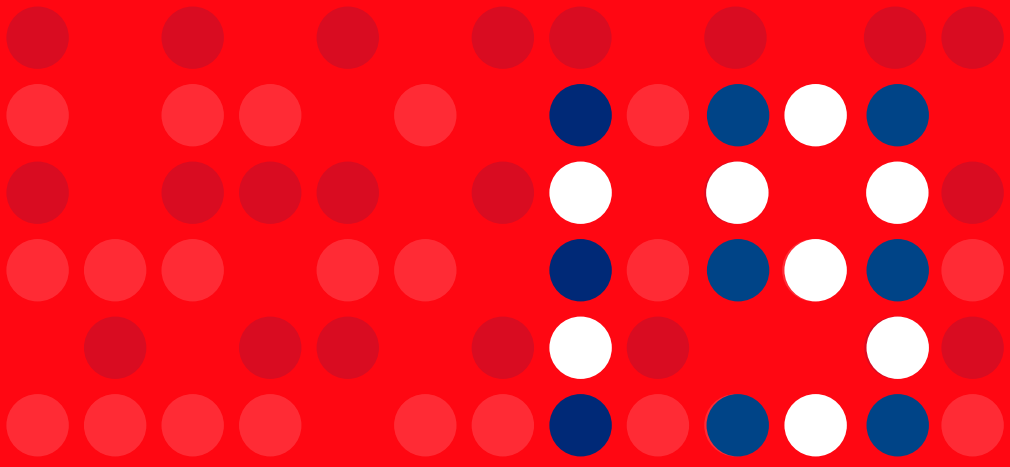
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2019



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.

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.

SHM contributes to the knowledge of HIV by studying the course of the infection and the effect of its treatment. To this end, SHM follows the treatment of every HIV-positive man, woman and child in care in the Netherlands and registered in the national observational HIV cohort, ATHENA. Continuous collection of data is carried out at 24 HIV treatment centres and subcentres and 4 paediatric HIV centres in the Netherlands. Patient data are collected and entered into the database in a pseudonymised form for storage and analysis. In this way SHM is able to comprehensively map the HIV epidemic and HIV treatment outcomes 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.

www.hiv-monitoring.nl

HIV Monitoring

Monitoring Report 2019

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 (in a new window) if they are a url (e.g., http://www.cdc.gov/hiv/guidelines/).

Reference numbers

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

Guide to buttons

Content page

Next chapter

Preceding chapter

You can also navigate using the bookmarks.

Acknowledgements

Authors: Ard van Sighem, Ferdinand Wit, Anders Boyd, Colette Smit, Amy Matser, Peter Reiss

Co-authors: Joop Arends, Ward van Bilsen, Kees Brinkman, Ashley Duits, Suzanne Geerlings, Gonneke Hermanides, Jeroen van Kampen, Frank Kroon, Liesbeth van Leeuwen, Jeannine Nellen, Kees van Nieuwkoop, Eline Op de Coul, Jan Prins, Maria Prins, 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
hiv.monitoring@amc.uva.nl, www.hiv-monitoring.nl

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

Chamber of commerce no. 34160453

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

To cite this report, please use: van Sighem A.I., Wit F.W.N.M., Boyd A., Smit C., Matser A., Reiss P. Monitoring Report 2019. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring, 2019. Available online at www.hiv-monitoring.nl

ISBN/EAN: 978-90-806415-0-1
First edition: 13 November 2019
Editing: Sally H. Ebeling, Boston, MA, USA

Art Direction & DTP: Studio Zest, Wormer, the Netherlands

The monitoring of HIV-positive adults is a collaborative effort involving Stichting HIV Monitoring (SHM) and a total of 24 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 2019, the following health institutes were involved as centres for adult HIV care (in alphabetical order of city):

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

Note: MC Slotervaart and MC Zuiderzee were declared bankrupt on 25 October 2018. Data collection continued in both hospitals until final closure early 2019. Patient care for people living with HIV has since been transferred to other nearby HIV treatment centres, where data collection will continue.

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

Table of contents

Introduction

The Monitoring Report 2019 on Human Immunodeficiency Virus (HIV) Infection in the Netherlands is the 18th in the series published by Stichting HIV Monitoring (SHM). Based on pseudonymised data from the AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort, 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.

SHM has managed the ATHENA cohort since 2001. 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. Through this work, SHM makes an important contribution to the ultimate goal (both in the Netherlands and globally) of reducing the number of new HIV infections. The up-to-date, reliable and detailed data generated by SHM and published in this report play an important role in achieving this goal. The data provide a measure of how close we are to realising the goal, but they also provide the evidence-base by which HIV prevention and treatment can, and should, be further optimised.

The Netherlands has already achieved one of the goals set by the UNAIDS and WHO for 2020, namely the 90-90-90 goal (90% of people living with HIV know their HIV status, 90% of people who know they have HIV are receiving treatment, and 90% of people on treatment have an undectable viral load), and work continues to improve the current figures of 92-93-96. In this year's report, we show that the Netherlands is also on track to achieving another important UNAIDS and WHO 2020 goal, which states that there should be a reduction in the number of new infections of at least 75% between 2010 and 2020. These achievements reflect efforts in the Netherlands in recent years to promote the importance of timely diagnosis and treatment initiation, thereby contributing not only to improved health in the individual, but also to the prevention of new infections.

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 2018

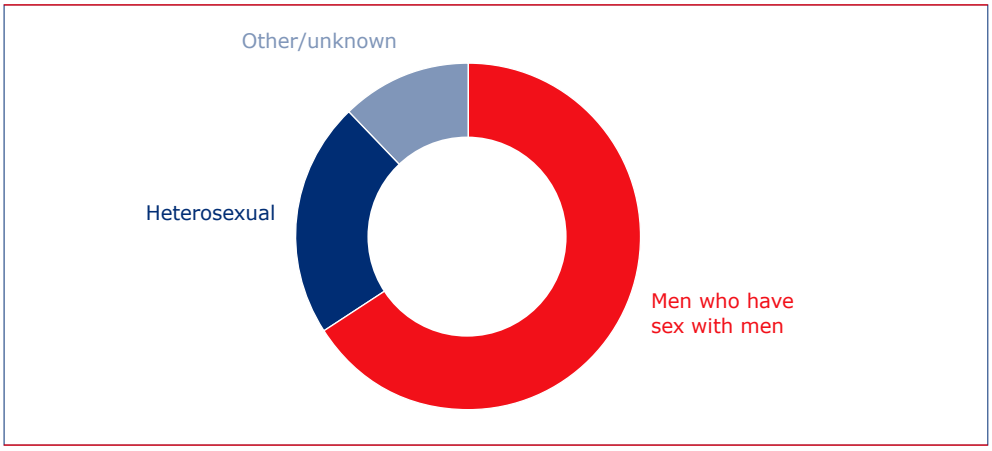
Trend of fewer new HIV diagnoses continues in 2018

Since 2008 there has been a decreasing trend in the annual number of newly-diagnosed HIV infections. This decreasing trend continued in 2018. The projected number of new diagnoses for 2018 is 664, compared with 749 in 2017.

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

In 2018, the majority (66%) of newly-diagnosed infections were in men who have sex with men (MSM), while 22% were acquired through heterosexual contact and around 12% through other or unknown modes of transmission.

Figure 1: Most likely route of HIV transmission in people newly-diagnosed in 2018.



People newly-diagnosed with HIV rapidly receive specialised care

Just 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, sexual health centre, 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 a number of observations. Firstly, our data show that the proportion of individuals with a previously negative HIV test has increased (74% of MSM, 30% of other men and 41% of women diagnosed in 2018 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 390 cells/mm^3 in 2018.

Number of newly-acquired infections is declining

The estimated number of newly-acquired HIV infections is declining and reached 320 in 2018 (compared with 440 in 2017). This downward trend over the years confirms that the Netherlands is on track to achieving the UNAIDS' fast-track target for 2020 of a 75% reduction in annual newly-acquired HIV infections since 2010.

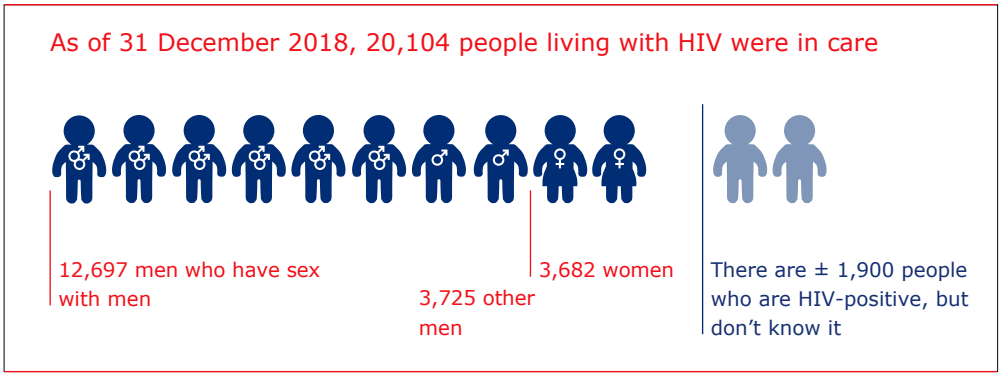
Late presentation for care remains a problem that needs attention

Despite the observed earlier diagnosis in certain groups, many people still present late for care, i.e., with an already markedly impaired immune system (CD4 count below 350 cells/mm^3) or even AIDS; in 2018, this was the case for 41% of MSM, 66% of other men and 45% of women.

How many people were in HIV care in 2018?

As of 31 December 2018, a total of 20,104 people living with HIV in the Netherlands (19,910 adults and 194 children and adolescents) were known to be in care in one of the 24 adult or 4 paediatric HIV treatment centres.

Figure 2: Number of people living with HIV and in care in the Netherlands in 2018.



Continuum of HIV care in 2018: 92-93-96

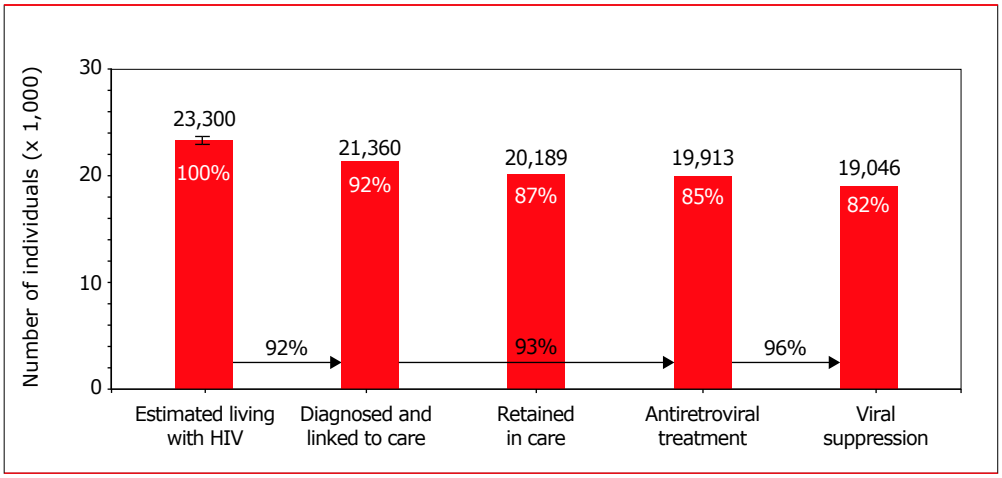
One of the goals of HIV treatment is to achieve viral suppression. The key steps that need to be achieved to reach viral suppression are illustrated in a continuum of HIV care. A continuum of care also gives a measure of progress towards achieving the UNAIDS 90-90-90 goals for HIV care by 2020.

The continuum of care for the Netherlands confirms that we have reached these goals (92-93-96 in 2018, see *Figure 3*):

- By the end of 2018, 23,300 individuals were estimated to be living with HIV, of whom an estimated 1,900 were still undiagnosed.
- In total, 21,360 individuals (**92%** 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 (19,913; **93%**), had started antiretroviral treatment, and 19,046 of those (**96%**) had achieved viral suppression.

This means that overall, 82% of the total estimated population living with HIV and 89% of those diagnosed and linked to care had a suppressed viral load by the end of 2018.

Figure 3: Continuum of HIV care for the total estimated HIV-positive population in the Netherlands by the end of 2018, based on UNAIDS 90-90-90 goals for 2020: 92-93-96.



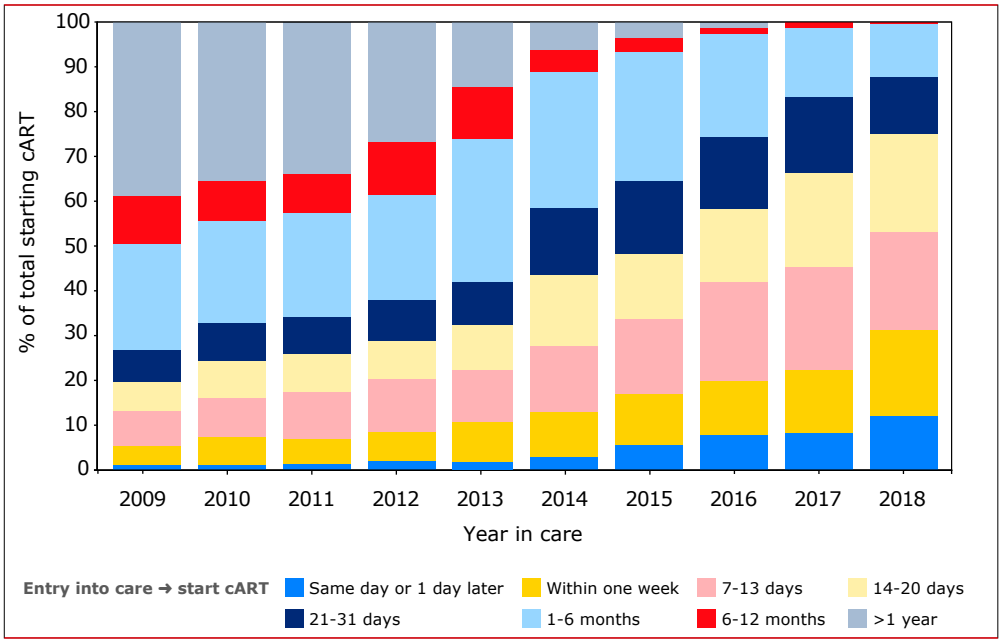
The figures for the Netherlands are impressive compared with other parts of the world. Nonetheless, in 2018 there were 664 new diagnoses and an estimated 1,900 people who remained undiagnosed. To achieve a significant decline in these numbers, novel transdisciplinary strategies are needed to simultaneously reduce the likelihood of HIV transmission in key populations at risk (including by provision of pre-exposure prophylaxis or PrEP), 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 2018, most people started HIV treatment within a month of entry into care

People are increasingly starting combination antiretroviral therapy (cART) soon after being diagnosed with HIV and entering care. In 2018, close to 90% of people started cART within one month of entry into care. Importantly, this was the case irrespective of the CD4 cell count at entry into care. In addition, in 2018, 3.5% started cART on the same day or the day after their HIV infection was diagnosed.

Figure 4: Time between entry into care and starting combination antiretroviral therapy (cART) for those starting cART between 2008–2018.



Legend: cART=combination antiretroviral therapy.

Most common cART regimens in 2018

Initial regimen

Just over 75% people started on an integrase inhibitor-containing regimen in 2018, with abacavir/lamivudine/dolutegravir and tenofovir alafenamide/emtricitabine/cobicistat-boosted elvitegravir being the most frequently-prescribed initial regimens in 2018.

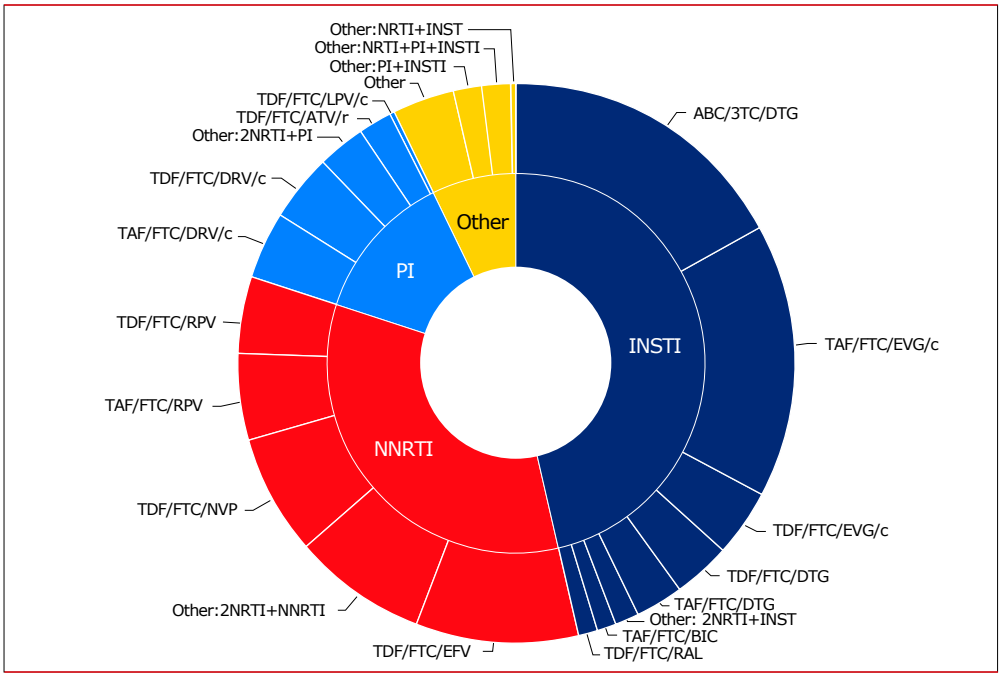
The likelihood of discontinuing or switching the initial regimen has been decreasing since 1996. As in previous years, toxicity continued to be a main reason for discontinuing or switching the initial regimen during the first year of treatment. Toxicity-related discontinuations were often due to neuropsychiatric,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

Integrase inhibitor–based cART used increasingly frequently

Integrase inhibitor-based cART continues to be further implemented on a large scale in the Netherlands: in 2018, 46% of all adults in care and on cART received an integrase inhibitor, compared with 39% in 2017. While 35% of the population on cART in 2018 received a backbone containing tenofovir disoproxil fumarate, new fixed-dose combinations have also led to an increase in the use of abacavir (35%) and tenofovir alafenamide (33%).

Among all HIV-positive individuals in care and on treatment in 2018, the majority (92.8%) received a cART regimen based on two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with an integrase inhibitor (46.6%), a non-NRTI (NNRTI, 33.4%), or a protease inhibitor (14%) (*Figure* 5). The most commonly-prescribed regimens in 2018 were abacavir/lamivudine/dolutegravir (17.2%), tenofovir alafenamide/emtricitabine/cobicistat-boosted elvitegravir (15.6%), and tenofovir disoproxil /emtricitabine combined with efavirenz (9.4%) or nevirapine (7%).

Figure 5: Combination antiretroviral therapy (cART) use in 2018 by all HIV-positive individuals in care.



Legend: *3TC=lamivudine; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; BIC=bictegravir; 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 receiving cART for at least 12 months and in care in 2018, 98% had achieved viral suppression (viral load <200 copies/ml). Individuals who had been diagnosed with HIV before 1996 and who remained in care and on cART in 2018 (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 2018. 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.

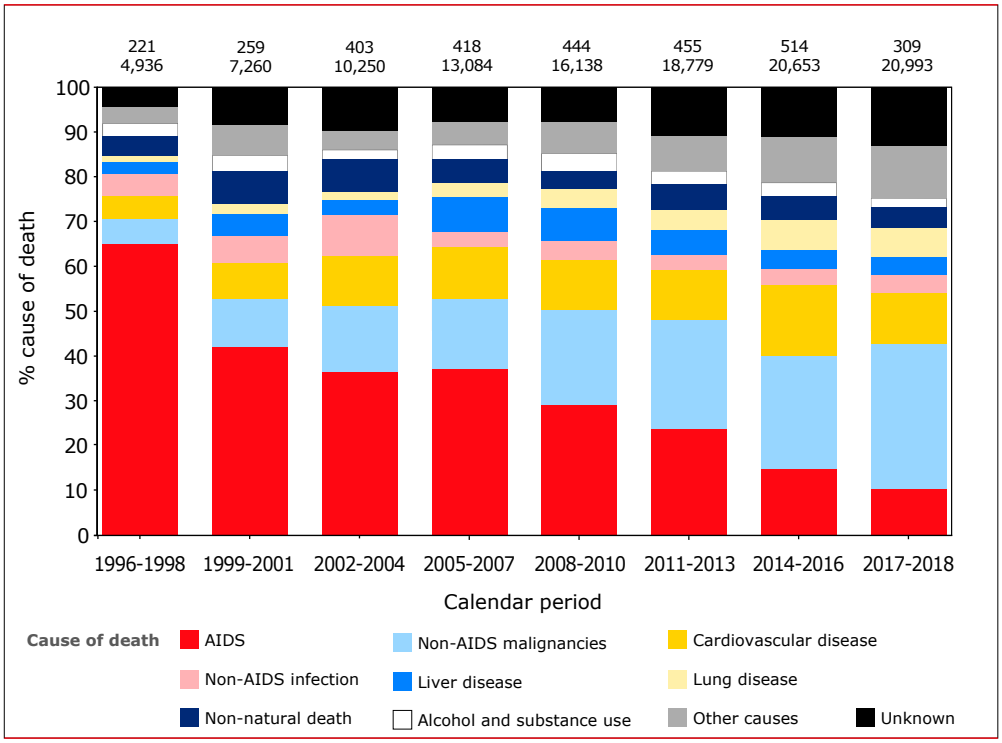
Morbidity and mortality

Sustained decline in AIDS-related death

Mortality remains low in HIV-positive individuals in care in the Netherlands. Since cART became available in the Netherlands in 1996, there has been a sustained decline in the risk of death from AIDS. Death is now increasingly likely to be caused by 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 entry into care, which once again stresses the importance of identifying and linking individuals to care earlier in the course of the infection.

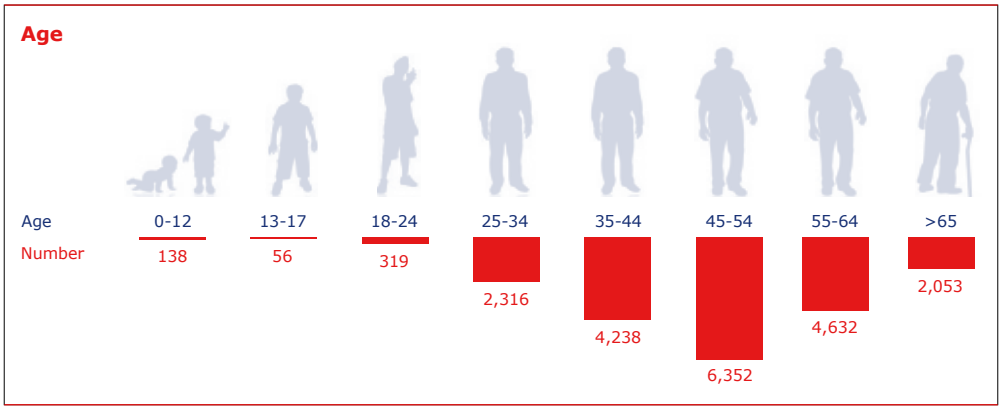
Figure 6: *Relative changes in cause of death in different calendar periods since the introduction of combination antiretroviral therapy (cART) in the Netherlands. Numbers above each bar represent the number of people at risk during that calendar period.*



Ageing and comorbidities

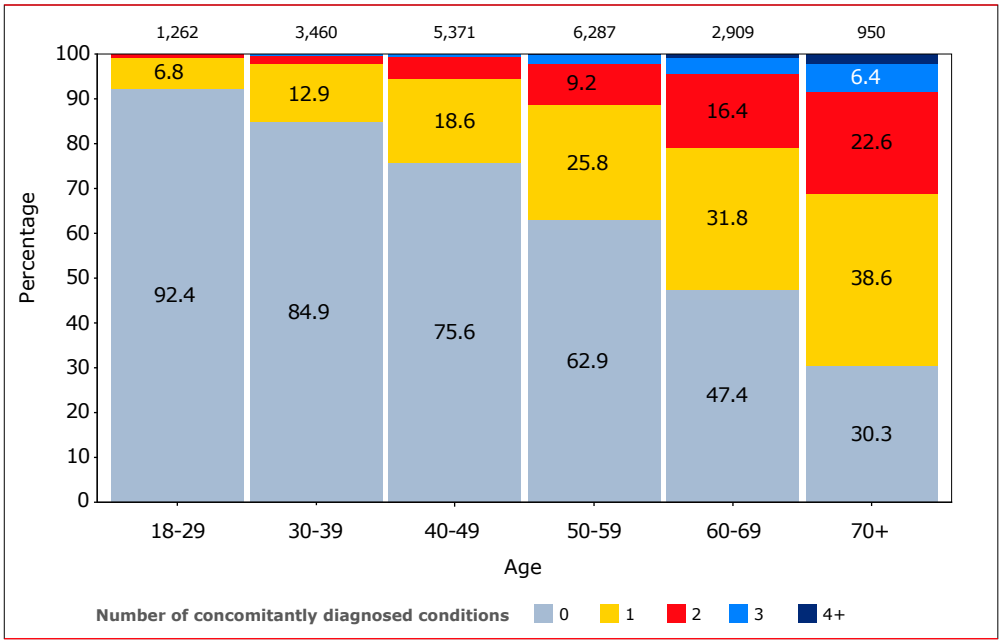
A substantial proportion of those people who were newly-diagnosed with HIV and entered HIV care in 2018 were older individuals; 24% were 50 years or older. At the same time, the overall population of people with HIV in care in the Netherlands also continues to age, with 50% currently older than 50 years (*Figure 7*).

Figure 7: *Age distribution of people living with HIV and in care in the Netherlands in 2018.*



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 2018. 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 cardiovascular risk only increased slightly over the period 2000-2018. This suggests that cardiovascular risk management has improved over time. Nonetheless, there remains significant room for further improvement, given the suboptimal use of statin therapy, antihypertensive therapy and low-dose acetylsalicylic acid use as secondary prevention following a myocardial infarction or ischaemic stroke, as well as the low, albeit slowly improving, uptake of these medications in the prevention of primary cardiovascular disease.

Non-AIDS malignancies

The most common non-AIDS malignancies are lung, anal, and head and neck cancers, as well as Hodgkin's lymphoma. The incidence rate of non-AIDS malignancies in the Netherlands has remained stable over time. However, when the increasing age of the HIV-positive population is taken into account, we observe a decline in the age-adjusted 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. Individuals who initiated ART within 12 months after their last HIV-negative test, had a lower risk of being diagnosed with a non-AIDS-defining malignancy, independent of their current CD4 cell count and other risk factors, suggesting an additional health benefit of early initiation of ART.

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, 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.

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 the standard of 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 5% having documented evidence of chronic infection and 3% having evidence of acute HCV infection at the time of the first diagnosis. Most individuals with HCV infection were male and from the Netherlands or other European countries.

Hepatitis B virus co-infection

The prevalence of chronic HBV infection has decreased over time as a result of increased HBV vaccination rates, together with the HBV-prophylactic effect of tenofovir and tenofovir alafenamide for the treatment of HIV. Six percent of individuals ever in care were found to have, or have had, chronic HBV infection.

HBV vaccination remains a priority

An estimated 34% of HIV-positive individuals overall had not been exposed to HBV and had not been successfully vaccinated. These individuals remain at risk of acquiring HBV if they are not taking a cART regimen including tenofovir or tenofovir alafenamide. These findings illustrate the importance of continuing our efforts to increase successful HBV vaccination rates, particularly in those who are not receiving tenofovir-containing cART.

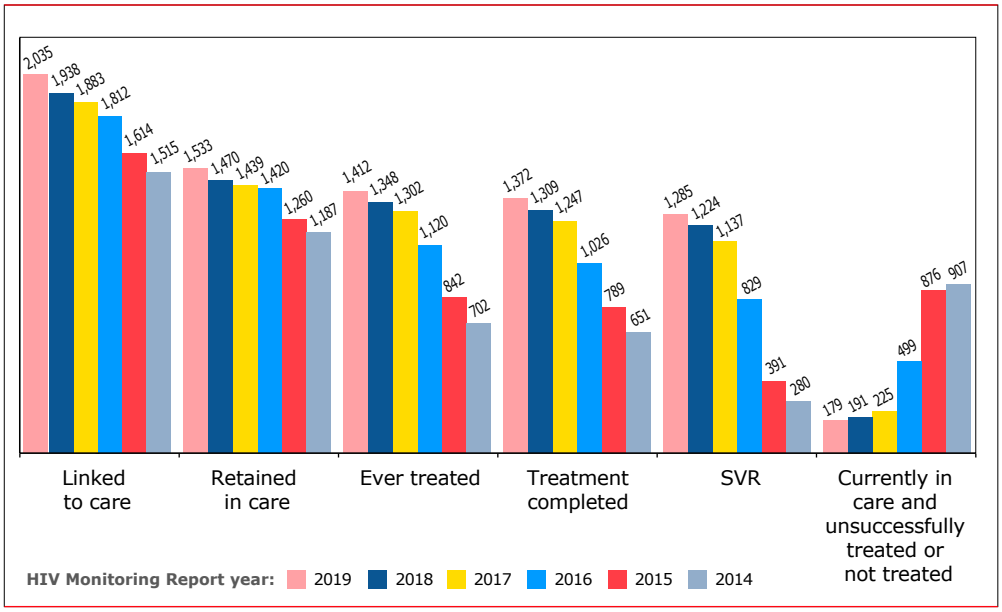
Risk of dying from HCV or HBV co-infection is decreasing

Overall, HIV-positive individuals with a chronic HCV or HBV co-infection remain at increased risk of liver-related morbidity and mortality. However, people diagnosed with chronic HCV or HBV have had a steadily decreasing risk of liver-related death since 2010. For those with chronic HBV infection, this is likely a result of increasingly effective HBV treatment through the use of tenofovir-containing cART that became more widespread in 2002.

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 effective treatment for HCV. By 31 December 2018, over 950 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*). However, not all individuals in need of treatment have yet received treatment with DAAs; this underlines the need for additional efforts to reach these people.

Figure 9: Hepatitis C virus continuum of care in people with HIV/HCV co-infection.



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 2018. 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 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 interventions to reduce HCV risk behaviours.

Pregnancies in women living with HIV-1 in the Netherlands

A total of 2,705 pregnancies were documented in 1,517 women in HIV care in the Netherlands. Of these women, 81% were born outside the Netherlands, mainly in sub-Saharan Africa (68%). Women who were born in the Netherlands were more likely to be aware of their HIV-positive status prior to conception than those born elsewhere (78% and 62%, respectively). In both groups, the most common mode of HIV acquisition was heterosexual contact (94%).

Fewer pregnancies

The number of pregnancies among women living with HIV-1 has been decreasing since 2009. This may be due to the increasing age of the women in HIV care, as well as a drop in national birth rates.

Higher detectable HIV RNA rates at the time of delivery in 2018

Almost all women (99%) were treated with antiretroviral therapy during pregnancy. As a result, maternal HIV RNA levels were below 50 copies/ml (i.e., undetectable) in 85% of the deliveries, and between 50-500 copies/ml in a further 10% of deliveries. However, we did see an increase in the proportion of women with detectable HIV RNA levels in 2018. This was primarily in women who were newly-diagnosed with HIV during pregnancy and consequently only

started treatment during pregnancy. Therefore, it is important that women who are newly-diagnosed with HIV during pregnancy are closely monitored.

Perinatal transmission of HIV now very rare in the Netherlands

Due to the high rates of successful treatment in women living with HIV, perinatal transmission of HIV is rare in the Netherlands, with only one reported case since 2015. The majority (69%) of children who acquired HIV perinatally were born outside the Netherlands. In the Netherlands, in women who receive treatment and have undetectable HIV RNA levels, the rate of vertical transmission is 0.18%.

Suboptimal viral suppression rates during the post-partum period

Following the new guideline recommendation in 2015 to prescribe cART to all individuals regardless of CD4 count, it is now also recommended that all pregnant women continue cART after pregnancy. Since 2015, of those women who continued using antiretroviral therapy after delivery, 12% had at least one detectable HIV RNA measurement in the year following delivery. This may reflect poorer treatment compliance during the post-partum period.

To achieve viral suppression during delivery and maintain treatment compliance in the post-partum period, women living with HIV who start cART during pregnancy require additional support, not only during pregnancy but also post-partum.

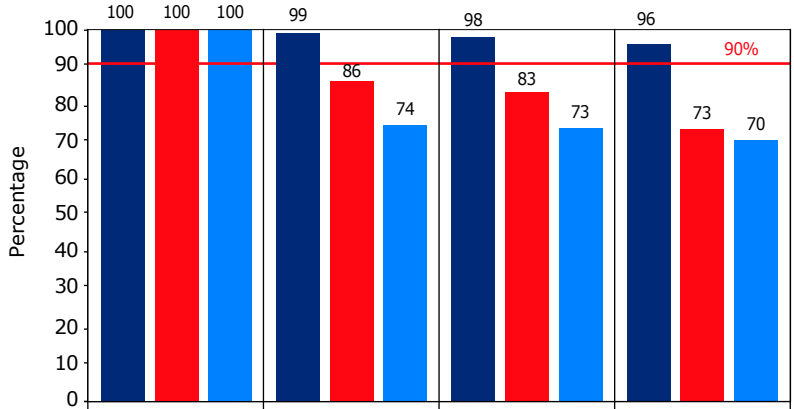
Children living with HIV

Of 504 children ever registered by SHM and who entered HIV care in the Netherlands, the majority (81%) remain in care. Of the children who are currently in care, 136 (27%) were born outside the Netherlands and adopted by Dutch parents.

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 in people who acquired HIV in childhood, as of 31 December 2018. The numbers on top of the bars indicate the proportion of individuals.



	Linked to care	Retained in care	On antiretroviral treatment	Virologically suppressed
Current age <18 years	195	194	191	187
Current age ≥18 years vertical transmission	140	121	116	102
Current age ≥18 years non-vertical transmission	125	93	91	88

Poorer viral suppression around transition to adult care

Of those individuals who were originally registered as a child, 81% were still in care in 2018, 52% of whom were older than 18 as of 31 December 2018. Of the children who had transitioned from paediatric to adult care, 20% 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 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

Comparing indicators to the national average

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. In this year's report, we also compared each centre's indicator to the national average, in a manner that takes into account the diverse mix of patients' geographical origin and routes of transmission that are found across centres.

In all centres the proportion of patients in care in 2018 who had initiated cART and had viral suppression were within the expected range of the national average.

High overall retention in care

Overall, retention in care was found to be high in most HIV treatment centres in the Netherlands, although in some centres 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. In fact, a median of 100% of all patients who entered care in 2016 and 2017 and who were retained in care in 2018 had initiated cART, while across all centres, more than 95% of patients in care in 2018 were on 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.

Amsterdam Cohort Studies

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS were started in 1984 shortly 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.

As of 31 December 2018, 2,888 MSM had been included in the ACS, of whom 607 were HIV-positive when they entered the study and 261 seroconverted during follow up. In 2018, 749 HIV-negative and 60 HIV-positive MSM remained in active follow up at the GGD Amsterdam, with an additional 197 HIV-positive MSM being followed at the MC Jan van Goyen or the DC Klinieken Lairesse-Hiv Focus Centrum in Amsterdam. In 2018, 92 additional HIV-negative MSM were recruited. The median age in this group was 28.1 years, while that of the total group of MSM in active follow up was 42.9 years at their last visit. The majority (83.7%) of the total group were born in the Netherlands and 85.7% were residents of Amsterdam. Finally, 75.9% of the participants had a college degree or higher. In 2018, 3 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 2018.

HIV in Curaçao

Over the years, an increasing proportion of individuals with HIV in care at the St Elisabeth Hospital in Willemstad in Curaçao have managed to achieve a suppressed viral load. 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. In addition, the proportion of people entering care with late-stage HIV infection remains high, although the proportion with advanced HIV disease appears to be decreasing.

Monitoring programme report

1. The HIV epidemic in the Netherlands

Ard van Sighem and Eline Op de Coul

Introduction

As of May 2019, 30,124 HIV-positive individuals had been registered by Stichting HIV Monitoring (SHM). Following registration, further clinical data were collected for 29,449 (97.8%) of the individuals, while the remaining 675 (2.2%) persons objected to the collection of their data. Among the 29,449 individuals with clinical data, 28,375 were registered in one of the HIV treatment centres in the Netherlands (*Figure 1.1*) and 1,246 were registered in the St. Elisabeth Hospital in Willemstad, Curaçao (see *Chapter 9*); 172 people had been registered both in the Netherlands and in Curaçao.

Of the 28,375 people registered in the Netherlands, the majority were diagnosed with HIV-1 (26,976; 95%). A small group of people, 100 in total, were diagnosed with HIV-2, while 67 people had antibodies against both HIV-1 and HIV-2. Serological results were not available in the SHM database for 1,232 individuals, a group that mostly comprised people who were registered before the official start of the AIDS Therapy Evaluation in the Netherlands (ATHENA) study and for whom only limited data were therefore 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 still in care at the end of 2018.

Back to Chapter 2 >

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

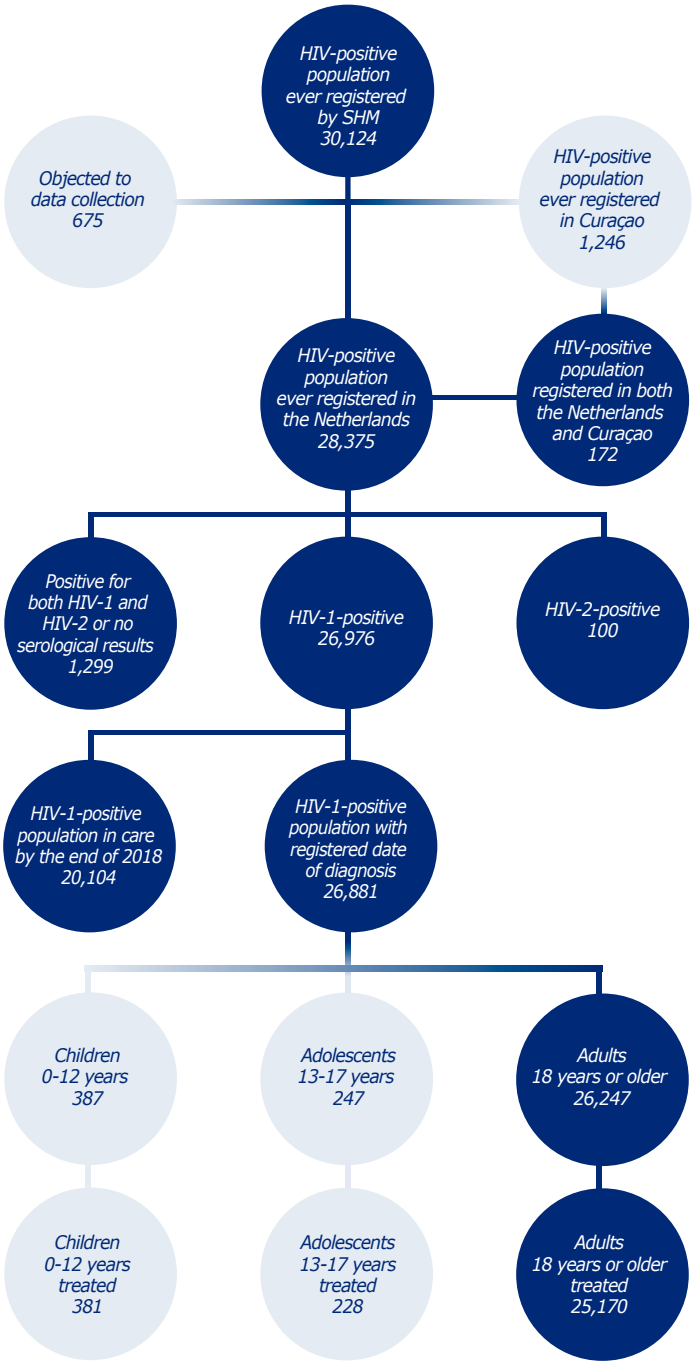
Infection	The moment an individual acquires an HIV infection. The time of infection is often unknown.
Diagnosis	The moment an individual is newly diagnosed with an HIV infection. The time of diagnosis can be weeks, months, or even years after infection.
Entry into care	The moment an HIV-positive individual is first linked to 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, 26,247 individuals were ever diagnosed with HIV-1 as adults and had a recorded date of diagnosis (*Figure 1.1*). The majority of these 26,247 adults were men who have sex with men (MSM; 15,829 (60%)), while 3,549 other men (14%) and 4,279 (16%) women reported having acquired their HIV infection through heterosexual contact (*Appendix Table 1.1*). For 775 (3%) individuals, the reported mode of transmission was injecting drug use, while for 330 (1%) individuals infection occurred through exposure to contaminated blood. Other and unknown modes of transmission accounted for the remaining 6% (1,485) of infections.

Figure 1.1: Overview of the HIV-positive population registered by Stichting HIV Monitoring (SHM) as of the end of 2018.

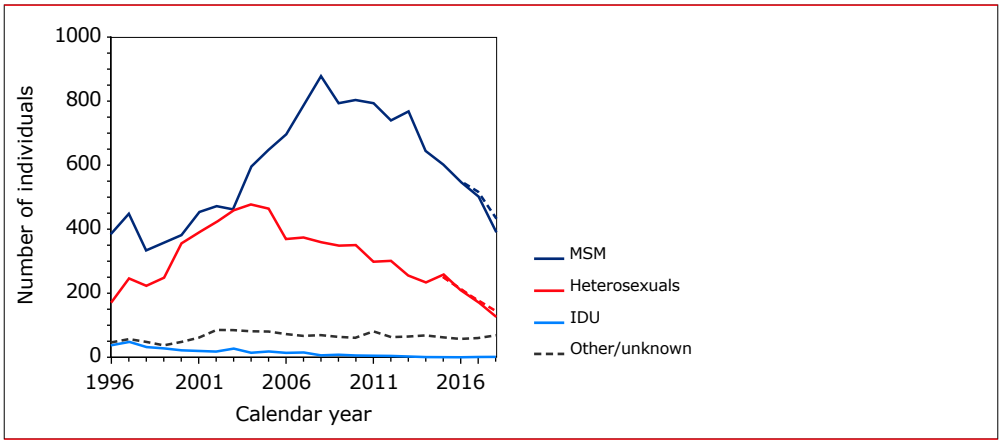


Decreasing number of diagnoses

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 2018, the decreasing trend continued and the number of new HIV diagnoses, taking into account a projected backlog[a] in registration of HIV cases, was approximately 664.

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 437 in 2018. In individuals who acquired their HIV infection via heterosexual contact, the number of new diagnoses has declined to approximately 150 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 2018, men who have sex with men (MSM) accounted for 66% of new diagnoses, infections via heterosexual contact for 22%, infections via injecting drug use (IDU) for 0%, and infections via other or unknown modes of transmission for 12% of the annual number of new diagnoses. The dotted lines indicate the number of diagnoses after the projected backlog in registration of HIV cases (3% in 2017, 11% in 2018) is taken into account (See Box 1.1).*



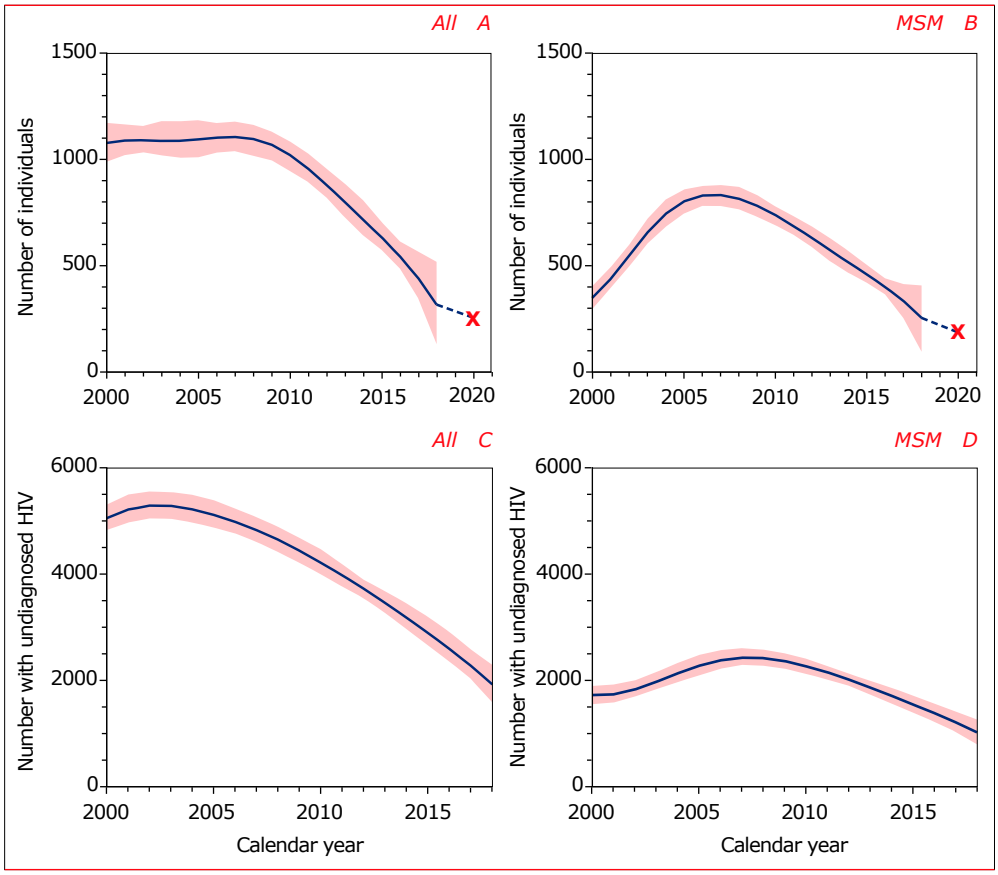
Legend: *MSM=men who have sex with men; IDU=injecting drug users.*

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 2017 and 11% in 2018.*

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 continuously over time to 320 (95% confidence interval (CI), 130-520) in 2018 (*Figure 1.3A*). In MSM, the annual number of newly-acquired HIV infections reached a peak of approximately 800 around 2007 and thereafter has continued to decrease to around 250 (95% CI, 90-410) in 2018 (*Figure 1.3B*). Since 2000, the number of people estimated to be living with undiagnosed HIV has also 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 in the entire HIV-positive population in the Netherlands (A, C) and in men who have sex with men (B, D). The cross indicates UNAIDS' target for 2020 of achieving a 75% reduction in the number of newly-acquired HIV infections since 2010.*

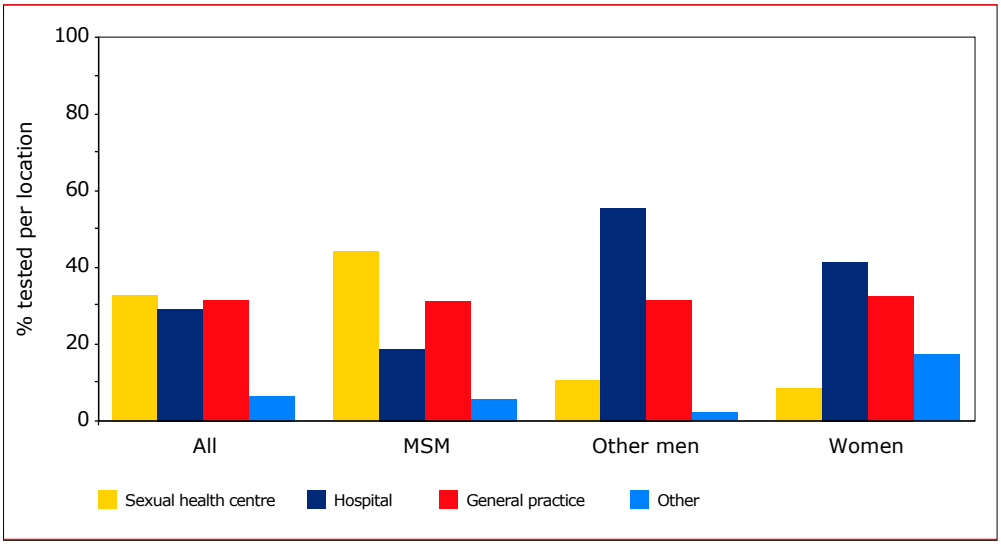


Towards a 75% reduction in newly-acquired HIV infections by 2020
In 2016, the United Nations General Assembly committed to achieving a 75% reduction by 2020 in the annual number of newly-acquired HIV infections compared with 2010[2,3]. The decreasing trend in the estimated annual number of newly-acquired infections in the Netherlands over the years shows that the Netherlands is on course to achieving this goal. In 2018, there were 320 newly-acquired HIV infections, which is a reduction of 69% compared to 2010. The UNAIDS' 2020 target (for the Netherlands implying 260 or fewer newly-acquired HIV infections in 2020) may already be reached in 2019 if current trends in the number of infections continue (*Figure 1.3A*). Among MSM, a reduction of 66% had been achieved by 2018 and, as in the overall population, the UNAIDS' 2020 target may also be met in 2019 (*Figure 1.3B*).

Setting in which HIV is diagnosed

Information on the setting in which HIV was diagnosed in the Netherlands was available for 1,991 (90%) of the 2,220 people diagnosed in 2016 or later, while 129 (6%) individuals were known to have been diagnosed abroad. Overall, 33% of these 1,991 individuals received their first HIV-positive test result at a sexual health centre, 29% at a hospital, and 32% at a general practice (*Figure 1.4*). Among those diagnosed at sexual health centres, 90% were MSM, 6% were other men, and 3% were women. These proportions are similar to those directly reported by sexual health centres in 2018[4].

***Figure 1.4:** Proportion of individuals diagnosed in 2016 or later, stratified by location of testing and transmission risk group.*



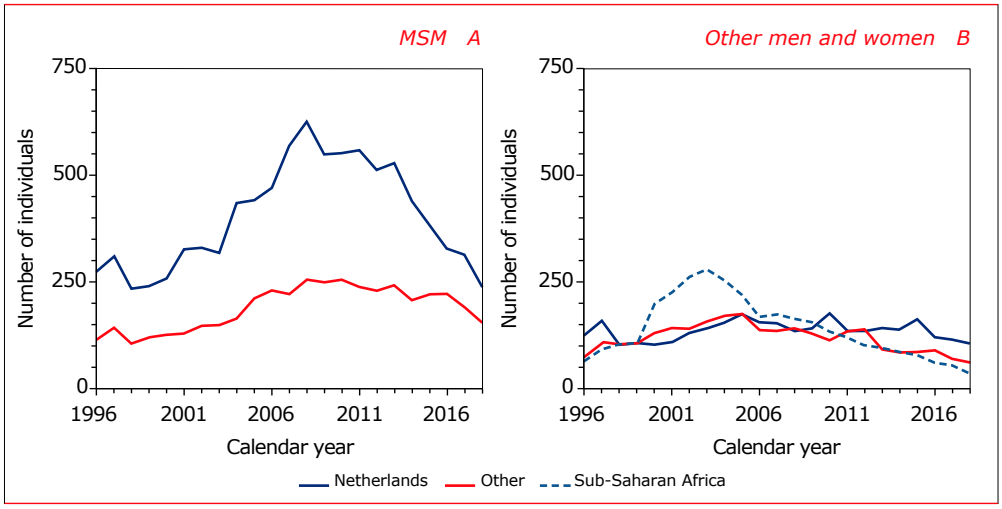
***Legend:** MSM=men who have sex with men.*

Geographical region of origin

In total, 11,552 (44%) people diagnosed with HIV as adults were born outside the Netherlands. Of the people who acquired HIV via homosexual contact, 68% 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, 2016), the proportion of MSM of Dutch origin was 61% (*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, 9% 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 2016 onwards, 48% of the newly-diagnosed women and other men were of Dutch origin, and 21% 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 1,480 MSM diagnosed in 2016 or later, 904 (61%) originated from the Netherlands, 181 (12%) from other European countries, 120 (8%) from South America, and 86 (6%) from the Caribbean. Among the other 740 people diagnosed in 2016 or later, 358 (48%) originated from the Netherlands, 59 (8%) from other European countries, 155 (21%) from sub-Saharan Africa, 69 (9%) from South America, 32 (5%) from the Caribbean, and 29 (4%) from south and south-east Asia. Note: data collection for 2017 and 2018 has not yet been finalised.*



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

Overall, 21% of the people newly diagnosed since 2016 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 14% and 12%, respectively, for people of Dutch origin and 30% 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 16% and 14%, respectively. Other PHS regions with at least 4% of new diagnoses since 2016 were Haaglanden (6%, including Den Haag), Utrecht (6%), Hart voor Brabant (5%, including Den Bosch and Tilburg), and Gelderland-Midden (4%, including Arnhem).

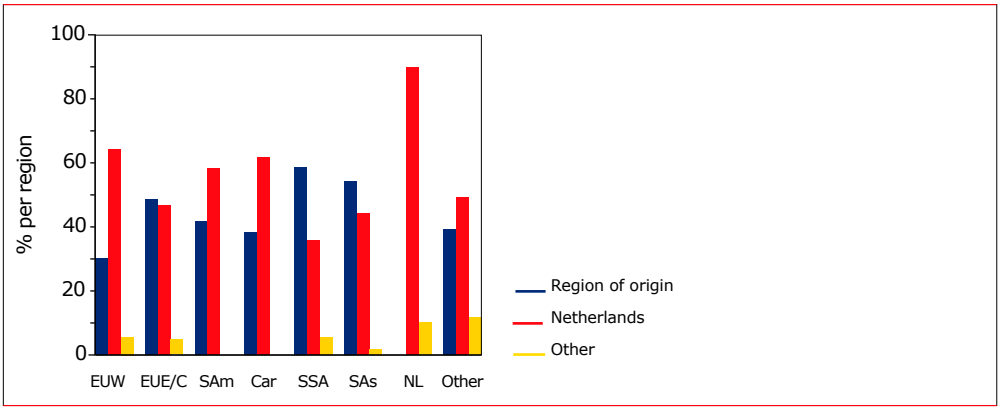
HIV diagnosis before arriving in the Netherlands

Since February 2018, SHM has been recording the date of arrival in the Netherlands for newly-registered HIV-positive individuals born abroad. Of the 1,075 people *newly-registered* in 2018 or up to May 2019, 472 (44%) were born in the Netherlands and 603 (56%) had been born abroad. In total, 307 (51%) foreign-born individuals were diagnosed after arrival and 286 (47%) were already diagnosed with HIV before moving to the Netherlands, while for the remaining 10 individuals born abroad, the date of arrival was not available yet. Among the 307 people diagnosed after arrival, the majority were diagnosed shortly before registration with SHM: 253 (82%) were diagnosed in 2018 or 2019, and 36 (12%) in 2017. In contrast, 70% of the people moving to the Netherlands with a diagnosed HIV infection were diagnosed before 2016. Including those migrants for whom the date of arrival was collected retrospectively, 400 people were known to have been diagnosed before moving to the Netherlands (*Appendix Table 1.1*).

Self-reported geographical region of HIV acquisition

In total, 1,658 (75%) of the individuals diagnosed in 2016 or later reported the most likely country where they acquired their HIV infection (*Figure 1.6*). Among people born in the Netherlands, the majority (90%) reported having acquired their HIV infection in the Netherlands, while among foreign-born individuals, 51% of those diagnosed in 2016 or later reported having acquired their HIV infection in the Netherlands.

Figure 1.6: Proportion of all HIV-1-positive adults diagnosed in 2016 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 2016 or later acquired their HIV infection in the Netherlands. Among other men and among women with a self-reported region of acquisition, 61% acquired HIV in the Netherlands, while 13% reported having acquired HIV in sub-Saharan Africa. The proportion of Dutch-born people who likely acquired HIV in the Netherlands was 93% for MSM, 79% for other men and 88% for women.

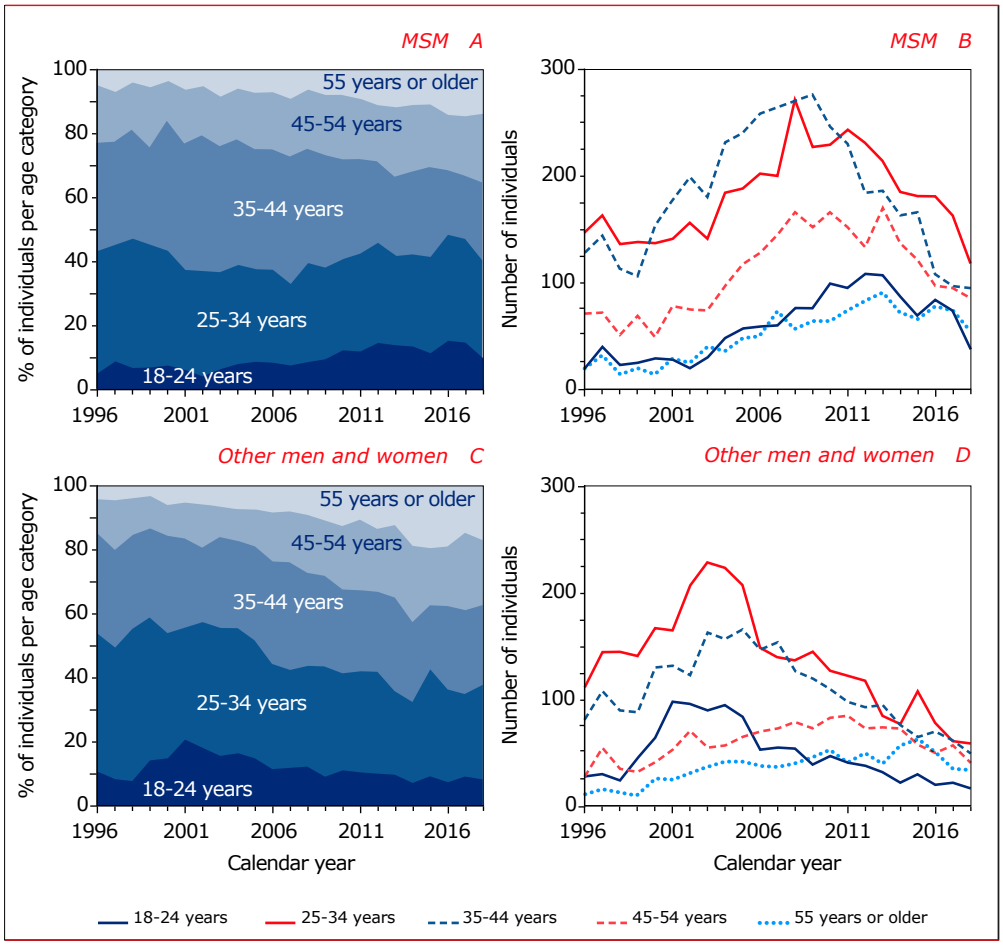
Increasingly older age at time of HIV diagnosis

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 2018, it was 40 (IQR 30-50) years. Over the entire period from 1996 through 2018, 16% of adults who received an HIV diagnosis were 50 years or older; in 2018, 24% were 50 years or older.

There were considerable age differences between MSM, other men, and women diagnosed in 2016 or later. MSM born in the Netherlands were diagnosed at a median age of 42 (30-53) years, while those of foreign origin were diagnosed at 32 (26-40) years. Among other people of Dutch origin, the median age at the time of diagnosis was 41 (31-53) years for women and 46 (32-55) years for men. Individuals born in sub-Saharan Africa (women: 37 years; men: 42 years) or elsewhere (women: 36 years; men: 39 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 2018, the proportion of MSM aged 45 years or older at the time of diagnosis increased from 24% to 36%, while these proportions were 15% and 37% for other individuals. During the same period, the proportion of individuals between 25 and 34 years of age decreased from 38% to 30% for MSM and from 43% to 30% for other individuals.*



Young adults

The annual 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 17 in 2018, or to 8% of the annual number of diagnoses (*Figure 1.7*). Among MSM, both the number and proportion of diagnoses among young adults increased over time and, in 2012, young adults accounted for 15% (108) of the diagnoses. Thereafter, the proportion of diagnoses among young MSM remained around this level, although the absolute number has decreased.

Entry into care

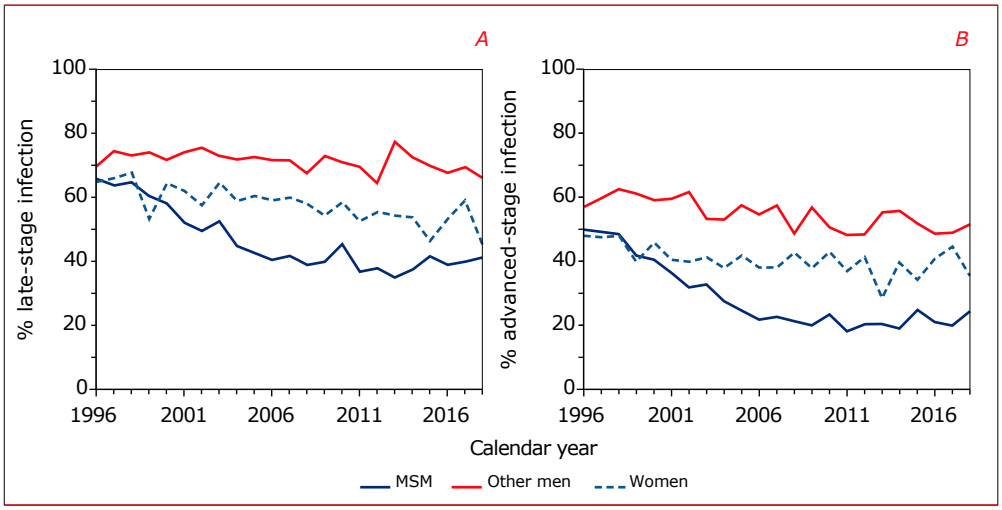
Of all individuals diagnosed with HIV in 2016 or later and for whom the setting in which they first tested HIV-positive was known (excluding those diagnosed abroad), 93% had entered care within 4 weeks of receiving their diagnosis and 96% within 6 weeks. The proportion in care within 6 weeks was 96% 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 (96%), at a general practice (96%), or at other locations (97%). Overall, the proportion in care within 6 weeks was similar for MSM (96%), other men (95%), 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 diagnosis

In total, 30% of the individuals with an HIV diagnosis from 1996 onwards had CD4 counts of 500 cells/mm^3 or higher at diagnosis, 20% had CD4 counts between 350 and 499 cells/mm^3, 20% had CD4 counts between 200 and 349 cells/mm^3, and 31% had CD4 counts below 200 cells/mm^3, while 15% had a concurrent AIDS diagnosis. For people diagnosed in 2016 or later, these proportions had improved somewhat and were 34%, 21%, 19%, and 26%, respectively; 13% had already been diagnosed with AIDS.

Overall, 52% of the individuals were diagnosed with HIV with an already late-stage HIV infection, i.e., with either a CD4 count below 350 cells/mm^3 or an AIDS-defining event regardless of CD4 count[5]. Over time, the proportion of late-stage HIV diagnoses decreased from 67% in 1996 to 47% in 2018 (*Figure 1.8*). In addition, the proportion of individuals diagnosed with advanced HIV disease, i.e., with a CD4 count below 200 cells/mm^3 or AIDS, has likewise decreased over time and was 32% in 2018.

Figure 1.8: Proportion of individuals classified as having (A) late-stage or (B) advanced-stage HIV infection at the time of diagnosis. From 1996 (2016) onwards, 52% (47%) were diagnosed with late-stage HIV infection: men who have sex with men (MSM) 44% (40%), other men 71% (66%), and women 58% (53%). Overall, 34% (29%) were diagnosed with advanced-stage HIV infection: MSM 26% (21%), other men 54% (48%), and women 40% (41%). 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. As a CD4 count measurement close to the time of diagnosis and before start of treatment was sometimes missing, the stage of the HIV infection could not be determined for all individuals. The proportion with unknown stage of HIV infection decreased from 33% in 1996 to 14% on average in 2016 or later.



Legend: MSM=men who have sex with men.

Late diagnosis by region of origin, age, and setting of diagnosis

Among individuals diagnosed with HIV in 2016 or later, 40% of MSM, 66% of other men, and 53% of women had a late-stage HIV infection. Late-stage HIV infection was most commonly found among people originating from sub-Saharan Africa (63%) or south and south-east Asia (62%), and among people originating from the Netherlands (62%) or from South America (59%) who acquired their HIV infection via other routes than homosexual contact (*Appendix Table 1.3*).

Older age at the time of diagnosis was also associated with a higher likelihood of late-stage HIV infection. Late-stage HIV was seen in 53% of MSM, 76% of other men, and 66% of women diagnosed in 2016 or later at 45 years of age or older, compared with 23% of MSM, 45% of other men, and 29% of women diagnosed at ages younger than 25 years (*Appendix Table 1.3*). Late-stage HIV was also observed

more often in people who received their HIV diagnosis at a hospital (77%) compared with those who were tested at a general practice (45%), a sexual health centre (24%), or another testing location (34%).

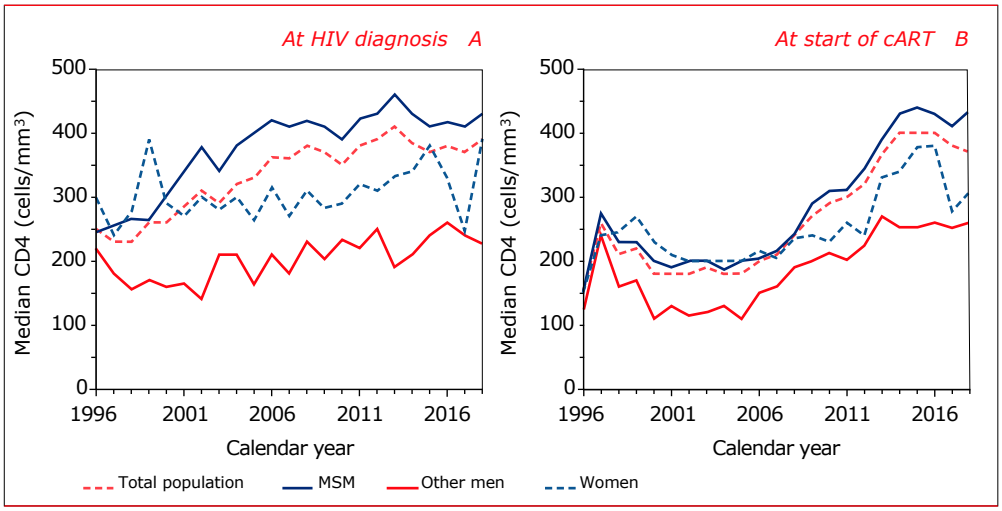
Impact of transient low CD4 cell counts early after infection

During the first few weeks after acquiring HIV, transient low levels of CD4 cell counts are common[6]. As a result, the stage of the infection may inadvertently be classified as late or advanced when individuals are diagnosed with HIV during this early phase of the infection. When people with a known HIV-negative test in the 6 months prior to HIV diagnosis were reclassified as not having a late-stage or advanced-stage HIV infection, the proportion of late-stage HIV infections among individuals diagnosed in 2016 or later changed from 47% to 43%. This decrease was mainly due to a decrease in late-stage HIV among MSM, from 40% to 34%, whereas among other men and among women, the proportion decreased by less than 2 percentage points. The change in the proportion of people diagnosed with advanced-stage HIV infection was more modest: 29% before and 28% after reclassification in people diagnosed in 2016 or later.

Earlier diagnosis

Between 1996 and 2018, median CD4 counts in the total adult population at the time of diagnosis increased from 250 to 390 cells/mm^3 (*Figure 1.9A*). This overall increase was mainly the result of a rise in CD4 counts in MSM, whereas CD4 counts in women and in other men showed more modest increases.

Figure 1.9: Changes over calendar time in median CD4 counts (A) at HIV diagnosis and (B) at the start of combination antiretroviral therapy (cART). (A) Between 1996 and 2018, CD4 counts at the time of diagnosis increased from 250 (interquartile range (IQR) 80–437) to 390 (IQR 150–594) cells/mm³ in the total adult population. The increase was most apparent for men who have sex with men (MSM): 245 (IQR 80–450) cells/mm³ in 1996 and 430 (IQR 218–602) cells/mm³ in 2018. 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 255 (IQR 59–538) and 390 (IQR 120–600) cells/mm³ in 2018. (B) In the total adult population, CD4 counts at the start of cART rose to 260 (IQR 130–392) cells/mm³ shortly after cART became available, decreased to a plateau of approximately 180 cells/mm³ between 2000 and 2005, and increased thereafter. In 2018, CD4 counts were 380 (IQR 160–602) cells/mm³ in the total population, 435 (IQR 216–658) cells/mm³ in MSM, 280 (IQR 50–490) cells/mm³ in other men, and 308 (IQR 120–545) 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.



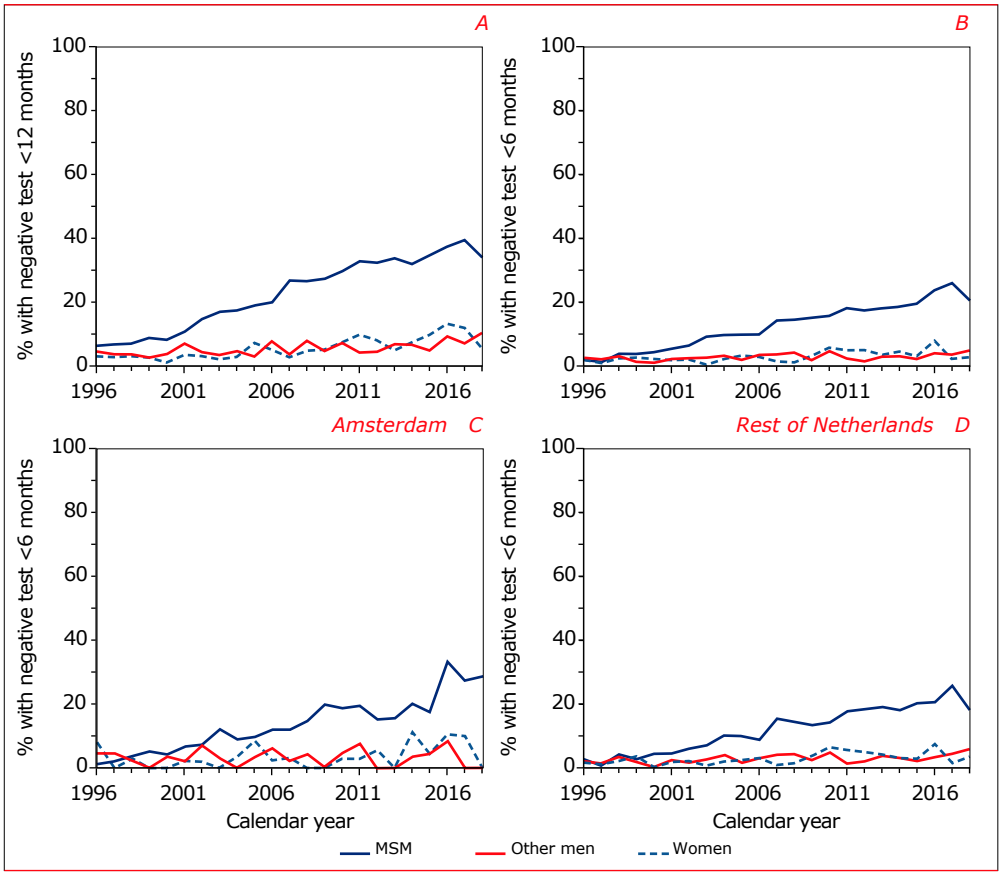
Legend: MSM=men who have sex with men; cART=combination antiretroviral therapy.

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, 32% had a negative test in the 12 months before diagnosis, while 18% had a negative test in the 6 months before diagnosis; by 2018, these proportions had increased to 34% and 21%, respectively. For other

men and for women however, the proportions with a recent infection between 2010 and 2018 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, 34% of men who have sex with men (MSM), 10% of other men, and 5% of women diagnosed in 2018 had a last negative test at most 12 months before diagnosis, whereas 21% of MSM, 5% of other men, and 3% of women had a last negative test at most 6 months before diagnosis.*



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

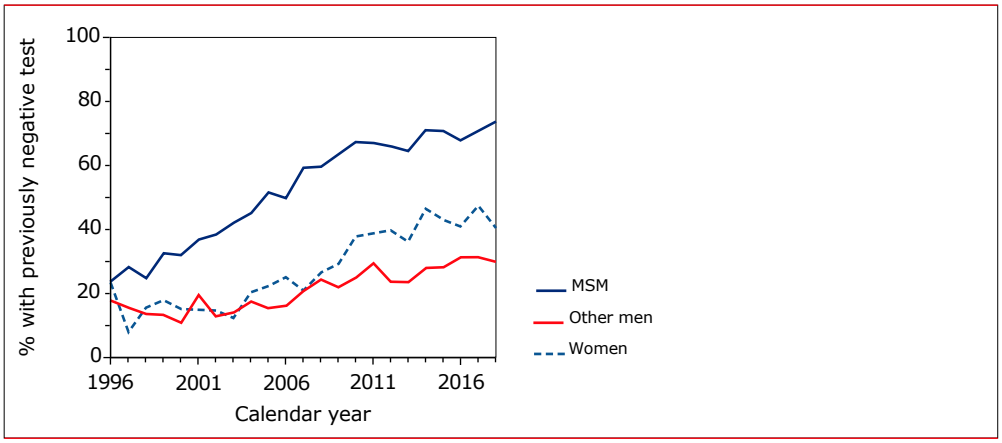
Amsterdam vs. rest of the Netherlands

Among those diagnosed in 2016 or later, the proportion of MSM with a known HIV-negative test in the 6 months before diagnosis was 31% in Amsterdam and 21% (i.e., lower) in the rest of the Netherlands, excluding Amsterdam (*Figure 1.10C; Figure 1.10D*). Among other men and among women, the proportion of recent infections did not differ between Amsterdam and the rest of the country.

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 2018, 74% of MSM, 30% of other men, and 41% 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 (88%), compared with 34% of those diagnosed in a hospital, 59% of those tested at a general practice, and 69% of those diagnosed elsewhere.

Figure 1.11: *Proportion of individuals diagnosed after a previously negative HIV test. Altogether, 74% of men who have sex with men (MSM), 30% of other men, and 41% of women diagnosed in 2018 had a previously negative HIV test.*



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

Treated population

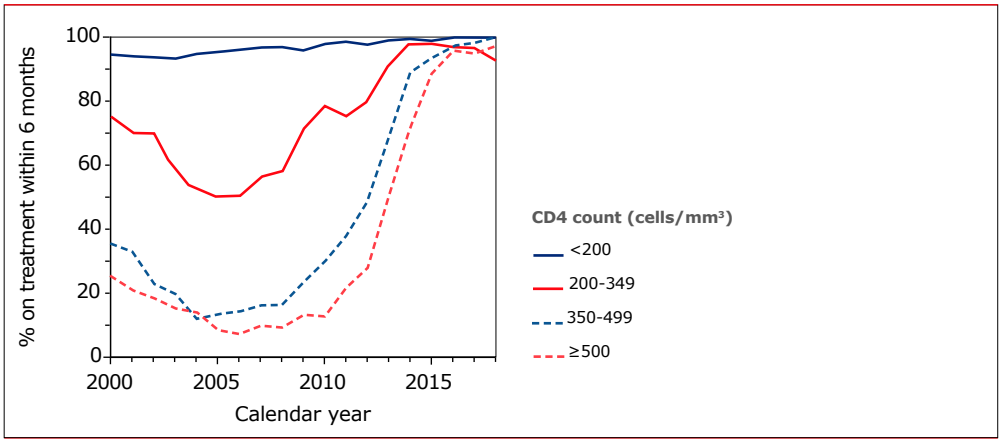
Of the 26,247 adults ever registered with an HIV-1 infection, 25,170 (96%) had started antiretroviral treatment by May 2019. Treatment and treatment outcomes are described in more detail in *Chapter 2*.

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 2018, median CD4 counts at the start of treatment had increased to 380 cells/mm^3. Of those starting cART in 2018, 28% of people started treatment at CD4 counts already below 200 cells/mm^3, 19% started at CD4 counts between 200 and 349 cells/mm^3, 17% started at CD4 counts between 350 and 499 cells/mm^3, and 35% 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 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 2018, for all CD4 strata, at least 90% of people who were diagnosed with HIV 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 1.1*).

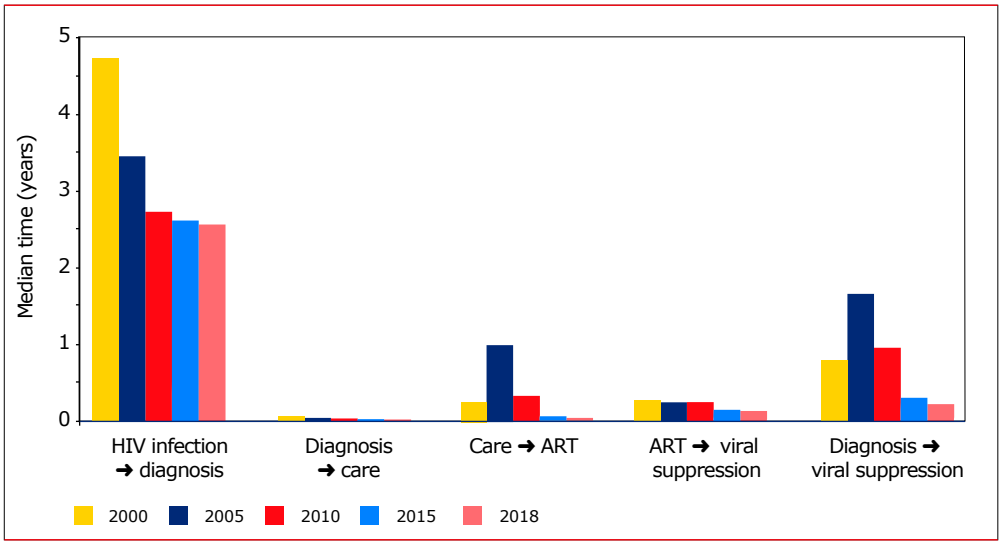
Figure 1.12: Proportion of individuals who started combination antiretroviral treatment (cART) within 6 months after HIV diagnosis by CD4 count at the time of diagnosis. Individuals were considered only if they had more than 6 months of follow up after diagnosis. Of all individuals diagnosed in 2016 or later, 100% of those with CD4 counts below 200 cells/mm³, 97% of those with CD4 counts between 200 and 349 cells/mm³, 98% of those with CD4 counts between 350 and 499 cells/mm³, and 96% of those with CD4 counts of 500 cells/mm³ or above had started cART within 6 months of diagnosis.



Time between HIV infection and viral suppression

People with a fully suppressed viral load do not transmit their virus to uninfected partners (undetectable equals untransmittable or U=U)[7,8,9]. 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[10]. 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 2018, 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 (1.2-4.7) years. During this same period, the median time from diagnosis to viral suppression decreased from 0.80 (IQR 0.40-3.64) years to 0.22 (0.15-0.38) 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.



Population – HIV-2

HIV-2-positive individuals

In total, 100 of the 28,375 registered HIV-positive individuals, including 46 men and 54 women, acquired an HIV-2 infection, of whom 21 were diagnosed in 2008 or later. The majority (80, or 80%) 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 (26 people) or Cape Verde (24 people). Only 21 individuals were born in the Netherlands, 15 of whom reported to have acquired their HIV infection in the Netherlands.

For the 84 individuals who were diagnosed in 1996 or later, the median CD4 count at the time of diagnosis was 305 (80-681) cells/mm^3. From 1996 onwards, 53% of the people were diagnosed with a late-stage HIV infection, and 42% were diagnosed with advanced HIV disease[5]. The distribution of CD4 counts at diagnosis appeared to be more bimodal than for HIV-1-positive individuals: 41% had CD4 counts below 200 cells/mm^3, 38% had CD4 counts of 500 cells/mm^3 or higher, while relatively few people (22%) had CD4 counts between 200 and 499 cell/mm^3.

HIV-2-positive people in care

A total of 65 people were still in clinical care, while 17 people had died, 6 had moved abroad, and 12 had no contact with HIV care in 2018. The median age of the people still in care was 61 (IQR 54-64) years; 56 (86%) individuals were 50 years or older. The majority (77%) of those in care had been living with HIV-2 for more than 10 years, while 28% had done so for more than 20 years.

In total, 42 people who were still in care by the end of 2018 had started combination antiretroviral treatment. The majority used a backbone of abacavir/lamivudine (16 individuals) or tenofovir/emtricitabine (12) in combination with dolutegravir (8) or a boosted protease inhibitor (20).

Of the 65 people who were still in care by the end of 2018, 54 had a most recent viral load measurement below 500 copies/ml, 3 had a viral load above 500 copies/ml, and 8 people had no available HIV-2 RNA result in 2018. Of the 23 individuals who were still in care and had not started cART, 18 had a viral load measurement below 500 copies/ml while the other 5 had no RNA result available in 2018. In this group of 23 people, CD4 cell counts were still high, with a median of 760 (570-1060) cells/mm^3.

HIV-1-positive people in care

Population in care

In total, 20,104 (75%) of the 26,976 HIV-1-positive individuals ever registered in the Netherlands, comprising 19,910 adults and 194 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 2018. People were considered to be in clinical care if they visited their treating physician in 2018 or had a CD4 count or HIV RNA measurement in that year and were still living in the Netherlands. Of the 6,872 people who, according to this definition, were not in care by the end of 2018, 3,120 (45%) were known to have died, and 1,839 (27%) to have moved abroad, while the remainder were either lost to follow up, only diagnosed with HIV in 2019, or had only moved to the Netherlands in 2019.

Table 1.1: Characteristics of the 20,104 HIV-1-positive individuals in clinical care by the end of 2018. An extended version of this table is available as Appendix Table 1.4.

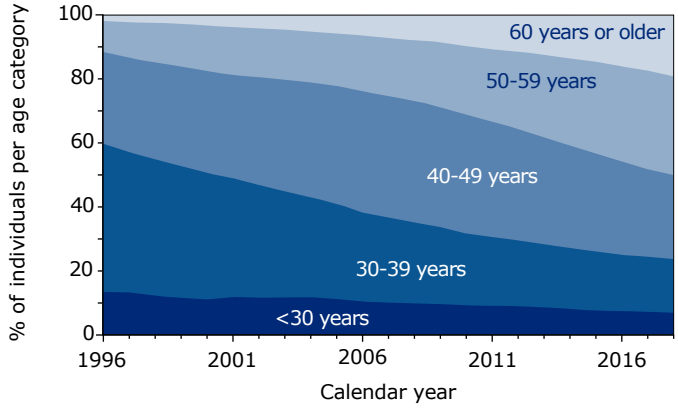
	Men (n=16,422, 82%)		Women (n=3,682, 18%)		Total (n=20,104)	
	n	%	n	%	n	%
Transmission						
MSM	12,697	77	-	-	12,697	63
Heterosexual	2,451	15	3,223	88	5,674	28
IDU	202	1	83	2	285	1
Blood/blood products	165	1	94	3	259	1
Other/unknown	907	6	282	8	1,189	6
Current age [years]						
0-12	61	0	77	2	138	1
13-17	31	0	25	1	56	0
18-24	235	1	84	2	319	2
25-34	1,869	11	447	12	2,316	12
35-44	3,199	19	1,039	28	4,238	21
45-54	5,187	32	1,165	32	6,352	32
55-64	4,025	25	607	16	4,632	23
65-74	1,530	9	178	5	1,708	8
≥75	285	2	60	2	345	2
Region of origin						
The Netherlands	10,836	66	1,129	31	11,965	60
Sub-Saharan Africa	1,084	7	1,484	40	2,568	13
Western Europe	925	6	118	3	1,043	5
South America	1,124	7	333	9	1,457	7
Caribbean	704	4	174	5	878	4
South and south-east Asia	483	3	239	6	722	4
Other	1,204	7	195	5	1,399	7
Unknown	62	0	10	0	72	0
Years aware of HIV infection						
<1	507	3	73	2	580	3
1-2	1,253	8	201	5	1,454	7
3-4	1,443	9	252	7	1,695	8
5-10	4,260	26	728	20	4,988	25
10-20	6,105	37	1,767	48	7,872	39
>20	2,827	17	645	18	3,472	17
Unknown	27	0	16	0	43	0

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

Ageing population

The median age of the population in clinical care by the end of 2018 was 50 (interquartile range [IQR] 41-58) 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 discussed earlier in this chapter. As a result, half of the people currently in care (50%) are 50 years or older, including 53% of men and 37% of women; 19% of the people are 60 years or older (*Appendix Table 1.4*). As the HIV-positive population continues to age, the number of individuals with age-related comorbidities also increases, 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 2018, these proportions were 7% and 50%, respectively, while 19% 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 age category: <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 2018 had been diagnosed with HIV a median of 11.3 (IQR 6.4-17.3) years previously. Thus, a large group (56%) of those in care have been living with HIV for more than 10 years, while 17% have done so for more than 20 years. The median time since diagnosis was 10.5 years for men who have sex with men (MSM), 12.0 years for other men, and 13.4 years for women. The majority of injecting drug users (94%) received their HIV diagnosis more than 10 years ago, which reflects how rare this mode of transmission has become as a result of the rapid and early adoption of harm reduction strategies in the Netherlands.

Antiretroviral treatment

In total, 99% of the individuals in care had started antiretroviral treatment, and 94% of them were currently using a once-daily regimen. Of the 262 (1%) individuals who had not yet started antiretroviral treatment by the end of 2018, 15 (5%) were known to have started treatment in 2019, while 110 (39%) other people were diagnosed with HIV in 2018 and their treatment had most likely not yet been recorded in the SHM database due to a delay in data collection. Antiretroviral treatment is discussed in more detail in *Chapter 2*.

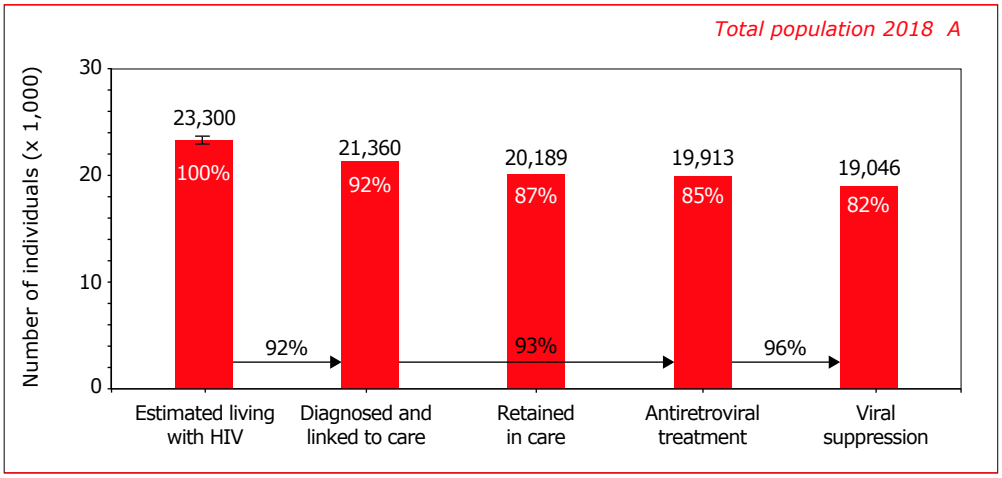
Clinical condition

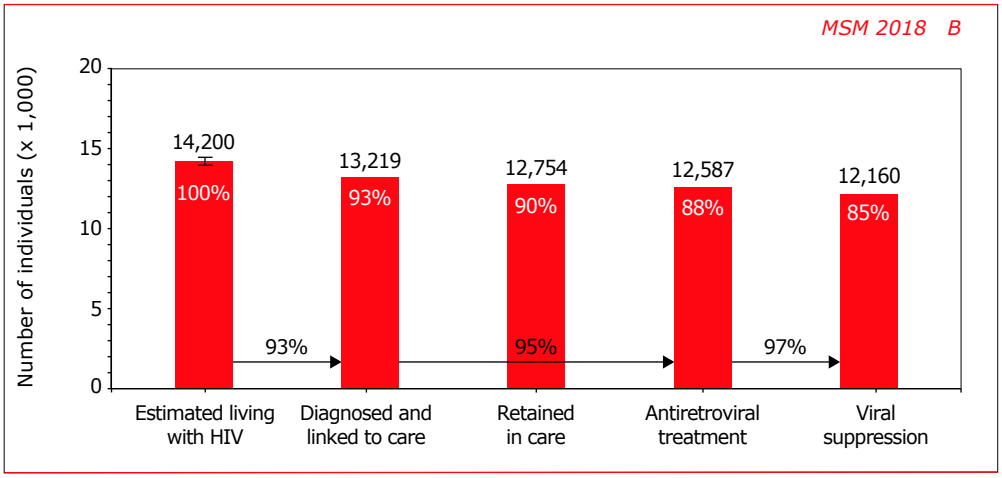
The median latest available CD4 count in 2018 of the people in care was relatively high at 680 (IQR 500-890) cells/mm^3, mainly as a result of treatment but partly also as a result of earlier diagnosis, as reported earlier in this chapter. CD4 counts were similar between MSM and women, being 692 (521-900) and 694 (510-922) cells/mm^3, respectively, but men who acquired HIV via other modes of transmission had lower CD4 counts at a median of 600 (410-820) cells/mm^3 (*Appendix Table 1.4*). For all people in care with a viral load measurement in 2018, 97% had a last measurement in that year below 200 copies/ml. Close to a quarter (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.

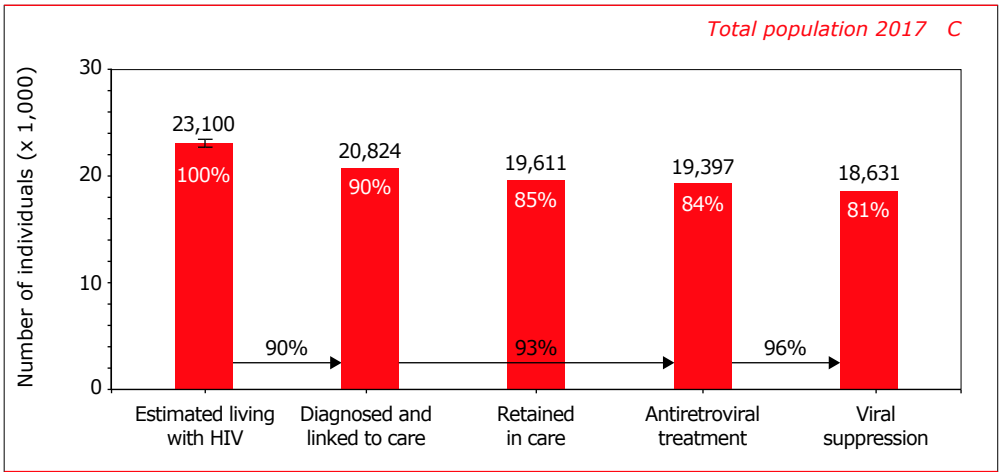
Continuum of HIV care

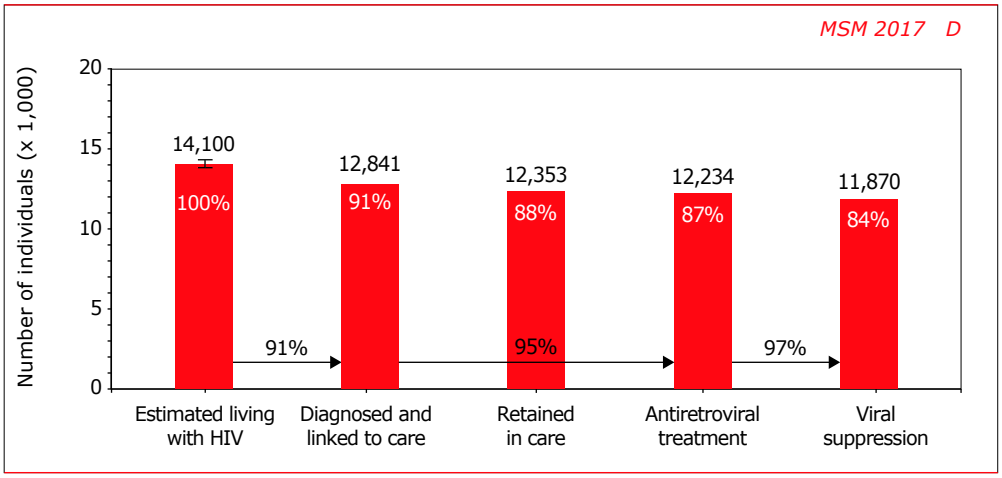
The total number of people living with HIV by the end of 2018 was 23,300 (95% confidence interval (CI) 23,000-23,700), including the estimated 1,900 (1,600-2,300) who were still undiagnosed[1]. Adjusted for registration delay, 21,360 individuals, or 92% of the total number estimated to be living with HIV, had been diagnosed, linked to care, and registered by SHM, of whom 20,189 individuals were considered to be retained in care (i.e., they had had at least one documented HIV RNA or CD4 count measurement or a clinic visit in 2018) (*Figure 1.15A*). The majority of these individuals (19,913, or 93% of those diagnosed and linked to care) had started antiretroviral treatment, and 19,046, or 96% of those treated, had a most recent HIV RNA measurement below 200 copies/ml. Overall, 82% of the total estimated population living with HIV and 89% 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 92-93-96[11]. Of the people still in care by the end of 2018, 14,015 (69%, or 76% 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 2018 and 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. Numbers were adjusted for a backlog in registration of HIV cases (3% in 2017, 11% in 2018).









Viral suppression

In total, 851 individuals (without adjustment for registration delay) had started treatment but did not have a suppressed viral load. On closer inspection, 301 (35%) of these individuals did not have a viral load measurement available in 2018. Of the 550 (65%) people with a viral load measurement and no viral suppression, 143 had only started antiretroviral treatment in 2018 and may not have had sufficient follow-up to achieve a documented suppressed viral load.

Lost to care

In total, 1,793 individuals were lost to care, of whom 654 (36%) before the end of 2008 and 1,139 (64%) after 2008. The 654 individuals who were lost to care in or before 2008 were excluded from the estimated number of people living with HIV and the number of people diagnosed and linked to care. It was assumed to be unlikely that these 654 individuals were still living in the Netherlands by the end of 2018 without needing care or antiretroviral treatment. Of the 1,139 individuals (1,171 with adjustment for registration delay) lost to care after 2008, i.e., the difference between the second (21,360) and third stage (20,189) in the care continuum, 74% were born outside the Netherlands, whereas this proportion was only 40% for those who were still in care by the end of 2018. 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 2018 was estimated to be 14,200 (14,000-14,500), of whom 1,000 (800-1,300) were still undiagnosed. Of these 14,200 MSM, 13,219 (93%) had been diagnosed and linked to care, 12,754 (90%) were still in care, 12,587 (88%) had started antiretroviral treatment, and 12,160 (85%) had a most recent HIV RNA below 200 copies/ml, or 93-95-97 in terms of the UNAIDS 90-90-90 target (*Figure 1.15B*). In total, 9,280 (73%, or 79% of those with a CD4 measurement) of MSM still in care by the end of 2018 had a CD4 count of 500 cells/mm^3 or higher at their last measurement in 2017 or 2018. Among women and other men still in care by the end of 2018, the proportion with viral suppression in 2018 was 92% and 93%, respectively, which was lower than among MSM (95%) (*Appendix Figure 1.2*).

Continuum of care by region of origin, age, and public health service region

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 1.3*). In terms of age, the proportion of people who were still in care by the end of 2018 was similar in all age groups. However, 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 1.4*). As a consequence, the proportion of people with viral suppression increased with age and was 74% among those aged 18 to 24 years and 94% in people 65 years of age or older, or 81% and 96%, respectively, of those who were still in care. Finally, 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 2017

We also re-estimated the continuum of HIV care for 2017 and found that, by the end of that year, 23,100 (22,900-23,400) people were living with HIV in the Netherlands, which was similar to the estimated 23,100 (22,700-23,600) reported in last year's Monitoring Report (*Figures 1.15C* and *1.15D*)[12]. 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 (19,397 compared to 19,289 last year) and the number with viral suppression (18,631 compared to 18,270) were somewhat higher in this year's report. This is due to having cleared the backlog in the collection of data on start of treatment and on viral load measurements in 2017. As a result, the 2017 estimate for the UNAIDS 90-90-90 target has been adjusted and has changed slightly from 90-93-95 in last year's report to 90-93-96 in this year's report. Similarly, when the 2018 HIV continuum of care is recalculated next year, it can be expected to undergo a comparable change compared to that reported in the present report.

Conclusions

Since 2008 there has been a steady decrease in the annual number of new HIV diagnoses to less than 800 new diagnoses in most recent years. This decreasing trend has continued in 2018 with approximately 664 new diagnoses in that year, although there is some uncertainty concerning this figure because, at the time of writing, not all people diagnosed in 2018 have yet been included in the SHM database. The decrease in HIV diagnoses is, in part, a consequence of a decrease in the estimated annual number of newly-acquired HIV infections. More than 40% of the new HIV diagnoses were in people born abroad and approximately half of foreign-born individuals for whom the date of arrival in the Netherlands was known had already been diagnosed before moving to the Netherlands. Hence, the number of HIV infections truly newly-diagnosed in the Netherlands may be considerably lower than reported.

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. This indicates that HIV-positive people are being diagnosed increasingly earlier in the course of their infection. In accordance, 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 diagnosed with late-stage 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 2018, more than 95% of individuals diagnosed with CD4 cells above 500 cells/mm^3 were on ART within 6 months after HIV diagnosis. 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 continued to both further surpass the UNAIDS 90-90-90 targets for 2020, and close in on achieving the UNAIDS 95-95-95 targets by 2030, with the current figures standing at 92-93-96[13]. In addition, the Netherlands is on course to achieving another UNAIDS' fast-track target for 2020, namely that of a 75% reduction in the annual number of newly-acquired HIV infections since 2010[2,3].

Recommendations

A re-assessment of the continuum of HIV care for 2017 showed that there was a considerable increase in the number of individuals who achieved viral suppression by the end of that year compared to what was reported in last year's report. To even more reliably monitor progress towards achieving UNAIDS' 95-95-95 goals for 2030, a more timely registration of viral load measurements would be needed, which could be markedly improved by further extending the automated import of laboratory measurements (LabLink) in the SHM database to all HIV treatment centres in the Netherlands. At present, LabLink only includes 14 of the 24 HIV treatment centres, although these do cover approximately 72% of all people followed by SHM.

Since 2018, SHM has been recording the date of arrival in the Netherlands for foreign-born individuals. A considerable proportion of these migrants appear to be diagnosed with HIV before arriving in the Netherlands. This will have an impact on the interpretation of the reported annual number of new HIV diagnoses in the Netherlands and, as a consequence, also on estimates of the number of newly-

acquired HIV infections. Not including migrants diagnosed before arrival allows a better estimation of the number of HIV infections newly-acquired *within the Netherlands*, which in turn provides more accurate information on how well the HIV epidemic is being controlled. In addition, at present, the estimate of the population with undiagnosed HIV in the Netherlands includes migrants diagnosed before arrival in the Netherlands, for whom no data of arrival has been recorded. Retrospective collection of the date of arrival is now being undertaken to improve this estimate.

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 larger proportion of people with viral suppression, and a smaller number living with undiagnosed HIV. In the third quarter of 2019, pre-exposure prophylaxis (PrEP) has become available on a national level for those at highest risk of acquiring HIV, thus importantly extending the set of available prevention measures. To fully curb the epidemic and achieve a sustained and steeper 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.

Worryingly, there still is a substantial number of individuals who are diagnosed with late-stage or advanced HIV infection. This is even the case among MSM, despite an increasing proportion in this group who have a confirmed diagnosis within a year of infection. Clearly, there remain groups of MSM and other populations who are not reached by existing prevention and testing approaches. Recently, a project called Last Mile was started within the HIV Transmission Elimination Amsterdam (H-TEAM) Initiative to improve our understanding of reasons and motivations for delayed testing in people presenting for care with late-stage HIV. Results of this first phase of the project will provide input for the design and implementation of integrated HIV testing and health check interventions aimed at, and developed together with, key affected populations.

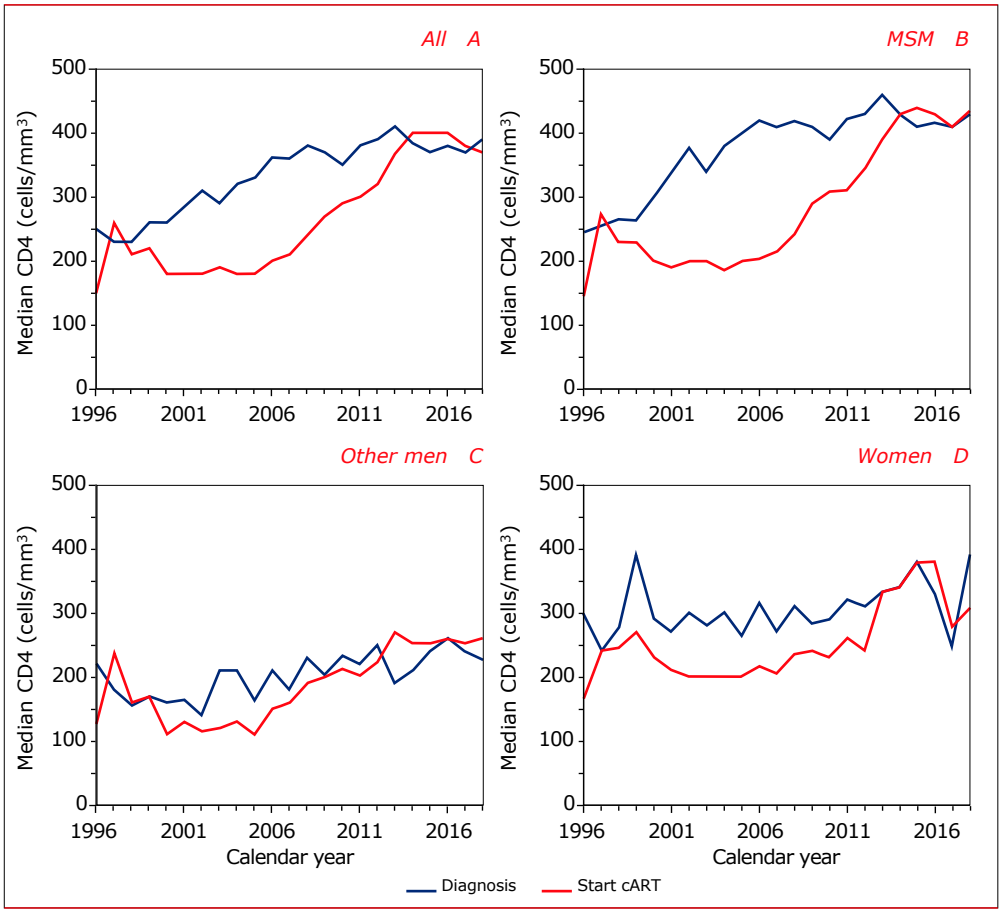
References

1. *ECDC HIV Modelling Tool [Software Application]. Version 1.3.0*. Stockholm: European Centre for Disease Prevention and Control; 2017. https://ecdc.europa.eu/en/publications-data/hiv-modelling-tool.
2. United Nations General Assembly. *Political Declaration on HIV and AIDS: On the Fast-Track to Accelerate the Fight against HIV and to End the AIDS Epidemic by 2030*. Vol 17020. New York; 2016. doi:10.1093/oxfordhb/9780199560103.003.0005
3. Joint United Nations Programme on HIV/AIDS (UNAIDS). *HIV Prevention 2020 Road Map. Accelerating Prevention to Reduce New Infections by 75%*. Geneva; 2017. http://www.unaids.org/sites/default/files/media_asset/hiv-prevention-2020-road-map_en.pdf.
4. Slurink IAL, van Aar F, Op de Coul ELM, et al. *Sexually Transmitted Infections in the Netherlands in 2018*. Bilthoven: National Institute for Public Health and the Environment, Ministry of Health, Welfare and Sport; 2019. doi:10.21945/RIVM-2019-0007
5. Antinori A, Coenen T, Costagiola D, et al. Late presentation of HIV infection: a consensus definition. *HIV Med*. 2011;12(1):61-64. doi:10.1111/j.1468-1293.2010.00857.x
6. Sasse A, Florence E, Pharris A, et al. Late presentation to HIV testing is overestimated when based on the consensus definition. *HIV Med*. 2016;17(3):231-234. doi:10.1111/hiv.12292
7. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *N Engl J Med*. 2011;365(6):493-505. doi:10.1056/NEJMoa1105243
8. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA*. 2016;316(2):171-181. doi:10.1001/jama.2016.5148
9. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *Lancet*. 2019;393(10189):2428-2438. doi:10.1016/S0140-6736(19)30418-0
10. Supervie V, Marty L, Lacombe J-M, Dray-Spira R, Costagliola D, FHDH-ANRS CO4 study group. Looking beyond the cascade of HIV care to end the AIDS epidemic: estimation of the time interval from HIV infection to viral suppression. *J Acquir Immune Defic Syndr*. 2016;33(0):1. doi:10.1097/QAI.0000000000001120

11. Joint United Nations Programme on HIV/AIDS (UNAIDS). *90-90-90 An Ambitious Treatment Target to Help End the AIDS Epidemic.*; 2014. http://www.unaids.org/en/resources/documents/2017/90-90-90.
12. van Sighem A, Boender S, Wit F, Smit C, Matser A, Reiss P. *Monitoring Report 2018. Human Immunodeficiency Virus (HIV) Infection in the Netherlands*. Amsterdam: Stichting HIV Monitoring; 2018.
13. Joint United Nations Programme on HIV/AIDS (UNAIDS). *Fast-Track Ending the AIDS Epidemic by 2030.*; 2014. http://www.unaids.org/sites/default/files/media_asset/JC2686_WAD2014report_en.pdf.

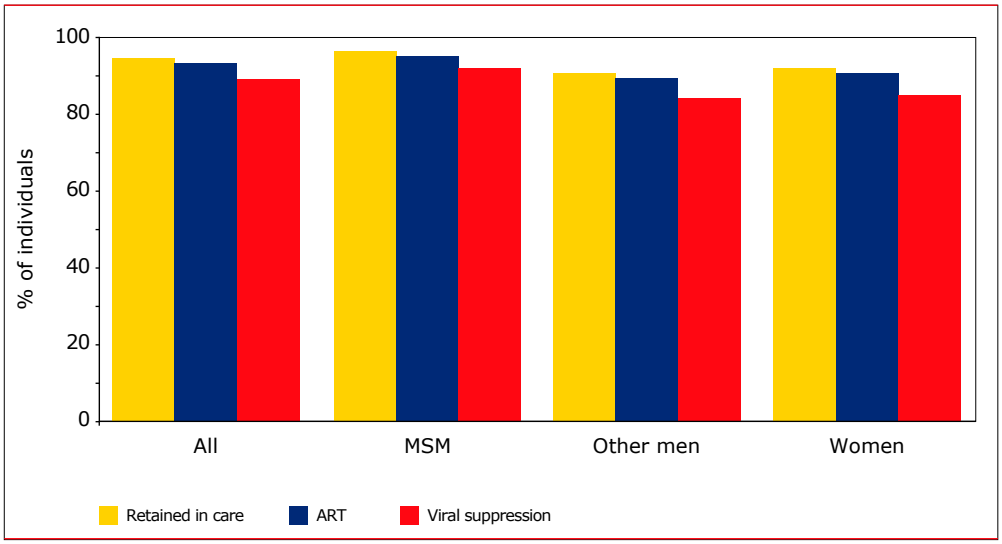
Appendix: supplementary figures and tables

Appendix Figure 1.1: *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.*



< Back to page 43

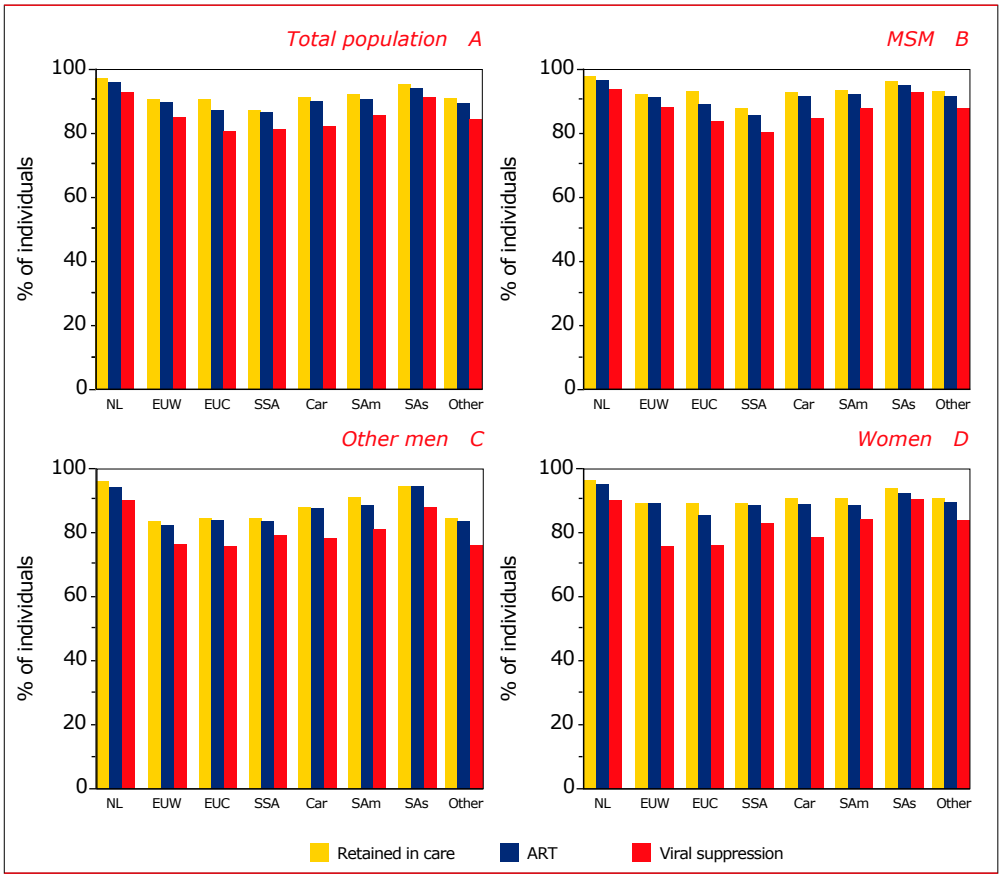
Appendix Figure 1.2: *Continuum of HIV care by transmission risk group. Proportions are given relative to the number of people diagnosed and linked to care.*



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

< Back to page 52

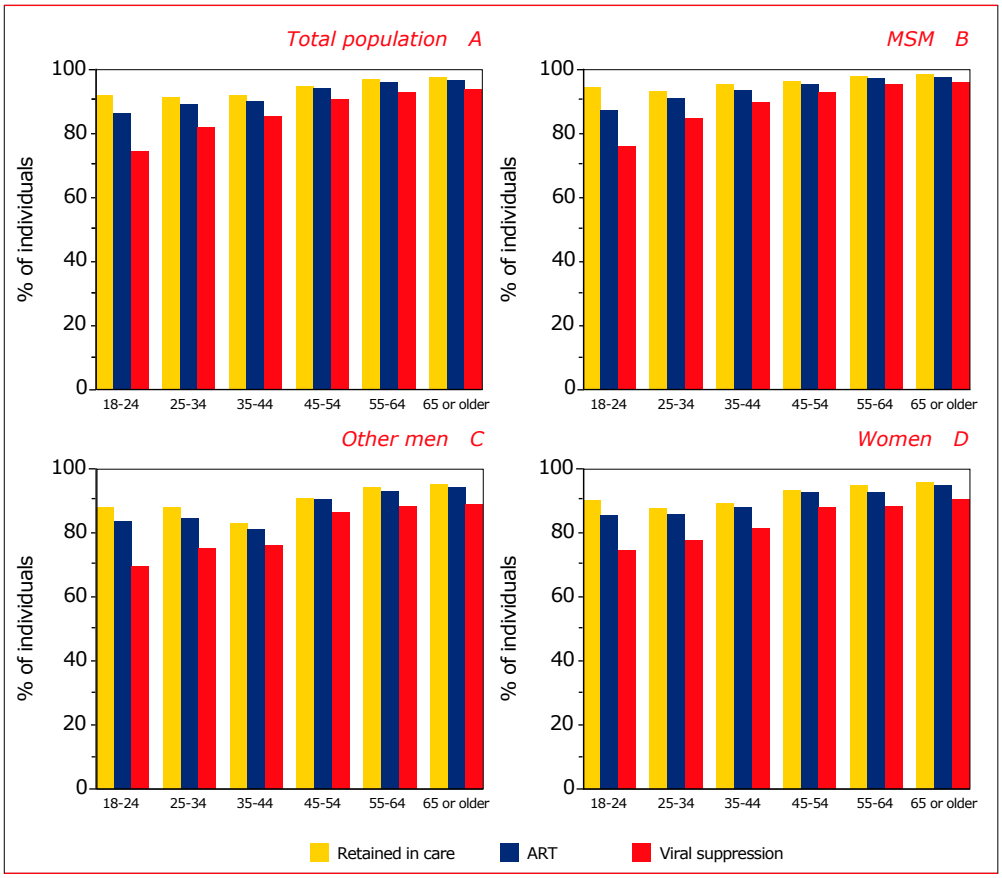
Appendix Figure 1.3: *Continuum of HIV care by region of origin for (A) the total HIV-1-positive population and for (B) men who have sex with men, (C) other men, and (D) women. Proportions are given relative to the number of people diagnosed and linked to care.*



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

< Back to page 52

Appendix Figure 1.4: *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=combination antiretroviral therapy.*

< Back to page 52

Appendix Table 1.1: *Annual number of HIV-1 diagnoses among children and 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. The last column shows the total number of diagnoses excluding migrants who were already diagnosed before moving to the Netherlands. Note: data collection for 2017 and 2018 had not yet been finalised at the time of writing.*

Year of	MSM	Heterosexual		IDU		Blood or blood products	
diagnosis	Men	Men	Women	Men	Women	Men	Women
≤1995	2,287	274	398	285	135	62	22
1996	386	90	83	31	8	3	4
1997	451	115	132	39	10	7	3
1998	337	109	115	25	8	6	6
1999	358	110	139	21	8	9	4
2000	382	163	193	18	5	3	4
2001	453	167	223	16	5	8	7
2002	475	168	255	16	3	15	7
2003	465	179	281	23	5	10	3
2004	596	207	271	11	4	4	4
2005	650	198	267	17	2	3	6
2006	697	164	205	10	5	5	7
2007	787	161	214	12	4	2	6
2008	878	177	183	6	1	5	3
2009	795	161	188	9	0	3	2
2010	804	182	169	6	1	6	2
2011	794	146	153	5	1	9	7
2012	739	152	150	5	1	4	3
2013	768	118	138	2	2	12	2
2014	644	112	122	1	1	7	5
2015	603	130	129	2	0	6	1
2016	548	102	108	1	0	9	3
2017	503	87	86	3	0	6	2
*2017**	*518*	*90*	*89*	*3*	*0*	*6*	*2*
2018	394	66	64	1	1	6	4
*2018**	*437*	*73*	*71*	*1*	*1*	*7*	*4*
2019	35	11	13	0	0	2	1
Total	**15,829**	**3,549**	**4,279**	**565**	**210**	**212**	**118**

**Projected numbers*

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

< Back to page 28

Other/unknown		<18 years of age		Total	Total excluding migrants
Men	Women	Men	Women		
167	46	54	39	3,769	3,753
35	6	14	3	663	662
40	8	8	10	823	819
30	7	8	8	659	649
19	6	11	13	698	692
38	4	16	29	855	852
41	6	15	33	974	973
61	3	18	21	1,042	1,040
60	13	17	21	1,077	1,070
66	8	14	13	1,198	1,189
63	9	11	10	1,236	1,221
58	3	8	12	1,174	1,161
53	7	9	13	1,268	1,260
56	6	13	18	1,346	1,326
51	9	14	15	1,247	1,230
48	6	21	18	1,263	1,243
62	4	14	10	1,205	1,183
47	10	9	13	1,133	1,115
47	5	6	4	1,104	1,071
49	8	6	8	963	926
51	5	7	7	941	907
42	4	7	6	830	785
48	5	4	2	746	706
49	*5*	*4*	*2*	*768*	*727*
54	5	2	2	599	581
60	*6*	*2*	*2*	*664*	*645*
5	1	0	0	68	67
1,291	**194**	**306**	**328**	**26,881**	**26,481**

Appendix Table 1.2: *Region of origin of the 26,247 adult HIV-1-positive individuals with a recorded date of diagnosis stratified according to year of HIV diagnosis.*

	MSM			Other men		
	<2016	≥2016	Total	<2016	≥2016	Total
The Netherlands	9,936	904	10,840	2,277	253	2,530
	69.2%	61.1%	68.4%	44.0%	57.1%	45.0%
Sub-Saharan Africa	210	28	238	1,342	64	1,406
	1.5%	1.9%	1.5%	25.9%	14.4%	25.0%
Western Europe	1,152	75	1,227	295	11	306
	8.0%	5.1%	7.8%	5.7%	2.5%	5.4%
Central Europe	333	85	418	169	20	189
	2.3%	5.7%	2.6%	3.3%	4.5%	3.4%
Eastern Europe	107	21	128	79	2	81
	0.7%	1.5%	0.8%	1.5%	0.5%	1.4%
South America	979	120	1,099	412	38	450
	6.8%	8.1%	6.9%	8.0%	8.6%	8.0%
Caribbean	576	86	662	246	19	265
	4.0%	5.8%	4.2%	4.8%	4.3%	4.7%
South and south-east Asia	423	61	484	130	9	139
	2.9%	4.1%	3.1%	2.5%	2.0%	2.5%
Other/unknown	633	100	733	224	27	251
	4.4%	6.8%	4.6%	4.3%	6.1%	4.5%

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

< Back to page 33

	Women		
	<2016	≥2016	Total
	1,220	105	1,325
	27.1%	35.4%	27.6%
	1,913	91	2,004
	42.5%	30.6%	41.7%
	230	2	232
	5.1%	0.7%	4.8%
	87	17	104
	1.9%	5.7%	2.2%
	55	7	62
	1.2%	2.4%	1.3%
	407	31	438
	9.0%	10.4%	9.1%
	242	13	255
	5.4%	4.4%	5.3%
	264	20	284
	5.9%	6.7%	5.9%
	86	11	97
	1.9%	3.7%	2.0%

Appendix Table 1.3: *Characteristics of the 894 individuals with a late-stage HIV infection among the 2,220 individuals diagnosed with HIV in 2016 or later. In total, as a result of missing CD4 cell counts at diagnosis, 320 (14%) individuals (223 MSM, 55 other men, and 42 women) could not be classified as having a late-stage HIV infection or not.*

	MSM (n=1,257)		Other men (n=388)		Women (n=255)		Total (n=1,900)	
	n	%	n	%	n	%	n	%
Overall	500	40	258	66	136	53	894	47
Age at entry [years]								
18-24	39	23	10	45	9	29	58	26
25-34	122	31	52	51	36	48	210	37
35-44	109	41	60	71	44	56	213	50
45-54	105	44	74	78	26	63	205	54
55-64	83	61	42	72	18	69	143	65
≥65	42	72	20	74	3	75	65	73
Region of origin								
The Netherlands	335	41	156	68	48	49	539	47
Sub-Saharan Africa	13	57	41	72	42	58	96	63
Western Europe	21	37	6	67	0	0	27	40
Central Europe	20	31	7	41	5	42	32	34
South America	32	36	20	63	14	54	66	45
Caribbean	24	33	9	60	5	42	38	38
South and south-east Asia	25	51	5	100	14	82	44	62
North Africa and Middle East	11	28	7	64	2	100	20	38
Other/unknown	19	39	7	64	6	43	32	43
Location of HIV diagnosis								
Sexual health centre	118	22	9	26	10	48	137	24
Hospital	167	72	172	82	80	77	419	77
General practice	161	45	58	54	26	35	245	45
Other/unknown	54	39	19	53	20	36	93	40

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

< Back to page 38

Appendix Table 1.4: Characteristics of the 20,104 people living with HIV and in care as of December 2018.

	MSM	Heterosexual		IDU	
	Men	Men	Women	Men	Women
	n=12,697	n=2,451	n=3,223	n=202	n=83
Current age [years]					
0–12	0	0	0	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%
13–17	1	0	2	0	0
	0.0%	0.0%	0.1%	0.0%	0.0%
18–24	170	8	39	1	0
	1.3%	0.3%	1.2%	0.5%	0.0%
25–34	1,526	208	400	5	1
	12.0%	8.5%	12.4%	2.5%	1.2%
35–44	2,554	438	972	30	11
	20.1%	17.9%	30.2%	14.9%	13.3%
45–54	4,013	835	1,076	66	22
	31.6%	34.1%	33.4%	32.7%	26.5%
55–64	3,066	664	514	88	46
	24.1%	27.1%	15.9%	43.6%	55.4%
65–74	1,169	242	165	12	2
	9.2%	9.9%	5.1%	5.9%	2.4%
≥75	198	56	55	0	1
	1.6%	2.3%	1.7%	0.0%	1.2%
Current age 50 years or older					
No	6,046	1,051	2,009	55	19
	47.8%	42.9%	62.3%	27.2%	22.9%
Yes	6,651	1,400	1,214	147	64
	52.4%	57.1%	37.7%	72.8%	77.1%
Current age 60 years or older					
No	10,165	1,885	2,809	157	59
	80.1%	76.9%	87.2%	77.7%	71.1%
Yes	2,532	566	414	45	24
	19.9%	23.1%	12.8%	22.3%	28.9%
Region of origin					
Netherlands	9,029	1,174	964	118	41
	71.1%	47.9%	29.9%	57,4%	49.4%
Sub-Saharan Africa	173	642	1,340	4	0
	1.4%	26.2%	41.6%	2.0%	0.0%

< Back to page 46

Blood or blood products		Other / unknown		Total	
Men	Women	Men	Women	Men	Women
n=165	n=94	n=907	n=282	n=16,422	n=3,682
0	0	61	77	61	77
0.0%	0.0%	6.7%	27.3%	0.4%	2.1%
0	0	30	23	31	25
0.0%	0.0%	3.3%	8.2%	0.2%	0.7%
4	2	52	43	235	84
2.4%	2.1%	5.7%	15.2%	1.4%	2.3%
20	9	110	37	1,869	447
12.1%	9.6%	12.1%	13.1%	11.4%	12.1%
27	25	150	31	3,199	1,039
16.4%	26.6%	16.5%	11.0%	19.5%	28.2%
52	29	221	38	5,187	1,165
31.5%	30.9%	24.4%	13.5%	31.6%	31.6%
34	21	173	26	4,025	607
20.6%	22.3%	19.1%	9.2%	24.5%	16.5%
21	6	86	5	1,530	178
12.7%	6.4%	9.5%	1.8%	9.3%	4.8%
7	2	24	2	285	60
4.2%	2.1%	2.6%	0.7%	1.7%	1.6%
78	52	507	227	7,737	2,307
47.3%	55.3%	55.9%	80.5%	47.1%	62.6%
87	42	400	55	8,685	1,375
52.7%	44.7%	44.1%	19.5%	52.9%	37.3%
123	77	723	265	13,053	3,210
74.5%	81.9%	79.7%	94.0%	79.5%	87.2%
42	17	184	17	3,369	472
25.5%	18.1%	20.3%	6.0%	20.5%	12.8%
106	17	409	107	10,836	1,129
64.2%	18.1%	45.1%	37.9%	66.0%	30.7%
29	37	236	107	1,084	1,484
17.6%	39.4%	26.0%	37.9%	6.6%	40.3%

	MSM	Heterosexual		IDU	
	Men	Men	Women	Men	Women
	n=12,697	n=2,451	n=3,223	n=202	n=83
Western Europe	784	80	66	20	25
	6.2%	3.3%	2.0%	9.9%	30.1%
South America	836	219	316	8	1
	6.6%	8.9%	9.8%	4.0%	1.2%
Caribbean	527	124	169	6	1
	4.2%	5.1%	5.2%	3.0%	1.2%
South and south-east Asia	396	37	219	9	1
	3.1%	1.5%	6.8%	4.5%	1.2%
Other	900	168	141	37	14
	7.1%	6.9%	4.4%	18.3%	16.9%
Unknown	52	7	8	0	0
	0.4%	0.3%	0.2%	0.0%	0.0%
Years aware of HIV infection					
<1	387	64	62	1	1
	3.0%	3.0%	1.9%	0.5%	1.2%
1–2	986	171	182	2	0
	7.8%	7.0%	5.6%	1.0%	0.0%
3–4	1,136	202	225	2	1
	8.9%	8.2%	7.%	1.0%	1.2%
5–10	3,428	591	641	6	3
	27.0%	24.1%	19.9%	3.0%	3.6%
10–20	4,576	1,084	1,594	63	20
	36.0%	44.2%	49.5%	31.2%	24.1%
>20	2,178	334	506	128	58
	17.2%	13.6%	15.7%	63.4%	6.9%
Unknown	6	5	13	0	0
	0.0%	0.2%	0.4%	0.0%	0.0%
Current CD4 count [cells/mm^3], median / IQR	698	600	690	586	626
	520–900	410–810	510–918	376–803	370–922
Current CD8 count [cells/mm^3], median / IQR	870	830	770	880	900
	642–1180	590–1140	560–1050	590–1200	690–1100

Blood or blood products		Other / unknown		Total	
Men	Women	Men	Women	Men	Women
n=165	n=94	n=907	n=282	n=16,422	n=3,682
4	3	37	24	925	118
2.4%	3.2%	4.1%	8.5%	5.6%	3.2%
4	10	57	6	1,124	333
2.4%	10.6%	6.3%	2.1%	6.8%	9.0%
3	4	44	0	704	174
1.8%	4.3%	4.9%	0.0%	4.3%	4.7%
10	15	31	4	483	239
6.1%	16.0%	3.4%	1.4%	2.9%	6.5%
9	8	90	32	1,204	195
5.5%	8.5%	9.9%	11.3%	7.3%	5.3%
0	0	3	2	62	10
0.0%	0.0%	0.3%	0.7%	0.4%	0.3%
6	4	49	6	507	73
3.6%	4.3%	5.4%	2.1%	3.1%	2.0%
14	5	80	14	1,253	201
8.5%	5.3%	8.8%	5.0%	7.6%	5.5%
11	5	92	21	1,443	252
6.7%	5.3%	10.1%	7.4%	8.8%	6.8%
26	12	209	72	4,260	728
15.8%	12.8%	23.0%	25.5%	25.9%	19.8%
44	41	338	112	6,105	1,767
26.7%	43.6%	37.3%	39.7%	37.2%	48.0%
61	27	126	54	2,827	645
37.0%	28.7%	13.9%	19.1%	17.2%	17.5%
3	0	13	3	27	16
1.8%	0.0%	1.4%	1.1%	0.2%	0.4%
565	655	594	798	675	690
413–780	510–920	402–810	520–1058	500–880	505–921
722	742	850	770	860	770
540–1114	607–1100	600–1200	570–1070	630–1174	560–1060

	MSM	Heterosexual		IDU	
	Men	Men	Women	Men	Women
	n=12,697	n=2,451	n=3,223	n=202	n=83
Current HIV RNA <200 copies/ml					
Not available	188	43	50	13	5
	1.5%	1.8%	1.6%	6.4%	6.0%
No	326	89	168	10	8
	2.6%	3.6%	5.2%	5.0%	9.6%
Yes	12,183	2,319	3,005	179	70
	96.0%	94.6%	93.2%	88.6%	84.3%
Current HIV RNA <100 copies/ml					
Not available	188	43	50	13	5
	1.5%	1.8%	1.6%	6.4%	6.0%
No	403	114	201	12	10
	3.2%	4.7%	6.2%	5.9%	12.0%
Yes	12,106	2,294	2,972	177	68
	95.3%	93.6%	92.2%	87.6%	81.9%
Ever AIDS	2,369	804	764	79	36
	18.7%	32.8%	23.7%	39.1%	43.4%
AIDS at diagnosis	1,230	558	438	18	7
	9.7%	22.8%	13.6%	8.9%	8.4%
Current treatment					
cART	12,528	2,423	3,172	199	83
	98.7%	98.9%	98.4%	98.5%	100.0%
Non-cART	11	1	3	0	0
	0.1%	0.0%	0.1%	0.0%	0.0%
Not started	158	27	48	3	0
	1.2%	1.1%	1.5%	1.5%	0.0%

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

Blood or blood products		Other / unknown		Total	
Men	Women	Men	Women	Men	Women
n=165	n=94	n=907	n=282	n=16,422	n=3,682
5	1	12	6	261	62
3.0%	1.1%	1.3%	2.1%	1.6%	1.7%
4	5	63	16	492	197
2.4%	5.3%	6.9%	5.7%	3.0%	5.4%
156	88	832	260	15,669	3,423
94.5%	93.6%	91.7%	92.2%	95.4%	93.0%
5	1	12	6	261	62
3.0%	1.1%	1.3%	2.1%	1.6%	1.7%
4	7	74	20	607	238
2.4%	7.4%	8.2%	7.1%	3.7%	6.5%
156	86	821	256	15,554	3,382
94.5%	91.5%	90.5%	90.8%	94.7%	91.9%
59	33	330	91	3,641	924
35.8%	35.1%	36.4%	32.3%	22.2%	25.1%
37	20	230	48	2,073	513
22.4%	21.3%	25.4%	17.0%	12.6%	13.9%
160	93	886	281	16,196	3,629
97.0%	98.9%	97.9%	99.6%	98.6%	98.6%
0	1	1	0	13	4
0.0%	1.1%	0.1%	0.0%	0.1%	0.1%
5	0	20	1	213	49
3.0%	0.0%	2.2%	0.4%	1.3%	1.3%

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 are living by the end of 2018. Proportions are given relative to the number of people diagnosed and linked to care.*

	Diagnosed and linked to care	Retained in care	
Public health service region	**n**	**n**	**%**
Groningen	576	542	94
Fryslân	340	328	96
Drenthe	269	247	92
IJsselland	333	321	96
Twente	422	410	97
Noord- en Oost-Gelderland	455	443	97
Gelderland Midden	702	680	97
Gelderland-Zuid	402	383	95
Flevoland	562	516	92
Regio Utrecht	1,223	1,152	94
Gooi & Vechtstreek	291	278	96
Hollands Noorden	424	402	95
Zaanstreek-Waterland	357	341	96
Amsterdam	6,169	5,875	95
Kennemerland	575	545	95
Hollands Midden	537	506	94
Haaglanden	1,619	1,536	95
Rotterdam-Rijnmond	2,470	2,301	93
Dienst Gezondheid & Jeugd ZHZ	308	287	93
Zeeland	228	211	93
West-Brabant	561	529	94
Hart voor Brabant	837	788	94
Brabant-Zuidoost	640	605	95
Limburg-Noord	385	361	94
Zuid Limburg	515	489	95
Unknown	159	113	71
Total	**21,360**	**20,189**	**95**

< Back to page 52

	Antiretroviral treatment		Viral suppression	
	n	%	n	%
	537	93	514	89
	325	96	315	93
	242	90	235	87
	319	96	314	94
	405	96	386	91
	435	96	416	91
	668	95	643	92
	379	94	363	90
	512	91	489	87
	1,114	91	1,089	89
	270	93	260	89
	397	94	379	89
	337	95	327	92
	5,806	94	5,553	90
	540	94	519	90
	498	93	481	90
	1,522	94	1,471	91
	2,256	91	2,117	86
	280	91	259	84
	205	90	194	85
	522	93	494	88
	787	94	743	89
	600	94	565	88
	359	93	344	89
	486	94	474	92
	111	69	102	64
	19,913	**93**	**19,046**	**89**

2. Response to combination antiretroviral therapy (cART)

Ferdinand Wit, Anders Boyd, Ard van Sighem, Kees Brinkman, Kees van Nieuwkoop, Anne Wensing, 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 guidelines of 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, including tuberculosis and AIDS, 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 no risk of onward sexual transmission of HIV; undetectable equals untransmittable, i.e., U=U[1,10,11,12,13,14]. Depending on the drugs employed, it may take as long as six months for the viral load to become undetectable. Moreover, sustained HIV suppression requires selection of appropriate treatment and adherence to treatment. HIV viral suppression should therefore be monitored and documented to assure both personal health and public health benefits.

Most guidelines list an unboosted integrase inhibitor as the third agent of preferred first-line cART regimens. Further treatment options include elvitegravir as a boosted integrase inhibitor, darunavir as a boosted protease inhibitor or rilpivirine as a non-nucleoside reverse transcriptase inhibitor (NNRTI, the latter only if viral load is <100,000 copies/ml). All aforementioned agents are used in combination with a double nucleoside backbone (either tenofovir/emtricitabine or abacavir/lamivudine)[9]. Additionally, tenofovir alafenamide (TAF) and tenofovir disoproxil

< Back to Chapter 1

fumarate (TDF) are two forms of tenofovir approved by the European Medicines Agency. TAF has 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 function and in people with osteoporosis or at risk for osteoporotic fractures[15,16]. Safety, ease of use, food effects, and potential for significant drug-drug interactions 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. Nevertheless, drug resistance mutations could develop if a given agent, even when combined with other agents, cannot sufficiently prevent the selective pressures driving resistance (i.e., low genetic barrier to resistance). Over time, accumulation of mutations in the HIV genome that are associated with drug resistance can prevent sustained viral suppression and thereby increase the risk of poor clinical outcomes[17,18,19,20,21,22,23].

This chapter reports on the prescription of, and responses to, cART in HIV-1 positive adults 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. We also analyse the presence of transmitted and acquired 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 26,173 registered adults (≥18 years at the time of diagnosis) with HIV-1 in the Netherlands

1. **Starting combination antiretroviral therapy**
   24,603 people were known to have initiated cART between January 1996 and December 2018.

2. **In care and on cART in the Netherlands in 2018**
   Out of 24,603 people who initiated cART between January 1996 and December 2018,
   ➔ 19,189 were in care and had a clinical visit in 2018;
   ➔ 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 24,603 people who initiated cART between January 1996 and December 2018,
   ➔ 6,729 initiated cART between January 2013 and December 2018;
   ➔ 5,508 people started 'common' and guideline-recommended initial regimens in 2013-2018: TDF/FTC/EFV (15.9%), TDF/FTC/RPV (10.9%), TDF/FTC/DRV/b (11.5%), TDF/FTC/EVG/c (16.4%), TDF/FTC/DTG (7.5%), ABC/3TC/DTG (23.4%), TAF/FTC/EVG/c (10.4%), TAF/FTC/RPV (0.8%), TAF/FTC/DTG (1.6%), TAF/FTC/DRV/c (1.0%), TAF/FTC/BIC (0.8%).

4. **Virological response**
   Out of 24,603 people who initiated cART between January 1996 and December 2018,
   ➔ 20,166 people were ART-naive, not pregnant at cART initiation, and had a viral load result after ≥3 months of cART initiation.

5. HIV drug resistance

Transmitted HIV drug resistance

As of January 2019, 7,401 HIV-1 sequences were obtained from 7,127 ART-naive people before initiating cART in 2003-2018.

➔ 25 people had pre-treatment integrase sequences available.

Acquired HIV drug resistance

As of January 2019, 3,802 HIV-1 sequences were obtained from 2,348 people who received cART for at least 4 months in 2000-2018.

➔ 2,518 sequences from 1,637 people who were ART-naive before initiating cART.

➔ 144 integrase sequences to assess resistance to INSTI class drugs were available from 122 people.

6. Immunological response

Out of the 24,603 people who initiated cART between January 1996 and December 2018

➔ 24,037 had CD4 cell count data available after initiating cART.

Legend: *ART=antiretroviral therapy; cART=combination antiretroviral therapy (defined as a combination of three antiretroviral drugs from two different antiretroviral drugs classes, or the use of selected combinations of two antiretroviral drugs for which there is sufficient efficacy data to support its use); 3TC=lamivudine; b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; ABC=abacavir; BIC=bictegravir; 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, 24,603 adults ever registered by SHM and followed in the ATHENA cohort were 18 years or older at the time of HIV-1 diagnosis and were known to have initiated cART between January 1996 and December 2018 (*Box 2.1*). Of these, 2,592 (10.5%) had prior exposure to mono or dual nucleoside-analogue antiretroviral therapy (ART) at the start of cART and 22,011 (89.5%) 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: 5,936 started between 1996 and the end of 2001, 5,326 between 2002 and the end of 2007, 6,612 between 2008 and the end of 2012, and 6,729 between 2013 and the end of 2018.

Table 2.1: Characteristics of people starting combination antiretroviral therapy in 1996–2018.

Year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2018	1996–2018
Total	n	5,936	5,326	6,612	6,729	**24,603**
DEMOGRAPHIC						
Age at cART initiation (years)	Median	37.6	38.6	40.3	39.2	**38.8**
	Q1	32.2	32.0	32.7	30.3	**31.8**
	Q3	44.6	45.7	48.0	48.9	**46.9**
Male (at birth)	n	4,827	3,896	5,615	5,824	**20,162**
	%	81.3	73.2	84.9	86.6	**82**
Transmission risk group						
Missing	n	2	4	5	13	**24**
	%	0.0	0.1	0.1	0.2	**0.1**
Men who have sex with men	n	3,469	2,546	4,377	4,644	**15,036**
	%	58.4	47.8	66.2	69.0	**61.1**
Heterosexual contact	n	1,656	2,220	1,791	1,628	**7,295**
	%	27.9	41.7	27.1	24.2	**29.7**
Injecting drug use	n	407	159	83	33	**682**
	%	6.9	3.0	1.3	0.5	**2.8**
Blood or blood products	n	107	67	47	65	**286**
	%	1.8	1.3	0.7	1.0	**1.2**
Vertical transmission	n	0	0	3	3	**6**
	%	0.0	0.0	0.1	0.0	**0.0**
Other/unknown	n	295	330	306	343	**1274**
	%	5.0	6.2	4.6	5.1	**5.2**
Region of origin						
Missing	n	29	20	18	34	101
	%	0.5	0.4	0.3	0.5	0.4
The Netherlands	n	3,566	2,567	3,963	3,966	14,062
	%	60.1	48.2	56.0	58.9	57.2
Western Europe/North America/Australia	n	679	412	474	405	1,970
	%	11.4	7.7	7.2	6.0	8.0
East/central Europe	n	87	135	252	411	885
	%	1.5	2.5	3.8	6.1	3.6
South America and the Caribbean	n	580	673	756	870	2879
	%	9.8	12.6	11.4	12.9	11.7
Sub-Saharan Africa	n	732	1,217	784	594	3,327
	%	12.3	22.9	11.9	8.8	13.5
Other*	n	263	302	365	449	1,379
	%	4.4	5.7	5.5	6.7	5.6

Year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2018	1996–2018
CLINICAL						
Recent infection	n	326	434	1,277	1,749	**3,786**
(within 12 months of diagnosis)	%	5.5	8.2	19.3	26.0	**15.4**
Ever tested HIV-negative	n	1,144	1,423	3,187	3,851	**9,605**
	%	19.3	26.7	48.2	57.2	**39.0**
CD4 cell count at start cART	Median	200	190	280	393	**260**
	Q1	80	90	170	230	**130**
	Q3	340	280	370	567	**400**
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**
(prior) AIDS at start cART	n	1,914	1,413	1,108	827	**5,262**
	%	32.2	26.5	16.8	12.3	**21.4**
ARV-naive at start cART	n	3,789	5,080	6,512	6,630	**22,011**
	%	63.8	95.4	98.5	98.5	**89.5**
Hepatitis B status at start of cART						
HBV-negative (HBsAg-negative)	n	5,295	4,859	6,101	5,985	**22,240**
	%	89.2	91.2	92.3	88.9	**90.4**
HBV-positive (HBsAg-positive)	n	369	315	315	175	**1,174**
	%	6.2	5.9	4.8	2.6	**4.8**
Unknown	n	272	152	196	569	**1,189**
	%	4.6	2.9	3.0	8.5	**4.8**
Hepatitis C status at start of cART						
HCV-negative	n	5,256	4,914	6,222	5,975	**22,367**
	%	88.5	92.3	94.1	88.8	**90.9**
HCV RNA-positive	n	81	131	135	96	**443**
	%	1.4	2.5	2.0	1.4	**1.8**
HCV Ab seropositive	n	146	64	44	26	**280**
	%	2.5	1.2	0.7	0.4	**1.1**
Unknown	n	453	217	211	632	**1,513**
	%	7.6	4.1	3.2	9.4	**6.2**
cART started during pregnancy	n	112	344	171	99	**726**
	%	1.9	6.5	2.6	1.5	**3.0**

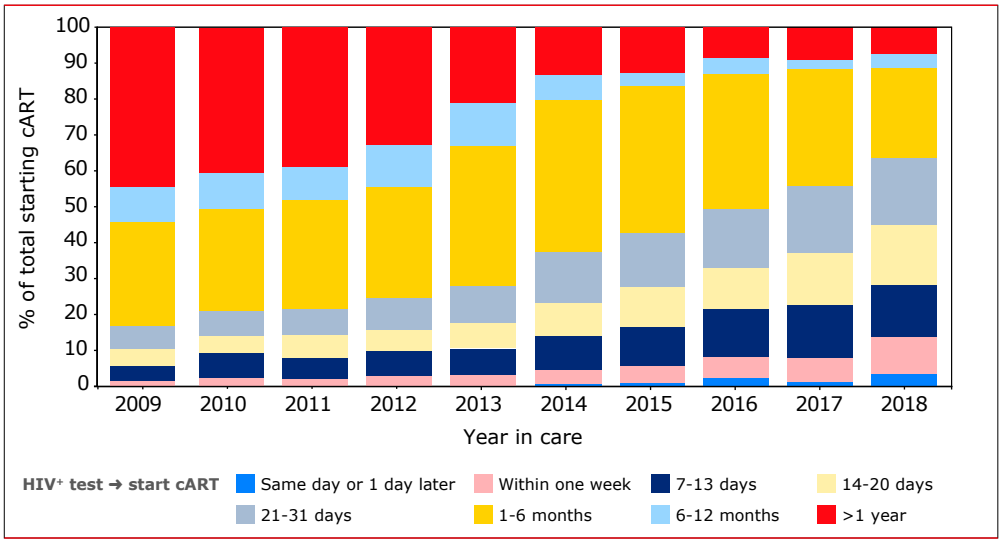
**The 48 people from other regions of origin who started in 2018 were from south-east Asia (n=22), North Africa and the Middle East (n=20), and Oceania and the Pacific (n=6).*

***Legend:** Ab=antibody; cART=combination antiretroviral therapy; ARV=antiretroviral; HBsAg=hepatitis b surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus.*

Of the 24,604 people who had initiated cART since January 1996, 20,162 (82.0%) were men, of whom 15,036 (74.6%) were men who have sex with men (MSM). Overall, 14,062 (57.2%) 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. Since 1996, 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 6-7.5% in 2015-2018. Simultaneously, the number of people from western Europe/North America/Australia slightly decreased from 11.5% in 1996-2001 to 5.6% in 2018, with a decrease in those from sub-Saharan Africa from 23.0% in 2002-2007 to 11.9% in 2008-2012 to 8.9% in 2013-2018.

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 134 days (interquartile range (IQR) 33-704) for those who entered care in 2011 to 105 days (IQR 30-505) in 2012, 65 days (IQR 27-279) in 2013, 42 days (IQR 21-107) in 2014, 36 days (IQR 18-51) in 2015, 30 days (IQR 14-55) in 2016, 27 days (IQR 14-48) in 2017, and 23 days (IQR 13-42) in 2018. The proportion of subjects initiating cART on the same day (or one day later) as their HIV-positive diagnosis increased from 0.5% in 2010, to 1.1% in 2015, 2.5% in 2016, 1.7% in 2017, and 3.5% in 2018. 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 2008-2018.*



**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 known 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 (IQR 90-280) in 2002-2007 to 280 cells/mm^3 (IQR 170-370) in 2008-2012 and to 393 cells/mm^3 (IQR 230-567) in 2013-2018 (p for trend <.0001). In 2018, the median CD4 cell count at the start of cART was 380 cells/mm^3 (IQR 163-606). Since 2016, both the number of people initiating cART per calendar year and the median CD4 cell count at cART initiation have decreased. This trend is likely due to the substantial group who were already in care but not on cART (because of their high CD4 cells counts) and subsequently initiated cART in 2015 and 2016 because of the 2015 guideline change recommending ART for all irrespective of CD4 count.

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 2018

Out of the 24,603 people who were known to have initiated cART between January 1996 and December 2018, 18,993 (77.2%) were alive, receiving cART, and had a visit for HIV care in the Netherlands in 2018. *Table 2.2* shows their treatment and clinical characteristics at their last clinic visit in 2018. Overall, 15,692 (82.6%) were men, and 12,310 (64.8%) were MSM. Their median age on 31 December 2018 was 50 (IQR 42-58) years. The majority (60.7%) originated from the Netherlands, followed by sub-Saharan Africa (11.6%) and South America and the Caribbean (11.5%).

Table 2.2: *Characteristics of people who had started combination antiretroviral therapy and were known to be in care in 2018.*

Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2018	All
Total	n	3,676	3,761	5,509	6,047	**18,993**
	%	19.4	19.8	29.0	31.8	**100**
Sex						
Male	n	2,956	2,775	4,709	5,252	**15,692**
	%	80.4	73.8	85.5	86.9	**82.6**
Female	n	720	986	800	795	**3,301**
	%	19.6	26.2	14.5	13.2	**17.4**
Age on 31 December 2018	Median	57.2	52.6	49.3	42.9	**50.5**
	Q1	52.3	46.2	41.4	33.8	**41.7**
	Q3	63.3	59.0	56.4	52.5	**58.0**
Transmission risk group						
No data	n	1	3	4	11	**19**
	%	0.03	0.08	0.07	0.2	**0.1**
Men who have sex with men	n	2,277	1,977	3,807	4,249	**12,310**
	%	61.9	52.6	69.1	70.3	**64.8**
Heterosexual contact	n	1,065	1,484	1,418	1,419	**5,386**
	%	29.0	39.5	25.7	23.5	**28.4**
Injecting drug use	n	134	64	48	22	**268**
	%	3.7	1.7	0.9	0.4	**1.4**
Blood or blood products	n	72	45	34	56	**207**
	%	2.0	1.2	0.6	0.9	**1.1**
Vertical transmission	n	.	.	2	3	**5**
	%	.	.	0.04	0.05	**0.03**
Other/unknown	n	127	188	196	287	**798**
	%	3.5	5.0	3.6	4.8	**4.2**
Region of origin						
No data	n	10	12	15	31	**68**

Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2018	All
	%	0.3	0.3	0.3	0.5	**0.4**
The Netherlands	n	2,309	2,008	3,531	3,685	**11,533**
	%	62.8	53.4	64.1	61.0	**60.7**
Western Europe/North America/Australia	n	337	217	326	321	**1,201**
	%	9.2	5.8	5.9	5.3	**6.3**
East/central Europe	n	47	93	187	361	**688**
	%	1.3	2.5	3.4	6.0	**3.6**
Latin America and the Caribbean	n	366	474	580	760	**2,180**
	%	10.0	12.6	10.6	12.6	**11.5**
Sub-Saharan Africa	n	423	737	564	486	**2,210**
	%	11.5	19.6	10.3	8.0	**11.6**
Other	n	184	220	306	403	**1,113**
	%	5.0	5.9	5.6	6.7	**5.9**
cART regimen						
TDF/FTC/EFV	n	229	507	758	289	**1,783**
	%	6.2	13.5	13.8	4.8	**9.4**
TDF/FTC/NVP	n	423	356	465	88	**1,332**
	%	11.5	9.5	8.4	1.5	**7.0**
TDF/FTC/RPV	n	90	133	294	309	**826**
	%	2.5	3.5	5.3	5.1	**4.4**
TDF/FTC/DRV/b	n	114	154	285	204	**757**
	%	3.1	4.1	5.2	3.4	**4.0**
TDF/FTC/ATV/r	n	69	85	159	63	**376**
	%	1.9	2.3	2.9	1.0	**2.0**
TDF/FTC/LPV	n	7	18	9	3	**37**
	%	0.2	0.5	0.2	0.1	**0.2**
TDF/FTC/EVG/c	n	57	98	159	434	**748**
	%	1.6	2.6	2.9	7.2	**4.0**
TDF/FTC/DTG	n	70	91	141	337	**639**
	%	1.9	2.4	2.6	5.6	**3.4**
TDF/FTC/RAL	n	33	46	79	44	**202**
	%	0.9	1.2	1.4	0.7	**1.1**
ABC/3TC/DTG	n	335	512	789	1,633	**3,269**
	%	9.1	13.6	14.3	27.0	**17.2**
TAF/FTC/EVG/c	n	325	450	784	1,404	**2,963**
	%	8.8	12.0	14.2	23.2	**15.6**
TAF/FTC/RPV	n	101	163	346	324	**934**
	%	2.8	4.3	6.3	5.4	**4.9**
TAF/FTC/DTG	n	81	77	166	229	**553**

Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2018	All
	%	2.2	2.1	3.0	3.8	**2.9**
TAF/FTC/DRV/c	n	152	139	202	234	**727**
	%	4.1	3.7	3.7	3.9	**3.8**
TAF/FTC/BIC	n	41	32	57	99	**229**
	%	1.1	0.9	1.0	1.6	**1.2**
Other: 2NRTI+NNRTI	n	612	419	366	85	**1,482**
	%	16.7	11.1	6.6	1.4	**7.8**
Other: 2NRTI+PI	n	143	167	154	76	**540**
	%	3.9	4.4	2.8	1.3	**2.8**
Other: 2NRTI+INSTI	n	63	59	75	51	**248**
	%	1.7	1.6	1.4	0.8	**1.3**
Other: NNRTI+INSTI	n	16	5	10	.	**31**
	%	0.4	0.1	0.2	.	**0.2**
Other: PI+INSTI	n	146	67	67	45	**325**
	%	4.0	1.8	1.2	0.7	**1.7**
Other: NRTI+PI+INSTI (3ARVs)	n	59	24	10	5	**98**
	%	1.6	0.6	0.2	0.1	**0.5**
Other: NRTI+PI+INSTI (4ARVs)	n	121	34	38	30	**223**
	%	3.3	0.9	0.7	0.5	**1.2**
Other	n	389	125	96	61	**671**
	%	10.6	3.3	1.7	1.0	**3.5**
CD4:CD8 ratio						
No data	n	445	498	720	1,390	**3,053**
	%	12.1	13.2	13.1	23.0	**16.1**
<0.50	n	629	550	742	1,166	**3,087**
	%	17.1	14.6	13.5	19.3	**16.3**
≥0.50 <1.00	n	1,684	1,857	2,714	2,356	**8,611**
	%	45.8	49.4	49.3	39.0	**45.3**
≥1.00	n	918	856	1,333	1,135	**4,242**
	%	25.1	22.8	24.2	18.8	**22.3**
CD4 count (cells/mm^3)						
No data	n	6	12	36	633	**687**
	%	0.2	0.3	0.7	10.5	**3.6**
<50	n	4	11	8	26	**49**
	%	0.1	0.3	0.2	0.4	**0.3**
50–199	n	67	67	56	204	**394**
	%	1.8	1.8	1.0	3.4	**2.1**
200–349	n	246	229	283	473	**1,231**
	%	6.7	6.1	5.1	7.8	**6.5**

Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2018	All
350–499	n	547	646	821	772	**2,786**
	%	14.9	17.2	14.9	12.8	**14.7**
500–749	n	1,260	1,392	2,097	1,728	**6,477**
	%	34.3	37.0	38.1	28.6	**34.1**
≥750	n	1,546	1,404	2,208	2,211	**7,369**
	%	42.1	37.3	40.1	36.6	**38.8**
Viral load <50 copies/ml						
No data	n	35	99	168	274	**576**
	%	1.0	2.6	3.15	4.5	**3.0**
Yes	n	3,230	3,180	4,733	4,906	**16,049**
	%	87.9	84.6	85.9	81.1	**84.5**
No	n	411	482	608	867	**2,368**
	%	11.2	12.8	11.0	14.3	**12.5**
Viral load <200 copies/ml						
No data	n	35	99	168	274	**576**
	%	1.0	2.6	3.1	4.5	**3.0**
Yes	n	3,580	3,572	5,254	5,534	**17,940**
	%	97.4	95.0	95.4	91.5	**94.5**
No	n	61	90	87	239	**477**
	%	1.7	2.4	1.6	4.0	**2.5**

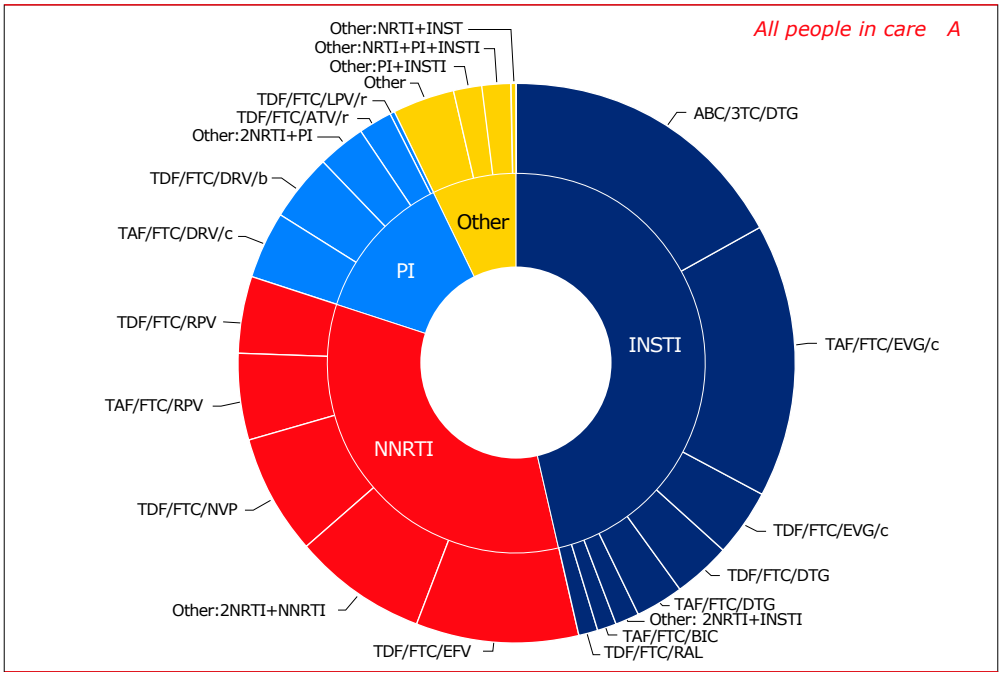
Legend: *3TC=lamivudine; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; ARVs=antiretroviral drugs; BIC=bictegravir; cART=combination antiretroviral therapy; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; 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.*

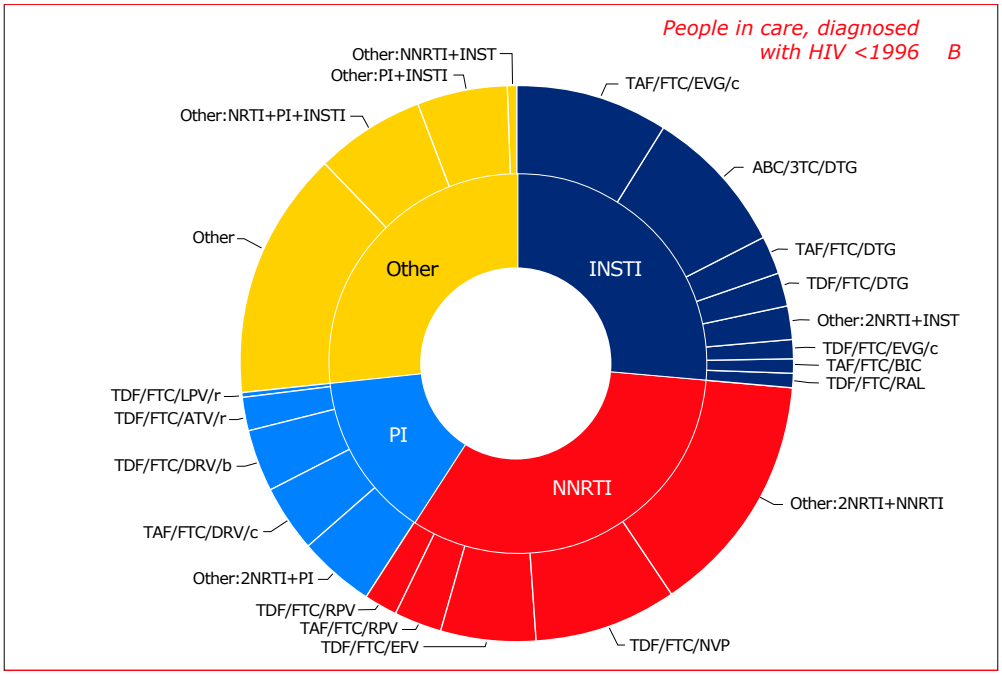
Among the 18,993 people in HIV care and on cART in 2018, the vast majority (92.8%) received a regimen based on two nucleoside analogue reverse transcriptase inhibitor (NRTIs), combined with either an integrase inhibitor (INSTI) (46.6%), an NNRTI (33.4%), or a protease inhibitor (PI) (12.7%). The distribution of cART use among the population in care in 2018 is presented in *Figure 2.2A*. The most common regimens were abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (17.2%), tenofovir alafenamide (TAF)/emtracitabine (FTC)/elvitegravir (EVG)/cobicistat (15.6%), and tenofovir disoproxil fumarate (TDF)/FTC combined with efavirenz (EFV) (9.4%) or nevirapine (NVP) (7.0%). Most people who initiated cART in 2018 did so with TAF/FTC/cobicistat-boosted EVG (25.0%) or ABC/3TC/DTG (23.4%). The proportion of the population in care in 2018 that uses TDF continues to decline (from 46.4% in 2017 to 35.3 in 2018); the proportion using TAF continues to increase (from 24.4%

of the population in care in 2017 to 33.2% in 2018). Zidovudine was still used by 206 individuals (1.1%, mostly in combination with lamivudine), didanosine by 2 (<0.1%), and stavudine by none. In total, 552 (2.9%) and 337 (1.8%) individuals used a cART regimen without any or with just a single NRTI. There were 526 individuals who used a 2-drug regimen (excluding pharmacological boosters): the most common 2-drug regimen were a combination of PI+INSTI (325, 61.8%), NRTI+INSTI (68, 12.9%), NRTI+PI (62, 11.8%), NNRTI+INSTI (31, 5.9%), and NNRTI+PI (19, 3.6%).

Of those with a plasma HIV RNA measurement in 2015-2018, 85.0% had a viral load <50 copies/ml, and 95.9% had a viral load <200 copies/ml. On the basis of the last available CD4 and CD8 cell count measurements in 2015-2018, 72.8% had a CD4 cell count of 500 cells/mm^3 or higher, and 24.4% had a CD4:CD8 ratio of 1 or higher.

Figure 2.2: Combination antiretroviral therapy (cART) use in 2018 by A) all people in care and B) people in care who were diagnosed with HIV <1996.





Legend: 3TC=lamivudine; /b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; cART=combination antiretroviral therapy; ABC=abacavir; ATV=atazanavir; BIC=bictegravir; 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 19,189 people in HIV care in the Netherlands in 2018, 3,757 (19.6%) had been diagnosed before the year 2000; of those, 3,158 (84.1%) were 50 years of age or older by the end of 2018. Furthermore, 1,933 (10.1%) were diagnosed before 1996, and 1,749 (90.5%) of those were 50 years or older by the end of 2018.

The data presented below focus on the 1,933 people who were diagnosed before 1996 (i.e., before the introduction of cART in the Netherlands, and thus considered *long-term HIV survivors*). Their median age at HIV diagnosis was 31 years (IQR 27-36). The majority were men (82.5%), and the main HIV transmission risk group was MSM (66.6%), followed by heterosexual contact (20.2%), injecting drug use (7.1%), and contaminated blood or blood products (2.4%); the remaining 3.7%

acquired HIV through another or an unknown transmission route. Most long-term survivors (65.8%) originated from the Netherlands, followed by western Europe, North America and Australia (13.8%), South America and the Caribbean (10.2%), sub-Saharan Africa (5.4%), and other regions (3.6%). At the start of cART, the median HIV viral load was 4.6 (IQR 3.9-5.1) $\log_{10}$ copies/ml (available for 1,462 people), and the median CD4 cell count was 240 (IQR 120-362) cells/mm^3 (available for 1,697 people). In total, 1,243 (64.3%) had a prior AIDS-defining event (CDC category C clinical event). The majority (57.8%) had initiated cART in 1996 or 1997 (35.7% and 22.0%, respectively), and 46.3% had received nucleoside analogue antiretroviral drugs as monotherapy or dual therapy before initiating cART.

As of 31 December 2018, the median age of these long-term survivors was 58 years (IQR 54-64). The majority (73.4%) received a dual NRTI backbone in combination with an NNRTI (32.7%), integrase inhibitor (26.6%), or protease inhibitor (14.1%). The most common regimens were TAF/FTC/EVG/c (9.1%), TDF/FTC/NVP (8.4%), ABC/3TC/DTG (8.4%), TDF/FTC/EFV (5.4%), and TAF/FTC/DRV/c (3.9%). Importantly, 26.6% 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 2015-2018), 2.1% had a CD4 cell count <200 cells/mm^3, 6.8% between 200 and 349 cells/mm^3, 17.5% between 350 and 499 cells/mm^3, 32.4% between 500 and 749 cells/mm^3, and 41.1% had 750 cells/mm^3 or higher. Furthermore, 23.1% had a CD4:CD8 ratio of 1 or higher. Of all long-term survivors receiving cART with a viral load measurement in 2018, viral suppression was high and comparable to the overall population in care: 89.1% had a viral load <50 copies/ml, and 97.1% 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 bictegravir, 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 of these new drugs/regimens in HIV treatment.

< Back to page 114

Box 2.2: Approval dates of new antiretroviral drugs/regimens for HIV treatment in the Netherlands in 2013–2018.

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
DTG/RPV (Juluca®)	May 21 , 2018
TAF/FTC/BIC (Biktarvy®)	June 25, 2018
Doravirine (Pifeltro®)	Nov 22, 2018
TDF/3TC/doravirine (Delstrigo®)	Nov 22, 2018

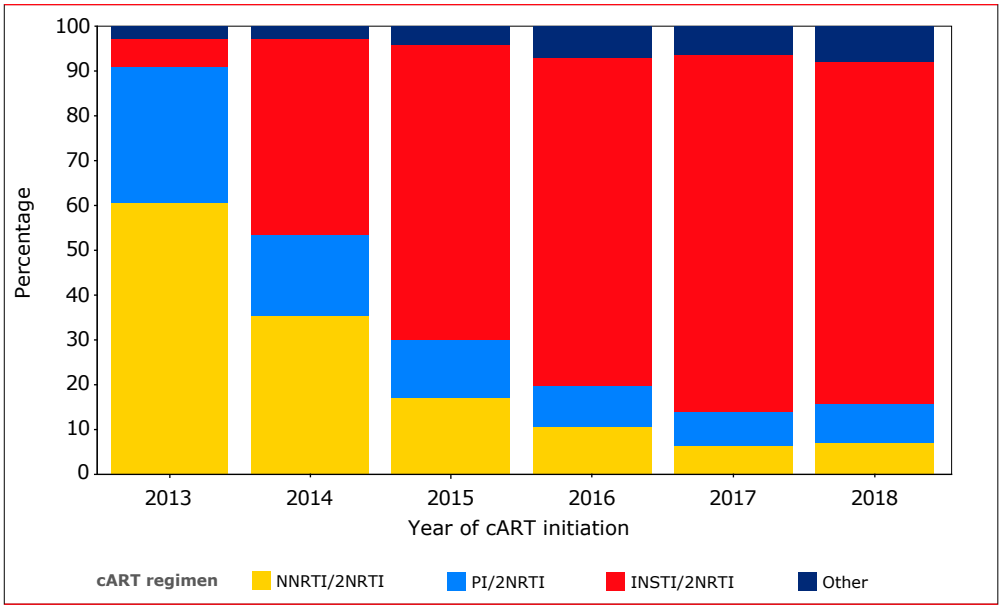
Legend: *3TC=lamivudine; ABC=abacavir; BIC = bictegravir; DTG=dolutegravir; DRV=darunavir; EVG=elvitegravir; FTC=emtricitabine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; RPV=rilpivirine.*
Source: *Medicines Evaluation Board and European Medicines Agency.*

Initial cART regimen

Out of 24,603 people who were known to have initiated cART between January 1996 and December 2018, 6,729 (27.4%) started cART between January 2013 and December 2018. *Figure 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 6.2% in 2013, to 44.1% in 2014, 65.4% in 2015, 72.8% in 2016, 79.4% in 2017, and then slightly decreased to 76.3% in 2018. EVG/c was introduced in the Netherlands at the end of 2013 and was used in 34.3%, 17.4%, 26.0%, 31.3%, and 27.3% of the initial regimens in 2014, 2015, 2016, 2017, and 2018, respectively. Dolutegravir was introduced in the Netherlands in 2014 and was used in 6.8%, 47.3%, 46.1%, 47.3%, and 39.6% of the initial regimens in 2014, 2015, 2016, 2017, and 2018, respectively. With the introduction of (boosted) elvitegravir, dolutegravir and bictegravir, the use of NNRTIs in the initial regimen decreased from 60.6% in 2013 to 35.2% in 2014, 16.9% in 2015, 10.6% in 2016, 6.2% in 2017, but increased slightly to 7.2% in 2018. The use of protease inhibitors in the

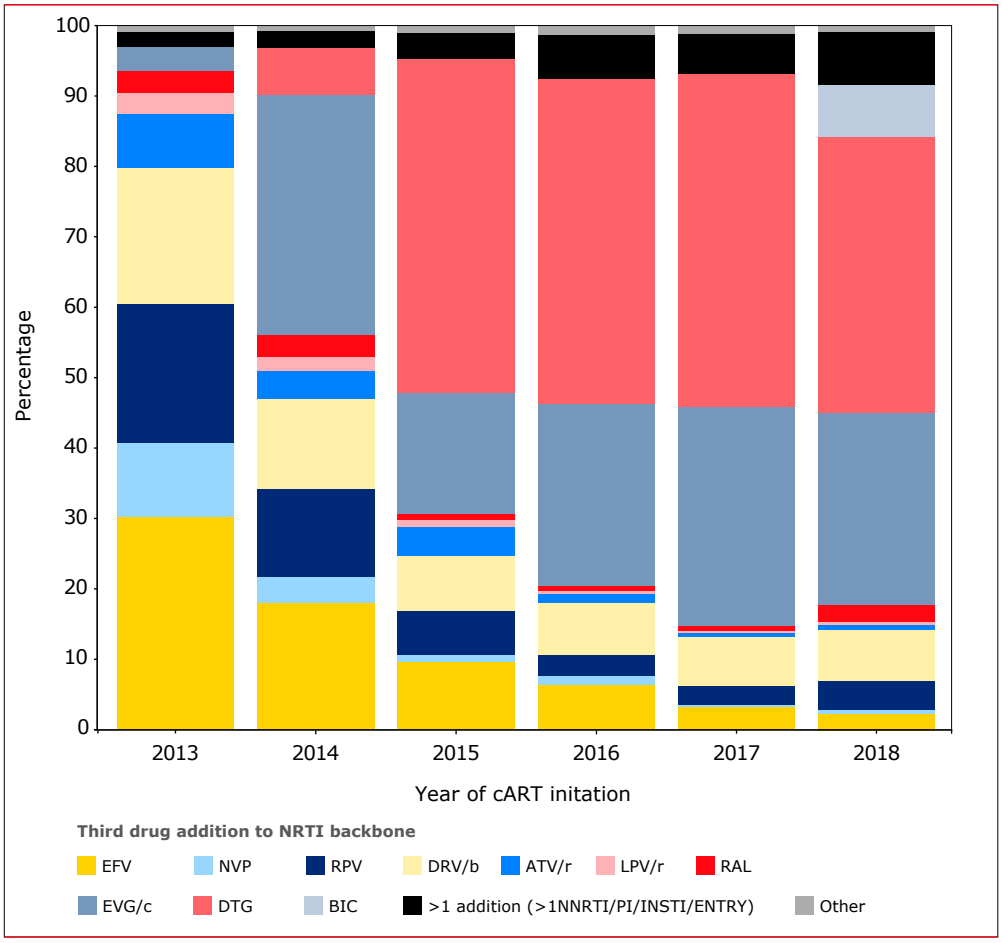
initial regimen decreased from 29.9% in 2013 to 7.7% in 2017 and increased slightly to 8.4% in 2018. In 2013-2018, 4.1% of people received more than one 'third-drug' addition to the NRTI backbone in their initial cART regimen, the majority of whom were people initiating cART during an acute HIV infection, with the regimen consisting of a PI (mainly boosted darunavir) plus an INSTI (mainly dolutegravir) with or without the addition of an NRTI.

Figure 2.3: Third-drug class additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2013-2018.



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

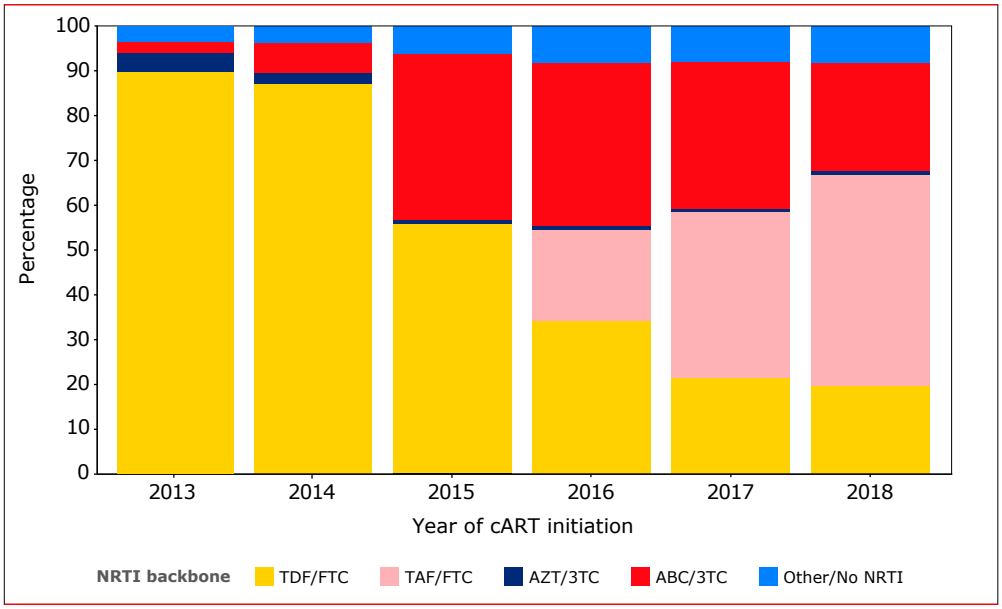
Figure 2.4: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2013-2018.



Legend: cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ATV=atazanavir; BIC=bictegravir; 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 NRTI backbone components of the initial cART regimens used between 2013 and 2018. 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 19.3%, 37.1% and 47.3% of the initial regimens in 2016, 2017 and 2018, respectively. At the same time, TDF use decreased from 89.5% in 2013 to 19.7% in 2018. The use of abacavir in combination with lamivudine, which was already available as a fixed-dose combination in Kivexa, became more frequently used after it was introduced as a once-daily fixed-dose combination with dolutegravir in Triumeq by the end of 2014. Its use increased from <3% of all initial regimens in 2013, to about a third of all initial regimens in 2015-2017, but decreased to 23.8% in 2018. The combination of zidovudine and lamivudine, often used by migrants who had already initiated cART before migrating to the Netherlands, further decreased to <1% since 2015.

Figure 2.5: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2013-2018.*



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 cART regimens initiated between 2013 and 2018 are presented in *Figure 2.6* and *Table 2.3*. In 2018, most people (39.5%) initiating cART received a dolutegravir-based regimen combined with either abacavir and lamivudine as part of the once-daily fixed-dose combination (23.2%), or they were provided with emtricitabine and tenofovir separately (tenofovir 15.6%; TDF 10.4%/TAF 5.2%). Additionally, 27.3% initiated an EVG/c-containing once-daily fixed-dose combination with emtricitabine and tenofovir (TDF 2.2%/TAF 25.1%). Raltegravir use in an initial regimen decreased to <1% between 2015 and 2017, but increased to 2.3% in 2018. The combination of ritonavir or cobicistat-boosted darunavir with tenofovir and emtricitabine was used in 7.2% of initial cART regimens in 2018: 2.0% based on TDF and 4.9% on 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*.

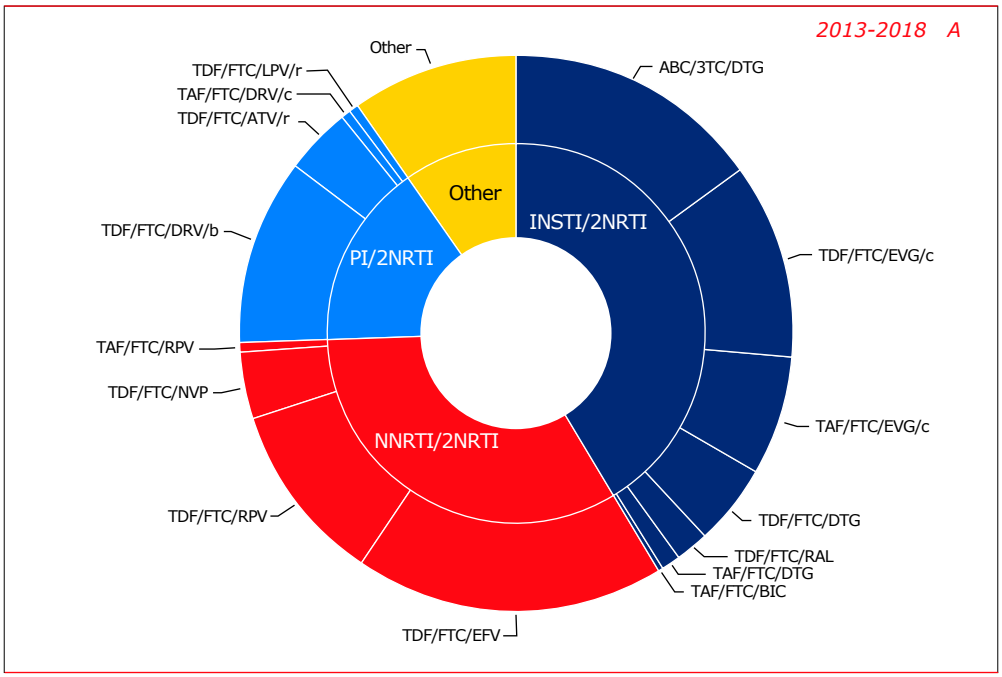
***Table 2.3:** Initial regimen in 2013–2018*

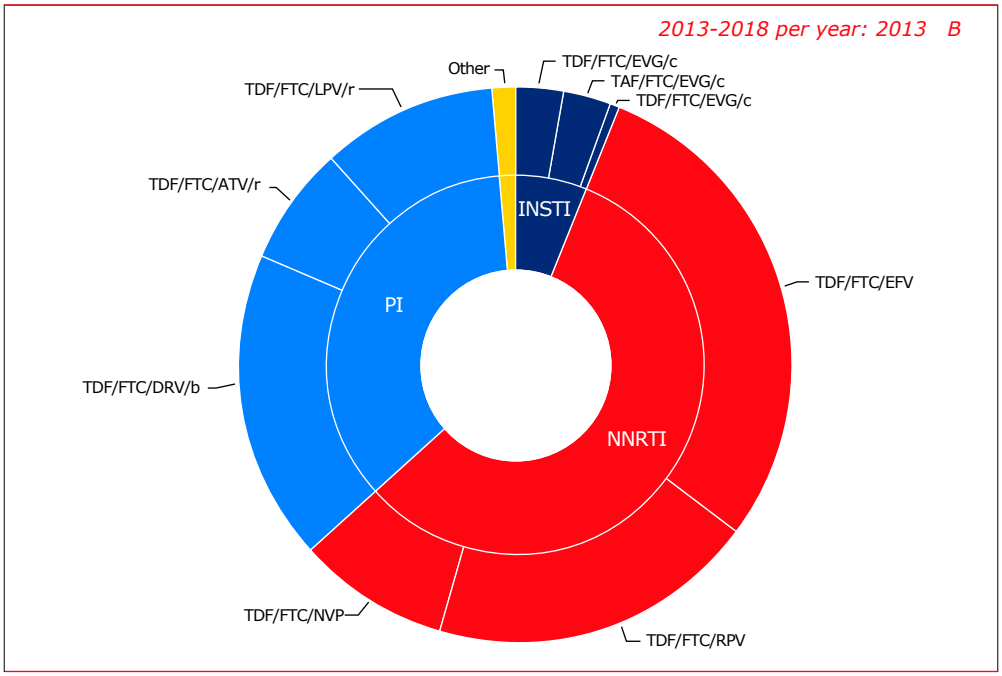
Regimen		2013	2014	2015	2016	2017	2018	2013–2018
Total	n	1,510	1,487	1,219	1,022	892	599	**6,729**
TDF/FTC/EFV	n	440	253	97	58	19	15	882
	%	29.1	17.0	8.0	5.7	2.1	2.5	13.1
TDF/FTC/NVP	n	132	35	7	8	2	2	186
	%	8.7	2.4	0.6	0.8	0.2	0.3	2.8
TDF/FTC/RPV	n	293	197	76	26	7	1	600
	%	19.4	13.3	6.2	2.5	0.8	0.2	8.9
TDF/FTC/DRV/b	n	275	159	91	62	34	12	633
	%	18.2	10.7	7.5	6.1	3.8	2.0	9.4
TDF/FTC/ATV/r	n	104	57	43	16	4	4	228
	%	6.9	3.8	3.5	1.6	0.5	0.7	3.4
TDF/FTC/LPV/r	n	19	5	8	1	.	.	33
	%	1.3	0.34	0.7	0.1	.	.	0.5
TDF/FTC/EVG/c	n	44	509	210	82	46	13	904
	%	2.9	34.2	17.2	8.0	5.2	2.2	13.4
TDF/FTC/DTG	n	.	39	139	101	77	62	418
	%	.	2.6	11.4	9.9	8.6	10.4	6.2
TDF/FTC/RAL	n	41	39	8	6	3	9	106
	%	2.7	2.6	0.7	0.6	0.3	1.5	1.6
ABC/3TC/DTG	n	.	62	435	361	290	140	1,288
	%	.	4.2	35.7	35.3	32.5	23.4	19.1

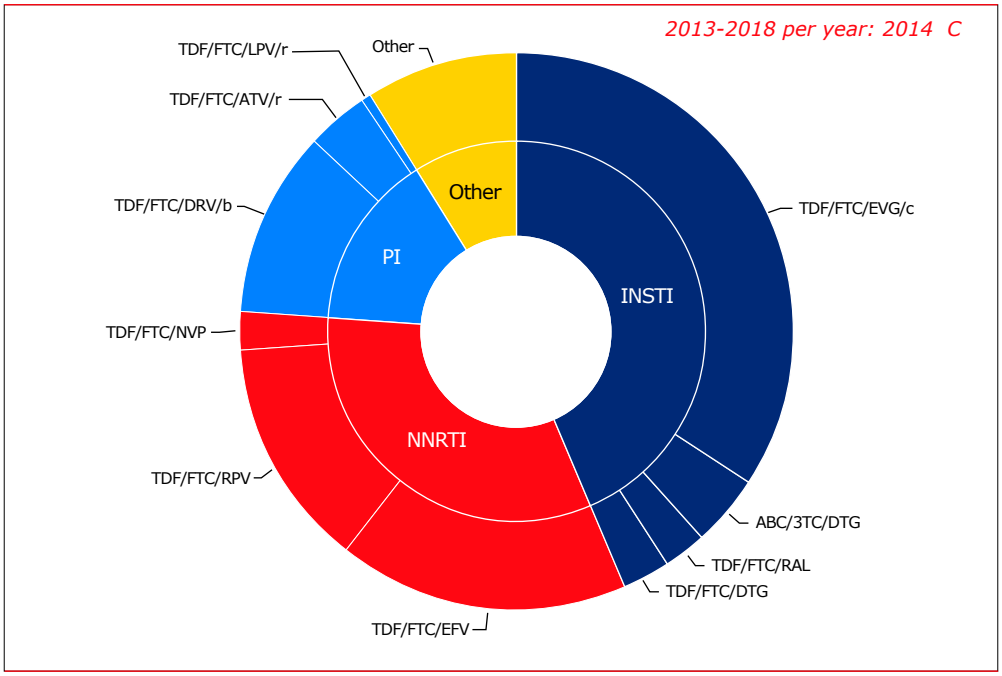
TAF/FTC/EVG/c	n	6	.	1	183	232	150	572
	%	0.4	.	0.1	17.9	26.0	25.0	8.5
TAF/FTC/RPV	n	.	.	.	4	16	24	44
	%	.	.	.	0.4	1.8	4.0	0.7
TAF/FTC/DTG	n	.	.	1	7	52	31	91
	%	.	.	0.1	0.7	5.8	5.2	1.4
TAF/FTC/DRV/c	n	.	.	.	2	26	29	57
	%	.	.	.	0.2	2.9	4.8	0.9
TAF/FTC/BIC	n	.	.	.	.	.	43	43
	%	.	.	.	.	.	7.2	0.6
Other: 2NRTI+NNRTI	n	53	40	26	13	12	1	145
	%	3.5	2.7	2.1	1.3	1.4	0.2	2.2
Other: 2NRTI+PI	n	56	46	19	13	5	5	144
	%	3.7	3.1	1.6	1.3	0.6	0.8	2.1
Other: 2NRTI+INSTI	n	9	7	2	3	8	9	38
	%	0.6	0.5	0.2	0.3	0.9	1.5	0.6
Other: PI+INSTI	n	.	.	5	7	6	3	21
	%	.	.	0.4	0.7	0.7	0.5	0.3
Other: NRTI+PI+INSTI (3ARVs)	n	1	3	2	.	1	1	8
	%	0.1	0.2	0.2	.	0.1	0.2	0.1
Other: NRTI+PI+INSTI (4ARVs)	n	10	20	41	58	49	43	221
	%	0.7	1.3	3.4	5.7	5.5	7.2	3.3

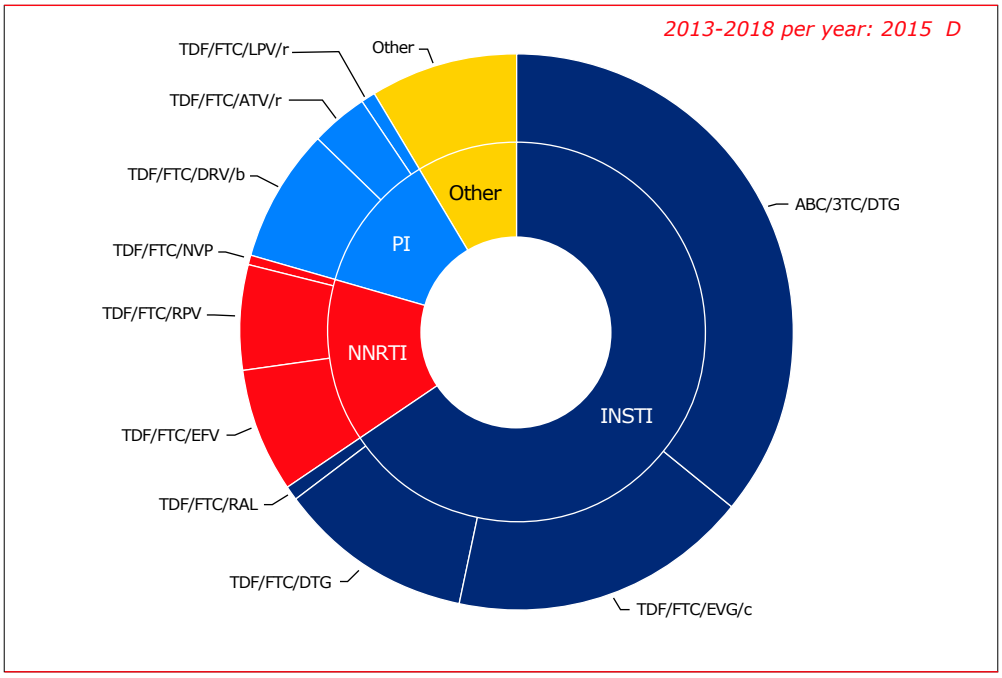
Legend: *ARVs=antiretroviral drugs; /b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; LPV=lopinavir; INSTI=integrase inhibitor; NRTI=nucleoside 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 regimen combinations in 2013-2018.

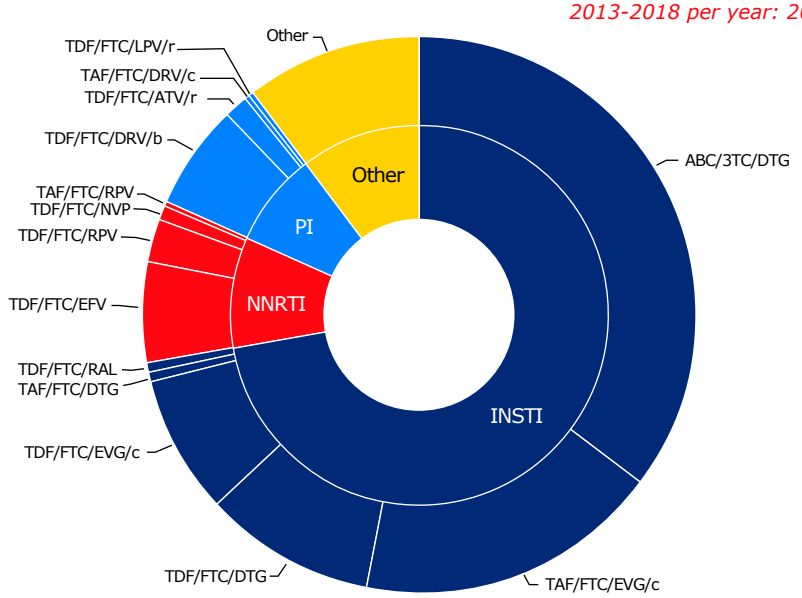




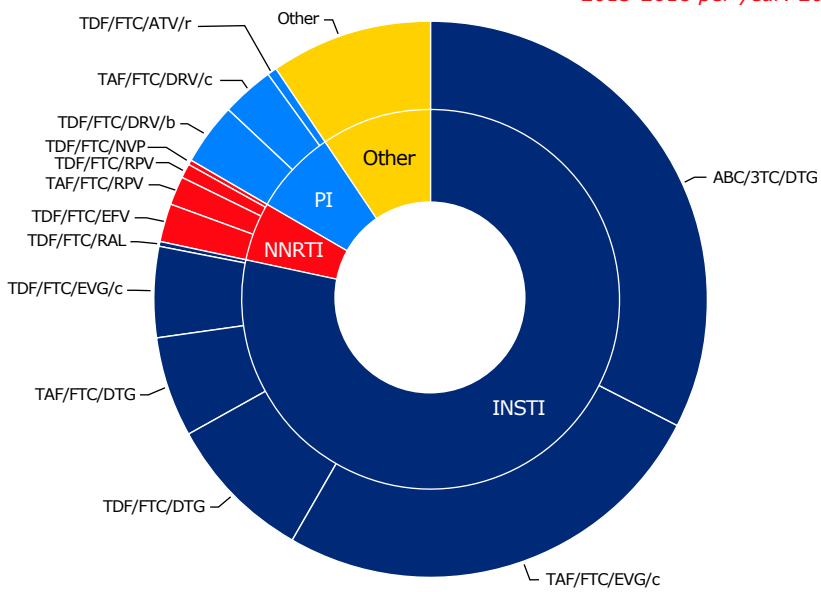

2013-2018 per year: 2014 C
TDF/FTC/LPV/r
Other
TDF/FTC/ATV/r
TDF/FTC/DRV/b
Other
PI
TDF/FTC/EVG/c
INSTI
TDF/FTC/NVP
NNRTI
TDF/FTC/RPV
ABC/3TC/DTG
TDF/FTC/RAL
TDF/FTC/DTG
TDF/FTC/EFV

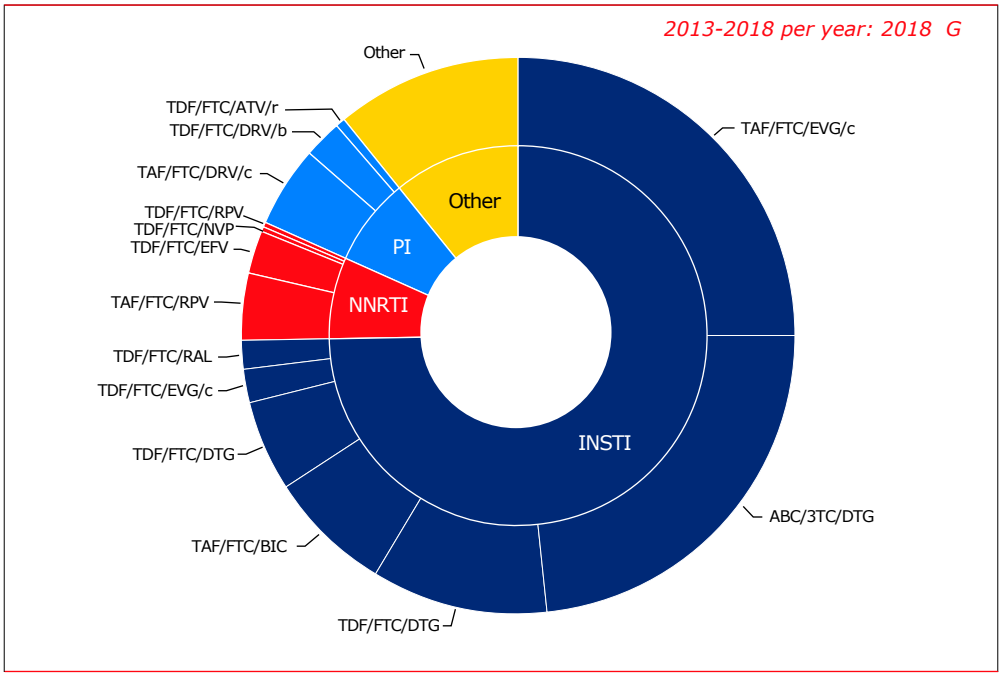

2013-2018 per year: 2015 D
TDF/FTC/LPV/r
Other
TDF/FTC/ATV/r
TDF/FTC/DRV/b
Other
PI
ABC/3TC/DTG
TDF/FTC/NVP
TDF/FTC/RPV
NNRTI
INSTI
TDF/FTC/EFV
TDF/FTC/RAL
TDF/FTC/DTG
TDF/FTC/EVG/c

2013-2018 per year: 2016 E



2013-2018 per year: 2017 F





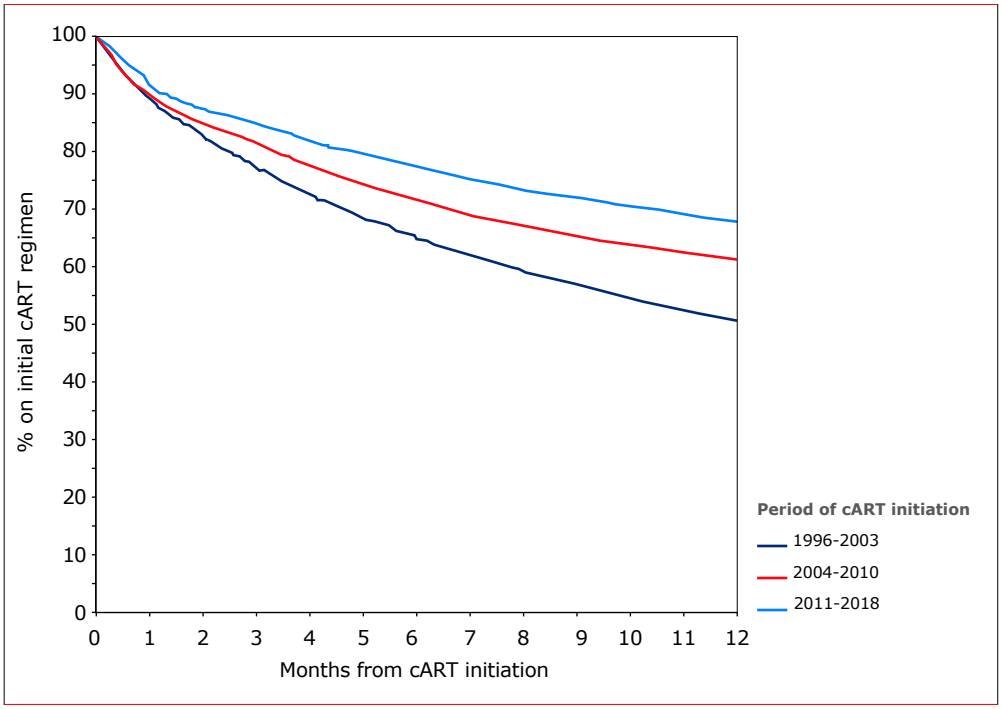
Legend: *3TC=lamivudine; ABC=abacavir; ATV=atazanavir; /b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; INSTI=integrase inhibitor; LPV=lopinavir; NNRTI=non-nucleoside 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 24,603 people who ever started cART between 1996 and 2018. 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. Likewise, the breakup of a (more expensive) single tablet regimen (STR) into (cheaper) generic components of the original STR, was also not considered a switch. A switch from one booster to another was also ignored. 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 1996-2018, 39.3% 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 2008-2018. 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).*



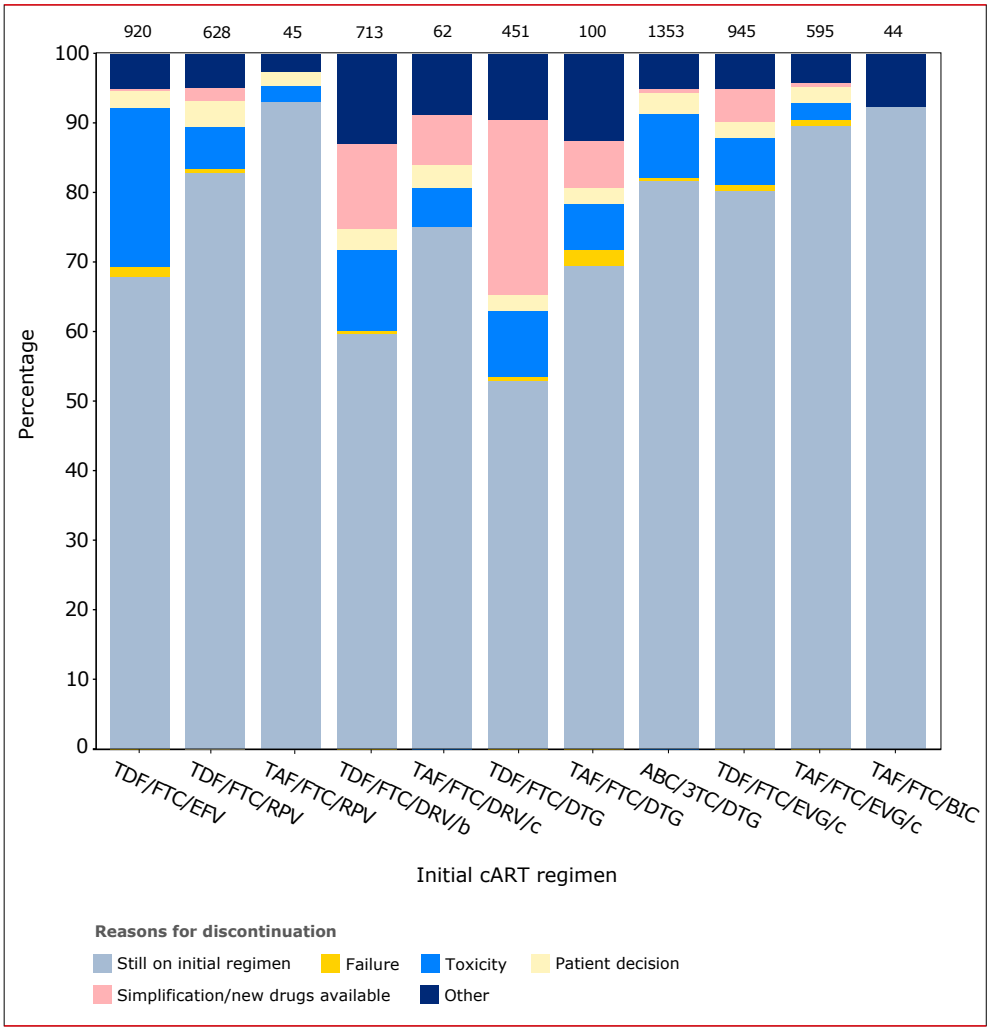
Legend: *cART=combination antiretroviral therapy*

Discontinuation of the initial cART regimen: 2013–2018

We further assessed the time to discontinuation of the initial regimen during the first year of treatment among the 5,508 people who started 'common' and guideline-recommended initial regimens in 2013-2018. Common and guideline-recommended regimens considered in this analysis were: tenofovir disoproxil fumarate/emtricitabine combined with efavirenz (TDF/FTC/EFV; 15.9%), rilpivirine (TDF/FTC/RPV; 10.9%), ritonavir-boosted or cobicistat-boosted darunavir (TDF/FTC/DRV/b; 11.5%), cobicistat-boosted elvitegravir (TDF/FTC/EVG/c; 16.4%), dolutegravir (TDF/FTC/DTG; 7.5%), or abacavir-lamivudine combined with dolutegravir (ABC/3TC/DTG; 23.4%), or tenofovir alafenamide/emtricitabine combined with cobicistat-boosted elvitegravir (TAF/FTC/EVG/c; 10.4%), rilpivirine (TAF/FTC/RPV; 0.8%), dolutegravir (TAF/FTC/DTG; 1.6%), cobicistat-boosted darunavir (TAF/FTC/DRV/c; 1.0%), bictegravir (TAF/FTC/BIC; 0.8%).

One year after cART initiation, 1,341 (24.4%) out of 5,508 who initiated one of these regimens had discontinued their initial regimen. The main reason for regimen discontinuation was toxicity (n=557; 41.5%), followed by simplification and/or availability of new drugs (n=254; 18.9%). 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, 6.3% discontinued their initial regimen for reasons of simplification and/or availability of new drugs in 2013, 14.2% in 2014, 27.6% in 2015, 24.5% in 2016, 19.6% in 2017 and 20.0% in 2018.

Figure 2.8: Reasons for discontinuation of the initial regimen during the first year of treatment 2013–2018, by regimen.

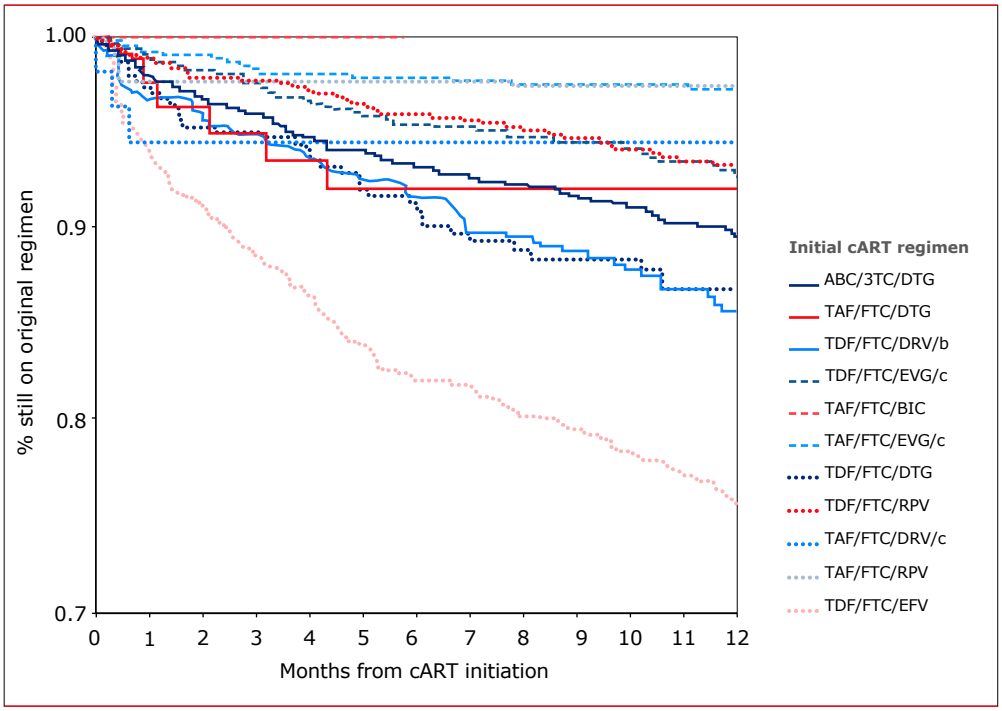


Legend: cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate. Numbers above the bars represent the total number of individuals using that particular regimen.

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 2013-2018, by regimen. Time was censored when the initial regimen was discontinued due to reasons other than toxicity (log-rank p<0.001).

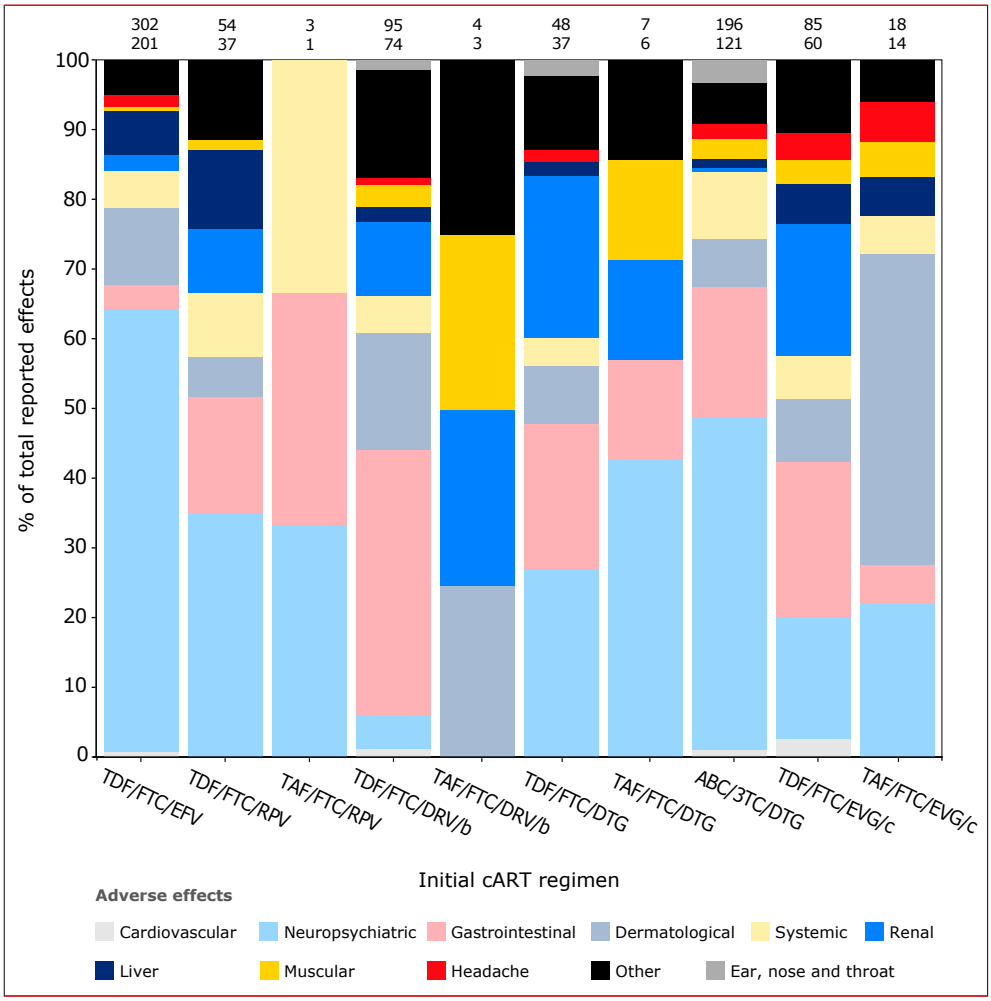


Legend: *cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir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

Adverse effects

Among the 557 who discontinued their initial cART regimen due to toxicity within a year, 709 adverse effects were recorded. The predominant effects were: 42.7% neuropsychiatric (mainly insomnia, mood changes, dizziness and depression), 15.3% gastrointestinal (mainly diarrhoea and nausea), 10.7% dermatological (rash due to medication, itching), 6.7% systemic (tiredness, apathy, loss of appetite), and 6.3% renal (renal insufficiency and increased serum creatinine). These adverse effects are stratified by cART regimen in *Figure 2.10*. Neuropsychiatric effects were associated with regimens containing efavirenz and dolutegravir and, to a lesser extent, rilpivirine and elvitegravir. Renal effects were mainly, but not exclusively, 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 2013–2018. The bars represent the distribution of 709 reported effects among 557 people, by regimen. Numbers above the bars represent the number of adverse events reported as reasons for discontinuing that particular regimen (top row) occurring in a certain number of individuals on that particular regimen (bottom row).



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; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.

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 24,603 adults have started cART since January 1996. For the current analysis of virological outcomes, we will focus on the 21,304 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 20,166 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 level.

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 2019 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[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].

Initial virological success

Out of 20,633 with a viral load test result after at least 3 months of cART initiation, 18,209 (88.3%) had a viral load measurement 6 months (±3 months) after cART initiation. Of these people, 15,316 (84.1%) 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 61.4% in those starting cART between 1996 and 2003, to 87.9% in those starting between 2004 and 2010, 92.1% in those starting between 2011 and 2017, and 95.0% in those starting in 2018.

Initial virological success of common initial cART regimens (2013–2018)

We analysed the initial virological success among the 4,114 adults who started a common or guideline-recommended cART regimen in 2013-2018 that was used frequently enough to allow for a meaningful analysis (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 2013-2018'), and had a viral load result after 6 months (±3 months) of cART initiation. In total, 94.2% (95% CI 93.5-94.9) of people achieved initial virological suppression, after a mean of 178 standard deviation (SD) 39 days. Overall, people receiving an integrase-inhibitor based regimen showed significantly higher rates of initial virological success: 94.5% (95% CI 94.5-96.1) of those on an integrase-inhibitor-based regimen had initial virological success, compared to 89.6% (95% CI 87.0-92.3) on a protease-inhibitor-based regimen and 93.9% (95% CI 92.5-95.4) on an 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. 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	616	15.0	341	12.9	97.9	96.4	99.5	Ref.
TDF/FTC/RPV	453	11.0	453	17.1	95.6	93.7	97.5	0.076
TDF/FTC/DRV/b	521	12.7	216	8.1	95.4	92.6	98.2	0.093
TDF/FTC/EVG/c	736	17.9	509	19.2	97.2	95.8	98.7	0.65
TDF/FTC/DTG	327	8.0	166	6.3	96.4	93.5	99.2	0.30
ABC/3TC/DTG	1037	25.2	700	26.4	97.6	96.4	98.7	0.70
TAF/FTC/EVG/c	424	10.3	268	10.1	97.4	95.5	99.3	0.65
cART regimen class								
NNRTI/2NRTI	1069	26.0	794	29.9	96.6	95.4	97.9	Ref.
PI/2NRTI	521	12.6	216	8.1	95.4	92.6	98.2	0.40
INSTI/2NRTI	2,524	61.4	1,643	61.9	97.3	96.5	98.1	0.32
All regimens	**4,114**	**100 .0**	**2,653**	**64.5**	**96.9**	**96.3**	**97.6**	

Legend: */b=boosted (cobicistat or ritonavir); /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; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.*

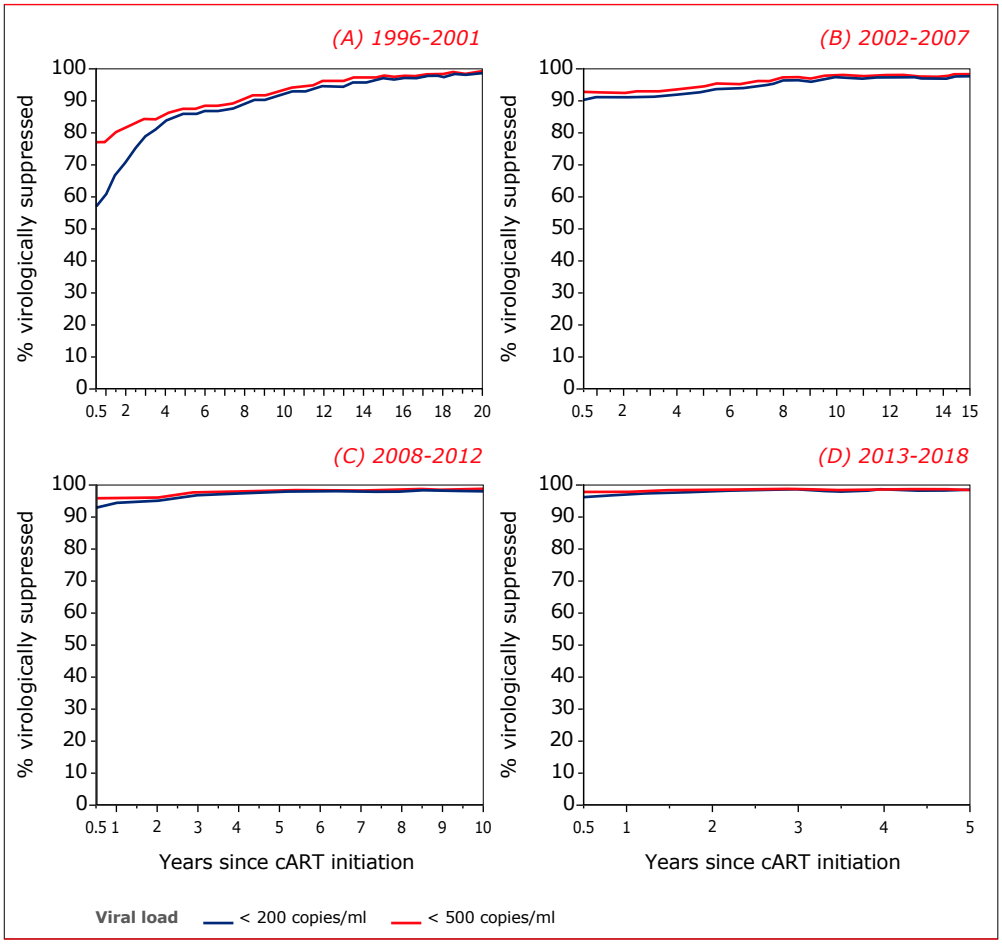
				By initial viral load at cART start			
						≥100,000 copies/ml	
		n	%	Initial viral success	95% CI low	95% CI high	p-value
	cART regimen						
	TDF/FTC/EFV	275	18.8	86.2	82.1	90.3	Ref.
	TDF/FTC/RPV	not recommended					
	TDF/FTC/DRV/b	305	20.9	85.6	81.6	89.5	0.83
	TDF/FTC/EVG/c	227	15.5	89.9	85.9	93.8	0.21
	TDF/FTC/DTG	161	11.0	88.8	83.9	93.7	0.48
	ABC/3TC/DTG	337	23.1	93.5	90.8	96.1	0.0031
	TAF/FTC/EVG/c	156	10.7	92.3	88.1	96.5	0.060
	cART regimen class						
	NNRTI/2NRTI	275	18.8	86.2	82.1	90.3	Ref.
	PI/2NRTI	305	20.9	85.6	81.6	89.5	0.83
	INSTI/2NRTI	881	60.3	91.5	89.6	93.3	0.010
	All regimens	**1,461**	**35.5**	**89.3**	**87.7**	**90.8**	

Viral suppression

We assessed long-term 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 and 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 2013-2018. 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 97.0% (95% CI 96.5-97.5) after 1 year of cART use to 98.2% (95% CI 97.7-98.7) after 4 years. The viral suppression rates over time during the full period (1996-2018) 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 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. It should be noted that 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 using the 2019 IAS-USA HIV drug resistance mutation list[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

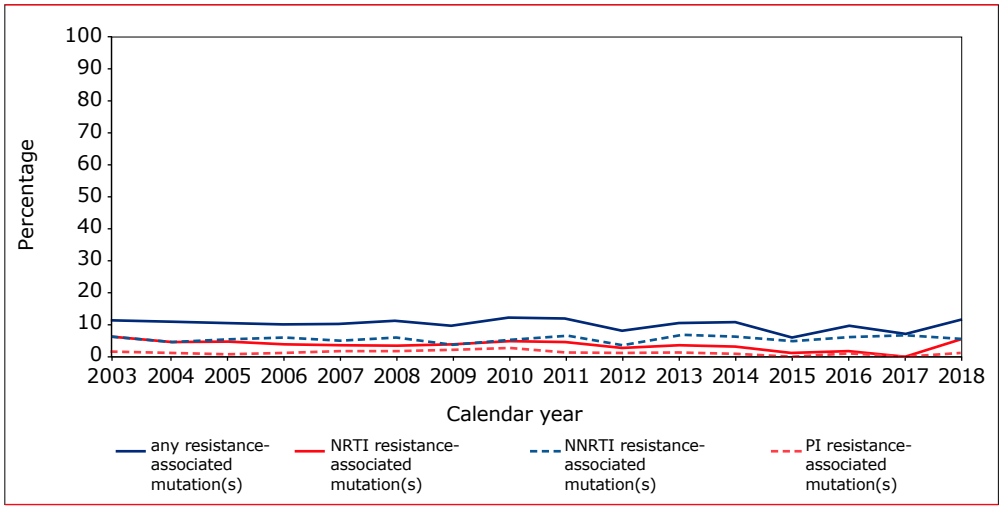
In the Netherlands, screening for HIV drug resistance at the time of entry into care has been incorporated in the treatment guidelines since 2003. Transmitted HIV drug resistance occurs when people acquire an HIV strain that harbours drug-resistance mutations. Drug-resistant variants of HIV may remain dormant in resting CD4 cells, awaiting more favourable replication conditions after treatment has started[28,29,30]. These dormant mutant variants might not be detected, which could make it difficult to distinguish between drug-susceptible versus drug-resistant strains[31]. 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 2019, 7,401 HIV-1 sequences had been obtained between 2003-2018 from 7,127 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 (68.6%) and, less often, women (14.5%). Most people with an available pre-treatment sequence originated from the Netherlands (60.8%) or sub-Saharan Africa (11.2%). The main HIV-1 subtype was B (76.5%), followed by non-B subtypes (23.5%), including recombinant form CRF_02AG (6.6%) and subtype C (4.8%).

Transmitted HIV drug resistance

In total, ≥1 major resistance mutation[24] was found in 768 (10.8%) of the people who were tested for resistance, including 296 (4.2%) with NRTI-associated resistance mutations, 412 (5.8%) with NNRTI-associated resistance mutations, and 130 (1.8%) with PI-associated resistance mutations. The prevalence of transmitted drug resistance was low and remained stable between 2003 and 2018 (*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 major drug resistance mutation detected before initiation of cART. The 2019 IAS–USA HIV drug resistance mutation list was used to score major drug resistance mutations[24]. NRTI=nucleotide/nucleoside reverse transcription inhibitor, NNRTI=non-NRTI, PI=protease inhibitor.*

In total, 189 (2.7%) screened for transmitted drug resistance harboured high-level resistance[25,26] to at least one antiretroviral drug; 32 (0.5%) to at least one NRTI, 139 (2.0%) 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; 2.3% (n=162) harboured high-level resistance in one drug class, 0.3% (n=18) in two drug classes, and <0.1% (n=5) 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

Twenty-five people had an integrase sequence available prior to cART initiation; all of them were ARV-naive. No major or minor INSTI resistance 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 2000-2018. If cART had been interrupted >2 weeks before the test, the sequence was excluded from the analysis.

In total, 3,802 HIV-1 sequences were obtained from 2,348 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 2.9-8.2). The main HIV-1 subtype was B (69.6%), followed by recombinant form CRF_02AG (10.0%) and subtype C (5.8%).

Overall, sequences from people pre-treated with monotherapy or dual therapy were disproportionally represented: 1,284 (33.8%) sequences were obtained from 711 (30.3%) pre-treated people, and 2,518 (66.2%) sequences were obtained from 1,637 (69.7%) ARV-naive people. However, over time this difference has become less distinct. In 2000, 73.2% of sequences were obtained from pre-treated people, compared with 36.6% in 2005 and less than 15% since 2010.

Out of all 3,802 sequences obtained at the time of HIV RNA >500 copies/ml, 2,553 (67.2%) harboured high-level resistance[25] to at least one antiretroviral drug. High-level NRTI resistance was detected in 2,195 (58.4%) sequences; of those, 1,829 (83.3% of 2,195) harboured high-level resistance to emtricitabine or lamivudine. Notably, of the 1,611 individuals ever identified as harbouring the M184V or M184I mutation and who were still in care in 2018, 1,100 (68.3%) were still on cART containing lamivudine and/or emtricitabine. In addition, 1,527 (40.6%) harboured high-level resistance to at least one NNRTI, and 998 (27.2%) to at least one PI.

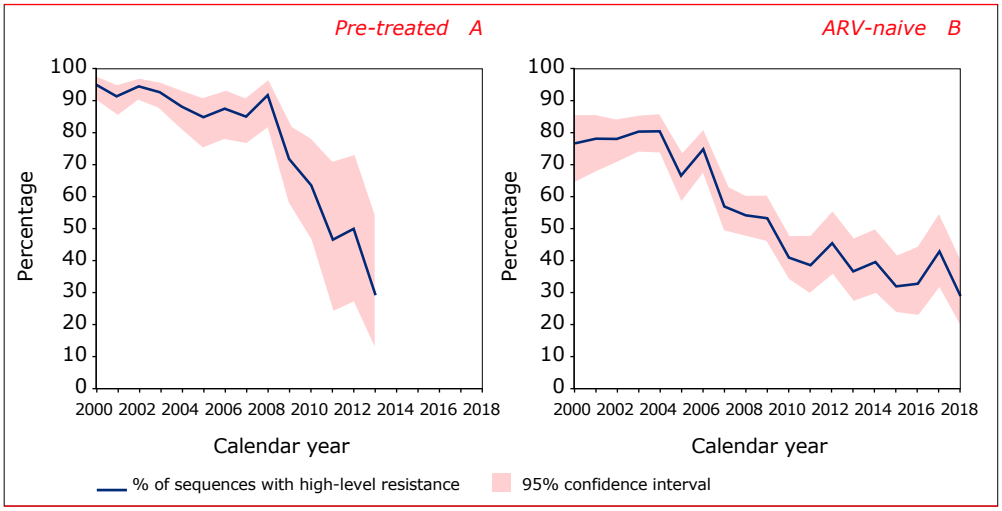
Differences in acquired HIV drug resistance between pre-treated and ARV-naive people

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 94.9% (95% CI 90.4-97.3) in 2000, 88.1% (95% CI 80.5-93.0) in 2004, 63.6% (95% CI 46.2-78.1) in 2010, and 29.4% (95% CI 12.8-54.2) in 2013 (*Figure 2.13A*). The availability of new drugs both in existing and new drug classes largely explains the decline since 2008[32]. In recent years (2014-2018), 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 76.6% (95% CI 64.7-85.4) of sequences in 2000, 74.7% (95% CI 67.4-80.8) in 2006, 45.5% (95% CI 36.0-55.3) in 2012, and 28.4% (95% CI 19.3-39.6) in 2018 (*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 (ARV) 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 (2014-2018) was too low to give meaningful proportions.*

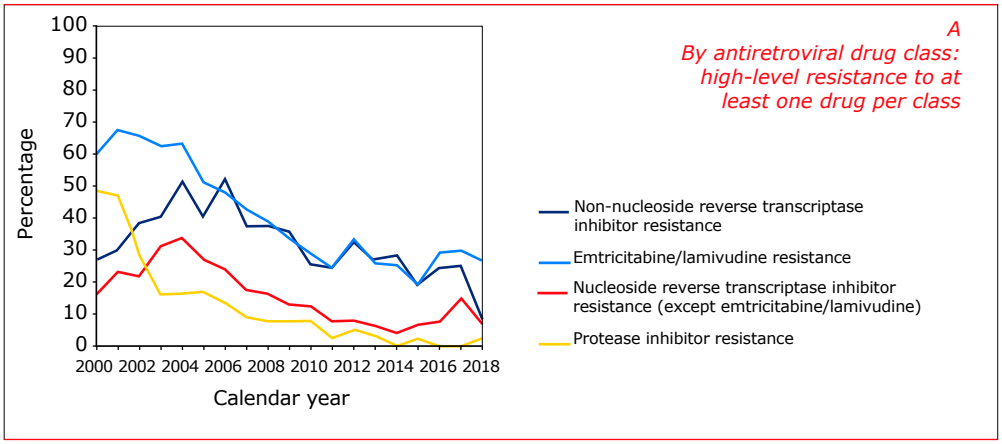
Acquired HIV drug resistance among previously ARV-naive people

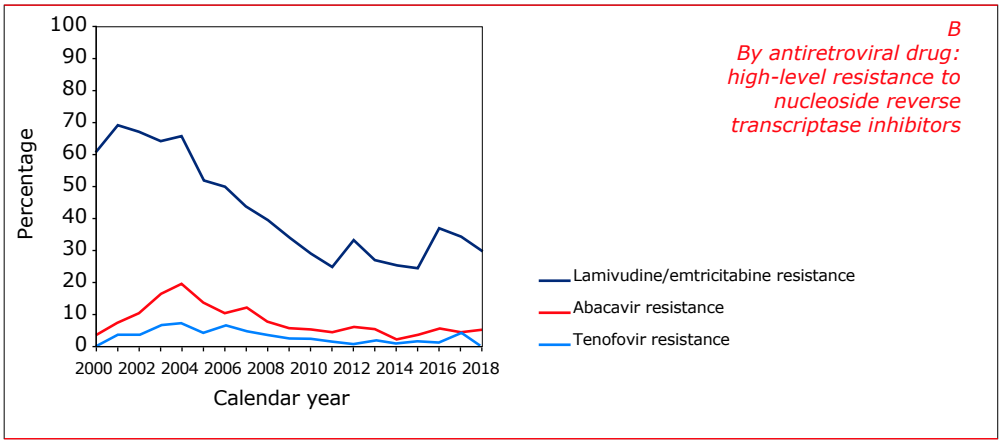
In the remainder of our analysis, we will focus solely on the 1,637 people who were ARV-naive before cART initiation. Overall, 1,543 (61.3%) out of all 2,518 sequences from previously ARV-naive people receiving cART harboured at least one major resistance mutation, associated with resistance to NRTI (n=1,243; 49.4%), NNRTI (n=962; 38.2%) or PI (n=338; 13.4%).

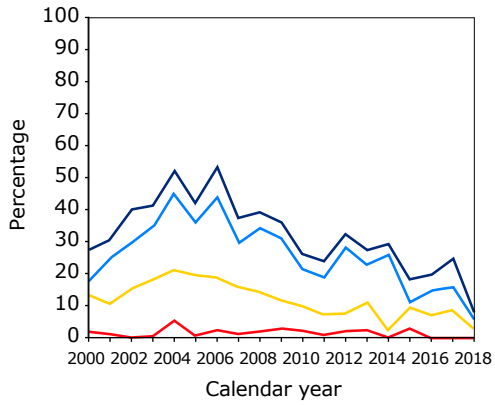
Figure 2.14A and *Table 2.5* present the annual proportion of sequences harbouring high-level resistance for each antiretroviral drug class. In 2000, 65.1% (95% CI 52.6-75.8), 27.0% (95% CI 17.5-39.2), and 48.4% (95% CI 36.5-60.5) of sequences harboured high-level resistance to at least one NRTI, NNRTI, or PI, respectively. The proportion of sequences with high-level of resistance declined over time for all drug classes. In 2009, 35.8% (95% CI 29.3-42.9), 35.8% (95% CI 29.3-42.9), and 7.9% (95% CI 4.8-12.7) of sequences harboured high-level resistance to at least one NRTI, NNRTI, or PI, respectively. In 2018, 26.8% (95% CI 17.8-38.2), 8.5% (95% CI 3.8-17.6), and 2.6% (95% CI 0.3-16.5) of sequences harboured high-level resistance to at least one NRTI, NNRTI or PI, respectively. The proportion of sequences with at least one resistance

mutation to all three drug classes (i.e., NRTI, NNRTI and PI) also declined over time from 6.3% (95% CI 2.4-15.5) in 2000 to 0% as of 2014. The annual proportions of sequences harbouring high-level resistance for individual antiretroviral drugs are presented in *Figure 2.14B-D* and *Appendix Table 2.3*, and the annual proportion of sequences harbouring at least one high-level resistance mutation to all three drug classes is presented in *Figure 2.14E*.

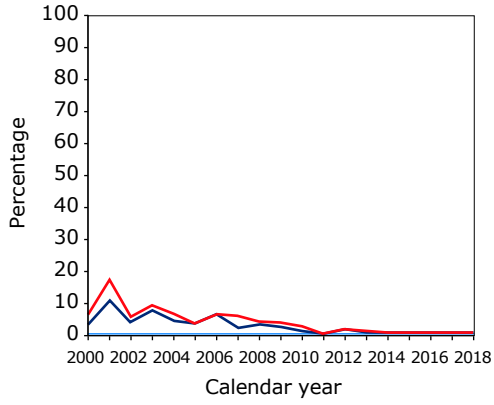
Figure 2.14: *The annual proportion of sequences with evidence of high-level resistance by drug class and antiretroviral drug, obtained at the time of virological failure when receiving combination antiretroviral therapy (cART), among previously antiretroviral drug-naive people.*



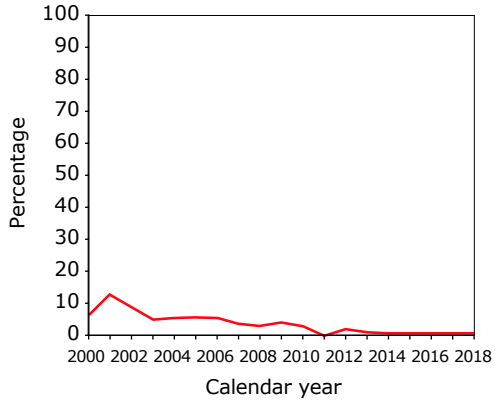




C
By antiretroviral drug: high-level resistance to non-nucleoside reverse transcriptase inhibitors



D
By antiretroviral drug: high-level resistance to protease inhibitors



E
By antiretroviral drug: high-level resistance to nucleoside reverse transcriptase inhibitors (NRTI), non-NRTIs and protease inhibitors

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*[37,38].

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	Nucleoside analogue reverse transcriptase inhibitors			Non-nucleoside reverse transcriptase inhibitors			Protease inhibitors		
	95% confidence interval			95% confidence interval			95% confidence interval		
Calendar year	%	low	high	%	low	high	%	low	high
2000	65.1	52.6	75.8	27.0	17.5	39.2	48.4	36.5	60.5
2001	75.6	65.4	83.5	30.2	21.5	40.7	47.1	36.7	57.6
2002	72.6	64.8	79.2	38.4	30.8	46.5	29.5	22.6	37.3
2003	71.4	64.6	77.3	40.6	33.9	47.7	16.3	11.7	22.3
2004	70.1	62.9	76.3	51.4	44.1	58.7	16.4	11.6	22.6
2005	58.2	50.4	65.7	40.5	33.1	48.3	17.1	12.0	23.8
2006	55.6	47.8	63.0	52.5	44.8	60.0	13.7	9.2	19.9
2007	47.6	40.5	54.8	37.4	30.8	44.6	9.1	5.7	14.1
2008	43.3	37.0	49.8	37.7	31.6	44.1	7.8	5.0	12.0
2009	35.8	29.3	42.9	35.8	29.3	42.9	7.9	4.8	12.7
2010	30.5	24.5	37.2	25.5	19.9	32.0	8.0	5.0	12.7
2011	27.2	19.8	36.1	24.6	17.5	33.3	2.7	0.9	7.9
2012	33.3	24.8	43.2	32.3	23.9	42.1	5.1	2.1	11.6
2013	27.2	19.1	37.1	27.2	19.1	37.1	3.4	1.1	10.2
2014	26.4	18.3	36.4	28.6	20.2	38.7	0.0	0.0	0.0
2015	22.3	15.3	31.4	19.4	12.9	28.2	2.3	0.6	8.6
2016	29.2	19.5	41.4	24.6	15.7	36.5	0.0	0.0	0.0
2017	35.8	25.3	47.9	25.4	16.4	37.1	0.0	0.0	0.0
2018	26.8	17.8	38.2	8.5	3.8	17.6	2.6	0.4	16.5

See Appendix Table 2.3 for antiretroviral drug-specific results.

Acquired integrase-inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on cART was relatively rare. The 144 integrase sequences that were available originated from 122 people who received cART for at least 4 months; 13 were pre-treated with monotherapy or dual therapy before initiating cART, and 109 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 9.0 years (IQR 2.9-13.9). 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 24 out of 122 people, which resulted in high-level resistance to at least one integrase inhibitor[24,25]. Among these 24 individuals, the following major INSTI resistance mutations were detected: N155H (n=10) and N155H/N (n=2); Y143R (n=3) and Y143Y/C (n=1); T66T/A (n=2), T66T/K (n=1), T66I (n=1); E92Q (n=3) and E92E/Q (n=1); Q148H (n=1, in combination with the G140S minor mutation); and R263K (n=1). Minor mutations detected were at position T66 (T66T/A, n=2), L74 (any mutation, n=6; L74I, n=5; L74M, n=1), T97 (any, n=2; T97A, n=2) and G140S (n=1).

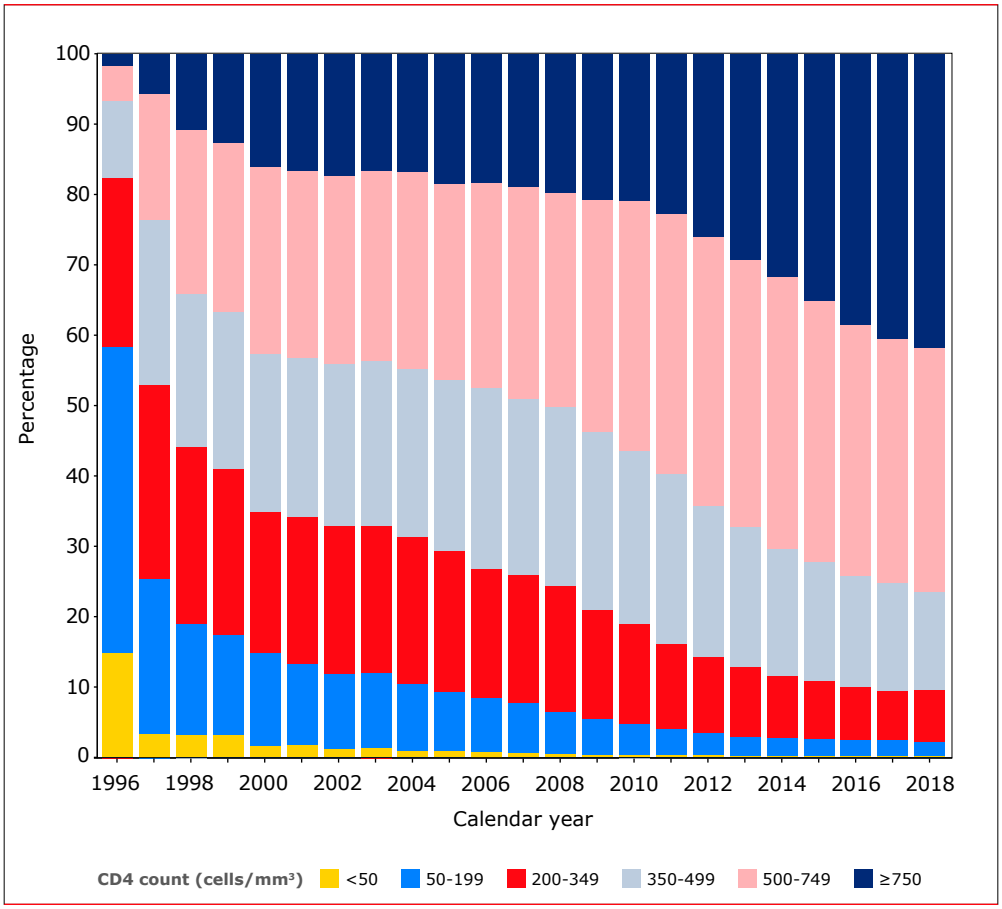
Immunological response

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[29,30,31,32,33]. 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[20]. 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 24,603 people known to have initiated cART between January 1996 and December 2018, CD4 cell count data were available after cART initiation for 24,037 (97.7%). *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 33.1% in 2002, 14.6% in 2012 and 9.7% in 2018 (*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 2,124 in 2009, to 1,744 in 2013, and 1,371 in 2018; see *Appendix Figure 2.3*. The drop in absolute number of people with low CD4 cell counts at the end of each calendar year, which has been observed since 2007, reflects the trend of starting cART at higher CD4 cell counts, more pronounced immune recovery with longer cART use, but also attrition due to the higher mortality rates in those with low CD4 counts.

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

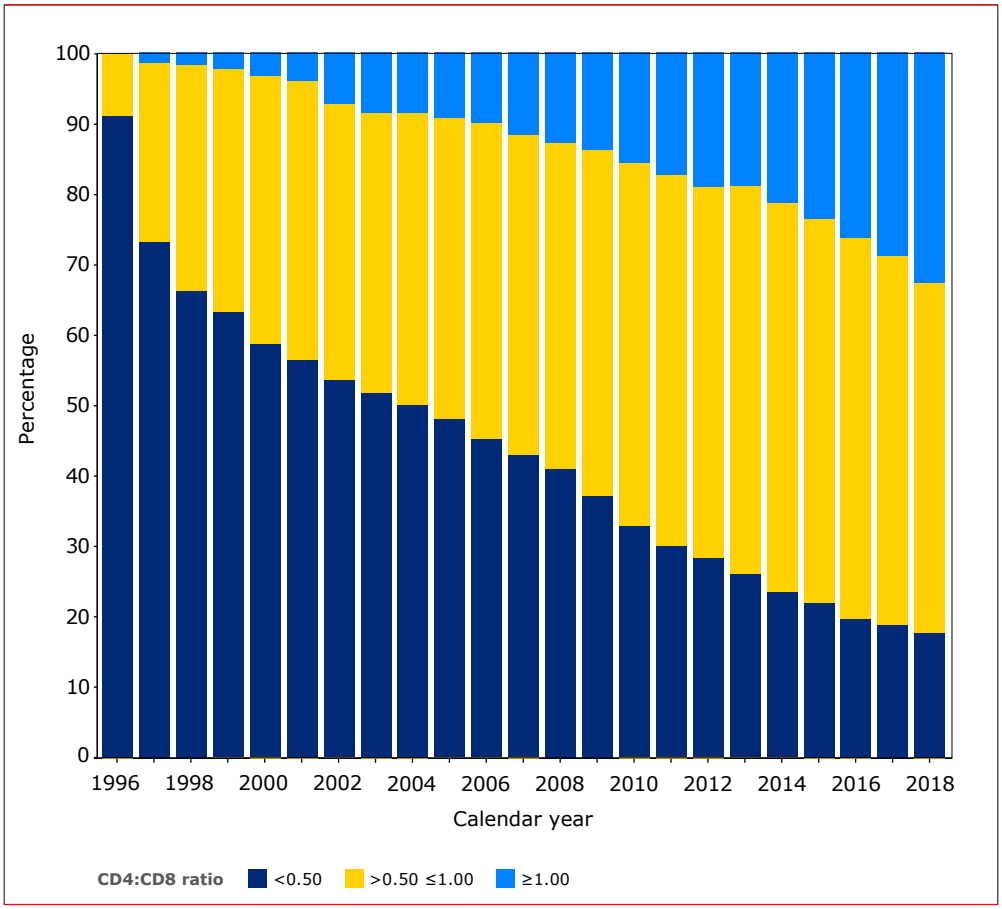


Legend: For each person, the last available CD4 cell count between January and December of each year, after starting cART, was selected (missing measurements/data not taken into account). Figures for 2018 may change slightly because data collection is not yet complete.

The percentage of those with a CD4:CD8 ratio of 1 or above increased from 2.4% in 1996-2001, to 9.1% in 2002-2007, to 15.6% in 2008-2012 and 25.0% in 2013-2018 (*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, 11.5% had a CD4 count of less than 500 cells/mm³, 33.1% had a CD4 count between 500-749 cells/mm³ and 55.5% had a CD4 count of ≥750 cells/mm³. When the CD4:CD8 ratio was ≥1, the median CD4 count was 780 cells/mm³ (IQR 610-990), and

remained fairly stable over time, with a median of 771 cells/mm^3 (IQR 596-1,010) in 1996-2001, 750 cells/mm^3 (IQR 570-961) in 2002-2007, median 730 cells/mm^3 (IQR 570-930) in 2008-2012 and median 810 cells/mm^3 (IQR 640-1,007) in 2013-2018.

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 (2013–2018)

We assessed the immunological response in people who started cART in more recent years: 5,528 people started cART in 2013-2018, 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 5,528 people who started cART in 2013-2018 and had sufficient immunological data available, 7.8% had CD4 counts <50 cells/mm^3, 13.5% had between 50 and 199 cells/mm^3, 20.1% had between 200 and 349 cells/mm^3, 25.8% had between 350 and 499 cells/mm^3, and 32.8% 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 normalisation of the CD4:CD8 ratio is strongly related to baseline CD4 cell count[46].

Figure 2.17: CD4 cell count over time after the start of combination antiretroviral therapy (cART) in 2013–2018.

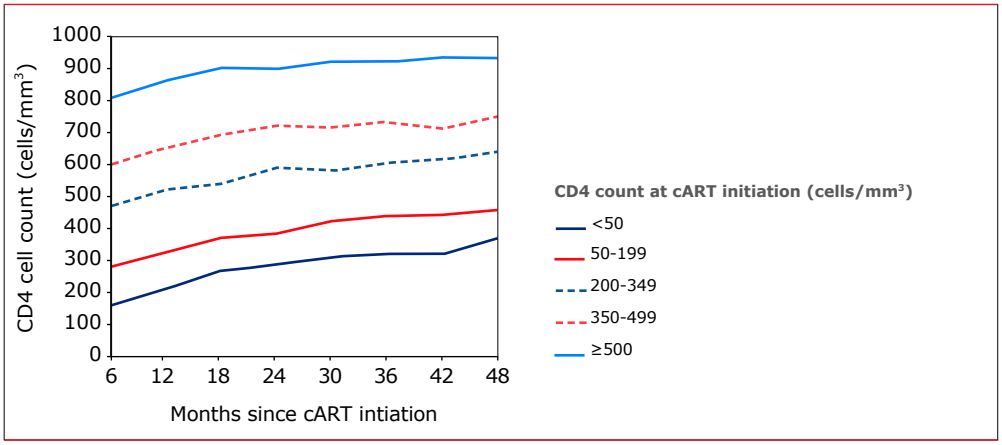
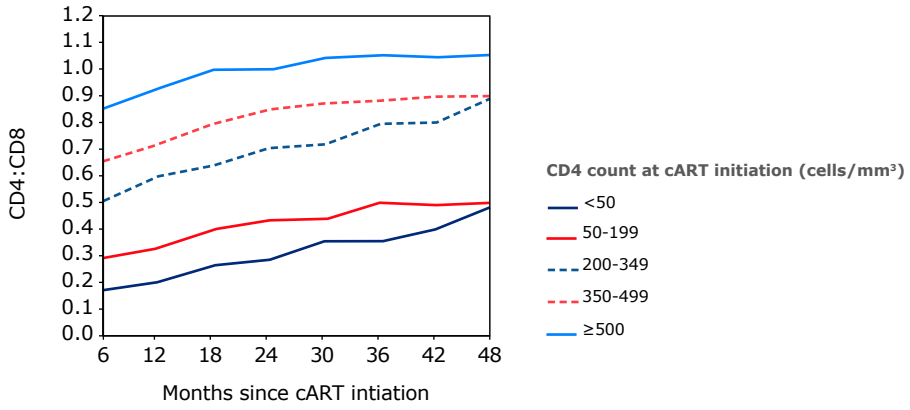


Figure 2.18: CD4:CD8 ratio over time after the start of combination antiretroviral therapy (cART) in 2013–2018.



Note: The presented immunological outcomes are based on available test results. For people with a low to moderate CD4 cell count (<350 cells/mm³), CD4 cell count testing is recommended at least twice a year[47]. When a person has a CD4 cell count >350 cells/mm³, 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 and peaked at a median of 420 cells/mm³ (IQR 220-600) in 2015, when new guidelines came out recommending rapid initiation of cART at any CD4 count. These changes in guidelines resulted in substantial numbers of individuals with preserved CD4 counts who, until that time, had postponed starting cART and who subsequently decided to initiate treatment. Since then, the median CD4 count at start of cART has decreased somewhat. Among HIV-positive individuals starting cART in 2018, the median CD4 cell count was 330 cells/mm³ (IQR 116-564). Immunological recovery was strongly related to the CD4 cell count at the start of cART.
- In 2018, the majority of individuals initiating cART did so within a month after diagnosis. Most persons who initiated cART in 2018 received TAF/FTC/EVG/c or ABC/3TC/DTG.

- 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 2018

- Integrase inhibitor-based cART has been further implemented on a large scale in the Netherlands. Integrase inhibitor-based cART was prescribed to 46% of those in care in 2018, compared with 39% in 2016[48].
- While 35% of the population on cART received TDF, newly-available fixed-dose combinations led to an increase in the prescription of ABC/3TC (23%) and TAF/FTC (33%) as the backbone.
- Of those receiving cART for at least 12 months and who had a plasma HIV RNA measurement in 2018, 98% had a viral load less than 200 copies/ml. Long-term survivors (i.e., individuals in care in 2018 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[49,50].
- Transmitted drug resistance is rare, and the overall prevalence is low and stable over time, in line with reported rates from other European countries[51].
- Integrase inhibitor resistance data are limited. No transmitted integrase inhibitor resistance was detected among 25 people tested up to 2018. Detected rates of acquired integrase inhibitor resistance among available sequences were very low, with only a few sequences showing major resistance to dolutegravir.

Immunological response

- After starting cART, the percentage of people with CD4 cell counts <350 cells/mm^3 dropped from 53.1% in 1997 to 33.1% in 2002, 14.6% in 2012 and 9.7% in 2018.
- The percentage of people with a CD4:CD8 ratio of 1 or above increased from 2.4% in 1996-2001, to 9.1% in 2002-2007, to 15.6% in 2008-2012 and 25.0% in 2013-2018.

References

1. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA*. 2016;316(2):171-181. doi:10.1001/jama.2016.5148
2. Cole SR, Hernan MA, Robins JM, et al. Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. *Am J Epidemiol*. 2003;158(7):687-694. doi:10.1093/aje/kwg206
3. European AIDS Clinical Society. European AIDS Clinical Society (EACS) Guidelines. *Version 9*. 2017;(October):72. doi:10.1002/oby.21371.
4. Shilaih M, Marzel A, Yang WL, et al. Genotypic resistance tests sequences reveal the role of marginalized populations in HIV-1 transmission in Switzerland. *Sci Rep*. 2016;6(May):27580. doi:10.1038/srep27580
5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Published 2016. Accessed July 14, 2016.
6. World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection.*; 2016.
7. Ryom L, Boesecke C, Bracchi M, et al. Highlights of the 2017 European AIDS Clinical Society (EACS) Guidelines for the treatment of adult HIV-positive persons version 9.0. *HIV Med*. 2018:1-7. doi:10.1111/hiv.12600
8. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis*. 2014;14(4):281-290. doi:10.1016/S1473-3099(13)70692-3
9. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *N Engl J Med*. 2011;365(6):493-505. doi:10.1056/NEJMoa1105243
10. Prevention Access Campaign. Consensus Statement: Risk of sexual transmission of HIV from a person living with HIV who has an undetectable viral load - Messaging Primer & Consensus Statement. 2017.
11. Nederlandse Vereniging van HIV Behandelaren. Het risico om hiv over te dragen is verwaarloosbaar klein indien de infectie goed behandeld wordt. May 3. http://nvhb.nl/2017/05/03/wetenschappelijk-onderzoek-toont-aan-dat-het-risico-om-hiv-over-te-dragen-verwaarloosbaar-klein-is-indien-de-infectie-goed-behandeld-wordt/. Published 2017.

12. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. 2000;342(13):921-929. doi:10.1056/NEJM200003303421303
13. Tovanabutra S, Robison V, Wongtrakul J, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. *J Acquir Immune Defic Syndr*. 2002;29(3):275-283.
14. Reynolds SJ, Makumbi F, Nakigozi G, et al. HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. *AIDS*. 2011;25(4):473-477. doi:10.1097/QAD.0b013e3283437c2b
15. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: Two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385(9987):2606-2615. doi:10.1016/S0140-6736(15)60616-X
16. Nederlandse Vereniging van HIV Behandelaren. 2.2. Keuze van antiretrovirale therapie bij naïeve volwassen patiënten. http://richtlijnhiv.nvhb.nl/index.php/2.2._Keuze_van_antiretrovirale_therapie_bij_naïeve_volwassen_patiënten. Published 2017.
17. Raboud JM, Rae S, Woods R, et al. Consecutive rebounds in plasma viral load are associated with virological failure at 52 weeks among HIV-infected patients. *AIDS*. 2002;16(12):1627-1632. doi:10.1097/00002030-200208160-00008
18. Karlsson AC, Younger SR, Martin JN, et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. *AIDS*. 2004;18(7):981-989. doi:10.1097/01.aids.0000125906.75228.f5
19. Hughes RA, Sterne JAC, Walsh J, et al. Long-term trends in CD4 cell counts and impact of viral failure in individuals starting antiretroviral therapy: UK Collaborative HIV Cohort (CHIC) study. *HIV Med*. 2011;12(10):583-593. doi:10.1111/j.1468-1293.2011.00929.x
20. van Lelyveld SF, Gras L, Kesselring A, et al. Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS*. 2012;26(4):465-474.
21. Zhang S, van Sighem A, Gras L, et al. Clinical significance of transient HIV type-1 viraemia and treatment interruptions during suppressive antiretroviral treatment. *Antivir Ther*. 2010;15(4):555-562.
22. Easterbrook PJ, Ives N, Waters A, et al. The natural history and clinical significance of intermittent viraemia in patients with initial viral suppression to <400 copies/ml. *AIDS*. 2002;16(11):1521-1527. doi:10.1097/00002030-200207260-00009
23. Raffanti SP, Fusco JS, Sherrill BH, et al. Effect of persistent moderate viremia on disease progression during HIV therapy. *J Acquir Immune Defic Syndr*. 2004;37(1):1147-1154. doi:00126334-200409010-00005 [pii]

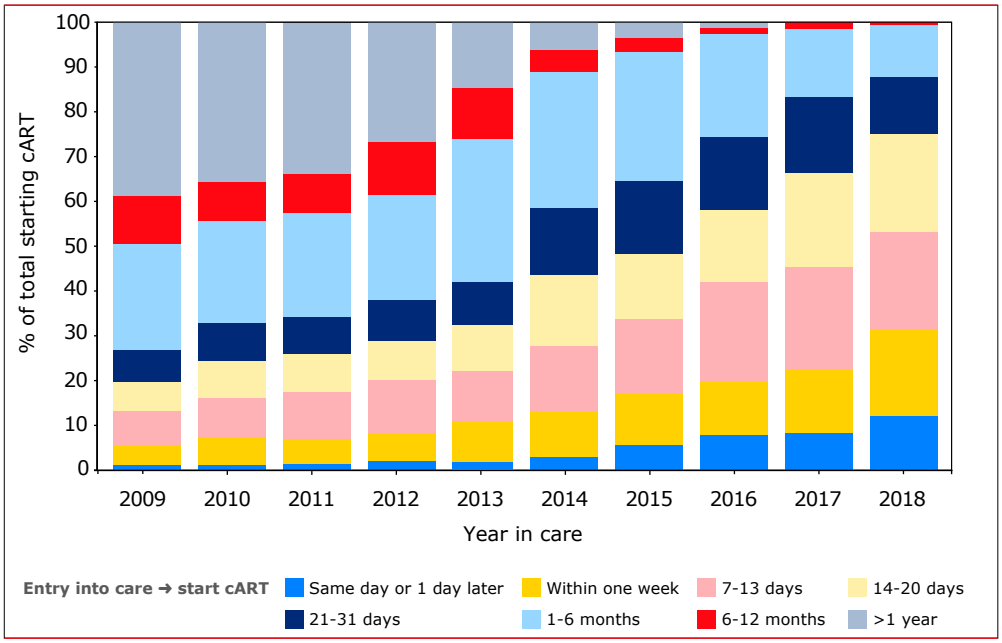
24. Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. *Resist Mut Update 2019;27(3) [In press]*
25. Stanford University. HIV Drug Resistance Database - Release Notes. https://hivdb.stanford.edu/page/release-notes/. Accessed September 18, 2017.
26. Liu TF, Shafer RW. Web resources for HIV type 1 genotypic-resistance test interpretation. *Clin Infect Dis*. 2006;42(11):1608-1618. doi:10.1086/503914
27. World Health Organization. *HIV Drug Resistance Report 2017*. Geneva: World Health Organization; 2017.
28. Barbour JD, Hecht FM, Wrin T, et al. Persistence of primary drug resistance among recently HIV-1 infected adults. *AIDS*. 2004;18(12):1683-1689.
29. Little SJ, Frost SDW, Wong JK, et al. Persistence of Transmitted Drug Resistance among Subjects with Primary Human Immunodeficiency Virus Infection. *J Virol*. 2008;82(11):5510-5518. doi:10.1128/JVI.02579-07
30. Bezemer D, De Ronde A, Prins M, et al. Evolution of transmitted HIV-1 with drug-resistance mutations in the absence of therapy: Effects on CD4+ T-cell count and HIV-1 RNA load. *Antivir Ther*. 2006;11(2):173-178.
31. Boukli N, Boyd A, Collot M, Meynard J-L, Girard P-M, Morand-Joubert L. Utility of HIV-1 DNA genotype in determining antiretroviral resistance in patients with low or undetectable HIV RNA viral loads. *J Antimicrob Chemother*. 2018;73(11):3129-3136. doi:10.1093/jac/dky316
32. Lange JM, Ananworanich J. The discovery and development of antiretroviral agents. *Antivir Ther*. 2014;19 Suppl 3:5-14. doi:10.3851/IMP2896
33. Gras L, Kesselring AM, Griffin JT, et al. CD4 cell counts of 800 cells/mm3 or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm3 or greater. *J Acquir Immune Defic Syndr*. 2007;45(2):183-192. doi:10.1097/QAI.0b013e31804d685b
34. Tsegaye A, Messele T, Tilahun T, et al. Immunohematological reference ranges for adult Ethiopians. *Clin Diagn Lab Immunol*. 1999;6(3):410-414.
35. Serrano-Villar S, Moreno S, Fuentes-Ferrer M, et al. The CD4:CD8 ratio is associated with markers of age-associated disease in virally suppressed HIV-infected patients with immunological recovery. *HIV Med*. 2014;15(1):40-49. doi:10.1111/hiv.12081
36. Serrano-Villar S, Pérez-Elías MJ, Dronda F, et al. Increased risk of serious non-AIDS-related events in HIV-infected subjects on antiretroviral therapy associated with a low CD4/CD8 ratio. *PLoS One*. 2014;9(1). doi:10.1371/journal.pone.0085798
37. Serrano-Villar S, Sainz T, Lee SA, et al. HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8+ T cell activation, and increased risk of non-AIDS morbidity and mortality. *PLoS Pathog*. 2014;10(5):e1004078. doi:10.1371/journal.ppat.1004078

38. Lo J, Abbara S, Shturman L, et al. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. *AIDS*. 2010;24(2):243-253. doi:10.1097/QAD.0b013e328333ea9e
39. O'Connor J, Smith C, Lampe FC, et al. Durability of viral suppression with first-line antiretroviral therapy in patients with HIV in the UK: an observational cohort study. *Lancet HIV*. 2017;3018(17):1-8. doi:10.1016/S2352-3018(17)30053-X
40. The Antiretroviral Therapy Cohort Collaboration (ART-CC). Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *Lancet HIV*. 2017;3018(17). doi:http://dx.doi.org/10.1016/
41. Effros RB, Fletcher C V, Gebo K, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. *Clin Infect Dis*. 2008;47(4):542-553. doi:10.1086/590150
42. Baker J V, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS*. 2008;22(7):841-848. http://www.ncbi.nlm.nih.gov/pubmed/18427202.
43. Baker J V, Peng G, Rapkin J, et al. Poor initial CD4+ recovery with antiretroviral therapy prolongs immune depletion and increases risk for AIDS and non-AIDS diseases. *JAIDS J Acquir Immune Defic Syndr*. 2008;48(5):541-546. doi:10.1097/QAI.0b013e31817bebb3
44. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008;372(9635):293-299. doi:10.1016/S0140-6736(08)61113-7
45. Lanoy E, May M, Mocroft A, et al. Prognosis of patients treated with cART from 36 months after initiation, according to current and previous CD4 cell count and plasma HIV-1 RNA measurements. *AIDS*. 2009;23(16):2199-2208. doi:10.1097/QAD.0b013e3283305a00
46. Hughes RA, May MT, Tilling K, et al. Long-term trends in CD4 cell counts, CD8 cell counts, and the CD4. *Aids*. 2018;32:1361-1367. doi:10.1097/QAD.0000000000001848
47. Nederlandse Vereniging van HIV Behandelaren. 4.1. Controles HIV-patiënten (polikliniek). Richtlijn HIV.
48. Boender TS, Sighem A van, Wit F, et al. Response to combination antiretroviral therapy (cART). In: *Human Immunodeficiency Virus (HIV) Infection in the Netherlands*. Amsterdam, the Netherlands: Stichting HIV Monitoring; 2016:48-93.
49. Scherrer AU, von Wyl V, Yang W-L, et al. Emergence of acquired HIV-1 drug resistance almost stopped in Switzerland: A 15-year prospective cohort analysis. *Clin Infect Dis*. 2016;62(10):1310-1317. doi:10.1093/cid/ciw128

50. Buchacz K, Baker R, Ward DJ, et al. Trends in decline of antiretroviral resistance among ARV-experienced patients in the HIV outpatient study: 1999-2008. *AIDS Res Treat*. 2012;2012. doi:10.1155/2012/230290
51. Hofstra LM, Sauvageot N, Albert J, et al. Transmission of HIV drug resistance and the predicted effect on current first-line regimens in Europe. *Clin Infect Dis*. 2016;62(5):655-663. doi:10.1093/cid/civ963

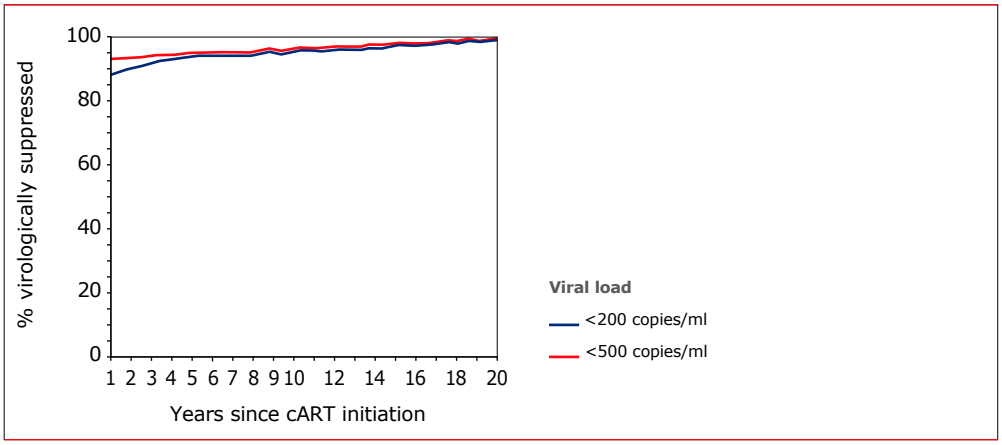
Appendix: supplementary figures and tables

Appendix Figure 2.1: Time between entry into HIV care and initiation of combination antiretroviral therapy (cART) of people starting cART in 2009–2018.



Legend: cART=combination antiretroviral therapy.

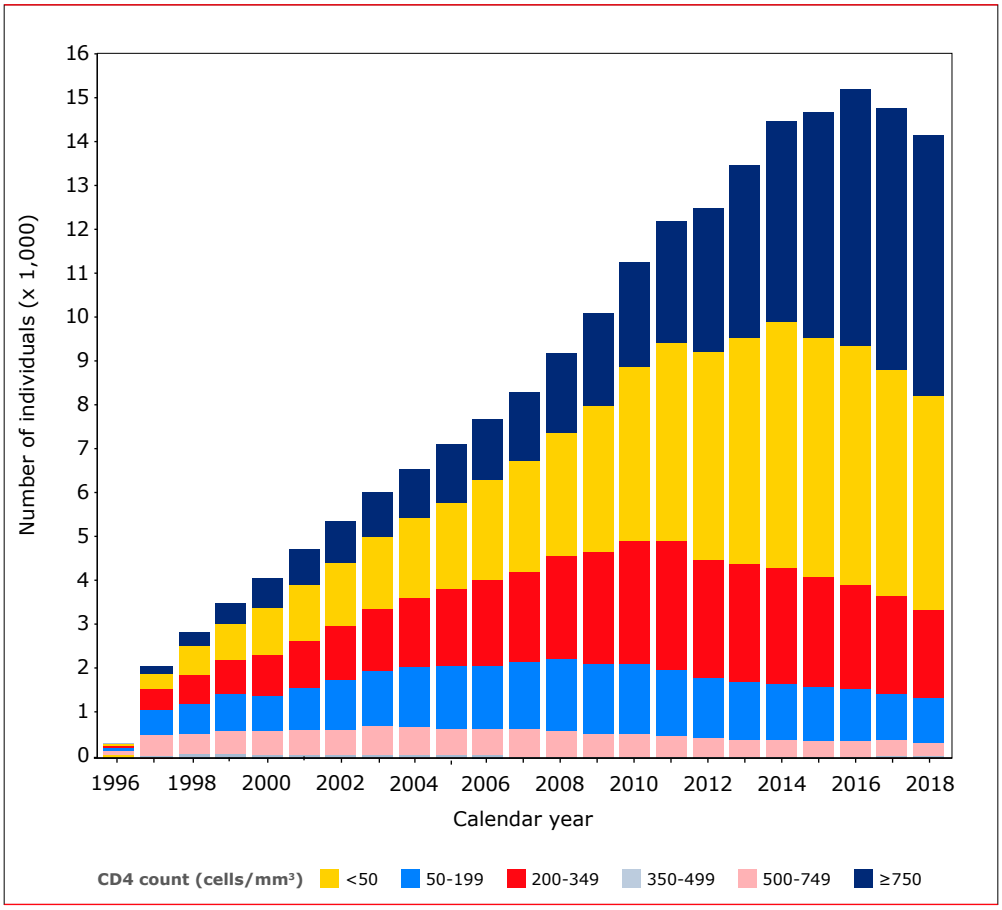
Appendix Figure 2.2: Viral suppression since initiation of combination antiretroviral therapy.



Legend: cART=combination antiretroviral therapy.

< Back to page 82

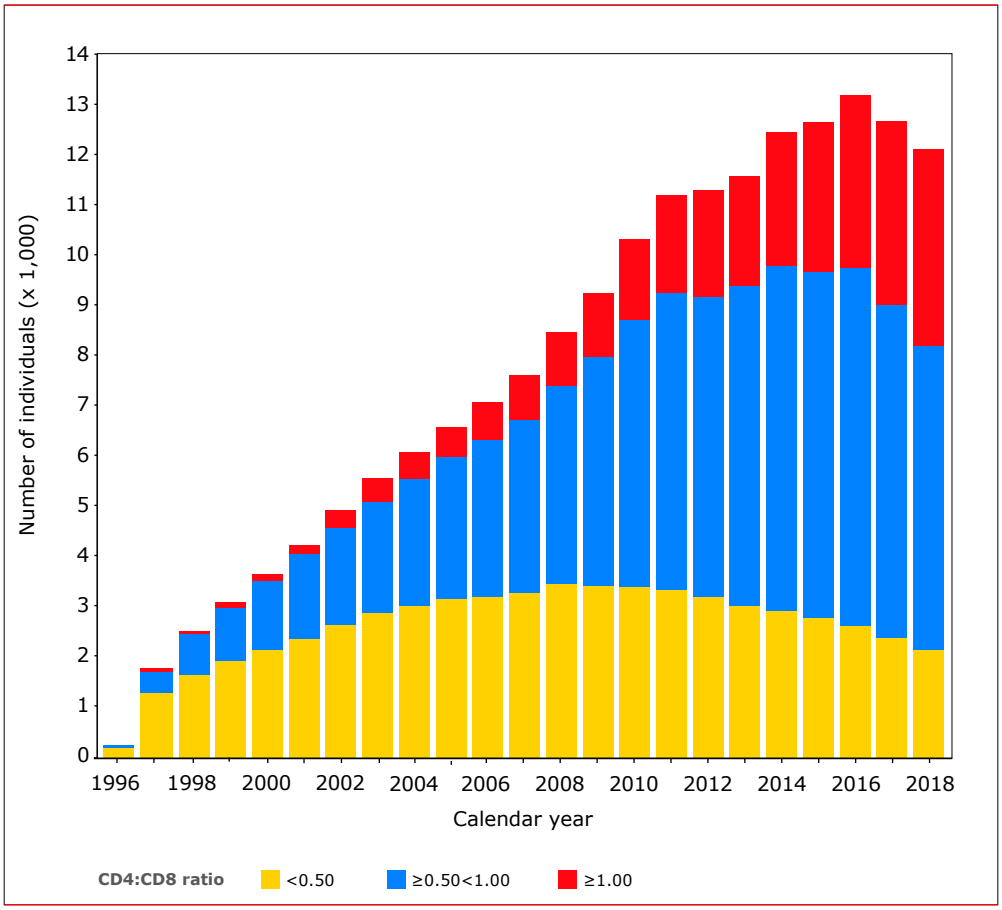
Appendix Figure 2.3: *Last available CD4 cell count (cells/mm³) in each calendar year after the start of combination antiretroviral therapy.*



Note: Numbers for 2018 may increase slightly because data collection is not yet complete.

< Back to page 121

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



Note: Numbers for 2018 may increase slightly because data collection is not yet complete.

< Back to page 122

Appendix Table 2.1: *Combination antiretroviral therapy (cART) regimen used by long-term HIV survivors in 2018.*

cART regimen	n	%
TDF/FTC/EFV	104	5.4
TDF/FTC/NVP	162	8.4
TDF/FTC/RPV	40	2.1
TDF/FTC/DRV/b	69	3.6
TDF/FTC/ATV/r	41	2.1
TDF/FTC/LPV/r	5	0.3
TDF/FTC/EVG/c	21	1.1
TDF/FTC/DTG	38	2.0
TDF/FTC/RAL	16	0.8
ABC/3TC/DTG	162	8.4
TAF/FTC/EVG/c	174	9.1
TAF/FTC/RPV	53	2.8
TAF/FTC/DTG	47	2.5
TAF/FTC/DRV/c	74	3.9
TAF/FTC/BIC	18	0.9
Other: 2NRTI+NNRTI	270	14.1
Other: 2NRTI+PI	83	4.3
Other: 2NRTI+INST	35	1.8
Other: NNRTI+INST	7	0.4
Other: PI+INSTI	102	5.3
Other: NRTI+PI+INSTI(3ARVs)	42	2.2
Other: NRTI+PI+INSTI(4ARVs)	79	4.1
Other	277	14.4
Total	**1,919**	**100**

Legend: *ARVs=antiretroviral drugs; /b=boosted cobicistat or ritonavir; /r=ritonavir-boosted; /c=cobicistat-boosted; 3TC=lamivudine; cART=combination antiretroviral therapy; ABC=abacavir; ATV=atazanavir; BIC=bictegravir; 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.*

< Back to page 90

Appendix Table 2.2: CD4 cell count at combination antiretroviral therapy (cART) initiation by calendar year 2013–2018.

Year of cART initiation	2013	2014	2015	2016	2017	2018	Total (2013–2018)
CD4 cell count available at cART initiation	1,366	1,334	1,074	862	668	224	**5,528**
CD4 cell count, median cells/mm³ (IQR)	370 (250–510)	410 (270–567)	420 (220–600)	410 (230–579)	370 (181–550)	330 (116–564)	**390 (230–560)**
CD4 cell count (cells/mm³)							
<50	92	74	86	79	60	38	**429**
	(6.7)	(5.6)	(8.0)	(9.2)	(9.0)	(17.0)	
50–199	163	161	161	109	116	37	**747**
	(11.9)	(12.1)	(15.0)	(12.7)	(17.4)	(16.5)	
200–349	341	257	180	157	136	41	**1,112**
	(25.0)	(19.3)	(16.8)	(18.2)	(20.4)	(18.3)	
350–499	408	380	249	201	148	42	**1,428**
	(29.9)	(28.5)	(23.2)	(23.3)	(22.2)	(18.8)	
≥500	362	462	398	316	208	66	**1,812**
	(26.5)	(34.6)	(37.1)	(36.7)	(31.4)	(29.5)	

< Back to page 124

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	64	60.9	10.3	7.4	3.6	10.3	0.0
2001	86	69.0	17.1	17.8	7.5	16.7	3.8
2002	146	67.1	10.9	14.6	10.7	17.8	3.6
2003	192	64.2	18.5	24.4	16.4	23.5	6.8
2004	178	65.7	17.7	23.1	19.7	26.3	7.5
2005	158	51.9	13.7	17.9	13.8	18.3	4.6
2006	162	50.0	9.3	14.8	10.4	18.9	6.6
2007	188	43.8	8.9	12.8	12.3	13.1	4.9
2008	231	39.6	7.4	11.0	7.9	14.1	3.7
2009	190	34.0	6.7	9.6	5.8	10.2	2.7
2010	200	29.1	5.8	8.0	5.5	9.1	2.6
2011	114	25.0	0.9	2.8	4.6	8.1	1.8
2012	99	33.3	0.0	2.1	6.4	8.2	1.1
2013	93	27.2	0.0	2.3	5.6	5.6	2.2
2014	91	25.6	1.1	2.3	2.3	3.4	1.1
2015	109	24.5	0.9	2.9	3.8	6.5	1.9
2016	73	37.0	1.4	1.4	5.8	5.8	1.4
2017	70	34.3	2.9	7.5	4.7	13.4	4.4
2018	74	29.7	0.0	0.0	5.5	5.4	0.0

< Back to page 117

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

Calendar year	Number of sequences	Nevirapine	Efavirenz	Etravirine	Rilpivirine
2000	64	27.4	17.5	1.9	13.3
2001	86	30.6	25.0	1.3	10.6
2002	146	40.0	29.7	0.0	15.4
2003	192	41.3	34.9	0.6	18.2
2004	178	52.0	44.9	5.4	21.2
2005	158	41.8	35.9	0.7	19.6
2006	162	53.1	43.9	2.4	18.8
2007	188	37.3	29.6	1.3	15.8
2008	231	39.2	34.2	2.0	14.4
2009	190	36.0	31.1	2.9	11.6
2010	200	26.2	21.5	2.2	10.0
2011	114	23.9	18.7	1.0	7.3
2012	99	32.3	28.0	2.2	7.6
2013	93	27.5	22.7	2.4	11.1
2014	91	29.2	26.1	0.0	2.3
2015	109	18.1	10.9	3.0	9.5
2016	73	19.7	14.7	0.0	7.1
2017	70	24.6	15.9	0.0	8.8
2018	74	8.1	5.6	0.0	2.7

C) High-level resistance to protease inhibitors.

Calendar year	Number of sequences	Nelfinavir	Saquinavir	Indinavir	Atazanavir	Fosam-prenavir	Lopinavir	Tipranavir	Darunavir
2000	64	48.4	8.1	5.1	6.6	6.3	3.3	1.6	0.0
2001	86	47.1	21.3	18.1	17.5	13.6	11.0	2.5	0.0
2002	146	29.9	10.1	6.7	5.8	5.1	4.2	0.0	0.0
2003	192	16.8	9.2	9.8	9.5	7.5	8.0	1.6	0.0
2004	178	15.4	6.5	6.6	6.9	5.2	4.7	0.6	0.0
2005	158	17.1	4.2	6.8	4.0	3.4	4.0	0.7	0.0
2006	162	13.0	5.7	7.5	7.0	5.1	6.8	2.5	0.0
2007	188	9.2	4.4	4.4	6.4	3.2	2.7	1.1	0.0
2008	231	6.6	3.5	4.9	4.4	4.8	3.6	0.4	0.0
2009	190	7.5	3.7	4.3	4.3	4.3	2.7	1.1	0.0
2010	200	6.6	3.1	4.1	3.0	4.1	1.6	0.0	0.0
2011	114	2.6	0.9	0.9	0.9	0.9	0.9	0.0	0.0
2012	99	5.1	2.1	2.1	2.0	2.0	2.0	0.0	0.0
2013	93	3.2	0.0	1.1	1.1	2.2	1.1	0.0	0.0
2014	91	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2015	109	1.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2016	73	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2017	70	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2018	74	1.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0

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

Ferdinand Wit, Marc van der Valk, and Peter Reiss

Introduction

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 is the case in HIV-negative individuals, traditional risk factors (e.g., tobacco use[19], alcohol abuse, and viral hepatitis co-infection[20]) also importantly contribute to the increased risk of certain non-AIDS comorbidities in people living with HIV.

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: 26,029 adults and an additional 406 individuals who were diagnosed with HIV as children and have since become adults, now totalling 26,435 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 having experienced any Centers for Disease Control (CDC) category C condition[23]). In contrast to what is usual in the United States, in our analyses a CD4 count below 200 cells/mm^3 in the absence of an AIDS-defining condition does not qualify as AIDS.

Diabetes mellitus, CVD (including myocardial infarction, stroke, coronary artery bypass grafting, coronary angioplasty or stenting, and carotid endarterectomy), and 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 Data Collection on Adverse Events of Anti-HIV Drugs (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 episodes of renal dysfunction that revert shortly after 3 months, and which do not represent true CKD.

Methods

For the analyses of incidence per calendar year and calendar 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 2011-2018, and standardised these according to the age distribution of the population during the period 2011-2018 (divided into the following 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

populations (period: 2011-2018) 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, having started cART within 12 months of being diagnosed with HIV, known time spent with CD4 count <200 cells/mm^3, known time spent 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.

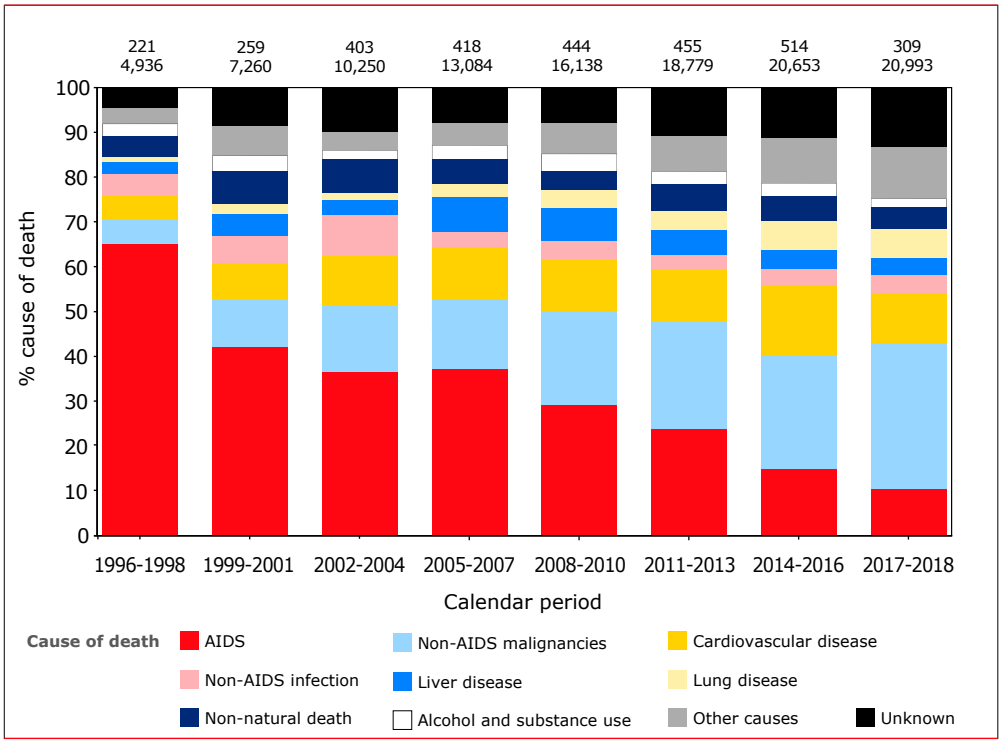
Mortality and AIDS

From 1996 onwards, the overall mortality rate in all 26,435 HIV-1-positive adults ever registered in the SHM database was 18.2 (95% confidence interval (CI) 13.5-23.9) per 1,000 person years of follow up (PYFU) in 1996 which declined to 8.4 (95% CI 7.1-9.9) per 1,000 PYFU in 2018 (*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 4.3 per 1,000 PYFU in 2018, when matched in terms of age and gender to our HIV-positive population. In the same group of 26,435 individuals, the incidence of AIDS decreased sharply from 120.4 (95% CI 107.9-133.9) in 1996 to 6.7 (95% CI 5.5-8.0) cases per 1,000 PYFU in 2018 (*Appendix Figure 3.1B*). 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 decreased from 14.1 (95% CI 9.8-19.6) per 1,000 PYFU in 1996 to 7.5 (95% CI 6.2-9.1) per 1,000 PYFU in 2018.

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 driven largely by the high number of individuals still presenting late for care with already advanced immune deficiency. Individuals who died of AIDS had lower CD4 counts (median 110 cells/mm^3 (interquartile

range, IQR 30-215)) when entering care compared to individuals who died of another cause (median 281 cells/mm^3, IQR 111-510). Thirty-three per cent of all individuals who died of AIDS between 2016 and 2018 had a CD4 cell count <50 cells/mm^3 when entering care. 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 (70%) than among individuals who entered care with less than 50 CD4 cells/mm^3 (38.9%). The time between entry into care and death was significantly shorter in individuals who died of AIDS (median 3.3 years, IQR 0.6-8.7) than in individuals who died of a non-AIDS cause (median 8.9 years, IQR 4.5-14.9; p<0.001). Conversely, the proportion and absolute number of deaths due to non-AIDS-defining conditions have significantly increased over time (*Figure 3.1*), primarily as a consequence of the increasing size and average age of the Dutch HIV-positive population.

Figure 3.1: *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 total number of deaths and the total 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 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) before 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).

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 individuals not born in the Netherlands with the exception of those born in Surinam or the Dutch Antilles) having been lost to follow up (*Appendix Table 3.4*). In native Dutch individuals and those from Surinam and the Dutch Antilles, 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 22.5 events per 1,000 PYFU of follow up. *Appendix Table 3.5* gives an overview of the AIDS events occurring between 1996 and 2018. The most common AIDS events between 2011 and 2018 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 (5%), AIDS dementia complex/HIV encephalopathy (3%) and cytomegalovirus-associated end organ disease (2%). 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 (although the likelihood was even higher if 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 still detectable, we also analysed the incidence of CDC-B and AIDS-defining events in the period between 2000 and 2018 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, in other words, focusing 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 opportunistic infection prophylaxis was not accounted for in this analysis. Only 'definitive' or 'probable' diagnoses were considered; 'possible' events or events with incomplete ascertainment were excluded from the analysis. Between 1 January 2000 and 31 December 2018, 22,768 individuals contributed a total of 181.9 thousand PYFU, during which 3,060 HIV-related events were diagnosed, resulting in an incidence rate of 16.8 events per 1,000 PYFU (1,878 CDC-B events, 10.3 events/1,000 PYFU; 1,182 CDC-C/AIDS events, 6.5 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 5.5 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 3.3 (2.9-3.8) and 2.0 (1.6-2.5)/1,000 PYFU, respectively. Note that the incidence in the over 750 cells/mm^3 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 2018.

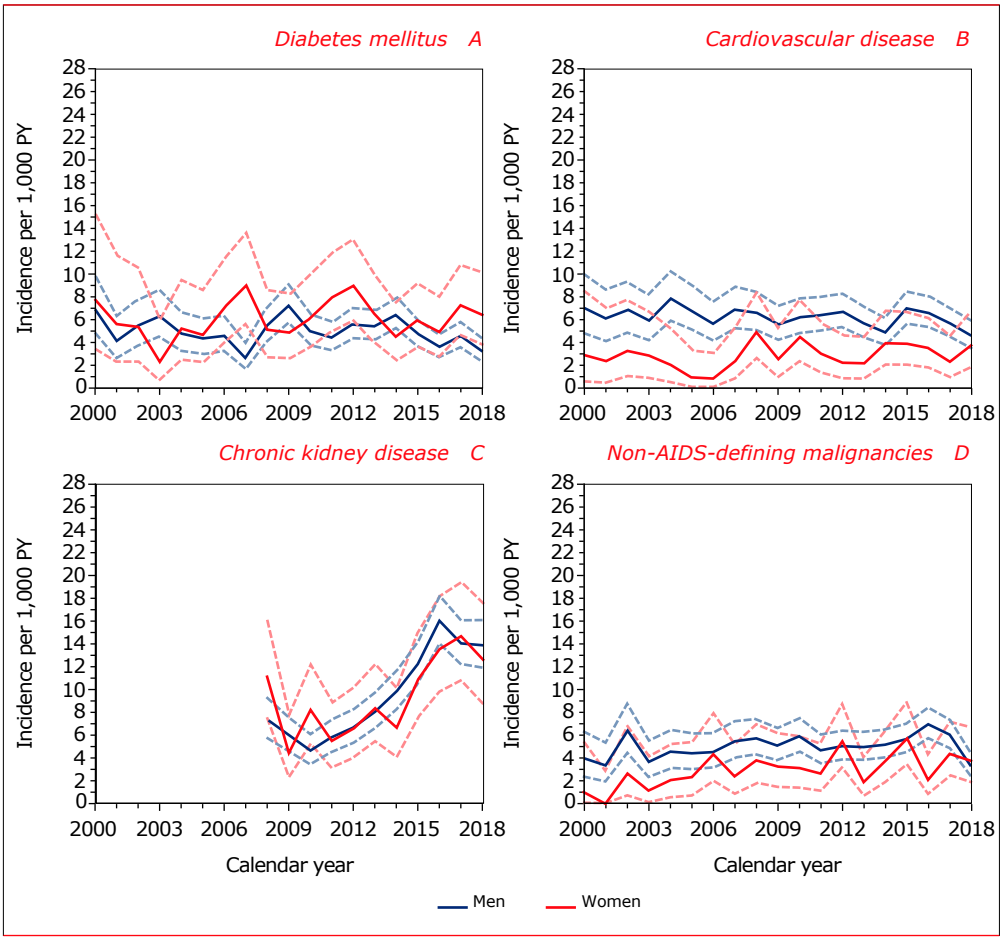
CD4 category (cells/mm³)	CDC events (n)	CDC-B events (n)	CDC-C events (n)	PYFU (x 1000)	Incidence rate CDC events (/1000 PY) (95% CI)	Incidence rate CDC-B events (/1000 PY) (95% CI)	Incidence rate CDC-C events (/1000 PY) (95% CI)
0-50	223	89	134	0.4	511 (446-583)	204 (164-251)	307 (257-364)
50-199	566	317	249	7.5	75.1 (69.0-81.5)	42.0 (37.5-46.9)	33.0 (29.1-37.4)
200-349	683	405	278	23.3	29.3 (27.2-31.6)	17.4 (15.7-19.2)	11.9 (10.6-13.4)
350-499	593	377	216	39.5	15.0 (13.8-16.3)	9.55 (8.61-10.6)	5.47 (4.77-6.25)
500-749	641	431	210	64.1	9.99 (9.24-10.8)	6.72 (6.10-7.39)	3.27 (2.85-3.75)
750+	354	259	95	47.0	7.53 (6.77-8.36)	5.51 (4.86-6.23)	2.02 (1.64-2.47)
Total	3,060	1,878	1,182	181.9	16.8 (16.2-17.4)	10.3 (9.86-10.8)	6.50 (6.13-6.88)

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 26,435 HIV-1-positive adults ever registered with SHM, 26,087 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 (separately for myocardial infarction and stroke), non-AIDS-defining malignancies (separately 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 26,087 individuals aged 18 years or older and in follow up in or after January 2000, a total of 1,248 (956 men and 292 women) were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.2A*) and, in 2018, was 3.2 (95% CI 2.3-4.3) per 1,000 PYFU of follow up in men and 6.4 (95% CI 3.8-10.1) 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 2011-2018 than in 2000-2005 and 2006-2010, whereas in women, the age standardised incidence in 2000-2005 and 2006-2010 was not significantly different from that in 2011-2018 (*Table 3.2*).

Demographic and clinical factors independently associated with an 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, a BMI greater than 25 kg/m^2 or below 18 kg/m^2, hypertension, a latest CD4 cell count below 200 cells/mm^3, pre-treatment with NRTIs prior to starting 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 2011-2018. 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 2011-2018 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	5.2 (4.5-6.1)	1.43 (1.23-1.64)	5.0 (3.7-6.6)	0.82 (0.59-1.06)
2006-2010	5.1 (4.5-5.8)	1.23 (1.08-1.39)	6.4 (5.1-7.9)	1.03 (0.81-1.25)
2011-2018	4.8 (4.4-5.2)	1 (reference)	6.5 (5.6-7.6)	1 (reference)

**Standardised according to the observed age distribution between 2011-2018.*

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

Cardiovascular disease

From January 2000 onwards, 1,340 individuals (1,197 men and 143 women) had a fatal or non-fatal cardiovascular event (688 had myocardial infarction, 476 stroke, 96 coronary artery bypass graft, 478 coronary angioplasty or stenting, and 11 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 2011-2018 (*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, having been pre-treated with NRTIs before starting 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 2011-2018, 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 in the model, the abacavir effect was only slightly attenuated, decreasing from an incidence risk ratio (IRR) of 1.56 to one of 1.42, p<0.001. Having an eGFR below 90 ml/min was independently associated with a higher risk of CVD; at 60-90 ml/min, the IRR was 1.07 (95% CI 0.93-1.24), p=0.35; at 30-60 ml/min the IRR was 1.80 (1.44-2.25), p<0.001; at 15-30 ml/min, the IRR was 4.21 (2.67-6.63) p<0.001; and at 0-15 ml/min the IRR was 4.42 (2.41-8.13), p<0.001.

From January 2000 onwards, 169 men and 14 women experienced a fatal or non-fatal secondary cardiovascular event (116 had myocardial infarction, 74 had stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2018 in men and women with a prior cardiovascular event was 27.9 (95% CI 23.9-32.4) and 17.2 (95% CI 9.4-28.9), 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: 36.4 events per 1,000 PYFU; SIR: 1.49, 95% CI 0.99-1.98) and 2006-2010 (crude rate: 28.2 events per 1,000 PYFU; SIR: 1.15, 95% CI 0.81-1.49) compared with the reference period 2011-2018 (crude rate: 23.9 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 2011–2018 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	6.8 (6.0–7.8)	1.70 (1.48–1.91)	2.3 (1.4–3.5)	1.07 (0.62–1.52)
2006–2010	6.2 (5.5–6.9)	1.29 (1.15–1.44)	3.1 (2.2–4.3)	1.26 (0.87–1.64)
2011–2018	6.0 (5.5–6.5)	1 (reference)	3.1 (2.5–3.9)	1 (reference)

**Standardised according to the observed age distribution between 2011–2018.*

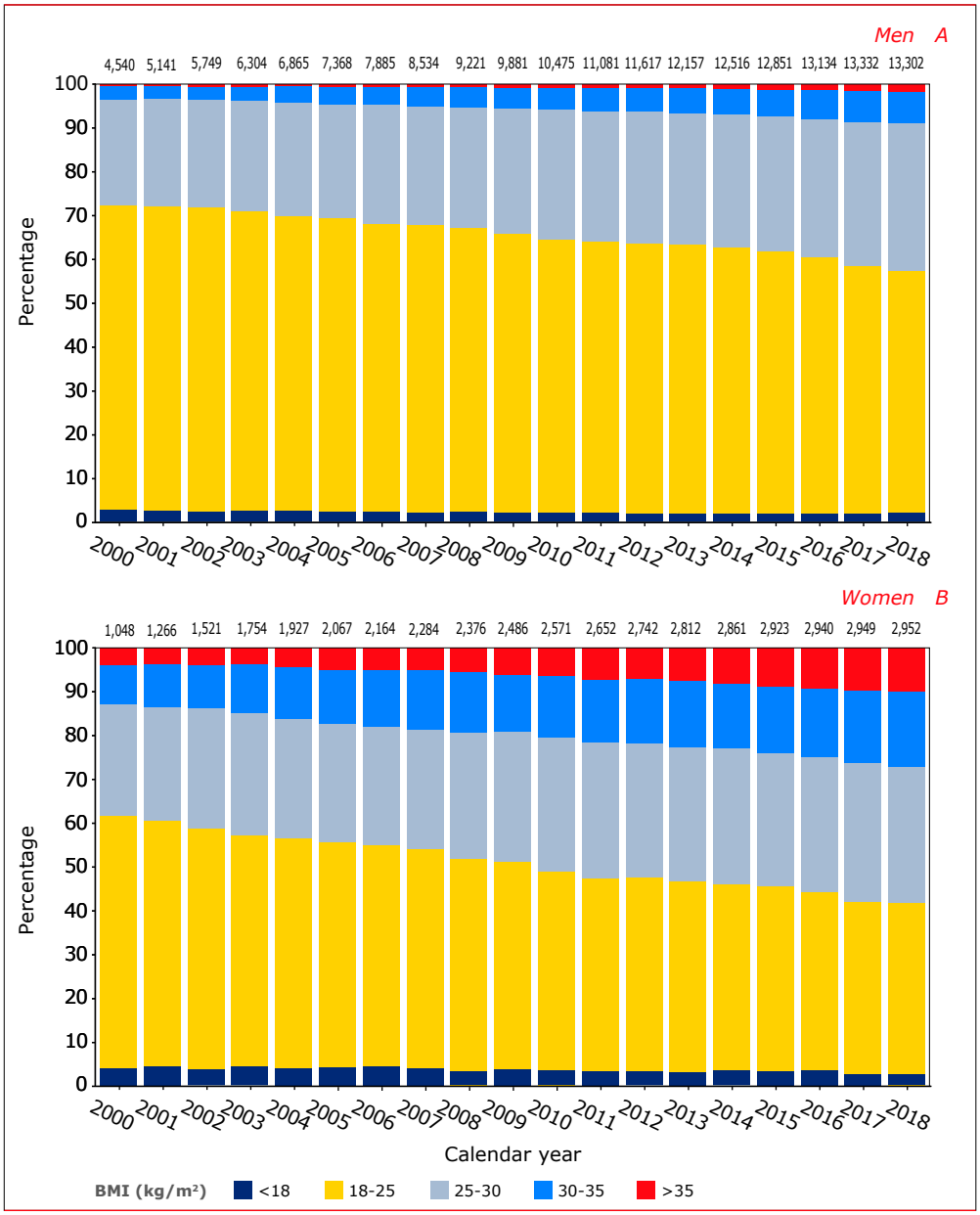
Legend: *CI=confidence intervals; PYFU=person years of follow up.*

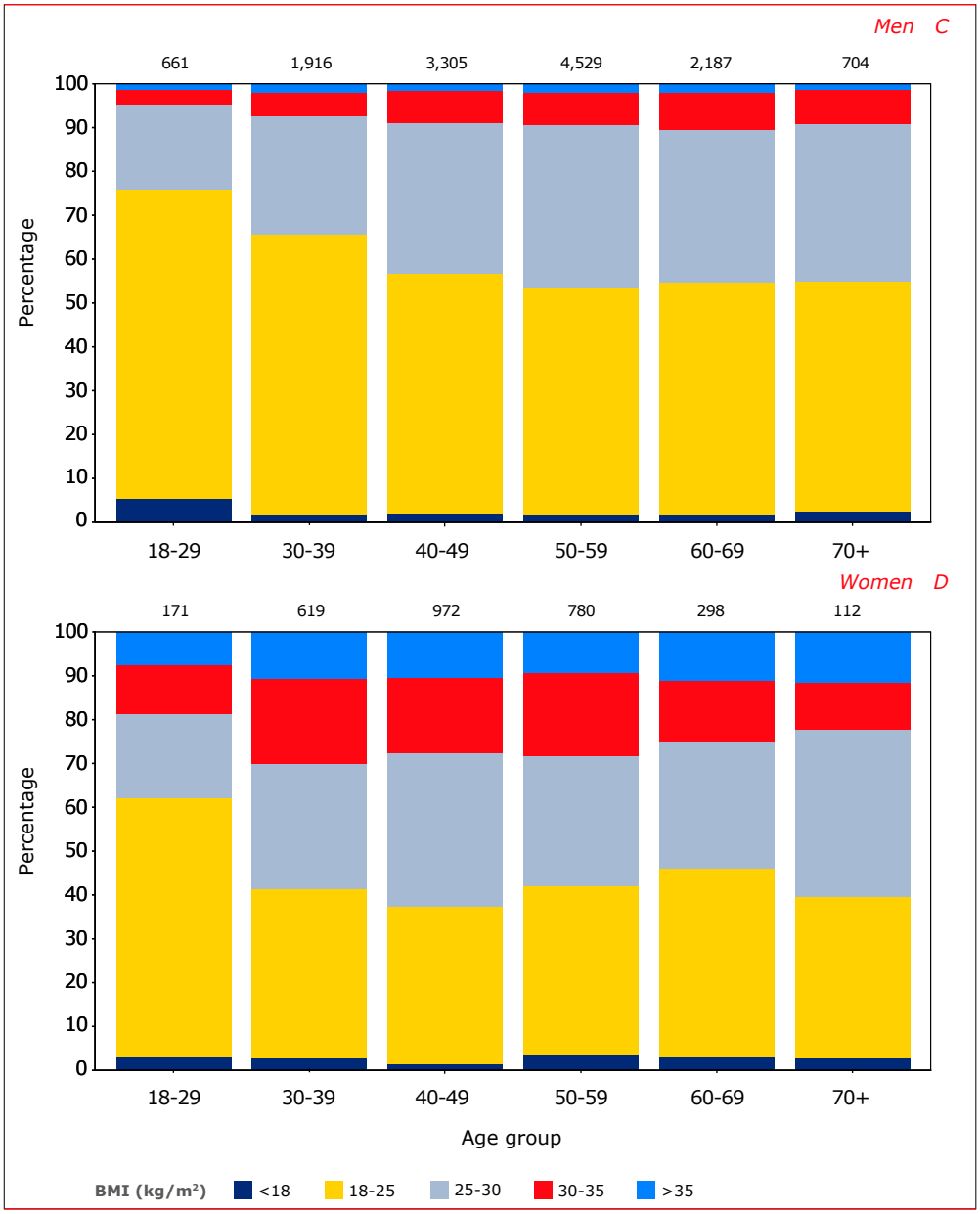
Trends in cardiovascular risk factors

Figures 3.3A and *3.3B* show that the distribution of body mass index (BMI) of both men and women in the HIV-1-positive population has increased over time. In 2018, the percentage of overweight (25-30 kg/m^2) and obese (class I: 30-35 and class II: ≥35 kg/m^2) men with an available BMI measurement was 34%, 7% and 2%, respectively. In women, these percentages were 31%, 17% and 10%, 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. *Figures 3.3C* and *3.3D* show the distribution of BMI over the age groups for men and women separately in 2018. Whereas in adult men of all age groups the proportion classified as obese (9%) was substantially lower than in the general Dutch male population (13.0%), in women of all age groups there was more obesity (27%) than in the general Dutch female population (16.9%)[25].

Figure 3.4A shows that, in 2018, 47% 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 2018, 23% of individuals not using antihypertensives had grade 1-3 hypertension (*Figure 3.4B*). For 3,249 of these 3,551 individuals, a 5-year cardiovascular disease (CVD) risk could be calculated with the recalibrated D:A:D study algorithm[26]. Of the 3,249 individuals, 5.3% 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[27]. *Figure 3.5* gives an overview of the cART-treated population's estimated risk of CVD over time. In 2000, the percentage of individuals at high (5-10%) or very high (≥10%) 5-year risk were 12% and 5%, respectively, which consistently increased to 20% and 12%, respectively, in 2018. The increase in the percentage of individuals at high or very high risk likely reflects the ageing of the population under study.

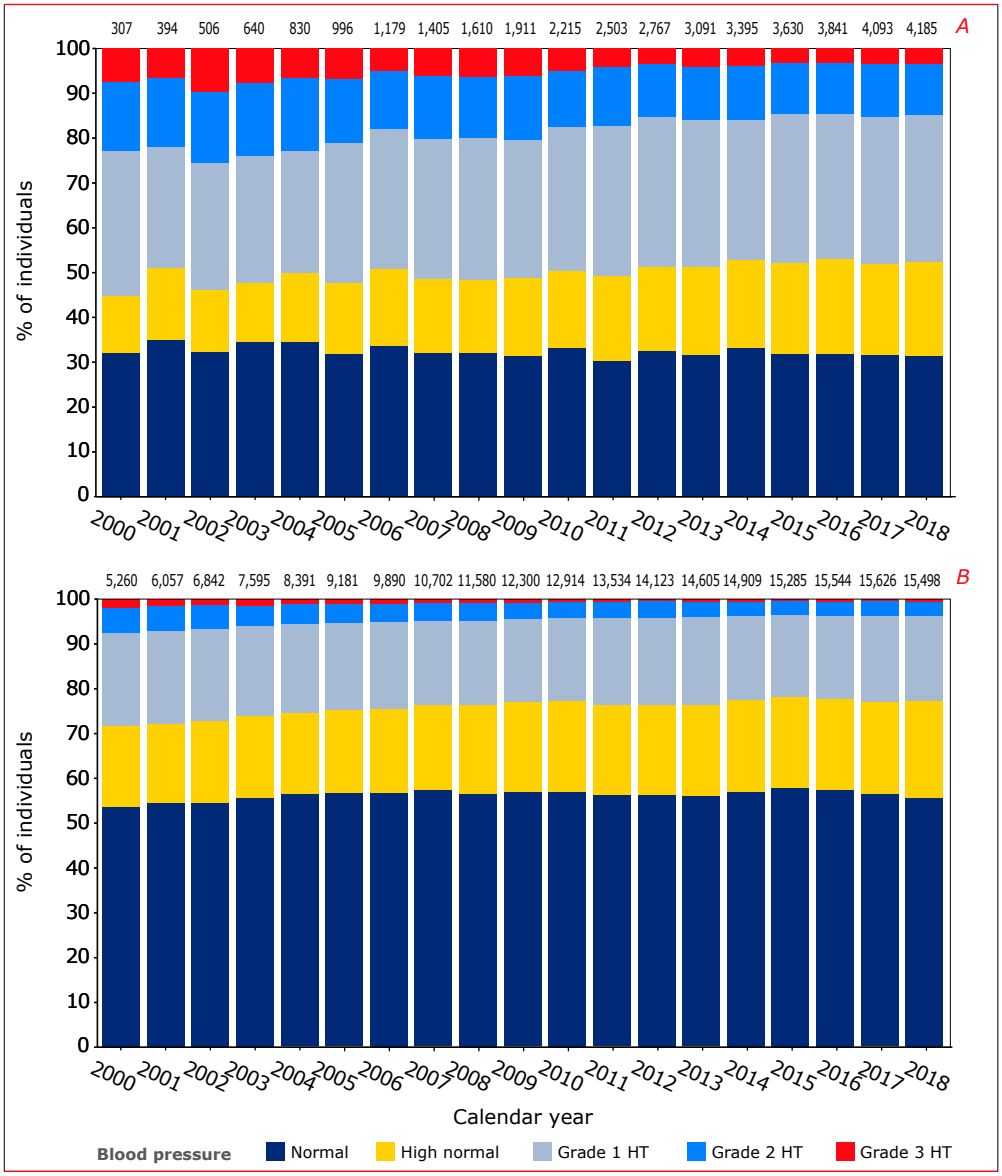
Figure 3.3: Distribution of the body mass index (BMI) at the end of each calendar year in (A) men and (B) women as a percentage of the total number of men and women with a known BMI in each year, and distribution of the BMI over the age groups for (C) men and (D) women in 2018. For each individual, the 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 (A & B) or age group (C & D).





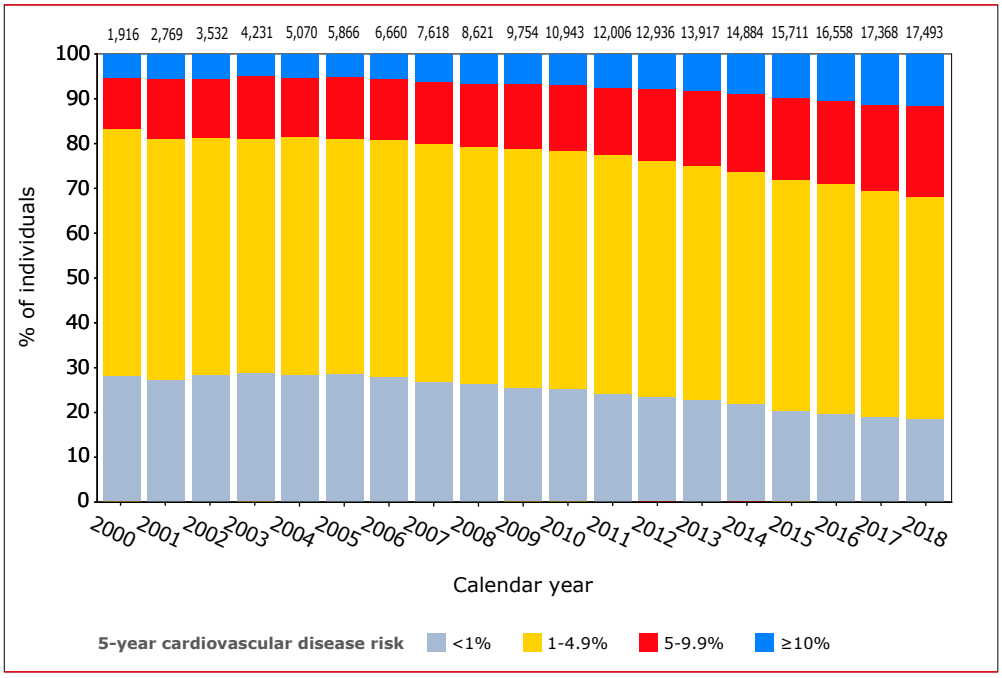
Legend: BMI=body mass index.

Figure 3.4: 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[28]). 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: BP=blood pressure; HT=hypertension.

Figure 3.5: 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[26]. 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.



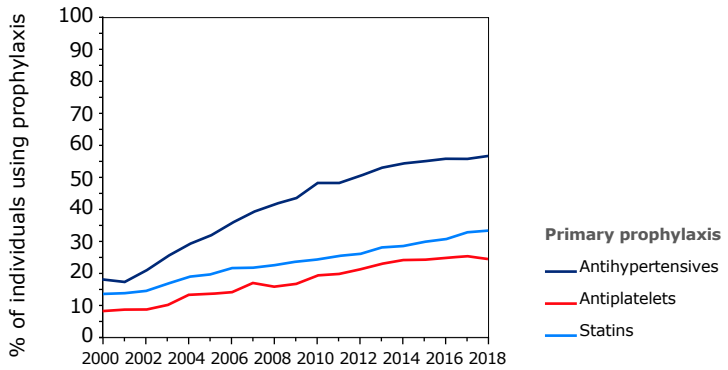
Use of primary or secondary prophylaxis for myocardial infarction or stroke

Primary prophylaxis

According to EACS guidelines, statin therapy should be offered to individuals with type 2 diabetes or a 10-year CVD risk ≥10%; 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 10-year CVD risk ≥20%; and acetylsalicylic acid should be offered to individuals aged 50 years or more with a 10-year CVD risk ≥20%[29].

Figure 3.6 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 2014, the overall proportion remains minimal and has remained stable during the last 4 years.

Figure 3.6: *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.*

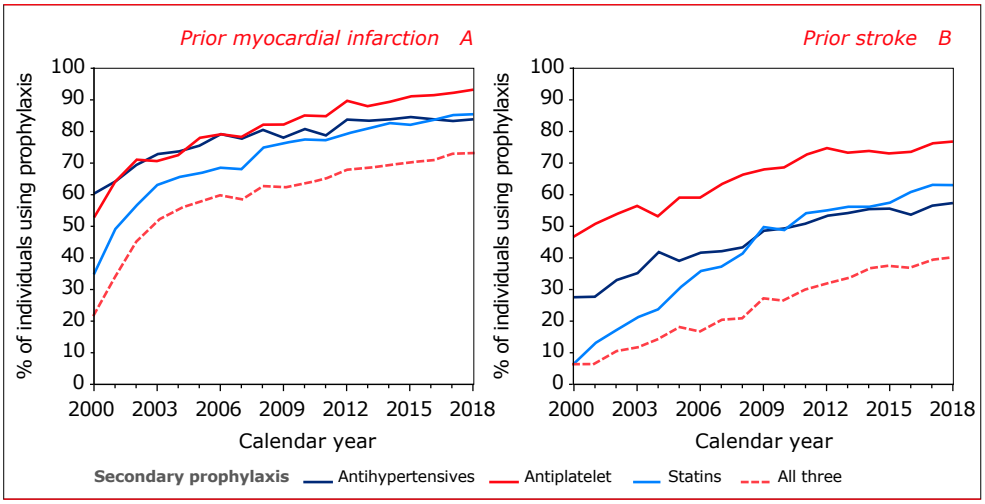


Secondary prophylaxis for myocardial infarction or stroke

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[30,31]. *Figure 3.7A* shows that the percentages of individuals using statins, acetylsalicylic acid/clopidogrel, or antihypertensives after a myocardial infarction increased between 2000 and 2018: in 2018, 86% of individuals with a prior myocardial infarction used statins, 84% used antihypertensives, and 93% used acetylsalicylic acid/clopidogrel. Although the use of statins and antihypertensives after an ischaemic stroke also

increased over time, in 2018 these medications were used less frequently after stroke than after a myocardial infarction (63% for statins, 77% for acetylsalicylic acid/clopidogrel, and 58% for antihypertensives) (*Figure 3.7B*).

Figure 3.7: *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[32]. 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[32,33]. However, because the CKD-EPI equation is the one most often used in clinical practice, 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 3.8*. The percentage of individuals with normal kidney function decreased over time from 76% in 2007 to 48% in 2018. This decrease was observed in both men and women (*Figure 3.9*). Typically, eGFR

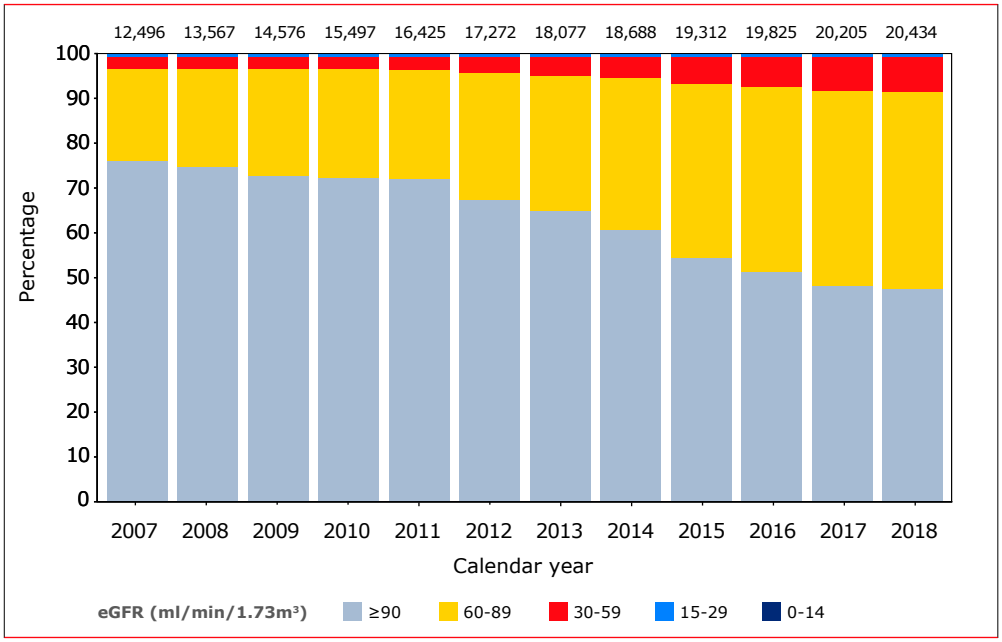
decreases with increased age, as shown in *Figure 3.10*, and therefore, the decrease in the proportion of individuals with normal function over time is likely to partly reflect the increasing age of individuals in care.

CKD incidence and risk factors

In individuals with an eGFR >60ml/min/1.73m^2 at inclusion in the analyses and without previously confirmed CKD, the crude incidence of CKD, defined as eGFR <60ml/min/1.73m^2 confirmed by a second test at least 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 (i.e., CKD already present in 2007) versus new-onset incident cases of CKD (i.e., no CKD observed in 2007) from 2008 onwards. In men, the incidence rose from 5.8 cases per 1,000 PYFU in the period 2008-2010 to 10.8 in 2011-2018, and in women the incidence rose from 8.2 to 10.1 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*).

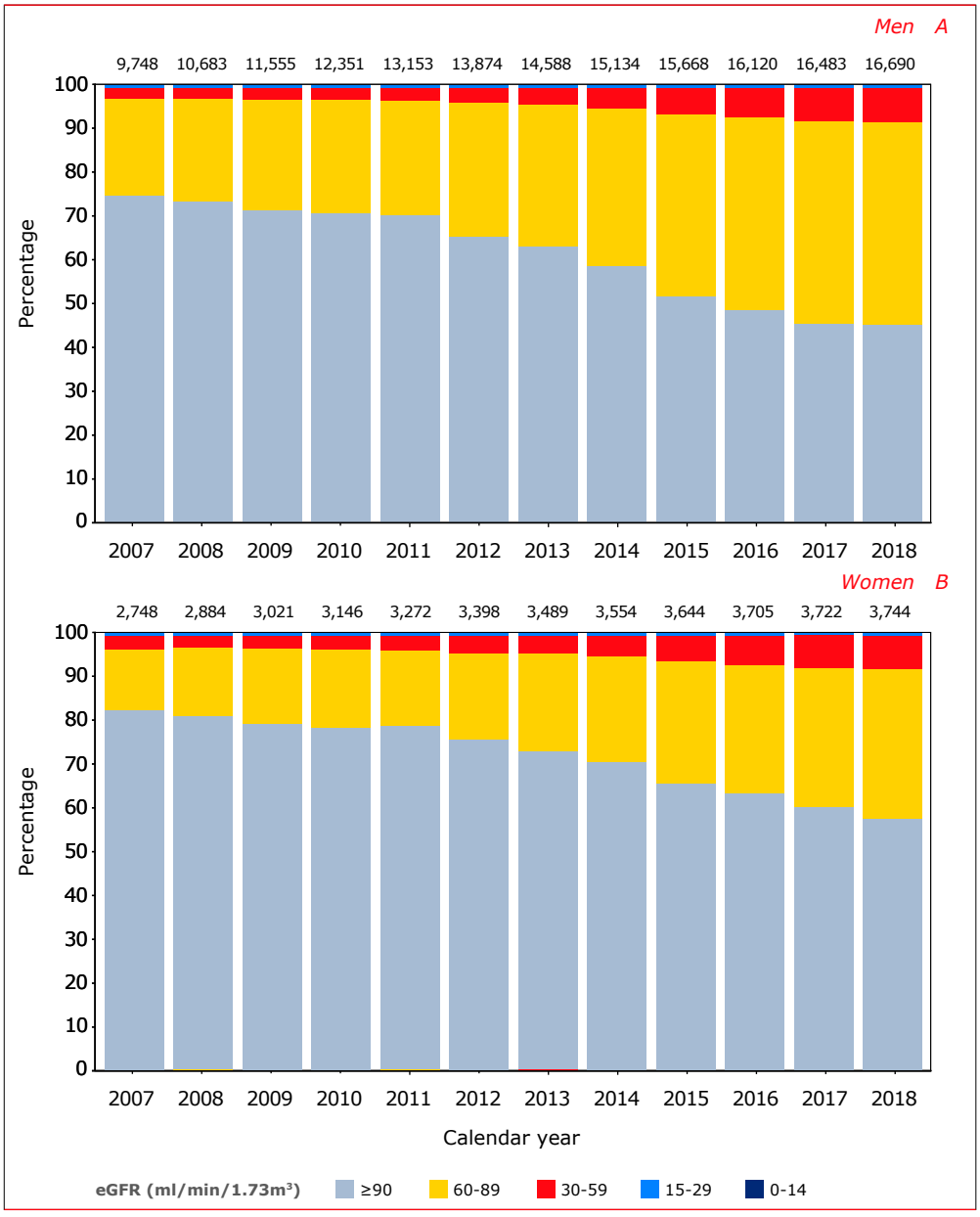
Risk factors for CKD included female gender, Dutch origin, low current CD4 cell count (<200 cells/mm^3), a prior AIDS diagnosis, belonging to the HIV transmission risk group of people who inject drugs, older age, lower body mass index, hypertension, diabetes mellitus, cardiovascular disease, pre-treatment with monotherapy and dual therapy with nucleoside analogues before the start of cART, and chronic HBV and HCV co-infection (*Appendix Table 3.7*). When current use of cobicistat, rilpivirine, dolutegravir and bictegravir were added to the model, the increased risk of CKD in the calendar period 2011-2018 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 ARV-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) and therefore do not truly reflect an increase in CKD.

Figure 3.8: 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 3.9: 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.



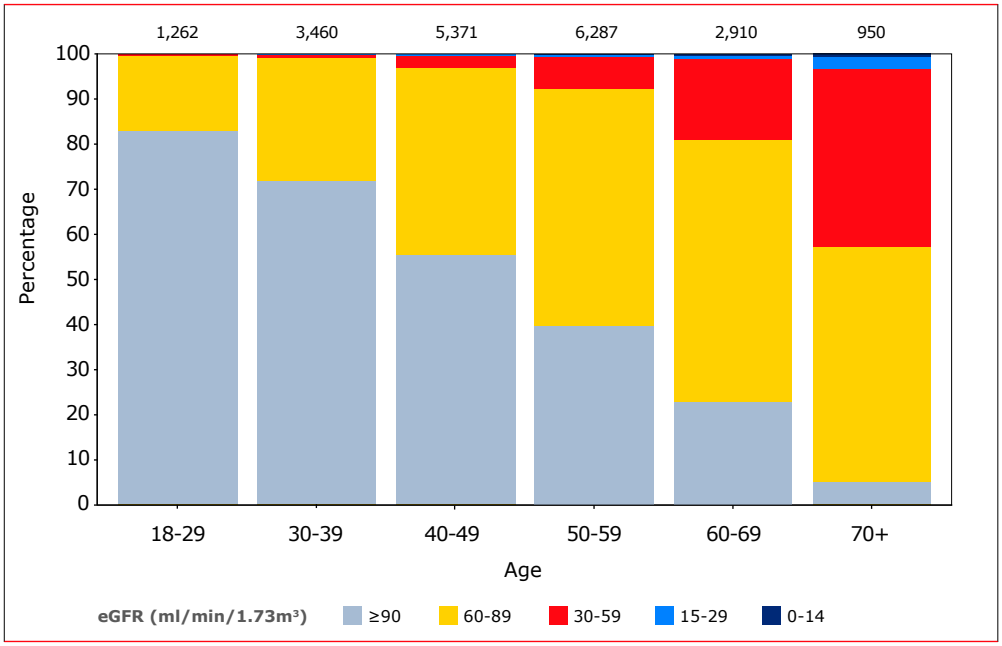
Legend: *eGFR=estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60-89 ml/min/1.73m²: mildly reduced; 30-59 ml/min/1.73m²: moderately reduced; 15-29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

Table 3.4: Crude chronic kidney disease incidence per 1,000 person years of follow up between 2008-2010 and between 2011-2018 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	5.8 (4.7-7.2)	0.67 (0.53-0.80)	8.2 (5.7-11.4)	1.20 (0.80-1.60)
2011-2018	10.8 (10.1-11.6)	1 (reference)	10.1 (8.6-11.8)	1 (reference)

**Standardised according to the observed age distribution between 2011-2018.*
***Legend:** CI=confidence interval; PYFU=person years of follow up.*

Figure 3.10: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2018 for different age categories. For each individual, the last available measurement in 2018 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.*

Non-AIDS-defining malignancies

Between 2000 and 2018, 1,495 diagnoses of non-AIDS-defining malignancy in 1,401 unique individuals were recorded in SHM's database. An additional 638 individuals 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 (18%), haematological malignancies (excluding AIDS-defining non-Hodgkin's lymphoma, 16%), invasive anal cancer (13%), intestinal cancer (excluding liver cancer, 11%), head and neck cancers (8%), and prostate cancer (8%). *Figure 3.11* shows the relative 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 3.12*, which shows the distribution of non-AIDS-defining malignancies with increasing age at cancer diagnosis.

Risk factors for non-AIDS-defining malignancies

The crude incidence of non-AIDS-defining malignancies (NADM) in men increased slightly from 5.8 cases per 1,000 PYFU in 2000-2005 to 6.5 cases per 1,000 PYFU in 2011-2018, and in women from 2.0 in 2000-2005 to 4.0 cases per 1,000 PYFU in 2011-2018 (*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 statistically significantly lower in the period 2011-2018 compared to 2000-2005 and 2006-2010 (*Table 3.6*). This lower age-standardised incidence in men may be due to a reduction 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 (borderline significantly) lower in the period 2011-2018 than in 2006-2010, but not 2000-2005 (*Table 3.6*).

Demographic and clinical factors independently 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*). Furthermore, people who had not yet started cART or who had been pre-treated with mono- or dual-nucleoside analogue RT inhibitors prior to starting CART had an independently increased risk for NADM compared with those who started cART while being treatment naïve (risk ratio (RR) 1.23 (1.04-1.46)). Of note, independent of all other risk factors investigated, people who initiated cART within 12 months of their last negative HIV test had a significantly lower risk for NADM (RR 0.46, 95% CI (0.27-0.80), p<0.001) than other treatment-naive people who started cART (i.e., those who either had an unknown duration of HIV infection or a duration of more than 12 months).

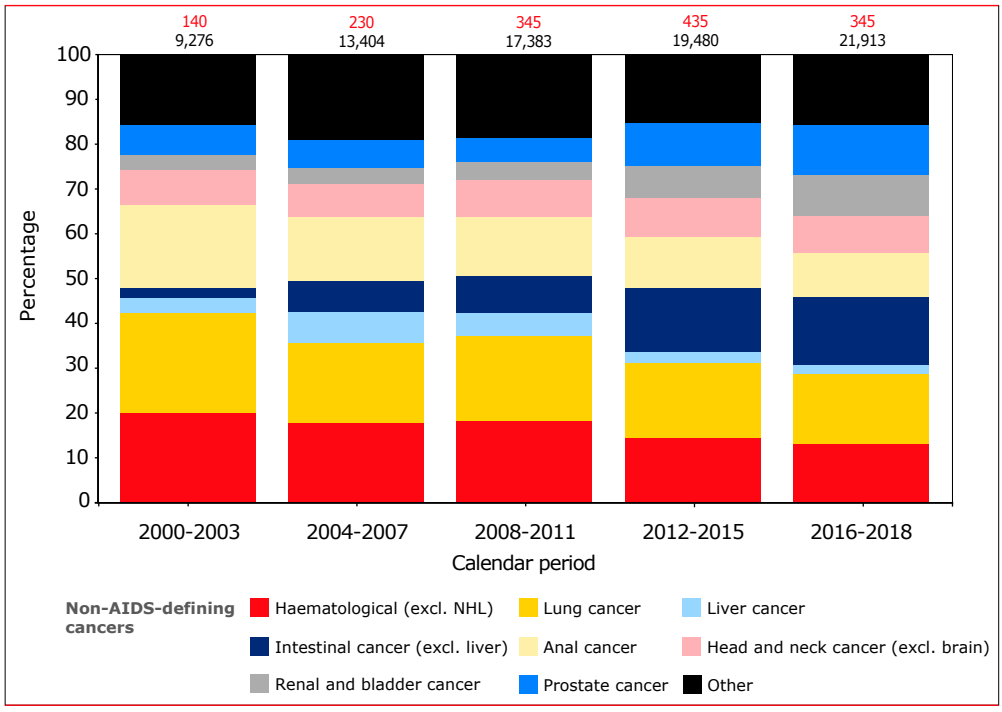
In the period from 1 January 2000 to 31 December 2018, the 5-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 50.1%, compared with 73.0% for CVD, 81.5% for DM, and 85.7% for CKD (*Appendix Figure 3.2*). In the same period, the

5-year survival rate of adults newly-entering care in one of the Dutch HIV treatment centres was 95.5%, and 82.1% 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

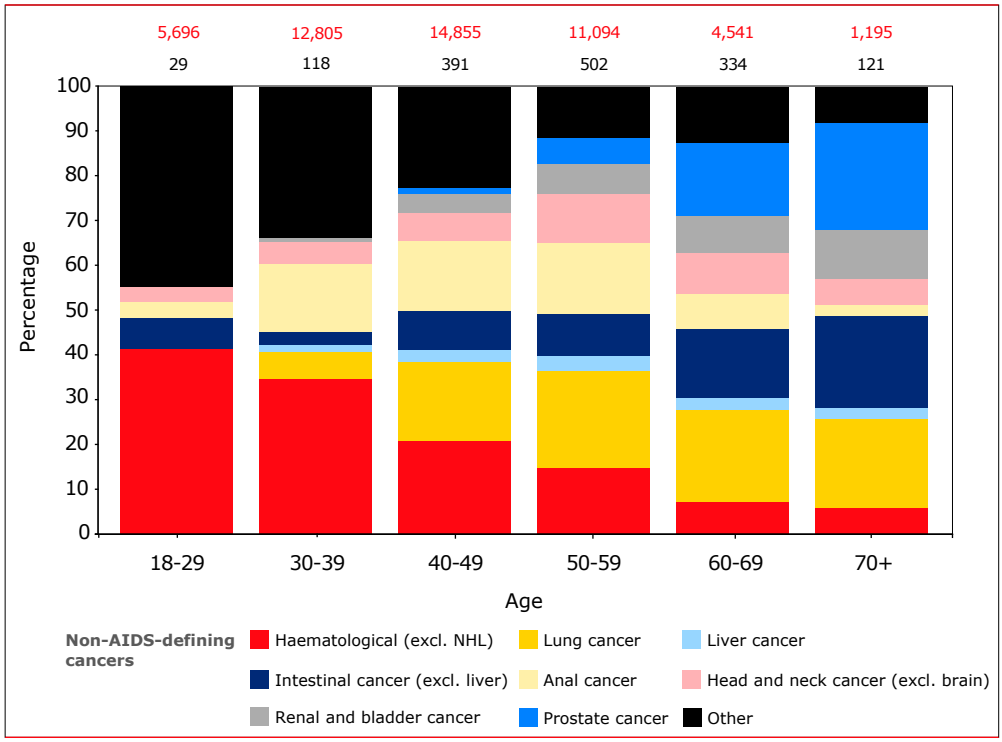
In total, 6 HIV-positive women and 182 HIV-positive men were diagnosed with anal cancer. Among HIV-positive men, the incidence of anal cancer fluctuated around 0.7 cases per 1,000 PYFU between 2000 and 2018 (*Figure 3.2G*). A 2015 study exploring the incidence of anal cancer among HIV-1-positive individuals 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=18) to analyse.

Figure 3.11: *Relative changes in non-AIDS-defining malignancies between 2000 and 2018 in HIV-1-positive individuals in the Netherlands. The numbers in red at the top of each bar represent the number of non-AIDS-defining cancer diagnoses during that calendar period, the numbers in black represent the number of individuals contributing data during that calendar year.*



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

Figure 3.12: Relative changes in non-AIDS-defining malignancies with increasing age in HIV-1-positive individuals in the Netherlands. The numbers in red at the top of each bar represent the number of cancer diagnoses in that age category, the numbers in black represent the number of individuals contributing data in that age category between 2000 and 2018.



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

Table 3.5: Most common non-AIDS-defining malignancies diagnosed between 2000-2018, excluding non-melanoma skin cancer and pre-malignant lesions found by cervical and anal screening.

Non-AIDS malignancy	Number of malignancies	%	5-year survival (%)
Lung cancer	263	17.6	14.2
Haematological cancer (excluding non-Hodgkin's lymphoma)	240	16.1	63.3
Anal cancer	188	12.6	62.1
Intestinal cancer (excluding liver)	162	10.8	36.3
Head and neck cancer (excluding brain)	124	8.3	57.1
Prostate cancer	120	8.0	78.0
Other cancers	90	6.0	48.8
Renal and bladder cancer	89	6.0	69.0
Malignant melanoma	64	4.3	69.4
Liver cancer	57	3.8	13.3
Breast cancer	39	2.6	82.6
Testicular cancer	31	2.1	89.1
Gynaecological cancer (excluding cervical)	23	1.5	66.0
Central nervous system (CNS) cancer	5	0.3	50.0

Table 3.6: Crude non-AIDS-defining malignancy incidence per 1,000 person years of follow up between 2000-2005, 2006-2010, and 2011-2018, 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	5.8 (5.0-6.6)	1.33 (1.15-1.51)	2.0 (1.2-3.1)	0.79 (0.44-1.15)
2006-2010	6.9 (6.2-7.6)	1.34 (1.19-1.48)	3.9 (2.9-5.2)	1.29 (0.94-1.64)
2011-2018	6.5 (6.1-7.0)	1 (reference)	4.1 (3.4-5.0)	1 (reference)

**Standardised according to the observed age distribution between 2011-2018.*

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

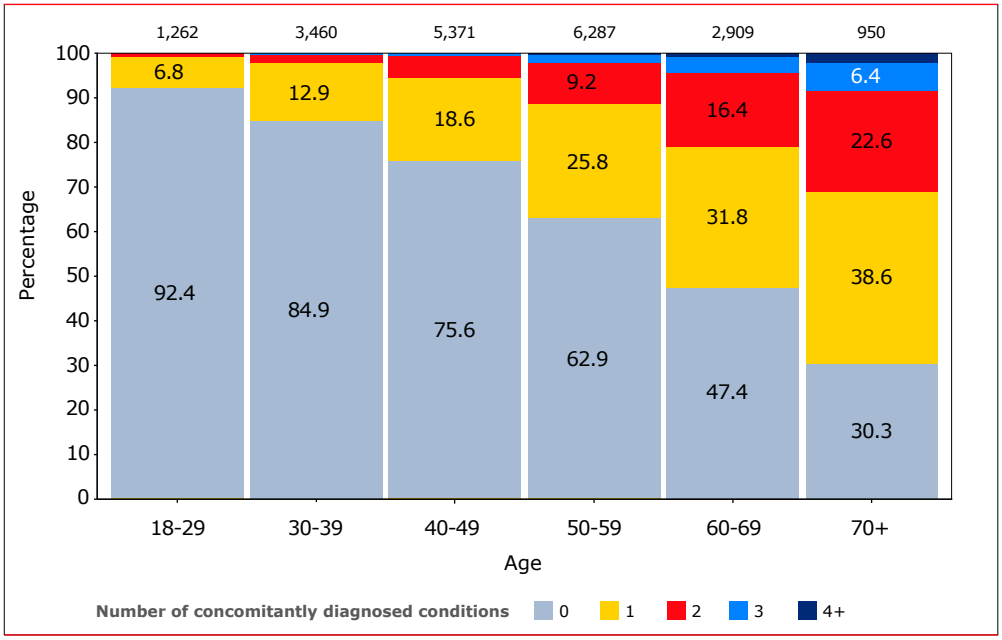
Multimorbidity

We investigated changes over time in the prevalence of non-AIDS multimorbidity. HIV infection itself and AIDS diagnoses did not contribute to the multimorbidity count. 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 (according to D:A:D diagnostic criteria); (6) hypertension, defined as the use of antihypertensive drugs and/or

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 to avoid over-diagnosis of both CKD in people using antiretroviral drugs that inhibit tubular secretion of creatinine and hypertension in those with borderline hypertension. Recurrences and non-primary CVD, stroke, and non-AIDS-defining malignancy events were not considered. Finally, CKD, hypertension and obesity could be reversible.

Figure 3.13 shows the distribution of the number of concomitantly diagnosed conditions in various age categories of the adult population in 2018. 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*). After adjusting for the variables listed in *Appendix Table 3.3*, multimorbidity was independently associated with increased risk of mortality (RR 2.21 (2.11-2.31, p<0.001, per additional comorbidity diagnosed).

Figure 3.13: *Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2018. 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.*



Polypharmacy, commonly defined as the concomitant use of 5 or more medications, is associated with adverse health outcomes, prescription errors, lower adherence, and an increased risk of clinically relevant pharmacological interactions and adverse drug reactions, especially in the elderly. At the end of each calendar year, we counted the number of registered comedications for each individual in active follow up. Antiretroviral agents are excluded from this count. We counted individual ATC codes (Anatomical Therapeutic Chemical classification system) of the comedications. Note that co-formulated combinations, such as cotrimoxazole, have a single ATC code and therefore increase the comedication count by 1.

In 2018, 24.1% of adults in active follow up had no recorded comedication use, while 34.1%, 15.3%, 9.2%, and 5.6% used 1, 2, 3, or 4 comedications, respectively. A further 11.8% used 5 or more non-antiretroviral comedications in addition to their cART regimen, which qualifies as polypharmacy. The prevalence of polypharmacy among adults has increased over calendar time (*Figure 3.14*): in 2000, just 3.0% of adults used 5 or more non-antiretroviral comedications in addition to their cART regimen. The main drivers for this increase in polypharmacy are the increasing age of the population and the increase in the number of chronic comorbidities. Older people (*Figure 3.15A*) and those with more comorbidities (*Figure 3.16*) used more comedications. There were some differences between men and women, with women using slightly more comedications than men, with the most pronounced differences between men and women in the youngest age groups (*Figure 3.15B*). Finally, in adults using cART in the period 2007-2018, polypharmacy was also associated with an increased risk of death (RR 2.52, 95% CI 2.24-2.85, p<0.001) independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities (i.e., multimorbidity). All comedications used by at least 250 adults patients in care in 2018 are listed in *Table 3.7*.

Table 3.7: use of comedications in 2018.

Comedication use in 2018	n	%
ATC group		
Vitamins	4,142	11.0
Lipid modifying agents	3,588	9.5
Drugs for acid related disorders	3,136	8.3
Agents acting on the renin-angiotensin system	2,769	7.3
Antithrombotic agents	2,296	6.1
Psychoanaleptic drugs	1,910	5.1
Mineral supplements	1,869	4.9
Drugs used in diabetes	1,570	4.2
Beta-blocking agents	1,458	3.9
Urological drugs	1,304	3.5
Calcium channel blockers	1,149	3.0
Psycholeptic drugs	1,097	2.9
Antibacterial drugs	1,020	2.7
Sex hormones and modulators of the genital system	962	2.5
Diuretic drugs	961	2.5
Drugs for obstructive airway diseases	860	2.3
Antiepileptic drugs	743	2.0
Anti-anaemic drugs	735	1.9
Analgesic drugs	679	1.8
Antiviral drugs	637	1.7
Cardiac therapy	499	1.3
Corticosteroids (systemic)	451	1.2
Nasal preparations	409	1.1
Antimycotic drugs	368	1.0
Drugs affecting bone structure and mineralisation	306	0.8
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents	296	0.8
Thyroid therapy	292	0.8
Other nervous system drugs	255	0.7

Figure 3.14: Number of comedications used over calendar time. The numbers at the top of each bar represent the number of individuals contributing data to that period. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per period.

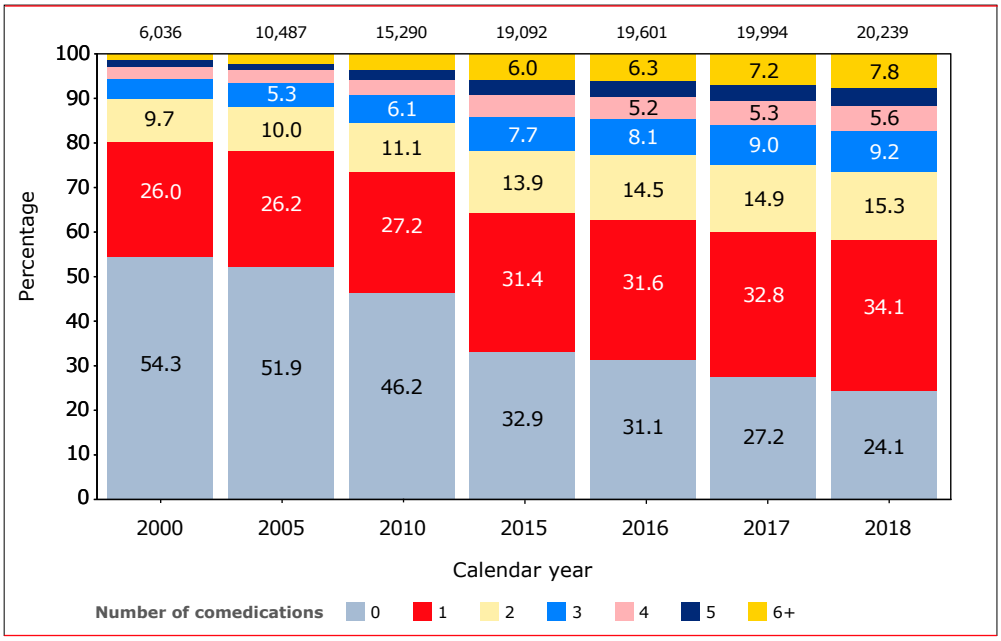
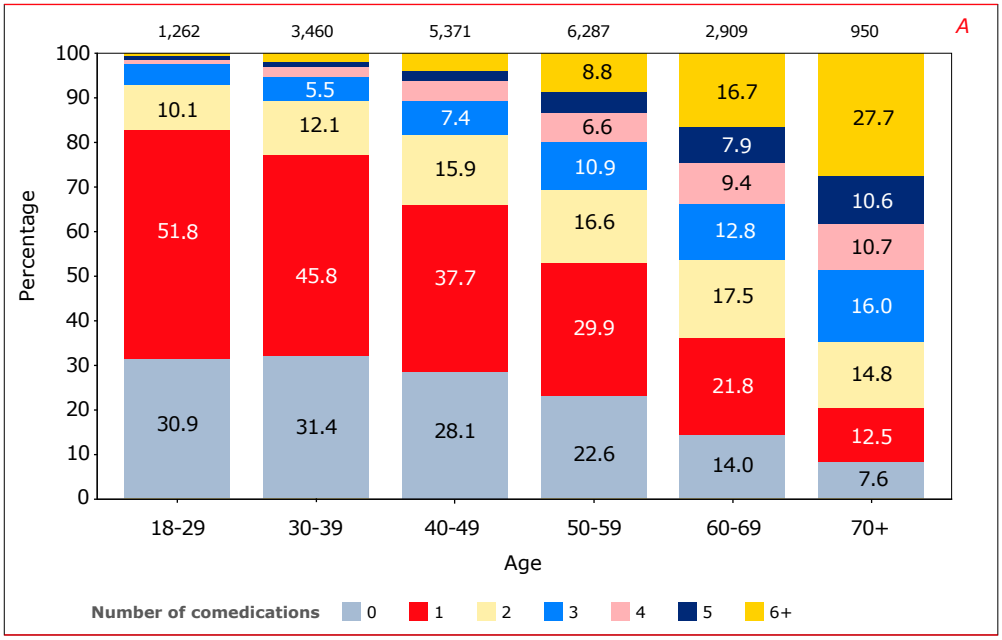


Figure 3.15: Number of comedications used by (A) age group and (B) gender. The numbers at the top of each bar represent the number of individuals contributing data to that age/gender category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



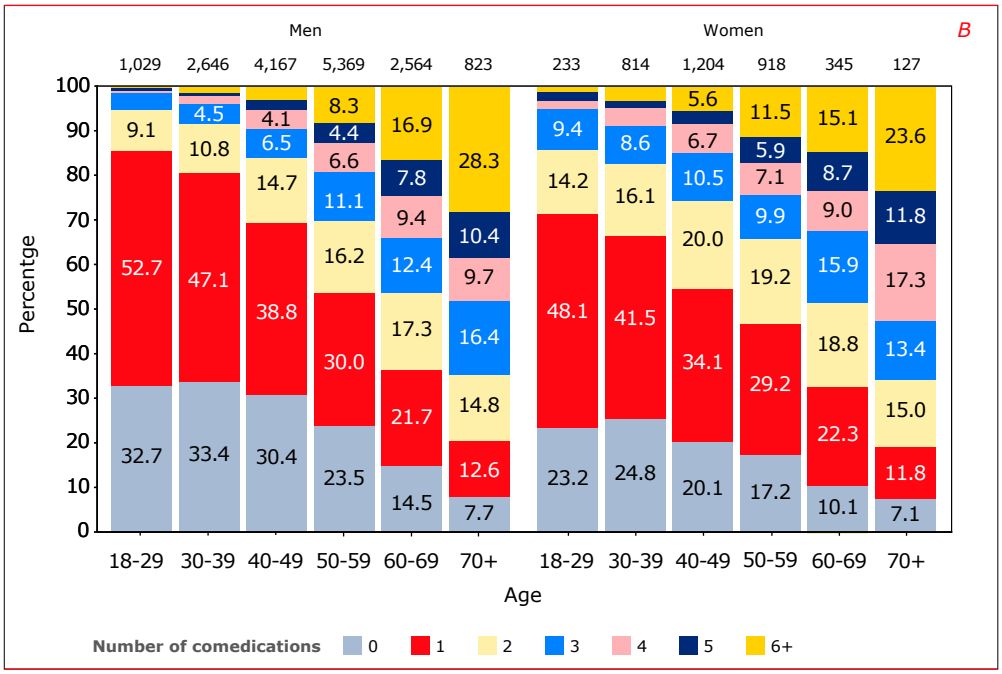
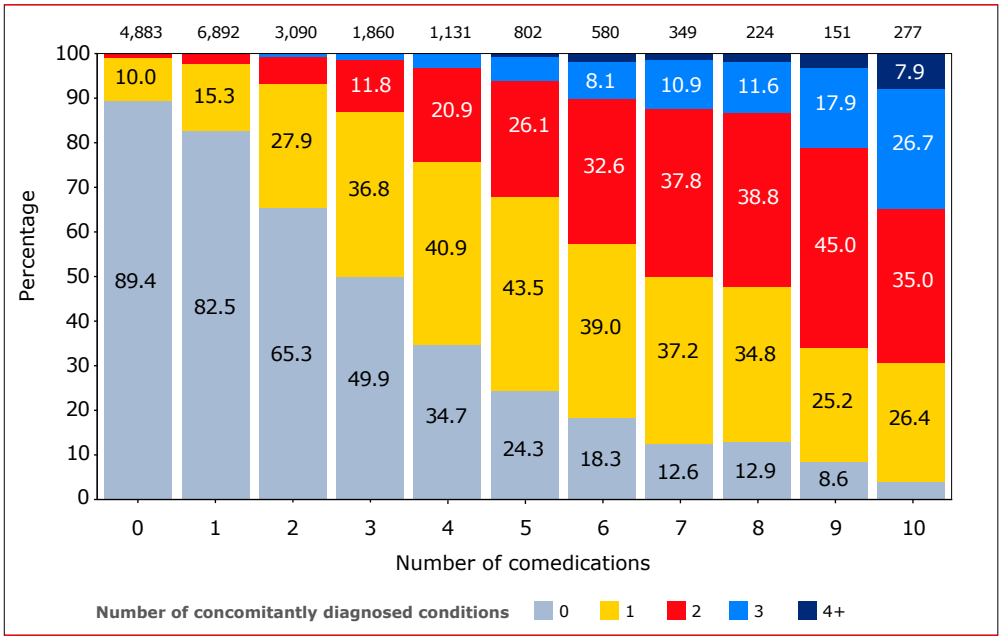


Figure 3.16: Number of comedications used by number of comorbidities diagnosed. The numbers at the top of each bar represent the number of individuals contributing data to that category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per category.



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 are mainly those who present 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 for diabetes mellitus and CVD were mainly those traditionally known to be associated with these conditions (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 2000-2018. 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, particularly 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. In our cohort, we found that obesity and overweight were significant risk factors for developing new-onset diabetes, but not cardiovascular disease, CKD or non-AIDS malignancies. Obese and overweight adults had a significantly lower risk of death than those with an ideal body weight, although this is likely biased by reverse causality, as body weight was included as a time-updated variable in our regression analyses.

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 also 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]. Moreover, renal impairment in the HIV-positive population is associated with an increased risk for cardiovascular disease[52]. The increase in 'CKD' in our population in recent years

appears to be largely caused by the increased use of dolutegravir, bictegravir, rilpivirine and cobicistat, all 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 (NADM) in the Netherlands are lung, anal, and head and neck cancer, as well as Hodgkin's lymphoma. The crude incidence of NADM in the Netherlands has remained stable over time, and we also observed a decline in age-standardised incidence of NADM in men. In addition, our analyses show that individuals diagnosed with NADM 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 NADM with increasing age[53,54,55,56]. Additional risk factors for NADM identified in our analyses were current or past smoking; a CD4 count below 350 cells/mm^3; not being on cART or having been pre-treated with NRTI before the start of cART; and a prior AIDS diagnosis. Other studies have also 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%. Moreover, individuals who had initiated cART earlier in infection, i.e., within 12 months of a last negative HIV test, had a significantly lower risk of NADM (RR 0.46, 95% CI 0.27-0.80, p=0.006), independent of other traditional and HIV-related risk factors.

Multimorbidity and polypharmacy

The prevalence of non-AIDS multimorbidity is slowly increasing, driven mainly by the increasing age of the cohort, and with women experiencing more comorbidities in each age group. Multimorbidity is independently associated with increased risk of mortality (RR 2.21 (2.11-2.31), per additional comorbidity diagnosed).

Polypharmacy, defined as the concomitant use of 5 or more medications, is becoming more prevalent, mainly because of the increased age of the cohort and the associated rise in prevalence of age-associated non-AIDS comorbidities. In 2000, 3.0% of adults used 5 or more non-antiretroviral comedications alongside their cART regimen and this steadily increased to 11.8% of adults in active follow up in 2018. The main drivers behind this increase in polypharmacy are the increasing age of the population and the increase in the number of chronic comorbidities per individual. In adults using cART in the period 2007-2018, polypharmacy was also associated with an increased risk of death (RR 2.52, 95% CI 2.24-2.85), independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities.

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[58,59,60]. Indeed, our own analyses show a markedly lower risk for non-AIDS malignancies in those who initiate cART early after infection.

The relatively poor 5-year survival rates following the diagnosis of several of the analysed non-AIDS-defining comorbidities compared with survival of people 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 have provided further insights into the independent contribution of HIV and HIV-associated factors, such as innate and adaptive immune and coagulation activation and inflammation. This will hopefully guide the development of interventions that target relevant pathophysiological mechanisms[9,61].

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. As the population of people living with HIV that is in care in the Netherlands continues to age, the co-morbidity burden continues to increase. In tandem with multimorbidity, the risk for polypharmacy is also strongly on the rise in recent years. Both multimorbidity and polypharmacy were independently associated with an increased risk of death. Adequate prevention and management of co-morbidities will become even more important as more people living with HIV are entering their 70s and 80s. Polypharmacy should also be adequately managed using of tools developed in geriatric medicine (e.g., START/STOPP and Beers) to limit the risk of complex drug-drug interactions, side effects, non-adherence and other severe adverse health outcomes.

Ageing, of course, strongly contributes to the risk of developing 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.

References

1. van Sighem AI, Gras LAJ, Reiss P, Brinkman K, de Wolf F, ATHENA national observational cohort study. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. *AIDS*. 2010;24(10):1527-1535. doi:10.1097/QAD.0b013e32833a3946
2. Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994-98: the EuroSIDA study. *Lancet*. 2000;356(9226):291-296. doi:10.1016/S0140-6736(00)02504-6
3. The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008;372(9635):293-299. doi:10.1016/S0140-6736(08)61113-7
4. Emery S, Neuhaus JA, Phillips AN, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. *J Infect Dis*. 2008;197(8):1133-44. doi:10.1086/586713
5. Mocroft A, Soriano V, Rockstroh J, et al. Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? *AIDS*. 2005;19(18):2117-2125
6. Bhaskaran K, Hamouda O, Sannes M, et al. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA*. 2008;300(1):51-59. doi:10.1001/jama.300.1.51
7. Lohse N, Hansen ABE, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. *Ann Intern Med*. 2007;146(2):87-95. doi:10.7326/0003-4819-146-2-200701160-00003
8. Bonnet F, Burty C, Lewden C, et al. Changes in cancer mortality among HIV-infected patients: the Mortalité 2005 Survey. *Clin Infect Dis*. 2009;48(5):633-639. doi:10.1086/596766
9. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis*. 2011;53(11):1120-1126. doi:10.1093/cid/cir627
10. Freiberg MS, Chang C-CH, Skanderson M, et al. The risk of incident coronary heart disease among veterans with and without HIV and hepatitis C. *Circ Cardiovasc Qual Outcomes*. 2011;4(4):425-432. doi:10.1161/CIRCOUTCOMES.110.957415

11. Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between hiv-infected and uninfected individuals: the AGE$_h$IV cohort study. *Clin Infect Dis*. 2014;59(12):1787-1797. doi:10.1093/cid/ciu701
12. Hsue PY, Deeks SG, Farah HH, et al. Role of HIV and human herpesvirus-8 infection in pulmonary arterial hypertension. *AIDS*. 2008;22(7):825-833. doi:10.1097/QAD.0b013e3282f7cd42
13. Arnsten JH, Freeman R, Howard AA, Floris-Moore M, Lo Y, Klein RS. Decreased bone mineral density and increased fracture risk in aging men with or at risk for HIV infection. *AIDS*. 21(5):617-623.
14. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS*. 2006;20(17):2165-2174. doi:10.1097/QAD.0b013e32801022eb
15. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. *J Clin Endocrinol Metab*. 93(9):3499-3504.
16. McCutchan JA, Wu JW, Robertson K, et al. HIV suppression by HAART preserves cognitive function in advanced, immune-reconstituted AIDS patients. *AIDS*. 2007;21(9):1109-1117. doi:10.1097/QAD.0b013e3280ef6acd
17. Robertson KR, Smurzynski M, Parsons TD, et al. The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS*. 2007;21(14):1915-1921. doi:10.1097/QAD.0b013e32828e4e27
18. Ances BM, Vaida F, Yeh MJ, et al. HIV infection and aging independently affect brain function as measured by functional magnetic resonance imaging. *J Infect Dis*. 201(3):336-340.
19. Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV cohort study: Associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst*. 2005;97(6):425-432. doi:10.1093/jnci/dji072
20. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet*. 2007;370(9581):59-67. doi:10.1016/S0140-6736(07)61050-2
21. Baker J V, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS*. 2008;22(7):841-848. http://www.ncbi.nlm.nih.gov/pubmed/18427202.
22. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296. doi:10.1056/NEJMoa062360

23. CDC Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report, 2005*. Vol Vol. 17. R. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2007. https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html.
24. Tripepi G, Jager KJ, Dekker FW, Zoccali C. Stratification for Confounding – Part 2: Direct and Indirect Standardization. *Nephron Clin Pract*. 2010;116(4):c322-c325. doi:10.1159/000319591
25. Gezondheidsenquête/Leefstijlmonitor CBS i.s.m. RIVM. Volwassenen met overgewicht en obesitas 2018. https://www.volksgezondheidenzorg.info/onderwerp/overgewicht/cijfers-context/huidige-situatie#node-overgewicht-volwassenen. Accessed September 12, 2019.
26. Friis-Møller N, Ryom L, Smith C, et al. An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. *Eur J Prev Cardiol*. 2016;23(2):214-223. doi:10.1177/2047487315579291
27. European AIDS Clinical Society. Guidelines. Version 8.0, October 2015. English edition. 2015. http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html.
28. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34(28):2159-2219. doi:10.1093/eurheartj/eht151
29. Rockstroh JK, Bhagani S, Benhamou Y, et al. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. *HIV Med*. 2008;9(2):82-88. doi:10.1111/j.1468-1293.2007.00535.x
30. Nederlands Huisartsen Genootschap. Beroerte. https://www.nhg.org/standaarden/samenvatting/beroerte. Published 2015.
31. Nederlands Huisartsen Genootschap Cardiovasculair Risicomanagement. https://www.nhg.org/standaarden/samenvatting/cardiovasculair-risicomanagement. Published 2016.
32. Mocroft A, Ryom L, Reiss P, et al. A comparison of estimated glomerular filtration rates using cockcroft-gault and the chronic kidney disease epidemiology collaboration estimating equations in HIV infection. *HIV Med*. 2014;15(3):144-152. doi:10.1111/hiv.12095
33. Vrouenraets SME, Fux CA, Wit FWNM, et al. A comparison of measured and estimated glomerular filtration rate in successfully treated HIV-patients with preserved renal function. *Clin Nephrol*. 2012;77(04):311-320. doi:10.5414/CN107214

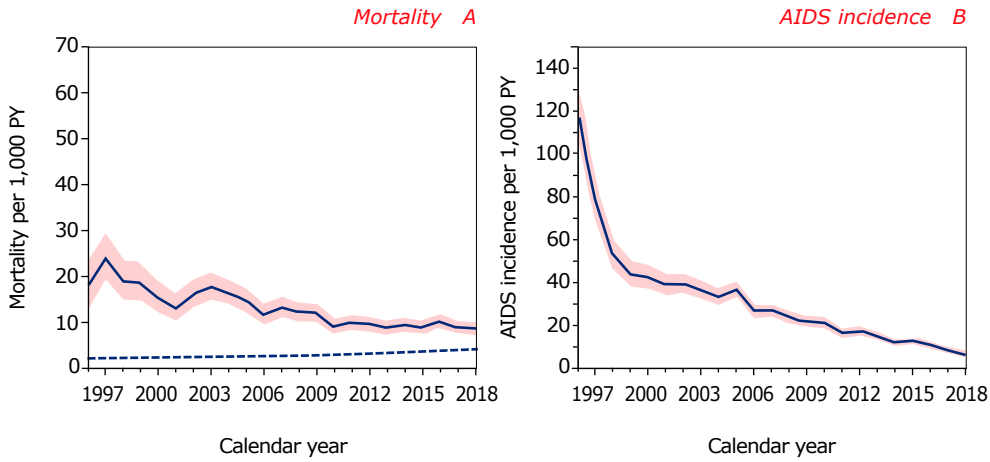
34. Richel O, Van RP, Zee D, Smit C, De Vries HJC, Prins JM. Anal cancer in the HIV-positive population: slowly declining incidence after a decade of cART. *J Acquir Immune Defic Syndr*. 2015;69(5):602-605. doi:10.1097/QAI.0000000000000675
35. Berenguer J, Alejos B, Hernando V, et al. Trends in mortality according to hepatitis C virus serostatus in the era of combination antiretroviral therapy. *AIDS*. 2012;26(17):2241-2246. doi:10.1097/QAD.0b013e3283574e94
36. Helleberg M, Kronborg G, Larsen CS, et al. Causes of death among Danish HIV patients compared with population controls in the period 1995-2008. *Infection*. 2012;40(6):627-634. doi:10.1007/s15010-012-0293-y
37. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: An observational study. *Lancet*. 2003;362(9377):22-29. doi:10.1016/S0140-6736(03)13802-0
38. Holtgrave DR. Causes of the decline in AIDS deaths, United States, 1995-2002: prevention, treatment or both? *Int J STD AIDS*. 2005;16(12):777-781. doi:10.1258/095646205774988109
39. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. All-cause mortality in treated HIV-infected adults with CD4 ≥500/mm^3 compared with the general population: evidence from a large European observational cohort collaboration. *Int J Epidemiol*. 2012;41(2):433-445. doi:10.1093/ije/dyr164
40. May MT, Gompels M, Delpech V, et al. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. *AIDS*. 2014;28(8):1193-1202. doi:10.1097/QAD.0000000000000243
41. Capeau J, Bouteloup V, Katlama C, et al. Ten-year diabetes incidence in 1046 HIV-infected patients started on a combination antiretroviral treatment. *AIDS*. 2012;26(3):303-314. doi:10.1097/QAD.0b013e32834e8776
42. Worm SW, Friis-Moller N, Bruyand M, et al. High prevalence of the metabolic syndrome in HIV-infected patients: impact of different definitions of the metabolic syndrome. *AIDS*. 2010;24(3):427-435.
43. Sabin CA, Reiss P, Ryom L, et al. Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration. *BMC Med*. 2016;14(1):61. doi:10.1186/s12916-016-0588-4
44. Ledergerber B, Furrer H, Rickenbach M, et al. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. *Clin Infect Dis*. 2007;45(1):111-119. doi:10.1086/518619
45. Brown TTT, Cole SSR, Li X, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch Intern Med*. 2005;165(10):1179-1184. doi:10.1001/archinte.165.10.1179

46. Kamara DA, Smith C, Ryom L, et al. Longitudinal analysis of the associations between antiretroviral therapy, viraemia and immunosuppression with lipid levels: the D:A:D study. *Antivir Ther*. 2016;(April 26). doi:10.3851/IMP3051
47. Yuh B, Tate J, Butt AA, et al. Weight change after antiretroviral therapy and mortality. *Clin Infect Dis*. 2015; 60(12):1852-1859.
48. Achhra AC, Mocroft A, Reiss P, et al. Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study. *HIV Med*. 2016;17(4):255-268. doi:10.1111/hiv.12294
49. Mocroft A, Neuhaus J, Peters L, et al. Hepatitis B and C co-infection are independent predictors of progressive kidney disease in hiv-positive, antiretroviral-treated adults. *PLoS One*. 2012;7(7):e40245-. doi:10.1371/journal.pone.0040245
50. Peters L, Grint D, Lundgren JD, et al. Hepatitis C virus viremia increases the incidence of chronic kidney disease in HIV-infected patients. *AIDS*. 2012;26(15):1917-1926. doi:10.1097/QAD.0b013e3283574e71
51. Ryom L, Mocroft A, Kirk O, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: The D:A:D Study. *J Infect Dis*. 2013;207(9):1359-1369. doi:10.1093/infdis/jit043
52. Ryom L, Lundgren JD, Ross M, et al. Renal Impairment and Cardiovascular Disease in HIV-Positive Individuals: The D:A:D Study. *J Infect Dis*. 2016;214(8):1212-1220. doi:10.1093/infdis/jiw342
53. Krishnan S, Schouten JT, Jacobson DL, et al. Incidence of non-AIDS-defining cancer in antiretroviral treatment-naïve subjects after antiretroviral treatment initiation: An ACTG longitudinal linked randomized trials analysis. *Oncology*. 2011;80(1-2):42-49. doi:10.1159/000328032
54. Powles T, Robinson D, Stebbing J, et al. Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection. *J Clin Oncol*. 2009;27(6):884-890. doi:10.1200/JCO.2008.19.6626
55. Sigel K, Wisnivesky J, Gordon K, et al. HIV as an independent risk factor for incident lung cancer. *AIDS*. 2012;26(8):1017-1025. doi:10.1097/QAD.0b013e328352d1ad
56. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: The swiss HIV cohort study. *Clin Infect Dis*. 2011;53(11):1130-1139. doi:10.1093/cid/cir626
57. Kesselring A, Gras L, Smit C, et al. Immunodeficiency as a risk factor for non-AIDS-defining malignancies in HIV-1-infected patients receiving combination antiretroviral therapy. *Clin Infect Dis*. 2011;52(12):1458-1465. doi:10.1093/cid/cir207

58. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: Results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis*. 2014;14(4):281-290. doi:10.1016/S1473-3099(13)70692-3
59. The TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med*. 2015;373(9):808-822. doi:10.1056/NEJMoa1507198
60. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373(9):795-807. doi:10.1056/NEJMoa1506816
61. High KP, Brennan-Ing M, Clifford DB, et al. HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. *J Acquir Immune Defic Syndr*. 2012;60 Suppl 1:S1-18. doi:10.1097/QAI.0b013e31825a3668

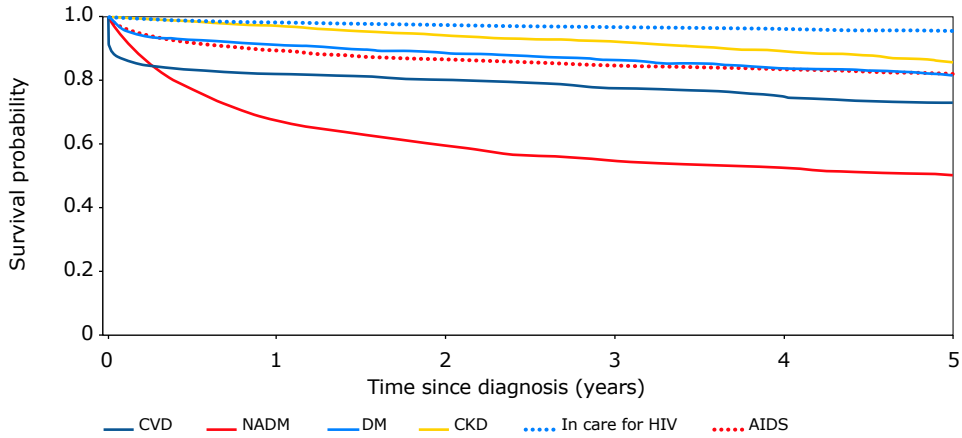
Appendix: supplementary figures and tables

Appendix Figure 3.1: *(A) Annual mortality and (B) incidence of AIDS in 26,435 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.*



< Back to page 142

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.*

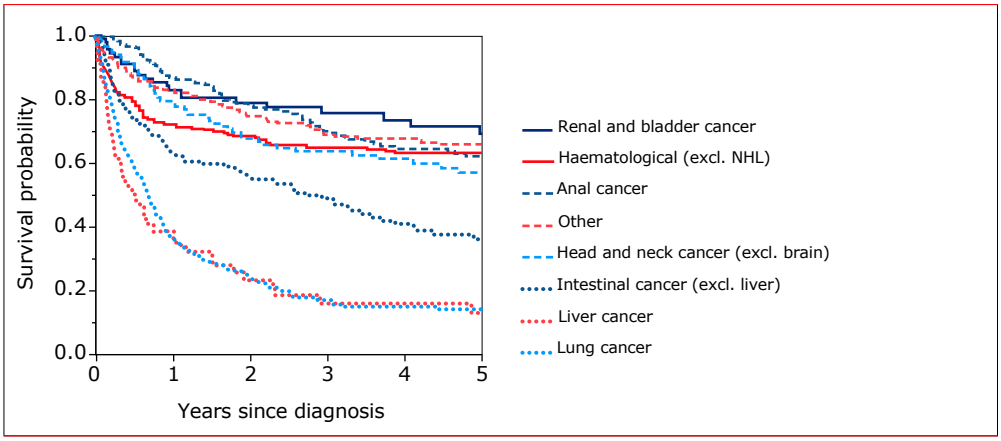


Time since diagnosis (years)	0	1	2	3	4	5
CVD	1,341	1,025	902	788	675	589
NADM	1,167	740	568	447	372	307
DM	1,253	1,062	945	842	736	631
CKD	1,889	1,546	1,245	971	754	591
In care for HIV	20,593	18,603	17,295	16,076	14,885	13,687
AIDS	3,377	2,852	2,625	2,425	2,224	2,039

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

< Back to page 163

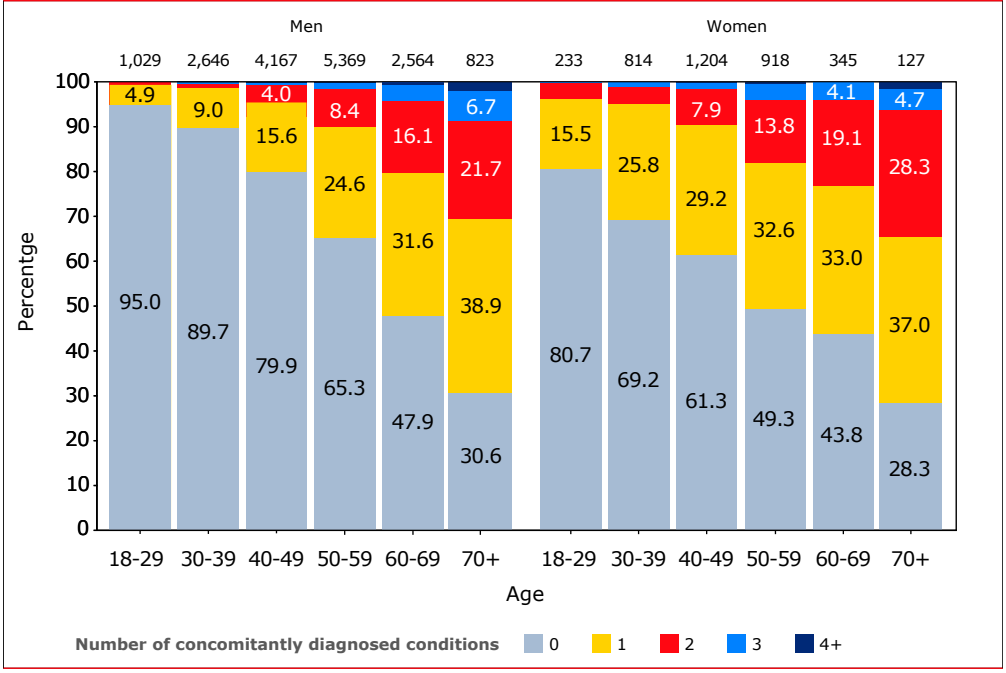
Appendix Figure 3.3: Estimated 5-year survival following the diagnosis of the most common non-AIDS-defining malignancies diagnosed between 1 January 2000 and 31 December 2018.



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

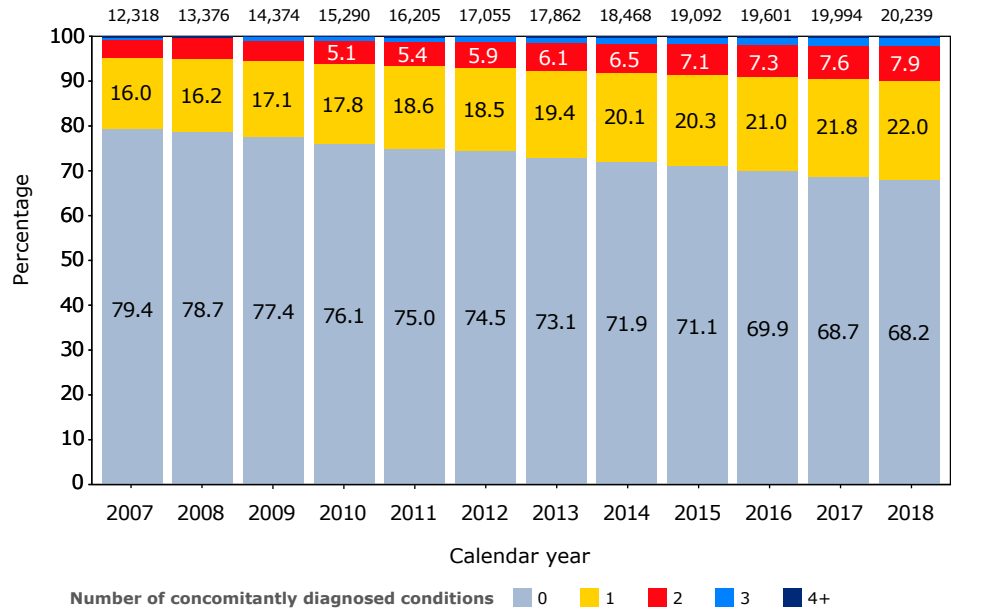
< Back to page 163

Appendix Figure 3.4: Prevalence of non-AIDS multimorbidity by gender in the adult population in 2018. 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.



< Back to page 166

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.



< Back to page 166

Appendix Table 3.1: Annual number of cases of death and first AIDS events among 26,435 HIV-1-positive individuals in the Netherlands recorded up to 31 December 2018.

	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	374	234	26	51	24
1997	316	153	52	87	63
1998	250	103	42	83	69
1999	232	113	55	91	89
2000	259	101	58	85	81
2001	260	127	63	83	79
2002	308	121	66	117	79
2003	314	140	73	142	117
2004	308	142	70	144	122
2005	375	175	88	143	117
2006	296	151	77	123	99
2007	332	168	91	152	127
2008	307	158	92	153	134
2009	304	139	77	162	143
2010	313	134	85	129	116
2011	255	119	75	151	135
2012	297	139	90	156	145
2013	260	125	90	148	139
2014	212	94	64	165	151
2015	238	115	91	159	152
2016	209	97	81	190	181
2017	174	73	63	169	161
2018	111	50	39	140	136

Legend: cART=combination antiretroviral therapy.

< Back to page 142

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 2011-2018.*

Causes of death	96-00	01-05	06-10	2011	2012	2013	2014	2015	2016	2017	2018
AIDS											
AIDS - infection	69	120	147	37	16	24	18	9	6	4	3
AIDS - malignancy	60	63	61	3	13	10	5	12	8	13	8
AIDS - unclassifiable	89	63	19	2	4	.	4	6	10	3	2
Subtotal	*218*	*246*	*227*	*42*	*33*	*34*	*27*	*27*	*24*	*20*	*13*
Non-AIDS malignancies	*30*	*95*	*135*	*31*	*43*	*37*	*41*	*40*	*49*	*62*	*39*
Cardiovascular disease											
Myocardial infarction	14	30	46	12	6	5	10	7	8	4	1
Stroke	3	11	13	2	4	1	1	3	7	3	3
Other CVD	6	24	26	10	5	6	16	13	16	10	13
Subtotal	*23*	*65*	*85*	*24*	*15*	*12*	*27*	*23*	*31*	*17*	*17*
Non-AIDS infection	*23*	*42*	*32*	*3*	*6*	*6*	*7*	*5*	*7*	*3*	*10*
Liver disease	*15*	*28*	*55*	*8*	*9*	*10*	*10*	*6*	*6*	*7*	*5*
Lung disease	*7*	*11*	*30*	*6*	*4*	*8*	*5*	*15*	*13*	*14*	*6*
Non-natural death											
Accident or violence	6	11	22	2	5	3	5	1	7	2	3
Suicide	12	25	11	6	7	3	4	8	3	6	3
Euthanasia	7	5	.	1	.	1	.	.	1	.	.
Subtotal	*25*	*41*	*33*	*9*	*12*	*7*	*9*	*9*	*11*	*8*	*6*
Alcohol and substance abuse	12	15	27	2	6	5	3	2	10	4	2
Other causes	21	29	42	10	13	12	18	14	19	15	21
Unknown	23	57	53	16	15	17	18	18	20	19	21
Total	**397**	**629**	**719**	**151**	**156**	**148**	**165**	**159**	**190**	**169**	**140**

< Back to page 142

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	1.32 (1.14-1.54)	<.001		0.93 (0.79-1.10)	0.413	
Region of birth						
Netherlands	1 (reference)		0.042	1 (reference)		0.028
Other	0.90 (0.81-1.00)	0.043		1.14 (1.01-1.29)	0.028	
HIV-1 transmission route						
Blood contact	0.72 (0.51-1.03)	0.069		0.83 (0.56-1.22)	0.334	
Heterosexual	1.05 (0.93-1.20)	0.437		0.83 (0.71-0.97)	0.018	
IDU	1.63 (1.34-1.99)	<.001		0.63 (0.48-0.82)	<.001	
MSM	1 (reference)		<.001	1 (reference)		<.001
Age*						
18-29	0.93 (0.67-1.30)	0.673	<.001	1.05 (0.85-1.29)	0.655	<.001
30-39	1 (reference)			1 (reference)		
40-49	1.54 (1.32-1.80)	<.001		1.08 (0.95-1.24)	0.228	
50-59	2.71 (2.31-3.17)	<.001		1.32 (1.14-1.54)	<.001	
60-69	4.76 (4.01-5.64)	<.001		1.37 (1.13-1.68)	0.002	
70+	10.38 (8.45-12.76)	<.001		1.75 (1.22-2.53)	0.003	
CD4 cell count**						
0-50	13.84 (11.42-16.77)	<.001	<.001	6.39 (5.12-7.99)	<.001	<.001
50-199	5.10 (4.40-5.90)	<.001		2.64 (2.23-3.14)	<.001	
200-349	2.18 (1.88-2.52)	<.001		1.56 (1.32-1.85)	<.001	
350-499	1.42 (1.22-1.65)	<.001		1.24 (1.05-1.48)	0.013	
500-749	1 (reference)			1 (reference)		
750+	0.88 (0.74-1.04)	0.138		1.09 (0.89-1.35)	0.399	
Per year longer on cART with HIV RNA >1,000 copies/ml	1.06 (1.04-1.08)	<.001	<.001	1.03 (1.01-1.06)	0.013	0.015
Treatment status at start cART						
Treatment-experienced	0.93 (0.83-1.03)	0.159		0.62 (0.55-0.71)	<.001	
Treatment-naive	1 (reference)			1 (reference)		
Prior AIDS event	1.76 (1.60-1.94)	<.001				
Hepatitis B virus positive	1.33 (1.15-1.54)	<.001		1.12 (0.92-1.36)	0.266	
Hepatitis C virus positive	1.53 (1.31-1.79)	<.001		1.35 (1.11-1.63)	0.002	

< Back to page 144

			Death			AIDS
	RR (95% CI)	p-value	Overall p-value	RR (95% CI)	p-value	Overall p-value
Body mass index*						
<18	3.17 (2.77-3.62)	<.001	<.001			
18-25	1 (reference)					
25-30	0.66 (0.58-0.74)	<.001				
30+	0.81 (0.67-0.98)	0.034				
Smoking status						
Current smoker	1.08 (0.94-1.24)	0.293	<.001	0.75 (0.66-0.85)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	2.20 (1.93-2.50)	<.001		0.89 (0.77-1.04)	0.135	
Early cART***	0.85 (0.58-1.26)	0.430		1.13 (0.85-1.52)	0.400	

**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 2018) 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)
0–50	46	2,614	17.6 (12.9–23.5)	2	195	10.2 (1.2–37.0)	8	183	43.7 (18.8–86.0)
050–199	190	9,266	20.5 (17.7–23.6)	10	501	20.0 (9.6–36.7)	35	1,087	32.2 (22.4–44.8)
200–349	410	20,531	20.0 (18.1–22.0)	17	1,011	16.8 (9.8–26.9)	76	1,608	47.3 (37.2–59.2)
350–499	537	37,724	14.2 (13.1–15.5)	34	1,626	20.9 (14.5–29.2)	109	3,107	35.1 (28.8–42.3)
500–749	721	82,976	8.7 (8.1–9.3)	48	3,902	12.3 (9.1–16.3)	179	6,989	25.6 (22.0–29.7)
750+	471	89,606	5.3 (4.8–5.8)	35	4,188	8.4 (5.8–11.6)	144	8,038	17.9 (15.1–21.1)

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

< Back to page 144

	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)
	7	1,733	4.0 (1.6-8.3)	23	410	56.1 (35.6-84.2)	6	92	65.0 (23.9-141.5)
	29	5,699	5.1 (3.4-7.3)	109	1,738	62.7 (51.5-75.7)	7	242	28.9 (11.6-59.6)
	76	13,070	5.8 (4.6-7.3)	212	4,097	51.7 (45.0-59.2)	29	744	39.0 (26.1-56.0)
	121	24,459	4.9 (4.1-5.9)	254	6,871	37.0 (32.6-41.8)	19	1,660	11.4 (6.9-17.9)
	206	56,336	3.7 (3.2-4.2)	266	12,621	21.1 (18.6-23.8)	22	3,128	7.0 (4.4-10.6)
	153	63,499	2.4 (2.0-2.8)	127	10,856	11.7 (9.8-13.9)	12	3,025	4.0 (2.0-6.9)

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 2011-2018.*

CDC event	1996-2000	2001-2005	2006-2010	2011-2015	2016-2018	Total	
	n	n	n	n	n	n	%
AIDS dementia complex / HIV encephalopathy	37	47	51	44	13	192	3.05
Bacterial pneumonia, recurrent	48	63	65	76	50	302	4.80
CMV ≥13 years	27	35	29	34	3	128	2.03
CMV colitis/proctitis	1	.	.	.	3	4	0.06
CMV meningo-encephalitis	.	.	.	.	1	1	0.02
CMV pneumonitis	.	.	.	.	4	4	0.06
CMV retinitis	30	20	12	11	7	80	1.27
Candidiasis trachea, bronchi, lungs	7	13	7	6	3	36	0.57
Candidiasis oesophageal	258	236	251	221	79	1,045	16.60
Cervical cancer	3	4	6	5	3	21	0.33
Coccidioidomycosis, disseminated or extrapulmonary	.	.	1	.	.	1	0.02
Cryptococcosis, disseminated or extrapulmonary	21	31	33	11	9	105	1.67
Cryptosporidiosis	22	12	10	12	2	58	0.92
Cystoisosporiasis	3	9	6	.	.	18	0.29
Wasting syndrome due to HIV	48	57	77	76	37	295	4.68
Herpes simplex virus, chronic ulcer	.	1	.	3	5	9	0.14
Herpes simplex virus	32	41	60	37	9	179	2.84
Histoplasmosis, disseminated or extrapulmonary	9	12	10	7	1	39	0.62
Kaposi's sarcoma	153	151	186	137	39	666	10.58
Leishmaniasis, visceral	.	1	2	2	2	7	0.11
Microsporidiosis	11	1	3	1	.	16	0.25
Mycobacterium, other species/unidentified (disseminated/extrapulmonary)	20	13	7	10	3	53	0.84
Mycobacterium, other species/unidentified (pulmonary)	.	3	4	10	3	20	0.32
Mycobacterium avium/kansasii (disseminated/ extrapulmonary)	25	19	28	9	6	87	1.38
Mycobacterium avium/kansasii (pulmonary)	.	1	.	.	4	5	0.08
Non-Hodgkin's lymphoma (NHL), AIDS-defining	59	86	81	94	32	352	5.59
Penicilliosis	.	.	1	.	.	1	0.02
Pneumocystis jirovecii extrapulmonary	1	1	3	.	.	5	0.08
Pneumocystis jirovecii pulmonary	335	297	326	263	117	1,338	21.25
Primary central nervous system lymphoma	8	5	9	7	4	33	0.52
Progressive multifocal leucoencephalopathy	18	25	35	23	3	104	1.65

< Back to page 144

CDC event	1996-2000	2001-2005	2006-2010	2011-2015	2016-2018	Total	
	n	n	n	n	n	n	%
Salmonella septicaemia, recurrent	2	.	.	.	.	2	0.03
Toxoplasmosis of the brain	70	97	55	42	17	281	4.46
Tuberculosis, extrapulmonary/disseminated	78	110	81	51	9	329	5.22
Tuberculosis, pulmonary	103	172	113	67	26	481	7.64
Total	**1,429**	**1,563**	**1,552**	**1,259**	**494**	**6,297**	**100.00**

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

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	12,055	0.5 (0.2-1.1)	25	6,515	3.8 (2.5-5.7)
30-39	85	41,457	2.1 (1.6-2.5)	78	15,707	5.0 (3.9-6.2)
40-49	280	67,825	4.1 (3.7-4.6)	99	14,971	6.6 (5.4-8.1)
50-59	330	49,565	6.7 (6.0-7.4)	62	6,966	8.9 (6.8-11.4)
60-69	204	18,648	10.9 (9.5-12.5)	20	2,373	8.4 (5.1-13.0)
70+	44	4,182	10.5 (7.6-14.1)	5	710	7.0 (2.3-16.4)

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	12,051	0.5 (0.2-1.1)	6	6,577	0.9 (0.3-2.0)
30-39	59	41,561	1.4 (1.1-1.8)	22	16,002	1.4 (0.9-2.1)
40-49	293	68,090	4.3 (3.8-4.8)	57	15,367	3.7 (2.8-4.8)
50-59	457	49,345	9.3 (8.4-10.2)	29	7,268	4.0 (2.7-5.7)
60-69	289	18,234	15.8 (14.1-17.8)	22	2,415	9.1 (5.7-13.8)
70+	91	3,949	23.0 (18.6-28.3)	7	694	10.1 (4.1-20.8)

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

< Back to page 146

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	4	8,930	0.4 (0.1-1.1)	4	3,539	1.1 (0.3-2.9)
30-39	39	25,952	1.5 (1.1-2.1)	10	9,908	1.0 (0.5-1.9)
40-49	179	47,323	3.8 (3.2-4.4)	57	11,526	4.9 (3.7-6.4)
50-59	433	39,729	10.9 (9.9-12.0)	113	5,856	19.3 (15.9-23.2)
60-69	506	15,333	33.0 (30.2-36.0)	93	1,790	52.0 (41.9-63.6)
70+	212	2,893	73.3 (63.7-83.8)	32	385	83.1 (56.8-117.2)

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	12,044	0.9 (0.5-1.6)	4	6,593	0.6 (0.2-1.6)
30-39	67	41,501	1.6 (1.3-2.1)	20	16,016	1.2 (0.8-1.9)
40-49	230	68,475	3.4 (2.9-3.8)	57	15,454	3.7 (2.8-4.8)
50-59	340	50,567	6.7 (6.0-7.5)	49	7,274	6.7 (5.0-8.9)
60-69	261	19,264	13.5 (12.0-15.3)	16	2,449	6.5 (3.7-10.6)
70+	99	4,152	23.8 (19.4-29.0)	9	727	12.4 (5.7-23.5)

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	12,067	0.1 (0.0-0.5)	2	6,599	0.3 (0.0-1.1)
30-39	27	41,649	0.6 (0.4-0.9)	6	16,049	0.4 (0.1-0.8)
40-49	185	68,477	2.7 (2.3-3.1)	25	15,519	1.6 (1.0-2.4)
50-59	247	50,327	4.9 (4.3-5.6)	17	7,376	2.3 (1.3-3.7)
60-69	164	19,147	8.6 (7.3-10.0)	9	2,479	3.6 (1.7-6.9)
70+	33	4,361	7.6 (5.2-10.6)	1	750	1.3 (0.0-7.4)

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	12,051	0.4 (0.1-1.0)	3	6,584	0.5 (0.1-1.3)
30-39	31	41,624	0.7 (0.5-1.1)	16	16,018	1.0 (0.6-1.6)
40-49	92	68,798	1.3 (1.1-1.6)	31	15,484	2.0 (1.4-2.8)
50-59	145	50,947	2.8 (2.4-3.3)	11	7,375	1.5 (0.7-2.7)
60-69	106	19,601	5.4 (4.4-6.5)	11	2,475	4.4 (2.2-8.0)
70+	46	4,423	10.4 (7.6-13.9)	6	738	8.1 (3.0-17.7)

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	12,067	0.0 (0.0.-0.3)
30-39	11	41,693	0.3 (0.1-0.5)
40-49	57	68,916	0.8 (0.6-1 .1)
50-59	77	51,217	1.5 (1.2-1.9)
60-69	24	20,008	1.2 (0.8-1.8)
70+	3	4,664	0.6 (0.1-1.9)

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	12,016	1.8 (1.1-2.8)	33	6,480	5.1 (3.5-7.2)
30-39	200	41,117	4.9 (4.2-5.6)	112	15,605	7.2 (5.9-8.6)
40-49	742	66,229	11.2 (10.4-12.0)	197	14,578	13.5 (11.7-15.5)
50-59	999	46,497	21.5 (20.2-22.9)	126	6,627	19.0 (15.8-22.6)
60-69	601	16,239	37.0 (34.1-40.1)	48	2,207	21.7 (16.0-28.8)
70+	178	3,173	56.1 (48.2-65.0)	16	587	27.3 (15.6-44.3)

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	1.22 (1.08-1.36)	<.001	.	1.68 (1.37-2.06)	<.001	.
Region of birth						
Netherlands	1 (reference)	.	0.649	1 (reference)	.	0.012
Other	1.02 (0.94-1.10)	0.649	.	0.85 (0.74-0.97)	0.013	.
HIV-1 transmission route						
MSM	1 (reference)	.	<.001	1 (reference)	.	<.001
Heterosexual	1.26 (1.14-1.39)	<.001	.	1.31 (1.13-1.52)	<.001	.
IDU	1.38 (1.12-1.70)	0.002	.	1.31 (0.95-1.82)	0.103	.
Blood contact	1.32 (1.02-1.72)	0.035	.	1.31 (0.87-1.97)	0.188	.
Age*						
18-29	0.58 (0.43-0.78)	<.001	<.001	0.47 (0.25-0.90)	0.022	<.001
30-39	1 (reference)	.	.	1 (reference)	.	.
40-49	2.04 (1.79-2.33)	<.001	.	2.70 (2.11-3.46)	<.001	.
50-59	3.74 (3.28-4.28)	<.001	.	5.61 (4.39-7.18)	<.001	.
60-69	6.35 (5.48-7.35)	<.001	.	9.73 (7.49-12.64)	<.001	.
70+	9.41 (7.75-11.44)	<.001	.	14.35 (10.45-19.70)	<.001	.
CD4 cell count**						
<50	4.08 (3.18-5.24)	<.001	<.001	3.10 (1.99-4.82)	<.001	<.001
50-199	1.84 (1.57-2.16)	<.001	.	1.54 (1.19-2.01)	0.001	.
200-349	1.27 (1.13-1.43	<.001	.	1.32 (1.10-1.59)	0.003	.
350-499	1.07 (0.97-1.19)	0.183	.	1.14 (0.97-1.34)	0.120	.
500-749	1 (reference)	.	.	1 (reference)	.	.
750+	1.16 (1.05-1.28)	0.003	.	1.35 (1.16-1.57)	<.001	.
Per year longer with CD4 <200 cells/mm^3	.	0.215	.	1.01 (0.97-1.05)	0.613	.
Prior AIDS event	1.25 (1.15-1.35)	<.001	.	1.14 (1.01-1.29)	0.040	.
Per year longer on cART while HIV RNA>1000 copies/ml	1.03 (1.00-1.05)	0.017	.	1.03 (0.99-1.06)	0.125	.
Treatment status						
Not (yet) started cART	1.19 (1.04-1.36)	0.012	<.001	0.98 (0.77-1.25)	0.875	0.021
Treatment-experienced at start cART	1.33 (1.21-1.47)	<.001	.	1.24 (1.07-1.45)	0.005	.
Treatment-naive at start	1 (reference)	.	.	1 (reference)	.	.
Per year longer on cART	1.01 (1.00-1.01)	0.228	.	1.00 (0.99-1.01)	0.900	.
Early cART within 12 months after last HIV-negative	0.89 (0.70-1.14)	0.352	.	1.16 (0.82-1.63)	0.404	.

< Back to page 149

	Non-AIDS-defining malignancy			Diabetes mellitus			CKD		
	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value
	1.05 (0.85–1.29)	0.653	.	1.19 (1.01–1.42)	0.042	.	0.62 (0.53–0.74)	<.001	.
	1 (reference)	.	0.019	1 (reference)	.	<.001	1 (reference)	.	<.001
	0.84 (0.73–0.97)	0.020	.	1.42 (1.25–1.62)	<.001	.	0.78 (0.70–0.88)	<.001	.
	1 (reference)	.	0.026	1 (reference)	.	<.001	1 (reference)	.	0.073
	0.99 (0.83–1.17)	0.886	.	1.54 (1.32–1.81)	<.001	.	1.00 (0.86–1.16)	0.998	.
	1.48 (1.07–2.06)	0.018	.	1.61 (1.13–2.30)	0.008	.	1.41 (1.04–1.90)	0.026	.
	1.65 (1.13–2.42)	0.010	.	1.64 (1.11–2.44)	0.014	.	1.33 (0.94–1.89)	0.112	.
	0.69 (0.41–1.17)	0.173	<.001	0.60 (0.40–0.89)	0.012	<.001	0.34 (0.15–0.81)	0.015	<.001
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	2.25 (1.75–2.89)	<.001	.	1.55 (1.28–1.88)	<.001	.	2.98 (2.18–4.07)	<.001	.
	4.33 (3.37–5.56)	<.001	.	2.40 (1.97–2.93)	<.001	.	8.18 (6.06–11.05)	<.001	.
	8.31 (6.38–10.83)	<.001	.	4.08 (3.26–5.10)	<.001	.	23.03 (17.01–31.17)	<.001	.
	14.70 (10.74–20.12)	<.001	.	4.06 (2.87–5.75)	<.001	.	45.09 (32.63–62.31)	<.001	.
	3.05 (1.86–5.00)	<.001	<.001	6.11 (4.29–8.70)	<.001	<.001	1.67 (0.88–3.17)	0.015	0.004
	2.06 (1.58–2.69)	<.001	.	1.95 (1.51–2.52)	<.001	.	1.61 (1.25–2.07)	<.001	.
	1.39 (1.15–1.69)	<.001	.	1.09 (0.90–1.33)	0.383	.	1.13 (0.95–1.34)	0.166	.
	1.09 (0.92–1.29)	0.332	.	0.97 (0.82–1.15)	0.740	.	1.02 (0.89–1.17)	0.810	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	0.97 (0.82–1.14)	0.682	.	1.16 (0.99–1.36)	0.059	.	0.93 (0.82–1.06)	0.267	.
	0.97 (0.93–1.00)	0.081	.	0.98 (0.94–1.02)	0.243	.	0.98 (0.95–1.02)	0.309	.
	1.27 (1.11–1.45)	<.001	.	1.34 (1.18–1.53)	<.001	.	1.14 (1.02–1.27)	0.018	.
	1.00 (0.97–1.04)	0.822	.	1.02 (0.98–1.05)	0.370	.	0.98 (0.95–1.01)	0.266	.
	1.28 (1.02–1.62)	0.035	0.007	1.42 (1.15–1.77)	0.001	<.001	0.41 (0.28–0.59)	<.001	<.001
	1.23 (1.04–1.46)	0.015	.	1.29 (1.08–1.54)	0.005	.	1.15 (0.99–1.34)	0.067	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	1.00 (0.99–1.02)	0.609	.	1.00 (0.99–1.02)	0.846	.	0.99 (0.98–1.00)	0.101	.
	0.46 (0.27–0.80)	0.006	.	0.92 (0.59–1.42)	0.694	.	0.94 (0.72–1.24)	0.676	.

	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*						
0-18	1.44 (1.17-1.78)	<.001	<.001	1.10 (0.78-1.56)	0.578	0.172
18-25	1 (reference)	.	.	1 (reference)	.	.
25-30	1.20 (1.10-1.31)	<.001	.	0.99 (0.86-1.13)	0.862	.
30+	1.88 (1.67-2.12)	<.001	.	1.05 (0.84-1.31)	0.650	.
Hepatitis B virus positive	1.17 (1.03-1.34)	0.019	.	1.02 (0.82-1.28)	0.832	.
Hepatitis C virus positive	1.04 (0.91-1.19)	0.542	.	0.99 (0.80-1.22)	0.918	.
Hypertension	1.14 (1.05-1.22)	<.001	.	1.19 (1.06-1.33)	0.004	.
Smoking status						
Current smoker	1.37 (1.25-1.50)	<.001	<.001	1.86 (1.61-2.15)	<.001	<.001
Never smoker	1 (reference)	.	.	1 (reference)	.	.
Past smoker	1.45 (1.32-1.60)	<.001	.	1.58 (1.35-1.85)	<.001	.
Calendar year period						
2000-2005	1.19 (1.06-1.33)	0.004	<.001	1.45 (1.21-1.74)	<.001	<.001
2006-2010	1.23 (1.13-1.35)	<.001	.	1.27 (1.10-1.47)	0.001	.
2011-2018	1 (reference)	.	.	1 (reference)	.	.
Recent use of ABC***		.	.	1.56 (1.38-1.77)	<.001	.
Per year longer on LOP/r		.	.	1.01 (0.99-1.03)	0.198	.
Per year longer on IDV		.	.	1.00 (0.99-1.01)	0.821	.
Per year longer on ZDV		.	.		.	.
Per year longer on d4T		.	.		.	.
Per year longer on ddI		.	.		.	.
Per year longer on TAF		.	.		.	.
Per year longer on TDF		.	.		.	.
Prior cardiovascular event		.	.		.	.
Prior diabetes		.	.		.	.
Current use of cobicistat		.	.		.	.
Current use of dolutegravir		.	.		.	.
Current use of rilpivirine		.	.		.	.
Current use of bictegravir		.	.		.	.

**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; TDF=tenofovir disoproxil fumarate; TAF=tenofovir alafenamide; RPV=rilpivirine; BIC=bictegravir; BMI: <18 kg/m² =underweight; 18-25 kg/m2=normal; 25-30 kg/m²=overweight; >30 kg/m²=severely overweight.*

	Non-AIDS-defining malignancy			Diabetes mellitus			CKD		
	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value
	1.99 (1.50–2.64)	<.001	<.001	1.34 (0.90–2.00)	0.152	<.001	1.59 (1.18–2.13)	0.002	0.021
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	0.83 (0.71–0.97)	0.017	.	2.17 (1.87–2.51)	<.001	.	1.09 (0.97–1.23)	0.138	.
	0.98 (0.77–1.25)	0.890	.	4.55 (3.83–5.41)	<.001	.	1.15 (0.97–1.37)	0.115	.
	1.64 (1.35–2.00)	<.001	.	1.08 (0.86–1.36)	0.498	.	1.45 (1.20–1.74)	<.001	.
	1.05 (0.84–1.31)	0.683	.	1.05 (0.83–1.32)	0.702	.	1.40 (1.19–1.65)	<.001	.
	0.94 (0.82–1.07)	0.333	.	1.19 (1.06–1.35)	0.004	.	1.13 (1.02–1.25)	0.019	.
	1.44 (1.23–1.69)	<.001	<.001	0.97 (0.84–1.13)	0.718	<.001	0.85 (0.75–0.96)	0.008	<.001
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	1.73 (1.47–2.04)	<.001	.	1.27 (1.08–1.48)	0.003	.	0.98 (0.87–1.11)	0.720	.
	0.88 (0.71–1.08)	0.212	0.021	1.19 (0.98–1.44)	0.082	0.091		.	.
	1.15 (0.98–1.33)	0.078	.	1.17 (1.00–1.36)	0.046	.	1.06 (0.92–1.23)	0.421	0.423
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.	1.01 (1.00–1.02)	0.092	.		.	.
		.	.	1.03 (1.00–1.06)	0.063	.		.	.
		.	.	1.06 (1.03–1.10)	<.001	.		.	.
		.	.		.	.	1.09 (0.94–1.27)	0.264	.
		.	.		.	.	1.01 (1.00–1.01)	0.245	.
		.	.		.	.	1.60 (1.35–1.89)	<.001	.
		.	.		.	.	1.37 (1.15–1.64)	<.001	.
		.	.		.	.	1.59 (1.34–1.89)	<.001	.
		.	.		.	.	3.36 (2.99–3.78)	<.001	.
		.	.		.	.	1.44 (1.18–1.76)	<.001	<.001
		.	.		.	.	10.26 (2.55–41.33)	0.001	0.017

Appendix Table 3.8: *Specific CDC-B and CDC-C (AIDS) events occurring in individuals on cART with undetectable viral load between 2000 and 2018.*

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Aspergillosis, invasive pulmonary	2	0.1%	0	0.0%
	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis oropharyngeal ≥13 years	681	21.8%	57	25.2%
	Candidiasis vulvovaginal, recurrent/ persistent	54	1.7%	1	0.4%
	Cardiomyopathy, HIV-related	3	0.1%	0	0.0%
	Cardiomyopathy, with HIV component	10	0.3%	1	0.4%
	Cervical dysplasia	538	17.2%	9	4.0%
	Diarrhoea, HIV-related ≥30 days	64	2.1%	1	0.4%
	Herpes zoster, multidermatomal	7	0.2%	0	0.0%
	Herpes zoster, recurrent/ unspecified multidermatomal	218	7.0%	10	4.4%
	Herpes zoster, recurrent unidermatomal	1	0.0%	1	0.4%
	HIV-associated nephropathy	20	0.6%	2	0.9%
	Fever of unknown origin / HIV-related fever	6	0.2%	0	0.0%
	Myelopathy, HIV-related	10	0.3%	0	0.0%
	Neuropathy, HIV-related	87	2.8%	2	0.9%
	Neuropathy, with HIV component	41	1.3%	1	0.4%
	Nocardiosis	1	0.0%	1	0.4%
	Oral hairy leucoplakia	51	1.6%	1	0.4%
	Pelvic inflammatory disease	4	0.1%	0	0.0%
	Thrombocytopenia, ≥13 years, HIV-related	94	3.0%	2	0.9%
	Thrombocytopenia, ≥13 years, with HIV component	6	0.2%	1	0.4%
	Weight loss (>10%) HIV-related or unknown origin	38	1.2%	2	0.9%
Subtotal		**1,937**	**62.1%**	**92**	**40.7%**
CDC-C events	AIDS dementia complex – HIV encephalopathy	45	1.4%	4	1.8%
	Bacterial pneumonia, recurrent	282	9.0%	15	6.6%
	CMV ≥13 years	19	0.6%	4	1.8%
	CMV oesophagitis	1	0.0%	1	0.4%
	CMV retinitis	15	0.5%	2	0.9%
	Candidiasis trachea, bronchi, lungs	9	0.3%	2	0.9%
	Candidiasis, esophageal	212	6.8%	24	10.6%
	Cervical cancer	8	0.3%	1	0.4%
	Coccidioidomycosis, disseminated/extrapulmonary	1	0.0%	0	0.0%

< Back to page 145

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%	1	0.2%	0	0.0%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
170	29.4%	140	20.1%	116	19.2%	124	18.9%	74	20.5%
5	0.9%	10	1.4%	17	2.8%	15	2.3%	6	1.7%
0	0.0%	0	0.0%	2	0.3%	0	0.0%	1	0.3%
3	0.5%	1	0.1%	2	0.3%	2	0.3%	1	0.3%
56	9.7%	121	17.4%	121	20.0%	144	22.0%	87	24.1%
6	1.0%	16	2.3%	11	1.8%	22	3.4%	8	2.2%
0	0.0%	2	0.3%	2	0.3%	1	0.2%	2	0.6%
24	4.2%	52	7.5%	45	7.5%	56	8.5%	31	8.6%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
3	0.5%	3	0.4%	4	0.7%	4	0.6%	4	1.1%
1	0.2%	2	0.3%	0	0.0%	1	0.2%	2	0.6%
4	0.7%	2	0.3%	0	0.0%	1	0.2%	3	0.8%
8	1.4%	16	2.3%	24	4.0%	22	3.4%	15	4.2%
7	1.2%	8	1.2%	9	1.5%	10	1.5%	6	1.7%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
14	2.4%	11	1.6%	8	1.3%	9	1.4%	8	2.2%
0	0.0%	1	0.1%	0	0.0%	2	0.3%	1	0.3%
20	3.5%	20	2.9%	20	3.3%	21	3.2%	11	3.0%
1	0.2%	3	0.4%	0	0.0%	1	0.2%	0	0.0%
5	0.9%	9	1.3%	7	1.2%	9	1.4%	6	1.7%
329	**56.9%**	**417**	**60.0%**	**388**	**64.2%**	**445**	**67.9%**	**266**	**73.7%**
8	1.4%	10	1.4%	8	1.3%	8	1.2%	7	1.9%
49	8.5%	76	10.9%	61	10.1%	59	9.0%	22	6.1%
4	0.7%	3	0.4%	5	0.8%	1	0.2%	2	0.6%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
5	0.9%	2	0.3%	5	0.8%	1	0.2%	0	0.0%
1	0.2%	4	0.6%	0	0.0%	1	0.2%	1	0.3%
51	8.8%	50	7.2%	35	5.8%	30	4.6%	22	6.1%
1	0.2%	2	0.3%	1	0.2%	3	0.5%	0	0.0%
0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
	Cryptococcosis extrapulmonary	16	0.5%	6	2.7%
	Cryptosporidiosis	10	0.3%	4	1.8%
	Cystoisosporiasis	1	0.0%	0	0.0%
	HIV wasting	16	0.5%	7	3.1%
	Herpes simplex virus, chronic ulcer	8	0.3%	0	0.0%
	Herpes simplex virus	62	2.0%	7	3.1%
	Histoplasmosis, disseminated or extrapulmonary	4	0.1%	3	1.3%
	Kaposi sarcoma	93	3.0%	5	2.2%
	Leishmaniasis, visceral	5	0.2%	1	0.4%
	Microsporidiosis	5	0.2%	2	0.9%
	Mycobacterium, other/unidentified (disseminated/extrapulmonary)	6	0.2%	1	0.4%
	Mycobacterium, other/unidentified (pulmonary)	5	0.2%	0	0.0%
	Mycobacterium avium / M. kansasii, disseminated/extrapulmonary	20	0.6%	5	2.2%
	Mycobacterium avium/kansasii, pulmonary	3	0.1%	0	0.0%
	non-Hodgkin's lymphoma, AIDS-defining	127	4.1%	7	3.1%
	Pneumocystis jirovecii, extrapulmonary	1	0.0%	0	0.0%
	Pneumocystis jirovecii, pulmonary	64	2.1%	16	7.1%
	Primary central nervous system lymphoma	5	0.2%	0	0.0%
	Progressive multifocal leucoencephalopathy	18	0.6%	4	1.8%
	Toxoplasmosis of the brain	17	0.5%	8	3.5%
	Tuberculosis, extrapulmonary/disseminated	36	1.2%	2	0.9%
	Tuberculosis, pulmonary	68	2.2%	3	1.3%
Subtotal		**1,182**	**37.9%**	**134**	**59.3%**
Total		**3,119**	**100.0%**	**226**	**100.0%**

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

CD4 category										
50–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
5	0.9%	3	0.4%	1	0.2%	1	0.2%	0	0.0%
0	0.0%	1	0.1%	3	0.5%	1	0.2%	1	0.3%
0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
5	0.9%	1	0.1%	2	0.3%	1	0.2%	0	0.0%
0	0.0%	0	0.0%	1	0.2%	5	0.8%	2	0.6%
6	1.0%	13	1.9%	16	2.6%	16	2.4%	4	1.1%
0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
10	1.7%	24	3.5%	21	3.5%	22	3.4%	11	3.0%
3	0.5%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
2	0.3%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
1	0.2%	3	0.4%	0	0.0%	1	0.2%	0	0.0%
2	0.3%	0	0.0%	2	0.3%	1	0.2%	0	0.0%
7	1.2%	4	0.6%	2	0.3%	1	0.2%	1	0.3%
0	0.0%	1	0.1%	0	0.0%	1	0.2%	1	0.3%
32	5.5%	33	4.7%	24	4.0%	24	3.7%	7	1.9%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
24	4.2%	10	1.4%	7	1.2%	6	0.9%	1	0.3%
1	0.2%	2	0.3%	1	0.2%	1	0.2%	0	0.0%
6	1.0%	4	0.6%	2	0.3%	2	0.3%	0	0.0%
3	0.5%	4	0.6%	1	0.2%	1	0.2%	0	0.0%
8	1.4%	7	1.0%	4	0.7%	10	1.5%	5	1.4%
15	2.6%	19	2.7%	14	2.3%	11	1.7%	6	1.7%
249	**43.1%**	**278**	**40.0%**	**216**	**35.8%**	**210**	**32.1%**	**95**	**26.3%**
578	**100.0%**	**695**	**100.0%**	**604**	**100.0%**	**655**	**100.0%**	**361**	**100.0%**

4. Viral hepatitis

Colette Smit, Anders Boyd, Marc van der Valk, Joop Arends, Peter Reiss

Box 4.1: Definitions of hepatitis C 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[1]
   Positive anti-HCV IgG with 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[1]
   Detectable HCV RNA in association with a rise in alanine aminotransferase (ALT) (>200 IU/l) with a documented normal ALT within the past 12 months.

Spontaneously cleared HCV infection

1. Individuals with a documented positive test result for HCV antibody, a subsequent negative HCV RNA test result and no prior history of medical treatment.
2. Individuals who did not fulfil the definition of acute HCV infection, but had a positive HCV RNA test result that became negative within 6 months without treatment.

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.

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.

Hepatitis C re-infection
Detectable HCV RNA after an earlier achieved SVR12 or SVR24, or spontaneous HCV clearance, or documentation of a new infection with a different genotype.

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 radiographically or endoscopically documented evidence of the presence of portal hypertension in terms of oesophageal varices, ascites, splenomegaly and reversal of portal blood flow and/or cirrhosis.

Definitive if:
Liver transplantation or presumptive combined with a pathology, histology 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[3,4,5]. In contrast, HCV and HBV co-infections are far more prevalent in HIV-positive individuals due to shared routes of transmission[6].

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)[7,8]. HBV infection can also directly lead to HCC without prior cirrhosis. Progression to severe liver disease takes, on average, 20 to 30 years in individuals mono-infected with HCV or HBV[9,10]. While 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 since become increasingly similar to that in HCV or HBV mono-infected individuals[11,12].

This chapter reports on the demographic and clinical characteristics, 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.

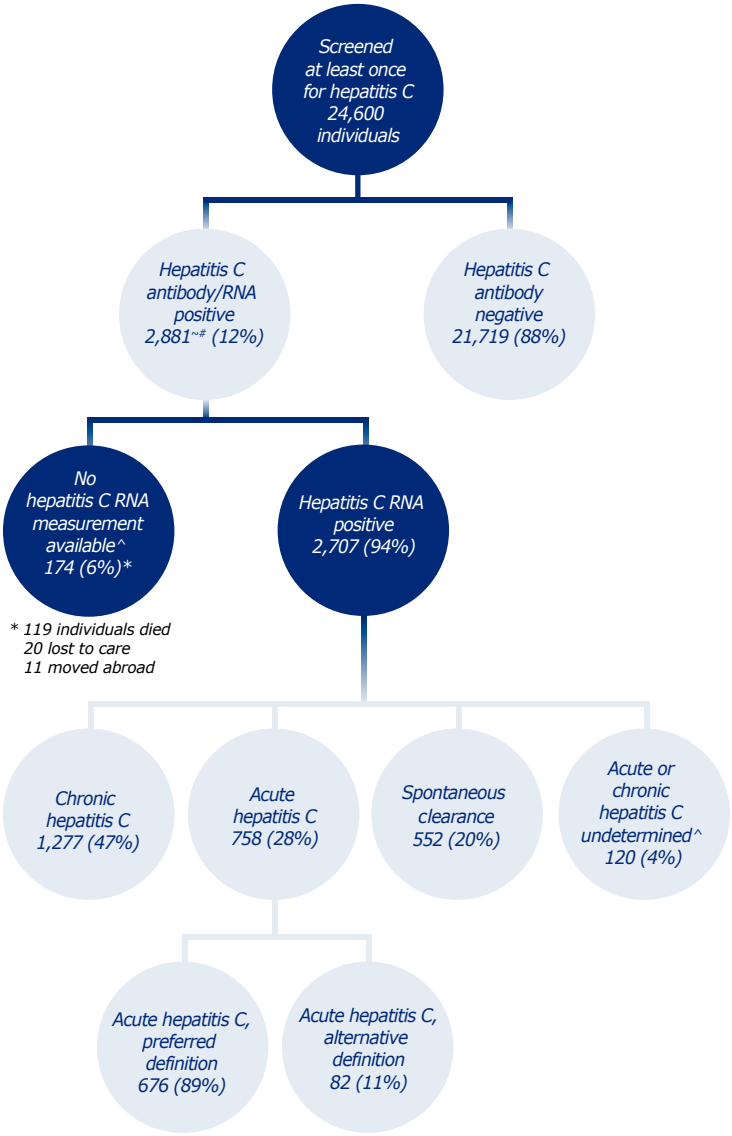
Population described in this chapter
All individuals ever registered up to 1 May 2019, based on the database lock in May 2019.

HCV

Demographic and clinical characteristics

As of May 2019, 26,247 HIV-1-positive adults (≥18 years of age at time of HIV-1 diagnosis) had ever been registered by Stichting HIV Monitoring (SHM) and in care in one of the HIV treatment centres in the Netherlands. Of those individuals, 24,600 (94%) were ever screened for HCV co-infection and 2,881 (12%) had a positive result with an HCV antibody test and/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 174 of these 2,881 individuals (6%). Of these 174 individuals, 119 are known to have died, 20 to have been lost to care, and 11 to have moved abroad; for the remaining 24 individuals with a positive HCV antibody test result, the reason for an undocumented HCV RNA was unknown. Of the remaining 2,707 individuals with positive HCV RNA test results, 758 (28%) were initially diagnosed with acute HCV infection that progressed to chronic infection and 1,277 (47%) were classified as already having chronic HCV infection (HCV RNA test result documented to have remained positive for more than 6 months after the first positive result at time of HCV diagnosis). Another 552 (20%) individuals had evidence of spontaneous clearance of HCV; the demographic characteristics of these are shown in *Appendix table 4.1*. The remaining 120 individuals of the 2,704 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.

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



~ including individuals who are HCV RNA positive, but with no known HCV antibody data
# including documented seroconversion
^ excluded from further analyses

The analyses described in the remainder of this section on HCV are therefore limited to the 2,035 individuals who could be definitively classified as having either chronic (n=1,277) or acute (n=758) HCV infection at the time of the primary HCV diagnosis. Most of these were male (81% and 99%, respectively), and the majority originated from the Netherlands (chronic: 737/1,277 [58%]; acute: 583/758 [77%]) (*Table 4.1*). Fifty-nine percent of the individuals ever registered and who had acquired HIV through injecting drug use (IDU) had a chronic HCV infection (436 of the total 739 people who use/used injecting drugs [PWID]). In the men who have sex with men (MSM) HIV transmission group, 3% had a chronic HCV infection (521 of the total of 15,041 MSM) and 5% had a documented acute HCV infection (715 of the total of 15,041 MSM). Finally, compared with individuals without acute or chronic HCV, those with spontaneous clearance of HCV more often were female, and less often Dutch ($p<0.001$) (*Table 4.1*).

Table 4.1: Demographic characteristics of individuals co-infected with HIV/hepatitis C virus (HCV) registered in the SHM database, 1998-2018.

	Total	Chronic HCV	Acute HCV
Total number of individuals screened for HCV	24,600	1,277	758
Male gender, n (%)	20,204 (82)	1,038 (81)	749 (99)
Region, n (%)			
Netherlands	13,835 (56)	737 (58)	583 (77)
Europe	1,634 (7)	200 (16)	65 (9)
Sub-Saharan Africa	3,348 (14)	44 (3)	11 (1)
Caribbean/South America	3,005 (12)	84(7)	46 (6)
South-east Asia	862 (3)	43 ()	18 (2)
Other	1,916 (8)	169 (13)	35 (5)
HIV transmission route, n (%)			
Men who have sex with men	15,041 (61)	521 (41)	715 (94)
Heterosexual	7,299 (30)	160 (13)	24 (3)
People who use/used injecting drugs	739 (3)	436 (34)	7 (1)
Other	1,548 (6)	160 (12)	12 (2)
cART, n (%)	23,586 (96)	1,222 (96)	754 (99)
HCV genotype (GT), n (%*)			
Total determined		1,147 (90)	680 (90)
GT 1		704 (55)	485 (71)
1a		423 (60)	404 (83)
1b		94 (13)	21 (4)
1c, 1a/b or not further specified		187 (27)	60 (12)
GT 2		55 (5)	37 (5)
GT 3		205 (18)	15 (2)
GT 4		181 (16)	142 (21)
GT 5&6		2 (0.1)	1 (2)
Deaths, n (%)	2,679 (11)	303 (24)	27 (4)

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

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

The HCV genotype was determined and documented in the clinical records of 1,147 of the 1,277 individuals (90%) with a chronic HCV infection. Of the individuals with a genotype determination, the majority (61%) were infected with HCV genotype 1 (n=704); of those persons, 60% were infected with genotype 1a (n=423) and 13% with genotype 1b (n=94). Five percent (n=55) were infected with HCV genotype 2, 18% (n=205) with genotype 3, and 16% (n=181) with genotype 4. One person was infected with genotype 5 and one with genotype 6.

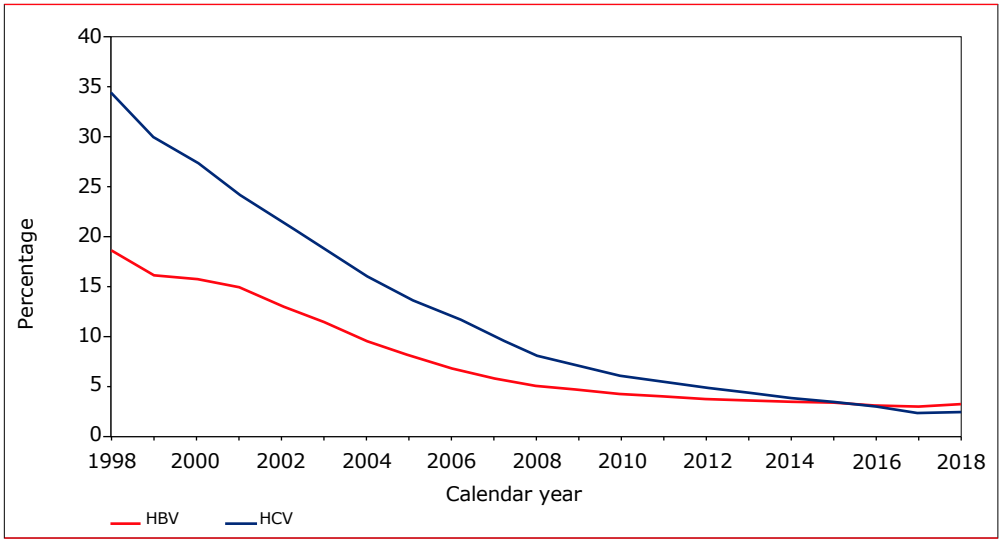
HCV genotype was also determined for 680 of the 758 individuals (90%) with an acute HCV infection. Individuals with an acute HCV infection were most likely to be infected with either genotype 1 (71%, n=485) or genotype 4 (21%, n=142). Of the 485 infected with genotype 1, 83% (404) were infected with genotype 1a and 4% (21) with genotype 1b.

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, 34% of the HIV-positive individuals in care had never 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 2018, only 2% of the individuals in care had never been screened for HCV co-infection (*Figure 4.2*). In 2018, unknown HCV status was relatively more common among individuals with heterosexually acquired HIV (206/5,682, 3.6%) or with another or unknown mode of HIV acquisition (41/866, 4.7%) and relatively less common among MSM (1.8%) and PWID (0.3%).

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

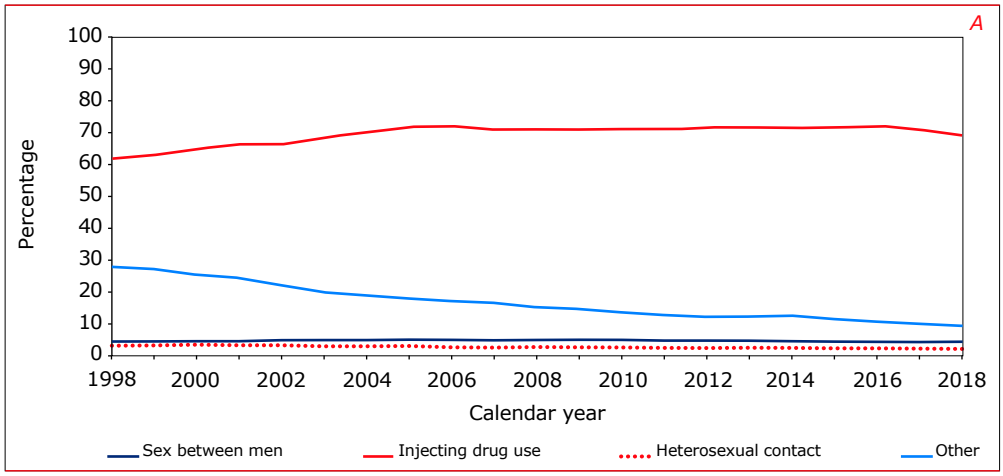


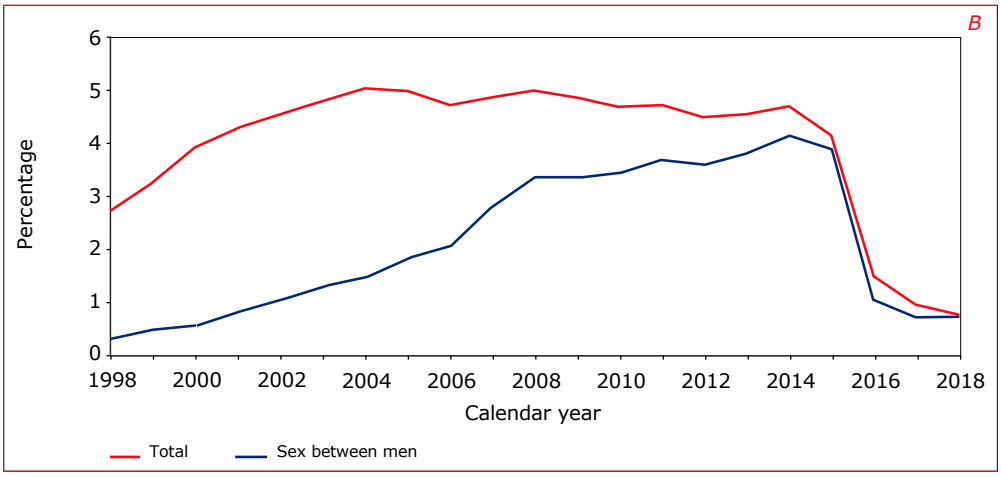
Legend: *HBV=hepatitis B virus; HCV=hepatitis C virus.*

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

The overall prevalence of ever being diagnosed with a chronic HCV co-infection among HIV-positive individuals ever registered decreased from 11.1% in 1998 to 4.8% in 2018, 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 61% and 72% over calendar years (*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 a diagnosis of 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 2.7% in 1998 and 5% in 2007, but it dropped to 0.8% in 2018. In MSM, the highest proportion of HCV RNA positivity was 4%; by 2018, 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 includes only cases of primary acute HCV infection (first diagnosis of HCV). The definition of acute HCV is consistent with the definition according to the European AIDS Treatment Network (NEAT) preferred criteria[1]. In addition, we expanded this definition with alternative criteria[1,2]. In brief, this alternative definition is based on detectable HCV RNA associated with an acute rise in alanine aminotransferase (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 regimen in the last 6 months. As SHM has only routinely collected ALT levels since 2012, the incidence of acute HCV according to the alternative criteria is reported from 2012 onwards.

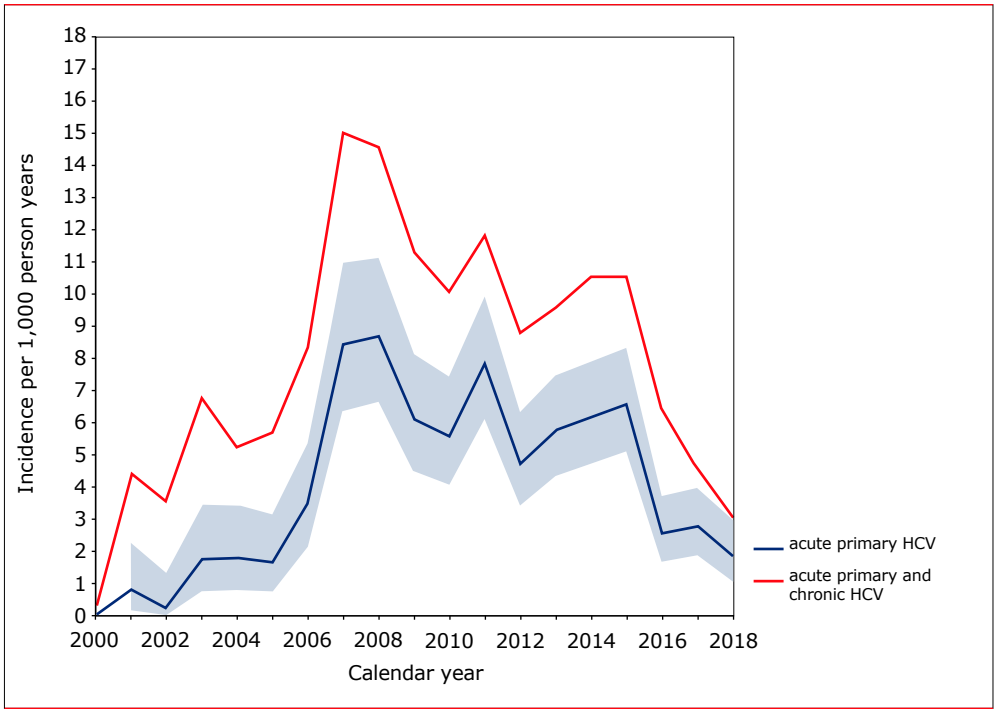
There were important differences in the incidence of the first diagnosis of acute HCV infection in terms of HIV transmission category. The vast majority of acute HCV infections occurred in MSM (715/758 [94%]). In PWID or former PWID, in contrast to the high prevalence of HCV, the overall incidence of acute HCV was low and occurred in only 7 cases. This is probably due to the high background prevalence of HCV infection in former PWID, together with injecting drug use having become very uncommon in the Netherlands. Twenty-four cases occurred among individuals who had acquired HIV heterosexually.

Figure 4.4 shows both the incidence of acute primary HCV infection and all newly diagnosed acute primary and chronic HCV diagnoses among MSM over time. The overall rate of acute HCV infection in this group was 4.5 per 1,000 person years (PY) (95% CI, 4.2-4.9). When the preferred NEAT acute HCV definition was used, the incidence increased from 0 diagnoses per 1,000 PY in 1998 to a peak of 8.4 and 8.7 per 1,000 PY in 2007 and 2008, respectively. The incidence, which was 6.5 diagnoses per 1,000 PY in 2015, after the start of increasing direct-acting

antiviral agents (DAA) uptake in 2014, declined to 2.6 in 2016 and then stabilised at 2.8 diagnoses per 1,000 PY in 2017.

As expected, incidence rates among MSM were higher when the preferred and alternative case definitions of acute HCV were combined, with incidence rates of 7.6 diagnoses per 1,000 PY in 2015, 3.7 in 2016 and 3.2 in 2017. The incidence of all newly-diagnosed HCV infections was higher during the overall observation period.

Figure 4.4: *Incidence of acute primary hepatitis C infection (blue line) and all acute primary and chronic HCV diagnoses (red line) among men who have sex with men per calendar year. Note: Low numbers in 2018 may be due to a delay in data collection.*



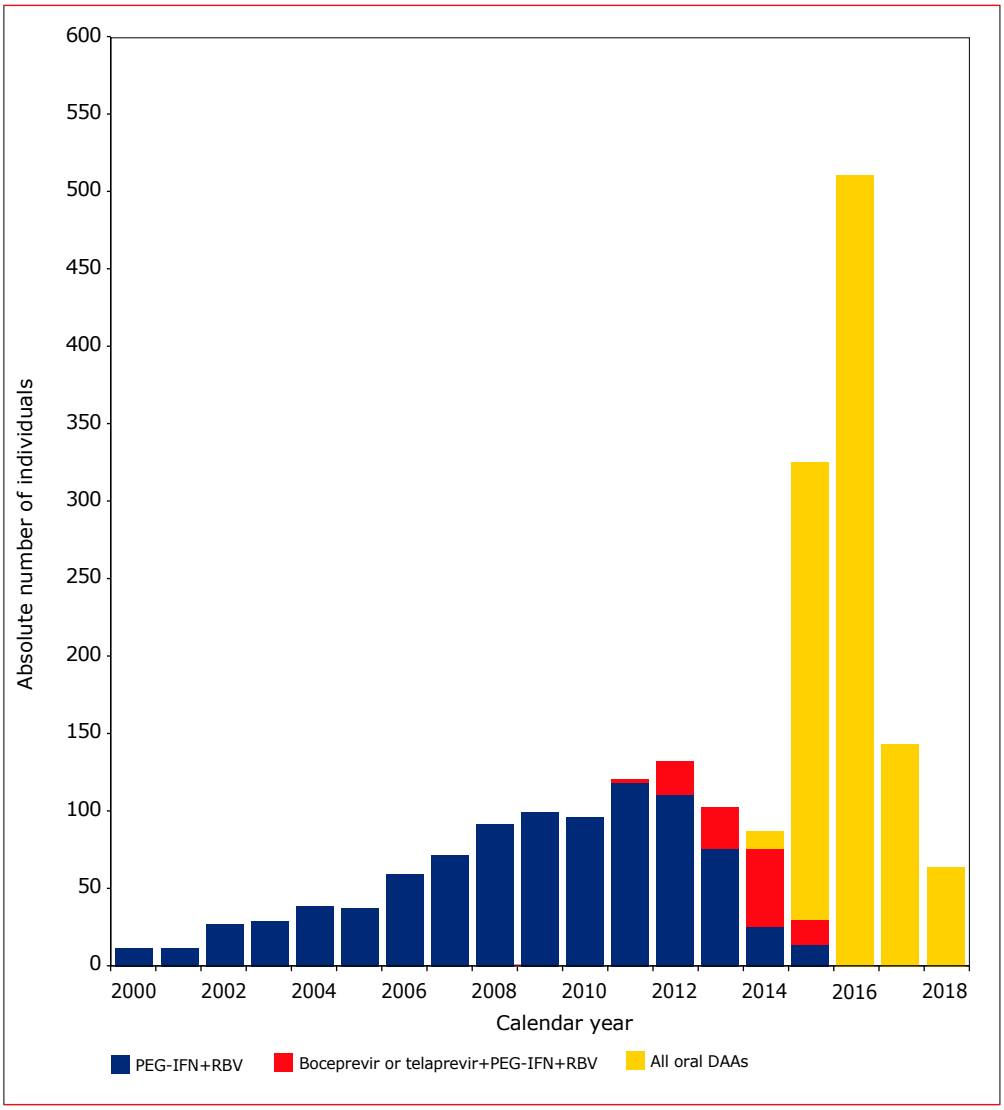
Legend: *HCV=hepatitis C virus; shaded area represents the 95% confidence interval.*

Treatment for HCV infection

The primary aim of HCV treatment is to achieve a sustained virological response (SVR)[13]. Treatment has changed markedly in recent years. In the past, 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 DAAs active against HCV genotype 1, became available in the Netherlands[14,15]. These agents were subsequently used as part of triple therapy that included one of those 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 individuals infected with HCV, including those with severe liver fibrosis and cirrhosis. Later, in November 2015, sofosbuvir was made available for all individuals infected with HCV regardless of their fibrosis status, and shortly thereafter, additional novel DAAs became available such as new HCV NS3/4A protease inhibitors (simeprevir, paritaprevir and grazoprevir), NS5A inhibitors (daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir and pibrentasvir) and an NS5B polymerase inhibitor (dasabuvir). An overview of DAA-containing HCV treatment combinations currently available in the Netherlands can be found at https://hcvrichtsnoer.nl/.

Figure 4.5 shows the absolute number of individuals who have started HCV treatment per calendar year. Among the 2,035 individuals ever diagnosed with chronic or acute HCV, 1,610 have ever received HCV treatment; of those, 448 have received HCV treatment more than once, including people who were unsuccessfully treated and those who re-acquired HCV after prior successful treatment.

Figure 4.5: Number of HIV/HCV co-infected individuals starting hepatitis C treatment per calendar year. Note: low numbers in 2018 may be due to a delay in data collection.



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

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

The outcome for 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 are no longer included in this report.

Treatment with novel DAAs

In total, at the time of the database lock on 1 May 2019, 961 individuals were known to have started a DAA regimen; 62 of those had been treated more than once with a DAA regimen. Reasons for receiving DAA treatment twice were: re-infection (n=26), no virologcial response during the first episode of DAA treatment (n=24), toxicity (n=2), and other reasons (n=6). Of the 1,026 DAA treatment episodes, 11 occurred in 2014, 296 in 2015, and 511 in 2016. The number of treatment episodes decreased to 143 in 2017 and 65 in 2018 (*Figure 4.5*).

The most frequently used DAA regimens were 1) sofosbuvir plus ledipasvir +/- RBV (n=532), and 2) sofosbuvir plus daclatasvir +/- RBV (n=245). Finally, 27 individuals who had previously been treated with DAAs are known to have died. The causes of death were liver disease (n=7), non-AIDS-defining malignancies (n=4), cardiovascular disease (n=3), non-AIDS-defining infection (n=3) and non-natural death (n=2); the remainder included alcohol and substance use, AIDS, lung disease, and unknown causes.

Outcome

HCV RNA data were collected up to 1 May 2019. At that point, 944 out of 1,026 treatment episodes had been completed with one of the DAA regimens, and sufficient time had elapsed since discontinuation of treatment to enable calculation of the SVR12 rate. In total, 919 of these 944 individuals achieved an SVR12 (97%), with the same rate for both treatment-naive and pre-treated individuals and for those with severe liver disease. Twenty-five individuals failed to achieve an SVR12. This group was not specifically different from the group that did achieve an SVR regarding HIV transmission mode, region of origin, CD4 cell counts, and HIV RNA.

Continuum of care for those with diagnosed HCV co-infection

Figure 4.6 shows the HCV continuum of care based on the number of persons known to be in HIV care as of 31 December 2018, with data from previous monitoring reports for 2014-2018 shown for comparison. Out of a total of 2,035 individuals linked to HIV care and diagnosed with HCV, 1,533 (75%) were retained in care, and 502 individuals were no longer in care (330 had died, 88 moved abroad and 84

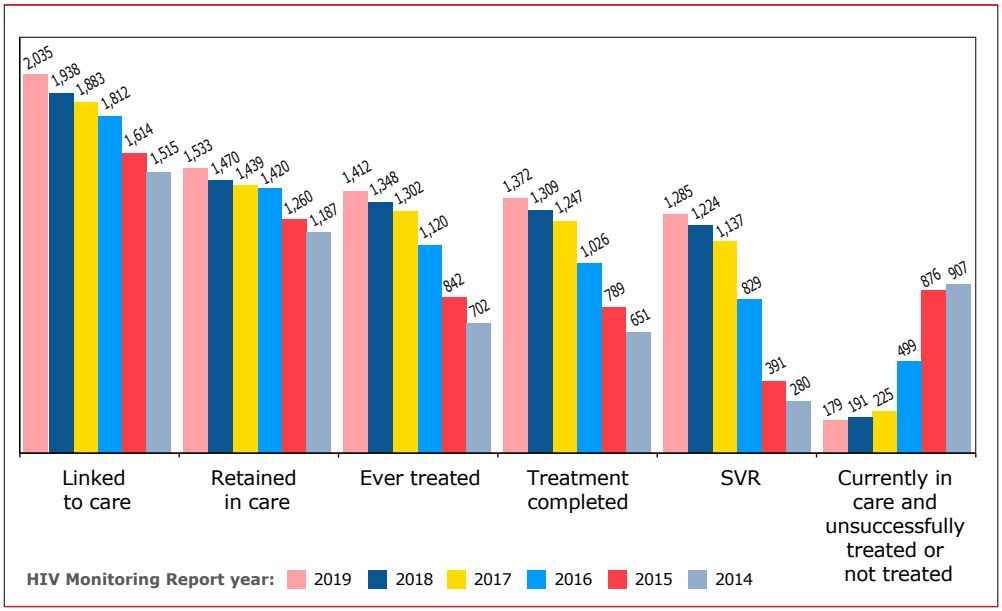
were lost to care). Of those still alive and in care, 1,412 (92%) had ever received treatment for HCV. Of the 1,412 individuals treated for HCV, 1,372 (97%) had completed HCV treatment, with enough data available to calculate the HCV treatment response (SVR12 for the DAAs and SVR24 for the older regimens). Overall, 1,285 of the 1,372 persons who completed treatment (94%) had achieved an SVR, including those who had achieved an SVR on a pegylated interferon-containing regimen.

As a result, 248 of the 1,533 individuals who were known to be alive and in care as of 31 December 2018 in one of the Dutch HIV treatment centres (16%) still needed HCV treatment:

- 121 individuals had never been treated for HCV; 116 of these were receiving cART for HIV during their last clinical visit, and 108 of these 121 individuals had an HIV RNA <100 copies/ml; the proportion untreated was higher among PWID (13%) or persons with an unknown HIV transmission mode (12%) compared to MSM (7%) (p=0.01).
- 56 had been unsuccessfully treated for HCV; 11 of these individuals had documented evidence of severe liver disease.
- 71 were still being treated or had insufficient time after treatment discontinuation to allow SVR calculation.

Of the 71 individuals for whom SVR could not yet be calculated due to insufficient time since treatment discontinuation, all had been treated with novel DAA combinations. For that reason, we extrapolated the observed DAA SVR rate of 97% to these individuals and assumed that 69 of the 71 will achieve SVR. This resulted in a more realistic estimate of individuals (248-69=179) who remained untreated or unsuccessfully treated.

Figure 4.6: Hepatitis C continuum of care.



Legend: SVR=sustained virological response.

HCV re-infection

Re-infection with HCV following successful treatment has been reported mainly in HIV-positive MSM[17,18,19], with high rates of re-infection found among MSM in the Netherlands, Germany[20] and the United Kingdom[21].

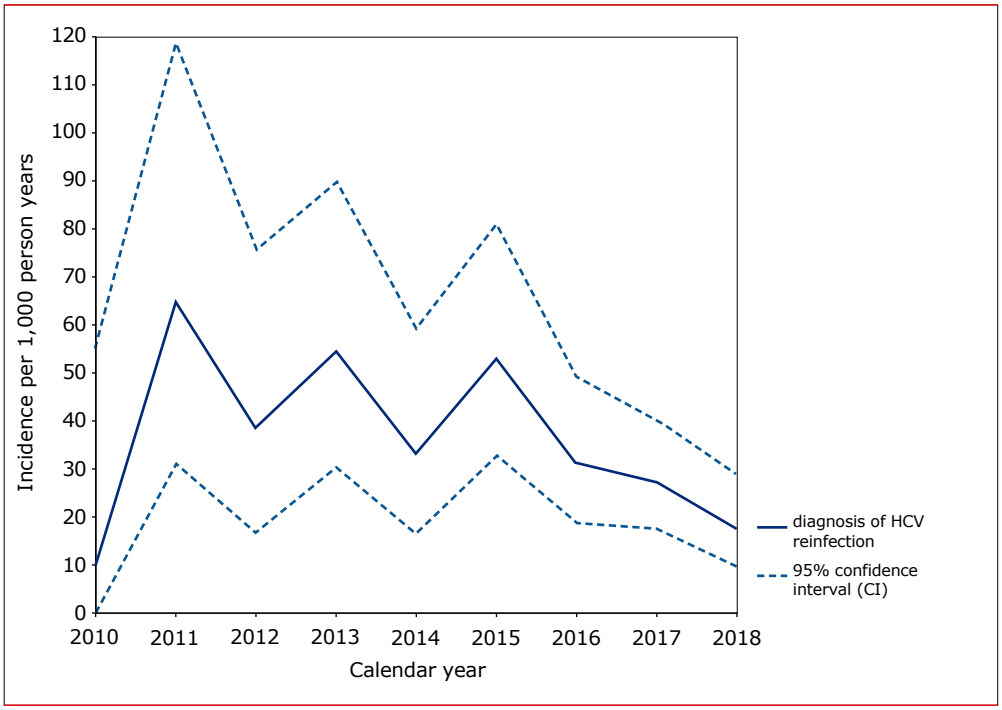
To identify possible HCV re-infection among HCV co-infected individuals, we selected the 1,450 individuals who had initially achieved an SVR after ever having received any type of HCV treatment. For these 1,450 individuals, the incidence of HCV re-infection was reported between 2010 and 2018. Follow-up time was calculated from the date of SVR, or if the SVR was achieved before 2010, from 1 January 2010 onward, until the earliest date of HCV re-infection, death, or last known contact.

Of these 1,450 individuals, 147 (10%) had documented detectable HCV RNA levels after having an earlier documented SVR, indicative of HCV re-infection. The median time between SVR and HCV re-infections that occurred from 2010 onwards was 1.6 years (IQR 0.9-3.5). For 49 of these 147 individuals (33%), an HCV genotype switch was reported, providing additional evidence of HCV re-infection.

Most individuals who became re-infected were MSM (131/147, 89%). Another five were PWID (5/147, 3%). For the remaining 8 individuals, documented HIV transmission routes were heterosexual contact (n=2) and unknown (n=6). Out of the 147 individuals with a re-infection, 126 were re-treated and the median time to re-treatment was 4.6 months (IQR; 2-16), with no difference between the pre- and post-DAA era; of those, 104 were re-treated with a DAA-containing regimen. In total, 110 of these 126 individuals achieved an SVR (96%). Among the 104 individuals who had been re-treated with a DAA-containing regimen, 93 achieved an SVR, and for 11 individuals SVR could not yet be determined.

The incidence of HCV re-infection was 26 re-infections per 1,000 PY (95%: 22-31) for the total population and 33 re-infections per 1,000 PY (95%: 27-39) for MSM. Because most re-infections occurred among MSM, the incidence of HCV re-infection after achieving an SVR over time is shown only for MSM (*Figure 4.7*). This incidence increased from 10 to 53 re-infections per 1,000 PY between 2010 and 2015, respectively, and then declined to 27 re-infections per 1,000 PY in 2017.

Figure 4.7: *Incidence of hepatitis C re-infection after earlier treatment-induced clearance among men who have sex with men, per calendar year. Note: Numbers in 2018 may be affected by a delay in data collection.*



Legend: *HCV=hepatitis C virus.*

HBV

Ninety-six percent of the 26,247[b] HIV-positive individuals ever registered in the SHM database had been screened for at least one serological marker of HBV (hepatitis B surface antigen [HBsAg], anti-hepatitis B surface [anti-HBs] antibodies, and/or anti-hepatitis B core [anti-HBc] antibodies). Screening for HBV infection in HIV-positive individuals in care has improved over calendar time. In 1999, 16% of individuals had not been screened for HBV infection (*Figure 4.2*). Since then, the proportion of HIV-positive individuals without HBV screening has decreased markedly, with just 3% of all HIV-positive individuals in care having no measured HBV serological markers in 2018 (*Figure 4.2*).

***Box 4.3:** Definitions of hepatitis B serological profiles.*

	HBV serological results		
	HBsAg	**Anti-HBs antibody**	**Anti-HBc antibody**
Active HBV infection*	Pos	–	–
Resolved HBV infection	Neg/ND	Pos	Pos
Isolated anti-HBc positive	Neg	Neg	Pos
Vaccinated†	Neg	Pos	Neg/ND
Non-immune‡	Neg/ND	Neg	Neg

**Ignoring anti-HBs antibody and anti-HBc antibody status*

†Alternative definition: HBsAg not determined (and assumed to be negative), anti-HBs antibody positive, and anti-HBc antibody negative

‡Alternative definition: HBsAg-negative, anti-HBs antibody negative, and anti-HBc antibody not determined (and assumed to be negative)

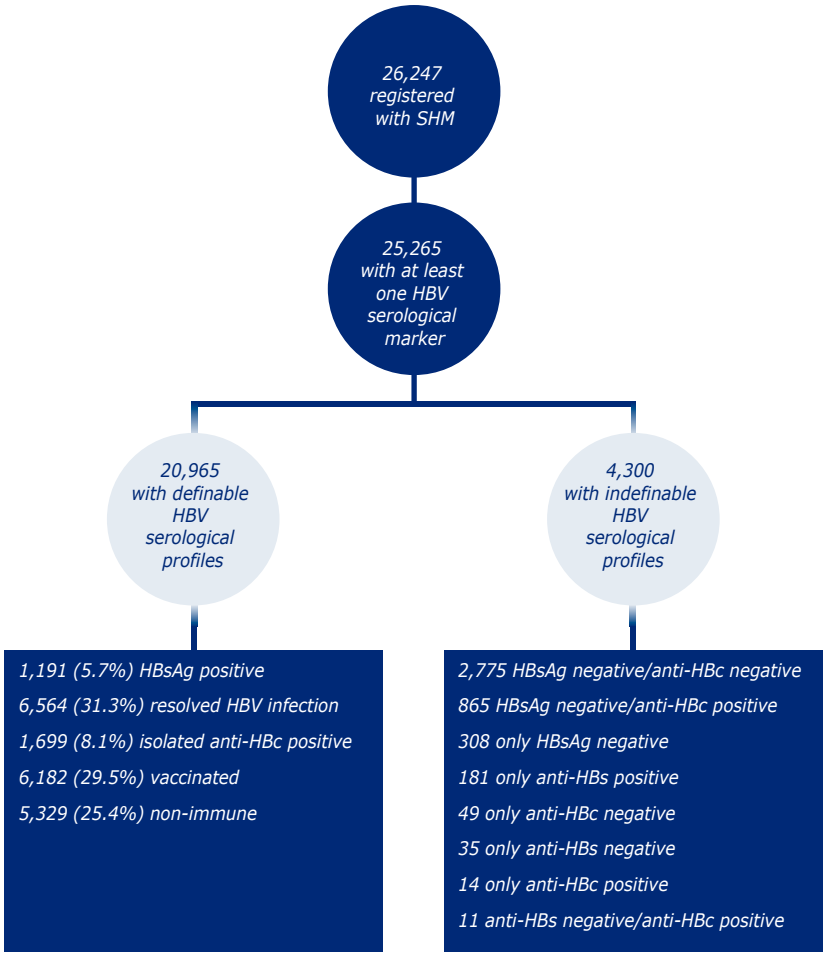
***Legend:** HBsAg=hepatitis B surface antigen; anti-HBs=anti-hepatitis B surface; anti-HBc=anti-hepatitis B core; Pos=positive; Neg=negative; HBV=hepatitis B virus; ND=not determined.*

HBV serological profiles

HBV serological profiles could be defined for 20,965 (83%) of the 25,265 screened individuals (*Figure 4.8*). A full HBV serological battery is not routinely performed in HIV-positive individuals. Therefore, any results from an HBV serological test were assumed to remain the same over time until the performance of a new serological test. The distribution of HBV serological profiles at the last visit are given in *Figure 4.8*. The remaining 4,300 (17%) individuals either did not have sufficient information to establish HBV serological profile (n=4,238) or were previously HBsAg-positive and no longer had anti-HBc antibodies (n=62). Demographic characteristics are compared between persons with definable HBV serological profiles in *Table 4.2*.

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.*

Figure 4.8: *Flowchart of HIV-positive individuals registered in the SHM database, 1999-2018, with testing for hepatitis B virus (HBV).*



Information obtained from most recent serological result.

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

Table 4.2: Demographic characteristics of HIV-positive individuals in care according to their hepatitis B virus (HBV) serological profile as registered in the SHM database, 1998-2018.

	HBV serological profile*, n (%)				
	Active HBV infection	Resolved HBV infection	Isolated anti-HBc positive	Vaccinated	Non-immune
Total number	1,191	6,564	1,699	6,182	5,329
Male gender	1,027 (86%)	5,663 (86%)	1,302 (77%)	5,325 (86%)	3,984 (75%)
Region of origin					
Netherlands	531 (45%)	3,617 (55%)	669 (39%)	3,813 (62%)	3,110 (58%)
Europe	77 (6%)	459 (7%)	122 (7%)	476 (8%)	289 (5%)
Sub-Saharan Africa	304 (26%)	991 (15%)	541 (32%)	463 (7%)	616 (12%)
Caribbean/South America	123 (10%)	782 (12%)	167 (10%)	714 (12%)	790 (15%)
South-east Asia	63 (5%)	264 (4%)	67 (4%)	194 (3%)	138 (3%)
Other	93 (8%)	451 (7%)	133 (8%)	522 (8%)	386 (7%)
HIV transmission group					
Men who have sex with men	683 (57%)	4,566 (70%)	751 (44%)	4,523 (73%)	2,538 (48%)
Heterosexual	361 (30%)	1,398 (21%)	609 (36%)	1,340 (22%)	2,312 (43%)
Injecting drug use	50 (4%)	223 (3%)	190 (11%)	59 (1%)	101 (2%)
Other	97 (8%)	377 (6%)	149 (9%)	260 (4%)	378 (7%)
cART	1,143 (96%)	6,343 (97%)	1,623 (96%)	6,017 (97%)	5,116 (96%)
Deaths	242 (20%)	917 (14%)	284 (17%)	283 (5%)	583 (11%)

**Based on information obtained from most recent serological result*

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

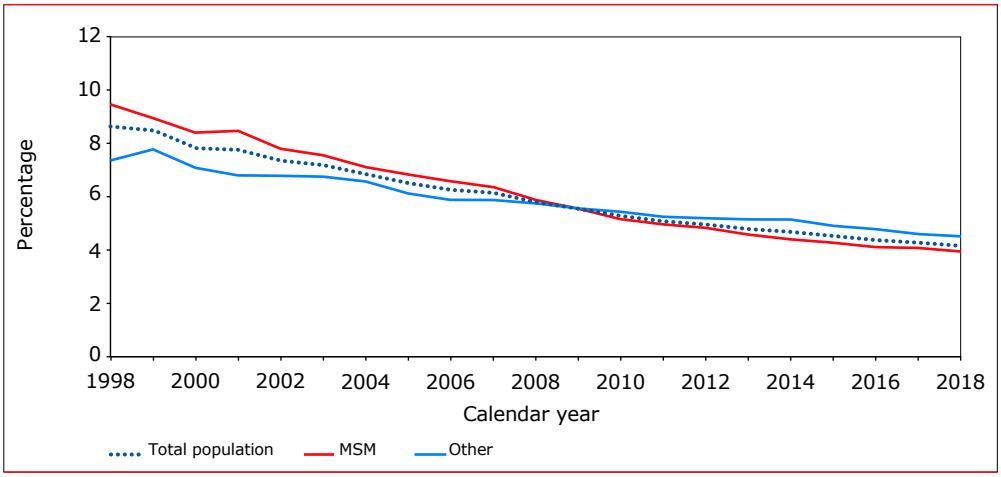
Individuals with active HBV infection

Of the 25,265 individuals screened for at least one HBV serological marker, a total of 1,551 (6%) ever had a positive HBsAg test result. Over time, 186 (12%) of these individuals resolved their HBV infection, i.e., they became HBsAg-negative and acquired anti-HBs antibodies; an additional 174 (11%) became HBsAg-negative without acquiring anti-HBs antibodies. The remaining 1,191 (77%) individuals continued clinical care with HBsAg-positive serology.

The prevalence of HBsAg-positive serology was 8.5% in 1998 and slowly decreased to 4.2% in 2018 (*Figure 4.9*). This decreasing prevalence could be the result of several factors, including lower numbers of individuals with incident HBV infection (as a result of increased vaccination coverage among MSM[22] and the preventive effect of HIV treatment with a cART regimen that includes tenofovir disoproxil fumarate (TDF)/tenofovir alafenamide fumarate (TAF)), individuals becoming HBsAg-negative

during treatment, and lower numbers of newly diagnosed HIV-positive individuals with HBsAg-positive serology[23]. As is the case for HCV co-infection, the proportion of HIV-positive individuals in care and chronically co-infected with HBV is considerably higher than that of the general Dutch population. Individuals co-infected with HBV were predominantly male (1,027/1,191, 86%), in line with those co-infected with HCV (*Table 4.2*). However, compared with 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 PWID.

Figure 4.9: *Prevalence of HBsAg-positive serology per calendar year.*



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

Treatment for chronic HBV infection

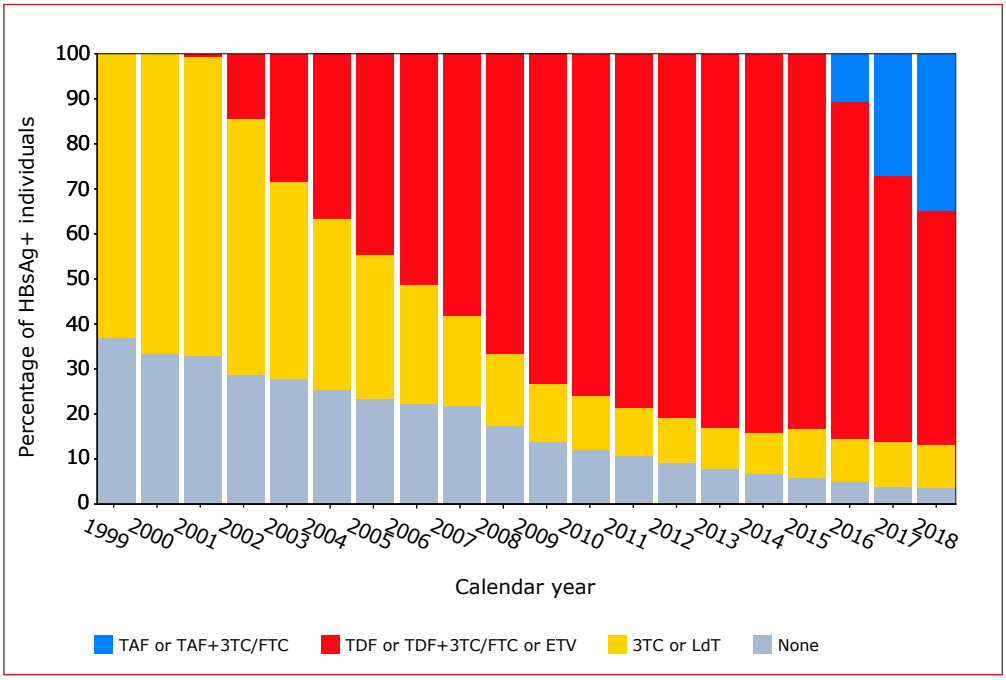
The treatment for chronic HBV infection aims to reduce viral replication. As HBV DNA is the parameter most directly influenced by therapy with either nucleoside or nucleotide analogues, HBV DNA undetectability is an appropriate surrogate marker for treatment response. Persistent lowering of HBV DNA levels to less than 20 IU/ml has also been shown to delay progression of liver fibrosis to cirrhosis[24]. Lowering HBV DNA levels may result in HBsAg negativity in a small 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 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 clinically important lowering of HBV DNA, thereby decreasing the risk of progression of liver fibrosis. A few antiviral agents used for treatment of HIV, such as lamivudine, emtricitabine and particularly TDF/TAF, are also active against HBV.

Of the 1,551 individuals with HIV in the SHM database who ever had an HBsAg-positive serological test result, 1,486 (96%) had ever received a cART regimen that included one or more agents with activity against both HIV and HBV. Reasons for the remaining 65 individuals not having received anti-HBV treatment included: death before being able to start treatment (n=16), recent entry into care (n=2), loss to follow up (n=41) and lack of sufficient information (n=6).

Most people with active HBV infection received treatment containing lamivudine in 1999-2000 (*Figure 4.10*). TDF-based cART (with or without lamivudine or emtricitabine) for combined HIV and HBV treatment was first used in 2002 (n=82/632, 13%) and became more commonly used than lamivudine in 2005. TAF-based cART (with or without lamivudine or emtricitabine) was first used in 2016 (n=130/1,206, 11%). In 2018, most co-infected individuals were receiving TDF-based cART (n=589/1,212, 49%), followed by TAF-based cART (n=399/1,212, 33%), lamivudine-based cART (n=171/1,212, 14%) or no anti-HBV-containing cART (n=53/1,212, 4%).

Figure 4.10: Anti-hepatitis B virus (HBV)-containing antiretroviral therapy per calendar year.



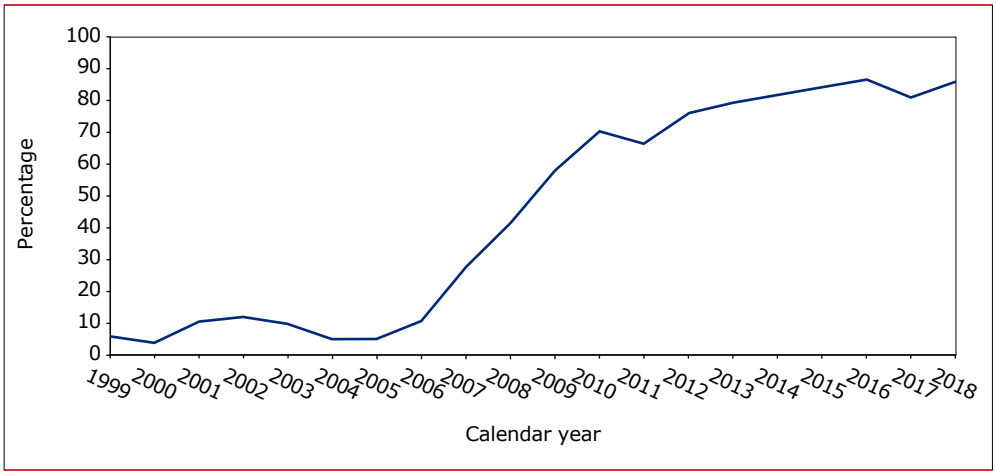
Legend: *TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; ETV=entecavir; 3TC=lamivudine; LdT=telbuvidine; FTC= emtricitabine.*

Note: *Anti-HBV agents were divided as none, 3TC or LdT, TDF or TDF+3TC/FTC or ETV, and TAF or TAF+3TC/FTC. 3TC and LdT should not be combined and TDF and ETV can be combined under special circumstances[25].*

In most individuals mono-infected with HBV, a persistently HBeAg-negative chronic HBV infection with undetectable HBV DNA confers a favourable long-term outcome, with low risk of cirrhosis and HCC[26]. We therefore examined the HBV DNA levels per calendar year in the population of individuals co-infected with HIV and HBV. In many treatment centres, HBV DNA is not routinely collected after the first negative HBV DNA result during treatment with TDF/TAF, provided that HIV RNA is undetectable. Therefore, for each year, HBV DNA measurements were available on average in 24% of individuals co-infected with HBV. *Figure 4.11* shows the proportion of those over time 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). In 1999-2005, at most, 18% of the individuals had an undetectable

HBV DNA level based on the detection limit of the assay used at the time of measurement. The percentage of individuals with an undetectable HBV DNA level became more common with increased use of TDF-containing cART and reached 80% in 2013. In 2018, 86% of individuals co-infected with HIV and HBV had an undetectable HBV DNA level. (*Figure 4.11*).

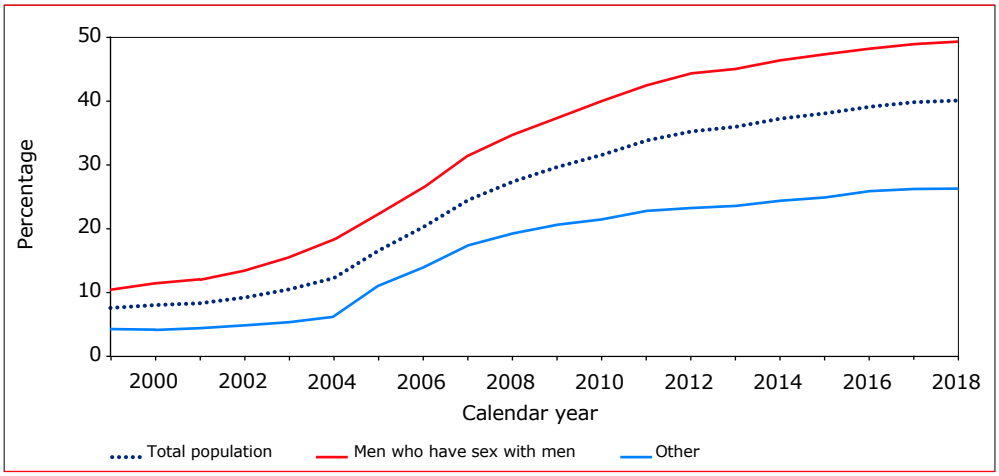
Figure 4.11: *Percentage of individuals with undetectable hepatitis B virus (HBV) DNA levels by assay with a detection limit of either <100, <200, <2000 IU/ml HBV DNA or <20 IU/ml per calendar year, regardless of HBeAg status.*



HBV vaccination in HIV-positive individuals

Of the 20,965 individuals with definable HBV serological profiles, 6,182 (29%) had serological evidence of HBV vaccination status at their last visit. HBV vaccination is not recommended for individuals with HBsAg positive and/or anti-HBc antibody positive serology. When individuals with negative HBsAg and anti-HBc antibody serology and without previous evidence of HBsAg-positive serology were considered, the prevalence of HBV vaccination status increased from 8% in 1999 to 40% in 2018 (*Figure 4.12*). The largest increase in HBV vaccination was observed in MSM compared to others, likely due to the national vaccination campaign targeting these individuals from 2002 onwards[22].

Figure 4.12: Prevalence of hepatitis B vaccination per calendar year.



Non-immune status in HIV-positive individuals

Of the 20,965 individuals with definable HBV serological profiles, 5,329 (25%) had serological evidence of being non-immune and non-exposed to HBV at their last visit. When the 4,300 individuals with indefinable HBV serological profiles were considered, 75 out of 287 with an anti-HBs antibody test did not have detectable anti-HBs antibodies, and 3,210 out of 4,013 without an anti-HBs antibody test were not reported to have been vaccinated by their treating physician. Thus, at most, 8,614 of 25,265 (34%) individuals screened for HBV remained susceptible to infection as of their last visit (*5,329* non-immune *plus 75* with indefinable HBV profile and anti-HBs antibody negative *plus 3,210* with indefinable HBV profile and missing data on anti-HBs antibody status and no physician-reported vaccination).

Individuals at risk, and MSM in particular, should be actively counselled about 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[27,28]. Data from SHM show that, of those people who remain at risk of acquiring HBV, 79% are currently being treated with a cART regimen that includes TDF or TAF; for MSM, this prevalence is 81%.

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 of those sources, were available for 1,681 of the 2,035 individuals with HCV co-infection and for 1,180 of the 1,551 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 492 (29%) of the individuals with HCV co-infection and in 256 (22%) of those with HBV co-infection (*Table 4.3*). Definitive severe chronic liver disease was documented for 117 individuals with an HCV co-infection (7%) and 69 (6%) with an HBV co-infection.

Table 4.3: *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	2,035	1,551
Severe chronic liver disease#	494 (29)**	256 (22)***
HCC	20 (1)	32 (2.1)
Liver transplantation	2 (0.1)	1 (0.1)
Deaths from any cause*	330 (16)	290 (19)
Liver-related deaths	71 (3)	47 (3)

**including liver-related death*

***based on 1,681 individuals with data on liver disease*

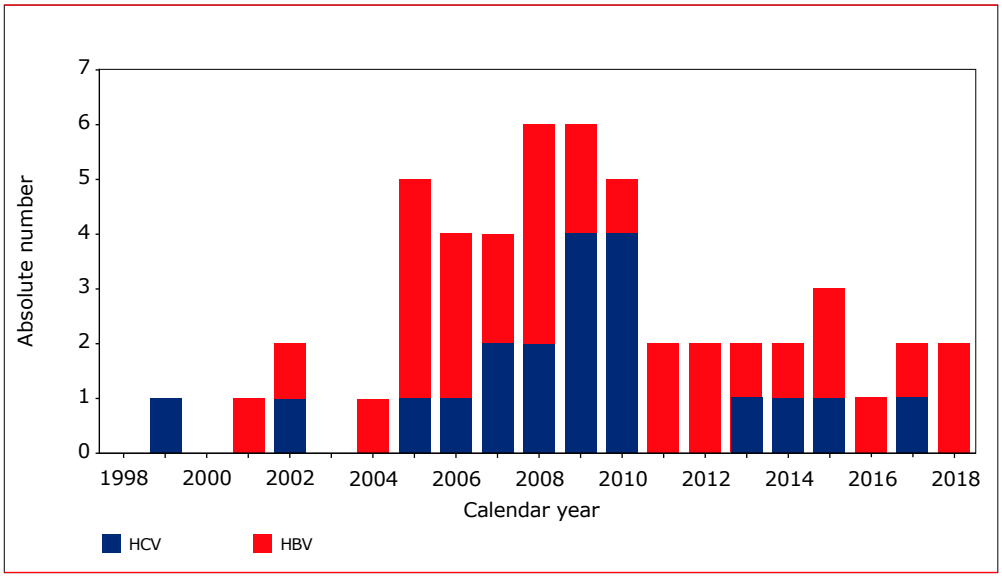
****based on 1,180 individuals with data on liver disease*

#including presumptive and definitive liver disease

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

Figure 4.13 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, 15 of whom were born in the Netherlands. HCC was found in 32 individuals (2.1%) with a chronic HBV co-infection, 18 of whom were born in the Netherlands, 9 in sub-Saharan Africa, 2 in Asia, and 1 each in South America, the United States, and Australia.

Figure 4.13: Absolute number of annually reported hepatocellular carcinoma cases over time.



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

Mortality

All-cause mortality

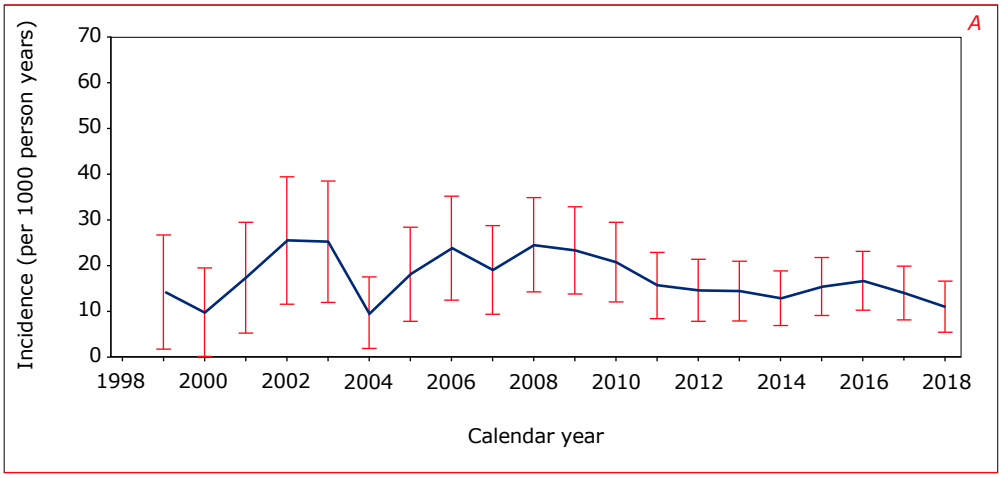
The overall proportion of those dying from any cause was 16% for the 1,938 individuals with an HCV infection and 19% for the 1,551 individuals with an HBV infection (*Table 4.3*). For individuals with HCV infection, the age- and gender-adjusted incidence rate of death from any cause was 16.4/1000 person years in 1998-2002, 20.1 in 2003-2011 and 14.2 from 2012 onwards (*Figure 4.14A*). In MSM with HCV infection, these incidence rates were 5.3/1000 person years in 1998-2002, 7.9 in 2003-2011, and 4.1 in 2012 onwards. In PWID with HCV infection, these incidence rates were 19.3/1000 person years in 1998-2002, 38.1 in 2003-2011, and 47.1 in 2012 onwards.

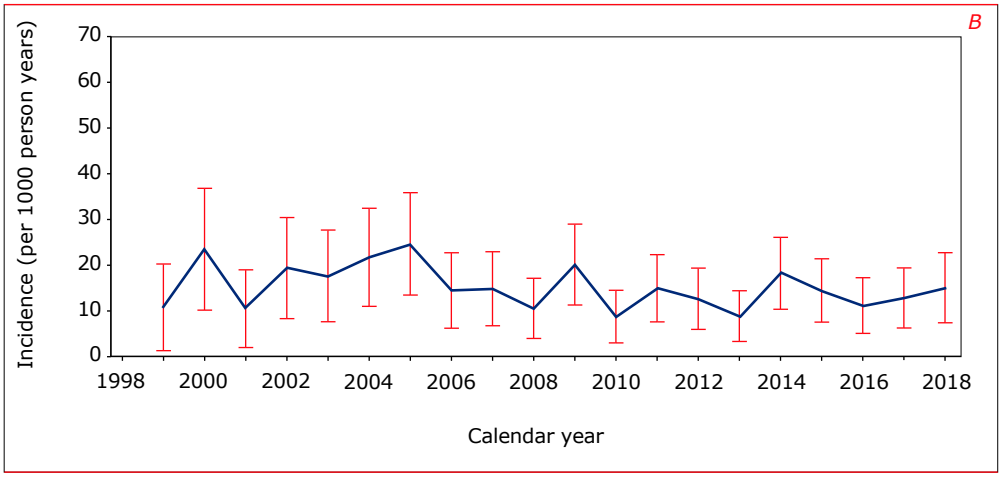
For individuals with HBV infection, the age- and gender-adjusted incidence rate of death from any cause was 16.0/1000 person years in 1998-2002, 16.1 in 2003-2011 and 13.4 from 2012 onwards (*Figure 4.14B*). In MSM with HBV infection, these incidence rates were 11.7/1000 person years in 1998-2002, 13.6 in 2003-2011, and 10.6 in 2012 onwards. In PWID with HCV infection, these incidence rates were 52.2/1000 person years in 1998-2002, 60.5 in 2003-2011, and 93.6 in 2012 onwards.

Liver-related mortality

In total, 118 individuals co-infected with hepatitis died of a liver-related cause (*Table 4.3*).

Figure 4.14: Annual age- and gender-adjusted all-cause mortality rate in 2,035 individuals positive for HIV1 who were ever diagnosed with (A) an acute or chronic HCV infection and (B) active hepatitis B virus infection.

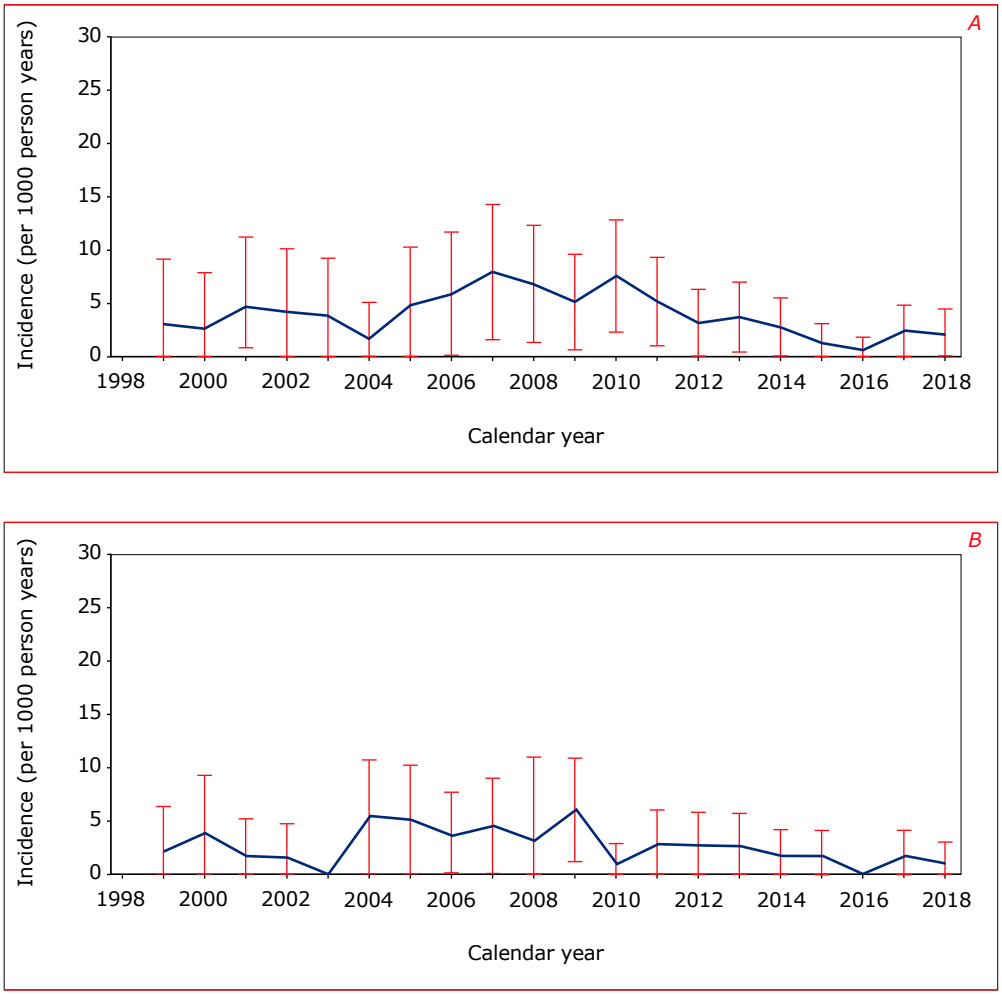




For individuals with HCV infection, the age- and gender-adjusted incidence rate of death from a liver-related cause was 3.2/1000 person years in 1998-2002, increasing to 5.7 in 2003-2011 and decreasing to 2.2 from 2012 onward (*Figure 4.15A*). In MSM with HCV infection, these incidence rates were 0/1000 person years in 1998-2002, 3.0 in 2003-2011, and 0.9 from 2012 onwards. In PWID with HCV infection, these incidence rates were 2.6/1000 person years in 1998-2002, 8.5 in 2003-2011, and 5.2 from 2012 onward.

For individuals with HBV infection, the age- and gender-adjusted incidence rate of liver-related death was 1.9/1000 person years in 1998-2002, increasing to 3.5 in 2003-2011 and decreasing to 1.7 from 2012 onward (*Figure 4.15B*). In MSM with HBV infection, these incidence rates were 2.4/1000 person years in 1998-2002, 3.2 in 2003-2011, and 1.6 from 2012 onward. In PWID with HBV infection, these incidence rates were 3.6/1000 person years in 1998-2002, 1.4 in 2003-2011, and 1.5 in 2012 onwards.

Figure 4.15: *Age- and gender-adjusted incidence rate of mortality related to liver disease for individuals infected with (A) hepatitis C virus or (B) hepatitis B virus, stratified by calendar year period.*



Conclusions

Screening for HCV and HBV co-infection in the HIV-positive population in the Netherlands continues to improve over time and nowadays is documented almost universally. Five percent of HIV-positive individuals ever registered between 1998 and 2018 in the SHM database were documented as being chronically infected with HCV and 3% 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 largely have been replaced in clinical practice by various novel DAAs. The number of HIV-positive individuals treated for HCV has rapidly increased. More than 1,000 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 decrease to 121 of HCV co-infected individuals remaining in need of HCV treatment. 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 2018. The rapidly increasing availability of novel interferon-free, highly effective combination antiviral regimens for HCV, together with optimised screening for HCV co-infection, with time will hopefully also 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 incidence of acute HCV infections in recent years. However, in line with earlier reports[17,21], 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 HBV co-infection. The prevalence of HBsAg-positive serostatus has decreased over time for all transmission groups, mostly as a result of increased HBV vaccination rates[22], together with the HBV-prophylactic effect of TDF/TAF in cART-treated individuals. Nonetheless, an estimated 32% of all HIV-positive individuals and 25% of MSM have either not been exposed to HBV or not been successfully vaccinated and may remain at risk of acquiring HBV. Since 79% of all individuals and 81% of MSM still at risk of acquiring HBV infection use a cART regimen that includes TDF/TAF, their risk could be essentially nil due to sustained chemoprophylaxis. The remaining 21% of the HIV-positive individuals ever registered and 19% of the MSM remain unprotected against HBV, which represents an estimated 6.5% of the total population of HIV-positive individuals screened for hepatitis B.

Among the HIV-positive individuals ever registered by SHM, 29% of the individuals chronically co-infected with HCV and 22% of the individuals chronically co-infected with HBV had evidence of severe chronic liver disease. 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 substantially since 2012. The overall mortality rate has decreased in individuals with HCV and HBV co-infections after 2012, yet the rate remains much higher for co-infected PWIDs compared to other transmission groups.

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, efforts should be ongoing to increase HBV vaccination rates among HIV-positive individuals who remain at increased risk of acquiring HBV, particularly those who are not receiving an antiretroviral regimen containing TDF or TAF or those previously not responding to vaccination[29]. 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 mortality related to liver disease among persons living with HIV. In addition, these novel regimens may have a beneficial impact on the risk of ongoing HCV transmission. The fact that DAA treatment uptake is lagging behind for a certain group of individuals shows that additional efforts are needed. This may include repeating an earlier approach by which SHM provides all HIV treatment centres with a pseudonymised list of untreated individuals, in order to draw specific attention to this group. Furthermore, additional research is recommended to provide more insight into the underlying reasons why treatment may be delayed in some individuals.

Importantly, regular HCV RNA screening among individuals who have been successfully treated for HCV infection is recommended to ensure early detection of new HCV infections; this is 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 monitoring the epidemiology of these infections and the response to existing and novel treatments but also to assessing the impact of treatment on reducing the burden of morbidity and mortality from chronic liver disease.

References

1. Rockstroh JK. Acute hepatitis C in HIV-infected individuals - recommendations from the NEAT consensus conference. *AIDS*. 2011;25(4):399-409. doi:10.1097/QAD.0b013e328343443b
2. Arends JE, Lambers FAE, van der Meer JTM, et al. Treatment of acute hepatitis C virus infection in HIV+ patients: Dutch recommendations for management. *Neth J Med*. 2011;69(1):43-49. http://www.ncbi.nlm.nih.gov/pubmed/21325703. Accessed August 28, 2018.
3. Hahné SJM, de Melker HE, Kretzschmar M, et al. Prevalence of hepatitis B virus infection in The Netherlands in 1996 and 2007. *Epidemiol Infect*. 2012;140(8):1469-1480. doi:10.1017/S095026881100224X
4. Nationaal Hepatitis Centrum. www.hepatitis.nl.
5. HepNed Study Group. Van Dijk M, Kracht PAM, Arends JE, et al. Retrieval of Chronic Hepatitis C Patients. A Manifesto for Action to Eliminate Hepatitis C in the Netherlands: The CELINE Project. *Neth J Med*. 2019;77(4):131-138.
6. Lincoln D, Petoumenos K, Dore GJ, Australian HIV Observational Database. HIV/HBV and HIV/HCV coinfection, and outcomes following highly active antiretroviral therapy. *HIV Med*. 2003;4(3):241-249. doi:10.1046/j.1468-1293.2003.00152.x
7. Heintges T, Wands J. Hepatitis C virus: epidemiology and transmission. *Hepatology*. 1997;26(3):1-6. doi:10.1002/hep.510260338
8. Lok AS. Chronic hepatitis B. *N Engl J Med*. 2002;346(22): 1682-3
9. Ikeda K, Saitoh S, Suzuki Y, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: A prospective observation of 2215 patients. *J Hepatol*. 1998;28(6):930-938. doi:10.1016/S0168-8278(98)80339-5
10. Posthouwer D, Makris M, Yee TT, et al. Progression to end-stage liver disease in patients with inherited bleeding disorders and hepatitis C: An international, multicenter cohort study. *Blood*. 2007;109(9):3667-3671. doi:10.1182/blood-2006-08-038349
11. Arends JE, Lieveld FI, Boeijen LL, et al. Natural history and treatment of HCV/HIV coinfection: Is it time to change paradigms? *J Hepatol*. 2015;63(5):1254-1262. doi:10.1016/j.jhep.2015.06.034
12. Lieveld FI, Smit C, Richter C, et al. Liver decompensation in HIV/Hepatitis B coinfection in the combination antiretroviral therapy era does not seem increased compared to hepatitis B mono-infection. *Liver Int*. 2019;39(3):470-483. doi:10.1111/liv.14000
13. European AIDS Clinical Society. Guidelines. Version 8.0, October 2015. English edition. 2015. http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html.
14. Zorg intstituut Nederland. www.zorginstituutnederland.nl.

15. Arends JE, van der Meer JTM, Posthouwer D, et al. Favourable SVR12 rates with boceprevir or telaprevir triple therapy in HIV/HCV coinfected patients. *Neth J Med*. 2015;73(7):324-330.
16. van Sighem AI, Boender TS, Wit FWNM, Smit C, Matser A, Reiss P. *Monitoring Report 2016. Human Immunodeficiency Virus (HIV) Infection in the Netherlands*. Amsterdam: Stichting HIV Monitoring; 2016.
17. Lambers FAE, Prins M, Thomas X, et al. Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM. *AIDS*. 2011;25(17):F21-7. doi:10.1097/QAD.0b013e32834bac44
18. den Hollander JG, Rijnders BJ, van Doornum GJJ, van der Ende ME. Sexually transmitted reinfection with a new hepatitis C genotype during pegylated interferon and ribavirin therapy. *AIDS*. 2005;19(6):639-640. http://www.ncbi.nlm.nih.gov/pubmed/15802989. Accessed August 26, 2016.
19. Berenguer J, Gil-Martin Á, Jarrin I, et al. Reinfection by HCV following effective all-oral DAA therapy in HIV/HCV-coinfected individuals. *AIDS*. December 2018. doi:10.1097/QAD.0000000000002103
20. Ingiliz P, Krznaric I, Stellbrink H-J, et al. Multiple hepatitis C virus (HCV) reinfections in HIV-positive men who have sex with men: no influence of HCV genotype switch or interleukin-28B genotype on spontaneous clearance. *HIV Med*. 2014;15(6):355-361. doi:10.1111/hiv.12127
21. Martin TCS, Martin NK, Hickman M, et al. Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM. *AIDS*. 2013;27(16):2551-2557. doi:10.1097/QAD.0b013e32836381cc
22. van Rijckevorsel G, Whelan J, Kretzschmar M, et al. Targeted vaccination programme successful in reducing acute hepatitis B in men having sex with men in Amsterdam, the Netherlands. *J Hepatol*. 2013;59(6):1177-1183. doi:10.1016/j.jhep.2013.08.002
23. Heuft MM, Houba SM, Van Den Berk GEL, et al. Protective effect of hepatitis B virus-active antiretroviral therapy against primary hepatitis B virus infection. *AIDS*. 2014;28(7):999-1005. doi:10.1097/QAD.0000000000000180
24. Xu B, Lin L, Xu G, et al. Long-term lamivudine treatment achieves regression of advanced liver fibrosis/cirrhosis in patients with chronic hepatitis B. *J Gastroenterol Hepatol*. 2015;30(2):372-378. doi:10.1111/jgh.12718
25. Ratcliffe L, Beadsworth MBJ, Pennell A, Phillips M, Vilar FJ. Managing hepatitis B/HIV co-infected: adding entecavir to truvada (tenofovir disoproxil/emtricitabine) experienced patients. *AIDS*. 2011;25(8):1051-1056. doi:10.1097/QAD.0b013e328345ef5e
26. Sharma SK, Saini N, Chwla Y. Hepatitis B virus: inactive carriers. *Virol J*. 2005;2:82. doi:10.1186/1743-422X-2-82

27. Quirk E, Graham H, Liu C, Rhee M, Piontkowsky D, Szwarcberg J. Reports of viral hepatitis B and C in HIV patients participating in clinical trials of elvitegravir/cobicistat/tenofovir DF/emtricitabine and cobicistat-boosted atazanavir plus tenofovir DF/emtricitabine. *Antivir Ther*. 2013;1 Suppl 38:A63.
28. Heuft MM, Houba SM, van den Berk GEL, et al. Protective effect of hepatitis B virus-active antiretroviral therapy against primary hepatitis B virus infection. *AIDS*. 2014;28(7):999-1005. doi:10.1097/QAD.0000000000000180
29. Machiels JD, Braam EE, van Bentum P, et al. Vaccination with Fendrix of prior nonresponding patients with HIV has a high success rate. *AIDS*. 2019;33(3):503-507. doi:10.1097/QAD.0000000000002085

Appendix: supplementary table

Appendix table 4.1: *Demographic characteristics of HIV/hepatitis C virus (HCV) co-infected individuals and those who spontaneously cleared HCV registered in the SHM database, 1998-2018.*

	Total HCV co-infected	Spontaneous clearance
Total number of individuals screened for HCV	2,035	552
Male gender, n (%)	1,787 (88)	437 (79)
Region of origin, n (%)		
Netherlands	1,320 (65)	281 (51)
Europe	265 (13)	78 (14)
Sub-Saharan Africa	55 (3)	58 (11)
Caribbean/South America	130(6)	67 (12)
South-east Asia	61 (3)	18 (32)
Other	204 (10)	50 (9)
HIV transmission route, n (%)		
Men who have sex with men	1,236 (60)	272 (49)
Heterosexual	184 (9)	101 (198)
People who use/used injecting drugs	443 (22)	114 (21)
Other	172 (8)	685 (132)
cART, n (%)	1,976(97)	524 (95)
Deaths, n (%)	330 (16)	86 (16)

< Back to page 206

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

Colette Smit, Tom Wolfs, Annemarie van Rossum

Box 5.1: Definitions

Child	An individual diagnosed with HIV and with a first visit in a Dutch HIV treatment centre 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 an HIV-positive child in care is notified to SHM by their treating physician or nurse and registered in the SHM database.
In care in 2018	Clinic visit or lab measurement in 2018.
ART	Antiretroviral therapy.
cART	Combination antiretroviral therapy: a combination of at least three antiretroviral drugs from two different antiretroviral drugs classes or at least three nucleoside reverse transcriptase inhibitors.
Viral suppression	Any viral load measurements <200 copies/ml, 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[1,2,3,4,5]. Immediate initiation of cART regardless of CD4 cell count or percentage is associated with higher survival rates of HIV-positive children when compared with children with delayed cART initiation based on CD4 cell count[6,7,8,9]. 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 irrespective of CD4 cell count, including all children[10].

< Back to Virological response

< Back to Chapter 6

In the Netherlands, children living with HIV generally receive healthcare at one of four paediatric HIV treatment centres. These children transition to adult HIV care when they reach 18 years of age. However, children who acquire HIV at an older age 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, while under the age of 18 (*Box 5.2*).

***Box 5.2:** Outline of the paediatric ATHENA cohort in the Netherlands: HIV-positive children (aged <18 years at the time of diagnosis and first visit in a Dutch HIV treatment centre) ever registered in the ATHENA cohort by 31 December 2018.*

Populations described in this chapter

1. Ever registered and in HIV care in the Netherlands before 18 years of age (n=504)
2. Population in care in 2018:
   - aged <18 years in 2018 (n=194): 189 with vertically-acquired HIV, 2 with non-vertically acquired HIV, and 3 with an unknown route of transmission.
   - aged ≥18 years in 2018 (n=214); 121 with vertically-acquired HIV, 86 with non-vertically acquired HIV, and 7 with an unknown route of transmission.
3. Specific populations:
   - adopted children (n=136)
   - children who have transferred to adult care (n=141)

Ever registered

As of 31 December 2018, 644 HIV-positive individuals diagnosed with HIV before the age of 18 years have been registered by SHM since the start of the registration in 1998. Of these 644 children, 504 children entered care in the Netherlands before 18 years of age. Those who entered Dutch HIV care only after they were 18 years or older (n=140) are not included in this chapter. Of the 504 children we report on, 387 entered care at a paediatric HIV treatment centre and 117 at an adult treatment centre. Those who entered care in an adult HIV treatment centre were predominantly diagnosed with HIV at an older age and had mostly acquired HIV through non-vertical transmission (*Table 5.1*).

Table 5.1: Demographic and HIV-related characteristics of 504 HIV-positive children ever registered by SHM and entering care in the Netherlands below the age of 18, as of 31 December 2018.

Characteristics	Vertically-acquired HIV infection*	Non-vertically-acquired HIV infection*	Route of transmission unknown*
Total	354	138	12
HIV treatment centre			
Paediatric care	346 (97)	31 (22)	10 (83)
Adult care	8 (3)	107 (78)	2 (17)
Gender			
Male	172 (49)	51 (37)	7 (58)
Female	182 (51)	87 (63)	5 (42)
Country of origin child			
The Netherlands	110 (31)	31 (22)	0
Sub-Saharan Africa	204 (58)	82 (59)	9 (75)
Other	40 (11)	25 (19)	3 (25)
Country of origin mother			
The Netherlands	32 (9)	2 (1)	1 (8)
Sub-Saharan Africa	187 (53)	13 (9)	6 (50)
Other/unknown	135 (38)	123 (89)	5 (42)
Age at HIV diagnosis	1.2 (0.3-4.0)	16.8 (16-17)	11.3 (5-14)
cART-treated	348 (98)	129 (93)	11 (92)
Therapy-naive at cART initiation	299 (84)	122 (88)	11 (92)
CD4 at cART initiation	543 (270-1190)	303 (196-412)	250 (75-522)
CD4 Z-score at cART initiation	-0.58 (-1.02–0.15)	-0.57 (-0.96–0.26)	-0.51 (-0.99–0.19)
VL (log copies/ml) at cART initiation	5.2 (4.5-5.8)	4.5 (4.0-5.2)	4.8 (4.5-5.3)

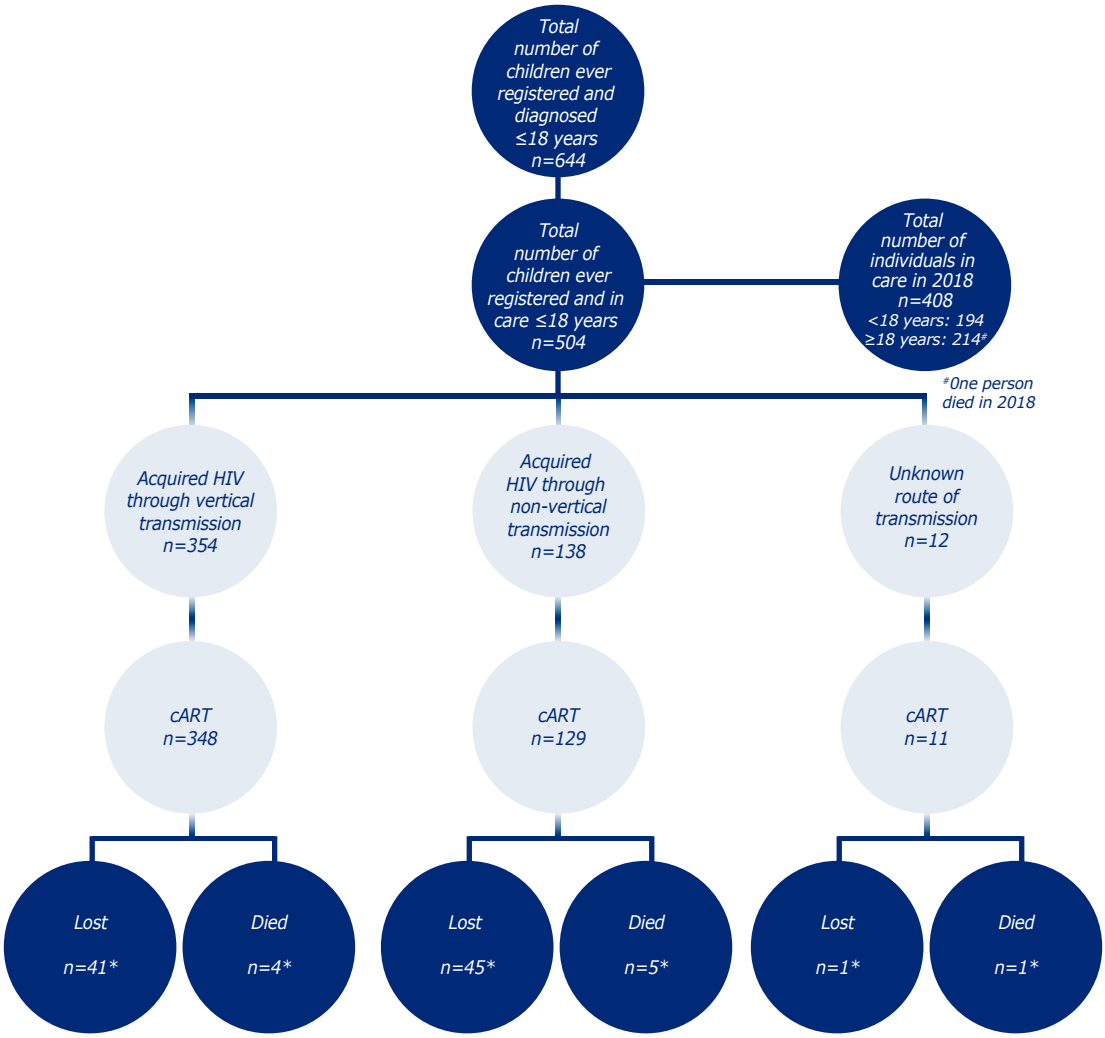
** Data are number (%) of children or median (interquartile range)*

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

Mode of transmission

The majority of the children 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 2018.*



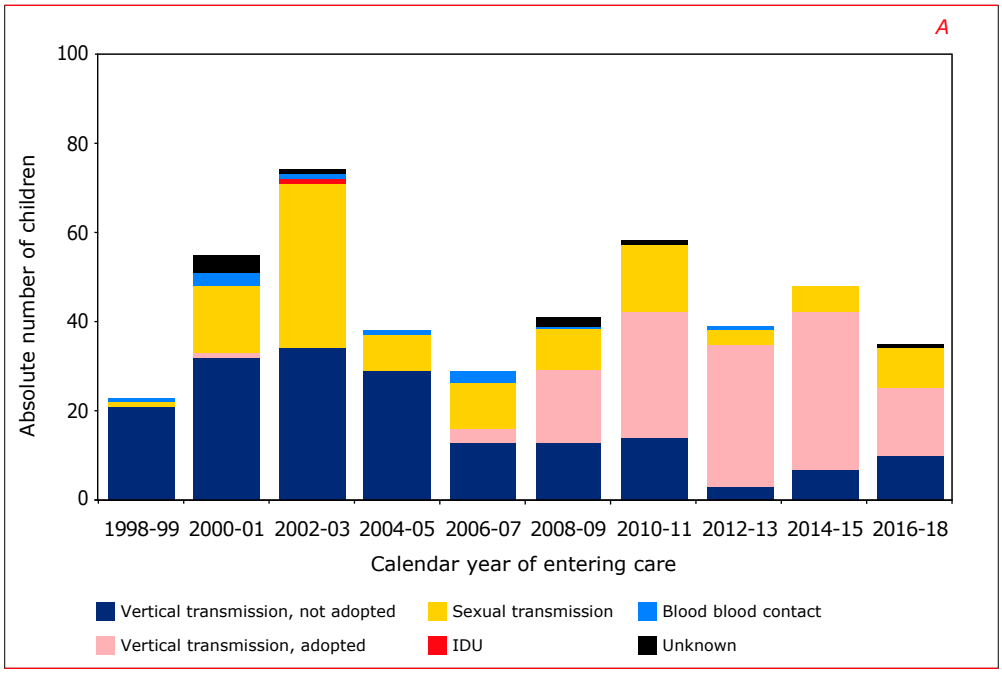
**of the total number of children who acquired HIV through vertical, non-vertical or an unknown route of transmission.*

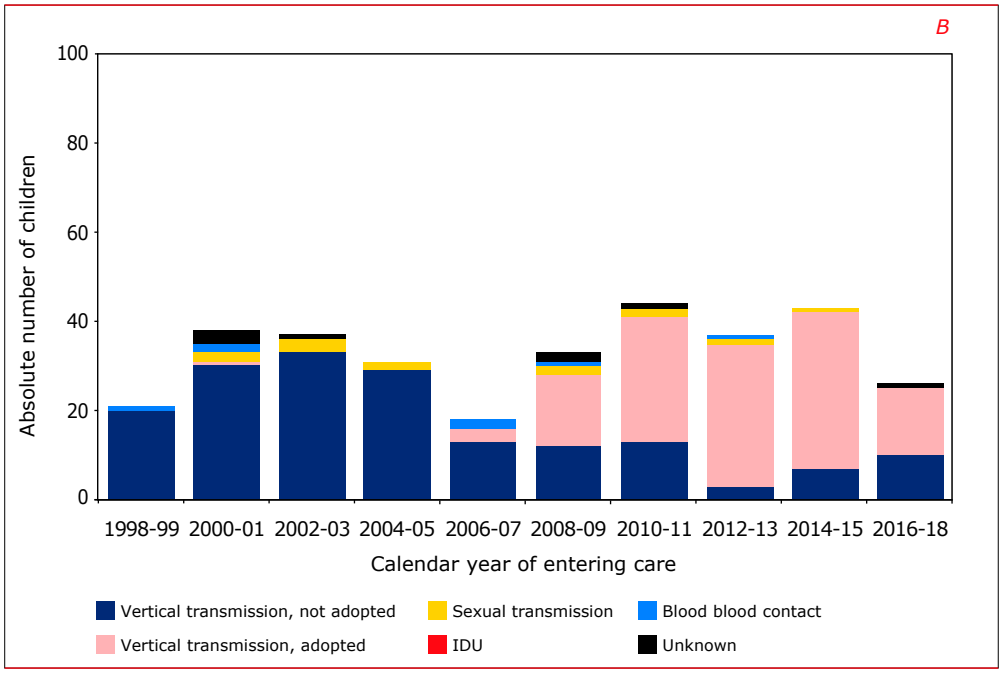
Legend: *cART=combination antiretroviral therapy.*

Children with vertically-acquired HIV

- In total 354 children had acquired HIV through vertical transmission.
- 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).
- 58% (n=204) of the children were born in sub-Saharan Africa.
- 31% (n=110) of the children were born in the Netherlands.
- In 9% of the children born in the Netherlands (10 out of 110), both parents originated from the Netherlands.
- Of children with vertically-acquired HIV, 97% received care in a paediatric HIV treatment centre in the Netherlands and the remaining 3% were seen in adult care.
- In total, 98% 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 1998-2018. A) total population, B) HIV paediatric care only.





Note: *low numbers in 2018 may be due to a delay in the treatment centre registering the child with SHM.*

Legend: *IDU=transmission through injecting drug use.*

Only a single case of HIV vertical transmission in the Netherlands since 2015

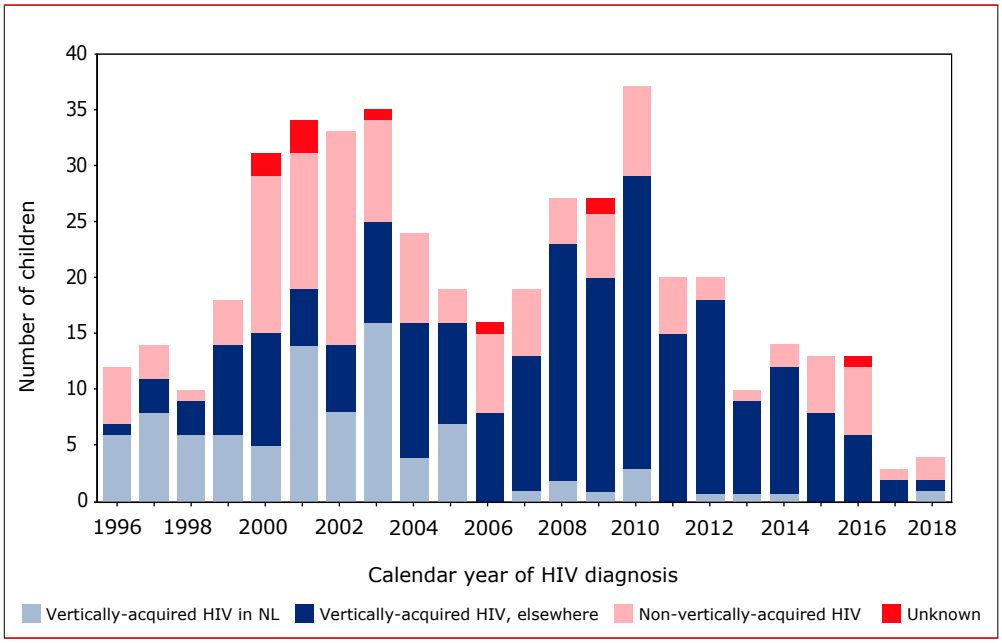
Vertical transmission of HIV has been reduced to close to zero in the Netherlands since 2015. *Figure 5.3* shows the number of newly-registered HIV diagnoses among children by year of diagnosis, according to mode of transmission and region of origin. As shown in the figure, vertical transmission of HIV in the Netherlands was relatively frequent prior to 2004 (16 cases in 2003), after which it markedly declined, with a single documented case of vertical transmission in the Netherlands in 2018.

The decline of vertical transmission in the Netherlands resulted from standard HIV screening among pregnant women, which was introduced nationally in 2004[11,12]. Since the introduction of this screening programme, 10 children who were born with HIV in the Netherlands have been reported to SHM. These 10 children are described briefly below:

- Seven children were born to mothers who only first tested positive themselves after giving birth; the mothers of five of these seven children had had a negative test result during the first trimester pregnancy screening and only acquired HIV later during their pregnancy.

- One child was born to a mother who was known to be HIV-positive, but who did not receive treatment during her pregnancy for an unknown reason.
- In one case, the mother was newly diagnosed with HIV and did start cART during pregnancy, 22 weeks after conception. Prior to initiating cART, the mother had detectable HIV RNA levels, but the last available HIV RNA measurement before delivery was undetectable (<50 copies/ml). This could suggest *in utero* transmission of HIV in this pregnancy.
- The remaining child was born to a mother whose HIV status during pregnancy was unknown, including any result of screening for HIV.

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 2018 may be due to a delay in registration.*

Children with non-vertically-acquired HIV

- In total, 138 children were registered with HIV infection acquired through non-vertical transmission, including 2 children newly-registered in 2018.
- The median age at their 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*):
  - 90 children had acquired HIV through heterosexual contact,
  - 28 children had acquired HIV through homosexual contact.
- Nineteen children had acquired HIV through contaminated blood or blood products. This mode of transmission was no longer reported from 1997 onwards among children born in the Netherland, and from 2009 onwards among all children, regardless of country of birth.
- The remaining child had acquired HIV through injecting drug use or accidentally through contaminated needles.
- Of the children with non-vertically-acquired HIV, 59% were born in sub-Saharan Africa.
- 81% received care in an adult HIV treatment centre.
- In total, 93% of the children had started cART.

Unknown route of HV-1 transmission

- For 12 HIV-positive children, the route of transmission was unknown.
- Their median age at diagnosis was 11.3 years (IQR 5-14).
- Ten children were in care at a paediatric HIV treatment centre.
- In total, 92% of these children had started cART.

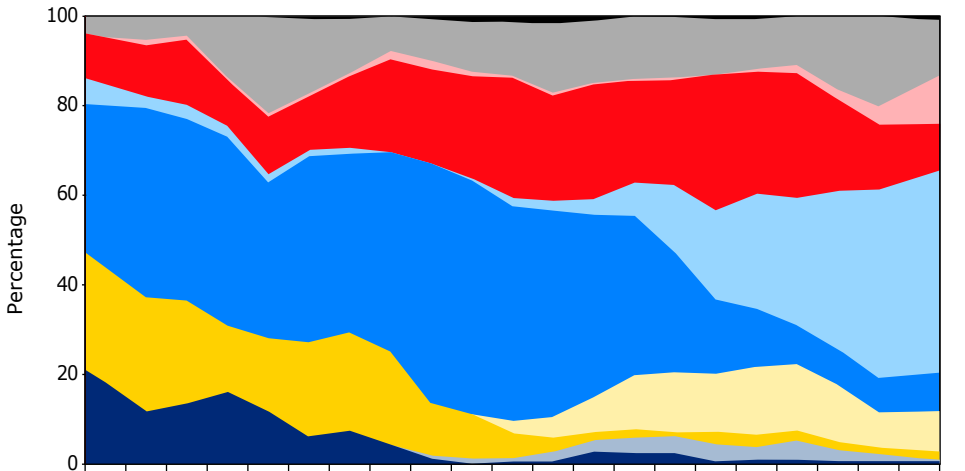
Newly registered in 2018

- 6 children first entered care in 2018.
- 4 of these children had vertically-acquired HIV and entered paediatric care.
- The other 2 children had acquired HIV through sexual contact and entered care in an adult HIV treatment centre; at that time they were older than 17 years.
- 3 children were born in the Netherlands; 1 child had acquired HIV through vertical transmission and 2 children through non-vertical transmission.
- 3 children were born in sub-Sahara Africa and all had vertically-acquired HIV. Two of these children had been adopted by Dutch parents.

Age distribution

The age distribution of children reveals some shifts between 1998 and 2008 (*Figure 5.4*). From 2008 onwards, there was an increase first in the proportion of children aged 0 to 5 years, and subsequently in thosed aged 5 to 12 from 2011 onwards. This is due to an increase in the rate of adoption of HIV-positive children in these age groups, as illustrated by the shaded areas in *Figure 5.4*. In 2018, about 83% 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	2018
	0	0	0	0	0	1	1	0	1	2	2	3	2	0	0	1	1	0	0	0	1
	3	4	4	17	34	28	20	13	16	20	22	30	27	29	29	27	25	25	38	46	31
	0	1	1	1	1	1	1	3	3	2	1	1	1	1	1	0	1	4	5	9	18
	7	9	14	13	20	20	27	35	36	41	49	46	50	48	50	65	60	65	48	34	24
	3	2	3	3	3	2	2	0	0	1	3	4	7	15	31	43	56	66	82	96	91
	24	33	39	53	54	69	67	75	92	94	88	90	80	75	57	36	29	20	19	18	17
	0	0	0	0	0	0	0	0	0	0	5	9	15	25	28	28	33	34	30	18	18
	17	20	22	19	26	35	37	35	20	18	10	6	4	4	2	6	6	5	4	3	4
	0	0	0	0	0	0	0	0	1	2	1	4	5	7	8	8	6	10	6	4	1
	12	9	13	20	18	10	12	7	2	0	1	1	5	5	5	1	2	2	1	1	1

Low mortality rates

The mortality rate among children registered between 1998 and 2018 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. AIDS was the reported cause of death for each of these boys, despite the fact that two of the boys were receiving cART. One boy had very low CD4 cell counts,

despite the use of cART and one boy died shortly after the start of cART with high levels of HIV RNA and low CD4 cell counts.

Treatment

Of the 504 children who were registered, 488 (98%) started cART. Of these 488 children, 439 (88%) were treatment-naive at the start of cART and 61 (11%) had previously been exposed to mono- or dual therapy (i.e., were pre-treated).

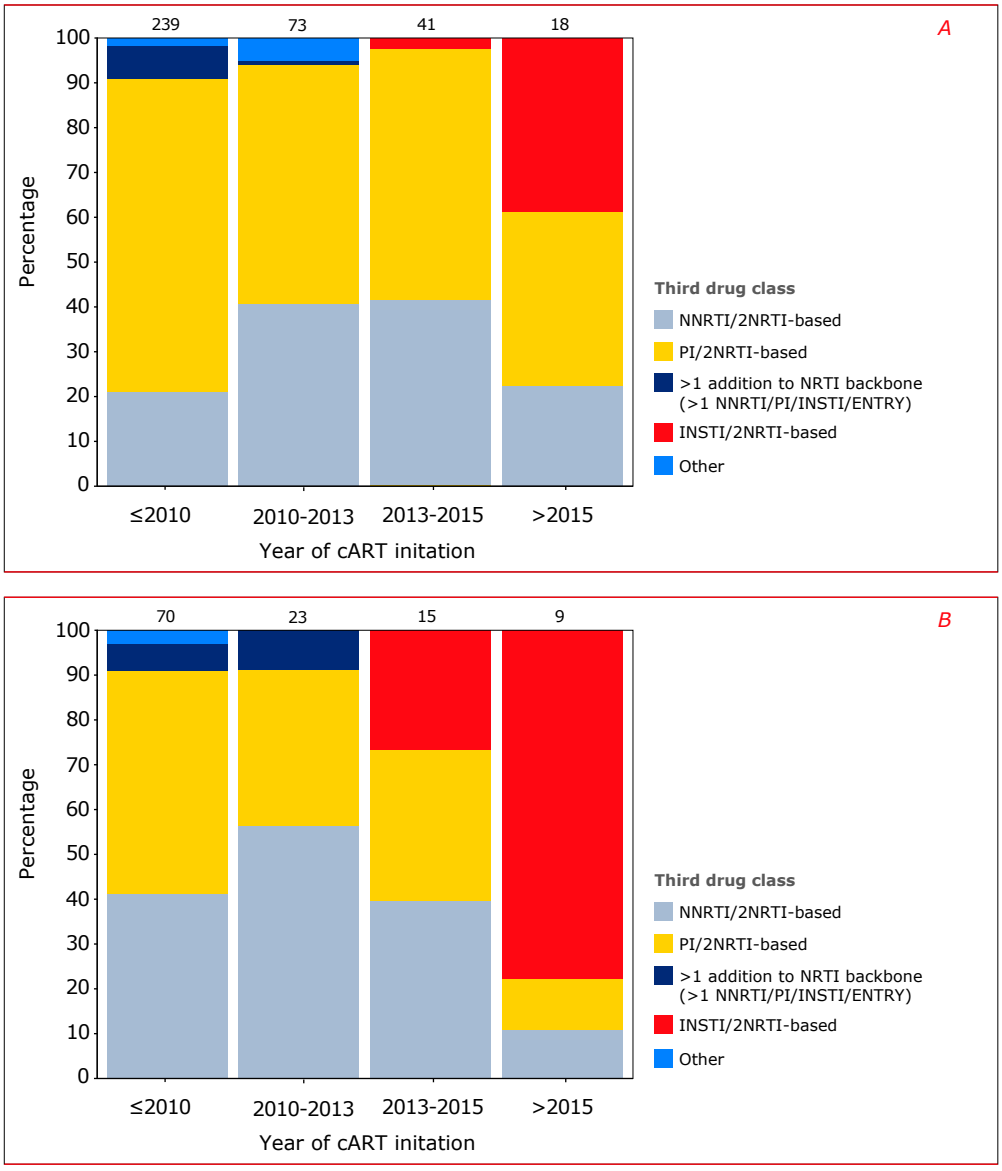
When assessing treatment, we included both pre-treated and treatment-naive children, grouped according to calendar year of starting cART: 309 children started a cART regimen before 2010, 96 started cART between 2010 and 2013, 83 started from 2013 onwards.

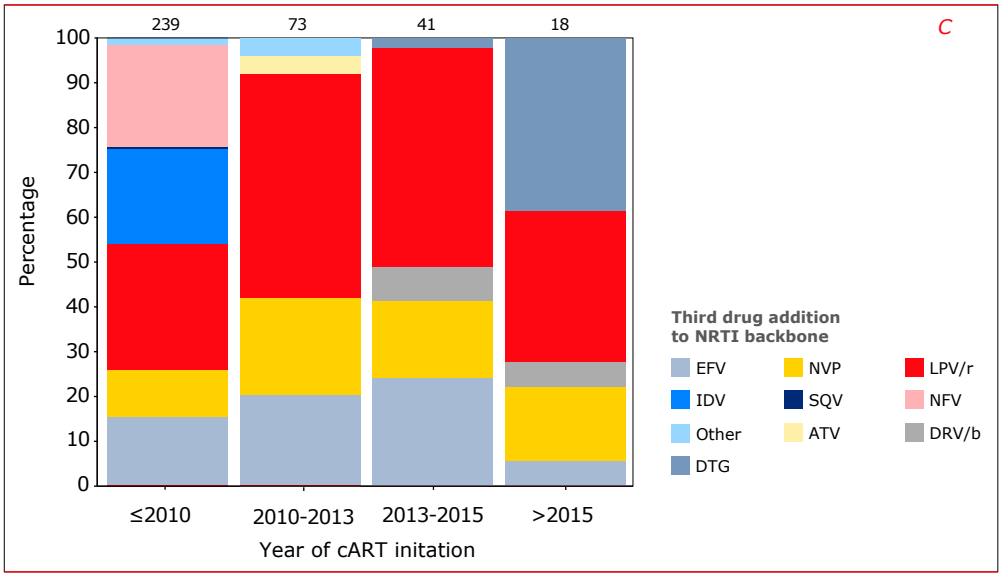
Of the children not treated with cART, 2 had only recently entered care, one had died shortly after entering care, 8 were lost to follow up and another 2 moved abroad. For another child the reason for not starting cART was recorded as being their one own decision and in another child who had low HIV RNA levels cART initiation was delayed until after transfer to adult care. Finally, for the remaining child, the reason for not initiating cART was unknown.

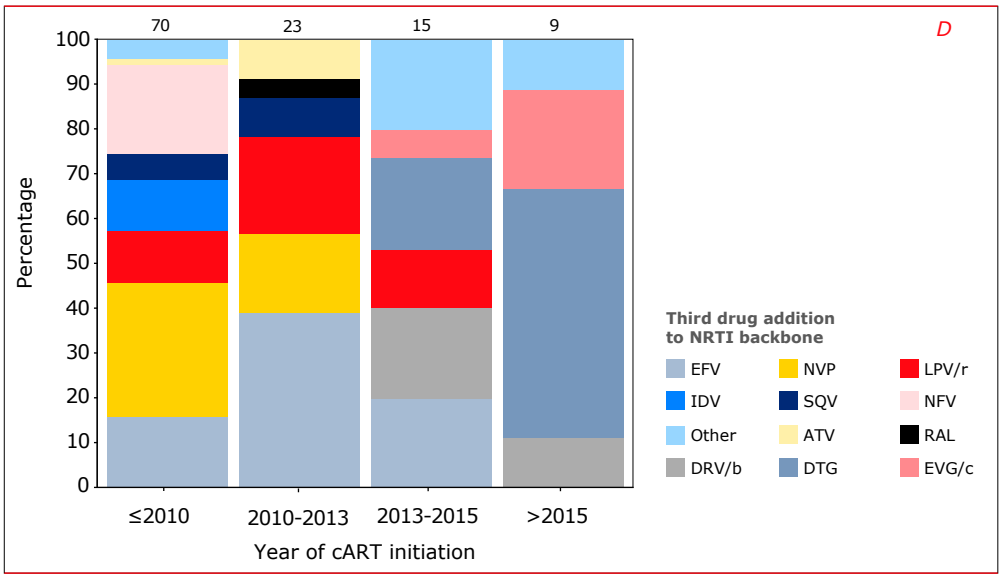
Initial combination antiretroviral regimen used

Overall, out of the 488 registered children who were known to have initiated cART, 58% were treated with a first-line cART regimen that included a protease inhibitor (PI) and two or more nucleoside reverse transcriptase inhibitors (NRTIs) and another 31% were treated with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimen with two or more NRTIs. *Figure 5.5* show the trends over time for the third-drug additions to the NRTI backbone as part of the initial cART regimens, stratified by calendar year of starting cART, and by being in care in a paediatric or adult HIV treatment centre. Among children in paediatric care, lopinavir was the most commonly-used protease inhibitor. In addition, following their introduction in 2013 and 2014, the integrase inhibitors dolutegravir and elvitegravir have also become part of an initial cART regimen in children, but were only prescribed to children older than 12 years of age.

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







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

Discontinuation of the initial cART regimen

The median time spent on an initial regimen among the 488 children who ever started cART was 17 months (IQR 4-41). Discounting weight-related dose changes, 433 children (88%) discontinued their first-line treatment regimen. The most important reasons for changing first-line cART included toxicity (15%) and simplification (22%). Virological failure accounted for 9% of the reasons for changing first-line cART therapy. Other reasons were low drug concentrations, decision by parents and/or child, research protocol-driven reasons, or unknown. The duration of time spent on an initial regimen was shorter for children who initiated cART in or after 2013 (median 14 months (IQR 6-25), likely the result of dolutegravir and elvitegravir becoming available as more attractive treatment options in 2013 and 2014.

Immunological response

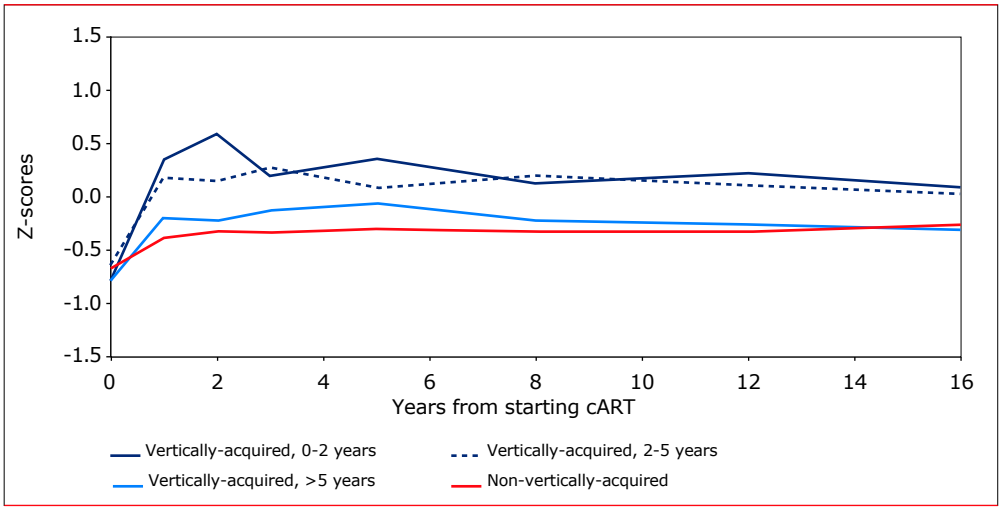
Earlier reports have shown that the clinical benefit of cART is strongly related to the degree to which the CD4 cell count recovers[13]. Long-term CD4 cell count changes were assessed among the 488 children who ever started cART. Children with vertically-acquired HIV were stratified according to age at the time of cART initiation, resulting in the following categories:
(1) vertically-acquired, 0-1 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[14], 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[15] 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.

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 with non-vertically-acquired HIV, these two groups were jointly analysed in a shared category.*

Figure 5.6 shows the changes in Z-scores for CD4 T-cell counts among HIV-positive children stratifying those with vertically-acquired HIV 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. However, the youngest children (aged below 5 years at time of cART initiation) had higher CD4-Z scores compared to children who were >5 years of age at time of cART initiation, and the CD4 Z-scores remained consistently higher among the youngest children.

Figure 5.6: *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 viral suppression used in this chapter is described in *Box 5.1*. Virological response to cART was assessed based on viral suppression (i.e., viral load <200 copies/ml) over a longer period of time (0-10 years).

For the current analysis, we included data from the 488 children registered and who had ever started cART. Children with vertically-acquired infection were stratified by age at cART initiation, as described earlier in this chapter.

Among the 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 period of cART initiation to account for changes in the use of cART regimens.

Figure 5.7 shows viral suppression rates by calendar period of cART initiation, from 1998-2009 and 2010-2018.

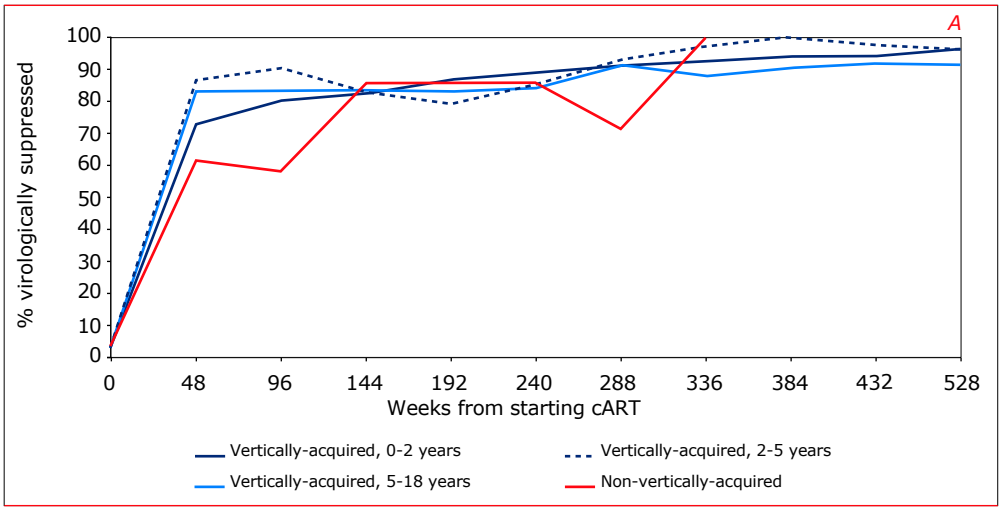
In those initiating cART between 1998 and 2009:

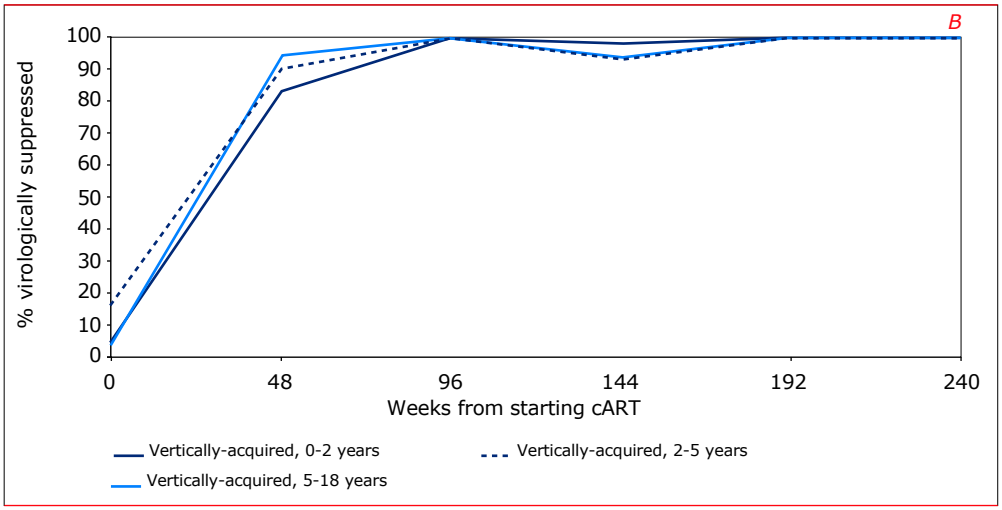
- Among children with vertically-acquired HIV and aged 0-2 years at time of cART initiation, viral suppression rates increased to 73% after one year of cART use, to 86% and 96% after 5 and 10 years, respectively.
- Among children with vertically-acquired HIV and aged 2-5 years at cART initiation, viral suppression rates increased to 87% after one year of cART use, to 85% and 96% after 5 and 10 years, respectively.
- Among children with vertically-acquired HIV and aged over 5 years at time of cART initiation, viral suppression rates increased to 87% after one year of cART use. However, ten-year viral suppression rates were lower (89%) compared with children less than 5 years of age at time of cART initiation.
- Among children with non-vertically-acquired HIV the five-year viral suppression rate was 86%. The 10-year viral suppression is not shown, due to the small number of children for whom such long term data could be calculated [*Figure 5.7A*].

In those initiating cART in or after 2010:

- Among those who started cART in or after 2010, the viral suppression rates were 100% in all groups after 5 years of cART use. However, among children with vertically-acquired HIV and aged 0-2 years at time of cART initiation, viral suppression rate after one year of cART use was 83% and lower than that in older children with vertically-acquired HIV. Importantly, due to the limited follow-up time between age at cART initiation and reaching 18 years of age for those with non-vertically acquired HIV, viral suppression rates are not presented for these children (*Figure 5.7B*).

Figure 5.7: Viral suppression since combination antiretroviral therapy initiation, by calendar period of therapy initiation: (A) 1998-2009 and (B) 2010-2018. Viral suppression is defined as any viral load measurements <200 copies/ml, except for time points in the past where tests were used with quantification limits higher than 200 copies/ml.





Legend: cART=combination antiretroviral therapy.

Currently in clinical care

Of the 504 HIV-positive children ever registered by SHM, 408 (76%) were still in clinical care in 2018 (*Figure 5.1*). Of the remaining 96 children no longer in care, 9 had died, 35 had moved abroad, and 52 were lost to follow up.

Currently in care and less than 18 years old

- Of the 408 individuals with HIV who entered care before the age of 18 years, 194 were still younger than 18 at the end of 2018.
- 192 children were in care in one of the paediatric HIV treatment centres.
- Their median age as of 31 December 2018 was 11 years (IQR 8-14).

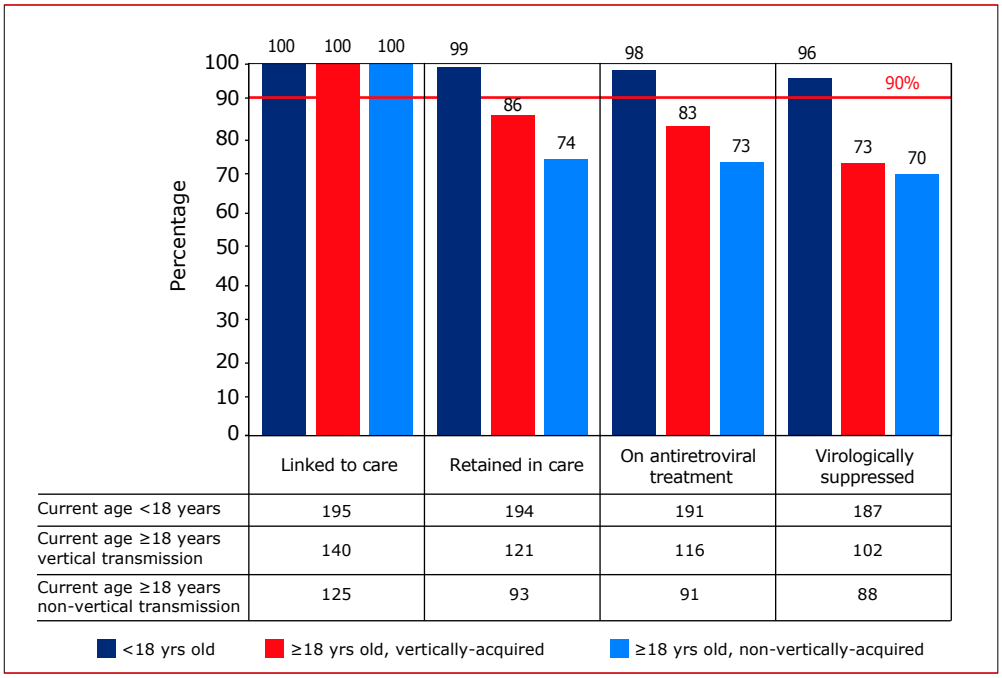
Currently in clinical care and 18 years or older

- The remaining 214 HIV-positive individuals who were first registered as a child were in care and older than 18 at the end of 2018.
- Their median age was 22 years (IQR 20-27) for those who had vertically-acquired HIV and 32 years (IQR 26-36) 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 2018, 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 5.8*).

Figure 5.8: Continuum of care by age and mode of HIV acquisition, as of 31 December 2018. The numbers above the bars indicate the proportion of individuals.



Individuals were stratified by age on 31 December 2018 and categorised as:

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

I Continuum of care: current age <18 years

- In total, 195 children less than 18 years old on 31 December 2018 were linked to care, registered by SHM, still alive, and not reported as having moved abroad.
- Of these children, 99% were retained in care (194/195); 192 children were receiving paediatric care. The single child that had been lost to follow up was born outside the Netherlands.
- During their last clinical visit in 2018, 98% (191/195) were using antiretroviral therapy.
- Overall, 96% of those linked to care and less than 18 years old had a most recent HIV RNA measurement below 200 copies/ml (187/195).

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

- 140 individuals who had acquired HIV through vertical transmission and who were over 18 years of age on 31 December 2018 were linked to care.
- Of these 140 individuals, 86% (121) were still in care as of 31 December 2018. The remaining 19 individuals had been lost to follow up, 11 of whom were born outside the Netherlands.
- 83% (116/140) were using antiretroviral therapy at their most recent clinical visit.
- 73% (102/140) had a most recent HIV RNA measurement below 200 copies/ml.

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

- 125 individuals were older than 18 by 31 December 2018 and had acquired HIV through non-vertical transmission.
- Of these, 93 (74%) were still in care as of 31 December 2018; 32 individuals had been lost to follow up, including 18 women originating from sub-Saharan Africa.
- 73% (91/125) were using antiretroviral therapy during their last registered clinical visit.
- and 70% (88/125) had a most recent HIV RNA measurement below 200 copies/ml.

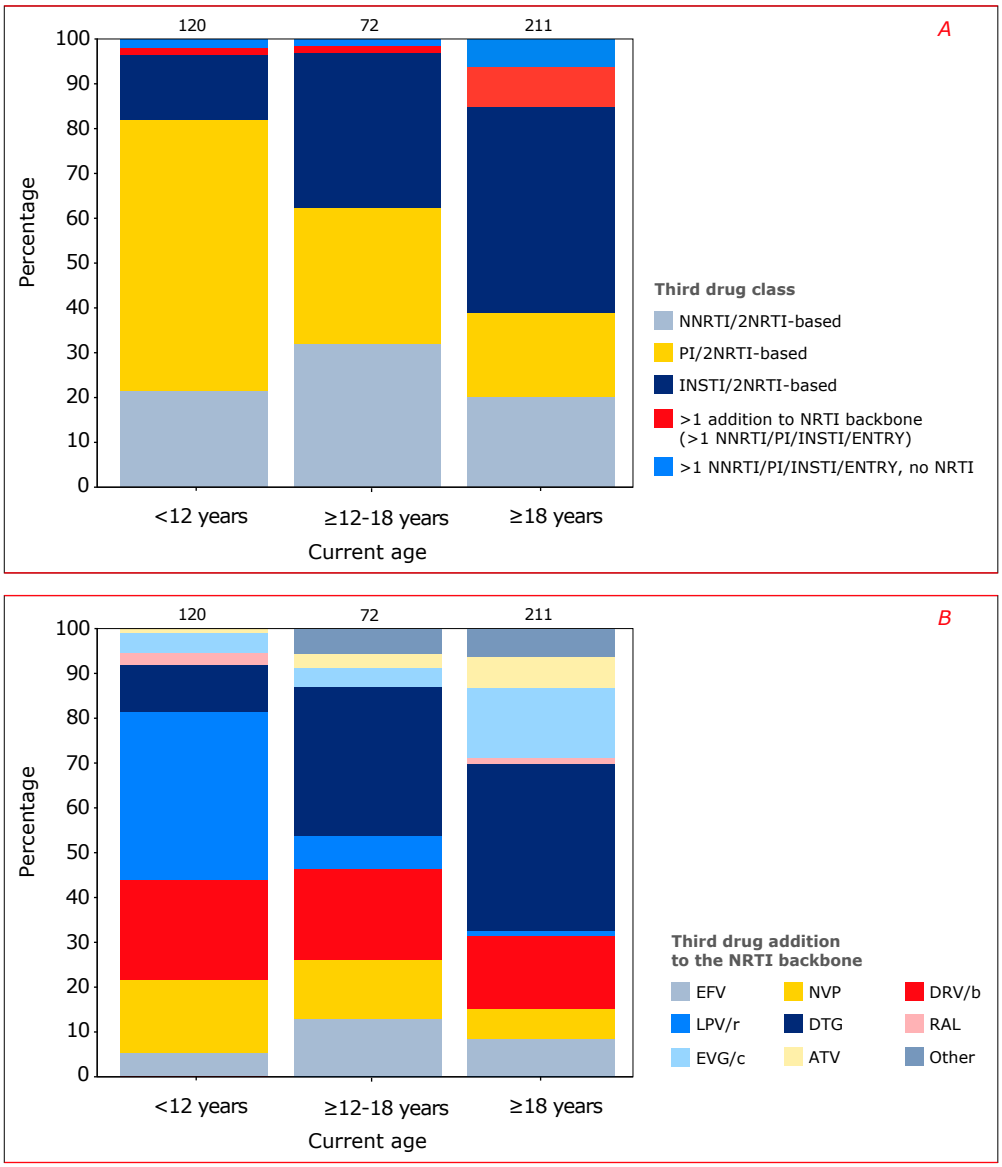
In care and on cART in 2018

Of the 408 people known to be in care in 2018 and aged less than 18 years, 396 (97%) were on cART by the end of 2018. The distribution of current cART use is shown in *Figure 5.9*, according to age on 31 December 2018.

Among those aged <12 years, a PI-containing regimen is currently used most often (61%), with lopinavir/ritonavir being the most common (37%). In children aged between 12 and 18 years, 32% are currently using an NNRTI-based regimens, 30% are using a PI-based regimen, and 35% are using an INSTI-based regimen. Among those who are currently using an INSTI-based regimen, dolutegravir was most commonly used (33%).

Among people who were diagnosed with HIV in childhood, but who are currently over 18 years of age, 46% are using an INSTI-based regimen, comprising mainly dolutegravir. There were no differences between those who started care in a paediatric HIV treatment center and those who did not.

Figure 5.9: 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: *ENTRY=entry inhibitor; INSTI=integrase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; 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.*

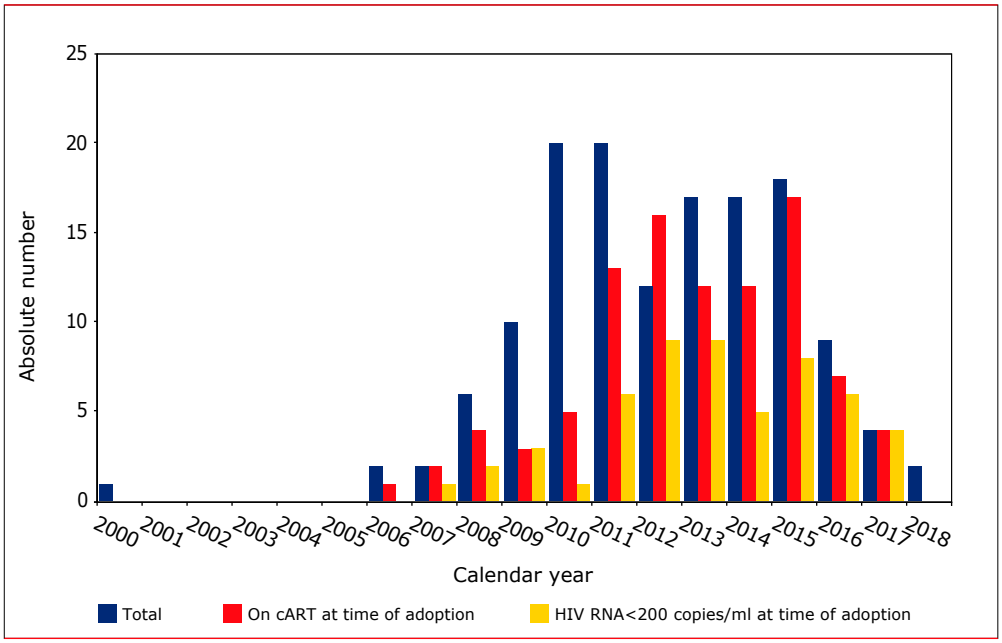
Special populations

Adopted children

Of the 504 children ever registered, 136 (27%) children were adopted by Dutch parents. The absolute number of children being adopted varied between 2 in 2006 and a maximum of 18 in 2015, with a decrease from 2016 onwards to 4 children in 2017 and 2 children in 2018 (*Figure 5.10*):

- Their median age at time of entering care in the Netherlands was 2.8 years (IQR 1.7-5.1).
- All but one child used cART during follow up in clinical care in one of the Dutch HIV treatment centres.
- In total, 96 (71%) children were already receiving cART before being adopted.
- 17 (13%) 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. However, the 2 children who were adopted in 2018 had no documented cART use at time of adoption. At the moment of entering care in the Netherlands, only 54 (40%) of the 136 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 8.4 years (IQR 6.2-10.8).
- All children who started cART are still on treatment, and 134/135 (99%) had an undetectable viral load (≤200 copies/ml) at the last known time point. The only individual with a detectable HIV RNA level was currently older than 18 and had transferred to an adult HIV treatment centre.

Figure 5.10: Number of HIV-positive children who entered paediatric care through adoption, by calendar year.



Legend: cART=combination antiretroviral therapy.

Transfer to adult care

Of the registered 504 children, 387 children initially received HIV care in one of the paediatric HIV treatment centres. As of 31 December 2018, 141 (36%) of these 387 children had transferred from paediatric to adult care because they had reached the age of 18.

The number of children who transferred to an adult centre varied from one child in 2000 to 20 in 2011, 11 in 2016, and 9 in 2018. The median age at transfer was 19.0 years (IQR 18.4-19.7). The median time in care after transfer is currently 5.1 years (IQR 2.5-8.0). Of the children who have transferred to adult care, 22 (16%) have been lost to follow up, six (4%) have since moved abroad, and 3 (2.1%) have died. The remaining 119 are currently alive and in care.

At their most recent clinical visit in 2018, 13 of the 119 individuals still in care (12%) had an HIV RNA level >200 copies/ml (median 2794; IQR 497-63,600).

At the time of transfer to an adult HIV treatment centre, 94 (80%) of the 117 children with an available HIV RNA measurement had an HIV RNA ≤200 copies/ml and 23 (20%) 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[16]. 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, 84% of the children had an HIV RNA level ≤200 copies/ml, compared to 80% of the young adults one year after their transfer. Of the 23 adolescents without viral suppression at time of transfer, 2 had died, 6 were no longer in care and 5 had a most recent HIV RNA >200 copies/ml. The remaining 10 adolescents were virally suppressed according to their last available HIV RNA measurement.

Weijsenfeld *et al.* explored the data on transition to adult care in our registry in more detail[17] and reported 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. Virological failure was associated with a low level of education and a lack of autonomy regarding medication adherence at the time of transitioning to adult care.

Summary

Of the 504 children diagnosed with HIV before the age of 18 and registered by SHM, 81% are still in care. A substantial proportion of the children newly registered since 2010 are children who have been adopted by Dutch parents. This has driven the observed increase in the proportion of children in care aged between 0 and 12 years old. It is worth noting that the annual number of newly-registered children who were adopted by Dutch parents has been decreasing since 2016.

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 one case reported since 2015. This reflects the success of standardised HIV screening during the first trimester of pregnancy[11]. 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. We observed low mortality rates in HIV-positive children in care in the Netherlands. Ninety-seven percent 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 the protease inhibitors lopinavir/ritonavir and

darunavir, 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 viral suppression rate after 5 years of cART use in HIV-positive children who initiated cART in or after 2010 cART is high (99% HIV-RNA <200 copies/ml), 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 2018 (96% versus 72%). Another important point is that almost all children (99%) 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 2018, 52% were older than 18 on 31 December 2018. The high rate of detectable HIV viral load in HIV-positive 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 is associated with an increased risk of virological failure.

Although universal screening for HIV early during pregnancy has resulted in vertical transmission of HIV having been reduced to close to zero in the Netherlands, health care providers should remain vigilant for the occasional incident maternal HIV infection which may occur later during pregnancy, and which, unnoticed, could result in vertical transmission.

References

1. Goetghebuer T, Haelterman E, Le Chenadec J, et al. Effect of early antiretroviral therapy on the risk of AIDS/death in HIV-infected infants. *AIDS*. 2009;23(5):597-604. doi:10.1097/QAD.0b013e328326ca37
2. Judd A, Chappell E, Turkova A, et al. Long-term trends in mortality and AIDS-defining events after combination ART initiation among children and adolescents with perinatal HIV infection in 17 middle- and high-income countries in Europe and Thailand: A cohort study. Deeks SG, ed. *PLOS Med*. 2018;15(1):e1002491. doi:10.1371/journal.pmed.1002491
3. Gibb DM. Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. *BMJ*. 2003;327(7422):1019-0. doi:10.1136/bmj.327.7422.1019
4. Gortmaker SL, Hughes M, Cervia J, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med*. 2001;345(21):1522-1528. doi:10.1056/NEJMoa011157
5. de Martino M, Tovo PA, Balducci M, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Italian Register for HIV Infection in Children and the Italian National AIDS Registry. *JAMA*. 2000;284(2):190-197.
6. Foster C, Pace M, Kaye S, et al. Early antiretroviral therapy reduces HIV DNA following perinatal HIV infection. *AIDS*. 2017;31(13):1847-1851. doi:10.1097/QAD.0000000000001565
7. Shiau S, Strehlau R, Technau K-G, et al. Early age at start of antiretroviral therapy associated with better virologic control after initial suppression in HIV-infected infants. *AIDS*. 2017;31(3):355-364. doi:10.1097/QAD.0000000000001312
8. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med*. 2008;359(21):2233-2244. doi:10.1056/NEJMoa0800971
9. Newell M-L, Patel D, Goetghebuer T, Thorne C. CD4 cell response to antiretroviral therapy in children with vertically acquired HIV infection: is it associated with age at initiation? *J Infect Dis*. 2006;193(7):954-962. doi:10.1086/500842
10. World Health Organization. Guidelines Guideline on When To Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV. *World Heal Organ*. 2015;(September):78. doi:978 92 4 150956 5
11. Boer K, Smit C, Van Der Flier M, De Wolf F. The comparison of the performance of two screening strategies identifying newly-diagnosed HIV during pregnancy. *Eur J Public Health*. 2011;21(5):632-637. doi:10.1093/eurpub/ckq157

12. Op de Coul ELM, Hahné S, van Weert YWM, et al. Antenatal screening for HIV, hepatitis B and syphilis in the Netherlands is effective. *BMC Infect Dis*. 2011;11(1):185. doi:10.1186/1471-2334-11-185
13. The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008;372(9635):293-299. doi:10.1016/S0140-6736(08)61113-7
14. Bunders M, Cortina-Borja M, Newell M-L, European Collaborative Study. Age-related standards for total lymphocyte, CD4+ and CD8+ T cell counts in children born in Europe. *Pediatr Infect Dis J*. 2005;24(7):595-600.
15. Comans-Bitter WM, De Groot R, Van den Beemd R, et al. Immunophenotyping of blood lymphocytes in childhood: Reference values for lymphocyte subpopulations. *J Pediatr*. 1997;130(3):388-393. doi:10.1016/S0022-3476(97)70200-2
16. Collins IJ, Foster C, Tostevin A, et al. Clinical status of adolescents with perinatal HIV at transfer to adult care in the UK/Ireland. *Clin Infect Dis*. 2017;64(8):1105-1112. doi:10.1093/cid/cix063
17. Weijsenfeld AM, Smit C, Cohen S, et al. Virological and social outcomes of HIV-infected adolescents and young adults in the Netherlands before and after transition to adult care. *Clin Infect Dis*. 2016;63(8):1105-1112. doi:10.1093/cid/ciw487

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

Colette Smit, Jeannine Nellen, Liesbeth van Leeuwen

Introduction

The most common route of HIV acquisition for children aged 0 to 15 years worldwide is transmission from an HIV-positive mother to her child[1]. Mother-to-child transmission (MTCT) can take place *in utero*, during labour and delivery, and postnatally during breastfeeding. Without intervention, the risk of MTCT varies between 15% and 45%[2,3]. However, since the introduction of combination antiretroviral therapy (cART) in pregnant women, the risk of MTCT has been dramatically reduced to less than 1%[4,5].

To ensure timely initiation of cART and thus reduce the risk of MTCT, it is important to ascertain a woman's HIV status during pregnancy. Therefore, in January 2004, the Netherlands introduced standardised voluntary HIV antibody testing for pregnant women during the first trimester of pregnancy[6].

In February 2018, Stichting HIV Monitoring launched a new data entry system, DataCapTree. The increased efficiency of this system has reduced the delay in pregnancy-related data collection and allowed previously reported pregnancies to be reviewed and supplemented with additional data. As a result, out of a total of 5,129 HIV-positive women in care in the Netherlands monitored by SHM between January 1996 and July 2019, 2,705 pregnancies were registered for 1,517 women.

Demographics

Maternal characteristics

Table 6.1 presents the characteristics of HIV-positive women with a registered pregnancy in the Netherlands. Of the 1,517 women with a documented pregnancy, 1,227 (81%) were of non-Dutch origin and 290 women (19%) originated from the Netherlands. The majority of women of non-Dutch origin were born in sub-Saharan Africa (n=839, 68%) or the Caribbean/Latin America region (n=210, 17%).

Women of Dutch origin were more likely than those of non-Dutch origin to be aware of their HIV infection before becoming pregnant (78% versus 62%, respectively, $p<0.001$). Furthermore, women of Dutch origin were slightly older at the time of their first registered pregnancy, with a median age of 30 years

(interquartile range (IQR) 27-35), compared with 29 years for non-Dutch women (IQR 25-34). In both groups of women, heterosexual contact was the most common mode of HIV acquisition (94%). Twelve women reported injecting drug use (IDU) as the mode of HIV acquisition. However, almost all transmissions by IDU in women with a documented pregnancy occurred before 2003, with just one occurring in 2010. Since then, there have been no further reports of HIV transmission by IDU. Finally, 14 pregnant women had acquired HIV by MTCT themselves.

Between 2000 and 2016, 31 mothers were documented to have died during follow up, with a median time between the onset of their last reported pregnancy and death of 5 years (IQR 3-10) and a median age at time of death of 36 years (IQR 30-40). For 5 women the cause of death was unknown. In those with a known cause of death, the most common causes were AIDS-related and non-AIDS related infection (n=13 and n=4, respectively). Other causes included non-AIDS related malignancies (n=3), lung disease (n=2) and liver disease (n=2). Two women died within one year after delivery. A total of 284 women were no longer in care; of these, 143 were known to have moved abroad and 141 were lost to follow up. Being lost to follow up was more common in women of non-Dutch origin (11%) than in those of Dutch origin (2%).

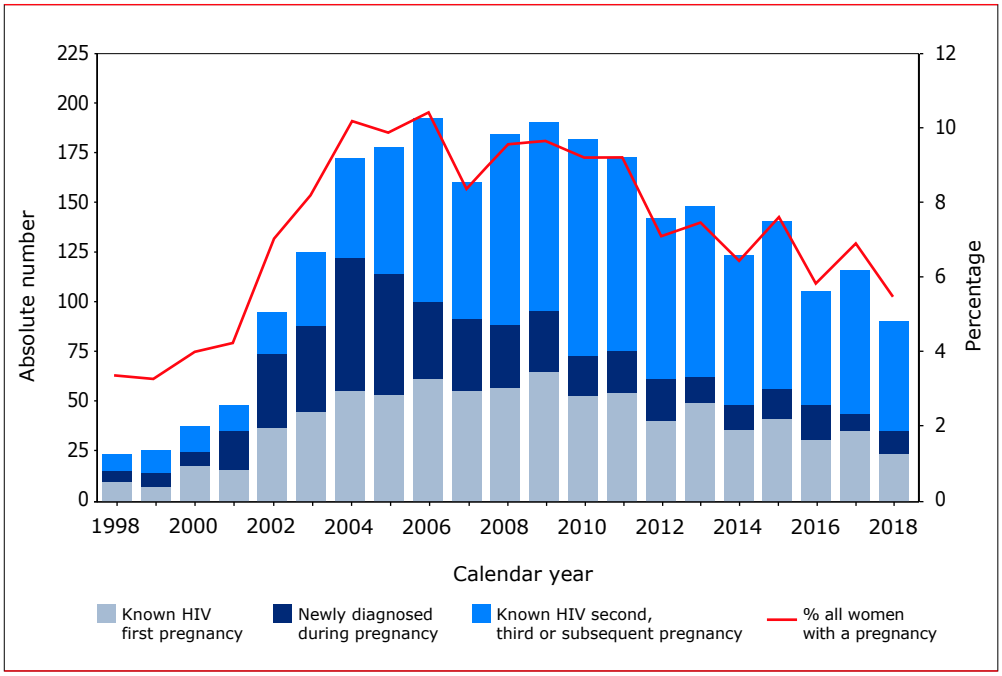
Trends in number of pregnancies in HIV-positive women

All women aged between 18 and 45 years were considered to be 'at risk' for pregnancy, and this group was therefore used to calculate the prevalence of pregnancies in women in care. The prevalence of pregnancies is shown in *Figure 6.1*.

The absolute annual number of pregnancies in women in care in the Netherlands varied between a minimum of 24 pregnancies in 1998 and a maximum of 193 in 2006 (*Figure 6.1*), with a decrease from 2009 onwards.

The number of women who were newly diagnosed with HIV during pregnancy increased from 6 in 1998 to 66 in 2004, and thereafter the number declined to approximately 13 annually after 2013. It should be noted that, between 2003 and 2005, there was a marked increase in new HIV diagnoses during pregnancy. This was likely the result of the introduction of standard HIV screening in the first trimester of pregnancy in Amsterdam in 2003, with subsequent extension to nationwide screening from 1 January 2004 onwards. Finally, the number of second, third or subsequent pregnancies in women already known to be HIV positive increased from 8 in 1998 to a maximum of 110 in 2010, and declined thereafter to approximately 75 annually (*Figure 6.1*).

Figure 6.1: Absolute number of first and subsequent pregnancies per year, stratified by known HIV infection at conception and newly diagnosed during pregnancy.



Pregnancy-related characteristics

Overall, 1,517 women accounted for 2,705 registered pregnancies. Forty-nine percent of the women had one registered pregnancy, 28% had two registered pregnancies, and 23% of the women had three or more registered pregnancies (*Table 6.1*).

Table 6.1: Characteristics of HIV-positive pregnant women registered and monitored by Stichting HIV Monitoring between 1 January 1996 and 1 July 2019.

	Total n (%)	Dutch n (%)	Non-Dutch n (%)
Maternal characteristics	1,517	290 (19)	1,227 (81)
HIV diagnosis before pregnancy (%)	985 (65)	225 (78)	760 62)
Age at start of first pregnancy occurring in HIV infection (years*)	29 (25-34)	30 (27-35)	29 (25-34)
HIV transmission route			
Heterosexual contact (%)	1,429 (94)	265 (91)	1,164 (95)
Other (%)	88 (6)	25 (9)	63 (5)
Total number of pregnancies	2,705	525	2180
Maximum number of pregnancies after HIV diagnosis			
1	738 (49)	148 (51)	590 (48)
2	422 (28)	80 (27)	342 (28)
3	218 (14)	35 (12)	183 (15)
≥4	139 (9)	27 (10)	112 (9)
Pregnancy outcome			
Partus (%)	1,972 (73)	383 (73)	1,589 (73)
Miscarriage (%)	213 (8)	51 (10)	162 (7)
Abortion (%)	502 (18)	91 (17)	411 (19)
Unknown (%)	18 (1)		18 (1)
Mode of delivery			
Vaginal	1,204 (61)	280 (73)	924 (58)
Caesarean	736 (37)	100 (26)	636 (40)
Unknown	32 (2)	3 (1)	29 (2)
Pregnancy duration			
≥37 weeks	1,635 (83)	320 (84)	1,315 (83)
32-37 weeks	224 (11)	43 (11)	181 (11)
<32 weeks	63 (3)	14 (4)	49(3)
Missing	50 (3)	6 (1)	46 (3)
Birth weight (grammes, IQR*)	3,065 (2,645-3,400)	3,095 (2,705-3,450)	3,060 (2,620-3,384)
Perinatal deaths	55 (3)	13 (3)	42 (3)
Start combination antiretroviral therapy in pregnancy			
Before pregnancy	1,230 (62)	248 (65)	982 (62)
During pregnancy	717 (36)	130 (34)	587 (37)
No combination antiretroviral therapy during pregnancy	25 (1)	5 (1)	20 (1)

	Total n (%)	Dutch n (%)	Non-Dutch n (%)
HIV RNA plasma levels before delivery			
HIV RNA available	1,930/1,972** (98)	379/383** (99)	1,551/1,589** (98)
Undetectable	1551 (80)	335 (89)	1,280 (83)
Detectable^	379 (20)	44 (11)	271 (17)

** Median, Interquartile Range (IQR)*

*** number of pregnancies after HIV diagnosis that resulted in birth*

^ based on the detection limit of the assay.

Pregnancy outcome

The 2,705 pregnancies resulted in 1,972 (73%) births (including both live births and stillbirths). Two hundred and thirteen pregnancies (8%) ended in miscarriage, and 502 (18%) ended through abortion. However, this may be an underestimation as not all miscarriages or terminations of pregnancies may have been reported. For the remaining 18 (1%) pregnancies, the outcome was unknown.

Pregnancy duration, preterm birth and perinatal death

A total of 1,972 pregnancies lasted at least 24 weeks and were therefore counted as resulting in a birth. The duration of pregnancy was known for 1,922 of these pregnancies. Overall, 1,635 (85%) pregnancies lasted at least 37 weeks, whereas 287 (15%) pregnancies resulted in preterm birth (defined as a pregnancy duration between 24 and 37 weeks). This preterm birth rate of 15% is higher than would be expected based on that in the general population, where preterm birth is reported in 7% of pregnancies[7].

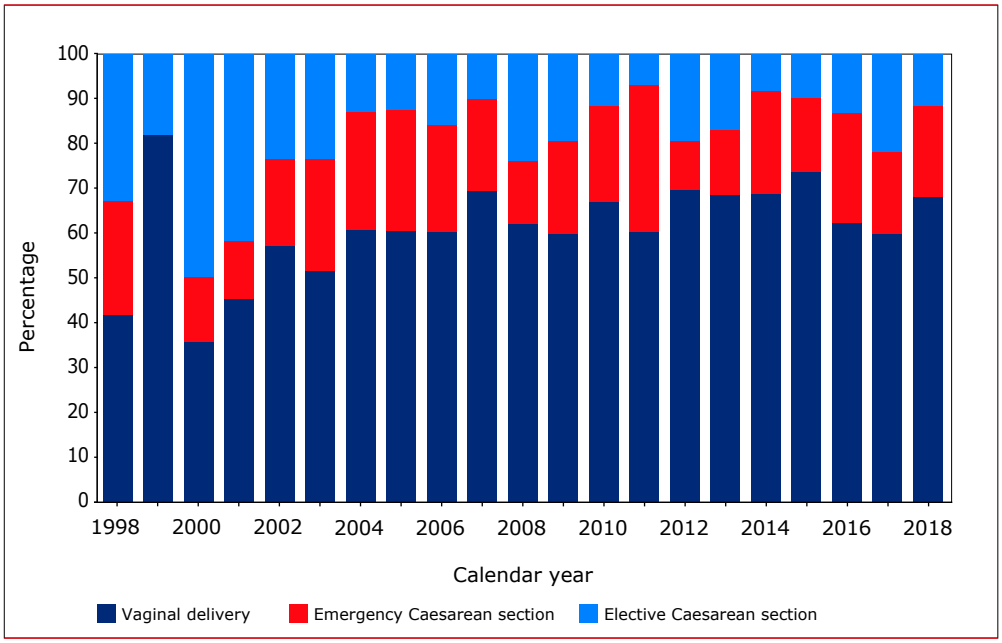
Perinatal death, including antepartum death, occurred in 3% (n=56) of the births. Congenital disorders were registered for 13 infants, three of whom died. No significant differences in pregnancy duration, birth weight, or perinatal death were found between women of Dutch and non-Dutch origin.

Mode of delivery

Providing viral suppression during pregnancy is achieved with cART, vaginal delivery is recommended for HIV-positive women[8,9]. However, in the presence of detectable HIV RNA levels at or near the time of delivery, elective Caesarean section is recommended to minimise the risk of MTCT: the European AIDS Clinical Society (EACS) guidelines state that elective Caesarean section should be carried out if HIV RNA levels are above 50 copies/ml in weeks 34-36 of pregnancy[10].

Figure 6.2 shows the trend in mode of delivery over time for the registered 1,972 pregnancies that lasted at least 24 weeks between 1998 and 2018. Overall, 61% of newborns were delivered vaginally; 73% of the women of Dutch origin delivered vaginally compared to 58% of the women of non-Dutch origin (p<0.001). Thirty-seven percent of newborns were delivered by Caesarean section, which was elective in 51% of cases. The proportion of elective Caesarean sections in first pregnancies decreased over time from 33% in 1998 to 12% in 2018 (Figure 6.2), which is equivalent to the level seen in the general population[7].

Figure 6.2: Modes of delivery over time.



Combination antiretroviral therapy use and response to treatment in pregnant women

From 1996 onwards, cART was used in almost all 1,972 pregnancies of at least 24 weeks duration: in 1,230 (62%) pregnancies, women were already using cART at the time of conception, while in 717 (36%) pregnancies, cART was first started during pregnancy. No cART use at any time during pregnancy was reported for just 25 pregnancies.

Figure 6.3A shows the most commonly used third-drug additions to the nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone as part of cART in pregnant women between 1998 and 2018. From 1998 to 2006, nelfinavir-containing and nevirapine-containing regimens were most commonly used (43% and 31%, respectively). Subsequently, from 2007 to 2014, the most commonly used regimen was a lopinavir/ritonavir-containing regimen (46%). Finally, from 2015 onward, atazanavir-containing regimens (28%) and darunavir-containing regimens (26%) were increasingly prescribed.

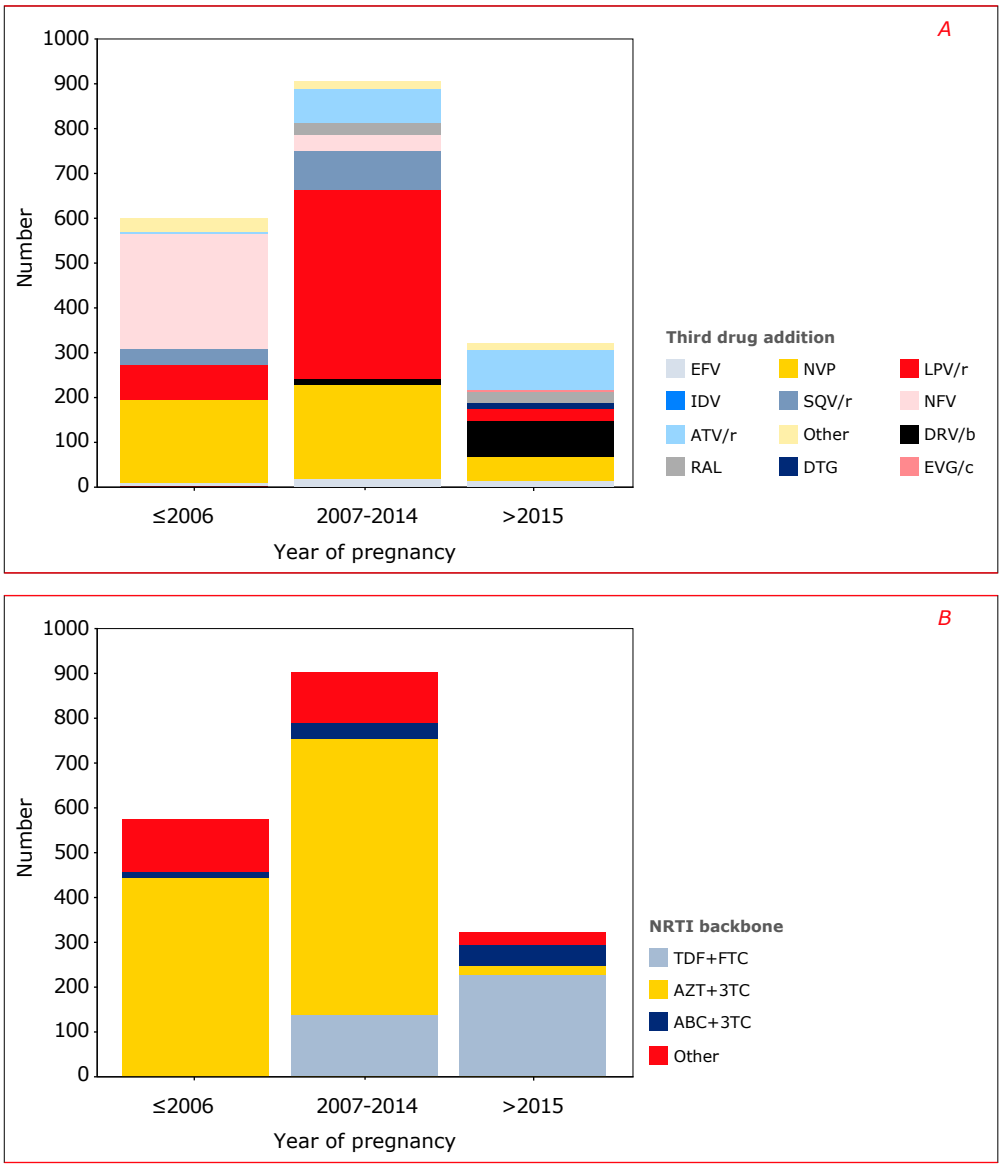
In May 2018, a potential safety signal was reported regarding dolutegravir and a possible relation with neural tube defects[11]. Between 2015 and 2018, dolutegravir was used *during conception* by 25 women in the Netherlands, of whom 22 switched to another regimen during pregnancy (median time between the conception and switch 6 weeks; IQR 5-9), and three continued dolutegravir during pregnancy. Of these 25 pregnancies, 23 live births, one stillbirth, and one perinatal death in the first week of life were reported. An additional 10 women initiated dolutegravir *during pregnancy* at a median of 22 weeks after conception (IQR 15-31), resulting in a total of 13 women using dolutegravir at time of birth. The 10 pregnancies in women who initiated dolutegravir during pregnancy resulted in 10 live births.

At the time of the safety alert in May 2018, three pregnant women were using dolutegravir: one woman gave birth shortly after the safety alert, and the other two women continued dolutegravir use during pregnancy. The above-mentioned stillbirth occurred in one of these pregnancies. No neural tube defects were documented in any of the infants born to women who used dolutegravir during conception or who initiated the drug later during pregnancy (including the stillbirth and perinatal death case). It should be noted that our report of dolutegravir use during pregnancy in 2018 may be incomplete due to a delay in data collection.

Figure 6.3B provides an overview of the components of the NRTI backbone used during pregnancy between 1998 and 2018. Until 2015, the most commonly prescribed backbone was the combination of zidovudine and lamivudine (AZT+3TC) (68% up to 2006 and 75% between 2007 and 2014). From 2015 onwards, there was a shift towards the combination of tenofovir and emtricitabine (TDF+FTC) (71%).

Due to the reduced antiviral activity of darunavir and elvitegravir when boosted with cobicistat, recommendations for the use of cobicistat-containing regimens during pregnancy changed in 2018, stating that cobicistat-containing regimens were no longer recommended during pregnancy[12]. However, in the Netherlands, cobicistat use at the time of delivery was not common in pregnant women at that time and has been documented in only 4 pregnancies since 2015.

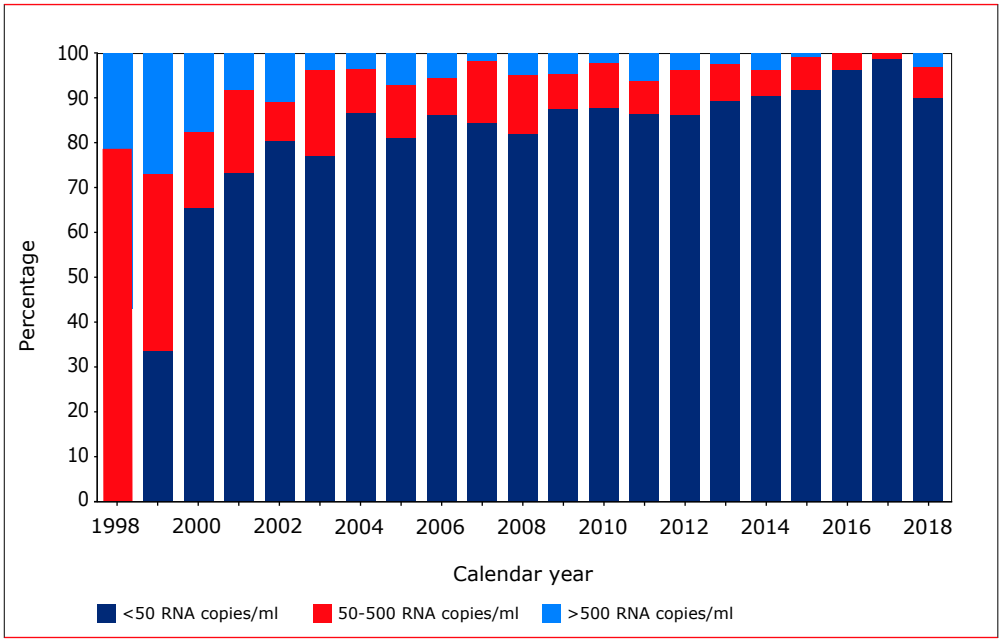
Figure 6.3: A) Third-drug additions and B) the nucleoside reverse transcriptase backbone used as part of the cART regimens during pregnancy in 1998-2018.



Legend: *3TC=lamivudine; /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; AZT=zidovudine; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; IDV=indinavir; LPV=lopinavir; NFV=nelfinavir; NVP=nevirapine; RAL=raltegravir; SQV=saquinavir; TDF=tenofovir disoproxil fumarate; NRTI=nucleoside analogue reverse transcriptase inhibitor.*

Figure 6.4 shows the percentage of women on cART and those with an undetectable viral load near delivery, based on the latest available viral load measurement prior to delivery; HIV RNA levels were categorised as <50 copies/ml, 50-500 copies/ml, and >500 copies/ml. Overall, for 85% of the births, the mothers had an HIV RNA level <50 copies/ml at the time of delivery, and 10% had an HIV RNA level between 50 and 500 copies/ml. The proportion of women with an HIV RNA <500 copies/ml at the time of delivery increased from 79% in 1999 to 100% in 2016 and 2017, but it decreased to 97% in 2018. This drop was driven by two women with HIV RNA >500 copies/ml and four women with HIV RNA of 50-500 copies/ml prior to delivery. Four of these six women had been diagnosed with HIV after only 7 to 36 weeks of pregnancy. All four initiated cART during pregnancy (two in the second trimester and two in the third trimester). The remaining two women had initiated cART in the past, but both had discontinued treatment before conception and restarted cART only during the second and third trimester of their pregnancies, respectively.

Figure 6.4: *Distribution of women using cART with latest HIV RNA levels <50 copies/ml, 50-500 copies/ml and >500 copies/ml prior to delivery.*



Mother-to-child transmission in children born in the Netherlands

As a result of the introduction of SHM's new data entry system, we were able to retrieve more data on vertical transmission than previously reported. Of the 1,972 children born from registered pregnancies in the Netherlands from 1996 onwards, 5 (0.25%) newborns were found to have vertically acquired HIV and were born to mothers diagnosed with HIV either prior to conception or during pregnancy. Data collected retrospectively about the pregnancy were also available for another five newborns with vertically acquired HIV. However, the mothers of these five infants were diagnosed with HIV only after delivery. As this chapter focuses specifically on pregnant women living with HIV and receiving care during pregnancy in one of the HIV treatment centres, these five children are not described in this chapter. They are, however, included in *Chapter 5* ('Children living with HIV in the Netherlands') of this report.

Further investigation of the five cases of MTCT in infants born to mothers diagnosed with HIV either prior to conception or during pregnancy revealed that these infants were born prior to 2015, before it was standard practice to initiate cART in all individuals regardless of CD4 count. In two cases, in 2000 and 2010, the mothers had not received cART during pregnancy. One of these women started cART only on the day of delivery. In three other cases, the mothers were newly diagnosed with HIV in 2000, 2002, and 2011, and started cART during pregnancy (during the 30th, 24th and 22nd week of pregnancy, respectively). Prior to initiating cART, all three mothers had detectable HIV RNA levels, but the last available HIV RNA measurement before delivery (with a minimum time before delivery of 4 days and a maximum of 6 weeks) was undetectable in all three cases (<50 copies/ml). This could suggest *in utero* transmission of HIV in these three pregnancies.

When these three vertical transmissions of HIV with a maternal HIV RNA level below 50 copies/ml prior to delivery were taken into account, the MTCT transmission rate in HIV RNA-suppressed pregnant women in the Netherlands came to 0.18% (3/1640), which is in line with other reports[13,14,15,16].

Postpartum follow up

Recommendations for the treatment of HIV have changed over time. Previously, the initiation of cART was based on the maternal CD4 cell count. As a result, a substantial proportion of women who did not need to start cART according to these early guidelines started cART for the first time only during pregnancy, with the sole purpose of reducing maternal HIV RNA to limit the MTCT risk. In many of these cases, cART was therefore discontinued after delivery. After 2015, general treatment guidelines were revised, and treatment for all individuals was

recommended regardless of CD4 cell count. Subsequently, all pregnant women have been advised to continue cART postpartum.

When investigating postpartum follow up, we focused on those women who were pregnant between 2015 and 2018 to ensure that the population reflected current guidelines. Postpartum follow up was defined as the first 12 months after delivery and was considered for all pregnancies with a minimum duration of 24 weeks. Here we describe treatment and virological suppression rates during the postpartum period, as well as breastfeeding rates.

Treatment

Of the 1,972 pregnancies lasting 24 weeks or longer, 338 occurred between 2015 and 2018. Of these 338 pregnancies, 81 were excluded from the analysis; 74 were excluded because of insufficient follow up between delivery and time of closure of the database and 7 because they were no longer in care (4 had moved abroad and 3 were reported as lost to follow up). All women used cART during their pregnancy. For the remaining 257 pregnancies in 227 women, cART was initiated before conception or during pregnancy in 78% and 22% of cases, respectively. In 38 of these 257 pregnancies, treatment was discontinued postpartum. In 23 of these 38 pregnancies, treatment was restarted after a median of 8 weeks (IQR 3-26 weeks). In the remaining 15 pregnancies, the women did not restart cART postpartum.

Virological outcome

Detectable viraemia postpartum was defined as at least one HIV RNA measurement above 50 copies/ml during the postpartum period. On the basis of this definition, detectable HIV RNA was observed in 21% of the 257 pregnancies. For the subset of women with documented continued postpartum use of cART, 12% had at least one HIV RNA level above 50 copies/ml. As expected, this proportion was higher in the 15 women who discontinued the use of cART postpartum, with 78% showing detectable HIV RNA levels. Despite treatment discontinuation, 8 women still had undetectable HIV RNA levels during the first year postpartum; 5 became detectable after this first year, and 3 women restarted cART although they had undetectable HIV RNA levels.

Breastfeeding

For the above-mentioned 257 pregnancies, breastfeeding was reported after 3 pregnancies and no breastfeeding after 230 pregnancies; such data was missing for the remaining 24 pregnancies. All three women who reported breastfeeding were using cART and had an undetectable HIV RNA postpartum, and no cases of vertical transmission were documented in any of the women who reported breastfeeding.

Summary and conclusions

The absolute number of pregnancies in HIV-1-positive women in care in the Netherlands has declined over time. This is probably a reflection of both the increasing age of women in follow up and the declining overall birth rate in the Netherlands[17]. Despite the high proportion of women with undetectable viraemia at the time of delivery, we did observe a somewhat increased proportion with detectable HIV RNA levels in 2018. This increase is concerning and should be closely monitored, particularly in women who are newly diagnosed with HIV after conception and therefore start cART only during pregnancy.

Due to the high proportion of women who now have an undetectable HIV RNA at the time of delivery, MTCT has become rare in the Netherlands. The overall MTCT rate in pregnant women using cART and having undetectable viraemia near the time of delivery was 0.18%, which is comparable to, or even slightly lower than, that reported in other western European countries[13,14,15,16].

Results of earlier studies analysing exposure to cART as an increased risk factor for preterm birth were conflicting[18]. However, more recent studies have reported declines in preterm births in women living with HIV attributed partly to the reduction in Caesarean sections to prevent vertical transmission of HIV[19,20]. Nevertheless, the proportion of preterm births in HIV-1-positive women in the Netherlands remains higher than that seen in the general population[7].

The proportion of HIV-positive women who delivered by Caesarean section in the Netherlands is comparable to the national rate of Caesarean sections. This finding suggests that the main reason for this type of delivery was not to reduce the risk of MTCT, but rather obstetric indications, such as foetal distress or insufficient dilation or expulsion. Moreover, a study in a large European cohort of HIV-positive pregnant women found that the proportion of Caesarean sections was somewhat higher than that seen in the Dutch population of HIV-positive women[20], suggesting that vaginal delivery has become more widely accepted in HIV-positive women in the Netherlands.

Finally, since 2015, cART has been recommended for all individuals regardless of CD4 cell count and, as such, is also recommended for women postpartum. From 2015 onward, 12% of women who continued to use cART postpartum had at least one episode of viraemia. This is possibly due to poorer adherence, which has previously been reported to deteriorate during the postpartum period[21,22,23,24,25,26].

Recommendations

As a result of changes in guidelines on HIV and pregnancy, cART is more likely to be started earlier in pregnancy. The earlier initiation of cART may lead to a greater number of women achieving an undetectable HIV RNA level earlier in their pregnancy and therefore near the time of delivery. However, exposure to cART in the first trimester may also be associated with a higher risk of preterm birth. Therefore, monitoring of pregnant women using cART during the first trimester of their pregnancy is important to gain more insight into the impact of cART exposure on birth weight and prematurity. In addition, women living with HIV who started cART during their pregnancy require a high level of support not only during pregnancy to ensure suppressed HIV RNA levels at the time of delivery, but also after delivery to maintain adherence to cART. Finally, although breastfeeding should not be actively recommended, women who decide to breastfeed should be followed closely with continuous support of treatment adherence, and both mother and infant should be monitored clinically and virologically[10,27].

References

1. UNAIDS. *Global Report: UNAIDS Report on the Global AIDS Epidemic 2012*. Vol UNAIDS/JC2. Joint United Nations Programme on HIV/AIDS (UNAIDS); 2012.
2. De Cock KM, Fowler MG, Mercier E, et al. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. *JAMA*. 2000;283(9):1175-1182.
3. Coll O, Hernandez M, Boucher CAB, et al. Vertical HIV-1 Transmission Correlates with a High Maternal Viral Load at Delivery. *J Acquir Immune Defic Syndr Hum Retrovirology*. 1997;14(1):26-30. doi:10.1097/00042560-199701010-00005
4. Boer K, Nellen J, Patel D, et al. The AmRo study: pregnancy outcome in HIV-1-infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. *BJOG An Int J Obstet Gynaecol*. 2007;114(2):148-155. doi:10.1111/j.1471-0528.2006.01183.x
5. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr*. 2002;29(5):484-494. doi:10.1097/00126334-200204150-00009
6. Mulder-Folkerts DKF, van den Hoek JAR, van der Bij AK, Boer K, Schutte MF, Coutinho RA. [Less refusal to participate in HIV screening among pregnant women in the Amsterdam region since the introduction of standard HIV screening using the opting-out method]. *Ned Tijdschr Geneeskd*. 2004;148(41):2035-2037.
7. Perined | Home. https://www.perined.nl/. Accessed September 5, 2017.

8. Rowland BL, Vermillion ST, Soper DE. Scheduled cesarean delivery and the prevention of human immunodeficiency virus transmission: A survey of practicing obstetricians. *Am J Obstet Gynecol*. 2001;185(2):327-331. doi:10.1067/mob.2001.116741
9. Stringer JS, Rouse DJ, Goldenberg RL. Prophylactic cesarean delivery for the prevention of perinatal human immunodeficiency virus transmission: the case for restraint. *JAMA*. 1999;281(20):1946-1949. doi:10.1001/jama.281.20.1946
10. European Aids Clinical Society Guidelines. http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf. Published 2018.
11. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med*. 2019;381(9):827-840. doi:10.1056/NEJMoa1905230
12. Boyd SD, Sampson MR, Viswanathan P, Struble KA, Arya V, Sherwat AI. Cobicistat-containing antiretroviral regimens are not recommended during pregnancy: viewpoint. *AIDS*. 2019;33(6):1089-1093. doi:10.1097/QAD.0000000000002163
13. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS*. 2008;22(8):973-981. doi:10.1097/QAD.0b013e3282f9b67a
14. Warszawski J, Tubiana R, Le Chenadec J, et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS*. 2008;22(2):289-299. doi:10.1097/QAD.0b013e3282f3d63c
15. Prieto LM, González-Tomé M-I, Muñoz E, et al. Low rates of mother-to-child transmission of HIV-1 and risk factors for infection in Spain: 2000-2007. *Pediatr Infect Dis J*. 2012;31(10):1053-1058. doi:10.1097/INF.0b013e31826fe968
16. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. *Clin Infect Dis*. 2015;61(11):civ578. doi:10.1093/cid/civ578
17. CBS. statline. http://statline.cbs.nl/.
18. Townsend C, Schulte J, Thorne C, et al. Antiretroviral therapy and preterm delivery-a pooled analysis of data from the United States and Europe. *BJOG An Int J Obstet Gynaecol*. 2010;117(11):1399-1410. doi:10.1111/j.1471-0528.2010.02689.x
19. Reitter A, Stücker AU, Linde R, et al. Pregnancy complications in HIV-positive women: 11-year data from the Frankfurt HIV Cohort. *HIV Med*. 2014;15(9):525-536. doi:10.1111/hiv.12142
20. Aebi-Popp K, Mulcahy F, Glass TR, et al. Missed opportunities among HIV-positive women to control viral replication during pregnancy and to have a vaginal delivery. *J Acquir Immune Defic Syndr*. 2013;64(1):58-65. doi:10.1097/QAI.0b013e3182a334e3

21. Laine C, Newschaffer CJ, Zhang D, Cosler L, Hauck WW, Turner BJ. Adherence to antiretroviral therapy by pregnant women infected with human immunodeficiency virus: a pharmacy claims-based analysis. *Obstet Gynecol*. 2000;95(2):167-173. doi:10.1016/S0029-7844(99)00523-2
22. Ickovics JR, Wilson TE, Royce RA, et al. Prenatal and postpartum zidovudine adherence among pregnant women with HIV Results of a MEMS substudy from the Perinatal Guidelines Evaluation Project. *J Acquir Immune Defic Syndr*. 2002;30(3):311-315. doi:10.1097/01.QAI.0000018001.56638.0A
23. Bardeguez AD, Lindsey JC, Shannon M, et al. Adherence to antiretrovirals among US women during and after pregnancy. *J Acquir Immune Defic Syndr*. 2008;48(4):408-417. doi:10.1097/QAI.0b013e31817bbe80
24. Mellins C a, Chu C, Malee K, et al. Adherence to antiretroviral treatment among pregnant and postpartum HIV-infected women. *AIDS Care*. 2008;20(8):958-968. doi:10.1080/09540120701767208
25. Rana AI, Gillani FS, Flanigan TP, Nash BT, Beckwith CG. Follow-up care among HIV-infected pregnant women in Mississippi. *J Women's Heal*. 2010;19(10):1863-1867. doi:10.1089/jwh.2009.1880
26. Huntington S, Thorne C, Newell M-L, et al. The risk of viral rebound in the year after delivery in women remaining on antiretroviral therapy. *AIDS*. 2015;29(17):2269-2278. doi:10.1097/QAD.0000000000000826
27. Kahlert C, Aebi-Popp K, Bernasconi E, et al. Is breastfeeding an equipoise option in effectively treated HIV-infected mothers in a high-income setting? *Swiss Med Wkly*. 2018;148(29-30). doi:10.4414/smw.2018.14648

7. Quality of care

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

Introduction

One of SHM's missions is to contribute to the quality of HIV care in the Netherlands. With the collection of pseudonymised data from individuals living with HIV in outpatient care in the 26 officially acknowledged HIV treatment centres during 2018, 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[2]. Using these guidelines as a basis, we defined a set of indicators, which are used to explore the quality of care in Dutch HIV treatment centres and gain insight into potential variation in outpatient care between HIV treatment centres.

***Box 7.1:** Definitions used in this chapter.*

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 is usually within a few weeks of HIV diagnosis.
Volume indicator	The number of people newly entering care for the first time in 2017 and 2018 for each treatment centre.

Outcome indicators	
Retention in care	I. Short-term retention: The percentage of people who entered care for the first time after being diagnosed with HIV in one of the HIV treatment centres in 2015 and 2016 and who were still alive and in care at least 18 months after entering care. Patients who died or moved abroad were excluded from this indicator. II. Long- term retention in care in 2018: the percentage of all individuals who had entered care during the period 2013-2016, had not moved abroad and had not died and had had a documented clinical visit in 2018.
Initiation of cART	I. Start of combination antiretroviral therapy (defined as a combination of at least three antiretroviral agents) within 6 months of entry into care in 2016 and 2017. II. The percentage of people who had initiated cART and were still in care in 2018.
Viral suppression	I. The percentage of treatment-naive people with a plasma HIV RNA level <400 copies/ml at 6 months after starting cART in 2017 (this definition of viral suppression is a requirement of the national certification process for HIV treatment centres in the Netherlands[1]). II. The percentage of all HIV-positive people on cART for at least 6 months in 2017 and 2018 with a plasma HIV RNA level <100 copies/ml. III. The percentage of all HIV-positive people in care in 2017 and 2018 with a plasma HIV RNA level <100 copies/ml.
Process indicators	
Prior to cART initiation	The percentage of people newly entering HIV care in 2016 and 2017 for whom data were available on plasma HIV RNA and CD4 count.
Following cART initiation	The percentage of people initiating cART in 2016 and 2017 for whom plasma HIV RNA and CD4 count were measured at least once within 13 months after cART initiation.

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[2]. These indicators were classified as volume, outcome or process indicators (*Box 7.1*).

As reported in earlier studies, both the number of patients in care (i.e., the centre 'volume') and the patient characteristics of a given centre (i.e. the patient 'mix') may have an impact on the reported indicators[3,4,5,6]. Regarding centre volume, a smaller number of patients in some HIV treatment centres could result in less informative percentages, as a single deviating score on an indicator can further increase the variation for a given indicator. For this reason, we compare each centre's indicator to the national average and provide statistical guidance as to whether a given centre falls below the national average. This assessment depends on the number of patients included when calculating the indicator (an overview of this method is provided in *Box 7.2*). Regarding patient mix, individual-level factors, such as age and mode of transmission, are known to be associated with several indicators. If performance indicators are different across centres, it could be that the variation in patient characteristics between centres are driving these differences. We therefore adjusted all indicators by year of birth and geographical origin/mode of transmission (*Box 7.2*).

Box 7.2: *Funnel plots to compare centres to the national average.*

What types of problems occur when evaluating indicators?	
Centres with fewer patients	Centres of smaller size are expected to have wider variation for any given indicator. This variation makes it difficult to determine if the indicator is truly higher or lower than what we would expect.
Patient mix	Individual-level factors, such as age and mode of transmission, are known to be associated with several indicators. If performance indicators are different across centres, it could be that the variation in patient characteristics between centres are driving these differences.

How can we account for these problems?	
Evaluating a centre's performance based on its size	We can determine whether the indicator of a centre (as a percentage) is *statistically* different to the national average. This statistical difference is partly determined by the number of individuals used to calculate the indicator.
Adjust for patient mix	We can adjust indicators based on several important features of the centre's patient population, such as year of birth and geographical origin/mode of HIV acquisition (Dutch men who have sex with men (MSM), Non-Dutch MSM, Dutch non-MSM, and Non-Dutch non-MSM).
What is a funnel plot? A funnel plot is a graphical depiction that allows us to view a centre's indicator compared to the national average. It can help account for the problems listed above. The following are key components of this plot:	
Patient size	The *x*-axis depicts the number of patients considered in a given indicator. For example, this number could be the total number of patients entering care in 2016, the total number of patients in care in 2018, etc.
Adjusted %	The *y*-axis depicts the percentage of patients who have achieved a given indicator. This indicator is adjusted for patient mix.
Centre's indicator	Dots depict each centre's indicator (adjusted %), which are plotted with respect to the number of patients included in the calculation of the indicator.
Comparison to the national average	A solid line depicts the national average. We can create boundaries that indicate (i) the highest indicator level a centre should achieve based on what we statistically expect from the national average ("upper" boundary) or (ii) the lowest indicator level a centre should achieve based on what we statistically expect from the national average ("lower" boundary). These boundaries make the form of a "funnel." The calculation of these boundaries is based on a statistical difference (±2 standard deviations) from the national average.

How is a funnel plot interpreted?	
When is an indicator lower than the national average?	If the centre's indicator falls below the "lower" boundary, then the centre has a lower-than-expected indicator compared to the national average.
When is an indicator higher than the national average?	This question will not be answered in the SHM report. The indicators will be high (ranging from 80-99%), making the "upper" boundary difficult to interpret. We will only provide the "lower" boundary.
Is it possible to determine a difference with so few patients?	Much like any statistical test, inference can be difficult when patient sizes are too small. If a centre size is small, the difference needed to find a statistically lower indicator would be very large. This means that the "lower" boundary could reach below 50%, which is far from a clinically meaningful indicator. In this report, we do not state if a centre's indicator is below the national average when there are fewer than 40 patients included.

Volume indicator

To meet the requirements of the national certification process for HIV treatment centres in the Netherlands (*Harmonisatie Kwaliteitsbeoordeling in de Zorgsector*, HKZ), HIV treatment centres are expected to enrol a minimum of approximately 20 new patients each year. Therefore, as a volume indicator, we quantified the number of patients newly entering care for the first time each year in 2017 and 2018 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 percentage of those patients who had entered care for the first time after being diagnosed with HIV in one of the Dutch HIV treatment centres in 2015 and 2016, and who were still alive and in care at least 18 months after entering care. Patients who were known to have

died or moved abroad were excluded from this retention in care indicator. During the observation period, approximately 9% of patients switched treatment centres; these patients were considered to be retained in care, since they were documented as having remained in care elsewhere and were not lost to follow up. However, to avoid double counting, they were assigned to their most recent treatment centre.

Long-term retention in care was defined as the percentage of all patients who had entered care during the period 2013-2016, had not moved abroad and had not died *and* had had a documented clinical visit in 2018. Again, patients switching treatment centres were considered to be retained in care and were assigned to their most recent treatment centre.

Initiation of cART describes: 1) among the patients who had entered care in 2016 and 2017, the percentage who had started cART within 6 months of entry into care; and 2) among all patients still in care in 2018, the percentage of patients who had ever initiated cART.

Viral suppression was assessed by three indicators:
The *first* indicator was defined as the percentage of treatment-naive patients with a plasma HIV RNA level <400 copies/ml at 6 months after starting cART in 2017. 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 percentage of viral suppression 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[1] during the development of *Zichtbare Zorg* (Visible Healthcare; ZiZo) indicators and HKZ.

The *second* indicator for viral suppression was the percentage 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 2017 and 2018.

The *third* viral suppression indicator was the percentage of all HIV-positive patients in care who have a last available HIV RNA level <100 copies/ml. This indicator was also calculated for the calendar years 2017 and 2018.

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 in 2016 and 2017. Only patients who entered care for the first time and were in care for at least 12 months were included; patients who had switched treatment centres were not counted as newly entering care, as they had remained in care elsewhere. Of note, patients who had been in care and started cART outside the Netherlands were excluded. The indicators were defined as the percentage of patients newly entering care in 2016 and 2017 for whom the following measurements were available in the 6 months after entry into care: CD4 and plasma HIV RNA.

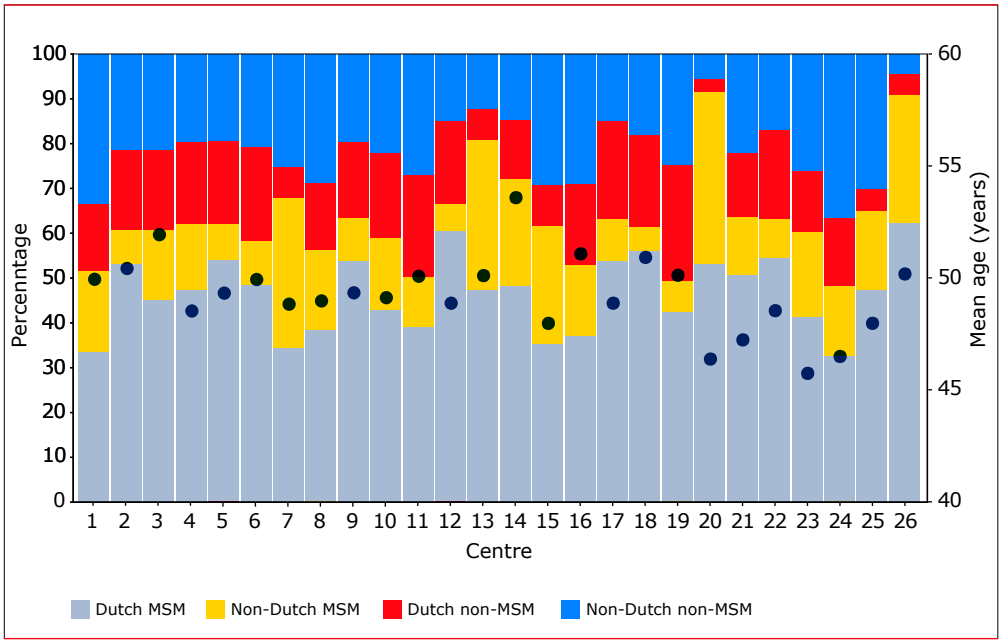
To calculate the process indicators *following cART initiation*, we included patients who had started cART in 2016 and 2017. The indicators were defined as the percentage of patients in whom the following measurements were carried out at least once within 13 months after cART initiation: CD4 cell count and plasma HIV RNA.

Results

Patient mix across centres

The characteristics of patients in care in 2018 are described per HIV treatment centre in *Figure 7.1* (patient 'mix'). To correct for patient 'mix', non-MSM (men who have sex with men) included both men and women. The largest geographical origin/mode of transmission group observed for almost all centres was Dutch MSM, ranging from 33 to 63% (median = 48%) of patients within centres. There was substantial variation across centres in the other geographical origin/mode of transmission groups (median, range across centres): Non-Dutch MSM (16%, 5% – 38%), Dutch non-MSM (17%, 3% – 25%), and Non-Dutch non-MSM (21%, 4% – 36%). The average age across centres ranged between 46 to 54 years (median = 49 years).

Figure 7.1: Description of the patient 'mix' for HIV-positive individuals in care in 2018 in the Netherlands.

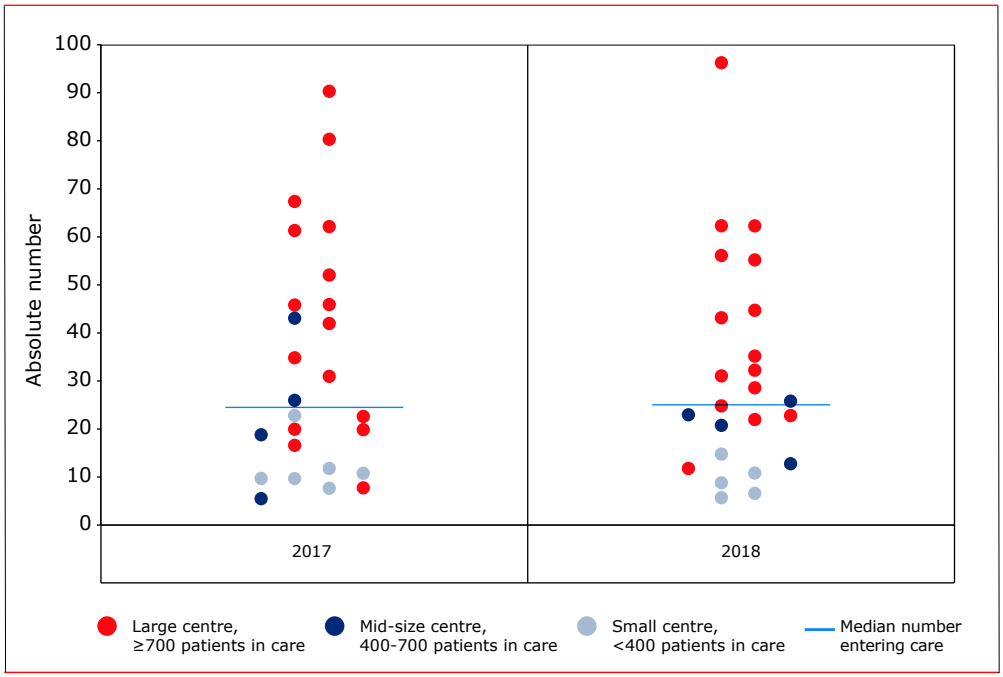


Note: *Percentage of individuals per centre is given in the bar chart according to geographical origin/mode of transmission group. Average age of patients per centre is given in black dots.*
Legend: *MSM=men who have sex with men.*

Volume indicator

The numbers of patients who newly entered care in 2017 and 2018 across the HIV treatment centres are shown in *Figure 7.2*. The median number of patients who entered care was 25 in 2017, and 31 in 2018, with a minimum number of 6 patients in both 2017 and 2018. In 2018, seven HIV treatment centres had fewer than 20 newly-entering patients.

Figure 7.2: Annual number of patients newly entering care per HIV treatment centre in the Netherlands in 2017–2018.



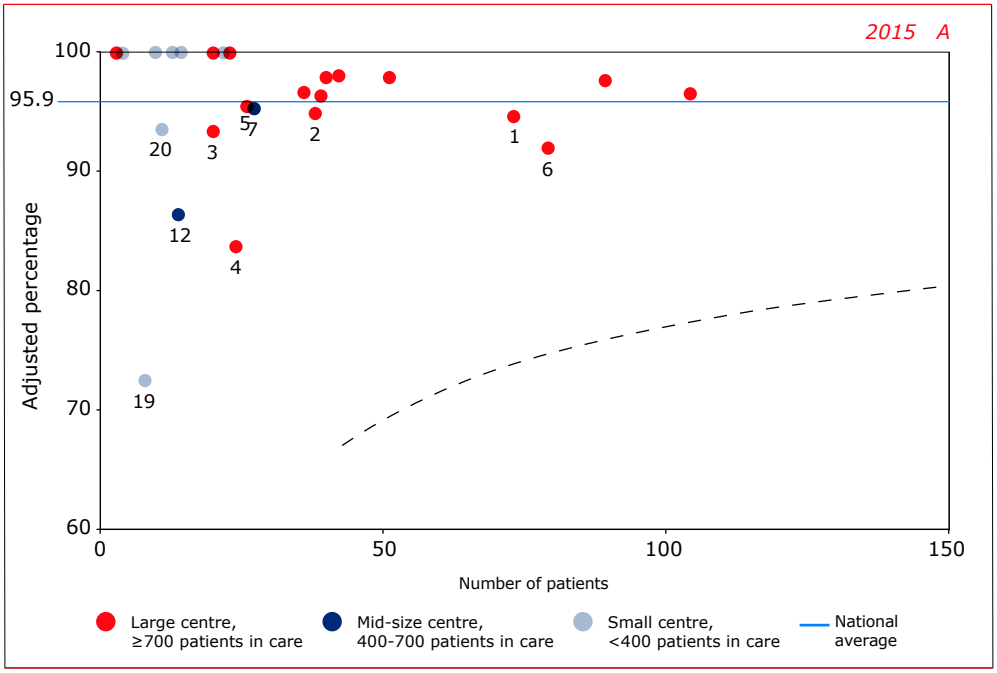
Outcome indicators

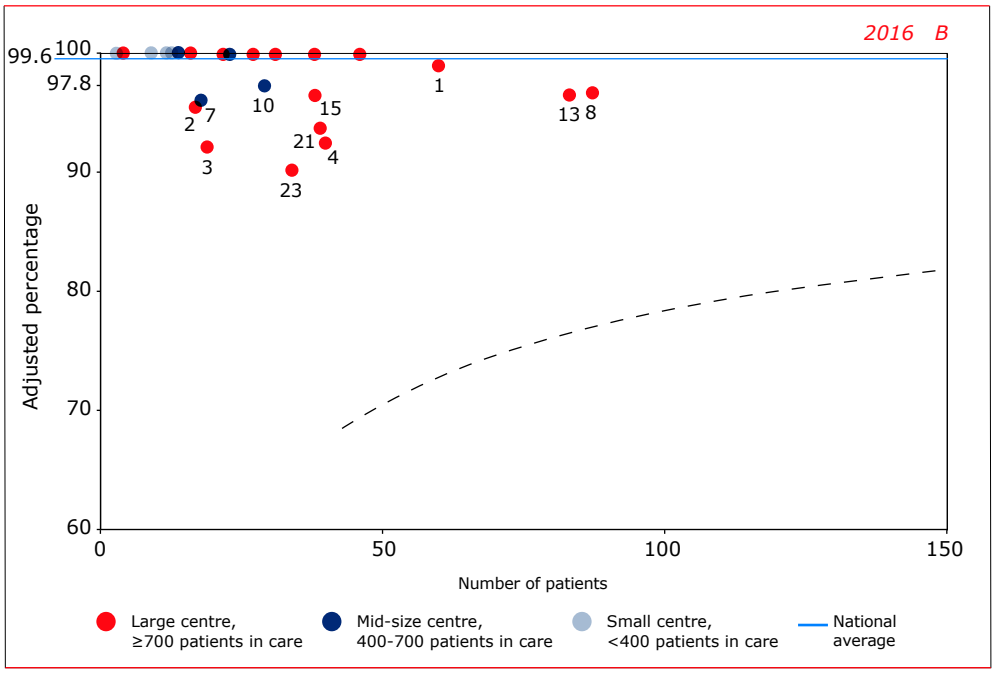
Retention in care

Across centres, the median unadjusted percentage of individuals with short-term retention was 97% (range = 75 – 100%) for patients entering care in 2015 and 100% (range = 89 – 100%) for those entering care in 2016. *Appendix Figure 7.1* shows the median unadjusted short-term retention rates for those who entered care between 2015-2016, stratified by MSM vs non-MSM and by patients' geographic region of origin. Median short-term retention rates in care were highest in Dutch MSM (100%, range = 88 – 100%), followed by Dutch non-MSM (100%, range = 75 – 100%), non-Dutch MSM (100%, range = 69 – 100%) and non-Dutch non-MSM (97%, range = 63 – 100%). *Figure 7.3A* shows the variation in adjusted percentage of short-term retention in care across treatment centres for patients who entered care in 2015 and 2016. This figure demonstrates that all centres with at least 40 patients entering care in 2015 and 2016 had adjusted percentages of short-term retention within the expected range when compared to the national level.

For all individuals in care as of 2018, the median unadjusted percentage of individuals with long term retention was 93% (range = 75 – 100%) across centres for patients entering care in 2013. This percentage increased as people entered care more recently, with a median percentage retained of 97% (range = 82 – 97%) for those entering care in 2016. *Figure 7.4* shows the adjusted percentage of individuals in long term retention-in-care per centre, according to the year in which patients entered care. Once again, all centres with at least 40 patients entering care in 2013, 2014, 2015 and 2016 had adjusted percentages of long term retention within the expected range when compared to the national level.

Figure 7.3: *Short-term retention in care, i.e., 18 months after entering care for those who entered care in A) 2015 and B) 2016. The percentage of individuals retained in care has been adjusted for patient mix and plotted as a function of the number of patients entered into care.*



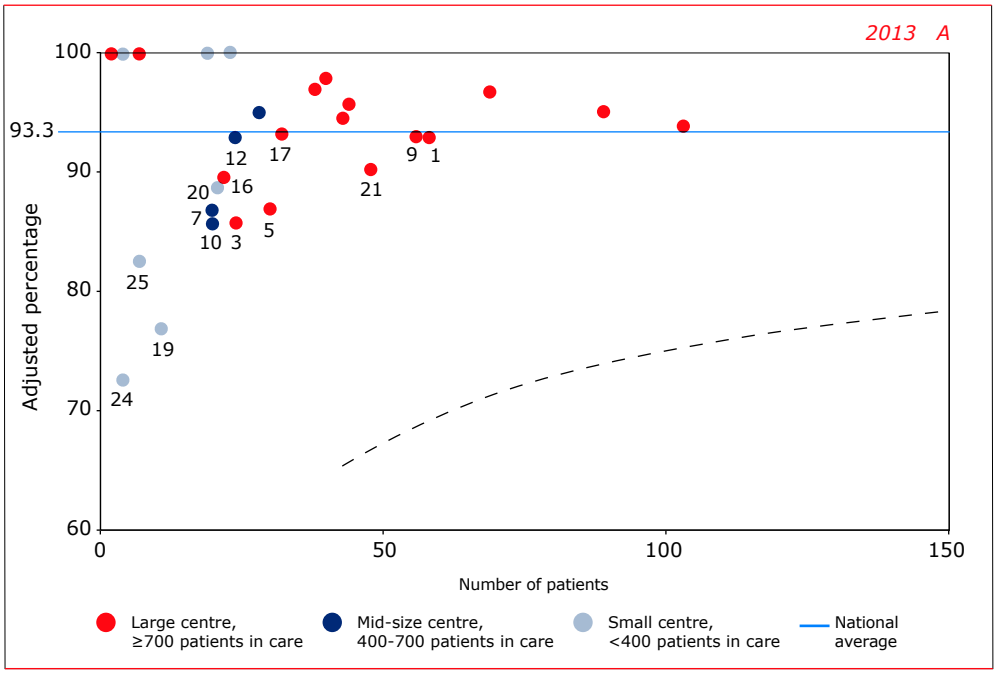


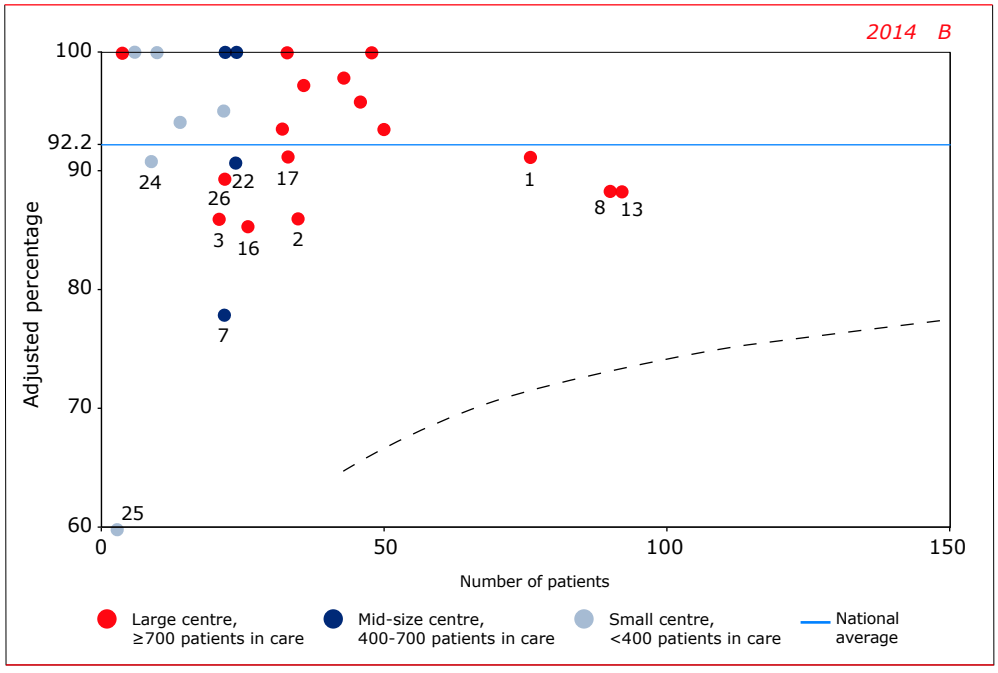
Legend: *Data points are labelled with centre numbers below the national average, which correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line.*

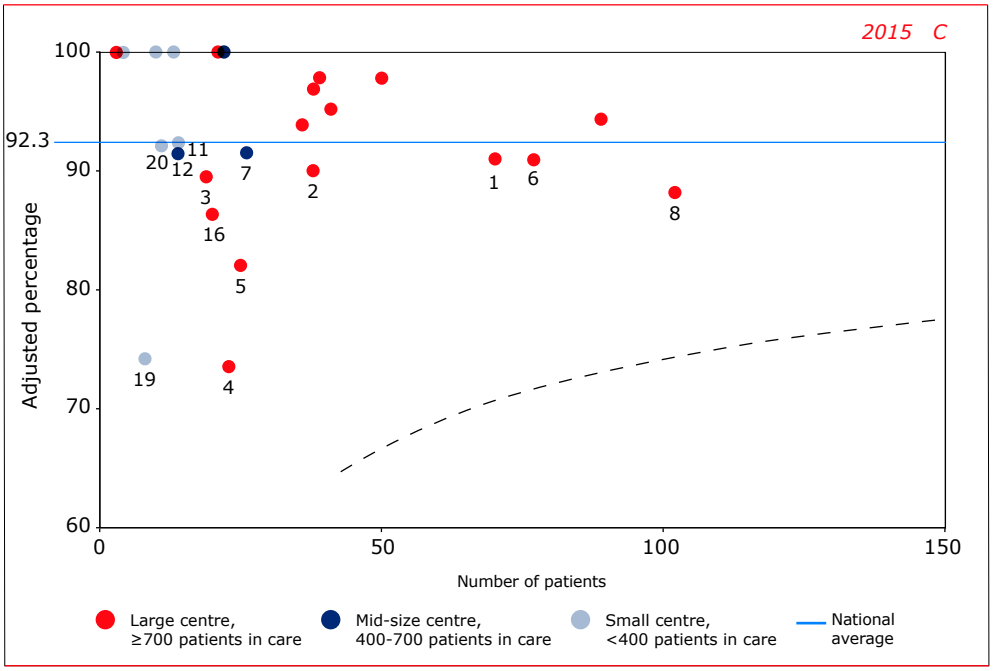
Initiation of cART

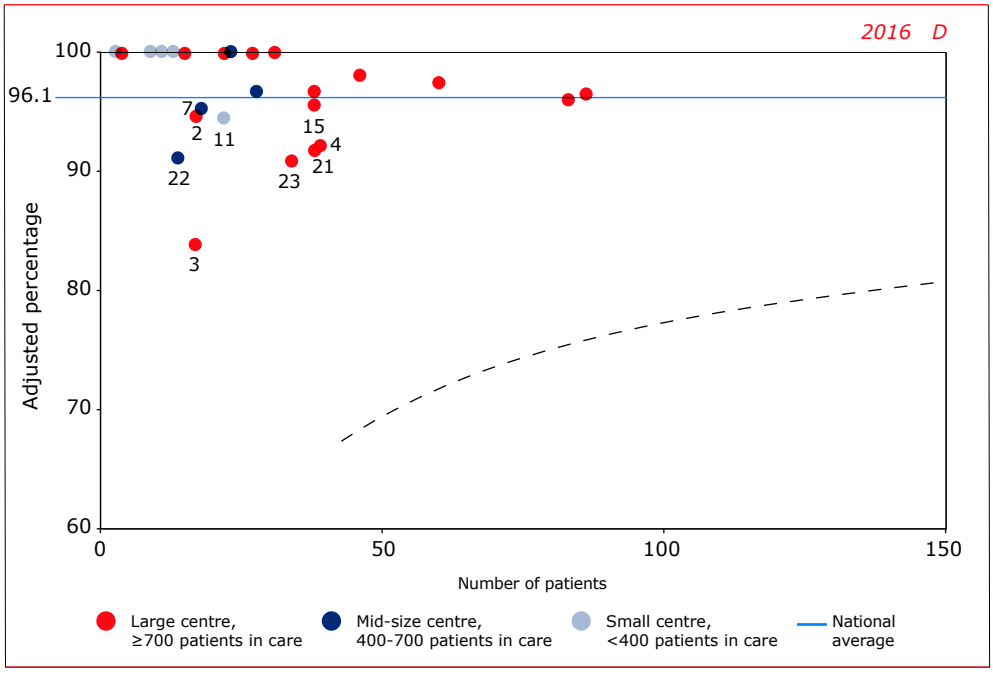
Across centres, the median unadjusted percentages of patients entering care in 2016 and 2017 who started cART within 6 months after entering care were both 100%. In terms of variation across HIV treatment centres, this percentage ranged between 71 – 100% in 2016 and 50 – 100% in 2017. *Figure 7.4* shows the adjusted percentages of patients starting cART within 6 months after entering care per centre, according to the year in which patients entered care. This figure demonstrates that all centres with at least 40 patients entering care in 2016 and in 2017 had adjusted percentages of patients starting cART within the expected range when compared to the national average.

Figure 7.4: Long-term retention in care, i.e., status in 2018 for those who entered care between (A-D) 2013-2016. The percentage of individuals retained in care has been adjusted for patient mix and plotted as a function of the number of patients entered into care.





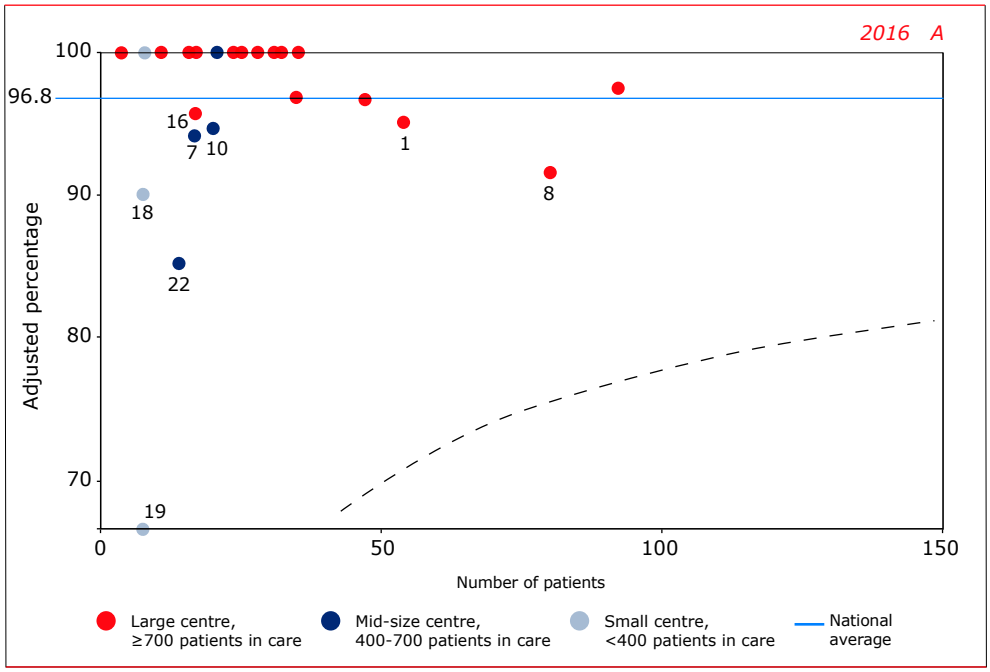


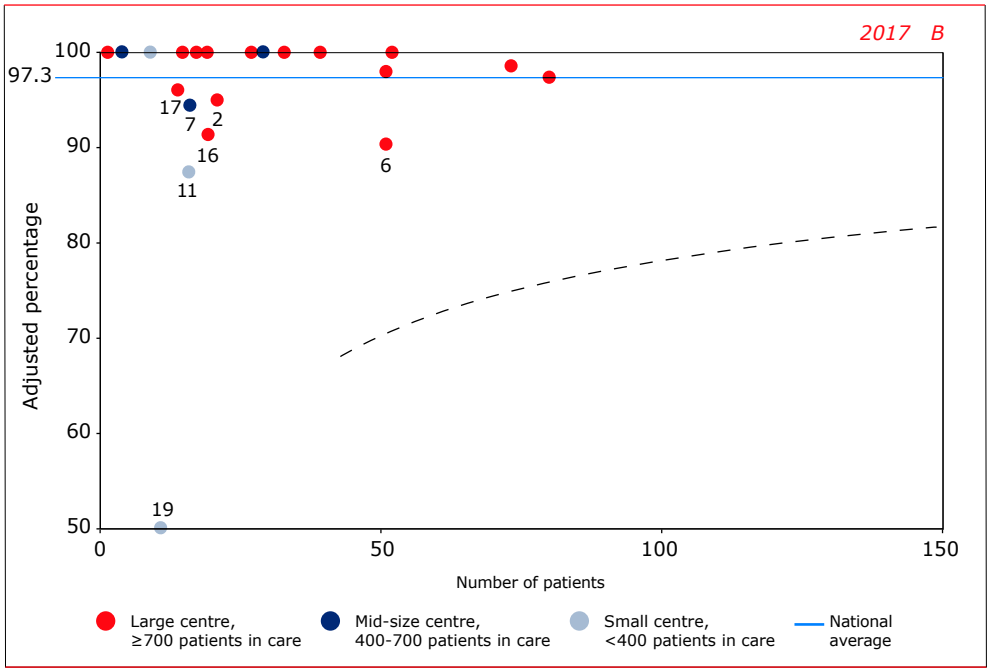


Legend: *Data points are labelled with centre numbers below the national average, which correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line.*

Among those who remained in care in 2018, the vast majority had initiated cART (across-centre median = 98%). This percentage was greater than 95% in all centres. *Figure 7.5* shows the adjusted percentages of patients in care in 2018 who had started cART per centre. All percentages were within the expected range when compared to the national average.

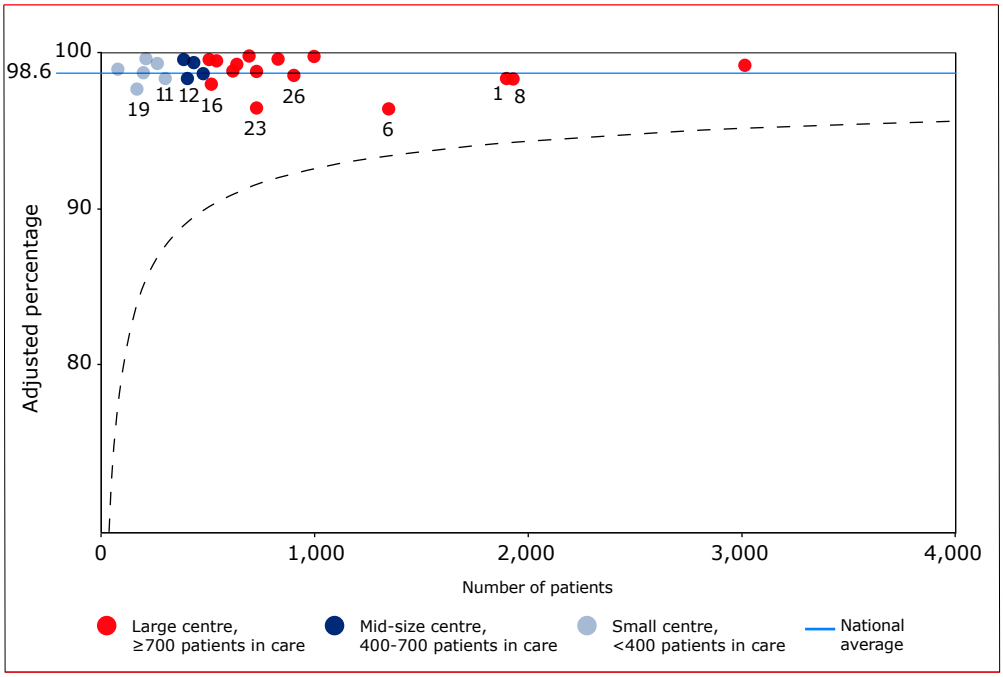
Figure 7.5: *The overall percentage of patients who entered care in A) 2016 and B) 2017 and started combination antiretroviral therapy (cART) within 6 months after entry. The percentage of individuals starting cART has been adjusted for patient mix and plotted as a function of the number of patients entered into care.*





Legend: *Data points are labelled with centre numbers below the national average, which correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line.*

Figure 7.6: The percentage of patients who entered care and who ever initiated cART and were still in care in 2018. The percentage of individuals starting cART has been adjusted for patient mix and plotted as a function of the number of patients still in care in 2018.

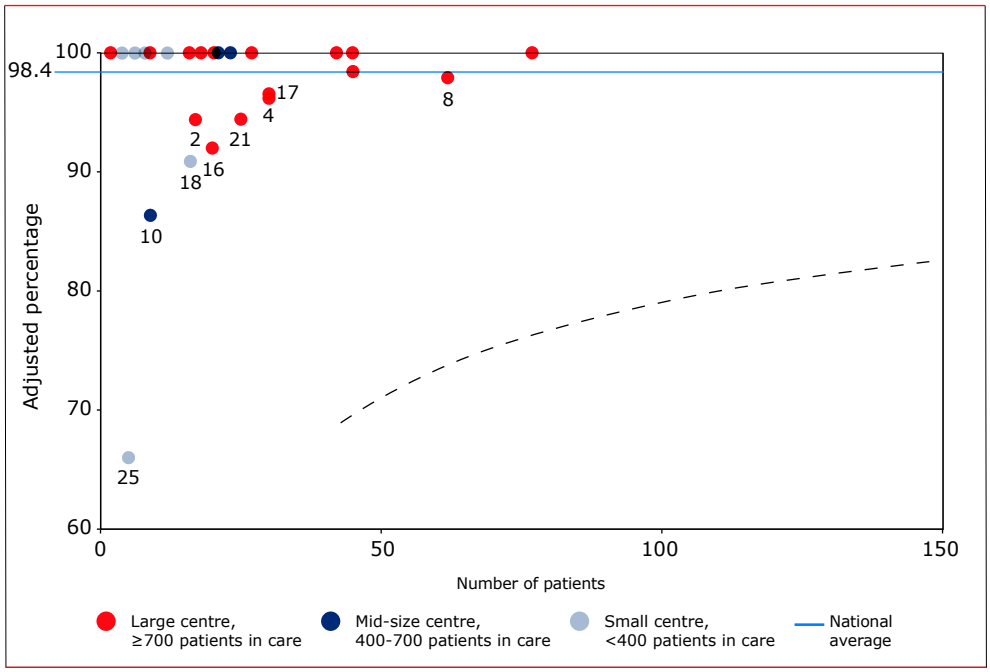


***Legend:** Data points are labelled with centre numbers below the national average, which correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line.*

Viral suppression

Viral suppression was assessed with *three* indicators. The *first* indicator is the percentage of treatment-naive patients with an HIV RNA level <400 copies/ml 6 months (minimum and maximum: 3-9 months) after the start of cART of patients newly initiating treatment in 2017, with follow up in 2018. The unadjusted percentage was 100% for 16 treatment centres and less than 90% (the minimum target of this indicator) for two centres. *Figure 7.7* shows the across-centre variation in adjusted percentage of patients who achieved viral suppression. This figure demonstrates that all centres with at least 40 patients newly initiating treatment in 2017 had adjusted percentages well within the expected range when compared to the national level.

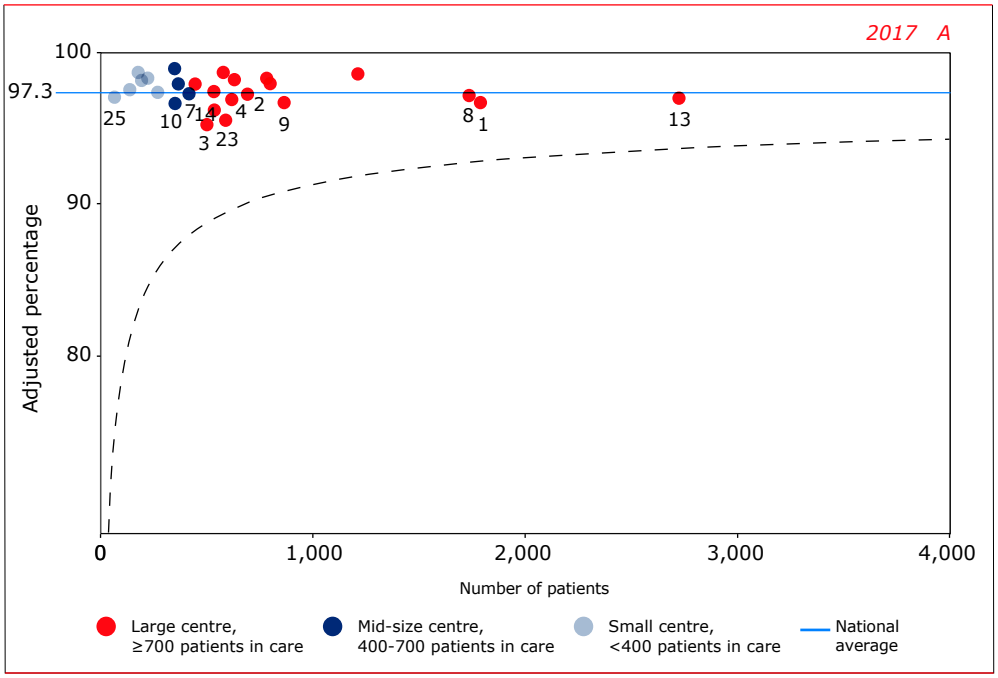
Figure 7.7: Percentage of treatment-naive patients with a plasma HIV RNA level <400 copies/ml at 6 months (minimum and maximum: 3-9 months) after having newly-initiated combination antiretroviral therapy (cART) in 2017 across all HIV treatment centres. The percentage of individuals with viral suppression has been adjusted for patient mix and plotted as a function of the number of patients newly initiating cART in 2017.

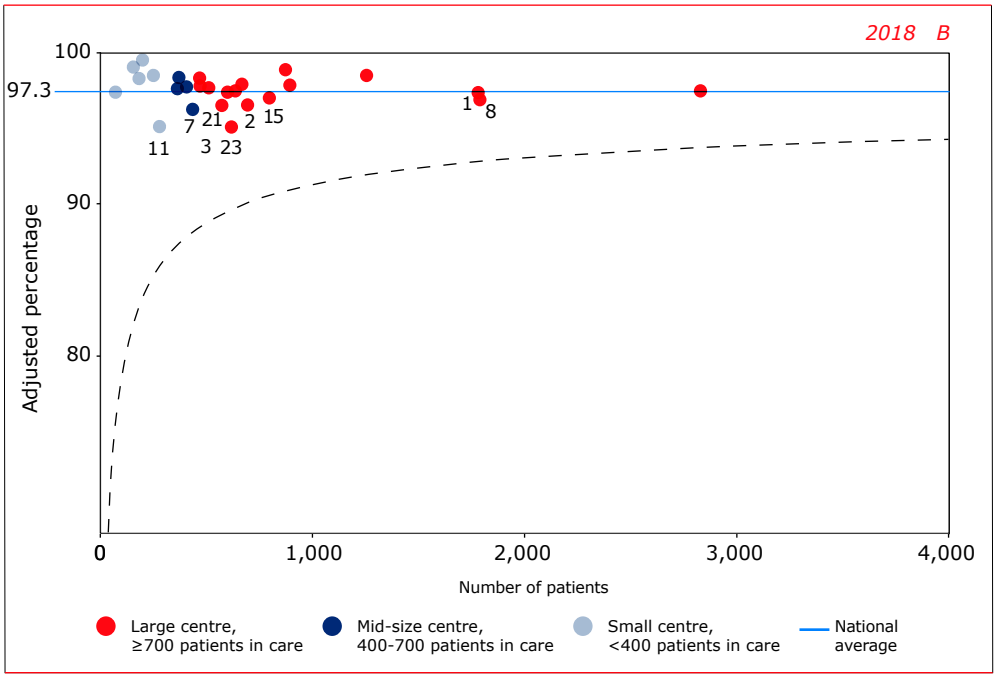


Legend: The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line. Data points are labelled with centre numbers below the national average, which correspond to Figure 7.1.

The *second* viral suppression indicator is the percentage 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 2017 and 2018. In both calendar years, the median unadjusted percentage was more than 90% (the minimum target of this indicator) across centres. *Figure 7.8A-B* shows the adjusted percentage of this viral suppression indicator per treatment centre, illustrating the limited variation across centres of different patient volume. All centres had adjusted percentages within the expected range when compared to the national level.

Figure 7.8: The percentage of all HIV-positive patients in care in A) 2017 and B) 2018, respectively, who had been on combination antiretroviral therapy (cART) for at least 6 months and who had an HIV RNA level <100 copies/ml. The percentage of individuals with viral suppression has been adjusted for patient mix and plotted as a function of the number of patients in care in 2017 and 2018 who had been on cART for at least 6 months.

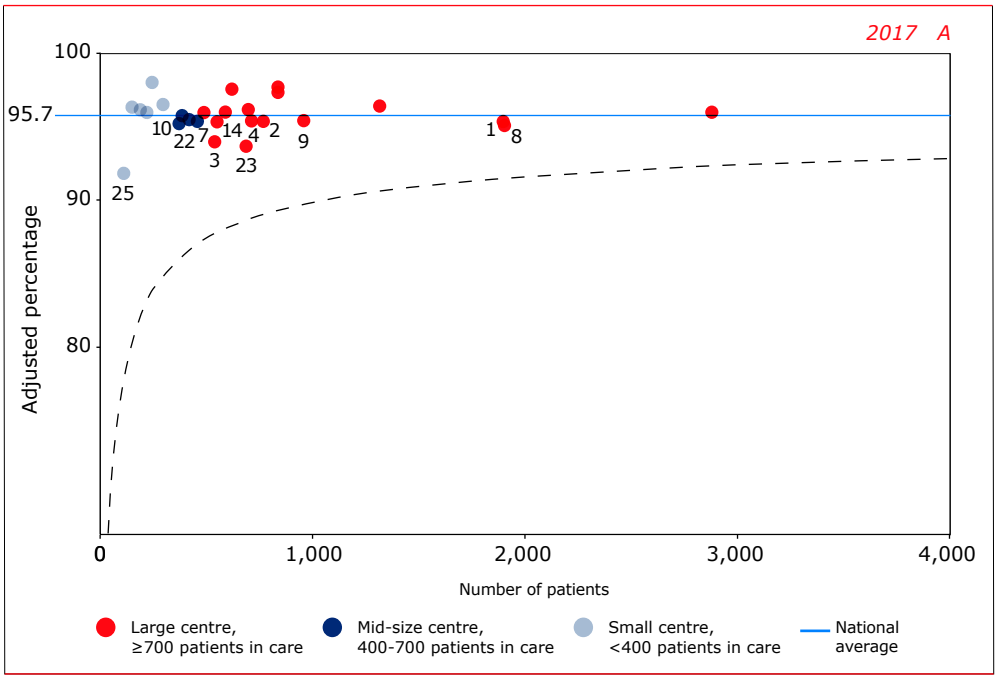


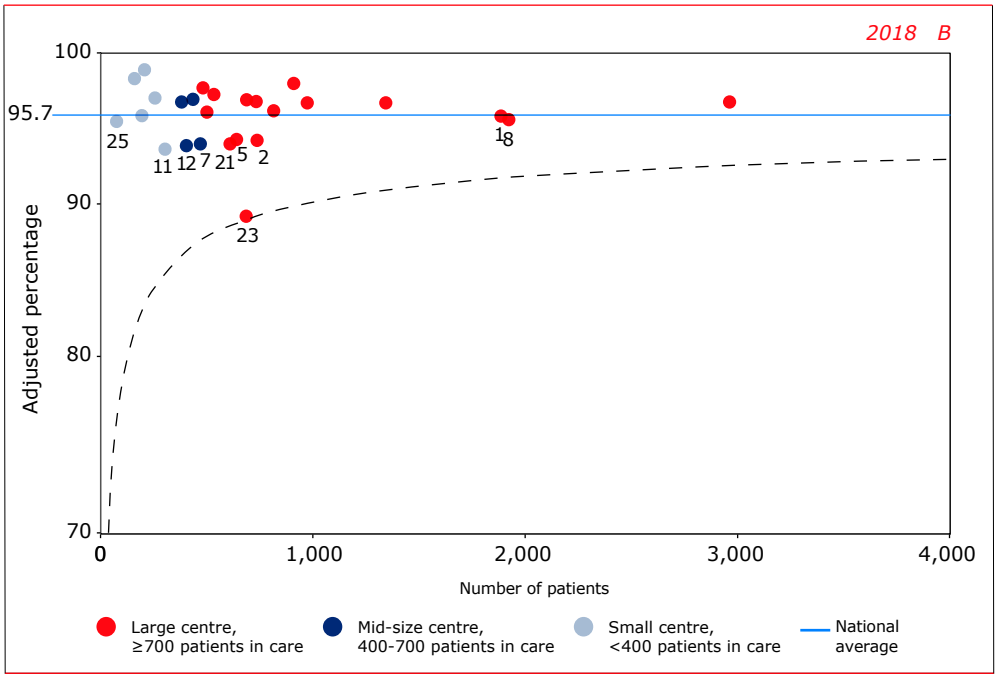


Legend: *Data points are labelled with centre numbers below the national average, which correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line.*

The *third* viral suppression indicator is the percentage of all HIV-positive patients in care who have a last available HIV RNA level <100 copies/ml. This indicator was calculated for the calendar years 2017 and 2018 and for all individuals who had an HIV RNA measurement (percentage without HIV RNA measurements: 1.6% in 2017 and 1.8% in 2018). Across centres, the median unadjusted percentage was 97% (range = 95 – 99%) in 2017 and 98% (range = 94 – 99%) in 2018. *Figure 7.9A-B* shows the adjusted percentage of this viral suppression indicator per treatment centre. All centres had adjusted percentages within the expected range when compared to the national level.

Figure 7.9: The percentage of all HIV-positive patients in care in A) 2017 and B) 2018, respectively, who had an HIV RNA level <100 copies/ml. The percentage of individuals with viral suppression has been adjusted for patient mix and plotted as a function of the number of patients in care in 2017 and 2018.





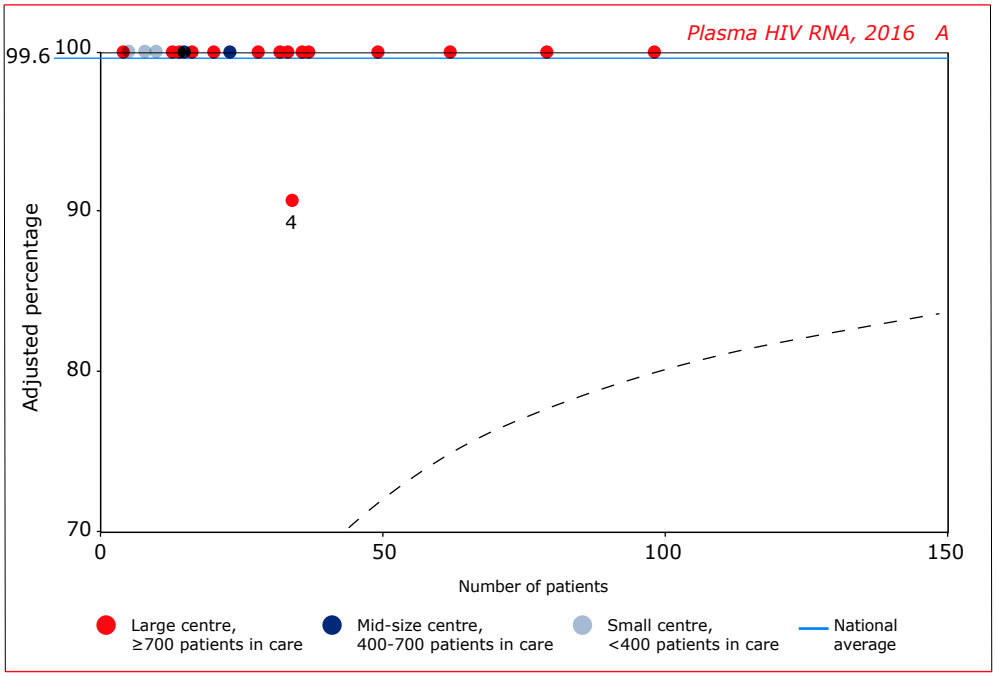
Legend: Data points are labelled with ccentre numbers below the national average, which correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line.

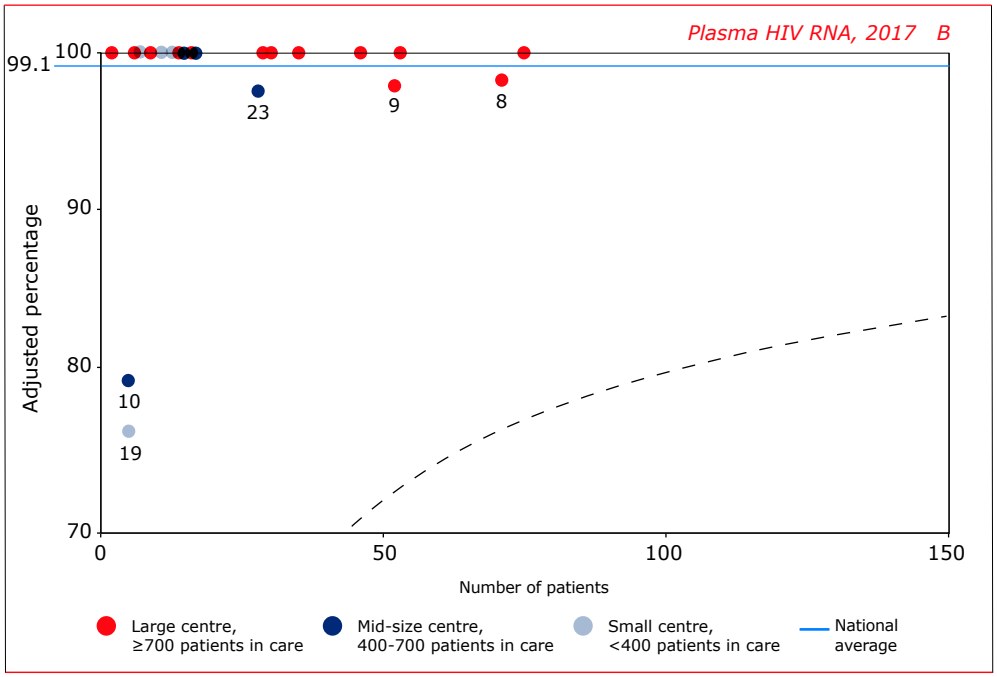
Process indicators

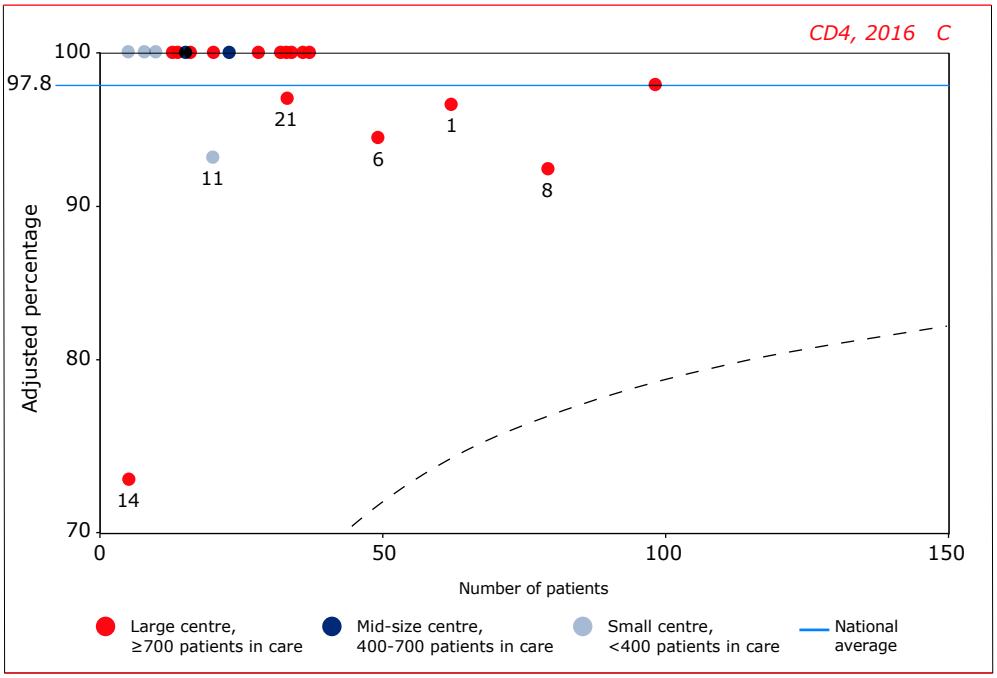
Prior to starting cART

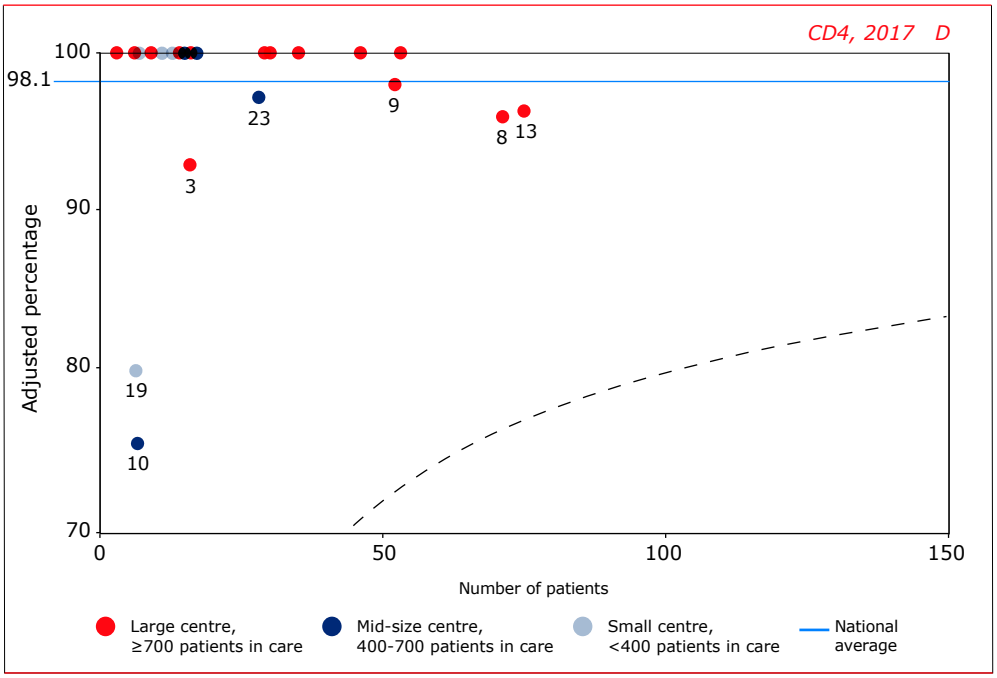
Process indicators were evaluated in patients who newly entered care in 2016 and 2017. Across centres, the median unadjusted percentage of these individuals having been tested for plasma HIV RNA and CD4 cell count within 6 months after entering care were respectively 100% (range = 91 – 100%) and 100% (range = 75 – 100%) in 2016 and 100% (range = 80 – 100%) and 100% (range = 80 – 100%) in 2017. *Figure 7.10A-D* shows the across-centre variation in adjusted percentage of individuals who had plasma HIV RNA and CD4 cell count measurements. This figure demonstrates that all centres with at least 40 patients entering care in 2016 and 2017 had adjusted percentages within the expected range when compared to the national level.

Figure 7.10: The percentage of patients who newly entered care in Dutch HIV treatment centres in 2016 and 2017, respectively, with assessment within 6 months of (A, B) plasma HIV RNA and (C, D) CD4 cell count. The percentage of individuals with plasma HIV RNA and CD4 cell count measurements has been adjusted for patient mix and plotted as a function of the number of patients entered into care.




Plasma HIV RNA, 2017 B
99.1
100
90
80
70
Adjusted percentage
23
9
8
10
19
0
50
100
150
Number of patients
Large centre, ≥700 patients in care
Mid-size centre, 400-700 patients in care
Small centre, <400 patients in care
National average


CD4, 2016 C
97.8
100
90
80
70
Adjusted percentage
21
1
6
11
8
14
0
50
100
150
Number of patients
Large centre, ≥700 patients in care
Mid-size centre, 400-700 patients in care
Small centre, <400 patients in care
National average

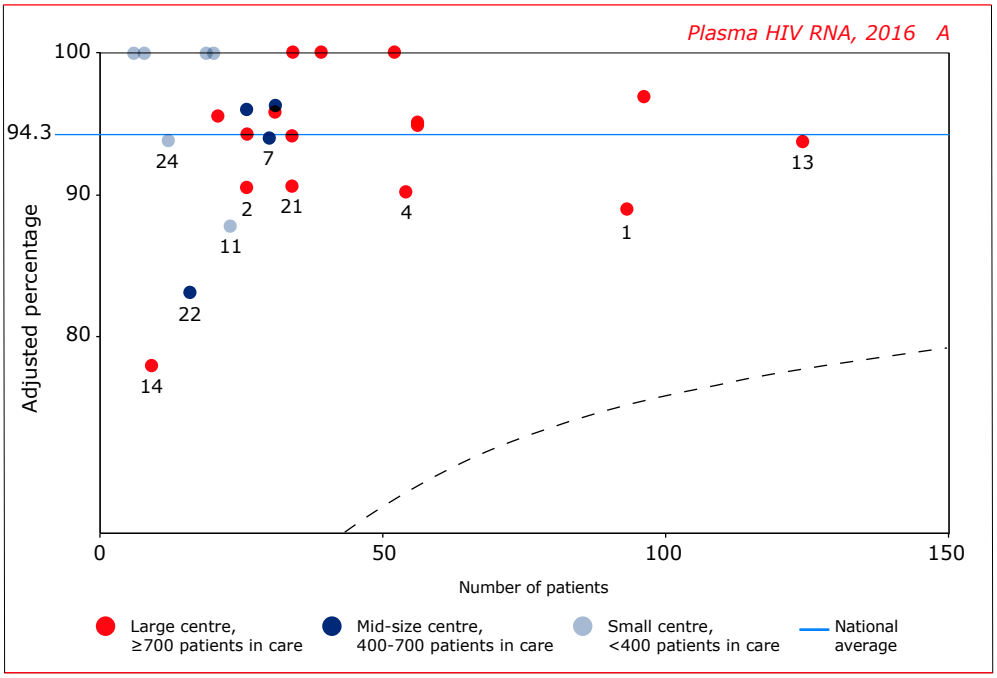


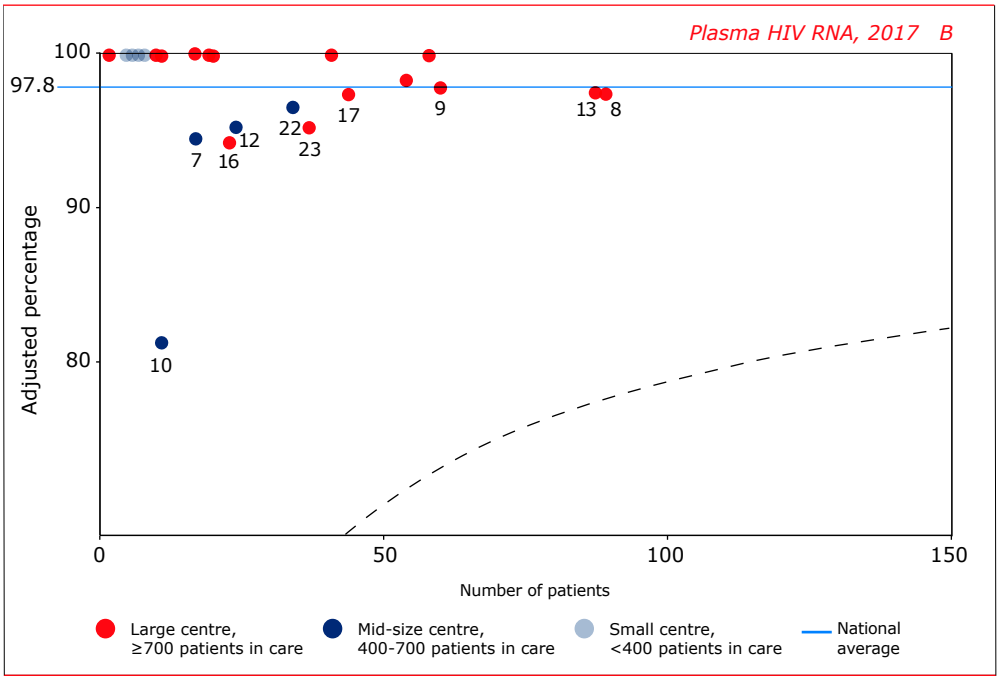
Legend: *Data points are labelled with centre numbers below the national average, which correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line.*

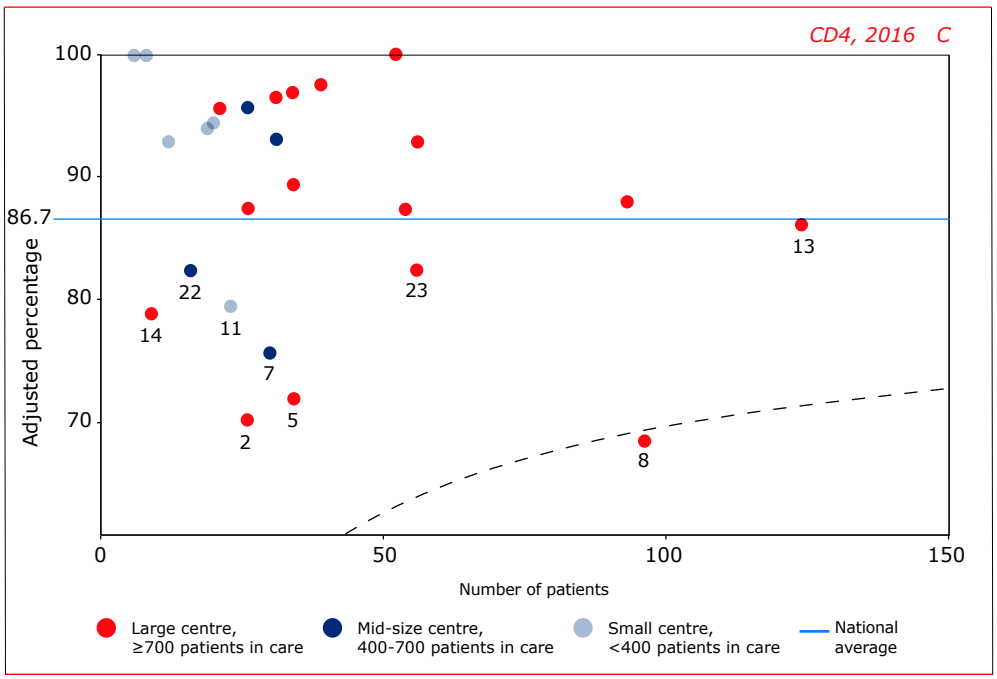
Following the start of cART

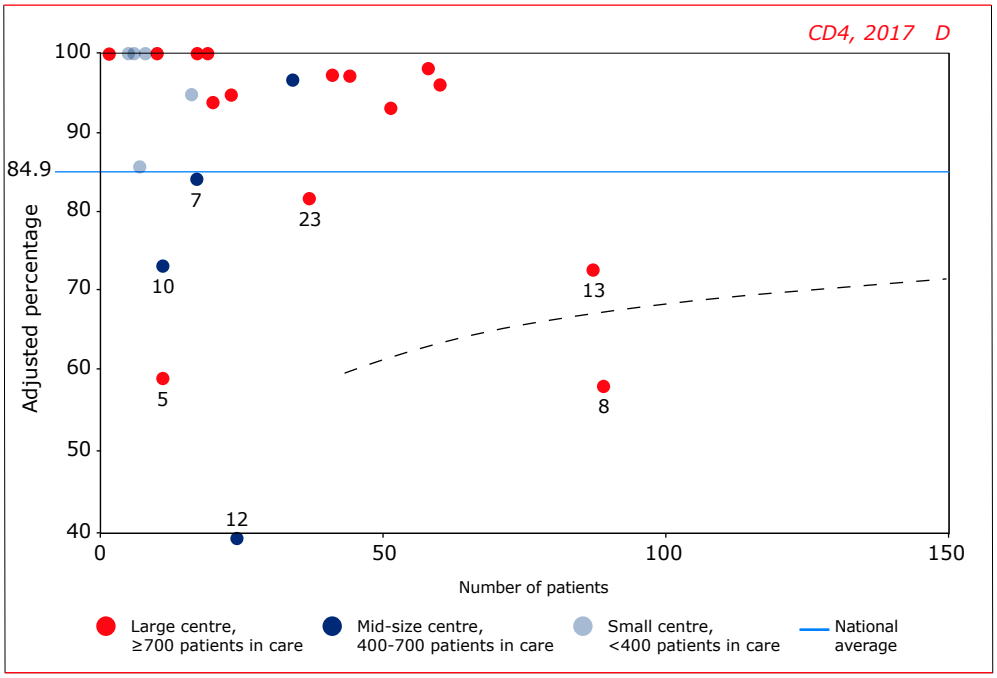
Process indicators were evaluated in patients who initiated cART in 2016 and 2017. Across centres, the median unadjusted percentage of these individuals having been tested for plasma HIV RNA and CD4 cell count within 13 months after initiating cART were respectively 95% (range = 78 – 100%) and 90% (69 – 100%) in 2016 and 100% (range = 82 – 100%) and 96% (58 – 100%) in 2017. *Figure 7.11A-D* shows the across-centre variation in adjusted percentage who had plasma HIV RNA and CD4 cell count measurements. This figure demonstrates that almost all centres with at least 40 patients entering care in 2016 and 2017 had adjusted percentages within the expected range when compared to the national level. One large-volume centre had a lower-than-expected percentage of individuals measured for CD4 cell count within 13 months after initiating cART in 2016 and 2017.

Figure 7.11: The percentage of patients in HIV treatment centres in the Netherlands who initiated combination antiretroviral therapy (cART) in 2016 and 2017, respectively, with assessment of (A, B) plasma HIV RNA and (C, D) CD4 cell count. The percentage of individuals with plasma HIV RNA and CD4 cell count measurements has been adjusted for patient mix and plotted as a function of the number of patients who initiated cART in 2016 and 2017.




Plasma HIV RNA, 2017 B
100
97.8
90
80
Adjusted percentage
10
7
16
12
22
23
17
9
13
8
0
50
100
150
Number of patients
Large centre, ≥700 patients in care
Mid-size centre, 400-700 patients in care
Small centre, <400 patients in care
National average


CD4, 2016 C
100
90
86.7
80
70
Adjusted percentage
14
22
11
7
2
5
23
13
8
0
50
100
150
Number of patients
Large centre, ≥700 patients in care
Mid-size centre, 400-700 patients in care
Small centre, <400 patients in care
National average



Legend: *Data points are labelled with centre numbers below the national average, which correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); only one large-volume centre falls below this line.*

Comparison between treatment centres and benchmarking

SHM has provided HIV treatment centres with the outcomes of centre-specific, ZiZo and HKZ-approved indicators since 2011. However, in 2017 and 2019, 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 serve as a useful benchmark, which centres can use to 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 2017. Although performance in terms of the HKZ indicator 'short-term viral suppression' is generally high, two small centres failed to achieve a score greater than 90% in 2017.

This year each treatment centre will again be provided with their unadjusted or adjusted centre-specific indicators benchmarked against the blinded scores of all other centres.

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 2018, 7 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. Five of these 7 centres had already failed to meet this particular criterion in 2017. Further discussion about the appropriateness of this standard seems warranted.
- After exclusion of patients who had died or moved abroad, both short-term and long-term retention-in-care rates are generally high. This is also the case when adjusting for patient mix.
- The percentage of patients initiating cART within 6 months after entering care has remained high for those entering care in 2016 and 2017, maintaining a median of 100%. The overall coverage of cART in 2018, regardless of time since entering care, is high across all centres despite variation in centre volume and patient mix.
- 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 volume and patient mix.
- Across centres, the median percentage of all patients in care with an HIV RNA level <100 copies/ml was 97% in 2017 and 98% in 2018. There was little variation in this percentage across centres after adjusting for patient mix.
- For every indicator, all centres were within the statistically expected range from the national average, while accounting for centre volume and patient mix, with only one exception.
- 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.
- The funnel plots provide a statistical interpretation of whether a centre performs within the expected range of the national average. Unfortunately, this interpretation becomes less reliable when a centre has only a limited number patients to be included in the indicator (i.e., less than 40 for the purpose of this report). Considering that many centres had fewer than 40 patients newly

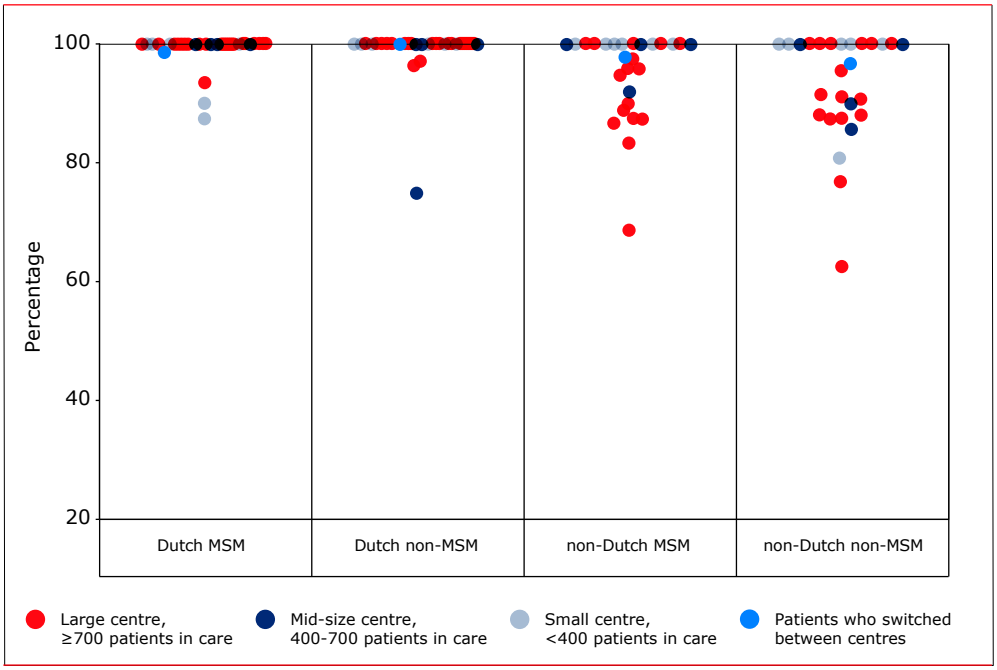
entering care in 2016-2018, they could not be feasibly compared to the national average. We therefore urge caution when comparing indicators of these small centres to the national average or even to fixed levels (e.g., 90%).

References

1. ZichtbareZorg. I*ndicatorengids HIV AIDS 2014*.; 2014.
2. Nederlandse Vereniging van HIV Behandelaren. Richtlijn HIV. http://richtlijnhiv.nvhb.nl/. Published 2017.
3. Engelhard EAN, Smit C, Van Sighem A, et al. Impact of HIV care facility characteristics on the cascade of care in HIV-infected patients in the Netherlands. AIDS. 2015;30(2):301-310. doi:10.1097/QAD.0000000000000938
4. Backus LI, Boothroyd DB, Phillips BR, et al. National Quality Forum Performance Measures for HIV/AIDS Care. *Arch Intern Med*. 2010;170(14):1239-1246. doi:10.1001/archinternmed.2010.234
5. Solomon L, Flynn C, Lavetsky G. Managed care for AIDS patients: is bigger better? *J Acquir Immune Defic Syndr*. 2005;38(3):342-347.
6. Gompels M, Michael S, Jose S, Hill T, et al. The use of funnel plots with regression as a tool to visually compare HIV treatment outcomes between centres adjusting for patient characteristics and size: a UK Collaborative HIV Cohort study. *HIV Med*. 2018;19(6).

Appendix: supplementary figures

Appendix Figure 7.1: Short-term retention-in-care by HIV transmission group and patients' region of origin for those who entered care between 2015-2016.



Legend: MSM=men who have sex with

Special reports

8. The Amsterdam Cohort Studies on HIV infection: annual report 2018

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 2018, the cohorts reached 34 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 34 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 are 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 2018

The cohort of men who have sex with men

As of 31 December 2018, 2,888 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 2,888 MSM, 607 were HIV-positive at entry into the study, and 261 seroconverted during follow up. In total, the GGD Amsterdam was visited 59,792 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 also 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 for future research. 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 2018, 749 HIV-negative and 60 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. All HIV-positive MSM at the GGD had filled in behavioural questionnaires. In addition to the HIV-positive MSM visiting the GGD Amsterdam, 197 HIV-positive participants have been followed outside the GGD Amsterdam at the MC Jan van Goyen or the DC Klinieken Lairesse-Hiv Focus Centrum in Amsterdam since 1999.

In 2018, 92 new HIV-negative MSM were recruited. The median age in this group was 28.1 years (interquartile range (IQR) 25.9-40.0), while that of the total group of MSM in active follow up was 42.9 years at their last visit (IQR 33.3-50.3). The majority (83.7%) of the total group were born in the Netherlands and 85.7% were residents of Amsterdam. Finally, 75.9% 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 high level of education, and 63.4% were born in the Netherlands.

ACS biobank

The ACS visits, together with data collection from several subgroup studies and affiliated studies embedded in the ACS, have resulted in a large collection of stored samples. The ACS biobank includes plasma/serum and PBMC samples collected within the context of the Primo-SHM study (a national randomised study comparing the effects of early temporary antiviral therapy with that of no therapy among people 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 mid-2018, the fourth round had been completed; 420 HIV positive and 457 HIV-negative participants had had a fourth visit. In the second half of 2018, preparations were made for the fifth round. By the end of 2018, 40 HIV-1-positive participants and 6 initially HIV-negative individuals had completed the fifth follow-up visit. Round 5 visits will continue through 2019 and will be completed mid-2020.

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.

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 2018, collection of anal and penile swabs from ACS participants continued and these are stored for future studies.

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, including 35 ACS participants who participated in the AMPrEP project at their own initiative. Participants were asked to return for follow-up visits one month after the PrEP start visit and then every three months. At every visit, participants fill in questionnaires on risk behaviour, adherence and general wellbeing and are screened for STI and HIV. Participants will be provided with PrEP until January 2020.

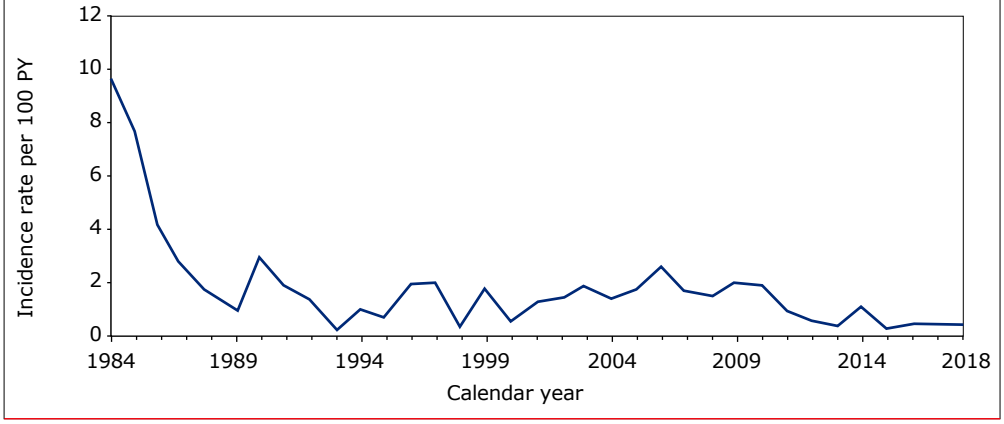
The AMPrEP project is part of the HIV Transmission Elimination Amsterdam (H-TEAM) initiative, a multidisciplinary and integrative approach to stop the epidemic.

The HIV epidemic

HIV incidence

In 2018, 3 MSM participating in the ACS seroconverted for HIV. The observed HIV incidence among MSM has remained relatively stable in recent years and was 0.5 per 100 person years in 2018. *Figure 8.1* shows the yearly observed HIV incidence rate for MSM from the start of the ACS through 2018, respectively.

Figure 8.1: *HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984–2018.*



Legend: *PY=person years.*

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

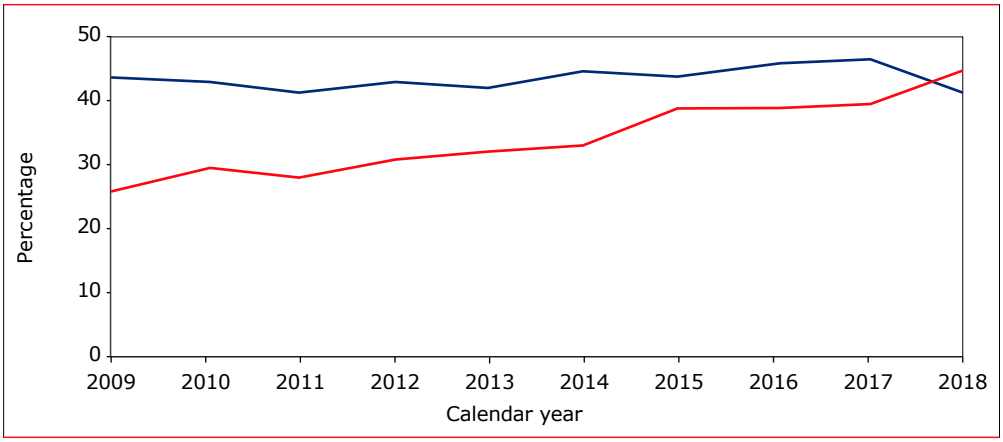
All 60 HIV-positive MSM in follow-up at the GGD were in HIV care.

Risk behaviour of MSM in ACS

Condomless anal sex (CAS) with a steady partner in the preceding six months was reported by 258/657 (39.3%) HIV-negative MSM in active follow up at their last cohort visit, compared with 257/659 (39.0%) who reported CAS with a casual

partner. Annual 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 8.2*). The use of pre-exposure prophylaxis has also increased over time since 2015. In 2018, 125/679 (18.4%) HIV-negative MSM in active follow up reported PrEP use in the preceding 6 months. CAS with a steady partner was reported by 45/121 (37.2%) MSM who used PrEP and 213/537 (39.7%) MSM who did not use PrEP. CAS with a casual partner was reported by 105/121 (86.8%) MSM who used PrEP and 152/539 (28.2%) MSM who did not use PrEP.

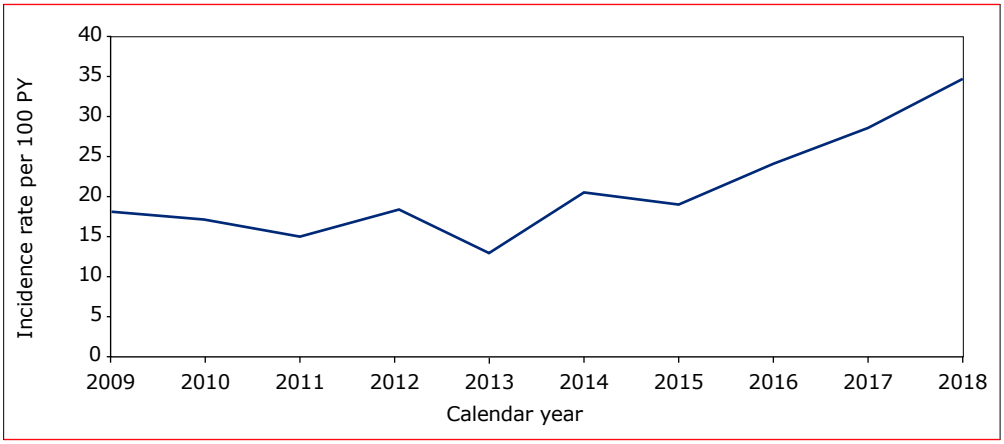
Figure 8.2: *Trend in proportion of condomless anal sex (CAS) with casual partners and steady partners among HIV-negative men who have sex with men (MSM) in the Amsterdam Cohort Studies (ACS), 2009-2018.*



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 2018, 726 MSM from the ACS were screened for STIs. The incidence rate of any STI (i.e., chlamydia, gonorrhoea and syphilis) was 34.5/100 person years in 2018 (95% confidence interval (CI) 28.6-41.7) among HIV-negative MSM. The incidence rate of any STI significantly increased between 2009-2018 (*Figure 8.3*). The incidence rate of any STI was 50.8/100 PY (95%-CI 31.6-81.7) among HIV-negative MSM who used PrEP and 31.1/100 PY (95%-CI 25.4-38.2) among HIV-negative MSM who did not report use of PrEP.

Figure 8.3: The incidence of any STI (i.e., chlamydia, gonorrhoea and syphilis) among HIV-negative MSM in the Amsterdam Cohort Studies (ACS), 2009-2018.



Legend: PY=person years.

ACS 2018 research highlights

Systemic DPP4 activity is reduced during primary HIV-1 infection and is associated with intestinal RORC+ CD4+ cell levels: a surrogate marker candidate of HIV-induced intestinal damage

Combined antiretroviral therapy (cART) transformed HIV-1 from a deadly disease into a chronic infection, but does not cure HIV infection. It also does not fully restore HIV-induced gut damage unless administered extremely early after infection. Additional biomarkers are needed to evaluate the capacity of therapies aimed at HIV remission/cure to restore HIV-induced intestinal immune damage and limit chronic inflammation. We aimed to identify a systemic surrogate marker whose levels would reflect gut immune damage such as intestinal Th17 cell loss starting from primary HIV-1 infection. We showed that soluble Dipeptidylpeptidase 4 (sDPP4) levels were strongly decreased in primary HIV-1 infection. Strikingly, sDPP4 levels in primary HIV-1 infection predicted time to AIDS. In the gut of SIV-infected non-human primates, DPP4 mRNA specifically correlated with RORC expression, a Th17 marker, in CD4+ cells from the intestine. We further demonstrated that sDPP4 activity levels were increased in animals treated with IL-21 and that this increase was associated with restoration of the Th17 compartment and reduced inflammation. Furthermore, DPP4 mRNA levels in small intestine CD4+ cells

positively correlated with circulating DPP4 activity. These data provide evidence that blood sDPP4 levels could be useful as a correlate for HIV-induced intestinal damage.
Ploquin MJ, Casrouge A, Madec Y, Noël N, Jacquelin B, Huot N, Duffy D, Jochems SP, Micci L, Lécuroux C, Boufassa F, Booiman T, Garcia-Tellez T, Ghislain M, Grand RL, Lambotte O, Kootstra N, Meyer L, Goujard C, Paiardini M, Albert ML, Müller-Trutwin M.
J Int AIDS Soc. 2018 Jul;21(7):e25144. doi: 10.1002/jia2.25144.

Immunogenicity in rabbits of HIV-1 SOSIP trimers from clades A, B, and C, given individually, sequentially, or in combination

A successful HIV-1 vaccine most probably requires a trimeric envelope glycoprotein (Env) component, as the Env trimer is the only viral protein on the surface of the virus and therefore the only target for neutralizing antibodies. Env trimers can induce strain-specific neutralizing antibodies but not yet broadly neutralizing antibodies. To try to broaden the antibody response, we immunized rabbits with soluble Env trimers from clade A, clade B, and clade C HIV-1 strains, using monovalent, multivalent, and sequential regimens. We found that when the Env trimers from different clades were delivered sequentially, the neutralizing antibody response could be cross-boosted, and this result provides the necessary clues on how to use Env trimers in vaccination experiments.
Torrents de la Peña A, de Taeye SW, Sliepen K, LaBranche CC, Burger JA, Schermer EE, Montefiori DC, Moore JP, Klasse PJ, Sanders RW.
J Virol. 2018 Mar 28;92(8). pii: e01957-17. doi: 10.1128/JVI.01957-17. Print 2018 Apr 15.

Incidence and clearance of anal high-risk HPV infection and their determinants among HIV-negative men who have sex with men over a period up to five years

The incidence and clearance of anal high-risk human papillomavirus (hrHPV) infections and determinants thereof among human immunodeficiency virus (HIV)-negative men who have sex with men (MSM) over a period of up to 5 years were assessed. Data from HIV-negative MSM who participated in the ACS in the period 2010-2015 were used. Anal self-swabs were collected during every 6-monthly visit, and were HPV genotyped using the SPF10-PCR DEIA/LiPA25-system-v1. Incidence rates (IRs) and clearance rates (CRs) of incident anal hrHPV infections were assessed by hrHPV type (types 16, 18, 31, 33, 45, 52, and 58). Determinants of transitions between uninfected and infected states were assessed by hrHPV type using a time-homogenous multi-state Markov model. This study included 713 HIV-negative MSM, with a median age of 37 years (interquartile range [IQR] 31-43) and a median number of study visits of 6 (IQR 2-7). The IRs of anal infections had a median of 5.2 per 100 person-years (range: 2.2-7.9) across types, with HPV16 having the highest IR. The CRs of incident anal hrHPV infections had a median of 53.7 per

100 person-years (range: 33.4-65.3) across types, with HPV16 having the lowest CR. Having had over 100 lifetime sex partners was significantly associated with incident anal hrHPV infections in multivariable analyses. The high incidence and low clearance rates of anal HPV16 infection, compared to other hrHPV types, is consistent with HPV16 being implicated in the large majority of anal cancer cases.
Marra E, Kovaleva A, Bruisten SM, Vermeulen W, Boyd A, Schim van der Loeff MF.
Clin Infect Dis. 2019 Apr 24;68(9):1556-1565. doi: 10.1093/cid/ciy738

Steering committee

In 2018, the steering committee met four times. Seven proposals for use of data and/or samples (serum/PBMC) were submitted to the committee: Five from the AMC Experimental Immunology, one from the AIGHD in collaboration with the GGD Amsterdam and one from GGD Amsterdam. One of the proposals involved collaborations with groups outside the ACS. All seven requests were approved, of which three after revisions recommended by the ACS steering committee.

Publications in 2018 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

Preexposure prophylaxis among men who have sex with men in the Amsterdam Cohort Studies: Use, eligibility, and intention to use
Coyer L, van Bilsen W, Bil J, Davidovich U, Hoornenborg E, Prins M, Matser A.
PLoS One. 2018 Oct 12;13(10):e0205663.

The effect of female sex on hepatitis C incidence among people who inject drugs: Results from Collaborative. the International Multicohort InC3
Esmaeili A, Mirzazadeh A, Morris MD, Hajarizadeh B, Sacks HS, et al. ; InC3 Collaborative.
Clin Infect Dis. 2018 Jan 6;66(1):20-28. doi: 10.1093/cid/cix768. MID:29020200.

Model projections on the impact of HCV treatment in the prevention of HCV transmission among people who inject drugs in Europe
Fraser H, Martin NK, Brummer-Korvenkontio H, Carrieri P, Dalgard O, et al.
J Hepatol. 2018 Mar;68(3):402-411.

Anal HPV 16 and 18 viral load: A comparison between HIV-negative and -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.

Incidence and clearance of anal high-risk HPV infection and their determinants among HIV-negative men who have sex with men over a period up to five-years
Marra E, Kovaleva A, Bruisten SM, Vermeulen W, Boyd A, Schim van der Loeff MF.
Clin Infect Dis. 2019 Apr 24;68(9):1556-1565. doi: 10.1093/cid/ciy738

Virological and serological predictors of anal high-grade squamous intraepithelial lesions among HIV-positive men who have sex with men
Marra E, Siegenbeek van Heukelom ML, Leeman A, Waterboer T, *et al.*
Clin Infect Dis. 2019 Apr 8;68(8):1377-1387. doi: 10.1093/cid/ciy719

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.

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):420-48.

Temporal trends of transmitted HIV drug resistance in a multinational seroconversion cohort
Olson A, Bannert N, Sönnerborg A, de Mendoza C, Price M, *et al.*; for CASCADE Collaboration in EuroCoord.
AIDS. 2018 Jan 14;32(2):161-169.

Systemic DPP4 activity is reduced during primary HIV-1 infection and is associated with intestinal RORC(+) CD4(+) cell levels: a surrogate marker candidate of HIV-induced intestinal damage
Ploquin MJ, Casrouge A, Madec Y, Noël N, Jacquelin B, *et al.*
J Int AIDS Soc. 2018 Jul;21(7):e25144. doi: 10.1002/jia2.25144.

Genomic variability of within-host hepatitis C variants in acute infection
Rodrigo C, Leung P, Lloyd AR, Bull RA, Luciani F, *et al.*; InC3 Collaborative.
J Viral Hepat. 2018 Dec 22.

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.;* 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.

Predictors of CD4 cell recovery following initiation of antiretroviral therapy among HIV-1 positive patients with well-estimated dates of seroconversion
Stirrup OT, Copas AJ, Phillips AN, Gill MJ, Geskus RB, et al.; CASCADE Collaboration in EuroCoord.
HIV Med. 2018 Mar;19(3):184-194. doi: 10.1111/hiv.12567

Immunogenicity in rabbits of HIV-1 SOSIP trimers from clades A, B, and C, given individually, sequentially, or in combination
Torrents de la Peña A, de Taeye SW, Sliepen K, LaBranche CC, Burger JA, *et al.*
J Virol. 2018 Mar 28;92(8). pii: e01957-17. doi: 10.1128/JVI.01957-17. Print 2018 Apr 15.

Detection of incident anal high-risk HPV-DNA in MSM: Incidence or reactivation?
Twisk DE, van der Sande MAB, van Eeden A, Heideman DAM, van der Klis FRM, *et al.*
J Infect Dis. 2018 Aug 24;218(7):1018-1026.

Infection pressure in men who have sex with men and their suitability to donate blood
Van Bilsen WPH, Zaaijer HL, Matser A, Hurk KVD, Slot E, *et al.*
Clin Infect Dis. 2019 Mar 5;68(6):1001-1008. doi: 10.1093/cid/ciy596

The evolution of subtype B HIV-1 tat in the Netherlands during 1985-2012
van der Kuyl AC, Gall A, Vink M, Zorgdrager F, Binter S, *et al.*; BEEHIVE Collaboration.
Virus Research (2018) 250: 51-64. https://doi.org/10.1016/j.virusres.2018.04.008

High proportions of liver fibrosis and cirrhosis in an ageing population of people who use drugs in Amsterdam, the Netherlands
Van Santen DK, Schim van der Loeff MF, Cartier van Dissel J, Martens JPD, van der Valk M, Prins M.
J Gastroenterol Hepatol. 2018 Oct;30(10):1168-1176. doi:10.1097/MEG.0000000000001213

Easy and accurate reconstruction of whole HIV genomes from short-read sequence data
Wymant C, Blanquart F, Gall A, Bakker M, Bezemer D, *et al.*
Virus Evolution: 2018 May 18;4(1):vey007. doi: 10.1093/ve/vey007

Theses in 2018 that include ACS data

Daniëla van Santen – 4 May 2018: Epidemiological studies on viral (co)-infections: human immunodeficiency virus, hepatitis C virus, and human papillomavirus. Supervisor: Prof. M. Prins; co-supervisors: Dr. R. B. Geskus & Dr. J. J. van der Helm.

Wijnand van den Boom – 9 May 2018: Casual sex, risk and context. HIV risk-reduction strategies among men who have sex with men. Supervisors: Prof. M. Prins & Prof. T.G.M. Sandfort; co-supervisors: Dr. E. Davidovich & Dr. I. G. Stolte.

Alba Torrents de la Peña – 29 June 2018: Structure-based stabilization of HIV-1 trimer vaccines. Supervisors: Prof. B. Berkhout & Prof. R. W. Sanders.

Elske Marra – 7 September 2018: Anal HPV infection & disease: common, easy to prevent, hard to treat. Supervisors: Prof. H.J.C. de Vries & Prof. J.M. Prins; co-supervisor: Dr. M.F. Schim van der Loeff.

9. Curaçao

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

Introduction

Since 2005, 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. Such a database 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 presents a concise overview of the current state of HIV treatment in Curaçao.

Population

In total, 1,246 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 (1,222; 98%), while 2 individuals were diagnosed with HIV-2, and 11 had antibodies against both HIV-1 and HIV-2. For 11 individuals, serological results on HIV type were not available in the SHM database.

People in clinical care

In total, 682 (56%) of the 1,222 registered HIV-1-positive individuals were known to be in clinical care by the end of 2018. People were considered to be in clinical care if they visited their treating physician in 2018 or had a CD4 count or HIV RNA measurement in that year and had not moved abroad. Of the 540 individuals who were not or no longer in clinical care, 183 (34%) were known to have died, and 93 (17%) to have moved abroad, while 11 people were only diagnosed with HIV in 2019, or only moved to Curaçao in 2019. Thus, 253 individuals were considered lost to care, equivalent to 27% of all HIV-1-positive individuals who were supposedly still alive and had not moved abroad.

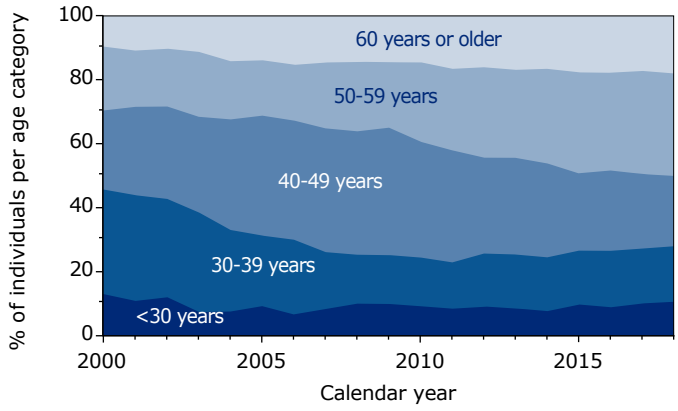
Ageing population

The median age of the population in care by the end of 2018 was 50 years (interquartile range (IQR) 38-57) 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, half of all people currently in care (50%) are 50 years or older, including 48% of men and 52% of women; 18% of the individuals are 60 years or

< Back Chapter 1

older. In contrast, the median age at the time of diagnosis decreased, from 38 (IQR 32-47) years in individuals diagnosed between 2000 and 2005 to 35 (27-46) years in those diagnosed in 2016 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 2018, these proportions were 11% and 50%, respectively, while 18% 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 care by the end of 2018 had been diagnosed with HIV a median of 8.8 (IQR 4.2-15.5) 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 7.4 years for men who have sex with men (MSM), 8.8 years for other men, and 9.6 years for women.

Table 9.1: Characteristics of the 682 HIV-1-positive individuals in clinical care in Curaçao by the end of 2018.

	Men (n=418, 61%)		Women (n=264, 39%)		Total (n=682)	
	n	%	n	%	n	%
Transmission						
MSM	177	42	-	-	177	26
Heterosexual	175	42	246	93	421	62
Other/unknown	66	16	18	7	84	12
Current age (years)						
0-17*	1	-	-	-	1	-
18-24	13	3	10	4	23	3
25-34	71	17	30	11	101	15
35-44	85	20	46	17	131	19
45-54	117	28	87	33	204	30
55-64	92	22	65	25	157	23
65-74	32	8	17	6	49	7
≥75	7	2	9	3	16	2
Country of origin						
Former Netherlands Antilles	343	82	174	66	517	76
Dominican Republic	8	2	42	16	50	7
Haiti	24	6	24	9	48	7
The Netherlands	13	3	1	0	14	2
Other	30	7	23	9	53	8
Years aware of HIV infection						
<1	30	7	16	6	46	7
1-2	55	13	23	9	78	11
3-4	52	12	23	9	75	11
5-10	105	25	73	28	178	26
10-20	125	30	91	34	216	32
>20	48	11	37	14	85	12
Unknown	3	1	1	0	4	1

**Data on children and adolescents are not yet collected.*

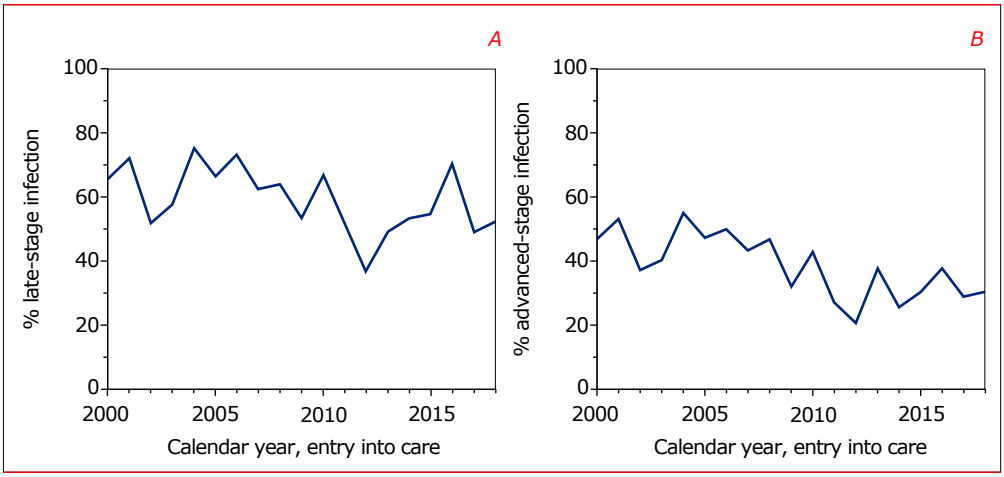
***Legend:** MSM=men who have sex with men.*

Late presentation and start of treatment

A large proportion of 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 was 64% among individuals entering care between 2000 and

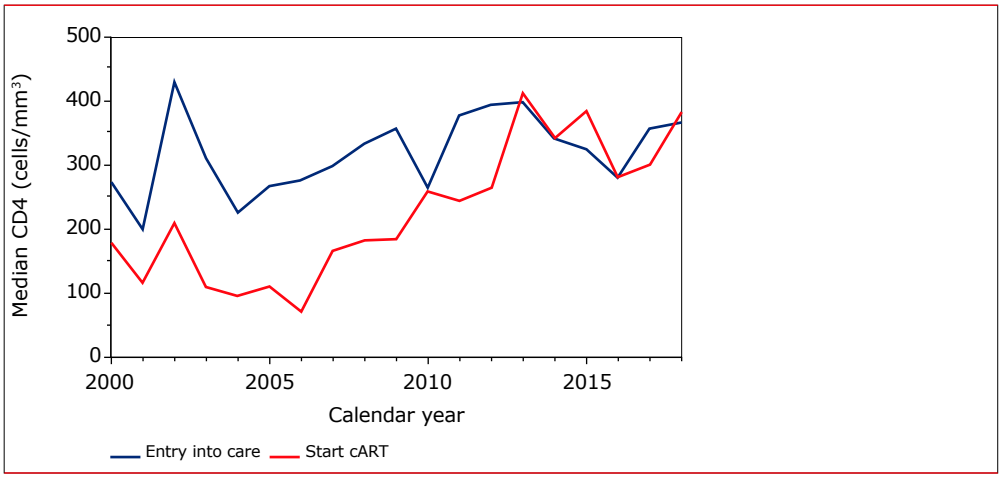
2005 and remained at a high level (58%) among those entering care in 2016 or later (*Figure 9.2A*). However, there appears to have been a decrease in the proportion of people presenting for care with advanced HIV disease, i.e., with a CD4 count less than 200 cells/mm^3 or AIDS. Between 2000 and 2005, 46% presented with advanced HIV, while this proportion was 33% among those presenting for care in 2016 or later (*Figure 9.2B*). 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 (2016) onwards, 59% (57%) presented with late HIV disease while 36% (30%) were advanced 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. As a pre-treatment CD4 count measurement close to the time of entry into care was sometimes missing, the stage of HIV infection could not be determined for 18% of individuals who have entered care since 2000.*



In recent years, there has been an increase in CD4 cell counts at the start of cART (*Figure 9.3*). Between 2016 and 2018, 29% of those for whom a CD4 count was available at the start of cART had less than 200 CD4 cells/mm^3, 24% had CD4 counts between 200 and 349 cells/mm^3, 25% had CD4 counts between 350 and 499 cells/mm^3, and 22% had CD4 counts of 500 cells/mm^3 or higher. During the same period, 95% 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 2018, the median CD4 count at the time of entry into care increased from 275 cells/mm³ (interquartile range (IQR) 144-449) to 368 (185-489) cells/mm³. During the same period, CD4 counts at start of cART increased from 180 (59-321) cells/mm³ to 383 (217-481) cells/mm³.

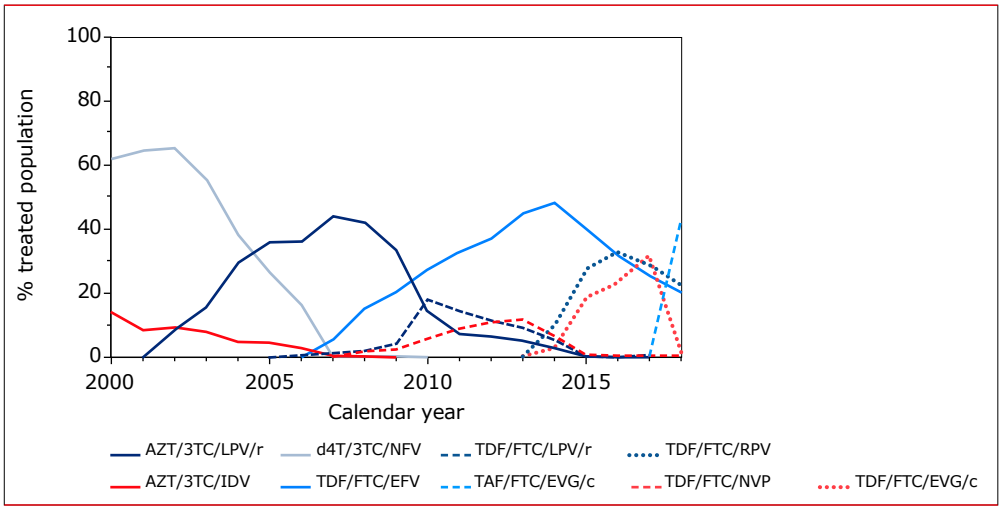


Legend: cART=combination antiretroviral therapy.

Combination treatment

In total, 1,121 (92%) of the 1,222 registered HIV-1-positive individuals had started antiretroviral treatment by May 2019 (*Appendix Table 9.1*). Over time, there have been clear shifts in the treatment regimens prescribed in Curaçao (*Figure 9.4*). Of the people who started antiretroviral treatment and were still in care by the end of 2018, 43% were being treated with tenofovir alafenamide/emtricitabine/cobicistat-boosted elvitegravir, 23% with tenofovir disoproxil/emtricitabine/rilpivirine, and 20% with tenofovir disoproxil/emtricitabine/efavirenz. The majority (96%) used a once-daily regimen, while 87% were treated with a fixed-dose single tablet regimen.

Figure 9.4: Percentage of individuals treated with antiretroviral therapy (ART) by specific regimens over calendar time. At the end of 2018, 43% of the people were receiving TAF/FTC/EVG/c, 23% RPV/TDF/FTC, and 20% TDF/FTC/EFV.

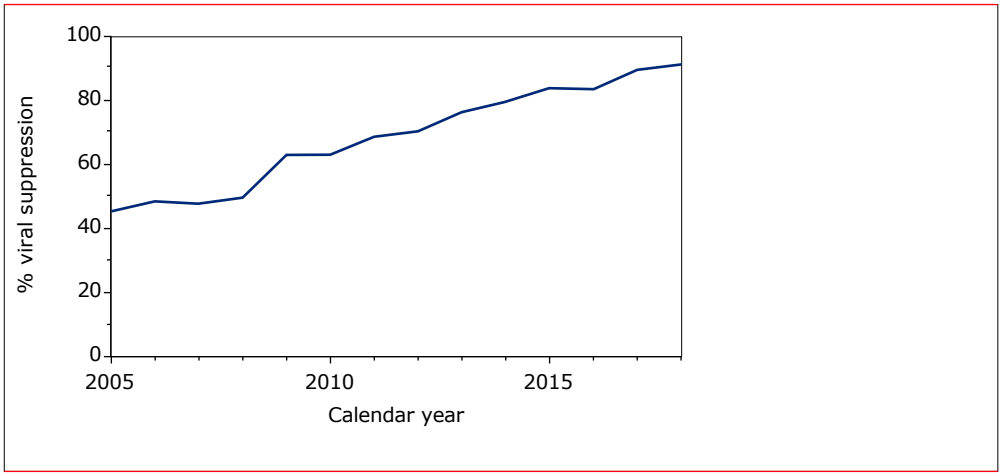


Legend: AZT=zidovudine; 3TC=lamivudine; LPV/r=ritonavir-boosted lopinavir; d4T=stavudine; NFV=nelfinavir TAF=tenofovir alafenamide; TDF=tenofovirdisoproxil fumarate; FTC=emtricitabine; RPV=rilpivirine; IDV=indinavir; EFV=efavirenz; NVP=nevirapine; EVG/c=cobicistat-boosted elvitegravir.

Treatment outcome

In the total population still in care, the median current CD4 count was 494 (IQR 356-694) cells/mm^3. CD4 counts were similar between MSM (524 (402-702) cells/mm^3) and women (514 (396-754) cells/mm^3), but men who acquired their infection via other or unknown modes of transmission had lower CD4 counts (441 (293-627) cells/mm^3). Among individuals with a viral load measurement, the proportion with HIV RNA levels less than 200 copies/ml increased from 45% in 2005 to 91% in 2018 (*Figure 9.5*).

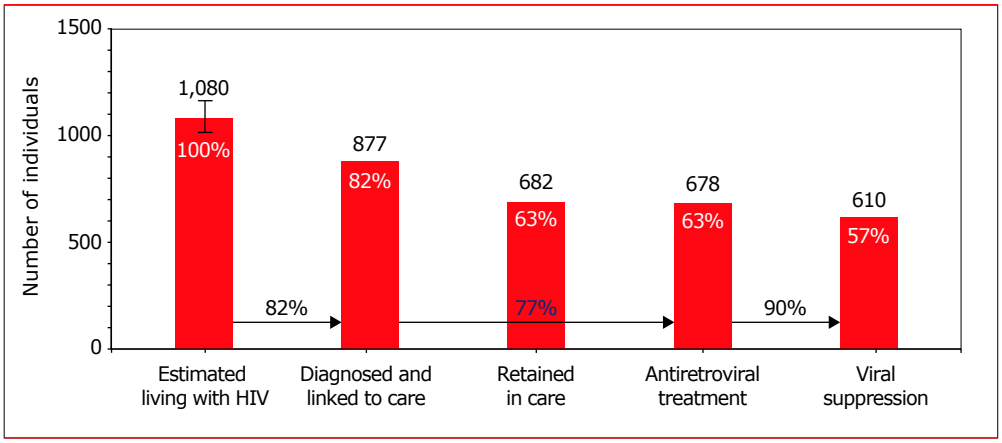
Figure 9.5: Proportion of people in care with HIV RNA <200 copies/ml at their last viral load measurement in each calendar year.



Continuum of HIV care

The total number of people living with HIV by the end of 2018, including those not yet diagnosed, was estimated to be 1,080 (95% confidence interval (CI) 1,000-1,160), of whom 200 (130-280) were still undiagnosed (*Figure 9.6*)[2]. In total, 877 individuals, or 82% 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, 682 (63%) people were still in care, i.e., they had had at least one HIV RNA or CD4 count measurement or a clinic visit in 2018. The majority of these individuals (678, or 77% of those diagnosed and linked to care) had started antiretroviral treatment. In total, 666 individuals, or 98% of those who started treatment, had an HIV RNA measurement available in 2018 and 610 (92%, or 90% of those treated) had a most recent HIV RNA below 200 copies/ml. Overall, 57% of the total estimated population living with HIV and 70% of 877 individuals 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 82-77-90: 82% of people living with HIV know their HIV status, 77% of all people diagnosed receive antiretroviral treatment, and 90% of people receiving treatment have a suppressed viral load[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 2018. 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.



Viral suppression

For 68 individuals who were known to have ever started treatment it was unknown if they had a suppressed viral load. On closer inspection, 12 (18%) of these individuals were found to have no documented RNA measurement available in 2018. Of the 56 (82%) people with a viral load measurement and no viral suppression, 14 had only started antiretroviral treatment in 2018 and may not have had sufficient follow up to achieve a documented suppressed viral load.

Antiretroviral treatment

Four individuals who were in care by the end of 2018 had not yet started antiretroviral treatment, although, at the time of writing, three of these people are known to have started treatment in 2019.

Lost to care

In total, 253 individuals were lost to care, of whom 58 (23%) before the end of 2008 and 195 (77%) after 2008. The 58 individuals who were lost to care before 2008 were excluded from the estimated number of people living with HIV and the number of people diagnosed and linked to care. It is unlikely that these 58 individuals are still living in Curaçao without needing care or antiretroviral treatment. Of the 195 individuals lost to care after 2008, i.e., the difference between the second (877) and third stage (682) in the care continuum, 60 (31%) were born outside the former Netherlands Antilles, including 26 in Haiti and 11 in the Dominican Republic,

whereas this proportion was slightly lower, 24%, for those who were still in care by the end of 2018. This suggests that some of those lost to care may actually have moved abroad, in particular back to their country of birth, but also shows that, overall, a considerable proportion of people were not retained in care.

Conclusion

Over the years, the quality of treatment offered to HIV-positive individuals in Curaçao has improved considerably, as evidenced by an increasing proportion of individuals with a suppressed viral load. In addition, timely registration of HIV RNA measurements in the SHM database has improved, enabling better monitoring of the progress towards achieving UNAIDS' 90-90-90 goals for 2020. However, the relatively high proportion of people lost to care is worrisome and may affect underreporting of death and/or outmigration. In addition, the proportion of people entering care with late-stage HIV infection remains high, although the proportion with advanced HIV disease appears to be decreasing.

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. Moreover, currently no data are regularly collected for HIV-positive children. As a result, data on children living with HIV in Curaçao are of unknown quality and can therefore not be used for strategic planning of HIV care for this specific population.

Early start of cART appears possible, but long-term continuous follow up should be guaranteed to optimise the effect of cART. The continuum of care for Curaçao illustrates 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, have died or moved abroad. 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.

Finally, a relatively large, albeit decreasing, proportion of individuals enter care late in the course of their infection. More efforts should be put into upscaling HIV screening and ensuring that people who test positive are quickly linked to care.

References

1. Antinori A, Coenen T, Costagiola D, et al. Late presentation of HIV infection: a consensus definition. *HIV Med*. 2011;12(1):61-64. doi:10.1111/j.1468-1293.2010.00857.x
2. *ECDC HIV Modelling Tool [Software Application]. Version 1.3.0*. Stockholm: European Centre for Disease Prevention and Control; 2017. https://ecdc.europa.eu/en/publications-data/hiv-modelling-tool.
3. Joint United Nations Programme on HIV/AIDS (UNAIDS). *90-90-90 An Ambitious Treatment Target to Help End the AIDS Epidemic.*; 2014. http://www.unaids.org/en/resources/documents/2017/90-90-90.

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 2017 and 2018 had not yet been finalised at the time of writing.

Calendar year	Diagnosis	Entry into care	Start cART
≤1999	252	180	91
2000	45	45	31
2001	36	41	42
2002	49	45	23
2003	59	54	25
2004	49	51	41
2005	53	62	48
2006	49	63	46
2007	43	43	45
2008	53	63	53
2009	52	58	56
2010	47	51	62
2011	58	57	51
2012	60	69	62
2013	70	60	82
2014	42	53	79
2015	48	49	53
2016	49	57	62
2017	40	50	56
2018	47	56	62
2019	6	6	9
Unknown	15	9	15
Total	**1,222**	**1,222**	**1,094**

< Back to page 328

Acknowledgements

Clinical centres

** denotes site coordinating physician*

Amsterdam UMC, AMC site, Amsterdam
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.

Amsterdam UMC, VUmc site, Amsterdam
HIV treating physicians: E.J.G. Peters*, M.A. van Agtmael, R.S. Autar, 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.

Emma Kinderziekenhuis (Amsterdam UMC, AMC site), Amsterdam
HIV treating physicians: T.W. Kuijpers, D. Pajkrt, H.J. Scherpbier.
HIV nurse consultants: C. de Boer, A. van der Plas, A.M. Weijsenfeld.

Admiraal De Ruyter Ziekenhuis, Goes
HIV treating physicians: M. van den Berge*, A. Stegeman.
HIV nurse consultants: S. Baas, L. Hage de Looff.
HIV clinical virologists/chemists: A. Buiting, A. Reuwer, J. Veenemans, B. Wintermans.

Catharina Ziekenhuis, Eindhoven
HIV treating physicians: M.J.H. Pronk*, H.S.M. Ammerlaan.
HIV nurse consultants: D.N.J. van den Bersselaar, E.S. de Munnik.
HIV clinical virologists/chemists: B. Deiman, A.R. Jansz, V. Scharnhorst, J. Tjhie, M.C.A. Wegdam.

DC Klinieken Lairesse – Hiv Focus Centrum
HIV treating physicians: A. van Eeden*, J. Nellen, M. van der Valk.
HIV nurse consultants: W. Brokking, L.J.M. Elsenburg, H. Nobel.
HIV clinical virologists/chemists: J. Schinkel.

ETZ (Elisabeth-TweeSteden Ziekenhuis), Tilburg
HIV treating physicians: M.E.E. van Kasteren*, M.A.H. Berrevoets, A.E. Brouwer.
HIV nurse consultants: A. Adams, R. van Erve, B.A.F.M. de Kruijf-van de Wiel, S. 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.

Erasmus MC, Rotterdam
HIV treating physicians: T.E.M.S. de Vries-Sluijs*, H.I. Bax, E.C.M. van Gorp, N.C. de de Jong-Peltenburg, M. de Mendonça Melo, E. van Nood,

J.L. Nouwen, B.J.A. Rijnders, C. Rokx, C.A.M. Schurink, L. Slobbe, A. Verbon.
HIV nurse consultants: N. Bassant, J.E.A. van Beek, M. Vriesde, L.M. van Zonneveld.
Data collection: J. de Groot.
HIV clinical virologists/chemists: C.A.B. Boucher, M.P.G Koopmans, J.J.A van Kampen.

Erasmus MC–Sophia, Rotterdam
HIV treating physicians: P.L.A. Fraaij, A.M.C. van Rossum, C.L. Vermont.
HIV nurse consultants: L.C. van der Knaap, E. Visser.

Flevoziekenhuis, Almere
HIV treating physicians: J. Branger*, R.A. Douma.
HIV nurse consultant: A.S. Cents-Bosma, C.J.H.M. Duijf-van de Ven.

HagaZiekenhuis, Den Haag
HIV treating physicians: E.F. Schippers*, C. van Nieuwkoop.
HIV nurse consultants: J.M. van IJperen, J. Geilings.
Data collection: G. van der Hut.
HIV clinical virologist/chemist: N.D. van Burgel.

HMC (Haaglanden Medisch Centrum), Den Haag
HIV treating physicians: E.M.S. Leyten*, L.B.S. Gelinck, F. Mollema.
HIV nurse consultants: S. Davids-Veldhuis, C. Tearno, G.S. Wildenbeest.
HIV clinical virologists/chemists: E. Heikens.

Isala, Zwolle
HIV treating physicians: P.H.P. Groeneveld*, J.W. Bouwhuis, A.J.J. Lammers.
HIV nurse consultants: S. Kraan, A.G.W. van Hulzen, M.S.M. Kruiper.
Data collection: G.L. van der Bliek, P.C.J. Bor.
HIV clinical virologists/chemists: S.B. Debast, G.H.J. Wagenvoort.

Leids Universitair Medisch Centrum, Leiden
HIV treating physicians: F.P. Kroon*, M.G.J. de Boer, H. Jolink, M.M.C. Lambregts, A.H.E. Roukens, H. Scheper.
HIV nurse consultants: W. Dorama, N. van Holten.
HIV clinical virologists/chemists: E.C.J. Claas, E. Wessels.

Maasstad Ziekenhuis, Rotterdam
HIV treating physicians: J.G. den Hollander*, R. El Moussaoui, K. Pogany.
HIV nurse consultants: C.J. Brouwer, J.V. Smit, D. Struik-Kalkman.
Data collection: T. van Niekerk.
HIV clinical virologists/chemists: O. Pontesilli.

Maastricht UMC+, Maastricht
HIV treating physicians: S.H. Lowe*, A.M.L. Oude Lashof, D. Posthouwer, M.E. van Wolfswinkel.
HIV nurse consultants: R.P. Ackens, K. Burgers, J. Schippers.
Data collection: B. Weijenberg-Maes.
HIV clinical virologists/chemists: I.H.M. van Loo, T.R.A. Havenith.

Medisch Centrum Leeuwarden, Leeuwarden
HIV treating physicians: M.G.A. van Vonderen*, L.M. Kampschreur.
HIV nurse consultants: S. Faber, R. Steeman-Bouma.
HIV clinical virologists/chemists: A. Al Moujahid.

Medisch Spectrum Twente, Enschede
HIV treating physicians: G.J. Kootstra*, C.E. Delsing.
HIV nurse consultants: M. van der Burg-van de Plas, L. Scheiberlich.

Noordwest Ziekenhuisgroep, Alkmaar
HIV treating physicians: W. Kortmann*, G. van Twillert*, R. Renckens.
HIV nurse consultant and data collection: D. Ruiter-Pronk, F.A. van Truijen-Oud.
HIV clinical virologists/chemists: J.W.T. Cohen Stuart, ER. Jansen, M. Hoogewerf, W. Rozemeijer, W. A. van der Reijden, J.C. Sinnige.

OLVG, Amsterdam
HIV treating physicians: K. Brinkman*, G.E.L. van den Berk, W.L. Blok, K.D. Lettinga, M. de Regt, W.E.M. Schouten, J.E. Stalenhoef, J. Veenstra, S.M.E. Vrouenraets.
HIV nurse consultants: G.F. Geerders, K. Hoeksema, M.J. Kleene, M. Knapen, I.B. van der Meché, E. Mulder-Seeleman, A.J.M. Toonen, S. Wijnands.
HIV clinical virologists: D. Kwa.

Radboudumc, Nijmegen
HIV treating physicians: R. van Crevel*, K. van Aerde, A.S.M. Dofferhoff, S.S.V. Henriet, H.J.M. ter Hofstede, J. Hoogerwerf, M. Keuter, O. Richel.
HIV nurse consultants: M. Albers, K.J.T. Grintjes-Huisman, M. de Haan, M. Marneef, R. Strik-Albers.
HIV clinical virologists/chemists: J. Rahamat-Langendoen, F.F. Stelma.
HIV clinical pharmacology consultant: D. Burger.

Rijnstate, Arnhem
HIV treating physicians: E.H. Gisolf*, R.J. Hassing, M. Claassen.
HIV nurse consultants: G. ter Beest, P.H.M. van Bentum, N. Langebeek.
HIV clinical virologists/chemists: R. Tiemessen, C.M.A. Swanink.

Spaarne Gasthuis, Haarlem
HIV treating physicians: S.F.L. van Lelyveld*, R. Soetekouw.
HIV nurse consultants: L.M.M. van der Prijt, J. van der Swaluw.
Data collection: N. Bermon.
HIV clinical virologists/chemists: W.A. van der Reijden, R. Jansen, B.L. Herpers, D. Veenendaal.

Medisch Centrum Jan van Goyen, Amsterdam
HIV treating physicians: D.W.M. Verhagen, F.N. Lauw.
HIV nurse consultants: M.C. van Broekhuizen, M. van Wijk.

Universitair Medisch Centrum Groningen, Groningen
HIV treating physicians:
W.F.W. Bierman*, M. Bakker, J. Kleinnijenhuis, E. Kloeze, A. Middel, D.F. Postma, E.H. Schölvinck, Y. Stienstra, C.L.A.R. Verhage, M. Wouthuyzen-Bakker.
HIV nurse consultants: A. Boonstra, H. de Groot-de Jonge, P.A. van der Meulen, D.A. de Weerd.
HIV clinical virologists/chemists:
H.G.M. Niesters, C.C. van Leer-Buter, M. Knoester.

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, E.M. Schadd, B.J. van Welzen.
HIV nurse consultants: K. Aarsman, B.M.G. Griffioen-van Santen, I. de Kroon.
Data collection: M. van Berkel, C.S.A.M. van Rooijen.
HIV clinical virologists/chemists:
R. Schuurman, F. Verduyn-Lunel, A.M.J. Wensing.

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:
E.O.W. Rooijakkers, D. van de Wetering.
HIV nurse consultants: A. Alberto.
Data collection: I. van der Meer.
HIV clinical virologists/chemists:
A. Rosingh, T. Halaby.

Composition of Stichting HIV Monitoring

SHM Board

Name	Position	Representing	Affiliation
Dr M. van der Valk	Chair	Dutch Association of HIV-Treating Physicians (NVHB)	Amsterdam UMC, AMC location Amsterdam
Dr Y.T.H.P. van Duijnhoven	Secretary	GGD GHOR Nederland	GGD Amsterdam
P.W.D. Venhoeven	Treasurer		Alexander Monro Ziekenhuis, Bilthoven
P. Brokx	Member	Hiv Vereniging	Hiv Vereniging, Amsterdam
J. Crasborn	Member	Zorgverzekeraars Nederland	Achmea, Zeist
Prof. K. Jager	Member	AMC-UvA	Amsterdam UMC, AMC location Amsterdam
P.E. van der Meer (until 1-9-19)	Member	Nederlandse Vereniging van Ziekenhuizen (NVZ)	Albert Schweizer Ziekenhuis, Dordrecht
J.J.Schoo (from 1-9-19)	Member	NVZ	Rijnstate, Arnhem
Prof. M.M.E. Schneider	Member	Nederlandse Federatie Universitair Medische Centra (NFU)	UMC Utrecht, Utrecht

SHM Advisory Board

Name	Affiliation
Prof. D.R. Kuritzkes (Chair)	Brigham and Women's Hospital, Boston, MA, USA
Dr J. Arends	UMC Utrecht, Utrecht
Prof. M. Egger	University of Bern, Switzerland
Prof. T.B.H. Geijtenbeek	Amsterdam UMC, AMC location, Amsterdam
Prof. B. Ledergerber	University Hospital Zurich, Switzerland
Prof. C. Sabin	University College, London, UK
P.J. Smit (until 24-4-19)	Hiv Vereniging, Amsterdam
R. Finkenflügel (from 24-4-19)	Hiv Vereniging, Amsterdam

SHM working group

Members

Name	Affiliation
Dr E.H. Gisolf	Rijnstate, Arnhem

Reviewers

Name	Affiliation
Dr J. Arends	UMC Utrecht, Utrecht
Dr W.F.W. Bierman	UMCG, Groningen
Prof. C.A.B. Boucher	Erasmus MC, Rotterdam
Prof. K. Brinkman	OLVG, Amsterdam
Dr D.M. Burger	Radboudumc, Nijmegen
Dr R. van Crevel	Radboudumc, Nijmegen
Dr S.P.M. Geelen	UMC Utrecht-WKZ, Utrecht
Dr G. Hermanides	Rode Kruis Ziekenhuis, Beverwijk
Prof. A.I.M. Hoepelman	UMC Utrecht, Utrecht
Dr S. Jurriaans	Amsterdam UMC, AMC location, Amsterdam
Dr F.C.M. van Leth	KNCV Tuberculosis Foundation, The Hague; AIGHD Amsterdam
Dr C. van Nieuwkoop	HagaZiekenhuis, Den Haag
Prof. J.M. Prins	Amsterdam UMC, AMC location, Amsterdam
Dr. B. Rijnders	Erasmus MC, Rotterdam
Dr C. Rokx	Erasmus MC, Rotterdam
Dr A.M.C. van Rossum	Eramus MC-Sophie Kinderziekenhuis, Rotterdam
Dr R. Schuurman	UMC Utrecht, Utrecht
Dr K. Sigaloff	Amsterdam UMC, VUmc location, Amsterdam
Dr J. Schouten	AIGHD, Amsterdam
Dr M. van der Valk	Amsterdam UMC, AMC location, Amsterdam

Hepatitis working group

Name	Affiliation
Dr J. Arends (Chair)	UMC Utrecht, Utrecht
Prof. K. Brinkman	OLVG, Amsterdam
Prof. A.I.M. Hoepelman	UMC Utrecht, Utrecht
Dr J. van der Meer	Amsterdam UMC, AMC location, Amsterdam
Dr. B. Rijnders	Erasmus MC, Rotterdam
Dr J. Schinkel	Amsterdam UMC, AMC location, Amsterdam
Dr E.F. Schippers	HagaZiekenhuis, Den Haag
Dr C. Smit	SHM, Amsterdam
Dr M. van der Valk	Amsterdam UMC, AMC location, Amsterdam
Dr T.E.M.S. de Vries-Sluijs	Erasmus MC, Rotterdam

Expert clinical and public health advisors

Name	Affiliation
Dr J. Arends	UMC Utrecht, Utrecht
Prof. K. Brinkman	OLVG, Amsterdam
Prof. A. Duits	Stichting Rode Kruis Bloedbank, Willemstad, Curaçao
Prof. S. Geerlings	Amsterdam UMC, AMC location, Amsterdam
Dr G. Hermanides	Rode Kruis Ziekenhuis, Beverwijk
Dr J. van Kampen	Erasmus MC, Rotterdam
Prof. F. Kroon	LUMC, Leiden
Dr L. van Leeuwen	Amsterdam UMC, AMC location, Amsterdam
Dr J. Nellen	Amsterdam UMC, AMC location, Amsterdam
Dr C. van Nieuwkoop	HagaZiekenhuis, The Hague
Dr E. Op de Coul	RIVM, Bilthoven
Prof. J.M. Prins	Amsterdam UMC, AMC location, Amsterdam
Dr A. van Rossum	Erasmus MC, Rotterdam
Dr M. van der Valk	Amsterdam UMC, AMC location, Amsterdam
Prof. A.M.J. Wensing	UMC Utrecht, Utrecht
Dr T. Wolfs	Wilhelmina Kinderziekenhuis, Utrecht.

SHM personnel

Director	P. Reiss MD, PhD
Deputy director	S. Zaheri MSc

Data analysis, reporting & research unit

Researchers	D.O. Bezemer PhD
	A. Boyd, PhD
	A.I. van Sighem PhD
	C. Smit PhD
	F.W.N.M. Wit MD, PhD

Data unit

Data management	M.M.J. Hillebregt MSc (coordinator)
	A.S. de Jong MSc
	T.J. Woudstra
Data quality staff	D. Bergsma MSc (coordinator)
	T. Rutkens
	L. van de Sande MA
	S. van der Vliet
Data protection officer	J.P. Feijt
Patient registration & data collection	L.G.M. de Groot-Berndsen (coordinator)

Data collectors	M. van den Akker Y.M. Bakker A. el Berkaoui M. Bezemer-Goedhart N.M. Brétin E.A. Djoechro MSc R. Regtop E.I. Kruijne C.R.E. Lodewijk E. Lucas L. Munjishvili MA F. Paling MSc B.M. Peeck MSc C.M.J. Ree Y.M.C. Ruijs-Tiggelman P.P. Schnörr MSc M.J.C. Schoorl MSc E.M. Tuijn-de Bruin D.P. Veenenberg-Benschop E.C.M. Witte
Communications unit	C.J. Ester PhD (manager) Y. de Waart
Human resources, finance & administration	I. Bartels (HR advisor) Y. de Waart (HR assistant) A.J.P.M. van der Doelen (controller) H.J.M. van Noort MSc (financial administrator) M.M.T. Koenen (office manager)

Publications & presentations

The publications and presentations listed below are those available since the publication of the Monitoring Report 2018.

Publications

Are European HIV cohort data within EuroCoord representative of the diagnosed HIV population?
Vourli G, Pharris A, Cazein F, Costagliola D, Dabis F, Del Amo J, Delpech V, Díaz A, Girardi E, Gourlay, Gunsenheimer-Bartmeyer B, Hernando V, Nikolopoulos G, Porter K, Rosińska M, Sabin C, Suligoi B, Supervie V, Wit F, Touloumi G.
AIDS. 2018 Oct 4. doi: 10.1097/QAD.0000000000002034. [Epub ahead of print]

Trends in human immunodeficiency virus diagnoses among men who have sex with men in North America, Western Europe, and Australia, 2000–2014
Chapin-Bardales J, Schmidt AJ, Guy RJ, Kaldor JM, McGregor S, Sasse A, Archibald C, Rank C, Casabona Barbarà J, Folch C, Vives N, Cowan SA, Cazein F, Velter A, an der Heiden M, Gunsenheimer-Bartmeyer B, Marcus U, Op de Coul ELM, van Sighem A, Aldir I, Cortes Martins H, Berglund T, Velicko I, Gebhardt M, Delpech V, Hughes G, Nardone A, Hall HI, Johnson AS, Sullivan PS.
Ann Epidemiol. 2018 Oct 9. pii: S1047-2797(18)30773-7. doi: 10.1016/j.annepidem.2018.09.006. [Epub ahead of print]

Do people living with HIV experience greater age advancement than their HIV-negative counterparts?
De Francesco D, Wit FW, Bürkle A, Oehlke S, Kootstra NA, Winston A, Franceschi C, Garagnani P, Pirazzini C, Libert C, Grune T, Weber D, Jansen EHJM, Sabin CA, Reiss P; The Co-morBidity in Relation to AIDS (COBRA) Collaboration.
AIDS. 2018 Oct 15. doi: 10.1097/QAD.0000000000002063. [Epub ahead of print]

Patterns of co-occurring comorbidities in people living with HIV
Francesco D, Verboeket SO, Underwood J, Bagkeris E, Wit FW, Mallon PWG, Winston A, Reiss P, Sabin CA; Pharmacokinetic and clinical observations in PeoPle Over fiftY (POPPY) study and the AGE_hIV cohort study.
Open Forum Infect Dis. 2018 Oct 24;5(11):ofy272. doi: 10.1093/ofid/ofy272. eCollection 2018 Nov.

Liver decompensation in HIV/hepatitis B coinfection in the cART era does not seem increased compared to hepatitis B mono-infection
Lieveld FI, Smit C, Richter C, van Erpecum KJ, Spanier BWM, Gisolf EH, Vrolijk JM, Siersema PD, Hoepelman AIM, Reiss P, Arends JE.
Liver Int. 2018 Nov 9. doi: 10.1111/liv.14000. [Epub ahead of print]

Reduced forced vital capacity among HIV-infected middle-aged individuals
Verboeket SO, Wit FW, Kirk GD, Drummond MB, van Steenwijk RP, van Zoest RA, Nellen JF, van der Loeff MFS, Reiss P; AGEh IV study group.
J Infect Dis. 2018 Nov 12. doi: 10.1093/infdis/jiy653. [Epub ahead of print]

Elimination prospects of the Dutch HIV epidemic among men who have sex with men in the era of preexposure prophylaxis
Rozhnova G, Heijne J, Bezemer D, van Sighem A, Presanis A, De Angelis D, Kretzschmar M.
AIDS. 2018 Nov 13;32(17):2615-2623. doi: 10.1097/QAD.0000000000002050.

Global temporal changes in the proportion of children with advanced disease at the start of combination antiretroviral therapy in an era of changing criteria for treatment initiation
Panayidou K, Davies M-A, Anderegg N, Egger M, and The IeDEA, COHERE, PHACS and IMPAACT 219C Collaborations Writing Group.
J Int AIDS Soc. 2018 Nov; 21(11): e25200.

Determinants of restoration of CD4 and CD8 cell counts and their ratio in HIV-1 positive individuals with sustained virological suppression on antiretroviral therapy
Gras L, May M, Ryder LP, Trickey A, Helleberg M, Obel N, Thiebaut R, Guest J, Gill J, Crane H, Lima VD, Monforte AD, Sterling TR, Miro J, Moreno S, Stephan C, Smith C, Tate J, Shepherd L, Saag M, Rieger A, Gillor D, Cavassini M, Montero M, Ingle SM, Reiss P, Costagliola D, Wit FWNM, Sterne J, de Wolf F, Geskus R; Antiretroviral Therapy Cohort Collaboration (ART-CC).
J Acquir Immune Defic Syndr. 2018 Dec 3. doi: 10.1097/QAI.0000000000001913. [Epub ahead of print]

Progression of liver fibrosis following acute hepatitis C virus infection in HIV-positive MSM
Newsum AM, Kooij KW, Boyd A, Smit C, Wit FWNM, van der Meer JTM, Prins M, Reiss P, van der Valk M; MOSAIC study group, ATHENA observational HIV cohort and NVHB-SHM hepatitis working group.
AIDS. 2019 Jan 14. doi: 10.1097/QAD.0000000000002138. [Epub ahead of print]

Predicting virological response to HIV treatment over time: a tool for settings with different definitions of virological response
Revell AD, Wang D, Perez-Elias MJ, Wood R, Tempelman H, Clotet B, Reiss P, van Sighem AI, Alvarez-Uria G, Nelson M, Montaner JS, Lane HC, Larder BA.
J Acquir Immune Defic Syndr. 2019 Feb 14. doi: 10.1097/QAI.0000000000001989. [Epub ahead of print]

Incidence of a first thrombotic event in people with HIV in the Netherlands: a retrospective cohort study
Borjas Howard JF, Rokx C, Smit C, Wit FWNM, Pieterman ED, Meijer K, Rijnders B, Bierman WFW, Vladimir Tichelaar YIG, on behalf of ATHENA observational HIV cohort investigators
The Lancet HIV, published online February 15 2019; DOI:https://doi.org/10.1016/S2352-3018(18)30333-3

Efficacy and safety of long-term Maraviroc use in a heterogeneous group of HIV-infected patients: a retrospective cohort study
Weehuizen JM, Wensing AMJ, Mudrikova T, Wit FWNM, Hoepelman AIM.
Int J Antimicrob Agents. 2019 Mar 1. pii: S0924-8579(19)30048-2. doi: 10.1016/j.ijantimicag.2019.02.018. [Epub ahead of print]

Cost-effectiveness of increased HIV testing among men who have sex with men in the Netherlands
Reitsema M, Steffers L, Visser M, Heijne J, Hoek AJV, Loeff MSV, Van Sighem A, Van Benthem B, Wallinga J, Xiridou M, Mangen MJ.
AIDS. 2019 Mar 15. doi: 10.1097/QAD.0000000000002199. [Epub ahead of print]

HIV-1 exposure and immune activation enhance sexual transmission of Hepatitis C virus by primary Langerhans cells
Nijmeijer BM, Sarrami-Forooshani R, Steba GS, Schreurs RRCE, Koekkoek SM, Molenkamp R, Schinkel J, Reiss P. Siegenbeek van Heukelom ML, van der Valk M, Ribeiro CMS, Geijtenbeek TBH.
J Int AIDS Soc. 2019; 22(3):e25268

Evaluating progress towards triple elimination of mother-to-child transmission of HIV, syphilis and hepatitis B in the Netherlands
Visser M, van der Ploeg CPB, Smit C, Hukkelhoven CWPM, Abbink F, van Benthem BHB, Op de Coul ELM.
BMC Public Health. 2019 Mar 29;19(1):353. doi: 10.1186/s12889-019-6668-6.

Albumin, white blood cell count, and body mass index improve discrimination of mortality in HIV-positive individuals
Tate JP, Sterne JAC, Justice AC; Veterans Aging Cohort Study (VACS) and the Antiretroviral Therapy Cohort Collaboration (ART-CC).
AIDS. 2019 Apr 1;33(5):903-912. doi: 10.1097/QAD.0000000000002140.

Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: Relevance for screening strategies
Wandeler G, Mauron E, Atkinson A, Dufour JF, Kraus D, Reiss P, Peters L, Dabis F, Fehr J, Bernasconi E, van der Valk M, Smit C, Gjærde LK, Rockstroh J, Neau D, Bonnet F, Rauch A; Swiss HIV Cohort Study, Athena Observational Cohort Study, EuroSIDA, ANRS CO3 Aquitaine Cohort.
J Hepatol. 2019 Apr 6. pii: S0168-8278(19)30226-0. doi: 10.1016/j.jhep.2019.03.032. [Epub ahead of print]

Challenges in modelling the proportion of undiagnosed HIV infections in Sweden
Andersson E, Nakagawa F, van Sighem A, Axelsson M, Phillips AN, Sönnerborg A, Albert J.
Euro Surveill. 2019;24(14):pii=1800203.

Predictive performance of cardiovascular disease risk prediction algorithms in people living with HIV
Van Zoest RA, Law M, Sabin CA, Vaartjes I, Van Der Valk M, Arends JE, Reiss P, Wit FW.
J Acquir Immune Defic Syndr. 2019 Apr 23. doi: 10.1097/QAI.0000000000002069. [Epub ahead of print]

Effect estimates in randomized trials and observational studies: comparing apples with apples
Lodi S, Phillips A, Lundgren J, Logan R, Sharma S, Cole SR, Babiker A, Law M, Chu H, Byrne D, Horban A, Sterne JAC, Porter K, Sabin C, Costagliola D, Abgrall S, Gill J, Touloumi G, Pacheco AG, van Sighem A, Reiss P, Bucher HC, Montoliu Giménez A, Jarrin I, Wittkop L, Meyer L, Perez-Hoyos S, Justice A, Neaton JD, Hernán MA; INSIGHT START Study Group and the HIV-CAUSAL Collaboration.
Am J Epidemiol. 2019 May 7. pii: kwz100. doi: 10.1093/aje/kwz100. [Epub ahead of print]

Piloting a surveillance system for HIV drug resistance in the European Union
van de Laar MJ, Bosman A, Pharris A, Andersson E, Assoumou L, Ay E, Bannert N, Bartmeyer B, Brady M, Chaix ML, Descamps D, Dauwe K, Fonager J, Hauser A, Lunar M, Mezei M, Neary M, Poljak M, van Sighem A, Verhofstede C, Amato-Gauci AJ, Broberg EK.
Euro Surveill. 2019 May;24(19). doi: 10.2807/1560-7917.ES.2019.24.19.1800390.

Low compliance with hepatocellular carcinoma screening guidelines in hepatitis B/C virus co-infected HIV-patients with cirrhosis
Willemse S, Smit C, Sogni P, Sarcletti M, Uberti-Foppa C, Wittkop L, Raben D, D'Arminio Monforte A, Dabis F, Van Der Valk M; Hepatocellular Carcinoma Screening Project Working Group for the Collaboration of Observational HIV on behalf of Epidemiological Research Europe (COHERE) In EuroCoord.
J Viral Hepat. 2019 May 28. doi: 10.1111/jvh.13146. [Epub ahead of print]

Emulating a trial of joint dynamic strategies: An application to monitoring and treatment of HIV-positive individuals
Caniglia EC, Robins JM, Cain LE, Sabin C, Logan R, Abgrall S, Mugavero MJ, Hernández-Díaz S, Meyer L, Seng R, Drozd DR, Seage Iii GR, Bonnet F, Le Marec F, Moore RD, Reiss P, van Sighem A, Mathews WC, Jarrín I, Alejos B, Deeks SG, Muga R, Boswell SL, Ferrer E, Eron JJ, Gill J, Pacheco A, Grinsztejn B, Napravnik S, Jose S, Phillips A, Justice A, Tate J, Bucher HC, Egger M, Furrer H, Miro JM, Casabona J, Porter K, Touloumi G, Crane H, Costagliola D, Saag M, Hernán MA
Stat Med. 2019 Jun 15;38(13):2428-2446. doi: 10.1002/sim.8120. Epub 2019 Mar 18.

Longitudinal virological outcomes and factors associated with virological failure in behaviourally HIV-infected young adults on combination antiretroviral treatment in the Netherlands, 2000-2015
Weijsenfeld AM, Blokhuis C, Stuiver MM, Wit FWNM, Pajkrt D; ATHENA observational HIV cohort.
Medicine (Baltimore). 2019 Aug;98(32):e16357. doi: 10.1097/MD.0000000000016357.

Serious clinical events in HIV-positive persons with chronic kidney disease (CKD)
Ryom L, Lundgren JD, Law M, Kirk O, El-Sadr W, Bonnet F, Weber R, Fontas E, Monforte AD, Phillips A, Reiss P, de Wit S, Hatleberg CI, Sabin C, Mocroft A; D:A:D study group.
AIDS. 2019 Aug 2. doi: 10.1097/QAD.0000000000002331. [Epub ahead of print]

Predictors of ischaemic and haemorrhagic strokes among people living with HIV: the D:A:D international prospective multicohort study
Hatleberg CI, Ryom L, Kamara D, De Wit S, Law M, Phillips A, Reiss P, D'Arminio Monforte A, Mocroft A, Pradier C, Kirk O, Kovari H, Bonnet F, El-Sadr W, Lundgren JD, Sabin C for the D:A:D Study Group
E Clinical Medicine EClinicalMedicine. 2019 Aug 11;13:91-100. doi: 10.1016/j.eclinm.2019.07.008.

Other publications

Sexually transmitted infections in the Netherlands in 2018
Slurink IAL, van Aar F, Op de Coul ELM, Heijne JCM, van Wees DA, Hoenderboom BM, Visser M, den Daas C, Woestenberg PJ, Götz HM, Nielen M, van Sighem AI, van Benthem BHB.
RIVM-2019-0007, Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

Presentations

Oral presentations

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

Predictive performance of cardiovascular disease risk equations in people living with HIV
van Zoest RA.
20th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV, New York, USA, 13-14 October 2018

Multimorbidity and risk of death differs by gender in people living with HIV in the Netherlands: the ATHENA cohort study
Wit F, van der Valk M, Gisolf J, Bierman W, Reiss P.
HIV Glasgow 2018, Glasgow, UK, 28-31 October 2018

The impact of M184V/I mutation on the efficacy of abacavir/lamivudine/dolutegravir regimens prescribed in treatment-experienced patients
Olearo F, Nguyen H, Bonnet F, Wandeler G, Stoeckle M, Bättig V, Cavassini M, Scherrer A, Schmid P, Bucher H, Günthard H, Böni J, Yerly S, D'Armino Monforte A, Zazzi M, Bellerive P, Rijnders B, Reiss P, Wit F, Kouyos R, Calmy A.
HIV Glasgow 2018, Glasgow, UK, 28-31 October 2018

HIV in Nederland anno 2018: wat gaat goed, wat kan beter?
van Sighem A, Wit F.
*Congres Soa*Hiv*Seks, Amsterdam, the Netherlands, 23 November 2018*

Introductions and transmission of different HIV-1 subtypes in the Netherlands
Bezemer D.
Amsterdam Cohort Studies meeting, Amsterdam, NL, 14 December 2018

Professor David Cooper Memorial Lecture. Antiretroviral therapy: advances and impact
Reiss P.
21st Bangkok International Symposium on HIV Medicine, Bangkok, Thailand, 16-18 January 2019

ECDC HIV Modelling Tool
van Sighem A.
ECDC/UNAIDS/WHO Regional Workshop for Europe HIV Estimates Workshop, Stockholm, Sweden, 20-22 March 2019

TasP effect from unrestricted DAA access suggested by trends in HCV incidence among the HIV-infected population in care in the Netherlands, on behalf of the ATHENA observational cohort
Smit C.
23rd International Workshop on HIV and Hepatitis Observational Databases, Athens, Greece, 28-30 March 2019

HIV transmission dynamics in the Netherlands – A combined mathematical model and phylogenetic analysis
Bezemer D.
Advanced Diagnostics for Infectious Disease at Molecular Diagnostics Europe, Lisbon, Portugal, 7-8 May 2019

Introductions and transmission of different HIV-1 subtypes in the Netherlands
Bezemer D.
RIVM Meeting on HIV/STI Modelling Bilthoven, the Netherlands, 4 April 2019

Introductions and transmission of different HIV-1 subtypes in the Netherlands
Bezemer D.
AIGHD Research Meeting, Amsterdam, the Netherlands, 1 February 2019

HIV in de regio
van Sighem A.
Eerste GGD-dag "NL naar 0 nieuwe hiv-infecties, Utrecht, the Netherlands, 10 April 2019

Gaten in het hiv-zorgcontinuüm
van Sighem A.
Soa-expertmeeting, Bilthoven, the Netherlands, 21 June 2019

Targeted screening and immediate start of treatment for acute HIV infection decreases time between HIV diagnosis and viral suppression among MSM at a Sexual Health Clinic in Amsterdam
Dijkstra M, van Rooijen MS, Hillebregt MM, van Sighem AI, Smit C, Hogewoning A, Heijman T, Hoornenborg E, Prins M, Prins JM, Schim van der Loeff MF, de Bree GJ, on behalf of the H-TEAM Initiative.
IAS 2019, Mexico City, Mexico, 21-24 July 2019

Poster presentations

The HIV continuum of care in Austria from 2010 to 2016: data and challenges
Leierer G, van Sighem A, Rieger A, Schmied B, Sarcletti M, Ollinger A, Haas B, Egle A, Rappold M, Zangerle R.
HIV Glasgow 2018, Glasgow, UK, 28-31 October 2018

Virologic and immunologic outcomes of integrase inhibitors (INSTIs) in RESPOND
Neesgaard B, Mocroft A, Zangerle R, Wit F , Youle M, Lampe F, Günthard H, Braun D, Necsoi C, De wit S, Law M, Petomenos K, Mussini C, Vincenzo S, Castagna A, d'Arminio Monforte A, Pradier C, Chkhartishvilli N, Tsertsvadza T, Reyes-Urueña J, Vehreschild JJ, Wasmuth JC, Stephan C, Llibre JM, Peters L, Pelchen-Matthews A, Vannappagari V, Gallant J, Greenberg L, Lundgren JD and Ryom Lon behalf of the RESPOND study group.
CROI 2019: Conference on Retroviruses and Opportunistic Infections, Boston, USA, 4-7 March 2019

Impact and determinants of comorbidity clusters in people living with HIV
De Francesco D, Verboeket SO, Underwood J, Wit FW, Bagkeris E, Mallon PWG, Winston A, Reiss P and Sabin CA for the POPPY study group.
CROI 2019: Conference on Retroviruses and Opportunistic Infections, Boston, USA, 4-7 March 2019

Variability in cognitive impairment over time in people with HIV and matched controls
De Francesco D, Sabin CA , Underwood J, Gisslen M, Wit FW, van Zoest RA, Schouten J, Geurtsen G, Schmand B, Portegies P, Reiss P and Winston A for the Co-morBidity in Relation to AIDS (COBRA) collaboration.
CROI 2019: Conference on Retroviruses and Opportunistic Infections, Boston, USA, 4-7 March 2019

Cognitive development in perinatally HIV-infected children on long-term treatment compared to healthy matched controls: a longitudinal cohort study
Van den Hof M, ter Haar AM, Scherpbier J, van der Lee JH, Reiss P, Wit FWNM, Oostrom KJ, Pajkrt D.
CROI 2019: Conference on Retroviruses and Opportunistic Infections, Boston, USA, 4-7 March 2019

HIV infection and risk of recurrent venous thromboembolism: a national cohort study
Rokx C, Borjas Howard J, Smit C, Wit F, Pieterman ED, Cannegieter S, Lijfering W, Meijer K, Reiss P, Bierman W, Tichelaar V, Rijders B.
CROI 2019: Conference on Retroviruses and Opportunistic Infections, Boston, USA, 4-7 March 2019

Estimating population characteristics at the time of acquiring HIV
van Sighem A, Op de Coul E, Reiss P, for the ATHENA national observational HIV cohort.
23rd International Workshop on HIV and Hepatitis Observational Databases, Athens, Greece, 28-30 March 2019

Cost-effectiveness of pre-exposure prophylaxis in MSM with event-driven and daily regimens
Reitsema M, Van Hoek AJ, Xiridou M, Wallinga J, Van Benthem B, Van Sighem A, Schim Van Der Loeff M, Prins M, Hoornenborg E.
STI & HIV 2019 World Congress, Vancouver, Canada, 14-17 July 2019

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 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 HIV. 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 virus infection 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 Vereniging
Dutch HIV association.

Immunological failure
A type of HIV treatment failure. There is no consensus on the definition of immunological failure. However, some experts define immunological failure as the failure to achieve and maintain adequate CD4 counts despite viral suppression.

Interferon
Interferons are naturally-occurring proteins (cytokines) produced by immune cells in response to an antigen, usually a virus. Although they don't directly kill viral cells, they boost the immune response by signalling neighbouring cells into action and inhibiting the growth of malignant cells. There are three types of interferons: alpha, beta, and gamma. Laboratory-made interferons are used to treat certain cancers and opportunistic infections. Addition of polyethylene glycol to interferons prolongs the half-life of interferon. Pegylated interferon alpha is used to treat chronic hepatitis C infection.

Mono-infection
When a person has only one infection.

Mortality
Mortality rate is a measure of the frequency of occurrence of death among a defined population during a specified time period.

MSM
Men who have sex with men.

Nederlandse Federatie Universitair Medische Centra (NFU)
Netherlands Federation of University Medical Centres.

Non-AIDS events
Diseases and clinical events that are not related to AIDS (i.e., that are not listed as being associated with AIDS by the Centers for Disease Control and Prevention) and include conditions such as malignancies, end-stage renal disease, liver failure, pancreatitis, cardiovascular disease.

Non-nucleoside reverse transcriptase inhibitor (NNRTI)
Antiretroviral HIV drug class. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind to and block HIV reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

Nucleoside reverse transcriptase inhibitor (NRTI)
Antiretroviral HIV drug class. Nucleoside reverse transcriptase inhibitors (NRTIs) block reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

Nucleotide
A building block of nucleic acids. DNA and RNA are nucleic acids.

Nucleotide reverse transcriptase inhibitor (NRTI)
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 virologic response (SVR12 or SVR24)
A measure of the response to hepatitis C virus (HCV) treatment. SVR12 or SVR24 indicates an undetectable level of HCV in blood 12 or 24 weeks, respectively, after completion of antiviral therapy for chronic HVC infection.

Sustained viral suppression
The continuous, long-term suppression of a person's viral load (HIV RNA), generally to undetectable levels, as the result of treatment with antiretroviral drugs.

Tolerability
The extent to which a drug's side effects can be tolerated by the patient.

Viraemia
The presence of a virus in the blood.

Virological failure
A type of HIV treatment failure. Virological failure occurs when antiretroviral therapy (ART) fails to suppress and sustain a person's viral load to less than 200 copies/ml. Factors that can contribute to 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 (ART) reduces a person's viral load (HIV RNA) to an undetectable level. Viral suppression does not mean a person is cured; HIV still remains in the body.

VWS
Dutch ministry of Health, Welfare and Sport.

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