is of paramount importance, not only for people living with HIV, but also from a public health perspective, to minimise the time between the moment a person acquires HIV and the point at which they achieve viral suppression[7]. 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 these three steps in the HIV care continuum (*Figure 1.13*). Between 2000 and 2017, 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 2.6 (1.3-4.8) years. During this same period, the median time from diagnosis to viral suppression decreased from 0.79 (IQR 0.40-3.58) years to 0.24 (0.15-0.41) years, mainly as a result of starting treatment earlier after entry into care.

Figure 1.13: 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, 98 of the 27,352 registered individuals, including 45 men and 53 women, acquired an HIV-2 infection, of whom 19 were diagnosed in 2008 or later. The majority (79, or 81%) of these people acquired their infection via heterosexual contact. HIV-2 is endemic in West Africa, and 66 people originated from this region, mostly from Ghana (25 people) or Cape Verde (24 people). Only 20 individuals were born in the Netherlands, 14 of whom reported to have acquired their HIV infection in the Netherlands. A total of 64 people were still in clinical care, 16 people had died, 6 had moved abroad, while 12 individuals had no contact with HIV care in 2017.

The median age of the people still in care was 60 (IQR 53-63) years; 83% 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 82 individuals who were diagnosed in 1996 or later, the median CD4 count at the time of diagnosis

was 340 (93-691) cells/mm^3. From 1996 onwards, 47% of the people were late presenters, and 38% presented for care with advanced HIV disease[3]. The distribution of CD4 counts at entry into care appeared to be more bimodal than for HIV-1-positive individuals: 37% had CD4 counts below 200 cells/mm^3, 40% had CD4 counts of 500 cells/mm^3 or higher, while relatively few people (23%) had CD4 counts between 200 and 499 cell/mm^3.

Treatment

In total, 60 HIV-2-positive individuals had ever started cART. Of the 40 of these individuals who were still in care by the end of 2017, 19 used a backbone of abacavir/lamivudine and 14 used tenofovir/emtricitabine. Additional drugs in the regimen included cobicistat-boosted or ritonavir-boosted darunavir in 17 individuals, ritonavir-boosted lopinavir in 8 individuals, atazanavir in 4 individuals (all ritonavir-boosted, except one), and dolutegravir in 11 individuals.

At start of cART, 25 individuals had HIV-2 RNA levels above 500 copies/ml, while 16 had levels below this threshold. Of the 64 people who were still in care, 56 had a most recent viral load measurement below 500 copies/ml, 2 had a viral load above 500 copies/ml, and 6 people had no available HIV-2 RNA result in 2016 or 2017. The 24 individuals who were still in care and had not, or not yet, started cART still had high CD4 counts with a median of 750 (520-945) cells/mm^3. All of the 20 non-treated individuals who had an HIV-2 RNA result in 2016 or 2017 had a viral load below 500 copies/ml.

HIV-1-positive people in care

Population in care

In total, 19,582 (75%) of the 25,988 registered HIV-1-positive individuals, comprising 19,390 adults and 192 minors less than 18 years of age, were known to be in clinical care (*Figure 1.1*; *Table 1.1*; *Appendix Table 1.4*) by the end of 2017. People were considered to be in clinical care if they visited their treating physician in 2017 or had a CD4 count or HIV RNA measurement in that year and they were still living in the Netherlands. Of the 6,406 people who, according to this definition, were no longer in care, 2,921 (46%) were known to have died, and 1,646 (26%) to have moved abroad, while 135 (2%) only entered HIV care in 2018 or were diagnosed with HIV in 2018.

Table 1.1: Characteristics of the 19,582 HIV-1-positive individuals in clinical care by the end of 2017. An extended version of this table is available as Appendix Table 1.4.

	Men (n=15,971, 82%)		Women (n=3,611, 18%)		Total (n=19,582)	
	n	%	n	%	n	%
Transmission						
MSM	12,378	78	-	-	12,378	63
Heterosexual	2,417	15	3,175	88	5,592	29
IDU	216	1	76	2	292	1
Blood (products)	166	1	95	3	261	1
Other/unknown	794	4	265	7	1,059	5
Current age [years]						
0-12	56	0	72	2	128	1
13-17	40	0	24	1	64	0
18-24	268	2	88	2	356	2
25-34	1,817	11	484	13	2,301	12
35-44	3,165	20	1,024	28	4,189	21
45-54	5,313	33	1,136	31	6,449	33
55-64	3,666	23	562	16	4,228	22
65-74	1,399	9	171	5	1,570	8
≥75	247	2	50	1	297	2
Region of origin						
The Netherlands	10,637	67	1,098	30	11,735	60
Sub-Saharan Africa	1,070	7	1,453	40	2,523	13
Western Europe	904	6	124	3	1,028	5
South America	1,070	7	330	9	1,400	7
Caribbean	663	4	172	5	835	4
South and south-east Asia	462	3	238	7	700	4
Other	1,108	7	186	5	1,294	7
Unknown	57	0	10	0	67	0
Years aware of HIV infection						
<1	563	4	82	2	645	3
1-2	1,327	8	230	6	1,557	8
3-4	1,552	10	239	7	1,791	9
5-10	4,355	27	766	21	5,121	26
10-20	5,623	35	1,725	48	7,348	38
>20	2,528	16	552	15	3,080	16
Unknown	23	0	17	0	40	0

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

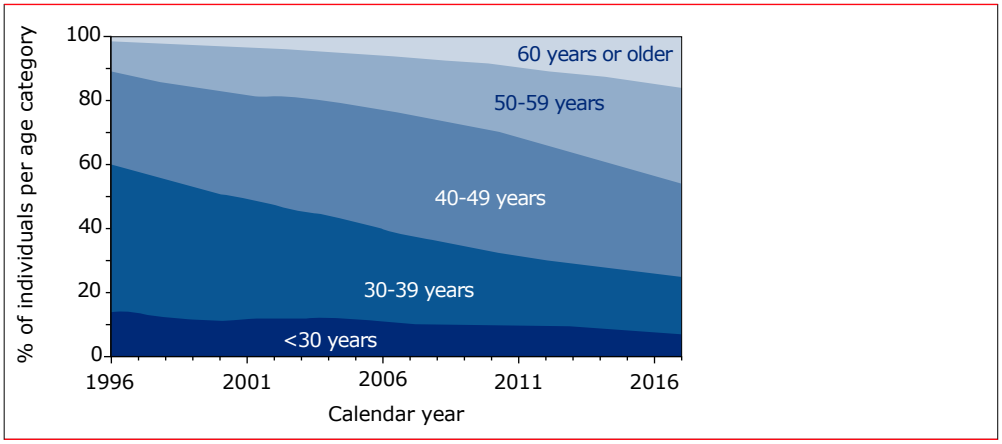
Loss to care

Of the 11,729 individuals who enrolled in HIV care between 2007 and 2016, 623 (5%) were lost to care before 2017 and were not reported as having died or moved abroad. The probability of being lost to care was lowest for people of Dutch origin: 5 years after enrolment 2% were estimated to no longer be in care. Of the individuals of sub-Saharan African origin, 15% of men and 9% of women were lost to care, as were 9% of men and 10% 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 11% less likely to be lost to care.

Ageing population

The median age of the population in clinical care by the end of 2017 was 50 (IQR 40-57) and has been increasing since 1996 (*Figure 1.14*). This increase in age is mainly a result of the improved life expectancy of people with HIV after the introduction of cART. In addition, people are being diagnosed at increasingly older ages, as has been discussed earlier in this chapter. As a result, almost half of people currently in care (48%) are 50 years or older, including 51% of men and 35% of women; 18% of the people are 60 years or older (*Appendix Table 1.4*). 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 1.14: *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 2017, these proportions were 7% and 48%, respectively, while 18% 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 2017 had been diagnosed with HIV a median of 10.6 (IQR 6.0-16.5) years previously. Thus, a large group (53%) of those in care have been living with HIV for more than 10 years, while 16% had done so for more than 20 years. The median time since diagnosis was 9.9 years for men who have sex with men (MSM), 11.6 years for other men, and 12.5 years for women. The majority of people who use/used injecting drugs (93%) received their HIV diagnosis more than 10 years ago, which reflects the greatly decreasing number of new infections occurring via this mode of transmission.

Antiretroviral treatment

In total, 98% of the individuals in care had ever started cART, of whom the majority, 93%, used a once-daily regimen. Of the 367 (2%) individuals who had not yet started cART, 29 (8%) used an antiretroviral regimen that was not classified as cART, and 132 (36%) were diagnosed with HIV in 2017 and their treatment had most likely not yet been recorded in the SHM database. Antiretroviral treatment is discussed in more detail in *Chapter 2*.

Clinical condition

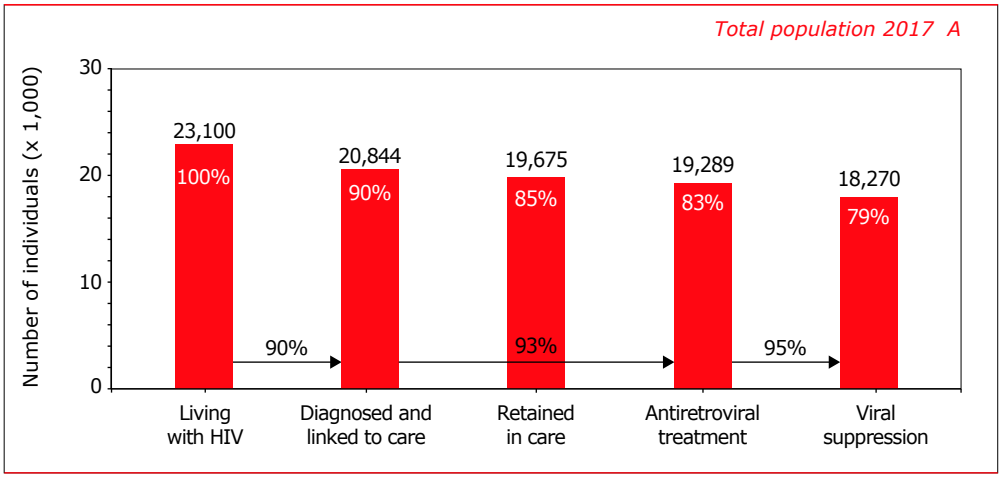
The median latest available CD4 count in 2017 of the people in care was relatively high at 670 (IQR 496-880) cells/mm^3, partly as a result of treatment and partly as a result of earlier diagnosis, as reported earlier in this chapter. CD4 counts were similar between MSM and women, but men who acquired HIV via other modes of transmission had lower CD4 counts (*Appendix Table 1.4*). For all people in care with a viral load measurement in 2017, their last measurement in that year was below 200 copies/ml for 96% and below 100 copies/ml for 95%. About one-fifth (23%) of the individuals had ever been diagnosed with an AIDS-defining disease; 57% of these people were diagnosed with AIDS concurrently with their HIV diagnosis.

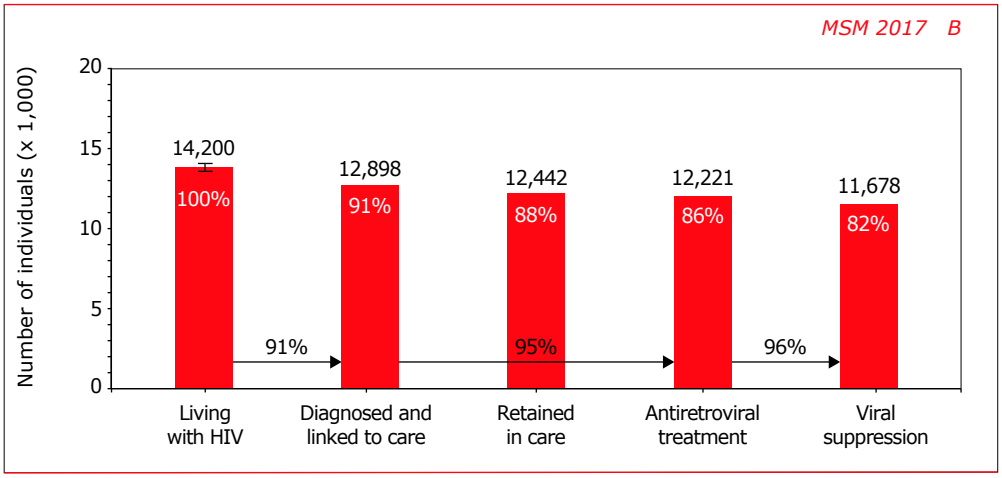
Continuum of HIV care

The total number of people living with HIV by the end of 2017, including those not yet diagnosed, was estimated at 23,100 (95% confidence interval [CI] 22,700-23,600), of whom 2,300 (1,900-2,700) were still undiagnosed[1]. Adjusted for registration delay, 20,844 individuals, or 90% of the total number estimated to be living with HIV, had been diagnosed, linked to care, and registered by SHM, while 19,675 individuals 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 2017) (*Figure 1.15A*). The majority of these individuals (19,289, or 93% of those diagnosed and linked to care) had started antiretroviral treatment, and 18,270, or 95% of those treated, had a most recent HIV RNA measurement below 200 copies/ml, irrespective of

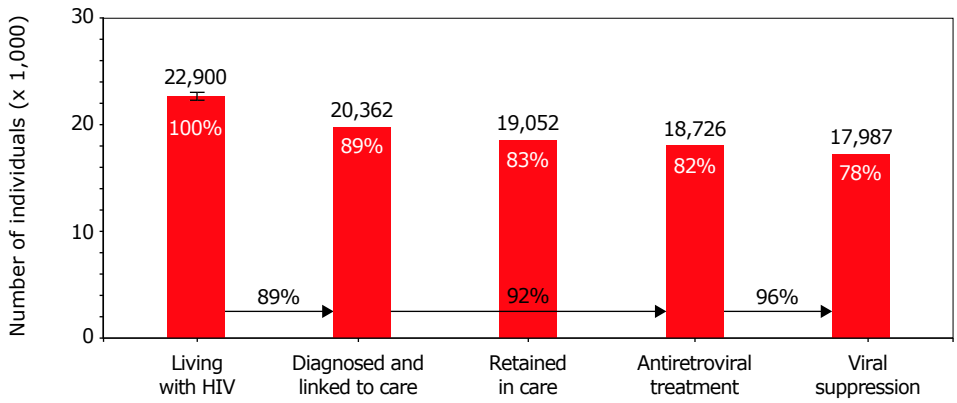
treatment. Overall, 79% of the total estimated population living with HIV and 88% of those diagnosed and ever linked to care had a suppressed viral load. Hence the Netherlands has reached the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 target for 2020 with the current estimate standing at 90-93-95[8]. Of the people still in care by the end of 2017, 13,686 (70%, or 75% of those with a CD4 measurement) had a most recent CD4 count of 500 cells/mm^3 or higher measured at most two years before.

Figure 1.15: 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 2017 and by the end of 2016. 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 2016, 11% in 2017).

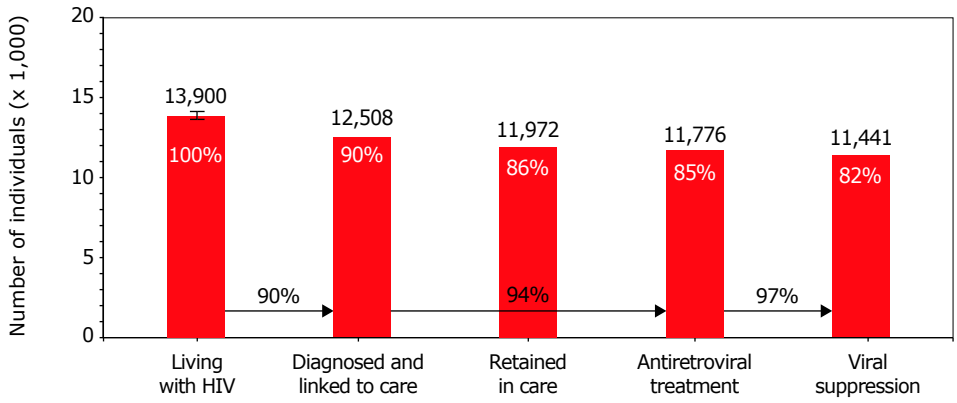




Total population 2016 *C*



MSM 2016 *D*



Lost to care

The estimated number of people living with HIV and the number of people diagnosed and linked to care excluded 573 individuals who had been diagnosed and linked to care, but were lost to care before the end of 2007, i.e. more than 10 years ago. It is unlikely that these 573 individuals are still living in the Netherlands without needing care or antiretroviral treatment. Of the 1,169 individuals lost to care (20,844 minus 19,675), 75% were born outside the Netherlands, whereas this proportion was only 40% for those who were still in care by the end of 2017. 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 at the end of 2017 was estimated to be 14,200 (14,000-14,500), of whom 1,300 (1,100-1,600) were still undiagnosed. Of these MSM estimated to be living with HIV, 12,898 (90%) had been diagnosed and linked to care, 12,442 (88%) were still in care, 12,221 (86%) had started cART, and 11,678 (82%) had a most recent HIV RNA below 200 copies/ml, or 91-95-96 in terms of the UNAIDS 90-90-90 target (*Figure 1.15B*). In total, 9,065 (73%, or 78% of those with a CD4 measurement) of MSM with a suppressed viral load had a CD4 count of 500 cells/mm^3 or higher at their last measurement in 2016 or 2017. Among women and other men, the proportion with a most recent HIV RNA below 200 copies/ml in 2017 was lower than in MSM (*Appendix Figure 1.3*).

Continuum of care by region of origin, age, and residence

Individuals of Dutch origin generally reached higher rates of engagement in the various stages of the care continuum than people originating from abroad (*Appendix Figure 1.4*). Moreover, the proportion of people who were still in care by the end of 2017 was similar between age groups, while the proportion who had started antiretroviral treatment increased from 86% of those diagnosed and linked to care among 18 to 24 year olds to 97% 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 77% among those aged 18 to 24 years and 93% in people 65 years of age or older, or 83% and 95%, respectively, of those who were still in care. Overall, engagement in the various stages of the care continuum was very similar between the 25 public health service regions in the Netherlands (*Appendix Table 1.5*).

Continuum of care 2016

We also re-estimated the continuum of HIV care for 2016 and found that, by the end of that year, 22,900 (22,700-23,300) people were living with HIV in the Netherlands, which was similar to the estimated 22,900 (22,400-23,400) reported in last year's Monitoring Report (*Figures 1.15C* and *1.15D*)[4]. While the number diagnosed and the number retained in care were very similar to last year's report, the number of those who started antiretroviral treatment (18,726 compared to 18,599 last year) and the number with viral suppression (17,987 compared to 17,580) were somewhat 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; this backlog may also be present in the reported continuum of HIV care for 2017. As a result, the estimate for the UNAIDS 90-90-90 target changed from 89-92-95 in last year's report to 89-92-96 in this year's report.

Conclusion

Since 2008 there has been a steady decrease in the annual number of new HIV diagnoses to less than 900 new diagnoses in most recent years. This decreasing trend continued in 2017 with approximately 750 new diagnoses in that year, although there is some uncertainty concerning this number of diagnoses because not all people diagnosed in 2017 have yet been included in the SHM database at the time of writing. The decrease in HIV diagnoses is, in part, 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^3. Conversely, the proportion diagnosed with evidence of a recent infection is increasing, although this is more evident among MSM than among other men and among women. In most recent calendar years, however, the downward trend in the proportion of MSM presenting with late or advanced HIV infection appears to have halted.

In recent years, testing for HIV appears to have become more frequent, because individuals with a positive test are more likely to have had a previous negative test. Testing rates appear to be highest among people who received a positive test result at a sexual health centre and lowest in those tested in a hospital. In addition, the population that tested positive for HIV in a hospital had the highest proportion of

late presenters. These observations illustrate that people tested at sexual health centres 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^3. In the most recent years, treatment uptake has also increased in individuals with high CD4 cells such that, in 2017, more than 90% of individuals diagnosed with CD4 cells above 500 cells/mm^3 were on cART within 6 months after entering HIV care. As a result of earlier treatment, in combination with increased testing and earlier diagnosis and a decreasing number of newly acquired HIV infections, the Netherlands has already reached the UNAIDS 90-90-90 targets for 2020 with the current estimate standing at 90-93-95. Hence, it is now time to aim for the next set of goals by UNAIDS: 95-95-95 by 2030[9].

Recommendations

A re-assessment of the continuum of HIV care for 2016 showed that there was an increase in the number of people on ART and in the number who achieved viral suppression by the end of that year compared to what was reported in last year's report. However, the difference between the number of people with viral suppression in this year's re-appraisal of 2016 and that reported last year was considerably smaller. This is most likely the result of having extended the automated import of laboratory measurements (LabLink) to 14 HIV treatment centres, which cover approximately 69% of all people followed by SHM. Nevertheless, to better monitor progress towards achieving UNAIDS' 95-95-95 goals for 2030, a more timely registration of start of treatment and viral load measurements would be needed. The latter could be markedly improved by further extending 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 people 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. The recent decision by the

Ministry of Health to make pre-exposure prophylaxis available to those at highest risk of acquiring HIV is therefore a very rational and welcome addition to our combination prevention toolbox in the Netherlands.

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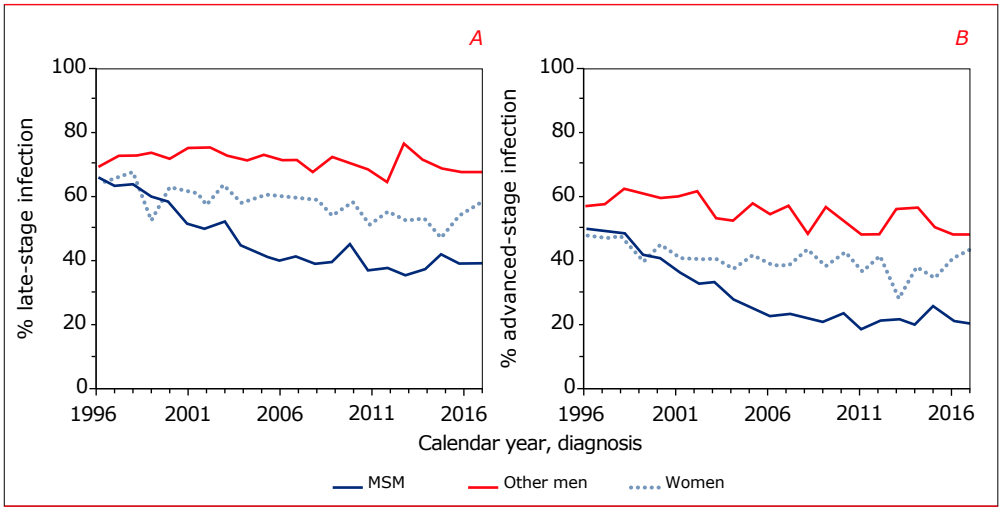
9. Joint United Nations Programme on HIV/AIDS (UNAIDS). *Fast-Track Ending the AIDS epidemic by 2030*. (2014). doi:ISBN 978-92-9253-063-1

Appendix: supplementary figures and tables

Appendix Figure 1.1: *Proportion of people classified as presenting with (A) late-stage or (B) advanced-stage HIV infection at the time of HIV diagnosis. From 1996 (2015) onwards, 52% (48%) were diagnosed with late-stage HIV infection: men who have sex with men (MSM) 44% (41%), other men 72% (68%), and women 59% (53%). Overall, 34% (30%) were diagnosed with advanced-stage HIV infection: MSM 26% (22%), other men 55% (49%), and women 40% (40%). Late-stage HIV infection: CD4 counts below 350 cells/mm³ or having AIDS, regardless of CD4 count. Advanced-stage HIV infection: CD4 counts below 200 cells/mm³ or having AIDS.*



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

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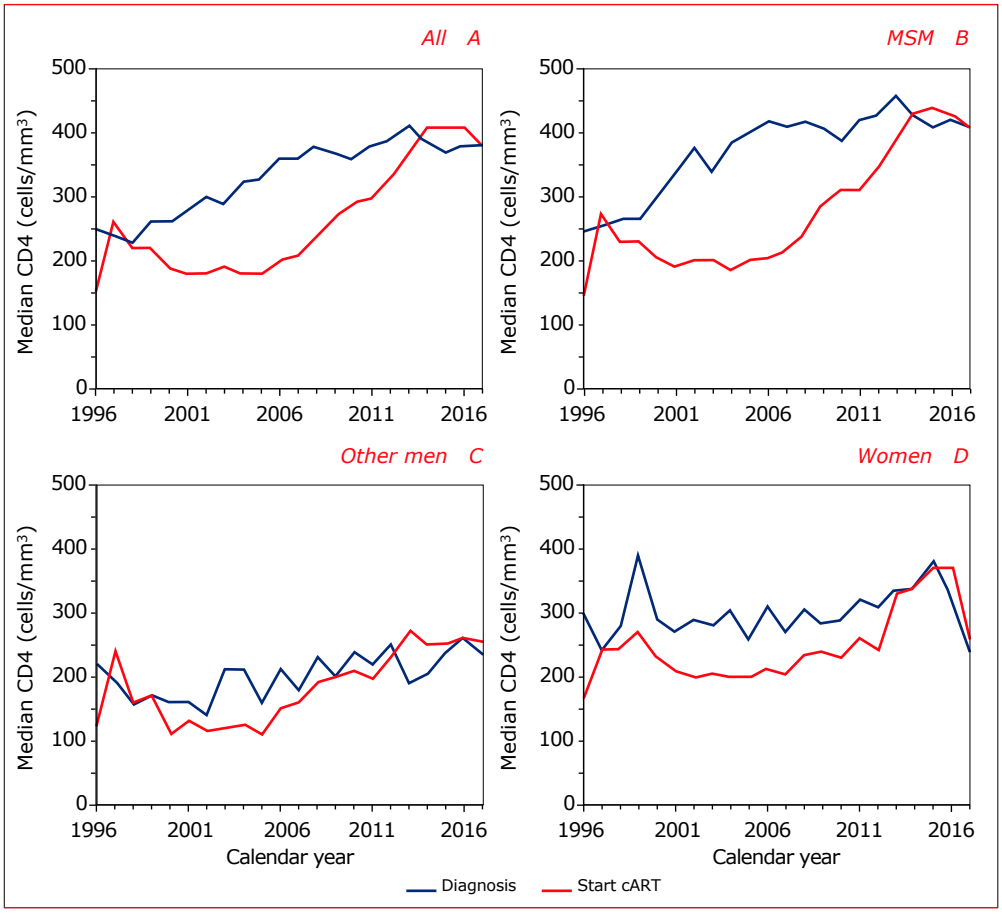
Appendix Figure 1.2: *Changes over calendar time in median CD4 counts at HIV diagnosis and at the start of combination antiretroviral therapy (cART) for (A) all individuals with an HIV-1 diagnosis, and for (B) men who have sex with men, (C) other men, and (D) women. The lines in each panel are a combination of Figures 1.9A and 1.9B.*



Legend: *cART=combination antiretroviral therapy.*

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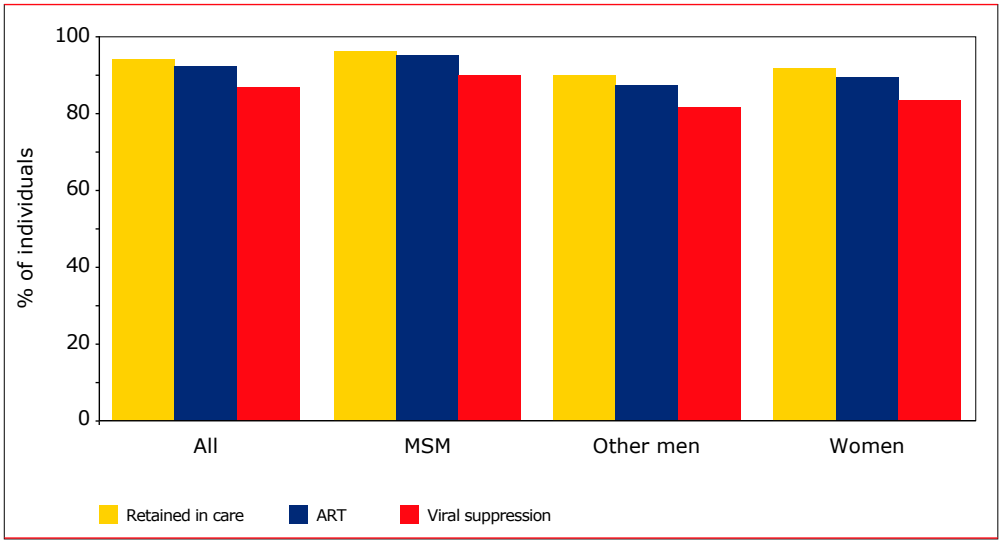
Appendix Figure 1.3: *Continuum of HIV care by transmission risk group. Proportions are given relative to the number of people diagnosed and linked to care.*



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

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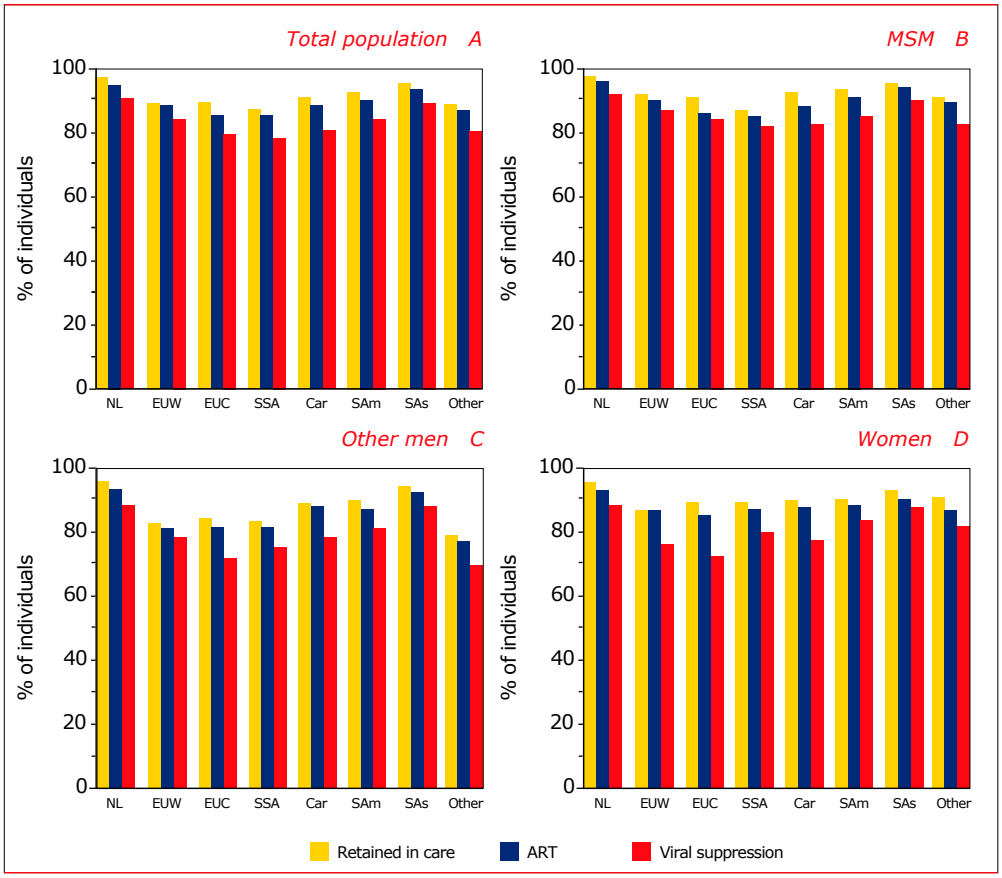
Appendix Figure 1.4: *Continuum of HIV care by region of origin for (A) the total HIV-1-positive population and for (B) men who have sex with men, (C) other men, and (D) women. Proportions are given relative to the number of people diagnosed and linked to care.*



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

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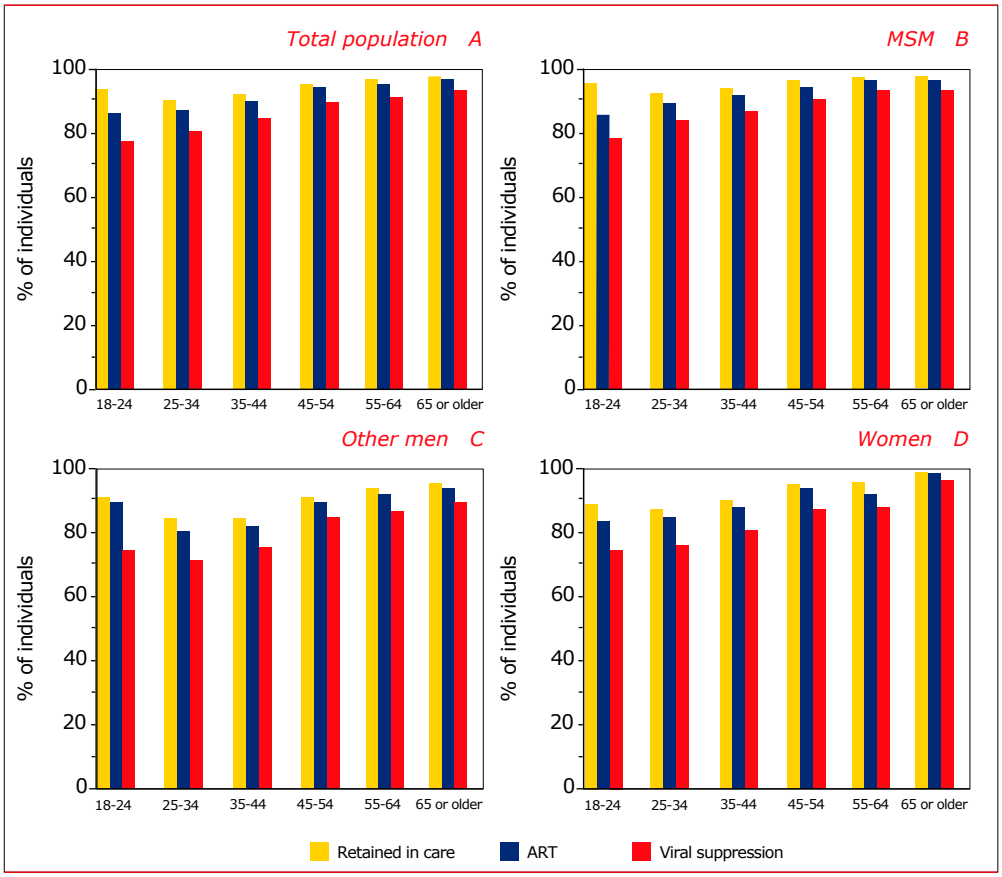
Appendix Figure 1.5: *Continuum of HIV care by age group for (A) the total HIV-1-positive population and for (B) men who have sex with men, (C) other men, and (D) women. Proportions are given relative to the number of people diagnosed and linked to care.*



Legend: *ART=antiretroviral therapy.*

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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) and individuals who acquired their HIV infection via heterosexual contact, injecting drug use (IDU), contact with contaminated blood, or other or unknown modes of transmission. Note: data collection for 2016 and 2017 had not yet been finalised at the time of writing.*

	MSM	Heterosexual		IDU	
Year of diagnosis	**Men**	**Men**	**Women**	**Men**	**Women**
≤1995	2,284	270	395	284	136
1996	386	90	83	31	8
1997	449	114	127	39	10
1998	334	108	113	23	7
1999	357	108	138	20	8
2000	382	163	195	18	5
2001	452	167	219	16	5
2002	474	168	251	16	3
2003	465	178	279	23	5
2004	591	204	264	11	4
2005	647	195	266	17	2
2006	692	164	201	10	5
2007	783	158	215	12	4
2008	870	178	181	6	1
2009	791	159	183	9	0
2010	802	181	168	6	1
2011	784	144	150	4	1
2012	732	148	149	6	1
2013	751	117	132	2	2
2014	626	111	119	1	0
2015	584	129	124	2	0
2016	523	101	103	1	0
*2016**	*539*	*104*	*106*	*1*	*0*
2017	465	81	76	2	0
*2017**	*516*	*90*	*84*	*2*	*0*
2018	57	5	8	0	0
Total	**15,281**	**3,441**	**4,139**	**559**	**208**

**Projected numbers*

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

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Blood or blood products		Other/unknown		Children		Total
Men	Women	Men	Women	Men	Women	
63	23	159	47	53	37	3,751
3	4	35	6	14	3	663
7	3	39	9	9	9	815
6	6	30	7	8	8	650
9	4	19	6	11	13	693
3	4	36	4	16	29	855
8	7	39	6	15	34	968
15	7	59	4	18	21	1,036
12	3	57	13	17	21	1,073
4	4	65	9	14	12	1,182
3	8	61	8	11	10	1,228
5	7	56	3	7	11	1,161
2	6	49	7	9	13	1,258
5	3	54	6	13	17	1,334
3	2	48	9	13	15	1,232
6	2	41	6	20	16	1,249
9	7	60	4	14	9	1,186
4	3	40	9	8	13	1,113
12	1	41	5	6	4	1,073
7	5	42	7	5	6	929
6	1	44	5	6	5	906
10	2	33	4	4	4	785
10	*2*	*34*	*4*	*4*	*4*	*809*
7	2	32	6	3	1	675
8	*2*	*36*	*7*	*3*	*1*	*749*
1	2	9	0	0	0	82
210	**116**	**1,148**	**190**	**294**	**311**	**25,897**

Appendix Table 1.2: *Region of origin of the 25,292 adult HIV-1-positive individuals with a recorded date of diagnosis stratified according to year of HIV diagnosis.*

	MSM			Other men		
	<2015	≥2015	Total	<2015	≥2015	Total
The Netherlands	9,555	1,027	10,582	2,147	268	2,415
	70.0%	63.0%	69.2%	43.9%	57.9%	45.1%
Sub-Saharan Africa	197	32	229	1,301	81	1,382
	1.4%	2.0%	1.5%	26.6%	17.5%	25.7%
Western Europe	1,091	83	1,174	284	11	293
	8.0%	5.1%	7.7%	5.8%	2.4%	5.5%
Central Europe	292	91	383	153	24	177
	2.1%	5.6%	2.5%	3.1%	5.2%	3.3%
Eastern Europe	99	14	113	67	4	71
	0.7%	0.9%	0.7%	1.4%	0.9%	1.3%
South America	930	118	1,048	393	28	421
	6.8%	7.2%	6.9%	8.0%	6.0%	7.9%
Caribbean	496	96	592	212	18	230
	3.6%	5.9%	3.9%	4.3%	3.9%	4.3%
South and south-east Asia	408	55	463	123	9	132
	3.0%	3.4%	3.0%	2.5%	1.9%	2.5%
Other/unknown	584	113	697	215	20	235
	4.3%	6.9%	4.6%	4.4%	4.3%	4.4%

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

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	Women		
	<2015	≥2015	Total
	1,159	127	1,286
	26.8%	38.1%	27.6%
	1,850	100	1,950
	42.8%	30.0%	41.9%
	227	5	232
	5.3%	1.5%	5.0%
	84	13	97
	1.9%	3.9%	2.1%
	51	5	56
	1.2%	1.5%	1.2%
	397	31	428
	9.2%	9.3%	9.2%
	218	12	230
	5.0%	3.6%	4.9%
	254	25	279
	5.9%	7.5%	6.0%
	80	15	95
	1.9%	4.5%	2.0%

Appendix Table 1.3: *Late presentation in the 2,828 individuals presenting for care in 2015 or later. In total, 103 individuals (78 MSM, 11 other men, and 14 women) could not be classified as a result of missing CD4 cell count at entry into care.*

	MSM (n=1,781)		Other men (n=536)		Women (n=408)		Total (n=2,725)	
	n	%	n	%	n	%	n	%
Overall	680	38	337	63	195	48	1,212	44
Age at entry [years]								
18-24	50	23	13	48	9	26	72	26
25-34	177	31	72	49	56	44	305	36
35-44	162	39	82	67	55	47	299	46
45-54	156	44	91	68	44	59	291	52
55-64	95	56	52	72	23	55	170	60
≥65	40	71	27	77	8	73	75	74
Region of origin								
The Netherlands	414	41	184	66	59	46	657	46
Sub-Saharan Africa	21	57	68	65	70	51	159	57
Western Europe	33	27	10	45	4	33	47	30
Central Europe	27	27	17	53	7	44	51	34
South America	54	36	17	61	20	49	91	41
Caribbean	55	44	12	48	2	17	69	42
South and South-East Asia	31	48	10	100	19	59	60	56
North Africa and Middle East	17	28	10	63	2	40	29	35
Location of testing								
Sexual health centre	156	24	18	46	10	33	184	26
Hospital	210	70	188	80	93	78	491	75
General practice	196	43	70	52	40	41	306	44
Other	20	31	8	50	26	42	54	38

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

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Appendix Table 1.4: Characteristics of the 19,582 people living with HIV and in care as of December 2017.

	MSM	Heterosexual		IDU	
	Men	Men	Women	Men	Women
	n=12,378	n=2,417	n=3,175	n=216	n=76
Current age [years]					
0–12	0	0	0	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%
13–17	2	0	1	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%
18–24	208	13	43	1	0
	1.7%	0.5%	1.4%	0.5%	0.0%
25–34	1,489	222	443	4	1
	12.0%	9.2%	14.0%	1.9%	1.3%
35–44	2,543	448	958	33	9
	20.5%	18.5%	30.2%	15.3%	11.8%
45–54	4,109	860	1,048	79	25
	33.2%	35.6%	33.0%	3.6%	32.9%
55–64	2,794	599	478	87	38
	22.6%	24.8%	15.1%	40.3%	50.0%
65–74	1,064	222	158	12	3
	8.6%	9.2%	5.0%	5.6%	3.9%
≥75	169	53	46	0	0
	1.4%	2.2%	1.4%	0.0%	0.0%
Current age 50 years or older					
No	6,101	1,123	2,047	69	16
	49.3%	46.5%	64.5%	31.9%	21.1%
Yes	6,277	1,294	1,128	147	60
	50.7%	53.5%	35.5%	68.1%	78.9%
Current age 60 years or older					
No	10,113	1,913	2,805	171	59
	81.7%	79.1%	88.3%	79.2%	77.6%
Yes	2,265	504	370	45	17
	18.3%	20.9%	11.7%	20.8%	22.4%

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Blood or blood products		Other / unknown		Total	
Men	Women	Men	Women	Men	Women
n=166	n=95	n=794	n=265	n=15,971	n=3,611
0	0	56	7	56	72
0.0%	0.0%	7.1%	27.2%	0.4%	2.0%
1	0	37	23	40	24
0.6%	0.0%	4.7%	8.7%	0.3%	0.7%
5	3	41	42	268	88
3.0%	3.2%	5.2%	15.8%	1.7%	2.4%
20	7	82	33	1,817	484
12.0%	7.4%	10.3%	12.5%	11.4%	13.4%
26	26	115	31	3,165	1,024
15.7%	27.4%	14.5%	11.7%	19.8%	28.4%
55	28	210	35	5,313	1,136
33.1%	29.5%	26.4%	13.2%	33.3%	31.5%
32	22	154	24	3,666	562
19.3%	23.2%	19.4%	9.1%	23.0%	15.6%
21	6	80	4	1,399	171
12.7%	6.3%	10.1%	1.5%	8.8%	4.7%
6	3	19	1	247	50
3.6%	3.2%	2.4%	0.4%	1.5%	1.4%
76	53	445	216	7,804	2,332
45.8%	55.8%	54.8%	81.5%	48.9%	64.6%
90	42	359	49	8,167	1,279
54.2%	44.2%	45.2%	18.5%	51.1%	35.4%
129	78	636	250	12,962	3,192
77.7%	82.1%	80.1%	94.3%	81.2%	88.4%
37	17	158	15	3,009	419
22.3%	17.9%	19.9%	5.7%	18.8%	11.6%

	MSM	Heterosexual		IDU	
	Men	Men	Women	Men	Women
	n=12,378	n=2,417	n=3,175	n=216	n=76
Region of origin					
Netherlands	8,898	1,145	941	125	36
	71.9%	47.4%	29.6%	57.9%	47.4%
Sub-Saharan Africa	166	648	1,318	4	0
	1.3%	26.8%	41.5%	1.9%	0.0%
Western Europe	761	82	69	24	25
	6.1%	3.4%	2.2%	11.1%	32.9%
South America	803	215	315	9	0
	6.5%	8.9%	9.9%	4.2%	0.0%
Caribbean	494	126	166	5	1
	4.0%	5.2%	5.2%	2.3%	1.3%
South and south-east Asia	379	38	219	9	1
	3.1%	1.6%	6.9%	4.2%	1.3%
Other	828	157	139	40	13
	6.7%	6.5%	4.4%	18.5%	17.1%
Unknown	49	6	8	0	0
	0.4%	0.2%	0.3%	0.0%	0.0%
Years aware of HIV infection					
<1	448	80	74	2	0
	3.6%	3.3%	2.3%	0.9%	0.0%
1-2	1,028	207	215	3	0
	8.3%	8.6%	6.8%	1.4%	0.0%
3-4	1,279	185	215	0	2
	10.3%	7.7%	6.8%	0.0%	2.6%
5-10	3,511	628	672	11	3
	28.4%	26.0%	21.2%	5.1%	3.9%
10-20	4,137	1,047	1,560	75	17
	33.4%	43.3%	49.1%	34.7%	22.4%
>20	1,969	267	426	125	54
	15.9%	11.0%	13.4%	57.9%	71.1%
Unknown	6	3	13	0	0
	0.0%	0.1%	0.4%	0.0%	0.0%
Current CD4 count [cells/mm^3], median / IQR	690	590	680	545	695
	520-889	412-810	493-892	371-819	402-894
Current CD8 count [cells/mm^3], median / IQR	870	830	770	835	881
	640-1,180	590-1,140	570-1,050	582-1,210	680-1,156

Blood or blood products		Other / unknown		Total	
Men	Women	Men	Women	Men	Women
n=166	n=95	n=794	n=265	n=15,971	n=3,611
104	18	365	103	10,637	1,098
62.7%	18.9%	46.0%	38.9%	66.6%	30.4%
31	39	221	96	1,070	1,453
18.7%	41.1%	27.8%	36.2%	6.7%	40.2%
4	4	33	26	904	124
2.4%	4.2%	4.2%	9.8%	5.7%	3.4%
5	10	38	5	1,070	330
3.0%	10.5%	4.8%	1.9%	6.7%	9.1%
5	5	33	0	663	172
3.0%	5.3%	4.2%	0.0%	4.2%	4.8%
8	13	28	5	462	238
4.8%	13.7%	3.5%	1.9%	2.9%	6.6%
9	6	74	28	1,108	186
5.4%	6.3%	9.3%	10.6%	6.9%	5.2%
0	0	2	2	57	10
0.0%	0.0%	0.3%	0.8%	0.4%	0.3%
6	2	27	6	563	82
3.6%	2.1%	3.4%	2.3%	3.5%	2.3%
16	3	73	12	1,327	230
9.6%	3.2%	9.2%	4.5%	8.3%	6.4%
15	5	73	17	1,552	239
9.0%	5.3%	9.2%	6.4%	9.7%	6.6%
24	13	181	78	4,355	766
14.5%	13.7%	22.8%	29.4%	27.3%	21.2%
48	48	316	100	5,623	1,725
28.9%	50.5%	39.8%	37.7%	35.2%	47.8%
54	24	113	48	2,528	552
32.5%	25.3%	14.2%	18.1%	15.8%	15.3%
3	0	11	4	23	17
1.8%	0.0%	1.4%	1.5%	0.1%	0.5%
605	734	599	810	670	690
387–800	525–947	410–840	610–1,120	491–870	500–910
753	877	837	760	860	770
552–1,100	610–1,050	599–1,160	516–1,047	630–1,180	570–1,060

	MSM	Heterosexual		IDU	
	Men	Men	Women	Men	Women
	n=12,378	n=2,417	n=3,175	n=216	n=76
Current HIV RNA <200 copies/ml					
No	361	102	179	7	4
	2.9%	4.2%	5.6%	3.2%	5.3%
Yes	11,631	2,218	2,897	191	67
	94.0%	91.8%	91.2%	88.4%	88.2%
Current HIV RNA <100 copies/ml					
No	462	130	223	8	6
	3.7%	5.4%	7.0%	3.7%	7.9%
Yes	11,530	2,190	2,853	190	65
	93.1%	90.6%	89.9%	88.0%	85.5%
Ever AIDS	2,340	783	753	85	30
	18.9%	32.4%	23.7%	39.4%	39.5%
AIDS at diagnosis	1,221	547	432	19	6
	9.9%	22.6%	13.6%	8.8%	7.9%
Current treatment					
cART	12,168	2,362	3,105	212	76
	98.3%	97.7%	97.8%	98.1%	100.0%
Non-cART	20	2	4	0	0
	0.2%	0.1%	0.1%	0.0%	0.0%
Not started	189	53	66	4	0
	1.5%	2.2%	2.1%	1.9%	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
	n=166	n=95	n=794	n=265	n=15,971	n=3,611
	9	7	50	18	529	208
	5.4%	7.4%	6.3%	6.8%	3.3%	5.8%
	154	86	722	238	14,9186	3,288
	92.8%	90.5%	90.9%	89.8%	93.4%	91.1%
	10	11	60	20	670	260
	6.0%	11.6%	7.6%	7.5%	4.2%	7.2%
	153	82	712	236	14,775	3,236
	92.2%	86.3%	89.7%	89.1%	92.5%	89.6%
	57	31	303	85	3,568	899
	34.3%	32.6%	38.2%	32.1%	22.3%	24.9%
	34	18	213	43	2,034	499
	20.5%	18.9%	26.8%	16.2%	12.7%	13.8%
	158	94	777	262	15,677	3,537
	95.2%	98.9%	97.9%	98.9%	98.2%	98.0%
	0	1	1	1	23	6
	0.0%	1.1%	0.1%	0.4%	0.1%	0.2%
	8	0	16	2	270	68
	4.8%	0.0%	2.0%	0.8%	1.7%	1.9%

Appendix Table 1.5: *Continuum of HIV care for the total HIV-1-positive population in the Netherlands diagnosed and linked to care, stratified by Public Health Service region in which people were living by the end of 2017. Proportions are given relative to the number of people diagnosed and linked to care.*

	Diagnosed and linked to care	Retained in care	
	n	n	%
Groningen	564	531	94
Fryslân	325	307	94
Drenthe	268	249	93
IJsselland	315	303	96
Twente	407	391	96
Noord- en Oost-Gelderland	439	422	96
Gelderland-Midden	662	639	97
Gelderland-Zuid	378	363	96
Flevoland	546	502	92
Regio Utrecht	1,179	1,113	94
Gooi & Vechtstreek	294	281	96
Hollands-Noorden	422	395	94
Zaanstreek-Waterland	347	339	98
Amsterdam	6,027	5,723	95
Kennemerland	567	533	94
Hollands-Midden	523	493	94
Haaglanden	1,582	1,502	95
Rotterdam-Rijnmond	2,419	2,242	93
Dienst Gezondheid & Jeugd ZHZ	304	282	93
Zeeland	206	189	92
West-Brabant	521	493	95
Hart voor Brabant	807	762	94
Brabant-Zuidoost	616	575	93
Limburg-Noord	356	335	94
Zuid-Limburg	500	479	96
Unknown	272	232	85
Total	**20,844**	**19,675**	**94**

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	Antiretroviral treatment		Viral suppression	
	n	%	n	%
	516	92	489	87
	304	93	286	88
	241	90	225	84
	297	94	292	93
	386	95	373	92
	409	93	399	91
	622	94	610	92
	359	95	327	87
	491	90	458	84
	1,068	91	1,063	90
	277	94	270	92
	382	90	371	88
	336	97	313	90
	5,645	94	5,321	88
	531	94	467	82
	481	92	463	89
	1,482	94	1,415	89
	2,169	90	2,011	83
	267	88	262	86
	184	89	163	79
	483	93	461	89
	758	94	713	88
	570	93	540	88
	331	93	311	88
	473	95	451	90
	228	84	214	79
	19,289	**93**	**18,270**	**88**

2. Response to combination antiretroviral therapy (cART)

Sonia Boender, Ferdinand Wit, Ard van Sighem, Kees Brinkman, Kees van Nieuwkoop, Anne Wensing and Peter Reiss

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 goals of cART are to prevent HIV disease progression, improve clinical outcomes and limit transmission[1,2]. Treatment guidelines across the globe recommend cART for all people with HIV, regardless of CD4 count. The decision to initiate cART should always include consideration of a person's comorbid conditions and his or her willingness and readiness to initiate therapy. Thus, although cART may be deferred because of clinical and/or psychosocial factors on a case-by-case basis, therapy should be initiated as soon as possible[3,4,5,6,7]. In general, the Dutch Association of HIV Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) follows the US Department of Health and Human Services guidelines.

Besides preventing clinical events, AIDS, and tuberculosis, the immediate start of cART is also more effective at preventing transmission of HIV than deferment of treatment until the CD4 count has dropped to ≤350 cells/mm^3 [8,9]. People living with HIV on cART with an undetectable viral load in their blood have a negligible to non-existent risk of sexual transmission of HIV; undetectable equals untransmittable, i.e. U=U [2,10,11,12,13,14]. 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. HIV viral suppression should therefore be continuously monitored and documented to assure both personal health and public health benefits.

Most guidelines list an integrase inhibitor as the third agent of preferred first-line cART regimens, along with the options of darunavir as a boosted protease inhibitor or rilpivirine as a non-nucleoside reverse transcriptase inhibitor (NNRTI) option (the latter only if viral load is <100,000 copies/ml), all in combination with a double nucleoside backbone (either tenofovir/emtricitabine or abacavir/lamivudine)[5]. Additionally, tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are two forms of tenofovir approved by the European Medicines Agency. TAF has

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fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. On the other hand, TDF use should be avoided in people with reduced renal functioning or risk thereof and in people with osteoporosis or at risk for osteoporotic fractures[15,16]. Safety, cost and access are among the factors to consider when choosing between these drugs. Finally, although still frequently used, efavirenz is no longer recommended as the preferred first-line cART regimen in the Netherlands, but remains an alternative[3,5,7].

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. High-level viraemia can lead to selection and accumulation of mutations in the HIV genome that are associated with drug resistance, which prevents successful viral suppression and thereby increases the risk of poor clinical outcomes[17,18,19,20,21,22,23].

This chapter reports 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 adults registered by Stichting HIV Monitoring (SHM) and enrolled in the ATHENA cohort, the database maintained by SHM. We also analyse the presence of HIV drug resistance. *Box 2.1* gives an overview of the number of people 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 23,893 registered adults (≥18 years at the time of diagnosis) with HIV-1 in the Netherlands

1. **Starting combination antiretroviral therapy**
   23,579 people were known to have initiated cART between January 1996 and December 2017.

2. **In care and on cART in the Netherlands in 2017**
   Out of 23,579 people known to have initiated cART between January 1996 and December 2017,
   ➔ 18,523 were in care and had a clinical visit in 2017;
   ➔ 3,812 of those were diagnosed with HIV before the year 2000, and 1,966 before 1996 (referred to as 'long-term HIV survivors').

3. **Changes in the use of initial cART regimen**
   Out of 23,579 people known to have initiated cART between January 1996 and December 2017,
   ➔ 5,767 initiated cART between January 2013 and December 2017;
   ➔ 4,630 initiated cART between January 2013 and December 2017 with a regimen composed of TDF/FTC in combination with EFV, RPV, DRV/b, EVG/c, or DTG; ABC/3TC/DTG; or TAF/FTC/EVG/c.

4. **Virological response**
   Out of 23,579 people known to have initiated cART between January 1996 and December 2017,
   ➔ 19,358 people were ARV-naive, not pregnant at cART initiation, and had a viral load result after ≥3 months of cART initiation.

   Initial virological success
   ➔ 15,645 individuals were ART-naive, not pregnant at cART initiation, and had a viral load result 6 months (±3 months) after cART initiation;
   ➔ 3,881 of those initiated tenofovir/FTC in combination with EFV, RPV, DRV/b, EVG/c, or DTG; ABC/3TC/DTG; or TAF/FTC/EVG/c in 2013-2017; and 3,456 of those also had viral load data available at the time of cART initiation.

5. **HIV drug resistance**

Transmitted HIV drug resistance

As of January 2018, 7,315 HIV-1 sequences were obtained from 6,981 ARV-naive people before initiating cART in 2003-2017.

➔19 people had pre-treatment integrase sequences available.

Acquired HIV drug resistance

As of January 2018, 4,242 HIV-1 sequences were obtained from 2,540 people who received cART for at least 4 months in 2000-2017.

➔ 2,816 sequences from 1,775 people who were ARV-naive before initiating cART.

➔ 107 integrase sequences were available from 89 people.

6. **Immunological response**

Out of the 23,578 people known to have initiated cART between January 1996 and December 2017

➔ 23,073 had CD4 cell count data available after initiating cART.

Legend: *ART=antiretroviral therapy (antiretroviral drug use that may prevent HIV from damaging the immune system by blocking the reproduction of HIV virus); 3TC=lamivudine; b=boosted (cobicistat or ritonavir); / c=cobicistat-boosted; cART=combination antiretroviral therapy (defined as a combination of three antiretroviral drugs from two different antiretroviral drugs classes); ABC=abacavir; ARVs=antiretroviral drugs; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.*

Starting combination antiretroviral therapy

In total, 23,578 adults ever registered by SHM and followed in the ATHENA cohort were aged 18 years or older at the time of HIV-1 diagnosis and were known to have initiated cART (defined as a combination of at least 3 antiretroviral agents) between January 1996 and December 2017 (*Box 2.1*). Of these, 2,538 (10.8%) had prior exposure to mono or dual antiretroviral therapy (ART) at the start of cART and 21,041 (89.2%) were ART-naive. The proportion of pre-treated persons initiating cART has decreased over time to <1%. In *Table 2.1*, we grouped people according to calendar year of starting cART: 5,928 started between 1996 and the end of 2001, 5,316 between 2002 and the end of 2007, 6,568 between 2008 and the end of 2012, and 5,767 between 2013 and the end of 2017. Those starting cART in 2018 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.

Table 2.1 Characteristics of people starting combination antiretroviral therapy in 1996–2017.

Year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2017	1996–2017
Total	n	5,928	5,315	6,569	5,767	**23,579**
DEMOGRAPHIC						
Age at cART initiation (years)	Median	37.6	38.6	40.4	39.3	**38.9**
	Q1	32.2	32.0	32.8	30.6	**31.9**
	Q3	44.6	45.7	48.0	49.0	**46.9**
Male (at birth)	n	4,819	3,889	5,578	4,996	**19,282**
	%	81.3	73.2	84.9	86.6	**81.8**
Transmission risk group						
Missing	n	4	7	5	11	**27**
	%	0.1	0.1	0.1	0.2	**0.1**
Men who have sex with men	n	3,475	2,546	4,357	4,038	**14,416**
	%	58.6	47.9	66.3	70.0	**61.1**
Heterosexual contact	n	1,650	2,209	1,784	1,404	**7,047**
	%	27.8	41.6	27.2	24.4	**29.9**
Injecting drug use	n	405	159	83	25	**672**
	%	6.83	2.99	1.26	0.43	**2.85**
Blood or blood products	n	106	69	47	53	**275**
	%	1.79	1.3	0.72	0.92	**1.17**
Vertical transmission	n	0	0	3	1	**4**
	%	0	0	0.1	<0.1	**<0.1**
Other/unknown	n	288	325	290	235	**1,138**
	%	4.9	6.1	4.4	4.1	**4.8**
Region of origin						
Missing	n	28	20	19	27	**94**
	%	0.5	0.44	0.3	0.5	**0.4**
The Netherlands	n	3,556	2,562	3,963	3,505	**13,586**
	%	60.0	48.2	60.3	60.8	**57.6**
Western Europe/North America/Australia	n	681	409	459	343	**1,892**
	%	11.5	7.7	7.0	6.0	**8.0**
East/central Europe	n	88	136	246	320	**790**
	%	1.5	2.6	3.7	5.6	**3.4**
South America and the Caribbean	n	582	673	745	697	**2,697**
	%	9.8	12.7	11.3	12.1	**11.4**
Sub-Saharan Africa	n	730	1,215	776	505	**3,226**
	%	12.3	22.9	11.8	8.8	**13.7**
Other*	n	263	300	361	370	**1,294**
	%	4.4	5.6	5.5	6.4	**5.5**

Year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2017	1996–2017
CLINICAL						
Recent infection	n	326	433	1,270	1,531	**3,560**
(within 12months of diagnosis)	%	5.5	8.2	19.3	26.6	**15.1**
Ever tested HIV-negative	n	1,141	1,421	3,176	3,353	**9,091**
	%	19.3	26.7	48.4	58.1	**38.6**
CD4 cell count at start cART	Median	200	190	280	394	**260**
	Q1	80	89	170	240	**126**
	Q3	340	280	369	560	**398**
HIV RNA (log_{10}) at start cART	Median	4.8	5.0	4.9	4.8	**4.9**
	Q1	4.2	4.5	4.4	4.2	**4.3**
	Q3	5.3	5.4	5.4	5.3	**5.3**
AIDS at start cART	n	1,911	1,411	1,104	695	**5,121**
	%	32.2	26.6	16.8	12.1	**21,72**
ARV-naive at start cART	n	3,773	5,073	6,478	5,717	**21,041**
	%	63.7	95.5	98.6	99.1	**89.2**
cART started during pregnancy	n	122	356	170	52	**700**
	%	2.1	6.7	2.6	0.9	**3.0**
Hepatitis B status at start of cART						
HBV-	n	5,279	4,836	6,056	5,68	**21,339**
	%	89.1	91.0	92.2	89.6	**90.5**
HBV+	n	368	317	317	163	**1165**
	%	6.2	6.0	4.8	2.8	**4.9**
Unknown	n	281	162	196	436	**1,075**
	%	4.7	3.1	3.0	7.6	**4.6**
Hepatitis C status at start of cART						
HCV-	n	5,245	4,885	6,204	5,371	**21,705**
	%	88.5	91.9	94.4	93.1	**92.1**
HCV RNA+	n	79	135	141	87	**442**
	%	1.3	2.5	2.2	1.5	**1.9**
HCV Ab+	n	146	65	42	27	**280**
	%	2.5	1.2	0.6	0.5	**1.2**
Unknown	n	458	230	182	282	**1,152**
	%	7.7	4.3	2.8	4.9	**4.9**

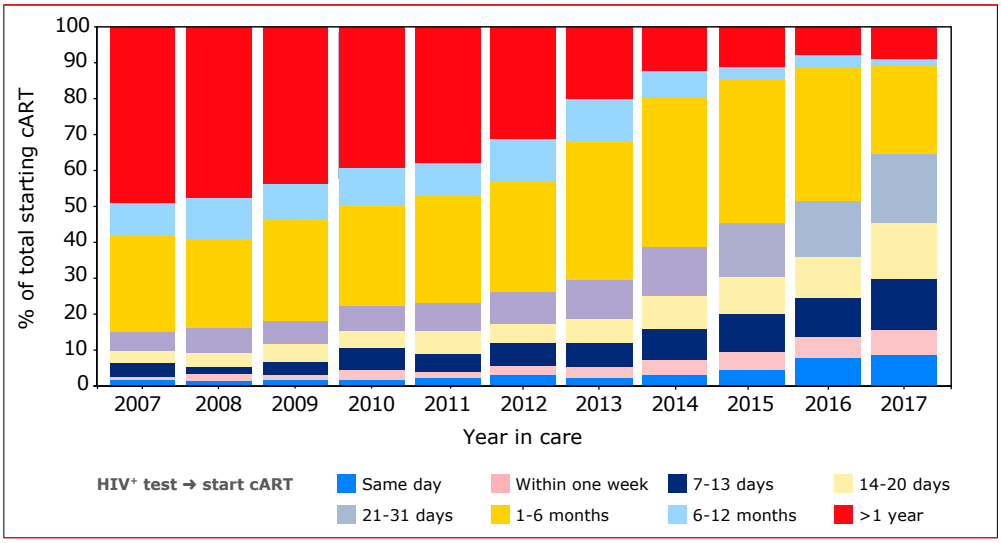
**The 63 people from other regions of origin who started in 2017 were from South-east Asia (n=29), North Africa and the Middle East (n=26), and Oceania and the Pacific (n=8).*

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

Of the 23,578 people who had initiated cART since January 1996, 19,282 were men (81.8%) of whom 14,416 (74.8%) were men who have sex with men (MSM). Overall, 13,586 (57.6%) originated from the Netherlands. Whereas the proportion of people from the Netherlands was stable over time, the region of origin for non-Dutch people changed over time. Over the past 20 years, there was a slight but steady increase in people from eastern and central Europe, from 2-3% until 2009, to 4-5% in 2010-2014 and to 6-7% in 2015-2017. Simultaneously, the number of people from western Europe/North America/Australia slightly decreased from 11.5% in 1996-2001 to 4.9% in 2017, with a decrease in those from sub-Saharan Africa from 23.0% in 2002-2007 to 11.9% in 2008-2012 to 8.8% in 2013-2017.

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 people 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 (interquartile range [IQR] 33-683) for those who entered care in 2011 to 98 days (IQR 30-491) in 2012, 65 days (IQR 41 21-106) in 2013, 41 days (IQR 21-106) in 2014, 35 days (IQR 17-76) in 2015, and 29 days (IQR 14-53) in 2016. In 2017, the time between an HIV-positive diagnosis and cART initiation further decreased to a median of 23 days (IQR 12-43). Likewise, the time between entering care and starting cART decreased over time (*Appendix Figure 2.1*).

Figure 2.1: Time between HIV diagnosis and initiation of combination antiretroviral therapy (cART) in persons starting cART in 2007–2017.*



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

Furthermore, the proportion of those with a previous negative HIV test increased over the years, and an increasing proportion of those starting cART had evidence of recent infection (i.e., within 12 months of a last negative HIV test). At the same time, there has been an increase in the median CD4 cell count at the start of cART, followed by stabilisation: from 190 cells/mm^3 (IQR89-280) in 2002-2007 to 280 cells/mm^3 (IQR 170-369) in 2008-2012 and to 394 cells/mm^3 (IQR 240-560) in 2013-2017 (p for trend <.0001). In 2017, the median CD4 cell count at the start of cART was 380 cells/mm^3 (IQR 202-554). Since 2016, both the number of people initiating cART per calendar year and the median CD4 cell count at cART initiation have slightly decreased. This trend is likely due to the substantial group who were already in care but not on cART (with high CD4 cells counts) and subsequently initiated cART under recent guideline changes.

Chapter 1 provides 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.

In care and on cART in the Netherlands in 2017

Out of the 23,578 people who were known to have initiated cART between January 1996 and December 2017, 18,523 (78.6%) were alive, receiving cART, and had a visit for HIV care in the Netherlands in 2017. *Table 2.2* shows their treatment and clinical characteristics in the year 2017. Overall, 15,265 (82.4%) were men, and 11,996 (64.8%) were MSM. The median age on 31 December 2017 was 50 (IQR 41-57) years. The majority (61.0%) originated from the Netherlands, followed by sub-Saharan Africa (11.9%) and South America and the Caribbean (11.3%).

Table 2.2: *Characteristics of people who started combination antiretroviral therapy and known to be in care in 2017.*

Calendar year of cART initiation		1996-2001	2002-2007	2008-2012	2013-2017	All
Total	n	3,773	3,843	5,597	5,310	**18,523**
	%	20.4	20.8	30.2	28.7	**100**
Sex						
Male	n	3,040	2,836	4,776	4,613	**15,265**
	%	80.6	73.8	85.3	86.9	**82.4**
Female	n	733	1,007	821	697	**3,258**
	%	19.4	26.2	14.7	13.1	**17.6**
Age on 31 December 2017	Median	56.3	51.6	48.3	42.6	**49.9**
	Q1	51.3	45.2	40.5	33.3	**41.3**
	Q3	62.4	58.1	55.5	51.9	**57.4**
Transmission risk group						
No data	n	2	6	4	10	**22**
	%	0.1	0.2	0.1	0.2	**0.1**
Men who have sex with men	n	2,341	2,024	3,855	3,776	**11,996**
	%	62.1	52.7	68.9	71.1	**64.8**
Heterosexual contact	n	1,,093	1,505	1,458	1,259	**5,315**
	%	29.0	39.2	26.1	23.7	**28.7**
Injecting drug use	n	136	68	53	19	**276**
	%	3.6	1.8	1.0	0.4	**1.5**
Blood or blood products	n	71	49	36	45	**201**
	%	1.9	1.3	0.6	0.9	**1.1**
Vertical transmission	n	.	.	2	1	**3**
	%	.	.	0.04	0.02	**0.02**
Other/unknown	n	130	191	189	200	**710**
	%	3.5	5.0	3.4	3.8	**3.8**
Region of origin						
No data	n	11	12	16	26	**65**
	%	0.3	0.3	0.3	0.5	**0.4**

Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2017	All
The Netherlands	n	2,362	2,042	3,588	3,308	**11,300**
	%	62.6	53.1	64.1	62.3	**61.0**
Western Europe/North America/Australia	n	344	229	325	286	**1,184**
	%	9.1	6.0	5.8	5.4	**6.4**
East/central Europe	n	51	96	186	284	**617**
	%	1.4	2.5	3.3	5.4	**3.3**
South America and the Caribbean	n	380	488	595	633	**2,096**
	%	10.1	12.7	10.6	11.9	**11.3**
Sub-Saharan Africa	n	432	755	581	433	**2,201**
	%	11.5	19.7	10.4	8.2	**11.9**
Other	n	193	221	306	340	**1,060**
	%	5.1	5.8	5.5	6.4	**5.7**
cART regimen						
TDF/FTC/EFV	n	269	602	921	305	**2,097**
	%	7.1	15.7	16.5	5.7	**11.3**
TDF/FTC/NVP	n	500	398	524	110	**1,532**
	%	13.3	10.4	9.4	2.1	**8.3**
TDF/FTC/RPV	n	104	170	382	380	**1,036**
	%	2.8	4.4	6.8	7.2	**5.6**
TDF/FTC/DRV/b	n	165	219	416	293	**1,093**
	%	4.4	5.7	7.4	5.5	**5.9**
TDF/FTC/ATV/r	n	104	130	225	74	**533**
	%	2.8	3.4	4.0	1.4	**2.9**
TDF/FTC/LPV	n	7	24	10	3	**44**
	%	0.2	0.6	0.2	0.1	**0.2**
TDF/FTC/EVG/c	n	64	103	181	503	**851**
	%	1.7	2.7	3.2	9.5	**4.6**
TDF/FTC/DTG	n	69	99	151	292	**611**
	%	1.8	2.6	2.7	5.5	**3.3**
TDF/FTC/RAL	n	47	48	89	44	**228**
	%	1.3	1.3	1.6	0.8	**1.2**
ABC/3TC/DTG	n	342	511	810	1,476	**3,139**
	%	9.1	13.3	14.5	27.8	**17.0**
TAF/FTC/EVG/c	n	285	386	642	1,110	**2,423**
	%	7.6	10.0	11.5	20.9	**13.1**
TAF/FTC/RPV	n	72	108	246	190	**616**
	%	1.9	2.8	4.4	3.6	**3.3**
TAF/FTC/DTG	n	59	46	109	146	**360**
	%	1.6	1.2	2.0	2.8	**1.9**

Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2017	All
TAF/FTC/DRV/c	n	68	61	82	78	**289**
	%	1.8	1.6	1.5	1.5	**1.6**
Other: 2NRTI+NNRTI	n	619	422	357	72	**1,470**
	%	16.4	11.0	6.4	1.4	**7.9**
Other: 2NRTI+PI	n	175	190	174	75	**614**
	%	4.6	4.9	3.1	1.4	**3.3**
Other: 2NRTI+INSTI	n	58	52	61	41	**212**
	%	1.5	1.4	1.1	0.8	**1.1**
Other: NNRTI+INSTI	n	8	5	4	.	**17**
	%	0.2	0.1	0.1	.	**0.1**
Other: PI+INSTI	n	121	55	57	31	**264**
	%	3.2	1.4	1.0	0.6	**1.4**
Other: NRTI+PI+INSTI (3ARVs)	n	72	30	19	6	**127**
	%	1.9	0.8	0.3	0.1	**0.7**
Other: NRTI+PI+INSTI (4ARVs)	n	105	33	29	20	**187**
	%	2.8	0.9	0.5	0.4	**1.0**
Other	n	460	151	108	61	**780**
	%	12.2	3.9	1.9	1.2	**4.2**
CD4:CD8 ratio						
No data	n	444	496	706	759	**2,405**
	%	11.8	12.9	12.6	14.3	**13.0**
<0.50	n	661	585	772	1,114	**3,132**
	%	17.5	15.2	13.8	21.0	**16.9**
≥0.50 <1.00	n	1,725	1,911	2,785	2,320	**8,741**
	%	45.7	49.7	49.8	43.7	**47.2**
≥1.00	n	943	851	1,334	1,117	**4,245**
	%	25.0	22.1	23.8	21.0	**22.9**
CD4 count (cells/mm^3)						
No data	n	28	41	85	95	**249**
	%	0.7	1.1	1.5	1.8	**1.3**
<50	n	7	11	12	23	**53**
	%	0.2	0.3	0.2	0.4	**0.3**
50–199	n	76	69	54	174	**373**
	%	2.0	1.8	1.0	3.3	**2.0**
200–349	n	249	237	296	449	**1,231**
	%	6.6	6.2	5.3	8.5	**6.7**
350–499	n	574	665	856	741	**2,836**
	%	15.2	17.0	15.3	14.0	**15.3**
500–749	n	1,272	1,403	2,111	1,683	**6,469**

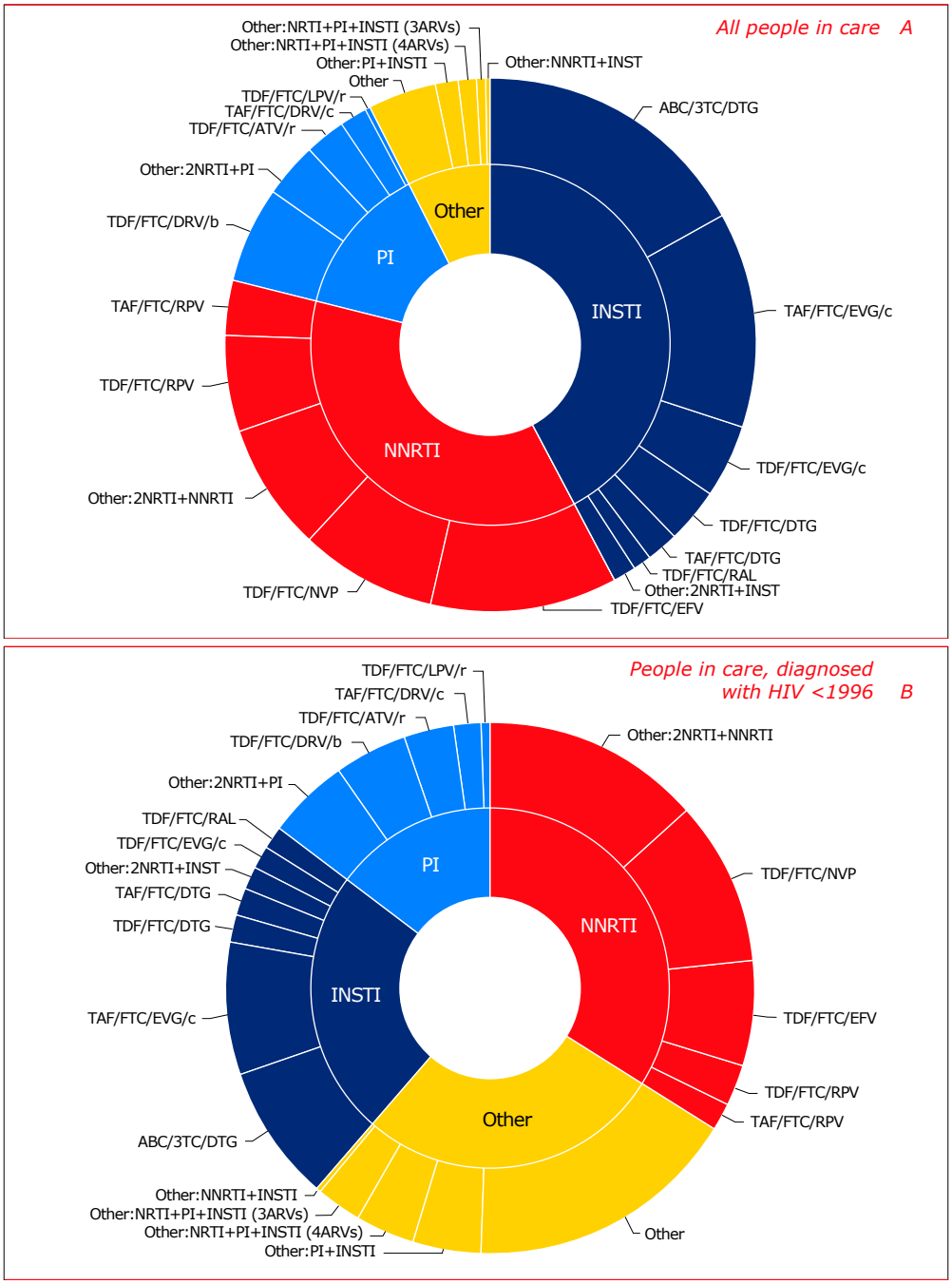
Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2017	All
	%	33.7	36.5	37.7	31.7	**34.9**
≥750	n	1,567	1,417	2,183	2,145	**7,312**
	%	41.5	36.9	39	40.4	**39.5**
Viral load <50 copies/ml						
No data	n	38	100	161	226	**525**
	%	1.0	2.6	2.9	4.3	**2.8**
<50 copies/ml	n	3,217	3,173	4,721	4,161	**15,272**
	%	85.3	82.6	84.4	78.4	**82.5**
Viral load <200 copies/ml						
No data	n	38	100	161	226	**525**
	%	1.0	2.6	2.9	4.3	**2.8**
<200 copies/ml	n	3,661	3,650	5,344	4,841	**17,496**
	%	97.0	95.0	95.5	91.2	**94.5**

Legend: *3TC=lamivudine; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; ARVs=antiretroviral drugs; cART=combination antiretroviral therapy; 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=nucleoside analogue reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; INSTI=integrase inhibitor.*

Among the 18,523 people in HIV care in 2017, the large majority (92.4%) received a regimen based on two nucleoside analogue reverse transcriptase inhibitor (NRTIs), combined with either an integrase inhibitor (INSTI) (42.2%), an NNRTI (36.4%), or a protease inhibitor (PI) (13.8%). The distribution of cART use among the population in care in 2017 is presented in *Figure 2.2A*. The most common regimens were abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (17.0%) and tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) combined with efavirenz (EFV) (11.3%) or nevirapine (NVP) (8.3%). Most people who initiated cART in 2017 did so with ABC/3TC/DTG (35.1%) or tenofovir alafenamide (TAF)/FTC/cobicistat-boosted elvitegravir-cobicistat (EVG/c; 31.2%). TDF was used by a large proportion of the population in care (46.4%); however, this proportion has decreased with an increase in the use of TAF (24.4% of the population in care in 2017).

Of those with a plasma HIV RNA measurement in 2015-2017, 82.5% had a viral load <50 copies/ml, and 94.5% had a viral load <200 copies/ml. On the basis of the last available CD4 and CD8 cell count measurements in 2015-2017, 74.4% had a CD4 cell count of 500 cells/mm^3 or higher, and 2.9% had a CD4:CD8 ratio of 1 or higher.

Figure 2.2: Combination antiretroviral therapy (cART) use in 2017: A) all people in care, and B) people in care who were diagnosed with HIV before 1996.



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

See Appendix Table 2.1 for a more detailed overview of the regimen used by people who were diagnosed with HIV before <1996.

Long-term HIV survivors

Out of 18,580 people in HIV care in the Netherlands in 2017, 3,812 (20.6%) were diagnosed before the year 2000; of those, 3,071 (80.6%) were 50 years of age or older by the end of 2017. Furthermore, 1,966 (10.6%) were diagnosed before 1996, and 1,718 (87.4%) of those were 50 years or older by the end of 2017.

The data presented below focus on the 1,966 people who were diagnosed before 1996 (i.e., before the introduction of cART, and thus considered long-term HIV survivors). Their median age at cART initiation was 31 years (IQR 26-36). The majority were men (82.4%), and the main HIV transmission risk group was MSM (66.4%), followed by heterosexual contact (20.1%), injecting drug use (7.1%), and contaminated blood or blood products (2.3%); the remaining 4.1% acquired HIV through another or an unknown transmission route. Most long-term survivors (65.2%) originated from the Netherlands, followed by western Europe, North America and Australia (13.9%), South America and the Caribbean (10.1%), sub-Saharan Africa (5.5%), and other regions (4.1%). At the start of cART, the median HIV viral load was 4.6 [IQR 3.8-5.1] $\log_{10}$ copies/ml (available for 1,497 people), and the median CD4 cell count was 240 [IQR 120-364] cells/mm^3 (available for 1,743 people). The majority (57.8%) had initiated cART in 1996 or 1997 (36.1% and 21.7%, respectively), and 46.5% had received antiretroviral drugs as monotherapy or dual therapy before initiating cART.

As of 31 December 2017, the median age of the long-term survivors was 57 years (IQR 53-63). The majority (72.3%) received a dual NRTI backbone in combination with an NNRTI (33.9%), integrase inhibitor (23.8%), or protease inhibitor (14.6%). The most common regimens were TDF/FTC/NVP (10.1%), ABC/3TC/DTG (8.3%), TAF/FTC/EVG/c (8.1%), TDF/FTC/EFV (6.5%), and TDF/FTC/DRV/b (boosted darunavir) (4.5%). Importantly, 27.2% 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 2015-2017), 2.2% had a CD4 cell count <200 cells/mm^3, 6.5% between 200 and 349 cells/mm^3, 17.8% between 350 and 499 cells/mm^3, 32.2% between 500 and 749 cells/mm^3,

and 40.4% had 750 cells/mm^3 or higher. Furthermore, 22.9% had a CD4:CD8 ratio of 1 or higher. Of all long-term survivors receiving cART with a viral load measurement in 2017, viral suppression was high and comparable to the overall population in care: 86.1% had a viral load <50 copies/ml, and 96.9% had a viral load <200 copies/ml.

Changes in the use of initial cART regimen

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

***Box 2.2:** Approval dates of new antiretroviral drugs for HIV treatment in the Netherlands in 2013–2017.*

Medicine	Authorisation date
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
TAF/FTC/DRV/cobicistat (Symtuza®)	September 21, 2017

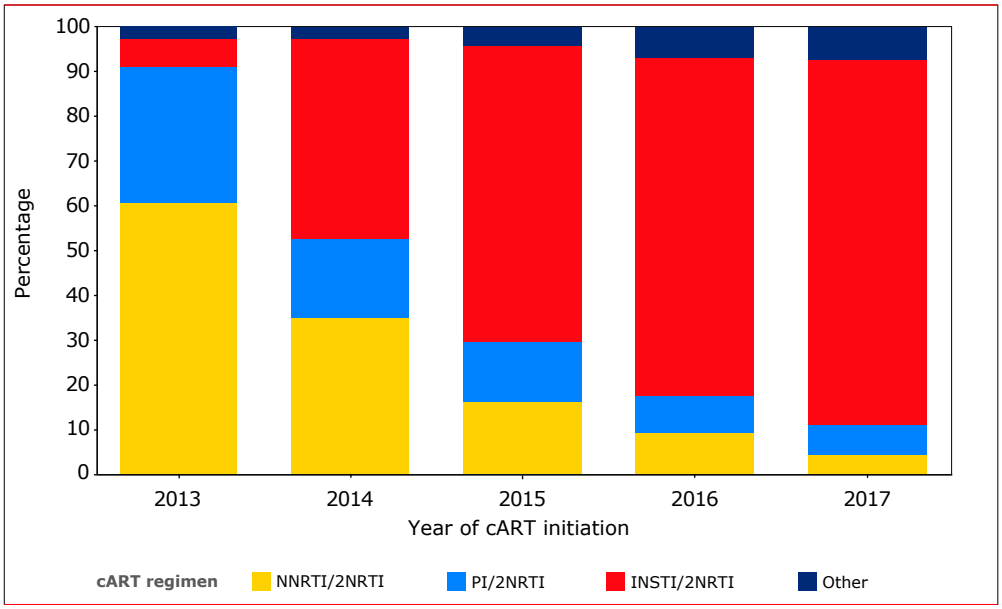
***Source:** Medicines Evaluation Board and European Medicines Agency.*
***Legend:** 3TC=lamivudine; ABC=abacavir; DTG=dolutegravir; DRV=darunavir; EVG=elvitegravir; FTC=emtricitabine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; RPV=rilpivirine.*

Initial cART regimen

Out of 23,578 people who were known to have initiated cART between January 1996 and December 2017, 5,767 (24.5%) started cART between January 2013 and December 2017. *Figures 2.3* and *2.4* show the trends over time in third-drug additions to the NRTI backbone used as 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 6.5% in 2013, to 44.4% in 2014, 65.8% in 2015, 75.3% in 2016, and 81.3% in 2017. EVG/c was introduced in the Netherlands at the end

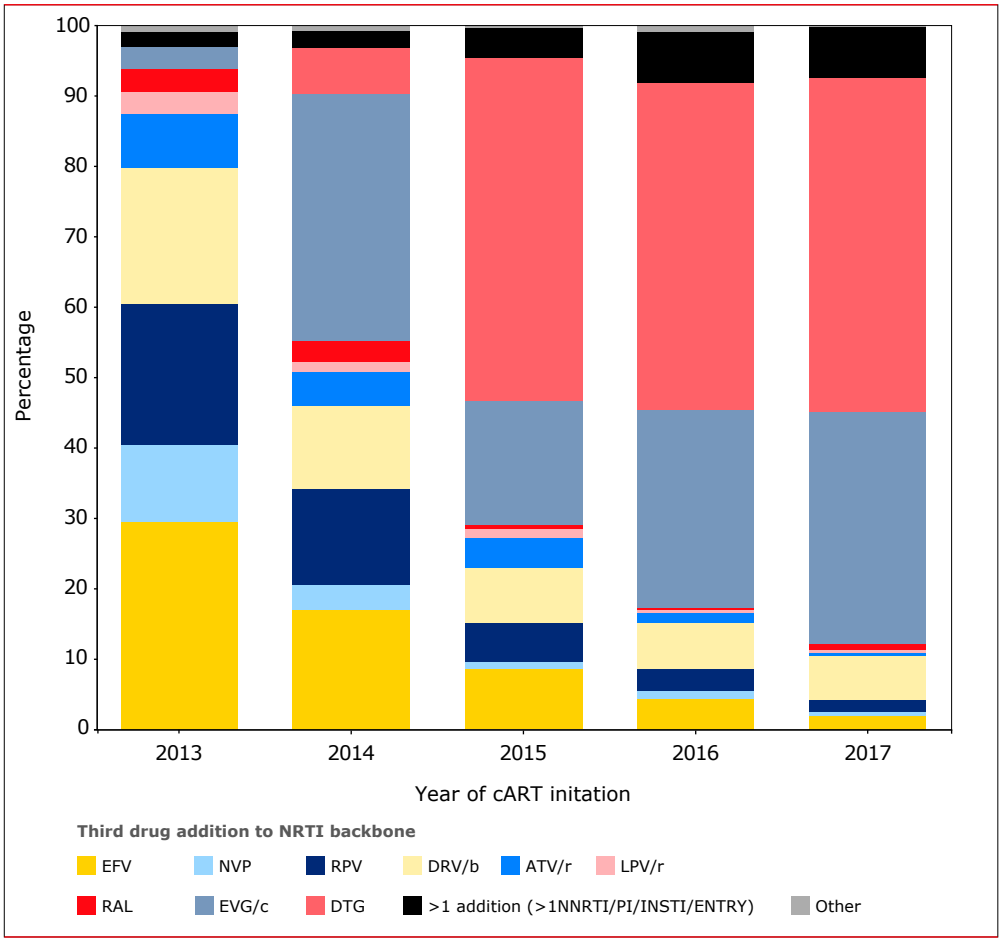
of 2013 and was used in 3.2%, 34.8%, 17.4%, 27.2%, and 33.0% of the initial regimens in 2013, 2014, 2015, 2016, and 2017, respectively. After its introduction in 2014, dolutegravir has become the predominant third-drug addition in the initial cART regimen and was used in up to 47% of initial regimens in 2015-2017. With the introduction of EVG/c and dolutegravir, the use of NNRTIs in the initial regimen decreased from ≥60% in 2013, to 35.0% in 2014, 16.4% in 2015, 9.4% in 2016, and 4.3% in 2017. The use of protease inhibitors in the initial regimen decreased from >30% in 2013 to 6.8% in 2017. In 2013-2017, 4% of people received more than one addition to the NRTI backbone in their initial cART regimen, the majority of whom were people initiating 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 2013-2017.*



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

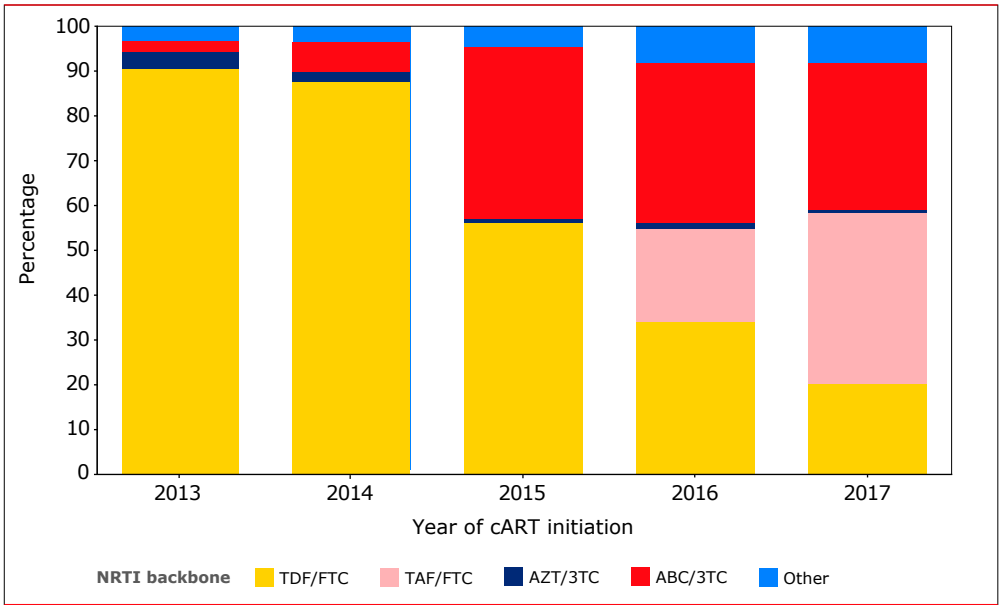
Figure 2.4: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2013-2017.



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 analogue reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NVP=nevirapine; PI=protease inhibitor; RAL=raltegravir; RPV=rilpivirine.*

Figure 2.5 provides an overview of the initial components of the NRTI backbone used between 2013 and 2017. The combination of tenofovir (TDF or TAF) and emtricitabine was the predominant backbone prescribed in initial cART regimens. Following its introduction at the end of 2015, TAF was prescribed in 20.0% and 37.9% of the initial regimens in 2016 and 2017, respectively. At the same time, TDF use decreased from 87-90% in 2013-2014 to 20.3% in 2017. 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 2013, to a third of all initial regimens in 2015-2017. The combination of zidovudine and lamivudine, often received by migrants, further decreased to <1% since 2015.

Figure 2.5: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2013-2017.*



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

The full cART regimens initiated between 2013 and 2017 are presented in *Figure 2.6* and *Table 2.3*. In 2017, most people (46.9%) initiating cART received a dolutegravir-based regimen combined with either abacavir and lamivudine as part of the once-daily fixed-dose combination (32.3%), or they were provided with emtricitabine and tenofovir separately (14.7%; TDF 8.3%/TAF 6.4%). Additionally, a third initiated an EVG/c-containing once-daily fixed-dose combination with emtricitabine and tenofovir (TDF 4.9%/TAF 9.0%). Raltegravir use in an initial regimen (not recommended in starting regimens because it needs to be taken twice daily), has decreased further to ~1% since 2015. The combination of ritonavir or cobicistat-boosted darunavir with tenofovir and emtricitabine was used in 6.2% of initial cART regimens in 2017: 3.9% based on TDF and 1.8% in the new once-daily fixed-dose combination with TAF. *Table 2.3* provides more detail on the 'other' initial regimens that are not further specified in *Figures 2.4-2.6*.

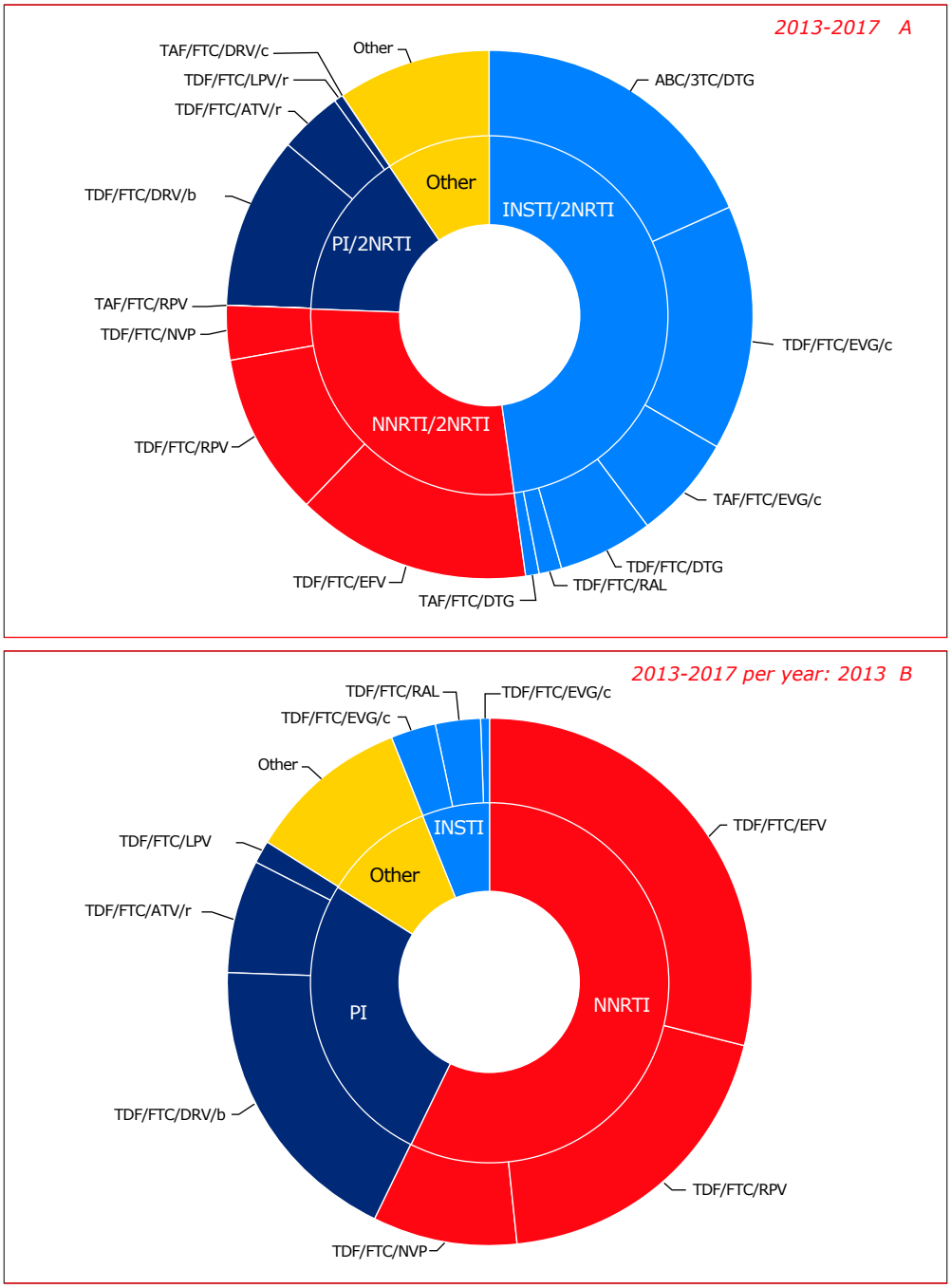
***Table 2.3:** Initial regimen in 2013–2017.*

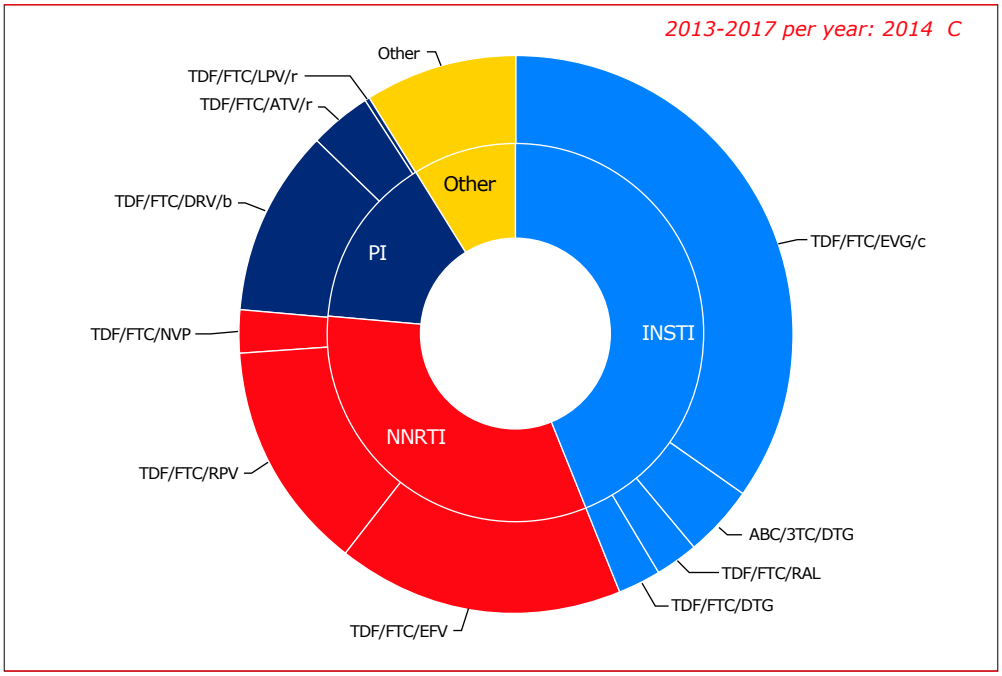
Regimen		2013	2014	2015	2016	2017	2013–2017
TDF/FTC/EFV	n	429	245	93	43	10	**820**
	%	28.9	16.8	7.9	4.5	1.5	**14.2**
TDF/FTC/NVP	n	131	35	7	9	2	**184**
	%	8.8	2.4	0.6	0.9	0.3	**3.2**
TDF/FTC/RPV	n	291	195	73	25	4	**588**
	%	19.6	13.4	6.2	2.6	0.6	**10.2**
TDF/FTC/DRV/b	n	273	157	90	56	26	**602**
	%	18.4	10.8	7.6	5.8	3.9	**10.4**
TDF/FTC/ATV/r	n	105	55	42	14	3	**219**
	%	7.1	3.8	3.6	1.5	0.4	**3.8**
TDF/FTC/LPV	n	18	5	8	1	.	**32**
	%	1.2	0.3	0.7	0.1	.	**0.6**
TDF/FTC/EVG/c	n	41	507	205	80	33	**866**
	%	2.7	34.8	17.4	8.3	4.9	**15.0**
TDF/FTC/DTG	n	.	36	137	96	56	**325**
	%	.	2.5	11.6	9.9	8.3	**5.6**
TDF/FTC/RAL	n	40	37	7	5	3	**92**
	%	2.7	2.5	0.6	0.5	0.4	**1.6**
ABC/3TC/DTG	n	.	61	425	355	218	**1,059**
	%	.	4.2	36.0	36.7	32.3	**18.4**
TAF/FTC/EVG/c	n	6	.	1	183	190	**380**
	%	0.4	.	0.1	18.9	28.2	**6.6**
TAF/FTC/RPV	n	.	.	.	3	7	**10**

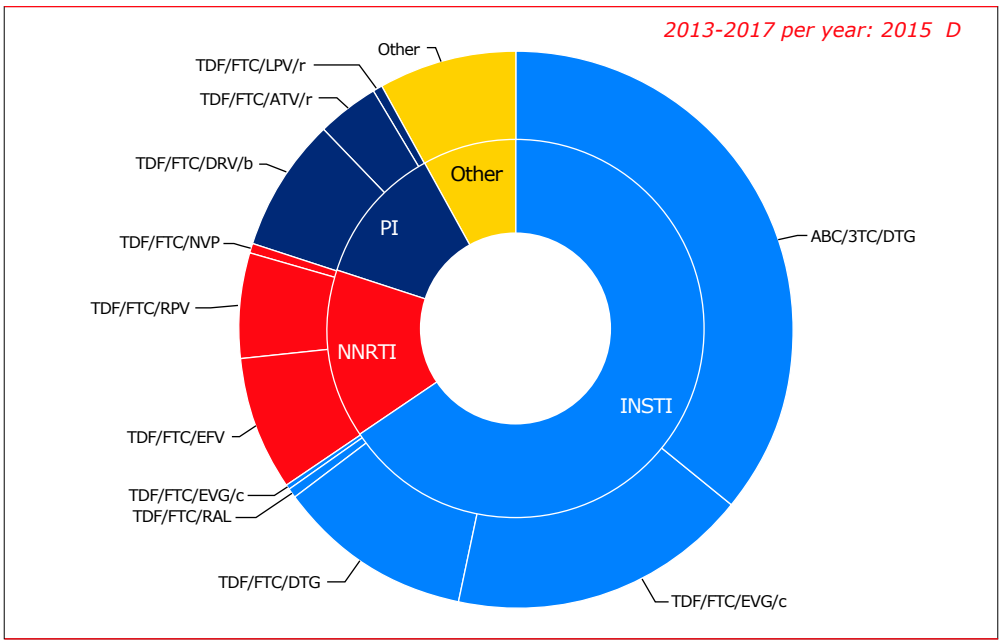
	%	.	.	.	0.3	1.0	**0.2**
TAF/FTC/DTG	n	.	.	.	6	43	**49**
	%	.	.	.	0.6	6.4	**0.9**
TAF/FTC/DRV/c	n	.	.	.	.	12	**12**
	%	.	.	.	.	1.8	**0.2**
Other:2NRTI+NNRTI	n	54	37	21	11	6	**129**
	%	3.6	2.5	1.8	1.1	0.9	**2.2**
Other:2NRTI+PI	n	55	45	19	11	5	**135**
	%	3.7	3.1	1.6	1.1	0.7	**2.3**
Other:2NRTI+INSTI	n	10	7	2	3	6	**28**
	%	0.7	0.5	0.2	0.3	0.9	**0.5**
Other: NRTI+PI+INSTI (3ARVs)	n	1	3	2	.	1	**7**
	%	0.1	0.2	0.2	.	0.2	**0.1**
Other: NRTI+PI+INSTI (4ARVs)	n	10	20	40	59	48	**177**
	%	0.7	1.4	3.4	6.1	7.1	**3.1**
Other	n	21	14	9	7	2	**53**
	%	1.4	1.0	0.78	0.7	0.3	**0.9**
Total	**n**	**1,485**	**1,459**	**1,181**	**967**	**675**	**5,767**
	%	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

Legend: *ARVs=antiretroviral drugs; 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; LPV=lopinavir; INSTI=integrase inhibitor; NRTI=nucleoside analogue reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NVP=nevirapine; PI=protease inhibitor; RPV=rilpivirine; RAL=raltegravir; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.*

Figure 2.6: Initial combination antiretroviral therapy regimens in A) 2013–107 and B–F) per individual year.




2013-2017 per year: 2014 C
Other
TDF/FTC/LPV/r
TDF/FTC/ATV/r
TDF/FTC/DRV/b
TDF/FTC/NVP
TDF/FTC/RPV
TDF/FTC/EFV
TDF/FTC/EVG/c
ABC/3TC/DTG
TDF/FTC/RAL
TDF/FTC/DTG
Other
PI
NNRTI
INSTI


2013-2017 per year: 2015 D
Other
TDF/FTC/LPV/r
TDF/FTC/ATV/r
TDF/FTC/DRV/b
TDF/FTC/NVP
TDF/FTC/RPV
TDF/FTC/EFV
TDF/FTC/EVG/c
TDF/FTC/RAL
TDF/FTC/DTG
ABC/3TC/DTG
TDF/FTC/EVG/c
Other
PI
NNRTI
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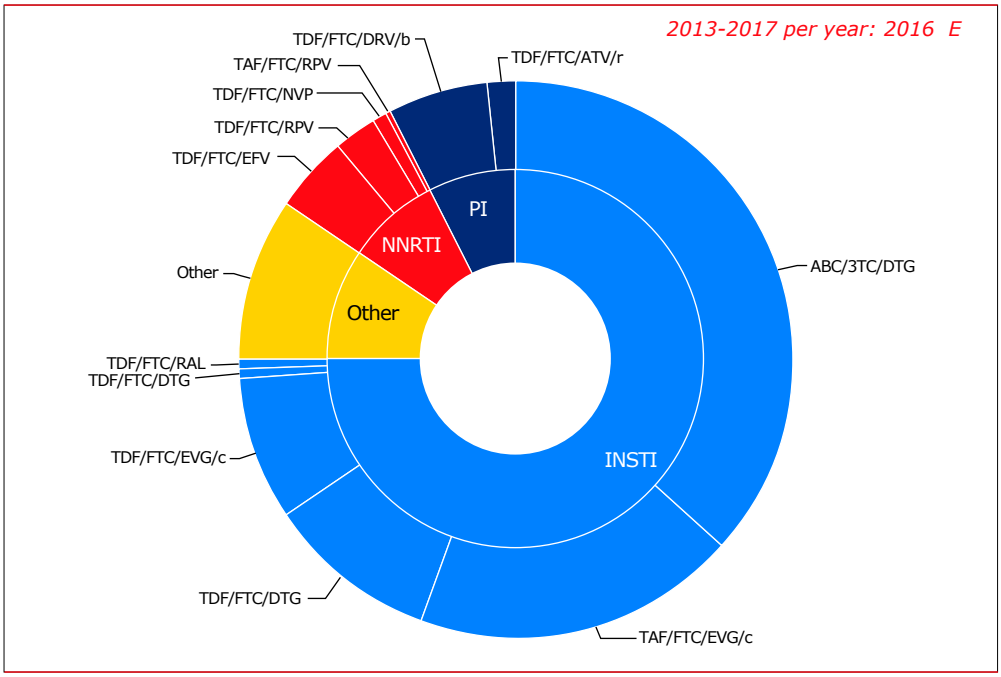
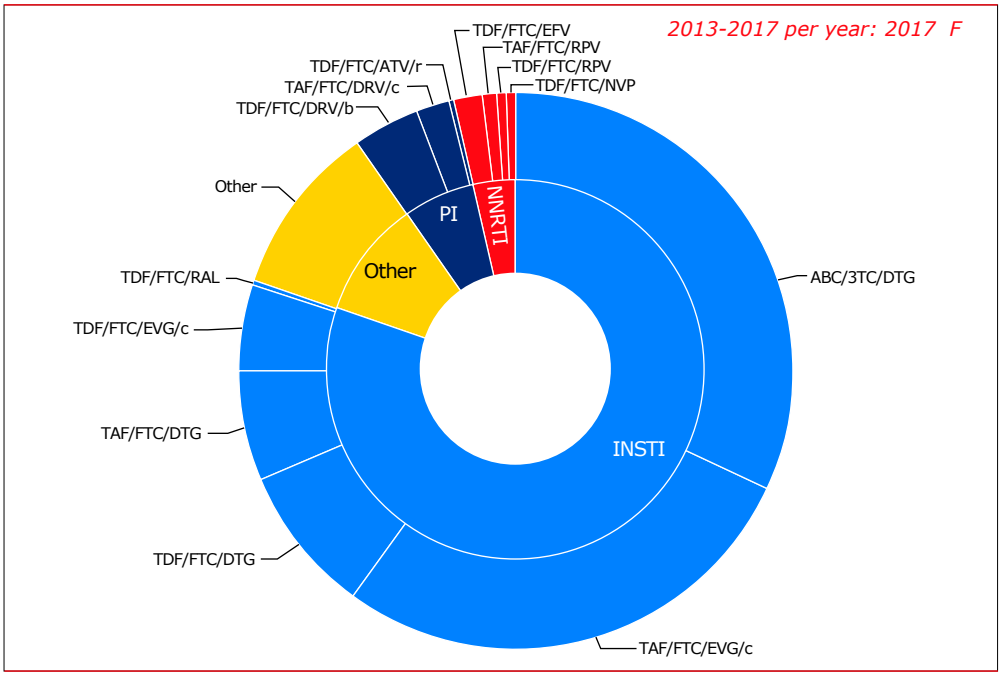

2013-2017 per year: 2016 E
TDF/FTC/DRV/b
TAF/FTC/RPV
TDF/FTC/NVP
TDF/FTC/RPV
TDF/FTC/EFV
TDF/FTC/ATV/r
PI
NNRTI
Other
Other
ABC/3TC/DTG
TDF/FTC/RAL
TDF/FTC/DTG
TDF/FTC/EVG/c
INSTI
TDF/FTC/DTG
TAF/FTC/EVG/c


2013-2017 per year: 2017 F
TDF/FTC/EFV
TAF/FTC/RPV
TDF/FTC/ATV/r
TDF/FTC/RPV
TAF/FTC/DRV/c
TDF/FTC/NVP
TDF/FTC/DRV/b
Other
PI
NNRTI
Other
TDF/FTC/RAL
ABC/3TC/DTG
TDF/FTC/EVG/c
TAF/FTC/DTG
INSTI
TDF/FTC/DTG
TAF/FTC/EVG/c

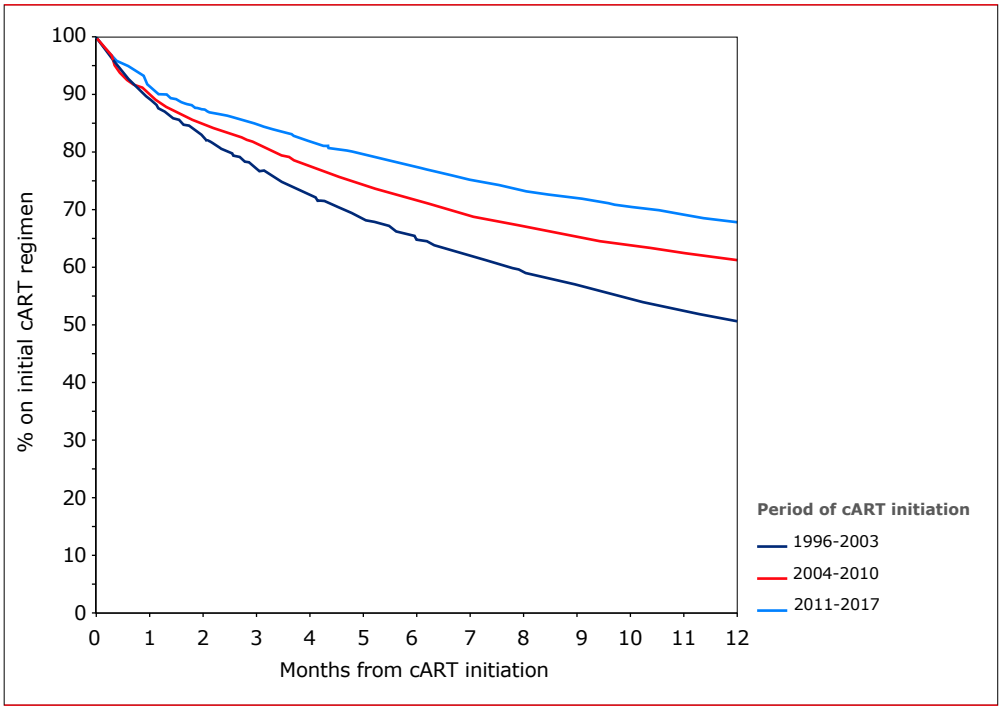
Legend: *3TC=lamivudine; ABC=abacavir; ATV=atazanavir; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; INSTI=integrase inhibitor; LPV=lopinavir; NNRTI=non-nucleoside reverse transcriptase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

Discontinuation of the initial cART regimen

We assessed the time spent on the initial cART regimen among the 23,578 people who ever started cART. Discontinuation of the initial cART regimen was defined as a change in or discontinuation of ≥1 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 (EFV) 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 EFV/TDF/FTC to EVG/c/TDF/FTC was. One-year discontinuation rates are based on the Kaplan-Meier estimates.

In the period 1996-2017, 39.6% of persons discontinued their initial regimen within one year. The time on the initial regimen improved over the years: in 1996-2007, half discontinued their original regimen within a year, compared to approximately a third who discontinued their initial regimen in 2006-2017. The time spent on the initial regimen during the first year of cART stratified by 5-year periods is shown in *Figure 2.7*.

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



Legend: cART=combination antiretroviral therapy

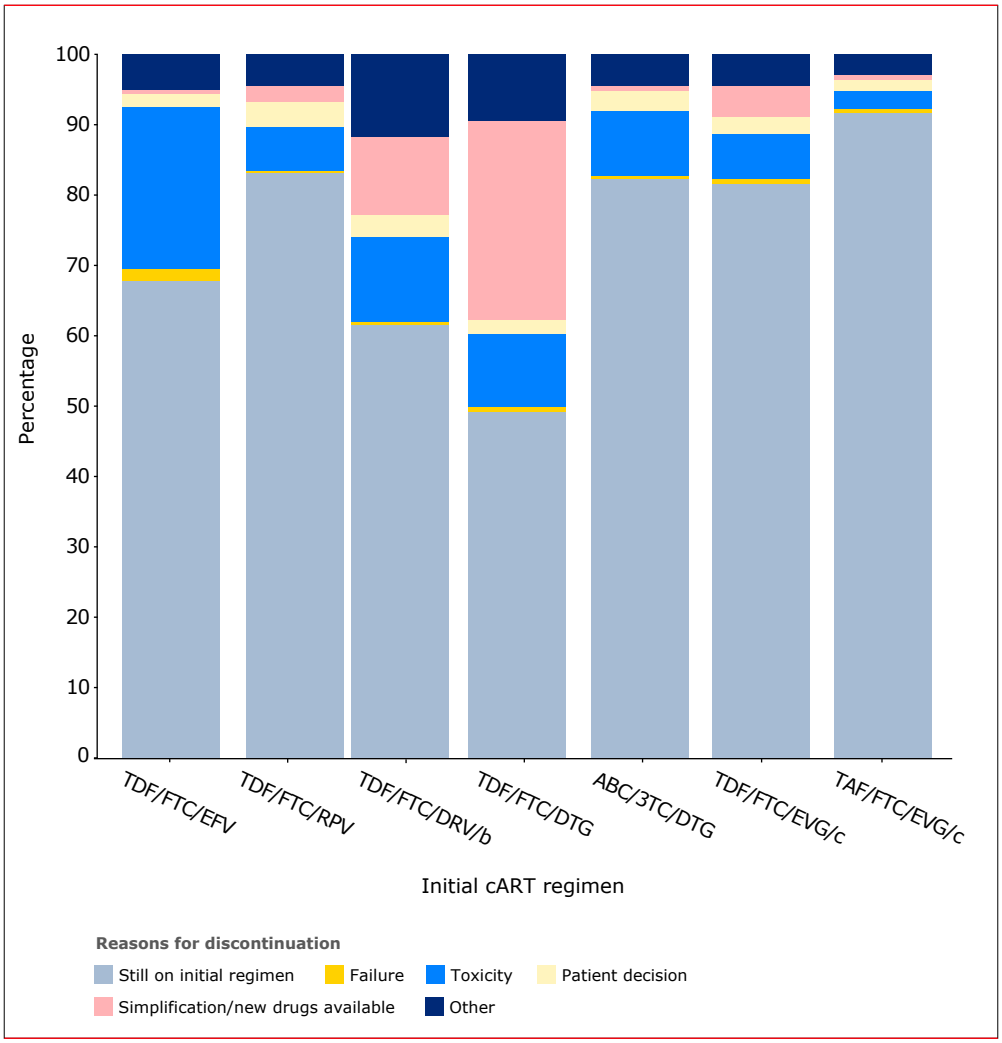
Discontinuation of the initial cART regimen: 2013-2017

We further assessed the time to discontinuation of the initial regimen during the first year of treatment among 4,630 people who started common initial regimens in 2013-2017. Common regimens considered in this analysis were: tenofovir/emtricitabine combined with efavirenz (TDF/FTC/EFV; 17.8%), rilpivirine (TDF/FTC/RPV; 12.7%), ritonavir-boosted or cobicistat-boosted darunavir (TDF/FTC/DRV/b; 13.0%), cobicistat-boosted elvitegravir (TDF/FTC/EVG/c; 18.7% and TAF/FTC/EVG/c; 8.2%), dolutegravir (TDF/FTC/DTG; 7.0%), or abacavir-lamivudine combined with dolutegravir (ABC/3TC/DTG; 22.9%).

One year after cART initiation, 1,129 (24.4%) out of 4,630 who initiated one of these regimens had discontinued their initial regimen. The main reason for regimen discontinuation was toxicity (n=490; 43.4%), followed by simplification and/or availability of new drugs (n=215; 19.0%). 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, 6.4% discontinued their initial regimen for reasons of simplification and/or availability of new drugs in 2013, 14.3% in 2014, 28.1% in 2015, 24.4% in 2016, and 22.7% in 2017.

Figure 2.8: *Reasons for discontinuation of the initial regimen during the first year of treatment 2013–2017, by regimen.*

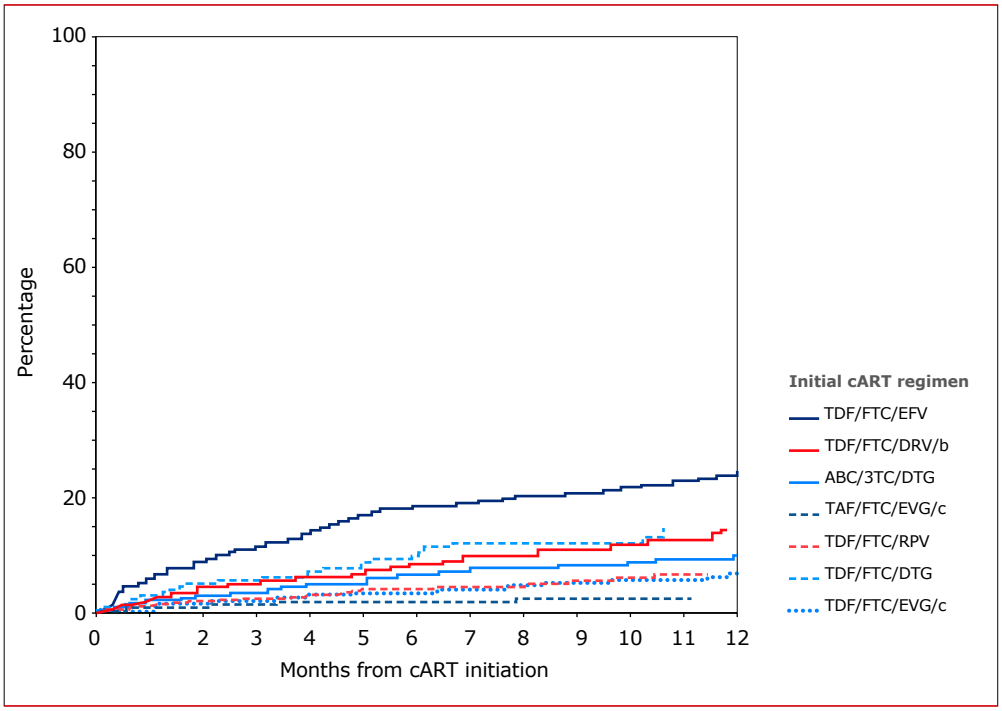


Legend: *cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.*

Discontinuation of the initial cART regimen due to toxicity

The time until discontinuation of the initial regimen due to toxicity during the first year of treatment, by regimen, is presented in *Figure 2.9*.

Figure 2.9: *Kaplan-Meier estimate of the time on initial regimen until modification due to toxicity 2013-2017, by regimen. Time was censored when the initial regimen was discontinued due to reasons other than toxicity (log-rank p<0.001).*

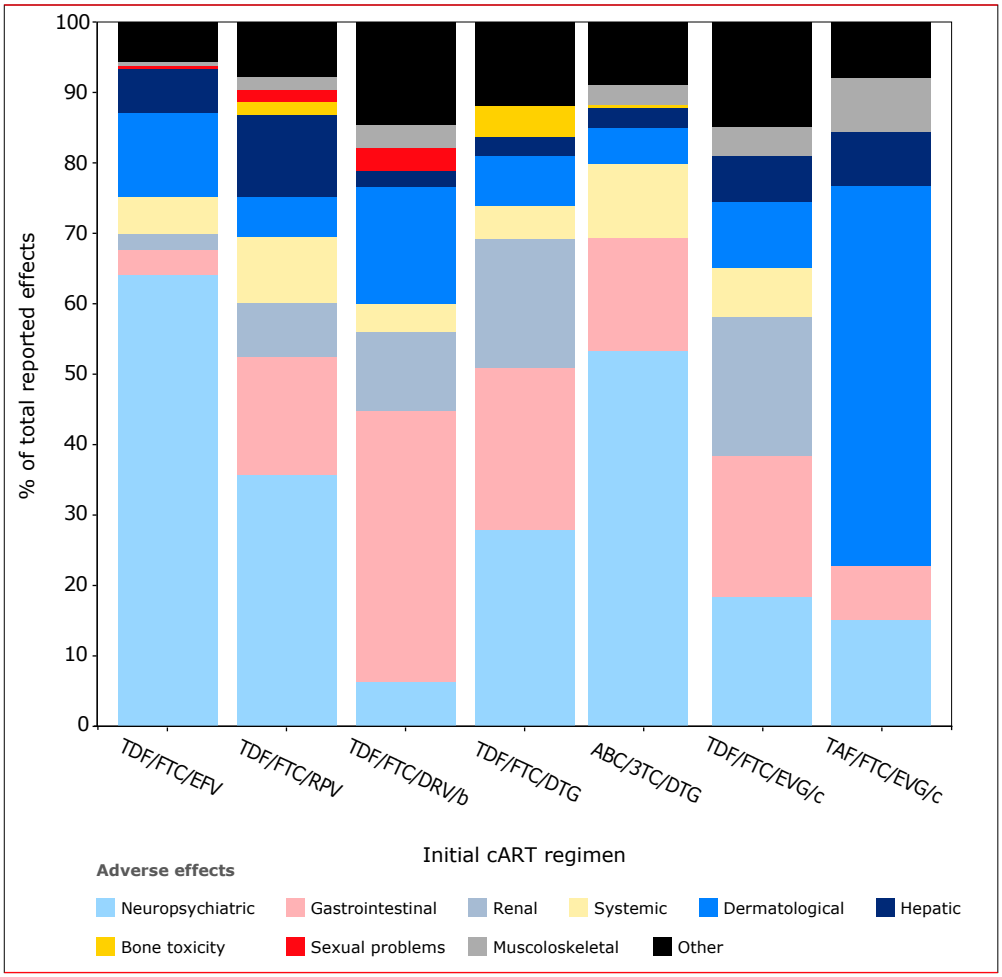


Legend: *cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.*

Adverse effects

Among the 490 who discontinued their initial cART regimen due to toxicity within a year, 709 adverse effects were recorded. The predominant effects were: 43.7% neuropsychiatric (mainly insomnia, mood changes, dizziness and depression), 14.7% gastrointestinal (mainly diarrhoea and nausea), 10.7% dermatological (rash due to medication, itching), 6.8% systemic (tiredness, apathy, loss of appetite), and 6.1% renal (renal insufficiency and increased serum creatinine). These adverse effects are stratified by cART regimen in *Figure 2.10*. Neuropsychiatric effects were associated with TDF/FTC/EFV, ABC/3TC/DTG (but less for TDF/FTC/DTG), and TDF/FTC/RPV. Hepatic effects were mainly reported by people discontinuing TDF/FTC/ATV/r (atazanavir plus ritonavir). Renal effects were only reported by people who discontinued TDF-based cART.

Figure 2.10: Adverse effects associated with initial regimen discontinuation due to toxicity, during the first year of treatment 2013–2017. The bars represent the distribution of 709 reported effects among 490 people, by regimen.



Legend: cART=combination antiretroviral therapy; 3TC=lamivudine; ABC=abacavir; b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EGV=elvitegravir; FTC=emtricitabine; NRTI=nucleoside analogue reverse transcriptase inhibitor; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil.

Note: The discontinuation rates and reasons for discontinuation are descriptive by nature and should be interpreted with caution. The choice of the initial cART regimen depends on personal 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 23,579 adults have started cART since January 1996. For the current analysis of virological outcomes, we will focus on the 20,387 adults who were ART-naive and not pregnant at the time of cART initiation (because cART may have been interrupted at the end of the pregnancy). We also excluded people without an appropriate 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 19,358 people. The main definitions for virological outcomes used in this chapter are summarised in *Box 2.3*.

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 combination antiretroviral therapy (cART).
The viral load measurement closest to 6 months (±3 months) 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.

HIV drug resistance

Transmitted HIV drug resistance
At least one resistance-associated mutation detected among people who never received antiretroviral drugs and had not started cART.
The 2017 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutation[24].

Acquired HIV drug resistance
High-level resistance to at least one antiretroviral drug, detected at the time of HIV 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[25,26].

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Initial virological success

Out of 19,358 with a viral load test result after at least 3 months of cART initiation, 15,645 (80.8%) had a viral load measurement 6 months (±3 months) after cART initiation. Of these people, 13,642 (87.2%) achieved initial virological success, i.e., a plasma viral load <100 HIV RNA copies/ml (*Box 2.3*). The percentage of people with initial virological success has improved over time, from 73.1% (95% CI 71.4-74.7) in those starting cART between 1996 and 2003, to 88.1% (95% CI 87.3-88.9) in those starting between 2004 and 2010, 91.9% (95% CI 941.2-92.6) in those starting between 2011 and 2016, and 94.3% (95% CI 92.2-96.4) in those starting in 2017.

Initial virological success of common initial cART regimens (2013–2017)

We analysed the initial virological success among the 3,881 adults who started a common cART regimen in 2013-2017 (TDF/FTC/EFV; TDF/FTC/RPV; TDF/FTC/DRV/b; TDF/FTC/EVG/c; TAF/FTC/EVG/c; TDF/FTC/DTG; and ABC/3TC/DTG); described under 'Changes in use of initial antiretroviral therapy 2013-2017'), and had a viral load result after 6 months (±3 months) of cART initiation. In total, 94.0% (95% CI 93.3-94.8) of people achieved initial virological suppression, after a mean of 179 (SD 39) days. Overall, people receiving an integrase-inhibitor based regimen showed significantly higher rates of initial virological success: 95.3% (95% CI 94.4-96.2) of those on an integrase-inhibitor-based regimen had initial virological success, compared to 90.1% (95% CI 87.5-92.6) on a protease-inhibitor-based regimen and 93.4% (95% CI 91.9-94.9) on a NNRTI-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 (</≥100,000 copies/ml), cART regimen, and regimen class through logistic regression analysis. Out of 3,881 individuals, viral load data were available for 3,456 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 above. The effect of cART regimen on the initial virological suppression rates was strongest in people with a viral load ≥100,000 copies/ml at cART initiation (*Table 2.4*).

Table 2.4: Initial virological success rates (see definition in Box 2.3) by initial regimen, and initial viral load at cART start. Population characteristics, which may be associated with the initial prescribed regimen, were not taken into account in this analysis.

	Total		By initial viral load at cART start					
					<100,000 copies/ml			
	n	%	n	%	Initial viral success	95% CI low	95% CI high	p-value
cART regimen								
TDF/FTC/EFV	556	16.0	311	14.0	98.1	96.5	99.6	Ref.
TDF/FTC/RPV	358	10.4	358	16.1	95.3	93.0	97.5	0.015
TDF/FTC/DRV/b	497	14.3	211	9.5	95.7	93.0	98.5	0.105
TDF/FTC/EVG/c	696	20.0	484	21.7	97.7	96.4	99.1	0.718
TDF/FTC/DTG	248	7.2	131	5.9	98.5	96.4	99.1	0.409
ABC/3TC/DTG	821	23.8	557	25.0	97.1	95.7	98.5	0.633
TAF/FTC/EVG/c	280	8.0	178	8.0	98.3	96.4	100.0	0.424
cART regimen class								
NNRTI/2NRTI	914	26.5	669	30.0	96.6	95.2	97.9	Ref.
PI/2NRTI	497	14.4	211	9.5	95.7	93.0	98.5	0.259
INSTI/2NRTI	2,045	59.2	1,350	60.5	97.6	96.8	98.4	0.066
All regimens	**3,456**	**100.0**	**2,230**	**64.5**	**97.1**	**96.4**	**97.8**	

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

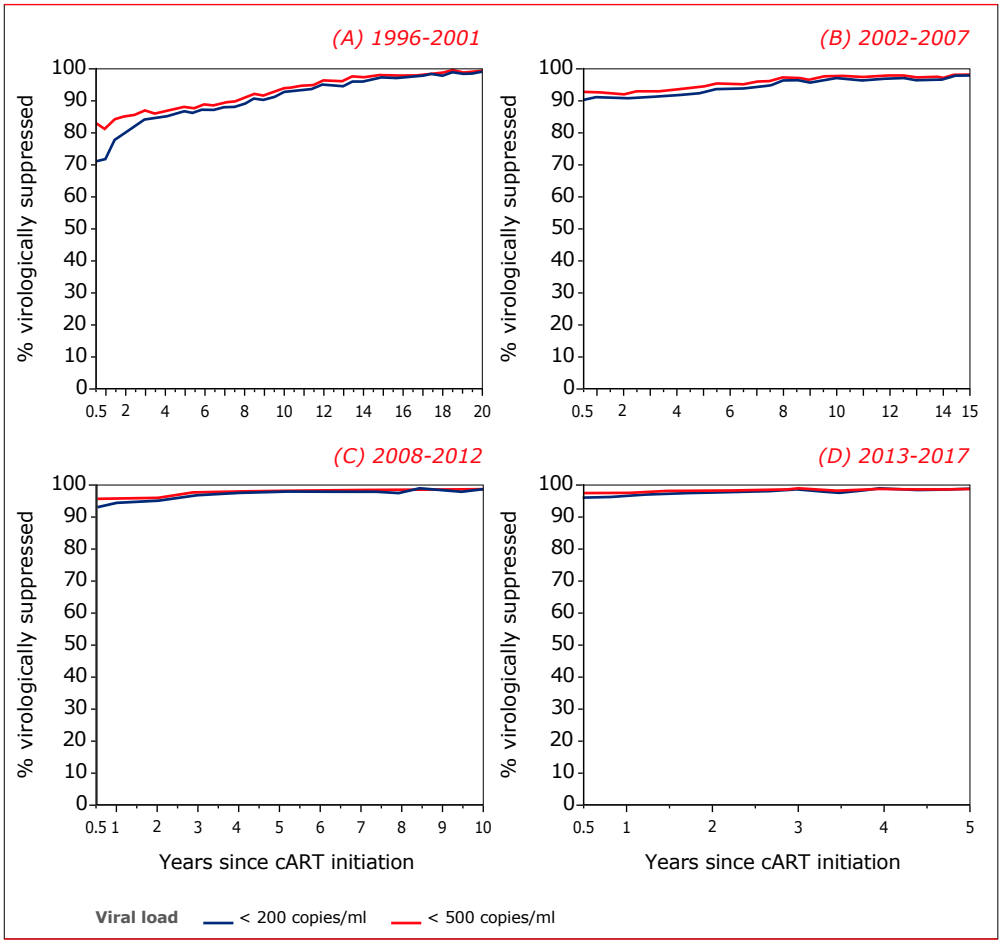
				By initial viral load at cART start			
				≥100,000 copies/ml			
		n	%	Initial viral success	95% CI low	95% CI high	p-value
	cART regimen						
	TDF/FTC/EFV	245	20.0	87.8	83.6	91.9	Ref.
	TDF/FTC/RPV	not recommended					
	TDF/FTC/DRV/b	286	23.3	85.7	81.6	89.7	0.026
	TDF/FTC/EVG/c	212	17.3	90.6	86.6	94.5	0.677
	TDF/FTC/DTG	117	9.5	88.0	82.1	93.9	0.491
	ABC/3TC/DTG	264	21.5	93.6	90.6	96.5	0.028
	TAF/FTC/EVG/c	102	8.3	91.2	85.7	96.7	0.588
	cART regimen class						
	NNRTI/2NRTI	245	20.0	87.8	83.6	91.9	Ref.
	PI/2NRTI	286	23.3	85.7	81.6	89.7	0.068
	INSTI/2NRTI	695	56.7	91.4	89.3	93.5	0.010
	All regimens	**1,226**	**35.5**	**89.3**	**87.6**	**91.0**	

Viral suppression

We assessed longitudinal viral suppression rates (i.e., viral load <200 copies/ml) over time on cART during 6-month intervals among adults with a viral load test result after cART initiation. The viral load measurement after at least 3 months of cART, closest to each 6-month time point (±3 months) was included in the analysis, irrespective of the viral load of that time point.

Figure 2.11 shows viral suppression rates by calendar period of cART initiation: 1996-2001, 2002-2007, 2008-2012 and 2013-2017. In line with the initial virological success rates, the long-term viral suppression rates likewise improved over time. In people initiating cART in or after 2013, suppression rates ranged from 96.8% (95% CI 96.3-97.4) after 1 year of cART use to 98.9% (95% CI 98.3-99.5) after 4 years. The viral suppression rates over time during the full period (1996-2017) are shown in *Appendix Figure 2.2*.

Figure 2.11: Viral suppression since combination antiretroviral therapy (cART) initiation, by calendar period of therapy initiation.



Legend: cART=combination antiretroviral therapy.

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

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[27].

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

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[24]. 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[25,26]. The definitions of transmitted and acquired HIV drug resistance used in our analyses are summarised in *Box 2.3*. The number of sequences and people included in each of the analyses is outlined in *Box 2.1*.

Screening for drug-resistant HIV before treatment initiation

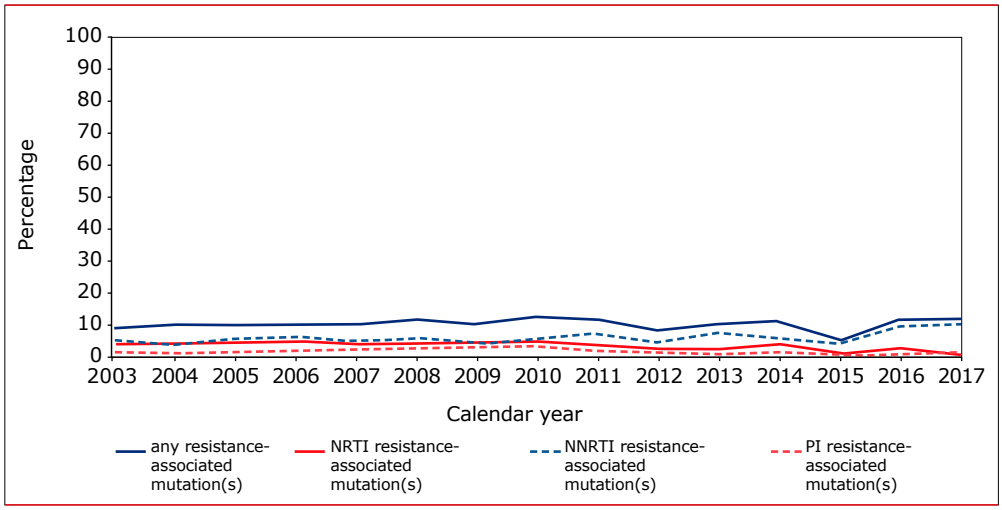
In the Netherlands, screening for HIV drug resistance at the time of entry into care has been incorporated in the treatment guidelines since 2003. Transmitted HIV drug resistance occurs when people acquire an HIV strain that harbours drug-resistance mutations. Although a drug-resistant virus strain may revert to a drug-susceptible virus, drug-resistant variants of HIV may remain dormant in resting CD4 cells, awaiting more favourable replication conditions after treatment has started[28,29,30]. Therefore, ideally, the presence of transmitted resistance should be identified as close to the moment of infection as possible in people who are antiretroviral (ARV)-naive before initiating cART.

As of January 2018, 7,315 HIV-1 sequences were obtained between 2003-2017 from 6,981 ARV-naive people before initiating cART. If someone had more than one sequence available before cART initiation, we selected the first available sequence (closest to the date of HIV-1 diagnosis) for further analysis to limit the effect of back mutation. Of those for whom pre-treatment drug-resistance data was available, the majority were MSM (66.2%) and, less often, women (14.2%). Most people with an available pre-treatment sequence originated from the Netherlands (57.7%) or sub-Saharan Africa (11.5%). The main HIV-1 subtype was B (75.8%), followed by non-B subtypes (24.2%), including recombinant form CRF_02AG (7.1%) and subtype C (5.2%).

Transmitted HIV drug resistance

In total, ≥1 resistance-associated major mutation[24] was found in 723 (10.4%) of the people who were tested for resistance, including 265 (3.8%) with NRTI-associated resistance mutations, 391 (5.6%) with NNRTI-associated resistance mutations, and 127 (1.8%) with PI-associated resistance mutations. The prevalence of transmitted drug resistance was low and remained stable between 2003 and 2017 (*Figure 2.12*).

Figure 2.12: The annual proportion of people with evidence of transmitted HIV drug resistance over time.



Legend: *Transmitted drug resistance was defined as the presence of at least one resistance-associated mutation detected before initiation of cART. The 2017 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[24].*

In total, 151 (2.2%) screened for transmitted drug resistance harboured high-level resistance[25,26] to at least one antiretroviral drug; 25 (0.4%) to at least one NRTI, 124 (1.8%) to at least one NNRTI and 30 (0.4%) to at least one PI. On the basis of the available resistance data, >97% were fully susceptible to all antiretroviral drugs; 1.8% (n=127) harboured high-level resistance in one drug class, 0.3% (n=20) in two drug classes, and 0.1% (n=4) to 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 people with resistance to all three classes, fully efficacious cART combinations can often still be constructed.

Integrase inhibitor resistance before HIV treatment initiation

Nineteen people had an integrase sequence available prior to cART initiation; all of them were ARV-naive. No major or minor integrase resistance-associated mutations were detected.

Acquired HIV drug resistance

The overall viral suppression rates of people receiving cART are very high and continue to improve in the Netherlands (see section 'Virological response'). However, acquired HIV drug resistance can still be detected in a subset of people 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 4 months of cART in 2000-2017. If cART had been interrupted >2 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 someone had more than one sequence available in any given calendar year.

In total, 4,242 HIV-1 sequences were obtained from 2,540 people who received cART for at least 4 months. The number of sequences and people included in each subsequent analysis are outlined in *Box 2.1*. The median time between initial start of cART and resistance testing was 5.2 years [IQR 2.9-8.1]. The main HIV-1 subtype was B (70.3%), followed by recombinant form CRF_02AG (8.7%) and subtype C (6.8%).

Overall, sequences from people pre-treated with monotherapy or dual therapy were disproportionally represented: 1,426 (33.6%) sequences were obtained from 765 (30.1%) pre-treated people, and 2,816 (66.4%) sequences were obtained from 1,775 (69.9%) ARV-naive people. However, over time this difference has become

less distinct. In 2000, 72.0% of sequences were obtained from pre-treated people, compared with 33.7% in 2005 and less than 15% since 2010.

Out of all 4,242 sequences obtained at the time of HIV RNA >500 copies/ml, 2,842 (67.0%) harboured high-level resistance[25,26] to at least one antiretroviral drug. High-level NRTI resistance was detected in 2,421 (57.1%) sequences; of those, 2,065 (85.3% of 2,421) harboured high-level resistance to emtricitabine or lamivudine. In addition, 1,688 (39.8%) harboured high-level resistance to at least one NNRTI, and 1,120 (26.4%) to at least one PI.

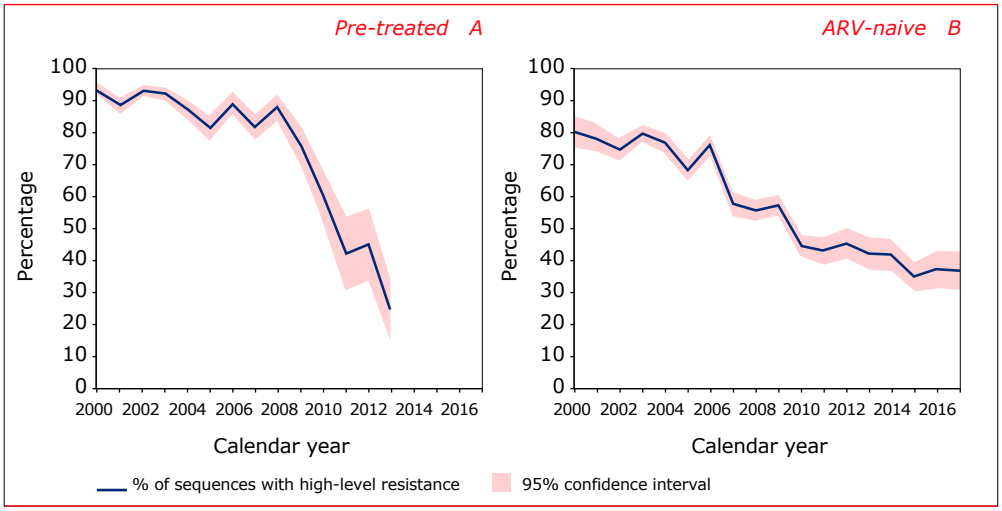
Previous antiretroviral drug exposure

The occurrence of acquired resistance was different for sequences obtained from pre-treated people than for those from people who were ARV-naive before initiating cART.

Among pre-treated people, the annual proportion of sequences harbouring high-level resistance to at least one drug was 93.8% (95% CI 91.9-95.7) in 2000, 87.3% (95% CI (84.2-90.4) in 2004, 60.0% (95% CI 51.6-68.4) in 2010, and 23.9% (95% CI 14.3-33.3) in 2013 (*Figure 2.13A*). The availability of new drugs both in existing and new drug classes largely explains the decline since 2008[31]. In recent years (2014-2017), both the number of pre-treated people and the number of sequences from pre-treated people were too low to provide meaningful proportions.

Among previously ARV-naive people, high-level resistance to at least one drug was detected among 80.0% (95% CI 75.0-85.0) of sequences in 2000, 75.9% (95% CI 72.6-79.3) in 2006, 45.4% (95% CI 40.6-50.2) in 2012, and 36.6% (95% CI 30.9-42.4) in 2017 (*Figure 2.13B*). Over time, the difference in acquired drug resistance detected among pre-treated and ARV-naive people has disappeared.

Figure 2.13: The annual proportion of sequences with evidence of high-level resistance to any antiretroviral drug, obtained at the time of virological failure when receiving combination antiretroviral therapy (cART), by prior antiretroviral drug exposure, among A) people who were pre-treated, and B) previously antiretroviral drug-naive people. The shaded area represents the 95% confidence interval.



Note: The number of sequences from pre-treated people in recent years (2014-2017) was too low to give meaningful proportions.

Legend: ARV=antiretroviral therapy (antiretroviral drug use that may prevent HIV from damaging the immune system by blocking the reproduction of HIV virus).

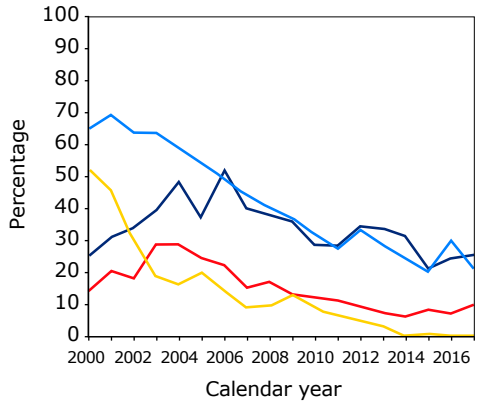
Acquired HIV drug resistance among previously ARV-naive people

In the remainder of our analysis, we will focus solely on the 1,775 people who were ARV-naive before cART initiation. Overall, 1,773 (63.0%) out of all 2,816 sequences from previously ARV-naive people receiving cART harboured at least one major resistance mutation, associated with resistance to NRTI (n=1,427; 50.7%), NNRTI (n=1,106; 39.3%) or PI (n=428; 15.2%).

In *Figure 2.14A* and *Table 2.5*, the annual proportion of sequences harbouring high-level resistance is presented for each antiretroviral drug class. In 2000, 64.6% (95% CI 58.6-70.6), 24.6% (95% CI 19.2-30.0), and 52.3% (95% CI 46.1-58.6) of sequences harboured high-level resistance to at least one NRTI, NNRTI, or PI, respectively. The proportion of sequences with high-level of resistance declined over time for all drug classes. In 2009, 36.4% (95% CI 33.1-39.6), 35.9% (95% CI 32.7-39.2), and 12.7% (95% CI 10.5-15.0) of sequences harboured high-level resistance to at least one NRTI, NNRTI, or PI, respectively. In 2017, 21.1% (95% CI 16.2-26.0), 25.4% (95% CI 20.2-30.6),

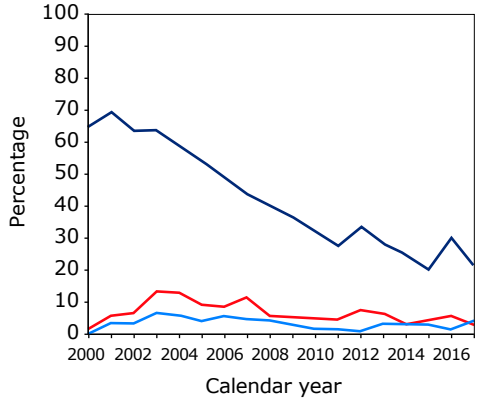
and 0.0% (95% CI 0.0-0.0) of sequences harboured high-level resistance to at least one NRTI, NNRTI or PI, respectively. The annual proportions of sequences harbouring high-level resistance for each antiretroviral drug are presented in *Figure 2.14B-D* and *Appendix Table 2.3*. Of note, drug resistance does not disappear when viral replication is successfully suppressed or re-suppressed.

Figure 2.14: *The annual proportion of sequences with evidence of high-level resistance by antiretroviral drug and drug class, obtained at the time of virological failure when receiving combination antiretroviral therapy (cART), among previously antiretroviral drug-naive people.*



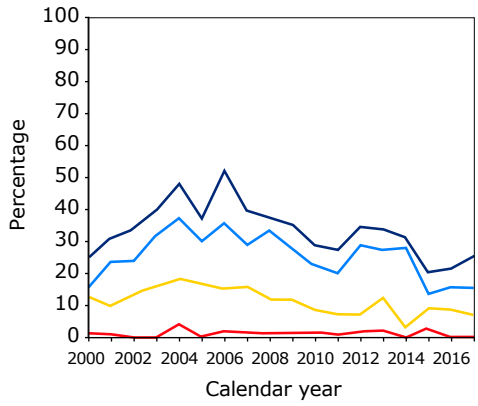
A
By antiretroviral drug class: high-level resistance to at least one drug per class

- Non-nucleoside reverse transcriptase inhibitor resistance
- Nucleoside reverse transcriptase inhibitor resistance (except emtricitabine/lamivudine)
- Emtricitabine/lamivudine resistance
- Protease inhibitor resistance

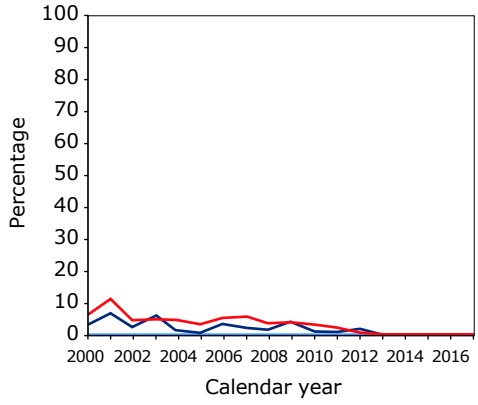


B
By antiretroviral drug: high-level resistance to at least one nucleoside reverse transcriptase inhibitor

- Lamivudine/emtricitabine resistance
- Abacavir resistance
- Tenofovir resistance



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

Legend: *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* [25,26].

Table 2.5: Acquired drug resistance: the annual proportion of available sequences with evidence of high-level resistance to at least one antiretroviral drug class after virological failure from people who received combination antiretroviral therapy and were previously antiretroviral drug-naive.

Drug class	NNRTI			NRTI			PI		
		95% CI			95% CI			95% CI	
Calendar year	%	low	high	%	low	high	%	low	high
2000	24.6	19.2	30.0	64.6	58.6	70.6	52.3	46.1	58.6
2001	30.7	25.7	35.6	69.3	64.4	74.3	45.5	40.1	50.8
2002	33.8	29.9	37.6	63.6	59.7	67.5	29.9	26.2	33.6
2003	39.3	36.0	42.7	63.5	60.2	66.8	18.5	15.8	21.2
2004	48.2	44.6	51.8	58.5	55.0	62.1	16.1	13.4	18.7
2005	36.9	33.3	40.6	54.0	50.2	57.7	19.9	16.9	22.9
2006	51.9	47.9	55.8	49.4	45.4	53.3	14.2	11.4	16.9
2007	39.8	36.2	43.3	44.0	40.4	47.6	8.9	6.8	11.0
2008	37.7	34.4	41.1	40.1	36.7	43.5	9.4	7.4	11.4
2009	35.9	32.7	39.2	36.4	33.1	39.6	12.7	10.5	15.0
2010	28.5	25.4	31.6	31.8	28.6	35.0	8.9	6.9	10.8
2011	28.1	24.3	32.0	27.4	23.6	31.3	6.7	4.5	8.8
2012	34.3	29.7	38.8	33.3	28.8	37.9	4.6	2.6	6.7
2013	33.7	28.8	38.6	28.4	23.8	33.1	3.2	1.4	5.0
2014	31.3	26.5	36.0	25.0	20.6	29.4	0.0	0.0	0.0
2015	21.1	17.2	25.0	20.2	16.3	24.0	0.9	0.0	1.8
2016	24.3	19.1	29.4	30.0	24.5	35.5	0.0	0.0	0.0
2017	25.4	20.2	30.6	21.1	16.2	26.0	0.0	0.0	0.0

See Appendix Table 2.3 for antiretroviral drug-specific results.

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

Acquired integrase-inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on cART was relatively rare. The 107 integrase sequences that were available originated from 89 people who received cART for at least 4 months; 14 were pre-treated with monotherapy or dual therapy before initiating cART, and 75 were ARV-naive before initiating cART. Most people had initiated cART years before; the median time between initial cART initiation and testing for integrase inhibitor resistance was 10.1 years [IQR 3.0-14.4]. For each person, we used the most recent sequence for further analysis.

At least one acquired major mutation associated with integrase inhibitor resistance was detected in 15 out of 89 people, which resulted in high-level resistance to at least one integrase inhibitor[24,25]. Among the 15, the following mutations were detected: N155H (n=6) and N155HN (n=1), associated with resistance to elvitegravir and raltegravir; Y143R (n=3) and Y143YC (n=1), associated with resistance to raltegravir; and T66TA (n=2) and T66TK (n=1), associated with resistance to elvitegravir. The remaining sequence harboured the Q148H mutation in combination with the G140S minor mutation, which is associated with resistance to all three currently available integrase inhibitors: dolutegravir (intermediate resistance), elvitegravir (high-level resistance) and raltegravir (high-level resistance). Minor mutations detected were at position L74 (any mutation, n=10; L74I, n=7; L74M, n=2; L74ILM, n=1), T97 (any, n=6; T97A, n=5; T97TA=1), G140S (n=1), and R263K (n=1).

Immunological response

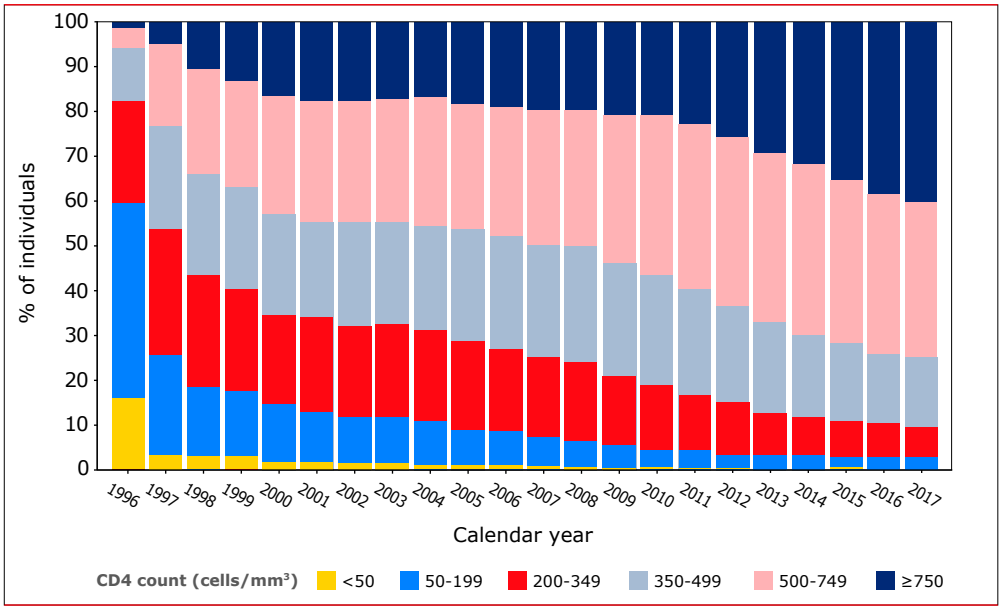
After initiation of cART, most people suppress HIV RNA to levels below the limit of detection, and this is accompanied by an increase in CD4 cell count. Failure to suppress viraemia is associated with poorer recovery of CD4 cell count[19,32]. However, incomplete recovery of CD4 cell count may also occur 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[33]. Normal CD4 cell counts in people without HIV are on average approximately 800 cells/mm^3, but vary according to factors such as age, ethnicity, sex, and smoking behaviour[34]. 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[35,36,37,38,39,40]. The clinical benefit of cART is strongly related to the level of recovery of the immune status (also see *Chapter 3*)[41,42,43,44,45].

Immunological response – by calendar year

Out of the 23,579 people who were known to have initiated cART between January 1996 and December 2017, CD4 cell count data were available after cART initiation for 23,073. *Figures 2.15* and *2.16* show the last known CD4 cell count and CD4:CD8 ratio of all people in HIV care for each calendar year. After starting cART, the percentage of people with CD4 cell counts <350 cells/mm^3 dropped from 53.1% in 1997 to 33.11% in 2002, 14.6% in 2012 and 9.7% in 2017 (*Figure 2.15*). Likewise, the absolute number of people with CD4 cell counts <350 cells/mm^3 at the end of each calendar year decreased from 2,112 in 2009, to 1,737 in 2013, and 1,296 in 2017; see *Appendix Figure 2.3*. The drop in absolute number of people 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.

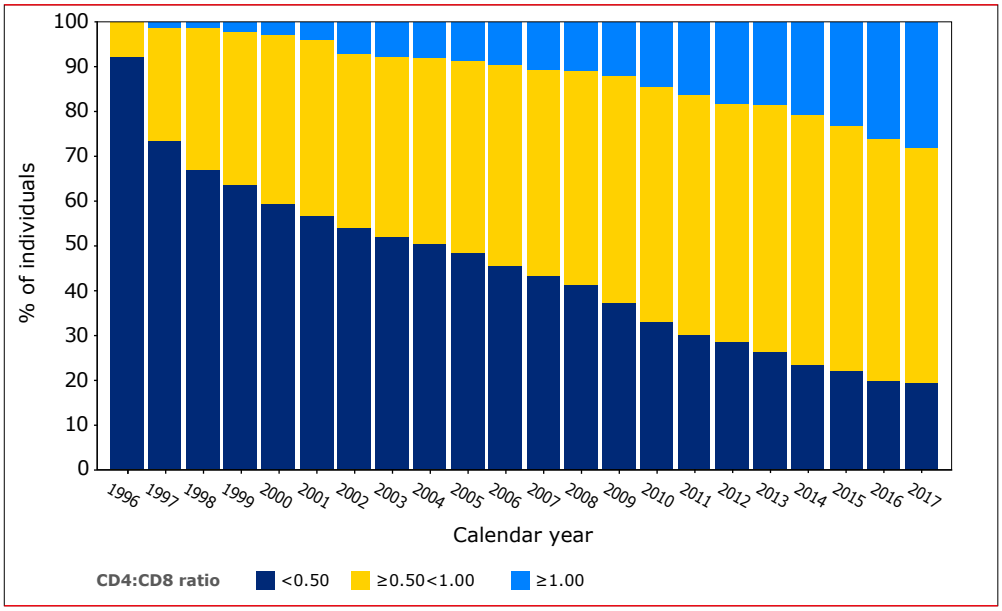
Figure 2.15: Last available CD4 cell count of the treated population by calendar year.



Legend: *For each person, the last available CD4 cell count between January and December of each year, after starting cART, was selected (missing measurements/data not taken into account). Figures for 2017 may change slightly because data collection is not yet complete.*

The percentage of those with a CD4:CD8 ratio of 1 or above increased from 2.5% in 1996-2001, to 9.0% in 2002-2007, to 14.9% in 2008-2012 and 23.5% in 2013-2017 (*Figure 2.16*). The absolute number of people in these CD4:CD8 categories per calendar year is plotted in *Appendix Figure 2.4*. Of all CD4:CD8 ratio measurements ≥1, 12.1% had a CD4 count of less than 500 cells/mm³, 33.6% had a CD4 count between 500-749 cells/mm³ and 54.3% had a CD4 count of ≥750 cells/mm³. When the CD4:CD8 ratio was ≥1, the median CD4 count was 778 cells/mm³ [IQR 600-980], and remained fairly stable over time, with a median of 771 cells/mm³ [IQR 596-1,010] in 1996-2001, 450 cells/mm³ [IQR 570-970] in 2002-2007, median 730 cells/mm³ [IQR 570-940] in 2008-2012 and median 800 cells/mm³ [IQR 630-1,000] in 2013-2017.

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



Legend: For each person, the last available CD4 cell count between January and December of each year, after starting cART, was selected.

Immunological response – after cART initiation

The immunological response to cART for both HIV-1 and HIV-2 infection has recently been well-studied in two international cohort collaboration studies, which include Dutch data from the ATHENA cohort. In the first study, the COHERE in EuroCoord collaboration evaluated the CD4 cell response to cART for HIV-1 infection and proposed reference curves that may be used as an additional tool for clinicians when evaluating responses to cART[46]. In the second study, the COHERE in EuroCoord and the ACHIeV2e Study Group aimed to assess CD4 cell recovery following first-line cART in people with HIV-2 compared to people with HIV-1[47]. A summary of both studies and the link to the web tool for the CD4 cell count reference curve can be found in *Box 2.4*.

Box 2.4: International collaborations.

Global trends in CD4 cell count at the start of cART[48]

In a large global cohort collaboration by International Epidemiology Databases to Evaluate AIDS (IeDEA) and COHERE, based on 951,855 people with HIV aged ≥16 years, the global trends in CD4 cell counts at cART initiation among adults from low-income, lower-middle-income, upper-middle-income, and high-income countries were investigated.

Overall, the modelled median CD4 cell count at the start of cART increased from 2002 to 2015 from 78 to 287 cells/mm^3 in low-income countries, from 99 to 234 cells/mm^3 in lower-middle-income countries, from 71 to 311 cells/mm^3 in upper-middle-income countries, and from 161 to 327 cells/mm^3 in high-income countries.

The study results show that median CD4 cell counts at the start of cART have increased in all country income groups over the last few years, and the proportion of people starting cART with severe immunodeficiency has decreased. However, the median CD4 cell count at cART start generally remained below 350 cells/mm^3 in 2015 and the decline in severe immunodeficiency appears to have plateaued in some countries. Substantial additional efforts and resources will be needed to achieve early diagnosis, rapid linkage to care, and prompt initiation of cART globally.

Box 2.4: International collaborations (continued).

Reference curves for CD4 T-cell count response to cART[46]

On behalf of COHERE in EuroCoord, Bouteloup *et al.* aimed to provide 'reference curves' for CD4 T-cell responses during the first 12 months of cART for people with virological suppression, according to their characteristics at cART initiation. Data from 27 cohorts across 35 European countries, including the ATHENA cohort in the Netherlands, were included in the analysis. A total of 28,992 people aged ≥18 years who initiated cART for the first time between 1 January 2005 and 1 January 2010 and who had at least one available measurement of CD4 count and a viral load ≤50 HIV-1 RNA copies/ml 6 months after cART initiation were included in the study.

The median CD4 T-cell count at treatment initiation was 249. The median observed CD4 counts at 6, 9 and 12 months were 382, 402 and 420 cells/mm^3, respectively. The two main factors explaining the variation of CD4 count after 6 months were AIDS stage and CD4 count at cART initiation. A CD4 count increase of ≥100 cells/ml was generally required for people to maintain a CD4 count at the same percentile as when they started, with slightly higher gains required for those who started with CD4 counts in the higher percentiles.

In conclusion, the study proposes reference curves for the CD4 count that may be used as an additional tool by the clinician when evaluating responses to cART.

A web tool is available at http://shiny.isped.u-bordeaux.fr/CD4refcurves

Box 2.4: International collaborations (continued).

CD4 cell count response to first-line cART: HIV-2 compared to HIV-1[47]

The COHERE collaboration in EuroCoord and the ACHIeV2e Study Group aimed to assess CD4 cell recovery following first-line cART in people with HIV-2 compared to HIV-1. ART-naive adults with HIV were included, if they started first-line cART (without NNRTIs or fusion inhibitors) between 1997 and 2011.

Overall, the study included 185 people with HIV-2 and 3,0321 people with HIV-1 with a median age of 46 years and 37 years, respectively. Median observed pretreatment CD4 cell counts/mm^3 were 203 (95% CI 100-290) in people with HIV-2 and 223 (100-353) in people with HIV-1. Mean observed CD4 cell count changes from start of cART to 12 months were +105 (95% CI 77-134) in people with HIV-2 and 202 (199-205) in people with HIV-1; an observed difference of 97 cells/mm^3 in one year. Overall, in adjusted analysis, the mean CD4 cell increase was 25 CD4 cells/mm^3/year lower in people with HIV-2 than into people with HIV-1.

In conclusion, a poorer CD4 cell increase during first-line cART was observed in people with HIV-2 infection than with HIV-1, even after adjustment for pretreatment viral load and other potential confounders. These results underscore the need to identify more potent therapeutic regimens or strategies against HIV-2.

Box 2.4: International collaborations (continued).

Effect of immediate initiation of cART in people with HIV aged ≥50 years[49]

Clinical guidelines recommend immediate initiation of cART for all people with HIV. However, those guidelines are based on trials of relatively young participants. On behalf of the HIV-CAUSAL Collaboration of HIV cohorts from Europe and the Americas, including the ATHENA cohort, Lodi *et al.* aimed to estimate the 5-year risk of all-cause mortality and non-AIDS mortality among ART-naive, AIDS-free people aged between 50 and 70 years.

The study included 9,596 people, with median age of 55 (IQR 52–60) years and CD4 count of 336 (182–513) cells/mm^3 at baseline. The 5-year risk of all-cause mortality was 0.40% (95% CI 0.10-0.71) lower for the general population with HIV, and 1.61% (0.79-2.67) lower for US veterans when comparing immediate initiation vs initiation at CD4 <350 cells/mm^3. The 5-year risk of non-AIDS mortality was 0.17% (95% CI 0.07-0.43) lower for the general population with HIV, and 1% (0.31-2.00) lower for US veterans when comparing immediate initiation vs initiation at CD4 <350 cells/mm^3.

In conclusion, immediate initiation of cART seems to be beneficial in reducing all-cause mortality in people who are AIDS-free and aged 50 years or older, despite their low baseline CD4 count. More effort should be made to diagnose HIV earlier, particularly in older people to ensure timely initiation of treatment and follow up for concomitant comorbidities, thereby maximising the benefit of early treatment for HIV.

2013–2017

We further assessed the immunological response in people who started cART in more recent years: 5,266 people started cART in 2013-2017, and CD4 cell count data were 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 5,266 people who started cART in 2013-2017, 7.4% had CD4 counts <50 cells/mm^3, 13.3% had between 50 and 199 cells/mm^3, 20.6% had between 200 and 349 cells/mm^3, 26.3% had between 350 and 499 cells/mm^3, and 32.4% had 500 or more CD4 cells/mm^3 at the time of cART initiation. The CD4 cell count at cART initiation has increased and stabilised in recent years (*Appendix Table 2.2*).

The CD4 cell count and CD4:CD8 ratio trajectories following cART initiation are plotted in *Figures 2.17* and *2.18* by CD4 cell count at cART initiation. The median CD4

cell counts and CD4:CD8 ratios increased after cART initiation. Both depended on the CD4 cell count at cART initiation and did not converge among the five baseline CD4 cell count strata. These observations are in line with a recent study by the Antiretroviral Therapy Cohort Collaboration (ART-CC), including ATHENA data, that showed that the likelihood of normalization of the CD4:CD8 ratio is strongly related to baseline CD4 cell count[50].

Figure 2.17: CD4 cell count over time after the start of combination antiretroviral therapy (cART) in 2013–2017.

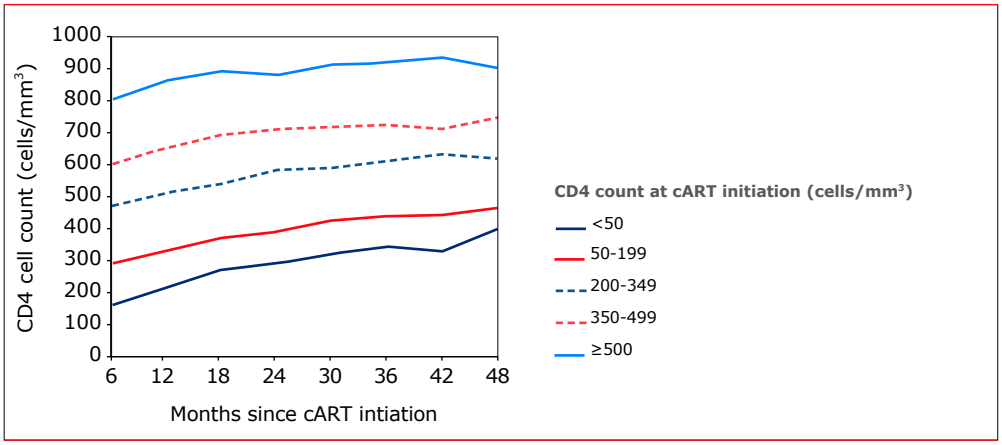
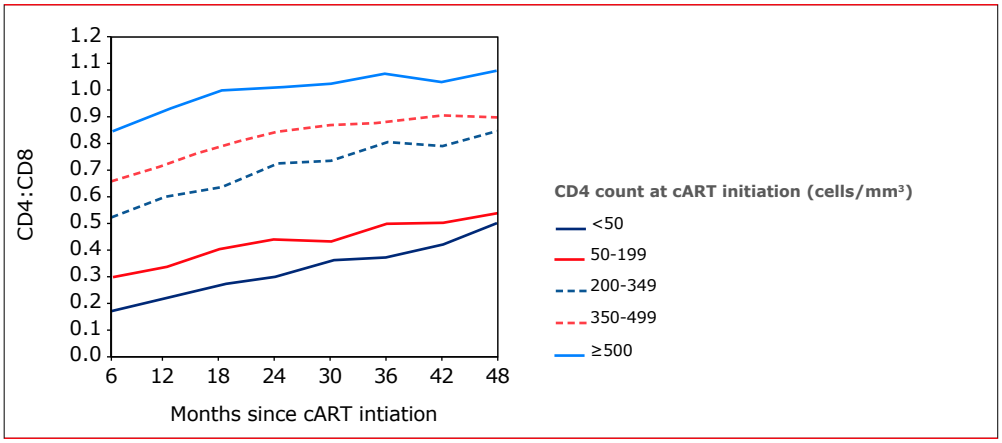


Figure 2.18: CD4:CD8 ratio over time after the start of combination antiretroviral therapy (cART) in 2013–2017.



Note: The presented immunological outcomes are based on available test results. For people with a low to moderate CD4 cell count (<350 cells/mm^3), CD4 cell count testing is recommended at least twice a year[51]. When a person has a CD4 cell count >350 cells/mm^3, the testing frequency may be reduced. Therefore, CD4 data from people achieving higher CD4 cell counts are disproportionally 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 2017, the median CD4 cell count was 380 cells/mm^3 [IQR 202-554]. Immunological recovery was strongly related to the CD4 cell count at the start of cART.
- In 2017, the majority of individuals initiating cART did so within a month after diagnosis. Most persons who initiated cART in 2017 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 neuropsychiatric problems, problems involving the gastrointestinal tract or liver, or a rash due to medication.

In care and receiving cART in 2017

- Integrase inhibitor-based cART has been further implemented on a large scale in the Netherlands. Integrase inhibitor-based cART was prescribed to 45% of those in care in 2017, compared with 39% in 2016[52].
- While 43% 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 for at least 12 months and who had a plasma HIV RNA measurement in 2017, 98% had a viral load less than 200 copies/ml. Long-term survivors (i.e., individuals in care in 2017 who were diagnosed with HIV before 1996) 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[53,54].
- Transmitted drug resistance is rare, and the overall prevalence is low and stable over time, in line with reported rates from other European countries[55].
- Integrase inhibitor resistance data are limited. No transmitted integrase inhibitor resistance was detected amongst 19 people tested in 2017. Detected rates of acquired integrase inhibitor resistance among available sequences were very low, with virtually no resistance to dolutegravir.

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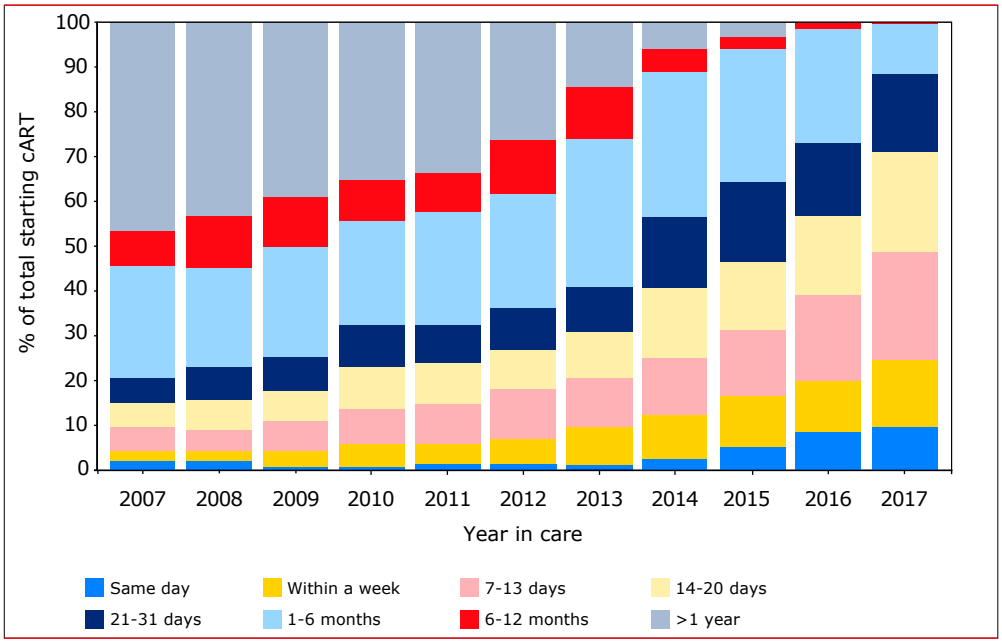
Appendix: supplementary figures and tables

Appendix Figure 2.1: *Time between entry into HIV care and initiation of combination antiretroviral therapy (cART) of people starting cART in 2007–2017*.*



Legend: *cART=combination antiretroviral therapy.*

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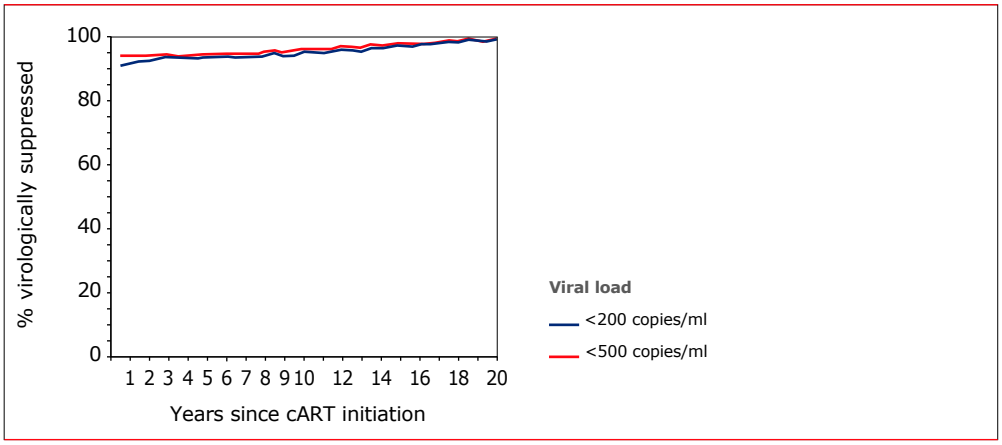
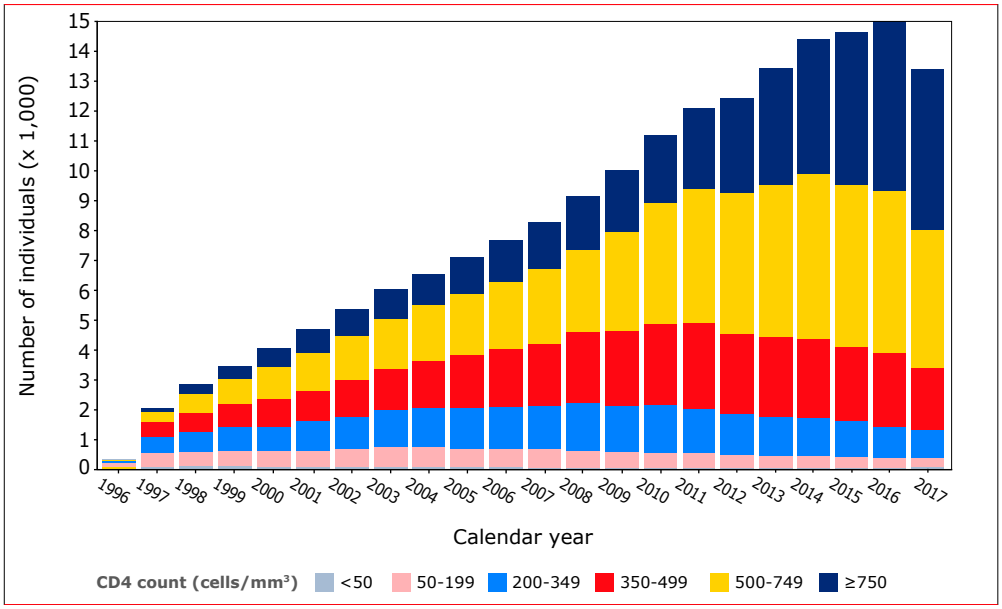
Appendix Figure 2.2: Viral suppression since initiation of combination antiretroviral therapy.



Legend: cART=combination antiretroviral therapy.

Appendix Figure 2.3: Last available CD4 cell count (cells/mm³) in each calendar year after the start of combination antiretroviral therapy.



Note: Numbers for 2017 may increase slightly because data collection is not yet complete.

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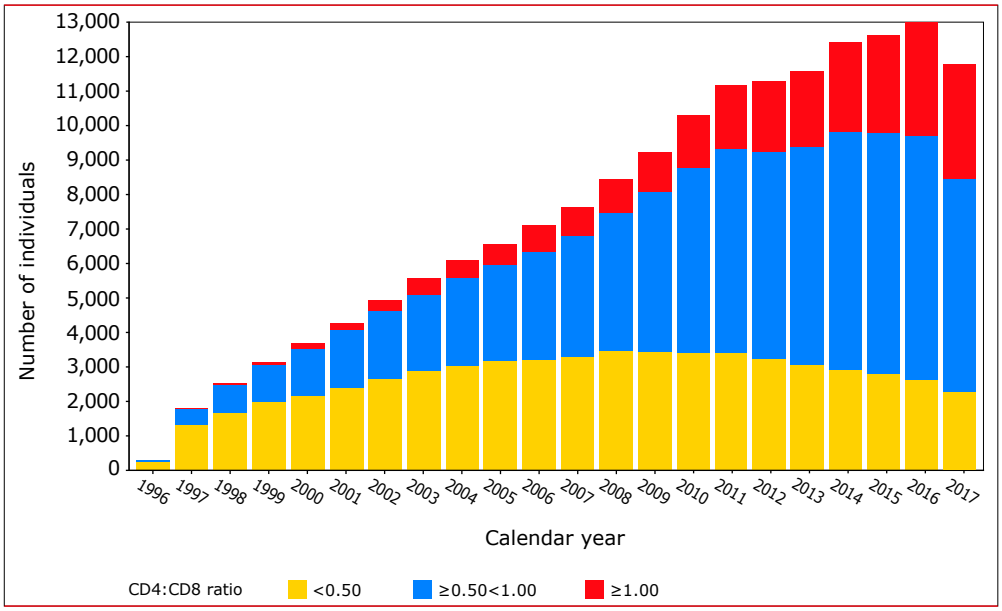
Appendix Figure 2.4: Last available CD4:CD8 ratio in each calendar year after the start of combination antiretroviral therapy.



Note: Numbers for 2017 may increase slightly because data collection is not yet complete.

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Appendix Table 2.1: Combination antiretroviral therapy (cART) regimen used by long-term HIV survivors in 2017.

cART regimen	n	%
TDF/FTC/EFV	127	6.5
TDF/FTC/NVP	198	10.1
TDF/FTC/RPV	46	2.3
TDF/FTC/DRV/b	89	4.5
TDF/FTC/ATV/r	60	3.1
TDF/FTC/LPV	6	0.3
TDF/FTC/EVG/c	27	1.4
TDF/FTC/DTG	36	1.8
TDF/FTC/RAL	23	1.2
ABC/3TC/DTG	163	8.3
TAF/FTC/EVG/c	159	8.1
TAF/FTC/RPV	35	1.8
TAF/FTC/DTG	33	1,7
TAF/FTC/DRV/c	35	1.8
Other: 2NRTI+NNRTI	264	13.4
Other: 2NRTI+PI	99	5.0
Other: 2NRTI+INSTI	27	1.4
Other: NNRTI+INSTI	5	0.3
Other: PI+INSTI	83	4.2
Other: NRTI+PI+INSTI (3ARVs)	52	2.6
Other: NRTI+PI+INSTI (4ARVs)	73	3.7
Other	326	16.6
Total	**1,966**	**100.0**

Legend: *ARVs=antiretroviral drugs; /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=nucleoside-analogue reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; INSTI=integrase inhibitor.*

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Appendix Table 2.2: *CD4 cell count at combination antiretroviral therapy (cART) initiation by calendar year 2013–2017.*

Year of cART initiation	2013	2014	2015	2016	2017	Total (2013–2017)
CD4 cell count available at cART initiation	1,347	1,323	1,049	800	38	**4,900**
CD4 cell count, median cells/mm³ [IQR]	370 [250–508]	410 [270–570]	410 [210–600]	400 [230–570]	176 [347–520]	**390 [40–557]**
CD4 cell count (cells/mm³)						
<50	92	74	86	75	37	**364**
	(6.8)	(5.6)	(8.2)	(9.4)	(9.7)	
50–199	160	159	159	104	71	**653**
	(11.9)	(12.0)	(15.2)	(13.0)	(18.6)	
200–349	336	255	179	153	85	**1,008**
	(24.9)	(19.3)	(17.1)	(19.1)	(22.3)	
350–499	404	377	243	183	82	**1,289**
	(30.0)	(28.5)	(23.2)	(22.9)	(21.5)	
≥500	355	458	382	285	106	**1,586**
	(26.4)	(34.6)	(36.4)	(35.6)	(27.8)	

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

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

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

Calendar year	Number of sequences	Emtricitabine/ lamivudine	Zidovudine	Stavudine	Abacavir	Didanosine	Tenofovir
2000	65	64.6	9.2	6.2	1.5	4.6	0.0
2001	88	69.3	12.5	13.6	5.7	12.5	3.4
2002	154	63.6	7.8	11.0	6.5	11.7	3.2
2003	211	63.5	14.2	19.4	13.3	17.1	6.6
2004	193	58.5	13.0	16.6	13.0	18.1	5.7
2005	176	54.0	9.1	11.9	9.1	13.6	4.0
2006	162	49.4	6.8	10.5	8.6	14.2	5.6
2007	191	44.0	5.2	8.4	11.5	11.5	4.7
2008	212	40.1	7.5	11.3	5.7	12.3	4.2
2009	220	36.4	6.4	8.6	5.0	7.3	2.7
2010	214	31.8	5.6	6.5	4.7	7.9	1.4
2011	135	27.4	2.2	5.2	4.4	8.1	1.5
2012	108	33.3	0.0	1.9	7.4	9.3	0.9
2013	95	28.4	0.0	3.2	6.3	6.3	3.2
2014	96	25.0	1.0	4.2	3.1	5.2	3.1
2015	109	20.2	1.8	4.6	4.6	7.3	2.8
2016	70	30.0	1.4	1.4	5.7	5.7	1.4
2017	71	21.1	1.4	5.6	2.8	9.9	4.2

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

Calendar year	Number of sequences	Nevirapine	Efavirenz	Etravirine	Rilpivirine
2000	65	24.6	15.4	1.5	12.3
2001	88	30.7	23.9	1.1	10.2
2002	154	33.8	24.0	0.0	13.6
2003	211	39.3	31.8	0.0	16.1
2004	193	48.2	37.3	4.1	18.1
2005	176	36.9	29.5	0.6	17.0
2006	162	51.9	35.8	1.9	15.4
2007	191	39.3	28.8	1.6	15.7
2008	212	37.7	33.5	1.4	12.3
2009	220	35.5	27.7	1.8	11.8
2010	214	28.5	22.4	1.4	8.9
2011	135	27.4	20.0	0.7	7.4
2012	108	34.3	28.7	1.9	7.4
2013	95	33.7	27.4	2.1	12.6
2014	96	31.3	28.1	0.0	3.1
2015	109	20.2	13.8	2.8	9.2
2016	70	21.4	15.7	0.0	8.6
2017	71	25.4	15.5	0.0	7.0

C) High-level resistance to protease inhibitors.

Calendar year	Number of sequences	Nelfinavir	Saquinavir	Indinavir	Atazanavir	Fosamprenavir	Lopinavir	Tipranavir	Darunavir
2000	65	52.3	6.2	4.6	6.2	3.1	3.1	1.5	0.0
2001	88	45.5	14.8	8.0	11.4	6.8	6.8	1.1	0.0
2002	154	29.9	7.8	4.5	4.5	2.6	2.6	0.0	0.0
2003	211	18.5	7.6	6.6	5.2	4.7	6.2	1.4	0.0
2004	193	15.0	3.6	4.7	4.7	3.1	1.6	0.5	0.0
2005	176	19.9	2.8	1.1	3.4	2.3	0.6	0.6	0.0
2006	162	13.6	4.9	4.9	5.6	3.7	3.7	1.9	0.0
2007	191	8.9	4.2	3.7	5.8	3.1	2.1	1.0	0.0
2008	212	8.0	2.8	2.8	3.8	4.2	1.9	0.5	0.0
2009	220	11.8	4.1	5.5	4.1	5.5	4.1	0.5	0.0
2010	214	7.5	3.3	3.3	3.3	4.2	1.4	0.0	0.0
2011	135	6.7	2.2	2.2	2.2	1.5	0.7	0.0	0.0
2012	108	4.6	1.9	2.8	0.9	0.9	1.9	0.0	0.0
2013	95	3.2	0.0	0.0	0.0	1.1	0.0	0.0	0.0
2014	96	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2015	109	0.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2016	70	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2017	71	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

3. Morbidity and mortality

Ferdinand Wit, Marc van der Valk and Peter Reiss

Introduction

Of the 25,761 HIV-1-positive adults and children ever registered in the Dutch national HIV registration and monitoring database up to 31 December 2017, 95.0% are currently on combination antiretroviral therapy (cART). Since the introduction of cART, the life expectancy of HIV-1-positive individuals has markedly improved; in a subgroup of recently-diagnosed, effectively-treated individuals, it has been shown to be similar to that of the general population in the Netherlands[1].

Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased[2], morbidity and/or mortality associated with non-AIDS-related diseases such as renal and liver disease, diabetes mellitus, myocardial infarction, stroke, osteoporosis, and non-AIDS-defining malignancies has increased among HIV-1 positive individuals during the cART era[3,4,5,6,7,8].

Various reports suggest that the risk of non-AIDS morbidity may be higher in HIV-positive individuals treated with antiretroviral therapy (ART) than in HIV-negative individuals of comparable age[9,10,11]. For example, pulmonary hypertension[12], bone disease, and non-traumatic bone fractures[13,14,15] 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[16,17,18]. Furthermore, as in HIV-negative individuals, traditional risk factors (e.g., tobacco use[19], alcohol abuse, and viral hepatitis co-infection[20]) 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 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 be driven partly by the use of cART, as well as by sustained residual HIV-associated immune activation and inflammation, despite effective cART[21,22].

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: 25,065 adults and an additional 459 individuals who entered care as children

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and have since become adults, now totalling 25,524 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[23]). A CD4 count below 200 cells/mm^3 in the absence of an AIDS-defining condition, in contrast to what is usual in the United States, does not qualify as AIDS in these analyses.

Diabetes mellitus is 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, is also 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, are defined according to criteria established by the D:A:D study, except that Castleman's disease is 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 wherever possible to establish the presence of any malignancy.

Chronic kidney disease (CKD) is 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, but 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.

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 more 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

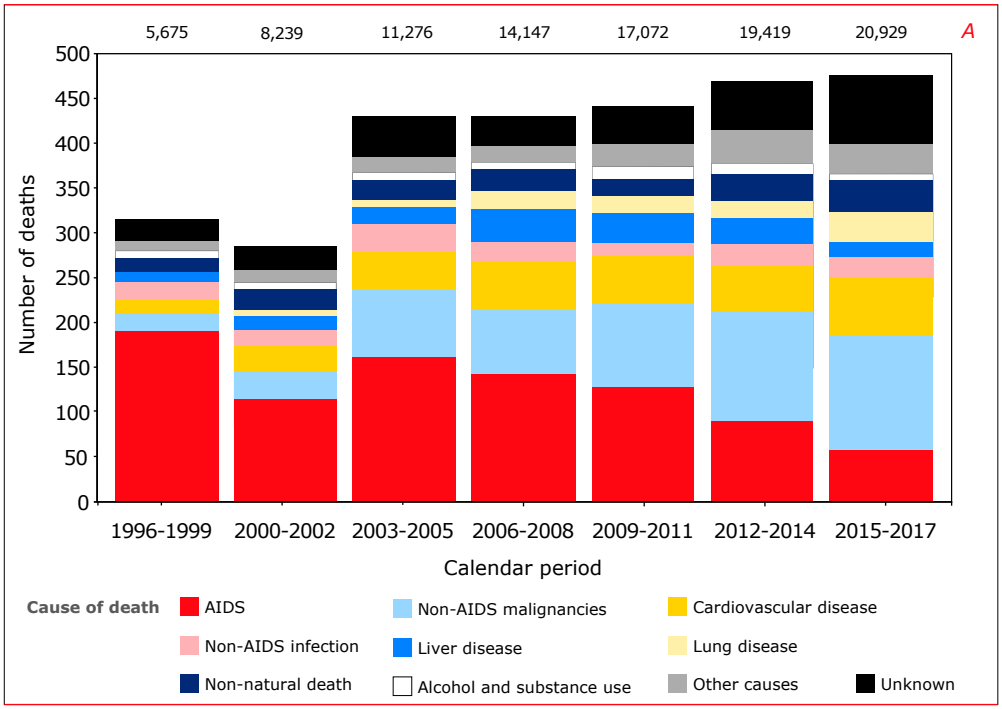
time, we also estimated the incidence rates for the periods 2000-2005, 2006-2010, and 2011-2017, and standardised these according to the age distribution of the population during the period 2011-2017 (divided into age classes 18-29, 30-39, 40-49, 50-59, 60-69, and ≥70 years) using the indirect method[24]. Indirect standardisation compares the incidence rates in the study and reference (period: 2011-2017) populations by applying the stratum-specific rates in the reference population to the study population. We investigated risk factors for AIDS, death, and 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-defining malignancy). CKD was not included in this combined endpoint as serum creatinine was not part of routine data collection before 2007. The baseline for treated and untreated HIV-1-positive individuals was defined as the date of HIV-1 diagnosis or January 2000, whichever occurred more recently. Subsequent follow-up time was divided into periods of 3 months. 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 3 months), body mass index, gender, region of birth, most likely mode of HIV-1 transmission, current age, known time with CD4 count <200 cells/mm^3, 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.

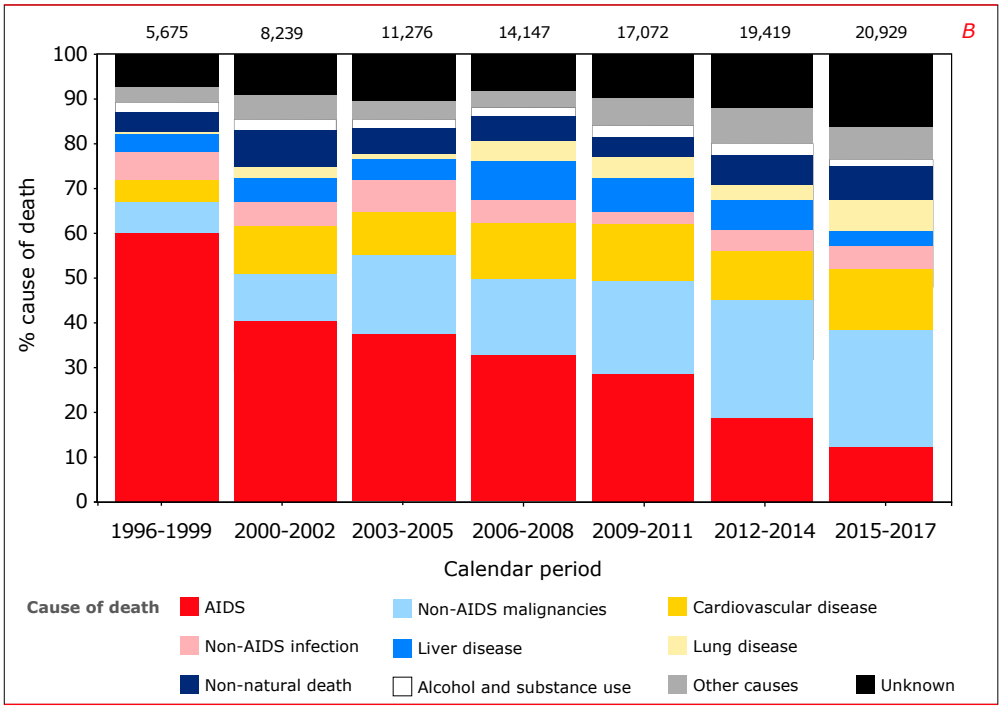
Mortality and AIDS

From 1996 onwards, the overall mortality rate in all 25,761 HIV-1-positive adults ever registered in the SHM was 17.7 (95% confidence interval [CI] 13.1-23.2) per 1,000 person years of follow up (PYFU) in 1996 and declined over time to 7.5 (95% CI 6.3-8.9) per 1,000 PYFU in 2017 (*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, which was 4.1 per 1,000 PYFU in 2017, 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 11.8 (95% CI 11.3-12.2) per 1,000 PYFU overall (period, 1996-2017) and 6.8 (95% CI 5.5-8.3) per 1,000 PYFU in 2017. In the same group of 25,761 individuals, the incidence of AIDS decreased sharply from 118.0 (95% CI 105.8-131.2) in 1996 to 6.7 (95% CI 5.5-8.0) cases per 1,000 PYFU in 2017 (*Appendix Figure 3.1B*).

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 2017 had a CD4 cell count <50 cells/mm^3 when entering care. Individuals who died of AIDS had lower CD4 counts (median 94 cell/mm^3 [interquartile range, IQR, 22-306]) when entering care compared to individuals who died of another cause (median 260 cells/mm^3 [IQR 92-474]). Among individuals who entered care with more than 300 CD4 cells/mm^3 and died of AIDS, the cause of death was relatively more likely to be an AIDS-related malignancy (27.7%) than among individuals who entered care with less than 50 CD4 cells/mm^3 (18.8%). The time between entry into care and death was significantly shorter in individuals who died of AIDS (median 3.4 years [IQR 0.6-8.9]) than in individuals who died of a non-AIDS cause (median 8.7 years [IQR 4.3-14.7], p<0.001). Conversely, the proportion and absolute number of deaths due to non-AIDS-defining conditions have significantly increased over time (*Figure 3.1A* and *B*), partly as a consequence of the increasing size and average age of the Dutch HIV-positive population.

Figure 3.1A and B: (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 at the 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 use/used injecting drugs (PWUID), 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, had spent more time with an HIV RNA level above 1,000 copies/ml while on cART, or had a current CD4 cell count less than 500 cells/mm^3 (although the risk of death was even higher when their CD4 cell count was less than 200 cells/mm^3). Of note, people with a CD4 cell count above 750 cells/mm^3 had a significantly lower mortality risk than those with a CD4 cell count between 500 and 750 cells/mm^3. People who had initiated cART early, i.e. within 12 months of their last negative HIV test or within 12 months after documented acute

HIV infection, had a borderline lower risk of death compared with those who initiated cART at a later time point or who had an unknown duration of HIV infection prior to initiation of cART. Note that this beneficial effect of early cART was independent of the CD4 cell count.

Although a lower mortality risk was observed in individuals of non-Dutch origin, this is likely due to a 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) having been 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.

The incidence of the first occurrence of any AIDS-defining event after entering care was 23.7 events per 1,000 PYFU of follow up. *Appendix Table 3.5* gives an overview of the AIDS events occurring between 1996 and 2017. The most common AIDS events between 2011 and 2017 were *Pneumocystis jirovecii* 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%), recurrent bacterial pneumonia (4%), AIDS dementia complex/HIV encephalopathy (3%) and cytomegalovirus-associated end organ disease (3%). Risk factors for AIDS-defining events are shown in *Appendix Table 3.3*. In the present analyses, we concentrate on the first occurrence of any AIDS-defining event after the 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^3 (but the likelihood was even higher when their CD4 cell count was below 200 or 50 cells/mm^3), had more than 1,000 HIV RNA copies/ml for a longer period of time while on cART, or were co-infected with the hepatitis C virus.

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 also analysed the incidence of CDC-B and AIDS-defining events in the period between 2000 and 2017 in individuals who had started cART at least 1 year before 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 those 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. Use of prophylaxis was not accounted for in this analysis. 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 2017, 21,984 individuals contributed a total of 151.4 thousand PYFU, during which 2,875 HIV-related events were diagnosed, resulting in an incidence rate of 19.0 events per 1,000 PYFU (1,787 CDC-B events, 11.8 events/1,000 PYFU; 1,088 CDC-C/AIDS events, 7.2 events/1,000 PYFU) (*Table 3.1*). As expected, the incidence rates were highest in the CD4 strata below 200 cells/mm^3. Although the incidence rates declined sharply in the higher CD4 strata, the incidence rates in the 200-349 and 350-499 cells/mm^3 strata remained substantial, with 11.9 and 6.2 AIDS-defining illnesses/1000 PYFU, respectively. The incidence rates of AIDS-defining illnesses in the CD4 strata of 500-749 and over 750 cells/mm^3 were 3.4 (3.0-4.0) and 2.3 (1.8-2.9)/1,000 PYFU, respectively. Note that the incidence in the 750+ stratum is statistically significantly lower than in the 500-749 cells/mm^3 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 (*Appendix Table 3.8* 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 while having an undetectable viral load between 2000 and 2016.*

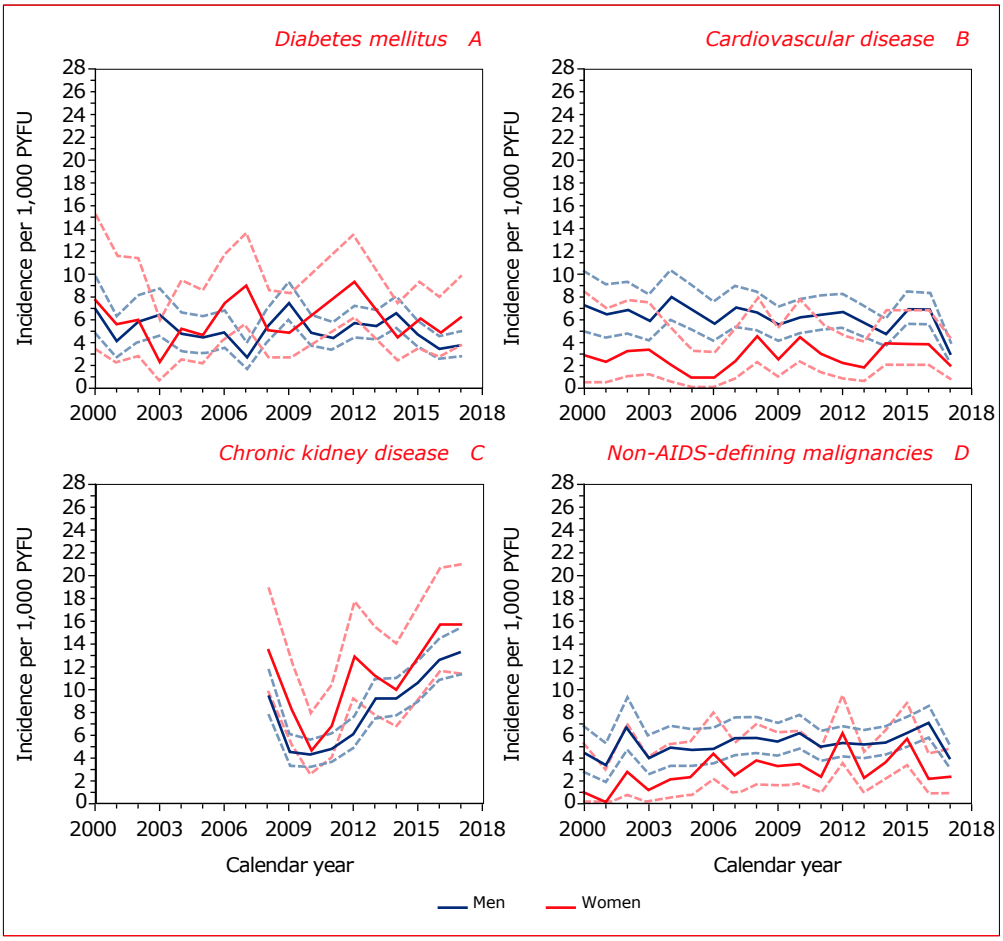
CD4 category (cells/mm^3)	CDC events (n)	CDC-B events (n)	CDC-C events (n)	PYFU (x 1,000)	Incidence rate CDC events (per 1,000 PYFU) (95% CI)	Incidence rate CDC-B events (per 1000 PYFU) (95% CI)	Incidence rate CDC-C events (per 1,000 PYFU) (95% CI)
0-49	212	88	124	0.4	506 (440-579)	210 (168-259)	296 (246-353)
50-199	556	312	244	7.3	76.5 (70.3-83.2)	43.0 (38.3-48.0)	33.6 (29.5-38.1)
200-349	657	400	257	22.2	29.6 (27.4-32.0)	18.0 (16.3-19.9)	11.6 (10.2-13.1)
350-499	580	363	217	36.9	15.7 (14.5-17.0)	9.83 (8.85-10.9)	5.88 (5.12-6.71)
500-749	604	417	187	58.3	10.4 (9.55-11.2)	7.15 (6.48-7.87)	3.21 (2.76-3.70)
750+	338	250	88	41.6	8.13 (7.29-9.05)	6.01 (5.29-6.81)	2.12 (1.70-2.61)
Total	**2,947**	**1,830**	**1,117**	**166.7**	**17.7 (17.0-18.3)**	**11.0 (10.5-11.5)**	**6.70 (6.31-7.11)**

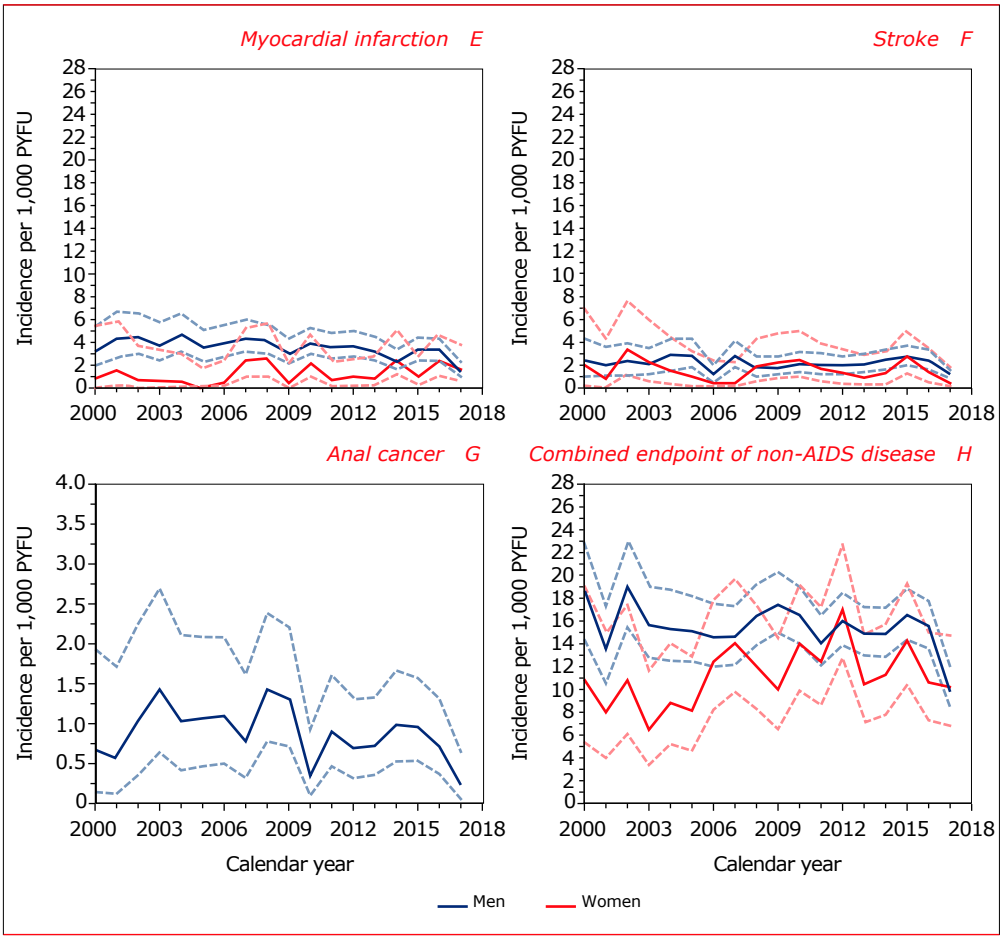
Legend: *CDC=Centers for Disease Control and Prevention Classification System for HIV Infection; CDC-B=moderately symptomatic HIV disease; CDC-C=AIDS-defining events; cART=combination antiretroviral therapy; PYFU=person years of follow up.*

Non-AIDS-defining events

Of the 25,761 HIV-1-positive adults ever registered with the Dutch national HIV registration and monitoring database, 25,178 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 (with separate reports for myocardial infarction and stroke), non-AIDS-defining malignancies (with a separate report for anal cancer), and CKD. We also present the incidence of the first occurrence of diabetes mellitus, cardiovascular disease, or non-AIDS-defining 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 the exception of anal cancer, which is presented for males only.*





Legend: *PYFU=person years of follow up.*

Diabetes mellitus

Of the 25,178 individuals aged 18 years or older and in follow up in or after January 2000, a total of 1,178 (906 men and 272 women) were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.2A*) and, in 2017, was 3.8 (95% CI 2.8-5.0) per 1,000 PYFU of follow up in men and 6.2 (95% CI 3.7-9.9) per 1,000 PYFU 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 2011-2017 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 2011-2017 (*Table 3.2*).

Demographic and clinical factors independently associated with increased risk of new-onset diabetes mellitus were male gender, non-Dutch origin (in particular people born in sub-Saharan Africa, South Asia, and the Caribbean), older age, having acquired HIV heterosexually or through injecting drug use, having a BMI greater than 25 kg/m^2 or below 18 kg/m^2, having hypertension, having a latest CD4 cell count below 200 cells/mm^3, being pre-treated with NRTIs at the start of cART, and a prior AIDS diagnosis (*Appendix Table 3.7*). Moreover, the risk of new-onset diabetes in the periods 2000-2005 and 2006-2010 was significantly higher than in the period 2011-2017. Finally, a longer time on zidovudine was also significantly associated with an increased risk.

Table 3.2: *Crude incidence of diabetes mellitus per 1,000 person years of follow up during 2000–2005, 2006–2010 and 2011–2017 and age-standardised incidence ratio (indirect method) with 95% confidence intervals.*

Calendar year	Men		Women	
	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)
2000–2005	5.4 (4.7–6.2)	1.42 (1.22–1.63)	5.0 (3.7–6.6)	0.81 (0.58–1.04)
2006–2010	5.2 (4.6–5.9)	1.22 (1.07–1.37)	6.5 (5.2–8.0)	1.03 (0.81–1.25)
2011–2017	4.9 (4.4–5.3)	1 (reference)	6.6 (5.5–7.7)	1 (reference)

**Standardised according to the observed age distribution between 2011–2017.*

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

Cardiovascular disease

From January 2000 onwards, 1,226 individuals (1,092 men and 134 women) had a fatal or non-fatal cardiovascular event (644 had myocardial infarction, 437 stroke, 85 coronary artery bypass graft, 415 coronary angioplasty or stenting, and 10 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 2011-2017 (*Table 3.3*).

In the analysis of risk factors, those associated with cardiovascular disease were male gender, Dutch origin, older age, acquiring HIV through MSM contacts or through injecting drug use, a latest CD4 cell count <350 cells/mm^3, having a prior AIDS diagnosis, being pre-treated with NRTIs at the start of cART, use of abacavir (either currently or in the last 6 months), current and past smoking, and presence of hypertension. Cardiovascular risk was also higher during 2000-2005 and 2006-2010 than during 2011-2017, 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 1.54 to one of 1.44, 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 1.28 (95% CI 1.09-1.52), p=0.003; at 30-60 ml/min the IRR was 1.80 (1.35-2.32), p<0.001; at 15-30 ml/min, the IRR was 5.19 (3.06-8.78) p<0.001; and at 0-15 ml/min the IRR was 4.37 (2.04-8.78), p<0.001.

From January 2000 onwards, 149 men and 11 women experienced a fatal or non-fatal secondary cardiovascular event (103 had myocardial infarction, 63 had stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2016 in men and women with a prior cardiovascular event was 27.8 (95% CI 23.5-32.6) and 15.6 (95% CI 7.8-27.9), respectively. The crude rate and age-standardised incidence ratio (SIR; indirect method) of secondary myocardial infarction and stroke per 1,000 PYFU did not change significantly during 2000-2005 (crude rate: 36.8 events per 1,000 PYFU; SIR: 1.58 95% CI 1.05-2.10) and 2006-2010 (crude rate: 27.9 events per 1,000 PYFU; SIR: 1.19, 95% CI 0.83-1.56) compared to the reference period 2011-2017 (crude rate: 22.9 events per 1,000 PYFU).

Table 3.3: Crude incidence of cardiovascular disease per 1,000 person years of follow up between 2000-2005, 2006-2010, and 2011-2017 and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Men		Women	
	Incidence/1000 PYFU (95%CI)	Standardised incidence ratio* (95% CI)	Incidence/1000 PYFU (95%CI)	Standardised incidence ratio* (95% CI)
2000-2005	6.9 (6.1-7.9)	1.77 (1.55-1.99)	2.4 (1.5-3.6)	1.15 (0.68-1.61)
2006-2010	6.2 (5.5-7.0)	1.32 (1.17-1.47)	3.2 (2.3-4.3)	1.30 (0.91-1.70)
2011-2017	5.8 (5.3-6.3)	1 (reference)	3.1 (2.4-3.9)	1 (reference)

**Standardised according to the observed age distribution between 2011-2017.*

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

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 11% in 2017 (*Figure 3.3*). In women, this figure decreased from 19% in 2000 to a minimum of 12% in 2007 and has since increased somewhat to 15% in 2017.

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 at the top of each bar represent the number of individuals contributing data during that calendar year.

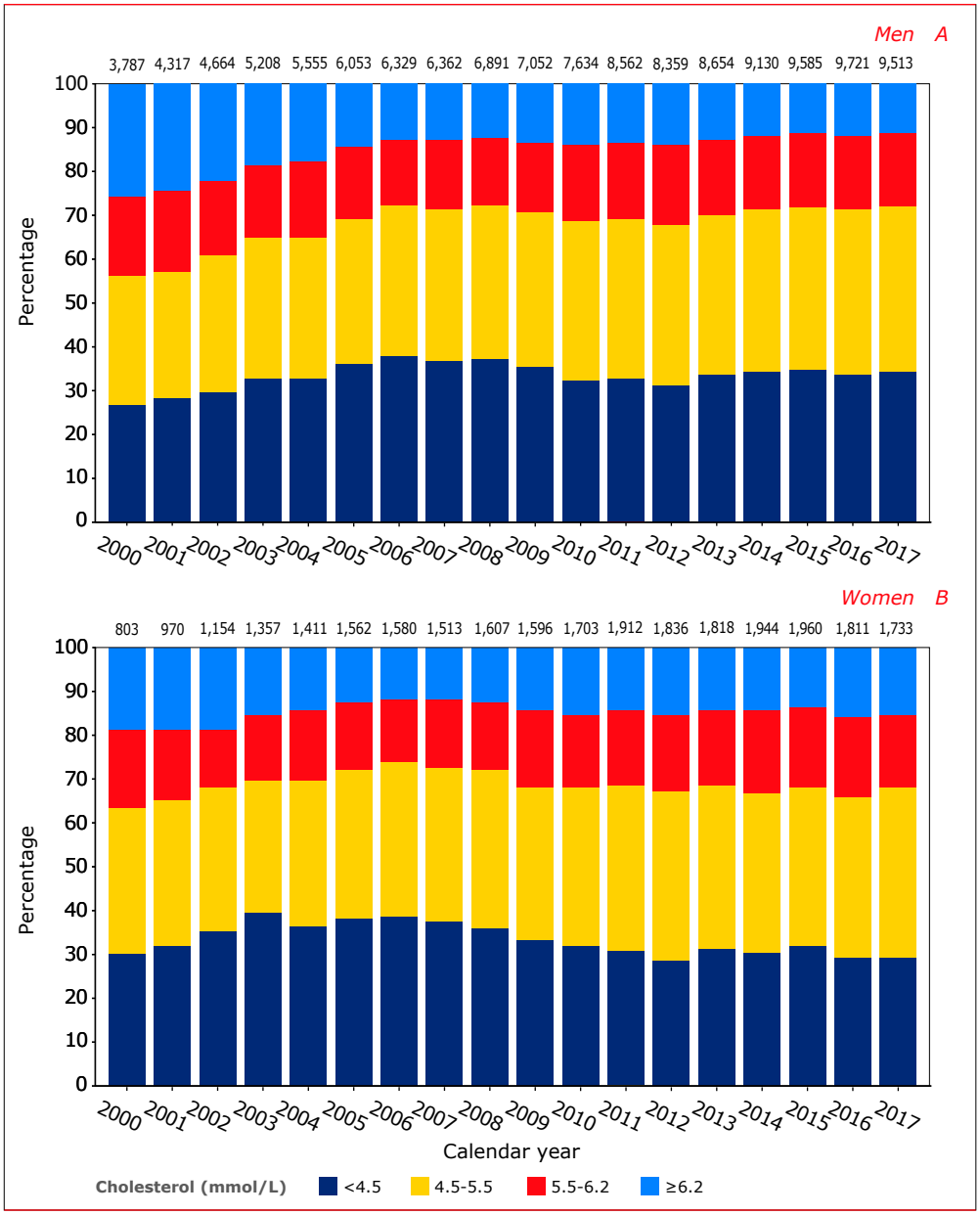
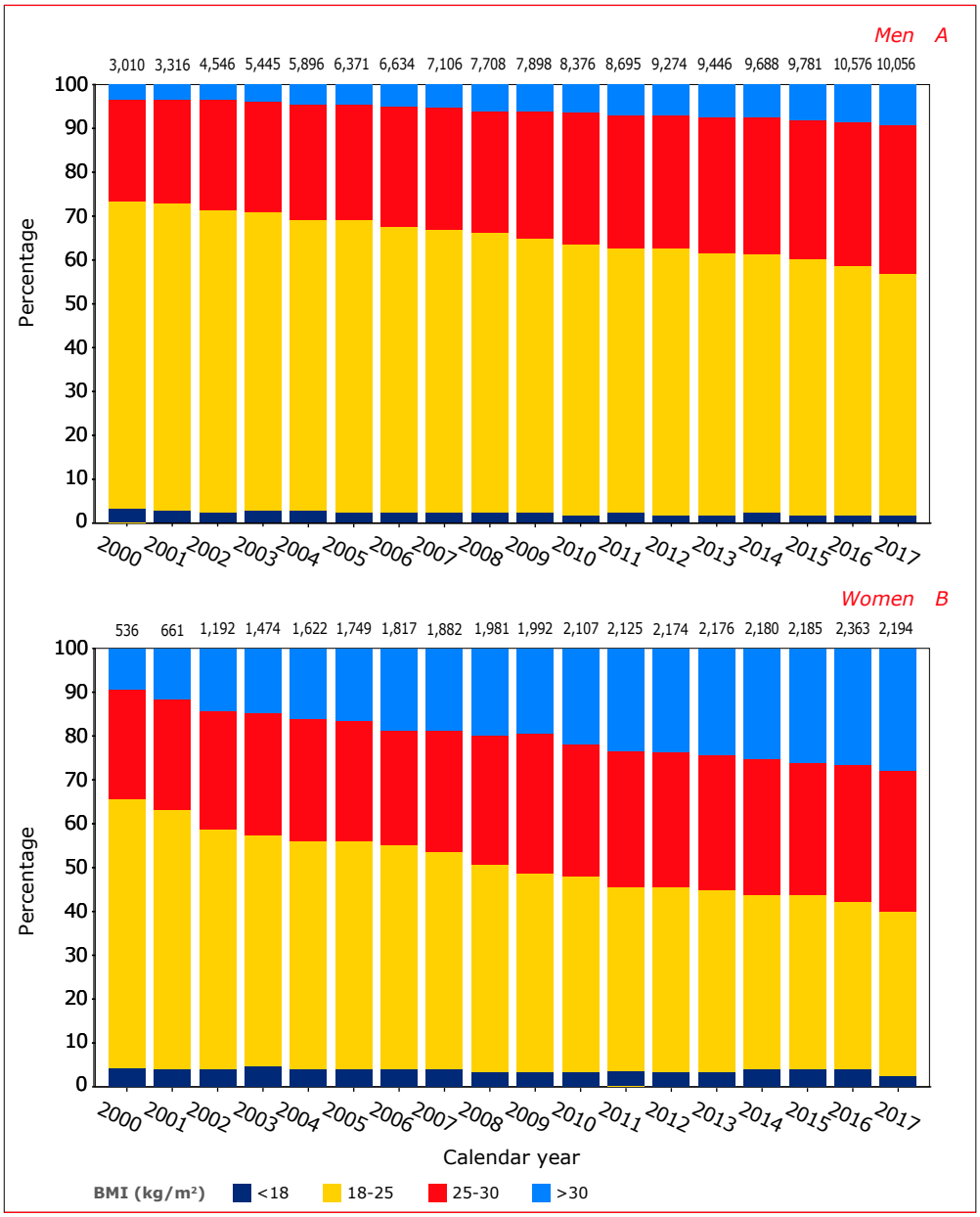


Figure 3.4 shows that the distribution of body mass index (BMI) of both men and women in the HIV-1-positive population has increased over time. In 2017, the percentage of overweight (25-30 kg/m^2) and obese (≥30 kg/m^2) men with an available BMI measurement was 34% and 9%, respectively. In women, these percentages were 31% and 29%, 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 analysis 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 start of cART, and that this effect was more marked in men than in women.

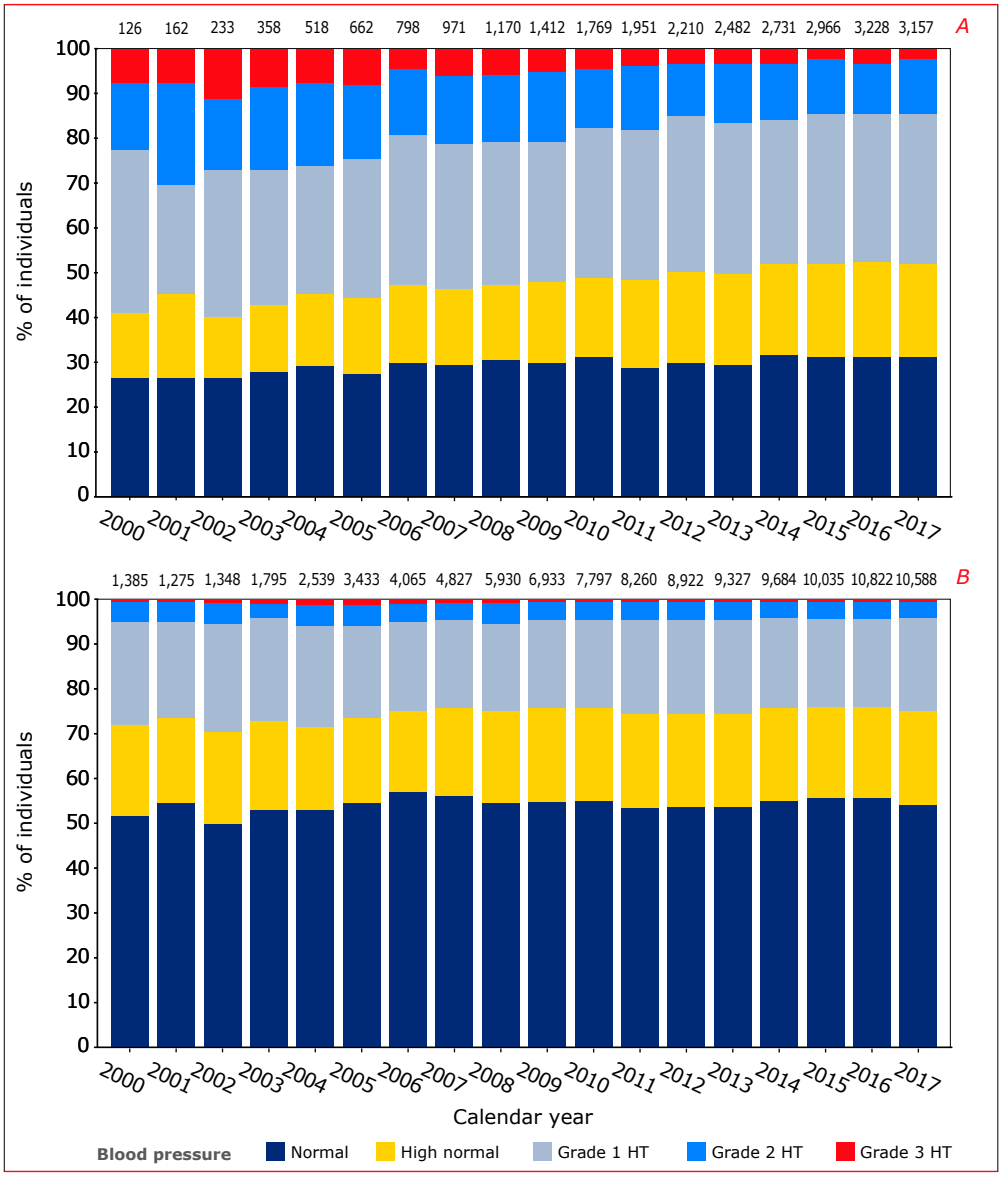
Figure 3.4: Distribution of the body mass index at the end of each calendar year in (A) men and (B) women as a percentage of the total number of men and women with a known BMI in each year. For each individual, the last available weight measurement in each year was selected. The numbers at the top of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



Legend: BMI=body mass index.

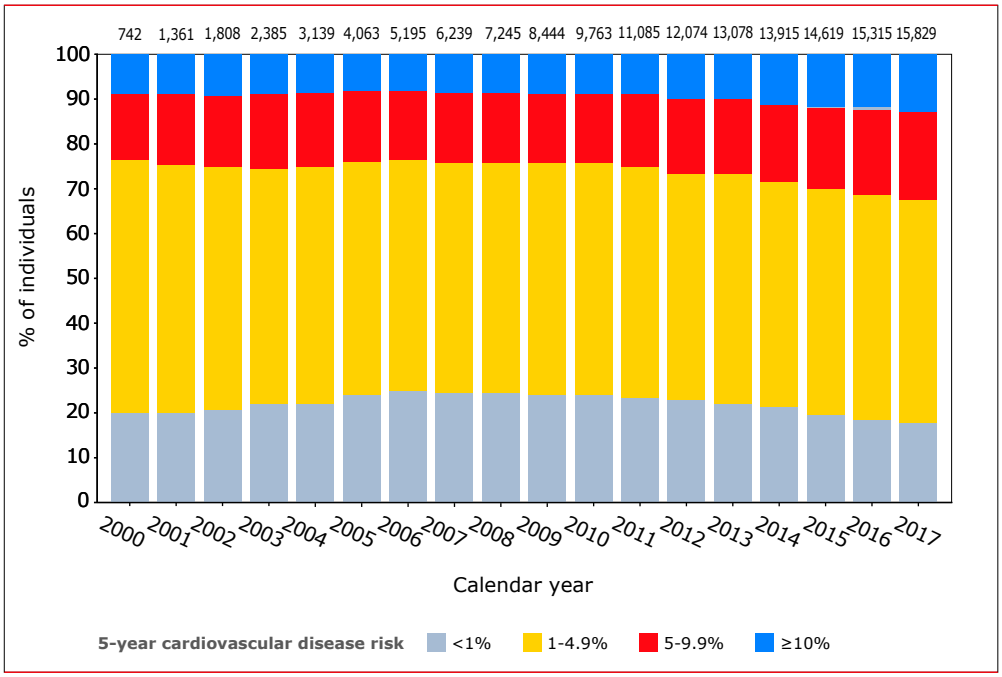
Figure 3.5A shows that, in 2017, 48% of those treated with antihypertensives still had grade 1 hypertension or higher. The figures above the bars show that, over time, an increasing number of individuals were using antihypertensives. In 2017, 2,632 (25%) individuals had grade 1-3 hypertension without specific treatment for this condition (*Figure 3.5B*). For 2,253 of these 2,632 individuals, a 5-year cardiovascular disease (CVD) risk could be calculated with the recalibrated D:A:D study algorithm[25]. Of the 2,253 individuals, 6.1% 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[26]. *Figure 3.6* gives an overview of the cART-treated population's estimated risk of CVD over time. From 2000 until 2012, the percentage of individuals at high (5-10%) or very high (≥10%) risk remained relatively stable at around 15% and 9%, respectively, but started to increase from 2013 to 2017 to 20% and 13%, respectively. The increase in recent years in the percentage of individuals at high or very high risk may reflect the ageing of the population under study.

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) those 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[27]). 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 at the top of each bar represent the number of individuals contributing data during that calendar year.



Legend: 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[25]. 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 over-represented. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.



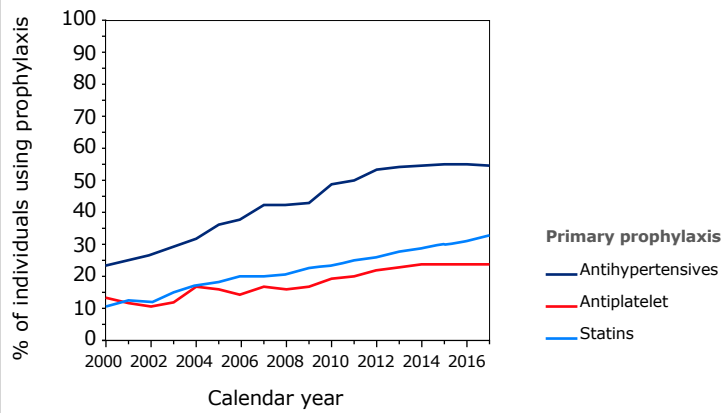
Use of primary or secondary prophylaxis for myocardial infarction or stroke

Primary prophylaxis

According to EACS guidelines, statin therapy should be offered to individuals with type 2 diabetes or a 5-year CVD risk ≥5%; angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, diuretics, and antihypertensives (verapamil or diltiazem) should be offered to individuals with a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and a 5-year CVD risk ≥10%; and acetylsalicylic acid should

be offered to individuals aged 50 years or more with a 5-year CVD risk ≥10%[28]. *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 somewhat since 2012. Although the percentage of individuals at high risk aged 50 years or older who used 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.*

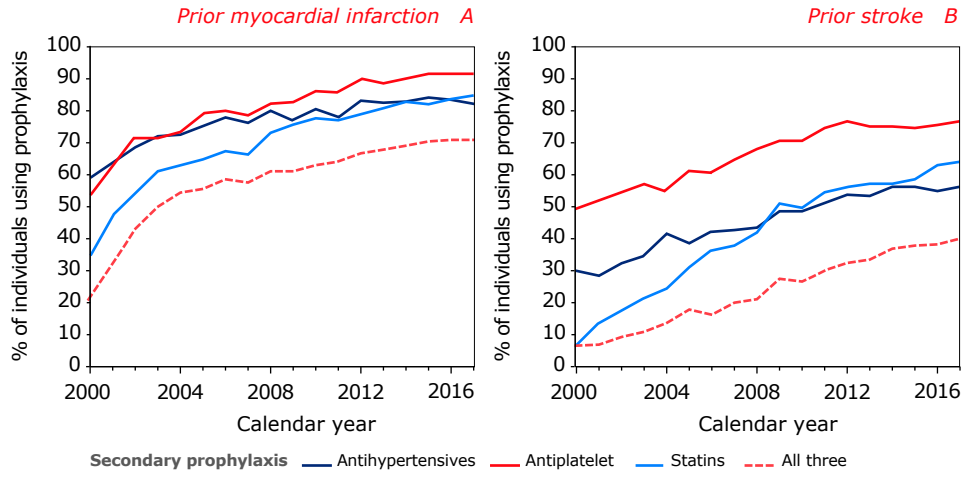


Secondary prophylaxis for myocardial infarction or stroke

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[29,30]. *Figure 3.8A* shows that the percentages of individuals using statins, acetylsalicylic acid/clopidogrel, or antihypertensives after a myocardial infarction increased between 2000 and 2017: in 2017, 85% of individuals with a prior myocardial infarction used statins, 82% used antihypertensives, and 92% used acetylsalicylic acid/clopidogrel. Although the use of statins and antihypertensives after an ischaemic stroke also

increased over time, in 2017 these medications were used less frequently after stroke than after a myocardial infarction (64% for statins, 77% for acetylsalicylic acid/clopidogrel, and 56% for antihypertensives) (*Figure 3.8B*).

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

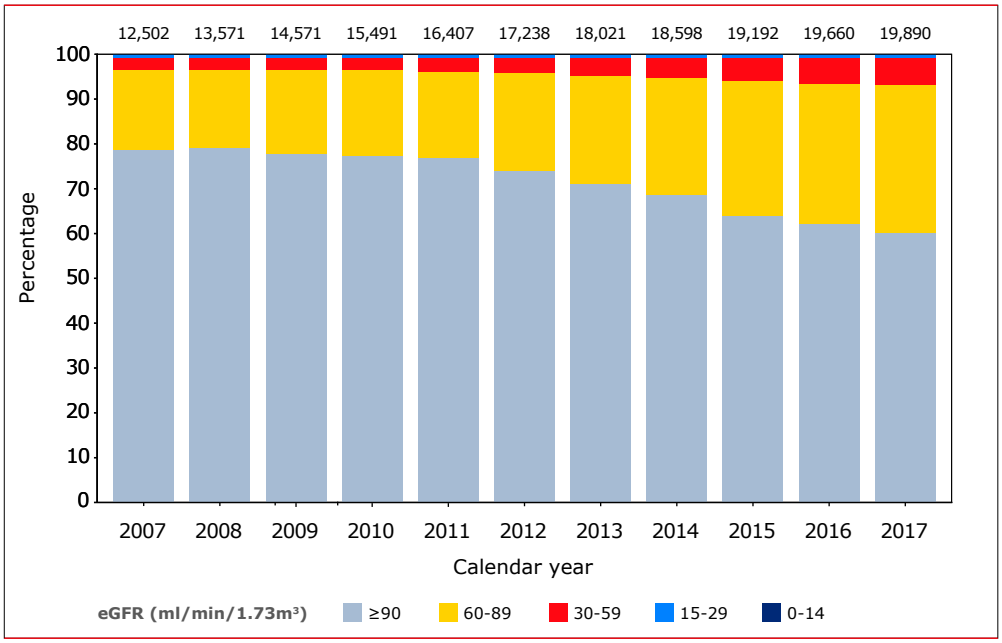


Chronic kidney disease

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[31]. 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[31,32]. 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^2 (≥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 60% in 2017. 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

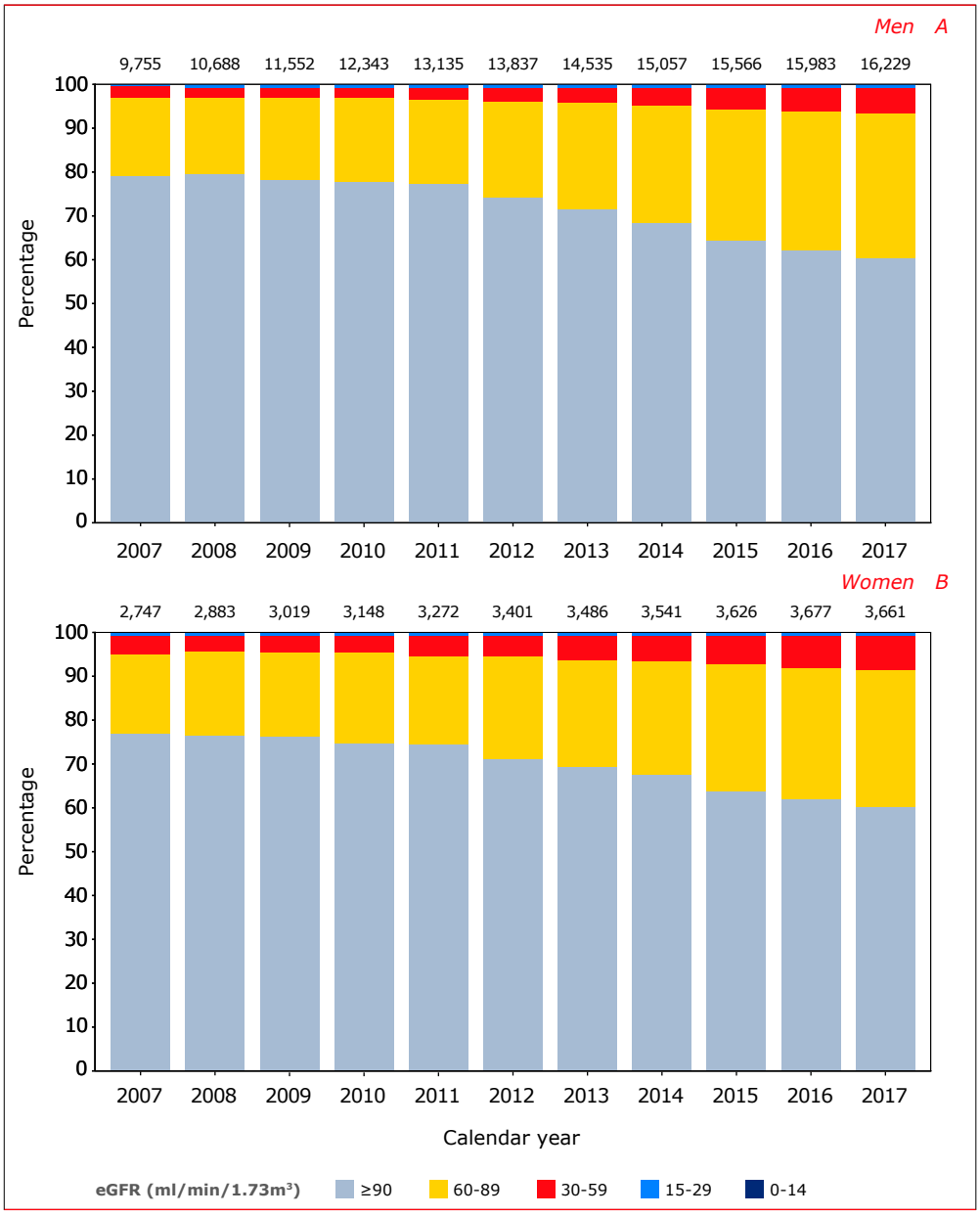
proportion of individuals with normal function over time is likely to partly reflect the increasing age of individuals in care.

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 at the top of each bar represent the number of individuals contributing data during that calendar year.



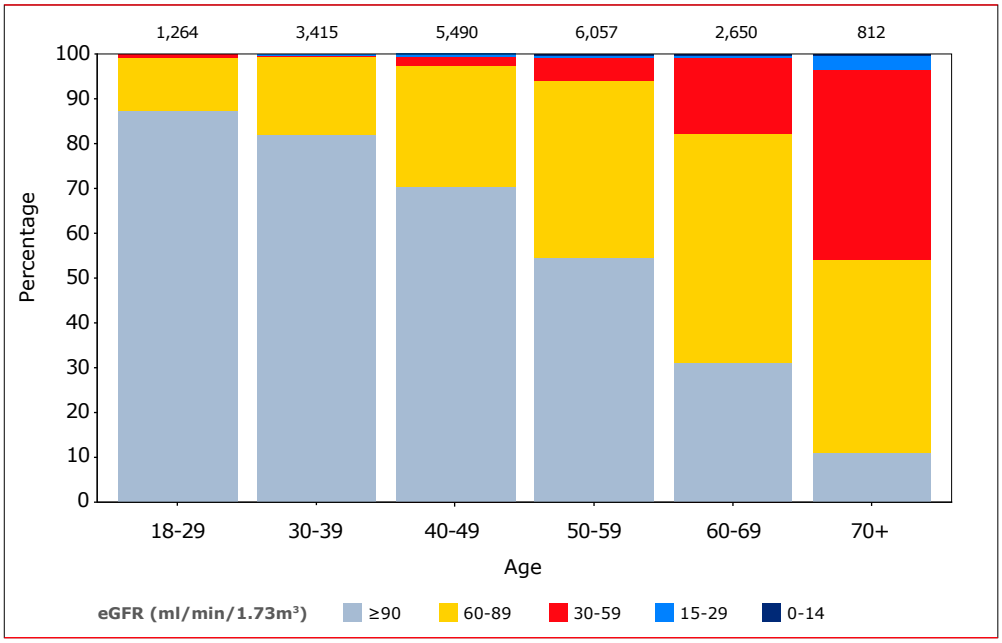
Legend: *eGFR=estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60-89 ml/min/1.73m²: mildly reduced; 30-59 ml/min/1.73m²: moderately reduced; 15-29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

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

Figure 3.11: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2017 for different age categories. For each individual, the last available measurement in 2017 was selected. The numbers at the 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/1.73m²: normal kidney function; 60-89 ml/min/1.73m²: mildly reduced; 30-59 ml/min/1.73m²: moderately reduced; 15-29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

In individuals with an eGFR >60ml/min/1.73m² at inclusion in the analyses and without previously confirmed CKD, the crude incidence of CKD, defined as eGFR <60ml/min/1.73m² confirmed by a second test at least 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 rose from 7.0 cases per 1,000 PYFU in the period 2008-2010 to 10.6 in 2011-2017, and in women the incidence rose from 9.8 to 14.4 cases per 1,000 PYFU during the same periods (*Table 3.4*). The standardised incidence ratio in men, but not in women, increased significantly over time (*Table 3.4*).

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	Men		Women	
	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)
2008-2010	7.0 (5.8-8.4)	0.78 (0.64-0.92)	9.8 (7.1-13.2)	0.89 (0.62-1.15)
2011-2017	10.6 (9.8-11.5)	1 (reference)	14.4 (12.4-16.6)	1 (reference)

**Standardised according to the observed age distribution between 2011-2017.*

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

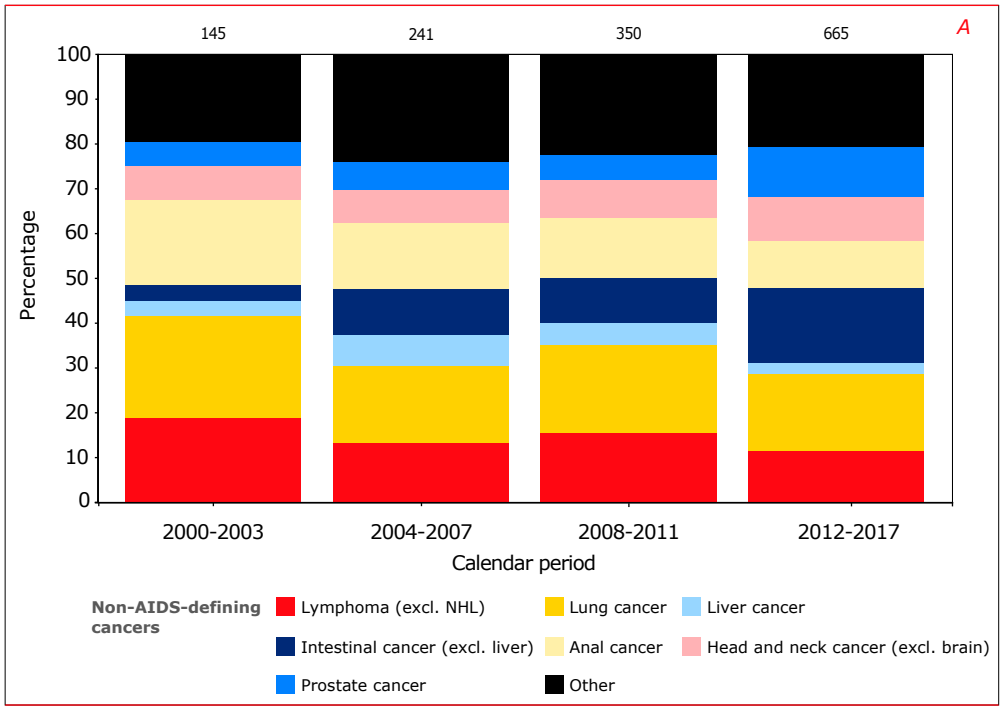
Risk factors for CKD included female gender, non-Dutch origin, low current CD4 cell count (<350 cells/mm^3), belonging to the HIV transmission risk group of people who inject drugs, older age, lower body mass index, diabetes mellitus, cardiovascular disease, being pre-treated with monotherapy and dual therapy with nucleoside analogues before the start of cART, and HBV co-infection (*Appendix Table 3.7*). When current use of cobicistat and dolutegravir were added to the model, the increased risk of CKD in the calendar period 2011-2016 disappeared in comparison to that in 2008-2010. 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).

Non-AIDS-defining malignancies

Between 2000 and 2017, 1,401 diagnoses of non-AIDS-defining malignancy in 1,307 unique individuals were recorded in SHM's database. An additional 581 patients were diagnosed with one or more non-melanoma skin cancers, but these were not included in the present analysis. *Table 3.5* shows the most common types of non-AIDS-defining cancer: lung cancer (17%), Hodgkin's lymphoma (13%), invasive anal cancer (12%), intestinal cancer (excluding liver cancer, 12%), head and neck cancers (9%), and prostate cancer (8%). *Figures 3.12A* and *B* show the relative and absolute changes in types of non-AIDS-defining cancers over time. The proportion of individuals with intestinal, prostate and renal cancer has increased over time,

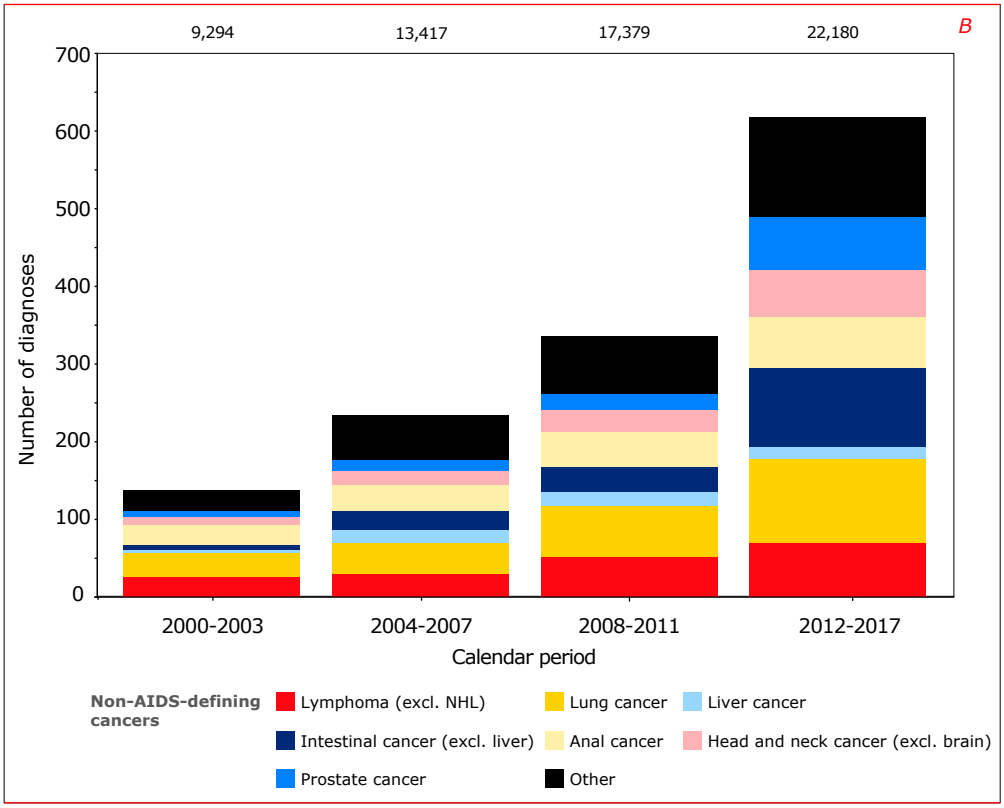
possibly reflecting the increasing age of the study population. This is further illustrated in *Figure 3.13*, which shows the distribution of non-AIDS-defining malignancies with increasing age at cancer diagnosis.

Figure 3.12A: *Relative changes in non-AIDS-defining malignancies between 2000 and 2017 in HIV-1-positive individuals in the Netherlands. The numbers at the top of each bar represent the number of non-AIDS-defining cancer diagnoses during that calendar period.*



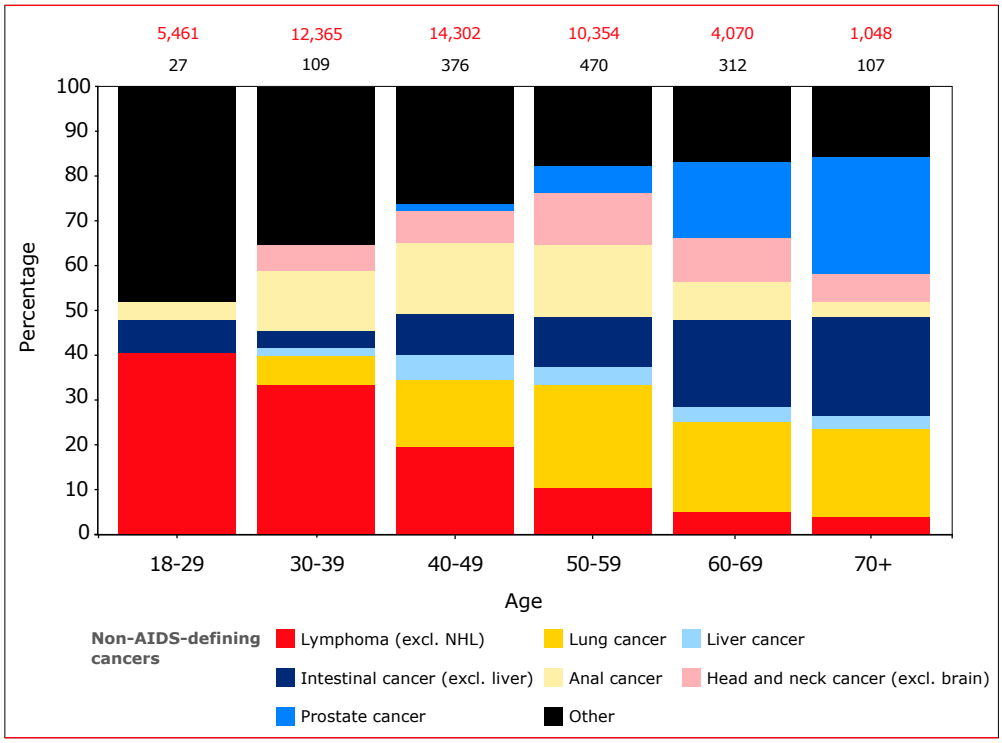
Legend: *excl.=excluding; NHL=non-Hodgkin's lymphoma.*

Figure 3.12B: Absolute number of non-AIDS-defining malignancies between 2000 and 2017 in HIV-1-positive individuals in the Netherlands. The numbers at the top of each bar represent the number of individuals at risk during that calendar period.



Legend: *excl.=excluding; NHL=non-Hodgkin's lymphoma.*

Figure 3.13: Relative changes in non-AIDS-defining malignancies with increasing age in HIV-1-positive individuals in the Netherlands. The numbers at the top of each bar represent the number of individuals at risk and the number of cancer diagnoses in that age category between 2000 and 2017.



Legend: excl.=excluding; NHL=non-Hodgkin's lymphoma.

The crude incidence of non-AIDS-defining malignancies in men increased slightly from 6.0 cases per 1,000 PYFU in 2000-2005 to 6.7 cases per 1,000 PYFU in 2011-2017, and in women from 2.0 in 2000-2005 to 4.0 cases per 1,000 PYFU in 2011-2017 (*Figure 3.2D*; *Appendix Table 3.6D*). However, when the changes in the age distribution of the HIV-positive population were taken into account, the age-standardised incidence in men was actually lower in the period 2011-2017 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 2011-2017 than in 2006-2010, but not 2000-2005.

Table 3.5: Most common non-AIDS-defining malignancies diagnosed between 2000-2017.

Non-AIDS-defining malignancy	Number of malignancies	%	5-year survival
Lung cancer	242	17.3	11.5
Lymphoma (excluding non-Hodgkin's lymphoma)	182	13.0	66.9
Anal cancer	169	12.1	63.2
Intestinal cancer (excluding liver)	166	11.8	31.4
Head and neck cancer (excluding brain)	120	8.6	57.9
Prostate cancer	107	7.6	78.5
Other cancers	89	6.4	48.5
Renal and bladder cancer	74	5.3	63.5
Malignant melanoma	56	4.0	67.4
Liver cancer	54	3.9	11.3
Leukaemia	42	3.0	40.8
Breast cancer	35	2.5	81.8
Testicular cancer	26	1.9	87.7
Gynaecological cancer (excluding cervical)	21	1.5	61.7
CNS cancer	18	1.3	28.9

Table 3.6: Crude non-AIDS-defining malignancy incidence per 1,000 person years of follow up between 2000-2005, 2006-2010, and 2011-2017, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Men		Women	
	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)
2000-2005	6.0 (5.2-6.8)	1.35 (1.17-1.52)	2.0 (1.2-3.1)	0.85 (0.47-1.24)
2006-2010	7.1 (6.4-7.9)	1.33 (1.19-1.47)	4.0 (3.0-5.3)	1.39 (1.01-1.76)
2011-2017	6.7 (6.2-7.2)	1 (reference)	4.0 (3.2-4.9)	1 (reference)

**Standardised according to the observed age distribution between 2011-2017.*

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

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^3), low body mass index, prior AIDS, chronic HBV co-infection, and current and/or past smoking (*Appendix Table 3.7*).

In the period from 1 January 2000 to 31 December 2017, the 5-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma

skin cancers and invasive anal cancers) was 47.3%, compared with 69.6% for CVD, 81.0% for DM, and 83.9% 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 82.2% 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*.

Anal cancer

In total, 3 HIV-positive women and 166 HIV-positive men were diagnosed with anal cancer. Among HIV-positive men, the incidence of anal cancer slowly decreased over time from 0.7 cases per 1,000 PYFU in 2000 to 0.2 cases per 1,000 PYFU in 2017 (*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, as both a lower nadir CD4 cell count and lower current CD4 cell count have each been associated with an increased risk of anal cancer[33]. 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 men who have sex with men (MSM) than in heterosexual men[34]. 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=14) to observe a decreasing trend in anal cancer in this group.

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

Of 6,124 therapy-naive individuals who started cART with less than 350 CD4 cells/mm^3 since 1996 and who had experienced at least 3 years of viral suppression on cART, 1,325 were classified as immunological non-responders (defined as having less than 350 CD4 cells/mm^3 after 3 years of viral suppression on cART) and 4,799 individuals were defined as having a good immunological response (a CD4 cell count of 350 cells/mm^3 or higher after 3 years of viral suppression on cART). We analysed the association between immunological response/non-response and the risk of the following endpoints: death, AIDS, non-AIDS-defining malignancy, diabetes mellitus, and cardiovascular disease. We considered only first events and excluded those individuals in whom a particular endpoint had already occurred prior to the start of the observation for this analysis (these were mainly prior AIDS events). Changes in immune status and/or plasma viraemia and/or use of cART after the initial 3 years of cART were ignored in this analysis – individuals remained in their original category of immunological responder/non-responder. The number

of events, crude incidence per 1,000 PYFU, 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 came close to reaching statistical significance for cardiovascular disease 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 (relative risk [RR] 1.38, 95% CI 1.09-1.75, p=0.009), but not with non-AIDS-defining malignancy (RR 1.28, 95% CI 0.95-1.73, p=0.11), AIDS (RR 1.20, 95% CI 0.76-1.91, p=0.43), diabetes mellitus (RR 0.80, 95% CI 0.57-1.13, p=0.20), or cardiovascular disease (RR 1.27, 95% CI 0.96-1.70, p=0.10). However, as the number of endpoints are small, these results should be interpreted with caution.

Table 3.7: *Crude incidence per 1,000 person 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/mm³ and after 3 years of virologically successful cART were either immunological responders (CD4 cell count ≥ 350 cells/mm³) or non-responders (CD4 cell count < 350 cells/mm³).*

Outcome	**Crude rate**			**Standardised rate***	
Immune response	Person years	Number of endpoints	Rate/1,000 PY (95% CI)	SIR (95% CI)	p-value
Death					
Responder (CD4 ≥350)	34,561	203	5.87 (5.09-6.74)	1 (reference)	.
Non-responder (CD4 <350)	10,458	108	10.33 (8.47-12.47)	1.34 (1.09-1.59)	0.009
AIDS					
Responder (CD4 ≥350)	26,074	83	3.18 (2.54-3.95)	1 (reference)	.
Non-responder (CD4 <350)	5,738	24	4.18 (2.68-6.22)	1.18 (0.71-1.66)	0.448
Non-AIDS-defining malignancy					
Responder (CD4 ≥350)	33,841	133	3.93 (3.29-4.66)	1 (reference)	.
Non-responder (CD4 <350)	10,169	64	6.29 (4.85-8.04)	1.27 (0.96-1.59)	0.085
Diabetes mellitus					
Responder (CD4 ≥350)	32,892	149	4.53 (3.83-5.32)	1 (reference)	.
Non-responder (CD4 <350)	9,928	43	4.33 (3.13-5.83)	0.82 (0.58-1.07)	0.160
Cardiovascular disease					
Responder (CD4 ≥350)	33,954	147	4.33 (3.66-5.09)	1 (reference)	.
Non-responder (CD4 <350)	10,128	71	7.01 (5.47-8.84)	1.27 (0.97-1.56)	0.076

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

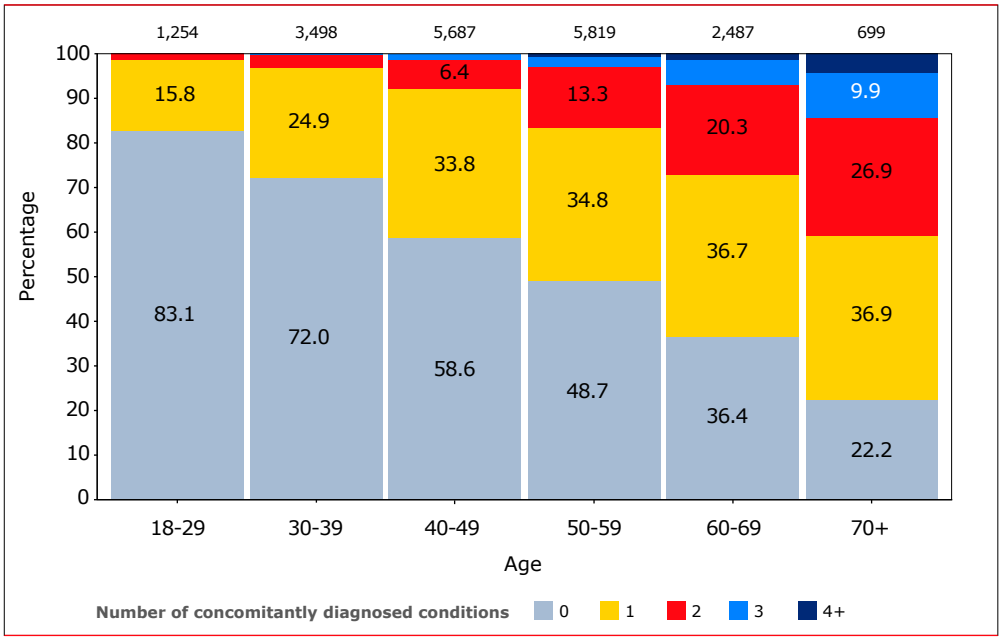
Legend: *SIR=standardised incidence ratio; 95% CI=95% confidence interval; PY=person years.*

Multimorbidity

We investigated changes over time in the prevalence of non-AIDS multimorbidity. HIV infection itself and AIDS diagnoses did not contribute to the multimorbidity score. The following comorbidities and conditions were taken into account: (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^2); (5) diabetes mellitus; (6) hypertension, defined as the use of antihypertensive drugs and/or a measured grade 2 (or higher) hypertension with systolic pressure ≥160 mmHg and/or diastolic pressure ≥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 so as to avoid overdiagnosis of both CKD in people using antiretroviral drugs that inhibit tubular secretion of creatinine and hypertension in those with borderline hypertension. Recurrences and second events of CVD, stroke, and non-AIDS-defining malignancies were not considered. Finally, CKD, hypertension and obesity could be reversible.

Figure 3.14 shows the distribution of the number of concomitantly diagnosed conditions in various age categories of the adult population in 2017. 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 2017. The numbers at the 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 reductions reported in studies from Spain[35], Denmark[36], several other European countries[37], and the USA[38]. The limited, but decreasing, number of individuals who still die of AIDS each year consists mainly of those presenting late for care with already advanced immunodeficiency. Nonetheless, overall, the 5-year survival after a first AIDS-defining condition was far greater than after a diagnosis of cardiovascular disease (CVD) or a non-AIDS-defining malignancy. 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 of 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^3 on treatment[39,40].

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[41] and myocardial infarction[42,43] 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). The observation that the age-standardised incidence ratios do not decline as much in women remains unexplained and needs further study. 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[41,44,45]. Several of these risk factors have been reported to be more prevalent among people living with HIV[19].

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 2000-2017. 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[46] (*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[47]. However, another study found that weight gain after starting cART was associated with an increased risk of diabetes, and, in those with a pre-antiretroviral therapy BMI in the normal range, with an increased risk of cardiovascular disease[48]. 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[49,50] and the use of tenofovir disoproxil fumarate, atazanavir/ritonavir, and lopinavir/ritonavir to be additional independent predictors of chronic renal impairment[51]. Renal impairment in the HIV-positive population is associated with an increased risk for cardiovascular disease[52]. 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[53,54,55,56]. 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^3) and a prior AIDS diagnosis. Other studies reported that the effect of immunodeficiency may be stronger for infection-related non-AIDS-defining malignancies[57]. The 5-year survival rate after

a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 47.3%.

Our analyses found no association between duration of cART and the incidence of non-AIDS-defining malignancies. On the other hand, a 2015 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, revealed an overall increase in the risk of non-AIDS-defining malignancies with longer exposure to a protease inhibitor-based cART regimen. This association was observed particularly for anal cance[58]. 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, further improvement can be made 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[59,60,61]. 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 analysed non-AIDS-defining comorbidities compared to survival of patients 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 Comorbidity and Aging with HIV (AGEhIV) 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 hopefully guide the development of interventions that target relevant pathophysiological mechanisms[9,62].

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[63].

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 high 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.

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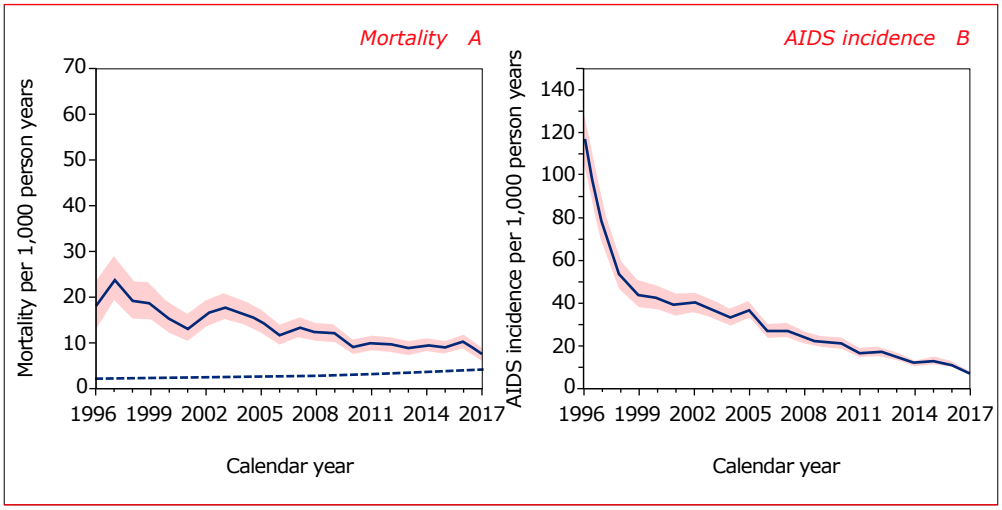
Appendix: supplementary figures and tables

Appendix Figure 3.1: *(A) Annual mortality and (B) incidence of AIDS in 25,524 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.*



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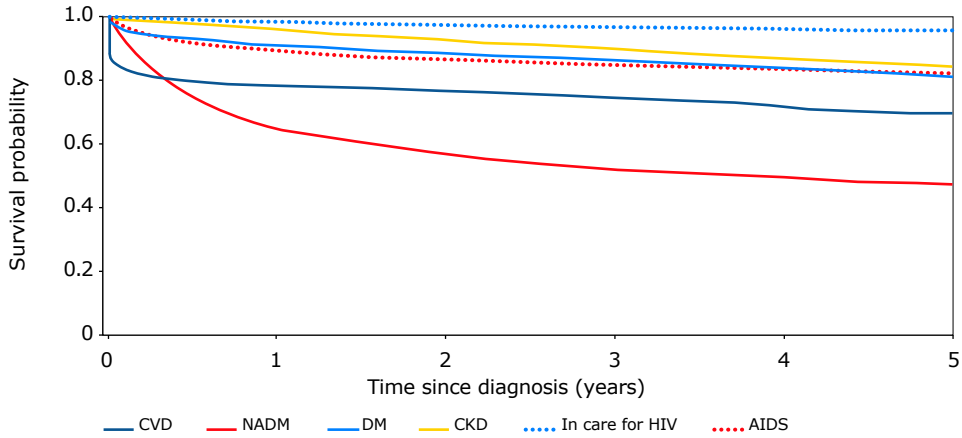
Appendix Figure 3.2: *Estimated 5-year survival following the diagnosis of cardiovascular disease, non-AIDS-defining malignancy, diabetes mellitus, chronic kidney disease. Two reference groups are included: survival from date of entry into HIV care (after 1 January 2000), and from date of first AIDS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



Time since diagnosis (years)	0	1	2	3	4	5
CVD	1,132	844	745	647	558	484
NADM	1,106	674	507	401	339	280
DM	1,186	1,004	888	791	675	577
CDK	1,657	1,287	1,011	801	631	482
In care for HIV	19,793	17,752	16,440	15,165	13,969	12,736
AIDS	3,681	3,097	2,847	2,581	2,394	2,192

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

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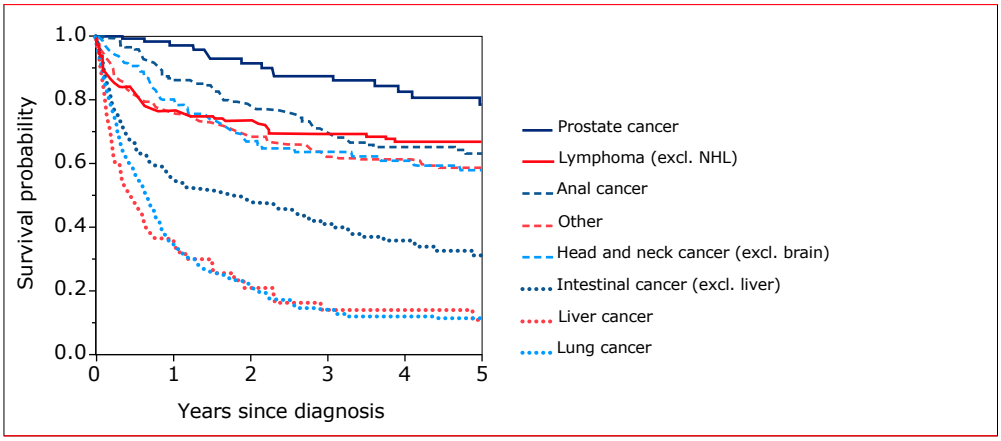
Appendix Figure 3.3: Estimated 5-year survival following the diagnosis of the most common non-AIDS-defining malignancies diagnosed between 1 January 2000 and 31 December 2017.



Legend: excl.-excluding; NHL=non-Hodgkin's lymphoma.

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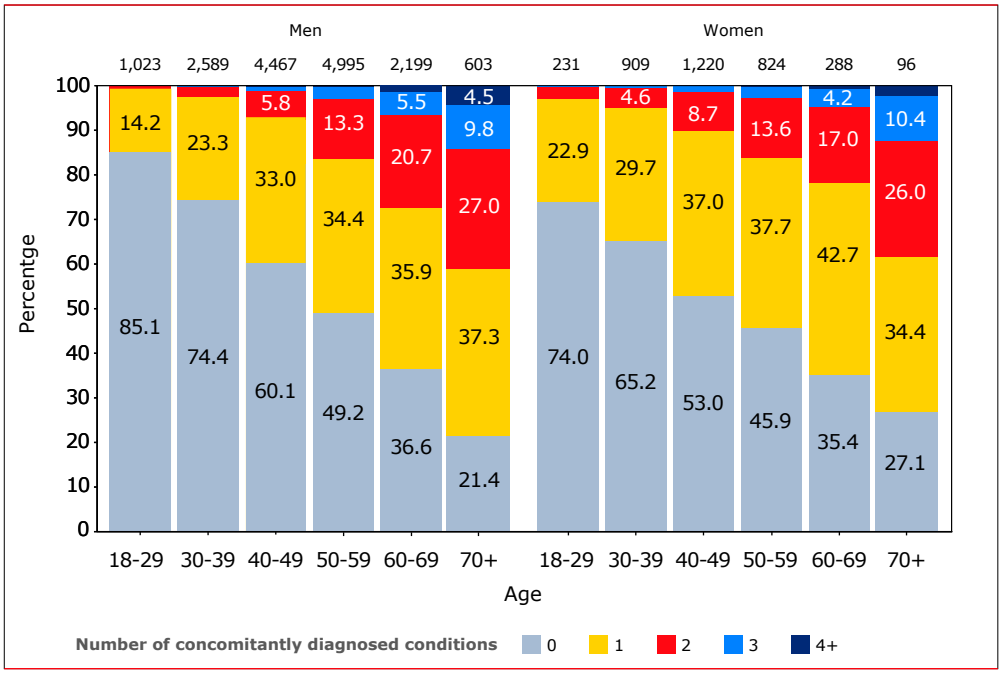
Appendix Figure 3.4: Prevalence of non-AIDS multimorbidity by gender in the adult population in 2017. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



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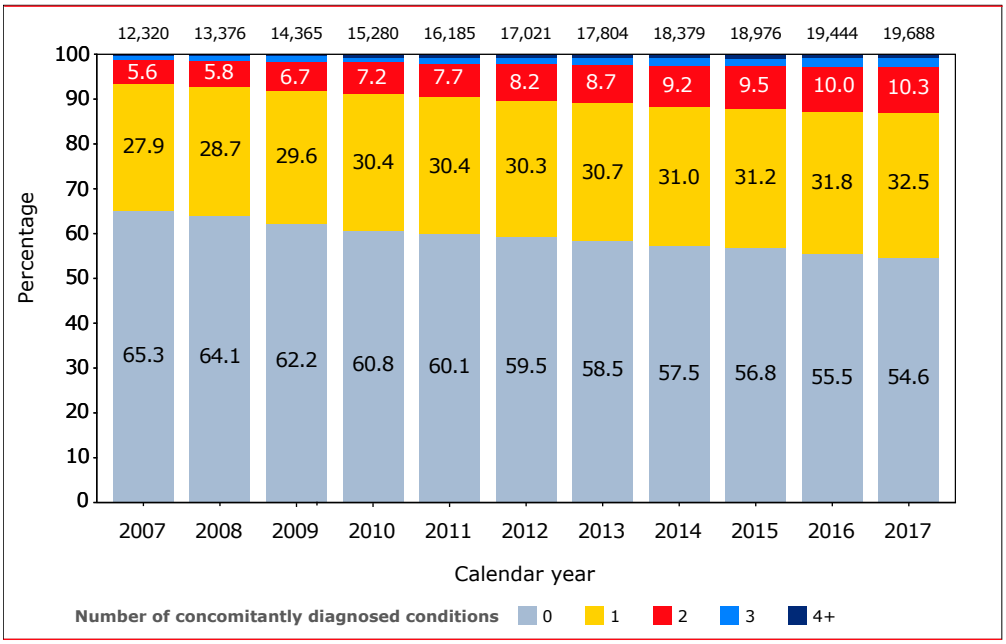
Appendix Figure 3.5: Prevalence of non-AIDS multimorbidity in the adult population. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per calendar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



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Appendix Table 3.1: Annual number of cases of death and first AIDS events among 25,524 HIV-1-positive individuals in the Netherlands recorded up to May 2017.

	AIDS			Death	
Calendar year	Number of AIDS events	AIDS ≥6 weeks after diagnosis	AIDS ≥4 weeks after start of cART	Number of deaths	Number of deaths ≥6 weeks after start of cART
1996	373	233	25	51	24
1997	312	154	52	87	63
1998	250	105	43	84	69
1999	235	116	56	92	90
2000	258	101	58	85	81
2001	259	127	63	83	79
2002	308	122	66	118	80
2003	315	140	73	142	117
2004	302	142	69	145	122
2005	378	177	89	142	116
2006	295	151	76	123	98
2007	332	170	91	152	126
2008	306	157	91	154	133
2009	302	138	76	161	142
2010	311	132	83	130	117
2011	256	121	75	151	135
2012	290	135	85	156	145
2013	257	124	90	149	140
2014	208	92	61	165	151
2015	233	113	90	161	153
2016	205	95	81	190	181
2017	114	32	26	126	119

Legend: cART=combination antiretroviral therapy.

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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 2011-2017.*

Causes of death	1996-2000	2001-2005	2006-2010	2011	2012	2013	2014	2015	2016	2017
AIDS										
AIDS - infection	68	119	149	35	15	23	17	7	1	.
AIDS - malignancy	58	63	61	3	13	10	5	13	4	.
AIDS - unclassifiable	97	65	20	3	4	.	4	9	16	10
Total	*223*	*247*	*230*	*41*	*32*	*33*	*26*	*29*	*21*	*10*
Non-AIDS malignancies	*30*	*96*	*134*	*32*	*43*	*38*	*41*	*39*	*48*	*39*
Cardiovascular disease										
Myocardial infarction	14	32	54	13	7	5	10	11	9	3
Stroke	4	11	14	3	4	3	4	3	7	2
Other CVD	6	20	16	8	4	3	12	10	16	3
Total	*24*	*63*	*84*	*24*	*15*	*11*	*26*	*24*	*32*	*8*
Non-AIDS infection	*24*	*42*	*31*	*4*	*7*	*6*	*10*	*6*	*12*	*7*
Liver disease	*17*	*30*	*62*	*8*	*9*	*10*	*11*	*6*	*5*	*4*
Lung disease	*4*	*11*	*33*	*7*	*4*	*9*	*5*	*14*	*13*	*8*
Non-natural death										
Accident or violence	6	11	21	1	5	3	5	2	7	1
Suicide	13	26	11	7	7	3	5	8	5	7
Euthanasia	3	3	2	2	.	1	1	.	.	4
Total	*22*	*40*	*34*	*10*	*12*	*7*	*11*	*10*	*12*	*12*
Alcohol and substance abuse	*10*	*13*	*19*	*1*	*4*	*4*	*4*	*2*	*5*	*1*
Other causes	*16*	*26*	*37*	*7*	*12*	*12*	*13*	*10*	*18*	*5*
Unknown	*29*	*62*	*56*	*17*	*18*	*19*	*18*	*21*	*24*	*32*
Total	**399**	**630**	**720**	**151**	**156**	**149**	**165**	**161**	**190**	**126**

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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
Risk factors						
Male gender	1.34 (1.16-1.55)	<.001		1.01 (0.86-1.19)	0.877	
Region of birth						
Netherlands	1 (reference)		<.001	1 (reference)		0.118
Other	0.80 (0.73-0.89)	<.001		1.10 (0.98-1.24)	0.117	
HIV-1 transmission route						
Blood contact	0.74 (0.52-1.03)	0.078		0.90 (0.60-1.34)	0.611	
Heterosexual	1.10 (0.97-1.24)	0.132		0.89 (0.76-1.04)	0.149	
IDU	1.63 (1.35-1.97)	<.001		0.64 (0.49-0.84)	0.001	
MSM	1 (reference)		<.001	1 (reference)		0.002
Age*						
18-29	0.81 (0.59-1.11)	0.188	<.001	1.01 (0.81-1.24)	0.961	0.002
30-39	1 (reference)			1 (reference)		
40-49	1.38 (1.20-1.60)	<.001		1.07 (0.94-1.22)	0.308	
50-59	2.42 (2.10-2.80)	<.001		1.25 (1.08-1.46)	0.003	
60-69	4.16 (3.54-4.88)	<.001		1.37 (1.12-1.68)	0.003	
70+	7.26 (5.94-8.87)	<.001		1.84 (1.17-2.89)	0.008	
CD4 cell count**						
0-50	16.92 (14.22-20.15)	<.001	<.001	6.19 (4.96-7.72)	<.001	<.001
50-199	5.20 (4.52-5.99)	<.001		2.69 (2.26-3.19)	<.001	
200-349	2.21 (1.92-2.54)	<.001		1.51 (1.27-1.79)	<.001	
350-499	1.41 (1.22-1.63)	<.001		1.17 (0.98-1.39)	0.084	
500-749	1 (reference)			1 (reference)		
750+	0.73 (0.61-0.86)	<.001		1.02 (0.82-1.27)	0.856	
Per year longer on cART with HIV RNA >1,000 copies/ml	1.05 (1.03-1.07)	<.001	<.001	1.03 (1.00-1.06)	0.037	0.040
Treatment status						
Treatment-experienced at start cART	1.12 (1.02-1.24)	0.023		0.59 (0.52-0.68)	<.001	
Treatment-naive at start	1 (reference)			1 (reference)		
Prior AIDS event	1.88 (1.72-2.06)	<.001				
Hepatitis B virus positive	1.35 (1.17-1.55)	<.001		1.00 (0.82-1.21)	0.994	
Hepatitis C virus positive	1.45 (1.24-1.68)	<.001		1.30 (1.06-1.59)	0.010	

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	Death			AIDS		
	RR (95% CI)	p-value	Overall p-value	RR (95% CI)	p-value	Overall p-value
Body mass index*						
<18	2.85 (2.51-3.24)	<.001	<.001			
18-25	1 (reference)					
25-30	0.69 (0.61-0.77)	<.001				
30+	0.84 (0.70-1.02)	0.075				
Smoking status						
Current smoker	1.46 (1.28-1.67)	<.001	<.001	0.76 (0.66-0.87)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	1.76 (1.53-2.04)	<.001		1.02 (0.86-1.22)	0.806	
Early cART***	0.67 (0.45-1.01)	0.055		0.95 (0.70-1.29)	0.752	

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 2017) by region of origin and time-updated CD4 cell count.*

	Total			Caribbean			Western Europe / North America		
Last CD4 count	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	61	2,654	23.0 (17.6-29.5)	1	129	7.7 (0.2-43.2)	16	226	70.7 (40.4-114.8)
50-199	202	9,077	22.3 (19.3-25.5)	7	459	15.3 (6.1-31.4)	41	1,033	39.7 (28.5-53.9)
200-349	404	18,246	22.1 (20.0-24.4)	17	787	21.6 (12.6-34.6)	72	1,455	49.5 (38.7-62.3)
350-499	509	36,725	13.9 (12.7-15.1)	26	1,606	16.2 (10.6-23.7)	100	3,310	30.2 (24.6-36.7)
500-749	680	78,438	8.7 (8.0-9.3)	46	3,350	13.7 (10.1-18.3)	169	6,562	25.8 (22.0-29.9)
750+	414	85,465	4.8 (4.4-5.3)	27	3,579	7.5 (5.0-11.0)	132	7,391	17.9 (14.9-21.2)

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

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	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	1,785	3.4 (1.2-7.3)	30	408	73.5 (49.6-104.9)	8	105	76.1 (32.8-149.9)
	31	5,626	5.5 (3.7-7.8)	116	1,687	68.8 (56.8-82.5)	7	273	25.7 (10.3-52.9)
	79	11,499	6.9 (5.4-8.6)	209	3,775	55.4 (48.1-63.4)	27	730	37.0 (24.4-53.8)
	109	23,568	4.6 (3.8-5.6)	253	6,863	36.9 (32.5-41.7)	21	1,377	15.3 (9.4-23.3)
	194	53,474	3.6 (3.1-4.2)	253	11,926	21.2 (18.7-24.0)	18	3,126	5.8 (3.4-9.1)
	130	61,918	2.1 (1.8-2.5)	115	9,874	11.6 (9.6-14.0)	10	2,703	3.7 (1.8-6.8)

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 2011-2017.*

CDC event	1996-2000	2001-2005	2006-2010	2011-2017	Total	
	n	n	n	n	n	%
AIDS dementia complex / HIV encephalopathy	39	47	53	52	191	3.13
Cervical cancer	3	4	7	4	18	0.30
Bacterial pneumonia, recurrent	48	64	66	106	284	4.66
CMV ≥13 years	27	35	29	37	128	2.10
CMV pneumonitis	.	.	.	1	1	0.02
CMV retinitis	30	20	12	15	77	1.26
Candidiasis trachea, bronchi, lungs	7	13	7	7	34	0.56
Candidiasis oesophageal	256	234	249	279	1,018	16.71
Coccidioidomycosis, disseminated or extrapulmonary	.	.	1	.	1	0.02
Cryptococcosis, disseminated or extrapulmonary	21	32	32	14	99	1.62
Cryptosporidiosis	21	12	10	12	55	0.90
Cystoisosporiasis	3	9	5	.	17	0.28
Wasting syndrome due to HIV	49	57	77	103	286	4.69
Herpes simplex virus, chronic ulcer	.	1	.	1	2	0.03
Herpes simplex virus	32	41	60	46	179	2.94
Histoplasmosis, disseminated or extrapulmonary	9	12	10	8	39	0.64
Kaposi's sarcoma	154	150	186	162	652	10.70
Leishmaniasis, visceral	.	1	2	4	7	0.11
Lymphoma, primary, central nervous system	6	3	7	5	21	0.34
Microsporidiosis	11	1	3	1	16	0.26
Mycobacterium, other species/unidentified (disseminated/extrapulmonary)	21	12	7	11	51	0.84
Mycobacterium, other species/unidentified (pulmonary)	.	3	4	12	19	0.31
Mycobacterium avium/kansasii (disseminated/extrapulmonary)	25	21	28	12	86	1.41
Non-Hodgkin's lymphoma (NHL), HIV-related	59	87	80	115	341	5.60
Penicilliosis	.	.	1	.	1	0.02
Pneumocystis jirovecii extrapulmonary	1	1	3	.	5	0.08
Pneumocystis jirovecii pulmonary	334	296	323	337	1,290	21.17
Progressive multifocal leucoencephalopathy	18	25	35	25	103	1.69
Salmonella septicaemia, recurrent	2	.	.	.	2	0.03
Toxoplasmosis of the brain	70	98	56	54	278	4.56
Tuberculosis, extrapulmonary/disseminated	79	110	82	55	326	5.35
Tuberculosis, pulmonary	102	171	111	82	466	7.65
Total	**1,427**	**1,560**	**1,546**	**1,560**	**6,093**	**100.00**

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.

	Men			Women		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	6	11,068	0.5 (0.2-1.2)	26	6,280	4.1 (2.7-6.1)
30-39	83	38,870	2.1 (1.7-2.6)	73	15,023	4.9 (3.8-6.1)
40-49	275	63,864	4.3 (3.8-4.8)	93	13,854	6.7 (5.4-8.2)
50-59	305	44,517	6.9 (6.1-7.7)	52	6,138	8.5 (6.3-11.1)
60-69	188	16,355	11.5 (9.9-13.3)	21	2,049	10.2 (6.3-15.7)
70+	40	3,488	11.5 (8.2-15.6)	5	576	8.7 (2.8-20.2)

Legend: n=number; PYFU=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.

	Men			Women		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	6	11,064	0.5 (0.2-1.2)	5	6,344	0.8 (0.3-1.8)
30-39	55	38,975	1.4 (1.1-1.8)	22	15,263	1.4 (0.9-2.2)
40-49	276	64,163	4.3 (3.8-4.8)	51	14,210	3.6 (2.7-4.7)
50-59	407	44,370	9.2 (8.3-10.1)	24	6,406	3.7 (2.4-5.6)
60-69	266	16,012	16.6 (14.7-18.7)	21	2,069	10.2 (6.3-15.5)
70+	79	3,272	24.1 (19.1-30.1)	7	567	12.3 (5.0-25.4)

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

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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.

	Men			Women		
Age	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**
18-29	33	7,901	4.2 (2.9-5.9)	10	3,302	3.0 (1.5-5.6)
30-39	90	23,283	3.9 (3.1-4.8)	25	9,099	2.7 (1.8-4.1)
40-49	148	43,392	3.4 (2.9-4.0)	71	10,278	6.9 (5.4-8.7)
50-59	264	35,022	7.5 (6.7-8.5)	109	5,010	21.8 (17.9-26.2)
60-69	345	13,501	25.6 (22.9-28.4)	75	1,433	52.3 (41.2-65.6)
70+	205	2,391	85.7 (74.4-98.3)	40	278	144.1 (102.9-196.2)

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

Appendix Table 3.6D: Incidence of non-AIDS-defining 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.

	Men			Women		
Age	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**
18-29	11	11,058	1.0 (0.5-1.8)	4	6,355	0.6 (0.2-1.6)
30-39	63	38,921	1.6 (1.2-2.1)	20	15,294	1.3 (0.8-2.0)
40-49	232	64,483	3.6 (3.1-4.1)	50	14,295	3.5 (2.6-4.6)
50-59	324	45,421	7.1 (6.4-8.0)	42	6,406	6.6 (4.7-8.9)
60-69	246	16,906	14.6 (12.8-16.5)	15	2,106	7.1 (4.0-11.7)
70+	86	3,434	25.0 (20.0-30.9)	8	599	13.4 (5.8-26.3)

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

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

	Men			Women		
Age	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**
18-29	1	11,080	0.1 (0.0-0.5)	2	6,362	0.3 (0.0-1.1)
30-39	25	39,052	0.6 (0.4-0.9)	6	15,323	0.4 (0.1-0.9)
40-49	175	64,509	2.7 (2.3-3.1)	26	14,349	1.8 (1.2-2.7)
50-59	225	45,234	5.0 (4.3-5.7)	15	6,495	2.3 (1.3-3.8)
60-69	154	16,784	9.2 (7.8-10.7)	9	2,127	4.2 (1.9-8.0)
70+	33	3,614	9.1 (6.3-12.8)	1	613	1.6 (0.0-9.1)

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

Appendix Table 3.6F: Incidence of stroke from 2000 onwards, according to gender and age.

	Men			Women		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	5	11,064	0.5 (0.1-1.1)	2	6,350	0.3 (0.0-1.1)
30-39	29	39,039	0.7 (0.5-1.1)	16	15,279	1.0 (0.6-1.7)
40-49	86	64,818	1.3 (1.1-1.6)	25	14,319	1.7 (1.1-2.6)
50-59	130	45,761	2.8 (2.4-3.4)	9	6,494	1.4 (0.6-2.6)
60-69	97	17,205	5.6 (4.6-6.9)	10	2,121	4.7 (2.3-8.7)
70+	40	3,665	10.9 (7.8-14.9)	6	606	9.9 (3.6-21.5)

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

Appendix Table 3.6G: Incidence of anal cancer in men from 2000 onwards, according to age.

	Men		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	0	11,080	0.0 (.-0.3)
30-39	10	39,099	0.3 (0.1-0.5)
40-49	53	64,919	0.8 (0.6-1.1)
50-59	69	46,014	1.5 (1.2-1.9)
60-69	21	17,557	1.2 (0.7-1.8)
70+	3	3,869	0.8 (0.2-2.3)

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

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

	Men			Women		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	22	11,031	2.0 (1.2-3.0)	33	6,249	5.3 (3.6-7.4)
30-39	194	38,552	5.0 (4.3-5.8)	109	14,911	7.3 (6.0-8.8)
40-49	738	62,362	11.8 (11.0-12.7)	182	13,496	13.5 (11.6-15.6)
50-59	931	41,820	22.3 (20.9-23.7)	106	5,853	18.1 (14.8-21.9)
60-69	563	14,268	39.5 (36.3-42.9)	49	1,905	25.7 (19.0-34.0)
70+	157	2,639	59.5 (50.6-69.6)	15	476	31.5 (17.7-52.0)

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

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

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value
Male gender	1.28 (1.15-1.43)	<.001	.	1.59 (1.29-1.97)	<.001	.
Region of birth						
Netherlands	1 (reference)	.	<.001	1 (reference)	.	0.009
Other	0.88 (0.82-0.95)	<.001	.	0.84 (0.73-0.96)	0.010	.
HIV-1 transmission route						
MSM	1 (reference)	.	<.001	1 (reference)	.	0.005
Heterosexual	0.94 (0.87-1.03)	0.175	.	1.24 (1.06-1.45)	0.009	.
IDU	1.03 (0.85-1.25)	0.735	.	1.33 (0.95-1.86)	0.094	.
Blood contact	0.75 (0.58-0.98)	0.035	.	1.39 (0.92-2.09)	0.113	.
Age*						
18-29	0.76 (0.58-0.99)	0.040	<.001	0.46 (0.24-0.89)	0.022	<.001
30-39	1 (reference)	.	.	1 (reference)	.	.
40-49	2.10 (1.85-2.38)	<.001	.	2.64 (2.06-3.38)	<.001	.
50-59	4.92 (4.34-5.57)	<.001	.	5.32 (4.15-6.83)	<.001	.
60-69	9.27 (8.12-10.58)	<.001	.	9.75 (7.49-12.70)	<.001	.
70+	18.88 (16.21-22.00)	<.001	.	14.30 (10.31-19.82)	<.001	.
CD4 cell count**						
<50	3.71 (2.99-4.60)	<.001	<.001	3.39 (2.22-5.17)	<.001	<.001
50-199	1.60 (1.40-1.83)	<.001	.	1.65 (1.27-2.14)	<.001	.
200-349	1.13 (1.02-1.24)	0.014	.	1.26 (1.04-1.53)	0.016	.
350-499	0.98 (0.91-1.07)	0.715	.	1.08 (0.91-1.27)	0.399	.
500-749	1 (reference)	.	.	1 (reference)	.	.
≥750	0.98 (0.91-1.06)	0.621	.	1.25 (1.06-1.46)	0.007	.
Per year longer with CD4 <200 cells/mm³	0.99 (0.98-1.01)	0.564	.	1.00 (0.97-1.04)	0.847	.
Prior AIDS event	1.21 (1.14-1.29)	<.001	.	1.15 (1.01-1.31)	0.031	.
Per year longer on cART while HIV RNA>1000 copies/ml	1.01 (0.99-1.03)	0.254	.	1.02 (0.98-1.06)	0.287	.
Treatment status						
Not (yet) started cART	1.13 (1.00-1.27)	0.049	<.001	1.07 (0.85-1.35)	0.580	0.021
Treatment-experienced at start cART	1.49 (1.38-1.61)	<.001	.	1.25 (1.07-1.47)	0.006	.
Treatment-naive at start	1 (reference)	.	.	1 (reference)	.	.
Per year longer on cART	1.02 (1.01-1.02)	<.001	.	1.00 (0.98-1.01)	0.922	.
Early cART within 12 months after last HIV-negative	0.87 (0.71-1.07)	0.177	.	1.09 (0.74-1.60)	0.661	.

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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
	1.15 (0.93–1.42)	0.201	.	1.25 (1.05–1.48)	0.014	.	0.50 (0.43–0.60)	<.001	.
	1 (reference)	.	0.008	1 (reference)	.	<.001	1 (reference)	.	<.001
	0.82 (0.71–0.95)	0.008	.	1.41 (1.24–1.61)	<.001	.	1.55 (1.38–1.75)	<.001	.
	1 (reference)	.	0.008	1 (reference)	.	<.001	1 (reference)	.	0.054
	1.05 (0.88–1.25)	0.580	.	1.53 (1.30–1.79)	<.001	.	1.03 (0.88–1.20)	0.754	.
	1.55 (1.11–2.15)	0.009	.	1.49 (1.04–2.14)	0.030	.	1.67 (1.23–2.25)	<.001	.
	1.71 (1.15–2.54)	0.008	.	1.48 (0.98–2.23)	0.064	.	1.06 (0.70–1.59)	0.786	.
	0.74 (0.44–1.25)	0.258	<.001	0.60 (0.40–0.88)	0.009	<.001	0.93 (0.63–1.37)	0.718	<.001
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	2.37 (1.84–3.06)	<.001	.	1.51 (1.25–1.83)	<.001	.	1.47 (1.16–1.87)	0.001	.
	4.67 (3.62–6.02)	<.001	.	2.34 (1.91–2.86)	<.001	.	3.69 (2.94–4.63)	<.001	.
	9.12 (6.96–11.95)	<.001	.	4.16 (3.32–5.21)	<.001	.	13.17 (10.46–16.57)	<.001	.
	15.88 (11.47–21.99)	<.001	.	4.43 (3.11–6.32)	<.001	.	41.95 (32.52–54.13)	<.001	.
	3.18 (1.98–5.13)	<.001	<.001	8.46 (6.19–11.56)	<.001	<.001	2.15 (1.33–3.48)	0.002	<.001
	2.15 (1.65–2.81)	<.001	.	2.21 (1.71–2.85)	<.001	.	1.62 (1.27–2.08)	<.001	.
	1.50 (1.24–1.81)	<.001	.	1.12 (0.91–1.37)	0.286	.	1.22 (1.02–1.45)	0.031	.
	1.10 (0.93–1.31)	0.256	.	0.99 (0.83–1.18)	0.882	.	1.04 (0.90–1.22)	0.577	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	0.87 (0.73–1.04)	0.119	.	1.14 (0.96–1.34)	0.129	.	0.98 (0.85–1.13)	0.776	.
	0.96 (0.92–0.99)	0.026	.	0.96 (0.92–1.00)	0.054	.	1.00 (0.97–1.04)	0.836	.
	1.27 (1.11–1.46)	<.001	.	1.30 (1.14–1.48)	<.001	.	1.10 (0.98–1.24)	0.113	.
	0.99 (0.95–1.03)	0.666	.	1.02 (0.98–1.05)	0.343	.	0.98 (0.95–1.01)	0.240	.
	1.44 (1.16–1.80)	0.001	<.001	1.80 (1.47–2.21)	<.001	<.001	0.70 (0.53–0.92)	0.012	0.002
	1.22 (1.03–1.45)	0.023	.	1.39 (1.18–1.65)	<.001	.	1.23 (1.05–1.45)	0.012	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	1.01 (0.99–1.02)	0.425	.	1.02 (1.00–1.04)	0.017	.	0.99 (0.98–1.00)	0.138	.
	0.58 (0.34–1.00)	0.048	.	0.88 (0.55–1.41)	0.596	.	0.99 (0.72–1.36)	0.945	.

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value
Body mass index*						
<18	1.39 (1.18-1.64)	<.001	<.001	1.15 (0.82-1.62)	0.408	0.003
18-25	1 (reference)	.	.	1 (reference)	.	.
25-30	1.11 (1.04-1.18)	0.003	.	0.99 (0.86-1.13)	0.839	.
30+	1.42 (1.28-1.57)	<.001	.	1.09 (0.87-1.36)	0.466	.
Hepatitis B virus positive	0.92 (0.82-1.04)	0.199	.	0.99 (0.79-1.25)	0.930	.
Hepatitis C virus positive	0.91 (0.81-1.03)	0.122	.	0.96 (0.76-1.20)	0.706	.
Hypertension	1.25 (1.17-1.33)	<.001	.	1.27 (1.12-1.44)	<.001	.
Smoking status						
Current smoker	1.22 (1.13-1.31)	<.001	<.001	1.87 (1.60-2.20)	<.001	<.001
Never smoker	1 (reference)	.	.	1 (reference)	.	.
Past smoker	1.43 (1.32-1.56)	<.001	.	1.54 (1.28-1.85)	<.001	.
Calendar year period						
2000-2005	0.96 (0.87-1.06)	0.402	0.309	1.53 (1.28-1.83)	<.001	<.001
2006-2010	1.03 (0.96-1.11)	0.398	.	1.29 (1.12-1.49)	<.001	.
2011-2017	1 (reference)	.	.	1 (reference)	.	.
Recent use of ABC***		.	.	1.54 (1.35-1.76)	<.001	.
Per year longer on LPV/r		.	.	1.01 (0.99-1.03)	0.236	.
Per year longer on IDV		.	.	1.00 (0.99-1.01)	0.658	.
Per year longer on ZDV		.	.		.	.
Per year longer on d4T		.	.		.	.
Per year longer on ddI		.	.		.	.
Per year longer on TDF		.	.		.	.
Prior cardiovascular event		.	.		.	.
Prior diabetes		.	.		.	.
Current use of cobicistat		.	.		.	.
Current use of dolutegravir		.	.		.	.

**Time-updated.*

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

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

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

	Non-AIDS-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
	1.88 (1.43-2.49)	<.001	<.001	1.40 (0.95-2.06)	0.086	<.001	4.66 (3.84-5.66)	<.001	<.001
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	0.80 (0.69-0.93)	0.003	.	2.04 (1.76-2.35)	<.001	.	0.42 (0.36-0.49)	<.001	.
	0.80 (0.61-1.03)	0.084	.	4.08 (3.44-4.85)	<.001	.	0.21 (0.15-0.29)	<.001	.
	1.60 (1.31-1.96)	<.001	.	1.11 (0.89-1.40)	0.357	.	1.31 (1.06-1.61)	0.012	.
	1.03 (0.82-1.30)	0.777	.	1.15 (0.91-1.45)	0.245	.	1.21 (1.00-1.47)	0.054	.
	1.03 (0.90-1.18)	0.674	.	1.19 (1.04-1.36)	0.011	.	0.94 (0.83-1.06)	0.305	.
	1.56 (1.32-1.84)	<.001	<.001	0.86 (0.74-1.01)	0.062	0.083	1.20 (1.04-1.38)	0.013	0.006
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	1.38 (1.14-1.67)	0.001	.	1.07 (0.90-1.27)	0.469	.	1.18 (1.01-1.38)	0.037	.
	0.89 (0.73-1.09)	0.251	0.031	1.27 (1.05-1.53)	0.013	0.016		.	.
	1.13 (0.98-1.32)	0.097	.	1.20 (1.04-1.40)	0.015	.	0.96 (0.83-1.11)	0.557	0.555
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.	1.01 (1.00-1.01)	0.020	.		.	.
		.	.	1.01 (0.99-1.02)	0.338	.		.	.
		.	.	1.00 (0.99-1.01)	0.374	.		.	.
		.	.		.	.	1.00 (0.99-1.01)	0.995	.
		.	.		.	.	1.68 (1.40-2.02)	<.001	.
		.	.		.	.	1.35 (1.10-1.66)	0.004	.
		.	.		.	.	1.71 (1.40-2.09)	<.001	.
		.	.		.	.	2.76 (2.39-3.20)	<.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 2017.*

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis, oropharyngeal	657	22.3%	57	26.9%
	Candidiasis, vulvovaginal	54	1.8%	1	0.5%
	Cervical dysplasia or carcinoma in situ	532	18.1%	9	4.2%
	Diarrhoea of unknown origin >1 month	66	2.2%	1	0.5%
	Fever of unknown origin >1 month	6	0.2%	0	0.0%
	Herpes simplex virus, mucocutaneous	19	0.6%	1	0.5%
	Herpes zoster, multidermatomal or 2+ episodes	219	7.4%	9	4.2%
	Myelopathy, HIV-related	11	0.4%	0	0.0%
	Neuropathy, peripheral, HIV-related	74	2.5%	1	0.5%
	Nocardiosis	1	0.0%	1	0.5%
	Oral hairy leukoplakia	50	1.7%	1	0.5%
	Pelvic inflammatory disease	4	0.1%	0	0.0%
	Thrombocytopenia, HIV-related	100	3.4%	5	2.4%
	Weight loss (> 10%) of unknown origin	36	1.2%	2	0.9%
Subtotal		**1,830**	**62.1%**	**88**	**41.5%**
CDC-C events	AIDS dementia complex / HIV encephalopathy	46	1.6%	5	2.4%
	Candidiasis, esophageal	201	6.8%	21	9.9%
	Candidiasis trachea, bronchi, lungs	9	0.3%	2	0.9%
	Cervical cancer, invasive	7	0.2%	1	0.5%
	Cytomegalovirus disease (not lymph node, liver or spleen)	19	0.6%	5	2.4%
	Cytomegalovirus retinitis	14	0.5%	2	0.9%
	Coccidioidomycosis, disseminated/ extrapulmonary	1	0.0%	0	0.0%
	Cryptococcosis extrapulmonary	16	0.5%	6	2.8%
	Cryptosporidiosis, chronic intestinal	9	0.3%	3	1.4%
	Herpes simplex virus: chronic bronchitis, pneumonitis, esophagitis	62	2.1%	6	2.8%
	Histoplasmosis, disseminated or extrapulmonary	4	0.1%	3	1.4%
	Isosporiasis, chronic intestinal (>1 month)	1	0.0%	0	0.0%
	Kaposi sarcoma	87	3.0%	5	2.4%
	Leishmaniasis, visceral	5	0.2%	1	0.5%
	Lymphoma, non-Hodgkin's lymphoma	113	3.8%	7	3.3%

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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%
166	29.9%	135	20.5%	101	17.4%	125	20.7%	73	21.6%
5	0.9%	10	1.5%	17	2.9%	15	2.5%	6	1.8%
54	9.7%	122	18.6%	123	21.2%	138	22.8%	86	25.4%
6	1.1%	16	2.4%	11	1.9%	23	3.8%	9	2.7%
1	0.2%	2	0.3%	0	0.0%	1	0.2%	2	0.6%
4	0.7%	1	0.2%	5	0.9%	4	0.7%	4	1.2%
26	4.7%	52	7.9%	46	7.9%	54	8.9%	32	9.5%
4	0.7%	2	0.3%	1	0.2%	1	0.2%	3	0.9%
8	1.4%	17	2.6%	24	4.1%	13	2.2%	11	3.3%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
13	2.3%	10	1.5%	9	1.6%	10	1.7%	7	2.1%
0	0.0%	1	0.2%	1	0.2%	1	0.2%	1	0.3%
19	3.4%	24	3.7%	18	3.1%	24	4.0%	10	3.0%
5	0.9%	8	1.2%	7	1.2%	8	1.3%	6	1.8%
312	**56.1%**	**400**	**60.9%**	**363**	**62.6%**	**417**	**69.0%**	**250**	**74.0%**
8	1.4%	10	1.5%	9	1.6%	7	1.2%	7	2.1%
50	9.0%	49	7.5%	33	5.7%	29	4.8%	19	5.6%
2	0.4%	3	0.5%	0	0.0%	1	0.2%	1	0.3%
1	0.2%	2	0.3%	1	0.2%	2	0.3%	0	0.0%
2	0.4%	3	0.5%	5	0.9%	1	0.2%	3	0.9%
5	0.9%	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%
6	1.1%	3	0.5%	0	0.0%	1	0.2%	0	0.0%
0	0.0%	1	0.2%	3	0.5%	1	0.2%	1	0.3%
6	1.1%	13	2.0%	17	2.9%	16	2.6%	4	1.2%
0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
0	0.0%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
9	1.6%	23	3.5%	20	3.4%	21	3.5%	9	2.7%
3	0.5%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
30	5.4%	25	3.8%	25	4.3%	21	3.5%	5	1.5%

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
	Lymphoma, primary, of brain	5	0.2%	0	0.0%
	Microsporidiosis	3	0.1%	1	0.5%
	MAI / M. kansasii, disseminated/extrapulmonary	21	0.7%	4	1.9%
	Mycobacterium, other/unidentified (disseminated/extrapulmonary)	6	0.2%	1	0.5%
	Pneumocystis jirovecii pneumonia	58	2.0%	15	7.1%
	Pneumonia, recurrent (in a 1-year period)	278	9.4%	15	7.1%
	Progressive multifocal leucoencephalopathy	17	0.6%	4	1.9%
	Toxoplasmosis of the brain	16	0.5%	5	2.4%
	Tuberculosis, extrapulmonary	36	1.2%	3	1.4%
	Tuberculosis, pulmonary	62	2.1%	4	1.9%
	Wasting syndrome due to HIV	15	0.5%	5	2.4%
	Other CDC C-event, specify	6	0.2%	0	0.0%
Subtotal		**1,117**	**37.9%**	**124**	**58.5%**
Total		**2,947**	**100.0%**	**212**	**100.0%**

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

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%	1	0.2%	0	0.0%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
8	1.4%	4	0.6%	2	0.3%	1	0.2%	2	0.6%
1	0.2%	3	0.5%	0	0.0%	1	0.2%	0	0.0%
20	3.6%	9	1.4%	8	1.4%	4	0.7%	2	0.6%
50	9.0%	70	10.7%	65	11.2%	55	9.1%	23	6.8%
6	1.1%	3	0.5%	2	0.3%	2	0.3%	0	0.0%
6	1.1%	3	0.5%	1	0.2%	1	0.2%	0	0.0%
7	1.3%	6	0.9%	5	0.9%	10	1.7%	5	1.5%
14	2.5%	19	2.9%	12	2.1%	8	1.3%	5	1.5%
6	1.1%	1	0.2%	2	0.3%	1	0.2%	0	0.0%
2	0.4%	1	0.2%	2	0.3%	0	0.0%	1	0.3%
244	**43.9%**	**257**	**39.1%**	**217**	**37.4%**	**187**	**31.0%**	**88**	**26.0%**
556	**100.0%**	**657**	**100.0%**	**580**	**100.0%**	**604**	**100.0%**	**338**	**100.0%**

4. Viral hepatitis

Colette Smit, Joop Arends, Peter Reiss and Clemens Richter

Box 4.1: Definitions of hepatitis B and C co-infection

Chronic hepatitis C virus (HCV) infection
Individuals who remain HCV RNA-positive for longer than 6 months after their first known positive HCV RNA test result.

Acute HCV infection[1,2]

1. *Case definition of acute hepatitis C virus according to preferred criteria*
   Positive anti-HCV IgG and a documented negative anti-HCV IgG within the previous 12 months.
   or:
   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
2. *Case definition of acute hepatitis C virus according to alternative criteria*
   Detectable HCV-RNA in association with a rise in alanine aminotransferase (ALT) (>200 U/l) with a documented normal ALT within the past 12 months and no changes in antiretroviral regimens within the last 6 months.

Spontaneously cleared HCV infection

1. Individuals with a documented positive test result for HCV antibody with a subsequent negative HCV RNA test result.
2. Individuals who fulfilled the above criteria for acute HCV and who subsequently had a negative HCV RNA test without having received HCV treatment.
3. Individuals 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.

SVR24
Sustained virological response, defined as a negative HCV RNA test result 24 weeks after treatment discontinuation in individuals treated for prior documented acute or chronic HCV infection.

SVR12
Sustained virological response, defined as a negative HCV RNA test result 12 weeks after treatment discontinuation in individuals treated for prior documented acute or chronic HCV infection.

Hepatitis C re-infection
Detectable HCV RNA more than 6 months after an SVR12 or SVR24, or spontaneous HCV clearance or documentation of a genotype switch.

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.

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.

Definitive if:
- combined with a pathology or transient elastography report documenting severe liver fibrosis or cirrhosis (metavir score F3-F4 or transient elastography stiffness ≥8kPa).

Background

Infection with hepatitis C virus (HCV) and hepatitis B virus (HBV) is generally uncommon in the Netherlands. It is estimated that 0.1 to 0.4 percent of the general Dutch population has evidence of ever having been exposed to HCV and that the same percentage has ever been exposed to HBV[3,4]. In contrast, HCV and HBV co-infections are far more prevalent in HIV-positive individuals due to shared routes of transmission[5].

Individuals with chronic HCV and HBV infection are at risk of developing liver fibrosis, which, in time, may lead to cirrhosis and can ultimately result in end-stage liver disease and hepatocellular carcinoma (HCC)[6,7]. 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[8,9]. Although liver fibrosis progression was faster in HIV co-infected 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[10].

In the era when treatment for HIV infection was either unavailable or insufficiently effective to achieve sustained suppression of viral replication, most individuals 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[11].

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.

Box 4.2: Viral hepatitis data in the ATHENA cohort in the Netherlands

Data used in this chapter
In 2018, Stichting HIV Monitoring launched a new data entry system, DataCapTree, which went live in February 2018 with an initial set of approved data collection protocols. However, the protocol for the collection of viral hepatitis data was delayed until the second half of 2018. For this reason, data used in this chapter are based on the database lock on 31 December 2017, rather than May 2018 as in from previous years.

Population described in this chapter
All individuals ever registered up to 31 December 2017.

HCV

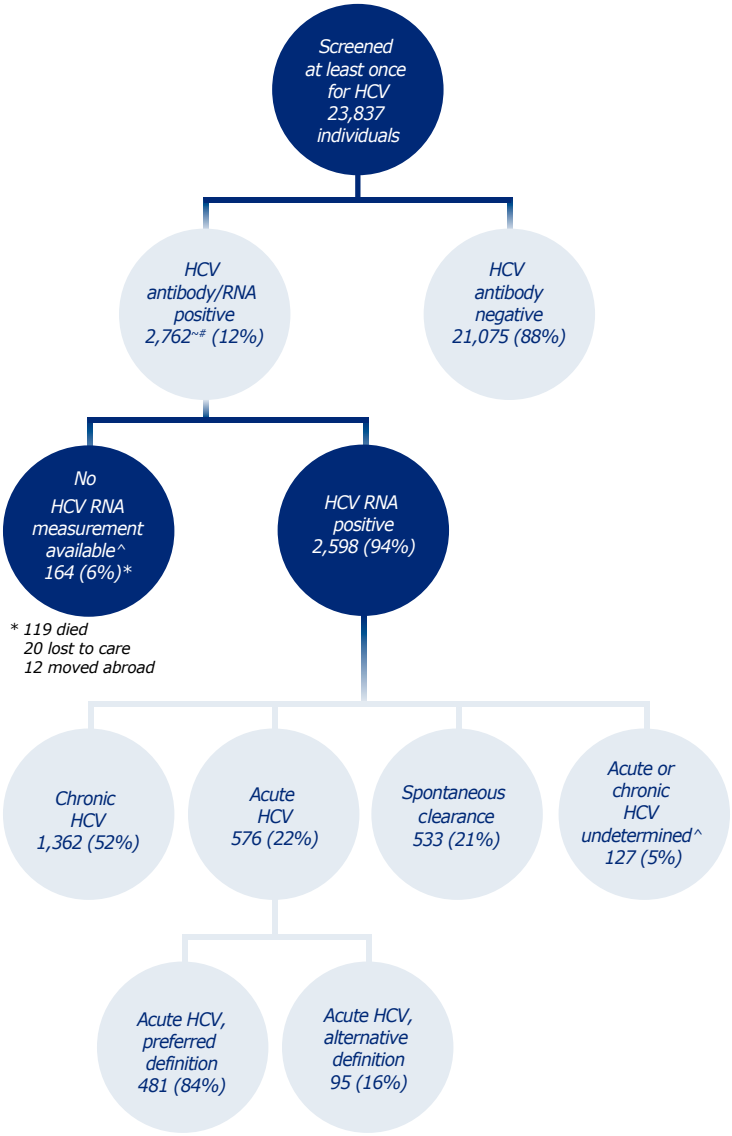
Demographic and clinical characteristics

In total, 2,762 (12%) of the 23,837 HIV-1-positive adults (≥18 years of age at time of HIV-1 diagnosis) in care who were ever screened for HCV co-infection had a positive result with an HCV antibody test or HCV RNA test. 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*). HCV RNA data were not documented in 164 of the 2,762 individuals (6%). Of these 164 individuals, 119 had died, 20 were lost to care, and 12 had moved abroad; for the remaining 13 individuals with a positive HCV antibody test result, the reason for an undocumented HCV RNA was unknown. Of the remaining 2,598 individuals with positive HCV RNA test results, 1,362 (52%) were classified as having a chronic HCV infection (HCV RNA test result documented to have remained positive for more than six months after the first positive result), and 576 (22%) were diagnosed with acute HCV infection (481 individuals were classified as having been diagnosed with an acute HCV infection based on the

preferred NEAT definition: documented anti-HCV IgG seroconversion or HCV RNA conversion within 12 months, and 95 individuals were classified based on the alternative definition: detectable HCV RNA with an acute rise in alanine amino-transferase [ALT]). Another 533 (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 2,598 with available HCV RNA data had one positive HCV RNA test result, but no registered follow-up results, rendering it impossible to determine whether their HCV infection was acute or chronic at the time of diagnosis. This group of individuals was therefore excluded from further analysis.

The analyses described in the remainder of this section on HCV are therefore limited to those individuals who could be definitively classified as having either chronic (n=1,362) or acute (n=576) HCV infection at the time of the primary HCV diagnosis. Most of these people with chronic or acute HCV infection were male (83% and 99%, respectively) and the majority originated from the Netherlands (chronic: 814/1,362 [60%]; acute: 451/576 [78%]) (*Table 4.1*). Sixty-two percent of the individuals ever registered and who had acquired HIV through injecting drug use (IDU) had a chronic HCV infection (450 of the total 728 people who use/used injecting drugs [PWUID]). In the men who have sex with men (MSM) HIV transmission group, 4% had a chronic HCV infection (617 of the total of 14,541 MSM) and 4% had a documented acute HCV infection (543 of the total of 14,541 MSM). Finally, compared with individuals with an acute primary HCV infection, those with spontaneous clearance of HCV were less likely to be male, originate from the Netherlands or belong to the MSM group (*Table 4.1*).

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



The HCV genotype was determined and documented in the clinical records of 1,232 of the 1,362 individuals (90%) with a chronic HCV infection. For 25 of these 1,232 genotype determinations, the genotype could not be successfully identified. Of those individuals for whom genotype determination was successful, the majority (61%) were infected with HCV genotype 1 (n=755); 61% were infected with genotype 1a (n=462) and 13% with genotype 1b (n=96). Five percent were infected with HCV genotype 2 (n=61), 16% were infected with genotype 3 (n=195), and 16% with genotype 4 (n=195). One person was infected with genotype 6.

HCV genotype was also determined for 537 of the 576 individuals (93%) with an acute HCV infection, with unsuccessful genotype identification in 22 out of these 537 individuals. Individuals with an acute HCV infection were most likely to be infected with either genotype 1 (67%) (n=359) or genotype 4 (21%, n=114). Of the 359 infected with genotype 1, 295 (82%) were infected with genotype 1a and 15 (4%) with genotype 1b. For the remaining 49 individuals with genotype 1, no differentiation between genotype 1a or 1b was available.

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	23,837	1,362	576	533
Male gender, n (%)	19,554 (82)	1,127 (83)	568 (99)	417 (78)
Region, n (%)				
Netherlands	13,590 (57)	814 (60)	451 (78)	274 (51)
Europe	1,578 (7)	208 (15)	46 (8)	75 (14)
Sub-Saharan Africa	3,279 (14)	45 (3)	8 (1)	57 (11)
Caribbean/South America	2,797 (12)	87 (6)	34 (6)	65 (12)
South-east Asia	828 (3)	44 (3)	12 (2)	16 (3)
Other	1,765 (7)	164 (12)	25 (4)	46 (9)
HIV transmission route, n (%)				
Men who have sex with men	14,541 (61)	617 (45)	543 (94)	255 (48)
Heterosexual	7,044 (30)	155 (11)	18 (3)	99 (19)
People who use/used injecting drugs	728 (3)	432 (32)	6 (1)	111 (21)
Other	1,524 (6)	158 (12)	9 (2)	68 (13)
cART, n (%)	22,645 (95)	1,307 (96)	571 (99)	507 (95)
HCV genotype (GT), n (%*)				
Total determined		1,232	537	
GT 1		755 (61)	359 (67)	
1a		*462*	*295*	
1b		*96*	*15*	
1c, 1a/b or not further specified		*197*	*49*	
GT 2		61 (5)	7 (5)	
GT 3		195 (16)	14 (3)	
GT 4		195 (16)	114 (21)	
Other		1 (0.1)	1 (0.2)	
Indeterminate		25 (2)	22 (4)	
Deaths, n (%)	2,489 (10)	291 (21)	21 (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.*

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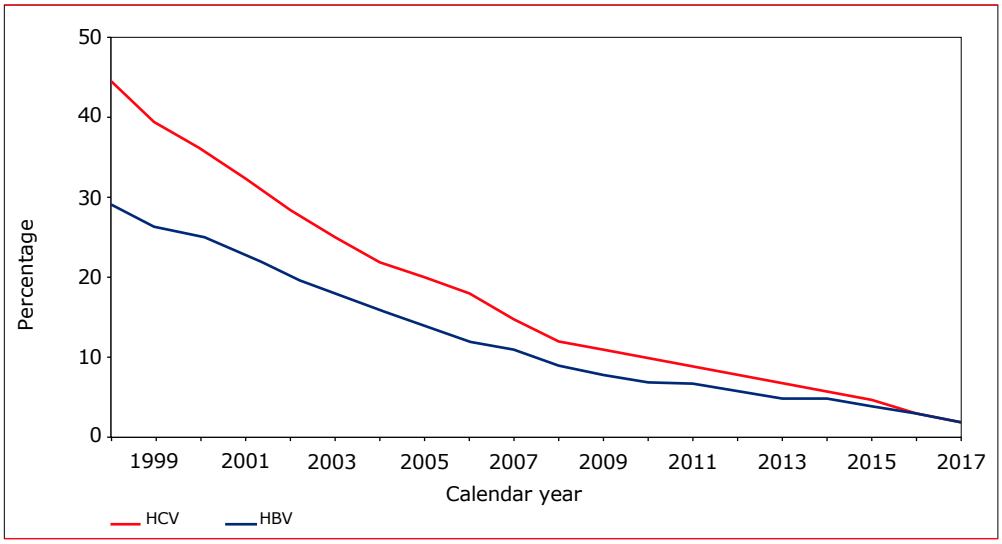
Changes over time

Testing for HCV over time

Screening for HCV infection among HIV-positive individuals ever registered has increased over calendar time. In 1998, 44% 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 and, in 2017, only 2% of the individuals in care had not been screened for HCV co-infection (*Figure 4.2*). Unknown HCV status was relatively more common among individuals with heterosexually acquired HIV (4.1%) or with an unknown route of HIV acquisition (4.5%) and relatively less common among MSM (1.8%). Additionally, the HCV co-infection status was known for all individuals with injecting drug use as the reported mode of HIV acquisition.

Figure 4.2: *Percentage of individuals in care with an unknown hepatitis B or hepatitis C status per calendar year of care.*



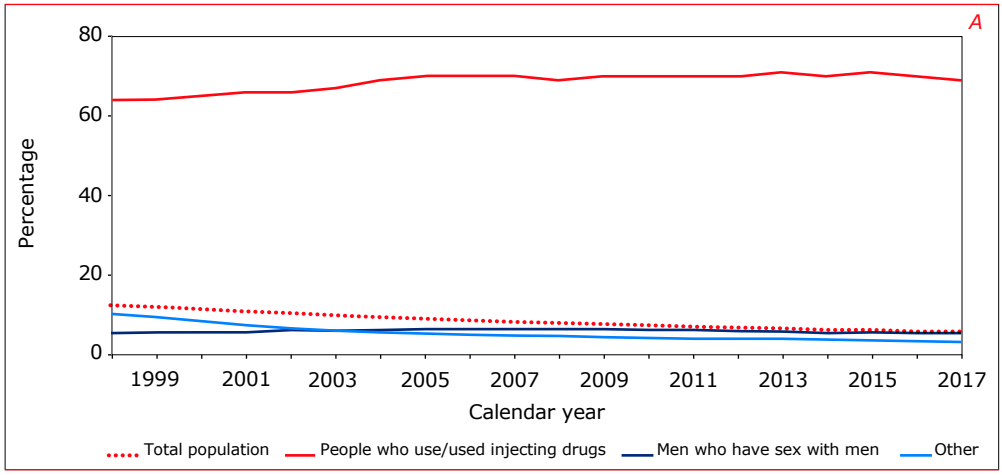
Legend: HBV=hepatitis B virus; HCV=hepatitis C virus.

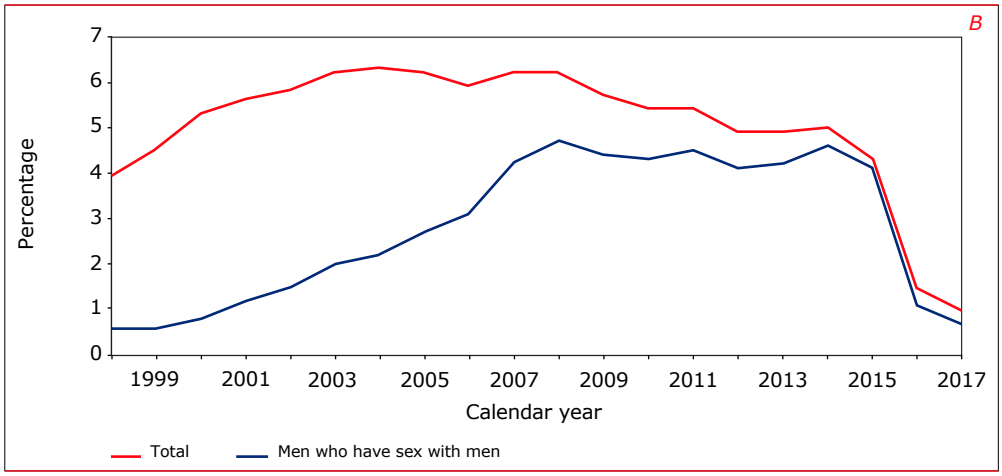
Prevalence of chronic HCV co-infection in individuals per calendar year

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 ever registered decreased

from 12.5% in 1998 to 5.8% in 2017, but was not equally distributed among HIV transmission categories. The highest prevalence was found among individuals who had acquired HIV by injecting drug use, and this number varied between 64% and 71% (*Figure 4.3A*).

Figure 4.3: *Prevalence of A) chronic hepatitis C virus (HCV) co-infection and B) detectable HCV RNA, per calendar year.*





Prevalence of individuals with detectable HCV RNA

Figure 4.3b shows the proportion of individuals with an active HCV infection over calendar time (defined as a time-updated positive HCV RNA test result), 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 a last available HCV RNA test result before the end of that calendar year. The overall proportion of individuals with detectable HCV RNA varied between 3.9% in 1998 and 6.2% in 2007, but dropped to 1.0% in 2017. In MSM, the highest proportion of HCV RNA positivity was observed in 2008, when 4.7% of the men had a positive HCV RNA test result; by 2017, the proportion of positive HCV RNA tests in this group had decreased sharply to 0.7%.

Incidence of acute HCV infection over time

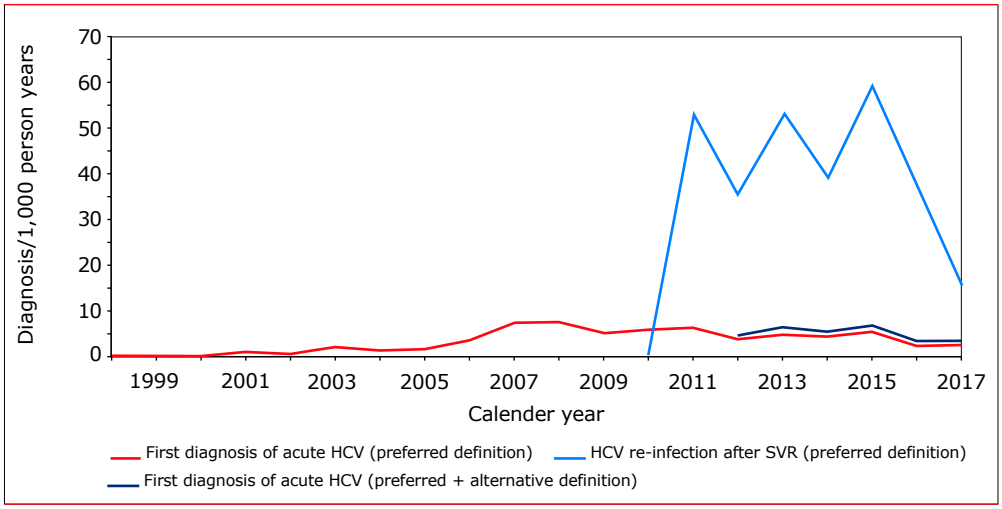
For the purpose of this analysis, the definition of acute HCV infection included cases of both primary acute HCV infection (first diagnosis of HCV) and HCV re-infection. The definition of acute HCV is consistent with the definition according to the NEAT preferred criteria[1]. In addition, in this year's report, we expanded this definition with alternative criteria[1,2]. In brief, this definition is based on detectable HCV-RNA in association with an acute rise in ALT greater than five times the upper limit of normal (>200 U/l) and with a documented normal ALT within the past 12 months, together with no change in antiretroviral regimens in the last 6 months. Since SHM has routinely collected ALT levels since 2012, the incidence of acute HCV according to the alternative criteria is reported from 2012 onwards.

Appendix *Table 4.1* presents the number of acute HCV infections and re-infections per calendar year. There were important differences in the incidence of the first diagnosis of acute HCV infection in terms of HIV transmission categories. The vast majority of acute HCV infections occurred in MSM (543/576 [94%]). In IDU or former IDU, in contrast to the high prevalence of HCV, the overall incidence was low (3.6/1,000 person years [PY], 95% confidence interval [CI] 1.60-7.20). This is probably due to the high background prevalence of HCV infection in former IDU, together with injecting drug use having become very uncommon in the Netherlands. Among individuals who acquired HIV heterosexually, the overall incidence of acute HCV was 0.3/1000 PY (0.2-0.5).

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 4.2 per 1,000 PY (95% CI 3.9-4.6). Based on the preferred NEAT acute HCV definition, this incidence increased from 0 diagnoses per 1,000 PY in 1998 to 5.2 diagnoses per 1,000 PY in 2015, with a peak in 2007 and 2008 of 7.3 and 7.4 acute HCV infections per 1,000 PY, respectively.

In 2017, the incidence of the first diagnosis of acute HCV infection was 2.4 per 1,000 PY. As expected, incidence rates among MSM were higher when the preferred and alternative acute HCV case definitions were combined, the incidence rate was 4.5 diagnoses per 1000 PY in 2012, 6.6 in 2015 and 3.3 in 2017.

Figure 4.4: *Incidence of acute hepatitis C infection among men who have sex with men, per calendar year. Note: Low numbers in 2017 may be due to a delay in data collection.*



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

Treatment for HCV infection

The primary aim of HCV treatment is to achieve a sustained virological response (SVR)[12]. Treatment for HCV infection has changed markedly in recent years. In the past, HCV treatment consisted of interferon alpha (IFN alpha), and subsequently pegylated interferon alpha (PEG-IFN alpha), in combination with ribavirin (RBV) for a period of 24 or 48 weeks, depending on HCV genotype. However, in April 2012, the first generation HCV NS3/4a protease inhibitors (PI) boceprevir and telaprevir, two direct-acting antivirals (DAAs) active against HCV genotype 1, became available in the Netherlands[13,14]. These agents were subsequently used as part of triple therapy that included one of these two agents, together with PEG-IFN alpha and RBV. Subsequently, the HCV NS5B polymerase inhibitor sofosbuvir was introduced in the Netherlands in 2014. Initially, due to government restrictions, sofosbuvir was only reimbursed for a defined group of HCV-infected individuals, including those with severe liver fibrosis and cirrhosis. Later, in November 2015, sofosbuvir was made available for all HCV-infected individuals regardless of their fibrosis

status, and shortly after additional novel DAAs became available such as new HCV NS3/4A protease inhibitors (simeprevir, paritaprevir and grazoprevir), NS5A inhibitors (daclatasvir, ledipasvir, ombitasvir, elbasvir and velpatasvir) and an NS5B polymerase inhibitor (dasabuvir). *Table 4.2* provides an overview of all DAA-containing HCV treatment combinations currently available in the Netherlands[15].

Table 4.2: *Overview of treatment regimens available as of 31 December 2017, 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
Sofosbuvir/velpatasvir	2016	All	12 weeks

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

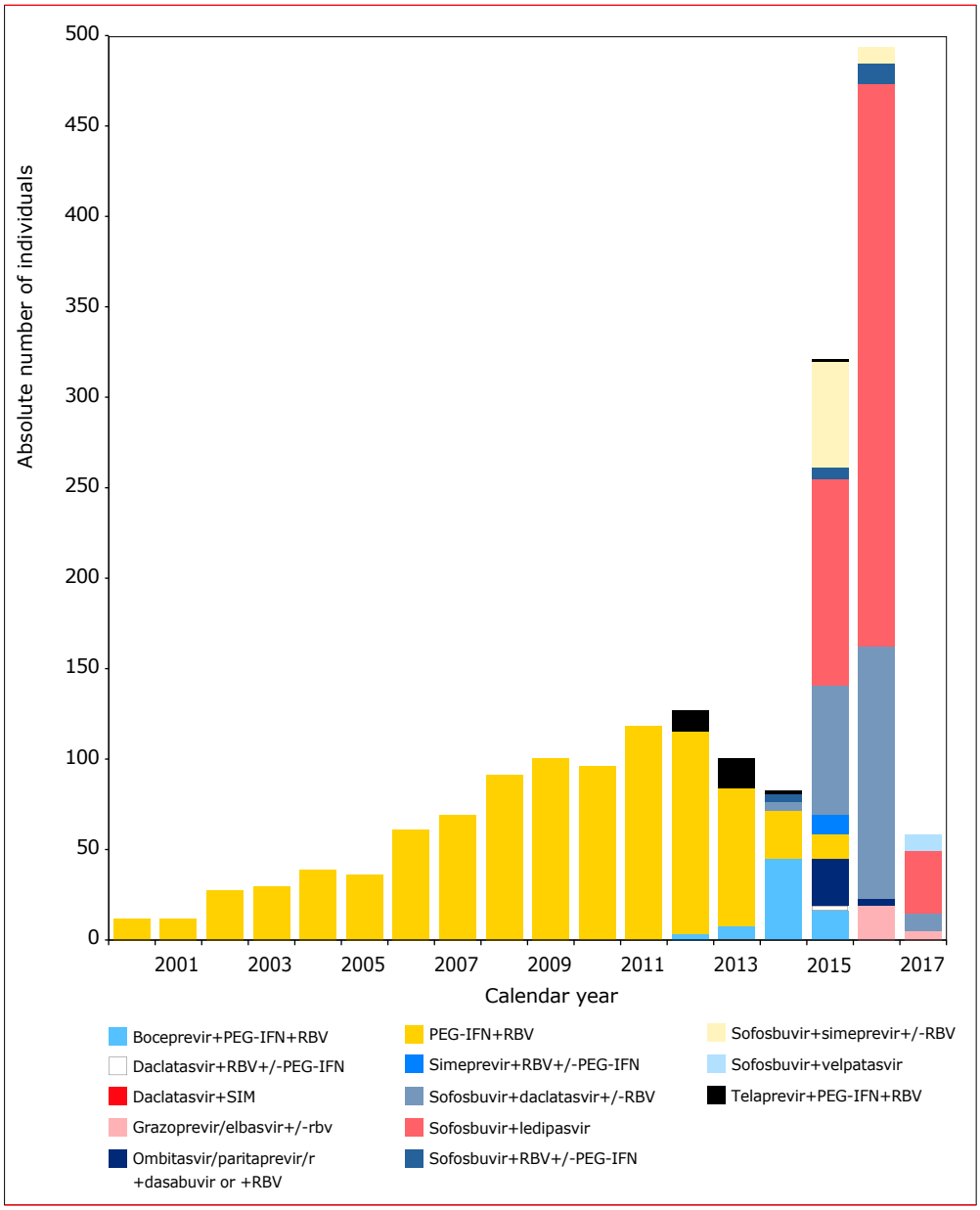
Legend: *DAA=direct-acting antiviral agent; HCV=hepatitis C; RBV=ribavirin; PEG-IFN=pegylated interferon; r=ritonavir.*

Figure 4.5 shows the absolute number of individuals who have started HCV treatment per calendar year. In total, 1,507 individuals have ever received HCV treatment; of those, 323 have received HCV treatment more than once, including people who were unsuccessfully treated and those who re-acquired HCV after previously successful treatment.

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

The outcome of people treated with the former PEG-IFN regimens was described in detail in SHM's 2016 monitoring report[16]. As these regimens have not been used since 2016 due to the availability of more novel DAAs, they will no longer be included in the current report.

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



Note: Low numbers in 2017 may be due to the use of data from the database lock of 31 December 2017, rather than that of May 2018 as in previous years, possibly resulting in a larger backlog in data collection.

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

Treatment with novel DAAs

In total, at the time of database lock on 31 December 2017, 838 individuals were known to have started a DAA regimen, 13 of whom had been treated twice with a DAA regimen. Reasons for receiving DAA treatment twice were: re-infection (n=3), no SVR achieved during the first episode of DAA treatment (n=8), and patient's decision to discontinue the first episode of DAA treatment (n=2). Of these 838 individuals, 9 had started their treatment in 2014, 292 in 2015, and the remaining 537 had started in either 2016 or 2017.

Table 4.3 provides an overview of the DAAs used. The most frequently-used DAA regimens were 1) sofosbuvir plus ledipasvir +/- RBV (n=461), which was prescribed to 311 individuals with HCV genotype 1 and 114 with genotype 4, and 2) sofosbuvir plus daclatasvir +/- RBV (n=228), which was prescribed to 128 individuals with genotype 1 and 51 with genotype 3. Finally, 16 individuals who had previously been treated with DAAs had died, with liver disease being the reported underlying cause of death in 4 individuals.

Table 4.3: Overview of responses (SVR12) to regimens containing novel direct-acting antivirals (DAAs) used by hepatitis C/HIV co-infected individuals in care in the Netherlands, based on data available as of 31 December 2017.

Regimen	n	HCV genotype (GT)	Severe chronic liver disease (see definition)	Treatment completed and SVR12* (n/total number individuals with available HCV RNA test results)	Treatment completed and SVR12* among individuals with severe chronic liver disease (n/total number individuals with available HCV RNA test results)
Sofosbuvir+ledipasvir+/-RBV	461		130	418/430 (97%)	119/123 (97%)
GT 1		311			
GT 2		5			
GT 3		6			
GT 4		114			
other		11			
unknown		14			
Sofosbuvir+daclatasvir+/-RBV	228		103	206/213 (97%)	91/93 (98%)
GT 1		128			
GT 2		9			
GT 3		51			
GT 4		23			
other		6			
unknown		11			
Sofosbuvir+simeprevir +/-RBV	66		53	64/64 (100%)	52/52 (100%)
GT 1		51			
GT 3		1			
GT 4		13			
other		1			
Sofosbuvir++RBV+/- PEG-IFN	19		8	17/17 (100%)	7/7 (100%)
GT 1		1			
GT 2		12			
GT 3		2			
GT 4		2			
other		1			
unknown		1			

Regimen	n	HCV genotype (GT)	Severe chronic liver disease (see definition)	Treatment completed and SVR12* (n/total number individuals with available HCV RNA test results)	Treatment completed and SVR12* among individuals with severe chronic liver disease (n/total number individuals with available HCV RNA test results)
Paritaprevir/r/ombitasvir +/- dasabuvir or RBV	32		9	30/32 (94%)	9/9 (100%)
GT 1		14			
GT 4		5			
other		3			
unknown		10			
Simeprevir+PEG-IFN+RBV	10		2	10/10 (100%)	2/2 (100%)
GT 1		4			
GT 4		5			
unknown		1			
Daclatasvir+RBV +/- PEG-IFN	4		2	3/3 (100%)	1/1 (100%)
GT 1		2			
GT 3		1			
unknown		1			
Simeprevir+daclatasvir	1		1	1/1 (100%)	1/1 (100%)
GT 1		1			
Grazoprevir/elbasvir	22		5	18/19 (95%)	5/5 (100%)
GT 1		13			
GT 4		8			
unknown		1			
Sofosbuvir/velpatasvir	8		3	1/1 (100%)	0
GT 1		2			
GT 2		1			
GT 3		2			
GT 4		2			
unknown		1			
Total	**851**		**316**	**768/790 (97%)**	**287/293 (98%)**

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

***Legend:** PEG-IFN=pegylated interferon; RBV=ribavirin; r=ritonavir; GT=HCV genotype; DAA=direct-acting antiviral agent; SVR12=sustained virological response result 12 weeks after treatment discontinuation.*

Outcome

HCV RNA data were collected up to 31 December 2017. At that point, 790 individuals had completed treatment with one of these regimens, and sufficient time had elapsed since discontinuation of treatment to enable calculation of the SVR12 (sustained virological response defined as a negative HCV RNA test result 12 weeks after treatment discontinuation) rate (*Table 4.3*). In total, 768 of these 790 individuals achieved an SVR12 (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-two individuals failed to achieve an SVR12, and failure occurred among all genotypes. This group was not specifically different from the group that did achieve an SVR and, due to the small group size, it is not possible to draw any further conclusions regarding failure to achieve an SVR.

Continuum of care for those with diagnosed HCV co-infection

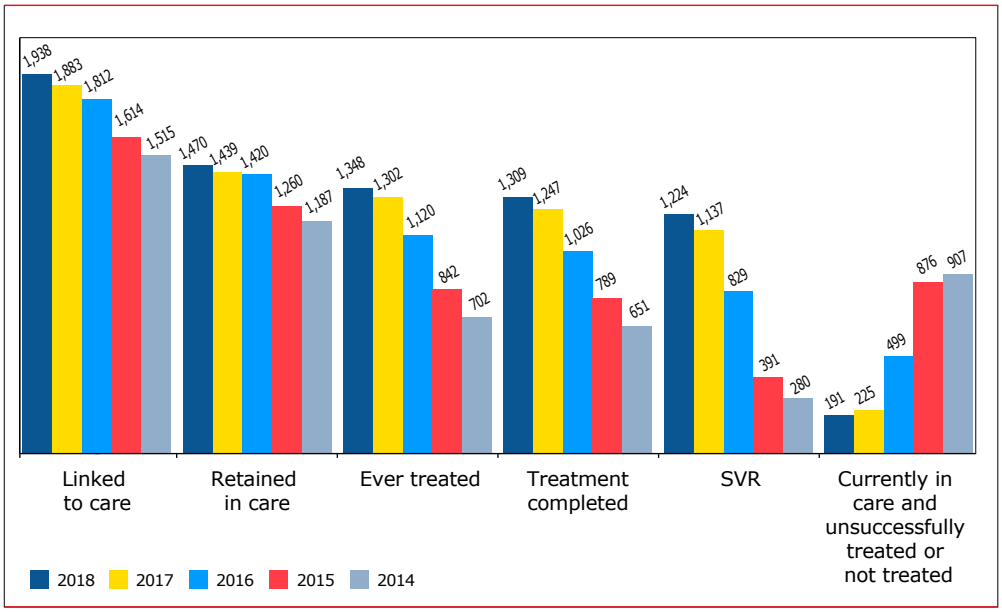
Figure 4.6 shows the continuum of care for individuals with an HCV co-infection, based on the number known to be in care as of 31 December 2017, with data from previous monitoring reports for 2014 (data cut-off 1 June 2014), 2015 (data cut-off 15 September 2015), 2016 (data cut-off 1 May 2016) and 2017 (data cut-off 1 May 2017) shown for comparison. Out of a total of 1,938 individuals linked to HIV care and diagnosed with HCV, 1,470 (76%) were retained in care, and of these, 1,348 (92%) had ever received treatment for HCV. Of the 1,348 individuals treated for HCV, 1,309 (97%) had completed HCV treatment and had data available with which HCV treatment response could be calculated (SVR12 for the DAAs and SVR24 for the older regimens). Overall, 1,224 of the 1,309 (94%) people who completed treatment had achieved an SVR, including those who had achieved an SVR on a pegylated interferon-containing regimen.

As a result, 246 of the 1,470 individuals (21%) who were alive and in care as of 31 December 2017 in one of the Dutch HIV treatment centres were still in need of treatment:

- 122 individuals had not been not treated for HCV; 90% of these were receiving cART for HIV, and 87% of these 122 individuals had an HIV RNA <100 copies/ml;
- 67 had been unsuccessfully treated for HCV;
- 57 were still being treated or had insufficient time after treatment discontinuation to allow SVR calculation.

All 57 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 57 individuals (n=55 individuals) will eventually be successfully treated. This resulted in an estimated number of 246-55=191 individuals who remain untreated or unsuccessfully treated.

Figure 4.6: Hepatitis C continuum of care.



Legend: SVR=sustained virological response.

Compared with the continuum of care presented in SHM's 2017 monitoring report, the continuum of care in this year's report shows that an additional 46 individuals have received HCV treatment, resulting in an increase in HCV/HIV co-infected individuals ever having been treated for HCV from 59% in 2014 to 92% in this year's report. Furthermore, since last year's report, an additional 87 individuals have documented evidence of cure. Finally, the total number of individuals who remain in need of HCV treatment has decreased from 225 in the 2017 monitoring report to 191 in the present report.

HCV re-infection

Re-infection with HCV following successful treatment has been reported mainly in HIV-positive MSM[17,18], with high rates of re-infection found among MSM in the Netherlands, Germany[19] and the United Kingdom[20].

To identify possible HCV re-infection among HCV co-infected individuals, we selected the 1,333 individuals who had initially achieved an SVR after ever having received any type of HCV treatment. For these 1,333 individuals, the incidence of HCV reinfection was reported between 2010 and 2017. Follow-up time was calculated from the date of SVR, or if the SVR had been achieved before 2010, from 1 January 2010 onward, until the earliest date of HCV re-infection, death, or last known contact.

Of these 1,333 individuals, 151 (11%) had documented detectable HCV RNA levels after having an earlier documented SVR (*Appendix Table 4.1*), indicative of HCV re-infection. For 61 of these 151 individuals (40%), an HCV genotype switch was reported, providing additional evidence of HCV re-infection.

The majority of individuals who became newly HCV RNA-positive after successful treatment for HCV (based on SVR) were MSM (134/151, 89%). A further six were PWUID (6/151, 4%). For the remaining 11 individuals, the HCV transmission route was unknown. However, documented HIV transmission routes were heterosexual contact (n=2), blood-blood contact (n=5) and unknown (n=4). Out of the 151 individuals with a re-infection, 108 were re-treated; of those, 83 were re-treated with a DAA-containing regimen. In total, 89 of these 108 individuals achieved an SVR. Among the 83 individuals who had been re-treated with a DAA-containing regimen, 79 achieved an SVR and for four individuals the SVR was not yet available.

The incidence of HCV reinfection was 31 re-infections per 1,000 PY (95%: 25-37) for the total population and 40 infections per 1,000 PY (95%: 33-48) for MSM. Because the majority of re-infections occurred among MSM, the incidence of HCV re-infection after achieving an SVR over time is shown only for MSM (*Figure 4.4*). This incidence increased from 0 to 59 infections per 1,000 PY between in 2010 and 2015 and then declined to 15 re-infections per 1,000 PY in 2017. All re-infections that were documented in 2016 and 2017 occurred in MSM.

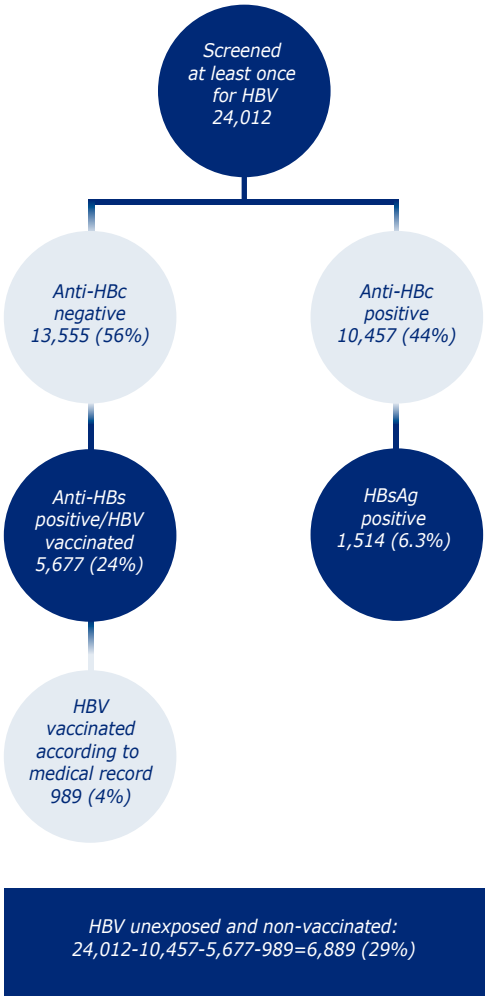
HBV

Forty-four percent of the 24,012[b] 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. The remaining 56%

b The total number of people screened for HBV differs from the total number screened for HCV, as not all those screened for HBV are also screened for HCV.

(n=13,555) tested negative for anti-HBc. Of these individuals, 24% (5,677) were anti-hepatitis B surface antigen-positive (anti-HBs+), indicating that they had been successfully vaccinated against HBV (*Figure 4.7*). In terms of route of HIV acquisition, this rate was 28% for MSM, 17% for heterosexuals and only 7% for PWUID. For 989 individuals (4%) who had not been tested for anti-HBs, the HIV-treating physician had noted HBV vaccination in the medical record; 751 of these individuals were MSM.

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.*

Overall, therefore, approximately 29% of the HIV-positive individuals ever registered remain at risk of HBV infection because they have not been exposed to HBV, have not been vaccinated, or have been unsuccessfully vaccinated (24,012 minus 10,457 exposed minus 5,677 with serological evidence of successful vaccination minus 989 former successful vaccination otherwise documented=6,889 [29% of 24,012]).

Furthermore, 21% of HIV-positive MSM remain at risk (100% minus 45.3% exposed minus 28.5% serological evidence of successful vaccination minus 5.2% former successful vaccination otherwise documented=21%). 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[21,22]. Data from SHM show that, of those people who remain at risk of acquiring HBV, 56% are currently being treated with a cART regimen that includes TDF or TAF; for MSM this prevalence is 63%.

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 1,514 of the 24,012 (6.3%) HIV-positive individuals ever screened for HBV. As for HCV co-infection, this rate is considerably higher than that of HBV infection in the general Dutch population. Individuals co-infected with HBV were predominantly male (1,306/1,514, 86%), in line with those co-infected with HCV (*Table 4.4*). However, compared to people 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. Finally, HBV co-infection was less common than HCV co-infection among PWUID.

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	24,012	1,514
Male gender	19,576 (82%)	1,306 (86%)
Region		
Netherlands	13,641 (57%)	748 (49%)
Europe	1,579 (7%)	9 (6%)
Sub-Saharan Africa	3,400 (14%)	343 (23%)
Caribbean/South America	2,807 (12%)	161 (11%)
South-east Asia	842 (4%)	66 (4%)
Other	1,743 (7%)	104 (7%)
HIV transmission group		
Men who have sex with men	14,475 (60%)	899 (59%)
Heterosexual	7,253 (30%)	436 (29%)
Injecting drug use	730 (3%)	69 (5%)
Other	1,554 (6%)	110 (7%)
cART	22,774 (95%)	1,441 (95%)
Deaths	2,646 (11%)	268 (18%)

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, 29% of the individuals had not been screened for the presence of HBV infection (*Figure 4.2*). Since then, the proportion of HIV-positive individuals with an unknown HBV status has decreased markedly, with just 2% of all HIV-positive individuals in care having an unknown HBV status in 2017 (*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 2017. The highest prevalence was found in MSM: in 1998, 11% of MSM had chronic HBV co-infection, and this figure decreased to 6.0% in 2017 (*Figure 4.8*). This decreasing prevalence of chronic HBV co-infection could be the result of increasing HBV vaccination rates (*Figure 4.9*), together with the preventive effect of HIV treatment with a cART regimen that includes TDF/TAF.

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

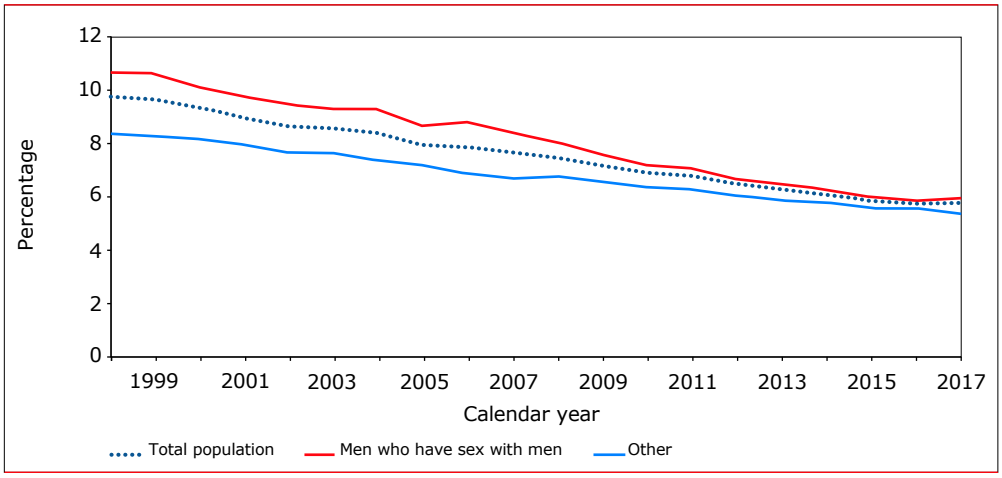
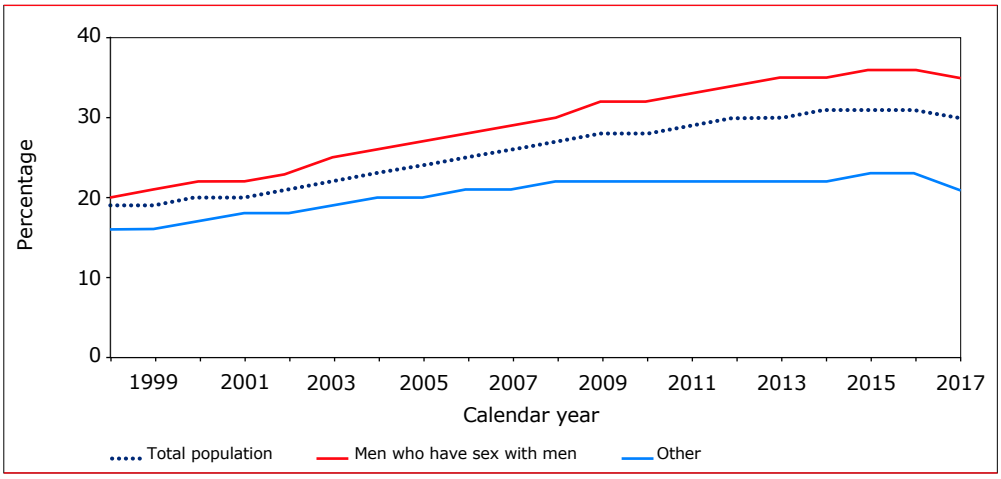


Figure 4.9: Prevalence of hepatitis B vaccination per calendar year.



Treatment for chronic HBV infection

The aim of treatment for chronic HBV infection is to reduce virus replication. As HBV DNA is the parameter most directly influenced by therapy with either nucleoside or nucleotide analogues, HBV DNA undetectability is the best surrogate marker for treatment response, and persistent lowering of HBV DNA levels to less than 20 IU/ml has also been shown to delay progression of liver fibrosis to

cirrhosis[23]. Chronic HBV infection is defined by the presence of hepatitis B surface antigen (HBsAg+). Lowering HBV DNA levels may result in HBsAg negativity in a subgroup of individuals. Persistent HBsAg negativity, together with the development of anti-HBs antibodies, is known as HBs seroconversion and 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 TDF/TAF, are also active against HBV.

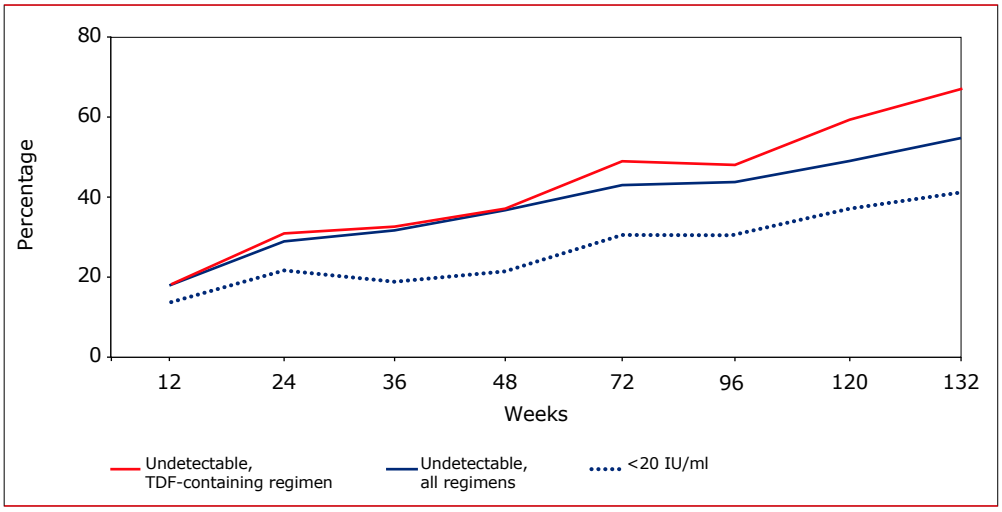
Of the 1,514 individuals with HIV in the SHM database who were co-infected with chronic HBV, 1,438 (95%) had ever received a cART regimen that included one or more agents with activity against both HIV and HBV. Reasons for the remaining 76 individuals not having received anti-HBV treatment included: death before being able to start treatment (n=16), recent entry into care (n=4), loss to follow up (n=42) and lack of sufficient information (n=14).

Most people treated for HBV (n=756/1,438, 53%) initially received lamivudine. Of those treated with lamivudine, 294 (39%) switched to a regimen containing tenofovir plus lamivudine after a median of 1.7 years (IQR 0.5-4.2) of prior exposure to lamivudine monotherapy for HBV and 222 (29%) switched to a regimen containing tenofovir plus emtricitabine after a median of 1.5 years (IQR 0.5-4.0). The remaining 240 individuals did not have a documented switch to a regimen containing TDF or TAF, 169 of whom were still in care in 2017. For 666 of 1,438 individuals (46%), their initial cART regimen included TDF and one additional agent with activity against HBV; for 114 of these 666 individuals (17%), the additional agent was lamivudine, and for 552 individuals (83%) the additional agent was emtricitabine; another 16 individuals started with a TAF-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[24]. We therefore examined the HBV DNA levels in the population of individuals co-infected with HIV and HBV. HBV DNA measurements were available for 1,063 (74%) out of the 1,438 treated HBV co-infected individuals. *Figure 4.10* shows the proportion with 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 37% after the first year of treatment, with an increase to 44% two years after the start of treatment and 55% three years after the start of treatment. The percentage of people with an HBV DNA level less than 20 IU/ml was 22% one year after the start of treatment, 31% after two years, and 41% after three years. In terms of individuals who were using a tenofovir-containing cART regimen, 67% of individuals with HBV DNA follow-up data had an undetectable HBV DNA level after three years of receiving treatment (*Figure 4.10*).

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.*

Among the 1,438 individuals whose cART regimen ever included one or more agents with activity against HBV, 533 of the 1,052 people with an available test result (51%) had a documented positive test result for HBeAg. Of these 533 individuals, 368 (69%) were re-tested, with 188 (51%) converting from HBeAg positivity to HBeAg negativity and 107 (29%) developing HBe antibodies. In total,

520 (53%) of the 982 individuals with HBsAg serology available during HBV treatment and who were HBsAg positive at time of treatment initiation became HBsAg negative. In addition, 136 (15%) of the 882 individuals with a documented negative HBs-antibody test result became HBs-antibody-positive, i.e., underwent an HBs seroconversion.

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

Liver-related morbidity

Additional data from liver biopsy pathology reports, transient elastography, radiology reports, or a combination, were available for 1,600 of the 1,938 individuals with chronic or acute HCV co-infection and for 1,149 of the 1,514 individuals with an HBV co-infection. Review of these additional data showed that severe chronic liver disease according to our definition was considered to be present (presumptive and definitive categories combined) in 667 (34%) of the individuals with HCV co-infection, and in 396 (26%) of those with HBV co-infection (*Table 4.5*). Definitive severe chronic liver disease was documented for 165 individuals with an HCV co-infection and 75 with an HBV co-infection.

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	1,983	1,514
Severe chronic liver disease#	667 (34)	396 (26)
HCC	20 (1.0)	26 (1.7)
Liver transplantation	2 (0.1)	1 (0.07)
Deaths from any cause*	312 (16)	268 (18)
Liver-related deaths	69 (3.5)	47 (3.1)

**including liver-related death*

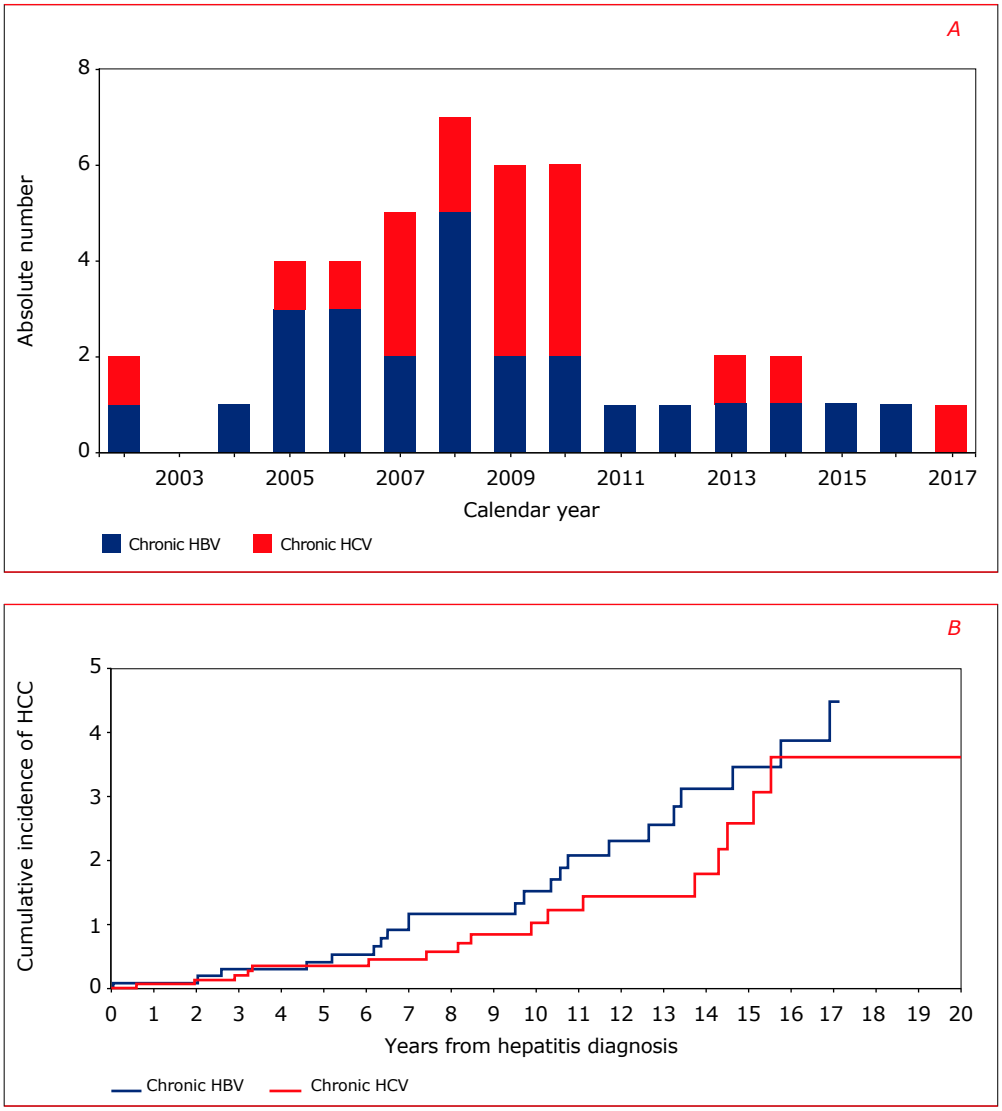
#including presumptive and definitive liver disease

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

Figure 4.11A shows that the annual number of new HCC diagnoses declined from 2010 onwards. HCC was diagnosed in 20 out of 1,362 individuals (1.4%) with a chronic HCV co-infection, of whom 15 were born in the Netherlands. HCC was found in 26 individuals (1.7%) with a chronic HBV co-infection, 15 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 1.7% (95% CI 0.9-2.7%) of individuals with HCV co-infection and in 1.2% (95% CI 0.6-2.3%) of those with chronic HBV co-infection. It should be noted that the exact moment of acquiring the 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 HCC cases over time and B) cumulative incidence of hepatocellular carcinoma (HCC) 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. Follow-up time was measured from the date of hepatitis diagnosis to the date of last contact, diagnosis of HCC, or 31 December 2017.



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

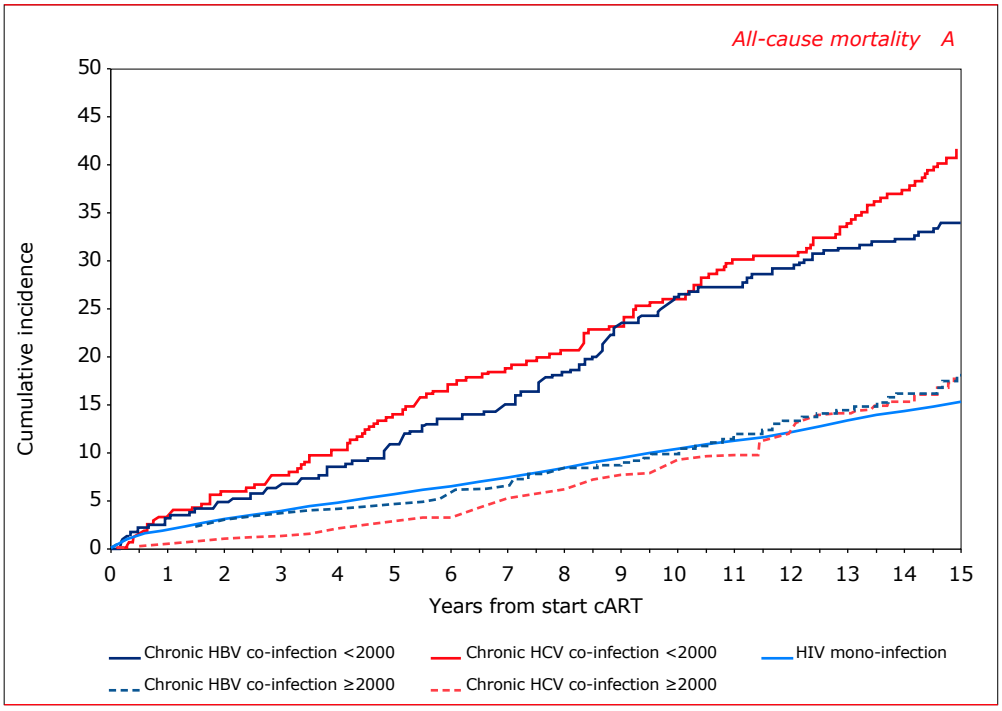
Mortality

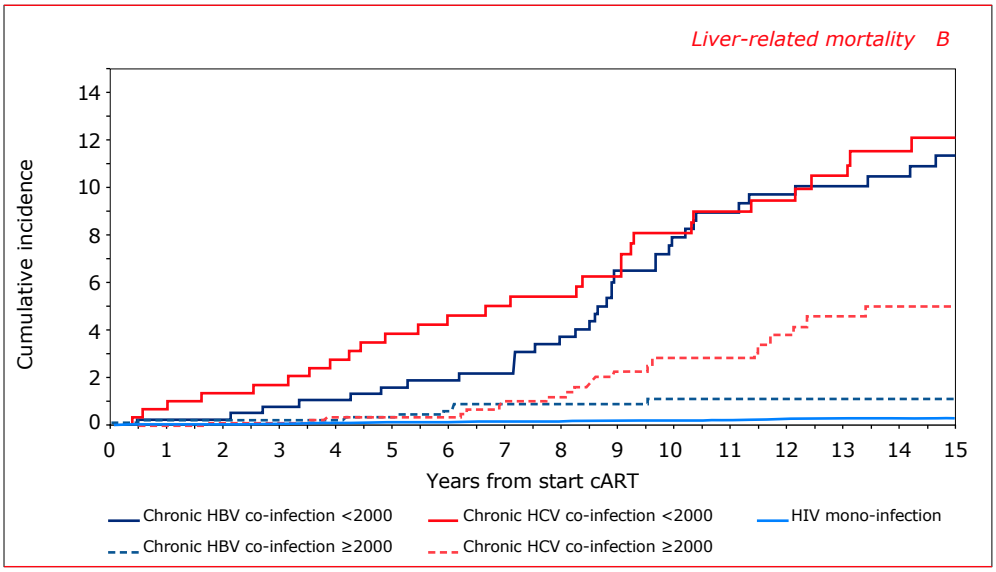
All-cause mortality

The overall rate of death from any cause was 16% for the 1,938 individuals with an HCV infection and 18% for the 1,514 individuals with an HBV infection (*Table 4.5*). The cumulative incidence of death from any cause was higher among people who were diagnosed with HCV or HBV before 2000 compared with those who were diagnosed in later calendar years (*Figure 4.12A*). 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 than in HIV mono-infected individuals. For people with an HCV co-infection diagnosed after 2000, the adjusted overall risk of death was non-significantly higher than in HIV mono-infected individuals.

Moreover, after adjustment for differences in demographic and clinical characteristics, the overall risk of death was significantly higher for both individuals with a chronic HBV co-infection diagnosed before 2000 and those diagnosed with HBV after 2000 than for HIV mono-infected individuals (*Table 4.6*).

Figure 4.12: Cumulative incidence of (A) all-cause mortality and (B) liver-related mortality, stratified by calendar year period. The Kaplan-Meier estimate was used to determine the time to death. The follow-up time was measured from the date of HIV diagnosis to the date of last contact, death or 31 December 2017.





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

Liver-related mortality

In total, 116 individuals co-infected with hepatitis died of a liver-related cause (*Table 4.5*). Ten years after cART initiation, 8% (95% CI 5-12) of chronically HCV co-infected individuals who were 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, 8% of individuals diagnosed before 2000 died of a liver-related cause (95% CI 6-12), which dropped to 3% (95% CI 2-5) in those diagnosed after 2000 (*Figure 4.12B*).

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 26.9 (95%: 16.0-45.2) in individuals diagnosed with HBV before 2000 to an HR of 4.09 (95%: 1.90-8.82) 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 17.7 (95% CI: 9.30-33.5) in individuals diagnosed with HCV before 2000 to an HR of 8.75 (95%CI: 4.95-15.5) in individuals diagnosed with HCV from 2000 onwards.

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 31 December 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	1.94 (1.58-2.40)		17.6 (9.29-33.5)	
HIV/chronic HCV, ≥2000	1.23 (0.99-1.54)		8.74 (4.95-15.48)	
HIV/chronic HBV, <2000	1.90 (1.59- 2.27)		26.9 (16.0-45.2)	
HIV/chronic HBV, ≥2000	1.27 (1.04-1.56)		4.09 (1.90-8.82)	

**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.*

Conclusion

Screening for HCV and HBV co-infection in the HIV-positive population in the Netherlands continues to improve over time. While, in 1998, approximately 39% of the individuals in care had not been screened for HBV or HCV co-infection, today the presence or absence of these co-infections is documented for almost all HIV-positive individuals. Six percent of HIV-positive individuals ever 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 800 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. 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[16]. Overall, a rapid reduction in the prevalence of an active HCV infection has been achieved, with prevalence in MSM having declined to less than 1% in 2017. 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[17,20], HCV re-infection after successful treatment has been observed. Although the rate of re-infection has declined in the most recent years, ongoing transmission of HCV persists.

Six percent of the HIV-positive individuals ever in care had a 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 TDF/TAF in cART-treated individuals. Nonetheless, an estimated 29% of all HIV-positive individuals and 21% of MSM have either not been exposed to HBV or not been successfully vaccinated and may remain at risk of acquiring HBV. However, 56% of all individuals and 63% of MSM still at risk of acquiring HBV infection use a cART regimen that includes TDF/TAF and may therefore be at a substantially lower risk due to sustained chemoprophylaxis. The remaining 44% of the HIV-positive individuals ever registered and 37% of the MSM remain unprotected against HBV, which represents an estimated 12.6% 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[6,7]. Among the HIV-positive individuals ever registered by SHM, 34% of the chronically HCV co-infected individuals and 26% of the chronically HBV 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, people with chronic HCV or HBV co-infection remain at increased risk of having a liver-related cause of death, although this risk has declined significantly for people 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 who are at increased risk of acquiring 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 HCV RNA screening among individuals who have been successfully treated for HCV infection is recommended to ensure 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.

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Appendix: supplementary table

Appendix Table 4.1: Absolute number of acute HCV diagnoses per calendar year among HIV-1 positive individuals ever registered.

	Acute primary HCV, preferred criteria	Acute primary HCV, alternative criteria	HCV re-infection	Total
≤2002	16	2	0	**18**
2003	5	0	0	**5**
2004	7	0	1	**8**
2005	8	1	1	**10**
2006	20	2	4	**26**
2007	41	1	2	**44**
2008	56	3	5	**64**
2009	41	1	7	**49**
2010	44	4	7	**55**
2011	50	6	23	**79**
2012	27	9	14	**50**
2013	44	16	18	**78**
2014	38	12	18	**68**
2015	49	17	29	**95**
2016	20	13	20	**53**
2017	15	8	8	**31**
total	**481**	**95**	**157**	**733**

Legend: HCV=hepatitis C virus

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

Colette Smit, Tom Wolfs and Annemarie van Rossum

Box 5.1: Definitions

Child	An individual diagnosed with HIV before the age of 18.
Infection	The moment a child acquires an HIV infection.
Diagnosis	The moment a child is newly diagnosed with HIV.
Registration	The moment a HIV-positive child in care is notified to SHM by their treating physician or nurse and registered in the SHM database.
In care in 2017	Clinic visit or lab measurement in 2017.
ART	Antiretroviral therapy: use of an antiretroviral drug that may prevent HIV from damaging the immune system by blocking HIV replication.
cART	Combination antiretroviral therapy: a combination of three antiretroviral drugs from two different antiretroviral drugs classes.
Initial virological success	Two consecutive HIV RNA levels below 100 copies/ml, except for time points in the past where tests were used with quantification limits of 200, 400, 500 or 1000 copies/ml[1].
Viral suppression	Any viral load measurements <200 copies/ml, at least three months after cART initiation, except for time points in the past where tests were used with quantification limits higher than 200 copies/ml.

Background

Combination antiretroviral therapy (cART) has dramatically decreased morbidity and mortality in HIV-positive children worldwide[2,3,4,5,6]. Moreover, early initiation of cART has been proven to be particularly beneficial in improving the survival of HIV-positive children[7,8,9,10]. As such, 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[11].

In the Netherlands, children living with HIV generally receive healthcare at one of four paediatric HIV treatment centres. These children will transition to adult HIV care upon reaching 18 years of age. However, children who acquire HIV at an older age and through non-vertical transmission are more likely to enter care at an adult HIV treatment centre. Diagnosis, treatment and follow up of all these children is monitored by Stichting HIV Monitoring (SHM).

Here we report on the demographics, clinical characteristics, and long-term virological and immunological response to treatment in HIV-positive children ever cared for in one of the paediatric and/or adult HIV treatment centres in the Netherlands (*Box 5.2*).

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Box 5.2: Outline of the paediatric ATHENA cohort in the Netherlands: HIV-positive children (aged <18 years at the time of diagnosis) ever registered in the ATHENA cohort by 31 December 2017.

Data used in this chapter

In 2018, Stichting HIV Monitoring launched a new data entry system, DataCapTree, which went live in February 2018 with an initial set of approved data collection protocols. The protocol for the collection of paediatric data was delayed until the second half of 2018. For this reason, data used in this chapter are based on the database lock of 31 December 2017, rather than May 2018 as in previous years. As a result, this year's earlier database lock for paediatric data may result in a certain degree of underreporting of data compared to previous years.

Populations described in this chapter

1. Ever registered (n=603)
2. Population in care in 2017:
   - aged <18 years in 2017 (n=183)
   - aged ≥ 18 years in 2017 (n=281)
3. Specific populations:
   - adopted children
   - children who transfer to adult care

Ever registered

As of 31 December 2017, 603 HIV-positive children had ever been registered by SHM since 1998, representing an increase of 13 children compared with last year's report. Of the 603 ever-registered HIV positive children, 358 children entered care at a paediatric HIV treatment centre. The remaining 245 entered care at an adult HIV treatment centre. This group was predominantly diagnosed with HIV at an older age and had mostly acquired HIV through non-vertical transmission (*Table 5.1*). Both groups of HIV-positive children, i.e., those who entered care at a paediatric HIV treatment centre and those who entered care at an adult HIV treatment centre, will be discussed in this chapter.

Table 5.1: Demographics and characteristics of 603 HIV-positive children ever registered in the Netherlands as of 31 December 2017.

Characteristics	Vertically-acquired HIV infection*	Non-vertically-acquired HIV infection*	Route of transmission unknown*
Total	335	247	21
HIV treatment centre			
Child care	321 (96)	28 (11)	9 (43)
Adult care	14 (4)	219 (89)	12 (57)
Gender			
Male	164 (49)	116 (47)	13 (62)
Female	171 (51)	131 (53)	8 (38)
Country of origin child			
The Netherlands	109 (33)	60 (24)	1 (5)
Sub-Saharan Africa	181 (54)	121 (49)	12 (57%)
Other	45 (13)	66 (27)	8 (38%)
Country of origin mother			
The Netherlands	23 (6)	6 (3)	1 (5)
Sub-Saharan Africa	181 (54)	33 (13)	5 (24)
Other/unknown	131 (39)	208 (84)	15 (71)
Age at HIV diagnosis	1.2 (0.3-4.0)	16.8 (16-17)	15.7 (12-17)
CDC** event at HIV diagnosis			
CDC-b	30 (9)	10 (4)	2 (10)
CDC-c	56 (17)	13 (5)	2 (10)
cART-treated	324 (97)	227 (92)	20 (95)
Therapy-naive at cART initiation	281 (84)	185 (75)	19 (90)
CD4 at cART initiation	527 (270-1,164)	290 (162-410)	293 (40-350)
CD4 Z-score at cART initiation	-0.62 (-1.05—0.16)	-0.62 (-10.4—0.26)	-0.51 (-1.12—0.24)
VL (log copies/ml) at cART initiation	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)*

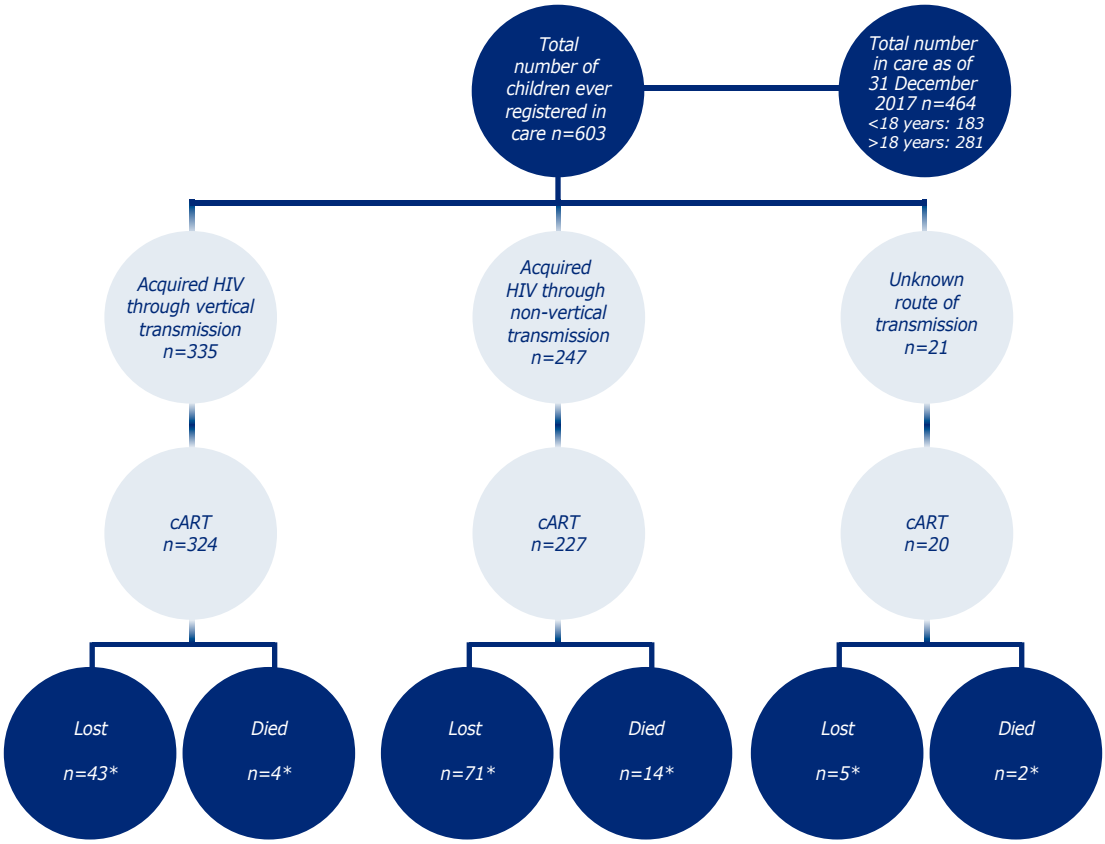
** *Categories as defined by the Centers for Disease Control and Prevention (CDC).*

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

Mode of transmission

The majority of the children ever registered had acquired HIV through vertical transmission or through sexual contact. The reported mode of HIV transmission is shown in *Figure 5.1*. *Figure 5.2* shows the number of newly-registered children per calendar year of entering care, according to the mode of HIV transmission and, for those with vertically-acquired HIV, according to whether or not they were adopted at the time of registration.

Figure 5.1: Overview of HIV-positive children registered by Stichting HIV Monitoring as of 31 December 2017.



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

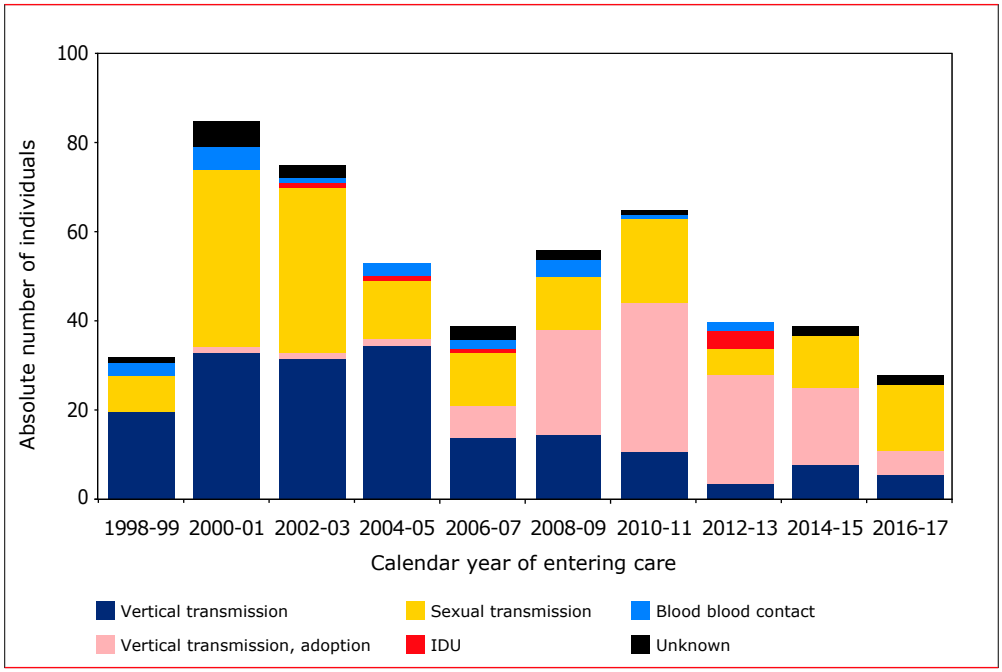
***Legend:** cART=combination antiretroviral therapy.*

Children with vertically-acquired HIV

- In total 335 children had acquired HIV through vertical transmission, representing an increase of 5 children compared with the end of 2016. None of these 5 children were born in the Netherlands.
- The median age at the first reported HIV-positive test result, including self-reported tests in the country of origin, was 1.2 years (interquartile range [IQR] 0.3-4.0 years).
- 54% (n=181) of the children were born in sub-Saharan Africa.

- 33% (n=109) of the children were born in the Netherlands.
- Only 10% of the children born in the Netherlands (11 out of 109) had parents who both originated from the Netherlands.
- Of children with vertically-acquired HIV, 96% received care in a paediatric HIV treatment centre in the Netherlands and the remaining 4% were seen in adult care.
- In total, 97% of the children had a documented cART start date.

Figure 5.2: Number of HIV-positive children by year of entering care in the Netherlands, stratified by HIV transmission mode and, for those who had acquired HIV through vertical transmission, by whether or not they had been adopted during the period 1998-2017.



Note: low numbers in 2017 may be due to a delay in the treatment centre registering the child with SHM.
***Legend:** IDU=transmission through injecting drug use.*

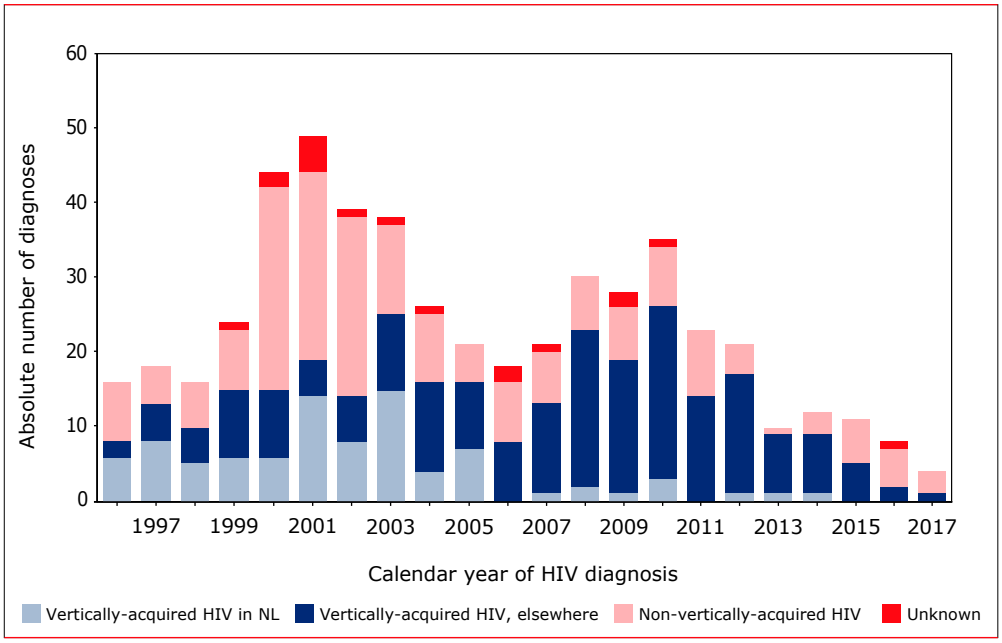
No vertical transmission of HIV in the Netherlands since 2015

Vertical transmission of HIV has been reduced to zero in the Netherlands since 2015. *Figure 5.3* shows the number of newly-registered HIV diagnoses among children by year of diagnosis, according to mode of transmission and region of origin. As shown in the figure, vertical transmission of HIV 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 since 2015.

The decline of vertical transmission in the Netherlands is most likely due to HIV screening among pregnant women, which was introduced nationally in 2004[12,13]. Since the introduction of this screening programme, 9 children born with HIV in the Netherlands have been reported to SHM. These 9 children are described briefly below:

- Six children were born to mothers who only first tested positive themselves after giving birth; the mothers of four of these six children had a negative test result during the first trimester pregnancy screening and acquired HIV only later during their pregnancy.
- One child was born to a mother who was known to be HIV-positive, but who was not receiving treatment during her pregnancy for an unknown reason.
- The remaining two children were born to mothers without a known screening or known HIV status during pregnancy.

Figure 5.3: Number of registered HIV diagnoses among children, according to year of HIV diagnosis, route of transmission, and region of origin.



Note: low numbers in 2017 may be due to a delay in registration.

Children with non-vertically-acquired HIV

- In total, 247 children were ever registered with HIV infection acquired through non-vertical transmission, including 8 children newly-registered in 2017.
- The median age at first reported HIV-positive test result was 16.8 years (IQR 16-17).
- The main route of HIV transmission was sexual contact (*Figure 5.2*):
  - 136 children had acquired HIV through heterosexual contact,
  - 55 children had acquired HIV through homosexual contact.
- 47 children had acquired HIV through contaminated blood or blood products. This mode of transmission was no longer reported from 2002 onwards among children born in the Netherland, and from 2013 onwards among any children, regardless of country of birth.
- The remaining 9 children had acquired HIV through injecting drug use or accidentally through contaminated needles.
- Of the children with non-vertically-acquired HIV, 49% were born in sub-Saharan Africa.
- About 89% received care in an adult HIV treatment centre.
- In total, 92% of the children had started cART.

Unknown route of HV-1 transmission

- For 21 HIV-positive children, the route of transmission was unknown.
- Their median age at diagnosis was 15.7 years (IQR 12-17).
- Nine children were in care at a paediatric HIV treatment centre.
- All children had started cART.

Newly registered in 2017

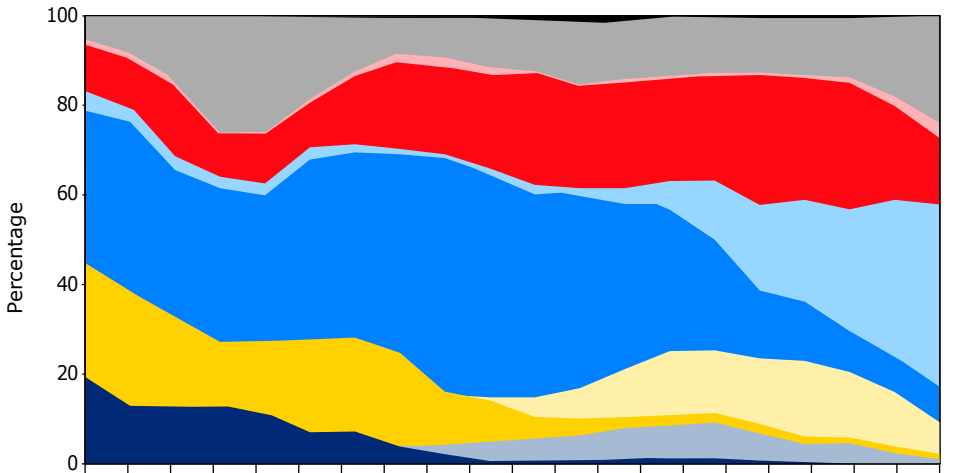
In 2017, thirteen children were newly-registered with SHM:

- Nine had entered care in 2017; the remaining 4 children had already entered care before 2017, but were only registered with SHM in 2017.
- Five had acquired HIV vertically, and 8 through sexual contact.
  - All 5 newly-registered children who had acquired HIV vertically were born outside the Netherlands; 2 of these children had been adopted by Dutch parents.
  - Five of the 8 children with non-vertically-acquired HIV were born in South America or the Caribbean and the remaining 3 children were born in various other regions outside the Netherlands.
- Four of the newly-registered children entered paediatric care and had vertically-acquired HIV. The other 9 children were in care in an adult HIV treatment centre, 8 of whom had acquired HIV through sexual contact and one who had acquired HIV vertically but had been diagnosed abroad and was older than 16 when entering care in the Netherlands.

Age distribution

During the period from 1998 through to 2017, the proportion of children below 12 years of age decreased gradually until 2008 (*Figure 5.4*). However, from 2008 onwards, there was a slight increase in the proportion of children aged between 0 and 5 years. This is due to an increase in the rate of adoption of HIV-positive children in this age group, illustrated by the shaded areas in *Figure 5.4*. In 2017, about 85% of the children aged 12 years or below were adopted.

Figure 5.4: Time-dependent age distribution of HIV-positive children in care over time. The shaded areas represent the proportion of adopted children.



	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
	0	0	0	0	0	1	1	0	0	1	2	3	2	0	0	1	1	0	0	0
	4	7	17	40	43	31	20	14	17	21	22	30	29	31	29	28	29	30	38	44
	0	1	1	1	1	1	2	3	3	2	1	1	1	1	1	0	1	3	4	6
	8	10	19	15	20	20	27	35	36	41	50	48	53	52	53	67	60	62	46	27
	3	2	3	3	3	3	2	1	1	1	3	3	7	14	28	41	51	61	74	75
	25	33	39	54	56	71	72	77	94	95	90	92	81	73	56	35	29	20	17	14
	0	0	0	0	0	0	0	0	0	1	8	15	25	33	32	33	37	32	25	13
	18	22	24	22	27	37	36	35	21	19	11	8	4	5	4	5	4	3	4	2
	0	0	0	0	0	0	0	1	4	7	8	12	14	16	18	13	8	8	5	2
	14	11	15	20	19	12	13	7	4	1	2	1	4	3	3	2	2	2	0	0

Low mortality rates

The mortality rate among children ever registered between 1998 and 2017 is very low. Three children (0.5%) have died at less than 18 years of age since the start of registration. These three boys were born outside the Netherlands and died before 2010. Two boys died of AIDS, despite receiving cART. The third boy did not receive cART and died very short after entering care in the Netherlands.

Treatment

Among the 603 children who were ever registered, 571 (95%) had initiated cART. Of these 571 children, 485 (85%) were treatment-naive at the start of cART and 86 (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 zero in 2016 and 2017.

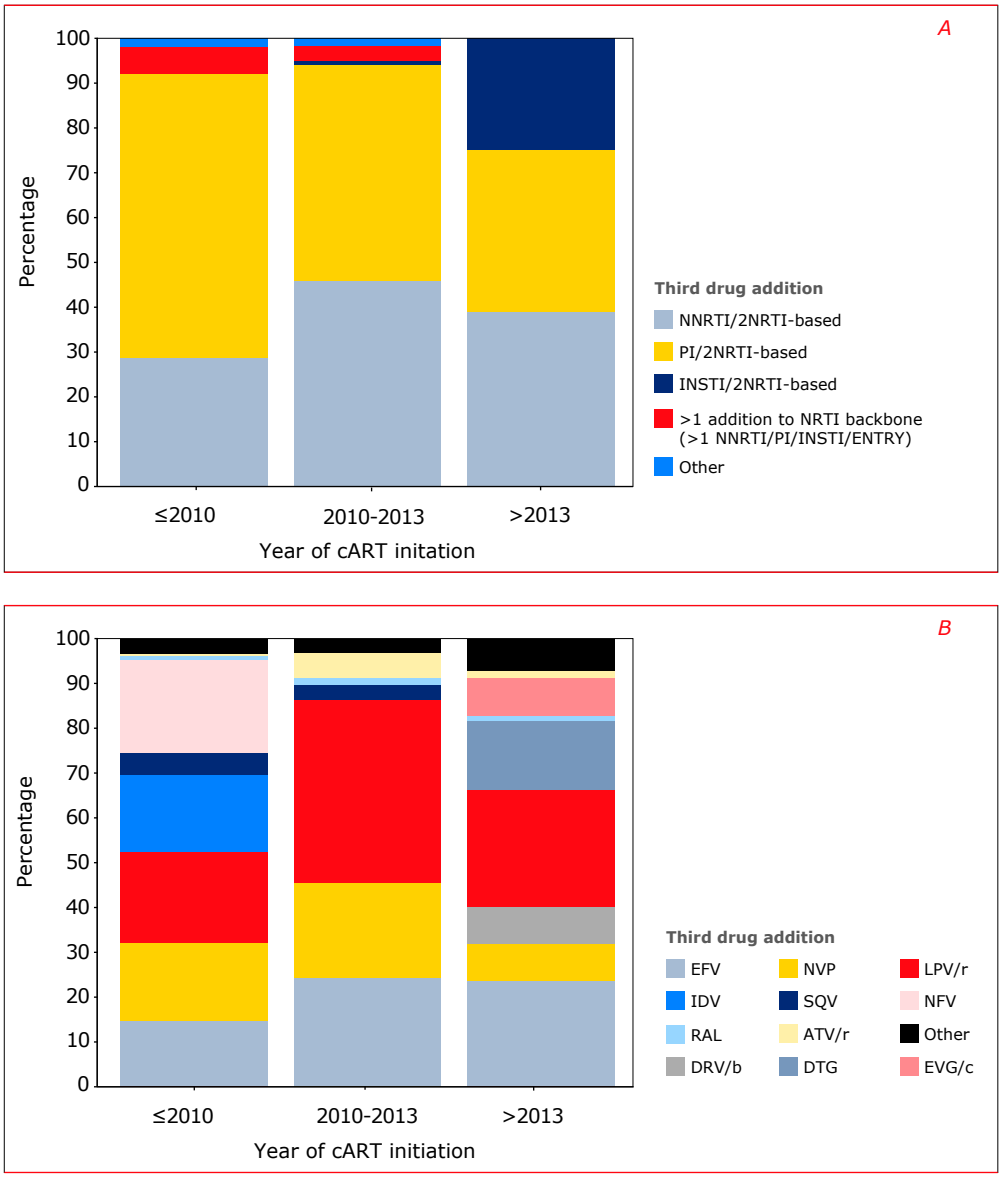
When assessing treatment, we included both pre-treated and treatment-naive children, grouped according to calendar year of starting cART: 399 had started a cART regimen before 2010, 97 had started between 2010 and 2013, and 75 had started cART from 2013 onwards.

Among those children not treated with cART, 6 had recently entered care, one had died shortly after entering care, and another 9 had been in care for less than one year.

Initial combination antiretroviral therapy regimen use

Overall, out of the 571 ever-registered children who were known to have initiated cART, 57% were treated with a first-line cART regimen that included a protease inhibitor (PI) and two or more nucleoside analogue reverse transcriptase inhibitors (NRTIs) and another 34% were treated with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimen with two or more NRTIs. *Figures 5.5A* and *5.5B* 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[14], but 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[1,15,16,17]. With the introduction of dolutegravir and elvitegravir in 2013 and 2014, these integrase inhibitors have also become part of the initial cART regimens.

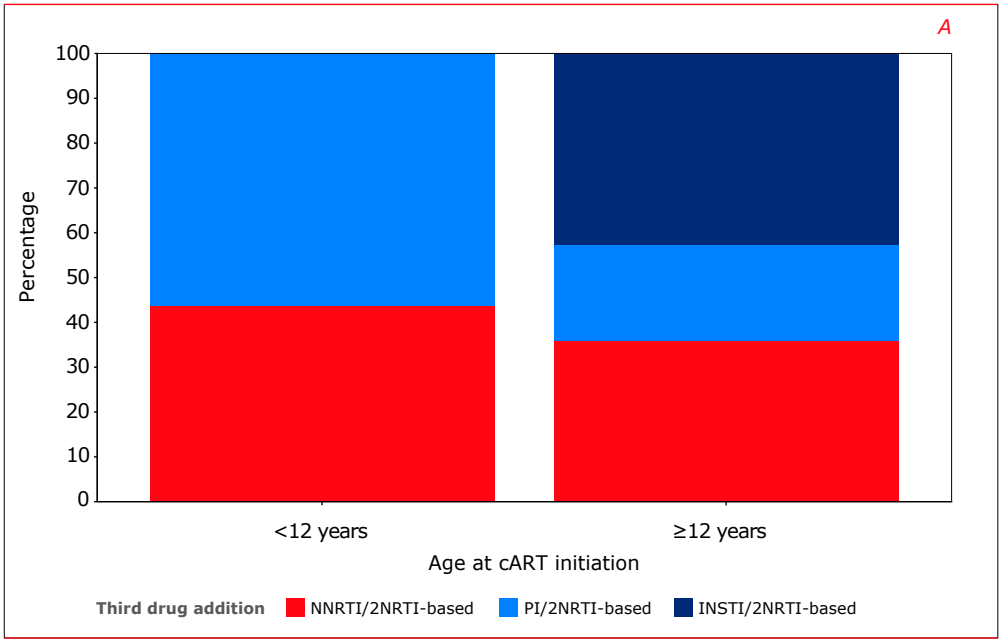
Figure 5.5: Third-drug additions to the nucleoside analogue reverse transcriptase backbone used as part of the initial cART regimen, stratified by calendar year period, according to (A) antiretroviral class and (B) specific drug.

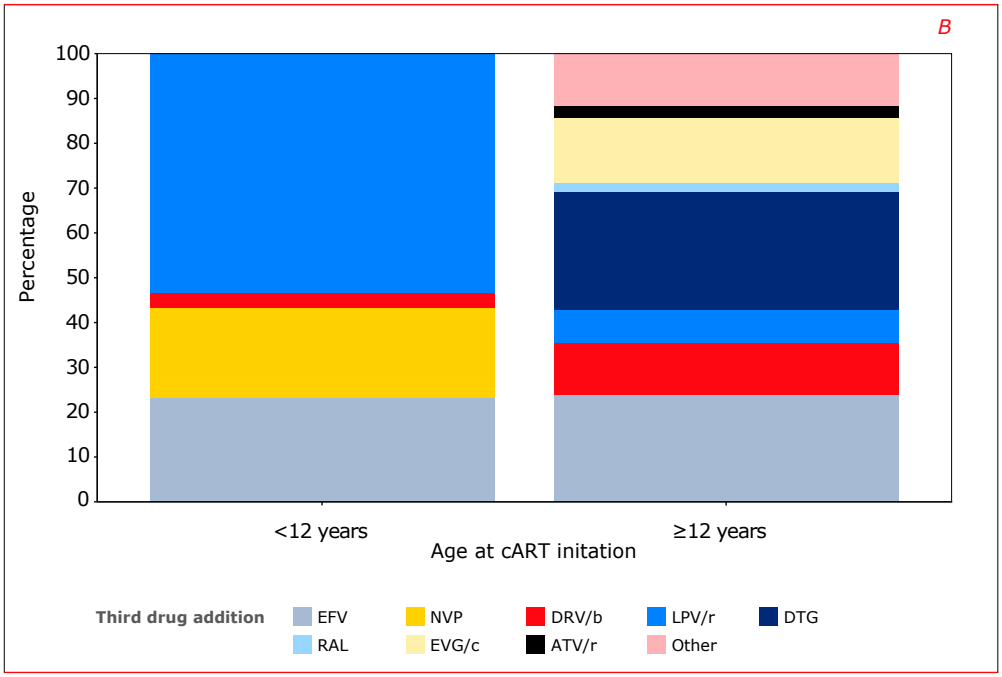


Legend: cART=combination antiretroviral therapy; ENTRY=entry inhibitor; INSTI=integrase inhibitor; NRTI= nucleoside analogue reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; EFV=efavirenz; NVP= nevirapine; LPV/r=ritonavir-boosted lopinavir;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

Figures 5.6A and *5.6B* further specify these third-drug additions to the NRTI backbone according to the age of starting cART in 2013-2016. Between 2013 and 2016, more than 50% of children below 12 years of age at the time of cART initiation used lopinavir/ritonavir and none of the children used an integrase inhibitor in their initial regimen. Among older children (≥12 years), there was more variation in the third-drug additions of the initial regimen, including the use of integrase inhibitors (24% dolutegravir and 14% elvitegravir).

Figure 5.6: *Third-drug additions to the nucleoside analogue 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 analogue reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; EFV=efavirenz; NVP= nevirapine; LPV/r=ritonavir-boosted lopinavir; RAL=raltegravir; ATV/r=ritonavir-boosted atazanavir; DTG=dolutegravir; EVG/c=cobicistat-boosted elvitegravir; DRV/b=cobicistat/ ritonavir-boosted darunavir.*

Discontinuation of the initial cART regimen

We assessed the time spent on the initial regimens among the 571 children who ever started cART. The median time spent on an initial regimen was 14 months (IQR 3.1-33.9). Discounting weight-related dose changes, 451 children (79%) discontinued their first-line treatment regimen. The most important reasons for changing first-line cART regimens included toxicity (20%), simplification (18%), and parental non-adherence (2%). Virological failure accounted for 10% of the reasons for changing first-line cART therapy. Other reasons were low drug concentrations, decisions by parents and/or child, research protocol-driven reasons, or unknown.

Immunological response

Earlier reports have shown that the clinical benefit of cART is strongly related to the degree to which the CD4 cell count recovers[18]. To investigate long-term CD4 cell count changes among the 571 children who ever started cART, we stratified the children with vertically-acquired HIV according to age at the time of cART initiation.

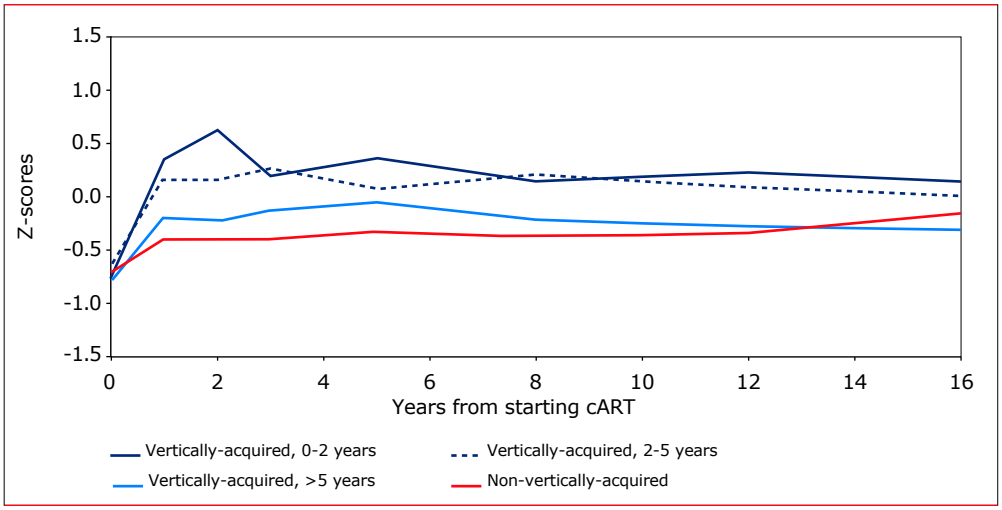
These categories were as follows:
(1) vertically-acquired, 0-2 year,
(2) vertically-acquired, 2-5 years,
(3) vertically-acquired, 5-18 years,
(4) non-vertically-acquired or unknown mode of HIV transmission[c], 5-18 years.

Given that normal CD4 cell counts in younger children are highly age-dependent[19], it is more appropriate to analyse time-dependent CD4 count trajectories, expressing CD4 counts as Z-scores, in which counts are standardised in relation to age. CD4 Z-scores, which represent the standard deviation from the reference values for HIV-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[20] 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 is 1 standard deviation below the age-specific median of the HIV-negative population.

Figure 5.7 shows the changes in Z-scores for CD4 T-cell counts among HIV-positive children stratified by age at initiation of cART. The youngest children (less than two years of age at cART initiation) had the highest absolute CD4 cell counts at cART initiation, but the age-adjusted CD4 Z-scores did not differ significantly between groups. In the first two years after cART initiation, CD4 Z-scores increased significantly in all children. This increase was lower in the groups of children aged 5-18 years at cART initiation with both vertically and non-vertically-acquired HIV than in the group of children less than two years of age with vertically-acquired HIV.

c The number of children with an unknown route of HIV transmission is too small to include as a separate category in this analysis. As these children had the same age distribution as those who with non-vertically-acquired HIV, these two groups were jointly analysed in a shared category.

Figure 5.7: Changes in Z-scores for CD4 T-cell counts among HIV-positive children stratified by age at initiation of combination antiretroviral therapy (cART).



Legend: cART=combination antiretroviral therapy.

Virological response

The main definition for virological outcomes used in this chapter are described in *Box 5.1*. Virological response to cART was assessed in two ways: firstly, based on initial virological success (i.e., two consecutive HIV RNA levels below 100 copies/ml), and secondly, based on viral suppression (i.e., viral load <200 copies/ml) over a longer period of time (1-10 years).

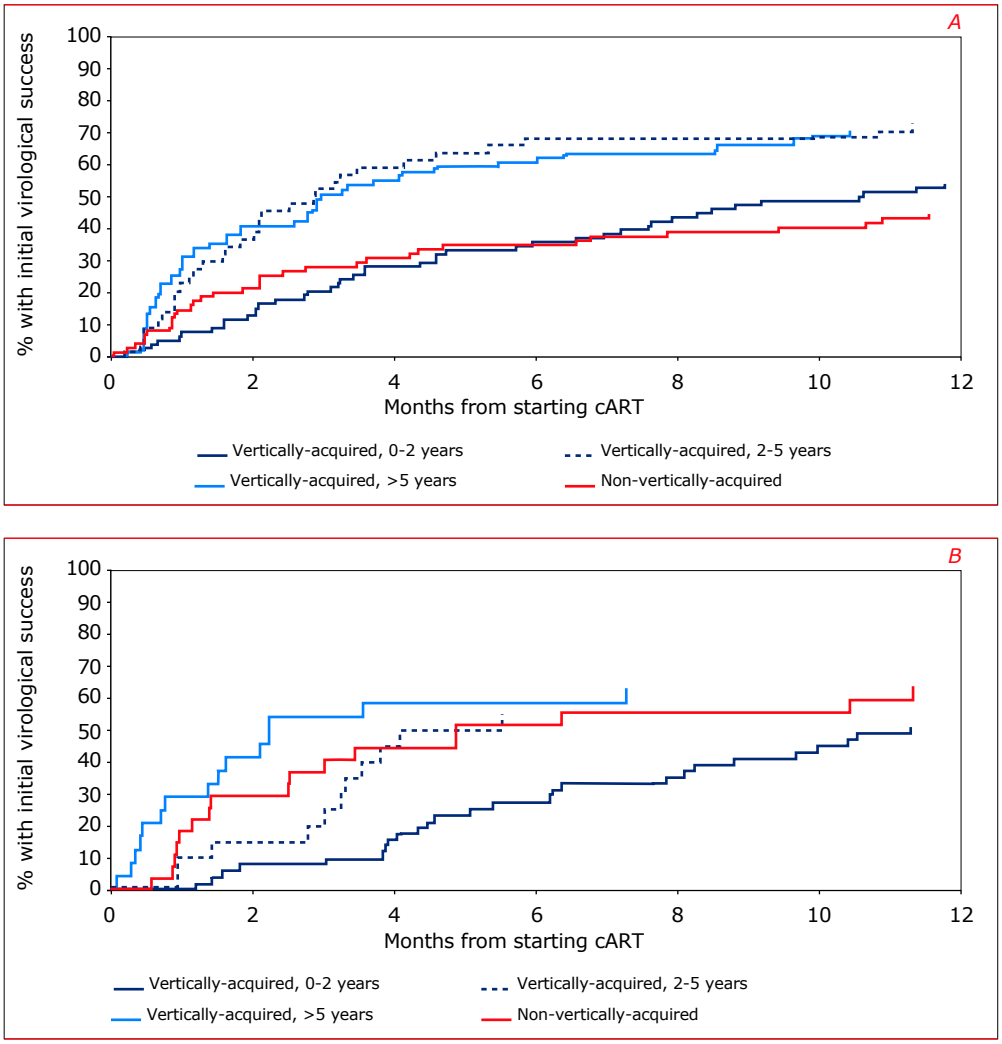
For the current analysis, we included data from the 571 children ever registered and who had ever started cART. Children were stratified by age at cART initiation (these are the same groups as those presented in the paragraph on immunological response to cART).

I. Initial virological success

Among children who started cART before 2010, the poorest virological responses were observed in those less than two years of age (54% reached initial virological success 12 months after the start of cART) and in those with non-vertically acquired HIV (55%). The best responses were among children aged two to four years old (75%) and those aged five years old or above who had vertically-acquired HIV (72%) (*Figure 5.8A*).

Figure 5.8B shows the time to initial virological success among children who initiated cART in or after 2010. In this group, 53% of the children less than two years of age and 60% of those aged between 2 and 5 years of age achieved an undetectable HIV RNA within 12 months. Higher initial virological success rates were observed among children aged five years or above with vertically-acquired HIV (63%).

Figure 5.8: *Kaplan-Meier estimates of the percentage of HIV-positive children with initial virological success (<100 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 2010-2017.*



Legend: *cART=combination antiretroviral therapy.*

II. Long term viral suppression

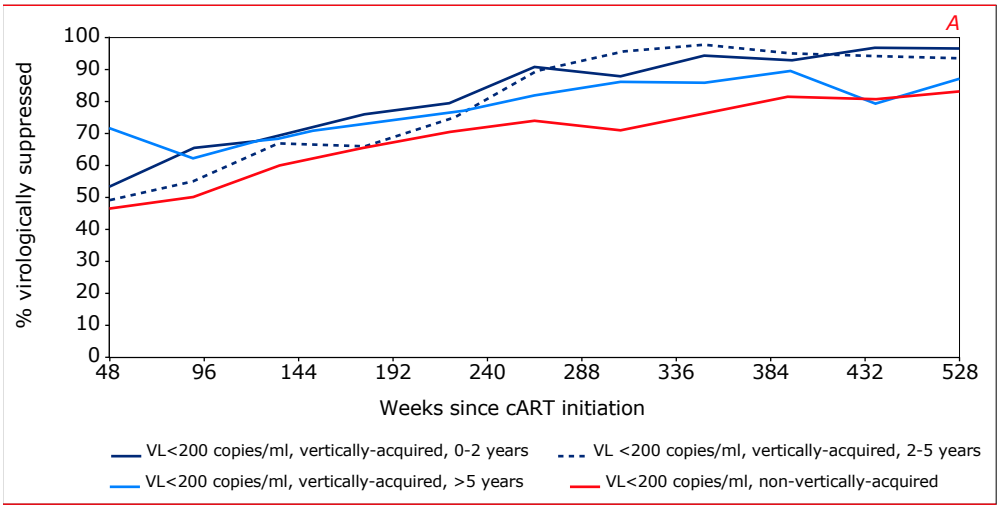
Among the 571 children who ever started cART, we assessed longitudinal viral suppression rates over time on cART during 24-week intervals. Viral load measurements closest to each 24-week time point (±12 weeks) were included in the analysis. Viral suppression rates were stratified by calendar year of cART initiation, to account for changes in the use of cART regimens.

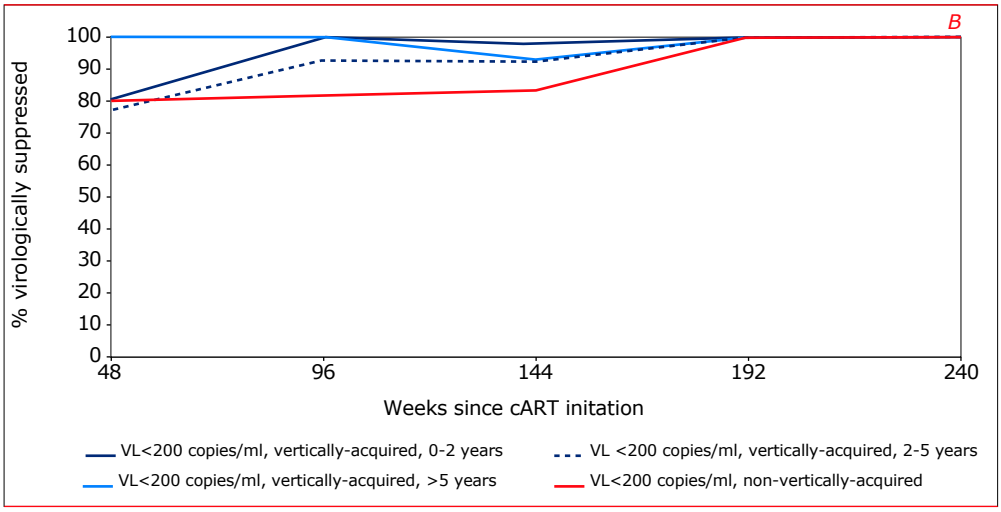
Figure 5.9 shows viral suppression rates by calendar period of cART initiation: 1998-2009 and 2010-2017.

In those initiating cART between 1998 and 2009:

- Among children with vertically-acquired HIV and aged 0-2 years at time of cART initiation: viral suppression rates increased from 53% after one year of cART use to 79% and 97% after 5 and 10 years, respectively.
- Among children with vertically-acquired HIV and aged 2-5 years at cART initiation: viral suppression increased from 49% after one year of cART use to 74% and 94% after 5 and 10 years, respectively.
- Ten-year viral suppression rates were lower for children with vertically-acquired HIV and aged over 5 years of age and for those with non-vertically acquired HIV (79% and 80%, respectively [*Figure 5.9A*]).
- 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 5 years of cART use (*Figure 5.9B*).

Figure 5.9: Viral suppression since combination antiretroviral therapy initiation, by calendar period of therapy initiation: (A) 1998–2010 and (B) 2010–2017.





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

The less favourable initial virological success among the youngest children that has also previously been described by others[18] might be due to difficulties in performing regular dosing adjustments in young children[19], but also due to the higher pre-cART viral loads in younger children[20]. Although we observed a poorer initial virological success during the first year of treatment among children who were aged less than 2 years at the time of cART initiation, their long-term viral suppression rate improved over time and most of these children had suppressed HIV RNA after 10 years of cART use.

Currently in clinical care

Of the 603 HIV-positive children ever registered by SHM, 464 (77%) were still in clinical care at the end of 2017 (*Figure 5.1*). Of the remaining 139 children no longer in care, 20 had died, 49 had moved abroad, and 70 were lost to follow up.

Currently in care and less than 18 years old

- Of the 464 children still in care, 183 were aged <18 years at the end of 2017.
- Their median age as of 31 December 2017 was 11 years (IQR 7-15).

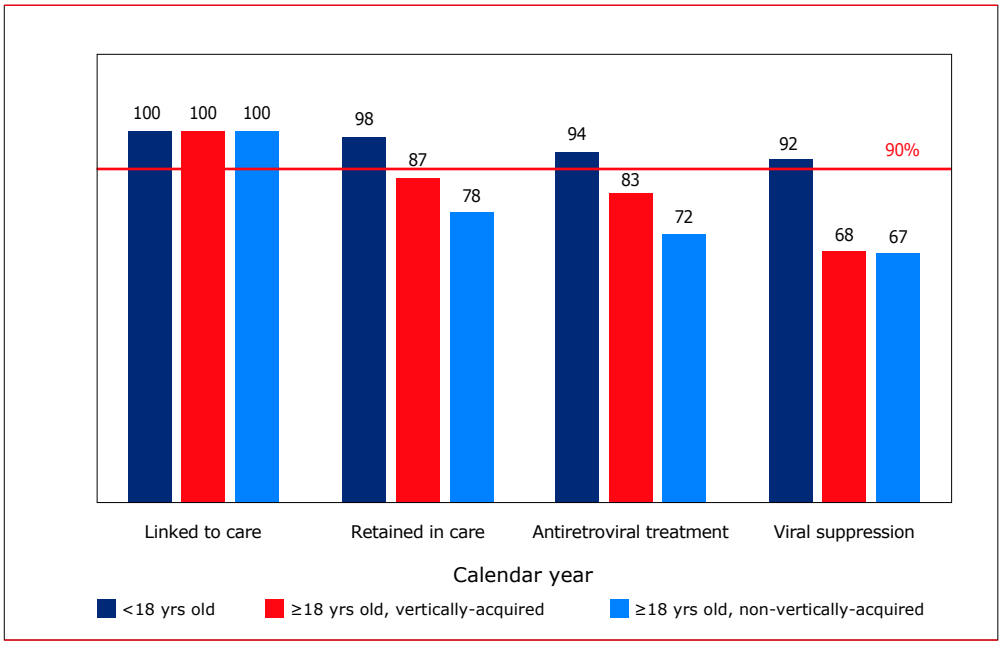
Currently in clinical care and 18 years or older

- 281 individuals who were registered as a child were in care and over 18 at the end of 2017.
- Their median age was 23 years (IQR 20-26) for those who had vertically acquired HIV and 32 years (IQR 26-35) for those with non-vertically-acquired HIV.

Continuum of care

On the basis of the total number of HIV-positive children ever registered by SHM, still alive on 31 December 2017, and not reported to have moved abroad or to have died, a 'continuum of care' was constructed. This continuum of care depicts engagement in HIV care across a number of key indicators, the last one being the number of children with a most recent HIV RNA measurement below 200 copies/ml (*Figure 5.10*).

Figure 5.10: Cascade of care by age and mode of HIV acquisition, as of 31 December 2017. The numbers above the bars indicate the proportion of individuals.



Individuals were stratified by age on 31 December 2017 and further categorised as:

I. current age <18 years (the number of children currently less than 18 years old with non-vertical acquisition of HIV was too small (n=5) for stratification by mode of acquisition in this age group).
II. current age ≥18 years and vertically-acquired HIV; and
III. current age ≥18 years and non-vertically-acquired HIV.

I. Continuum of care: current age <18 years

- In total, 187 children less than 18 years old on 31 December 2017 were linked to care, registered by SHM, still alive, and not reported as having moved abroad.
- Of these 187 children, 98% were retained in care (183/187). The remaining 4 children had been lost to follow up, all of whom were born outside the Netherlands.
- During their last clinical visit in 2017, 94% (176/183) were using antiretroviral therapy.
- Overall, 92% of those linked to care and less than 18 years old had a most recent HIV RNA measurement below 200 copies/ml (172/187).

II. Continuum of care: current age ≥18 years with vertically-acquired HIV

- 127 individuals who had acquired HIV through vertical transmission and who were over 18 years of age on 31 December 2017 were linked to care.
- Of these 127 individuals, 87% (110) were still in care as of 31 December 2017. The remaining 17 individuals had been lost to follow up, 10 of whom were born outside the Netherlands.
- 83% (106/127) were using antiretroviral therapy at their most recent clinical visit.
- 68% (86/127) had a most recent HIV RNA measurement below 200 copies/ml.

III. Continuum of care: current age ≥18 years with non-vertically-acquired HIV

- 219 individuals were older than 18 by 31 December 2017 and had acquired HIV through non-vertical transmission.
- Of these 219 individuals, 171 (78%) were still in care as of 31 December 2017; 48 individuals had been lost to follow up, including 24 women originating from sub- Saharan Africa.
- 72% (157/219) were using antiretroviral therapy during their last registered clinical visit.
- and 67% (147/219) had a most recent HIV RNA measurement below 200 copies/ml.

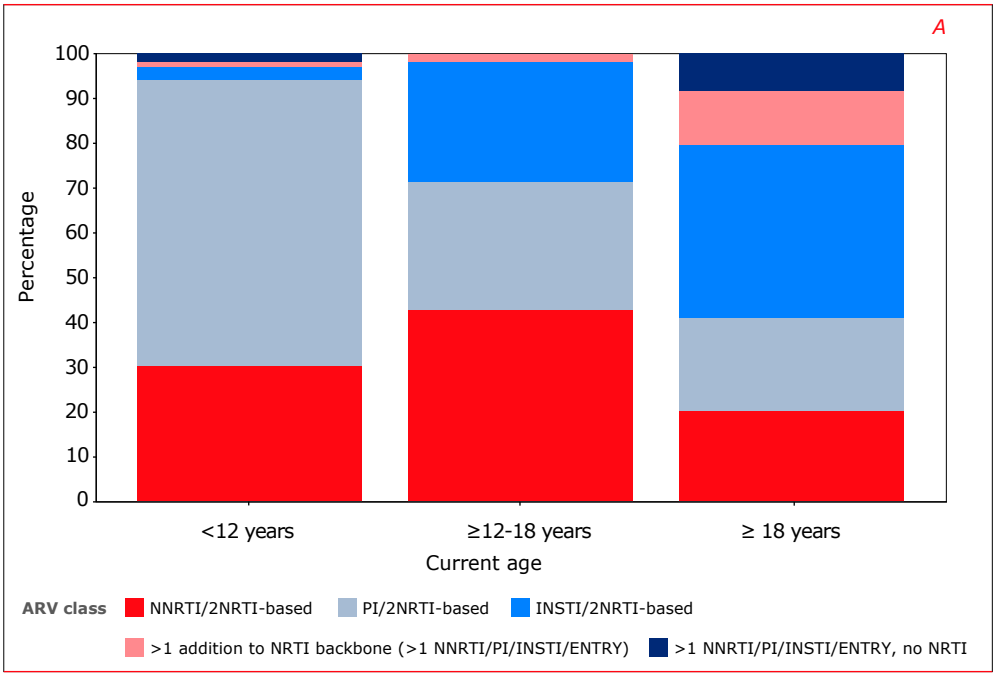
In care and on cART in 2017

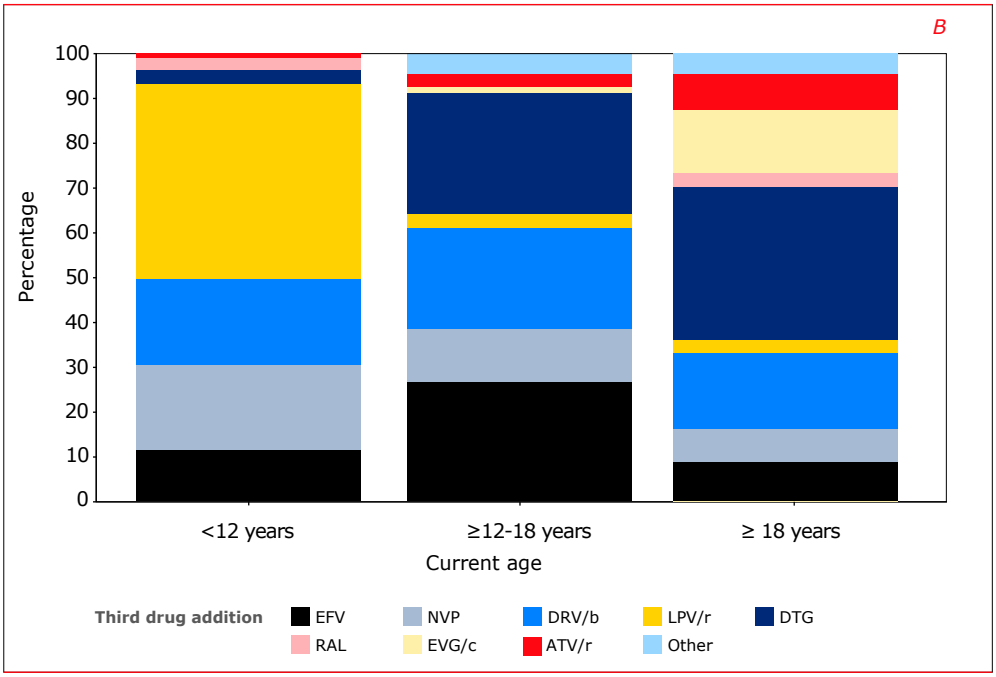
Of the 464 people known to be in care in 2017, 439 (95%) received cART in 2017. The distribution of current cART use is shown in *Figure 5.11*, according to age on 31 December 2017. Among those aged <12 years, a PI-containing regimen is currently used most often (64%), with lopinavir/ritonavir being the most common (43%).

In children aged between 12 and 18 years, 43% are currently using an NNRTI-based regimens, 28% are using a PI-based regimen, and 27% are using an INSTI-based regimen. Among those who are currently using an INSTI-based regimen, 27% use dolutegravir and another 27% use efavirenz.

Among people who were diagnosed with HIV in childhood, but who are currently over 18 years of age, 38% are using an INSTI-based regimen, comprising mainly dolutegravir.

Figure 5.11: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the current regimen, stratified by current age: (A) antiretroviral class and (B) specific drug.





Legend: *ARV=antiretroviral drug; ENTRY=entry inhibitor; INSTI=integrase inhibitor; NRTI=nucleoside analogue reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; 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.*

Special populations

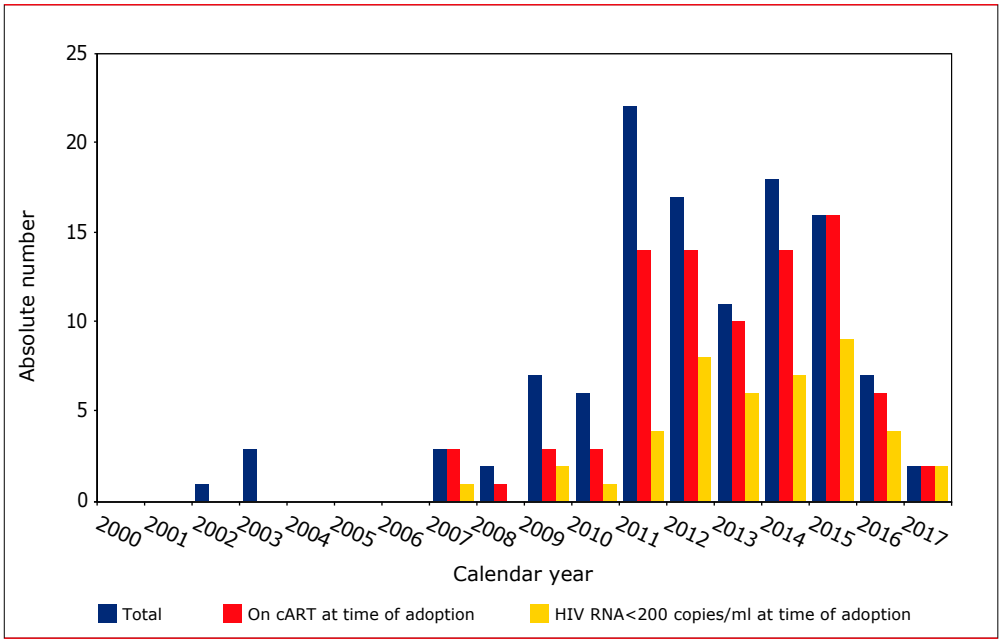
Adopted children

Of the 603 children ever registered, 115 children were adopted by Dutch parents (*Figure 5.12*):

- Their median age at time of entering care in the Netherlands was 2.7 years (IQR 6.4-4.7).
- 113 children ever used cART during follow up in clinical care in one of the Dutch HIV treatment centres.
- In total, 88 children were already receiving cART before being adopted.
- 9 children had been treated with monotherapy or dual therapy before the start of cART.
- The proportion of children receiving treatment prior to adoption increased over time, and was 100% for children adopted in 2017.

- At the moment of entering care in the Netherlands, only 44 (38%) of the 115 children had a viral load <200 copies/ml, and this proportion did not increase substantially over time.
- All children are currently alive and in care, and their median current age is 8.8 years (IQR 6.4-10.9).
- All children who started cART are still on treatment, and all 113 (100%) had an undetectable viral load (≤200 copies/ml) at the last known time point.

Figure 5.12: Number of HIV-positive children who entered paediatric care through adoption, by calendar year.



Legend: cART=combination antiretroviral therapy.

Individuals who transfer to adult care

Of the ever-registered 603 children, 358 children initially received HIV care in one of the paediatric HIV treatment centres. As of 31 December 2017, 128 (36%) of these 358 children had transferred from paediatric to adult care because they had reached 18 years of age.

The number of children who transferred to an adult centre varied from one child in 2000 to 20 in 2011, 11 in 2016, and 5 in 2017. The median age at transfer was 19.0 years (IQR 18.4-19.8). The median time in care after transfer was 4.8 years

(IQR 2.5-7.3). Of the children who transferred to adult care, 13 (10%) were lost to follow up, seven (5%) have since moved abroad, and two (1.6%) have died. The remaining 106 are currently alive and in care.

At their most recent clinical visit in 2017, 18 of the 106 individuals still in care (17%) had an HIV RNA level >200 copies/ml (median 5,180, IQR 1,740-60,000). The majority of these people were young women (58%) with vertically-acquired HIV (89%) and who were not originally from the Netherlands.

At the time of transfer to an adult HIV treatment centre, 89 (79%) of the 113 children with an available HIV RNA measurement had an HIV RNA ≤200 copies/ml and 24 (21%) had an HIV RNA level>200 copies/ml. These rates are comparable to results from the UK, which found that three quarters of the adolescents were virologically suppressed at time of transition[21]. We also observed comparable proportions of undetectable HIV RNA levels in the year before and after transfer to adult care: one year before transfer to adult care, 83% of the children had an HIV RNA level ≤200 copies/ml, compared to 80% of the young adults one year after their transfer.

Of those 24 adolescents without viral suppression at time of transfer, 1 had died, 6 were no longer in care and 7 had a most recent HIV RNA >200 copies/ml. The remaining 10 individuals had suppressed HIV RNA levels at their most recent HIV RNA measurement.

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 Weijsenfeld *et al.,* who confirmed an increased risk of virological failure between 18-19 years of age, with this risk being concentrated around the time of transitioning to adult care. Characteristics found to be significantly associated with virological failure were a low level of education and a lack of autonomy regarding medication adherence at the time of transitioning to adult care[22].

Summary

Among the 603 children diagnosed with HIV before the age of 18 and ever registered by SHM, 77% are still in care. A substantial proportion of the children newly registered since 2010 are children who have been adopted by Dutch parents, and this drives the small increase observed in the proportion of children in care aged between 0 and 5 years old.

The majority of children with vertically-acquired HIV were born outside the Netherlands. Vertical transmission of HIV within the Netherlands has become extremely rare, with no cases reported since 2015. This reflects the success of standardised HIV screening in the first trimester of pregnancy[12]. This measure does not, however, completely prevent vertical transmission from occurring. Physicians should therefore remain alert to the possibility of incident HIV acquisition later during pregnancy in women who tested HIV-negative during the first trimester and should also be aware of possible signs of primary HIV infection. Given the low prevalence (between 0.04% and 0.08%)[13] of primary HIV infection among pregnant women in the Netherlands, standardised repeat screening during pregnancy is not likely to be cost effective.

We observed low mortality rates in HIV-positive children in care in the Netherlands. The majority of HIV-positive children ever in care in the Netherlands have received cART. Over time, the initial cART regimens have changed and, in more recent years, mostly include lopinavir/ritonavir, and efavirenz, as well as the integrase inhibitors dolutegravir and elvitegravir in children 12 years of age or older.

Long-term immunological outcomes after initiating cART were poorer in children who started cART when they were five years of age or older. Moreover, although a less favourable initial virological response was seen in the youngest children, the overall viral suppression rate of HIV-positive children receiving cART is high and continues to improve over time, including among the youngest children.

The continuum of care shows a high retention-in-care rate among children currently aged less than 18 years. However, young people who have reached 18 years of age or above are more likely to be lost to follow up. Moreover, compared with children who are still below 18 years of age, a substantially lower proportion of those aged 18 years or above had suppressed HIV RNA levels by the end of 2017. It is also worth noting that all children who were adopted by Dutch parents had currently suppressed HIV RNA levels.

Of those individuals who were originally registered as a child and were still in care in 2017, 61% were older than 18 on 31 December 2017. The majority of these young

people are on cART. The high rate of detectable HIV viral load in these individuals around the time of transitioning to adult care is of concern. Although viral suppression rates have improved over time, resulting in relatively more young people being virally suppressed during their most recent clinical visit, there remains a group of young people who are unable to achieve HIV RNA suppression despite cART use.

Recommendations

The provision of care for children living with HIV in the Netherlands has resulted in generally favourable outcomes, with a low mortality rate and good long-term virological and immunological responses to treatment. An increasing proportion of the children have reached the age of 18 or older and have transitioned to adult care. Special attention is needed for this group, as this period of transition seems to be associated with an increased risk of virological failure. Although no cases of vertical HIV transmission within the Netherlands have been documented since 2015, there remains a need for awareness of the potential for incident HIV infections during pregnancy to ensure vertical transmission of HIV remains at zero.

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

In February 2018, Stichting HIV Monitoring launched a new data entry system, DataCapTree. The initial set of data collection protocols implemented in DataCapTree did not include data on pregnancies in women living with HIV in the Netherlands. Collection of this information was not initiated until later in 2018 and, consequently, at the time of writing this report, insufficient data were available on pregnancies in women living with HIV in 2017 to allow us to carry out informative analyses. We therefore refer our readers to the HIV Monitoring Report of 2017, which provides a comprehensive overview of pregnancies in women living with HIV in the Netherlands up to the end of 2016. An update will be provided in next year's report.

7. Quality of care

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

Box 7.1: Definitions

Diagnosis	The moment an individual is newly diagnosed with an HIV infection. The time of diagnosis can be weeks, months, or years after infection.
Registration	The moment an HIV-positive individual in care is notified to SHM by their treating 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 individuals is registered with SHM.
Entry into care	The moment an HIV-positive individual is first seen for care in an HIV treatment centre, which is usually within a few weeks of HIV diagnosis.
Volume indicator	The number of people newly entering care for the first time between 2012 and 2016 for each treatment centre.
Outcome indicators *Retention in care*	I. Short term retention: The proportion of people who entered care at an HIV treatment centre between 2012 and 2017 for the first time after diagnosis and who were still in care, had not moved and had not died at least 18 months after entering care II. Retention in care in 2017: the proportion of people who had not moved, had not died and had a clinical visit in 2017, stratified by year of entering care (2012-2017).

Initiation of cART	I. Start of combination antiretroviral therapy (defined as a combination of three antiretroviral drugs from two different antiretroviral drug classes) within 6 months of entry into care. II. The proportion of people who had entered care between 2012 and 2016, had initiated cART, and were still in care in 2017.
Viral suppression	I. The proportion of treatment-naive people with a plasma HIV RNA level <400 copies/ml at 6 months after the start of cART. II. The proportion of all HIV-positive people on cART for at least 6 months with a plasma HIV RNA level <100 copies/ml. III. The proportion of people who entered HIV care between 2012 and 2016, were still in care in 2017, and had a plasma HIV RNA level <100 copies/ml.
Process indicators *Prior to cART initiation*	The proportion of people newly entering HIV care for whom data were available on CD4 count, plasma HIV RNA, total cholesterol, and screening for the presence of hepatitis C virus (HCV) co-infection and hepatitis B virus (HBV) co-infection in the 6 months after entry into care.
Following cART initiation	I. The proportion of people in whom CD4 cell count, plasma HIV RNA and total cholesterol measurements were carried out at least once within approximately 12 months after cART initiation. II. The proportion of men who have sex with men (MSM) who were HCV-negative at entry into care and in whom repeat HCV screening was carried out within approximately 18 months after the initial HCV negative test. III. The proportion of MSM for whom syphilis serology was repeated within approximately 18 months after the first assessment at entry into care.

Box 7.2: Data used in this chapter

DataCapTree: impact of new data entry system launched in 2018 on 2017 data
In 2018, Stichting HIV Monitoring launched a new data entry system, DataCapTree, which went live in February 2018 with an initial set of approved data collection protocols. Data included in this new data entry system at the time of the May 2018 database lock were used in this chapter to describe patients newly entering care, the initiation of cART and retention in care rates. However, as the laboratory data were not yet fully up to date by May 2018, the decision was made to use data from the database lock of 31 December 2017 (from the previous data entry system, Oracle Clinical) for those indicators that include laboratory measurements. As data collection over the previous year standardly continues through the months of January to May in the subsequent year, the use of laboratory data from an earlier database lock may mean that the backlog in data collection over 2017 might be slightly greater than in previous years.

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 individuals living with HIV in outpatient care in the currently 26 officially acknowledged HIV treatment centres, SHM provides a nationwide overview of the outcome of care for individuals living 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 people in the Netherlands[1]. Using these guidelines as a basis, we defined a set of indicators with which to explore the quality of care in Dutch HIV treatment centres and 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 (DHHS) HIV/AIDS practice guidelines. These indicators were classified as volume, outcome or process indicators.

As reported in earlier studies, the number of patients in care (i.e., the centre volume) may have an impact on the reported indicators[2,3,4]. In particular, a smaller number of patients in some HIV treatment centres could result in less informative proportions, as a single deviating score on an indicator could result in a wide range of scores for a given indicator. 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 (red dots): ≥700 patients (11 centres); medium-sized (blue dots): 400-700 patients (9 centres); small (grey dots): ≤400 patients (6 centres). Patients who switched between centres are presented as a green dot (*retention in care* indicator only).

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 number 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 each year between 2012 and 2017 for each treatment centre.

Outcome indicators

The outcome indicators included *retention in care*, *initiation of cART* and *achievement of viral suppression*. For the purpose of the current analysis, we defined short-term and long term retention in care as follows:

Short term retention in care was defined as the proportion 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 who were still alive and in care at least 18 months after entering care. Patients who died were excluded from the retention in care indicators.

Retention in care in 2017 was defined as the proportion of patients who had not moved, had not died, and had had a clinical visit in 2017, stratified by year of entering care (2012-2015). During the observation period, approximately 14% of patients switched treatment centres; these patients were considered to be retained in care, since they were documented as having remained in care and were not lost to follow up. However, to avoid double counting, they were not assigned to a particular centre, but were included in a separate category.

Initiation of cART describes, in the first place, the overall proportion of patients who had entered care between 2012 and 2016 and who had started cART within 6 months of entry into care. This indicator was stratified by CD4 cell count at entry into care: CD4 ≥500 cells/mm^3, CD4 350-500 cells/mm^3 and CD4 <350 cells/mm^3. Secondly, the initiation of care indicator describes the proportion of patients who had ever initiated cART among those who entered care between 2012 and 2016 and who were still in care in 2017.

Viral suppression was assessed by three indicators. The first indicator was defined as the proportion of treatment-naive patients with a plasma HIV RNA level <400 copies/ml at 6 months after the start of cART. The HIV RNA measurement closest to 6 months after the start of cART was chosen, with a minimum window of 3 months and a maximum of 9 months. The target suppression rate was set at ≥90%. This indicator, developed using the Delphi method, is part of the HKZ certification process and was defined jointly with the NVHB[5] during the development of *Zichtbare Zorg* (Visible Healthcare; ZiZo) indicators and HKZ.

The second indicator for viral suppression was the proportion of all HIV-positive patients on cART for at least 6 months with a plasma HIV RNA level <100 copies/ml. This indicator was calculated for the calendar years 2012-2017.

The third indicator for viral suppression was the proportion of all HIV-positive patients who entered care between 2012 and 2016 and who were still in care in 2017 with a most recent plasma HIV RNA level below <100 copies/ml, regardless of cART use.

Process indicators

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

To calculate the process indicators prior to cART initiation, we included all patients who had entered care between 2012 and 2016. Only patients who had 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 proportion of patients newly entering care between 2012 and 2016 for whom the following measurements were available in the 6 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 virus (HBV) co-infection. In terms of cholesterol measurements, patients were stratified according to age the at time of entering care (<50 years and ≥50 years).

To calculate the process indicators following cART initiation, we included patients who had started cART in 2012-2016. The indicators were defined as the proportion 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 MSM. The first of these indicators was calculated for MSM who were HCV-negative at entry into care in 2012-2015. We calculated the proportion with repeat HCV serology or HCV RNA within approximately 18 months after the date of their HCV negative test result. 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.

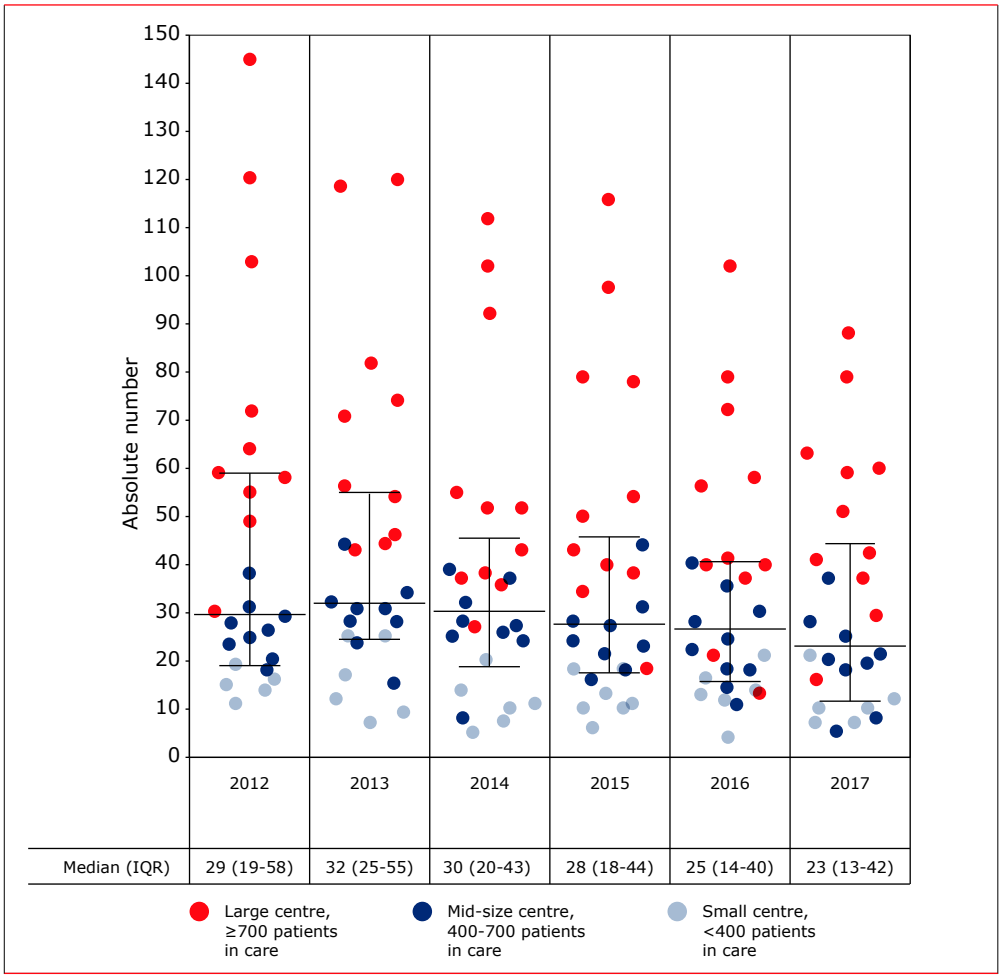
The second of the MSM-specific indicators was derived for all MSM who entered care in 2012-2015, and describes the proportion of men for whom syphilis serology was repeated within approximately 18 months after the first time syphilis was assessed.

Results

Volume indicator

The numbers of patients who newly entered care in 2012-2017 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 23 in 2017 and shows a small decrease over time. The minimum number ranged from 11 patients in 2012 to 4 in 2016 and 5 in 2017. In 2017, ten HIV treatment centres had fewer than 20 newly-entering patients.

Figure 7.1: Annual number of patients newly entering care per HIV treatment centre in the Netherlands in 2012–2017.



Legend: IQR=interquartile range.

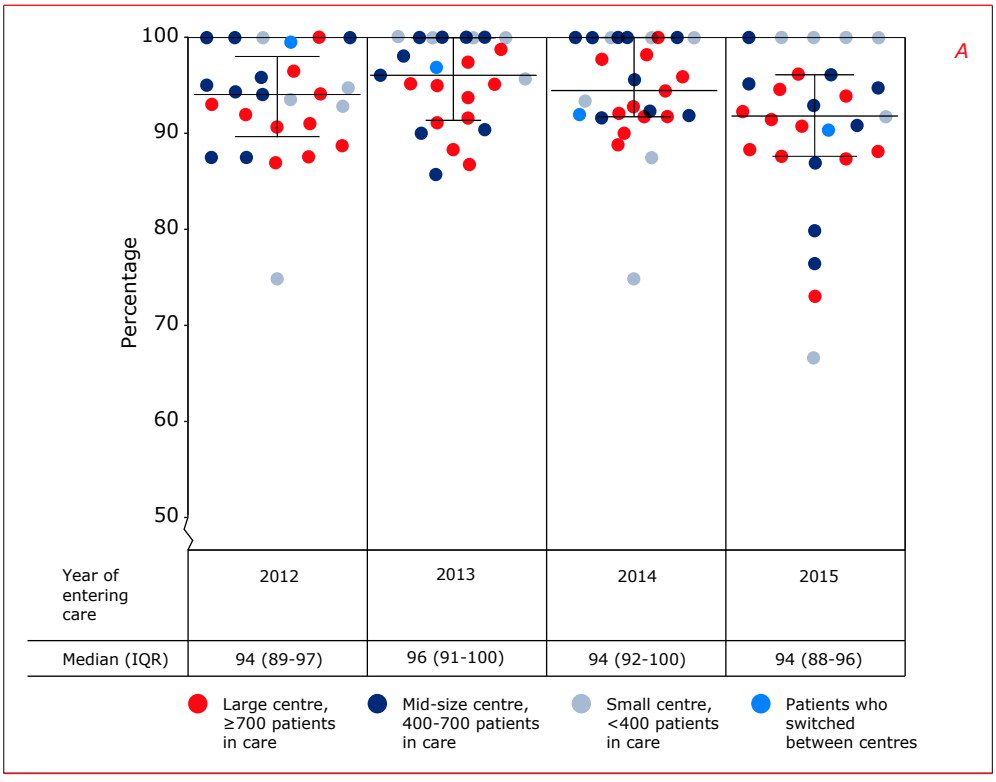
Retention in care

Figure 7.2A shows the variation in retention in care rate across treatment centres for patients who entered care between 2012-2015. The median retention rates varied between 94% and 92%, with a minimum of 67% and a maximum of 100%.

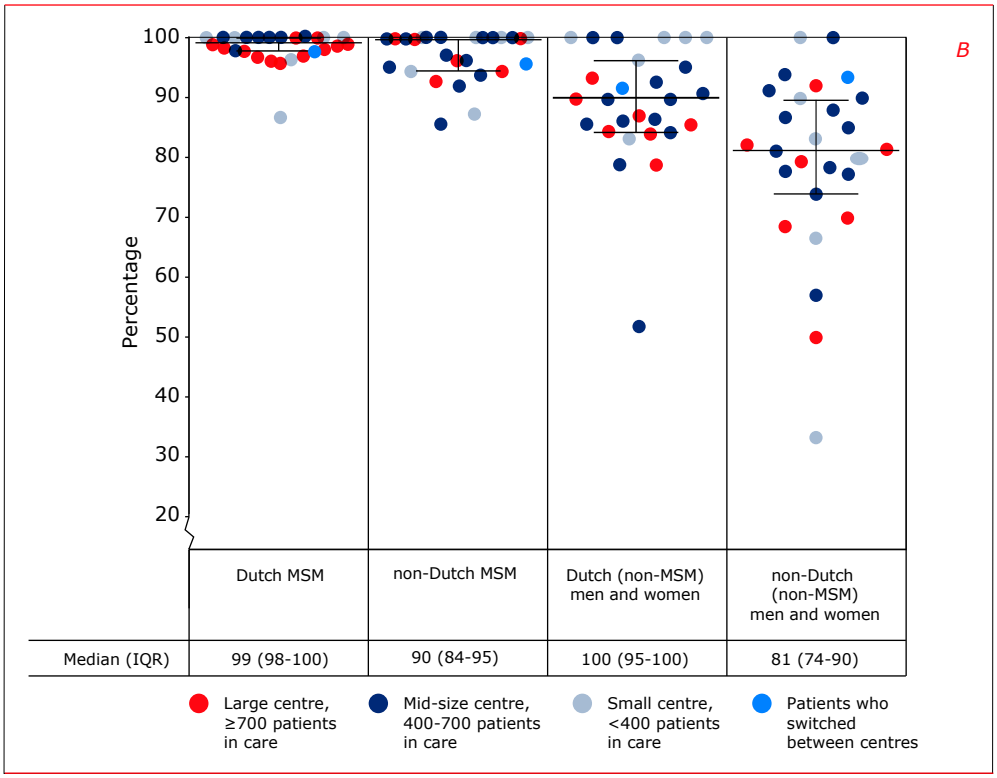
Figure 7.2B shows the retention rates for those who entered care between 2012-2015, stratified by MSM vs non-MSM and by patients' region of origin (Dutch vs non-Dutch). Retention in care rates were highest in Dutch MSM (99%) and Dutch (non-MSM) male and female patients (100%) compared with non-Dutch MSM (90%) and non-Dutch (non-MSM) male and female patients (81%), respectively (Chi square test p<0.0001). Lower retention rates were observed among non-Dutch MSM from western European countries other than the Netherlands and women from eastern Europe or an unknown region of origin.

Figure 7.2C shows the long term retention-in-care rates. Among patients who entered care in 2012, the median retention-in-care rate in 2017 was 84%. This rate increased when people entered care more recently, with a median retention rate of 95% for those who entered care in 2016.

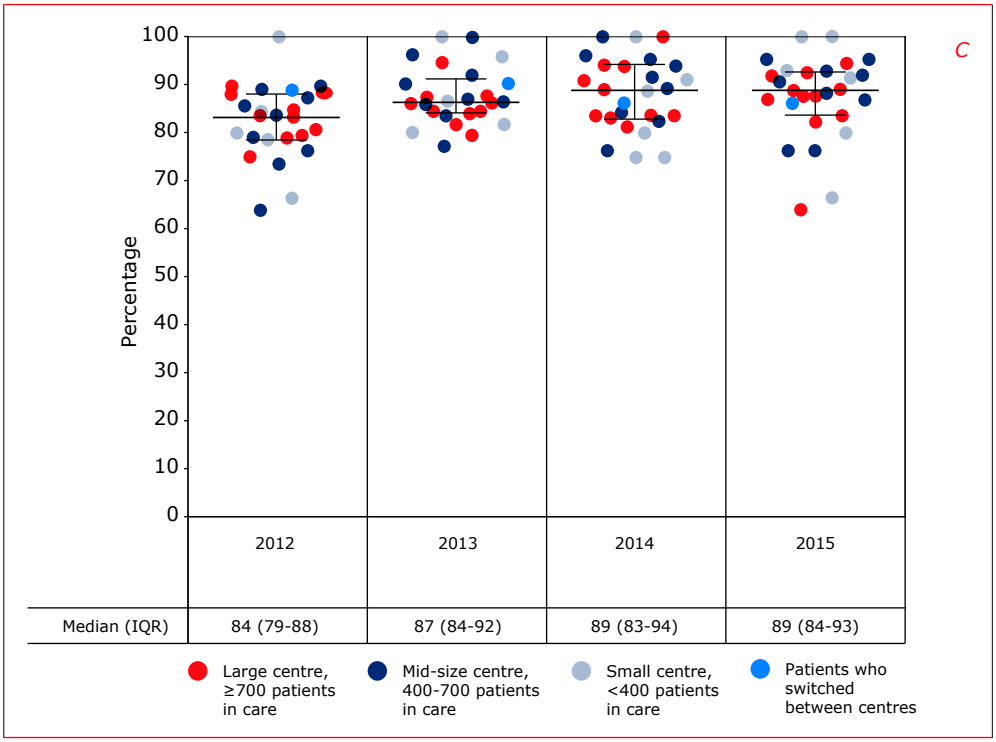
Figure 7.2: *Retention in care: A) 18 months after entering care, over time by year of entering care, B) by HIV transmission group and patients' region of origin, C) in 2017 for those who entered care between 2012–2015. Retention rates are presented as the median and interquartile range across all HIV treatment centre.*



Legend: *IQR=interquartile range.*



Legend: *IQR=interquartile range.*



Legend: *IQR=interquartile range.*

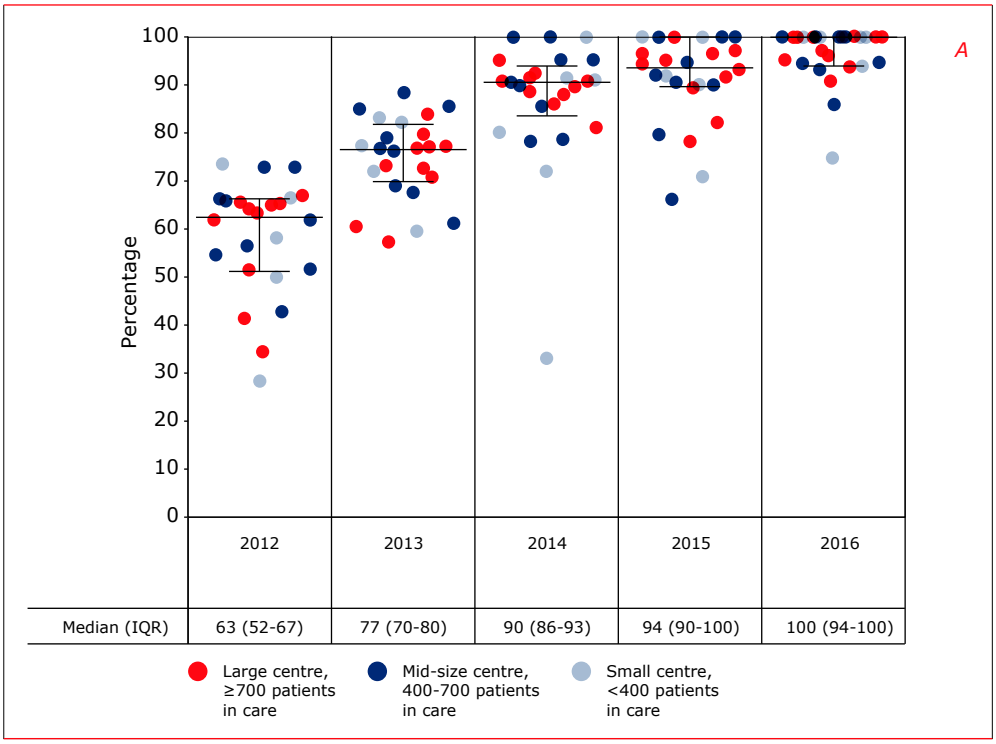
Initiation of cART

Figure 7.3A shows the proportions of patients starting cART within 6 months after entering care. Overall, a median of 63% of the patients who entered care in 2012 started cART within 6 months of entry, and this proportion increased to a median of 100% among those who entered care in 2016. In terms of variation across HIV treatment centres, the lowest proportion of patients starting cART within 6 months was 29% for 2012 and 75% in 2016.

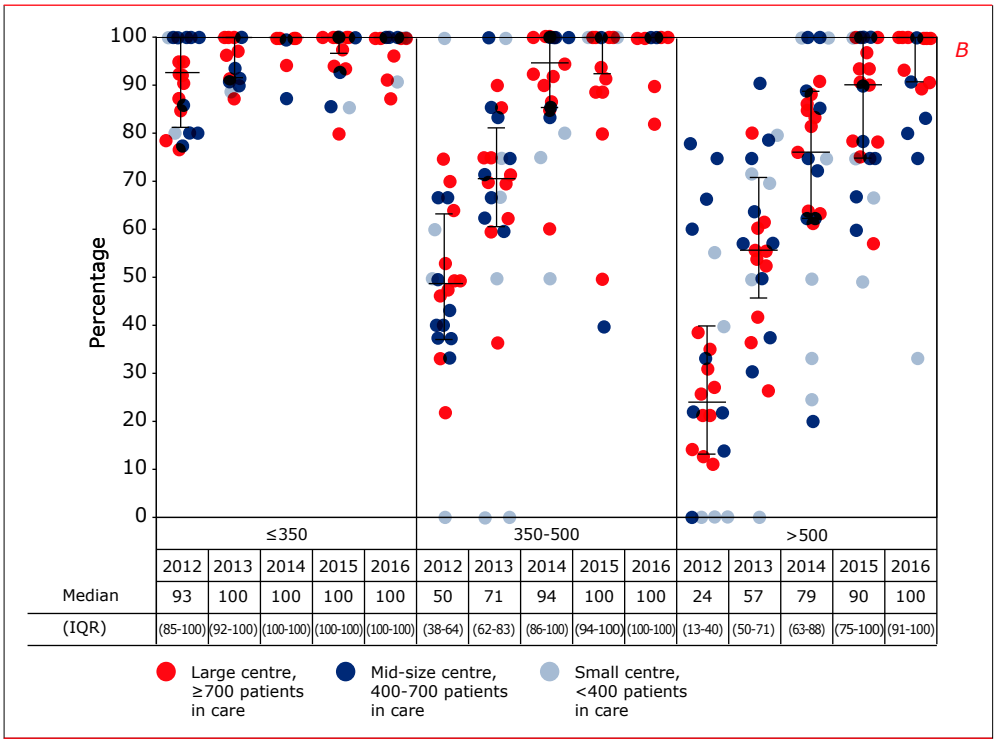
When stratified by CD4 cell count, the proportion of patients starting cART within 6 months of entering care was lower for the CD4 cell category >500 cells/mm^3, compared with that of <350 cells/mm^3 (*Figure 7.3B*). This difference between CD4 cell categories became smaller over time, and in 2016 the median proportions of patients starting cART within 6 months was 100% for all CD4 cell count strata; nonetheless, considerable variation remained between HIV treatment centres. This variation was greatest for individuals who entered care with more than 500

CD4 cells/mm^3. Among those who entered care between 2012 and 2016 and remained in care in 2017, almost everyone had initiated cART (98%). This proportion was greater than 90% in all centres (*Figure 7.3C*).

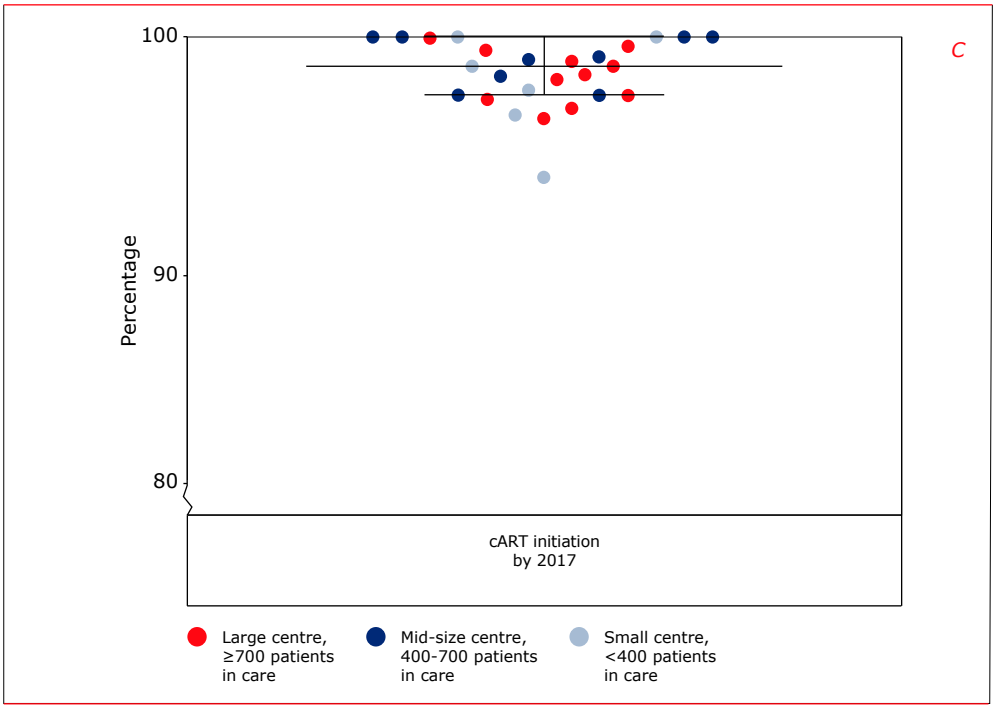
Figure 7.3: *The proportion of patients who entered care between 2012–2016 and started combination antiretroviral therapy (cART) within 6 months after entry: A) overall, B) by CD4 cell count at entry, C) the proportion who newly entered care between 2012–2016 and who initiated cART and were still in care in 2017.*



Legend: *IQR=interquartile range.*



Legend: *IQR=interquartile range.*

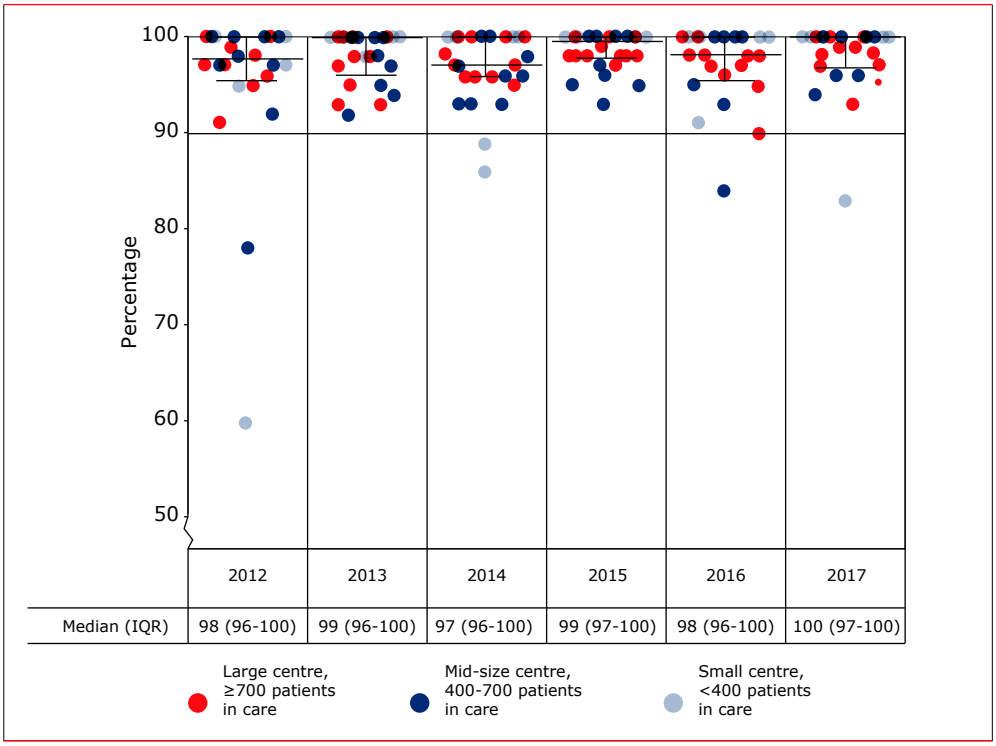


Legend: *cART=combination antiretroviral therapy.*

Viral suppression

Viral suppression was assessed with three indicators. The first indicator is the proportion 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. *Figure 7.4* shows the viral suppression rates for patients newly initiating treatment during the period 2012-2017. The median rates varied from 97% to 100% in this period. In 2017, in one small treatment centre, less than 90% of the treatment-naive patients had achieved an HIV RNA <400 copies/ml within 6 (3-9) months after starting cART.

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



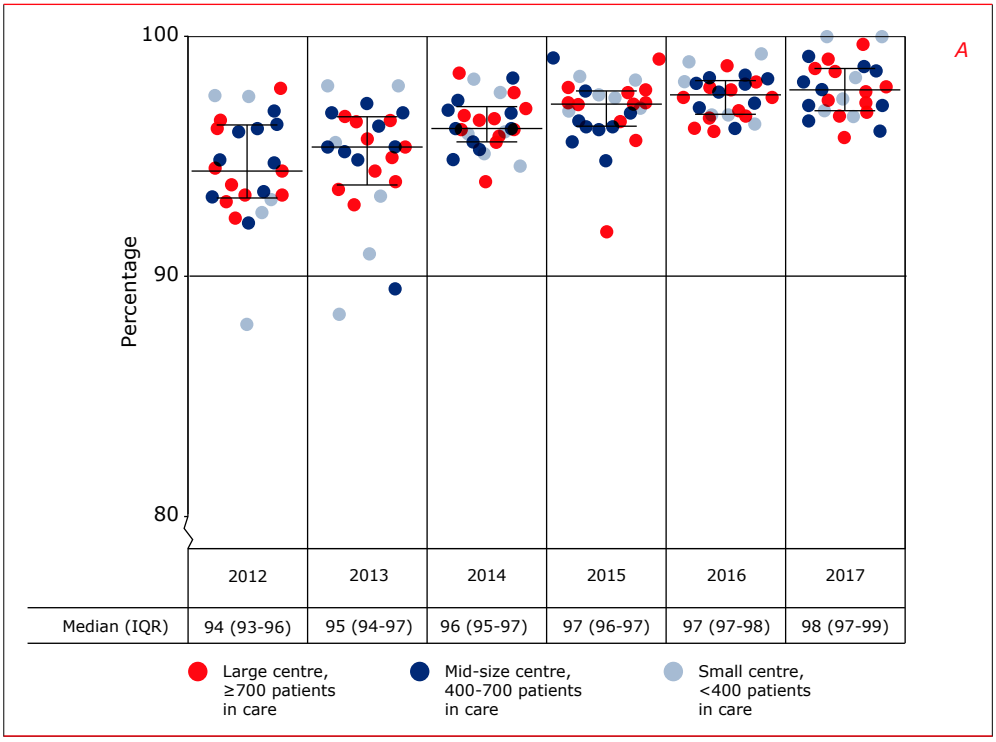
***Legend:** IQR=interquartile range.*

The second viral suppression indicator is the proportion of all HIV-positive patients in care who have been on cART for at least 6 months and have a last available HIV RNA level <100 copies/ml. This indicator was calculated for the calendar years 2012-2017 (*Figure 7.5A*). In all calendar years, the median proportion was more than 90%, with limited variation according to centre size.

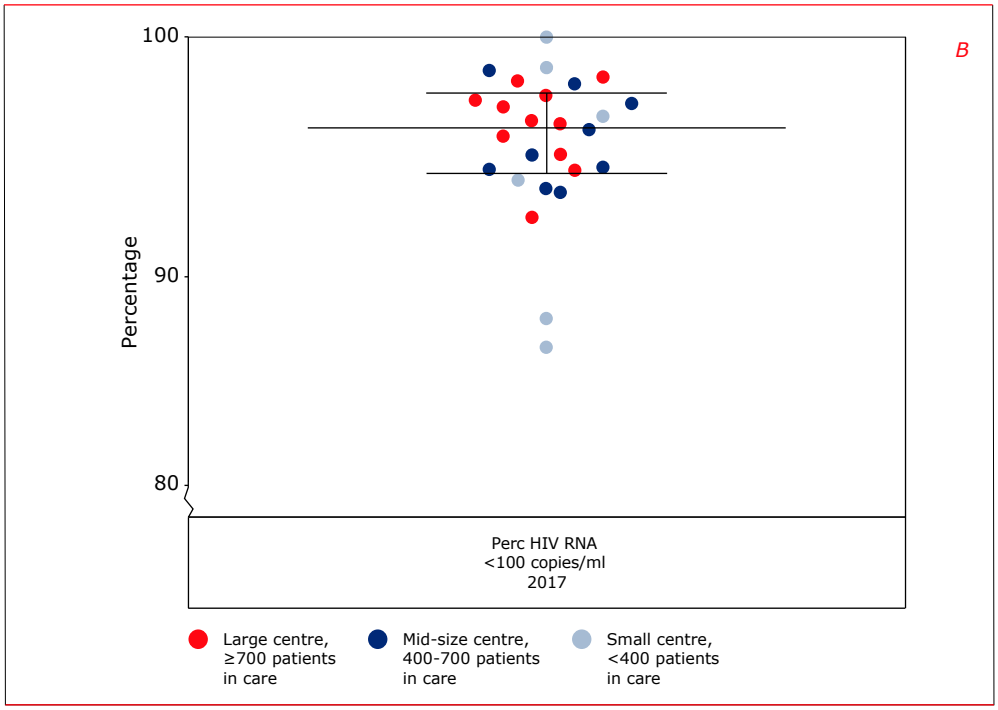
Overall, and not stratified by treatment centre, the proportion of patients with long-term viral suppression was slightly lower in those of non-Dutch origin than in those originating from the Netherlands (96% vs 98%, p=0.001). Moreover, MSM had higher suppression rates after more than 6 months of cART use than non-MSM (98% vs 95%, p<0.0001).

Figure 7.5B shows the proportion of patients who entered care between 2012-2016, were still in care in 2017, and had a last available HIV RNA level <100 copies/ml, regardless of cART use. Overall 96% of the patients in care in 2017 had an HIV RNA level<100 copies/ml, although this rate was below 90% for two HIV treatment centres.

Figure 7.5: *A) The proportion of all HIV-positive patients in care who had been on combination antiretroviral therapy (cART) for at least 6 months and who had an HIV RNA level <100 copies/ml. This indicator was calculated for each calendar year during the period 2012-2017 and is presented as the proportion across all HIV treatment centres; B) The proportion of HIV-positive patients who entered care between 2012-2016 and who are still in care in 2017 with an HIV RNA level <100 copies/ml.*



Legend: *IQR=interquartile range.*



Process indicators

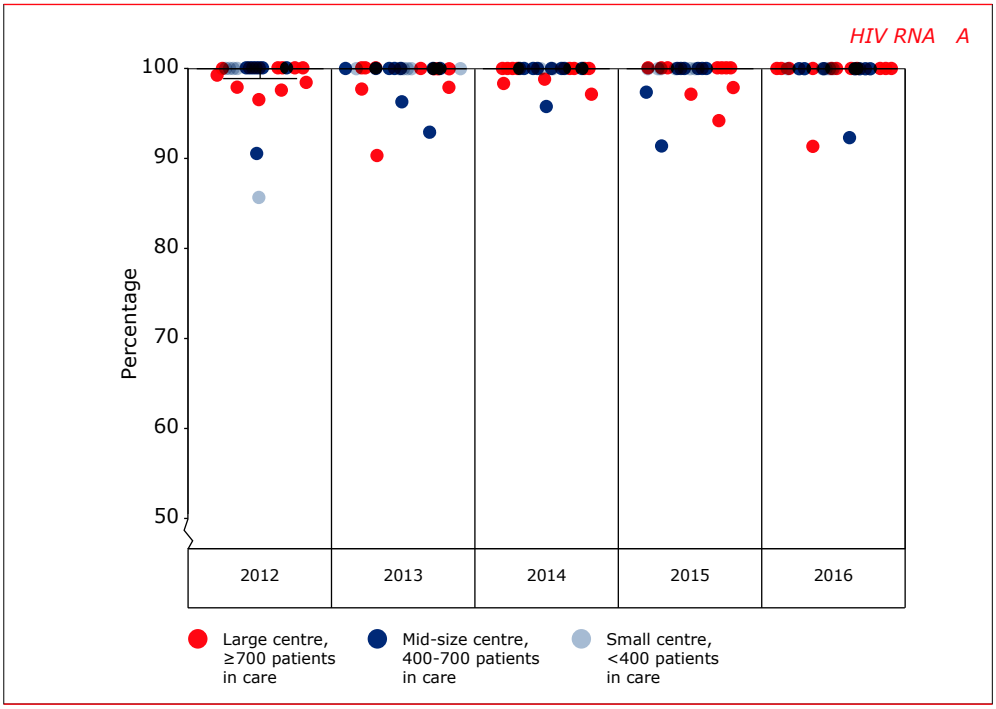
Prior to starting cART

Figure 7.6 shows the variation between Dutch HIV treatment centres in terms of measuring plasma HIV RNA, CD4 cell count, and total cholesterol (stratified by age at first visit), as well as HCV and HBV screening, in patients who newly entered care in 2012-2016. The median rates of testing for plasma HIV RNA and CD4 cell count within 6 months after entering care were stable over time and greater than 90% in all years. However, there was considerable inter-centre variation in those patients with a cholesterol measurement. This variation was greater in patients below 50 years of age at the time of their first clinical visit than in those above 50 years. Although, in the majority of centres all patients above 50 years of age had a cholesterol measurement, there remained some centres in which less than 90% of patients above 50 years of age had an available cholesterol measurement.

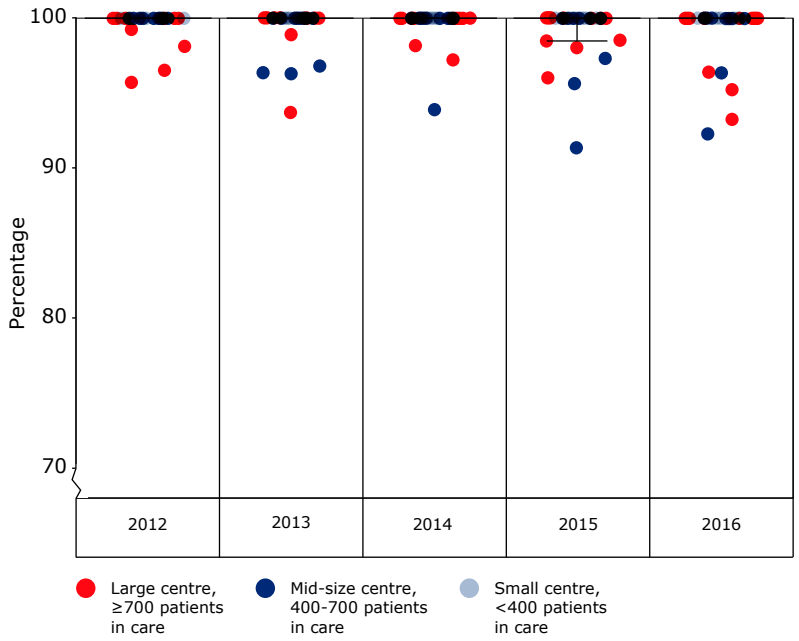
In terms of HCV screening, the median proportions of patients being screened improved over time from 87% in 2012 to 94% in 2016. The maximum proportion of patients screened for HCV was 100% in all years, while the minimum rates were between 54% (2014) and 73% (2015). Overall, patients who were screened for HCV during their first year in care were more likely to be MSM (p=0.004), although one centre did have a minimum HCV screening rate of 64% among MSM. Of those patients who were not screened for HCV (regardless of HIV transmission mode) during their first months in care, 47% were subsequently tested for HCV: for this group the median time between entry in care and their first HCV test was 17 months (IQR=13-28 months).

The median proportion of patients screened for HBV also increased over time from 90% in 2012 to 93% in 2016. However, observed minimum rates were 55% in 2013 and 33% in 2016.

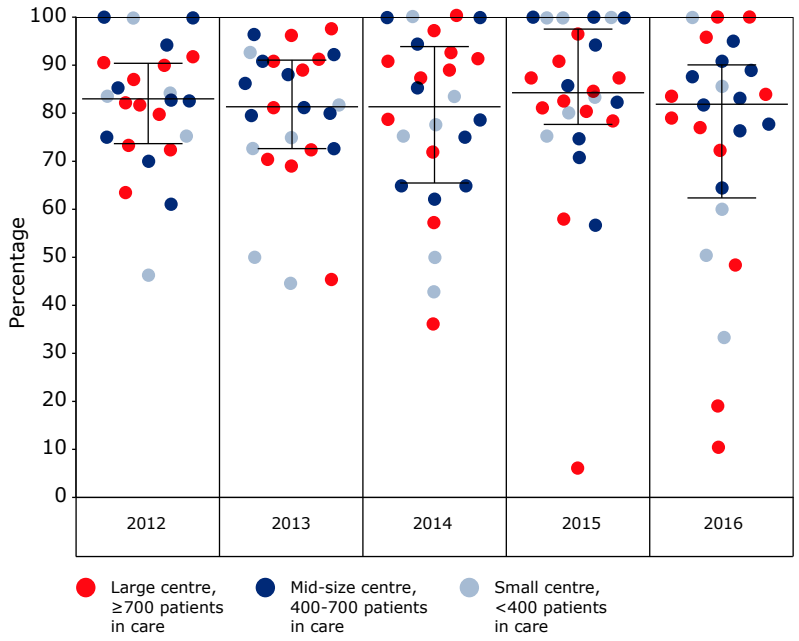
Figure 7.6: Proportions of patients who newly entered care in Dutch HIV treatment centres in 2012–2016, with assessment within 6 months of (A) HIV RNA, (B) plasma CD4 cell count, (C) total cholesterol in patients aged <50 year at entry in care, (D) total cholesterol in patients aged ≥50 year at entry in care, (E) hepatitis C and (F) hepatitis B.



CD4 B

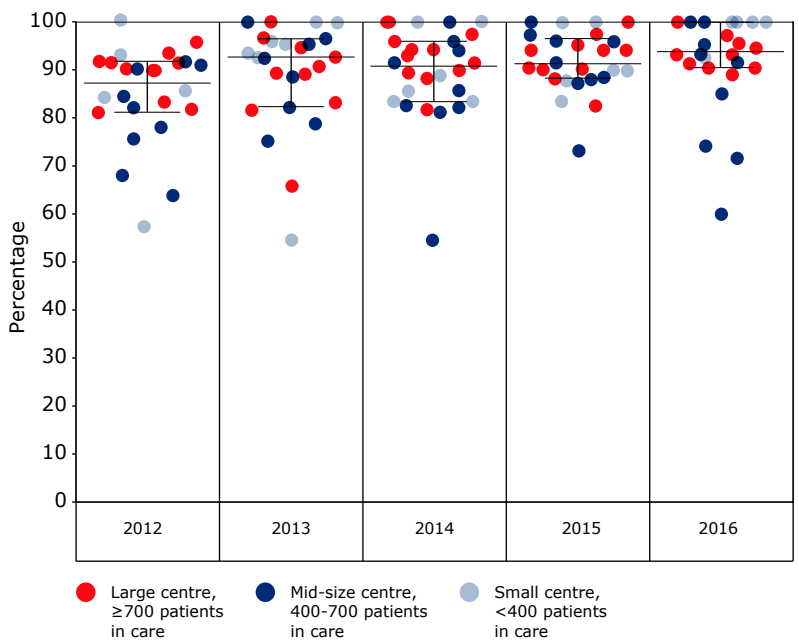


Total cholesterol <50 years C

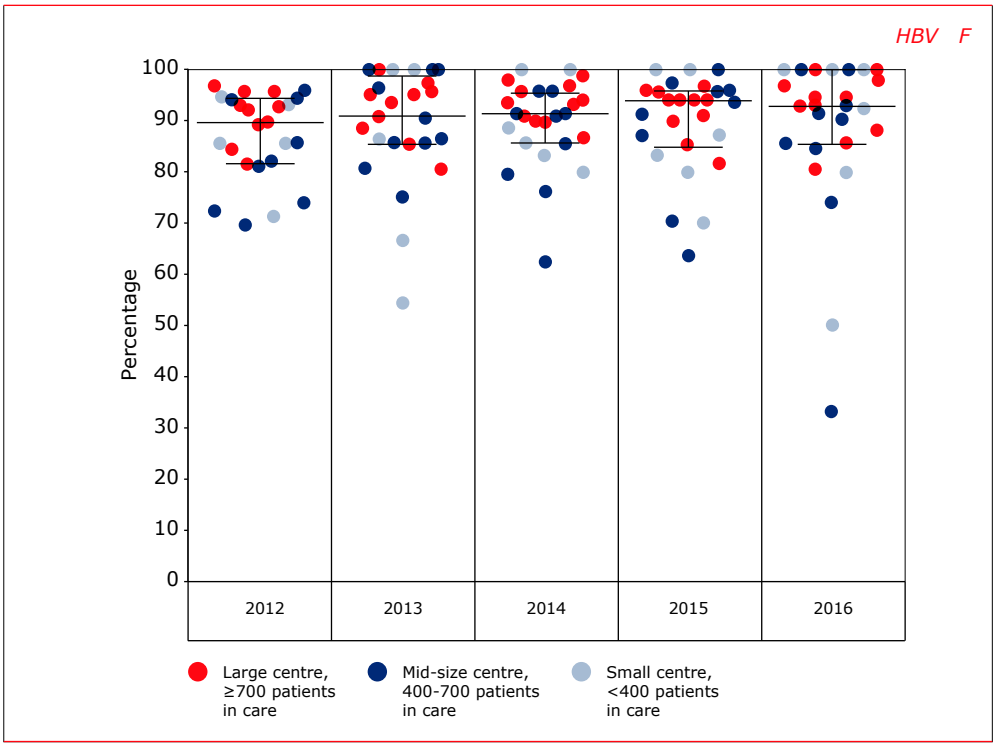


Total cholesterol ≥50 years D

HCV E



Legend: *HCV=hepatitis C virus.*

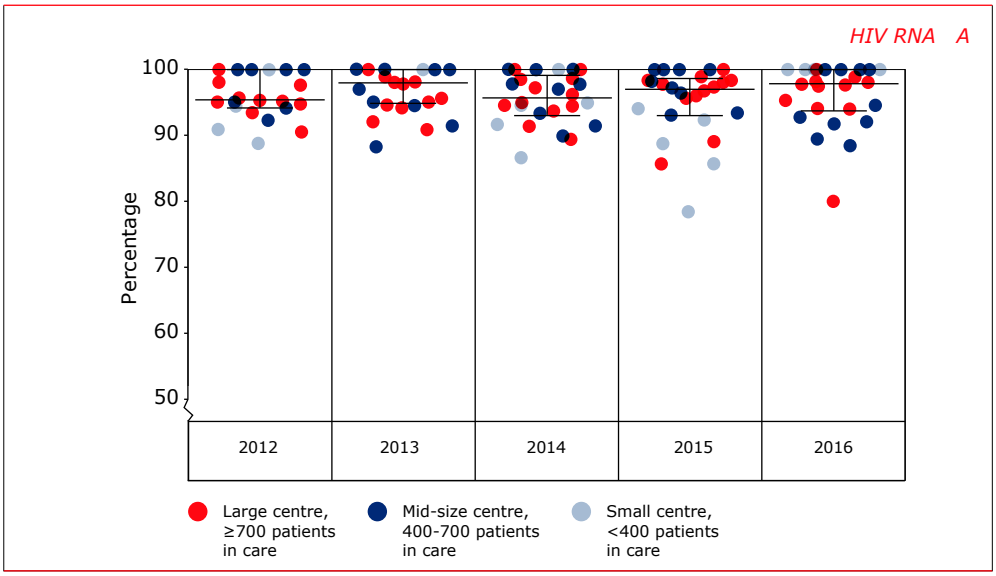


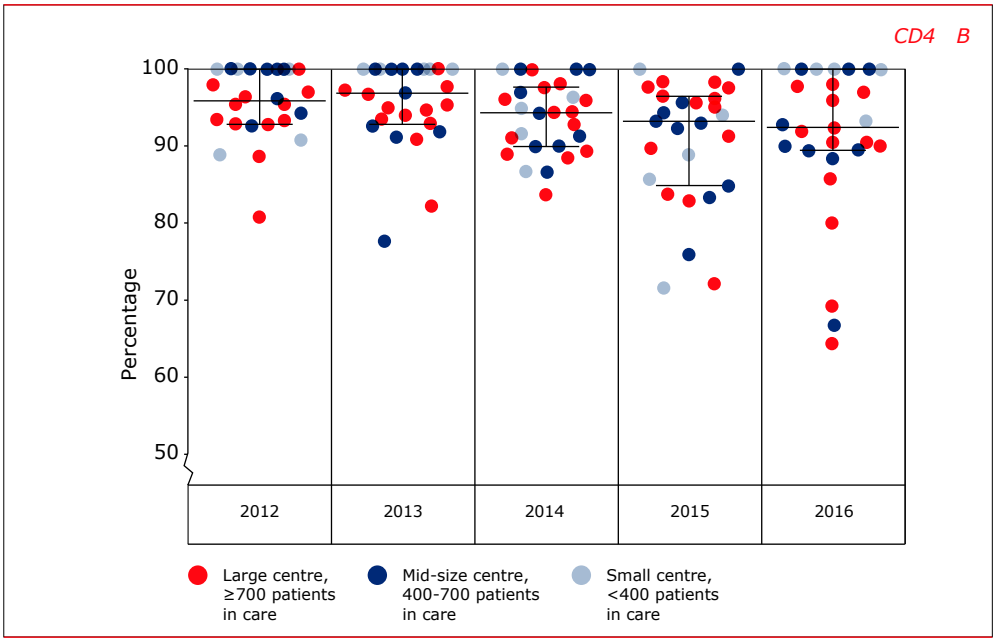
Legend: HBV=hepatitis B virus.

Following the start of cART

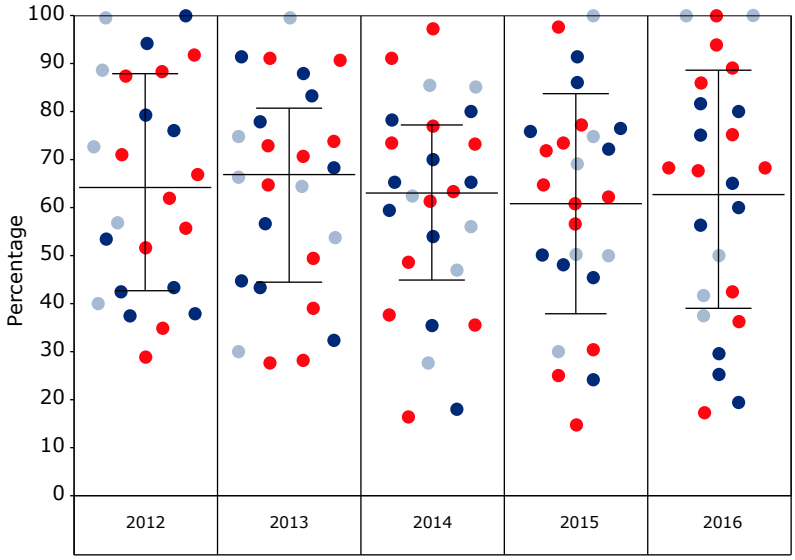
Figure 7.7 shows the variation between HIV treatment centres in the Netherlands in terms of assessing plasma HIV RNA, CD4 cell count, and total cholesterol, stratified by age, once within 13 months after cART initiation for all patients who initiated cART between 2012 and 2016 and who were still in care 12 months after starting cART. The median proportion of patients with an HIV RNA measurement remains stable high over time. However, the median proportion of patients with a CD4 cell measurement has decreased over time, from 81% in 2012 to 64% in 2016. Finally, the assessment of total cholesterol following treatment initiation varied greatly between treatment centres, irrespective of centre size and time-updated age (*Figure 7.7C* and *7.7D*).

Figure 7.7: Proportions of patients in HIV treatment centres in the Netherlands who initiated combination antiretroviral therapy (cART) in 2012–2016, with assessment of (A) HIV RNA, (B) plasma CD4 cell count, (C) total cholesterol in patients aged <50 year at entry in care, (D) total cholesterol in patients aged ≥50 year at entry in care within 13 months after start of cART.

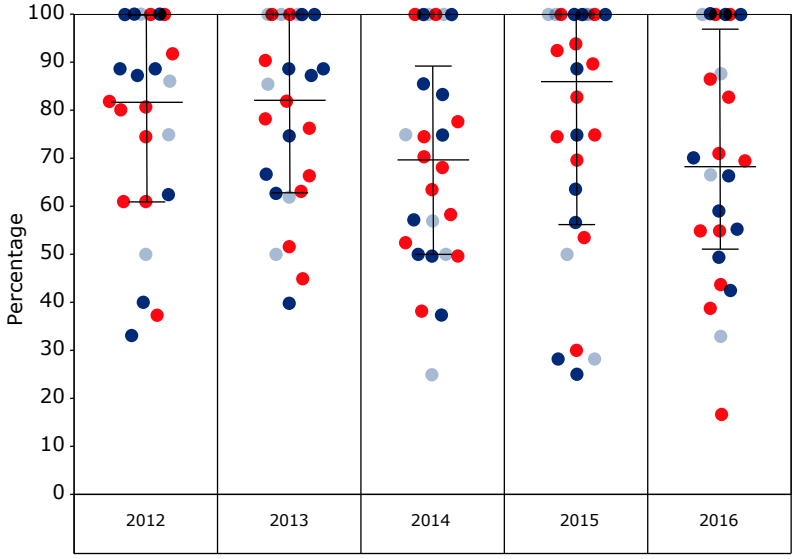




Total cholesterol <50 years C



Total cholesterol ≥50 years D

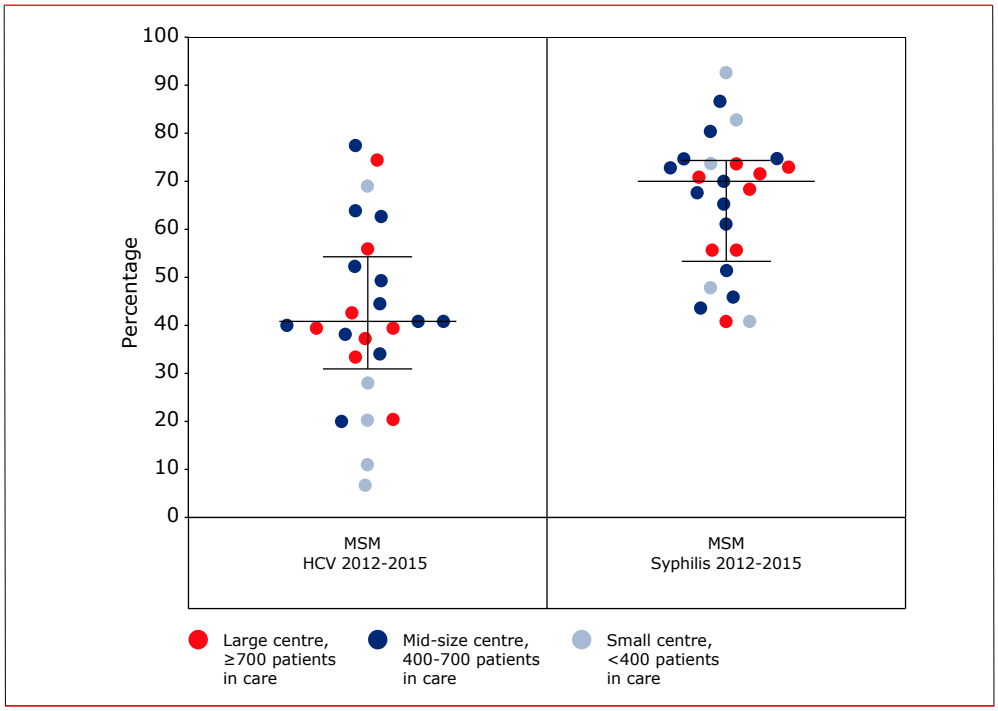


Repeat screening for hepatitis C and syphilis in MSM

To assess repeat screening for hepatitis C virus and syphilis in MSM, 18 months of follow up after the first documented HCV serology test date is required. We therefore used 2015, rather than 2016, as the most recent year of entry.

Between 2012 and 2015, 2,765 MSM newly entered care; of those, 2,518 (95%) were screened for the presence of HCV in the first year after entering care. Sixty-one (2%) of these 2,518 MSM tested positive for HCV. The remaining 2,457 (98%) MSM were HCV-negative when they entered HIV care, and this group was included in the calculation of the repeat HCV screening rate. *Figure 7.8* depicts the rate of repeat HCV screening within 18 months after the first screening among MSM who were HCV-negative at entry into care. This figure shows considerable variation in the rate of repeat HCV screening. The median rate of repeat HCV antibody or HCV RNA testing in MSM who were HCV-negative at entry into care was 42%; the maximum rate was 78%, while one centre carried out repeat HCV tests in only 7% of MSM who were HCV-negative at entry into care. In total 1,372/2,457 MSM were not repeatedly screened for the presence of HCV. Of note, for 12 of these 1372 (1%) MSM, repeat HCV screening could not be documented despite the presence of at least one elevated ALAT measurement (≥200 u/l, 5x40 u/l) during the observation period, possibly indicating acute HCV infecton[6]. A large degree of variation was also observed between HIV treatment centres for repeat syphilis screening among MSM during follow up. The maximum rate of patients undergoing repeat syphilis screening was 93%, and the minimum was 41%, with the median being 70%.

Figure 7.8: Rates of repeat screening for hepatitis C virus (HCV) among men who have sex with men (MSM) who were HCV-negative at entry in care and for syphilis among all MSM who entered care in one of the HIV treatment centres in 2012 and 2015.



Legend: HCV=hepatitis C virus.

Changes in performance over time

SHM has provided HIV treatment centres with the outcomes of centre-specific, ZiZo and HKZ-approved indicators since 2011. However, in 2017, SHM also provided each centre with a number of the indicators described in this chapter, in a manner that allowed the centres to compare their indicators with the blinded scores of other centres. Subsequently, several centres approached SHM for more specific data regarding their scores.

In the context of quality of HIV care in the Netherlands, the data presented in this chapter may therefore serve as a useful benchmark with which to compare centres and identify potential aspects for improvement. It is likely too early to observe an effect of this benchmarking, as most of the recent indicator scores are only reported through 2016. Nonetheless, general improvements in performance over time have

been observed for earlier initiation of cART, as well as for HBV and HCV screening prior to cART initiation. On the other hand, a decline was observed over time in the performance of CD4 measurements after cART initiation, and the overall assessment of cholesterol remains low over time. Finally, although, performance in terms of the HKZ indicator 'short term viral suppression' is generally high, one centre failed to achieve a score greater than 90% on more than one occasion.

This year each treatment centre will again be provided with their centre-specific indicators benchmarked against the blinded scores of all other centres. This will allow treatment centres to potentially identify elements of care that may be further improved.

Key findings and conclusions

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

- In 2017, 10 HIV treatment centres did not meet the criterion of seeing a minimum of 20 new patients per year, as required by the current HKZ standards for HIV treatment centres in the Netherlands. Seven of these centres had already failed to meet this particular criterion in 2016.
- After exclusion of patients who had died, overall and treatment centre-specific retention-in-care rates 18 months after entering care are generally high. However, lower retention rates were observed for patients of non-Dutch origin (both for MSM and non-MSM) than for patients born in the Netherlands. This is in line with the continuum of care presented in *Chapter 1* of this report.
- Over time, the proportion of patients initiating cART within 6 months after entering care has clearly increased, reaching a median of 100% for those who entered care in 2017. However, considering that current guidelines recommend treatment for all patients regardless of CD4 count[1], it is worth noting that the rates for starting cART within 6 months were still relatively lower in patients who entered care with a CD4 cell count >500 CD4 cells/mm^3. This effect was observed in small, mid-sized, and large treatment centres and indicates a need for further improvement.
- Regardless of time since entering care, a median of 99% of all patients who had entered care between 2012 and 2016 and who were retained in care in 2017 had initiated cART.
- 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.

- A median of 96% of the patients who had entered care between 2012 and 2016 and who were retained in care in 2017 had an HIV RNA level <100 copies/ml.
- In MSM who had entered care between 2012 and 2015 and who were HCV-negative at entry into care, the rate of repeat HCV screening varied widely. However, these findings should be interpreted with some caution for two reasons. Firstly, national guidelines[1] currently only recommend repeat screening for HCV in those MSM who report behaviour which continues to put them at risk of sexually acquired HCV. However, SHM does not collect data on risk-taking behaviour and we were therefore unable to account for this in our analyses. Secondly, the variation in repeat HCV screening may be explained by physicians applying a policy of targeted screening based on the presence of incident transaminase elevations as an indicator of liver damage. This notion is supported by the observation that the majority of those MSM not screened for HCV did not have elevated transaminase levels.
- In MSM who entered care between 2012 and 2015, repeat syphilis screening also varied considerably. As with HCV, this variation may reflect differences in screening policy between centres, possibly based on the assessment of risk-taking behaviour. However, as SHM does not collect data on risk-taking behaviour, we were unable to account for this in our analyses.
- Quality of care covers several aspects of health care[7,8]. As such, the wide range of indicators used in these analyses 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, incidentally, some of the reported variation may be due to missing data.

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Special reports

8. The Amsterdam Cohort Studies on HIV infection: annual report 2017

Amy Matser, Ward van Bilsen 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 2017, the cohorts reached 33 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 33 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 also become an important component of the ACS research programme.

From the outset, research in the ACS has taken a multidisciplinary approach, integrating epidemiology, social science, virology, immunology, and clinical medicine in one study team. This unique collaboration has been highly 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 Amsterdam University Medical Centers (Academic Medical Center [AMC] site): Departments of Medical Microbiology, Experimental Immunology, and Internal Medicine [Division of Infectious Disease]; the Emma Kinderziekenhuis (paediatric HIV treatment centre); Stichting HIV Monitoring (SHM); MC Jan van Goyen: Department of Internal Medicine; and the Hiv Focus Centrum (DC Klinieken Lairesse). From the start, Sanquin Blood Supply Foundation has been involved

in the ACS and, since 2007, has provided financial support for 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 Netherlands 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 2017

The cohort of men who have sex with men

As of 31 December 2017, 2,796 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 also collected for diagnostic tests and storage. Of the 2,796 MSM, 607 were HIV-positive at entry into the study, and 253 seroconverted during follow up. In total, the GGD Amsterdam was visited 58,410 times by MSM.

From 1984 until 1985, men who had had sexual contact with a man in the preceding six months were enrolled independent of their HIV status. In the period 1985 – 1988, 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 preceding six months. From 1988 to 1998, the cohort was also open for HIV-positive MSM. During the period 1995–2004, only men aged ≤30 years with at least one male sexual partner in the previous six months could enter the study. From 2005 to 2013, recruitment has been open to MSM of all ages with at least one sexual partner in the preceding six months.

Since 2013, HIV-negative men of all age groups have been eligible to participate in the ACS if they live in or are closely connected with the city of Amsterdam and have had at least one male sexual partner in the preceding six months. In line

with the advice issued by the international scientific advisory committee in 2013, the cohort now makes additional efforts to recruit young HIV-negative MSM (age ≤30 years).

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 MC Jan van Goyen. 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. Blood samples from these participants are stored. 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 2017, 701 HIV-negative and 73 HIV-positive MSM were in active follow up at the GGD Amsterdam; in other words, these men had visited the cohort at least once in the current or preceding year. Of the 73 HIV-positive MSM, 73 had filled in behavioural questionnaires. In addition to the HIV-positive MSM visiting the GGD Amsterdam, 256 HIV-positive MSM were followed outside the GGD Amsterdam at the MC Jan van Goyen or the DC Klinieken Lairesse-Hiv Focus Centrum in Amsterdam. Behavioural questionnaires were filled in by 35 of these men. In 2017, 60 new HIV-negative MSM were recruited. The median age in this group was 29.5 years (interquartile range [IQR] 25.7-34.3), while that of the total group of MSM in active follow up was 42.5 years at their last visit (IQR 34.7-49.5). The majority (85.0%) of the total group were born in the Netherlands and 83.8% were residents of Amsterdam. Finally, 75.3% of the participants had a college degree or higher.

The cohort of drug users

As of 31 December 2016, 1,680 PWUD were included in the ACS and contributed 28,194 visits. In 2014, the cohort was closed for new participants. Regular follow up of drug users continued until February 2016. All PWUD who had ever participated in the ACS were then invited for an end-of-study interview and follow up of PWUD was successfully ended in July 2016. 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 college degree or higher, 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 comparing the effects of early temporary antiviral therapy with that of no therapy among patients who presented with primary HIV-1 infection at the AMC HIV outpatient clinic and ACS seroconverters). These samples are stored at the AMC. At present, 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$_h$IV cohort study

The AGEhIV cohort study (a collaboration between the AMC Departments of Infectious Diseases and Global Health, the 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 ≥45 years, and to determine the extent to which comorbidities, their risk factors and their relation to quality of life differ between HIV-positive and HIV-negative 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-negative participants from similar risk groups through the STI clinic at the GGD Amsterdam (n=486) or the ACS (n=64). All participants were aged ≥45 years and were as comparable as possible with respect to age, gender, ethnicity, and risk behaviour. By the end of 2017, 340 HIV-1-positive participants and 308 initially HIV-negative individuals had completed the fourth follow-up visit. The fourth visits will be completed in the first half of 2018, and the fifth study round will start in the fall of 2018.

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 MC Jan van Goyen. 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.

H2M2 study

In 2015, a study based on the H2M cohort was initiated to identify potential predictors for high-grade anal intra-epithelial neoplasia (HGAIN) in the HIV-positive MSM population. This study, the H2M2, is an Aidsfonds-supported project and a collaboration between the GGD Amsterdam, AMC, DC Klinieken Lairesse, the RIVM-CIb, DDL Diagnostic Laboratory, VUmc and the DKFZ German Cancer Research Center. The study includes a subset of the HIV-positive ACS participants (n=19). Analyses showed that among 193 HIV-positive MSM, persistence of an HPV type in the preceding years was strongly associated with an HGAIN caused by that type. Neither HPV-specific antibodies, nor the HPV viral load of anal infections was predictive for HGAIN. Analyses among a larger group of HIV-positive MSM showed that there are no demographic, behavioural, or HIV-related variables that usefully may predict the presence of HGAIN.

H2M3 study

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. 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 analyses of anal samples have been conducted. This study found that a quarter of MSM had not cleared an anal HPV-16 infection after three 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. Thus, even in highly pre-exposed men, the incidence rate of hrHPV infections is high. In 2017, collection of anal and penile swabs from ACS participants continued and these will be stored for future studies. The H2M3 study is a collaboration between GGD Amsterdam, ACS, and Crucell.

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 2017, 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 were provided with PrEP until June 2018.

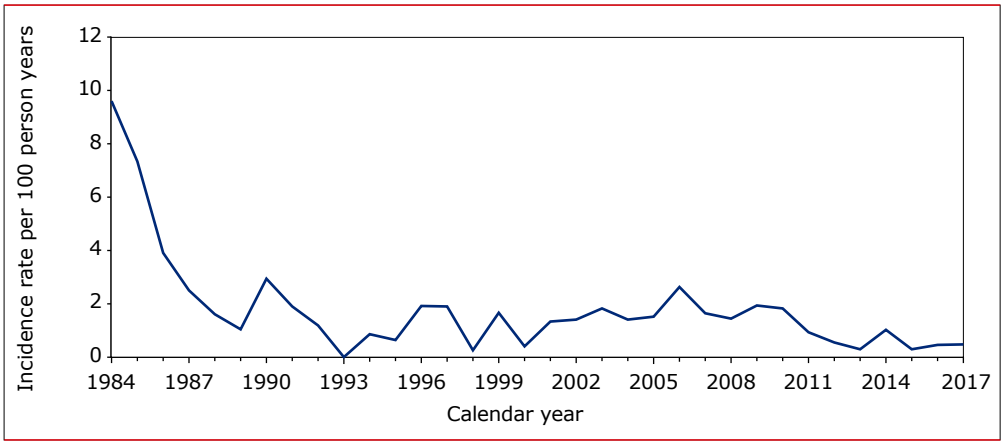
The AMPrEP project is part of the HIV Transmission Elimination Amsterdam (H-TEAM) initiative, a multidisciplinary and integrative approach to stop the epidemic (www.hteam.nl).

The HIV epidemic

HIV incidence

In 2017, 2 MSM participating in the ACS seroconverted for HIV. The observed HIV incidence among MSM has remained relatively stable in recent years and was 0.5 per 100 person years in 2017. *Figure 1* shows the yearly observed HIV incidence rate for MSM from the start of the ACS through 2017, respectively.

Figure 1: HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984–2017.



Transmission of therapy-resistant HIV strains

In 2018, no surveillance of transmission of drug-resistant HIV-1 strains was performed.

Combination antiretroviral therapy (cART) uptake

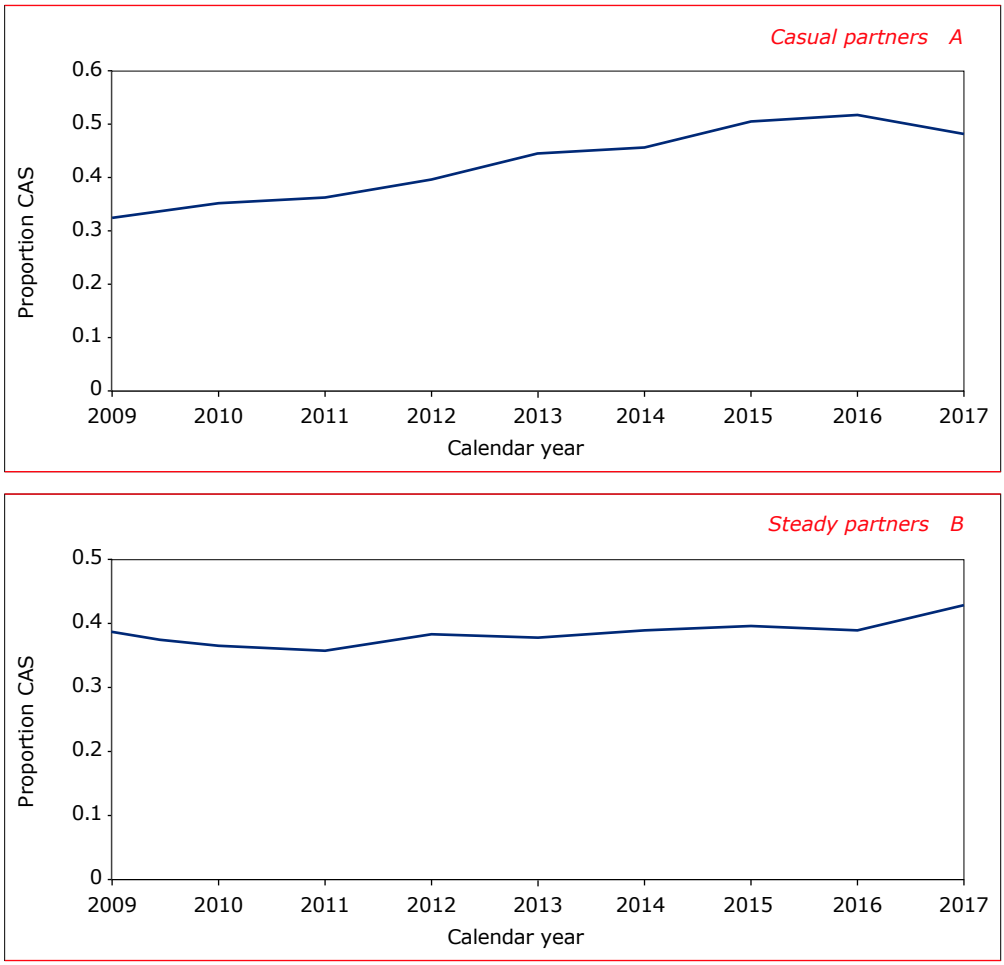
Of the 344 HIV-positive MSM included in the ACS, treatment data were available for 329 MSM in 2017. Of these, 306 (94%) received some form of antiretroviral therapy in 2017.

Risk behaviour of MSM in ACS

Condomless anal sex (CAS) with a steady partner was reported by 256/583 (43.9%) HIV-negative MSM in active follow up at their last cohort visit, compared with 209/461 (45.3%) who reported CAS with a casual partner.

Trends in CAS among HIV-negative MSM participating in the ACS, especially CAS with casual partners, continue to show a gradual increase from 2009 onwards. (*Figure 2*). The use of pre-exposure prophylaxis was reported by 60/655 (9.2%) HIV-negative MSM in active follow up.

Figure 2: *Trend in proportion of condomless anal sex (CAS) with A) casual partners and B) steady partners among HIV-negative men who have sex with men (MSM) in the Amsterdam Cohort Studies (ACS), 2009-2017.*



Legend: *CAS=condomless anal sex,*

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 2017, 684 MSM from the ACS were screened for STIs. The overall prevalence of any STI (i.e., chlamydia, gonorrhoea, syphilis, and HCV) was 14.9% (93/625) among HIV-negative MSM and 39.0% (23/59) among HIV-positive MSM.

ACS 2017 research highlights

DC-SIGN polymorphisms associate with risk of hepatitis C virus infection among men who have sex with men but not among injecting drug users

We aimed to identify whether genetic polymorphisms within L-SIGN or DC-SIGN correlate with hepatitis C virus (HCV) susceptibility. A men who have sex with men (MSM) and an injecting drug users (IDU) cohort of HCV cases and multiple-exposed uninfected controls were genotyped for numerous L-SIGN and DC-SIGN polymorphisms. DC-SIGN single nucleotide polymorphisms (SNPs) –139, –871, and –939 correlated with HCV acquisition in the MSM cohort only. When the same SNPs were introduced into a transcription activity assay they demonstrated a reduction in expression with predicted alteration in binding of transcription factors. DC-SIGN promoter SNPs correlated with risk of HCV acquisition via sexual but not IDU exposure, likely through modulation of mRNA expression levels.

Steba GS, Koekkoek SM, Vanhommerig JW, Brinkman K, Kwa D, Van Der Meer JTM, Prins M, Berkhout B, Tanck M, Paxton WA, Molenkamp R, Schinkel J; MSM Observational Study of Acute Infection with Hepatitis C (MOSAIC) Study Group and Amsterdam Cohort Studies (ACS).

J Infect Dis. 2018 Jan 17;217(3):353-357. doi: 10.1093/infdis/jix587

HIV and hepatitis C treatment uptake among people who use drugs participating in the Amsterdam Cohort Studies, 1985–2015

HIV-positive people who use drugs (PWUD) start antiretroviral therapy (ART) later than other risk groups, and among HCV-positive PWUD, HCV treatment uptake is low. Since 2014, HCV direct-acting antivirals (DAAs) are available and reimbursed in the Netherlands. Temporal trends in ART and HCV-treatment uptake among PWUD in the ACS from 1985 through 2015 were described. Treatment uptake was defined by: treatment initiation (the proportion initiating any kind of ART/HCV treatment when treatment-naïve) and coverage (the proportion ever treated for HIV/HCV) among all HIV-/HCV-RNA-positive PWUD. Each was calculated per calendar year. We estimated the cumulative probability of ART uptake in the pre-

cART (<1996) and cART era (January 1, 1996) among HIV seroconverters, with all-cause mortality as a competing risk. Of 1,305 PWUD, 263 (20.2%) were HIV-antibody positive and 810 (62.1%) were HCV-antibody positive, at study entry. ART coverage increased over time, from 5.7% in 1990 and 42.2% in 1996 to 91.7% in 2015. The proportion initiating ART ranged from 4.8% in 1990 to 33.3% in 2011. At 8 years after HIV seroconversion, 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 but lower among HIV-coinfected (23.5%) than HCV-monoinfected PWUD (52.5%). In 2015, 3.0% initiated HCV treatment with DAAs. We observed an increase in ART and HCV-treatment coverage among PWUD over time. As expected, ART uptake was higher in the cART era than the pre-cART era. Although in 2015 HCV treatment coverage was relatively high, DAA uptake was still low.
van Santen DK, van der Helm JJ, Lindenburg K, Schim van der Loeff M, Prins M. *Int J Drug Policy.2017 Sep;47:95-101. doi: 10.1016/j.drugpo.2017.05.026. Epub 2017 Jun 9.*

Steering committee

In 2017, the steering committee met three times. Nine proposals for use of data and/or samples (serum/PBMC) were submitted to the committee: Two from the AMC Medical Microbiology department, five from the AMC Experimental Immunology, and two from GGD Amsterdam. Three of the proposals were collaborations with groups outside the ACS. Seven requests were approved of which two after major revisions recommended by the ACS steering committee; for the remaining 2 proposals, pilot experiments were requested.

Publications in 2017 that include ACS data

Sexual risk behaviour trajectories among MSM at risk for HIV in Amsterdam, the Netherlands
Basten M, Heijne JCM, Geskus R, Den Daas C, Kretzschmar M, Matser A.
AIDS. 2018 Jun 1;32(9):1185-1192. doi: 10.1097/QAD.0000000000001803

Reference curves for CD4 T-cell count response to combination antiretroviral therapy in HIV-1-infected treatment-naïve patients
Bouteloup V, Sabin C, Mocroft A, Gras L, Pantazis N, *et al.* 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

From clinical sample to complete genome: comparing methods for the extraction of HIV-1 RNA for high-throughput deep sequencing
Cornelissen M, Gall A, Vink M, Zorgdrager F, Binter S, *et al.* BEEHIVE Consortium.
Virus Res. 2017 Jul 15;239:10-16. doi: 10.1016/j.virusres.2016.08.004. Epub 2016 Aug 4

NK cells in self-limited HCV infection exhibit a more extensively differentiated, but not memory-like, repertoire
de Groen RA, Groothuismink ZMA, van Oord G, Kootstra NA, Janssen HLA, *et al.*
J Viral Hepat. 2017 Nov;24(11):917-926. doi: 10.1111/jvh.12716. Epub 2017 May 17

Analysis of resistance-associated substitutions in acute hepatitis C virus infection by deep sequencing across six genotypes and three continents
Eltahla AA, Rodrigo C, Betz-Stablein B, Grebely J, Applegate T, *et al.* InC3 Study Group.
J Viral Hepat. 2017 Jan;24(1):37-42. doi: 10.1111/jvh.12615. Epub 2016 Sep 25

Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study
European Union HCV Collaborators.
Lancet Gastroenterol Hepatol. 2017 May;2(5):325-336. doi: 10.1016/S2468-1253(17)30045-6. Epub 2017 Mar 15

HIV-1 blocks the signaling adaptor MAVS to evade antiviral host defense after sensing of abortive HIV-1 RNA by the host helicase DDX3
Gringhuis SI, Hertoghs N, Kaptein TM, Zijlstra-Willems EM, Sarrami-Forooshani R, *et al.*
Nat Immunol. 2017 Feb;18(2):225-235. doi: 10.1038/ni.3647. Epub 2016 Dec 26

Anal HPV 16 and 18 viral load: a comparison between HIV-negative and HIV-positive MSM and association with persistence
Marra E, King A, van Logchem E, van der Weele P, Mooij SH, *et al.*
J Med Virol. 2018 Jan;90(1):76-83. doi: 10.1002/jmv.24898. Epub 2017 Oct 17

Design and crystal structure of a native-like HIV-1 envelope trimer that engages multiple broadly neutralizing antibody precursors in vivo
Medina Ramirez M, Garces F, Escolano A, Skog P, de Taeye SW, *et al.*
J Exp Med. 2017 Sep 4;214(9):2573-2590. doi: 10.1084/jem.20161160. Epub 2017 Aug 28

Multiplex flow cytometry-based assay to study the breadth of antibody responses against E1E2 glycoproteins of hepatitis C virus
Merat SJ, van de Berg D, Bru C, Yasuda E, Breij E, *et al.*
J Immunol Methods. 2018 Mar;454:15-26. doi: 10.1016/j.jim.2017.07.015. Epub 2017 Aug 30

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. 2018 Jan;19(1):42-48. doi: 10.1111/hiv.12536. Epub 2017 Jul 25

Spontaneous clearance of hepatitis C virus infection among human immunodeficiency virus-infected men who have sex with men
Newsum AM, Schinkel J, van de Laar TJW, van der Meer JTM, Prins M.
Open Forum Infect Dis. 2017 Jun 16;4(2):ofx090. doi: 10.1093/ofid/ofx090. eCollection 2017 Spring

Phylogenetic analysis of full-length, early infection, hepatitis C virus genomes among people with intravenous drug use: the InC(3) Study
Rodrigo C, Eltahla AA, Bull RA, Luciani F, Grebely J, *et al.*; InC3 Collaborative.
J Viral Hepat. 2017 Jan;24(1):43-52. doi: 10.1111/jvh.12616. Epub 2016 Nov 3

DC-SIGN polymorphisms associate with risk of hepatitis C virus infection among men who have sex with men but not among injecting drug users
Steba GS, Koekkoek SM, Vanhommerig JW, Brinkman K, Kwa D, *et al.*
J Infect Dis. 2018 Jan 17;217(3):353-357. doi: 10.1093/infdis/jix587

Lack of decline in hepatitis C virus incidence among HIV-positive men who have sex with men during 1990-2014
van Santen DK, van der Helm JJ, Del Amo J, Meyer L, D'Arminio Monforte A, *et al.*; CASCADE Collaboration in EuroCoord.
J Hepatol. 2017 Aug;67(2):255-262. doi: 10.1016/j.jhep.2017.03.038. Epub 2017 Apr 12

HIV and hepatitis C treatment uptake among people who use drugs participating in the Amsterdam Cohort Studies, 1985-2015
van Santen DK, van der Helm JJ, Lindenburg K, Schim van der Loeff M, Prins M.
Int J Drug Policy. 2017 Sep;47:95-101. doi: 10.1016/j.drugpo.2017.05.026. Epub 2017 Jun 9

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, *et al.* On half of the COHE in EuroCoord and ACHIeV2e Study Group.
J Antimicrob Chemother. 2017 Oct 1;72(10):2869-2878. doi: 10.1093/jac/dkx210

Theses in 2017 that include ACS data

S.W. de Taeye – 9 March 2017: Stabilization of HIV-1 envelope glycoprotein trimers to induce neutralizing antibodies. University of Amsterdam. Supervisors: Prof. B. Berkhout & Prof. R.W. Sanders

9. Curaçao

Diederik van de Wetering, Gonneke Hermanides, Ashley Duits and 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 exist in this relatively small Caribbean setting. This special report endeavours to present a concise overview of the current state of HIV treatment in Curaçao.

Population

In total, 1,105 HIV-positive individuals ever registered by SHM have been followed in the St. Elisabeth Hospital in Curaçao. Of these people, the majority were diagnosed with HIV-1 (1,079; 98%), while 2 individuals were diagnosed with HIV-2, and 11 had antibodies against both HIV-1 and HIV-2. For 13 individuals, serological results on HIV type were not available in the SHM database. In total, 1,064 of the people with HIV-1 had a recorded date of diagnosis.

People in clinical care

In total, 650 (60%) of the 1,079 registered HIV-1-positive individuals were known to be in clinical care by the end of 2017. People were considered to be in clinical care if they visited their treating physician in 2017 or had a CD4 count or HIV RNA measurement in that year and were still living in Curaçao. Of the 429 individuals who were no longer in clinical care, 176 (41%) were known to have died and 10 (2%) to have moved abroad, while 8 people only entered HIV care in 2018 or were diagnosed with HIV in 2018. Thus, 235 patients, or 22% of all registered HIV-1-positive individuals, were considered lost to care. Among individuals entering care between 2007 and 2016, the probability of being lost to care five years after enrolment was lower for people originating from the former Dutch Antilles (25%) than for those originating from Haiti or the Dominican Republic (35%) or from elsewhere (31%).

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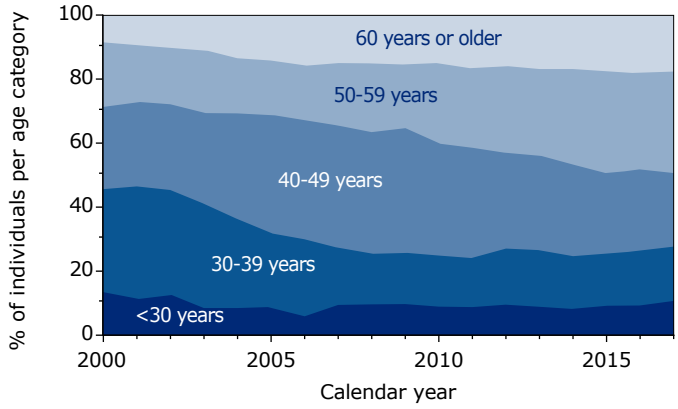
Ageing population

The median age of the population in clinical care by the end of 2017 was 50 years (interquartile range [IQR] 39-57) 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 (49%) are 50 years or older, including 49% of men and 50% of women; 17% of the individuals are 60 years or older. In contrast, the median age at diagnosis was 39 (IQR 33-49) years between 2000 and 2005 and decreased to 34 (26-46) years in individuals diagnosed in 2015 or later.

Figure 9.1: *Increasing age of the HIV-1-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 29% were 50 years or older. In 2017, these proportions were 11% and 49%, 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 2017 had been diagnosed with HIV a median of 8.6 (IQR 4.2-14.9) years previously. Thus, a large group (44%) of those in care had been living with HIV for more than 10 years, while 12% had done so for more than 20 years (*Table 9.1*). The median time since diagnosis was 7.2 years for men who have sex with men (MSM), 8.5 years for other men, and 9.5 years for women.

Table 9.1: Characteristics of the 650 HIV-1-positive individuals in clinical care in Curaçao by the end of 2017.

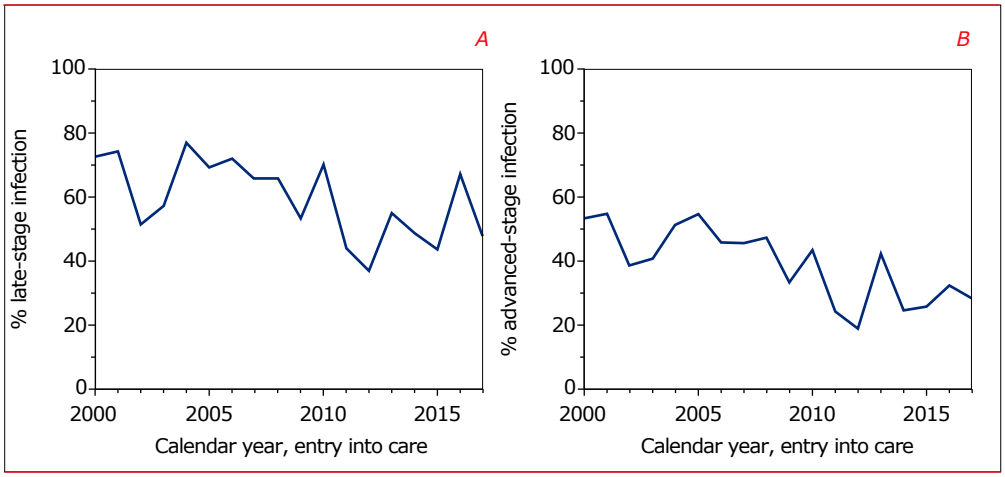
	Men (n=400, 62%)		Women (n=250, 38%)		Total (n=650)	
	n	%	n	%	n	%
Transmission						
MSM	164	41	-	-	164	25
Heterosexual	178	45	233	93	411	63
Other/unknown	58	15	17	7	75	12
Current age (years)						
0-12	0	0	0	0	0	0
13-17	0	0	0	0	0	0
18-24	18	5	8	3	26	4
25-34	64	16	32	13	96	15
35-44	82	21	42	17	124	19
45-54	116	29	90	36	206	32
55-64	81	20	51	20	132	20
65-74	32	8	18	7	50	8
≥75	7	2	9	4	16	2
Country of origin						
Former Netherlands Antilles	331	83	161	64	492	76
Dominican Republic	7	2	40	16	47	7
Haiti	20	5	30	12	50	8
The Netherlands	12	3	0	0	12	2
Other	30	8	19	8	49	8
Years aware of HIV infection						
<1	22	6	10	4	32	5
1-2	59	15	24	10	83	13
3-4	52	13	28	11	80	12
5-10	96	24	69	28	165	25
10-20	127	32	83	33	210	32
>20	41	10	35	14	76	12
Unknown	3	1	1	0	4	1

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

Late presentation and start of treatment

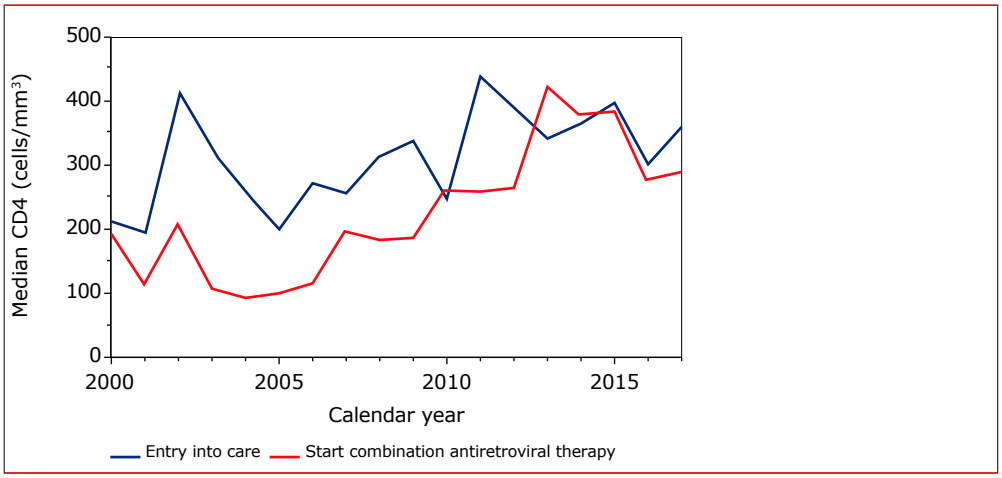
Overall, 59% of the 896 people who have entered care since 2000 were late presenters, i.e., individuals either presenting for care with a CD4 count below 350 cells/mm^3 or presenting with an AIDS-defining event regardless of CD4 count[1]. The proportion of late presenters has gradually decreased over time such that 55% of individuals entering care in 2015 or later were late presenters (*Figure 9.2*). In addition, the proportion of people presenting for care with advanced HIV disease, i.e., with a CD4 count less than 200 cells/mm^3 or AIDS, has also decreased over time and has been at an average of 32% since 2015. Altogether, 12% of the individuals who entered care since 2000 presented with an AIDS-defining disease.

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 (2015) onwards, 59% (55%) presented with late HIV disease while 39% (32%) were advanced-stage presenters. Late-stage HIV infection: CD4 counts below 350 cells/mm^3 or having AIDS, regardless of CD4 count. Advanced-stage HIV infection: CD4 counts below 200 cells/mm^3 or having AIDS.*



In recent years, there has been an increase in CD4 cell counts at the start of cART (*Figure 9.3*). Between 2015 and 2017, 30% of those for whom a CD4 count was available at the start of cART had less than 200 CD4 cells/mm^3, 23% had CD4 counts between 200 and 349 cells/mm^3, 21% had CD4 counts between 350 and 499 cells/mm^3, and 25% had CD4 counts of 500 cells/mm^3 or higher. During the same period, 94% of the people entering care received treatment within six months, irrespective of their CD4 count.

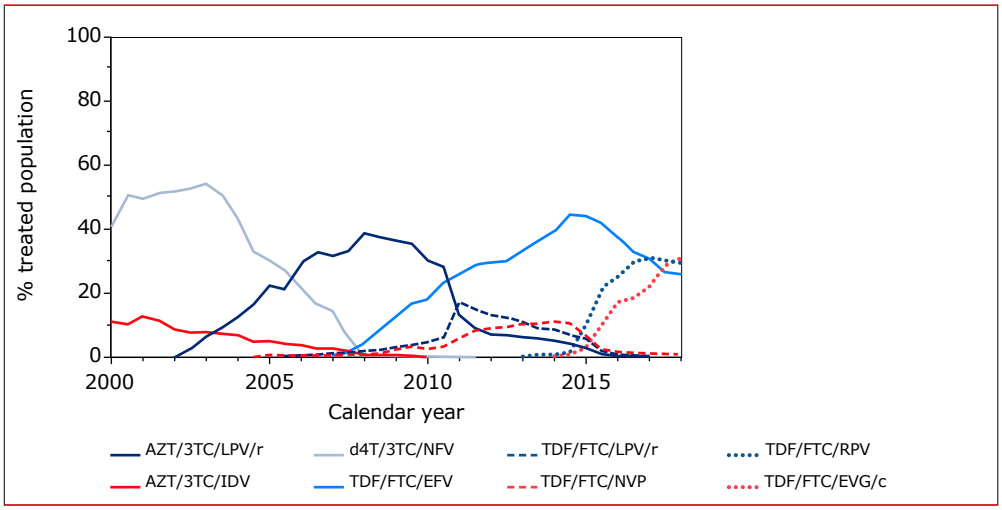
Figure 9.3: Changes over calendar time in median CD4 counts at entry into care and at the start of combination antiretroviral therapy (cART). Between 2000 and 2017, the median CD4 count at the time of entry into care increased from 214 cells/mm³ (interquartile range [IQR], 105–407) to 360 (189–459) cells/mm³. During the same period, CD4 counts at start of cART increased from 195 cells/mm³ (69–336) to 292 (138–477) cells/mm³.



Combination treatment

In total, 946 (88%) of the 1,079 registered HIV-1-positive individuals 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 mainly prescribed. At the end of 2017, the most commonly prescribed regimens were a combination of tenofovir/emtricitabine with either rilpivirine, efavirenz, or cobicistat-boosted elvitegravir. Of the people who started cART and were still in care by the end of 2017, 31% were being treated with tenofovir/emtricitabine/cobicistat-boosted elvitegravir, 30% with tenofovir/emtricitabine/rilpivirine, and 26% with tenofovir/emtricitabine/efavirenz. The majority (96%) used a once-daily regimen, while 88% were treated with a fixed-dose drug combination.

Figure 9.4: Percentage of individuals treated with combination antiretroviral therapy (cART) by specific regimens over calendar time. At the end of 2017, 31% of the people were receiving TDF/FTC/EVG/c, 30% RPV/TDF/FTC, and 26% TDF/FTC/EFV.

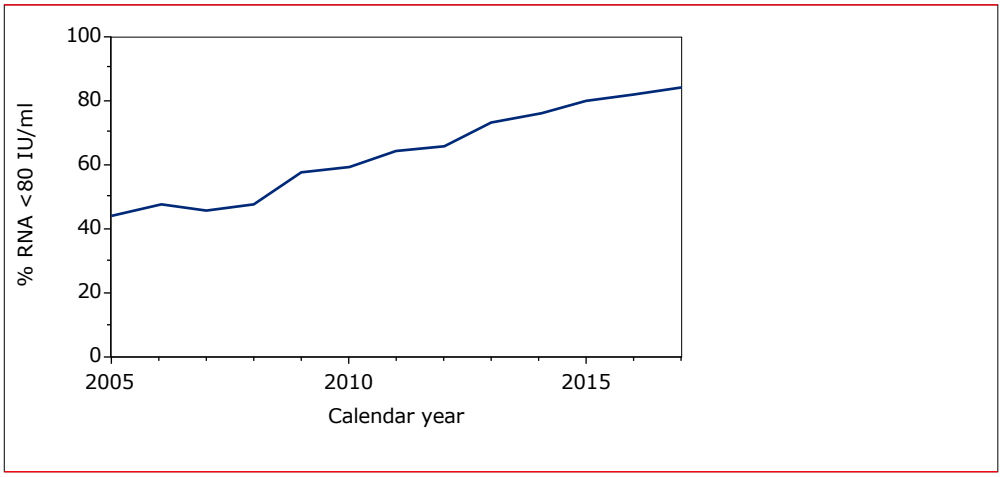


Legend: AZT=zidovudine; 3TC=lamivudine; LPV/r=ritonavir-boosted lopinavir; d4T=stavudine; NFV=nelfinavir; TDF=tenofovir disoproxil fumarate; FTC=emtricitabine; RPV=rilpivirine; IDV=indinavir; EFV=efavirenz; NVP=nevirapine; EVG/c=cobicistat-boosted elvitegravir.

Treatment outcome

In the total population still in care, the median current CD4 count was 500 (IQR 361-679) cells/mm^3. CD4 counts were similar between MSM (536 [IQR 404-702] cells/mm^3) and women (532 [413-741] cells/mm^3), but men who acquired their infection via other or unknown modes of transmission had lower CD4 counts (433 [298-607] cells/mm^3). Among individuals with a viral load measurement, the proportion with viral suppression, i.e., HIV RNA levels less than 80 IU/ml increased from 44% in 2005 to 84% in 2017 (*Figure 9.5*).

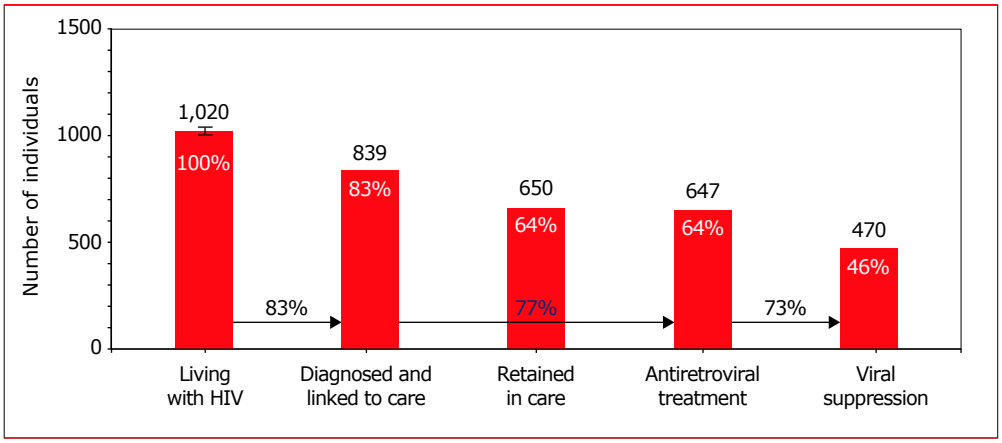
Figure 9.5: Proportion of people in care with HIV RNA <80 IU/ml at their last viral load measurement in each calendar year.



Continuum of HIV care

The total number of people living with HIV by the end of 2017, including those not yet diagnosed, was estimated at 1,020 (95% confidence interval [CI] 980-1,080), of whom 180 (140-240) were still undiagnosed (*Figure 9.6*)[2]. These 1,020 people did not include individuals who were known to have died or moved abroad or who were lost to care before the end of 2007, i.e., more than 10 years ago. In addition, this number did not include people who had an HIV diagnosis but had not yet been linked to care and registered by SHM. In total, 839 individuals, or 83% of the total number estimated to be living with HIV, had been diagnosed, linked to care, and registered by SHM, and were not recorded in the SHM database as having died or moved abroad. Altogether, 650 (64%) people were still in care, i.e., they had had at least one HIV RNA or CD4 count measurement or a clinic visit in 2017. The majority of these individuals (647, or 77% of those diagnosed and linked to care) had started antiretroviral treatment. In total, 561 individuals, or 86% of those in care, had an HIV RNA measurement available in 2017 and 470 (84%, or 73% of those treated) had a most recent HIV RNA below 80 IU/ml. Overall, 46% of the total estimated population living with HIV and 56% of those diagnosed and ever linked to care had a suppressed viral load. In terms of the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 target for 2020, the current estimate for Curaçao stands at 83-77-73, or 83-77-84 when taking into account that data on HIV RNA measurements for 2017 may not yet be complete in the database[3].

Figure 9.6: Continuum of HIV care for the total estimated HIV-1-positive population estimated to be living with HIV in Curaçao by the end of 2017. 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.



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 suboptimal, as illustrated by the relatively low proportion of individuals with a suppressed viral load. Finally, the high proportion lost to care is concerning and may affect 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. Currently, no data are regularly collected for HIV-positive children. As a result, the data available on children living with HIV in Curaçao cannot be used for strategic planning of HIV care for this specific population. Earlier this year a new SHM data collection system was implemented, which is expected to further increase the quality of the collected data items once it is fully operational.

Early start of cART in people living with HIV in Curaçao appears possible, but long-term continuous follow up should be guaranteed to optimise the effect of cART. The continuum of care for Curaçao illustrates, for example, that while almost everyone who is still in care has started antiretroviral treatment, too many individuals are lost to care. In part, this may be explained by people who, unknown to SHM, no longer live in Curaçao. To address this issue, efforts have recently been stepped up to trace people who miss their scheduled appointment in the hospital. As a result, retention in care is expected to improve in the near future. In addition, the proportion of people in care for whom at least one viral load measurement in 2017 is available in the SHM database is relatively low. A more timely registration of HIV RNA measurements is needed to better monitor the progress towards achieving the UNAIDS' 90-90-90 goals for 2020. Finally, a relatively large, albeit decreasing, proportion of individuals enter care late in the course of their infection. More efforts should therefore be invested in upscaling HIV screening and ensuring that people who test positive are quickly linked to care.

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2. *ECDC HIV modelling tool [software application]. Version 1.3.0.* (European Centre for Disease Prevention and Control, 2017).
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Appendix: supplementary table

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 2016 and 2017 had not yet been finalised at the time of writing.

Calendar year	Diagnosis	Entry into care	Start cART
≤1999	232	171	84
2000	40	41	31
2001	34	41	38
2002	47	42	20
2003	55	53	22
2004	46	47	37
2005	43	55	44
2006	47	58	41
2007	38	42	43
2008	46	50	46
2009	49	55	50
2010	43	48	56
2011	53	53	46
2012	56	63	59
2013	65	56	75
2014	39	47	72
2015	43	45	48
2016	48	59	60
2017	36	45	52
2018	4	8	10
Unknown	15	–	12
Total	**1,079**	**1,079**	**946**

Legend: cART=combination antiretroviral therapy.

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Acknowledgements

Clinical centres

* denotes site coordinating physician

Academic Medical Centre of the University of Amsterdam (AMC-UvA)**
HIV treating physicians: M. van der Valk*, S.E. Geerlings, A. Goorhuis, J.W. Hovius, B. Lempkes, F.J.B. Nellen, T. van der Poll, J.M. Prins, P. Reiss, M. van Vugt, W.J. Wiersinga, F.W.M.N. Wit.
HIV nurse consultants: M. van Duinen, J. van Eden, A. Hazenberg, A.M.H. van Hes, F.J.J. Pijnappel, S.Y. Smalhout, A.M. Weijsenfeld.
HIV clinical virologists/chemists: S. Jurriaans, N.K.T. Back, H.L. Zaaijer, B. Berkhout, M.T.E. Cornelissen, C.J. Schinkel, K.C. Wolthers.

Emma Kinderziekenhuis (AMC-UvA), Amsterdam
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HIV nurse consultants: C. de Boer, A. van der Plas, A.M. Weijsenfeld.

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HIV clinical virologists/chemists: M. Damen.

ETZ (Elisabeth-TweeSteden Ziekenhuis), Tilburg
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HIV nurse consultants: A. Adams, B.A.F.M. de Kruijf-van de Wiel, S.J. Keelan-Pfaf, B. van de Ven.
Data collection: B.A.F.M. de Kruijf-van de Wiel, B. van der Ven.
HIV clinical virologists/chemists: A.G.M. Buiting, J.L. Murck, 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.
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HIV nurse consultants: M. van der Burg-van de Plas, H. Heins.

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HIV clinical virologists: D. Kwa.

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HIV clinical pharmacology consultant: D. Burger.

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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, A. Middel, E.H. Scholvinck, Y. Stienstra, C.L. Vermont, KM. 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.

Universitair Medisch Centrum 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, M.J.A. de Regt, E.M. Schadd, M.W.M. Wassenberg, M.A.D. van Zoelen.
HIV nurse consultants: K. Aarsman, B.M.G. Griffioen-van Santen, 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, K.C.E. Sigaloff.
HIV nurse consultants: M. Heitmuller, L.M. Laan.
HIV clinical virologists/chemists: C.W. Ang, R. van Houdt, M. Jonges, A.M. Pettersson, J. van Prehn.

Wilhelmina Kinderziekenhuis, UMC Utrecht, Utrecht
HIV treating physicians: L.J. Bont, S.P.M. Geelen, Y.G.T. Loeffen, T.F.W. Wolfs.
HIV nurse consultants: N. Nauta.

Sint Elisabeth Hospitaal, Willemstad, Curaçao
HIV treating physicians: J.F. Schattenkerk, F. Muskiet, R. Voigt, D. van de Wetering.
HIV nurse consultants: I. van der Meer.

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Prof. K. Brinkman	OLVG, Dept. of Internal Medicine, Amsterdam
Prof. S. Geerlings	AMC, Dept. of Internal Medicine, Amsterdam
Prof. F. Kroon	LUMC, Dept. of Infectious Diseases, Leiden
Dr. L. van Leeuwen	AMC, Dept. of Obstetrics and Gynaecology, Amsterdam
Dr. J. Nellen	AMC, Dept. of Internal Medicine, Amsterdam
Dr. C. van Nieuwkoop	HagaZiekenhuis, Dept. of Internal Medicine, The Hague
Dr. E. Op de Coul	RIVM, Bilthoven
Prof. J.M. Prins	AMC, Dept. of Internal Medicine, Amsterdam
Dr. C. Richter	Rijnstate, Dept. of Internal Medicine, Arnhem
Dr. A. van Rossum	Erasmus MC, Paediatric Infectious Diseases and Immunology, Rotterdam
Dr. M. van der Valk	AMC, Dept. of Internal Medicine, Amsterdam
Dr. A.M.J. Wensing	UMCU, Dept. of Virology, Utrecht
Dr. T. Wolfs	Wilhelmina Kinderziekenhuis, Utrecht.

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 (until 30 June 2018)
	A.I. van Sighem PhD
	C. Smit PhD
	F.W.N.M. Wit PhD

Data unit

Data management	M.M.J. Hillebregt MSc (coordinator)
	A.S. de Jong MSc
	T.J. Woudstra
Quality control, helpdesk & protocol management	S. Grivell MSc (protocol & helpdesk coordinator)
Data quality staff	D. Bergsma MSc
	R. Meijering MSc
	M.S. Raethke MSc
	T. Rutkens
Data protection officer	M.M.B. Tuk-Stuster
Patient registration & data collection	L.G.M. de Groot-Berndsen (coordinator)
	M.M.B. Tuk-Stuster (patient registration administrator)

Data collection	M. van den Akker Y.M. Bakker A. el Berkaoui M. Bezemer-Goedhart N. Brétin E. Djoechro R. Regtop J. Geerlinks J. Koops MSc (until 30 June 2018) E.I. Kruijne C.R.E. Lodewijk E. Lucas R. van der Meer MA L. Munjishvili MA F. Paling MSc B.M. Peeck MSc C.M.J. Ree Y.M.C. Ruijs-Tiggelman M.J.C. Schoorl MSc P. Schnörr L. van de Sande E.M. Tuijn-de Bruin D.P. Veenenberg-Benschop S. van der Vliet S.J. Wisse MSc (until 30 June 2018) E.C.M. Witte
Communications unit	C.J. Ester PhD (manager) M.J. Sormani (until 30 April 2018)
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)

Publications & presentations

The publications and presentations listed below are those available since the publication of the Monitoring Report 2017.

Publications

Lack of decline in hepatitis C virus incidence among HIV-positive men who have sex with men during 1990-2014
van Santen DK, van der Helm JJ, Del Amo J, Meyer L, D'Arminio Monforte A, Price M, Béguelin CA, Zangerle R, Sannes M, Porter K, Geskus RB, Prins M; CASCADE Collaboration in EuroCoord.
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Higher prevalence and faster progression of chronic kidney disease in human immunodeficiency virus-infected middle-aged individuals compared with human immunodeficiency virus-uninfected controls
Kooij KW, Vogt L, Wit FWNM, van der Valk M, van Zoest RA, Goorhuis A, Prins M, Post FA, Reiss P; AGE$_h$IV Cohort Study.
Infect Dis. 2017 Sep 15;216(6):622-631. doi: 10.1093/infdis/jix202

CD4:CD8 ratio and CD8 count as prognostic markers for mortality in human immunodeficiency virus-infected patients on antiretroviral therapy: The Antiretroviral Therapy Cohort Collaboration (ART-CC)
Trickey A, May MT, Schommers P, Tate J, Ingle SM, Guest JL, Gill MJ, Zangerle R, Saag M, Reiss P, Monforte AD, Johnson M, Lima VD, Sterling TR, Cavassini M, Wittkop L, Costagliola D, Sterne JAC; Antiretroviral Therapy Cohort Collaboration (ART-CC).
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Time to switch to second-line antiretroviral therapy in children with HIV in Europe and Thailand
Collins IJ; European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) study group in EuroCoord.
Clin Infect Dis. 2017 Sep 26. doi: 10.1093/cid/cix854. [Epub ahead of print]

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Clinical Infectious Diseases, cix858, https://doi.org/10.1093/cid/cix858

Structural brain abnormalities in successfully treated HIV infection: associations with disease and cerebrospinal fluid biomarkers
Van Zoest RA, Underwood J, De Francesco D, Sabin CA, Cole JH, Wit FW, Caan MWA, Kootstra NA, Fuchs D, Zetterberg H, Majoie CBLM, Portegies P, Winston A, Sharp DJ, Gisslén M, Reiss P; Co-morBidity in Relation to AIDS (COBRA) Collaboration.
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Antiretroviral pill count and clinical outcomes in treatment naive patients with HIV
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Cardiovascular disease (CVD) and chronic kidney disease (CKD) event rates in HIV-positive persons at high predicted CVD and CKD risk: A prospective analysis of the D:A:D observational study
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High treatment uptake in HIV/HCV-coinfected patients after unrestricted access to direct-acting antivirals in the Netherlands
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Substantial heterogeneity in progress toward reaching the 90–90–90 HIV target in the WHO European region
Porter K, Gourlay A, Attawell K, Hales D, Supervie V, Touloumi G, Rosinska M, Vourli G, van Sighem A, Pharris A, Noori T; ECDC Dublin Declaration Monitoring Network.
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Non-Hodgkin lymphoma risk in adults living with HIV across five continents: a multicohort study
Rohner E; AIDS-defining Cancer Project Working Group of IeDEA, COHERE in EuroCoord. The ATHENA (AIDS Therapy Evaluation in the Netherlands) national observational HIV cohort.
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Boender TS, Smit C, Sighem AV, Bezemer D, Ester CJ, Zaheri S, Wit FWNM, Reiss P; ATHENA national observational HIV cohort.
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Other publications

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Poster presentations

The impact of increased STI testing on the spread of HIV and gonorrhoea among men who have sex with men
Reitsema MT, Wallinga J, van Benthem BH, van Sighem AI, van der Loeff MFS, Xiridou M.
Epidemics 6, Sitges, Spain, 29 November-1 December 2017

Serum albumin as a long term predictor of serious non-AIDS events
Ronit A, Hatleberg CI, Ryom L, Bonnet F, El-Sadr WM, Reiss P, Weber R, Pradier C, de Wit S, Law M, D'Arminio Monforte A, Lundgren JD, Phillips A, Sabin C.
CROI 2018: Conference on Retroviruses and Opportunistic Infections, Boston, USA, 4-7 March 2018

Determinants of cognitive function differ in a European and a Korean cohort
de Francesco D, Winston A, Choi YJ, van Zoest R, Underwood J, Schouten J, Ku NS, Kim WJ, Reiss P, Sabin C.
CROI 2018: Conference on Retroviruses and Opportunistic Infections, Boston, USA, 4-7 March 2018

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Substantial decline in virological failure after combination antiretroviral treatment (cART) initiation in treatment-naive HIV-positive adults in the Netherlands from 1996 to 2016
Boender TS, on behalf of ATHENA.
22nd International Workshop on HIV Observational Databases, Fuengirola, Spain, 22-23 March 2018

Acute hepatitis C infection among HIV-positive adults in the Netherlands: a capture-recapture analysis of two national databases
Boender TS.
22nd International Workshop on HIV Observational Databases, Fuengirola, Spain, 22-23 March 2018

Efficacy and safety of IFN-free DAA HCV therapy in HIV/HCV co-infected persons: Results from a pan-European study
Lundgren J on behalf of EuroSIDA in RESPOND consortium.
22nd International Workshop on HIV Observational Databases, Fuengirola, Spain, 22-23 March 2018

Effect estimates of randomized trials and observational studies: comparing apples with apples
Lodi S on behalf of HIV-CAUSAL Collaboration.
22nd International Workshop on HIV Observational Databases, Fuengirola, Spain, 22-23 March 2018

Withholding primary PCP prophylaxis in virally suppressed HIV patients: A trial emulation in COHERE
Furrer H on behalf of COHERE in EuroCoord.
22nd International Workshop on HIV Observational Databases, Fuengirola, Spain, 22-23 March 2018

Pulmonary function in controlled HIV-infection: lower forced vital capacity but similar 1-second forced expiratory volume among those with limited smoking experience
Verboeket S on behalf of $AGE_{h}IV$.
22nd International Workshop on HIV Observational Databases, Fuengirola, Spain, 22-23 March 2018

Long-term growth in HIV-infected children and adolescents on ART in Europe and Thailand
Crichton S on behalf of EPPICC.
22nd International Workshop on HIV Observational Databases, Fuengirola, Spain, 22-23 March 2018

The paediatric continuum of HIV care in the Netherlands: from diagnosis in childhood to viral suppression in adulthood
Smit C on behalf of ATHENA.
22nd International Workshop on HIV Observational Databases, Fuengirola, Spain, 22-23 March 2018

CD4/CD8 ratio and risk of Kaposi sarcoma in people living with HIV achieving suppressed viraemia on antiretroviral therapy
Caby F on behalf of COHERE.
22nd International Workshop on HIV Observational Databases, Fuengirola, Spain, 22-23 March 2018

PrEP for MSM can result in reductions in HIV transmission and can be cost-effective, even with a small decrease in condom use
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Late presenters drive the non-ART cost of HIV-care
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Many introductions but little transmission of HIV-1 non-B subtypes amongst heterosexuals in the Netherlands
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Heterogeneity in pulmonary function indices by HIV status and cumulative smoking intensity among well-controlled HIV-infected persons compared to HIV-uninfected participants in the AGE$_h$IV cohort
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HCV treatment cascade in the Netherlands: DAA uptake varies by key population, effectiveness of HIV treatment and co-medication use
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Incidence, timing and outcome of IRIS in relation to specific opportunistic infections – the ATHENA cohort study
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Non-nucleoside reverse transcriptase inhibitor-based combination antiretroviral therapy is associated with lower cell-associated HIV RNA and DNA levels as compared with therapy based on protease inhibitors
Pasternak AO, Kootstra N, Vroom J, Wit FWNM, de Bruin M, de Francesco D, Sabin C, Winston A, Prins JM, Reiss P, Berkhout B, on behalf of The Co-morBidity in Relation to Aids (COBRA) Collaboration and the MEMS Cohort Study.
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Earlier HIV diagnosis among men who have sex with men in Amsterdam following interventions to increase awareness of early HIV infection
van Sighem A, de Bree G, Davidovich U, Zuilhof W, van Bijnen A, Verdult F, Dijkstra M, Heijman T, Hogewoning A, Op de Coul E, van Bergen J, Schim van der Loeff M, Reiss P, HIV Elimination Amsterdam (H-TEAM) Initiative and the ATHENA National HIV Cohort.
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The paediatric continuum of HIV care in the Netherlands: from diagnosis in childhood to viral suppression in adulthood
Smit C, Wolfs T, Boender TS, van Rossum A, Reiss P, on behalf of the ATHENA observational cohort.
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Substantial decline in virological failure after combination antiretroviral treatment (cART) initiation in treatment-naïve HIV-positive adults in the Netherlands from 1996 to 2016
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Evaluating progress towards triple elimination of mother-to-child transmission of HIV, syphilis and hepatitis B in the Netherlands, 2012-2015
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Does HIV-seroconversion affect the serum N-glycans profile, one possible biomarker of ageing? Insights from a longitudinal study
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Cost-effectiveness of increased HIV testing among Dutch MSM
Mangen MJ.
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Oral presentations

The effectiveness of a guided Internet-based self-help intervention for people with HIV and depressive symptoms: A randomized controlled trial
Van Luenen S, Garnefski N, Spinhoven P, Kraaij V.
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The cascade of care: how to make predictions for the early steps?
van Sighem A.
Ülkemizde HIV Epidemiyolojisinin Güncel Durumu ve Önleme Stratejileri, Istanbul, Turkey, 14 October 2017

The hepatitis C continuum of care among HIV infected individuals in EuroSIDA
Amele S, on behalf of EuroSIDA.
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HIV and ageing: using cohort data to separate the myths from reality
Van Zoest R, Schouten J.
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Use of integrase inhibitors is an independent risk factor for immune reconstitution inflammatory syndrome (IRIS) in HIV-1 late presenters: An ATHENA Cohort Study
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Meer inzicht in de hiv-epidemie met de ECDC HIV modelling tool [Greater insight into the HIV epidemic using the ECDC HIV modelling tool]
van Sighem A.
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Living positive with HIV: A randomized controlled trial of a guided Internet-based self-help intervention for people with HIV and depressive symptoms
Van Luenen S, Kraaij V, Spinhoven P, Garnefski N.
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Many introductions but little transmission of HIV 1 non B subtypes in the Netherlands
Bezemer D, Hall M, van Sighem A, Reiss P, Fraser C, Ratmann O.
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Geospatial analysis and mapping of new HIV diagnoses, late presentations and GP testing practices in Amsterdam
Böhnke L, Vu T, van Bergen J, van Sighem A, Groot Bruinderink M, Op de Coul E, Kroone M, Reiss P, Heidenrijk M, de Bree GJ.
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The HIV epidemic in the Netherlands: an update
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Cost-effectiveness of increased HIV testing among men who have sex with men in the Netherlands
Reitsema M, Steffers L, Wallinga J, van Benthem B, Visser M, de Munnik S, van Sighem, Schim van der Loeff M, Xiridou M, Mangen MJM.
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Estimating HIV incidence and the undiagnosed HIV population in the European Union/European Economic Area
van Sighem A, Pharris A, Quinten C, Noori T, Amato-Gauci A.J. and the ECDC HIV/AIDS Surveillance and Dublin Declaration Networks.
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Serious clinical outcomes in HIV-positive persons with chronic kidney disease (CKD)
Ryom L, on behalf of the DAD study.
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HCV treatment cascade: highest DAA uptake for MSM receiving cART
Smit C on behalf of ATHENA.
22nd International Workshop on HIV Observational Databases, Fuengirola, Spain, 22-23 March 2018

Earlier HIV diagnosis in Amsterdam after implementation of an early HIV infection awareness campaign
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Effectiveness of transmitted drug resistance testing on the risk of clinical outcomes
Lodi S on behalf of HIV-CAUSAL Collaboration.
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HIV-1 transmission dynamics in the Netherlands
Bezemer D.
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Importance of investing in data collection to guide the response
van Sighem A.
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HIV modelling
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Estimating the number of people living with undiagnosed HIV – the Netherlands
van Sighem A.
European HIV Network meeting, Berlin, Germany, 23-25 April 2018

Models for case surveillance settings – ECDC model
van Sighem A and Quinten C.
UNAIDS Reference Group on Estimates, Modelling and Projections, Atlanta, GE, United States, 30-31 May 2018

Country case studies for incidence estimation – Netherlands
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Acute hepatitis C bij mensen met hiv: melding & registratie [Acute hepatitis C in people living with HIV: reporting and registration]
Boender TS.
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The ECDC HIV Modelling Tool: estimating the first stage in the HIV care continuum
van Sighem A.
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Mortality and COD among HIV+ persons by ART experience in the Netherlands
van Sighem A.
UNAIDS Reference Group on Estimates, Modelling and Projections, Bern, Switzerland, 17-19 September 2018

Terminology

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

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

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

AIGHD
Amsterdam Institute for Global Health and Development.

Antibody
An immune system protein formed in response to invading disease agents such as viruses, fungi, bacteria, and parasites. Usually antibodies defend the body against invading disease agents, however, the HIV antibody does not give such protection.

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

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

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

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

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

cART
Combination antiretroviral treatment.

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

CDC
US Centers for Disease Control and Prevention.

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

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.

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 association.

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 analogue reverse transcriptase inhibitor (NRTI)
Antiretroviral HIV drug class. Nucleoside analogue reverse transcriptase inhibitors (NRTIs) block reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

Nucleotide
A building block of nucleic acids. DNA and RNA are nucleic acids.

Nucleotide reverse transcriptase inhibitor (NtRTI)
A type of antiretroviral (ARV) HIV drug. Nucleotide reverse transcriptase inhibitors (NtRTIs) interfere with the HIV life cycle in the same way as NRTIs. Both block reverse transcription. NtRTIs are included in the NRTI drug class.

NVHB
Dutch Association of HIV-Treating Physicians (Nederlandse Vereniging van HIV Behandelaren).

Person year
A measure of time used in medical studies 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.

Pseudonymisation
Pseudonymisation is a privacy-enhancing technique that replaces personal identifiers with coded data. Certain identifiers (such as gender and age) are included in the record, but personal information is removed or replaced by a randomised string of characters. The data collected from people living with HIV are stored in SHM's database in a pseudonymised form. Pseudonymisation takes place within the HIV treatment centre and the key to the code is only available to the HIV treating physician.

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

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

RIVM
The Netherlands' National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu).

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

SHM
Stichting HIV Monitoring, the Dutch HIV Monitoring Foundation.

Sustained virological response (SVR12 or SVR24)
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 fails to suppress and sustain a person's viral load to less than 200 copies/ml. Factors that can contribute to virological 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 virological control
When antiretroviral therapy 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