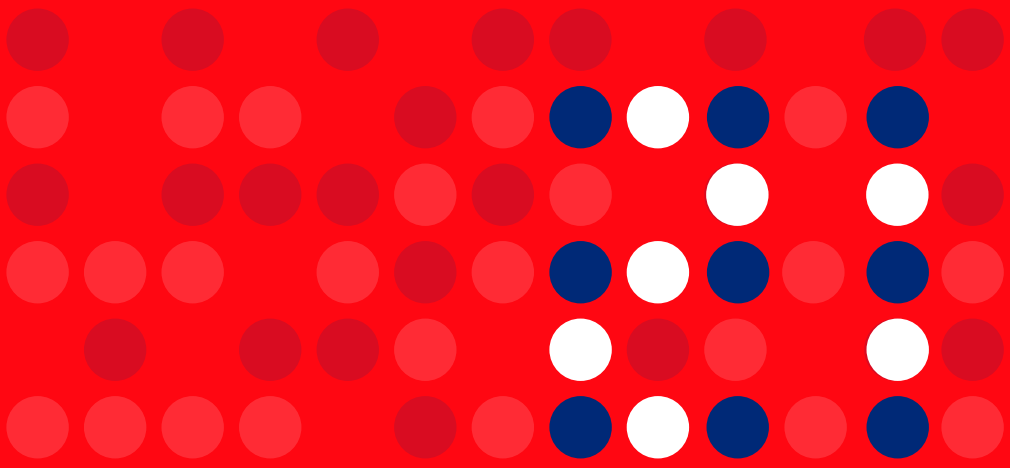
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2021



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

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Monitoring Report 2021

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

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Acknowledgements

Authors: Ard van Sighem, Ferdinand Wit, Anders Boyd, Colette Smit, Amy Matser, Marc van der Valk

Co-authors: Judith Branger, Kees Brinkman, Mark Claassen, Ashley Duits, Suzanne Geerlings, Gonneke Hermanides, Lia van der Hoek, Marije Hofstra, Jeffrey Koole, Neeltje Kootstra, Liesbeth van Leeuwen, Tania Mudrikova, Jeannine Nellen, Kees van Nieuwkoop, Eline Op de Coul, Maria Prins, Peter Reiss, Bart Rijnders, Esther Rooijakkers, Annemarie van Rossum, Berend van Welzen, Anne Wensing, Diederik van de Wetering, Tom Wolfs

Production and support: Sacha Boucherie, Wim Don, Mireille Koenen, Yunka de Waart

For digital copies: www.hiv-monitoring.nl
For printed copies, send email to:
hiv.monitoring@amsterdamumc.nl

Visiting address: stichting hiv monitoring, Tafelbergweg 51, 1105 BD Amsterdam, the Netherlands

Chamber of commerce no. 34160453
Correspondence to: Marc van der Valk, hiv.monitoring@amsterdamumc.nl

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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 2020 the following health institutes were recognized 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 ADRZ (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

In 2020 the following health institutes were recognized as centres for paediatric HIV care:

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

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Introduction

The 2021 Monitoring Report on Human Immunodeficiency Virus (HIV) Infection in the Netherlands is the 20th 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 effects of treatments. It also describes quality of care in HIV treatment centres, and includes special reports on HIV in Curaçao and on the Amsterdam Cohort Studies. Due to the COVID-19 pandemic this year's Monitoring Report also includes a special report on COVID-19.

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 is on course to meet the Joint United Nations Programme on HIV/AIDS (UNAIDS) targets for HIV care for 2025, namely the 95-95-95 goals (95% of people living with HIV know their HIV status, 95% of people who know they have HIV are receiving treatment, and 95% of people on treatment have an undetectable viral load). This year's data show that, in 2020, each of the eight public sexual health surveillance regions reached, or surpassed 90-90-90, with the country as a whole standing at 93-94-95. This means that the Netherlands is also closing in on achieving the national HIV targets of 95-95-95 by 2022. Among men who have sex with men (MSM), the 95-95-95 goal has already been achieved; in 2020, the percentages were 96-96-96. In 2020, the Netherlands reached another important UNAIDS and World Health Organization (WHO) 2020 goal, which stated that the number of new infections should be reduced by at least 75% between 2010 and 2020. SHM data reveal that, in 2020, the number of estimated newly-acquired infections dropped by 82 percent, from 950 in 2010 to 180 in 2020. Among MSM, there was a drop of 91 percent over the same period, from 700 to 60. 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 year 2020 was, due to the COVID-19 pandemic, an unusual year. The national lockdowns and limited access to both centres for sexual health and general practitioners, may have influenced the number of new diagnoses. The years to come will tell what the impact of the COVID-19 pandemic has been. SHM is proud to report that the COVID-19 pandemic did not harm the quality of care for people living with HIV. The data only show a shift from physical consultations to consultations by phone or via internet. Also, people living with a well-controlled HIV, do not appear to be at greater risk of getting a severe Sars-Cov-2 infection than the general population. We do see a higher risk of serious infection in people living with HIV with low CD4 cell counts, and in people with multiple comorbidities.

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

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

Finally, we extend our 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 impacted communities that we can further our insight into the many facets of HIV and HIV treatment. This not only improves the care for people living with HIV in the Netherlands, but also provides guidance for HIV prevention.

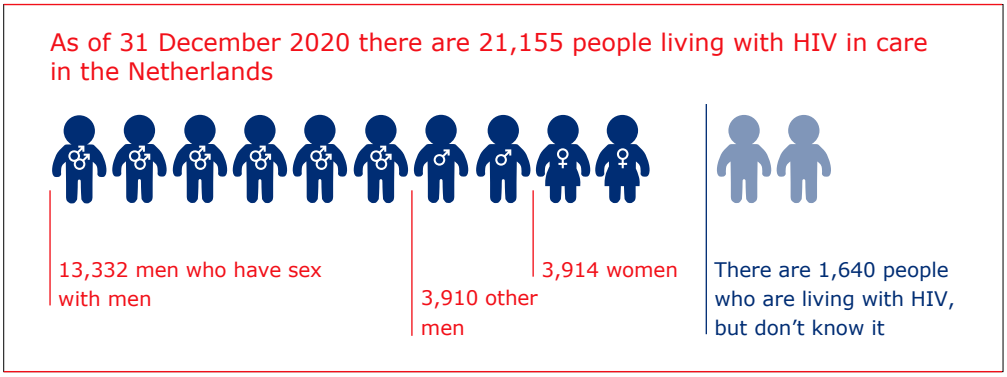
Marc van der Valk MD PhD
Sima Zaheri MSc

Board of Directors, stichting hiv monitoring

Executive summary

The HIV epidemic in the Netherlands in 2020

Figure 1: Number of people living with HIV and in care in the Netherlands in 2020.



The number of people with HIV and in care

As of 31 December 2020, 24,000 people were estimated to be living with HIV in the Netherlands (*Figure 1*). Of those, 21,155 were in care in one of the 24 adult or four paediatric HIV treatment centres.

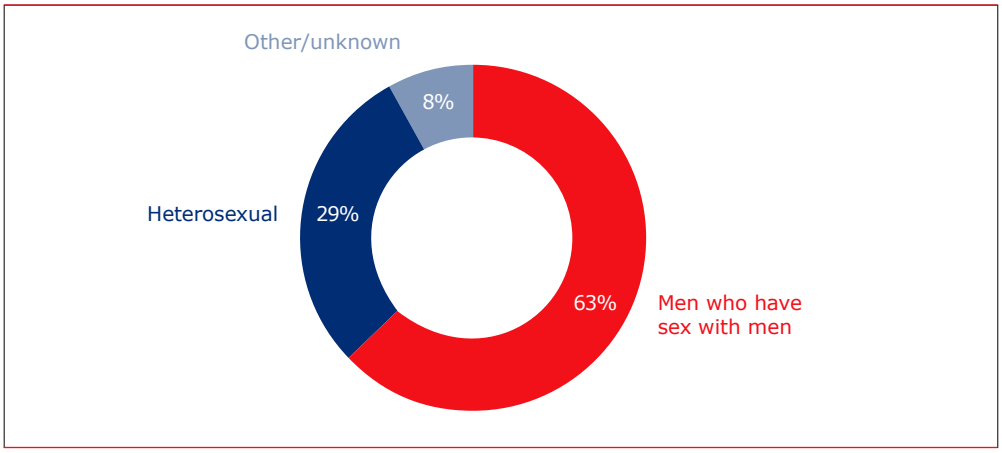
The trend of fewer new HIV diagnoses continued in 2020

Since 2008, the annual number of newly-diagnosed HIV infections has fallen steadily, and this trend continued in 2020. The projected number of new diagnoses for 2020 is 411, compared with 660 in 2018 and 604 in 2019. This means that the Netherlands is on track to meet its national HIV target to halve the number of new diagnoses in 2022, compared with 2015 (when there were 894). In addition, 173 individuals living with HIV who were born abroad arrived in the Netherlands in 2020, with a documented HIV diagnosis prior to arrival.

The majority of new HIV diagnoses continued to be among men who have sex with men

In 2020, the majority (63%) of newly-diagnosed infections were in men who acquired HIV via sex with other men (MSM), while 29% were acquired through heterosexual contact, and 8% through other or unknown modes of transmission (*Figure 2*).

Figure 2: Overview of the newly-diagnosed infections in 2020 divided into transmission groups.



Most people newly diagnosed with HIV had rapid access to specialised care

The majority of people newly diagnosed with HIV in 2020 (95%) entered specialised HIV care within four weeks of their diagnosis. This rate remained similar, regardless of where the diagnosis was made (i.e., hospital, general practice, sexual health centre, or other test location).

The decline in the number of newly-acquired infections continued in 2020

The estimated number of newly-acquired HIV infections has been declining, and reached 180 in 2020; a reduction of 82%, compared with the 2010 figure of 950. This downward trend confirmed that the Netherlands has achieved the UNAIDS fast-track target for 2020 – a 75% reduction in the number of annual, newly-acquired HIV infections, compared to 2010. Among MSM, the number of newly-acquired HIV infections fell by 91%, from 700 in 2010 to 60 in 2020, surpassing the UNAIDS target.

Late diagnosis remains a problem that needs attention

Many people are diagnosed with late-stage HIV infection; in other words, with an already markedly-impaired immune system (CD4 count below 350 cells/mm^3) or even AIDS. In 2020, this was the case for 42% of MSM, 71% of other men, and 67% of women. Although newly-diagnosed MSM had the lowest proportion of late-stage HIV infections, they accounted for 103 (50%) of all 205 individuals diagnosed with late-stage HIV in 2020.

Early diagnosis occurred mainly among MSM

Although diagnosis with late-stage HIV infection is common, a considerable proportion of people receive their HIV diagnosis early in the course of their infection. In total, 33% of MSM diagnosed in 2020 had a previously negative HIV test at most 12 months before diagnosis; these proportions remained much lower in other men (8%) and in women (9%).

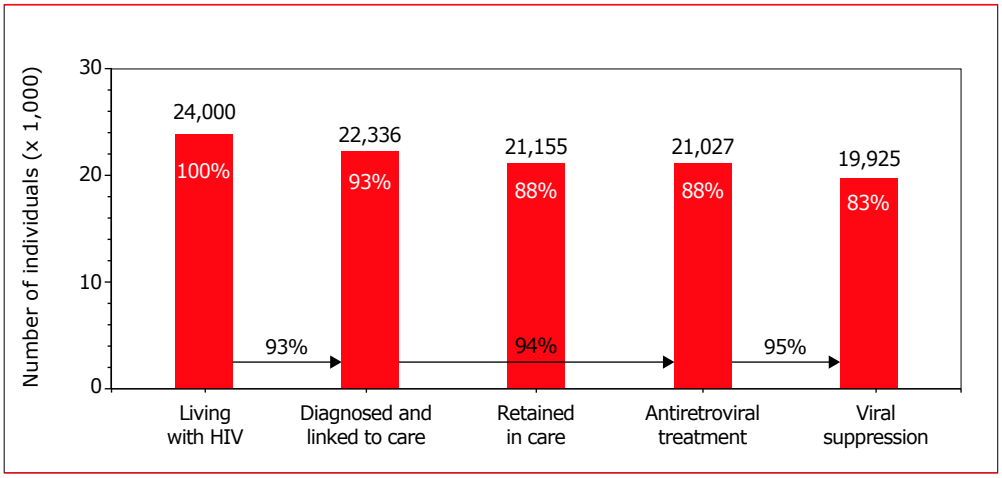
Continuum of HIV care in 2020: 93–94–95 – the Netherlands is on course to meet targets

One of the key goals of HIV treatment is to achieve viral suppression. The steps involved in reaching suppression are illustrated in a continuum of HIV care, which also gives a measure of progress towards achieving the UNAIDS 95-95-95 goals for HIV care by 2025.

The continuum of care for the Netherlands in 2020, confirmed that each of these goals is within reach (93-94-95, see *Figure 3*). The Netherlands is also closing in on achieving the national HIV targets of 95-95-95 by 2022.

- By the end of 2020, 24,000 individuals were estimated to be living with HIV, of whom an estimated 1,640 were still undiagnosed.
- In total, 22,336 of the 24,000 (93%) 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 (21,027; 94%), had started antiretroviral treatment, and 19,925 of those (95%) had achieved viral suppression.
- Overall, 83% 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 2020.

Figure 3: Continuum of HIV care for the total estimated population living with HIV in the Netherlands by the end of 2020, based on UNAIDS 95-95-95 goals for 2025: 93-94-95.



All STI surveillance regions closing in on the 95-95-95 targets

In 2020, all eight STI surveillance regions in the Netherlands were closing in on UNAIDS's 95-95-95 targets for 2025. The proportion of people living with HIV with a suppressed viral load, including those remaining undiagnosed, varied between 81% and 85%. More than half (54%) of all people estimated to be living with HIV were in Noord-Holland/Flevoland and in Zuid-Holland Zuid.

Many people with HIV live in the four largest cities

In total, 10,370 (43%) people with HIV were estimated to be living in the four largest cities (Amsterdam, Rotterdam, Den Haag, and Utrecht) in 2020. Of these 10,370 individuals, it was estimated that 560 have yet to be diagnosed.

The figures for the Netherlands are impressive compared with other parts of the world. Nonetheless, in 2020, there were 411 new diagnoses and an estimated 1,640 people who remained undiagnosed. To achieve a significant further 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 (cART).

Information on the prior use of pre-exposure prophylaxis (PrEP) is now being collected
SHM has started collecting PrEP-related data from the electronic medical records (EMRs) of individuals newly diagnosed with HIV and first entering care: this information was retrospectively collected for individuals who newly entered care between January 2018 and June 2019. By July 2021, data had been collected for 1,987 individuals.

In 1,545 (77.8%) EMRs, no mention was made about prior use of PrEP, whereas in 442 (22.2%) EMRs, information was available on prior use of PrEP. The proportion of individuals for whom information on prior use of PrEP was available increased from 9.3% in 2018, to 24.8% in 2019, to 32.2% in 2020, to 52.8% in the first half of 2021.

Of the 442 individuals for whom information on prior use of PrEP was available, 60 (13.6%) were men who reported prior use of PrEP.

- 52/60 (86.7%) reported that their most likely route of HIV acquisition was through sexual contact with other men.
- 31/60 (51.7%) obtained PrEP through a healthcare provider in the Netherlands, 11 (18.3%) through a buyers club / internet / store outside of the Netherlands, six (10.0%) through a healthcare provider outside of the Netherlands, and two (3.3%) from a friend living with HIV who donated some of his own medication. For 10 men no information was available.
- Regular periodic medical check-ups while using PrEP were performed in 31/60 (51.7%) of the cases, no check-ups were done in eight (13.3%), and for 21 (35.0%) men no information was available.
- For 37/60 (61.7%), it was reported that they had used PrEP after the last negative HIV test performed while using PrEP.

For 38 (63.3%) of the men who reported using PrEP when first entering HIV care, a genotypic resistance test was done. Resistance-associated mutations (M184V/I), possibly associated with the use of the antiretroviral agents that had been used as PrEP, were detected in seven of these 38 men (18.4%). Six of these seven men obtained their PrEP through a Dutch healthcare provider, and all seven men reported that they had continued to use PrEP after their last negative HIV test performed while using PrEP. All of these seven men started cART containing an integrase inhibitor, and six of them achieved full viral suppression. These data underscore the importance of (continued) access to formal PrEP services, including regular monitoring while on PrEP, for all those who need it. SHM will continue to work with the HIV treatment centres to collect information on prior use of PrEP in all individuals newly entering care.

COVID-19 in people living with HIV in the Netherlands

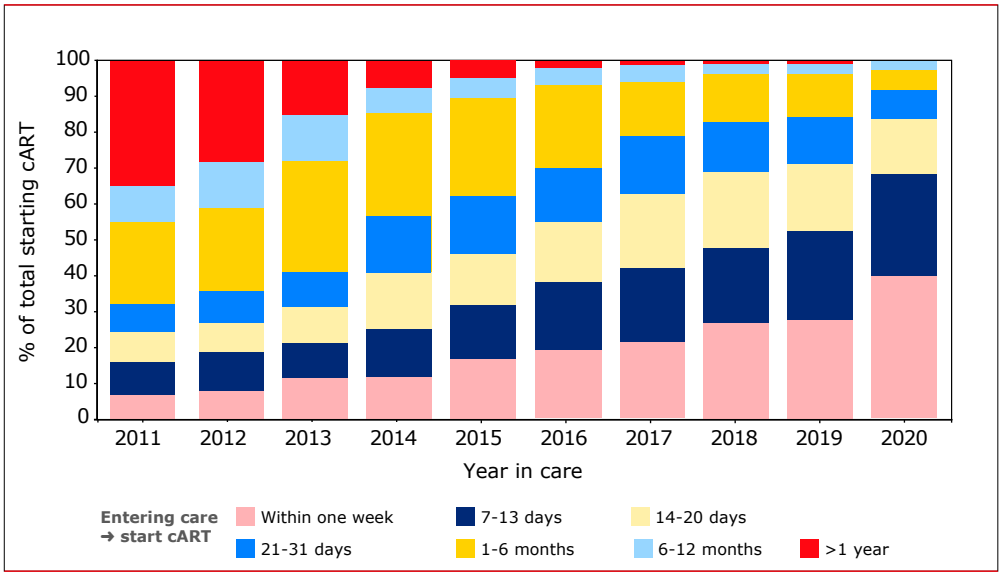
We recorded 1,308 COVID-19 events in people living with HIV in the Netherlands in the period prior to 6 September 2021. In total, 109 (8.3%) individuals were hospitalised, with 18/109 (1.4%) requiring ICU admission. Independent risk factors for hospitalisation for COVID-19 among people living with HIV were higher age, migrant status (with higher risk in individuals originating from sub-Saharan Africa or, to a lesser extent, from Latin America), obesity (BMI over 30 kg/m^2), having a current CD4 cell count below 500 cells/mm^3 (the risk was even higher when the CD4 cell count was below 200 cells/mm^3), and having had a prior AIDS-defining Illness.

In total, 19 (1.4%) of the 1,308 people living with HIV diagnosed with SARS-CoV-2 were reported to have died as a direct result of COVID-19. The observed mortality rates in people living with HIV diagnosed with COVID-19 were very low in those aged below 50 years. In the older age strata, the mortality rates quickly increased. In those hospitalised for COVID-19, the observed mortality rate was 11.0%, in those admitted to the ICU, it was 27.8%. However, in all age groups, mortality strongly clustered in individuals who either had multiple general risk factors (i.e., comorbidities), or those with poorer responses on ART (i.e., a low current or nadir CD4 cell count, a prior AIDS-defining condition, or a plasma HIV-1 viral load above 200 cps/ml). Furthermore, migrants born in sub-Saharan Africa or Latin America (including the Caribbean) appeared to be at increased risk of hospitalisation and death independent of age, comorbidities and HIV-related parameters.

Combination antiretroviral therapy (cART) in adults

The period between people being diagnosed with HIV and entering care, and starting combination antiretroviral therapy (cART), continues to decline. In 2020, 92% of people started cART within one month of entry into care, and 98% did so within six months of entry into care. Importantly, this was the case, irrespective of their CD4 cell count at entry into care.

Figure 4: Time between entry into care and starting combination antiretroviral therapy (cART) for those starting cART in 2011–2020.



Legend: cART=combination antiretroviral therapy.

Most common cART regimens in 2020

Initial regimen

Of the people who started cART in 2020, 84% received a regimen containing an integrase inhibitor; the most frequently prescribed were tenofovir alafenamide/emtricitabine/bictegravir and tenofovir disoproxil/emtricitabine/dolutegravir.

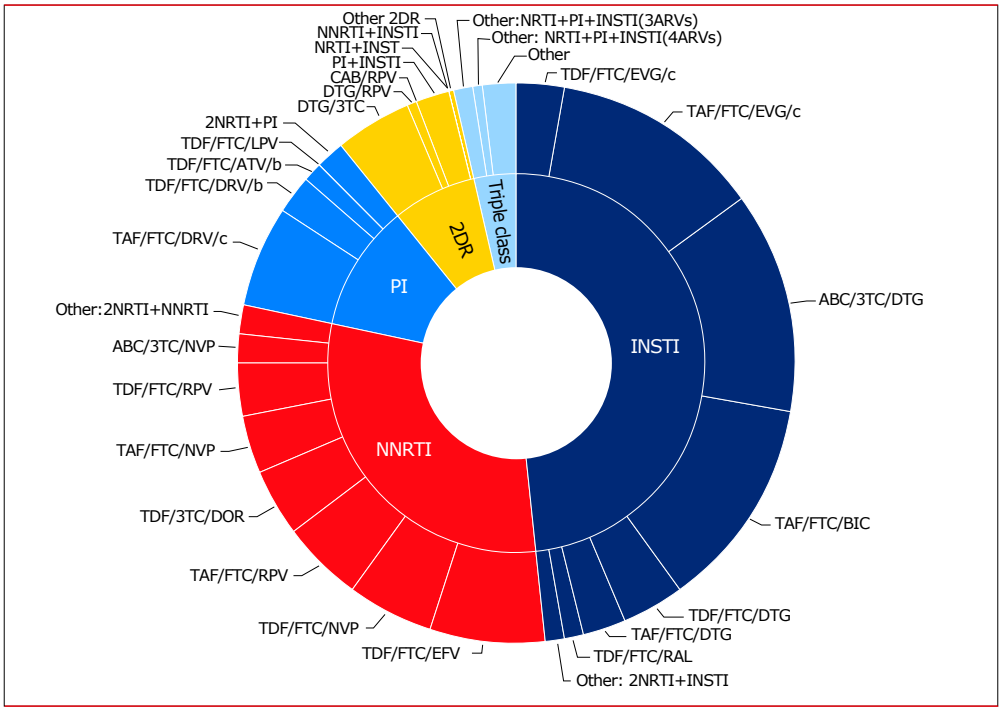
Compared to the first decade of the cART era, discontinuation of the initial regimen has become less common over time. In the past decade, the discontinuation rate has remained stable. However, the reasons for switching have continued to change, with virological failure a very rare event nowadays. In recent years, many switches were driven by the wish for regimen simplification and pre-emptive modifications because of the availability of new regimens that are perceived to have better long-term safety profiles.

The use of integrase inhibitor–based cART has been rising among all individuals living with HIV

Integrase inhibitor-based cART continues to be further implemented on a large scale in the Netherlands: in 2020, 58% of all adults in care and on cART received an integrase inhibitor, compared to 39% in 2017, 46% in 2018, and 50% in 2019. Thirty-one percent of the population on cART in 2020 received a backbone containing tenofovir disoproxil; new fixed-dose combinations have also led to an increase in the use of tenofovir alafenamide (44%), while the use of abacavir (17%) has decreased.

Among all individuals living with HIV in care and on treatment in 2020, the majority (89.4%) received a cART regimen based on two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with an integrase inhibitor (48.4%), a non-NRTI (NNRTI, 30.0%), or a protease inhibitor (PI, 10.9%) (*Figure 5*). The most commonly-prescribed regimens in 2020 were abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (12.7%), tenofovir alafenamide (TAF)/FTC/bictegravir (BIC) (12.3%), tenofovir alafenamide (TAF)/FTC/elvitegravir (EVG)/cobicistat (12.3%), tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/efavirenz (EFV) (6.8%), and tenofovir alafenamide (TAF)/emtricitabine (FTC)/darunavir (DRV)/cobicistat (5.9%). Dual regimens mostly consisting of one Integrase strand transfer inhibitors (INSTI), plus either one PI, one INSTI or one NNRTI, were used by 7.3% of all individuals living with HIV in care and on treatment in 2020.

Figure 5: Combination antiretroviral therapy (cART) use in 2020.



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; DOR=doravirine; 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.*

Virological response was excellent, 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 2020, 98% had achieved viral suppression (viral load below 200 copies/ml).

Changing cART landscape

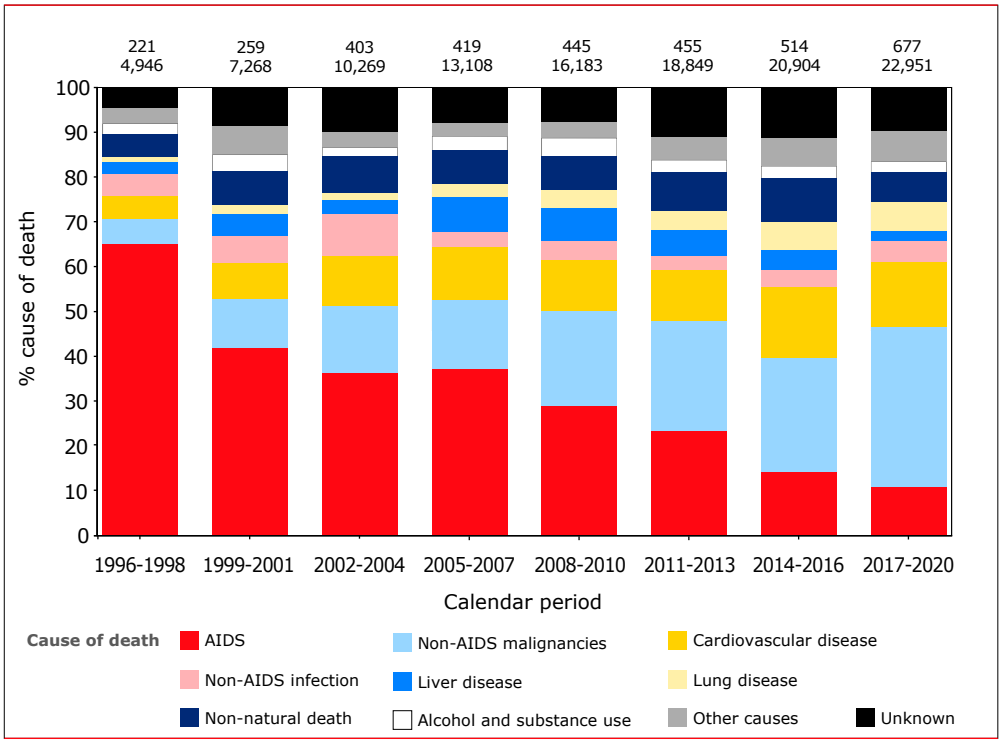
Following revised HIV treatment guidelines, prompt cART initiation continued to become more common in 2020. In recent years, the introduction of new, integrase inhibitor-based, once-daily, fixed-dose combinations has changed the landscape of cART use in the Netherlands. All currently-recommended regimens are durable.

Morbidity and mortality

The downward trend in AIDS-related deaths continued in 2020

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*).

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.*



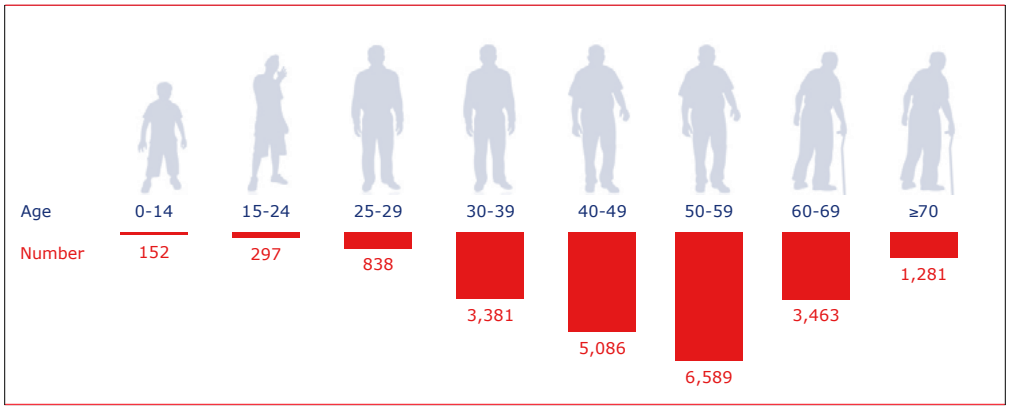
Legend: *cART=combination antiretroviral therapy.*

Ageing and comorbidities

The reported number of AIDS-related deaths remained relatively stable at around 20 cases per year between 2016 and 2020. Those that did occur, were largely driven by late entry into care. This once again stresses the importance of identifying and linking individuals to care earlier in the course of their infection. Otherwise, achieving the national HIV target of zero AIDS-related deaths by 2022 is unlikely to be achieved.

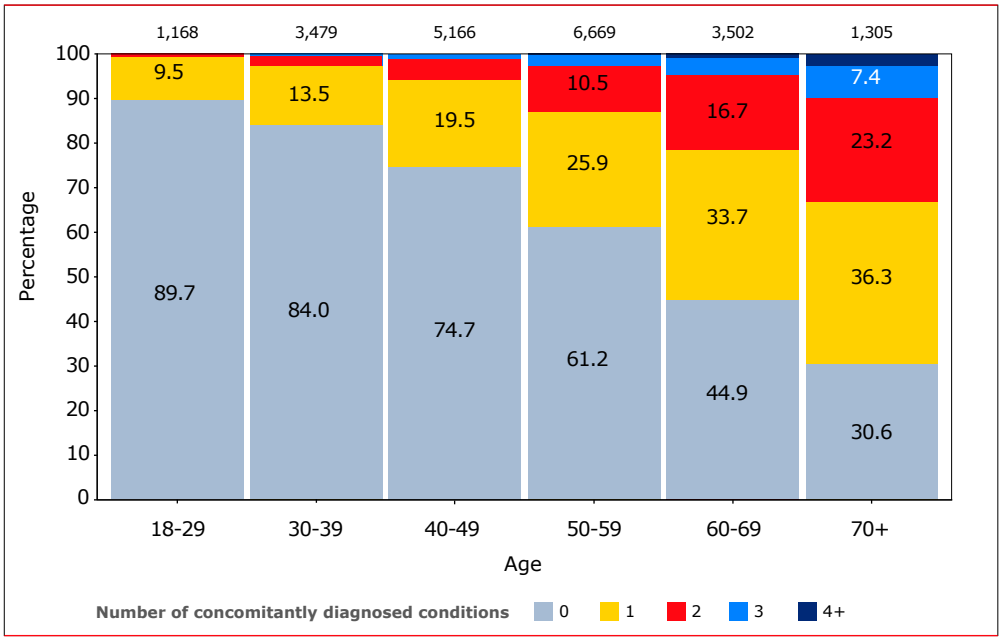
A substantial proportion of the people who were newly diagnosed with HIV and entered HIV care in 2020, were older individuals; 26% were 50 years or older. The overall population of people with HIV in care in the Netherlands also continues to age, with 54% older than 50 years on 31 December 2020 (*Figure 7*).

Figure 7: *Age distribution of people living with HIV and in care in the Netherlands in 2020.*



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 was the rising proportion of individuals with multiple comorbidities, the risk of which is known to be greater in those with HIV (*Figure 8*).

Figure 8: Prevalence of non-HIV/AIDS multimorbidity in adults in HIV care in 2020. Numbers on top of the bars represent the number of individuals contributing data to that age category.



The data showed only a slight increase in cardiovascular risk

As a result of the increasing average age of the population living with HIV, the proportion at high cardiovascular risk continued to slowly increase in 2000-20. However, age-standardised incidence rates of cardiovascular diseases have continued to decline over the years. 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 remained stable

The most common non-AIDS malignancies are lung, haematological, gastro-intestinal, anal, prostate, and head and neck cancers. Non-AIDS malignancies are now the most important cause of death in people living with HIV. The crude incidence rate of non-AIDS malignancies in the Netherlands is slowly increasing

over time. However, when the increasing age of the population living with HIV is taken into account, we observed 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 of 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 people living with HIV. This is particularly relevant for older individuals and those at increased risk of comorbidity.

Viral hepatitis 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 individuals living with HIV 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 individuals living with HIV.

Approximately 11% 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 their first diagnosis. Most individuals with HCV infection were male and from the Netherlands or other European countries.

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.

Hepatitis D virus screening in individuals with hepatitis B virus is low
Guidelines from the European Association for the Study of the Liver recommend that any individual with chronic HBV infection should be screened for hepatitis D virus (HDV). Despite these recommendations, only 13% of individuals with HBV infection had been tested for HDV infection by 2020. Attempts should be made to identify individuals with HDV, considering that more effective medication to treat this infection is increasingly available.

HBV vaccination remains a priority
An estimated 42% of individuals living with HIV in the Netherlands had not been exposed to HBV and had not been successfully vaccinated by the end of 2020. Of these, 18% were not taking a cART regimen including tenofovir or tenofovir alafenamide and thus remained at risk of acquiring HBV. Efforts to increase successful HBV vaccination rates, particularly in those who are not receiving tenofovir-containing cART, are essential for protecting individuals from HBV infection, as stated in the 2022 national HIV targets.

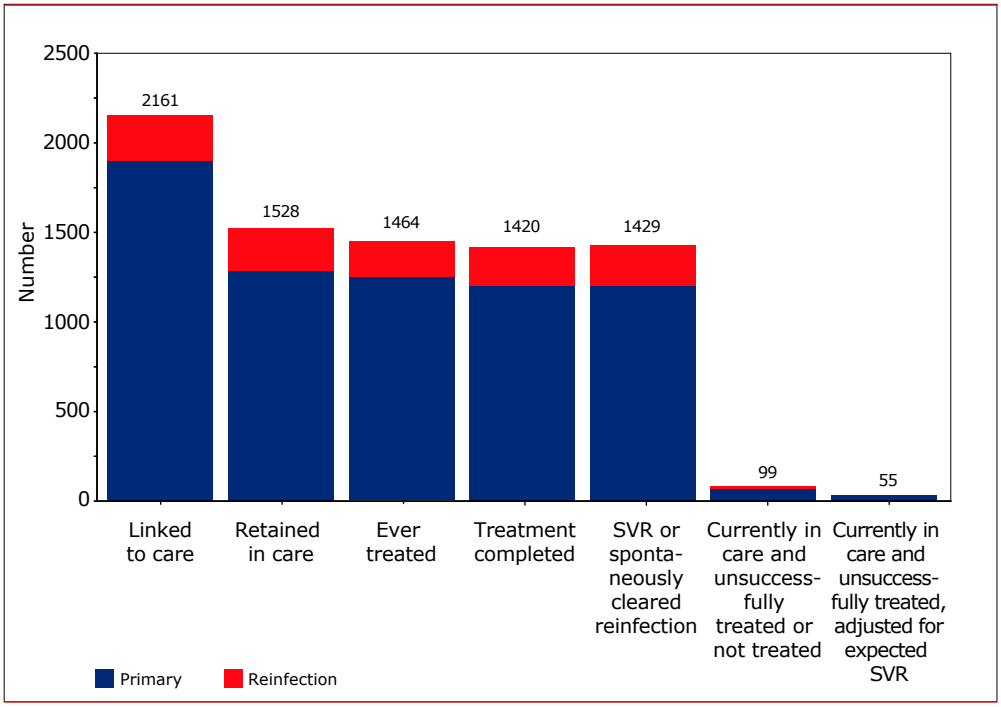
Risk of dying from HCV or HBV co-infection continued to decrease

Overall, individuals living with HIV and a chronic HCV or HBV co-infection, remain at increased risk of liver-related morbidity and mortality. However, since 2010, the risk of people diagnosed with chronic HCV or HBV dying a liver-related death has steadily decreased. 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 individuals living with HIV with HCV co-infection have now received effective treatment for HCV. By 31 December 2020, over 1,100 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. When retreatment was taken into account, the sustained virological response after the last course of treatment was 99%. These developments have resulted in a low number of HCV co-infected individuals in need of treatment (*Figure 9*).

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 incidence of acute HCV infections observed in the recent years, together with the rapid decline in the prevalence of active HCV infections. In MSM, the prevalence of active HCV infections decreased to 0.29% in 2020. 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 completely ceased.

Regular HCV screening among sexually-active MSM is recommended
Effective HCV treatment will limit the impact of HCV co-infection on long-term, liver-related morbidity and mortality; however, this effect should be monitored. To further 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. Such measures are key if we are to achieve the 2022 national HIV target of optimally protecting individuals at risk of being infected with HCV.

Hepatitis A virus testing and immunity

Fifty-six percent of individuals living with HIV ever registered in the SHM database have been screened for HAV (hepatitis A). Of those screened, 67% had a positive anti-HAV antibody test result (i.e., protected against HAV through vaccination or from prior infection), and this percentage was comparable across transmission groups. Of note, among MSM living with HIV under the age of 40, 43% of those who had been screened did not have anti-HAV antibodies. Given the European-wide outbreak of HAV among sexually-active MSM in 2017, these individuals should be prioritised for HAV vaccination.

Pregnancies among women living with HIV in the Netherlands

In total, 562 pregnancies were documented in 429 women receiving HIV care in the Netherlands in 2016-20. Of these women, 72% were born outside the Netherlands, mainly in sub-Saharan Africa (63%). The most common mode of HIV acquisition was heterosexual contact (90%).

Pregnant women may fail to have undetectable HIV RNA at the time of delivery

All women were treated with antiretroviral therapy during pregnancy. As a result, maternal HIV RNA levels were below 50 copies/ml (i.e., undetectable) in 96% of the deliveries, and between 50-500 copies/ml in a further 3% of deliveries. However, a number of women had detectable HIV RNA levels around the time of delivery. Almost half of them were only newly diagnosed with HIV during the course of their pregnancy, and therefore started treatment later during their pregnancy. This reinforces the importance of close monitoring of women newly diagnosed with HIV during pregnancy.

Perinatal transmission of HIV is now very rare in the Netherlands

Due to the high rates of successful treatment in women living with HIV, perinatal transmission of HIV was rare in the Netherlands between 2016 and 2020. In the Netherlands, in women who receive treatment, the rate of vertical transmission was 0.27%.

Viral suppression rates during the post-partum period were suboptimal

Following changes to treatment guidelines in 2015, it is now recommended that all pregnant women continue cART after delivery. Nonetheless, of the women who continued using antiretroviral therapy after delivery between 2016-20, 11% had at least one detectable HIV RNA measurement in the year following delivery. Of these women, 34% had more than one detectable HIV RNA measurement. This may reflect poorer treatment compliance during the post-partum period.

Additonal support

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.

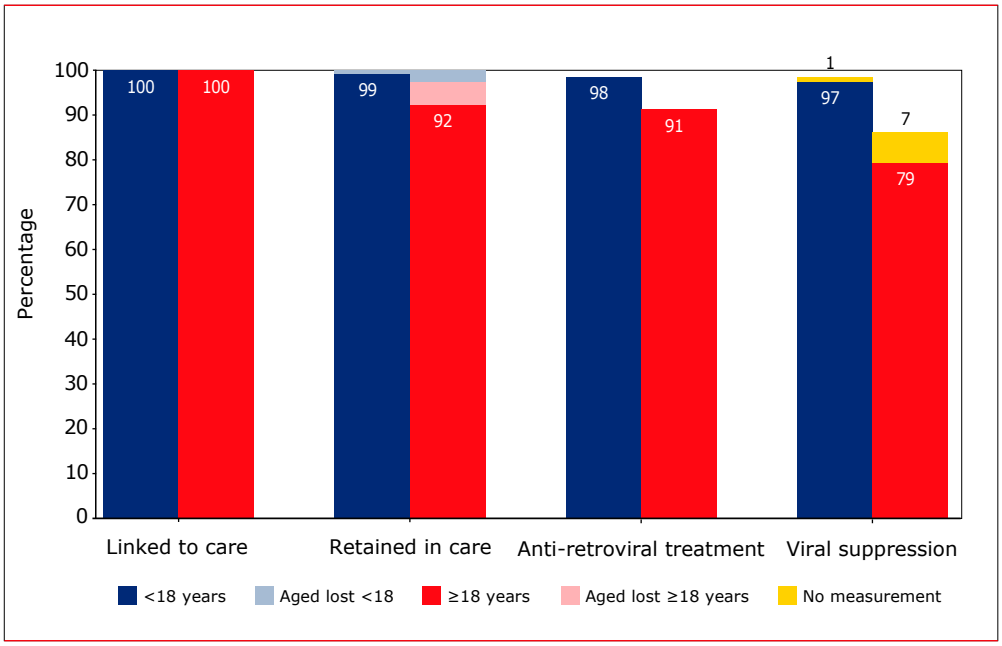
Children living with HIV

Of 393 children who were diagnosed with HIV below the age of 15 years, and who entered care in the Netherlands before they were 18 years, 338 (86%) remained in care and 178 were under the age of 18 by the end of 2020. Of the children who were in care and under 18 years of age, 136 (76%) were born outside the Netherlands and had been adopted by Dutch parents.

Outcomes for children living with HIV were generally favourable

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

Figure 10: Continuum of care by age, as of 31 December 2020. The numbers in and above the bars indicate the proportion of individuals.



Poorer viral suppression rates were seen around the time of transition to adult care

Of the individuals who were originally registered as a child, 86% were still in care in 2020, and 41% of these were over the age of 18 years by 31 December 2020. Of the children who transitioned from paediatric to adult care, 20% had an HIV RNA level above 200 copies/ml at the time of transition, suggesting challenges for these adolescents with respect to treatment adherence.

Optimisation of long-term care for adolescents and young adults

The large proportion of adolescents with inadequately-suppressed viraemia around the time of transitioning to adult care, illustrates that long-term care for this particularly vulnerable group of young individuals can be further optimised.

Quality of care

Retention in care has been improving

For many centres, short-term retention has been high for individuals entering care. Overall retention has also witnessed a median increase of 12% over the past five years, even in 2020, when the COVID-19 pandemic began. Nevertheless, the overall retention rate for non-Dutch MSW and non-Dutch women in 2020, was considerably lower than other groups after adjusting for age. The reasons for this finding are unclear.

Earlier start of cART and high rates of viral suppression

Across most centres, people started 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 their CD4 count. In fact, a median of 97% and 98% of all patients who entered care in 2018 and 2019, respectively, and who were retained in care in 2020, had initiated cART, while across all centres, more than 95% of patients in care in 2020 were on cART.

Viral suppression rates in the first six 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 there.

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 (*Nederlandse Vereniging van HIV Behandelaren*, NVHB). We also compared each centre's indicator to the national average, in a manner that took into account the diverse mix of patient geographical origins and modes of HIV transmission found across centres.

In all centres, the proportion of patients in care in 2020, who had initiated cART and had viral suppression, were high and within the expected range of the national average.

Impact of the COVID-19 pandemic

The COVID-19 pandemic did not appear to substantially affect continuing care across centres in the Netherlands. No centre saw a decrease in overall retention of more than 2% between 2020 and 2019, even though centres were more commonly opting for consultations via telephone or email than for physical consultations. Nevertheless, among individuals in care in 2020, there was a decrease of more than 5% in plasma HIV RNA testing in two centres and a decrease of more than 5% in CD4 cell count testing in 11 centres.

Amsterdam Cohort Studies

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS were initiated 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.

By 31 December 2020, 2,901 MSM had been included in the ACS, of whom 607 were HIV-positive when they entered the study, and 263 seroconverted during follow up. In 2020, 699 HIV-negative and 53 MSM living with HIV remained in active follow up at the *Gemeentelijke Gezondheidsdienst Amsterdam* (GGD Amsterdam). In 2020, two new HIV-negative MSM, who were 28.7 and 48.4 years of age at inclusion, were recruited. The median age of the total group of MSM in active follow up was 44.5 (interquartile range [IQR] 34.0-55.9) years at their last cohort visit. The majority were born in the Netherlands and were residents of Amsterdam (83.4% and 88.8%, respectively). In total, 77.2% of the participants had a college degree or higher. In 2020, none of the MSM participating in the ACS seroconverted for HIV; consequently, the observed HIV incidence was 0 per 100 person years.

HIV in Curaçao in 2020

Over the years, an increasing proportion of individuals with HIV in care at the Curaçao Medical Center in Willemstad (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 remained high.

Monitoring programme report

1. The HIV epidemic in the Netherlands

Ard van Sighem, Eline Op de Coul, Ferdinand Wit

Key findings

- In 2020, 24,000 people were estimated to be living with HIV in the Netherlands.
- The estimated number of people living with an undiagnosed HIV infection decreased from 3,950 in 2010 to 1,640 in 2020, a reduction of 59%.
- The estimated annual number of newly-acquired HIV infections, using the ECDC HIV Platform tool, decreased from 950 in 2010 to 180 in 2020, a reduction of 82%. During the same period, the number of newly-acquired infections among men who reported sex with men as most likely mode of transmission (MSM) fell by 91%, from 700 in 2010 to 60 in 2020.
- Of the approximately 411 people with an HIV diagnosis in 2020, 258 (63%) were MSM and 119 (29%) were men and women who acquired their HIV through heterosexual contact.
- In 2020, 26% of all people newly diagnosed were aged 50 years or older at the time of diagnosis; 9% were between 15 and 24 years of age. Of the 21,087 HIV-1-positive people in care by the end of 2020, 54% were 50 years or older and 22% were 60 years or older.
- Of the 442 individuals for whom information on prior use of pre-exposure prophylaxis (PrEP) was available, 60 (13.6%) reported prior use of PrEP, and 382 (86.4%) did not.
- For 38 (62.1%) men who reported having used PrEP when first entering HIV care, a genotypic resistance test was done; a 184V mutation was found in seven (19.4%).
- In total, 24% of the people newly diagnosed in 2018 or later, were diagnosed within 12 months of HIV infection; in MSM, this proportion was 34%.
- From 2018 onwards, 776 (50%) individuals were diagnosed with late-stage HIV infection: 401 (41%) MSM, 229 (68%) other men, and 146 (61%) women; these proportions have barely changed over the past decade.
- Among those diagnosed in 2018 or later, late-stage HIV was seen in 52% of MSM, 81% of other men, and 77% of women diagnosed at 50 years of age or older, compared with 24% of MSM, 50% of other men, and 41% of women diagnosed below the age of 25 years.

Introduction

As of May 2021, 31,921 individuals with HIV had been registered by stichting hiv monitoring (SHM). Following registration, further clinical data were collected for 31,120 (97.5%) of the individuals; the remaining 801 (2.5%) objected to the collection of their data. Among the 31,120 individuals with clinical data, 30,015 were registered with one of the HIV treatment centres in the Netherlands (*Figure 1.1*) and 1,306 were registered with the Curaçao Medical Center in Willemstad, Curaçao (see *Chapter 9*); 201 people were registered both in the Netherlands and in Curaçao.

Of the 30,015 people registered in the Netherlands, the majority were diagnosed with HIV-1 (28,745; 96%). A small group of people, 101 in total, were diagnosed with HIV-2, while 63 people had antibodies against both HIV-1 and HIV-2. Serological results were not available in the SHM database for 1,106 individuals; most of these people were registered before the official start of the AIDS Therapy Evaluation in the Netherlands (ATHENA) study, so only limited data were collected on them.

The first part of this chapter focuses on the characteristics of HIV-1-positive individuals at the time of diagnosis and on HIV-1-positive individuals who were still in care at the end of 2020. New in this year's report is a brief overview of HIV-1-positive trans people. The chapter concludes by briefly considering the HIV-2-positive population.

Box 1.1: Infection, diagnosis, entry into care, and registration.

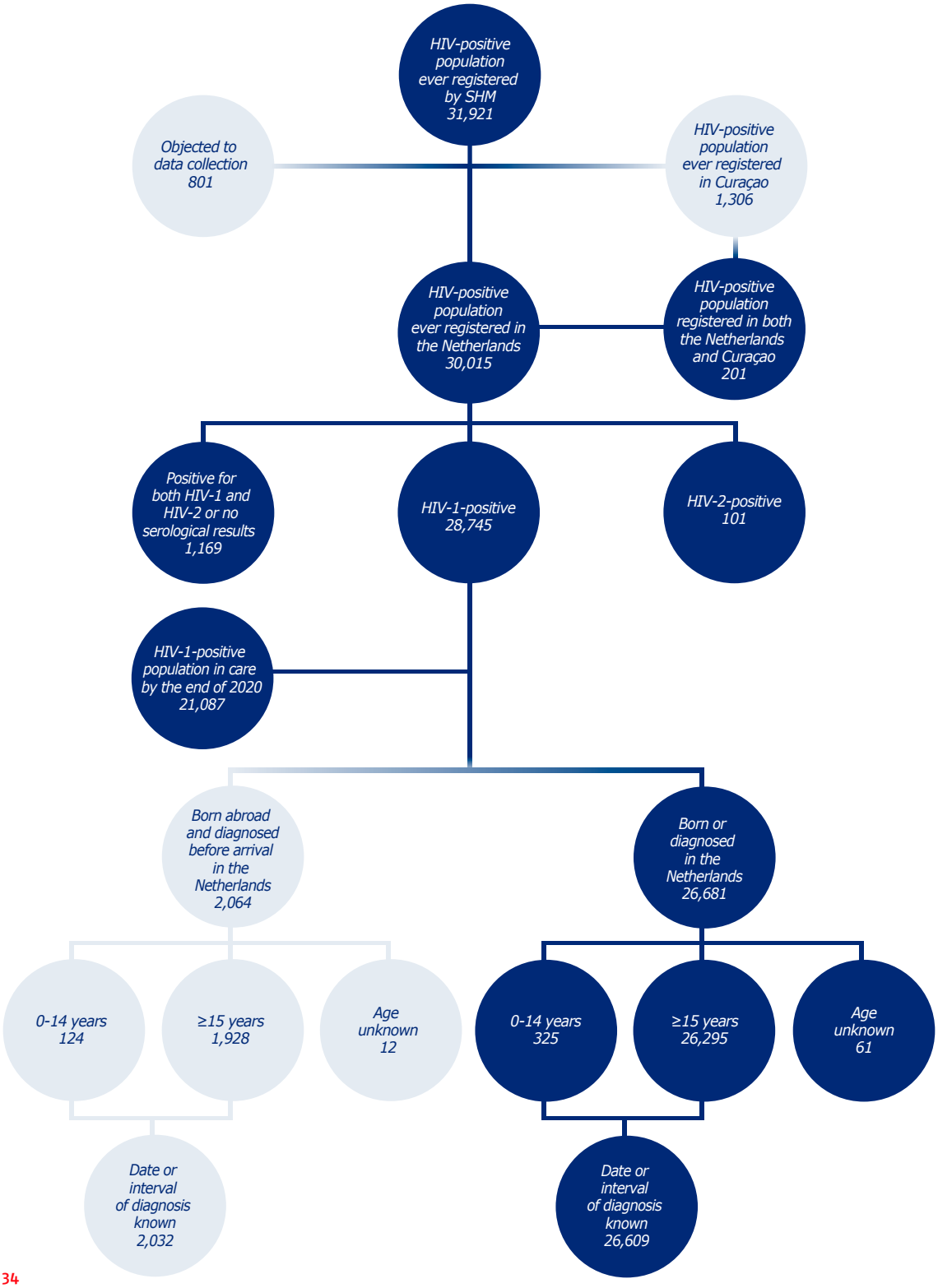
Infection	The moment an individual acquires HIV. The time of infection is often unknown.
Diagnosis	The moment an individual is newly diagnosed with HIV. The time of diagnosis can be weeks, months, or years after infection.
Entry into care	The moment an individual living with HIV is first seen for care in an HIV treatment centre, which is usually within a few weeks of HIV diagnosis.
Registration	The moment an individual with HIV in care is reported to SHM by their treating HIV physician or nurse and is 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 individual living with HIV is registered with SHM.

HIV-1

Individuals living with HIV-1

Of the 28,745 individuals in the Netherlands who were ever diagnosed with HIV-1, 2,064 (7%) were born abroad and had a documented HIV diagnosis prior to arrival in the Netherlands (*Figure 1.1*). These 2,064 individuals have been excluded from the analyses on newly-diagnosed individuals later in this section. The remaining 26,681 individuals were newly diagnosed while living in the Netherlands, or their date of arrival in the country has not yet been recorded in the SHM database.

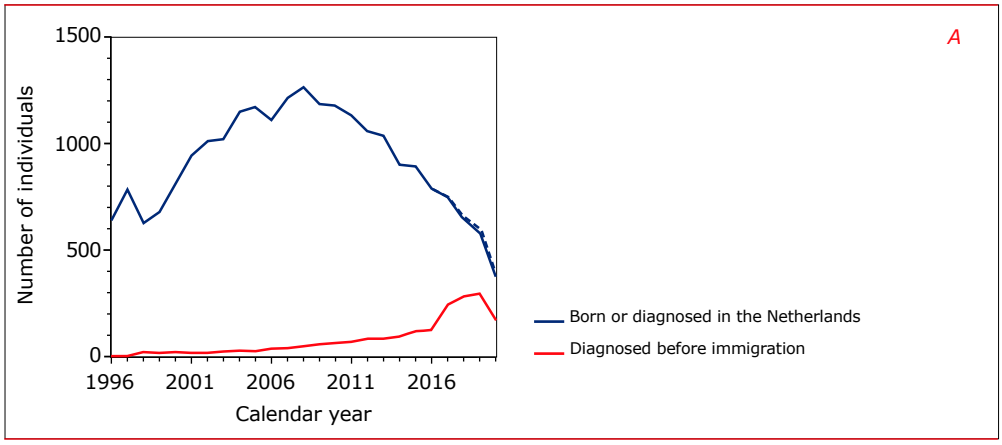
Figure 1.1: *Overview of the population with HIV registered by stichting hiv monitoring (SHM) at the end of 2020.*

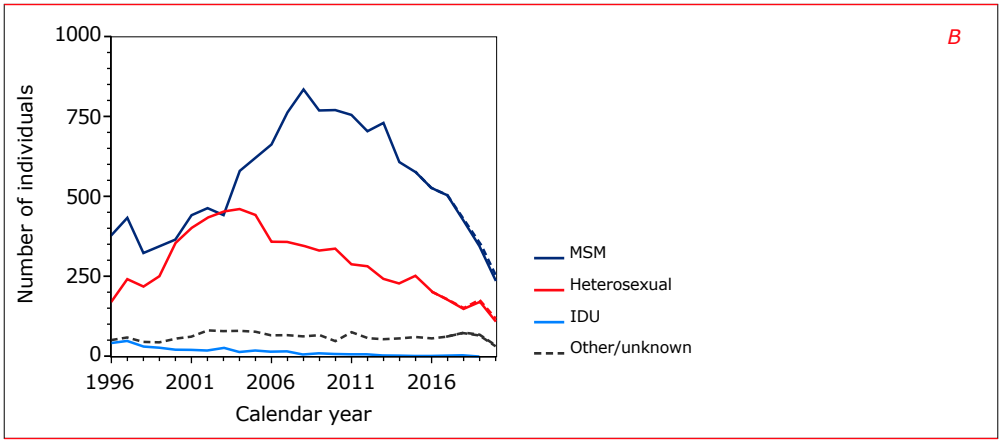


Individuals diagnosed before arriving in the Netherlands

In total, 2,064 individuals who were born abroad had a documented HIV-1 diagnosis before arriving in the Netherlands; 763 arrived in the Netherlands in 2018 or later (*Figure 1.2A*). So far, SHM has registered 173 migrants who arrived in 2020. Information on diagnosis abroad and date of arrival in the Netherlands has been recorded for all newly-registered individuals since early 2018, but is not yet available for everyone included in the SHM database. So far, retrospective data collection has prioritised people with an HIV diagnosis in 2010 or later. As a result, information on pre-arrival diagnosis was available for 71% (3,311) of migrants diagnosed in 2010 or later compared to 63% in last year's report[1]; this percentage falls to 33% (2,797) for those diagnosed before 2010, compared to 18% last year.

Figure 1.2: *(A) Annual number of individuals newly diagnosed with HIV-1 in the Netherlands (by year of diagnosis) or with documented diagnosis abroad before moving to the Netherlands (by year of arrival), and (B) annual number of individuals newly diagnosed with HIV-1 in the Netherlands and aged 15 years or older at the time of diagnosis, according to the most likely mode of transmission. In 2020, infections via sex between men (MSM) accounted for 63% of the annual number of new diagnoses, infections via heterosexual sex for 29%, infections via injecting drug use (IDU) for 0%, and infections via other or unknown modes of transmission for 8%. Dashed lines indicate the number of diagnoses after adjusting for a delay in notification to SHM.*





Legend: *MSM=sex between men; IDU=injecting drug use.*

Table 1.1: Annual number of HIV-1 diagnoses per transmission risk group, including individuals who acquired their HIV infection via sex between men (MSM), heterosexual sex, injecting drug use (IDU), contact with contaminated blood, or other or unknown modes of transmission. Numbers with an asterisk are adjusted to reflect a delay in notification to SHM and due to rounding may not add up to the total number reported in the last column.

Year of diagnosis	MSM	Heterosexual		IDU	
	Men	Men	Women	Men	Women
≤1995	2,153	270	394	276	132
1996	377	87	83	33	9
1997	434	114	128	38	10
1998	323	105	114	23	8
1999	344	110	140	19	7
2000	365	155	198	17	4
2001	441	167	234	14	6
2002	464	172	262	14	3
2003	442	179	274	22	5
2004	579	196	265	9	5
2005	621	191	252	14	3
2006	663	161	198	9	5
2007	763	157	201	11	4
2008	836	170	176	5	1
2009	769	159	172	9	0
2010	771	176	161	5	1
2011	756	142	146	5	1
2012	704	139	143	6	1
2013	731	116	126	1	2
2014	608	113	115	1	0
2015	577	129	123	1	0
2016	527	101	102	1	0
*2016**	*528*	*101*	*102*	*1*	*0*
2017	504	94	83	3	0
*2017**	*507*	*95*	*84*	*3*	*0*
2018	425	76	71	1	1
*2018**	*433*	*77*	*72*	*1*	*1*
2019	344	87	84	1	0
*2019**	*357*	*90*	*87*	*1*	*0*
2020	238	56	54	0	0
*2020**	*258*	*61*	*58*	*0*	*0*
2021	38	8	9	0	0
Total	**15,797**	**3,630**	**4,308**	**538**	**208**

** Numbers adjusted for a delay in notification.*

***Legend:** MSM=sex between men; IDU=injecting drug use.*

Blood or blood products		Other/unknown		<15 years of age		Total
Men	Women	Men	Women	Men	Women	
64	22	152	43	36	23	3,565
4	4	36	6	9	1	649
8	3	40	8	5	6	794
6	4	29	6	6	5	629
10	4	23	7	7	8	679
5	5	38	7	6	10	810
8	6	43	4	8	12	943
13	7	58	3	12	3	1,011
9	4	54	12	11	11	1,023
4	4	63	9	10	5	1,149
6	4	59	8	9	5	1,172
5	6	51	4	3	5	1,110
2	5	51	8	5	5	1,212
6	2	49	5	7	10	1,267
3	2	50	11	4	8	1,187
5	0	37	5	9	9	1,179
10	6	54	5	3	6	1,134
4	4	41	8	4	6	1,060
13	0	39	2	4	2	1,036
8	4	35	9	3	5	901
5	2	48	5	2	2	894
10	2	39	5	2	0	789
10	*2*	*39*	*5*	*2*	*0*	*790*
5	3	49	5	0	1	747
5	*3*	*49*	*5*	*0*	*1*	*752*
5	5	58	5	1	0	648
5	*5*	*59*	*5*	*1*	*0*	*660*
8	2	48	7	0	1	582
8	*2*	*50*	*7*	*0*	*1*	*604*
5	4	17	6	0	0	380
5	*4*	*18*	*7*	*0*	*0*	*411*
0	1	2	1	0	0	59
231	**115**	**1,263**	**204**	**166**	**149**	**26,609**

Of the 763 migrants who arrived in 2018 or later with a documented pre-arrival HIV diagnosis, 463 (61%) were men who reported sex with men (MSM) as the most likely mode of transmission, 139 (18%) were other men, and 161 (21%) were women. The median age at the time of arrival was 35 (interquartile range [IQR] 29-41) years; 83 (11%) were below 25 years of age, including 21 children younger than 15 years, while 58 (8%) were 50 years of age or older. In total, 167 (22%) migrants originated from sub-Saharan Africa, 141 (18%) from South America, 112 (15%) from western Europe, 79 (10%) from eastern Europe, 78 (10%) from central Europe, 47 (9%) from the Caribbean, and 47 (9%) from south and southeast Asia. The most commonly reported countries of origin (with at least 25 individuals living with HIV arriving in the Netherlands) were Brazil (51, 7%), Poland (40, 5%), Russian Federation (38, 5%), and the United States (25, 3%).

The majority (665, or 88%) of the 763 individuals had already started antiretroviral treatment before arriving in the Netherlands. By the time they entered HIV care in the Netherlands, their median CD4 counts were 620 (IQR 437-840) cells/mm^3, while 631 individuals had HIV RNA levels below 200 copies/ml (84% of the 751 with a viral load measurement available).

Individuals newly diagnosed in the Netherlands

Of the 26,681 individuals who were living in the Netherlands at the time of their HIV-1 diagnosis, or whose date of arrival in the country had not yet been recorded in the SHM database, 325 (1%) were diagnosed as children under 15 years of age: they are described in more detail in *Chapter 5*. Among the 26,609 individuals for whom the date or period of diagnosis was known, 26,294 (99%) were diagnosed at 15 years of age or older; 15,797 (60%) were men who acquired their HIV infection through sex with men, while 3,630 (14%) other men and 4,308 (16%) women reported having acquired their infection through heterosexual sex (*Table 1.1*). For 746 (3%) individuals, the reported mode of transmission was injecting drug use, while for 346 (1%) individuals, infection occurred through exposure to contaminated blood. Other and unknown modes of transmission accounted for the remaining 1,698 (6%) HIV diagnoses.

Decreasing number of diagnoses

From the 1990s until 2008, the annual number of new diagnoses increased from approximately 650 to almost 1,270 (*Table 1.1; Figure 1.2A*). Since 2009, the annual registered number of new diagnoses has steadily declined. In 2020, that downward trend continued and the number of new HIV diagnoses was approximately 411. This number takes into account a projected backlog[a] in registration of HIV cases.

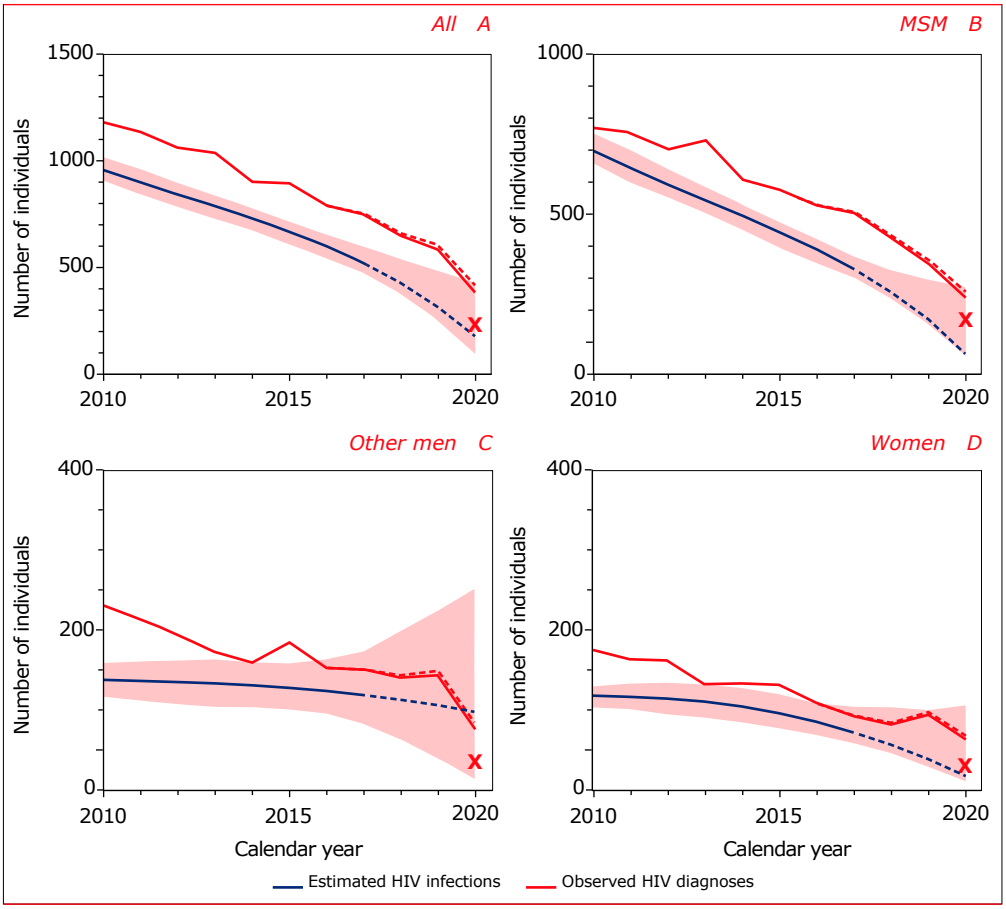
In MSM, the annual number of diagnoses was approximately 380 in 1996 and increased to almost 840 in 2008 (*Figure 1.2B*). Thereafter, the number of diagnoses gradually decreased to approximately 258 in 2020. In individuals who acquired their HIV infection via heterosexual sex, the annual number of new diagnoses has declined to approximately 119 in 2020. Finally, injecting drug use is now rarely reported as the most likely mode of transmission, which reflects the decreasing popularity of injecting drugs.

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. The estimated number of infections decreased from 950 (95% confidence interval [CI] 910-1,020) in 2010 to 180 (CI 90-430) in 2020 (*Figure 1.3A*), which is a reduction of 82% (54-90). This shows that the Netherlands has reached one of the United Nations 2020 targets: a 75% reduction in the annual number of new infections compared with 2010[2,3]. During the same period, the number of newly-acquired HIV infections among MSM fell by 91% (63-92), from 700 (660-750) in 2010 to 60 (60-270) in 2020 (*Figure 1.3B*).

a *As it may take some time before people living with HIV are registered in the SHM database by their treating physician, there is a backlog for the most recent calendar years. Based on past trends in registration, adjustment factors for 2016-2020 were estimated using the European Centre for Disease Prevention and Control (ECDC) HIV Platform Tool*[13].

Figure 1.3: *Observed annual number of HIV diagnoses (red) and estimated annual number of newly-acquired HIV infections (blue) in the total population (A), in men who have sex with men (B), in other men (C), and in women (D), according to European Centre for Disease Prevention and Control (ECDC) HIV Platform tool[13]. The cross indicates the UNAIDS' target for 2020 of achieving a 75% reduction in the number of newly-acquired HIV infections since 2010. The red dashed lines represent the number of diagnoses after adjusting for the delay in notification to SHM, while the blue dashed lines indicate that estimates in 2018 and later are still uncertain.*



Legend: *MSM=sex between men.*

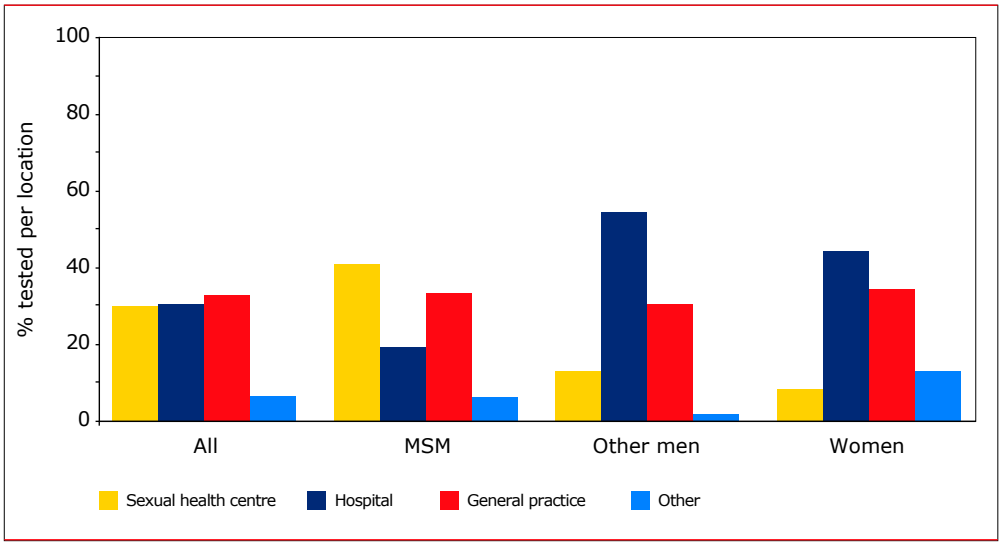
In other men, the estimated number of newly-acquired infections in 2010 was 140 (95% CI 120-160), which was similar to the estimated number of 120 (100-130) in women. The number of infections in other men has changed comparatively little over time – it was 100 (10-250) in 2020, a decrease of 29% (*Figure 1.3C*). In contrast, the estimated number of infections among women decreased by 85% (0-90) to 20 (10-110) in 2020 (*Figure 1.3D*).

It is worth noting that in all four populations, the uncertainty around the estimates is relatively large, especially for the most recent calendar years. One reason for this is that estimates of the number of infections in these years are quite sensitive to the observed number of diagnoses in 2019 and 2020. For this year's estimates we did not take into account the observed diagnoses in 2020 because we noticed that they tended to be below the long-term trend in most recent years, in particular among other men (*Figure 1.3C*). This lower number of diagnoses may be a consequence of the COVID-19 pandemic and the partial lockdown in 2020, which disrupted testing services for HIV at sexual health centres, and possibly also the registration of people in the SHM database. However, in the estimation process, we still used 2020 data on people diagnosed with HIV who had a concurrent AIDS diagnosis, because we presumed their clinical symptoms were severe enough not to delay their HIV diagnosis.

Setting in which HIV is diagnosed

Information on the setting in which HIV was diagnosed in the Netherlands was available for 1,583 (95%) of the 1,667 people diagnosed in 2018 or later, while 66 (4%) individuals were known to have been diagnosed abroad. Overall, 30% of these 1,583 individuals received their first HIV-positive test result at a sexual health centre, 31% at a hospital, and 33% at a general practice (*Figure 1.4*); in 2020, these proportions were 30%, 29%, and 35%, respectively. Among those diagnosed at sexual health centres, 86% were MSM, 9% were other men, and 4% were women, which was similar to the proportions directly reported by sexual health centres[4].

Figure 1.4: Proportion of individuals diagnosed in 2018 or later, stratified by location of testing and transmission risk group.

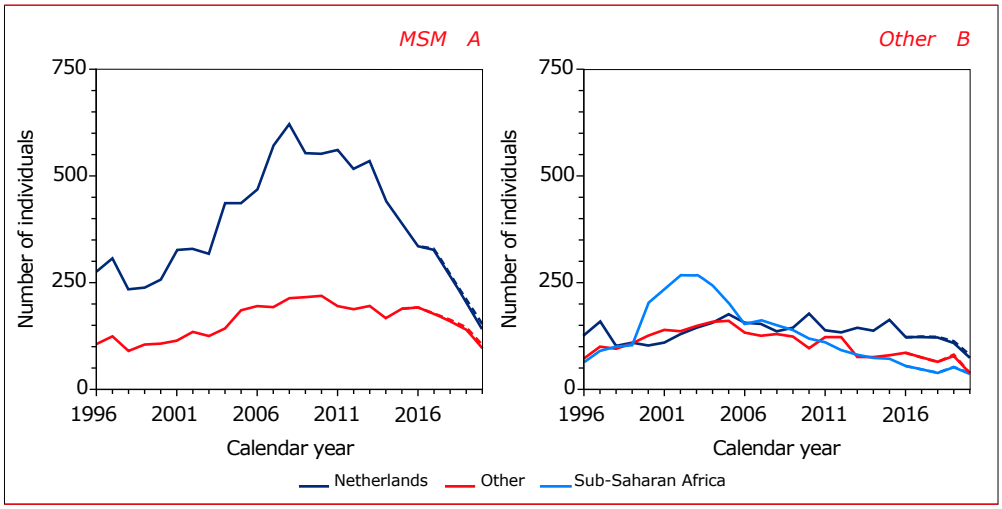


Legend: MSM=sex between men.

Geographical region of origin

In total, 10,904 (42%) people diagnosed with HIV-1 at 15 years of age or older were born outside the Netherlands. Of the men who acquired HIV via sex with men (MSM), 71% originated from the Netherlands, 10% from other European countries, 7% from South America, and 4% from the Caribbean (*Figure 1.5A*). In recent years (i.e., for diagnoses in, or after, 2018), the proportion of MSM of Dutch origin was 63%, while slight increases were observed in the proportion of MSM from central Europe, South America, and the Caribbean.

Figure 1.5: *Annual number of diagnoses by region of origin among: (A) men who acquired HIV via sex with men (MSM), and (B) other people aged 15 years or older at the time of diagnosis. Of the 1,045 MSM diagnosed in 2018 or later, 637 (61%) originated from the Netherlands, 125 (12%) from other European countries, 105 (10%) from South America, and 65 (6%) from the Caribbean. Of the other 622 people diagnosed in 2018 or later, 307 (49%) originated from the Netherlands, 64 (10%) from other European countries, 130 (21%) from sub-Saharan Africa, 47 (8%) from South America, 29 (5%) from the Caribbean, and 18 (3%) from south and southeast Asia.*



Legend: *MSM=sex between men.*

Among women and other men, only 39% originated from the Netherlands, while 32% originated from sub-Saharan Africa, 8% from South America, 5% from the Caribbean, and 4% from south and southeast Asia (*Figure 1.5B*). From 2018 onwards, 49% of the newly-diagnosed women and other men were of Dutch origin, and 21% originated from sub-Saharan Africa.

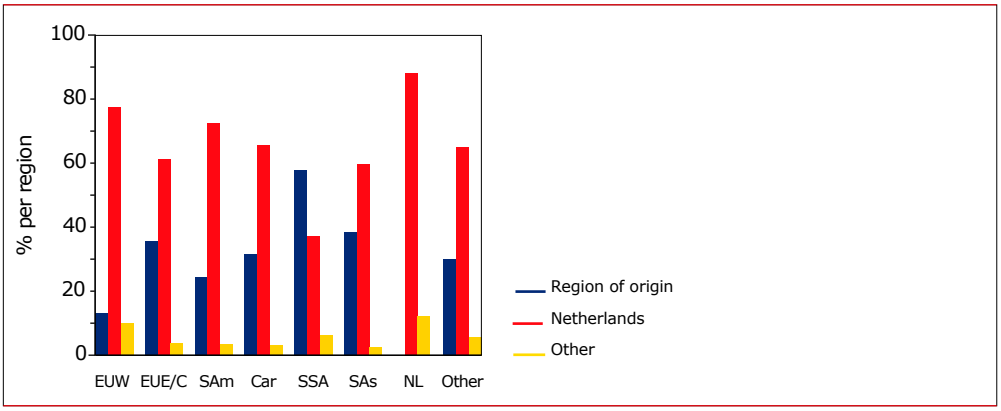
Overall, 22% of the people newly diagnosed since 2018, were living in the Amsterdam public health service (PHS) region at the time of diagnosis, and 13% were living in the Rotterdam-Rijnmond PHS region. These proportions were 15% and 11%, respectively, for people of Dutch origin and 30% and 16%, respectively, for people originating from other countries. Among MSM, 25% were living in Amsterdam at the time of diagnosis and 13% were living in Rotterdam, while among other men and among women, 17% were living in Amsterdam and 13% in Rotterdam. Other PHS regions with at least 5% of the new diagnoses since 2018 were Haaglanden (7%, including Den Haag) and Utrecht (6%).

Self-reported geographical region of HIV-1 acquisition

In total, 1,244 (75%) of those diagnosed in 2018 or later at 15 years of age or older, named the country in which they were most likely to have acquired their HIV-1 infection (*Figure 1.6*). Among people born in the Netherlands, the majority (88%) reported having acquired their HIV infection in the Netherlands, while among foreign-born individuals, 61% of those diagnosed in 2018 or later reported having acquired their HIV infection in the Netherlands.

The majority (86%) of MSM diagnosed in 2018 or later, who named the likely country of infection, reported that they acquired their HIV-1 infection in the Netherlands. Among other men and among women, 66% reported the Netherlands, and 11% sub-Saharan Africa. The proportion of Dutch-born people who likely acquired HIV in the Netherlands was 91% for MSM, 75% for other men, and 91% for women.

Figure 1.6: *Proportion of all HIV-1-positive individuals aged 15 years or older and diagnosed in 2018 or later per region of origin, who reported acquiring 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 southeast Asia; NL=the Netherlands; Other=other regions of origin.*

Increasingly older age at time of HIV diagnosis

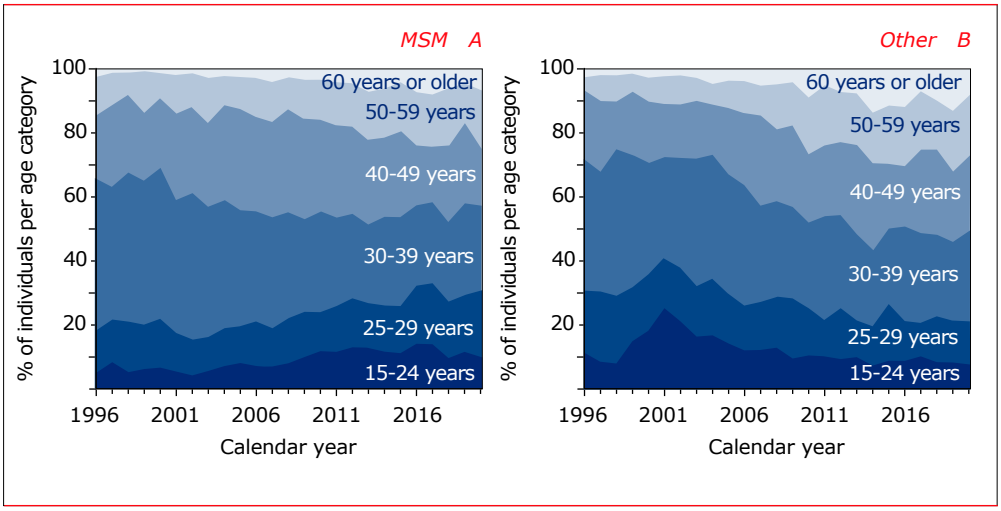
The age at which individuals are diagnosed with HIV has been slowly increasing over time. In 1996, the median age at the time of diagnosis was 36 (interquartile range [IQR] 30-43) years; in 2020, it was 39 (IQR 29-50) years. In 1996-2020, 17% of individuals who received an HIV diagnosis were aged 50 years or older; in 2020, 26% were 50 years or older (*Figure 1.7*)[5].

There were some age differences between MSM, other men, and women diagnosed in 2018 or later. MSM born in the Netherlands were diagnosed at a median age of 43 (IQR 31-53) years, while MSM of foreign origin were diagnosed at a much younger median age of 32 (27-42) years. Other men and women of Dutch origin were of similar age at the time of diagnosis as Dutch MSM: 44 (33-56) years for men and 40 (29-53) years for women. Foreign-born men other than MSM were 41 (32-50) years of age at the time diagnosis, which was somewhat older than the median age of 38 (30-45) years for foreign-born women. In 2020, 25% of MSM, 27% of other men, and 28% of women were 50 years or older at the time of diagnosis.

Young people

Between 1996 and 2020, 11% of the individuals who received an HIV diagnosis at 15 years of age or older were under 25 years of age (*Figure 1.7*). In 2020, 35 young people were diagnosed with HIV, which was 9% of all people diagnosed with HIV that year. The number of young individuals diagnosed in 2020 was 24 (10%) among MSM, five (6%) among other men, and six (9%) among women.

Figure 1.7: *Age distribution at the time of diagnosis among HIV-1-positive: (A) men who acquired HIV via sex with men (MSM), and (B) other men and women. In 1996-2020, the proportion of individuals between 15 and 29 years of age changed from 18% to 31% for MSM, and from 31% to 21% for other individuals. During the same period, the proportion of MSM aged 50 years or older at the time of diagnosis changed from 15% to 25%, while these proportions were 7% and 17% for other individuals.*



Legend: *MSM=sex between men.*

Entry into care

Of the individuals diagnosed with HIV in 2018 or later for whom the diagnosis setting was known, 82% entered care within two weeks of diagnosis, 95% within four weeks, and 97% within six weeks; for individuals diagnosed in 2020, these proportions were 85%, 97%, and 98%, respectively. The proportion in care within four weeks was 95% for individuals who received their first HIV-positive test at a sexual health centre, and similar for those who tested HIV-positive in a hospital (97%), at a general practice (94%), or at other locations (92%). The proportion in care within four weeks did not differ between MSM, other men, and women (98%), but increased with age at the time of diagnosis: 90% of individuals diagnosed at 15-24 years were in care within four weeks, compared to 95% of those diagnosed at 25-49 years of age, and 99% of those diagnosed at 50 years of age or older. The proportion in care within four weeks of diagnosis was larger among individuals born in the Netherlands (97%), than among those born abroad (92%).

Late diagnosis

Overall, 50% of the individuals diagnosed in 2018 or later had a late-stage HIV infection at the time of diagnosis; in other words, a CD4 count below 350 cells/mm^3 or an AIDS-defining event regardless of CD4 count[6]. Over time, the proportion of late-stage HIV diagnoses decreased from 67% in 1996 to a nadir of 43% in 2013, and then increased to 52% in 2020 (*Figure 1.8*). The proportion of individuals diagnosed with advanced HIV disease (i.e., with a CD4 count below 200 cells/mm^3 or AIDS), has likewise changed over time and was 33% in 2020. Although the downward trend in these *proportions* appears to have halted after 2013, the *number* of individuals diagnosed with late-stage or advanced-stage HIV infection continued to decline, albeit gradually. It is worth noting that although newly-diagnosed MSM had the lowest proportion of late-stage HIV infections, they accounted for 401 (52%) of all 776 individuals diagnosed with late-stage HIV in 2018 or later.

Figure 1.8: *Number and proportion of individuals classified as having: (A, B) late-stage, or (C, D) advanced-stage HIV infection at the time of diagnosis. In 2020, 189 (52%) individuals were diagnosed with late-stage HIV infection: 95 (42%) men who acquired HIV via sex with men (MSM), 52 (71%) other men, and 42 (67%) women; adjusting for reporting delay, 205 (52%) individuals: 103 (42%) MSM, 56 (71%) other men, and 45 (67%) women. During the same year, 119 (33%) individuals were diagnosed with advanced-stage HIV infection: 49 (22%) MSM, 36 (49%) other men, and 34 (54%) women; adjusting for reporting delay, 129 (33%) individuals: 53 (22%) MSM, 39 (49%) other men, and 37 (54%) women. 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. From 2018 onwards, the stage of infection was unknown for 111 (7%) individuals.*

Legend: *MSM=sex between men.*

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

Among individuals diagnosed with HIV in 2018 or later, 401 (41%) MSM, 229 (68%) other men, and 146 (61%) women had a late-stage HIV infection. Late-stage HIV infections, in relative terms, were most common among people originating from sub-Saharan Africa (72%, or 101 individuals), from Central Europe (56%, or 55 individuals), or from south and southeast Asia (55%, 31 individuals), and among people originating from the Netherlands (59%, or 420 individuals), from North Africa and the Middle East (73%, or 19 individuals), or from South America (71%, or 60 individuals) who acquired their HIV infection via other routes than sex between men (*Table 1.2*).

Older age at the time of diagnosis was also associated with a higher proportion of late-stage HIV infection. Late-stage HIV was seen in 52% of MSM, 81% of other men, and 77% of women diagnosed in 2018 or later at 50 years of age or older, compared with 24% of MSM, 50% of other men, and 41% of women diagnosed below the age of 25 years (*Table 1.2*). Late-stage HIV was also observed more often in people who received their HIV diagnosis at a hospital (79%), than among those who were tested at a general practice (46%), a sexual health centre (28%), or another testing location (40%).

Table 1.2: Characteristics of the 776 individuals with a late-stage HIV infection among the 1,667 individuals diagnosed with HIV in 2018 or later. In total, as a result of missing CD4 cell counts at diagnosis, it was not possible to classify whether 111 (7%) individuals (65 MSM, 35 other men, and 11 women), had a late-stage HIV infection. For each of the four groups (MSM, other men, women, and total), percentages represent the proportion with late-stage infection of the total number of individuals diagnosed in each category listed in the first column.

	Men (n=980)		Other men (n=3,337)		Women (n=239)		Total (n=1,556)	
	n	%	n	%	n	%	n	%
Overall	401	41	229	68	146	61	776	50
Age at diagnosis (years)								
15-24	24	24	9	50	12	41	45	30
25-29	50	29	16	41	17	45	83	33
30-39	106	41	53	62	45	67	204	50
40-49	109	48	61	73	32	60	202	55
50-59	79	49	53	82	28	76	160	61
≥60	33	59	37	80	12	80	82	70
Region of origin								
The Netherlands	251	41	124	64	45	49	420	47
Sub-Saharan Africa	11	61	38	84	52	68	101	72
Western Europe	22	49	4	80	0	-	26	52
Central Europe	26	46	17	71	12	67	55	56
South America	33	34	17	77	10	63	60	45
Caribbean	20	35	5	36	9	69	34	40
South and southeast Asia	16	41	5	100	10	83	31	55
North Africa and Middle-East	8	27	10	77	1	50	19	42
Other/unknown	14	41	9	60	7	70	30	51
Location of HIV diagnosis								
Sexual health centre	103	26	12	30	11	55	126	28
Hospital	129	70	149	86	85	83	363	79
General practice	134	42	55	57	36	46	225	46
Other/unknown	35	39	13	50	14	36	62	40

***Legend:** MSM=sex between men.*

Impact of transient low CD4 cell counts early after infection

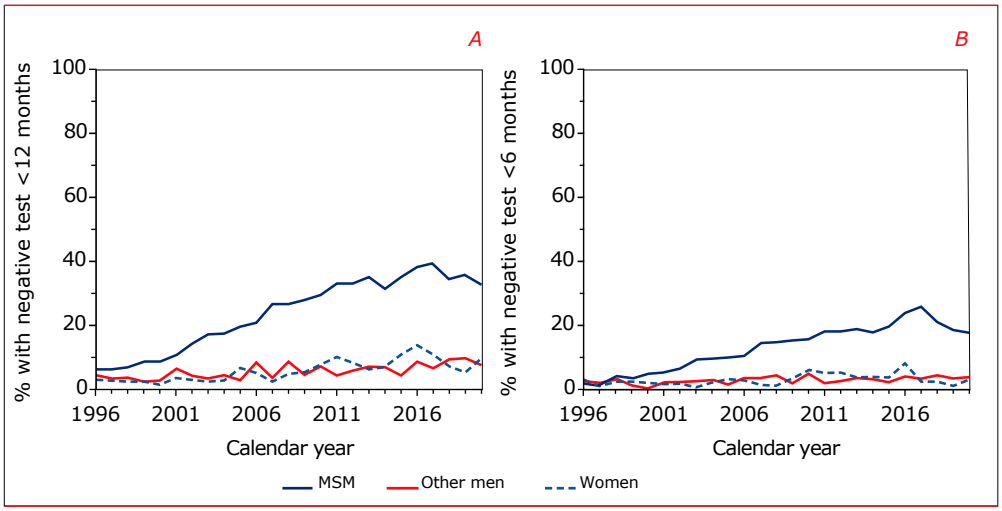
During the first few weeks after acquiring HIV, transient low levels of CD4 cell counts are common[7]. As a result, the stage of the infection may inadvertently be classified as late or advanced when individuals are diagnosed during this early phase of HIV infection. When people with a known HIV-negative test in the six 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 2018 or later changed from 50% to 47%. This decrease was mainly due to a drop in late-stage HIV among MSM (from 41% to 36%) whereas among other men and among women, the proportion decreased by at most a percentage point. The change in the proportion of people diagnosed with advanced-stage HIV infection was more modest: 32% before and 31% after reclassification in people diagnosed in 2018 or later.

Recent infection

Although many individuals are diagnosed with a late-stage HIV infection, a considerable proportion of people with an HIV diagnosis receive it early in the course of their infection. In total, among the individuals diagnosed in 2018 or later, 24% had a negative test in the 12 months prior to diagnosis, while 13% had a negative test in the six months prior to diagnosis (*Figure 1.9*). Among MSM, the proportion with a negative test in the 12 or six months prior to their HIV diagnosis, was 34% and 19%, respectively, for those diagnosed in 2018 or later. The proportion of MSM with a known HIV-negative test in the six months prior to their diagnosis was 26% in the Amsterdam PHS region, 24% in Rotterdam-Rijnmond, and 15% in the rest of the Netherlands. For other men and for women, however, the proportions with a recent infection were considerably lower, and among those diagnosed in 2018 or later, only 8% had a negative test in the 12 months prior to their diagnosis, while 3% had a negative test in the six months prior to diagnosis; these proportions did not differ between Amsterdam, Rotterdam-Rijnmond, and the rest of the country.

Figure 1.9: *Proportion of people diagnosed who had: (A) a last negative test at most 12 months prior to their diagnosis, or (B) a last negative test at most six months prior to their diagnosis. In total, 33% of men who acquired their HIV infection through sex with men (MSM), 8% of other men, 9% of women, and 24% of all individuals diagnosed in 2020 had a last negative test at most 12 months before diagnosis, whereas 17% of MSM, 4% of other men, 3% of women, and 12% of all individuals had a last negative test at most six months before diagnosis.*

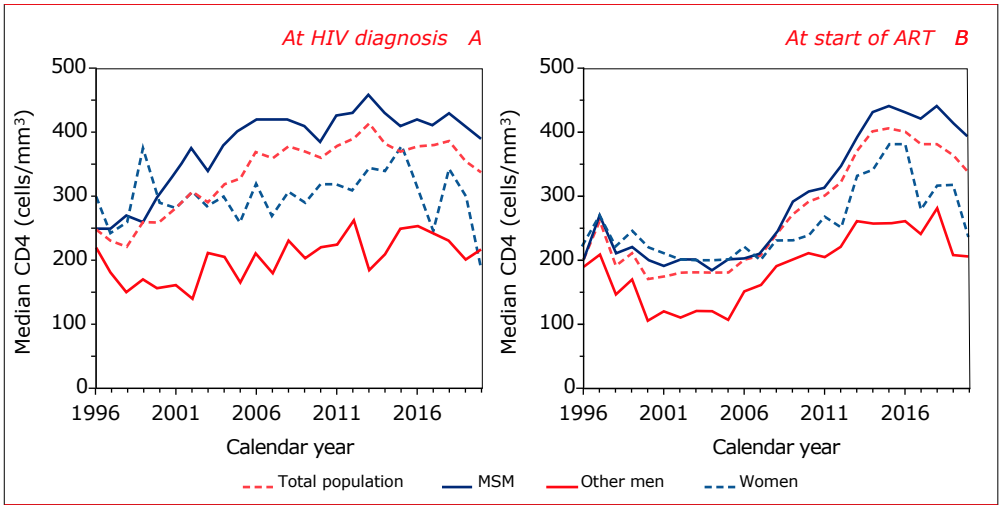


Legend: *MSM=sex between men.*

The proportion of people with a recorded previously negative HIV test increased from 22% in 1996 to 56% in 2020. MSM were more likely to have a previously negative HIV test than other men and women. In 2020, 69% of MSM, 35% of other men, and 34% of women newly diagnosed with HIV had a recorded previous test with a negative result. The proportion with a known previously negative test was highest among those diagnosed at a sexual health centre (78%), compared with 26% of those diagnosed in a hospital, 59% at a general practice, and 77% who were diagnosed elsewhere.

Between 1996 and 2020, median CD4 counts at the time of diagnosis increased from 250 to 338 cells/mm^3 (*Figure 1.10A*). 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 1.10: *Changes over calendar time in median CD4 counts: (A) at HIV diagnosis, and (B) at the start of antiretroviral treatment (ART). (A) In 1996-2020, CD4 counts at the time of diagnosis increased from 250 (interquartile range [IQR] 80-434) to 338 (IQR 152-566) cells/mm³ in the total population diagnosed at 15 years of age or older. The increase was most apparent for men who acquired their HIV infection through sex with men (MSM): 249 (IQR 80-450) cells/mm³ in 1996 and 390 (IQR 240-600) cells/mm³ in 2020. CD4 counts in other men and in women were 220 (IQR 40-410) and 300 (IQR 129-445) cells/mm³, respectively, in 1996, and 218 (IQR 58-478) and 187 (IQR 64-470) cells/mm³ in 2020. (B) In the total population, CD4 counts at the start of ART were approximately 180 cells/mm³ between 2000 and 2005, and increased thereafter. In 2020, CD4 counts were 335 (IQR 160-559) cells/mm³ in the total population, 390 (IQR 240-583) cells/mm³ in MSM, 205 (IQR 50-450) cells/mm³ in other men, and 231 (IQR 60-470) cells/mm³ in women.*



Legend: *MSM=sex between men; ART=antiretroviral treatment.*

Prior use of pre-exposure prophylaxis

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral agents by HIV-negative people to prevent HIV acquisition. In the Netherlands, the roll-out of the formal PrEP program at the municipal health centres (GGD) started in September 2019, but informal use through buyers' clubs or prescription, and monitoring through other healthcare providers, including as part of the AMPrEP study in Amsterdam, started several years earlier. People at high risk of HIV acquisition are eligible for the official PrEP program.

In consultation and collaboration with the Dutch Association of HIV-Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB), and Dutch Nurses' Association's HIV/AIDS nurse consultants unit (*Verpleegkundigen & Verzorgenden Nederland – Verpleegkundig Consulenten Hiv*, V&VN VCH), since July 2019, SHM has prospectively collected PrEP-related data from the electronic medical records (EMRs) for individuals newly diagnosed with HIV and first entering care. Also, SHM retrospectively collected available information on prior use of PrEP from individuals who newly entered into care between January 2018 and June 2019. By 30 June 2021, data had been collected from 1,987 EMRs; only 442 (22.2%) of which specifically mentioned whether there was prior use of PrEP or not. The proportion of individuals for whom information on prior use of PrEP was available increased from 9.3% in 2018, to 24.8% in 2019, to 32.2% in 2020, to 52.8% in the first half of 2021.

The demographic characteristics of the group for whom information on prior use of PrEP was available showed little variation: 25.5% of MSM vs. 18.2% of other men and women; and 24.3% of individuals born in the Netherlands vs. 20.2% of migrants. They were also slightly younger in age (median 37.6 years, IQR 29.0-48.6) than individuals without PrEP information in their EMRs (median 38.5 years, IQR 29.2-49.5).

Of the 442 individuals for whom information on prior use of PrEP was available, 60 (13.6%) reported prior use of PrEP, and 382 (86.4%) did not. Prior use of PrEP was reported by none of the 53 cisgender women, none of the 13 transwomen, 59 (15.7%) of 375 cisgender men (24 [11.1%] of 216 men born in the Netherlands, and 35 [22.0%] of 159 migrant men), and one (of a total of one) transman. Of the 59 cismen and one transmen who reported prior use of PrEP, the most likely route of HIV acquisition was through sexual contact with other men in 52 (86.7%) men, sexual contact with women in one (1.7%) man, sexual contact with women and other men in four (6.7%) men, tattoo/piercing in one (1.7%) man, and was unknown in two (3.3%) men. The 60 men who reported prior use of PrEP were younger (median 31.2, IQR 26.2-39.7 years) than the men who did not (median 38.1, IQR 29.5-49.8 years).

Of the 60 men who reported prior use of PrEP, 31 (51.7%) obtained it from a healthcare provider in the Netherlands (15 via a family practitioner, 12 via the GGD and three via an HIV treatment centre; for one there was no information). Eleven (18.3%) men obtained it from a buyers club/internet/store outside of the Netherlands, six (10.0%) from a healthcare provider outside of the Netherlands, and two (3.3%) from a friend living with HIV who donated some of his own medication; for ten (16.7%) men, there was no information available. Co-formulated tenofovir disoproxil/emtricitabine was used by 34 men, one man reported use of dolutegravir (obtained through a friend living with HIV) and another reported using Genvoya (obtained through an unspecified route). Information on the specific antiretrovirals used was not available for the other 24 men. Daily PrEP use was reported by 17 (28.3%) men, on-demand use by 14 (23.3%) men, and intermittent use (i.e., a fixed schedule but not seven days a week), was reported by six (10.0%) men. For 23 (38.3%) men, there was no information available.

Regular periodic medical checkups while using PrEP were performed by the GGD (15 men, 25.0%), HIV treatment centres (six men, 10.0%), family practitioners (eight men, 13.3%), or by a medical specialist other than an HIV treatment centre (two men, 3.3%). No checkups were performed for eight (13.3%) men, and for 21 (35.0%) men there was no information available. Thirty-seven (61.7%) men reported using PrEP after their last negative HIV test, while 12 (20.0%) didn't. There was no information available for 11 (18.3%) men. For 38 (63.3%) men who reported using PrEP when first entering HIV care, a genotypic resistance test was done. In 13 (34.2%) of these 38 men, resistance-associated mutations were detected: seven harboured a M184V/I mutation, while one man had unspecified RT resistance mutations. In one of the patients harbouring a M184V mutation, there was inconclusive evidence he might also have had a K65R mutation. Furthermore, tests detected 10I, 35D in the protease gene (n=1), A98G in the RT gene (n=1), V106I in the RT (n=1), L10V, K20I, E35D, H69M, and L89M in the protease gene (n=1), and V106I in the RT, plus A71I, V77I, and I93L in the protease gene (n=1); these might be naturally occurring polymorphisms and are probably unrelated to the prior use of PrEP.

It is noteworthy that all but one man in whom resistance mutations were detected had indicated that they had continued the use of PrEP for a while after their last HIV-negative test. These 13 men had previously received medical check-ups at a municipal health center (n=4), an HIV-treatment center (n=4), family practitioner (n=1), and one men (who obtained PrEP through a buyers club) had never been medically monitored during PrEP use, and for four men no information was available. The moment of the last use of PrEP for these 13 men was in 2018 (n=3), 2019 (n=3), 2020 (n=6), and 2021 (n=1).

For 56 of the 60 men who reported prior use of PrEP, data on their first-line cART were available. All eight men with evidence of clinically-relevant RT mutations started a regimen containing an integrase inhibitor. Five of the eight men combined the integrase inhibitor with a protease inhibitor and the remaining three men combined the integrase inhibitor with two nucleoside-analogue reverse transcriptase inhibitors (tenofovir, emtricitabine with either dolutegravir [n=1] or bictegravir [n=2]).

Of the remaining 48 men with no baseline resistance test available, or whose test showed no evidence of clinically-relevant RT mutations, 45 initiated a preferred first-line regimen containing two NRTIs, plus either an integrase inhibitor (n=30), a PI (n=2), an integrase inhibitor plus a PI (n=14), or a non-nucleoside RT inhibitor (n=2).

None of the first-line regimens were discontinued due to a lack of virological efficacy. One of the eight men with evidence of clinically-relevant RT mutations did not have an optimal virological treatment response. Three months after starting on Biktarvy, his plasma viral load was found to be undetectable, but, in the following two-year period, all eight recorded measurements showed detectable viremia; the highest recorded value was 253 copies/ml. Among the 48 men with no baseline resistance test available, those with a viral load measurement at least four months after the initiation of cART showed an adequate initial virological treatment response (below 200 copies/ml), with no subsequent viral breakthrough recorded.

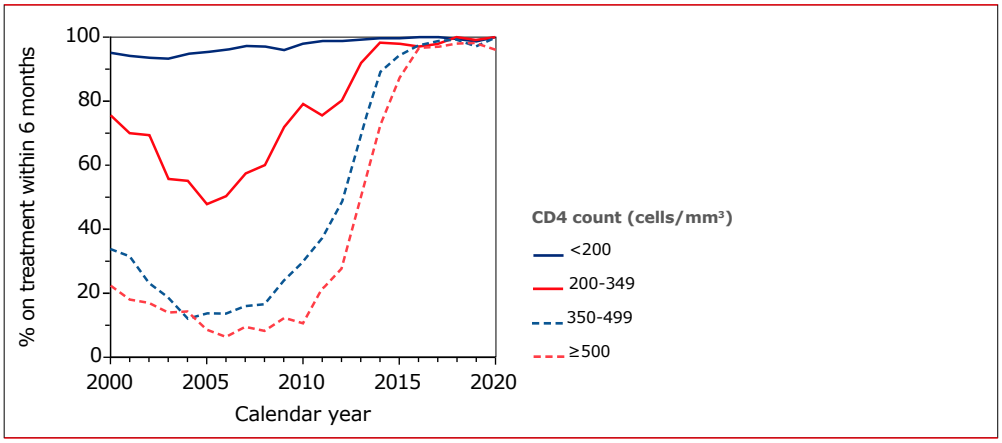
The percentage of individuals for whom information on prior PrEP use could be retrieved from the medical records is steadily increasing. SHM will continue to work with the HIV treatment centers to (retrospectively) collect information on prior use of PrEP in all individuals newly entering care.

Antiretroviral treatment

Of the 26,294 individuals diagnosed at 15 years of age or older, 25,407 (97%) had started antiretroviral treatment by May 2021. Over the past few years, increasingly, antiretroviral treatment has been initiated earlier in the course of an HIV infection, as evidenced by higher CD4 counts at the start of treatment since the mid-2000s (*Figure 1.10B*). In 2020, median CD4 counts at the start of treatment increased to 335 cells/mm^3. Treatment and treatment outcomes are described in more detail in *Chapter 2*.

The main reason for starting treatment late (i.e., at low CD4 counts), appears to be a late diagnosis, because most people who can start treatment at high CD4 counts now do so. Prior to 2015, individuals with higher CD4 counts were less likely to start treatment within six months of diagnosis, but, in 2015, treatment guidelines changed to recommend immediate initiation of antiretroviral treatment, regardless of CD4 count[8]. In 2020, for all CD4 strata, at least 95% of people who were diagnosed with HIV that year started treatment within six months (*Figure 1.11*).

Figure 1.11: *Proportion of individuals who started antiretroviral treatment (ART) within six months of their HIV diagnosis by CD4 count at the time of diagnosis. Individuals were considered only if they had more than six months of follow up after diagnosis. Of all individuals diagnosed in 2018 or later, 99% of those with CD4 counts below 200 cells/mm^3, 100% of those with CD4 counts between 200 and 349 cells/mm^3, 98% of those with CD4 counts between 350 and 499 cells/mm^3, and 98% of those with CD4 counts of 500 cells/mm^3 or above had started ART within six months of diagnosis.*



Time between HIV infection and viral suppression

People with a suppressed viral load do not transmit their virus to uninfected partners (undetectable equals untransmittable, or U=U)[9-11]. 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[12]. However, to reach viral suppression, people living with HIV must first be diagnosed, then linked to care, and subsequently start treatment.

Over time, significant improvements have been realised in several of these steps in the HIV care continuum. Between 2010 and 2020, the median time from diagnosis to viral suppression decreased from 0.84 (IQR 0.38-2.60) years to 0.17 (IQR 0.12-0.29) years, or from 10.1 (IQR 4.5-31.2) months to 2.1 (IQR 1.5-3.5) months. This was mainly due to starting treatment earlier after entry into care, and more rapidly reaching viral suppression after starting treatment. The time from infection to diagnosis was the greatest contributing factor to the delay between acquiring HIV and achieving viral suppression and was estimated to be a median of 2.8 (IQR 1.3-5.1) years in 2020.

Population in care

In total, 21,087 (73%) of the 28,745 HIV-1-positive individuals ever registered in the Netherlands were known to be in clinical care by the end of 2020 (*Figure 1.1*; *Table 1.3*). People were considered to be in clinical care if they had visited their treating physician in 2020, or had a CD4 count or HIV RNA measurement in that year, and were still living in the Netherlands. Of the 7,658 people who, according to this definition, were not in care by the end of 2020, 3,490 (46%) had died, 1,840 (53%) of them before the end of 2010. Another 2,099 (27%) had moved abroad, including 676 (32%) who did so before the end of 2010. The remainder were either lost to care (1,961), were only diagnosed with HIV in 2021 (59), moved to the Netherlands in 2021 (16), or newly entered care in 2021 (33). Of the people who moved abroad, 1,612 (77%) had RNA levels below 200 copies/ml at their last viral load measurement; in those lost to care, that figure was 1,221 (62%).

Table 1.3: Characteristics of the 21,087 HIV-1-positive individuals in clinical care by the end of 2020.

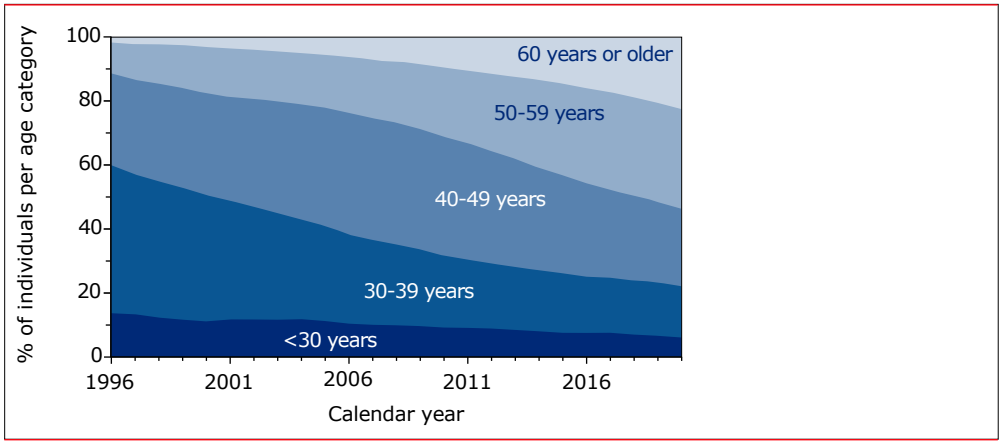
	Men (n=17,184, 81%)		Women (n=3,803, 19%)		Total (n=21,087)	
	n	%	n	%	n	%
Transmission						
MSM	13,289	77	-	-	13,289	63
Heterosexual	2,530	15	3,403	87	5,933	28
IDU	192	1	78	2	270	1
Blood/blood products	182	1	110	3	292	1
Other/unknown	991	6	312	8	1,303	6
Current age (years)						
0-15	65	0	87	2	152	1
15-24	208	1	89	2	297	1
25-29	706	4	132	3	838	4
30-39	2,642	15	739	19	3,381	16
40-49	3,866	22	1,220	31	5,086	24
50-59	5,570	32	1,019	26	6,589	31
60-69	3,006	17	457	12	3,463	16
≥70	1,121	7	160	4	1,281	6
Region of origin						
The Netherlands	11,054	64	1,179	30	12,233	58
Sub-Saharan Africa	1,097	6	1,560	40	2,657	13
Western Europe	979	6	115	3	1,094	5
South America	1,268	7	350	9	1,618	8
Caribbean	756	4	191	5	947	4
South and southeast Asia	532	3	248	6	780	4
Other	1,417	8	245	6	1,662	8
Unknown	81	0	15	0	96	0
Years aware of HIV infection						
<1	311	2	61	2	372	2
1-2	1,075	6	186	5	1,261	6
3-4	1,339	8	215	6	1,554	7
5-10	4,047	24	667	17	4,714	22
10-20	6,908	40	1,841	47	8,749	41
>20	3,480	20	917	23	4,397	21
Unknown	24	0	16	0	40	0

***Legend:** MSM=sex between men; IDU=injecting drug use.*

Ageing population

The median age of the population in clinical care by the end of 2020 was 51 (IQR 41-59) and has been increasing since 1996 (*Figure 1.12*). This increase in age is mainly a result of the improved life expectancy of people living with HIV following the introduction of combination antiretroviral treatment. In addition, people are being diagnosed at increasingly older ages, as discussed earlier in this chapter. As a result, approximately half of the people currently in care (54%) are 50 years or older, including 56% of men and 42% of women; 22% are 60 years or older. As the population living with HIV 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 1.12: *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 12% were 50 years or older. In 2020, these proportions were 6% and 54%, respectively, while 22% of individuals in care were 60 years of age or older. The proportion of individuals in clinical care as of 31 December each calendar year is shown according to age category: <30 years of age, 30-39 years, 40-49 years, 50-59 years, and 60 years or older.*



Duration of infection

People in clinical care by the end of 2020 were known to be HIV-positive for a median of 12.5 (IQR 7.4-18.6) years. Therefore, a large group (62%) of those in care have been living with HIV for more than 10 years, while 21% have done so for more than 20 years. The median time since diagnosis was 11.9 years for men who acquired HIV via sex with men (MSM), 13.0 years for other men, and 14.7 years for women. The majority of individuals who acquired their HIV infection via injecting drug use (94%) received their HIV diagnosis more than 10 years ago, which reflects how rare this mode of transmission has become since the Netherlands' rapid and early adoption of harm reduction strategies in the 1980s.

Treated population

By the end of 2020, 99% of the individuals in care had started antiretroviral treatment, and 95% of them were using a once-daily regimen. Of the 124 (1%) individuals who had not yet started antiretroviral treatment by the end of 2020, seven (6%) were known to have started treatment in 2021, while 32 (26%) were diagnosed with HIV in 2020, so it is likely their treatment has yet to be recorded in the SHM database. Antiretroviral treatment is discussed in more detail in *Chapter 2*.

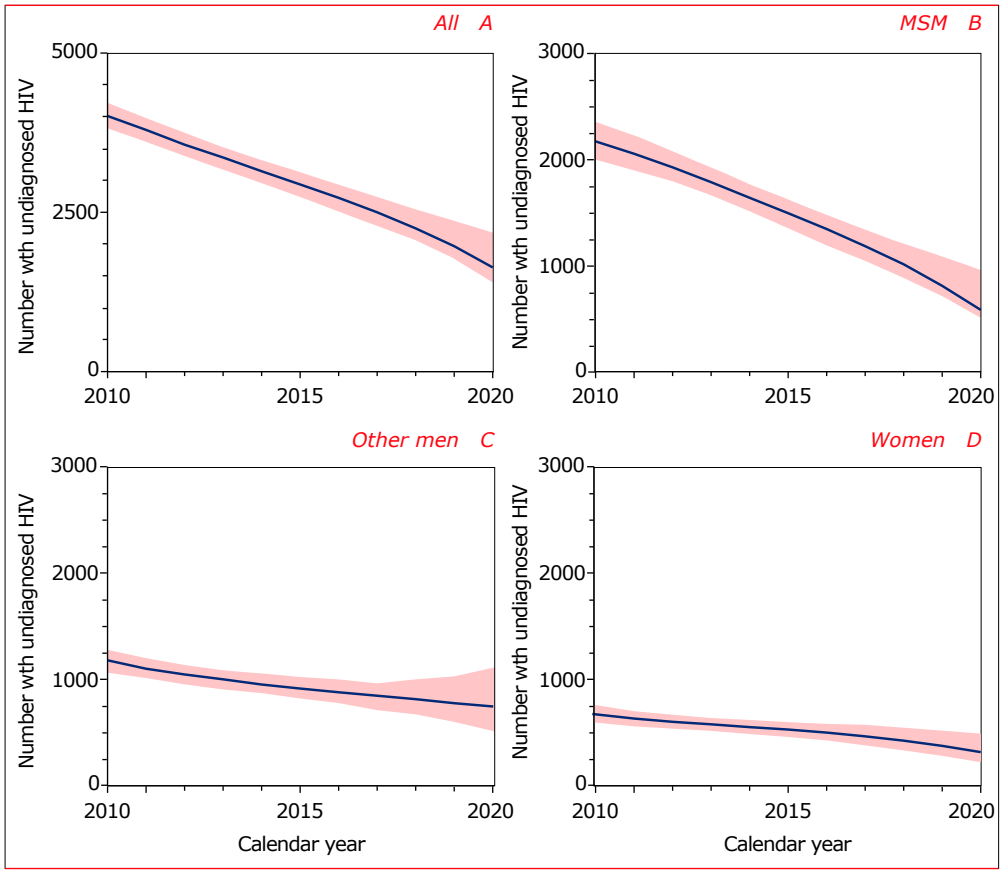
Clinical condition

The most recent median CD4 count in 2020 for people in care was 700 (IQR 513-920) cells/mm^3. This is mainly a result of effective antiretroviral treatment, but also partly reflects earlier diagnosis. Most recent CD4 counts were similar between MSM and women, being 722 (IQR 540-930) and 703 (IQR 510-930) cells/mm^3, respectively, but men who acquired HIV via other modes of transmission had lower CD4 counts at a median of 620 (IQR 430-850) cells/mm^3. Of the people in care with an HIV-1 viral load measurement in 2020, 98% had a last measurement in that year below 200 copies/ml and 96% had a last measurement below 50 copies/ml. More than one fifth (22%) of the individuals had ever been diagnosed with an AIDS-defining disease; 57% were diagnosed with AIDS concurrently with their HIV diagnosis.

Undiagnosed population

The estimated number of people with an undiagnosed HIV infection decreased from 3,950 (95% CI 3,770-4,200) in 2010 to 1,640 (95% CI 1,400-2,180) in 2020, representing a reduction of 59% (95% CI 46-66) (*Figure 1.13A*). This decrease was mostly driven by MSM, among whom the number of undiagnosed HIV cases fell by 73% (56-78) from 2,170 (2,000-2,360) in 2010 to 590 (500-960) by the end of 2020 (*Figure 1.13B*). Among other men, the estimated number with undiagnosed HIV was 1,170 (1,070-1,280) in 2010 and 740 (510-1,110) in 2020, while in women these numbers were 670 (590-760) and 310 (220-490), respectively (*Figures 1.13C* and *1.13D*).

Figure 1.13: *Estimated number of people living with undiagnosed HIV in the Netherlands: (A) overall, (B) men who acquired HIV through sex with men (MSM), (C) other men, and (D) women, according to the European Centre for Disease Prevention and Control (ECDC) HIV Platform tool[13].*

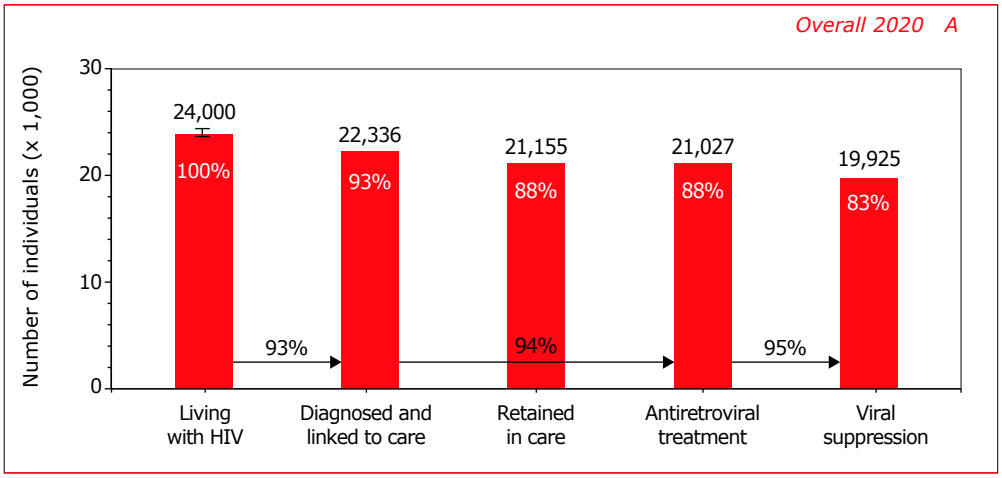


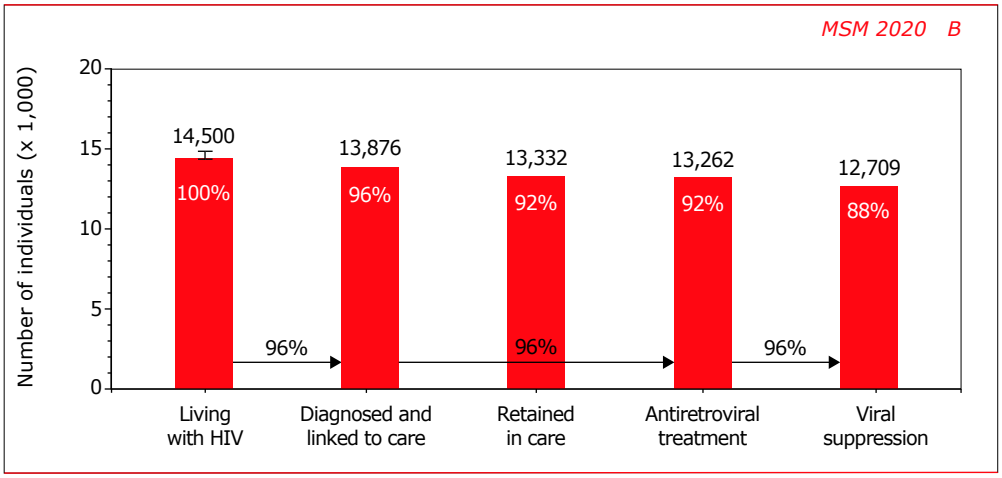
Legend: *MSM=sex between men.*

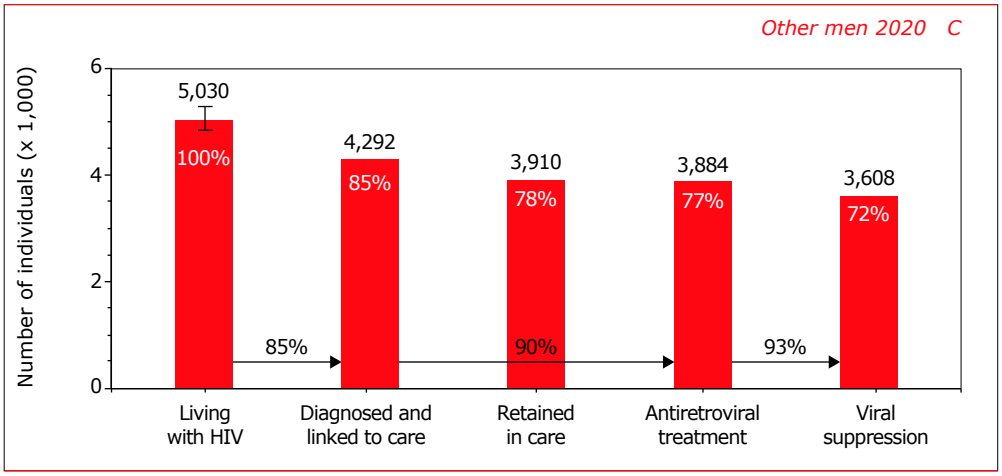
Continuum of HIV care – national level

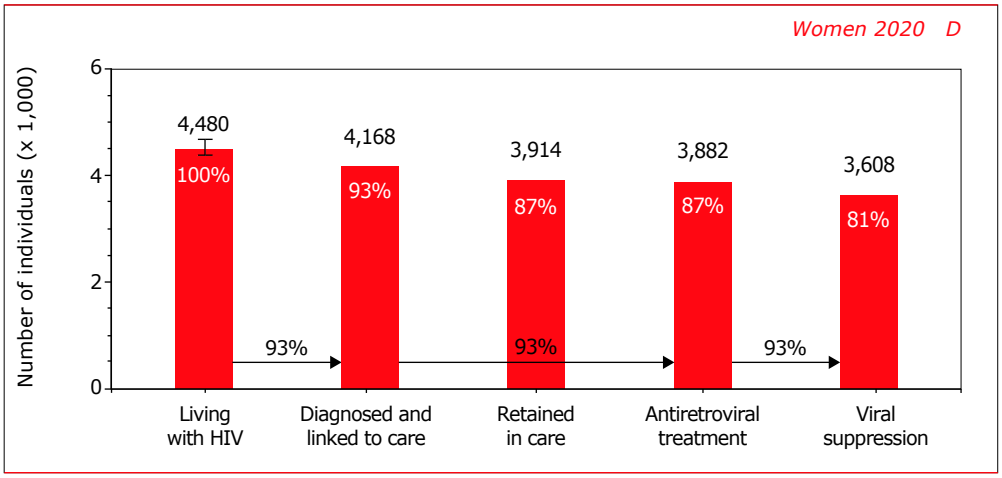
The total number of people living with HIV by the end of 2020 was 24,000 (95% CI 23,600-24,200), including the estimated 1,640 (1,400-2,180) who remained undiagnosed[13]. Adjusted for registration delays, 22,336 individuals, or 93% of the total number estimated to be living with HIV, had been diagnosed, linked to care, and registered by SHM, of whom 21,155 individuals were considered to be retained in care (i.e., they had at least one documented HIV RNA or CD4 count measurement, or a clinic visit in 2020) (*Figure 1.14A*). The majority of these individuals (21,027, or 94% of those diagnosed and linked to care), had started antiretroviral treatment, and 19,925, or 95% of those treated, had a most recent HIV RNA measurement below 200 copies/ml, and 19,464 (93%) a measurement below 50 copies/ml. Overall, 83% of the total estimated population living with HIV and 89% of those diagnosed and ever linked to care had a suppressed viral load. That means that, by 2020, the Netherlands had almost reached the Joint United Nations Programme on HIV/AIDS (UNAIDS) 95-95-95 target for 2025, with the estimate standing at 93-94-95. Of the people still in care by the end of 2020, 14,752 (70%, or 77% of those with a CD4 measurement), had a most recent CD4 count of 500 cells/mm^3 or higher, which was measured, at most, two years earlier.

Figure 1.14: Continuum of HIV care for people estimated to be living with HIV in the Netherlands by the end of 2020: (A) the total HIV-1-positive population, (B) men who acquired HIV via sex with men (MSM), (C) other men, and (D) women. Percentages at the top of the bars are calculated relative to the number living with HIV, while percentages at the bottom correspond to the UNAIDS' 95-95-95 targets for 2025. Numbers were adjusted to reflect reporting delays.









Legend: *MSM=sex between men.*

Viral suppression

In total, 1,094 individuals (without adjusting for registration delays) had started treatment but did not have a suppressed viral load by the end of 2020. On closer inspection, 697 (64%) of these individuals did not have a viral load measurement available in 2020, which is approximately twice as many as the 339 individuals without a viral load measurement in 2019 (as reported in last year's report[1]). This increase was observed in almost all HIV treatment centres, including those with automated import of laboratory measurements into the SHM database.

It may therefore be related, in part, to a reduction in out-patient clinic visits during the partial COVID-19 pandemic lockdown. In total, 610 (88%) of the 697 individuals without a viral load measurement in 2020 had an RNA level below 200 copies/ml at their last measurement in 2019.

Of the 397 (36%) people with a viral load measurement and no viral suppression, 58 (15%) had not yet started treatment by the time of their last available viral load measurement in 2020. Another 22 (6%) had only started treatment in the six months prior to that last measurement and may not have had sufficient follow up to achieve a documented suppressed viral load.

Lost to care

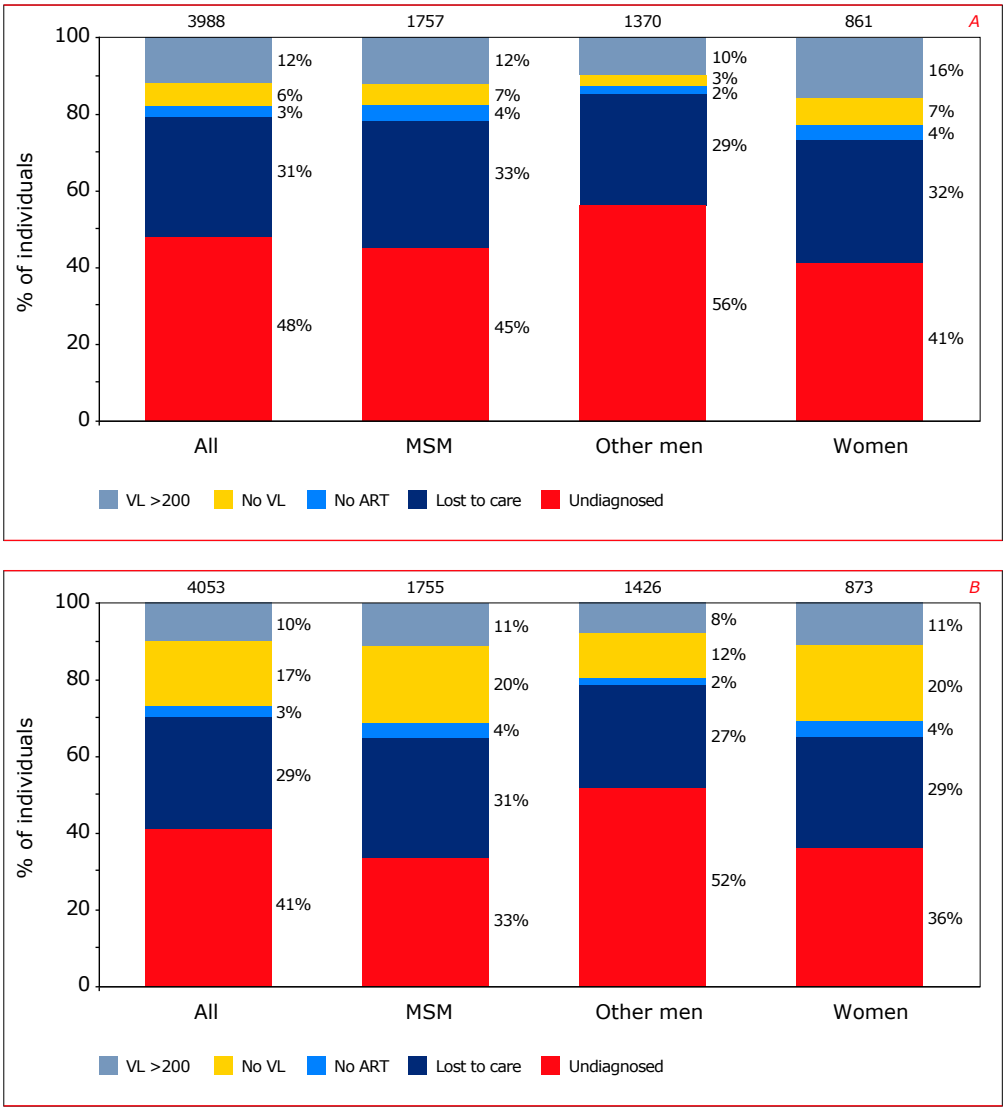
In total, 1,961 individuals were lost to care by the end of 2020, of whom 815 (42%) were lost before the end of 2010, 686 (35%) in 2011-17, 193 (10%) before the end of 2018, and 267 (14%) before the end of 2019[b]. The 815 individuals who were lost to care in or before 2010, were excluded from the estimated number of people living with HIV and the number of people diagnosed and linked to care. It was assumed to be unlikely that these 815 individuals were still living in the Netherlands by the end of 2020 without needing care or antiretroviral treatment during that ten-year period. Of the 1,146 individuals lost to care after 2010, 68% were born outside the Netherlands; this proportion was only 42% for those who were still in care by the end of 2020. This suggests that some of those lost to care may have moved abroad; in particular, back to their country of birth.

Transmittable levels of virus

The number of individuals living with HIV likely to have an unsuppressed viral load by the end of 2020 was estimated to be 4,053, which is the difference between the first and the last stage in the HIV care continuum. These individuals may still pass HIV onto uninfected individuals. *Figure 1.15B* shows their distribution across the gaps between successive stages in the care continuum; about two in five people (41%) have HIV but are not yet aware of their infection. The number of 4,053 is likely to be an overestimate of the true number with an unsuppressed viral load in the Netherlands. As discussed above, some of the 29% who were lost to care may have moved abroad and may be receiving HIV care outside the Netherlands. In addition, 17% of the people had no viral load measurement in 2020 but, since they all started antiretroviral treatment, it is likely that many have viral load levels below 200 copies/ml.

b *In addition to the 1,961 individuals lost to care there were 33 individuals who had already been diagnosed by the end of 2020 and were living in the Netherlands but entered care in 2021. These 33 individuals (34 with adjustment for registration delay), as well as the 1,146 lost to care after 2010 (1,147 with adjustment), are counted in the first and second stage of the continuum but not in the other stages.*

Figure 1.15: *Estimated number of people living with HIV likely to have an unsuppressed viral load: (A) by the end of 2019, or (B) by the end of 2020, stratified by successive stages in the HIV care continuum.*



Legend: *ART=antiretroviral treatment; MSM=sex between men; VL=viral load.*

Continuum of care in MSM, other men, and women

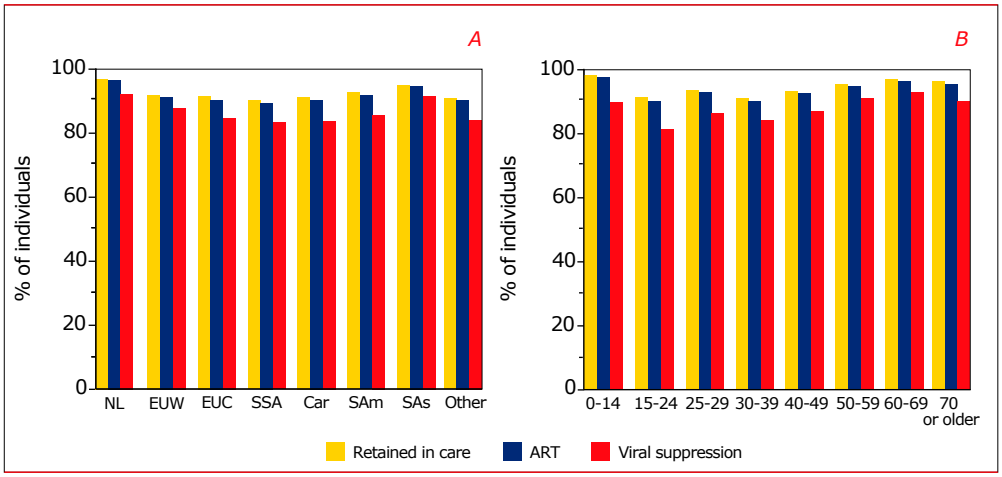
The number of MSM living with HIV at the end of 2020 was estimated to be 14,500 (95% CI 14,400-14,800), of whom 590 (500-960) had yet to be diagnosed. Of these 14,500 MSM, 13,876 (96%) had been diagnosed and linked to care, 13,332 (92%) were still in care, 13,262 (92%) had started antiretroviral treatment, and 12,709 (88%) had a most recent HIV RNA below 200 copies/ml, or 96-96-96 in terms of the 2025 UNAIDS 95-95-95 target, meaning that in MSM, the UNAIDS targets were met by 2020 (*Figure 1.14B*). In total, 9,766 (73%, or 80% of those with a CD4 measurement) of MSM still in care by the end of 2020 had a CD4 count of 500 cells/mm^3 or higher at their last measurement in 2019 or 2020.

Among other men, the estimated number living with HIV in 2020 was 5,030 (95% CI 4,810-5,400), including 740 (510-1,110) who were not yet diagnosed (*Figure 1.14C*). In total, 4,292 (85%) men had been diagnosed and linked to care, 3,910 (78%) were still in care, 3,884 (77%) had started treatment, and 3,608 (72%) had a suppressed viral load below 200 copies/ml. The number of women living with HIV was estimated to be 4,480 (4,390-4,660), of whom 310 (220-490) were not yet diagnosed (*Figure 1.14D*). Of these women, 4,168 (93%) had been diagnosed and linked to care, 3,914 (87%) were still in care, 3,882 (87%) had started treatment, and 3,608 (81%) had a suppressed viral load. Among women and other men still in care by the end of 2020, the proportion with viral suppression was 92%, which was lower than among MSM (95%).

Continuum of care by region of origin and age

Individuals of Dutch origin generally engaged more with the various stages of the care continuum than people from other countries (*Figure 1.16A*). Engagement with all stages of the care continuum was highest among the youngest age group. Levels of engagement were generally lower in the other age groups, but both the proportion of people who were still in care and the proportion who had started antiretroviral treatment by the end of 2020, increased with age, and exceeded 95% in people aged 50 years or older (*Figure 1.16B*). As a consequence, the proportion of people with viral suppression also increased with age; rising from 82% among those aged 15 to 24 years, to more than 90% for people aged 50 years or older.

Figure 1.16: Continuum of HIV care: (A) by region of origin, and (B) by age group for the total HIV-1-positive population. 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 southeast Asia; Other=other regions of origin; ART=antiretroviral treatment.

Continuum of care 2019

We also re-estimated the continuum of HIV care for 2019 and found that, by the end of that year, 24,000 (95% CI 23,800-24,400) people were living with HIV in the Netherlands, which was similar to the estimated 23,700 (23,400-24,100) reported in last year's report[1]. While the number diagnosed (22,071 compared to 21,969), the number retained in care (20,824 compared to 20,710), and the number of those who started antiretroviral treatment (20,698 compared to 20,478) were very similar to last year's report, the number with viral suppression (19,989 compared to 19,625) was somewhat higher in this re-estimation of the figures. This is due to the fact that the backlog in the collection of data on start of treatment and on viral load measurements in 2019, has now been mostly cleared. As a result, the 2019 estimate for the UNAIDS 95-95-95 target has been adjusted and has changed slightly from 93-93-96 in last year's report, to 92-94-97 in this year's report. When the 2020 HIV continuum of care is recalculated next year, a comparable change is expected.

Figure 1.15A shows the distribution across the gaps in the care continuum for the 3,988 individuals who were likely to have an unsuppressed viral load by the end of 2019. Proportions of people lost to care, not yet on antiretroviral treatment, or with a viral load measurement above 200 copies/ml were similar to 2020 figures. However, the proportion of individuals with undiagnosed HIV was larger in 2019 (48%) than in 2020 (41%), with 1,970 (95% CI 1,780-2,370) individuals yet to be diagnosed by the end of 2019, compared to 1,640 by the end of 2020. In contrast, the proportion without a viral load measurement was smaller (6%) in 2019 than in 2020 (17%), which, as mentioned before, may be related to a reduction in outpatient clinic visits during the COVID-19 pandemic, and clearing the backlog in data collection on viral load measurements.

Continuum of HIV care – regional level

We also determined the continuum of care, including the first stage of people estimated to be living with HIV, for the eight STI surveillance regions[c] in the Netherlands, and for the four largest cities in the country (*Table 1.4*). More than half (54%) of all people estimated to be living with HIV by the end of 2020 were in Noord-Holland/Flevoland and in Zuid-Holland Zuid, which include the cities of Amsterdam and Rotterdam. In these two regions, 720 (47%) people were estimated to be living with undiagnosed HIV. All eight regions had reached or surpassed the UNAIDS' 90-90-90 targets for 2020, and the proportion of all people living with HIV who had a suppressed viral load, including those yet to be diagnosed, varied between 81% and 85%. Engagement in the various stages of the care continuum among those diagnosed and linked to care was similar between the 25 public health service regions in the Netherlands (*Table 1.5*).

c *Reporting to the national STI surveillance system is organised in eight regions, which each consist of one or more public health service regions (see also Table 1.5).*

Table 1.4: *Continuum of care by the end of 2020 for the total HIV-1-positive population living in the Netherlands in each of the eight sexually-transmitted infection (STI) surveillance regions, or in one of the four major cities. For each region or city, percentages on the first row are relative to the estimated number of people living with HIV, while those on the second row correspond to UNAIDS' 95-95-95 targets. For 190 individuals diagnosed and linked to care, region of residence was unknown.*

	Estimated living with HIV		Diagnosed and linked to care	
	Undiagnosed	Total		
	n	n	n	%
Region				
Noord	110	1,340	1,231	92
	90-220	1,320-1,450		*92*
Oost	220	2,690	2,469	92
	170-330	2,640-2,800		*92*
Utrecht	110	1,420	1,303	92
	70-190	1,380-1,500		*92*
Noord-Holland/Flevoland	420	9,090	8,670	95
	310-570	8,980-9,240		*95*
Zuid-Holland Noord	130	1,810	1,680	93
	100-230	1,780-1,910		*93*
Zuid-Holland Zuid	300	3,780	3,477	92
	220-390	3,700-3,870		*92*
Zeeland/Brabant	170	2,530	2,354	93
	120-250	2,480-2,610		*93*
Limburg	70	1,030	958	93
	40-130	1,000-1,090		*93*
Total	1,540	23,680	22,144	93
	1,370-1,820	23,520-23,970		*93*
City				
Amsterdam	300	6,420	6,120	95
	220-400	6,340-6,520		*95*
Rotterdam	130	2,080	1,950	94
	80-200	2,030-2,150		*94*
Den Haag	80	1,290	1,212	94
	60-150	1,270-1,360		*94*
Utrecht	50	580	533	92
	30-110	570-650		*92*
Total	560	10,370	9,813	95
	460-700	10,280-10,510		*95*

Retained in care		Antiretroviral treatment		Viral suppression	
n	%	n	%	n	%
1,173	88	1,169	87	1,115	83
			95		*95*
2,385	89	2,368	88	2,262	84
			96		*96*
1,244	88	1,234	87	1,192	84
			95		*97*
8,208	90	8,167	90	7,725	85
			94		*95*
1,607	89	1,598	88	1,505	83
			95		*94*
3,284	87	3,253	86	3,054	81
			94		*94*
2,213	88	2,203	87	2,097	83
			94		*95*
904	88	903	88	855	83
			94		*95*
21,019	89	20,895	88	19,804	84
			94		*95*
5,802	90	5,775	90	5,496	86
			94		*95*
1,832	88	1,812	87	1,706	82
			93		*94*
1,160	90	1,150	89	1,082	84
			95		*94*
507	87	502	87	488	84
			94		*97*
9,300	90	9,240	89	8,772	85
			94		*95*

Table 1.5: Continuum of HIV care for the total HIV-1-positive population in the Netherlands diagnosed and linked to care, stratified by the public health service region in which people were living at the end of 2020. 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**	**%**
Noord			
Groningen	599	572	95
Fryslân	354	339	96
Drenthe	278	262	94
Oost			
IJsselland	369	359	97
Twente	444	428	96
Noord- en Oost-Gelderland	494	481	97
Gelderland Midden	745	715	96
Gelderland-Zuid	417	402	96
Utrecht			
Regio Utrecht	1,303	1,244	95
Noord-Holland/Flevoland			
Flevoland	571	532	93
Gooi & Vechtstreek	298	285	96
Hollands Noorden	459	430	94
Zaanstreek-Waterland	389	372	96
Amsterdam	6,365	6,038	95
Kennemerland	588	551	94
Zuid-Holland Noord			
Haaglanden	1,680	1,607	96
Zuid-Holland Zuid			
Hollands Midden	566	535	95
Rotterdam-Rijnmond	2,599	2,449	94
Dienst Gezondheid & Jeugd ZHZ	312	300	96
Zeeland/Brabant			
Zeeland	237	223	94
West-Brabant	587	558	95
Hart voor Brabant	861	812	94
Brabant-Zuidoost	670	620	93
Limburg			
Limburg-Noord	401	375	94
Zuid Limburg	557	529	95
Unknown	192	136	71
Total	**22,336**	**21,155**	**95**

	Antiretroviral treatment		Viral suppression	
	n	%	n	%
	570	95	539	90
	338	95	327	92
	261	94	249	90
	358	97	352	95
	424	95	407	92
	479	97	461	93
	709	95	667	90
	399	96	374	90
	1,234	95	1,192	91
	530	93	505	89
	283	95	271	91
	428	93	379	83
	370	95	342	88
	6,008	94	5,719	90
	548	93	509	86
	1,598	95	1,505	90
	530	94	498	88
	2,428	93	2,278	88
	295	95	278	89
	222	94	194	82
	554	94	523	89
	810	94	779	90
	617	92	600	90
	375	94	351	87
	528	95	504	90
	132	69	121	63
	21,027	**94**	**19,925**	**89**

In total, 10,370 (95% CI 10,280-10,510) people living with HIV were estimated to be living in the four largest cities in the Netherlands; 43% of the total number of people in the country living with HIV. Of these 10,370 people, 560 (460-700) were estimated to be undiagnosed (34% of the national estimate of 1,640 individuals with an undiagnosed HIV infection). Of the four cities, Amsterdam had the largest population of people living with HIV; an estimated 6,420 (6,340-6,520) individuals, of whom 300 (220-400) were still undiagnosed (*Table 1.4*). Of the 10,370 people living with HIV in the four largest cities, 9,813 (95%) had been diagnosed and linked to care, 9,240 (89%, or 94% of those diagnosed) had started antiretroviral treatment, and 8,772 (85%, or 95% of those on treatment) had a suppressed viral load. All four cities had reached or surpassed the UNAIDS' 90-90-90 targets for 2020 with the current combined estimate for the cities standing at 95-94-95.

As shown in *Tables 1.4* and *1.5*, some of the regions have relatively small numbers of people living with HIV. Estimates of the undiagnosed population are based on observed annual numbers of newly-diagnosed HIV infections and on the CD4 count distribution at the time of diagnosis. With an increasingly smaller annual number of diagnoses, estimates become more sensitive to year-on-year fluctuations in newly-diagnosed infections. As a result, the relative uncertainty in the estimates becomes larger. In this respect, it is reassuring that the total estimated number of 1,540 (95% CI 1,370-1,820) individuals living with undiagnosed HIV across the eight STI surveillance regions, is close to the number of 1,640 (1,400-2,180) we have estimated for the total nationwide population. Another source of uncertainty that is not quantified in the estimates, is that information on the region or city where people are living, is only recorded when people first enrol in care, or move to another HIV treatment centre. People moving in or out of a region or city without changing their HIV treatment centre, will not have their region of residence updated in the SHM records.

Trans people

Of the 28,745 individuals with an HIV-1 infection, 222 were trans people; 212 (95%) transwomen and 10 (5%) transmen. In this group of 222 individuals, the most commonly-reported regions of origin were South America (81, 36%), the Caribbean (47, 21%), the Netherlands (43, 19%), and south and southeast Asia (24, 11%). Interestingly, many of the trans people originated from only a few specific countries. Among the 81 individuals from South America, there were 21 people from Ecuador, 19 from Brazil, 10 from Venezuela, and nine from Suriname. Most frequently reported countries of origin in the Caribbean were the former Netherlands Antilles (18) and Cuba (12), while 12 people from south and southeast Asia originated from Thailand.

In total, 52 trans people, or 29% of those born abroad, had a documented HIV-1 diagnosis before moving to the Netherlands. The majority (37) of these 52 people had already started antiretroviral treatment before arrival. A viral load measurement around the time of arrival was available for 31 people, and showed that 19 (61%) had a viral load below 200 copies/ml.

Among the 40 trans individuals diagnosed in 2018 or later while living in the Netherlands, 12 were diagnosed with a late-stage HIV infection, which is 34% of the 35 people for whom the stage of infection could be classified. In total, among the individuals diagnosed in 2018 or later, 13 had a negative HIV test in the 12 months prior to diagnosis, seven of them in the six months prior to diagnosis. The 40 trans people were relatively young at the time of their HIV diagnosis, with a median age of 29 (IQR 28-35) years, and most of them (32) were born abroad.

In total, 174 (78%) of the 222 HIV-1-positive trans individuals were known to be in clinical care by the end of 2020. Of the 48 people who were not in care anymore, ten had died, including four who died of AIDS, and 14 had moved abroad. The remainder were either lost to care (20), were only diagnosed with HIV in 2021 (three), or only moved to the Netherlands in 2021 (one). In total, 11 of the people who moved abroad and 11 of those lost to care had RNA levels below 200 copies/ml at their last viral load measurement.

The majority of people in clinical care (169, or 97%), had started antiretroviral treatment by the end of 2020. Two other individuals started treatment in 2021. Of the 169 people in care with a viral load measurement in 2020, 156 (92%) had a last measurement in that year below 200 copies/ml; this proportion was 94% when considering individuals who had started treatment. The most recent CD4 count in 2020 of the people in care stood at a median of 710 (IQR 528-990) cells/mm^3, which was comparable to the CD4 counts in the total population in care.

HIV-2

In total, 101 of the 30,015 registered individuals with HIV, acquired an HIV-2 infection (46 men and 55 women); 17 of these were diagnosed in 2011 or later. The majority (80, or 79%), acquired their infection via heterosexual sex. HIV-2 is endemic in West Africa, and 65 people originated from this region, mostly from Ghana (25 people) or Cape Verde (24 people). Twenty-two individuals were born in the Netherlands.

By the end of 2020, a total of 62 people were still in clinical care, 20 had died, seven had moved abroad, and 12 had no contact with HIV care during that year. The median age of the people still in care was 61 (IQR 53-65) years; 53 (85%) individuals were 50 years or older. The majority (79%) of those in care had been living with HIV-2 for more than 10 years, while 37% had been living with it for more than 20 years.

Of the 62 people still in care, 43 had a most recent viral load measurement below 500 copies/ml, three had a viral load above 500 copies/ml, and 16 people had no available HIV-2 RNA result in 2020. Most people in care (39, 63%), had started antiretroviral treatment. Of the 23 individuals who were still in care but had yet to start treatment, 15 had a viral load measurement below 500 copies/ml, while only one individual had a viral load above 500 copies/ml; the other seven people had no RNA measurement in 2020. CD4 counts in the group of 62 people in care were a median of 660 (IQR 450-880) cells/mm^3.

Conclusions

Since 2008, there has been a steady decrease in the annual number of new HIV diagnoses – in recent years, the figure has fallen below 700. This downward trend continued in 2020 with approximately 411 new diagnoses, although there is some uncertainty concerning this figure because, at the time of writing, not all people diagnosed in 2020 were registered in the SHM database. The decrease in HIV diagnoses is, in part, a consequence of a fall in the estimated annual number of newly-acquired HIV infections. However, as a result of disrupted testing services in 2020, due to the partial lockdown in response to COVID-19, the number of diagnoses in 2020 may be somewhat lower than expected if we look at the long-term declining trend.

Although the number of consultations at sexual health centres in 2020 was 30% less than in 2019[4], our data did not show a reduction in the proportion diagnosed with HIV at these locations. One reason for the absence of such a reduction may be that consultations were only 18% lower in 2020 for MSM, which is the group in which the majority of HIV infections are diagnosed. Also, decreased testing for HIV was partially offset by stricter triaging.

A large proportion (50%) of newly-diagnosed individuals already had late-stage HIV infection (i.e., CD4 counts below 350 cells/mm^3 or AIDS) at the time of diagnosis. The somewhat higher proportions with late-stage HIV in 2020 may be a result of scaled-back testing services and stricter triaging, which increased the likelihood that people with symptoms of late-stage HIV were diagnosed, rather than people

without symptoms. Nevertheless, our data show that the downward trend in the proportion diagnosed with late-stage HIV has halted and numbers may even be increasing. This may, however, be a consequence of earlier diagnosis in other groups: the rapid diagnosis of people with early HIV infection, in combination with decreasing numbers of people newly acquiring an HIV infection, mean the undiagnosed population is mainly comprised of people who have been living with HIV for longer periods. Therefore, the observed proportion with late-stage HIV is the result of underlying dynamics in transmission and diagnosis and may be less suitable as an indicator of late-stage HIV. The absolute number diagnosed with late-stage HIV is more useful and this number is still steadily, albeit gradually, decreasing.

In recent years, almost all newly-diagnosed individuals started antiretroviral treatment within six months of diagnosis, irrespective of the stage of their HIV infection. This earlier treatment, combined with increased testing, earlier diagnosis and a decreasing number of newly-acquired HIV infections, has resulted in the Netherlands continuing to surpass the UNAIDS' 2020 targets of 90-90-90. The Netherlands is now close to achieving the UNAIDS' 2025 targets of 95-95-95, with the current figures standing at 93-94-95[14]. In MSM, the 95-95-95 target has already been reached, in part as a consequence of a 91% decrease in annual numbers of newly-acquired HIV infections, compared with 2010[2,3].

National Action Plan on STIs, HIV and Sexual Health 2017–2022

One of the goals set by the National Action Plan on STIs, HIV and Sexual Health is to achieve a 50% reduction in the annual number of newly-diagnosed HIV infections by 2022, compared with 2015 figures[15]. In 2020, there were approximately 411 newly-diagnosed infections, which is a reduction of 54%, compared to the 894 diagnoses in 2015. Although this means this specific goal has already been reached, some caution is warranted as the number of diagnoses in 2020 may have been below the long-term decreasing trend in diagnoses due to reduced testing services during the 2020 partial lockdown.

A second goal in the National Action Plan is to reach the Joint United Nations Programme on HIV/AIDS' (UNAIDS) 95-95-95 target by 2022, three years earlier than the UNAIDS' target year of 2025. By the end of 2020, the overall estimate in the Netherlands stood at 93-94-95, while in MSM the National Action Plan target had been reached (96-96-96). Earlier diagnosis of people living with HIV and retaining people in care will both be key to reaching and surpassing this specific goal in all groups affected by HIV.

Recommendations

A reassessment of the continuum of HIV care for 2019, showed a considerable increase in the number of individuals who achieved viral suppression by the end of that year, compared to the figures reported in last year's report. To more reliably monitor progress towards achieving the UNAIDS' 95-95-95 goal for 2025, a more timely registration of viral load measurements is needed. This can be markedly improved by further extending the automated import of laboratory measurements (LabLink) into the SHM database to all HIV treatment centres in the Netherlands. At present, LabLink is available for 19 of the 24 HIV treatment centres, which together treat approximately 74% of all people followed by SHM.

One of the care continuum indicators that is not performing as well as some others, is the proportion of people who are still in care. In total, 1,961 individuals who were diagnosed in or before 2020, and had been registered with SHM, were marked as lost to care (i.e., they did not visit their HIV physician or nurse in 2020, but they were not known to have died or moved abroad). The large proportion of people born abroad among those lost to care suggests that some may have left the Netherlands and are now receiving care in a different country. Since most individuals who are not receiving care, and treatment, will have an unsuppressed viral load, it is important to more accurately quantify the number truly lost to care, and better understand possible underlying reasons.

The decrease in the number of new HIV diagnoses is likely, in part, to be the result of various positive developments mentioned earlier in this chapter. These include 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) became 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. Major steps towards achieving this goal would be lifting the current restrictions on community-based and home-based HIV testing, which is planned for next year, and increasing awareness of sexual risk behaviour.

Worryingly, a substantial number of individuals are diagnosed with late-stage or advanced HIV infection. This is even the case among MSM, despite a high proportion being diagnosed within a year of infection. Clearly, there are groups of MSM and other populations that the existing prevention and testing approaches do not reach. Recently, a project called Last Mile was started within the HIV Transmission Elimination Amsterdam Initiative (H-TEAM) to improve our understanding of the reasons and motivations for delayed testing in people presenting for care with late-stage HIV. Data from this first phase of the project showed important factors for receiving a late-stage HIV diagnosis were people's personal relationship with health professionals, low-risk perceptions, fear related to the outcome of testing, and also institutional barriers and missed opportunities during client-provider interactions[16]. These findings 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.

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Special report

COVID-19 in people living with HIV in the Netherlands

Ferdinand Wit, Peter Reiss, Marc van der Valk

In this special chapter, we report on the consequences of the COVID-19 pandemic on the population of people living with HIV in the Netherlands. In the first section, we focus on the incidence of, and risk factors for severe COVID-19 in people living with HIV. The second section discusses the impact the COVID-19 pandemic has had on HIV care in general.

Incidence, risk factors, and outcomes of COVID-19 in people living with HIV

Background

The first documented case of SARS-CoV-2 infection in the Netherlands was on 27 February 2020[1]. By September 2021, an estimated cumulative 1.9 million Dutch individuals had acquired a SARS-CoV-2 infection, resulting in about 18,000 deaths[1]. The majority of SARS-CoV-2 infections result in a self-limiting disease with minor or mild symptoms. However, certain groups are at increased risk of severe COVID-19, hospitalisation, and death; for example, older individuals, men, certain ethnic groups, people with lower socio-economic status, and people diagnosed with certain ageing-associated, non-communicable comorbidities like obesity, hypertension, renal dysfunction, diabetes mellitus, and cardiovascular disease. People with certain inborn immunodeficiency syndromes, haematological malignancies, solid organ transplants, and people receiving immunosuppressive treatment are also at increased risk of severe outcomes. Currently, there are insufficient data available to confirm whether people living with HIV are at greater risk of developing severe COVID-19 than the general population: some studies suggest the risk is similar[2-8], while others suggest an increased risk of severe outcomes[9-13]. However, while most of these studies adjusted their analyses for age, sex, ethnicity, and comorbidities, many were conducted using data from general COVID cohorts, and missed detailed information on important HIV-related parameters, like use of antiretroviral therapy, plasma HIV-1 viremia, prior AIDS diagnoses, and current and nadir CD4 cell counts. Therefore, it also remains unclear whether, if people living with HIV are at greater risk of developing severe COVID-19, those risks are driven by differences in demographic characteristics, a high prevalence of non-HIV-related comorbidities, and/or HIV-related parameters. Many of the risk factors for severe COVID-19 in the general population are more prevalent in people living with HIV.

We describe the incidence, risk factors, and outcomes of COVID-19 in people living with HIV in the Netherlands using data collected up to 6 September 2021.

Methods

Stichting hiv monitoring (SHM) records relevant HIV-related and ART-related data, including diagnosis of, and hospitalisations for COVID-19, for all consenting people living with HIV in the Netherlands. SHM uses automated electronic queries of electronic medical records (EMR) in the HIV treatment centres to quickly identify new diagnoses of, and hospitalisations for COVID-19 and prioritises data collection on these events. However, data collection does not happen in real time, so delays remain between the COVID-19 event happening, the information being recorded in the EMR in the treatment centres, and the moment the data is captured by SHM and becomes available for analysis.

Details regarding diagnosis, disease severity, hospitalisations, and outcomes of COVID-19 are also collected. SHM data collection of COVID-19 events is based on the WHO International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) COVID-19 case report forms[14]. Hospitalised patients are the main focus of our data collection, as individuals with COVID-19 who are not admitted to hospital, rarely have reliable, detailed information documented in their EMR in HIV treatment centres for SHM to capture. SHM has not (yet) established links to other COVID-19 providers and cohorts/datasets, so direct comparisons with other patient populations cannot currently be made. Data on SARS-CoV-2 vaccination are also not yet available.

Objective measures of COVID-19 disease severity could often not be recorded by SHM, as these data were not systematically recorded in EMRs, especially for people who weren't hospitalised. In addition, detailed information on COVID-19 disease severity was often not available for patients who had been hospitalised for COVID-19, if the hospital differed from the one in which they received their HIV care. Therefore, we used data on hospitalisation for COVID-19 as a proxy for COVID-19 disease severity: cases of COVID-19 were classified as 'very severe' (admission to an intensive care unit [ICU]), 'severe' (requiring hospitalisation but no ICU admission), 'moderate' (requiring a visit to the emergency room but no hospitalisation), or 'mild' (requiring no medical care, or care by the family practitioner only).

Risk factors for (very) severe COVID-19 (hospitalisation and death), were investigated using multivariable logistic regression including relevant demographics (age, sex, region of origin), general risk factors (comorbidities), and HIV-related parameters.

Findings

By 6 September 2021, SHM had collected data on 1,308 probable (SARS-CoV-2 PCR-negative but with a strong clinical suspicion, n=19, 1.5%), and definitively-diagnosed (SARS-CoV-2 PCR-positive, n=1,289, 98.5%) SARS-CoV-2 infections in people living with HIV (*Table SR1*). An additional 201 possible COVID-19 events were reported by individuals who experienced mild symptoms but had no positive SARS-CoV-2 PCR test; these mostly occurred in the early months of the pandemic in 2020, when SARS-CoV-2 testing was not (widely) available. None of the 201 possible events resulted in hospitalisation and they are not further considered in this report.

Of the 1,308 recorded COVID-19 events, 109 (8.3%) resulted in hospitalisation; 18 (1.4%) of which required ICU admission. An additional 37 (2.8%) individuals presented with COVID-19 at an emergency room but required no hospitalisation, and the remaining 1,162 (88.8%) individuals remained at home.

The characteristics of the overall population living with HIV in care in the Netherlands in 2020 is described in *Chapter 2*, *Table 2.2*. Compared to the total population living with HIV, those who were hospitalised for COVID-19 were older, were more likely to have acquired HIV through heterosexual contact (both men and women), and were more likely to be born in sub-Saharan Africa or Latin America (including the Caribbean). Overall, men were not more likely than women to be hospitalised for COVID-19; the percentage of men among hospitalised patients (75.9%) was even somewhat lower than in the total population living with HIV (82.2%).

Regarding HIV-related characteristics, there were only minor differences between people living with HIV who were diagnosed with COVID-19, and the total population living with HIV, with the overwhelming majority being on ART, with a plasma HIV-1 viral load below 200 cps/mL, and a high median CD4 cell count well above 500 cells/mm^3. There were, however, noticeable differences between people diagnosed with COVID-19 who were hospitalised and those who weren't hospitalised; for example, the former had generally been HIV-positive for longer, but this is most likely driven by the fact that those who were hospitalised were on average eight years older. Furthermore, those who were hospitalised had lower current and nadir CD4 cell counts, and had more frequently had a prior AIDS diagnosis, compared to those not hospitalised (*Table SR1*).

Table SR1: Characteristics of individuals diagnosed with COVID-19.

	Hospitalised	Emergency room visit, but not hospitalised	Not hospitalised
n	109	37	1,162
Age, years	57.0 (51.2-65.2)	53.2 (46.6-58.7)	49.1 (40.1-56.9)
Male sex	75.9%	70.3%	81.7%
HIV transmission category			
MSM	42.6%	37.8%	67.4%
Other men	33.3%	32.4%	14.3%
Women	24.1%	29.7%	18.3%
Region of origin			
Netherlands / Europe / North America	45.0%	43.2%	59.2%
Sub-Saharan Africa	22.0%	13.5%	10.9%
Latin America / Caribbean	22.0%	16.2%	18.0%
Years known to be HIV positive	15.8 (9.9-22.5)	13.2 (9.6-19.6)	11.9 (6.9-17.2)
On ART	99.0%	100%	99.3%
HIV viral load >200 cps/mL	5 (4.7%)	3 (8.3%)	22 (1.9%)
Viral load (when detectable) in cps/mL	40,000 (6,049-62,743)	3,935 (557-43,000)	1,046 (588-52,488)
Current CD4 count, mm^3	559 (396-821)	600 (490-780)	718 (539-890)
Nadir CD4 count, mm^3	176 (60-275)	240 (74-353)	266 (140-398)
Prior AIDS diagnosis	38.0%	21.6%	18.1%

Legend: n (%) or median (IQR), as appropriate; MSM=men who have sex with men; cps/ml=copies per millilitre; ART=antiretroviral therapy.

Table SR2: Prevalence of comorbidities among people living with HIV who were diagnosed with COVID-19.

	Hospitalised	Emergency room presentation	Not hospitalised
Number of individuals with available data	100 of 109 (91.7%)	37 of 37 (100%)	1,122 of 1,162 (96.6%)
Obesity (BMI>30 kg/m²)	28 (28.0%)	3 (8.1%)	165 (14.7%)
Diabetes mellitus type 2	17 (17.0%)	3 (8.1%)	47 (4.2%)
Cardiovascular disease	8 (8.0%)	2 (5.4%)	22 (2.0%)
Stroke	9 (9.0%)	2 (5.4%)	19 (1.7%)
Hypertension (grade 2+ or on medication)	17 (17.0%)	4 (10.8%)	65 (5.79%)
Non-AIDS-defining malignancy	8 (8.0%)	1 (2.7%)	26 (2.3%)
Chronic kidney disease (eGFR<60 ml/min)	6 (6.0%)	2 (5.4%)	7 (0.6%)
Multimorbidity count			
0	39 (39.0%)	26 (70.3%)	833 (74.2%)
1	35 (35.0%)	9 (24.3%)	236 (21.0%)
2 or more	26 (26.0%)	2 (5.4%)	53 (4.7%)

Legend: *BMI=body mass index; eGFR=estimated glomerular filtration rate in millilitres per minute.*

Table SR2 shows the distribution of selected comorbidities among individuals diagnosed with COVID-19. All investigated comorbidities were much more prevalent among the group that was hospitalised, resulting in a higher total multimorbidity count in the hospitalised group.

Multivariable logistic regression showed that independent risk factors for hospitalisation for COVID-19 among people living with HIV were higher age, migrant status (with higher risk in individuals originating from sub-Saharan Africa or, to a lesser extent, from Latin America), obesity (BMI over 30 kg/m²), having a current CD4 count below 500 cells/mm³ (the risk was even higher when the CD4 cell count was below 200 cells/mm³), and having had a prior AIDS-defining illness (*Table SR3*). All other demographic, comorbidity, HIV-related and ART-related parameters investigated were not independently associated with a higher risk of being hospitalised following a diagnosis of COVID-19. It is noteworthy that since the moment that people living with HIV became eligible for the national SARS-CoV-2 vaccination program in April 2021, there has been a strong reduction in COVID-19-related diagnoses and hospitalisations among the population living with HIV. In May 2021, only seven hospitalisations were recorded, another one in July 2021, and there have been none since.

The median duration of hospitalisation was six (interquartile range [IQR] 3-14) days. Individuals who were admitted to the ICU remained hospitalised for a median of 25 (IQR 9-40) days; the median duration of hospitalisation was 28 (IQR 14-51) days in those who survived.

In total, 19 (1.4%) of the 1,308 people living with HIV diagnosed with SARS-CoV-2 were reported to have died as a direct result of COVID-19. The observed mortality rates in the various age groups were: 0% (n=0) in 304 aged 18-39 years, 0.3% (n=1) in 342 aged 40-49 years, 0.7% (n=3) in 417 aged 50-59 years, 2.8% (n=5) in 182 aged 60-69 years, 12.0% (n=6) in 50 aged 70-79 years, and 50% (n=4) in eight aged 80 years and over. For five individuals, age was unknown. Of the 19 individuals that died, 12 (of a total of 109, 11.0%) had been hospitalised for COVID-19 (five of whom had been admitted to the ICU [out of a total of 18, 27.8%]), two had visited the emergency room (out of a total of 37, 5.4%), and five had not been hospitalised (out of a total of 1,162, 0.4%). Of the seven individuals who had not been hospitalised and had died, five were known to be living in a nursing home prior to their COVID-19 diagnosis. Of the remaining two individuals who had not been hospitalised, but who died of COVID-19, one individual was a stroke survivor with three additional major comorbidities, and one individual was a 60-year-old woman from sub-Saharan Africa, with no known comorbidities, a good treatment response on ART, a current CD4 between 200 and 250, and a nadir CD4 cell count below 100.

Table SR3: *Independent predictors of hospitalisation among people living with HIV who were diagnosed with COVID-19.*

Risk factor	OR (95% CI)	P-value
Age (per 10 years increase)	1.9 (1.1-2.3)	<0.0001
Region of origin		
Europe / North America	1	
Sub-Saharan Africa	2.9 (1.6-5.4)	0.0007
Latin America	1.7 (0.9-2.9)	0.086
Obese (BMI>30)	2.2 (1.3-3.7)	0.0018
Current CD4 count, cells/mm^3		
0-199	5.9 (2.4-14.7)	0.0001
200-499	1.9 (1.1-3.0)	0.013
500+	1	
Prior AIDS diagnosis	1.9 (1.2-3.0)	0.0061

Legend: *BMI=body mass index.*

Table SR4 shows the demographics, HIV-related characteristics, and comorbidities of those who died from COVID-19, compared to those who survived. As expected, there were very substantial differences.

Because of the low number of COVID-19-related deaths, statistical power to formally explore risk factors using regression analysis is low. Exploratory multivariable logistic regression models showed that independent risk factors for COVID-19-related mortality were higher age, having a sub-Saharan African or Latin American origin, having a higher number of concomitantly diagnosed comorbidities, having a current CD4 count below 500/mm^3 (with the risk being even higher when the CD4 cell count was below 200/mm^3), and having a detectable plasma HIV-1 viral load of more than 200 cps/ml *(Table SR5*). However, because of low statistical power, these findings should be interpreted with caution; the observed associations are based on very few observations and hence the model's estimates are likely inflated. SARS-CoV-2 vaccinations among people living with HIV not only resulted in a drop in COVID-19-related hospitalisations, but a similar strong reduction in COVID-19-related deaths. The last COVID-19-related death was recorded in April 2021.

Table SR4: *Characteristics of individuals diagnosed with COVID-19 who died from COVID-19 compared to those who survived.*

	Survived	Died of COVID-19
Number of individuals	1,289	19
Age, years	49.9 (40.5-57.5)	70.1 (64.9-78.5)
Male sex	80.9%	79.0%
HIV transmission category		
MSM	64.9%	42.1%
Other men	16.0%	36.8%
Women	19.1%	21.1%
Region of origin		
Netherlands / Europe / North America	57.8%	42.1%
Sub-Saharan Africa	11.9%	15.8%
Latin America / Caribbean	18.0%	36.8%
Years known HIV-positive	12.2 (7.1-17.6)	18.7 (13.6-23.5)
On ART	99.3%	100%
HIV viral load <200 cps/mL	97.7%	94.7%
Current CD4 cell count, cells/mm^3	708 (525-889)	391 (250-719)
Nadir CD4 cell count, cells/mm^3	260 (130-390)	119 (62-200)
Prior AIDS diagnosis	19.5%	36.8%
Comorbidities		
Number of individuals with available data	1,242 of 1,289	18 of 19
Obesity (BMI>30)	15.6%	16.7%
Diabetes mellitus	5.0%	27.8%
Cardiovascular disease	2.3%	16.7%
Stroke	1.9%	33.3%
Hypertension (grade 2+ or on medication)	6.1%	55.6%
Non-AIDS-defining malignancy	2.6%	16.7%
Chronic kidney disease (eGFR<60 ml/min)	0.8%	27.8%
Multimorbidity count		
0	72.1%	16.7%
1	22.4%	16.7%
2	4.8%	38.9%
3	0.7%	11.1%
4 or more	0.1%	16.7%

Legend: *n (%) or median (IQR), as appropriate; MSM=men who have sex with men; cps/ml=copies per millilitre; ART=antiretroviral therapy; BMI=body mass index; eGFR=estimated glomerular filtration rate in millilitres per minute.*

Table SR5: Independent predictors of mortality among people living with HIV who were diagnosed with COVID-19.

Risk factor	OR (95% CI)	P-value
Age (per 10 years increase)	8.9 (3.7-21.0)	<0.0001
Region of origin		
European / North America	1	
Sub-Saharan Africa	6.1 (0.8-22.9)	0.078
Latin America	4.8 (1.0-22.9)	0.048
Number of concomitantly diagnosed comorbidities (per 1 comorbidity increase)	2.9 (1.5-5.6)	0.0017
Current CD4 count (cells/mm^3)		
0-199	12.2 (1.4-105.4)	0.023
200-499	7.3 (1.7-32.3)	0.0080
500+	1	
HIV-1 viral load >200 copies/mL	11.0 (1.9-64.3)	0.0077

Impact of the COVID-19 pandemic on HIV care in the Netherlands

The COVID-19 pandemic has had an unprecedented impact on healthcare systems in virtually every country in the world, including on the delivery of care in HIV treatment centres in the Netherlands. Many members of HIV treatment teams were, and are still actively engaged in frontline COVID-19 care. Serious restrictions were put in place on access to standard HIV care at times when hospitals were experiencing peak hospitalisation rates for COVID-19.

In 2020, there were approximately 411 newly-diagnosed HIV infections, a figure that was lower than expected based on numbers in previous years. This may be the result of disrupted testing services, due to the partial lockdown in response to COVID-19 in 2020, but it could also be, in part, the result of a backlog in notifying SHM of new HIV diagnoses. Aside from this, the impact of COVID-19-related restrictions on the HIV epidemic appears to have been limited. For instance, of those diagnosed in 2020, 30% received their first HIV-positive test result at a sexual health centre, 29% at a hospital, and 35% at a general practice. These proportions are the same as those reported for 2019.

At times, HIV care providers were required to severely restrict the number of non-emergency routine visits to HIV outpatient clinics. Nevertheless, 91.9% of individuals in care had a documented contact with their HIV care provider in 2020 (either via a physical consultation, telemedicine or contact by email), compared to 89.7% in 2019. There were only slight decreases in the percentage of individuals still in care receiving plasma HIV RNA and CD4 cell count testing. The percentage

tested at least once for plasma HIV RNA was 98.9% in 2019 and 96.7% in 2020, and the percentage tested at least once for CD4 cell count was 80.6% in 2019 and 74.8% in 2020. These percentages are compared across centres in *Chapter 7*.

Since the start of the COVID-19 pandemic, there has been a large shift from standard-of-care, six-monthly visits at the HIV outpatient clinics to telemedicine using phone and video calls. The percentage of patients who had a physical consultation with an HIV specialist decreased from 93.4% in 2019 to 45.2% in 2020. The percentage of patients who had a physical consultation with another specialist, consultant, or nurse consultant/specialist similarly decreased from 32.5% in 2019 to 19.0% in 2020. In contrast, the percentage of patients who had a non-physical consultation with any type of healthcare professional increased from 12.5% in 2019 to 63.8% in 2020. Most of these consultations occurred over the telephone or via email (94.4%) and a few occurred virtually using video consultation (1.6%) or other means (5.1%). The differences in how each centre transitioned from physical to non-physical consultations can be found in *Chapter 7*.

In *Chapter 2*, we observed that despite restrictions on routine HIV care, there was a further decrease in the time between HIV diagnosis and the start of cART (*Figures 2.1A* and *2.1B*). The median CD4 count at cART initiation was 344 cells/mm^3 (IQR 160-560), which is consistent with the observed trend in the preceding years. Of all adults in HIV care and on cART, 2.9% had no HIV-1 viral load measurement available in 2020. Of the individuals with an available measurement, 97.6% had an HIV-1 viral load below 200 copies/mL, which is not dissimilar to previous years' figures (*Table 2.2*). We observed a decrease in the number of treatment changes in 2020, compared to previous years. Between 2015 and 2019, the proportion of all patients on cART who made at least one change to their cART regimen fluctuated between 22.2% and 26.6% per calendar year; in 2020, this proportion decreased substantially to 16.4%. The distribution of the recorded reasons for switching cART were very similar to those reported for preceding years.

In *Chapter 3*, we describe HIV-related and non-HIV-related morbidity and (all-cause) mortality. Only 12 COVID-19-related deaths were recorded in 2020 (and, to date, nine COVID-19-related deaths in 2021). The observed all-cause mortality rate in people living with HIV in the period 2017-19 was stable between 8.4 and 8.5 deaths per 1,000 person years of follow up, but, in 2020, this increased slightly to 9.0 deaths per 1,000 person years of follow up (*Figure 3.1*). However, it should be noted that because of the increased average age of the population living with HIV in the Netherlands, the difference between the observed all-cause mortality rate, and the expected age-matched and gender-matched mortality rate, continued to decrease, also in 2020, in accordance with long-term trends.

The observed time trends in the incidence of major non-AIDS-defining comorbidities (diabetes mellitus, chronic kidney disease, non-AIDS-defining malignancies, myocardial infarction, stroke, and anal cancer) were not significantly different in 2020 compared to preceding years (*Figures 3.3A-G*).

Discussion

We recorded 1,308 COVID-19 events in people living with HIV in the Netherlands in the period prior to 6 September 2021. In total, 109 (8.3%) individuals were hospitalised, with 18/109 (1.4%) requiring ICU admission. These rates are likely inflated as, at the beginning of the pandemic, SARS-CoV-2 PCR testing was only available for severely ill individuals presenting at a hospital. Furthermore, not every symptomatic individual will have presented for SARS-CoV-2 testing, and probably a substantial proportion of SARS-CoV-2-infected individuals will have had asymptomatic disease. Because of these limitations, the observed rate of severe COVID-19 disease (i.e., hospitalisation and death), represents an upper bound. Not until well-designed seroprevalence studies have been conducted will we be able to reliably estimate what proportion of people living with HIV who acquire a SARS-CoV-2 infection go on to develop severe COVID-19 disease.

The observed mortality rates in people living with HIV diagnosed with COVID-19 were very low in those aged below 50 years. In the older age strata, the mortality rates quickly increased. In those hospitalised for COVID-19, the observed mortality rate was 11.0%, in those admitted to the ICU, it was 27.8%. However, in all age groups, mortality strongly clustered in individuals who either had multiple general risk factors (i.e., comorbidities), or those with poorer responses on ART (i.e., a low current or nadir CD4 count, a prior AIDS-defining condition, or a plasma HIV-1 viral load above 200 cps/mL). Furthermore, migrants born in sub-Saharan Africa or Latin America (including the Caribbean) appeared to be at increased risk of hospitalisation and death independent of age, comorbidities and HIV-related parameters. However, because of the very limited number of events, there is still the possibility of residual confounding.

As these estimated mortality rates are based on an incomplete dataset, they should be interpreted with caution. Hospitalisations and deaths because of COVID-19 are generally more quickly communicated to SHM than mild cases, and most asymptomatic cases of SARS-CoV-2 infection will have gone completely undiagnosed, probably resulting in an overestimation of the mortality rate in the group that was not hospitalised. The observed mortality rate of 0.4% in the group that was not hospitalised was further inflated by the fact that four of

the five reported COVID-19-related deaths in this group occurred in individuals in poor health living in nursing homes, and in one individual that was living at home but suffered from serious disability as the result of a prior stroke.

Migrants appear to be at increased risk of severe and fatal COVID-19 disease. In the general population, several migrant and ethnic groups are currently substantially less likely to be vaccinated. It should be noted that virtually all observed COVID-19-related mortality occurred before people living with HIV became eligible for the national SARS-CoV-2 vaccination programme, and hence a lower vaccination rate cannot explain the increased risk of mortality in migrants. However, HIV care providers should prioritise pro-actively addressing misinformation, misunderstandings, genuine concerns, and other barriers to COVID vaccination in these high-risk groups.

As comorbidities are important risk factors for severe COVID-19, and are more prevalent in people living with HIV than in the general population, vaccination is also a vitally important strategy for lowering the burden of severe COVID-19 disease in these high-risk individuals. It is expected that the high vaccination rate in the Dutch population living with HIV will prevent large numbers contracting SARS-CoV-2 and being hospitalised. However, the unvaccinated will remain at risk of severe COVID-19. It is currently unknown what proportion of people living with HIV may have an insufficient immune response to the currently-available SARS-CoV-2 vaccines, but several formal studies are underway to document the rate of and risk factors for SARS-CoV-2 vaccine failure in people living with HIV.

The COVID-19 pandemic has had an unprecedented impact on the delivery of HIV health care in the HIV treatment centres in the Netherlands. We observed no obvious deviations from the long-term trends in the number of newly-diagnosed people living with HIV, or in the time between diagnosis and entry into care and start of cART. However, only continued monitoring will make it clear whether, in the coming year(s), there will be a larger than expected number of people diagnosed with HIV, and whether a higher proportion of them will be late presenters with severely-decreased CD4 cell counts at the moment of entering HIV care.

There was a large increase in the proportion of consultations by (video) phone and emails in 2020. Laboratory monitoring was performed less often in 2020 than in preceding years, however, the vast majority of people living with HIV had an HIV-1 viral load measurement at least once during 2020. The proportion of people living with HIV on ART with a plasma HIV-1 viral load below 200 copies/mL in 2020 was very similar to preceding years, indicating that, for the majority on cART, there do not seem to have been major disruptions in their access to and ability to use cART.

There was also no significant increase in the all-cause mortality rate in 2020, compared to preceding years. There were likewise no changes in the long-term trends in the incidence of major non-HIV-related comorbidities in 2020. This suggests that there has been no significant underdiagnosis of these events in people living with HIV in 2020. However, only continued monitoring of the outcomes will show whether, in the coming year(s), the incidence (and disease stage at diagnosis) of these outcomes will increase.

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2. Response to combination antiretroviral therapy

Ferdinand Wit, Anders Boyd, Ard van Sighem, Kees Brinkman, Kees van Nieuwkoop, Anne Wensing, Marc van der Valk

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 the initiation of cART as soon as possible in all people newly diagnosed with HIV, regardless of CD4 count. The decision to initiate cART should always include consideration of a person's comorbid conditions and willingness and readiness to initiate therapy[3-7]. In general, the guidelines of the Dutch Association of HIV Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) follow the US Department of Health and Human Services guidelines[8].

Besides preventing clinical events, including tuberculosis and AIDS, the immediate start of cART is also more effective at preventing transmission of HIV than deferral of treatment until the CD4 count has dropped to a level equal to or below 350 cells/mm^3 [9,10]. People living with HIV on cART with an undetectable viral load in their blood have no risk of onward sexual transmission of HIV, (i.e., undetectable equals untransmittable, or U=U[11-16]). Depending on the drugs employed, it may take as long as six months for the viral load to become undetectable. Sustained HIV suppression requires selection of appropriate treatment and adherence to treatment. HIV viral suppression should therefore be monitored and documented to ensure both personal health and public health benefits.

Treatment with cART generally results in sustained suppression of HIV viral load to levels below the reported threshold. Nevertheless, drug resistance mutations may develop if a given agent, even when combined with other agents, cannot sufficiently prevent the selective pressures driving resistance. Over time, accumulation of mutations in the HIV genome that are associated with drug resistance can prevent sustained viral suppression, thereby increasing the risk of poor clinical outcomes[17-23].

In this chapter, 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[24]. 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.*

Between 1996 and the end of 2020, a cumulative total of 28,745 individuals (aged 15 years or older at the time of diagnosis) were registered by SHM as living with HIV-1 in the Netherlands

1. **Starting combination antiretroviral therapy**
   26,806 people were known to have initiated cART between January 1996 and December 2020.

2. **In care and on cART in the Netherlands in 2020**
   Of the 26,806 people who initiated cART between January 1996 and December 2020,
   ➔ 20,479 were in care by the end of 2020.

3. **Changes in the use of the initial cART regimen**
   Of the 26,806 people who initiated cART between January 1996 and December 2020,
   ➔ 5,389 initiated cART between January 2015 and December 2020.
   ➔ The most frequently used guideline-recommended initial regimens in 2015-20 were: ABC/3TC/DTG (25.8%), TDF/FTC/DTG (12.5%), TAF/FTC/EVG/c (12.3%), TAF/FTC/BIC (10.8%), TDF/FTC/EVG/c (7.1%), TDF/FTC/EFV (5.0%), TDF/FTC/DRV/b (4.3%), TAF/FTC/DRV/c (2.7%), TDF/FTC/RPV (2.5%), and TAF/FTC/DTG (2.5%).

4. **Virological response**
   Of the 26,806 people who initiated cART between January 1996 and December 2020,
   ➔ 22,675 people were ART-naive, not pregnant at cART initiation, and had an HIV viral load result within six months (plus or minus three months) of cART initiation.

5. HIV drug resistance

Transmitted HIV drug resistance

As of December 2020, 8,158 HIV-1 sequences had been obtained from 7,863 ART-naive people prior to initiation of cART in 2003-20.

➔ 8,149 reverse transcriptase sequences were available from 7,857 individuals.

➔ 7,758 protease sequences were available from 7,473 individuals.

➔ 42 integrase sequences were available from 42 individuals.

Acquired HIV drug resistance

As of December 2020, 4,298 HIV-1 sequences had been obtained from 2,596 people who received cART for at least four months in 2000-20.

➔ 2,959 sequences were from 1,868 people who had been ART-naive before initiating cART.

➔ 4,248 reverse transcriptase sequences were available from 2,578 individuals.

➔ 4,132 protease sequences were available from 2,495 individuals.

➔ 208 integrase sequences were available from 168 individuals.

6. Immunological response

Of the 26,806 people who initiated cART between January 1996 and December 2020,

➔ 26,330 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; ABC=abacavir; BIC=bictegravir; /b=booster; /c=cobicistat; 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, 26,806 individuals ever registered by SHM and followed in the ATHENA cohort were 15 years or older at the time of HIV-1 diagnosis, and were known to have initiated cART between January 1996 and December 2020 (*Box 2.1*). Of these, 2,135 (8.0%) had prior exposure to mono- or dual- nucleoside-analogue antiretroviral therapy (ART) at the start of cART, and 24,671 (92.0%) were ART-naive. The proportion of pre-treated people starting cART has decreased over time to less than 1%, and nowadays mostly consists of people who were diagnosed and started on ART abroad. In *Table 2.1*, we have grouped people by calendar year of cART initiation: 9,562 started in 1996-2005, 6,066 in 2006-10, 7,081 in 2011-15, and 4,097 in 2016-20.

Table 2.1 Characteristics of people starting combination antiretroviral therapy in 1996-2020.

Year of cART initiation		1996-2005	2006-2010	2011-2015	2016-2020	1996-2020
Number of individuals		9,562	6,066	7,081	4,097	**26,806**
DEMOGRAPHIC						
Age at cART initiation (years)	Median	37.5	40.2	39.4	37.7	38.6
	Q1	31.8	32.9	30.9	29.1	31.4
	Q3	44.6	47.3	48.3	49.0	46.9
Male sex (at birth)	n	7,338	4,936	6,120	3,485	21,879
	%	76.7	81.4	86.4	85.1	81.6
Transmission risk group						
Missing	n	8	8	12	13	41
	%	0.1	0.1	0.1	0.3	0.1
Men who have sex with men	n	5,010	3,722	4,877	2,664	16,273
	%	52.4	61.4	68.9	65.0	60.7
Heterosexual contact	n	3,306	1,870	1,750	1,053	7,979
	%	34.6	30.8	24.7	25.7	29.8
Injecting drug use	n	538	108	42	27	715
	%	5.6	1.8	0.6	0.7	2.7
Blood or blood products*	n	170	49	67	51	337
	%	1.8	0.8	1.0	1.2	1.3
Vertical transmission	n	2	4	3	4	13
	%	0.02	0.1	0.04	0.1	0.05
Unknown	n	528	305	330	285	1,448
	%	5.5	5.0	4.7	7.0	5.4
Region of origin						
Missing	n	48	18	27	42	135
	%	0.5	0.3	0.4	1.0	0.5
The Netherlands	n	5,162	3,405	4,202	2,095	14,864
	%	54.0	56.1	59.3	51.1	55.5
Western Europe/North America/Australia	n	945	499	485	213	2,142
	%	9.9	8.2	6.9	5.2	8.0
Eastern/central Europe	n	177	201	374	377	1,129
	%	1.9	3.3	5.3	9.2	4.2
Latin America and the Caribbean	n	1,030	717	892	631	3,270
	%	10.8	11.8	12.6	15.4	12.2
Sub-Saharan Africa	n	1,706	879	658	407	3,650
	%	17.8	14.5	9.3	10.0	13.6
Other	n	494	347	443	332	1,616
	%	5.2	5.7	6.3	8.1	6.0

Year of cART initiation		1996–2005	2006–2010	2011–2015	2016–2020	1996–2020
CLINICAL						
Recent infection	n	581	932	1,704	1,044	4,261
(within 12 months of diagnosis)	%	6.1	15.4	24.1	25.5	15.9
Ever having tested HIV-negative	n	1,986	2,468	3,883	2,248	10,585
	%	20.8	40.7	54.8	54.9	39.5
CD4 cell count at start of cART	Median	190	244	355	381	270
	Q1	80	140	220	190	130
	Q3	320	330	500	570	410
HIV RNA (log_{10}) at start of cART	Median	4.9	5.0	4.8	4.8	4.9
	Q1	4.3	4.4	4.3	4.1	4.3
	Q3	5.3	5.4	5.3	5.4	5.3
(Prior) AIDS at start of cART	n	2,961	1,149	924	543	5,577
	%	31.0	18.9	13.1	13.3	20.8
Prior mono- or dual-NRTI treatment	n	2,030	54	26	25	2,135
at start of cART	%	21.2	0.9	0.4	0.6	8.0
Hepatitis B status at start of cART						
HBV-negative (HBsAg-negative)	n	8,584	5,576	6,460	3,455	24,075
	%	89.8	91.9	91.2	84.3	89.8
HBV-positive (HBsAg-positive)	n	596	321	208	100	1,225
	%	6.2	5.3	2.9	2.4	4.6
Unknown	n	382	169	413	542	1,506
	%	4.0	2.8	5.8	13.2	5.6
Hepatitis C status at start of cART						
HCV-negative	n	8,631	5,751	6,803	3,892	25,077
	%	90.3	94.8	96.1	95.0	93.6
HCV RNA-positive	n	171	134	103	63	471
	%	1.8	2.2	1.5	1.5	1.8
HCV Ab seropositive	n	194	45	43	21	303
	%	2.0	0.7	0.6	0.5	1.1
Unknown	n	566	136	132	121	955
	%	5.9	2.2	1.9	3.0	3.6
cART started during pregnancy	n	404	229	137	73	843
	%	4.2	3.8	1.9	1.8	3.1

virus; HCV=hepatitis C virus; NRTI=nucleoside analogue reverse transcriptase inhibitor.

* *In recent years, the category 'blood or blood products' mainly contains people who have reported coming into contact with blood from other people (via fights, biting or tattoo shops) as the only possible risk factor for HIV acquisition, although this has rarely been proven by HIV testing of the purported source. Iatrogenic transmission of HIV through contaminated blood or blood products in the Netherlands is extremely rare.*

** *In recent decades, most cases of pre-treatment with mono- or dual-NRTI therapy prior to initiation of cART occurred in people who were diagnosed and started ART abroad before migrating to the Netherlands, and in people who inadvertently used PEP or PrEP while being HIV-positive, or because of medication errors.*

Legend: *cART=combination antiretroviral therapy; cART=combination antiretroviral therapy; HBV=hepatitis B*

Of the 26,806 people known to have initiated cART since January 1996, 21,879 (81.6%) were men, of whom 16,273 (74.4%) were men who have sex with men (MSM). Overall, 14,864 (55.5%) 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. From 1996 onwards, there was a slight, but steady increase in people from eastern and central Europe; from 2-3% prior to 2010, to 5.3% in 2011-15, and 9.2% in 2016-20. Simultaneously, the number of people from western Europe/North America/Australia decreased slightly from 9.9% in 1996-2005, to 5.2% in 2016-20. This was also true for sub-Saharan Africa; the number declined from 17.8% in 1996-2005, to 9.9% in 2016-20.

Prompt initiation of cART following the first seropositive HIV test has increased over time, reflecting implementation and uptake of evolving HIV treatment guidelines (*Figure 2.1A*). Among people with an accurate date of HIV diagnosis and who started cART in the Netherlands, the median time between an HIV-positive diagnosis and cART initiation shifted from 141 days (interquartile range [IQR] 34-729) for those who entered care in 2011, to 36 days (IQR 17-83) in 2015; 25 days (IQR 11-47) in 2018; 22 days (IQR 9-46) in 2019; and 18 days (IQR 8-37) in 2020. The time between entering care and starting cART decreased over time (*Figure 2.1B*), with the majority of newly diagnosed ART-naïve people entering care in the Netherlands initiating cART within one month. In 2020, 77.5% of individuals initiated cART within one month, while 15.2%, 3.3% and 4.1% of newly diagnosed ART-naïve individuals who initiated cART in the Netherlands did so either 1-5 months, 6-12 months, or more than one year after their HIV diagnosis, respectively (*Figure 2.1A*). People originating from sub-Saharan Africa, the Caribbean, and central and eastern Europe were overrepresented among those starting more than six months after HIV diagnosis. The delay between testing HIV-positive and initiating cART was mostly driven by a long period between HIV diagnosis and entering care, as 92.0% of people initiating cART in 2020 did so within one month of entering care (*Figure 2.1B*). All designated HIV treatment centres in the Netherlands have a policy to arrange for the first consultation within a couple of days; usually just a single working day after being contacted by the newly diagnosed person or their referring healthcare provider.

Figure 2.1A: Time between HIV diagnosis and initiation of combination antiretroviral therapy (cART) in people starting cART in 2011–2020.*

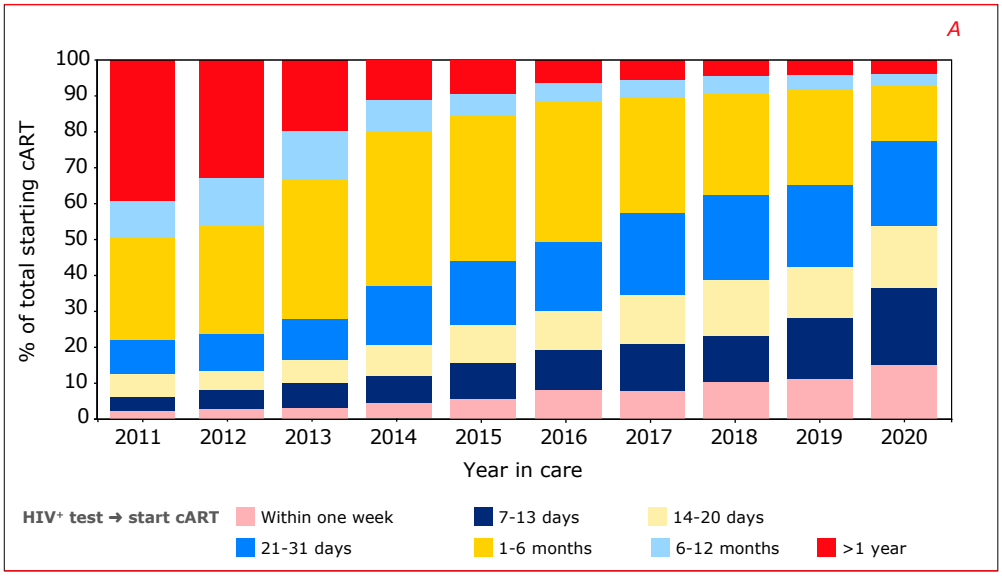
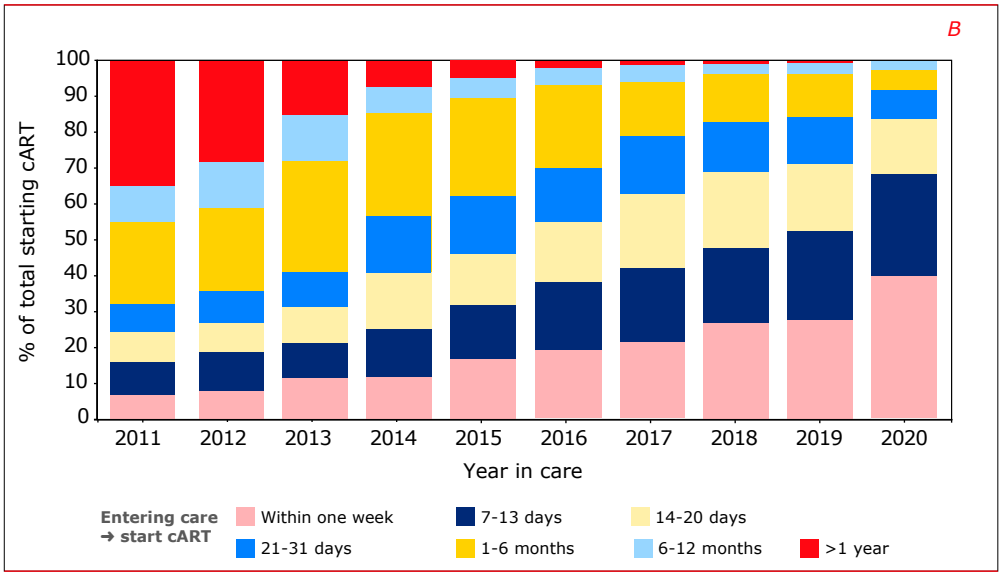


Figure 2.1B: Time between entry into HIV care and initiation of combination antiretroviral therapy (cART) for people starting cART in 2011–2020.*



Legend: cART=combination antiretroviral therapy.

The proportion of individuals newly diagnosed with HIV who have a known previous negative HIV test has increased over the years, from 20.8% in the period 1996-2005, to 40.7% in 2006-10, 54.8% in 2011-15, and 54.9% in 2016-20. In addition, an increasing proportion of those starting cART showed evidence of recent infection (i.e., within 12 months of a last negative HIV test); the percentage of 6.1% in 1996-2005 rose to 15.4% in 2006-10, 24.1% in 2011-15, and 25.5% in 2016-20. Over the same time period, there was an increase in the median CD4 cell count at the start of cART: from 190 cells/mm^3 (IQR 80-320) in 1996-2005, to 244 cells/mm^3 (IQR 140-330) in 2006-10, 355 cells/mm^3 (IQR 220-500) in 2011-15, and 381 cells/mm^3 (IQR 190-570) in 2016-20. In 2015, the median CD4 cell count at cART initiation peaked at 412 (IQR 270-560) and has since continued to decrease slightly each year to 344 cells/mm^3 (IQR 160-560) in 2020. This trend is likely due to the substantial group already in care but not on cART (because of their high CD4 cells counts), who subsequently initiated cART en masse in 2015 and 2016, when the 2015 guideline change recommended ART for all, irrespective of CD4 count. At the start of cART, 20.8% of individuals had already been diagnosed with an AIDS-defining condition; 90.9% had a CD4 cell count below 350 cells/mm^3, and 76.5% had a CD4 cell count below 200 cells/mm^3.

Chapter 1 provides more detailed information on changing trends in the CD4 cell count at the start of cART, and additional aspects of the continuum of HIV care.

In care and on cART in the Netherlands in 2020

Of the 26,806 people known to have initiated cART between January 1996 and December 2020, 20,251 (75.6%) were alive, still receiving cART, and had a recorded visit for HIV care in the Netherlands in 2020. A total of 228 people were still alive but (temporarily, and for various reasons) not on cART anymore and have therefore been excluded from the analyses in this paragraph – most of these individuals had medical, psychiatric, and/or psycho-social issues that temporarily prevented them from using their cART, and expected to re-start cART once those issues were sufficiently resolved. *Table 2.2* shows the treatment and clinical characteristics of all individuals on ART at the last clinic visit in 2020. Overall, 16,651 (82.2%) were men, and 13,033 (64.4%) were MSM. Their median age on 31 December 2020 was 51.5 (IQR 42.0-59.3) years. The majority (58.9%) originated from the Netherlands, followed by Latin America / the Caribbean (12.1%) and sub-Saharan Africa (11.8%).

Table 2.2: Characteristics of people receiving combination antiretroviral therapy and known to be in care in 2020.

Year of cART initiation		1996–2005	2006–2010	2011–2015	2016–2020	All
Total	n	5,886	4,663	6,007	3,695	**20,251**
	%	29.1	23.0	29.7	18.3	**100**
Male sex	n	4,469	3,809	5,215	3,158	**16,651**
	%	75.9	81.7	86.8	85.5	**82.2**
Age on 31 December 2019	Median	57.4	52.5	47.3	40.9	**51.5**
	Q1	51.5	45.4	38.7	32.0	**42.0**
	Q3	63.6	59.1	56.0	51.7	**59.3**
Transmission risk group						
No data	n	5	5	7	12	**29**
	%	0.1	0.1	0.1	0.3	**0.1**
Men who have sex with men	n	3,309	3,030	4,256	2,438	**13,033**
	%	56.2	65.0	70.9	66.0	**64.4**
Heterosexual contact	n	2,043	1,359	1,438	934	**5,774**
	%	34.7	29.1	23.9	25.3	**28.5**
Injecting drug use	n	170	54	19	16	**259**
	%	2.9	1.2	0.3	0.4	**1.3**
Blood or blood products	n	108	36	49	47	**240**
	%	1.8	0.8	0.8	1.3	**1.2**
Vertical transmission	n	1	3	2	4	**10**
	%	0.02	0.06	0.03	0.1	**0.05**
Other/unknown	n	250	176	236	244	**906**
	%	4.3	3.8	3.9	6.6	**4.5**
Region of origin						
No data	n	22	12	23	36	**93**
	%	0.4	0.3	0.4	1.0	**0.5**
The Netherlands	n	3,383	2,834	3,759	1,958	**11,934**
	%	57.5	60.8	62.6	53.0	**58.9**
Western Europe/North America/Australia	n	453	287	351	174	**1,265**
	%	7.7	6.2	5.8	4.7	**6.3**
Eastern/central Europe	n	101	136	288	313	**838**
	%	1.7	2.9	4.8	8.5	**4.1**
Latin America and the Caribbean	n	639	541	708	563	**2,451**
	%	10.9	11.6	11.8	15.2	**12.1**
Sub-Saharan Africa	n	956	575	503	348	**2,382**
	%	16.2	12.3	8.4	9.4	**11.8**
Other	n	332	278	375	303	**1,288**
	%	5.6	6.0	6.2	8.2	**6.4**

Year of cART initiation		1996–2005	2006–2010	2011–2015	2016–2020	All
cART regimen						
TDF/FTC/EFV	n	404	551	375	42	**1,372**
	%	6.9	11.8	6.2	1.1	**6.8**
TDF/FTC/NVP	n	515	303	189	9	**1,016**
	%	8.8	6.5	3.2	0.2	**5.0**
TDF/FTC/RPV	n	132	124	325	29	**610**
	%	2.2	2.7	5.4	0.8	**3.0**
TDF/3TC/DOR	n	157	200	239	172	**768**
	%	2.7	4.3	4.0	4.7	**3.8**
TDF/FTC/DRV/b	n	123	131	166	53	**473**
	%	2.1	2.8	2.8	1.4	**2.3**
TDF/FTC/ATV/b	n	68	69	55	11	**203**
	%	1.2	1.5	0.9	0.3	**1.0**
TDF/FTC/LPV	n	8	9	1	1	**19**
	%	0.1	0.2	0.02	0.03	**0.1**
TDF/FTC/EVG/c	n	89	98	304	92	**583**
	%	1.5	2.1	5.1	2.5	**2.9**
TDF/FTC/DTG	n	125	92	193	331	**741**
	%	2.1	2.0	3.2	9.0	**3.7**
TDF/FTC/RAL	n	44	47	57	29	**177**
	%	0.8	1.0	1.0	0.8	**0.9**
ABC/3TC/DTG	n	499	500	883	684	**2,566**
	%	8.5	10.7	14.7	18.5	**12.7**
TAF/FTC/RPV	n	211	225	420	90	**946**
	%	3.6	4.8	7.0	2.4	**4.7**
TAF/FTC/DRV/c	n	338	287	356	216	**1,197**
	%	5.7	6.2	5.9	5.9	**5.9**
TAF/FTC/EVG/c	n	475	526	919	561	**2,481**
	%	8.1	11.3	15.3	15.2	**12.3**
TAF/FTC/DTG	n	118	115	145	147	**525**
	%	2.0	2.5	2.4	4.0	**2.6**
TAF/FTC/BIC	n	523	465	621	873	**2,482**
	%	8.9	10.0	10.3	23.6	**12.3**
TAF/FTC/NVP	n	378	223	94	4	**699**
	%	6.4	4.8	1.6	0.1	**3.5**
ABC/3TC/NVP	n	231	73	48	1	**353**
	%	3.9	1.6	0.8	0.03	**1.7**

Year of cART initiation		1996–2005	2006–2010	2011–2015	2016–2020	All
DTG/3TC	n	198	194	275	222	**889**
	%	3.4	4.2	4.6	6.0	**4.4**
DTG/RPV	n	60	19	20	4	**103**
	%	1.0	0.4	0.3	0.1	**0.5**
CAB/RPV*	n	3	2	2	9	**16**
	%	0.05	0.04	0.03	0.2	**0.1**
2DR:NNRTI+INST	n	6	.	2	.	**8**
	%	0.1	.	0.03	.	**0.04**
2DR:PI+INSTI	n	2	1	1	1	**5**
	%	0.03	0.02	0.02	0.03	**0.02**
2DR:NRTI+INSTI	n	180	85	40	11	**316**
	%	3.1	1.8	0.7	0.3	**1.6**
Other:2NRTI+NNRTI	n	143	103	75	8	**329**
	%	2.4	2.2	1.3	0.2	**1.6**
Other:2NRTI+PI	n	94	63	61	23	**241**
	%	1.6	1.4	1.0	0.6	**1.2**
Other:2NRTI+INST	n	94	63	61	23	**241**
	%	1.6	1.4	1.0	0.6	**1.2**
Other:2DR	n	52	14	15	4	**85**
	%	0.9	0.3	0.3	0.1	**0.4**
Other:NRTI+PI+INSTI(3ARVs)	n	57	5	5	4	**71**
	%	1.0	0.1	0.1	0.1	**0.4**
Other:NRTI+PI+INSTI(4ARVs)	n	141	32	24	22	**219**
	%	2.4	0.7	0.4	0.6	**1.1**
Other	n	270	48	45	17	**380**
	%	4.6	1.0	0.8	0.5	**1.9**
CD4:CD8 ratio						
No data	n	742	575	847	553	**2,717**
	%	12.6	12.3	14.1	15.0	**13.4**
<0.50	n	915	607	691	887	**3,100**
	%	15.6	13.0	11.5	24.0	**15.3**
≥0.50 <1.00	n	2,542	2,147	2,632	1,365	**8,686**
	%	43.2	46.0	43.8	36.9	**42.9**
≥1.00	n	1,687	1,334	1,837	890	**5,748**

Year of cART initiation		1996–2005	2006–2010	2011–2015	2016–2020	All
	%	28.7	28.6	30.6	24.1	**28.4**
CD4 count (cells/mm³)						
No data	n	18	12	18	26	**74**
	%	0.3	0.3	0.3	0.7	**0.4**
<50	n	10	7	4	21	**42**
	%	0.2	0.2	0.1	0.6	**0.2**
50–199	n	101	52	60	152	**365**
	%	1.7	1.1	1.0	4.1	**1.8**
200–349	n	377	243	278	370	**1,268**
	%	6.4	5.2	4.6	10.0	**6.3**
350–499	n	888	676	732	577	**2,873**
	%	15.1	14.5	12.2	15.6	**14.2**
500–749	n	2,047	1,703	1,969	1,080	**6,799**
	%	34.8	36.5	32.8	29.2	**33.6**
≥750	n	2,445	1,970	2,946	1,469	**8,830**
	%	41.5	42.3	49.0	39.8	**43.6**
Viral load <50 copies/ml						
No data	n	25	31	66	460	**582**
	%	0.4	0.7	1.1	12.5	**2.9**
Yes	n	5,203	4,121	5,277	2,677	**17,278**
	%	88.4	88.4	87.9	72.5	**85.3**
No	n	658	511	664	558	**2,391**
	%	11.2	11.0	11.1	15.1	**11.8**
Viral load <200 copies/ml						
No data	n	25	31	66	460	**582**
	%	0.4	0.7	1.1	12.5	**2.9**
Yes	n	5,749	4,556	5,840	3,055	**19,200**
	%	97.7	97.7	97.2	82.7	**94.8**
No	n	112	76	101	180	**469**
	%	1.9	1.6	1.7	4.9	**2.3**

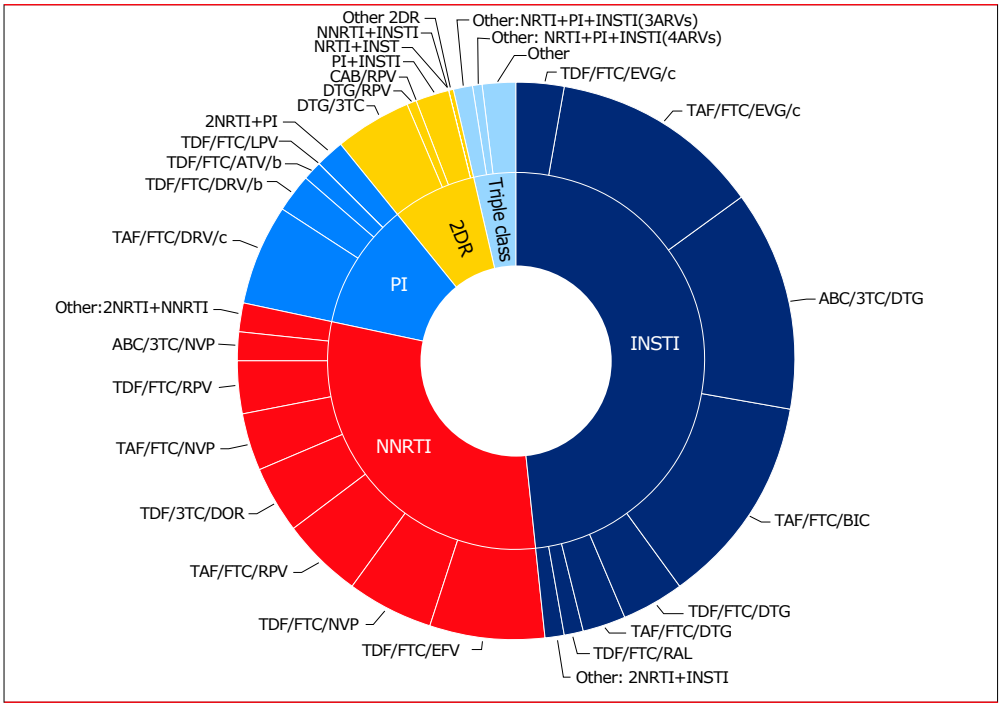
** All patients using this combination were participating in a clinical trial.*

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; DOR=doravirine; 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 20,251 people in HIV care and on cART in 2020, the vast majority (89.4%) received a regimen based on two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with either an integrase inhibitor (INSTI) (48.4%), a non-nucleoside reverse transcriptase inhibitor (NNRTI) (30.0%), or a protease inhibitor (PI) (10.9%). The distribution of cART use among the population in care in 2020 is presented in *Figure 2.2A*. The most frequently used regimens (used by at least 5% of the population) were abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (12.7%), tenofovir alafenamide (TAF)/FTC/bictegravir (BIC) (12.3%), tenofovir alafenamide (TAF)/FTC/elvitegravir (EVG)/cobicistat (12.3%), tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/efavirenz (EFV) (6.8%), tenofovir alafenamide (TAF)/emtricitabine (FTC)/darunavir (DRV)/cobicistat (5.9%), and tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/nevirapine (NVP) (5.0%). The proportion of the population in care in 2020 using TDF declined over time (from 46.4% in 2017, to 35.3% in 2018, 31.9% in 2019, and 30.8% in 2020), while the proportion using TAF continued to increase (from 24.4% of the population in care in 2017, to 33.2% in 2018, 42.1% in 2019, and 43.7% in 2020). Zidovudine was still used by 128 individuals (0.6%, mostly in combination with lamivudine). In total, 650 (3.2%) and 1,099 (5.4%) individuals used a cART regimen without any NRTI or with just a single NRTI. There were 1,484 (7.3%) individuals who used a two-drug regimen (excluding pharmacological boosters): the most common two-drug regimens were a combination of NRTI+INSTI (894, 60.2%, of which 99.6% used lamivudine and 99.8% dolutegravir); PI+INSTI (378, 25.5%, of which 98.4% used darunavir plus either dolutegravir (87.8%), or raltegravir (12.2%)); NNRTI+INSTI (127, 8.6%, of which 93.7% used rilpivirine, 86.6% used dolutegravir, and 12.6% used cabotegravir); NNRTI+PI (16, 1.1%).

Of those with a plasma HIV RNA measurement in 2020, 87.8% had a viral load below 50 copies/ml, and 97.6% had a viral load below 200 copies/ml. On the basis of the last available CD4 and CD8 cell count measurements in 2015-20, 77.5% had a CD4 cell count of 500 cells/mm^3 or higher, and 32.8% had a CD4:CD8 ratio of 1 or higher.

Figure 2.2: Combination antiretroviral therapy (cART) use in 2020.



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; DOR=doravirine; 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.*

Changes in the use of the initial cART regimen

Data from recent clinical trials on new antiretroviral drugs, 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 combination regimens 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.

Box 2.2: Approval dates of new antiretroviral drugs/regimens for HIV treatment in the Netherlands in 2013–2020.

Medicine	Authorisation date
TDF/FTC/EVG/cobicistat (Stribild®)	24 May 2013
DTG (Tivicay®)	16 January 2014
ABC/3TC/DTG (Triumeq®)	01 September 2014
DRV/cobicistat (Rezolsta®)	19 November 2014
TAF/FTC/EVG/cobicistat (Genvoya®)	19 November 2015
TAF/FTC (Descovy®)	21 April 2016
TAF/FTC/RPV (Odefsey®)	21 June 2016
TAF (Vemlidy®)	09 January 2017
TAF/FTC/DRV/cobicistat (Symtuza®)	21 September 2017
DTG/RPV (Juluca®)	21 May 2018
TAF/FTC/BIC (Biktarvy®)	25 June 2018
Doravirine (Pifeltro®)	22 November 2018
TDF/3TC/Doravirine (Delstrigo®)	22 November 2018
3TC/DTG (Dovato®)	03 July 2019
Cabotegravir (Vocabria®)	17 December 2020
Rilpivirine (Rekambys®)	17 December 2020

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

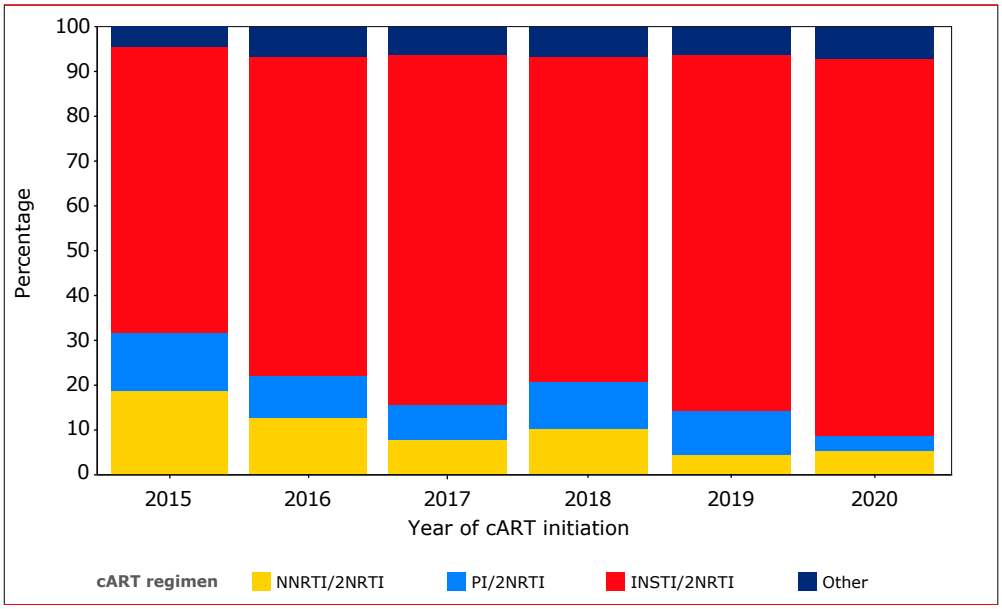
Source: *Medicines Evaluation Board http://english.cbg-meb.nl/ and European Medicines Agency http://www.ema.europa.eu/*

Initial cART regimen

Of the 26,806 people known to have initiated cART between 1996 and 2020, 5,389 (20.1%) started cART between January 2015 and December 2020. *Figures 2.3* and *2.4* show the trends over time in third-drug additions to the NRTI backbone used as part of their initial cART regimen. The use of integrase inhibitors in combination with an NRTI backbone as initial therapy, continued to rise from 63.8% in 2015, to 71.0% in 2016, 78.0% in 2017, 72.1% in 2018, 79.0% in 2019, and 83.7% in 2020 (89.4% including other INSTI-containing regimens). EVG/c was used in 17.2%, 25.2%, 30.5% and 24.1% of the initial regimens in 2015, 2016, 2017, and 2018, respectively, before its use dropped sharply to 3.2% in 2019 and 1.6% in 2020. Dolutegravir was used in 49.4%, 51.4%, 51.5%, 44.3%, 33.7%, and 42.7% of the initial regimens in 2015, 2016, 2017, 2018, 2019, and 2020, respectively. Bictegravir was introduced in the Netherlands in 2018 and was used in 7.1%, 46.4%, and 45.9% of the initial regimens in 2018, 2019, and 2020, respectively. The use of NNRTIs in the initial regimen

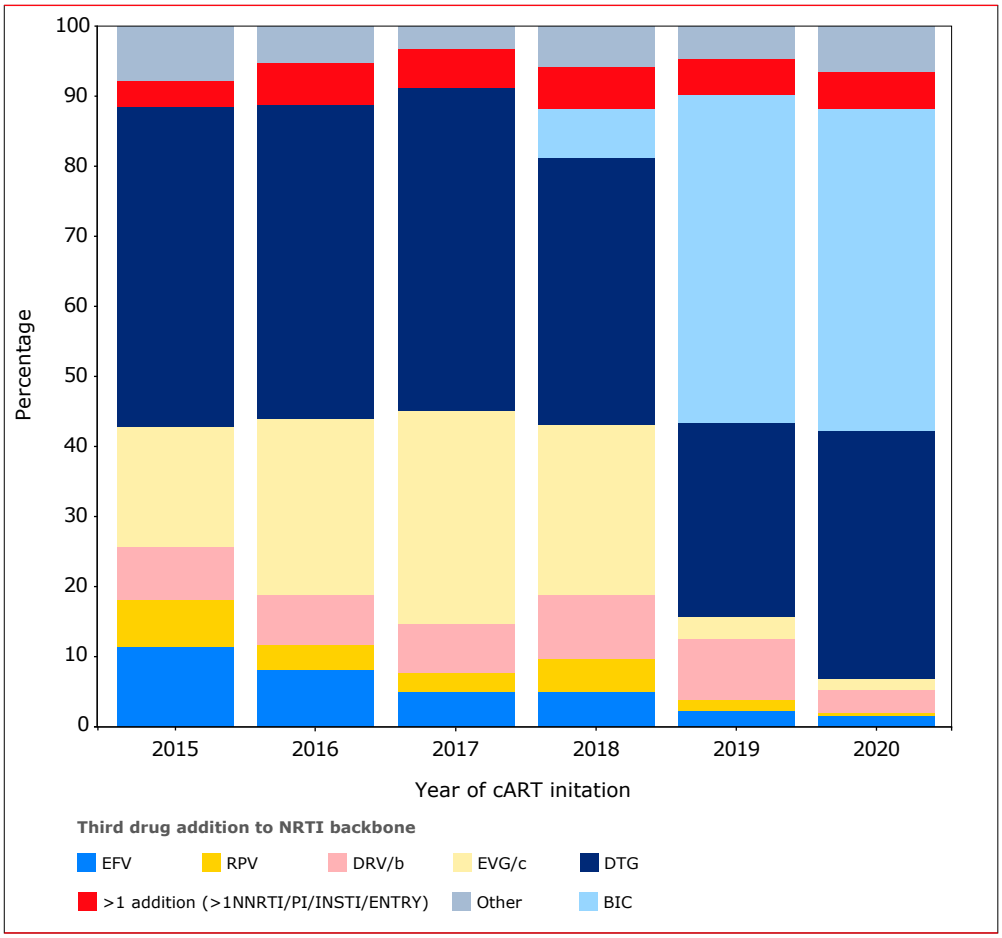
decreased from 18.9% in 2015 to 12.9% in 2016, 7.9% in 2017, 10.4% in 2018, 4.6% in 2019, and 5.5% in 2020. The use of PIs in the initial regimen decreased from 12.9% in 2015 to 9.2% in 2016, 7.8% in 2017, 10.5% in 2018, 9.9% in 2019, and 3.4% in 2020. In 2015-20, 4.9% of individuals received more than 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), plus two NRTIs. *Figure 2.4* shows all third-drug additions to the nucleoside reverse transcriptase backbone that were used in at least 5% of individuals for one or more years as part of the initial regimen during the period 2015-20. The use of nevirapine, atazanavir, lopinavir, raltegravir, and doravirine as third-drug additions to initial regimens did not exceed 5% in any year in the period 2015-20. As a result, those regimens have been included in the category 'other' in *Figure 2.4*.

Figure 2.3: *Third-drug class additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2015-2020.*



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 2015-2020.

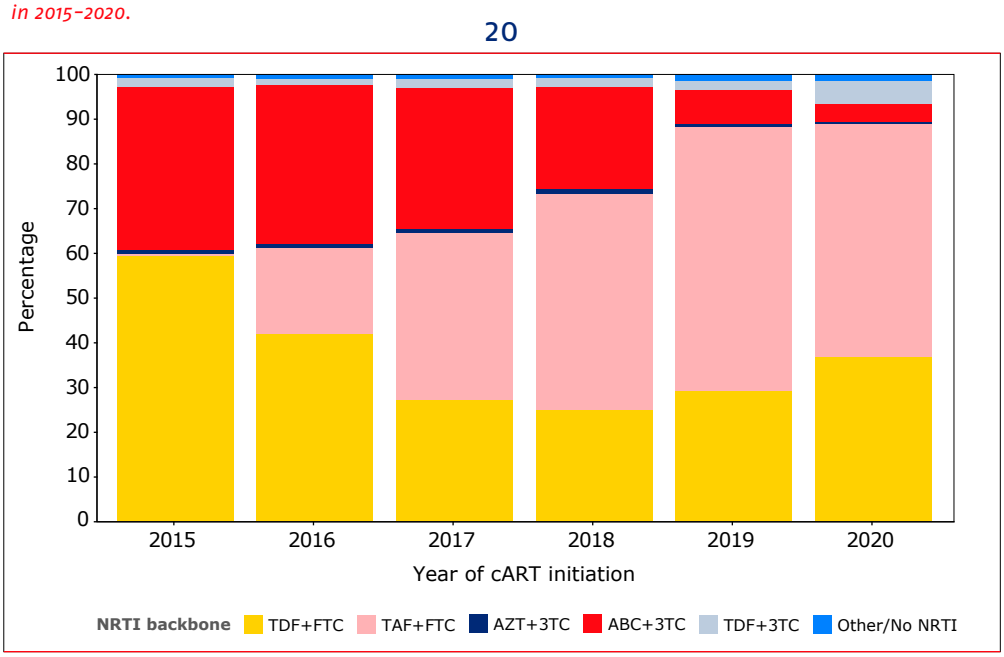


Legend: cART=combination antiretroviral therapy; b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; ENTRY=entry inhibitor; INSTI=integrase inhibitor; NRTI=nucleoside analogue reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; RPV=rilpivirine.

Figure 2.5 provides an overview of the NRTI backbone components of the initial cART regimens used in 2015-20. The combination of tenofovir (TDF or TAF) and emtricitabine was the predominant backbone prescribed. Following its introduction at the end of 2015, TAF was prescribed in 19.0%, 37.6%, 48.3%, 59.4%,

and 52.0% of the initial regimens in 2016, 2017, 2018, 2019, and 2020, respectively. At the same time, TDF use decreased from 61.2% in 2015 to 27.0% in 2018, and then increased to 31.4% in 2019 and 41.7% in 2020, probably because of a sharp decrease in the use of abacavir-containing NRTI backbones in 2019 and 2020. The use of abacavir in combination with lamivudine decreased from 36.5% of all initial regimens in 2015 to 35.8% in 2016, 31.6% in 2017, and 22.9% in 2018, after which there was a sharp decrease to 7.7% in 2019 and 4.1% in 2020. The combination of zidovudine and lamivudine, which is still sometimes used by migrants who initiated cART before arriving in the Netherlands, has further decreased to less than 1% since 2016 (n=1 in 2020).

Figure 2.5: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2015–2020.*



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 in 2015-20 are presented in *Figure 2.6* and *Table 2.3*. In 2020, the most frequently used initial regimen was TAF/FTC/bictegravir (45.9%). Dolutegravir-containing initial regimens were used in 35.8% of cases: combined with either abacavir and lamivudine as part of the once-daily, fixed-dose

combination (1.2%), or provided with emtricitabine and tenofovir separately (TDF 29.1%/TAF 1.9%). Additionally, 4.1% initiated a doravirine-containing once-daily, fixed-dose combination with lamivudine and tenofovir (TDF). Elvitegravir/c, darunavir/b, or raltegravir use in an initial regimen was 1.6%, 4.2%, and 0.7%, respectively, in 2020. *Table 2.3* provides more detail on the 'other' initial regimens that are not further specified in *Figures 2.4-2.6*.

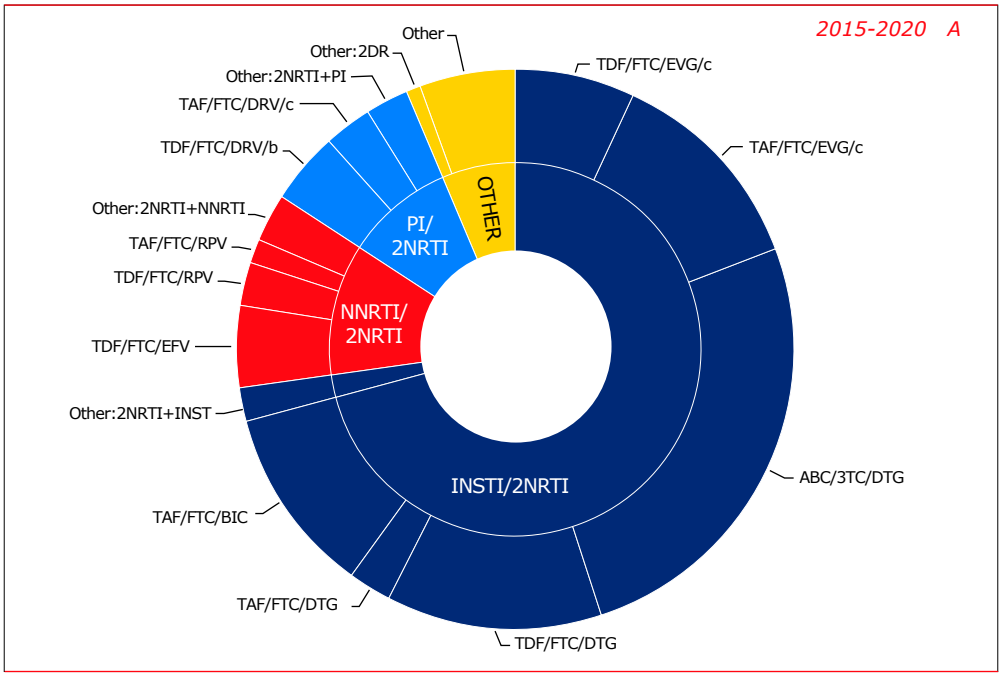
***Table 2.3:** Initial regimens in 2015–2020.*

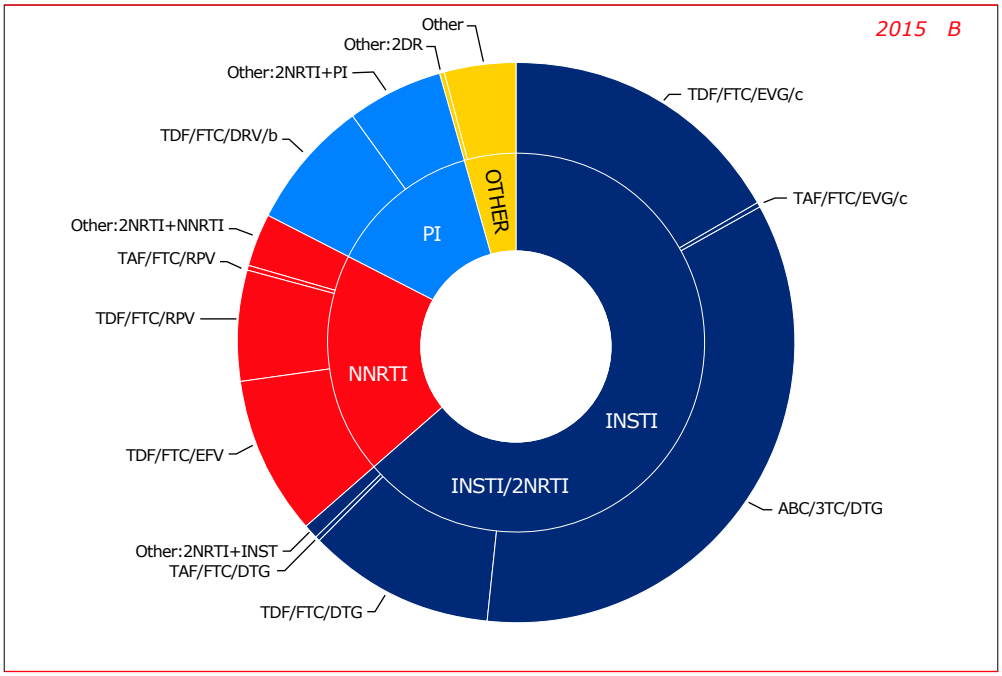
		2015	2016	2017	2018	2019	2020	2015–2020
n		1,292	1,119	998	855	689	436	5,389
Regimen								
TDF/FTC/EFV	n	117	75	29	30	12	4	267
	%	9.06	6.7	2.91	3.51	1.74	0.92	4.95
TDF/FTC/NVP	n	7	9	2	2	1	.	21
	%	0.54	0.8	0.2	0.23	0.15	.	0.39
TDF/FTC/RPV	n	85	34	8	3	3	.	133
	%	6.58	3.04	0.8	0.35	0.44	.	2.47
TDF/3TC/DOR	n	.	.	.	.	4	16	20
	%	.	.	.	.	0.58	3.67	0.37
TDF/FTC/DRV/b	n	94	69	36	13	16	6	234
	%	7.28	6.17	3.61	1.52	2.32	1.38	4.34
TDF/FTC/ATV/b	n	45	17	4	6	6	.	78
	%	3.48	1.52	0.4	0.7	0.87	.	1.45
TDF/FTC/LPV/r	n	8	2	1	.	.	.	11
	%	0.62	0.18	0.1	.	.	.	0.2
TDF/FTC/EVG/c	n	217	88	54	17	5	.	381
	%	16.8	7.86	5.41	1.99	0.73	.	7.07
TDF/FTC/DTG	n	143	105	90	85	122	127	672
	%	11.07	9.38	9.02	9.94	17.71	29.13	12.47
TDF/FTC/RAL	n	10	8	6	13	8	3	48
	%	0.77	0.71	0.6	1.52	1.16	0.69	0.89
ABC/3TC/DTG	n	446	386	305	186	48	18	1,389
	%	34.52	34.5	30.56	21.75	6.97	4.13	25.77
ABC/3TC/NVP	n	1	1	1	.	.	.	3
	%	0.08	0.09	0.1	.	.	.	0.06
TAF/FTC/RPV	n	1	6	18	38	6	2	71
	%	0.08	0.54	1.8	4.44	0.87	0.46	1.32
TAF/FTC/DRV/c	n	.	1	31	62	43	8	145
	%	.	0.09	3.11	7.25	6.24	1.83	2.69

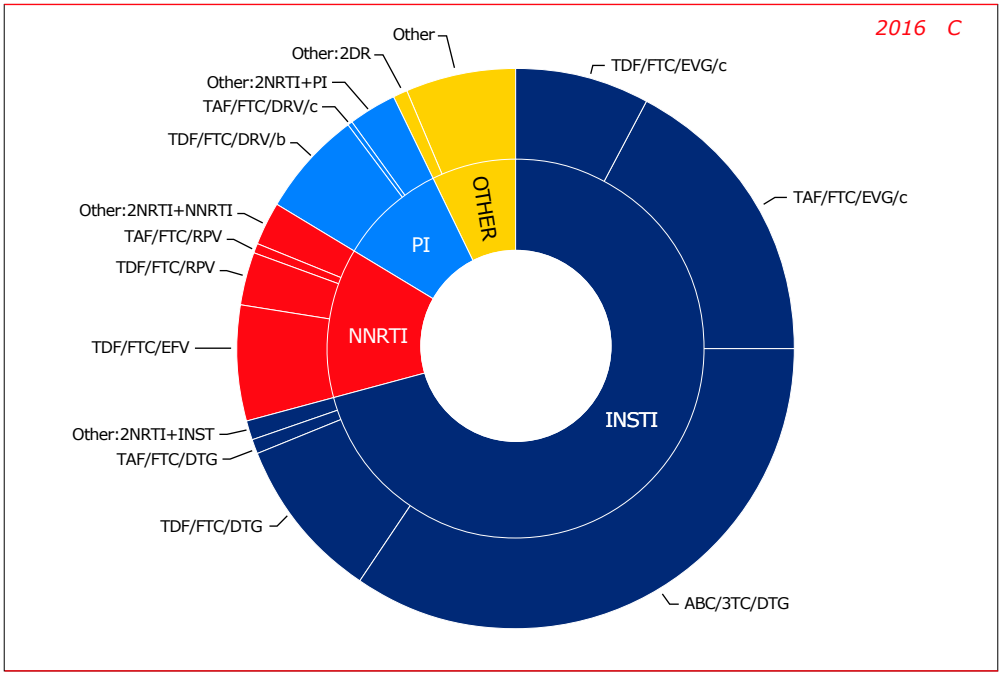
		2015	2016	2017	2018	2019	2020	2015–2020
n		1,292	1,119	998	855	689	436	5,389
Regimen								
TAF/FTC/EVG/c	n	5	194	250	189	17	7	662
	%	0.39	17.34	25.05	22.11	2.47	1.61	12.28
TAF/FTC/DTG	n	1	9	56	47	14	5	132
	%	0.08	0.8	5.61	5.5	2.03	1.15	2.45
TAF/FTC/BIC	n	.	.	2	61	320	200	583
	%	.	.	0.2	7.13	46.44	45.87	10.82
DTG/3TC	n	.	1	1	2	3	6	13
	%	.	0.09	0.1	0.23	0.44	1.38	0.24
DTG/RPV	n	.	.	.	.	1	.	1
	%	.	.	.	.	0.15	.	0.02
2DR: PI+INSTI	n	5	8	7	4	2	2	28
	%	0.39	0.71	0.7	0.47	0.29	0.46	0.52
Other: 2NRTI+NNRTI	n	34	19	21	16	7	2	99
	%	2.63	1.7	2.1	1.87	1.02	0.46	1.84
Other: 2NRTI+PI	n	19	14	7	9	3	1	53
	%	1.47	1.25	0.7	1.05	0.44	0.23	0.98
Other: 2NRTI+INST	n	2	4	15	19	10	5	55
	%	0.15	0.36	1.5	2.22	1.45	1.15	1.02
Other: NRTI+PI+INSTI (3ARVs)	n	2	1	1	1	1	.	6
	%	0.15	0.09	0.1	0.12	0.15	.	0.11
Other: NRTI+PI+INSTI (4ARVs)	n	42	57	52	49	33	23	256
	%	3.25	5.09	5.21	5.73	4.79	5.28	4.75
Other	n	8	11	1	3	4	1	28
	%	0.62	0.98	0.1	0.35	0.58	0.23	0.52

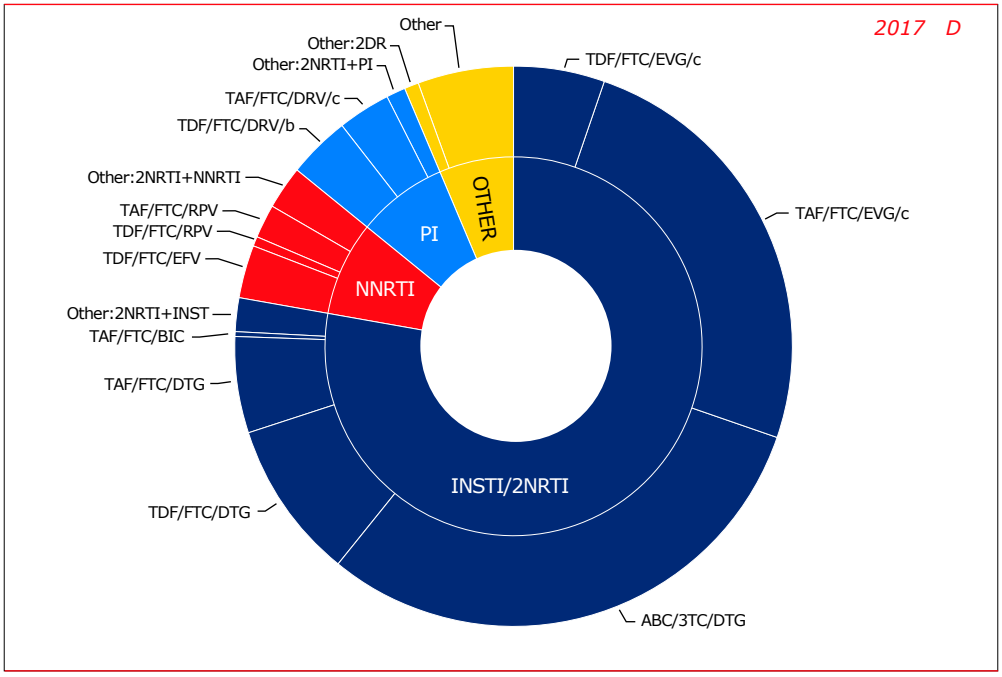
Legend: *ARVs=antiretroviral drugs; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; ATV=atazanavir; BIC=bictegravir; CI=confidence interval; DOR=doravirine; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine;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

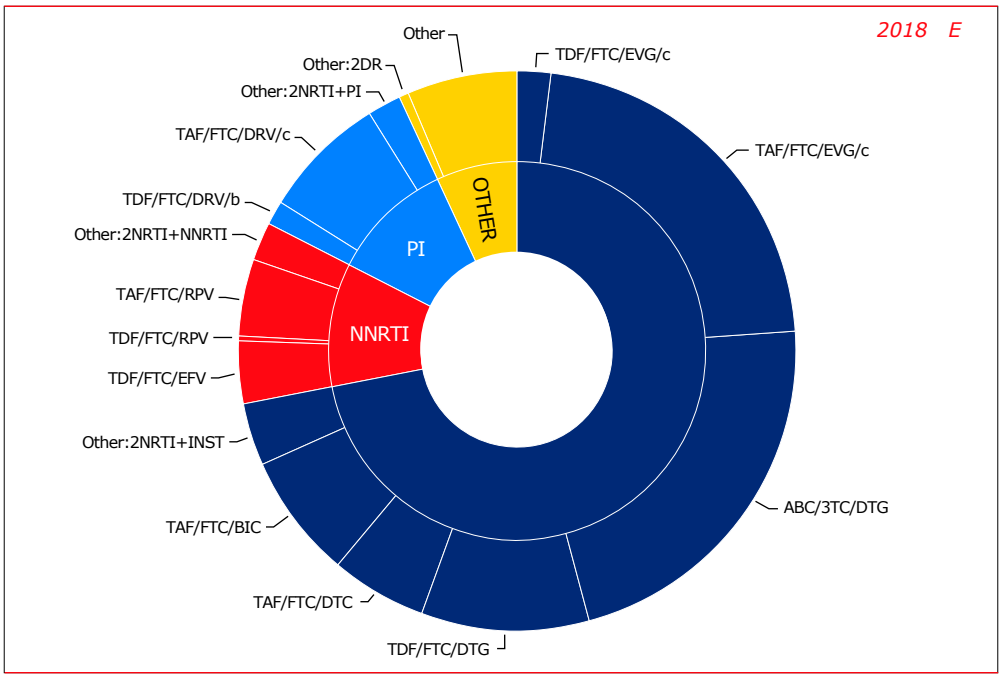
Figure 2.6: The initial combination antiretroviral therapy regimens given in 2015–2020 A) in total and B) by year.

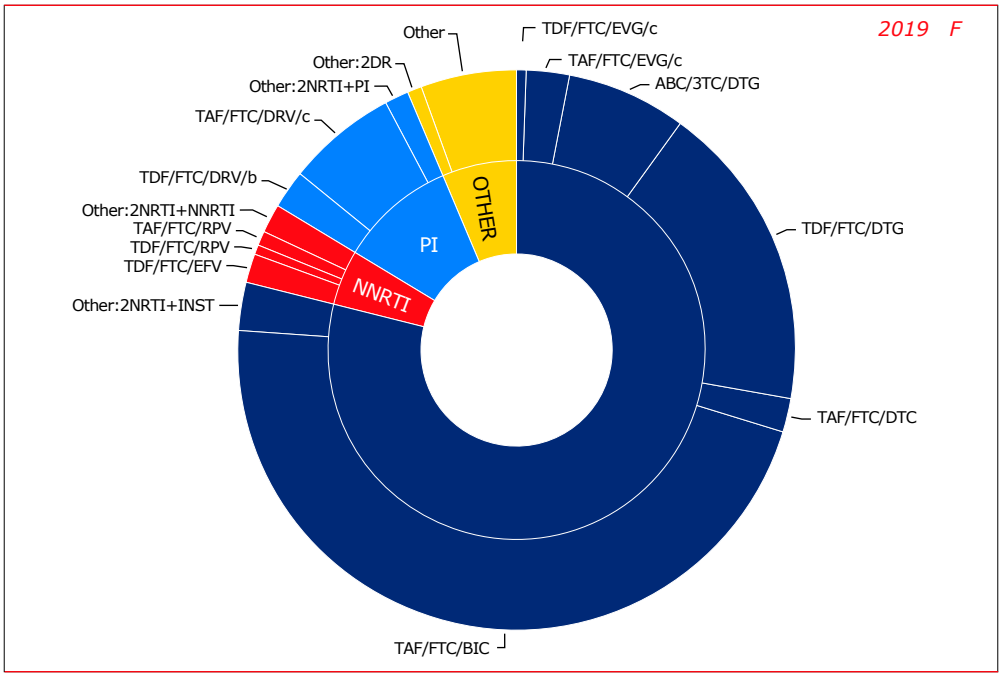


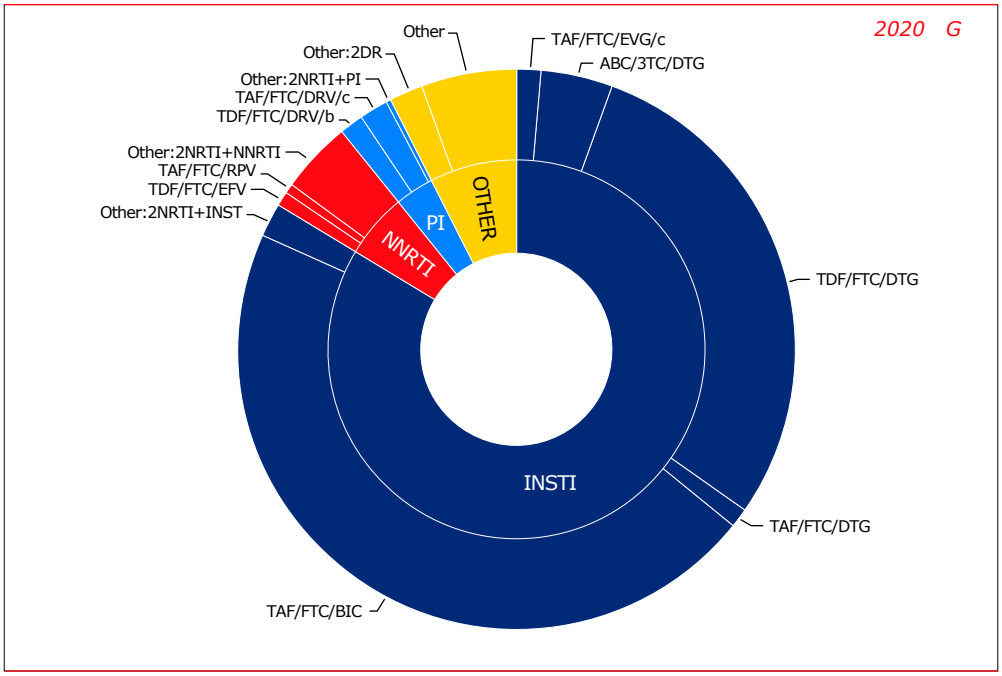



2016 C
Other
Other:2DR
Other:2NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/DRV/b
Other:2NRTI+NNRTI
TAF/FTC/RPV
TDF/FTC/RPV
TDF/FTC/EFV
Other:2NRTI+INST
TAF/FTC/DTG
TDF/FTC/DTG
TDF/FTC/EVG/c
TAF/FTC/EVG/c
ABC/3TC/DTG
OTHER
PI
NNRTI
INSTI


2017 D
Other
Other:2DR
Other:2NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/DRV/b
Other:2NRTI+NNRTI
TAF/FTC/RPV
TDF/FTC/RPV
TDF/FTC/EFV
Other:2NRTI+INST
TAF/FTC/BIC
TAF/FTC/DTG
TDF/FTC/DTG
TDF/FTC/EVG/c
TAF/FTC/EVG/c
ABC/3TC/DTG
OTHER
PI
NNRTI
INSTI/2NRTI


2018 E
Other
Other:2DR
Other:2NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/DRV/b
Other:2NRTI+NNRTI
TAF/FTC/RPV
TDF/FTC/RPV
TDF/FTC/EFV
Other:2NRTI+INST
TAF/FTC/BIC
TAF/FTC/DTC
TDF/FTC/DTG
TDF/FTC/EVG/c
TAF/FTC/EVG/c
ABC/3TC/DTG
OTHER
PI
NNRTI


2019 F
Other
Other:2DR
Other:2NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/DRV/b
Other:2NRTI+NNRTI
TAF/FTC/RPV
TDF/FTC/RPV
TDF/FTC/EFV
Other:2NRTI+INST
TAF/FTC/BIC
TDF/FTC/EVG/c
TAF/FTC/EVG/c
ABC/3TC/DTG
TDF/FTC/DTG
TAF/FTC/DTC
OTHER
PI
NNRTI



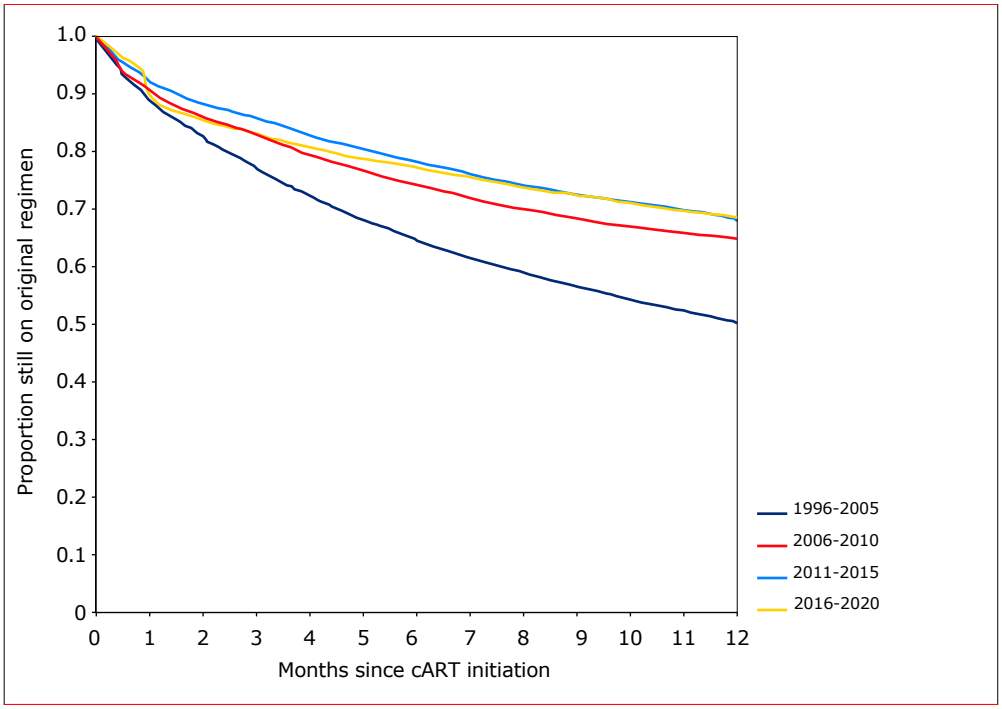
Legend: *3TC=lamivudine; ABC=abacavir; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; INSTI=integrase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor;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

Discontinuation of the initial cART regimen

For the 26,806 people who started cART between 1996 and 2020, we assessed the time spent on that initial cART regimen. Discontinuation was defined as a change in, or discontinuation of one or more of the drugs included in the regimen. Simplification to a fixed-drug combination formulation containing the same drugs was not considered a discontinuation. 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 fixed-dose TDF/FTC to the fixed drug combination EFV/TDF/FTC was not considered discontinuation of the initial regimen, however, 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 1996-2020, 38.9% of individuals discontinued their initial regimen within one year; the length of time they remain on it has improved over the years: in 1996-2005, 49.9% discontinued it within a year, compared to 35.1% in 2006-10, 32.0% in 2011-15, and 30.6% in 2016-20. *Figure 2.7* shows the time to the first modification of the initial regimen during the first year of cART, stratified by five-year calendar periods.

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



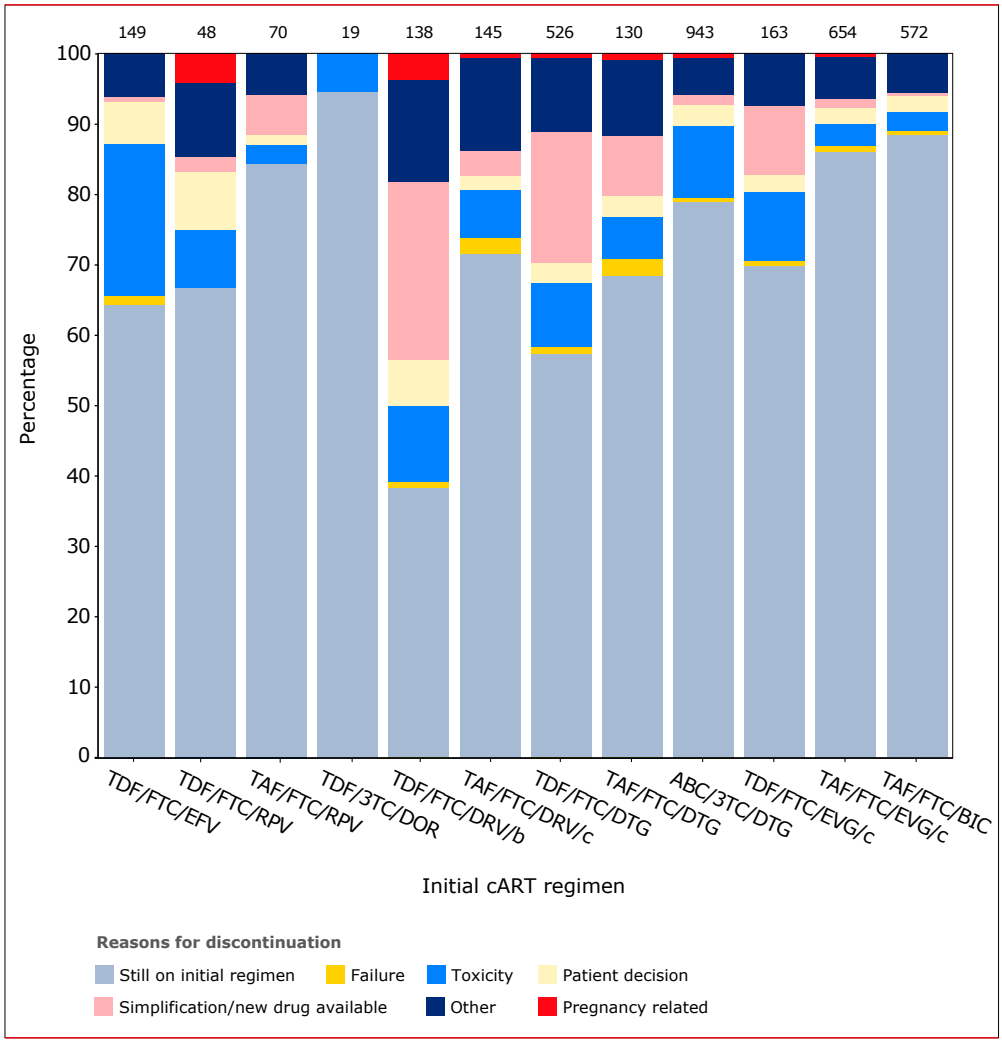
Legend: *cART=combination antiretroviral therapy.*

Discontinuation of the initial cART regimen: 2016–2020

We further assessed the time to discontinuation of the initial regimen during the first year of treatment among the 3,557 people who started 'common' and guideline-recommended initial regimens in 2016-20. The regimens considered in this analysis were: tenofovir disoproxil fumarate/emtricitabine combined with efavirenz (TDF/FTC/EFV, 4.2%); rilpivirine (TDF/FTC/RPV, 1.4%); ritonavir-boosted or cobicistat-boosted darunavir (TDF/FTC/DRV/b, 3.9%); cobicistat-boosted elvitegravir (TDF/FTC/EVG/c, 4.6%); dolutegravir (TDF/FTC/DTG, 14.8%); tenofovir disoproxil fumarate/lamivudine combined with doravirine (TDF/3TC/DOR, 0.5%); abacavir-lamivudine combined with dolutegravir (ABC/3TC/DTG, 26.5%); tenofovir alafenamide/emtricitabine combined with cobicistat-boosted elvitegravir (TAF/FTC/EVG/c, 18.4%); rilpivirine (TAF/FTC/RPV, 2.0%); dolutegravir (TAF/FTC/DTG, 3.7%); cobicistat-boosted darunavir (TAF/FTC/DRV/c, 4.1%); and bictegravir (TAF/FTC/BIC, 16.1%).

One year after cART initiation, 874 (24.6%) of the 3,557 individuals using one of these initial regimens, had discontinued it. The main reason for this discontinuation was toxicity (267, 30.6%), followed by simplification and/or availability of new drugs (192, 22.0%). The availability of new, once-daily, fixed-dose combinations contributed to an increase in initial regimen discontinuation due to simplification and/or availability of new drugs, especially for those receiving TDF/FTC/DTG, and TDF/FTC/DRV/b (*Figure 2.8*). In total, 23.4% of all discontinuations were for reasons of simplification and/or availability of new drugs in 2016, 20.0% in 2017, 18.6% in 2018, 23.5% in 2019, and 28.4% in 2020. The nature and severity of toxicities leading to discontinuation have changed considerably over the decades. Because of the availability of a large number of potent and well-tolerated recommended and alternative regimens, as well as the very low risk of viral breakthrough following a switch, the threshold for modifying the initial (or any) regimen has become much lower over the years. Furthermore, in recent years, the regimens TDF/FTC/DTG and TDF/FTC/DRV/b have frequently been used as an initial 'induction' regimen in treatment-naïve patients because of their potent antiretroviral activity and high genetic barrier to resistance, with the explicit intention to quickly switch to a single tablet 'maintenance' regimen, (typically a single tablet regimen), after the plasma HIV-1 viral load has become undetectable.

Figure 2.8: Reasons for discontinuation of the initial regimen during the first year of treatment in 2016–2020, by regimen. Numbers above the bars represent the total number of individuals using that particular regimen.

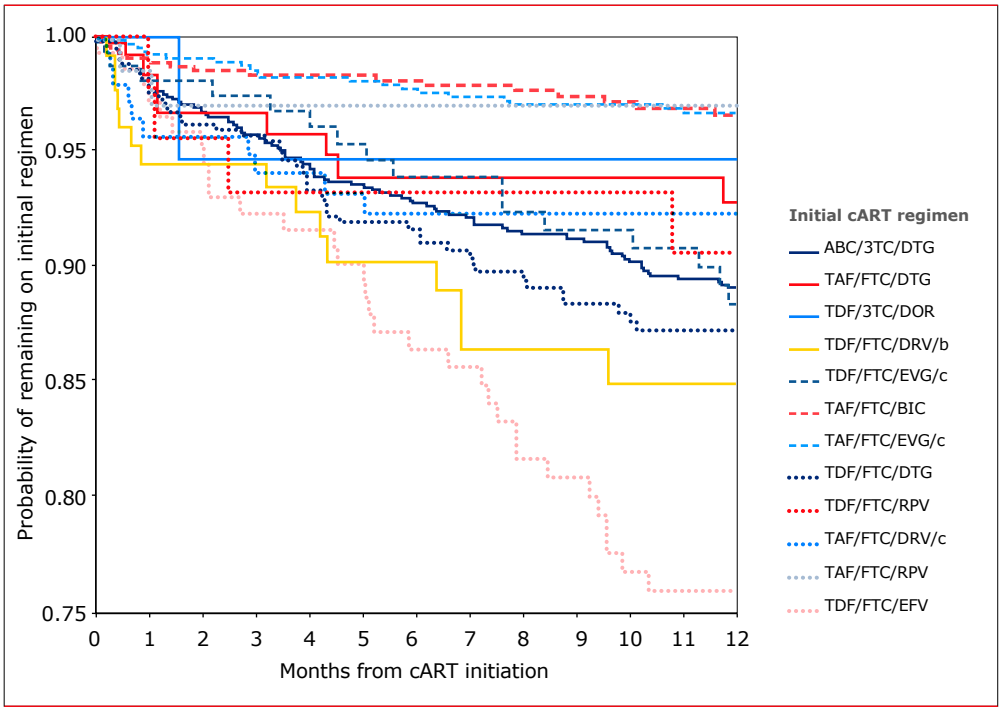


Legend: cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DOR=doravirine; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide;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

Discontinuation of the initial cART regimen due to toxicity

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

Figure 2.9: *Kaplan-Meier estimate of the time on initial regimen until modification due to toxicity in 2016-2020, by regimen. Time was censored when the initial regimen was discontinued due to reasons other than toxicity (log-rank p<0.001).*



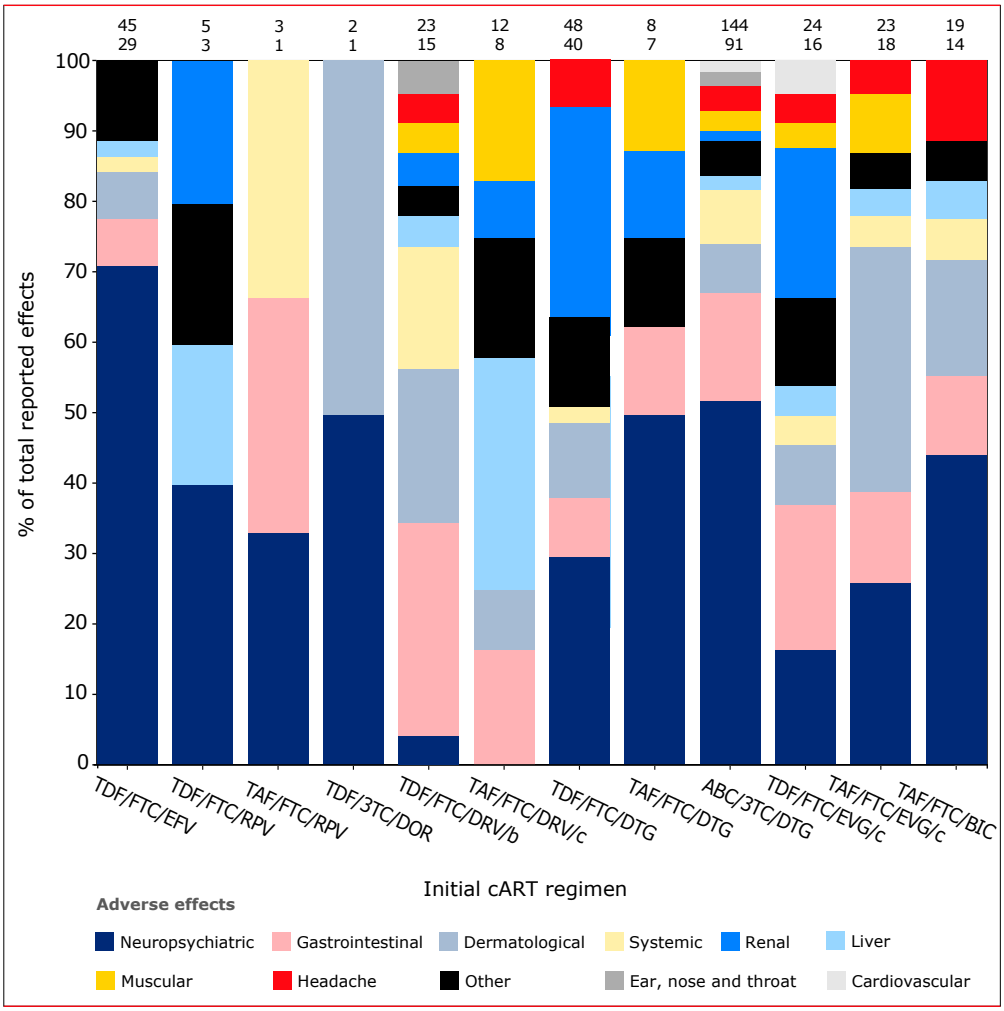
Legend: *cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir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

Adverse effects

Among the 267 individuals who discontinued their initial cART regimen within a year due to toxicity, 356 adverse effects were recorded. The predominant effects were: 41.6% neuropsychiatric (mainly insomnia, mood changes, dizziness, and depression), 14.0% gastrointestinal (mainly diarrhoea and nausea), 10.7% dermatological (rash due to medication, itching), 7.0% renal (renal insufficiency and increased serum creatinine), and 5.9% systemic (tiredness, apathy, and loss of appetite). 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 in 2016–2020. The bars represent the distribution of 356 reported effects among 267 people, by regimen. Numbers above the bars represent 1) the number of adverse events reported as reasons for discontinuing that particular regimen (top row), and 2) the number of individuals using that particular regimen who experienced those events (bottom row).



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 that are 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.

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

Virological response

In the Netherlands, a total of 26,806 adults started cART between January 1996 and December 2020. For the analysis of virological outcomes in this section, we have focused on the 23,290 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 have also excluded people without an appropriate viral load test result within at least three months of cART initiation. Results are therefore restricted to the remaining 22,675 individuals. 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 below 100 copies/ml within six months of starting combination antiretroviral therapy (cART).
The viral load measurement closest to six months (plus or minus three months) after cART initiation was included in the analysis, irrespective of the viral load level.

Viral suppression

Any viral load measurements below 200 copies/ml, after at least three months of cART initiation.

HIV drug resistance

Transmitted HIV drug resistance

At least one resistance-associated mutation detected among individuals who had never received antiretroviral drugs and had not started cART.
The 2019 International Antiviral Society-USA (IAS-USA) HIV drug resistance mutation list was used to score major resistance-associated mutations[25].

Acquired HIV drug resistance

High-level resistance to at least one antiretroviral drug, detected at the time of an HIV viral load above 500 copies/ml, among people receiving cART for at least four months.
The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.9-1) was used to infer antiretroviral drug susceptibility and resistance scores[26,27].

Initial virological success

Of the 22,675 individuals with a viral load test result within at least three months of cART initiation, 19,692 (86.8%) had a viral load measurement six months (plus or minus three months) after cART initiation. Of these people, 16,678 (84.7%) achieved initial virological success (i.e., a plasma viral load below 100 HIV RNA copies/ml [*Box 2.3*]). That percentage has improved over time, from 68.2% in those starting cART between 1996 and 2004, to 87.9% in 2005-10, 92.3% in 2011-19, and 93.9% in those starting in 2020.

Initial virological success of common initial cART regimens (2013–2020)

We analysed initial virological success among the 5,454 adults who started a common or guideline-recommended cART regimen in 2013-20, who used it frequently enough to allow for a meaningful analysis (TDF/FTC/EFV; TDF/FTC/RPV; TDF/FTC/DRV/b; TDF/FTC/DTG; TDF/FTC/EVG/c; TAF/FTC/RPV; TAF/FTC/DRV/c; TAF/FTC/BIC; TAF/FTC/DTG; TAF/FTC/EVG/c; and ABC/3TC/DTG), and had a viral load result within six months (plus or minus three months) of cART initiation. In total, 94.1% (95% confidence interval [CI] 93.5-94.7) of individuals achieved initial virological suppression, after a mean of 179 (standard deviation [SD] 39) days. Overall, people receiving an integrase inhibitor or NNRTI-based regimen showed significantly higher rates of initial virological success: 94.1% (95% CI 92.7-95.4) of those on an integrase inhibitor-based regimen and 95.0% (95% CI 94.2-95.7) on a NNRTI-based regimen, compared to 89.6% (95% CI 87.2-91.9) on a protease inhibitor-based regimen.

Using logistic regression analysis, we further evaluated the initial virological success rates stratified by viral load at cART initiation (below, as well as equal to or above 100,000 copies/ml), cART regimen, and regimen class. Stratified analysis of initial virological success based on viral load at cART initiation, showed superior virological outcomes for INSTI-based regimens, compared to both NNRTI-based and protease inhibitor-based regimens in people with a viral load at or above 100,000 copies/ml at cART initiation (*Table 2.4*). However, there were no significant differences between the three regimen classes in people with a viral load below 100,000 copies/mL at cART initiation. Population characteristics, which may be associated with the initial prescribed regimen, were not taken into account in this analysis.

Table 2.4: *Initial virological success rates (see definition in Box 2.3), by initial regimen and initial viral load at cART initiation in 2013–2020.*

	Total		By initial viral load at cART initiation					
					<100,000 copies/ml			
	n	%	n	%	Initial viral success	95% CI low	95% CI high	p-value
cART regimen								
TDF/FTC/EFV	633	11.6	346	10.1	98.0	96.5	99.5	Ref.
TDF/FTC/RPV	463	8.5	463	13.5	95.2	93.3	97.2	0.045
TDF/FTC/DRV/b	545	10.0	225	6.6	95.6	92.9	98.2	0.10
TDF/FTC/EVG/c	765	14.0	528	15.4	97.3	96.0	98.7	0.55
TDF/FTC/DTG	564	10.3	290	8.5	97.2	95.4	99.1	0.54
ABC/3TC/DTG	1,223	22.4	820	24.0	97.0	95.8	98.1	0.33
TAF/FTC/RPV	52	1.0	52	1.5	100	100	100	0.99
TAF/FTC/DRV/c	116	2.1	51	1.5	100	100	100	0.99
TAF/FTC/EVG/c	551	10.1	340	9.9	97.4	95.6	99.1	0.59
TAF/FTC/DTG	98	1.8	48	1.4	95.8	90.2	100	0.36
TAF/FTC/BIC	444	8.1	256	7.5	97.7	95.8	99.5	0.78
Regimen class								
NNRTI/2NRTI	1,148	21.1	861	25.2	96.6	95.4	97.8	Ref.
PI/2NRTI	661	12.1	276	8.1	96.4	94.2	98.6	0.84
INSTI/2NRTI	3,645	66.8	2,282	66.7	97.2	96.5	97.9	0.41
All regimens	**5,454**	**100**	**3,419**	**62.7**	**97.0**	**96.4**	**97.6**	

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

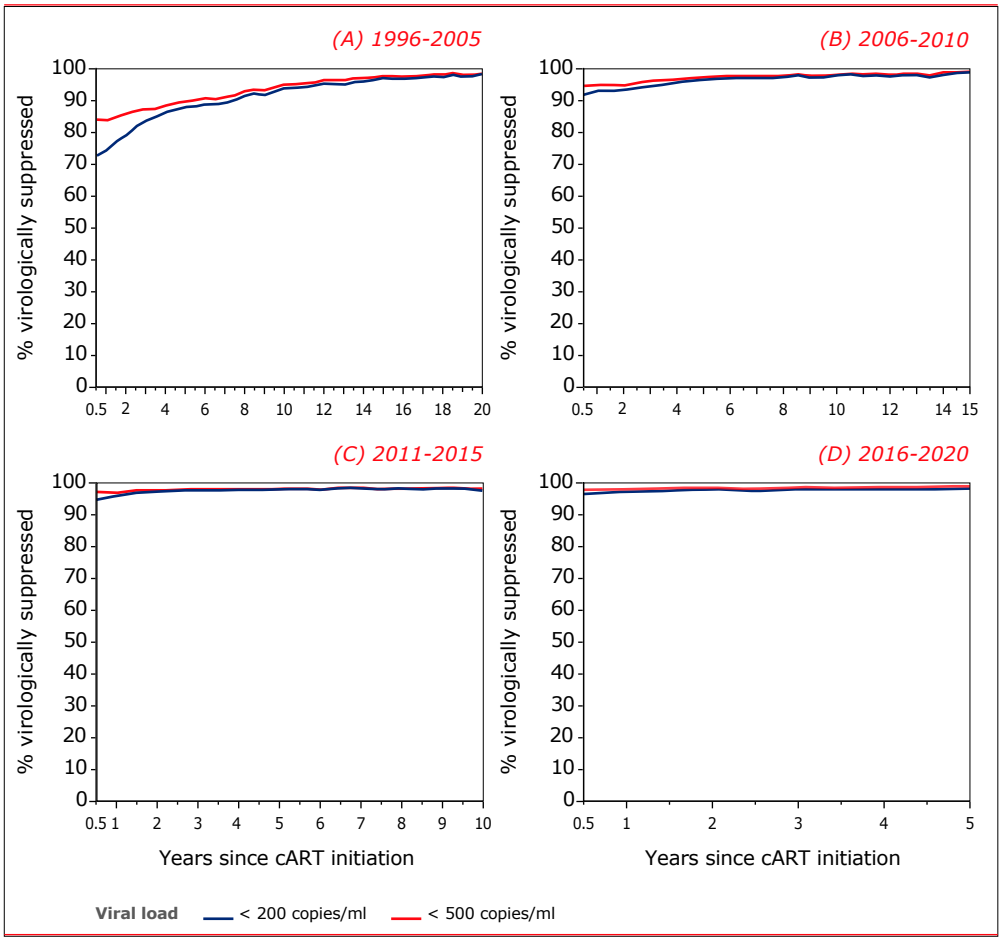
		By initial viral load at cART initiation					
		≥100,000 copies/ml					
		n	%	Initial viral success	95% CI low	95% CI high	p-value
	cART regimen						
	TDF/FTC/EFV	287	14.1	86.4	82.4	90.4	Ref.
	TDF/FTC/RPV	not recommended					
	TDF/FTC/DRV/b	320	15.7	85.0	81.1	88.9	0.62
	TDF/FTC/EVG/c	237	11.7	89.9	86.0	93.7	0.23
	TDF/FTC/DTG	274	13.5	90.1	86.6	93.7	0.17
	ABC/3TC/DTG	403	19.8	92.1	89.4	94.7	0.017
	TAF/FTC/RPV	not recommended					
	TAF/FTC/DRV/c	65	3.2	83.1	74.0	92.2	0.49
	TAF/FTC/EVG/c	211	10.4	91.5	87.7	95.2	0.082
	TAF/FTC/DTG	50	2.5	92.0	84.5	99.5	0.28
	TAF/FTC/BIC	188	9.2	92.0	88.1	95.9	0.062
	Regimen class						
	NNRTI/2NRTI	287	14.1	86.4	82.4	90.4	Ref.
	PI/2NRTI	661	18.9	84.7	81.1	88.3	0.53
	INSTI/2NRTI	3,645	67.0	91.2	89.7	92.7	0.013
	All regimens	**2,035**	**37.3**	**89.3**	**87.9**	**90.7**	

Viral suppression

We assessed long-term viral suppression rates (i.e., viral load below 200 copies/ml), during six-month intervals among adults on cART with a viral load test result after cART initiation. The viral load measurement after at least three months of cART, closest to each six-month time point (plus or minus three months), was included in the analysis, irrespective of the viral load.

Figure 2.11 shows viral suppression rates by calendar period of cART initiation: 1996-2005, 2006-10, 2011-15, and 2016-20. In line with the initial virological success rates, the long-term viral suppression rates improved over time. In people initiating cART in, or after 2015, suppression rates ranged from 97.4% (95% CI 96.8-97.9) after one year of cART use, to 98.3% (95% CI 97.4-99.1) after four years.

Figure 2.11: *Viral suppression following combination antiretroviral therapy (cART) initiation, by calendar period of therapy initiation; A) 1996-2005, B) 2006-2010, C) 2011-2015, and D 2016-2020.*



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

Legend: *cART=combination antiretroviral therapy.*

HIV drug resistance

Box 2.3: Definitions of virological response and HIV drug resistance.

HIV drug resistance

Transmitted HIV drug resistance
At least one major resistance-associated mutation detected among individuals who had 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[25].

Acquired HIV drug resistance
High-level resistance to at least one antiretroviral drug, detected at the time of an HIV viral load above 500 copies/ml, among people receiving cART for at least four months.
The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.9-1) was used to infer antiretroviral drug susceptibility and resistance scores[26,27].

Preventing, monitoring and responding to HIV drug resistance is a key component of comprehensive and effective HIV care. When antiretroviral therapy does not result in complete suppression of viral replication, HIV drug resistance can occur: mutations in the genetic structure of HIV detrimentally affect the ability of a particular drug, or combination of drugs, to block replication of the virus. All current antiretroviral drugs, including newer classes, are at risk of becoming partially or fully inactive due to the emergence of drug-resistant virus[28].

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 section 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 separate sections. Of note, SHM does not receive drug resistance data from all HIV treatment centres and laboratories; therefore, presented figures might not be representative of the full population in HIV care.

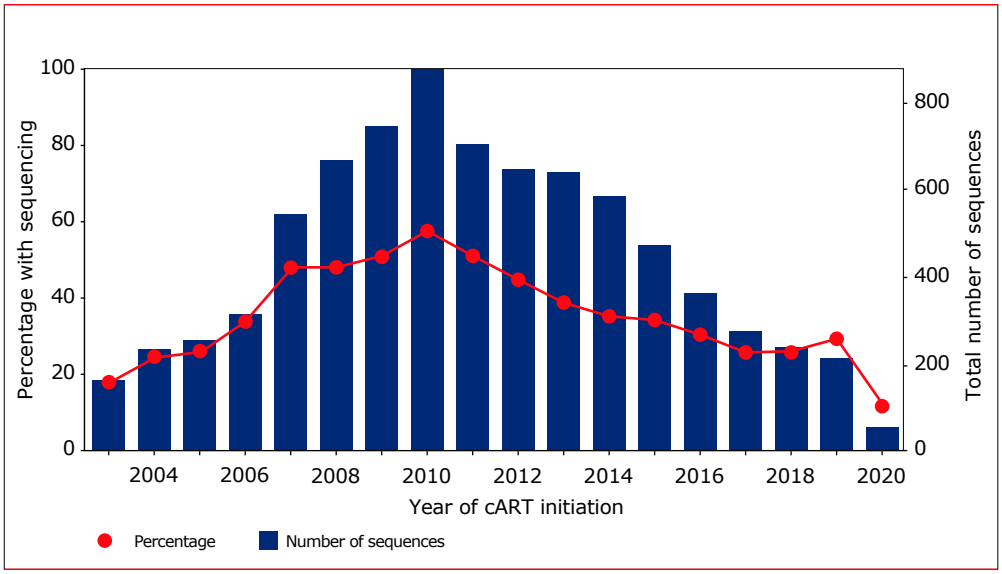
We evaluated the presence of mutations in the HIV genome that are associated with drug resistance. The 2019 International Antiviral Society-USA (IAS-USA) HIV drug resistance mutation list was used to score major resistance-associated mutations[25]. Furthermore, we assessed the association between these mutations and the susceptibility to antiretroviral drugs. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.9-1) 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[26,27]. 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

Since 2003, the Dutch treatment guidelines have included a recommendation to screen for HIV drug resistance at the time of entry into care. Transmitted HIV drug resistance occurs when people acquire an HIV strain that harbours drug-resistant mutations. Drug-resistant variants of HIV may remain dormant in resting CD4 cells, awaiting more favourable replication conditions after treatment has started[29-31]. These dormant mutant variants may not be detected, which can make it difficult to distinguish between drug-susceptible and drug-resistant strains[32]. Ideally, the presence of transmitted resistance should be identified as close as possible to the moment of infection in people who are antiretroviral (ARV)-naive before initiating cART.

In total, 8,158 HIV-1 sequences were obtained between 2003 and 2020 from 7,863 ARV-naive people before they initiated cART. The number of sequences and the percentage of ARV-naive people with sequencing before cART initiation peaked in 2010 and have steadily declined since then (*Figure 2.12*). The decline in the number of sequences in 2020 is likely due to a backlog in relaying sequence data to the SHM; it is too early to determine whether the reduced capacity at virology departments across the Netherlands during the COVID-19 pandemic had any influence. 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 our analysis, to limit the effect of back mutation. Of those with pre-treatment drug-resistance data, the majority were MSM (67.7%), while (14.8%) were women. Most people with an available pre-treatment sequence originated from the Netherlands (60.0%), or sub-Saharan Africa (11.1%). The main HIV-1 subtype was B (75.3%), followed by non-B subtypes (24.7%), including recombinant form CRF_02AG (6.6%), subtype C (5.1%), and CRF_01AE (3.4%).

Figure 2.12: The annual number of sequences and the percentage of ARV-naive people with sequencing before cART.

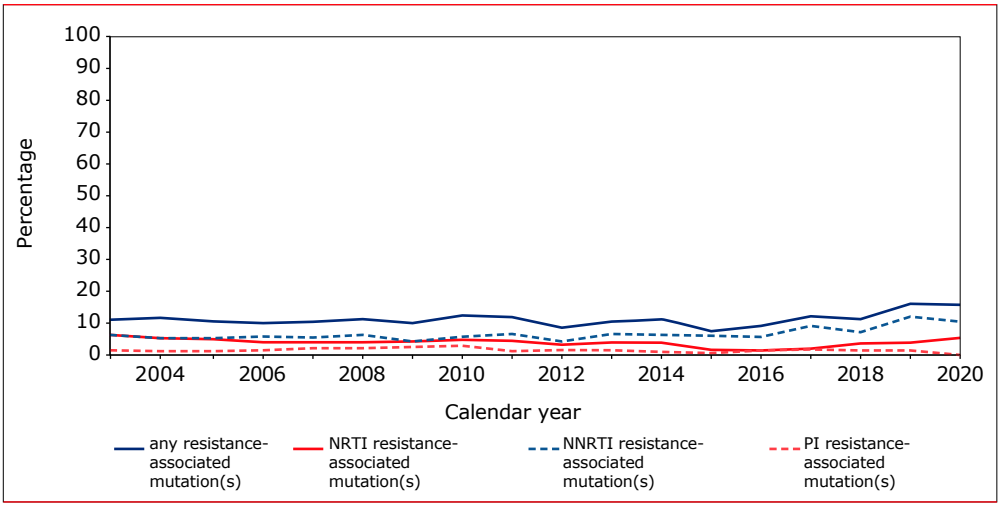


Legend: cART=combination antiretroviral therapy.

Transmitted HIV drug resistance

In total, at least one or more major resistance-associated mutation[25] was found in 859 (10.9%) of the people tested for resistance, including 321 (4.1%) with NRTI-associated resistance mutations, 474 (6.0%) with NNRTI-associated resistance mutations, and 140 (1.8%) with PI-associated resistance mutations. The prevalence of transmitted drug resistance was low and remained stable between 2003 and 2020 (*Figure 2.13*).

Figure 2.13: The annual percentage of people with evidence of transmitted HIV drug resistance over time. Transmitted drug resistance was defined as the presence of at least one resistance-associated mutation detected before initiation of cART. The 2019 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[25].



Legend: NRTI=nucleotide/nucleoside reverse transcription inhibitor; NNRTI=non-NRTI; PI=protease inhibitor; RAS=resistance associated substitution.

In total, 225 (2.9%) individuals screened for transmitted drug resistance harboured high-level resistance[26,27] to at least one antiretroviral drug; 41 (0.5%) to at least one NRTI, 166 (2.1%) to at least one NNRTI, and 34 (0.5%) to at least one PI. On the basis of the available resistance data, more than 97% were fully susceptible to all antiretroviral drugs; 2.5% (195) harboured high-level resistance in one drug class, 0.3% (22) in two drug classes, and less than 0.1% (five) 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 still often be constructed.

Integrase inhibitor resistance before HIV treatment initiation

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

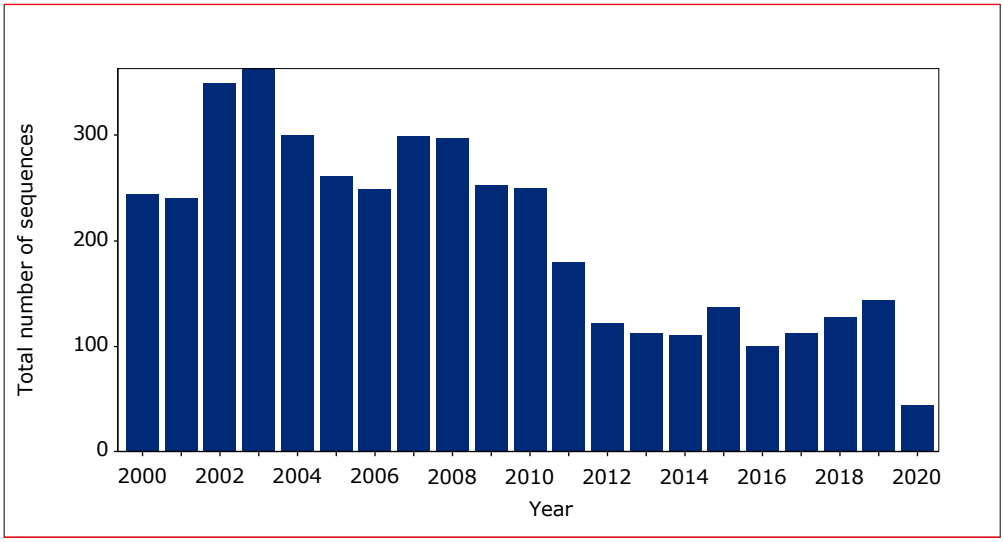
Acquired HIV drug resistance

The overall viral suppression rates of people receiving cART are very high and continue to improve in the Netherlands (see section *Virological response*). However, acquired-HIV drug resistance is still detectable 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 above 500 copies/ml, and resistance test results available after at least four months of cART in 2000-20. If cART had been interrupted more than two weeks before the test, the sequence was excluded from the analysis.

In total, 4,298 HIV-1 sequences were obtained from 2,596 people who received cART for at least four months. The number of sequences and people included in each subsequent analysis are outlined in *Box 2.1*. The number of sequences in this group was consistently above 200 between 2000 and 2010, substantially declined in 2011, then continued to decline slightly until 2019 (*Figure 2.14*). There was a considerable decline in 2020. The median time between initial start of cART and resistance testing was 5.5 years (IQR 3.0-8.8). The main HIV-1 subtype was B (67.8%), followed by recombinant form CRF_02AG (10.9%), and subtype C (5.8%).

Figure 2.14: *The annual number of HIV-1 sequences in people who received cART for at least four months.*



Overall, sequences from people pre-treated with monotherapy or dual therapy were disproportionally represented: 1,339 (31.2%) sequences were obtained from 728 (28.0%) pre-treated people, and 2,959 (68.8%) sequences were obtained from 1,868 (72.0%) ARV-naive people. However, over time this difference became less distinct: in 2000, 73.0% of sequences were obtained from pre-treated people, compared with 36.4% in 2005, and less than 16% from 2010 onwards.

Of the 4,298 sequences obtained when the HIV RNA was above 500 copies/ml, 2,735 (63.6%) harboured high-level resistance to at least one antiretroviral drug. High-level NRTI resistance was detected in 2,750 (64.0%) sequences; of those, 2,368 (86.1%) harboured high-level resistance to emtricitabine or lamivudine. Notably, of the 1,721 individuals ever identified as harbouring the M184V or M184I mutation who were still in care in 2020, 1,158 (67.3%) were still on cART containing lamivudine or emtricitabine, and 908/1,158 (78.4%) had undetectable HIV-RNA at their last visit. In addition, 1,640 (38.6%) harboured high-level resistance to at least one NNRTI, and 1,027 (24.9%) to at least one PI.

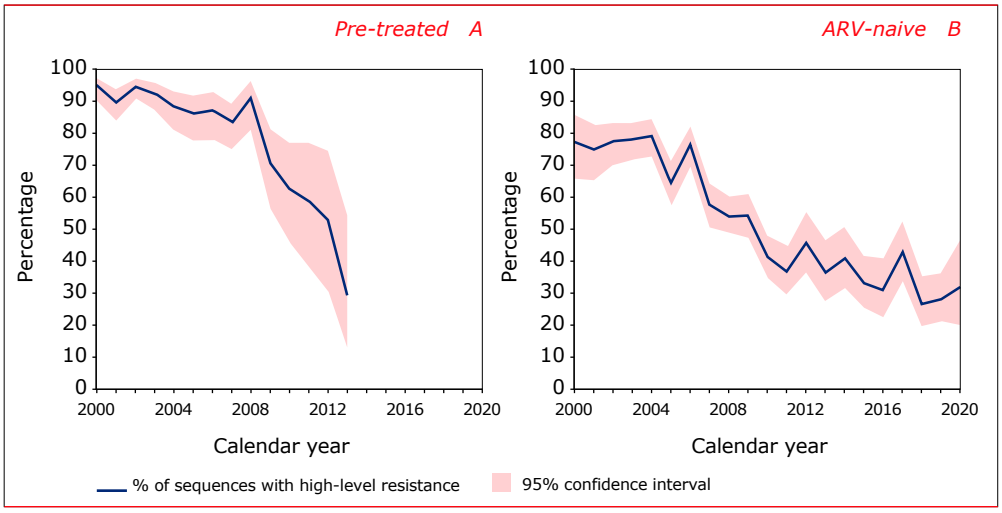
Previous antiretroviral drug exposure

The occurrence of acquired resistance was different for sequences obtained from people with mono NRTI therapy or dual NRTI therapy, than for those from people who were ARV-naive before initiating cART.

Among pre-treated people, the annual percentage of sequences harbouring high-level resistance to at least one drug was 94.9% (95% CI 90.6-97.4) in 2000, 88.5% (95% CI 81.2-93.2) in 2004, 62.9% (95% CI 46.0-77.1) in 2010, and 29.4% (95% CI 12.8-54.2) in 2013 (*Figure 2.15A*). The availability of new drugs, both in existing and new drug classes, largely explains the decline since 2008[33]. In recent years (2014-20), both the number of pre-treated people, and the number of sequences from pre-treated people, were too low to provide meaningful percentages.

Among previously ARV-naive people, high-level resistance to at least one drug was detected among 77.3% (95% CI 65.7-85.8) of sequences in 2000, 76.5% (95% CI 69.5-82.2) in 2006, 45.7% (95% CI 36.4-55.3) in 2012, and 31.8% (95% CI 19.8-46.8) in 2020 (*Figure 2.15B*). Over time, the difference in acquired drug resistance detected among pre-treated and ARV-naive people has disappeared.

Figure 2.15: The annual percentage 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 with mono or dual nucleoside-analogue RT inhibitors (NRTIs), 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 2014-2020 was too low to give meaningful percentages.

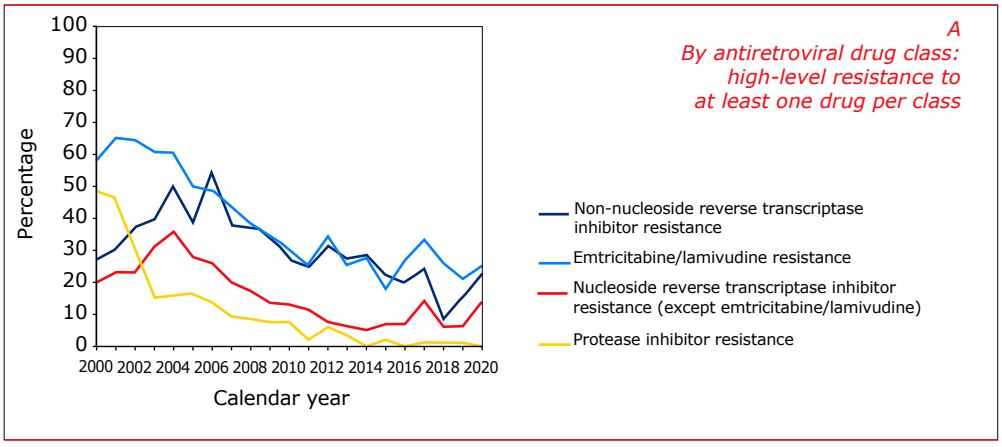
Acquired HIV drug resistance among previously ARV-naive people

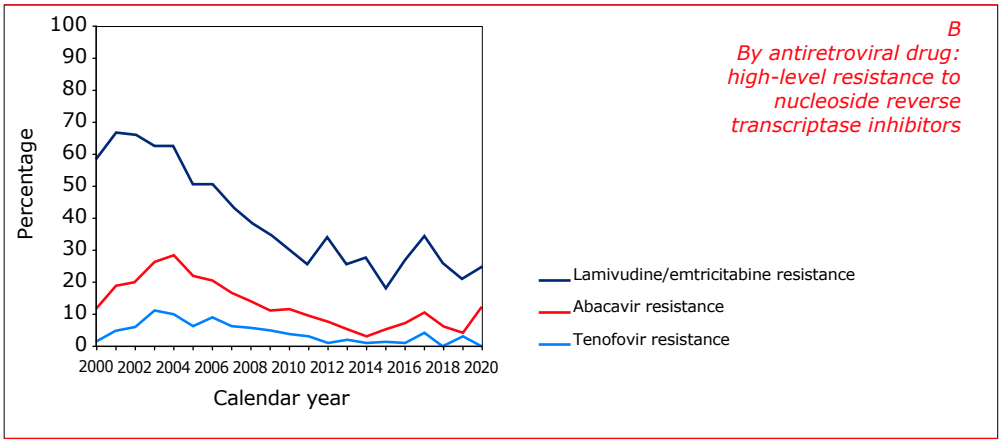
In the remainder of our analysis, we focus solely on the 1,868 people who were ARV-naive before cART initiation. Overall, 1,743 (58.9%) of the 2,959 sequences from previously ARV-naive people receiving cART harboured at least one major resistance mutation, associated with resistance to NRTI (1,388; 46.9%), NNRTI (1,080; 36.5%), or PI (363; 12.3%).

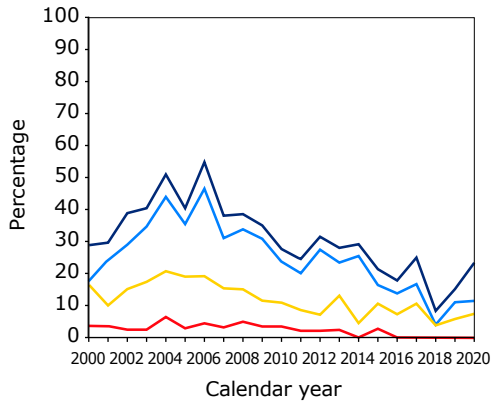
In *Figure 2.16A* and *Table 2.5*, the annual percentage of sequences harbouring high-level resistance is presented for each antiretroviral drug class. In 2000, 67.7% (95% CI 55.5-78.9), 27.7% (95% CI 18.2-39.7), and 48.5% (95% CI 36.7-60.4) of sequences harboured high-level resistance to at least one NRTI, NNRTI, or PI, respectively. The percentage of sequences with high-level resistance declined over time for all drug classes. In 2009, 36.8% (95% CI 30.4-43.7), 34.8% (95% CI 28.6-41.7), and 7.5% (95% CI 4.5-12.0) of sequences harboured high-level resistance to at least one NRTI, NNRTI, or PI, respectively. In 2020, 25.0% (95% CI 14.4-39.7), 22.7% (95% CI 12.7-37.3), and 0% of sequences harboured high-level resistance to at least one NRTI, NNRTI or PI, respectively. The percentage of sequences with at least one resistance mutation to all three drug classes (i.e., NRTI, NNRTI, and PI), also declined over time: from 9.1% (95% CI 4.1-18.8) in 2000 to 0% in

2014. The annual percentages of sequences harbouring high-level resistance to individual antiretroviral drugs are presented in *Figure 2.16B-D* and *Appendix Table 2.1A-C*, and annual percentages of sequences harbouring at least one high-level resistance mutation to all three drug classes in *Figure 2.16E*. Of note, drug resistance does not disappear when viral replication is successfully suppressed or re-suppressed, but instead remains viably archived in the viral reservoir.

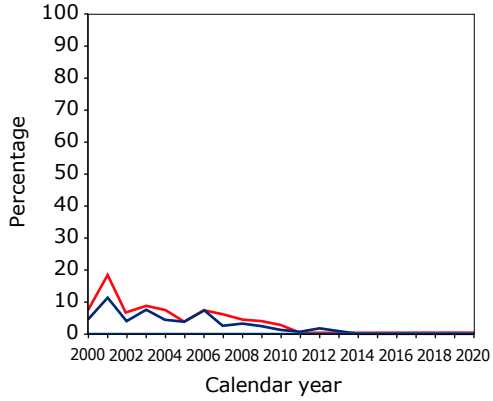
Figure 2.16: *The annual percentages of sequences with evidence of high-level resistance by drug class and antiretroviral drug, obtained at the time of virological failure when receiving combination antiretroviral therapy (cART), among previously antiretroviral drug-naive people. Results are shown by A) antiretroviral drug class: high-level resistance to at least one drug within class, B) antiretroviral drug: high-level resistance to nucleoside reverse transcriptase inhibitors, C) antiretroviral drug: high-level resistance to non-nucleoside reverse transcriptase inhibitors, D) antiretroviral drug: high-level resistance to protease inhibitors, and E) high-level resistance to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors.*



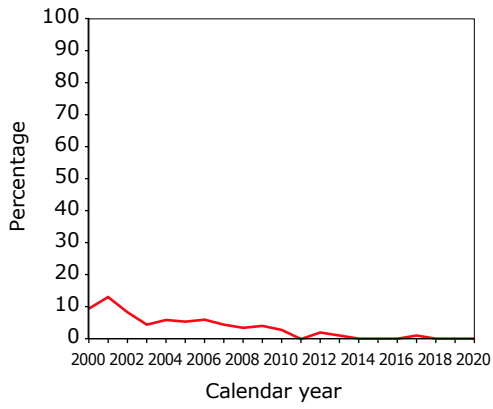




C
By antiretroviral drug: high-level resistance to non-nucleoside reverse transcriptase inhibitors



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



E
High-level resistance to nucleoside reverse transcriptase inhibitors (NRTI), non-NRTIs and protease inhibitors

Note: *The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.9-1) 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*[26,27].
Legend: *NRTIs=nucleoside analogue reverse transcriptase inhibitors.*

Table 2.5: Acquired drug resistance: the annual percentage 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. See Appendix Table 2.1 for antiretroviral drug-specific results.

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	67.7	55.5	77.9	27.7	18.2	39.7	48.5	36.7	60.4
2001	72.8	62.9	80.9	29.3	21.0	39.4	46.2	36.2	56.4
2002	71.6	64.0	78.2	37.4	30.2	45.3	30.3	23.6	38.0
2003	69.2	62.4	75.2	39.8	33.3	46.7	15.1	10.7	20.7
2004	69.0	62.0	75.2	50.3	43.1	57.4	16.0	11.4	22.0
2005	56.6	49.0	64.0	38.6	31.5	46.2	16.3	11.4	22.7
2006	57.6	50.1	64.9	54.1	46.6	61.5	13.6	9.2	19.7
2007	48.7	41.8	55.7	37.9	31.4	45.0	9.2	5.9	14.2
2008	43.1	37.0	49.5	37.2	31.3	43.5	8.4	5.5	12.6
2009	36.8	30.4	43.7	34.8	28.6	41.7	7.5	4.5	12.0
2010	31.6	25.8	38.1	27.0	21.5	33.3	7.5	4.6	11.9
2011	27.2	20.8	34.7	24.7	18.6	32.0	1.9	0.6	5.8
2012	34.3	25.9	43.8	31.4	23.3	40.9	5.7	2.6	12.1
2013	26.3	18.4	36.1	27.4	19.4	37.2	3.4	1.1	9.9
2014	28.6	20.5	38.3	28.6	20.5	38.3	0		
2015	20.3	14.0	28.6	22.0	15.5	30.4	1.9	0.5	7.4
2016	26.7	18.5	37.1	19.8	12.7	29.5	0		
2017	37.4	28.4	47.3	24.2	16.8	33.6	1.2	0.2	7.8
2018	25.9	18.6	34.8	8.0	4.2	14.7	1.2	0.2	7.9
2019	22.4	15.9	30.5	15.2	9.9	22.6	1.0	0.1	7.0
2020	25.0	14.4	39.7	22.7	12.7	37.3	0		

Acquired integrase inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on cART was relatively rare. The available 208 integrase sequences originated from 168 people who received cART for at least four months; 17 were pre-treated with monotherapy or dual NRTI therapy before initiating cART, and 151 were ARV-naive before initiating cART. Most people had initiated cART years before; the median time between initial cART initiation and testing for integrase inhibitor resistance was 10.4 years (IQR 3.7-15.0). For each person, we used the most recent sequence in our analysis.

At least one acquired major mutation associated with integrase inhibitor resistance was detected in 29 of the 168 individuals, which resulted in high-level resistance to at least one integrase inhibitor[25,26]. Among the 29, the following major INSTI resistance mutations were detected (numbers are given in parenthesis): N155H (14) and N155H/N (two); Y143R (three) and Y143Y/C (one); T66I (one); E92Q (four) and E92E/Q (one); Q148H (one, in combination with the G140S minor mutation); and R263K (one). Minor mutations detected were at position L74: any mutation (six); L74I (five); L74M (one); T97 (any, four; T97A, four); T66 other than T66I (any, three; T66T/A, two; T66T/K, one); and G140S (one). Six of the 29 patients who harboured a high-level resistance mutation to INSTI had ever received INSTI-monotherapy.

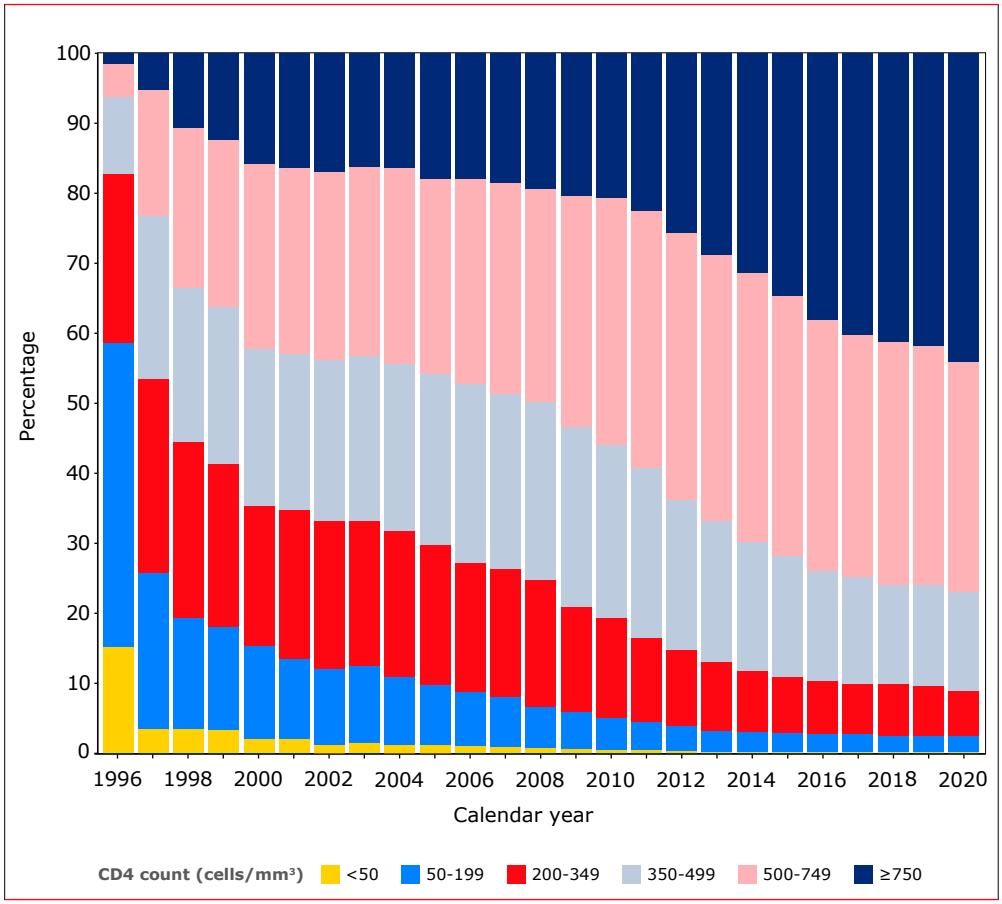
Immunological response

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 viremia is associated with poorer recovery of CD4 cell count[34,35]. However, incomplete recovery of CD4 cell count (i.e., having a CD4 count persistently below 350 cells/mm^3), 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[36]. 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[37]. 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[38-43]. The clinical benefit of cART is strongly related to the level of recovery of the immune status (also see *Chapter 3*)[44-48].

Immunological response – by calendar year

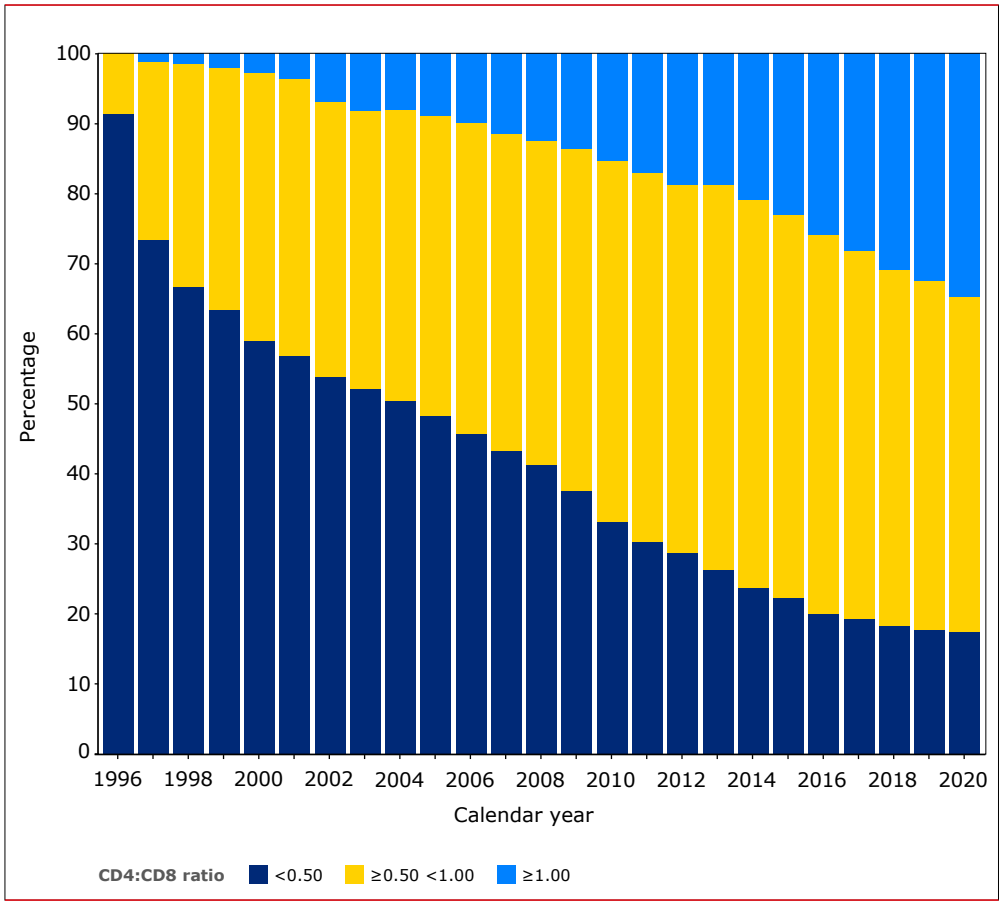
Of the 26,806 people known to have initiated cART between January 1996 and December 2020, CD4 cell count data after cART initiation were available for 26,330 (98.2%). *Figures 2.17* and *2.18* show the last known CD4 cell count and CD4:CD8 ratio of all people in HIV care for each calendar year. After starting cART, the percentage of people with CD4 cell counts below 350 cells/mm^3 dropped from 53.3% in 1997 to 29.7% in 2005, 19.2% in 2010, 11.0% in 2015, and 9.0% in 2020 (*Figure 2.17*). The decrease in the percentage of people with low CD4 cell counts at the end of each calendar year results from the trend of starting cART at higher CD4 cell counts, more pronounced immune recovery with longer cART use, continually-declining virological failure rates, and attrition by the higher mortality rates in those with low CD4 counts.

Figure 2.17: Last available CD4 cell count of the treated population by calendar year (missing measurements/ data were not taken into account). Figures for 2020 may change slightly as data collection is not yet complete.



The percentage of those with a CD4:CD8 ratio of one or above increased from 1.2% in 1997 to 2.8% in 2000, 8.8% in 2005, 15.3% in 2010, 23.1% in 2015, and 34.6% in 2020 (*Figure 2.18*). Of all CD4:CD8 ratio measurements equal to or above one, 10.4% had a CD4 count of less than 500 cells/mm^3, 32.1% had a CD4 count between 500-749 cells/mm^3, and 57.5% had a CD4 count equal to or above 750 cells/mm^3. When the CD4:CD8 ratio was equal to or above one, the median CD4 count was 800 cells/mm^3 (IQR 621-1,000).

Figure 2.18: Last available CD4:CD8 ratio in each calendar year after the start of combination antiretroviral therapy (cART).



Immunological response – after cART initiation (2016–2020)

We also assessed the immunological response in people who started cART more recently (i.e., in 2016-20), and had CD4 cell count data available at, and after cART initiation. The level of viral suppression and treatment interruptions after initiating cART were not taken into account in this analysis. Of the 3,210 people who started cART in 2016-20 and had sufficient immunological data available, 10.0% had CD4 counts below 50 cells/mm^3, 16.0% 50-199 cells/mm^3, 19.4% 200-349 cells/mm^3, 21.0% 350-499 cells/mm^3, and 33.5% equal to or above 500 CD4 cells/mm^3 at the time of cART initiation. The average CD4 cell count at cART initiation has decreased slightly in recent years (*Appendix Table 2.2*).

The CD4 cell count and CD4:CD8 ratio trajectories following cART initiation are plotted in *Figures 2.19* and *2.20* 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 study by the Antiretroviral TherapyCohort Collaboration (ART-CC), which included ATHENA data. It showed that the likelihood of normalisation of the CD4:CD8 ratio is strongly related to baseline CD4 cell count[49].

Figure 2.19: *CD4 cell count over time after the start of combination antiretroviral therapy (cART) in 2016–2020.*

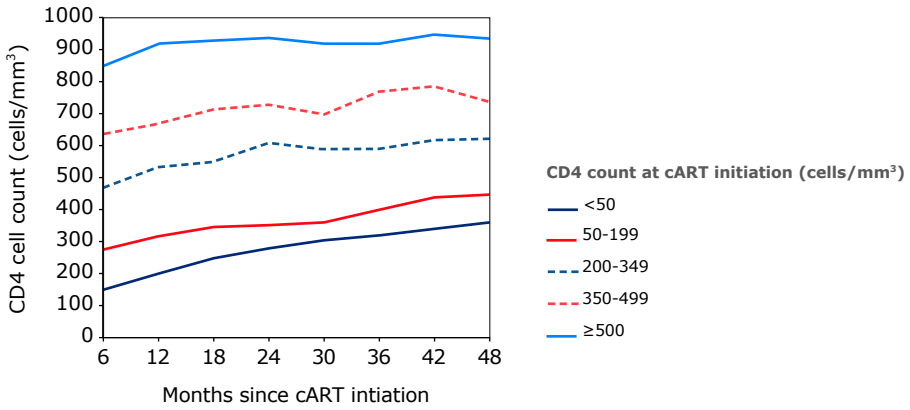
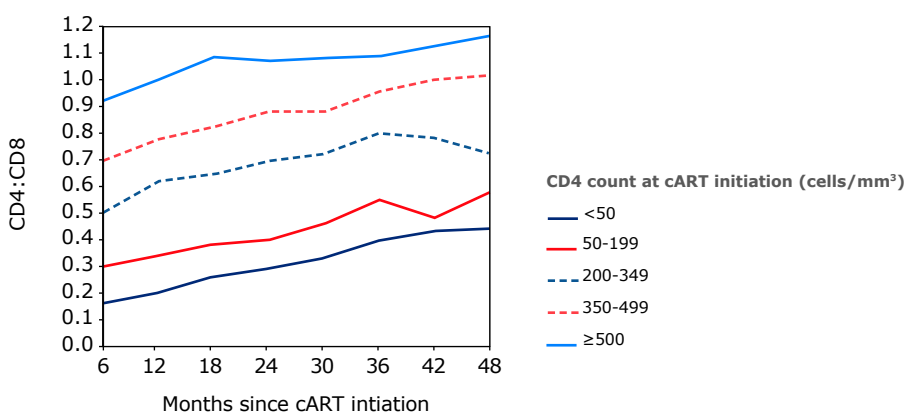


Figure 2.20: *CD4:CD8 ratio over time after the start of combination antiretroviral therapy (cART) in 2016–2020.*



Note: *The presented immunological outcomes are based on available test results. For people with a low to moderate CD4 cell count (below 350 cells/mm³), CD4 cell count testing is recommended at least twice a year[50]. When a person has a CD4 cell count above 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 and the initial regimen

- Rapid initiation of cART following a diagnosis of HIV infection, irrespective of CD4 cell count, has generally resulted in a shorter median time to initiation of cART following diagnosis.
- The CD4 cell count at cART initiation initially increased over time, peaking in the year 2015 at a median of 414 cells/mm^3 (IQR 220-600). This was when new guidelines were issued that recommended rapid initiation of cART at any CD4 count. Those guidelines resulted in substantial numbers of individuals with preserved CD4 counts, who had postponed starting cART, deciding to initiate treatment. Since then, the median CD4 count at the start of cART has continued to decrease. Among individuals living with HIV starting cART in 2020, the median CD4 cell count was 286 cells/mm^3 (IQR 99-500). Immunological recovery was better when cART was started at a higher CD4 cell count.
- In 2020, 89.4% of initial regimens contained an integrase inhibitor. The most frequently used initial regimen was bictegravir/emtricitamine/tenofovir alafenamine (45.9%). Dolutegravir-containing initial regimens were used in 42.7% of cases.
- Compared to the first decade of the cART era, discontinuation of the initial regimen has become less common over time. In the past decade, the discontinuation rate has remained stable. However, the reasons for switching have continued to change, with virological failure a very rare event nowadays. In recent years, many switches were driven by the wish for regimen simplification and pre-emptive modifications because of the availability of new regimens that are perceived to have better long-term safety profiles.
- 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 2020

- Integrase inhibitor-based cART has been implemented on a large scale in the Netherlands and was used by 48.4% of all individuals.
- The nucleoside analogue backbone used contained TDF in 30.8% of cases, ABC in 16.8%, and TAF in 43.7% of cases.
- In 2020, 7.3% used a two-drug regimen.
- Of those receiving cART for at least 12 months, who had a plasma HIV RNA measurement in 2019, 97.6% had a viral load below 200 copies/ml, and 96.9% had a viral load equal to or below 50 copies/ml.

Virological response and drug resistance

- The overall viral suppression rates of the population living with HIV receiving cART is high and has continued to improve. Among the limited number of individuals who experienced virological failure, the annual percentage with acquired drug resistance remained low; this is in line with findings in other high-income settings[51,52].
- Transmitted drug resistance was rare, and the overall prevalence was low and stable over time, in line with rates reported by other European countries[53].
- Integrase inhibitor resistance data remain limited. No transmitted integrase inhibitor resistance was detected among the 168 people tested by the end of 2020. Detected rates of acquired integrase inhibitor resistance among available sequences remained very low, with almost no significant resistance to dolutegravir.
- There was a considerably lower number of sequences available in 2020 than in other years; this could be due to restricted capacity at virology departments during the COVID-19 pandemic. The effect of limited sequencing should be evaluated in the future.

Immunological response

- In individuals using cART, the percentage of people with CD4 cell counts below 350 cells/mm^3 dropped from 53.3% in 1997 to 29.7% in 2005, 19.2% in 2010, 11.0% in 2015, and 9.0% in 2020.
- The percentage of those with a CD4:CD8 ratio of one or above increased from 1.2% in 1997 to 8.8% in 2005, 15.3% in 2010, 23.1% in 2015, and 34.6% in 2020.

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Appendix

Appendix Table 2.1A-C: *Acquired drug resistance: annual percentage of available sequences with evidence of high-level resistance after virological failure by antiretroviral drug, associated with people who received combination antiretroviral therapy and were previously antiretroviral drug-naive. Results are shown by A) high-level resistance to nucleoside reverse transcriptase inhibitors, B) high-level resistance to non-nucleoside reverse transcriptase inhibitors, and C) high-level resistance to protease inhibitors.*

A)

Calendar year	Number of sequences	Emtricitabine/ lamivudine	Zidovudine	Stavudine	Abacavir	Didanosine	Tenofovir
2000	65	58.5	14.8	10.7	11.7	12.3	1.7
2001	92	66.7	15.0	17.7	18.8	16.7	4.8
2002	155	66.2	12.4	15.2	19.9	18.6	6.3
2003	201	62.9	18.4	24.0	26.4	26.5	11.2
2004	187	62.8	18.8	22.1	28.3	28.7	10.1
2005	166	50.6	13.6	18.1	22.1	21.2	6.5
2006	170	50.9	10.8	16.8	20.5	22.1	9.0
2007	195	44.3	10.2	13.5	16.8	14.0	6.5
2008	239	39.1	7.6	11.5	14.3	15.1	5.9
2009	201	35.2	6.8	9.5	11.5	11.3	5.2
2010	215	30.4	5.4	8.4	11.7	12.1	3.9
2011	158	25.6	2.6	4.8	9.7	9.7	3.3
2012	105	34.3	0.0	2.0	7.9	7.8	1.0
2013	95	25.5	0.0	2.2	5.5	5.5	2.2
2014	98	27.8	1.0	3.1	3.2	4.1	1.1
2015	118	18.3	0.9	2.7	5.3	6.8	1.8
2016	86	26.7	1.2	2.5	7.1	4.9	1.2
2017	99	34.4	2.0	6.3	10.5	12.4	4.3
2018	112	25.9	0.0	0.0	6.3	5.4	0.0
2019	125	21.1	1.6	4.9	4.1	5.7	3.2
2020	44	25.0	2.3	2.3	12.2	9.8	0.0

B)

Calendar year	Number of sequences	Nevirapine	Efavirenz	Etravirine	Rilpivirine
2000	65	28.6	17.5	3.7	16.1
2001	92	29.7	24.4	3.5	9.9
2002	155	38.9	29.2	2.3	15.3
2003	201	40.4	34.2	2.4	17.5
2004	187	50.8	44.0	6.4	20.6
2005	166	40.3	35.3	2.8	18.9
2006	170	54.8	46.3	4.6	19.3
2007	195	38.0	31.1	3.1	15.2
2008	239	38.7	33.9	4.8	15.0
2009	201	35.0	30.7	3.4	11.4
2010	215	27.6	22.9	3.6	10.7
2011	158	24.5	20.1	2.1	8.7
2012	105	31.4	27.3	2.1	7.1
2013	95	28.0	23.3	2.4	12.9
2014	98	29.2	25.5	0.0	4.3
2015	118	21.2	16.1	2.8	10.5
2016	86	17.9	13.6	0.0	7.2
2017	99	25.0	16.9	0.0	10.5
2018	112	8.0	3.7	0.0	3.7
2019	125	15.2	10.9	0.0	5.7
2020	44	23.3	10.8	0.0	7.3

C)

Calendar year	Number of sequences	Nelfinavir	Saquinavir	Indinavir	Atazanavir	Fosamprenavir	Lopinavir	Tipranavir	Darunavir
2000	66	48.5	9.4	6.6	7.9	7.7	4.8	1.6	0.0
2001	91	46.7	21.3	18.2	18.8	14.0	11.5	3.5	0.0
2002	155	30.7	10.9	7.8	6.9	5.6	4.0	0.7	0.0
2003	199	15.7	8.3	8.9	8.7	6.7	7.2	1.6	0.0
2004	187	15.2	6.7	6.9	7.7	5.5	4.5	0.6	0.0
2005	166	16.3	3.9	6.5	3.8	3.2	3.8	0.6	0.0
2006	169	13.1	6.1	7.8	7.3	5.5	7.1	2.4	0.0
2007	195	9.4	4.8	4.3	6.2	3.1	2.6	1.0	0.0
2008	239	6.8	3.4	4.7	4.7	4.7	3.5	0.4	0.0
2009	201	7.1	3.5	4.1	4.1	4.1	2.6	1.0	0.0
2010	214	6.2	2.9	3.9	2.8	3.8	1.5	0.0	0.0
2011	156	1.9	0.6	0.6	0.6	0.6	0.6	0.0	0.0
2012	105	5.7	2.0	2.0	1.9	1.9	1.9	0.0	0.0
2013	89	3.4	0.0	1.1	1.1	2.2	1.1	0.0	0.0
2014	83	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2015	103	1.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2016	75	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2017	86	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2018	85	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2019	97	1.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0
2020	44	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Appendix Table 2.2: *CD4 cell count at combination antiretroviral therapy (cART) initiation by calendar year in 2016–2020.*

Year of cART initiation	2016	2017	2018	2019	2020	2016–2020
CD4 cell count available at cART initiation	926	822	687	540	235	**3,210**
CD4 cell count, median cells/mm³ (IQR)	410 (237–580)	380 (200–560)	373 (167–580)	354 (154–560)	286 (99–500)	**380 (185–570)**
CD4 cell count (cells/mm³)						
<50	8.9%	8.3%	11.5%	10.2%	16.2%	**10.0%**
50–199	12.2%	16.1%	16.6%	20.0%	20.4%	**16.0%**
200–349	18.4%	20.3%	18.6%	18.9%	23.4%	**19.4%**
350–499	23.1%	22.6%	19.5%	19.8%	14.5%	**21.0%**
≥500	37.5%	32.7%	33.8%	31.1%	25.5%	**33.5%**

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

3. Morbidity and mortality

Ferdinand Wit, Berend van Welzen, Marc van der Valk

Introduction

Since the introduction of combination antiretroviral therapy (cART) in 1996, the life expectancy of HIV-1-positive individuals has markedly improved; in a subgroup of recently-diagnosed, effectively-treated individuals, it was 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 has increased among HIV-1-positive individuals during the cART era[3-8]; for example, renal and liver disease, diabetes mellitus, myocardial infarction, stroke, osteoporosis, and non-AIDS-defining malignancies.

Various reports suggest that the risk of non-AIDS morbidity may be higher in individuals living with HIV treated with antiretroviral therapy (ART), than in HIV-negative individuals of comparable age[9-11]. For example, pulmonary hypertension[12], bone disease, and non-traumatic bone fractures[13-15], have each 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[16-18]. Just as with HIV-negative individuals, traditional risk factors (e.g., tobacco use[19], alcohol abuse, and viral hepatitis co-infection[20]), also 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 composition, 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 its causes for HIV-1-positive adults (18 years and older) using updated stichting hiv monitoring (SHM) data. We look at a total of 28,240 adult individuals ever registered by SHM – that breaks down as 27,760 adults and an additional 479 individuals who were diagnosed with HIV as children and have since become adults. 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 of the United States' Centers for Disease Control (CDC) category C conditions[23]. In contrast to what is usual in the US, in our analyses, a CD4 count below 200 cells/mm^3 in the absence of an AIDS-defining condition, does not qualify as AIDS.

The following are defined according to criteria established by the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study: 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). In addition, Castleman's disease is also considered a non-AIDS-defining malignancy.

Histological confirmation of malignancies is part of standard clinical practice in the Netherlands. As a result, pathology reports, wherever possible, have been used 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 six months or longer. In previous Monitoring Reports, we used a period of three months, but in the present Monitoring Report, we have extended the period to six months because of the large number of episodes of renal dysfunction that revert shortly after three months, and which do not represent true CKD.

Methods

For the analyses of incidence per calendar year and calendar period, we have considered 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 was most recent. 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 2000-10, 2011-15, and 2016-20. We standardised these estimates according to the age distribution of the population during the period 2016-20 (divided into the following age classes: 18-29, 30-39, 40-49, 50-59, 60-69, and 70 years or older), using the indirect method[24]. Indirect standardisation compares the incidence rates in the study and reference (period: 2016-20) populations by applying the stratum-specific rates in the reference population to the study population. We investigated risk factors for AIDS, death, and each of the non-AIDS events, as well as a combined non-AIDS endpoint

(defined as first occurrence of cardiovascular disease, diabetes mellitus, or non-AIDS-defining malignancy). CKD was not included in this combined endpoint as serum creatinine was not part of routine data collection before 2007.

The baseline for treated and untreated HIV-1-positive individuals was defined as the date of HIV-1 diagnosis or January 2000, whichever was most recent. Subsequent follow-up time was divided into periods of three months. Poisson regression models were used to estimate the independent association between risk factors and each endpoint. Models were adjusted for the most recent CD4 cell count (lagged by three months), body mass index, gender, region of birth, most likely mode of HIV-1 transmission, current age, having started cART within 12 months of the last negative HIV test, known time spent with CD4 count below 200 cells/mm^3, known time spent with plasma HIV RNA above 1,000 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

Mortality was investigated in all 28,240 HIV-1-positive adults ever registered in the SHM database. The mortality rate was 18.2 (95% confidence interval [CI] 13.5-23.9) per 1,000 person years of follow up (PYFU) in 1996, and declined to 8.9 (95% CI 7.4-10.5) per 1,000 PYFU in 2010. It has since remained stable at that 2010 level with an observed mortality rate of 9.0 (95% CI 7.7-10.5) in 2020 (*Figure 3.1A*). Despite this improvement over time, the mortality rate in HIV-1-positive adults remained well above the age-matched and gender-matched mortality observed in the general population in the Netherlands, which was 5.0 per 1,000 PYFU in 2020. This excess mortality can be only partly ascribed to individuals who already had AIDS at the time of their HIV diagnosis, even less so in recent years. When these individuals were excluded from the analysis, the mortality rate decreased from 14.1 (95% CI 9.8-19.6) per 1,000 PYFU in 1996 to 8.2 (95% CI 6.8-9.7) per 1,000 PYFU in 2020, still well above the observed mortality rates in the age-matched and gender-matched general population. *Appendix Figure 3.1* shows the five-year survival curves after diagnosis of the first AIDS-defining condition, compared to survival for all people with HIV as well as survival after diagnosis of several common, non-AIDS-defining comorbidities.

Observed underlying causes of death are presented in *Appendix Table 3.1*. Although the AIDS-related death rate has decreased significantly since the advent of cART, the continued occurrence of deaths due to AIDS is driven largely by the persistent high proportion of newly diagnosed HIV-positive individuals who present late for care with advanced immune deficiency. As such, the rate still falls short of the aim of zero AIDS-deaths by 2022, as stated in the Netherlands' National Action Plan on STIs, HIV and Sexual Health[25]. *Table 3.1* shows the characteristics of adults living with HIV who died of AIDS, compared to those who died of non-AIDS causes in the period 2010-20. Individuals who died of AIDS were more frequently female, non-MSM and/or migrants, more recently diagnosed with HIV, had been on cART for a shorter period of time, and had much lower CD4 counts at diagnosis, with 64.3% qualifying as a very late presenter (CD4 count below 200 cells/mm^3). In addition, these individuals had much lower nadir CD4 counts. In 56% of cases, they did not have controlled viremia, and 9.2% of this group was not using any ART at the time of death, either because ART had not been started or had been discontinued (*Table 3.1*). Among individuals who died of AIDS but did not classify as (very) late presenters (i.e., they had a CD4 count above 350 cells/mm^3 at diagnosis), the cause of death was relatively more likely to be an AIDS-related haematological malignancy, which are also known to occur in people on suppressive ART with high CD4 counts. The proportion and absolute number of deaths due to non-AIDS-defining conditions have increased significantly over time (*Figure 3.2*), primarily as a consequence of the ever increasing size and average age of the population of people with HIV in the Netherlands. People with HIV that were born in the Netherlands, MSM and men in general are overrepresented among those who died of non-AIDS causes, because people in these three (overlapping) categories have a higher average age compared to migrants, HIV transmission categories other than MSM, and women. Independent risk factors for death and for being diagnosed with an AIDS-defining condition are listed in *Appendix Table 3.2*.

Table 3.1: *Characteristics of adults with HIV who died of AIDS compared to adults with HIV who died of non-AIDS causes in the period 2010-2020.*

	Died of non-AIDS causes	Died of AIDS	p-value
Number of subjects	1,458 (83.2%)	294 (16.8%)	
Age	58.1 (50.4-66.6)	52.6 (44-60.4)	<.001
Male sex	1,278 (87.7%)	236 (80.3%)	0.001
Dutch origin	1,030 (70.6%)	178 (60.5%)	<.001
Men who have sex with men	820 (56.2%)	125 (42.5%)	<.001
Heterosexual men and women	364 (25.0%)	102 (34.7%)	<.001
Other transmission categories	274 (18.8%)	67 (22.8%)	0.125
Years since HIV diagnosis	13.8 (7.32-20.5)	5.93 (0.69-13.6)	<.001
Years since start of cART	11.4 (5.31-16.8)	2.05 (0.34-11.4)	<.001
CD4 at HIV diagnosis	280 (100-500)	109 (30-308)	<.001
Late presenter (CD4 <350 at entry in care)	831 (57.1%)	227 (78.8%)	<.001
Very late presenter (CD4 <200 at entry)	550 (37.7%)	189 (64.3%)	<.001
CD4 nadir	130 (50-240)	44 (10-100)	<.001
Last CD4 measured before death	460 (270-660)	110 (38-270)	<.001
Not undetectable at moment of death	248 (17.2%)	156 (56.3%)	<.001
Not on cART at moment of death	71 (4.9%)	27 (9.2%)	0.005

Legend: *cART=combination antiretroviral therapy. Data shown are n (%) for categorical variables and median (interquartile ranges) for continuous variables. CD4 counts are expressed as cells/mm³.*

Figure 3.1: *(A) Annual mortality and (B) incidence of AIDS in 28,240 HIV-1-positive individuals in the Netherlands after entry into HIV care 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 sex-matched individuals from the general population in the Netherlands.*

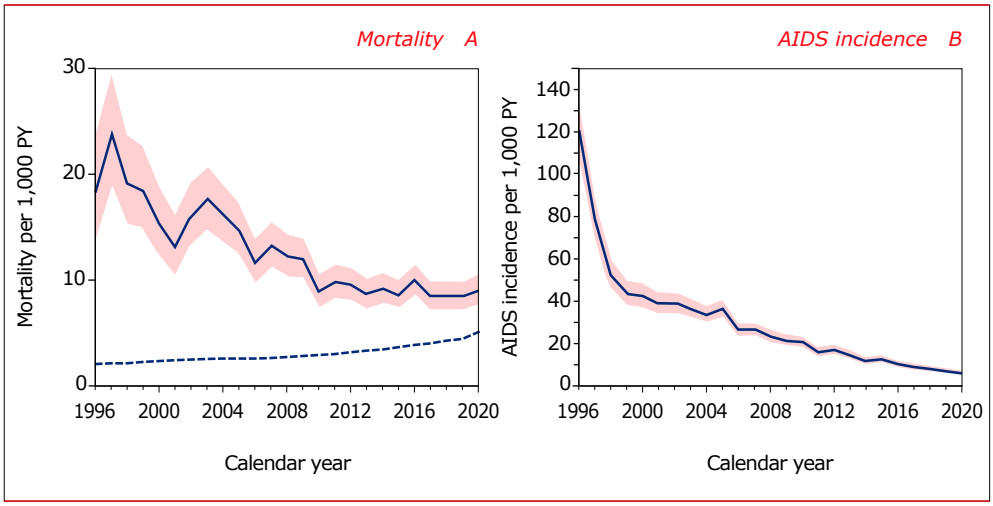
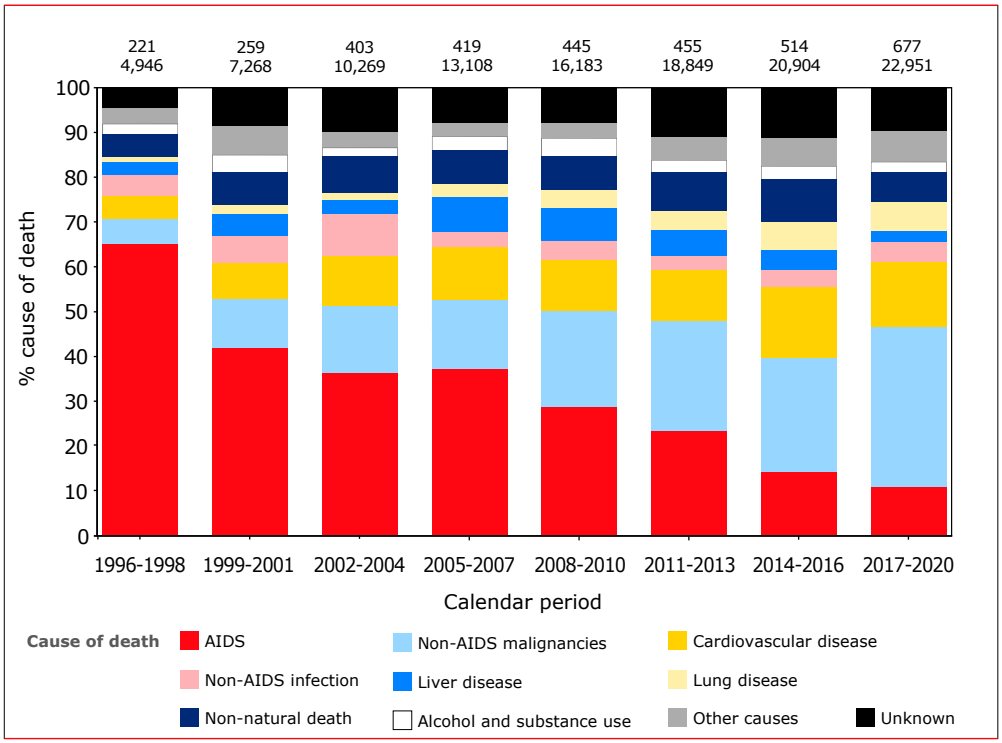


Figure 3.2: Relative changes in causes of death in different calendar periods since the introduction of combination antiretroviral therapy (cART) in the Netherlands. The numbers at the top of each bar represent the total number of deaths and the total number of individuals that were at risk during that calendar period. Mortality attributed to 'alcohol use' refers to deaths due to complications of alcohol-related liver cirrhosis.



We used Poisson regression analysis to examine factors associated with mortality in individuals from the moment they started cART. After correction for all variables listed in *Appendix Table 3.2*, including time-updated age and time-updated lagged CD4 cell counts, we found that, in general, risk of death was higher in men compared to women, and this risk increased as individuals grew older. It also increased if they belonged to the HIV transmission risk group of people who use/used injecting drugs (PWUID); had a prior AIDS diagnosis; were co-infected with the hepatitis B virus (HBV) or hepatitis C virus (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, with the risk of death progressively increasing in lower CD4 strata.

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, and other individuals not born in the Netherlands (with the exception of those born in Surinam or the Dutch Antilles), being lost to follow up (*Appendix Table 3.3*). In native Dutch individuals, and those from Surinam and the Dutch Antilles, the risk of becoming lost to follow up was not linked to their CD4 count. In contrast, people from all other non-Dutch groups were far more likely to become lost to follow up if they had very low CD4 counts. One explanation could be that those born overseas often return to their families in their country of origin when they experience a severe deterioration in health. As a result, it is likely that mortality rates in these groups have been considerably underestimated.

Individuals who had a psychiatric disease as the recorded underlying cause of death, and for whom the immediate cause of death was recorded as suicide, have been re-classified as 'suicide' for the current analysis (*Appendix Table 3.1*). The number of recorded suicides among people living with HIV in the Netherlands in the period 2011 to 2020 was stable at around ten recorded cases per calendar year, which is much higher than the known rates of suicide in the general Dutch population (which has 10.5 instances per 100,000 individuals per year compared to more than 40 in the population living with HIV)[26]. For patients with a serious somatic condition, who opted for euthanasia in the terminal disease stage, the underlying somatic condition was recorded as the cause of death. In the entire follow-up period from 1996 to 2020, a total of 138 instances of euthanasia were recorded; 33% of cases occurred in patients who died of AIDS, 41% in patients who died of non-AIDS-defining malignancies, and the remaining 26% in patients who died of other diseases. Our definition of euthanasia does not include the use of standard practice palliative care, like palliative sedation in the terminal phase of the underlying disease.

AIDS-defining events

In the group of 28,240 HIV-1-positive adults ever registered in the SHM database, the incidence of AIDS decreased sharply from 121.0 (95% CI 108.4-134.5) in 1996 to 6.2 (95% CI 5.1-7.5) cases per 1,000 PYFU in 2020 (*Figure 3.1B*). *Appendix Table 3.4* gives an overview of the AIDS events occurring between 1996 and 2020. The most common AIDS events between 2016 and 2020 were *Pneumocystis jirovecii* pneumonia (21% of all events); oesophageal candidiasis (17%); Kaposi's sarcoma (11%); tuberculosis (pulmonary 8%, extrapulmonary 5%); lymphoma (6%); recurrent bacterial pneumonia (5%); AIDS-related wasting (5%); toxoplasmosis of the brain (4%); AIDS dementia complex/HIV encephalopathy (3%); and cytomegalovirus-associated end organ disease (3%). Risk factors for AIDS-defining events are shown in *Appendix Table 3.2*.

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 HCV.

Because the main findings of the analysis of AIDS events after the start of cART were heavily influenced by events occurring shortly after the start of cART and/or while HIV-1 RNA was still detectable, we also analysed the incidence of CDC-B and AIDS-defining events in individuals who had started cART at least one 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, we focused on those individuals with an optimal response to cART. Events were classified into CD4 strata based on the current or 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. Between 1 January 2000 and 31 December 2020, 24,863 individuals contributed a total of 221.8 thousand PYFU, during which 3,423 CDC-B and/or AIDS-defining events were diagnosed. This resulted in an incidence rate of 15.4 events per 1,000 PYFU (2,110 CDC-B events, 9.5 events/1,000 PYFU; 1,313 CDC-C/AIDS events, 5.9 events/1,000 PYFU) (*Table 3.2*). 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 10.6 and 5.8 AIDS-defining illnesses/1,000 PYFU, respectively. The incidence rates of AIDS-defining illnesses in the CD4 strata of 500-749 and over 750 cells/mm^3 were 3.0 (95% CI 2.6-3.4) and 1.9 (95% CI 1.6-2.3) events/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 Herpes simplex virus (HSV) ulcers, and AIDS dementia complex (*Appendix Table 3.6* shows the type and number of HIV-related diagnoses by CD4 strata).

Table 3.2: CDC-B and CDC-C/AIDS events occurring between 2000 and 2020 in individuals on cART, while having an undetectable viral load.

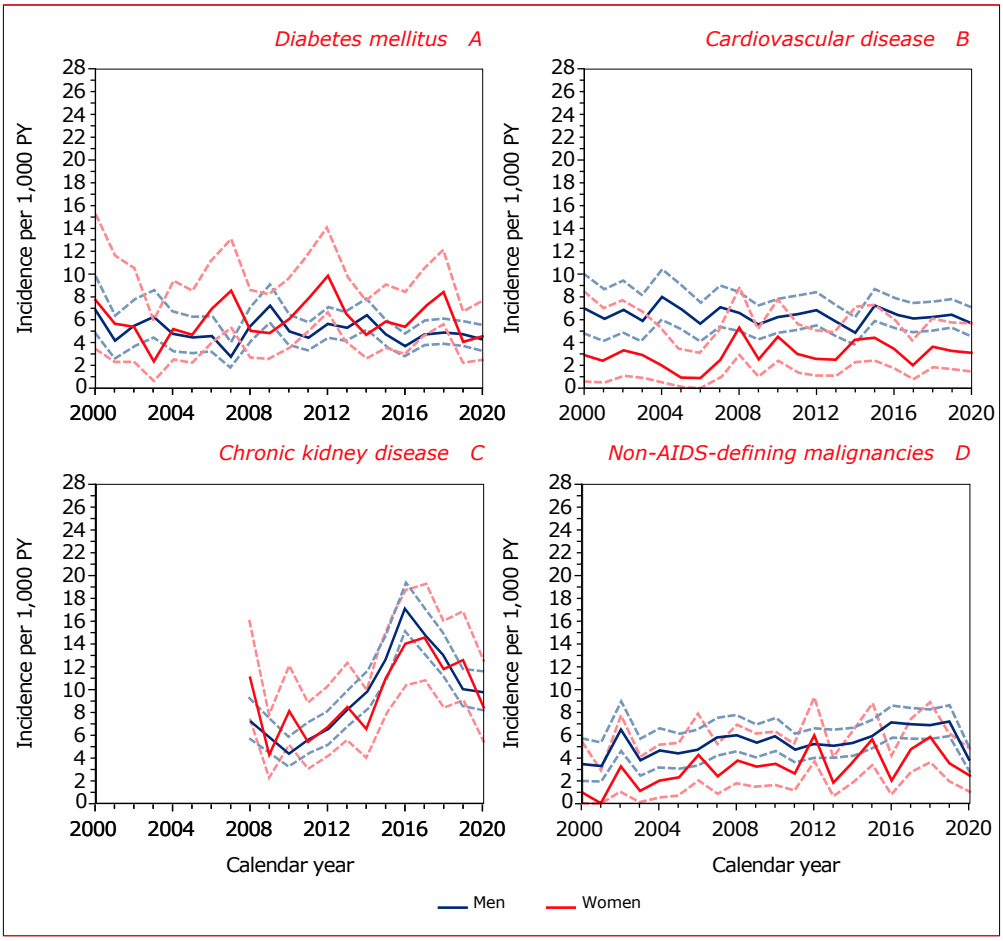
CD4 category (cells/mm³)	CDC events (n)	CDC B events (n)	CDC C events (n)	PYFU follow-up (x1000)	Incidence rate CDC events (/1000 PY) (95%CI)	Incidence rate CDC-B events (/1000 PY) (95%CI)	Incidence rate CDC-C events (/1000 PY) (95%CI)
0-49	224	93	131	0.5	481 (420-549)	200 (161-245)	282 (235-334)
50-199	636	348	288	8.0	79.2 (73.1-85.6)	43.3 (38.9-48.1)	35.8 (31.8-40.2)
200-349	719	442	277	26.1	27.5 (25.6-29.6)	16.9 (15.4-18.6)	10.6 (9.39-11.9)
350-499	659	397	262	45.5	14.5 (13.4-15.6)	8.73 (7.89-9.63)	5.76 (5.09-6.50)
500-749	738	504	234	78.4	9.41 (8.74-10.1)	6.43 (5.88-7.01)	2.98 (2.61-3.39)
750+	447	326	121	63.3	7.07 (6.43-7.75)	5.15 (4.61-5.75)	1.91 (1.59-2.29)
Total	**3423**	**2110**	**1313**	**221.8**	**15.4 (14.9-16.0)**	**9.51 (9.11-9.93)**	**5.92 (5.60-6.25)**

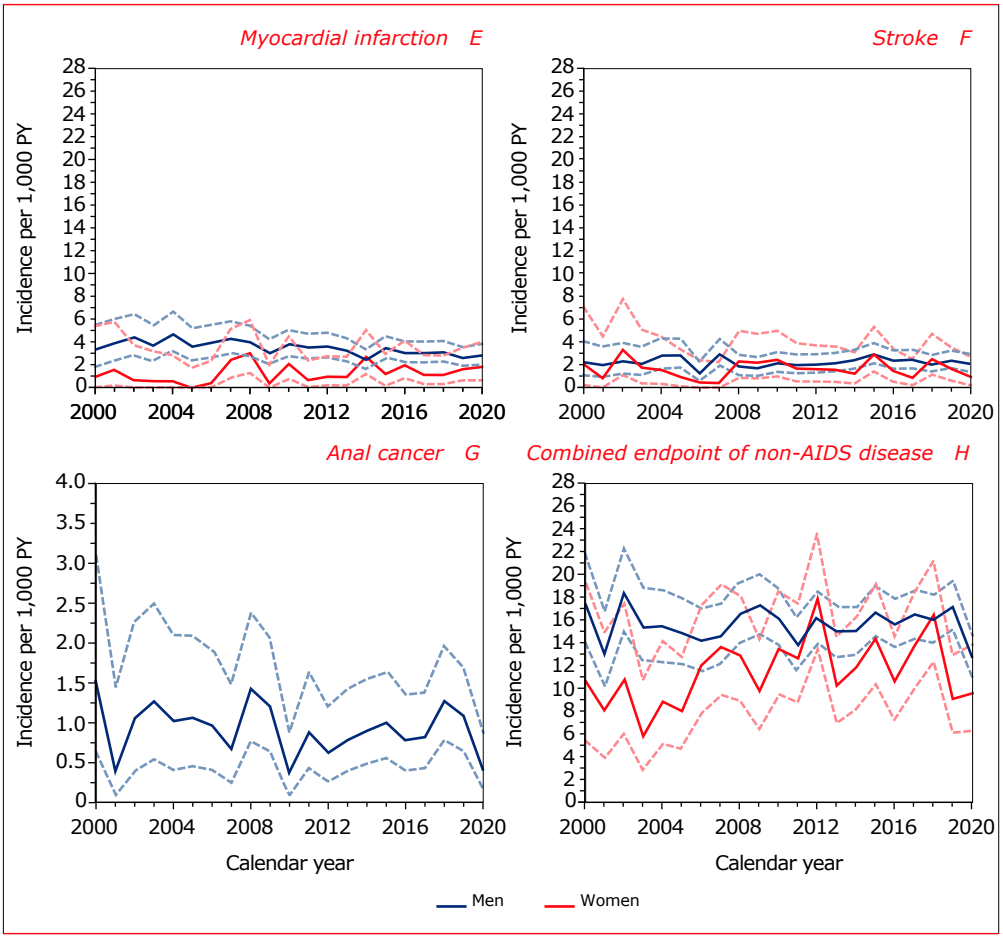
***Legend:** CDC=Centers for Disease Control and Prevention Classification System for HIV Infection; CDC-B=moderately symptomatic HIV disease; CDC-C=AIDS-defining events; cART=combination antiretroviral therapy; PYFU=person years of follow up.*

Non-AIDS-defining events

Of the 28,240 HIV-1-positive adults ever registered with SHM, 27,896 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 (both overall and 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 3.3*).

Figure 3.3: *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.*





Diabetes mellitus

Of the 27,896 individuals aged 18 years or older and in follow up in, or after January 2000, a total of 1,476 (1,140 men and 336 women) were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.3A*) and, in 2020, was 4.3 (95% CI 3.3-5.5) per 1,000 PYFU in men and 4.6 (95% CI 2.5-7.6) per 1,000 PYFU in women. In men, the age-standardised incidence ratio declined over time and was significantly lower in 2016-20 than in 2000-10 and 2011-15. Whereas, in women, the age standardised incidence in 2000-10 and 2011-15 was not significantly different from that in 2016-20 (*Table 3.3*).

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 group; acquiring 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 nucleoside analogue reverse transcriptase inhibitors (NRTIs) prior to starting cART; and a prior AIDS diagnosis (*Appendix Table 3.5*). Moreover, the risk of new-onset diabetes in the periods 2000-10 and 2011-15 was significantly higher than in the period 2016-20. A longer time on didanosine was also significantly associated with an increased risk.

Table 3.3: *Crude incidence of diabetes mellitus per 1,000 person years of follow up in 2000–2010, 2011–2015 and 2016–2020 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)
2000–2010	5.2 (4.7–5.7)	1.51 (1.36–1.65)	5.7 (4.8–6.8)	1.04 (0.86–1.22)
2011–2015	5.3 (4.8–5.9)	1.32 (1.18–1.46)	6.9 (5.6–8.3)	1.20 (0.97–1.43)
2016–2020	4.5 (4.1–5.0)	1 (reference)	6.0 (4.9–7.3)	1 (reference)

** Standardised according to the observed age distribution between 2016–2020.*

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

Cardiovascular disease

From January 2000 onwards, 1,613 individuals (1,441 men and 172 women) had a fatal or non-fatal cardiovascular event. Of these, 816 had a myocardial infarction, 572 a stroke, 119 a coronary artery bypass graft, 584 a coronary angioplasty or stenting, and 13 a carotid endarterectomy. The crude incidence over time remained stable and was lower in women than in men (*Figure 3.3B*). The standardised incidence ratio in men and women declined over time (*Table 3.4*).

In the analysis of risk factors, those associated with cardiovascular disease were: male gender; Dutch origin; older age group; acquiring HIV through MSM contacts or through injecting drug use; a latest CD4 cell count below 350 cells/mm^3; a prior AIDS diagnosis; pre-treatment with NRTIs before starting cART; use of abacavir (either currently or in the last six months); current and past smoking; and presence of hypertension. Estimated cardiovascular risk using the D:A:D algorithm was also higher during 2000-10 and 2011-15 than during 2016-20, independent of other variables included in the analysis (*Appendix Table 3.5*). 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 1.58 to 1.45, p<0.001. Compared to having an eGFR above 90 ml/min, having an eGFR below 60 ml/min was independently associated with a higher risk of CVD; at 60-90 ml/min, the IRR was 1.09 (95% CI 0.95-1.24), p=0.22; at 30-60 ml/min the IRR was 1.72 (1.41-2.10), p<0.001; at 15-30 ml/min, the IRR was 4.56 (3.08-6.73), p<0.001; and at 0-15 ml/min the IRR was 3.59 (2.01-6.42), p<0.001.

From January 2000 onwards, 207 men and 20 women experienced a fatal or non-fatal secondary cardiovascular event (129 had a myocardial infarction, 107 had a stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2020 in men and women with a prior cardiovascular event was 27.4 (95% CI 23.8-31.4) and 19.7 (95% CI 12.0-30.4), respectively. The crude rate and age-standardised incidence ratio (SIR; indirect method) of secondary myocardial infarction and stroke per 1,000 PYFU changed significantly during 2000-10 (crude rate: 30.9 events per 1,000 PYFU; SIR: 1.25, 95% CI 0.97-1.52), but not during 2011-15 (crude rate: 24.4 events per 1,000 PYFU; SIR: 0.98, 95% CI 0.73-1.22) compared with the reference period 2016-20 (crude rate: 24.9 events per 1,000 PYFU).

Table 3.4: *Crude incidence of cardiovascular disease per 1,000 person years of follow up in 2000–2010, 2011–2015, and 2016–2020 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)
2000–2010	6.5 (6.0–7.1)	1.56 (1.43–1.69)	2.8 (2.2–3.6)	1.56 (1.18–1.94)
2011–2015	6.3 (5.7–6.9)	1.20 (1.08–1.31)	3.4 (2.5–4.4)	1.33 (0.98–1.69)
2016–2020	6.2 (5.7–6.8)	1 (reference)	3.1 (2.3–4.0)	1 (reference)

** Standardised according to the observed age distribution in 2016–2020.*

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

Trends in cardiovascular risk factors

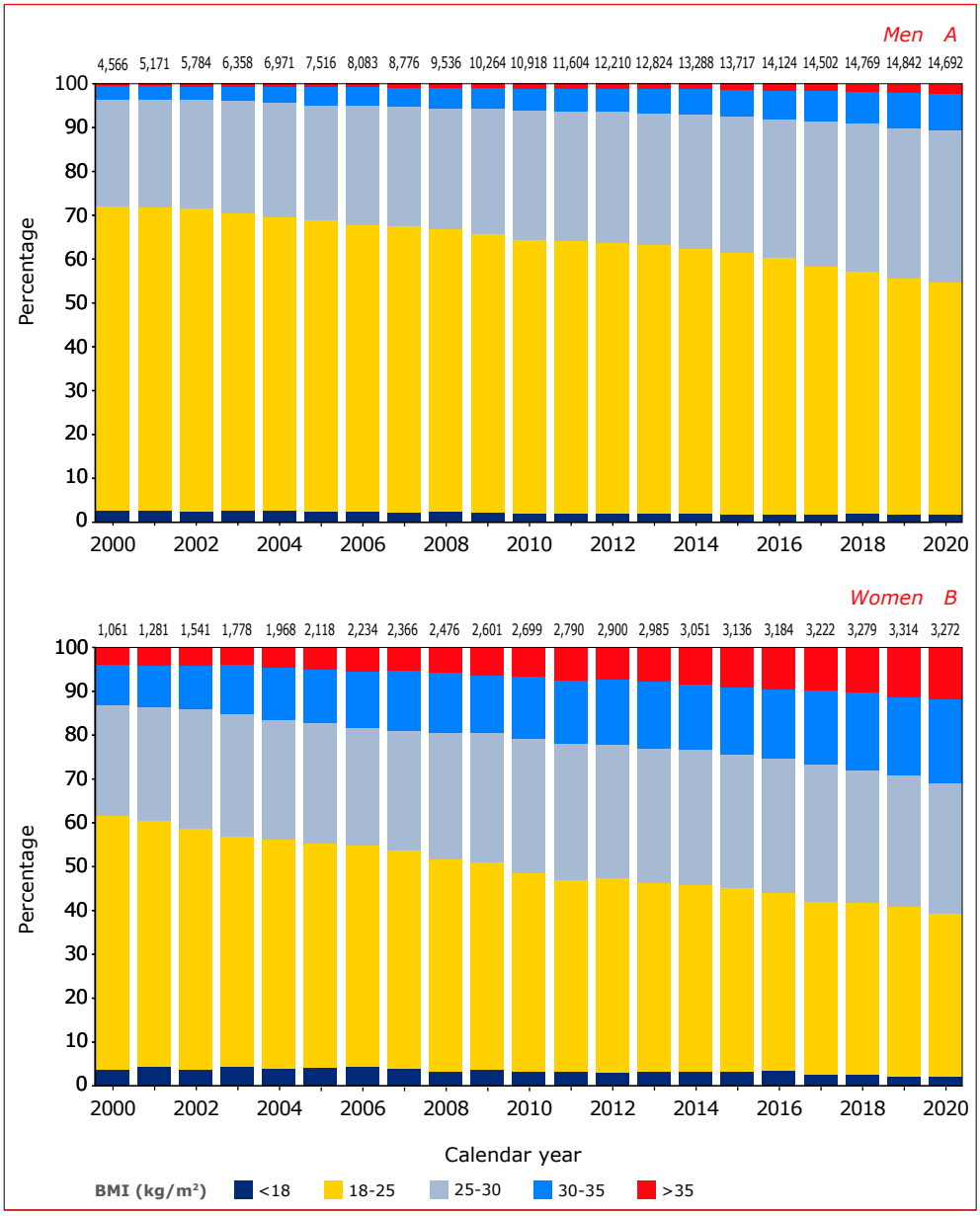
Figures 3.4A and *3.4B* show that the distribution of body mass index (BMI) of both men and women in the HIV-1-positive population has increased over time. In 2020, the proportion of men with available BMI data who were overweight (25-30 kg/m^2), or obese (WHO class I: 30-35 kg/m^2 and WHO class II/III: 35 kg/m^2 or over), was 34.6%, 8.5% and 2.2%, respectively. In women, these proportions were 29.9%, 19.3% and 11.7%, respectively.

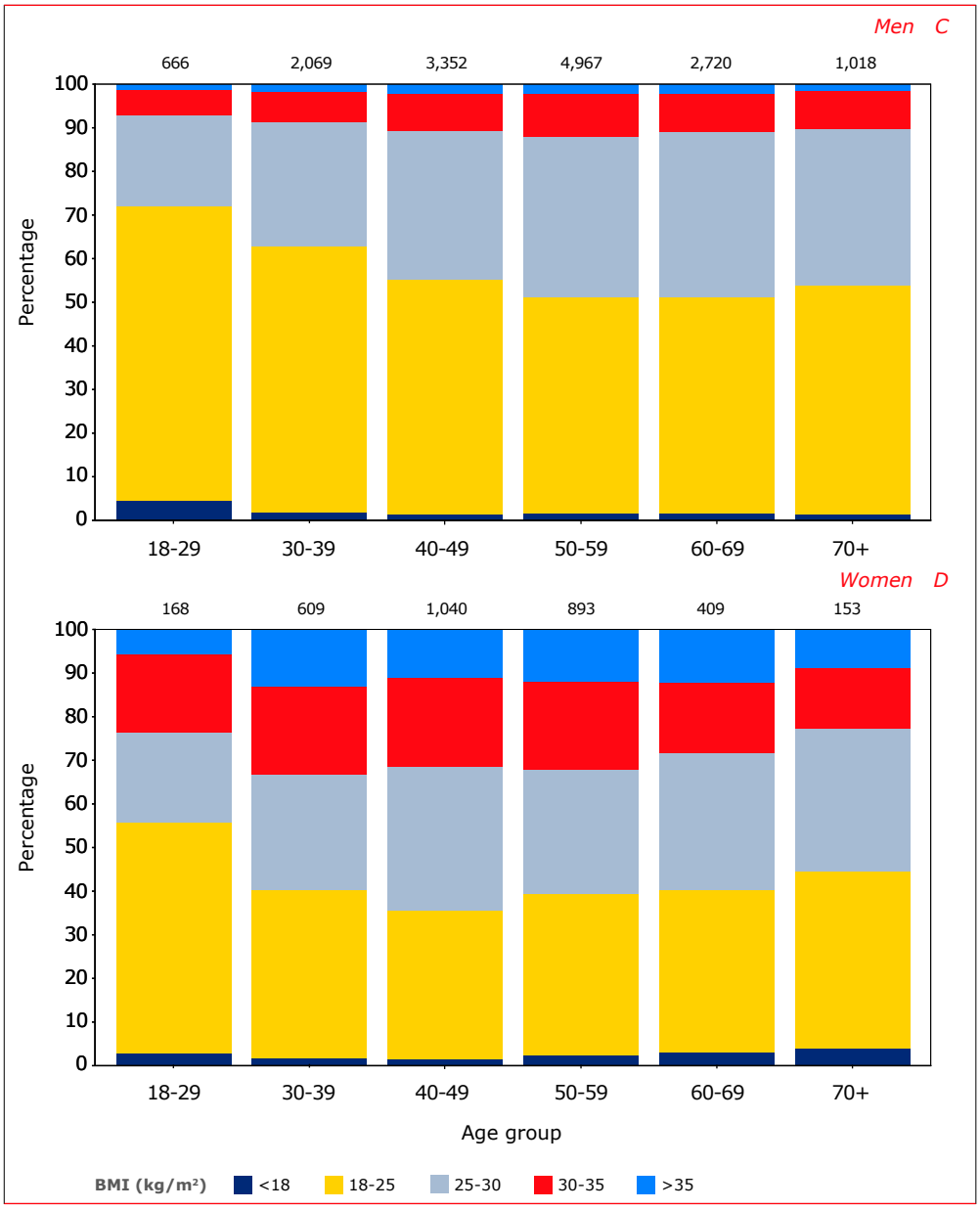
Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the population living with HIV. This analysis revealed that the increase was at least partially driven by changes over time in population demographic characteristics (age, region of origin, HIV transmission category) and time since first start of cART, and that this effect was more marked in men than in women.

With regard to specific antiretroviral agents, the use of bictegravir, dolutegravir, rilpivirine and tenofovir alafenamide were all independently associated with higher body weight. *Figures 3.4C* and *3.4D* show the distribution of BMI according to age groups in 2020 for men and women. Whereas in adult men of all age groups, the proportion classified as obese (10.7%) was somewhat lower than the proportion found in the general Dutch male population (12.3%), in women of all age groups there was more obesity (30.0%) than in the general Dutch female population (15.4%)[27]. There were substantial differences between native Dutch people, Western migrants and non-Western migrants: among males, 9.6% of Dutch men, 11.5% of Western migrants and 13.6% of non-Western migrants were obese, whereas in females, those figures were 21.5%, 20.1%, and 37.3%, respectively. Being obese (a BMI over 30) was independently associated with an increased risk of diabetes (IRR 5.13, 95% CI 4.38-6.00, p<0.001), but that was not the case with CVD, CKD or non-AIDS-defining malignancies (*Appendix Table 3.5*).

Figure 3.5A shows that, in 2020, 48.9% of those treated with antihypertensives still had grade 1 hypertension or higher. In 2020, 25.0% (4,031) of individuals not using antihypertensives had grade 1-3 hypertension (*Figure 3.5B*). For 3,745 (92.9%) of these individuals, a five-year cardiovascular disease (CVD) risk could be calculated with the recalibrated D:A:D study algorithm[28]: 219 (5.9%) had a five-year CVD risk of 10% or more; according to the European AIDS Clinical Society (EACS) guidelines, these individuals, in particular, should receive antihypertensive treatment[29]. *Figure 3.6* 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% or more) five-year risk were 11.7% and 5.6%, respectively, which steadily increased to 20.4% and 12.1%, respectively, in 2020. The increase in the percentage of individuals at high or very high risk likely reflects the ageing of the population being studied.

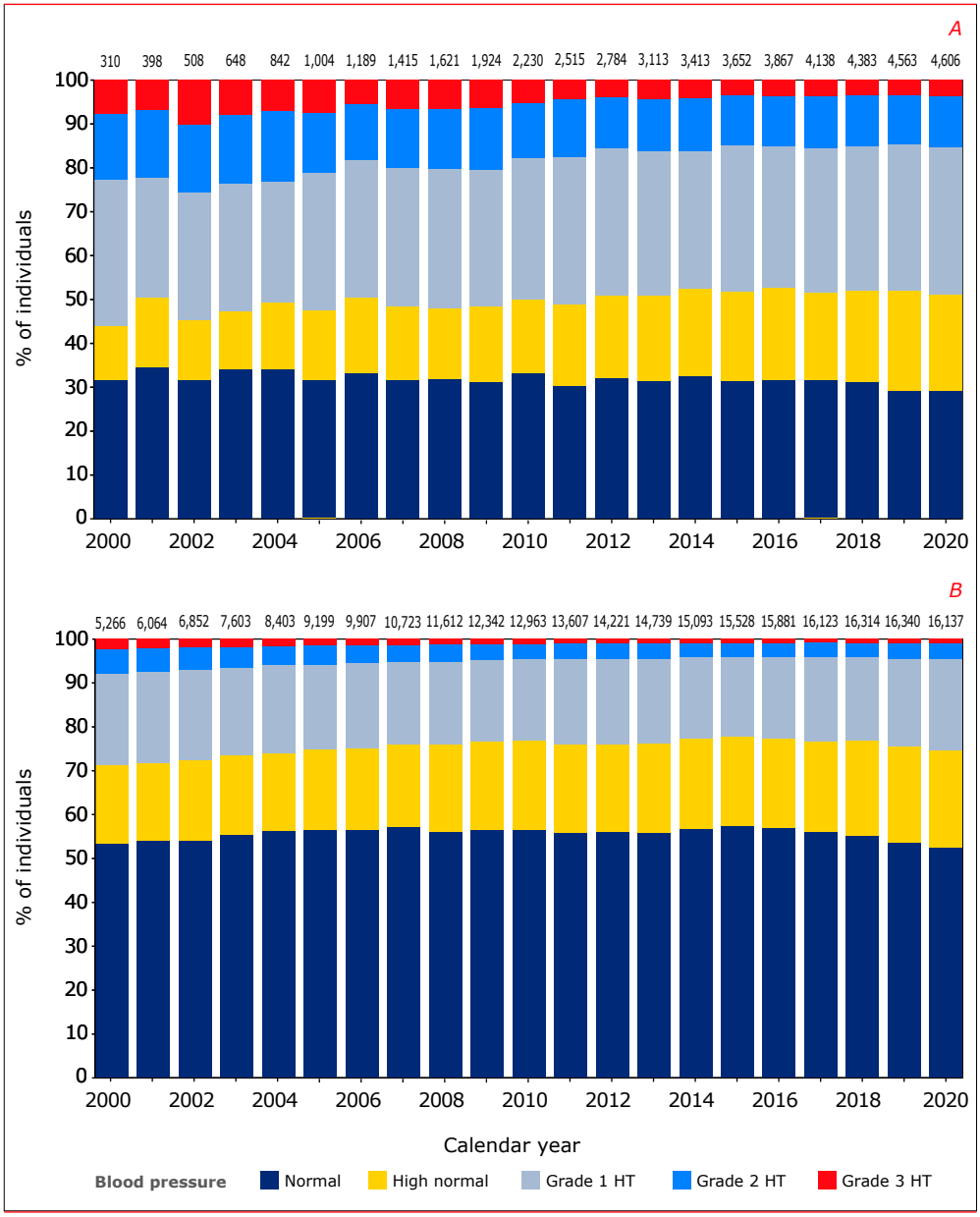
Figure 3.4: Distribution of the body mass index (BMI) at the end of each calendar year in (A) men, and (B) women, as a percentage of the total number of men and women with a known BMI in each year, and distribution of the BMI over the age groups for (C) men, and (D) women, in 2020. For each individual, 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 from that age group (C & D).





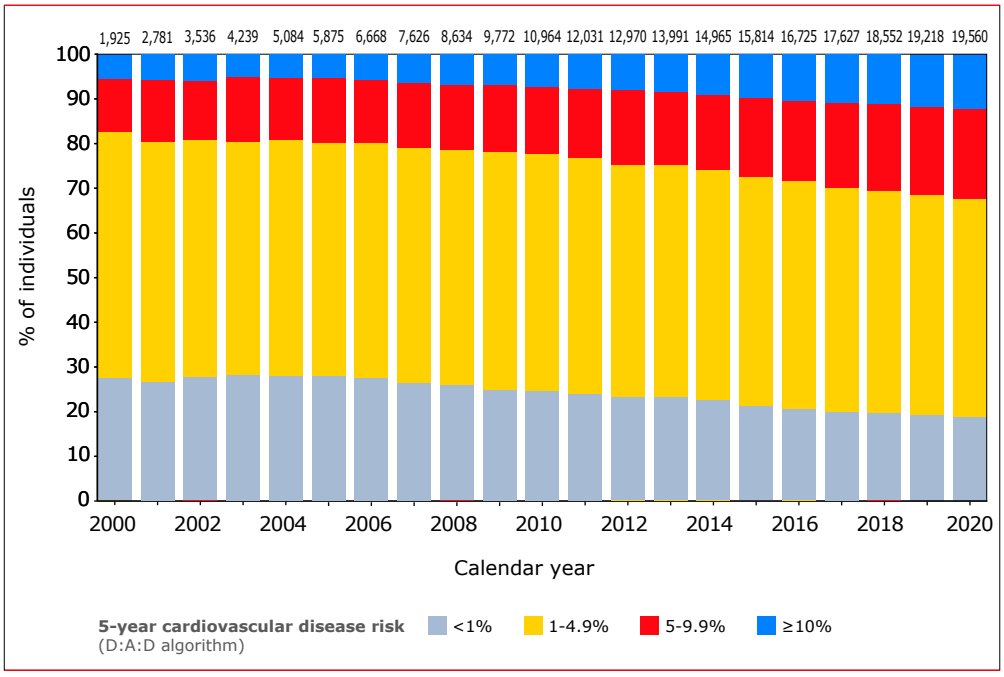
Legend: BMI=body mass index.

Figure 3.5: Distribution of graded blood pressure at the end of each calendar year in (A) individuals known to be receiving antihypertensive treatment, and (B) 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 by the European Society of Cardiology[30]. 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 3.6: Estimated five-year risk of coronary heart disease at the end of each calendar year according to the algorithm from the D:A:D: study[28]. 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.



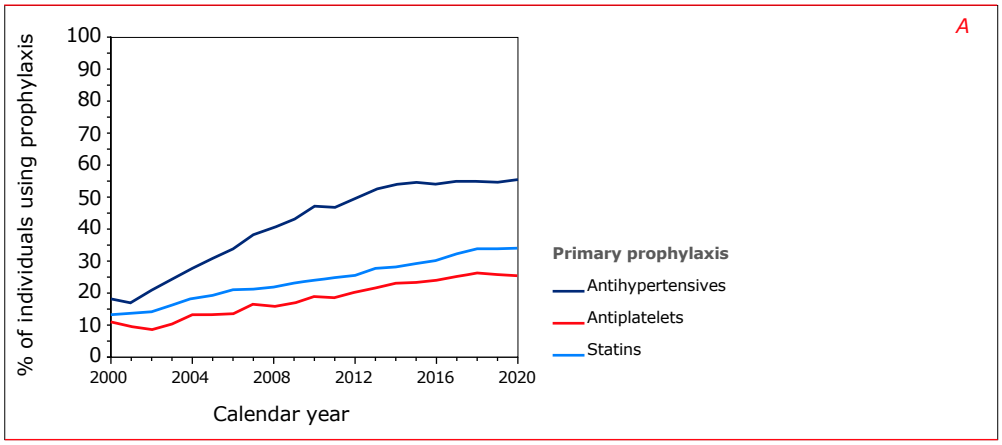
Use of primary or secondary preventive therapy for myocardial infarction or stroke

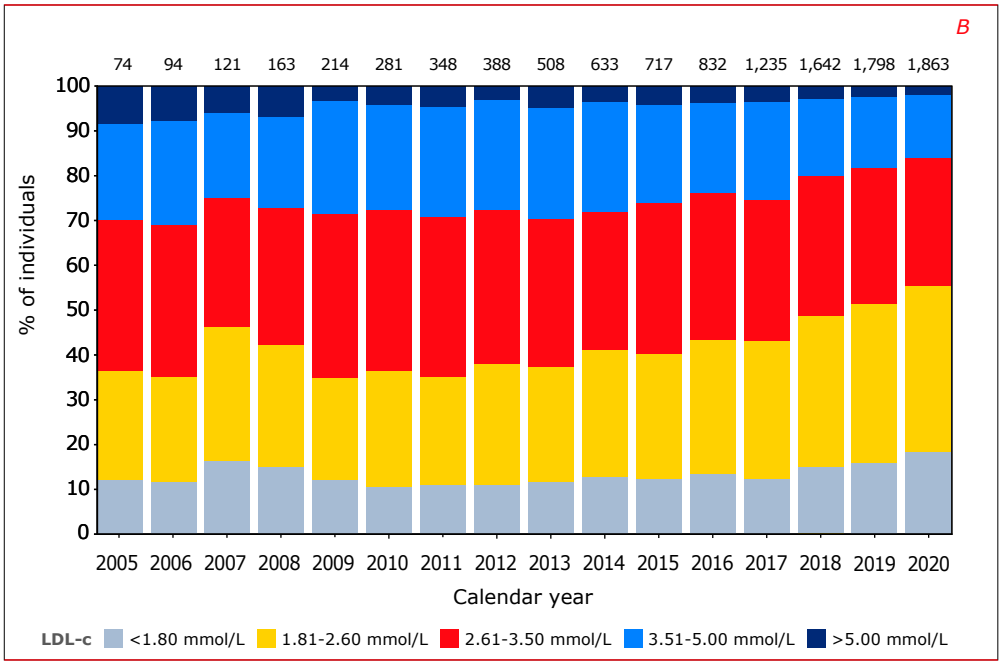
Primary prevention

According to EACS guidelines, statin therapy should be offered to individuals with type 2 diabetes or a ten-year CVD risk same or ≥10%. They also recommend that angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers (CCB), diuretics, and non-dihyropyridine CCB (verapamil or diltiazem) should be offered to individuals with a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and a ten-year CVD risk ≥20%. For individuals aged 50 years or more with a ten-year CVD risk ≥20%, acetylsalicylic acid is recommended[31]. In general, the Dutch cardiovascular risk management (CVRM) guidelines closely resemble the EACS guidelines, with the notable exception that the Dutch guidelines do not recommend the use of

acetylsalicylic acid in older people with increased CVD risk, but without prior clinical CVD[32]. *Figure 3.7A* shows trends in the use of these medications in individuals without a prior stroke, myocardial infarction, or cardiovascular surgical procedure. The percentage of individuals for whom primary prevention with statins and the above-mentioned antihypertensive agents (referred to collectively hereafter as antihypertensives) is recommended, has increased over time, although the curve for antihypertensives has levelled off somewhat since 2013. Although the percentage of individuals who were at high risk, aged 50 years or older, and used acetylsalicylic acid/clopidogrel as primary prevention, increased slowly prior to 2014, the overall proportion remained minimal and has remained stable during the last years. Only about half the individuals who received treatment with antihypertensive agents or statins for the primary prophylaxis of myocardial infarction or stroke reached treatment targets (below 2.6 mmol/l). *Figure 3.5A* shows that of all individuals using antihypertensive agents, only about half had a normal blood pressure in recent years. *Figure 3.7B* shows the distribution of LDL-cholesterol in subjects who use statins for primary CVD prophylaxis. The proportion of individuals with an LDL-c below 1.8 mmol/l or between 1.8 and 2.6 mmol/l was 12.2% and 24.3%, respectively, in 2005, and increased to 18.7% and 36.7%, respectively, in 2020.

Figure 3.7: *(A) 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 for primary prevention of myocardial infarction or stroke. (B) Distribution of LDL-cholesterol in individuals using statins for primary prevention of myocardial infarction or stroke.*

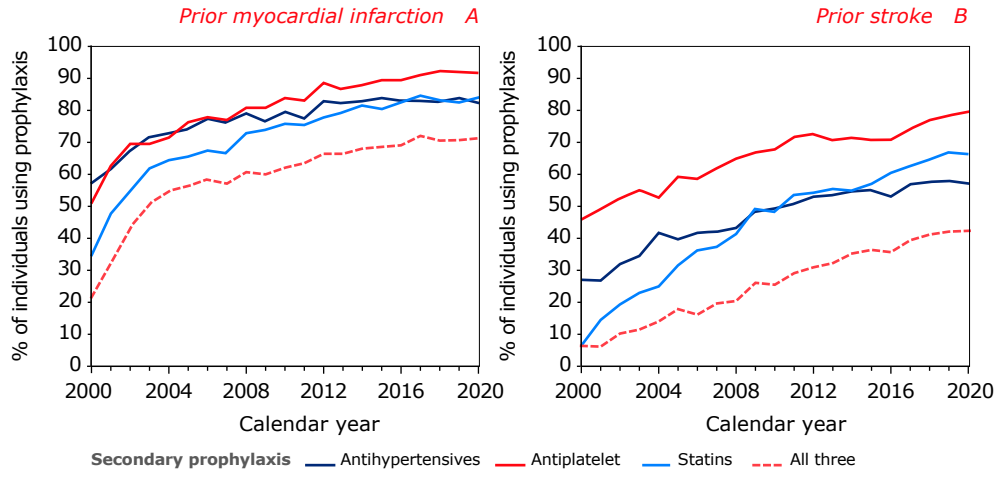




Secondary prophylaxis for myocardial infarction or stroke

According to all guidelines, individuals with a prior myocardial infarction or ischaemic stroke should receive lifelong treatment with statins, antihypertensives (ACE inhibitors, beta blockers or angiotensin receptor blockers), as well as low-dose acetylsalicylic acid/clopidogrel[33,34]. *Figure 3.8A* shows that the percentages of individuals using statins, acetylsalicylic acid/clopidogrel, or antihypertensives after a myocardial infarction increased between 2000 and 2020: in 2020, 84.0% of individuals with a prior myocardial infarction used statins, 82.5% used antihypertensives, and 91.8% used acetylsalicylic acid/clopidogrel. Although the use of statins and antihypertensives after an ischaemic stroke also increased over time, in 2020 these medications were used less frequently after a stroke than after a myocardial infarction (66.5% used statins, 57.4% used antihypertensives, and 79.7% used acetylsalicylic acid/clopidogrel) (*Figure 3.8B*).

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



Chronic kidney disease

Glomerular filtration rate (GFR) is a marker of renal function and is commonly estimated by one of three formulae, namely, the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations[35]. 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 individuals living with HIV[35,36]. 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 or above, normal kidney function; 60-89, mildly reduced; 30-59, moderately reduced; 15-29, severely reduced; and below 15, very severely reduced kidney function) is shown in *Figures 3.9A* and *3.9B* for men and women. The percentage of men with normal kidney function decreased over time from 74.5% in 2007, to 44.9% in 2020, and this pattern was similar in women. 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 due, in part, to the increasing age of individuals in care.

CKD incidence and risk factors

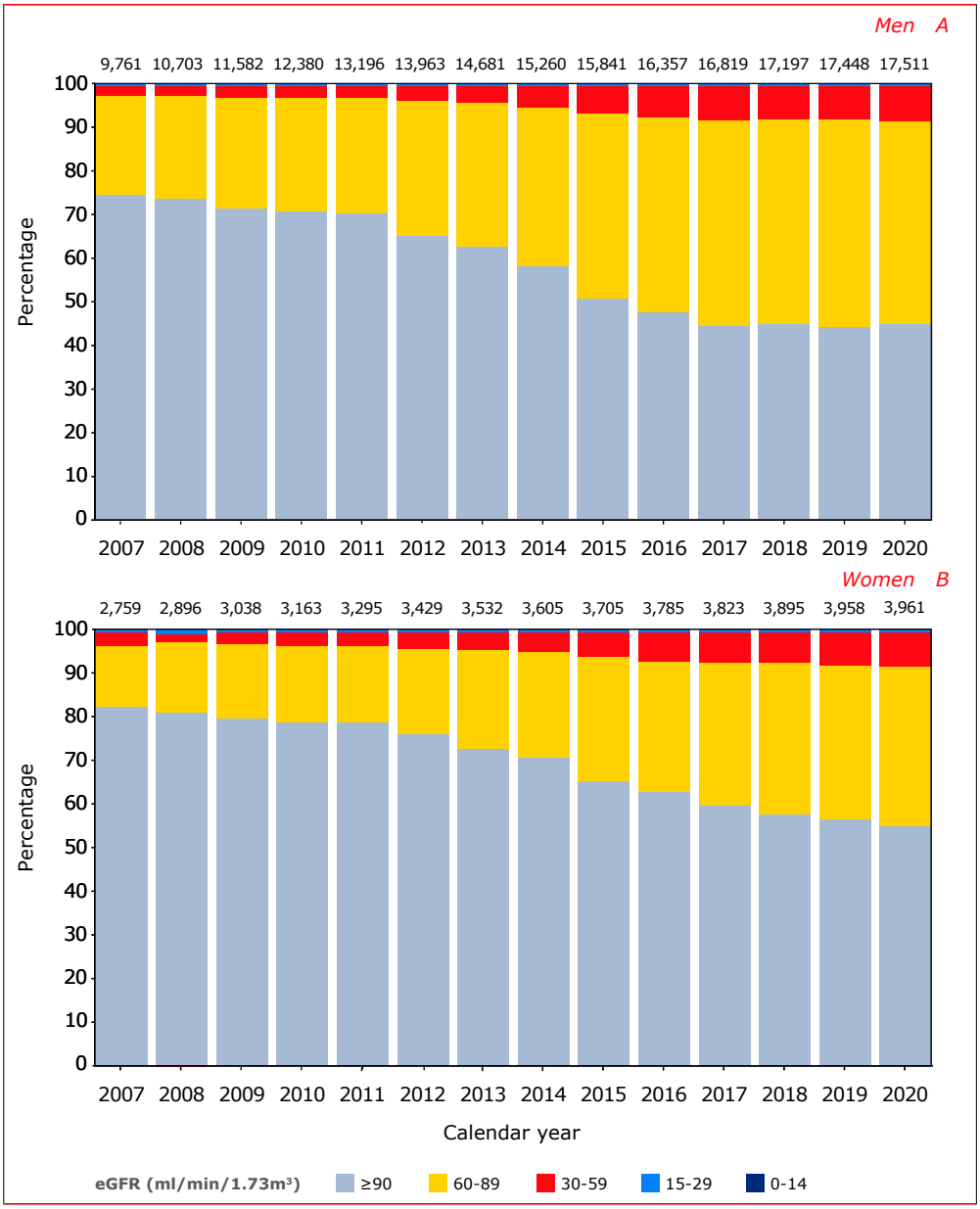
In individuals with an eGFR above 60ml/min/1.73m^2 at the time of inclusion in the analyses, who did not have a previously confirmed CKD, the crude incidence of CKD, defined as eGFR below 60ml/min/1.73m^2 confirmed by a second test at least 26 weeks later, varied over time (*Figure 3.3C*). Routine collection 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 7.1 cases per 1,000 PYFU in the period 2008-14 to 11.9 in 2015-20. In women, the incidence rose from 7.3 to 12.7 cases per 1,000 PYFU during the same periods (*Table 3.5*). The age-standardised incidence ratio in men and women increased significantly over time (*Table 3.5*).

Risk factors for CKD included: female gender; Dutch origin; low current CD4 cell count (below 200 cells/mm^3); a prior AIDS diagnosis; belonging to the HIV transmission risk group of people who inject drugs; older age group; 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 3.5*). When current use of cobicistat, rilpivirine, dolutegravir, and bictegravir were added to the model, the increased risk of CKD in the calendar period 2016-20 completely disappeared in comparison to 2008-10 and 2011-15. This strongly 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 true glomerular filtration rate (namely, organic cation transporter 2 (OCT2), and multidrug and toxin extrusion transporter (MATE1)) and is therefore not a true increase in CKD.

Tenofovir disoproxil fumarate (TDF) can cause true decreases of the GFR. We investigated changes in serum creatinine levels in subjects who switched from a stable (longer than 12 months) TDF-containing regimen to a TAF-containing regimen. We compared the serum creatinine levels measured in the three months prior to the switch, to serum creatinine levels measured at least six months after the switch. This analysis was limited to subjects who did not start or stop OCT2 / MATE1 inhibitors within the 12 months prior to, and six months following, the switch from TDF to TAF. A total of 393 subjects fulfilled the above criteria and switched from TDF to TAF because of renal toxicity / elevated serum creatinine. Another 2,916 subjects also fulfilled the above criteria but switched from TDF to TAF for other reasons. The 393 subjects who switched because of presumed TDF-

associated renal toxicity, had a median serum creatinine level of 115 (IQR 106-125) mmol/l prior to the switch, and showed a median change of -7 (IQR -16 to 0) mmol/l 6 months or longer after the switch. The 2,916 subjects who switched because of other reasons had a median serum creatinine level of 88 (IQR 77-100) mmol/l prior to the switch, and showed a median change of -1 (IQR -7 to +5) mmol/l 6 months or longer after the switch.

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.*



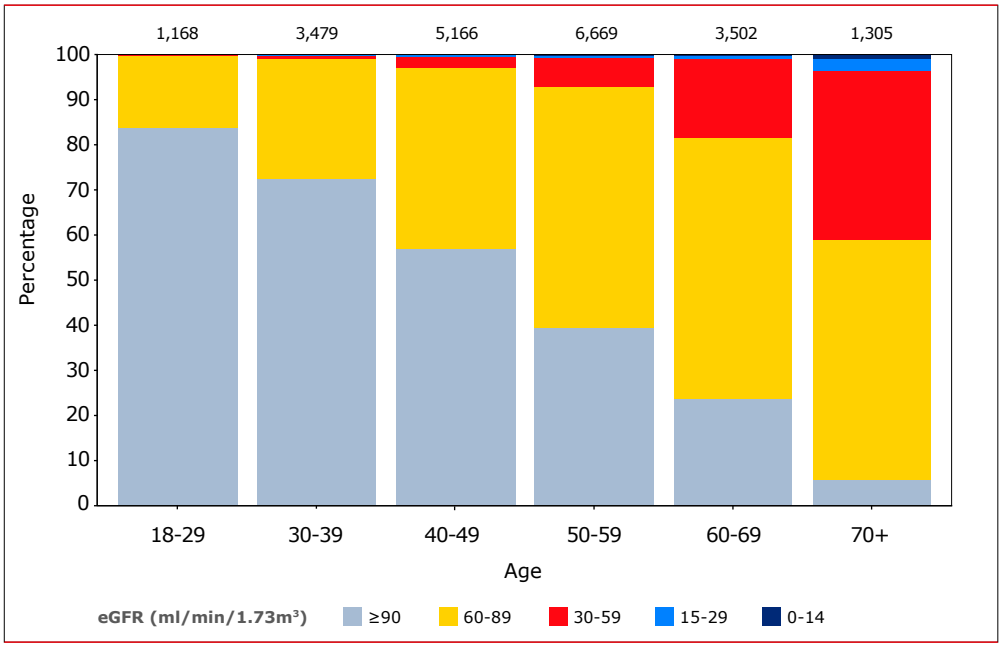
Legend: *eGFR=estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60–89 ml/min/1.73m²: mildly reduced; 30–59 ml/min/1.73m²: moderately reduced; 15–29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

Table 3.5: Crude chronic kidney disease incidence per 1,000 person years of follow up in 2008-2014, and 2015-2020, 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)
2008-2014	7.1 (6.4-7.9)	0.74 (0.66-0.82)	7.3 (5.8-9.1)	0.84 (0.66-1.02)
2015-2020	11.9 (11.1-12.8)	1 (reference)	12.7 (10.8-14.8)	1 (reference)

** Standardised according to the observed age distribution in 2015-2020.*
***Legend:** CI=confidence interval; PYFU=person years.*

Figure 3.10: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2020 for different age categories. For each individual, the last available measurement in 2019 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 2020, 1,920 diagnoses of non-AIDS-defining malignancies in 1,771 unique individuals were recorded in SHM's database. An additional 775 patients were diagnosed with one or more non-melanoma skin cancers, but these were not included in the present analysis. *Table 3.6* shows the most common types of non-AIDS-defining cancer: lung cancer (16.9%); haematological malignancies (excluding AIDS-defining non-Hodgkin's lymphoma, 14.2%); intestinal cancer (mainly oesophageal, gastric, intestinal, and rectal cancers, but excluding liver cancer, 13.5%); invasive anal cancer (not AIN, 11.9%); prostate cancer (9.4%); and head and neck cancers (8.3%). *Figure 3.11* shows the relative and absolute changes in types of non-AIDS-defining cancers over time. The proportion of individuals with intestinal, prostate, and renal cancer has increased over time, likely 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 and women is shown in *Figure 3.3D*. The age-standardised incidence in men was statistically significantly lower in the period 2016-20, compared to 2000-10, and borderline significantly lower compared to 2011-15 (*Table 3.7*). 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. The situation for women was similar – the age-standardised incidence was (borderline significantly) lower in the period 2016-20, than in 2000-10, and to a lesser extent in 2011-15 (*Table 3.7*).

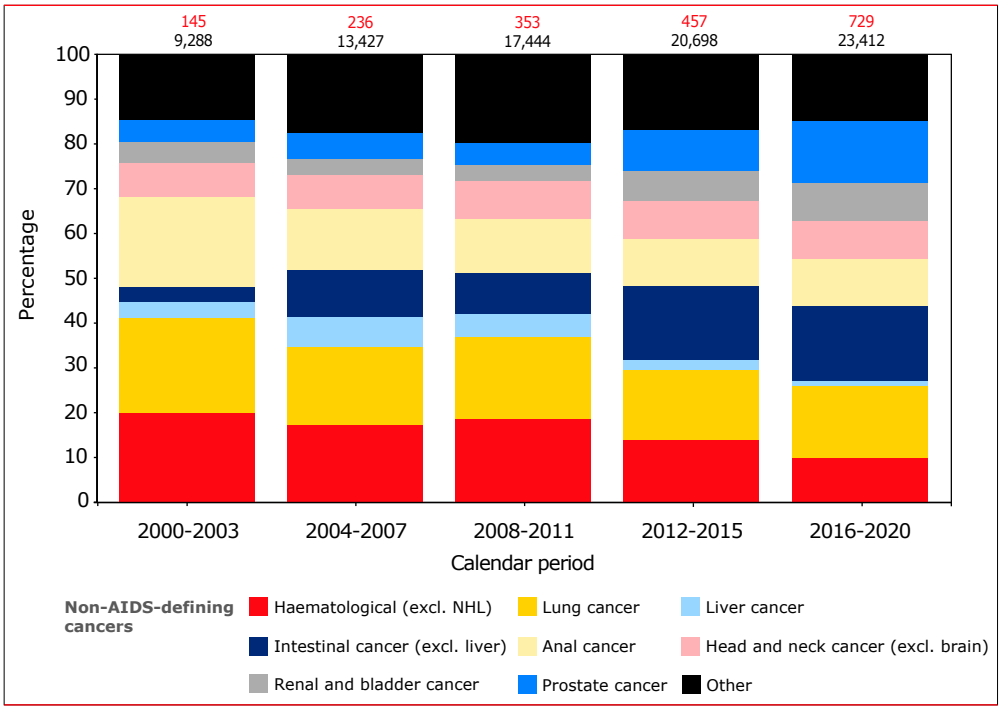
Demographic and clinical factors independently associated with an increased risk of a first non-AIDS-defining malignancy were: older age group; acquiring HIV-1 through injecting drugs or contact with blood or blood products; lower current CD4 cell count (CD4 below 350 cells/mm^3); low body mass index; prior AIDS; chronic HBV co-infection; and current or past smoking (*Appendix Table 3.6*). Furthermore, people who had been pre-treated with mono- or dual-NRTI-based regimes prior to starting cART, had an independently increased risk for NADM, compared with those who started cART while being treatment naïve (relative risk [RR] 1.22, 95% CI 1.05-1.42). 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 0.62, 95% CI 0.42-0.93) 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 2020, the five-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 49.8%, compared with 73.1% for CVD, 82.6% for DM, and 86.1% for CKD (*Appendix Figure 3.1*). In the same period, the five-year survival rate of all adults newly entering care in one of the Dutch HIV treatment centres was 95.6%, and 81.9% for those newly entering care with an AIDS diagnosis. The five-year survival rates following the most common non-AIDS-defining malignancies are shown in *Table 3.6* and *Appendix Figure 3.2*.

Anal cancer

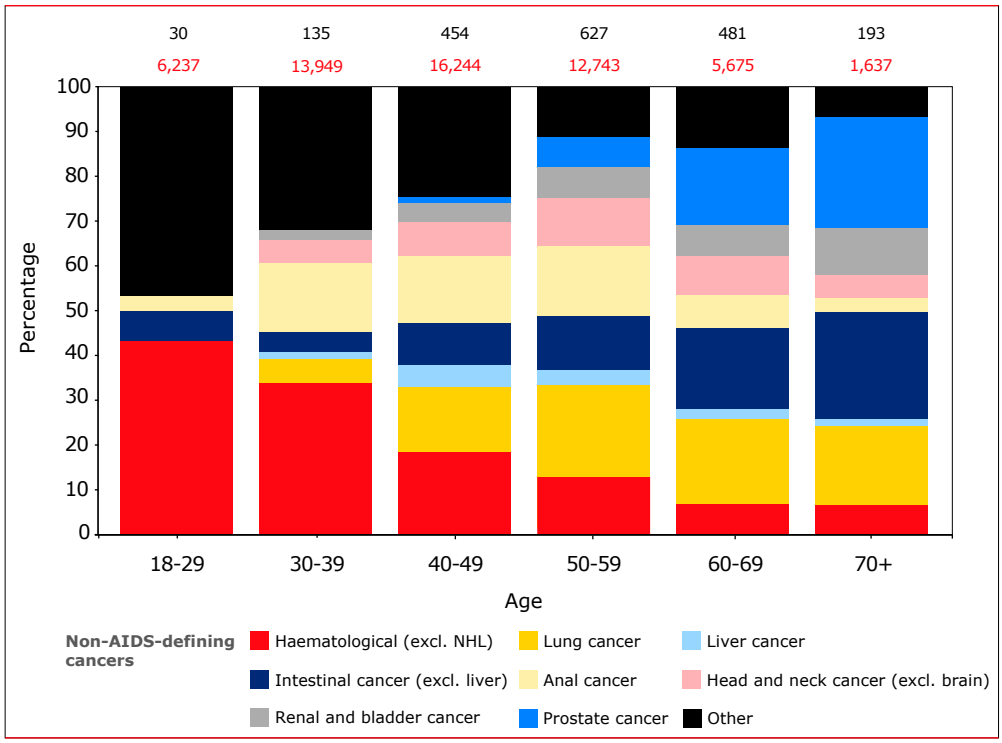
In total, 219 men living with HIV and 10 women living with HIV were diagnosed with anal cancer. Among men living with HIV, the incidence of anal cancer fluctuated between 0.4 and 1.5 cases per 1,000 PYFU between 2000 and 2020 (*Figure 3.3G*). A 2015 study exploring the incidence of anal cancer among 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[37]. 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=23) to analyse.

Figure 3.11: Relative changes in non-AIDS-defining malignancies between 2000 and 2020 in HIV-1-positive individuals in the Netherlands. The numbers at the top of each bar represent the number of non-AIDS-defining cancer diagnoses (top number) and the total number of individuals in care during that calendar period (bottom number).



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 living with HIV in the Netherlands. The numbers at the top of each bar represent the number of individuals at risk and the number of cancer diagnoses in that age category between 2000 and 2020.



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

Table 3.6: Most common non-AIDS-defining malignancies diagnosed in 2000-2020, 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	325	16.9	15.0
Hematological (excl. NHL)	272	14.2	64.7
Intestinal cancer (excl. liver)	259	13.5	32.8
Anal cancer	229	11.9	65.5
Prostate cancer	181	9.4	77.6
Head and neck cancer (excl. brain)	159	8.3	57.9
Renal and bladder cancer	120	6.3	62.9
Other cancers	102	5.3	45.8
Malignant melanoma	85	4.4	72.9
Liver cancer	60	3.1	14.8
Breast cancer	50	2.6	81.6
Testicular cancer	38	2.0	87.9
Gynecological cancer (excl. cervical)	27	1.4	69.2
CNS cancer	13	0.7	64.8

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

Table 3.7: Crude non-AIDS-defining malignancy incidence per 1,000 person years of follow up in 2000-2010, 2011-2015, and 2016-2020, 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)
2000-2010	6.6 (6.0-7.1)	1.29 (1.18-1.39)	3.2 (2.5-4.0)	1.26 (0.97-1.55)
2011-2015	6.6 (6.0-7.2)	1.01 (0.92-1.10)	4.3 (3.4-5.5)	1.13 (0.87-1.40)
2016-2020	7.9 (7.3-8.6)	1 (reference)	4.9 (3.9-6.0)	1 (reference)

** Standardised according to the observed age distribution in 2011-2020.*

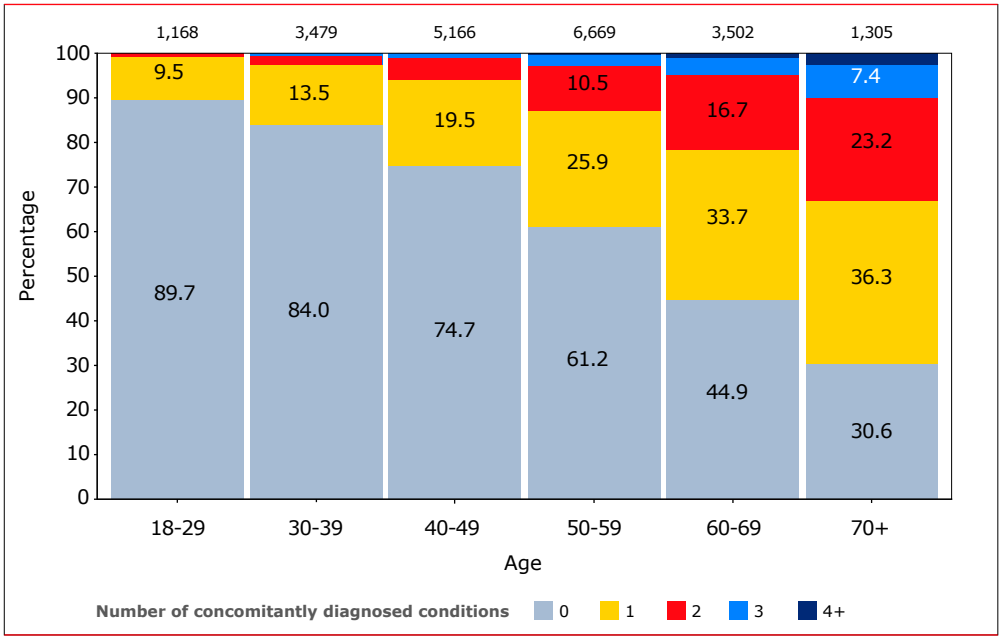
Legend: *CI=confidence intervals; PY=person years*

Multimorbidity

We investigated changes over time in the prevalence of non-AIDS multimorbidity. HIV infections 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 at or above 60 mmHg and/or diastolic pressure at or above 100 mmHg; and (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; this is to avoid overdiagnosis of 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.

Appendix Figure 3.4 shows the prevalence of each individual comorbidity over calendar time. *Figure 3.13* shows the distribution of the number of concomitantly-diagnosed conditions in various age categories of the adult population in 2020. The number of concomitant conditions was slightly higher in women than in men for all age categories (*Appendix Figure 3.3*). Moreover, although the average number of concomitant conditions has steadily increased over the past ten years due to 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 3.2*, multimorbidity was independently associated with increased risk of mortality (RR 2.20, 95% CI 2.12-2.30, $p<0.001$, per additional comorbidity diagnosed).

Figure 3.13: Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2020. 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

Polypharmacy, commonly defined as the concomitant use of five 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 count 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[a]) of the comedications. Note that coformulated combinations, such as cotrimoxazole, have a single ATC code and therefore increase the comedication count by one.

In 2020, 21.9% of adults in active follow up had no recorded comedication use, while 30.7%, 15.9%, 10.0%, and 6.8% used one, two, three, or four comedications, respectively. A further 14.7% used five or more non-antiretroviral comedications in addition to their cART regimen, which qualifies as polypharmacy. The prevalence

a *https://www.whocc.no/atc_ddd_index/*

of polypharmacy among adults has increased over time (*Figure 3.14*): in 2000, just 3.1% of adults used five or more non-antiretroviral comedications in addition to their cART regimen. The main drivers for this increase are the rising age of the population and the growth 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, while the most pronounced differences were to be found in the youngest age groups (*Figure 3.15B*). Finally, in adults using cART in the period 2007-20, polypharmacy was also associated with an increased risk of death (RR 2.23, 95% CI 2.00-2.49, $p<0.001$), independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities (i.e., multimorbidity). All co-medications used by at least 250 adults living with HIV in care in 2020 are listed in *Table 3.8*.

Table 3.8: Use of comedications in 2020.

Comedication use in 2020	n	%
ATC group		
Lipid modifying agents	4,042	8.7
Drugs for acid-related disorders	3,582	7.7
Agents acting on the renin-angiotensin system	3,052	6.6
Antithrombotic agents	2,601	5.6
Psycholeptics drugs (antipsychotics, anxiolytics, hypnotics, sedatives)	2,181	4.7
Psychoanaleptics (antidepressants, psychostimulants)	2,134	4.6
Mineral supplements	1,998	4.3
Drugs used in diabetes	1,877	4.0
Drugs for obstructive airway diseases	1,808	3.9
Urological drugs	1,604	3.5
Beta blocking agents	1,584	3.4
Calcium channel blockers	1,352	2.9
Antibacterial drugs	1,082	2.3
Sex hormones and modulators of the genital system	1,080	2.3
Diuretic drugs	1,022	2.2
Antianaemic drugs	1,007	2.2
Analgesic drugs	815	1.8
Antiepileptic drugs	781	1.7
Corticosteroids systemic	771	1.7
Antiviral drugs	721	1.6
Cardiac therapy	634	1.4
Nasal preparations	558	1.2
Topical dermatological corticosteroids	508	1.1
Antimycotic drugs	450	1.0
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents	444	1.0
Drugs affecting bone structure and mineralisation	405	0.9
Thyroid therapy	333	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.

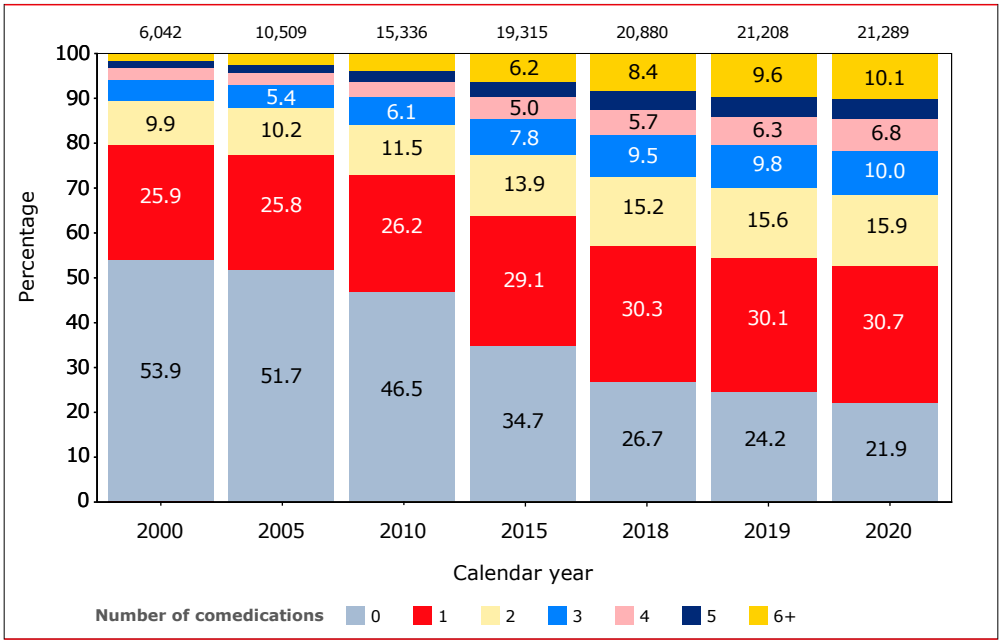
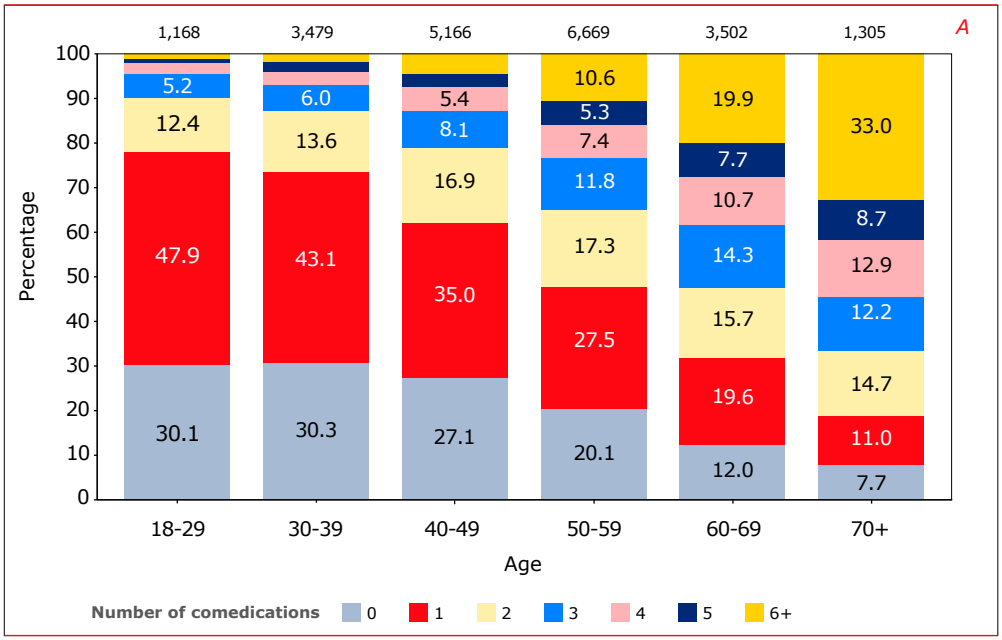


Figure 3.15: Number of comedications used by (A) age group, and (B) gender in 2020. The numbers at the top of each bar represent the number of individuals contributing data to that age/gender category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



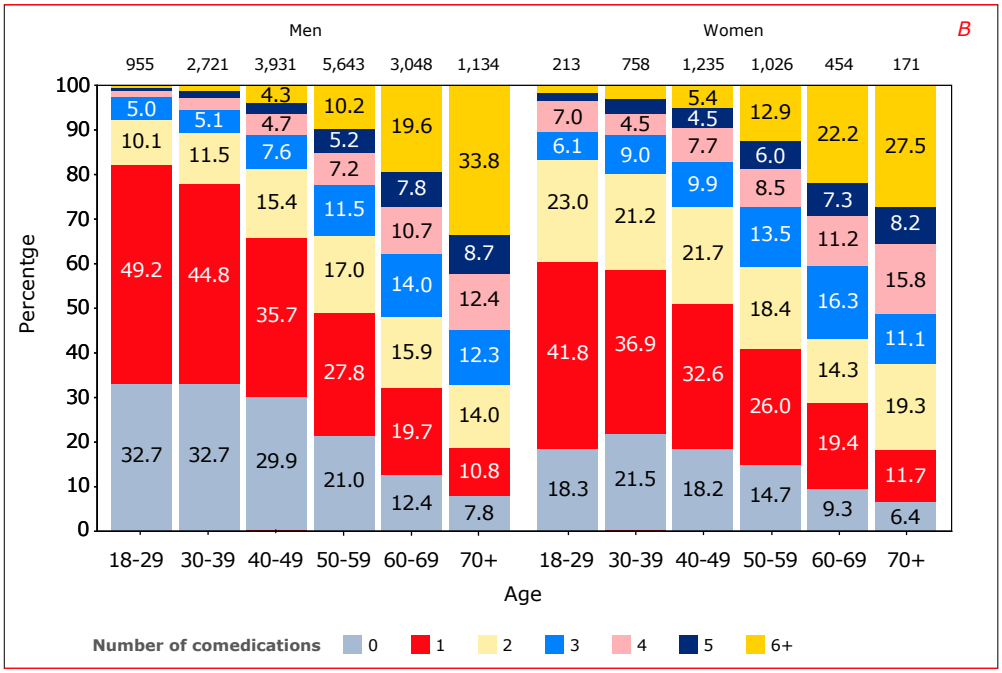
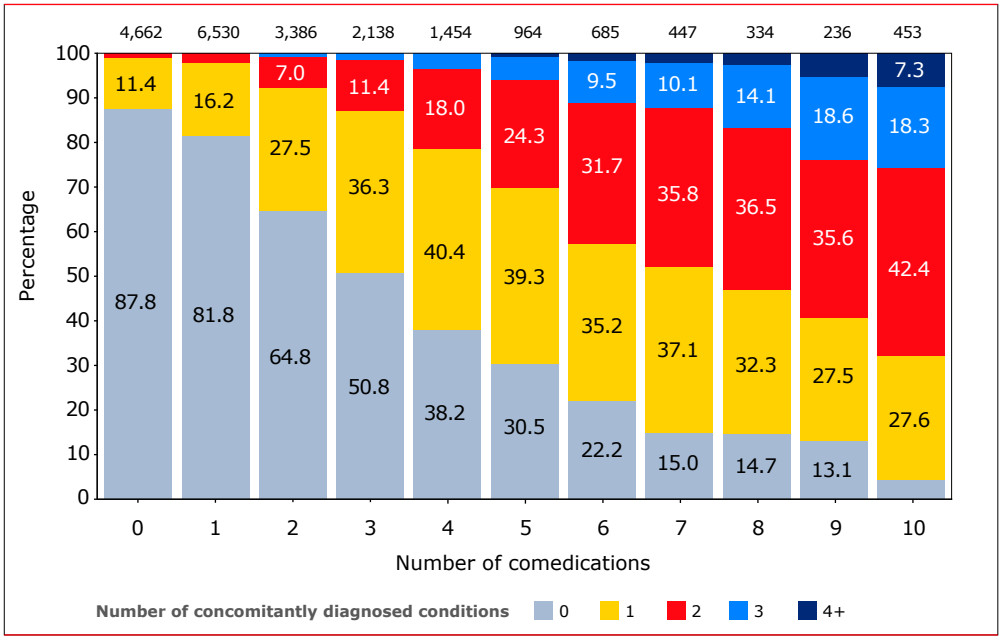


Figure 3.16: Number of comedications used in relation to the number of prevalent comorbidities. The numbers at the top of each bar represent the number of individuals contributing data to that category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per 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. The limited number of deaths from AIDS each year mainly occur among those who present late for care with already advanced immunodeficiency. The five-year survival rate after a first AIDS-defining condition is 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 non-AIDS malignancies and CVD 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, the mortality rate among people living with HIV in the Netherlands remains substantially higher than in the general Dutch population, although it is slowly approaching the general Dutch

population rate. Furthermore, several studies have found that mortality rates in individuals on treatment who achieve CD4 counts above 500 cells/mm^3 may even drop below general population rates[38,39].

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 CVD declined over time in men and women, while the age-adjusted incidence for diabetes mellitus only declined in men. This decline may suggest improved awareness, prevention (including switching from drugs associated with an increased risk of diabetes mellitus[40] and myocardial infarction[41,42]), and increased attention to managing traditional risk factors for these conditions. It may also reflect an increasing proportion of individuals living at high CD4 cell counts (because of the trend over time to start cART at higher CD4 cell counts, but also due to an increase in the proportion of individuals who have used cART long enough to reach high CD4 cell counts). The observation that the age-standardised incidence ratios for diabetes mellitus do not decline as much in women remains unexplained and needs further study – but the observed increasing average BMI and high prevalence of obesity in women might partially explain this observation. Finally, the risk factors observed for diabetes mellitus and CVD (including age, hypertension, smoking, and obesity), were similar to those previously reported in other studies[40,43,44]. Several of these risk factors are more prevalent among people living with HIV[19].

Cardiovascular risk factors

The proportion of adults living with HIV at high (5-10%), or very high (more than 10%) cardiovascular risk slowly increased from 11.7% and 5.6%, respectively, in 2000, to 20.4% and 12.1%, respectively, in 2020. This increase largely reflects the increased average age of the population. We observed that cardiovascular risk management has improved over time, as illustrated by the increasing use of statins and antihypertensives, 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[45] (*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 increased availability of preferred antiretroviral treatment options that do not contain pharmacological boosters that can interfere with these preventive medicines has made it easier to implement proper cardiovascular risk management.

The clinical significance of the increase in BMI over time, especially in women, requires further study. Recent results suggest that weight gain after starting cART is associated with lower mortality for normal-weight individuals, but they show no clear benefit for overweight or obese individuals[46]. 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[47]. 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 being overweight were significant risk factors for developing new-onset diabetes and CKD, but not cardiovascular disease and 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. Currently, analyses are underway in our cohort to look in depth at the relationship between weight gain on cART and the use of specific antiretroviral agents (the integrase strand transfer inhibitors and tenofovir alafenamide, in particular), while controlling for demographic characteristics, traditional risk factors, and confounders.

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 hypertension, were found to be at increased risk of CKD, as were individuals with advanced immunodeficiency. In addition, other studies have also reported hepatitis B and C virus co-infection[48,49], and the use of tenofovir disoproxil fumarate, atazanavir/ritonavir, and lopinavir/ritonavir, to be additional independent predictors of chronic renal impairment[50]. Moreover, renal impairment in the population living with HIV is associated with an increased risk of cardiovascular disease[51]. The increase in CKD in our population, 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, intestinal, anal, and head and neck cancer, as well as Hodgkin's lymphoma. The crude incidence of NADM has remained stable over time, and we also observed a decline in age-standardised incidence of NADM in men, and to a lesser extent in women. In addition, our analyses showed that individuals diagnosed with NADM a more likely to be older. This is in line with data from other cohorts, including the Swiss HIV cohort[49-52]. 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 reported that the effect of immunodeficiency may be stronger for infection-related non-AIDS-defining malignancies[56]. Importantly, 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 0.54, 95% CI 0.33-0.86, p=0.009), independent of other traditional and HIV-related risk factors. The five-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 50.1%.

Multimorbidity and polypharmacy

The prevalence of non-AIDS multimorbidity is slowly increasing, driven mainly by the increasing age of the cohort, and by women experiencing more comorbidities in each age group. Multimorbidity is strongly and independently associated with increased risk of mortality.

Polypharmacy, defined as the concomitant use of five or more medications in addition to cART, is becoming more prevalent, mainly because of the increased age of the cohort and the associated rise in the prevalence of age-associated, non-AIDS comorbidities. In 2000, 3.0% of adults used five or more non-antiretroviral comedications alongside their cART regimen, and this steadily increased to 14.7% of adults in active follow up in 2020. 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 2007-20, polypharmacy was also strongly and independently associated with an increased risk of death, independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities.

Recommendations

The proportion of individuals dying of AIDS in the Netherlands has markedly declined throughout the cART era, but to reach the goal of zero AIDS-deaths by 2022, it will be imperative to identify individuals earlier after infection, and rapidly link them to care for immediate start of treatment. This can also be expected to beneficially impact the incidence of comorbidities for which advanced immunodeficiency is a contributing risk factor[54-56]. Of note, our own analyses show a markedly lower risk for non-AIDS malignancies in those who initiate cART within the first year of infection.

The relatively poor five-year survival rates following the diagnosis of several of the analysed non-AIDS-defining comorbidities, compared with survival of all people newly entering care with an AIDS diagnosis, underlines the importance of primary prevention, early diagnosis and aggressive pursuit of treatment and secondary prevention of non-AIDS comorbidities in the population living with HIV. 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[9,60].

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 potentially 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 comorbidity burden continues to increase. In tandem with multi-morbidity, the risk for polypharmacy is also strongly on the rise in recent years. Both multimorbidity and polypharmacy were each independently associated with an increased risk of death. Adequate prevention and management of comorbidities will become even more important as more people living with HIV are entering their 70s and 80s. Polypharmacy should also be adequately managed using 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.

Awareness on the part of both physicians and people living with HIV of the role of modifiable, lifestyle-related risk factors (particularly in older individuals, or those otherwise at high risk of certain comorbidities), along with the appropriate management of these risk factors, offer considerable hope for lowering the comorbidity burden and ensuring healthy ageing in people living with HIV.

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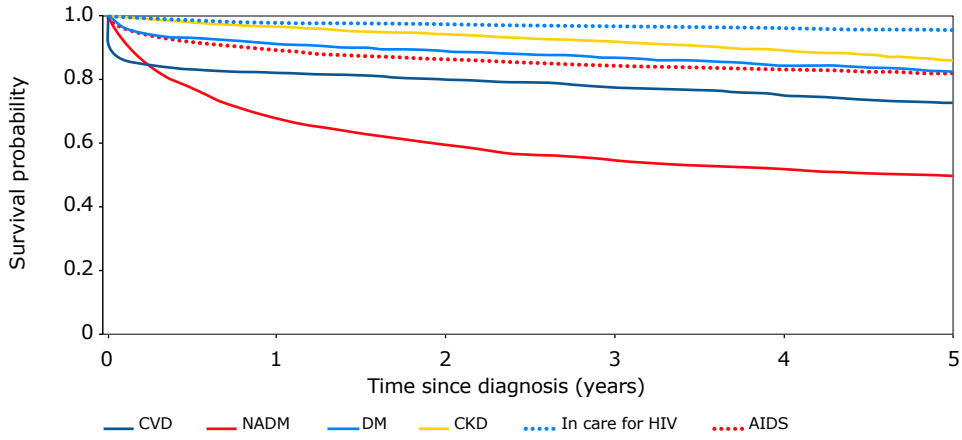
Appendix: supplementary figures and tables

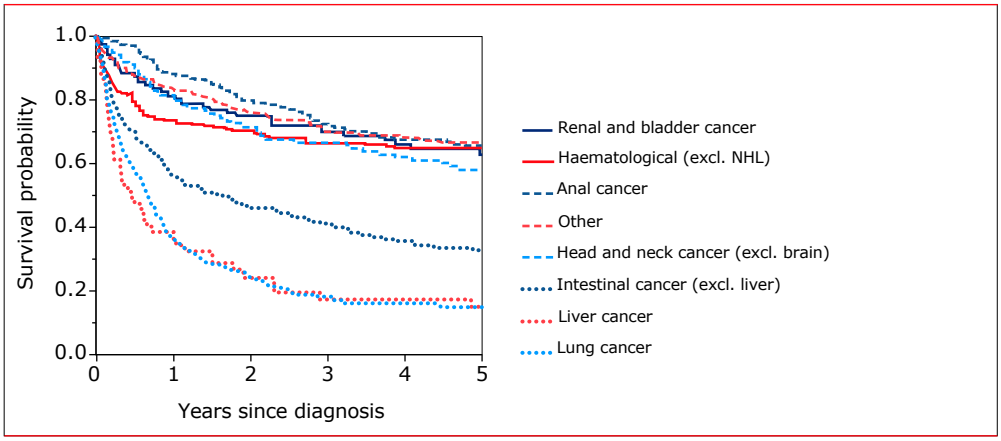
Appendix Figure 3.1: *Estimated five-year survival following the diagnosis of cardiovascular disease, non-AIDS-defining malignancy, diabetes mellitus, and chronic kidney disease. Two reference groups are included: survival from date of entry into HIV care (after 1 January 2000), and from date of first 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	1,616	1,258	1,116	973	859	745
NADM	1,490	966	762	616	507	422
DM	1,485	1,264	1,149	1,022	904	793
CKD	2,331	2,039	1,801	1,520	1,210	918
In care for HIV	22,348	20,524	19,211	18,017	16,837	15,714
AIDS	3,628	3,073	2,858	2,666	2,491	2,336

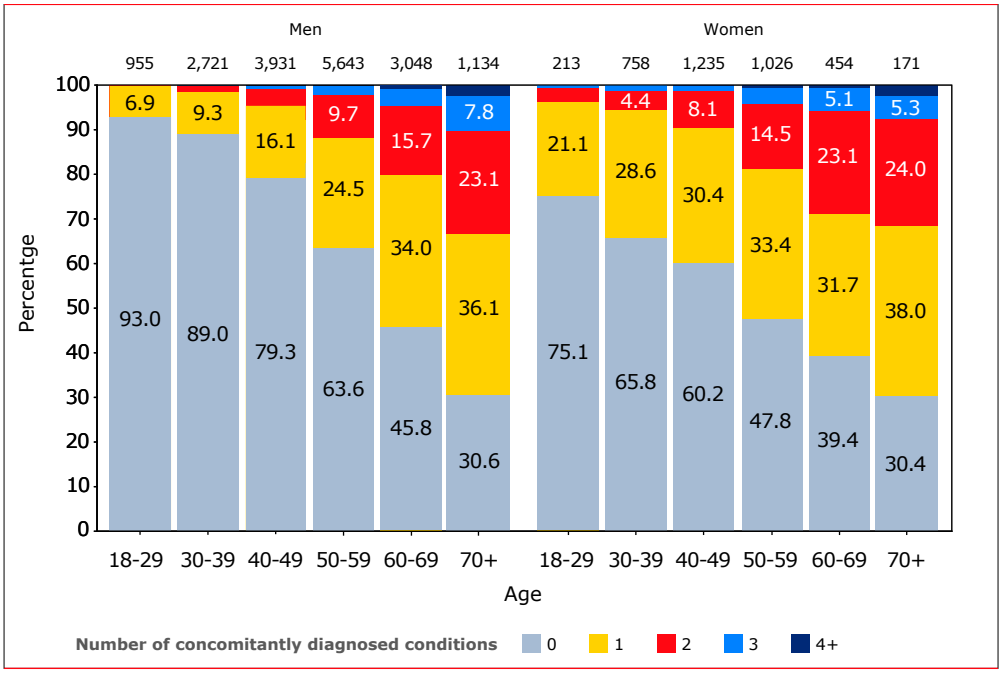
Legend: *KM=Kaplan-Meier; CVD=cardiovascular disease; NADM=non-AIDS defining malignancy; DM=diabetes mellitus; CKD=chronic kidney disease.*

Appendix Figure 3.2: *Estimated five-year survival following the diagnosis of the most common non-AIDS-defining malignancies diagnosed between 1 January 2000 and 31 December 2020.*

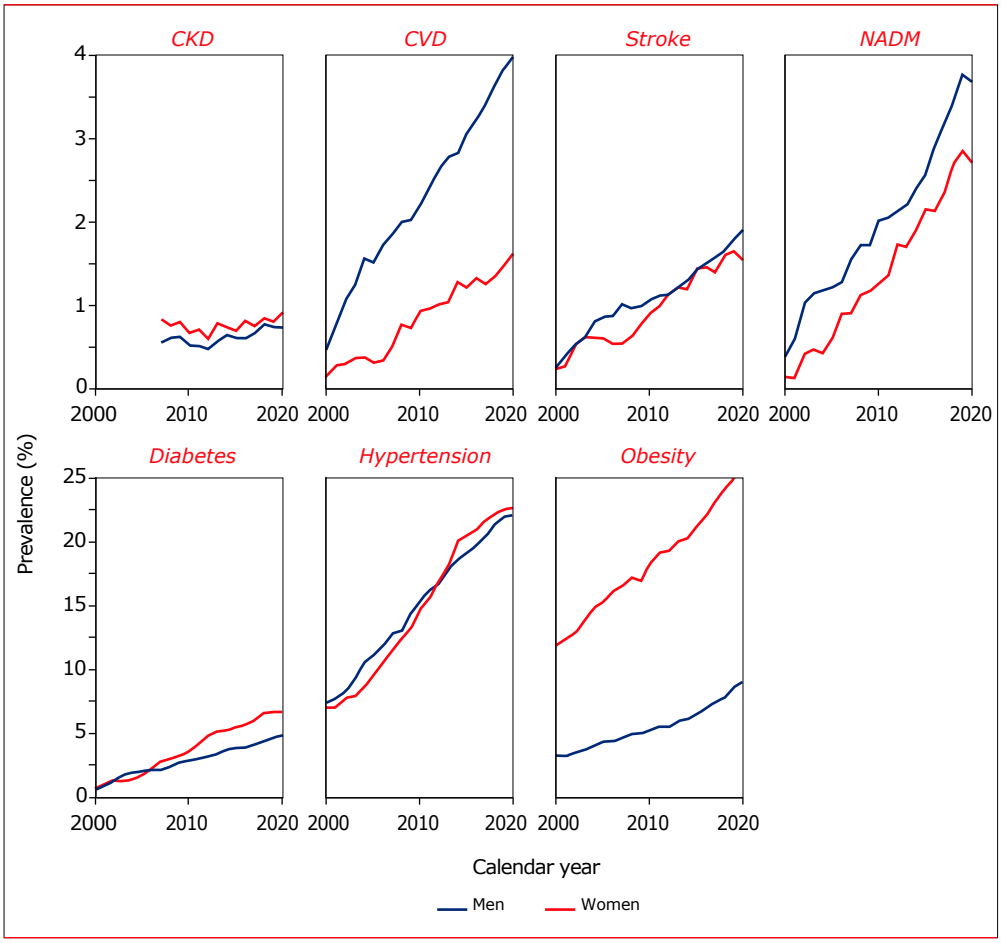


Legend: *KM=Kaplan-Meier; excl.=excluding; NHL=non-Hodgkin's lymphoma.*

Appendix Figure 3.3: *Prevalence of non-AIDS multimorbidity by gender in the adult population in 2020. 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.*

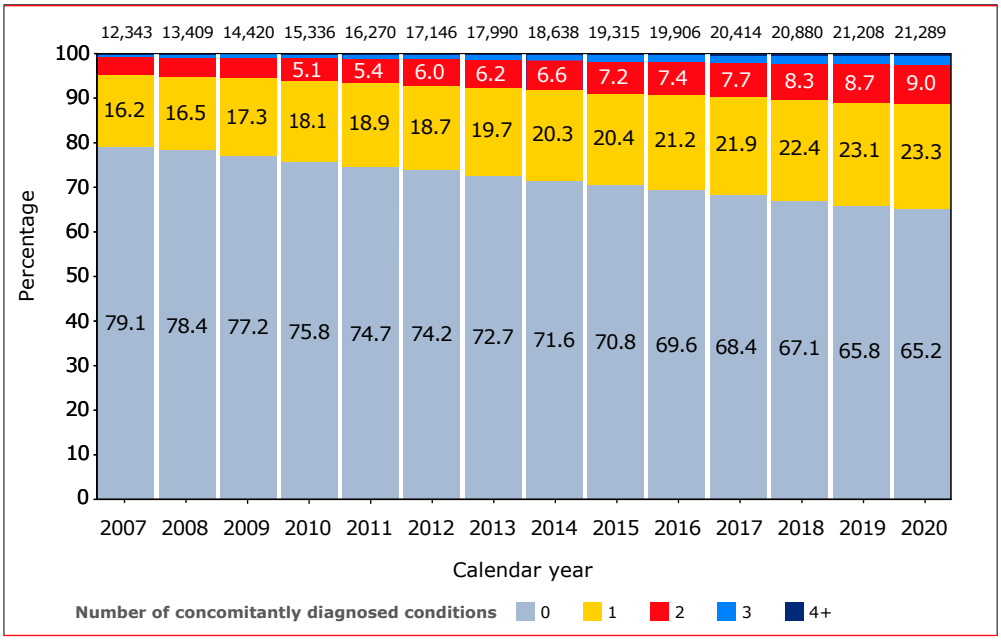


Appendix Figure 3.4: *Prevalence of non-AIDS comorbidities in the adult population between 2000 and 2020.*



Legend: *CKD=chronic kidney disease; CVD=cardiovascular disease; NADM=non-AIDS-defining malignancies.*

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.



Appendix Table 3.1: *Absolute number of causes of death among HIV-1-positive individuals during the periods 1996-2000, 2001-2005, 2006-2010, and 2011-2020.*

	Calendar period								
Causes of death	**96-00**	**01-05**	**06-10**	**11-15**	**2016**	**2017**	**2018**	**2019**	**2020**
AIDS									
AIDS - infection	69	120	148	103	6	4	4	7	4
AIDS - malignancy	60	63	61	43	8	13	10	11	5
AIDS - unclassifiable	89	63	19	15	10	3	4	5	4
Subtotal	*218*	*246*	*228*	*161*	*24*	*20*	*18*	*23*	*13*
Non-AIDS malignancies	*30*	*95*	*136*	*193*	*49*	*62*	*48*	*75*	*60*
Cardiovascular disease									
Myocardial infarction	14	30	46	40	8	4	2	12	15
Stroke	3	11	13	11	7	3	3	2	3
Other CVD	6	24	26	50	16	10	16	12	13
Subtotal	*23*	*65*	*85*	*101*	*31*	*17*	*21*	*26*	*31*
Non-AIDS infection	*23*	*42*	*32*	*27*	*7*	*3*	*10*	*6*	*14*
Liver disease	*15*	*28*	*55*	*43*	*6*	*7*	*8*	.	*1*
Lung disease	*7*	*11*	*30*	*38*	*13*	*14*	*9*	*15*	*6*
Non-natural death									
Accident or violence	6	11	22	16	7	2	4	1	1
Suicide	12	30	30	52	10	12	11	4	12
Euthanasia	7	5	.	2	1	.	.	.	.
Subtotal	*25*	*46*	*52*	*70*	*18*	*14*	*15*	*5*	*13*
Alcohol and substance abuse	12	15	27	18	10	4	4	2	4
Other causes	21	24	23	43	13	8	18	10	11
Unknown	23	57	53	84	20	18	21	12	11
Total	**397**	**629**	**721**	**778**	**191**	**167**	**172**	**174**	**164**

Legend: *CVD=cardiovascular disease.*

Appendix Table 3.2: 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	1.28 (1.12-1.47)	<.001		0.96 (0.82-1.13)	0.655	
Region of birth						
Netherlands	1 (reference)		0.140	1 (reference)		0.098
Other	0.93 (0.84-1.02)	0.142		1.10 (0.98-1.24)	0.098	
HIV-1 transmission route						
Blood contact	0.77 (0.55-1.06)	0.111		0.85 (0.59-1.22)	0.385	
Heterosexual	1.05 (0.94-1.19)	0.392		0.90 (0.77-1.04)	0.147	
IDU	1.61 (1.34-1.94)	<.001		0.72 (0.56-0.93)	0.013	
MSM	1 (reference)		<.001	1 (reference)		0.031
Age*						
18-29	0.90 (0.65-1.24)	0.506	<.001	1.08 (0.88-1.33)	0.449	<.001
30-39	1 (reference)			1 (reference)		
40-49	1.50 (1.29-1.75)	<.001		1.09 (0.95-1.24)	0.218	
50-59	2.65 (2.28-3.08)	<.001		1.34 (1.16-1.56)	<.001	
60-69	4.78 (4.07-5.61)	<.001		1.39 (1.15-1.68)	<.001	
70+	10.50 (8.72-12.64)	<.001		2.04 (1.48-2.81)	<.001	
CD4 cell count**						
0-50	14.20 (11.83-17.05)	<.001	<.001	6.74 (5.39-8.42)	<.001	<.001
50-199	5.06 (4.42-5.80)	<.001		2.82 (2.39-3.34)	<.001	
200-349	2.14 (1.87-2.45)	<.001		1.64 (1.40-1.93)	<.001	
350-499	1.38 (1.21-1.58)	<.001		1.26 (1.07-1.49)	0.006	
500-749	1 (reference)			1 (reference)		
750+	0.86 (0.74-0.99)	0.040		1.15 (0.95-1.39)	0.151	
Per year longer on cART with HIV RNA >1,000 copies/ml	1.05 (1.03-1.07)	<.001	<.001	1.03 (1.01-1.06)	0.018	0.020
Treatment status at start cART						
Treatment-experienced	0.96 (0.87-1.06)	0.446		0.63 (0.55-0.72)	<.001	
Treatment-naive	1 (reference)			1 (reference)		
Prior AIDS event	1.73 (1.58-1.89)	<.001				
Hepatitis B virus positive	1.26 (1.10-1.44)	0.001		1.13 (0.93-1.37)	0.221	
Hepatitis C virus positive	1.58 (1.37-1.83)	<.001		1.23 (1.02-1.48)	0.027	

			Death			AIDS
	RR (95% CI)	p-value	Overall p-value	RR (95% CI)	p-value	Overall p-value
Body mass index*						
0–18	3.07 (2.70–3.49)	<.001	<.001			
18–25	1 (reference)					
25–30	0.67 (0.61–0.75)	<.001				
30+	0.86 (0.72–1.01)	0.073				
Smoking status						
Current smoker	1.10 (0.97–1.25)	0.129	<.001	0.76 (0.67–0.86)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	2.04 (1.82–2.30)	<.001		0.94 (0.81–1.09)	0.408	
Early cART***	0.86 (0.61–1.20)	0.376		1.18 (0.90–1.55)	0.232	

** Time-updated.*

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

**** cART started within 12 months of the 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 3.3: *Lost to follow up (no follow up after 31 December 2019) 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	47	2,713	17.3 (12.7–23.0)	2	218	9.2 (1.1–33.1)	8	177	45.2 (19.5–89.0)
050–199	199	9,866	20.2 (17.5–23.2)	12	726	16.5 (8.5–28.9)	35	1,068	32.8 (22.8–45.6)
200–349	415	22,053	18.8 (17.1–20.7)	16	1,058	15.1 (8.6–24.6)	83	1,901	43.7 (34.8–54.1)
350–499	562	43,264	13.0 (11.9–14.1)	37	1,821	20.3 (14.3–28.0)	125	3,699	33.8 (28.1–40.3)
500–749	816	93,993	8.7 (8.1–9.3)	60	4,533	13.2 (10.1–17.0)	202	7,640	26.4 (22.9–30.3)
750+	563	107980	5.2 (4.8–5.7)	43	5,409	7.9 (5.8–10.7)	171	9,545	17.9 (15.3–20.8)

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

	Netherlands			Sub-Saharan Africa			South and south-east Asia		
	n	PY	Incidence/ 1,000 PY (95% CI)	n	PY	Incidence/ 1,000 PY (95% CI)	n	PY	Incidence/ 1,000 PY (95% CI)
	4	1,755	2.3 (0.6–5.8)	27	445	60.6 (40.0–88.2)	6	117	51.3 (18.8–111.6)
	31	5,983	5.2 (3.5–7.4)	110	1,757	62.6 (51.5–75.5)	11	333	33.0 (16.5–59.1)
	82	13,985	5.9 (4.7–7.3)	208	4,330	48.0 (41.7–55.0)	26	781	33.3 (21.8–48.8)
	128	28,324	4.5 (3.8–5.4)	250	7,598	32.9 (28.9–37.2)	22	1,822	12.1 (7.6–18.3)
	251	63,147	4.0 (3.5–4.5)	281	14,626	19.2 (17.0–21.6)	22	4,047	5.4 (3.4–8.2)
	201	77,065	2.6 (2.3–3.0)	130	12,500	10.4 (8.7–12.3)	18	3,461	5.2 (3.1–8.2)

Appendix Table 3.4: *Absolute number of first AIDS events among HIV-1-positive individuals during the periods 1996-2000, 2001-2005, 2006-2010, 2011-2015 and 2016-2020.*

CDC event	1996-2000	2001-2005	2006-2010	2011-2015	2016-2020	Total	
	n	n	n	n	n	n	%
AIDS dementia complex - HIV encefalopathy	37	47	51	44	18	197	2.95
Bacterial pneumonia, recurring	48	64	66	77	88	343	5.14
CMV colitis/proctitis	1	.	1	1	3	6	0.09
CMV disease	26	35	29	33	3	126	1.89
CMV meningo-encefalitis	.	.	.	.	1	1	0.01
CMV pneumonitis	.	.	.	.	11	11	0.16
CMV retinitis	30	20	12	12	10	84	1.26
Candidiasis lungs/bronchial/trachea	7	13	7	6	7	40	0.60
Candidiasis oesophagitis	260	238	251	223	134	1106	16.56
Cervical cancer, invasive	3	4	6	4	4	21	0.31
Coccidioimycosis, extrapulmonary / disseminated	.	.	1	.	.	1	0.01
Cryptococcosis, extrapulmonary / disseminated	21	31	33	11	11	107	1.60
Cryptosporidiosis	22	12	11	12	2	59	0.88
Cystoisosporiasis	3	9	6	.	.	18	0.27
HIV wasting	50	57	77	78	57	319	4.78
HSV chronic ulcer	1	1	1	3	18	24	0.36
HSV oesophagitis	.	.	.	.	1	1	0.01
HSV pneumonitis	.	.	.	.	1	1	0.01
Herpes simplex virus	32	41	59	37	9	178	2.67
Histoplasmosis, extrapulmonary / disseminated	9	12	10	7	2	40	0.60
Kaposi's sarcoma	153	153	187	139	85	717	10.74
Leishmaniasis visceral	.	1	2	2	2	7	0.10
Microsporidiosis	11	1	3	1	.	16	0.24
Mycobacterium avium/kansasii, extrapulmonary / disseminated	25	19	28	9	7	88	1.32
Mycobacterium avium/kansasii, pulmonary	1	2	.	1	7	11	0.16
Mycobacterium other / unspecified, extrapulmonary / disseminated	20	13	8	10	3	54	0.81
Mycobacterium other / unspecified, pulmonary	.	3	4	9	4	20	0.30
Non-Hodgkin`s lymphoma (NHL)	58	86	80	94	60	378	5.66
Penicilliosis	.	.	1	.	.	1	0.01
Pneumocystis jirovecii extrapulmonary	1	1	3	.	1	6	0.09
Pneumocystis jirovecii pneumonia	334	300	325	263	184	1406	21.06
Primary CNS lymphoma	8	4	9	6	4	31	0.46

CDC event	1996–2000	2001–2005	2006–2010	2011–2015	2016–2020	Total	
	n	n	n	n	n	n	%
Progressive multifocal leucoencefalopathy	18	25	35	24	7	109	1.63
Salmonella sepsis, recurring	2	.	.	1	.	3	0.04
Toxoplasmosis of the brain	70	97	55	42	26	290	4.34
Tuberculosis, extrapulmonary / disseminated	79	111	80	53	23	346	5.18
Tuberculosis, pulmonary	104	175	116	73	43	511	7.65
Total	**1434**	**1575**	**1557**	**1275**	**836**	**6677**	**100.00**

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

Appendix Table 3.5: 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	1.26 (1.13-1.41)	<.001	.	1.71 (1.41-2.07)	<.001	.
Region of birth						
Netherlands	1 (reference)	.	0.049	1 (reference)	.	0.165
Other	1.08 (1.00-1.16)	0.049	.	0.92 (0.82-1.04)	0.167	.
HIV-1 transmission route						
MSM	1 (reference)	.	<.001	1 (reference)	.	0.021
Heterosexual	1.19 (1.09-1.30)	<.001	.	1.20 (1.05-1.39)	0.010	.
IDU	1.33 (1.10-1.61)	0.004	.	1.20 (0.88-1.63)	0.240	.
Blood contact	1.26 (0.99-1.61)	0.060	.	1.18 (0.80-1.74)	0.414	.
Age*						
18-29	0.61 (0.46-0.80)	<.001	<.001	0.51 (0.28-0.94)	0.032	<.001
30-39	1 (reference)	.	.	1 (reference)	.	.
40-49	2.00 (1.76-2.26)	<.001	.	2.69 (2.11-3.42)	<.001	.
50-59	3.69 (3.25-4.19)	<.001	.	5.86 (4.62-7.44)	<.001	.
60-69	6.34 (5.52-7.27)	<.001	.	9.76 (7.60-12.55)	<.001	.
70+	10.30 (8.67-12.22)	<.001	.	16.98 (12.74-22.62)	<.001	.
CD4 cell count**						
0-50	3.99 (3.10-5.13)	<.001	<.001	3.26 (2.10-5.05)	<.001	<.001
050-199	1.81 (1.56-2.11)	<.001	.	1.64 (1.28-2.09)	<.001	.
200-349	1.28 (1.15-1.43)	<.001	.	1.34 (1.13-1.59)	<.001	.
350-499	1.05 (0.95-1.15)	0.327	.	1.06 (0.91-1.23)	0.465	.
500-749	1 (reference)	.	.	1 (reference)	.	.
750+	1.14 (1.04-1.24)	0.004	.	1.22 (1.07-1.40)	0.004	.
Per year longer with CD4<200 cells/mm^3	0.99 (0.97-1.01)	0.498	.	1.00 (0.97-1.04)	0.846	.
Prior AIDS event	1.21 (1.13-1.30)	<.001	.	1.13 (1.01-1.26)	0.041	.
Per year longer on cART while HIV RNA>1000 cp/mL	1.02 (1.00-1.04)	0.073	.	1.02 (0.99-1.05)	0.184	.
Treatment status						
Not (yet) started cART	1.17 (1.02-1.33)	0.024	<.001	1.01 (0.80-1.28)	0.915	0.013
Treatment-experienced at start cART	1.29 (1.18-1.41)	<.001	.	1.24 (1.08-1.43)	0.003	.
Treatment-naive at start	1 (reference)	.	.	1 (reference)	.	.
Per year longer on cART	1.01 (1.00-1.02)	0.025	.	1.00 (0.99-1.02)	0.632	.
Early cART within 12 months after last HIV-negat	0.83 (0.66-1.03)	0.089	.	1.08 (0.80-1.47)	0.611	.

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
1.07 (0.89-1.29)	0.463	.	1.28 (1.09-1.51)	0.003	.	0.62 (0.54-0.72)	<.001	.
1 (reference)	.	0.052	1 (reference)	.	<.001	1 (reference)	.	<.001
0.88 (0.78-1.00)	0.053	.	1.49 (1.32-1.68)	<.001	.	0.77 (0.69-0.86)	<.001	.
1 (reference)	.	0.060	1 (reference)	.	<.001	1 (reference)	.	0.072
0.98 (0.84-1.14)	0.762	.	1.46 (1.26-1.69)	<.001	.	0.99 (0.87-1.13)	0.915	.
1.33 (0.99-1.80)	0.059	.	1.59 (1.14-2.23)	0.007	.	1.45 (1.10-1.91)	0.009	.
1.51 (1.06-2.14)	0.022	.	1.64 (1.14-2.35)	0.008	.	1.29 (0.94-1.78)	0.111	.
0.65 (0.39-1.09)	0.104	<.001	0.64 (0.44-0.94)	0.024	<.001	0.27 (0.11-0.68)	0.006	<.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
2.25 (1.78-2.84)	<.001	.	1.50 (1.25-1.80)	<.001	.	3.16 (2.35-4.24)	<.001	.
4.18 (3.31-5.27)	<.001	.	2.37 (1.96-2.86)	<.001	.	8.63 (6.49-11.47)	<.001	.
8.74 (6.86-11.14)	<.001	.	3.79 (3.07-4.68)	<.001	.	23.80 (17.88-31.68)	<.001	.
15.01 (11.36-19.84)	<.001	.	4.36 (3.23-5.89)	<.001	.	44.21 (32.63-59.88)	<.001	.
3.04 (1.89-4.88)	<.001	<.001	6.01 (4.19-8.62)	<.001	<.001	1.09 (0.49-2.46)	0.829	<.001
2.05 (1.61-2.61)	<.001	.	1.80 (1.39-2.32)	<.001	.	1.72 (1.36-2.17)	<.001	.
1.37 (1.15-1.63)	<.001	.	1.14 (0.94-1.37)	0.181	.	1.21 (1.04-1.41)	0.016	.
1.09 (0.94-1.27)	0.271	.	1.00 (0.85-1.17)	0.952	.	1.03 (0.91-1.17)	0.637	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
0.90 (0.78-1.05)	0.173	.	1.32 (1.15-1.52)	<.001	.	0.96 (0.86-1.08)	0.526	.
0.99 (0.95-1.02)	0.377	.	0.99 (0.96-1.03)	0.688	.	0.99 (0.96-1.01)	0.312	.
1.19 (1.06-1.34)	0.004	.	1.31 (1.16-1.47)	<.001	.	1.14 (1.03-1.26)	0.009	.
1.00 (0.97-1.03)	0.915	.	1.02 (0.99-1.05)	0.239	.	0.97 (0.94-1.00)	0.070	.
1.20 (0.96-1.51)	0.114	0.011	1.42 (1.14-1.75)	0.001	<.001	0.41 (0.28-0.59)	<.001	<.001
1.22 (1.05-1.42)	0.008	.	1.31 (1.11-1.53)	<.001	.	1.16 (1.01-1.33)	0.033	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
1.00 (0.99-1.02)	0.654	.	1.01 (0.99-1.02)	0.312	.	0.98 (0.98-0.99)	0.002	.
0.62 (0.42-0.93)	0.020	.	0.70 (0.45-1.09)	0.111	.	0.99 (0.79-1.25)	0.928	.

	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 (1.19-1.75)	<.001	<.001	1.23 (0.90-1.67)	0.195	0.006
18-25	1 (reference)	.	.	1 (reference)	.	.
25-30	1.22 (1.12-1.32)	<.001	.	1.02 (0.91-1.16)	0.693	.
30+	1.97 (1.77-2.19)	<.001	.	1.17 (0.97-1.42)	0.100	.
Hepatitis B virus positive	1.20 (1.07-1.36)	0.003	.	1.02 (0.83-1.25)	0.827	.
Hepatitis C virus positive	1.04 (0.92-1.18)	0.508	.	1.04 (0.86-1.26)	0.689	.
Hypertension	1.14 (1.07-1.22)	<.001	.	1.20 (1.08-1.34)	<.001	.
Smoking status						
Current smoker	1.40 (1.29-1.52)	<.001	<.001	1.83 (1.60-2.08)	<.001	<.001
Never smoker	1 (reference)	.	.	1 (reference)	.	.
Past smoker	1.46 (1.34-1.60)	<.001	.	1.53 (1.32-1.76)	<.001	.
Calendar year period						
2000-2010	1.30 (1.18-1.44)	<.001	<.001	1.50 (1.29-1.75)	<.001	<.001
2011-2015	1.18 (1.08-1.28)	<.001	.	1.27 (1.11-1.45)	<.001	.
2016-2020	1 (reference)	.	.	1 (reference)	.	.
Recent use of ABC***		.	.	1.58 (1.41-1.78)	<.001	.
Per year longer on LOP/r		.	.	1.01 (0.99-1.02)	0.267	.
Per year longer on IDV		.	.	1.00 (0.99-1.01)	0.972	.
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; 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
1.90 (1.46-2.46)	<.001	<.001	1.33 (0.91-1.96)	0.142	<.001	1.46 (1.10-1.93)	0.009	0.022
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
0.87 (0.76-0.99)	0.034	.	2.22 (1.93-2.54)	<.001	.	1.13 (1.02-1.26)	0.018	.
0.94 (0.76-1.17)	0.594	.	5.13 (4.38-6.00)	<.001	.	1.15 (0.99-1.34)	0.076	.
1.58 (1.32-1.89)	<.001	.	1.09 (0.88-1.34)	0.438	.	1.42 (1.20-1.68)	<.001	.
1.09 (0.89-1.32)	0.416	.	1.00 (0.81-1.25)	0.977	.	1.33 (1.14-1.54)	<.001	.
0.97 (0.87-1.09)	0.649	.	1.17 (1.04-1.31)	0.007	.	1.12 (1.03-1.23)	0.013	.
1.55 (1.34-1.78)	<.001	<.001	0.99 (0.86-1.14)	0.925	<.001	0.81 (0.72-0.91)	<.001	<.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
1.79 (1.55-2.07)	<.001	.	1.29 (1.12-1.49)	<.001	.	1.02 (0.91-1.13)	0.781	.
0.94 (0.80-1.11)	0.467	0.743	1.46 (1.23-1.74)	<.001	<.001	1.27 (1.07-1.51)	0.006	<.001
0.96 (0.84-1.10)	0.550	.	1.38 (1.19-1.60)	<.001	.	1.32 (1.17-1.48)	<.001	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	.	.		.	.		.	.
	.	.		.	.		.	.
	.	.		.	.		.	.
	.	.	1.02 (1.00-1.03)	0.020	.		.	.
	.	.	1.02 (0.99-1.05)	0.176	.		.	.
	.	.	1.06 (1.03-1.09)	<.001	.		.	.
	.	.		.	.	1.00 (0.98-1.01)	0.550	.
	.	.		.	.	1.01 (1.00-1.01)	0.159	.
	.	.		.	.	1.59 (1.37-1.85)	<.001	.
	.	.		.	.	1.30 (1.11-1.53)	0.001	.
	.	.		.	.	1.69 (1.47-1.94)	<.001	.
	.	.		.	.	3.25 (2.90-3.65)	<.001	.
	.	.		.	.	1.33 (1.11-1.59)	0.002	.
	.	.		.	.	1.89 (1.41-2.55)	<.001	.

Appendix Table 3.6: *Specific CDC-B and CDC-C (AIDS) events occurring in individuals on cART with undetectable viral load between 2000 and 2020.*

		All events		0-50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Aspergillosis, invasive pulmonary	9	0.3%	1	0.4%
	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis oropharyngeal	754	22.0%	60	26.7%
	Candidiasis vulvovaginal, frequent/persistent	54	1.6%	1	0.4%
	Cardiomyopathy, HIV-related	5	0.1%	0	0.0%
	Cardiomyopathy, with HIV-related component	14	0.4%	1	0.4%
	Cervical dysplasia	553	16.1%	7	3.1%
	Diarrhea, HIV-related >=30 days	63	1.8%	1	0.4%
	Fever e.c.i. / HIV-related	6	0.2%	0	0.0%
	HIV-associated nephropathy (HIVAN)	21	0.6%	2	0.9%
	Herpes zoster, multidermatomal	13	0.4%	0	0.0%
	Herpes zoster, recurring / multidermatomal unspecified	217	6.3%	8	3.6%
	Herpes zoster, unidermatomal recurrent	11	0.3%	2	0.9%
	Myelopathy, HIV-related	10	0.3%	0	0.0%
	Neuropathy, HIV-related	101	2.9%	1	0.4%
	Neuropathy, with HIV-related component	72	2.1%	1	0.4%
	Nocardiosis	2	0.1%	1	0.4%
	Oral Hairy Leucoplakia (OHL)	53	1.5%	1	0.4%
	Pelvic inflammatory disease	9	0.3%	0	0.0%
	Thrombocytopenia, HIV-related	101	2.9%	4	1.8%
	Thrombocytopenia, with HIV-related component	12	0.3%	2	0.9%
	Weight loss >10%, HIV-related / unknown cause	38	1.1%	1	0.4%
Subtotal		**2119**	**61.7%**	**94**	**41.8%**
CDC-C events	AIDS dementia complex - HIV encephalopathy	45	1.3%	4	1.8%
	Bacterial pneumonia, recurring	309	9.0%	13	5.8%
	CMV disease	19	0.6%	4	1.8%
	CMV esophagitis	2	0.1%	1	0.4%
	CMV retinitis	17	0.5%	4	1.8%
	Candidiasis lungs/bronchial/trachea	10	0.3%	2	0.9%
	Candidiasis esophagitis	233	6.8%	24	10.7%
	Cervical cancer, invasive	10	0.3%	1	0.4%
	Coccidioimycosis, extrapulmonary / disseminated	1	0.0%	0	0.0%
	Cryptococcosis, extrapulmonary / disseminated	16	0.5%	6	2.7%
	Cryptosporidiosis	10	0.3%	4	1.8%
	Cystoisosporiasis	1	0.0%	0	0.0%

CD4 category										
050–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
3	0.5%	0	0.0%	1	0.2%	2	0.3%	2	0.4%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
191	29.9%	151	21.0%	123	18.6%	136	18.4%	93	20.7%
5	0.8%	7	1.0%	17	2.6%	19	2.6%	5	1.1%
1	0.2%	1	0.1%	2	0.3%	0	0.0%	1	0.2%
3	0.5%	1	0.1%	2	0.3%	5	0.7%	2	0.4%
54	8.5%	125	17.4%	108	16.4%	152	20.5%	107	23.8%
4	0.6%	19	2.6%	12	1.8%	19	2.6%	8	1.8%
1	0.2%	2	0.3%	0	0.0%	1	0.1%	2	0.4%
4	0.6%	3	0.4%	4	0.6%	3	0.4%	5	1.1%
2	0.3%	4	0.6%	2	0.3%	2	0.3%	3	0.7%
25	3.9%	51	7.1%	44	6.7%	56	7.6%	33	7.3%
0	0.0%	0	0.0%	2	0.3%	3	0.4%	4	0.9%
4	0.6%	1	0.1%	1	0.2%	1	0.1%	3	0.7%
7	1.1%	16	2.2%	28	4.2%	29	3.9%	20	4.5%
8	1.3%	11	1.5%	15	2.3%	26	3.5%	11	2.4%
0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
14	2.2%	10	1.4%	10	1.5%	10	1.4%	8	1.8%
0	0.0%	4	0.6%	0	0.0%	3	0.4%	2	0.4%
18	2.8%	21	2.9%	21	3.2%	25	3.4%	12	2.7%
1	0.2%	4	0.6%	0	0.0%	4	0.5%	1	0.2%
5	0.8%	10	1.4%	6	0.9%	10	1.4%	6	1.3%
351	**54.9%**	**442**	**61.5%**	**398**	**60.3%**	**506**	**68.4%**	**328**	**73.1%**
7	1.1%	9	1.3%	11	1.7%	7	0.9%	7	1.6%
53	8.3%	73	10.2%	80	12.1%	62	8.4%	28	6.2%
3	0.5%	3	0.4%	6	0.9%	1	0.1%	2	0.4%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
4	0.6%	5	0.7%	3	0.5%	1	0.1%	0	0.0%
1	0.2%	4	0.6%	1	0.2%	1	0.1%	1	0.2%
54	8.5%	56	7.8%	37	5.6%	37	5.0%	25	5.6%
2	0.3%	1	0.1%	2	0.3%	4	0.5%	0	0.0%
0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
6	0.9%	2	0.3%	1	0.2%	1	0.1%	0	0.0%
0	0.0%	1	0.1%	3	0.5%	1	0.1%	1	0.2%
0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
	HIV wasting	16	0.5%	4	1.8%
	HSV chronic ulcer	23	0.7%	1	0.4%
	HSV pneumonitis	1	0.0%	0	0.0%
	Herpes simplex virus	62	1.8%	7	3.1%
	Histoplasmosis, extrapulmonary / disseminated	4	0.1%	3	1.3%
	Kaposi's sarcoma	113	3.3%	5	2.2%
	Leishmaniasis visceral	5	0.1%	1	0.4%
	Microsporidiosis	5	0.1%	1	0.4%
	Mycobacterium avium/kansasii, extrapulmonary / disseminated	21	0.6%	5	2.2%
	Mycobacterium avium/kansasii, pulmonary	3	0.1%	0	0.0%
	Mycobacterium other / unspecified, extrapulmonary / disseminated	8	0.2%	3	1.3%
	Mycobacterium other / unspecified, pulmonary	5	0.1%	0	0.0%
	Non-Hodgkin`s lymphoma (NHL)	148	4.3%	9	4.0%
	Pneumocystis jirovecii extrapulmonary	1	0.0%	0	0.0%
	Pneumocystis jirovecii pneumonia	68	2.0%	13	5.8%
	Primary CNS lymphoma	5	0.1%	1	0.4%
	Progressive multifocal leukoencephalopathy	18	0.5%	5	2.2%
	Toxoplasmosis of the brain	19	0.6%	5	2.2%
	Tuberculosis, extrapulmonary / disseminated	45	1.3%	2	0.9%
	Tuberculosis, pulmonary	70	2.0%	3	1.3%
Subtotal		**1313**	**38.3%**	**131**	**58.2%**
Total		**3432**	**100.0%**	**225**	**100.0%**

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

	CD4 category									
	050–199		200–349		350–499		500–749		750+	
	n	%	n	%	n	%	n	%	n	%
	8	1.3%	1	0.1%	2	0.3%	1	0.1%	0	0.0%
	3	0.5%	1	0.1%	2	0.3%	11	1.5%	5	1.1%
	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
	7	1.1%	12	1.7%	16	2.4%	15	2.0%	5	1.1%
	0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
	14	2.2%	23	3.2%	28	4.2%	31	4.2%	12	2.7%
	3	0.5%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
	3	0.5%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
	7	1.1%	5	0.7%	2	0.3%	2	0.3%	0	0.0%
	0	0.0%	1	0.1%	0	0.0%	1	0.1%	1	0.2%
	2	0.3%	2	0.3%	0	0.0%	1	0.1%	0	0.0%
	2	0.3%	0	0.0%	2	0.3%	1	0.1%	0	0.0%
	41	6.4%	32	4.5%	30	4.5%	25	3.4%	11	2.4%
	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
	29	4.5%	10	1.4%	9	1.4%	5	0.7%	2	0.4%
	1	0.2%	2	0.3%	1	0.2%	0	0.0%	0	0.0%
	7	1.1%	3	0.4%	2	0.3%	1	0.1%	0	0.0%
	7	1.1%	4	0.6%	2	0.3%	1	0.1%	0	0.0%
	9	1.4%	5	0.7%	8	1.2%	11	1.5%	10	2.2%
	14	2.2%	21	2.9%	14	2.1%	10	1.4%	8	1.8%
	288	**45.1%**	**277**	**38.5%**	**262**	**39.7%**	**234**	**31.6%**	**121**	**26.9%**
	639	**100.0%**	**719**	**100.0%**	**660**	**100.0%**	**740**	**100.0%**	**449**	**100.0%**

4. Viral hepatitis

Anders Boyd, Colette Smit, Bart Rijnders, Mark Claassen, Marc van der Valk

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% of the general Dutch population has evidence of exposure to HCV or HBV[1,2]. Infection with hepatitis D virus (HDV), which requires HBV infection, is even less common in the Netherlands and is more often found in individuals from specific, high-endemic regions (e.g., west/central Africa and eastern Europe)[3]. In contrast, HCV, HBV and HBV/HDV co-infections are far more prevalent in individuals living with HIV due to shared routes of transmission[4].

Individuals with chronic HCV and HBV infection are at risk of developing liver fibrosis, which, in time, may lead to cirrhosis and/or result in end-stage liver disease or hepatocellular carcinoma (HCC)[5,6]. Progression to severe liver disease takes, on average, 20 to 30 years in individuals mono-infected with HCV or HBV[7,8]. While progression of liver disease was faster in HIV co-infected people 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[9,10]. Meanwhile, co-infection with HBV-HDV is known to be highly associated with severe liver-related outcomes compared to HBV mono-infection[11], with accelerated progression to end-stage liver disease in individuals living with HIV, despite effective cART[12].

Infection with hepatitis A virus (HAV) or hepatitis E virus (HEV) is more frequent in the Netherlands compared to HBV and HCV. Both are transmitted by way of the intestine and can cause acute inflammatory liver disease that can usually resolve without treatment[13,14]. In the Netherlands, outbreaks of HAV infection are mostly observed in specific groups, such as men who have sex with men (MSM), with some onward transmission[15], whereas markers of previous HEV infection can be detected in roughly 10% of the general population[16]. HAV and HEV infections rarely cause death in adults, yet a small minority of individuals infected with HEV will develop chronic infection and/or damage to tissues/organs outside the liver (e.g., neuralgic amyotrophy, Guillain-Barre syndrome, meningoencephalitis, glomerulonephritis, and thrombocytopenia)[17]. HEV infection more commonly persists and develops into chronic infection in immunocompromised individuals, who are then at increased risk of developing ongoing symptoms[14].

This chapter reports on the demographic and clinical characteristics, severe chronic liver disease and mortality rates, and responses to treatment with regards to viral hepatitis infections in individuals living with HIV.

Hepatitis C virus (HCV)

Box 4.1: Definitions of hepatitis C infection.

Primary HCV infection
First documented HCV infection.

Chronic HCV infection
Individuals who remain HCV RNA-positive for longer than six months after their first known positive HCV RNA test result.

Acute HCV infection[18,19]

1. Case definition of acute HCV according to *preferred* criteria[18]:
   Positive anti-HCV IgG with a documented negative anti-HCV IgG within the past 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 past 12 months.
2. Case definition of acute HCV according to *alternative* criteria[18]:
   Detectable HCV RNA in association with a rise in alanine aminotransferase (ALT) (above 200 IU/l) with a documented normal ALT within the past 12 months.

Spontaneously-cleared HCV infection
Individuals with a documented positive test result for HCV antibody or RNA, a subsequent negative HCV RNA test result, and without a history of medical treatment. Spontaneous clearance was distinguished as either 'definitive' (two consecutive negative HCV-RNA test results after a positive HCV antibody or RNA test result), or 'possible' (one negative HCV-RNA test result following an earlier positive HCV antibody or RNA test result).

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 reinfection
Detectable HCV RNA after an earlier achieved SVR12 or SVR24, or after 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-documented 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 there is:
- a liver transplantation, or
- presumptive evidence, combined with a pathology, histology, or transient elastography report documenting severe liver fibrosis or cirrhosis (Metavir score F3-F4 or transient elastography stiffness ≥8kPa).

HCV screening over time

In the Netherlands, the national guidelines for the treatment and monitoring of HIV recommend HCV screening during the first clinical visit after HIV diagnosis, and additional annual HCV screening for MSM who report HCV-related risk-taking behaviour[20]. Screening for HCV infection among the individuals living with HIV ever registered with SHM has increased over calendar time. Ninety-six percent of the 28,223[a] individuals living with HIV ever registered in the SHM database have been screened at least once for HCV; anti-HCV or HCV RNA. In 2000, 27% of the individuals living with HIV in care had never been screened for the presence of HCV infection in that specific calendar year. However, over time, a strong and steady increase in the percentage of individuals with a known HCV status has been observed, and, in 2020, only 1.6% of the individuals in care had never been screened for HCV co-infection (*Figure 4.1A*). In 2020, unknown HCV status was relatively more common among individuals with heterosexually-acquired

a *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.*

HIV (3.0%), or with another or unknown mode of HIV acquisition (4.5%), and relatively less common among MSM (0.8%) and people who inject drugs (PWID) or former PWID (0.4%).

Follow-up screening

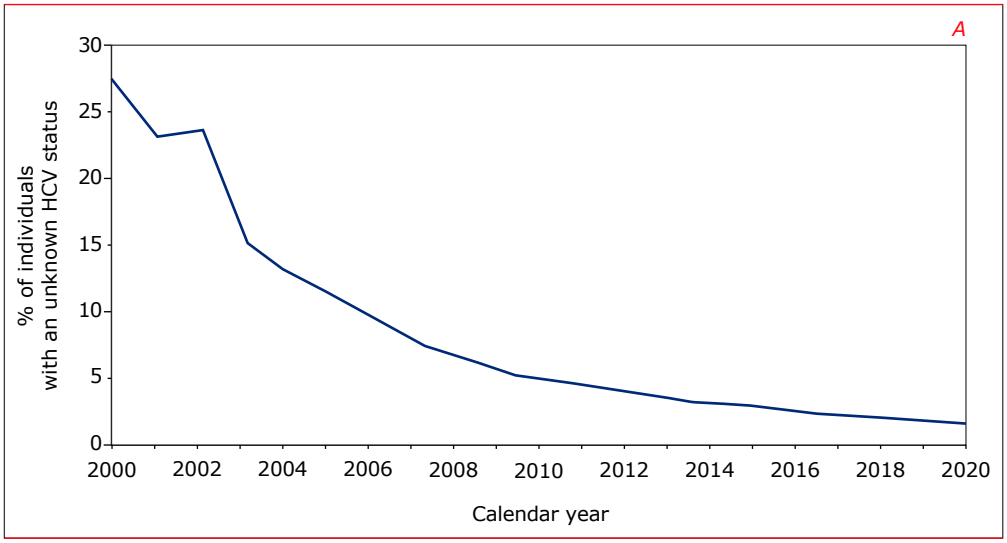
Among individuals who had a negative first HCV test and who remained in care, 77% had a second HCV test at some point during follow up. This proportion was highest for MSM, of whom 86% had at least a second HCV test, and lowest for individuals who acquired HIV through heterosexual contact (61%).

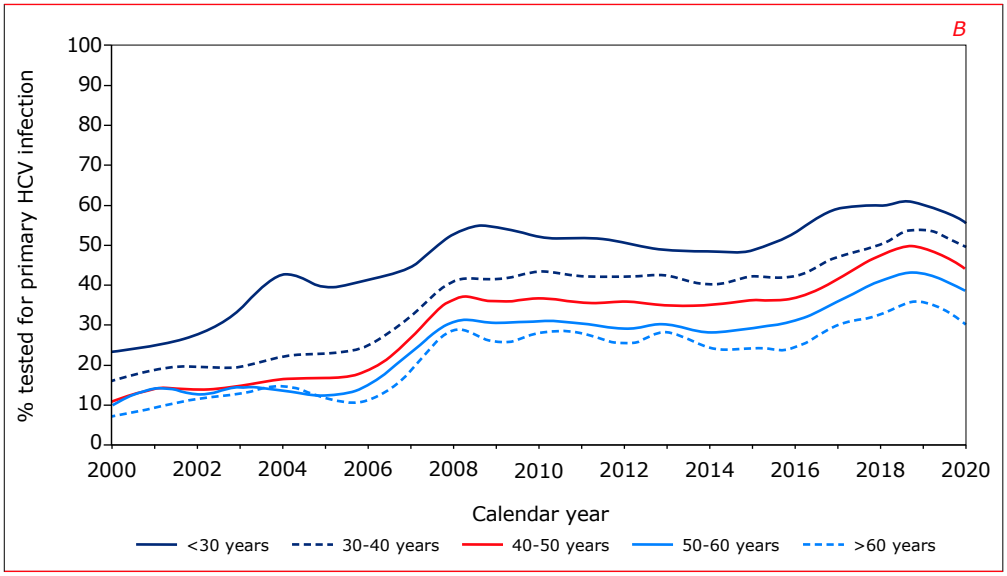
Most HCV infections are observed among MSM[21]; therefore, the following analysis on testing frequency is reported for MSM only. Overall, the percentage of HCV seronegative MSM with at least one HCV test in a calendar year increased over time, from 13% in 2000 to 27% in 2007, and 48% in 2019. However, testing frequency among HCV seronegative MSM decreased to 40% in 2020. When testing was stratified by age, the highest percentage of testing was seen among MSM under 30 years of age, and testing decreased with increasing age (*Figure 4.1B*). Nevertheless, the median age for diagnosis of acute HCV was 43 years (IQR 36-39) (*Table 4.2*), while in the age range 40-50 years, 51% and 44% had at least one test in 2019 and 2020, respectively. Although reasons for screening or lack of screening are unknown, the lower testing frequency in 2020 may be related to the COVID-19 pandemic, which led to a reduction in services at many of the HIV treatment centres (*Chapter 7*).

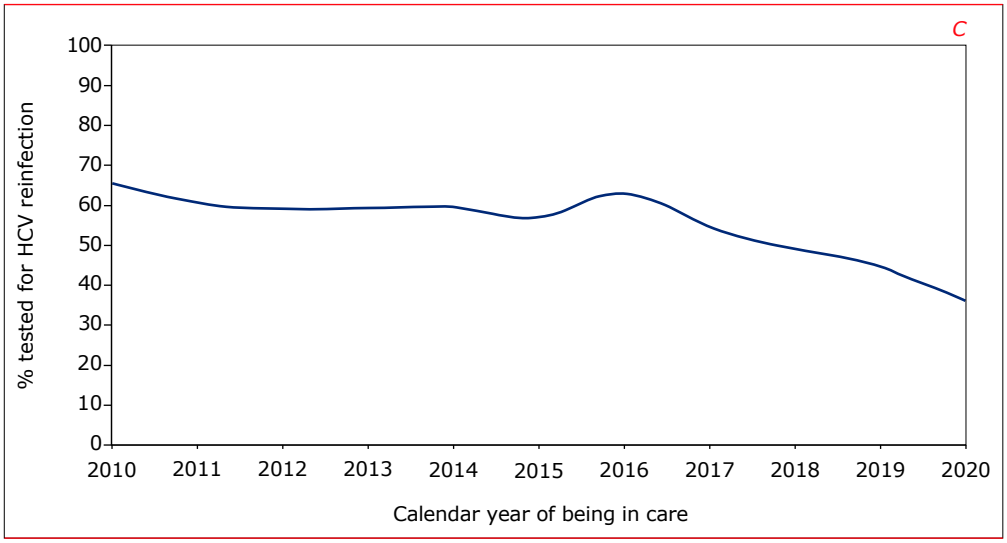
Screening for HCV RNA among those at risk of HCV reinfection is an important factor in identifying HCV reinfection. Among MSM living with HIV at risk of reinfection after treatment-induced, or spontaneous clearance of HCV, the percentage of men with an HCV RNA test during a calendar year varied between 55% and 66% in 2010-16, but declined to 45% in 2019, and 36% in 2020 (*Figure 4.1C*). It is worth noting that these data may include MSM who are not considered at risk of HCV reinfection by their treating physician, as data on HCV-related risk-taking behaviour are not available to SHM. Also of note, is that repeated HCV screening among MSM at risk of HCV reinfection might be guided by a policy of targeted screening, based on the presence of incident transaminase elevations as an indicator of liver damage. This might be reflected by the observed higher proportion of repeated HCV screening among MSM with elevated transaminase levels. In those at risk of HCV reinfection and incident transaminase elevations, the overall percentage of men with an HCV test following this elevated transaminase level was 71% in 2012-2020[b]; unlike the observed decrease in testing in the total population of MSM at risk of reinfection, the testing frequency after an elevated transaminase level was higher in 2020 compared to 2019 (*Figure 4.1D*).

b *Transaminase data became routinely available from 2012 onwards.*

Figure 4.1: *(A) The percentage of individuals in care with an unknown hepatitis C status per calendar year of care, (B) the percentage of men who have sex with men (MSM) who were susceptible to primary HCV infection with an HCV test, stratified by age, (C) the percentage of MSM at risk of HCV reinfection with an HCV RNA test, and (D) the percentage of MSM at risk of HCV reinfection with an HCV RNA test following an incident elevated transaminase level.*






C
% tested for HCV reinfection
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90
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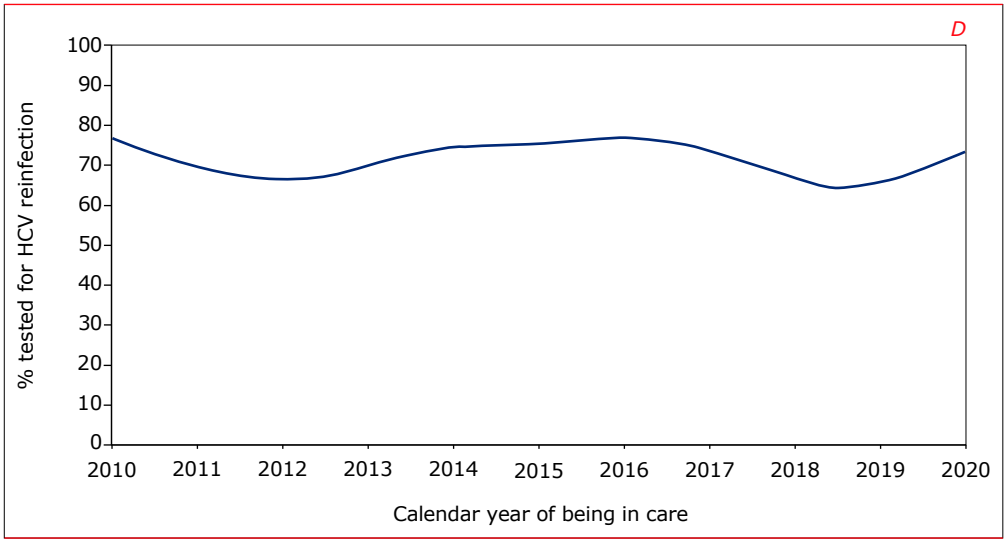
Calendar year of being in care


D
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2019
2020
Calendar year of being in care

HCV-positive individuals

As of May 2021, 28,223 HIV-1-positive adults (aged 15 years or older at the time of their HIV-1 diagnosis) had been registered by the stichting hiv monitoring (SHM). Of those individuals, 26,984 (96%) were ever screened for HCV co-infection and had been in care at one of the HIV treatment centres in the Netherlands: 3,051 (11%) had a positive result with an HCV antibody test and/or HCV RNA test. This confirms that HCV is far more prevalent among the population living with HIV than is estimated for the general Dutch population (*Figure 4.2*). HCV RNA data were not documented in 169 of the 3,051 cases (6%). Of these 169 individuals, 115 have died, 25 have been lost to care, and 11 have moved abroad; the reason for an undocumented HCV RNA in the remaining 18 individuals is unknown.

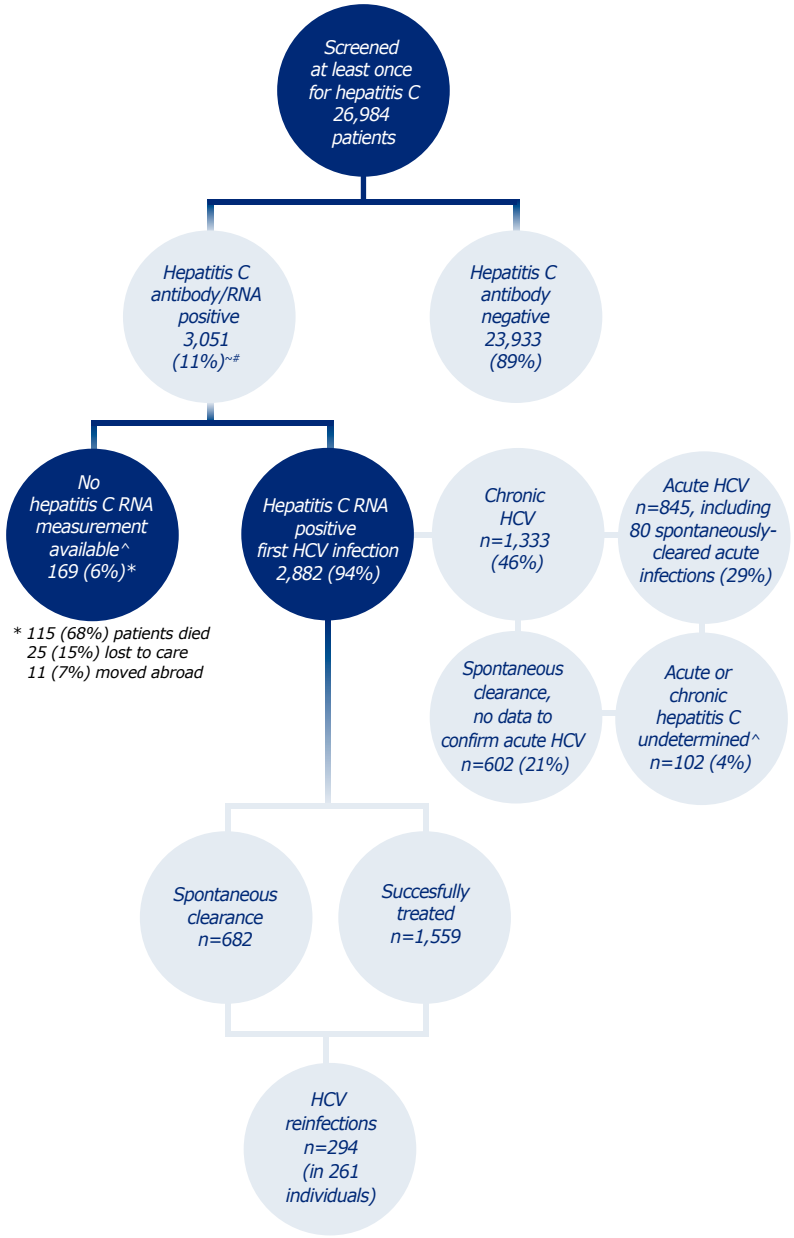
In total, 2,882 individuals were diagnosed with an HCV infection, confirmed by documented HCV RNA data:

- 845 (29%) were initially diagnosed with an acute HCV infection:
  - 80 spontaneously cleared their infection
  - 765 became chronic HCV infections, or were treated within six months of diagnosis.
- 1,333 (46%) were classified as having a chronic HCV infection at the time of their diagnosis.
- 602 (21%) had evidence of spontaneous clearance of HCV but could not be classified as having an acute HCV infection at the time of their HCV diagnosis.

The remaining 102 individuals 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 has therefore been excluded from the analysis. The majority (n=92) of individuals with no HCV follow-up data were no longer in care in 2020.

In total, 1,559 of the individuals with a primary HCV infection had a treatment-induced clearance of their primary HCV infection (including old and new treatment regimens). Another 682 individuals spontaneously cleared their primary HCV infection. In total, 294 HCV reinfections after clearance occurred in 261 individuals. The majority (75%) of those with a primary infection who are not at risk of an HCV reinfection (i.e., those without SVR or spontaneous clearance of HCV) are no longer in care. The paragraph describing the continuum of HCV care gives more detail on those who remain in care, without clearance of their HCV infection.

Figure 4.2: Flowchart of individuals living with HIV tested at least once for hepatitis C virus (HCV).



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

Spontaneous clearance of HCV

In total, 682 individuals spontaneously cleared their HCV infection. Among the 845 individuals with primary acute hepatitis, 80 (9%) cases of spontaneous clearance were observed. Another 602 cases of spontaneous clearance were observed among individuals who could not be classified as having a primary acute infection. Compared to all individuals with HCV co-infection, those with spontaneous clearance of HCV were more likely to be female, less likely to be Dutch, and more likely to be from sub-Saharan Africa (p<0.001) (*Table 4.1*).

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, 1998-2020.*

	Total HCV co-infected	Spontaneous clearance
Total number of individuals	2,780	682 (25)
Age at HCV diagnosis (median, IQR)	40 (34-47)	41 (35-48)
HCV status		
Chronic HCV	1,333	
Acute HCV	765	
Definitive clearance	274	274
Possible clearance	328	328
Spontaneous clearance after confirmed primary acute infection	80	80
Male gender, n (%)	2394 (86)	557 (82)
Region, n (%)		
Netherlands	1694 (61)	354 (52)
Europe	358 (13)	89 (13)
Sub-Saharan Africa	120 (4)	61 (9)
Caribbean/South America	214 (8)	74 (11)
Southeast Asia	88 (3)	24 (4)
Other	306 (11)	80 (12)
HIV transmission route, n (%)		
Men who have sex with men	1,634 (59)	370 (54)
Heterosexual	310 (11)	116 (17)
People who use/used injecting drugs	579 (21)	124 (18)
Other	257 (9)	72 (11)
cART, n (%)	2696 (97)	657 (96)
Deaths, n (%)	479 (17%)	106 (16)

Demographic characteristics of individuals with acute or chronic HCV infection at the time of HCV diagnosis

In total, 2,178 individuals could be definitively classified as having either chronic (n=1,333), or acute (n=845) HCV infection at the time of their primary HCV diagnosis. Most of these were male (81% and 99%, respectively), and the majority originated from the Netherlands (chronic: 751/1,333 [57%]; acute: 646/845 [76%]) (*Table 4.2*). Fifty-eight percent of the registered individuals who acquired HIV through injecting drug use (IDU), had a chronic HCV infection (449 of the total 773 PWID or former PWID). In the MSM HIV transmission group (16,432), 3% (546) had a chronic HCV infection and 5% (794) had a documented acute HCV infection.

The HCV genotype was determined and documented in the clinical records of 1,198 of the 1,333 (96%) individuals with a chronic HCV infection. Of the individuals with a genotype determination, the majority (62%, n=742) were infected with HCV genotype 1; 61% (n=451) with genotype 1a, and 14% (n=101) with genotype 1b. For 25% of the people infected with genotype 1, the subtype was not further specified. Five percent (n=59) were infected with HCV genotype 2, 17% (n=209) with genotype 3, and 16% (n=186) with genotype 4. One person was infected with genotype 5 and one with genotype 6.

HCV genotype was also documented for 739 of the 845 (88%) individuals with an acute HCV infection. They were most likely to be infected with either genotype 1 (72%, n=529) or genotype 4 (21%, n=155). Of the 529 infected with genotype 1, 84% (n=445) were infected with genotype 1a and 5% (n=23) with genotype 1b. For 14% of the people infected with genotype 1, the subtype was not further specified.

Table 4.2: Demographic characteristics of individuals co-infected with HIV/hepatitis C virus (HCV) registered in the SHM database, 1998-2020.

	Total	Chronic HCV	Acute HCV
Total number of individuals screened for HCV	26,984	1,333 (5)	845 (3)
Age at baseline (median, IQR)	40 (34-47)	39(33-45)	43 (36-49)
Male gender, n (%)	22,123(82)	1,078 (81)	838 (99)
Region of origin, n (%)			
Netherlands	14,809 (55)	751 (57)	646 (76)
Europe	1,802 (7)	207 (16)	69 (8)
Sub-Saharan Africa	3,636 (13)	49 (4)	11 (1)
Caribbean/South America	3,370 (12)	91(7)	52 (6)
Southeast Asia	960 (4)	44 (3)	24 (3)
Other	2,407 (9)	191 (14)	43 (5)
HIV transmission route, n (%)			
Men who have sex with men	16,432 (61)	546 (41)	794 (94)
Heterosexual	7,993 (30)	169 (13)	27 (3)
People who use/used injecting drugs	773 (3)	449 (34)	8 (1)
Other	1749 (6)	167 (12)	16 (2)
cART, n (%)	26,110 (97)	1,278(96)	841 (99)
HCV genotype (GT), n (%*)			
Total determined		1,198 (89)	739(87)
GT 1		742 (62)	529(72)
1a		451	445
1b		101	23
1c, 1a/b or not further specified		190	61
GT 2		59 (5)	38 (5)
GT 3		209 (17)	16 (2)
GT 4		186 (16)	155 (21)
GT 5 or 6		2 (0.1)	1 (<1)
Deaths, n (%)	3,067 (11)	333 (25)	45 (5)

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

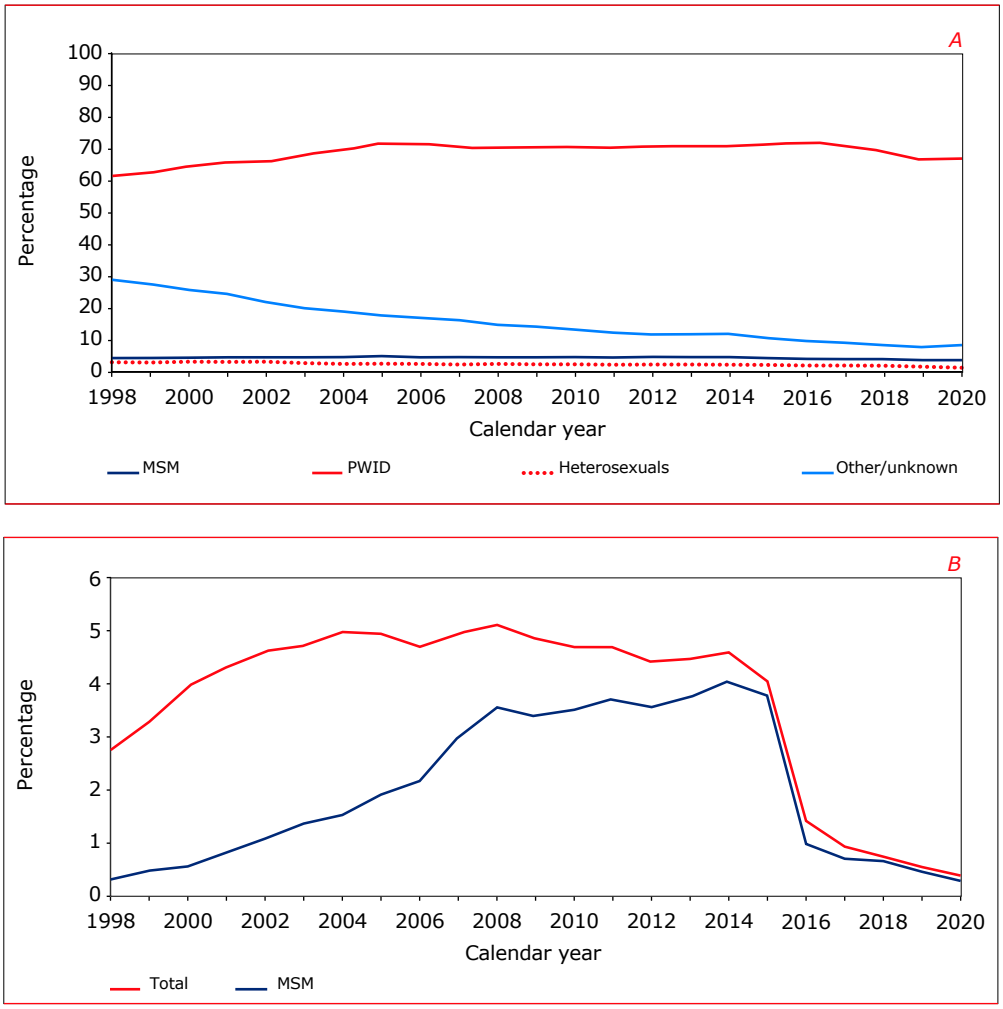
***Legend:** n=total for each category; (%)=percentage of the total for each column; HCV=hepatitis C virus; cART=combination antiretroviral therapy; GT=genotype.*

Changes over time

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 individuals living with HIV ever registered, decreased from 11.2% in 1998 to 4.3% in 2020, 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.*



Legend: *MSM: men who have sex with men; PWID: people who use/used injecting drugs.*

Prevalence of individuals with detectable HCV RNA

Figure 4.3B shows the percentage of individuals with a positive HCV RNA over calendar time. Individuals contributed follow-up time to the analysis if they were in care in a specific calendar year. The HCV RNA positivity was based on a last available HCV RNA test result before the end of that calendar year. The overall percentage of individuals with detectable HCV RNA varied between 2.7% in 1998 and 5.1% in 2008, before dropping to 0.4% in 2020. In MSM, the highest percentage of HCV RNA positivity was 4% in 2014; by 2020, the percentage of positive HCV RNA tests in this group had decreased sharply to 0.29%.

Incidence of new HCV infections over time

The incidence of primary infection is calculated for individuals with a first documented HCV infection, based on the date of their first positive HCV antibody or HCV RNA test result. This paragraph describes the incidence of acute HCV infection, including only cases of primary acute HCV infection (first diagnosis of HCV). The definition of acute HCV infection is consistent with the one given in the European AIDS Treatment Network (NEAT) preferred criteria[18]. We have also expanded this definition to include alternative criteria[18,19]. 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 (above 200 IU/l), and a documented normal ALT within the past 12 months, together with no change in antiretroviral regimen in the last six months. As SHM has only routinely collected ALT levels since 2012, incidence rates based on the alternative criteria are reported from 2012 onwards.

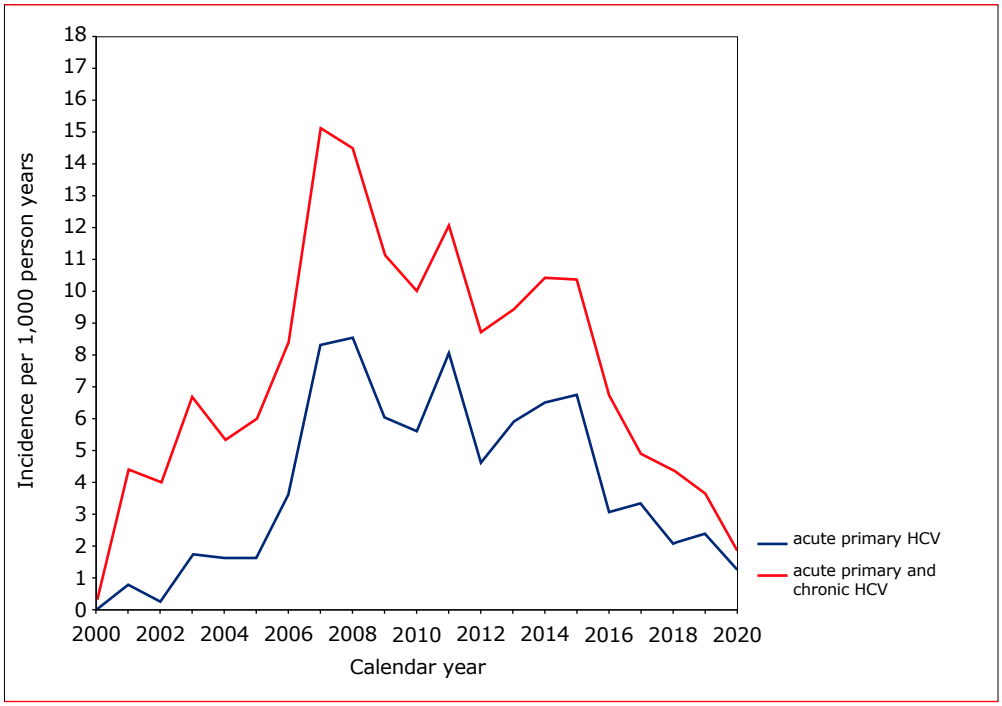
There were important differences in the incidence of the first diagnosis of acute HCV infection in terms of HIV transmission category. The vast majority of acute HCV infections occurred in MSM (n=794/845 [94%]). In contrast to the high prevalence of HCV in PWID or former PWID, the overall incidence of acute HCV in this group was low, occurring in only eight cases. This is probably due to the high background prevalence of HCV infection in former PWID, the fact that injecting drug use has become very uncommon in the Netherlands, and the effective harm-reduction programmes implemented in addictive care centres in the Netherlands. Twenty-seven cases occurred among individuals who had acquired HIV hetero-sexually.

Figure 4.4 shows both the incidence of acute primary HCV infection and all primary HCV diagnoses among MSM over time. The overall rate of primary HCV infection was 7.7 per 1,000 person years (PY) (95% CI 7.3-8.1). The incidence of primary infection increased from 0.28 (95% CI 0.01-1.58) to a peak of 15.1 (CI 12.3-18.4) in 2007

and decreased to 1.8 (CI 1.1-2.9) in 2020. When including those with an acute HCV infection, the overall rate of acute HCV infection among MSM was 4.2 per 1,000 PY (95% CI 3.9-4.5). When the preferred NEAT acute HCV definition was used, the incidence increased from 0 diagnoses per 1,000 PY in 2000, to a peak of 8.3 and 8.5 per 1,000 PY in 2007 and 2008, respectively. By 2015, the incidence was 6.8 diagnoses per 1,000 PY. It then declined to 3.0 in 2016, before further decreasing to 1.3 diagnoses per 1,000 PY in 2020.

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, 3.9 in 2016, and 1.5 in 2020.

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.*



Legend: *HCV=hepatitis C virus.*

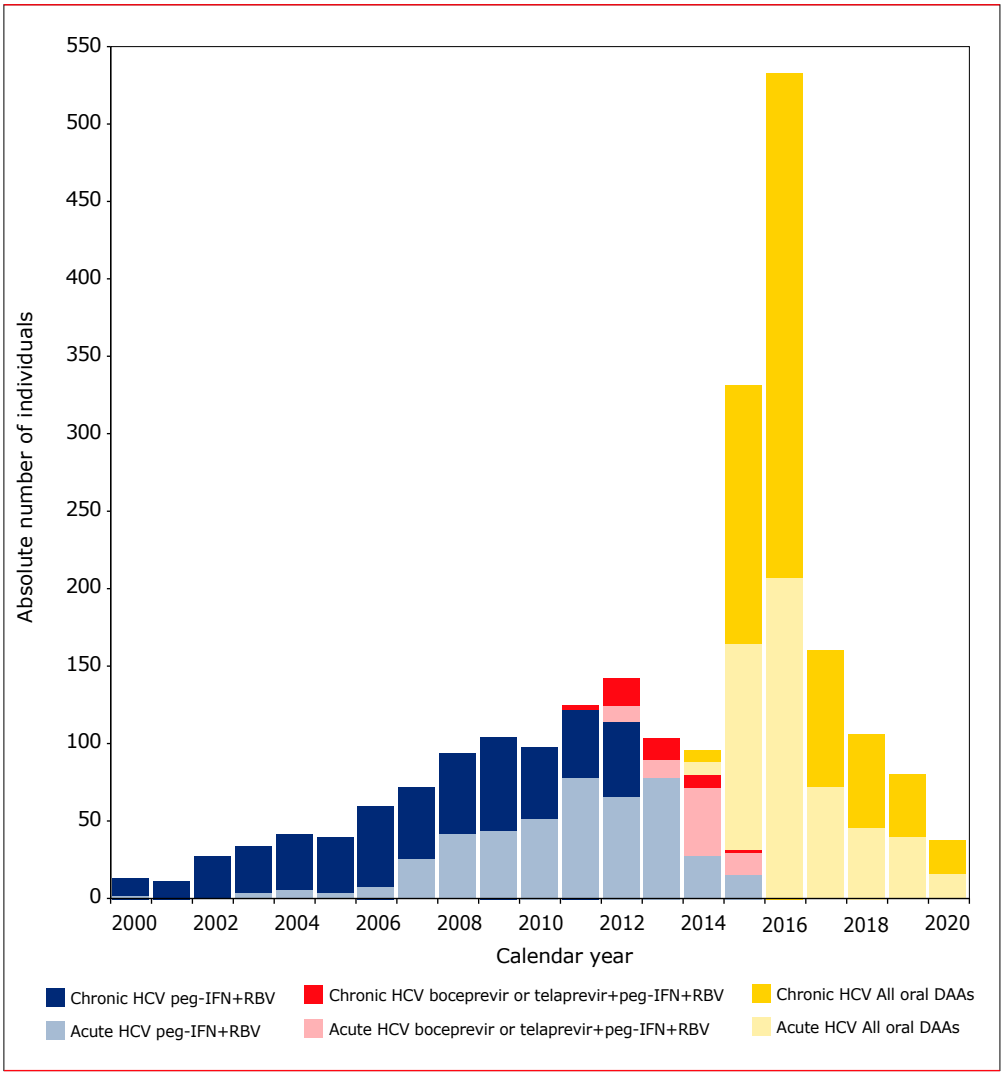
Treatment for HCV infection

The primary aim of HCV treatment is to achieve a sustained virological response (SVR)[22] and the treatments used have 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.

In April 2012, the first generation HCV NS3/4a protease inhibitors (PI) boceprevir and telaprevir, DAAs active against HCV genotype 1, became available in the Netherlands[23,24]. These agents were subsequently used as part of triple therapy that included one of those two agents, together with PEG-IFN alpha and RBV. In 2014, the HCV NS5B polymerase inhibitor sofosbuvir was introduced in the Netherlands. Initially, due to government restrictions, sofosbuvir was only reimbursed for a defined group of individuals with severe liver fibrosis and cirrhosis. In November 2015, sofosbuvir was made available for all individuals chronically infected with HCV, regardless of fibrosis state. Shortly thereafter, additional novel DAAs became available, such as new HCV NS3/4A protease inhibitors (simeprevir, paritaprevir, grazoprevir, glecaprevir, and voxilaprevir); 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. Of the individuals ever diagnosed with a primary chronic or acute HCV infection, or a reinfection, 1,769 have ever received HCV treatment; of those, 546 have received HCV treatment more than once (this includes people who were unsuccessfully treated and those who reacquired HCV after prior successful treatment). In total, 955 regimens with (peg-)interferon+RBV, 125 regimens with first generation PI, and 1,235 regimens with all oral DAAs were documented.

Figure 4.5: Number of HIV/HCV co-infected individuals starting hepatitis C treatment per calendar year, according to acute or chronic HCV infection at the time of diagnosis.



Legend: HCV=hepatitis C virus; 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 PEG-IFN-based regimens was described in detail in SHM's 2016 Monitoring Report[25]. 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 2021, 1,121 individuals were known to have started a DAA regimen; 100 of those had been treated more than once with a DAA regimen with, in total, 1,235 treatment episodes. The most common reasons for receiving DAA treatment more than once were: reinfection after earlier DAA treatment-induced clearance (n=52), and no SVR or discontinuation of first DAA treatment episode due to a lack of early virological response (n=29), or toxicity (n=6). Of the total 1,235 DAA treatment episodes, 17 occurred in 2014, 301 in 2015, and 532 in 2016. The number of treatment episodes has subsequently decreased to 38 in 2020 (*Figure 4.5*).

The most frequently used DAA regimens were 1) sofosbuvir plus ledipasvir +/- RBV (n=576); 2) sofosbuvir plus daclatasvir +/- RBV (n=253); and 3) pibrentasvir/glecaprevir (n=106). This last regimen was the one most commonly used in 2020. Forty-seven individuals who had previously been treated with DAAs are known to have died. The causes of death included liver disease (n=7), non-AIDS-defining malignancies (n=12), cardiovascular disease (n=5), non-AIDS-defining infection (n=4), and non-natural death (n=5). The remaining deaths (n=14) were related to alcohol and substance use, AIDS, lung disease, or the cause was unknown. The paragraph on mortality gives more details on mortality causes over time, including liver-related mortality.

Treatment outcomes

HCV RNA data were collected up to 1 May 2021. At that point, 1,178 out of 1,235 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 1,143 of the 1,178 treatment episodes (97%), SVR12 was achieved.
- No SVR was achieved in 29 treatment episodes among 27 individuals.
- For the remaining six treatment episodes, no follow-up data on SVR were available: three people died shortly after being treated, and there were no reported HCV RNA tests available to assess treatment outcome in three of the cases.

SVR rates were comparable for individuals who received HCV treatment for the first time and those with prior HCV treatment or severe liver disease. Higher SVR rates were found among MSM (98%), than among PWID or former PWID (93%), and individuals who acquired HIV through heterosexual contact (96%). Furthermore, no specific differences in SVR rates were observed regarding CD4 cell counts and HIV RNA at the time of DAA initiation.

Among the 27 individuals who did not achieve SVR:
- 17 were successfully retreated with a DAA regimen,
- eight were not retreated, and
- two were unsuccessfully retreated.

HCV reinfection

Reinfection with HCV following successful treatment or spontaneous clearance has been reported mainly in MSM living with HIV[26,27], with high rates of reinfection found among MSM in the Netherlands, Germany[28], and the United Kingdom[29].

To identify possible HCV reinfection among previously HCV co-infected individuals, we selected people who initially achieved an SVR after receiving any type of HCV treatment, and individuals with spontaneous clearance of HCV.

In total, 2,241 individuals were susceptible for HCV reinfection (1,559 after SVR, 682 after spontaneous clearance).

Of those 2,241 individuals, 294 reinfections among 261 individuals (12%) were documented: 179 after SVR and 115 after spontaneous clearance. The median time between SVR and HCV reinfection was 1.7 years (IQR 1.0-3.2), and between spontaneous clearance and reinfection it was 1.3 years (IQR 0.5-3.1).

Most individuals who became reinfected were MSM (225/261, 86%). Another 25 were PWID or former PWID (25/261, 10%). For the remaining 11 individuals, documented HIV transmission routes were heterosexual contact (three), blood-blood contact (three), and unknown (five).

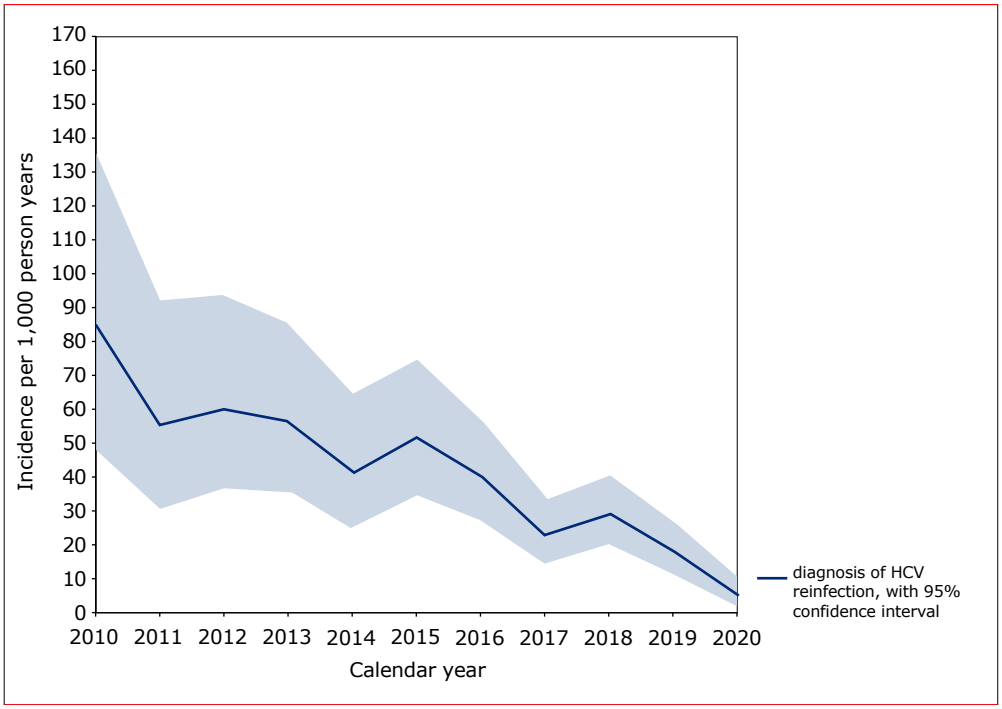
Of the 294 reinfections, 259 (88%) were retreated (193 with DAA, 66 with interferon+/-boceprevir/telaprevir) The median time to retreatment after reinfection diagnosis, stratified by calendar year of reinfection, was:
- Prior to 2015: 27.5 months (IQR 4.1-64.3).
- 2015-17: 3.1 months (IQR 1.6-7.6).
- From 2018: 2.5 months (IQR 1.5-4.0).

We calculated the incidence of reinfection between 2010 and 2020. Follow-up time was from the date of SVR, date of spontaneous clearance, or from 1 January 2010 onwards, until the earliest date of HCV reinfection, death, or last known contact.

The incidence of HCV reinfection for the total population was 23 reinfections per 1,000 PY (95%, confidence interval [CI] 20-26), and for MSM it was 31 reinfections per 1,000 PY (95%, CI 27-36).

Because most reinfections occurred among MSM, the incidence of HCV reinfection after achieving an SVR over time is shown only for MSM (*Figure 4.6*). This incidence decreased from 84 reinfections per 1,000 PY in 2010 to 52 in 2015, and then declined to 18 reinfections per 1,000 PY in 2019, and five in 2020. A stable decline in the incidence of reinfection in MSM has been seen since 2018. However, the effect of testing on the incidence of HCV reinfection cannot be completely excluded. Although HCV RNA testing after incident transaminase elevations showed an increase (*Figure 4.1D*), also during the beginning of the COVID-19 pandemic, the overall frequency of HCV RNA testing in MSM susceptible of reinfection has decreased (*Figure 4.1C*).

Figure 4.6: Incidence of hepatitis C reinfection after earlier treatment-induced clearance among men who have sex with men, per calendar year.



Note: numbers in 2020 may be affected by a delay in data collection.
Legend: HCV=hepatitis C virus.

Continuum of care for those with diagnosed HCV co-infection

Figure 4.7 shows the HCV continuum of care, based on the number of people known to be in HIV care as of 31 December 2020. Individuals were categorised according to their last documented HCV infection episode. In total, 2,161 individuals were linked to HIV care, 1,900 individuals had a primary HCV infection, and 261 individuals had a reinfection. Of those 2,161 individuals, 1,528 (71%) were retained in care, while 633 individuals were no longer in care (374 had died, 139 had moved abroad, and 120 were lost to care). Of those still alive and in care, 1,464 (96%) had received treatment for HCV (with DAAs or a pegylated interferon-containing regimen), and 1,420 (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, 1,413 of the 1,420 people who completed treatment (99%) had achieved an SVR, including those who had achieved an SVR on a pegylated interferon-containing

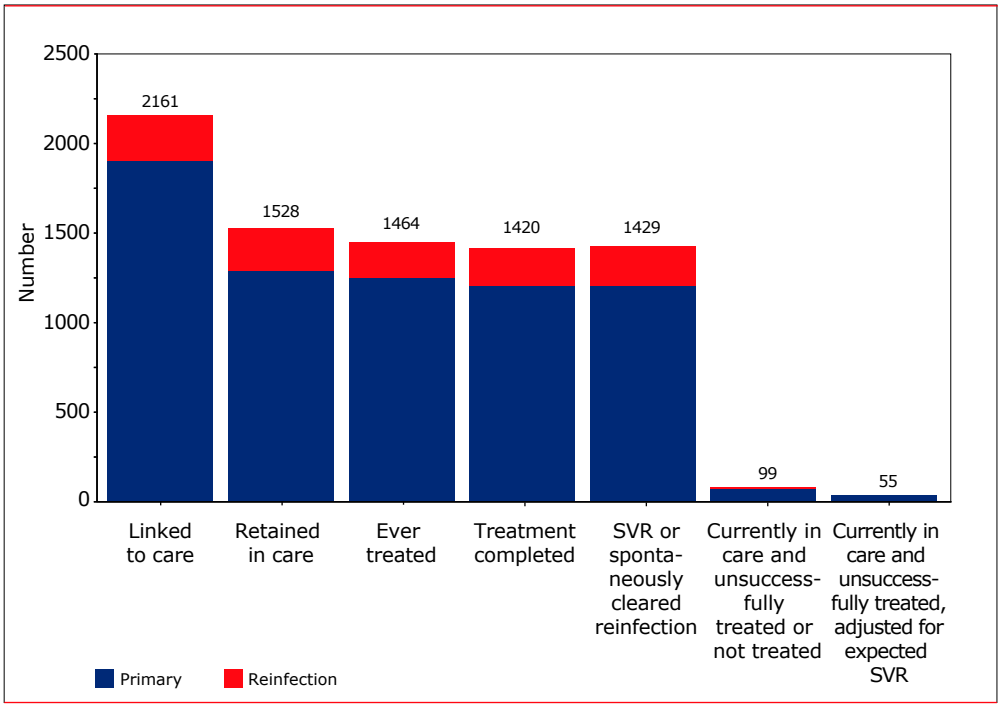
regimen and those who were retreated after earlier treatment failure. Another 16 individuals with HCV reinfection had a negative last HCV RNA test result, without documentation of HCV treatment. It is likely they spontaneously cleared their HCV infection, bringing the total of individuals with a treatment-induced or spontaneous clearance of their most recent HCV episode to 1,429.

As a result, 99 (6%) of the 1,528 individuals known to be alive and in care in one of the Dutch HIV treatment centres on 31 December 2020 were still in need of HCV treatment:

- 48 individuals had never been treated for HCV. The percentage untreated was higher among PWID (7%), people who acquired HIV through heterosexual contact (8%), and people with an unknown HIV transmission mode (7%), than among MSM (2%).
- Six had been unsuccessfully treated for HCV, including those who did not achieve an SVR on a pegylated interferon-containing regimen.
- 45 were still being treated or had insufficient time after treatment discontinuation to allow SVR calculation.

Of the 45 individuals for whom SVR could not yet be calculated, all had been treated with novel DAA combinations. For that reason, we have extrapolated the observed DAA SVR rate for these individuals and assumed that 44 of the 45 (97%) will achieve SVR. This results in a more realistic estimate of individuals (99-44=55) who have yet to be treated or were unsuccessfully treated.

Figure 4.7: Hepatitis C continuum of care.



Legend: SVR=sustained virological response.

Liver-related morbidity

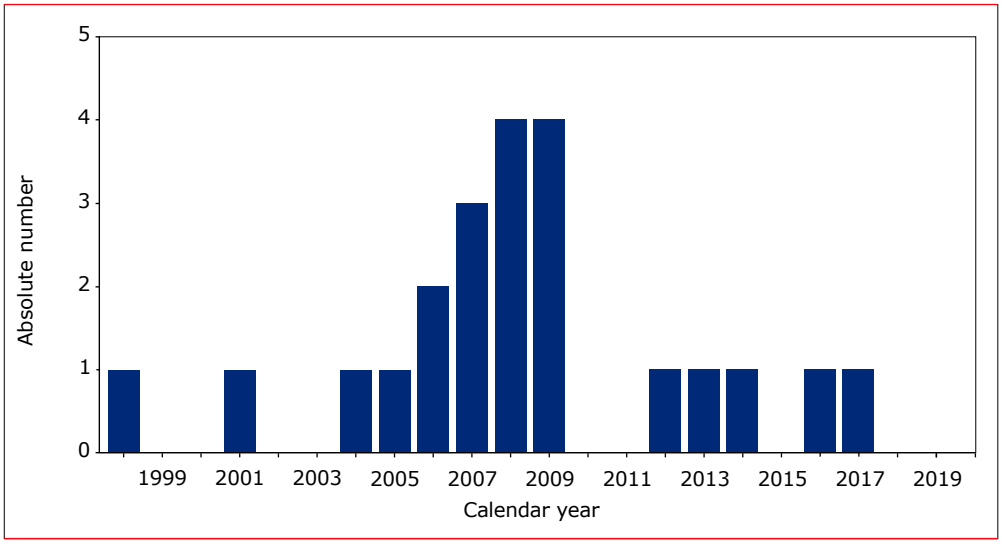
Data on liver-related morbidity are collected for all individuals living with HIV in follow up in the ATHENA cohort. In total, 1,149 cases of severe liver disease, according to our definition, were considered to be present (presumptive and definitive categories combined): 514 among individuals with HCV co-infection, 273 among individuals with HBV co-infection, 42 among individuals coinfected with HBV and HCV, and 404 among individuals living with HIV without documented HCV or HBV co-infection. This chapter reports on clinical characteristics and severe chronic liver disease with regards to HCV and/or HBV infection in individuals living with HIV; therefore, further analyses in this section are limited to those with viral hepatitis.

Liver-related morbidity in HCV

Additional data from liver biopsy pathology reports, transient elastography, radiology reports, or a combination of those sources, were available for 1,753 of the 2,098 individuals with HCV co-infection. Review of these additional data show that severe chronic liver disease was considered to be present (presumptive and definitive categories combined) in 514 (24%) of the individuals with HCV co-infection, and 29% of those with additional liver-related data. Definitive severe chronic liver disease was documented for 120 (7%) individuals with an HCV co-infection.

In total, 22 cases of hepatocellular carcinoma (HCC) were reported among individuals with HCV co-infection. *Figure 4.8* shows that the annual number of new HCC diagnoses declined from 2010 onwards. In 1998-2020, HCC was diagnosed in 22 of the 2,098 individuals (1.0%) with an HCV co-infection; 16 of those 22 were born in the Netherlands.

Figure 4.8: *Absolute number of annually-reported HCC cases among HCV co-infected individuals over time.*

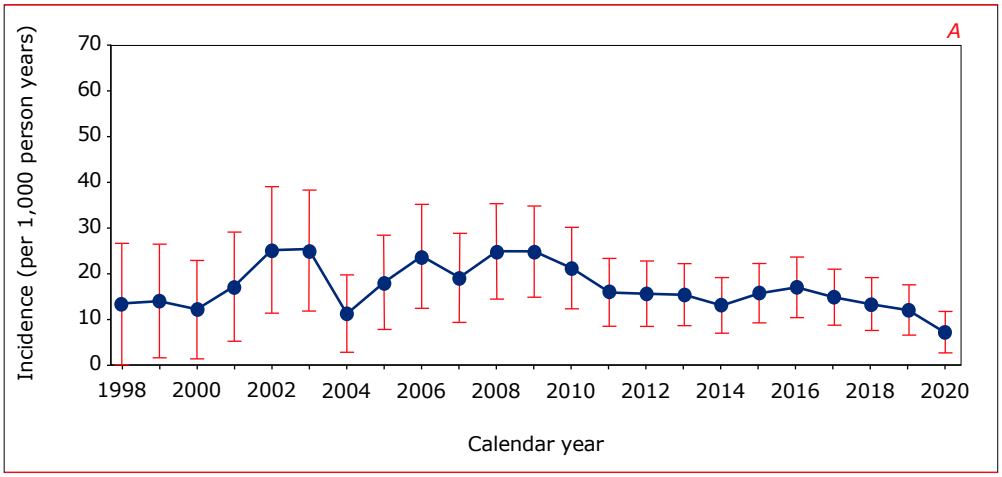


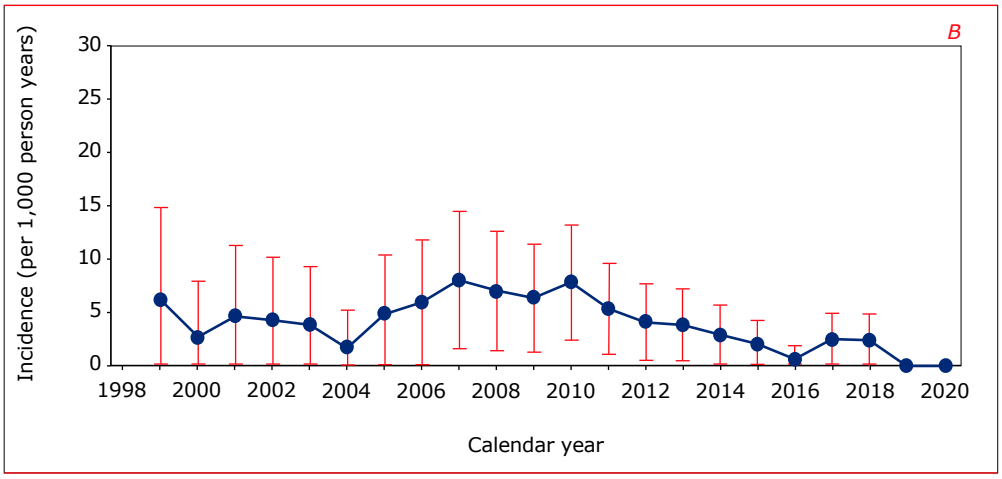
Mortality

All-cause mortality

Among the 2,098 individuals with an HCV infection, 18% died from any cause. For individuals with HCV infection, the incidence rate of death from any cause, adjusted for age and gender of the SHM population, was 17.2/1,000 PY in 1998-2002, 20.6 in 2003-11 and 13.9 from 2012 onwards (*Figure 4.9A*). In MSM with HCV infection, these incidence rates were 5.3/1,000 PY in 1998-2002, 8.9 in 2003-11, and 5.0 from 2012 onwards. In PWID with HCV infection, these incidence rates were 19.4/1,000 PY in 1998-2002, 38.4 in 2003-11, and 44.0 from 2012 onwards.

Figure 4.9: *Annual: (A) all-cause mortality rate, and (B) mortality related to liver disease (adjusted for age and gender of the SHM population), in 2,098 HIV-1-positive individuals who were ever diagnosed with an acute or chronic HCV infection.*





Note: *Individuals with acute or chronic HCV infection could be co-infected with HBV.*

Liver-related mortality

In total, 76 (4%) individuals co-infected with HCV died of a liver-related cause between 1998 and 2020. Other important causes of death among individuals with an HCV co-infection were non-AIDS malignancies (3%), AIDS (2%), and cardiovascular diseases (2%).

For individuals with HCV infection, the incidence rate of death from a liver-related cause, adjusted for age and gender of the SHM population, was 3.8/1,000 PY in 1998-2002, increasing to 5.9 in 2003-11, and decreasing to 2.0 from 2012 onwards (*Figure 4.9B*). In MSM with HCV infection, these incidence rates were 0/1,000 PY in 1998-2002, 3.5 in 2003-11, and 0.8 from 2012 onwards. In PWID with HCV infection, these incidence rates were 2.6/1,000 PY in 1998-2002, 8.5 in 2003-11, and 4.1 from 2012 onwards.

Hepatitis B virus (HBV)

Box 4.2: *Definitions of hepatitis B serological profiles.*

	HBV serological results		
	HBsAg	**Anti-HBs antibody**	**Anti-HBc antibody**
HBsAg positive*	Pos	–	–
HBsAg-negative phase with anti-HBs	Neg/ND	Pos	Pos
HBsAg-negative phase without anti-HBs	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.

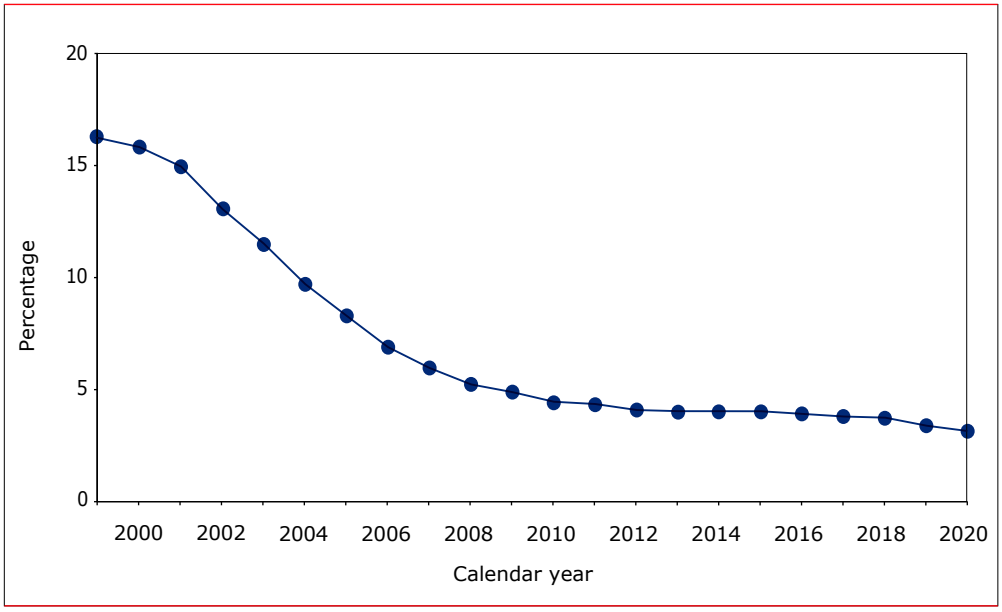
‡ Alternative definition: HBsAg-negative, anti-HBs antibody negative, and anti-HBc antibody not determined (and assumed to be negative).

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 screening

Ninety-six percent of the 28,223 individuals living with HIV ever registered in the SHM database have 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 individuals living with HIV in care has improved over calendar time. In 1999, 16% of individuals had not been screened for HBV infection (*Figure 4.10*). Since then, the percentage of individuals living with HIV without HBV screening has decreased markedly, with 3% of all individuals living with HIV in care having no measured HBV serological markers in 2020 (*Figure 4.10*).

Figure 4.10: *Percentage of individuals in care without any hepatitis B virus serological test per calendar year of care.*

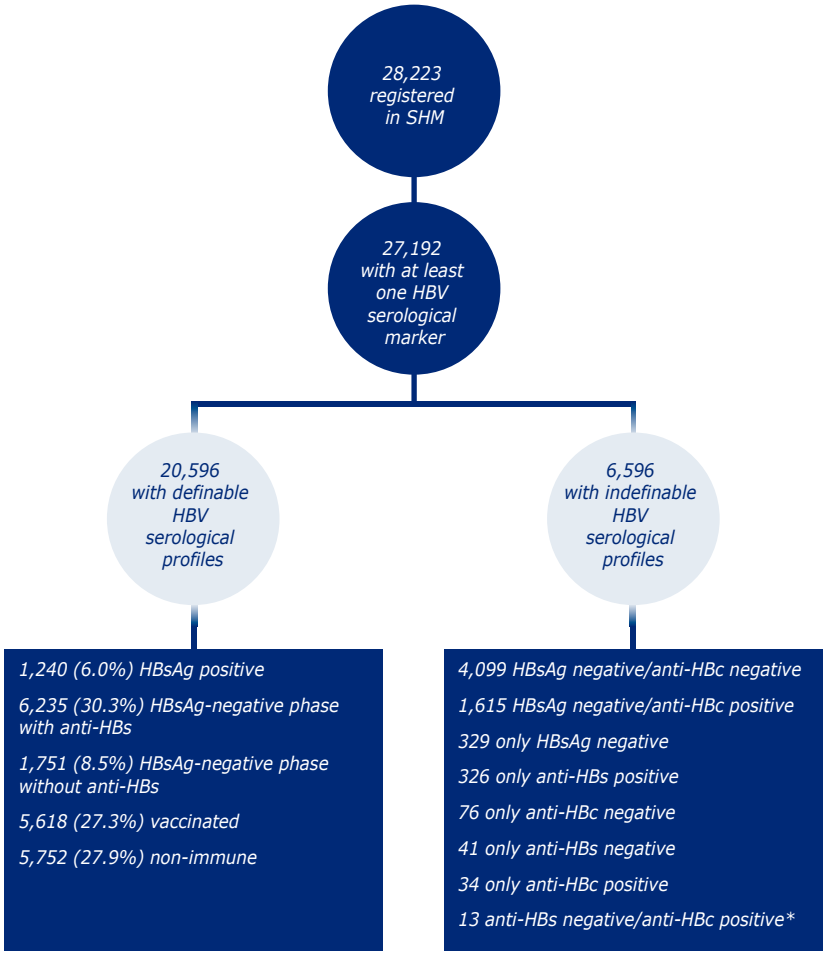


HBV serological profiles

HBV serological profiles could be defined for 20,596 (76%) of the 27,192 screened individuals (*Figure 4.11*). A full HBV serological battery is not routinely performed in individuals living with HIV; 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 4.11*. The remaining 6,596 (24%) individuals either had insufficient information to establish an HBV serological profile (n=6,533), or were previously HBsAg-positive, no longer had anti-HBc antibodies, and did not have anti-HBs

antibodies (n=63). The demographic characteristics of people with definable HBV serological profiles are compared in *Table 4.3*.

Figure 4.11: *Flowchart of individuals living with HIV registered in the SHM database, 1999–2020, with testing for hepatitis B virus (HBV). Information was obtained from the most recent serological result.*



** The 63 individuals who were HBsAg-positive and then lost HBsAg without a definable profile are not included.*
Legend: *Anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus.*

Table 4.3: Demographic characteristics of individuals living with HIV in care, according to their hepatitis B virus (HBV) serological profile as registered in the SHM database, 1998–2020.

	HBV serological profile*, n (%)				
	HBsAg positive	HBsAg-negative phase with anti-HBs	HBsAg-negative phase without anti-HBs	Vaccinated	Non-immune
Total number	1,240	6,235	1,751	5,618	5,752
Male gender	1,056 (85%)	5,342 (86%)	1,340 (77%)	4,833 (86%)	4,245 (74%)
Region of origin					
The Netherlands	529 (43%)	3,351 (54%)	705 (40%)	3,328 (59%)	3,320 (58%)
Europe	75 (6%)	444 (7%)	122 (7%)	428 (8%)	300 (5%)
Sub-Saharan Africa	313 (25%)	978 (16%)	546 (31%)	425 (8%)	686 (12%)
Caribbean/South America	140 (11%)	752 (12%)	171 (10%)	720 (13%)	847 (15%)
Southeast Asia	69 (6%)	264 (4%)	62 (4%)	159 (3%)	149 (3%)
Other	114 (9%)	446 (7%)	145 (8%)	558 (10%)	450 (8%)
HIV transmission group					
Men who have sex with men	701 (57%)	4,287 (69%)	791 (45%)	4,088 (73%)	2,709 (47%)
Heterosexual	390 (31%)	1,380 (22%)	611 (35%)	1,215 (22%)	2,513 (44%)
Injecting drug use	52 (4%)	208 (3%)	183 (10%)	52 (1%)	110 (2%)
Other	97 (8%)	360 (6%)	166 (9%)	263 (5%)	420 (7%)
cART	1,193 (96%)	6,051 (97%)	1,684 (96%)	5,514 (98%)	5,583 (97%)
Deaths	255 (21%)	976 (16%)	317 (18%)	319 (6%)	665 (12%)

** Based on information obtained from the 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 HBsAg-positive serology

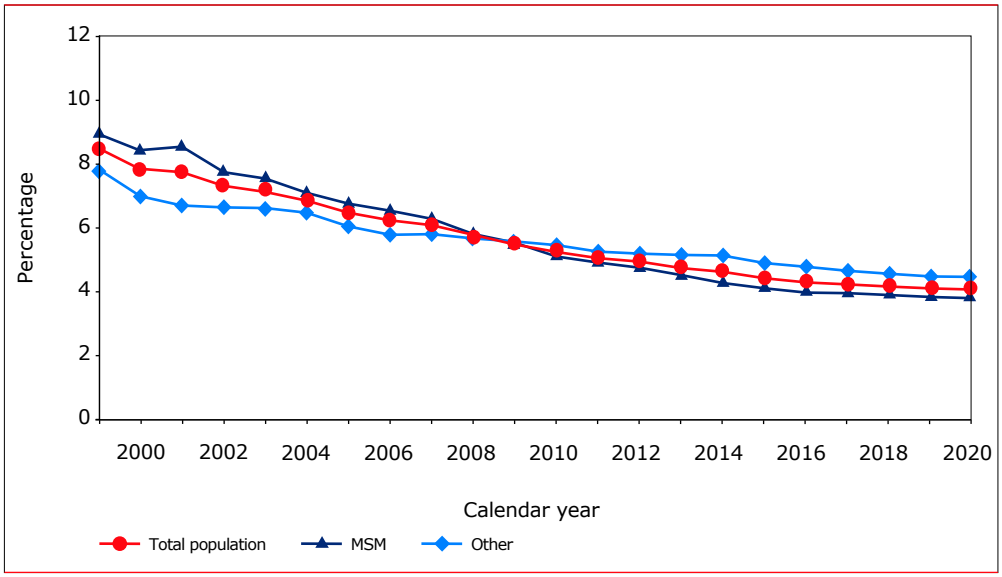
Prevalence of HBsAg-positive serology

Of the 27,192 individuals ever screened for at least one HBV serological marker, a total of 1,621 (6%) received a positive HBsAg test result. Over time, 183 (11%) of these individuals became HBsAg-negative and acquired anti-HBs antibodies (i.e., HBsAg-negative phase with anti-HBs) and an additional 198 (12%) became HBsAg-negative without acquiring anti-HBs antibodies (i.e., HBsAg-negative phase without anti-HBs). The remaining 1,240 (77%) individuals continued clinical care with HBsAg-positive serology.

The prevalence of HBsAg-positive serology was 8.5% in 1999, and slowly decreased to 4.1% in 2020 (*Figure 4.12*). This decline 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[30], 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 individuals living with HIV with HBsAg-positive serology[31].

As is the case for HCV co-infection, the percentage of individuals living with HIV in care and chronically co-infected with HBV is considerably higher than the rate found in the general Dutch population. Individuals co-infected with HBV were predominantly male (1,056/1,240; 85%), in line with those co-infected with HCV (*Table 4.3*). 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. HBV co-infection was also less common than HCV co-infection among PWID.

Figure 4.12: *Prevalence of HBsAg-positive serology per calendar year.*



Legend: *MSM=men who have sex with men; HBsAg=hepatitis B surface antigen.*

Presence of HBV–HDV infection

By 2020, 216/1,621 (13%) individuals with HBV infection had been tested for HDV infection (i.e., IgG or IgM anti-HDV antibodies or presence of HDV RNA). Of those individuals, 24 (11%) were identified with either past or current HDV infection; 12 of these 24 were tested for HDV RNA and six were found to have detectable HDV RNA, indicating active HDV infection.

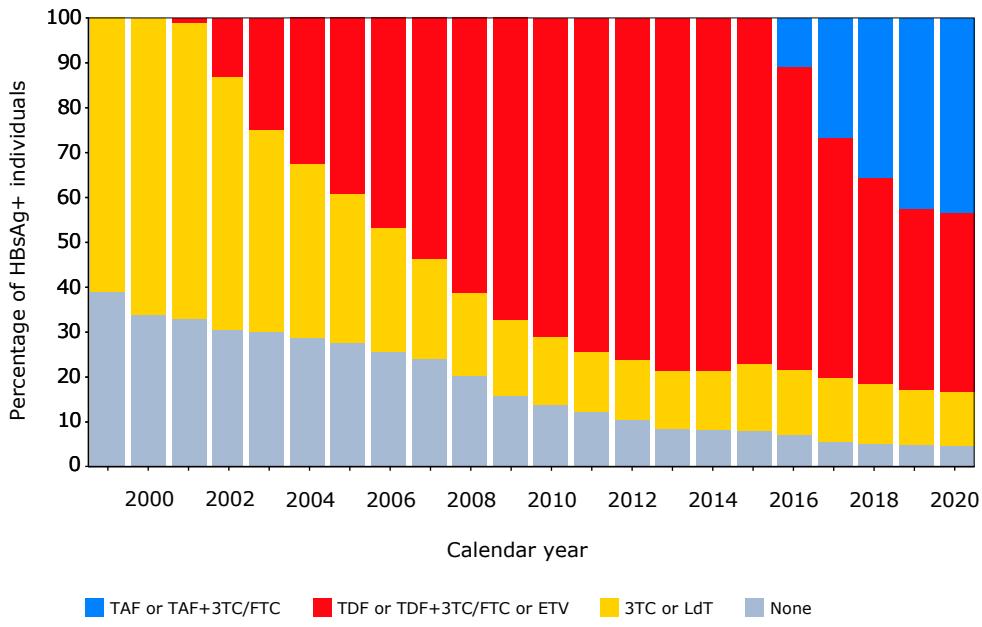
Treatment for chronic HBV infection

The treatment for chronic HBV infection aims to reduce viral replication of HBV. 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 has also been shown to reduce the risk of HCC and overall mortality in individuals with HIV-HBV co-infection[32,33]. A few antiviral agents used for treatment of HIV, such as lamivudine, and particularly TDF/TAF, are also active against HBV.

Of the 1,621 individuals with HIV in the SHM database who have ever had an HBsAg-positive serological test result, 1,557 (96%) received a cART regimen that included one or more agents with activity against both HIV and HBV. The reasons the remaining 64 individuals did not receive anti-HBV treatment included: death prior to start of treatment (n=16), recent entry into care (n=4), loss to follow up (n=40), or lack of sufficient information (n=4).

Most people with HBsAg-positive serology received treatment containing lamivudine in 1999-2000 (*Figure 4.13*). TDF-based cART (with or without lamivudine or emtricitabine) for combined HIV and HBV treatment was first used in 2002 (n=83/639, 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=132/1,215, 11%). In 2020, most HBV co-infected individuals were receiving TAF-based cART (n=550/1,264, 44%), closely followed by TDF-based cART (n=508/1,264, 40%), and lamivudine-based cART (n=149/1,264, 12%), or no anti-HBV-containing cART (n=57/1,264, 5%).

Figure 4.13: Anti-hepatitis B virus (HBV)-containing antiretroviral therapy per calendar year.



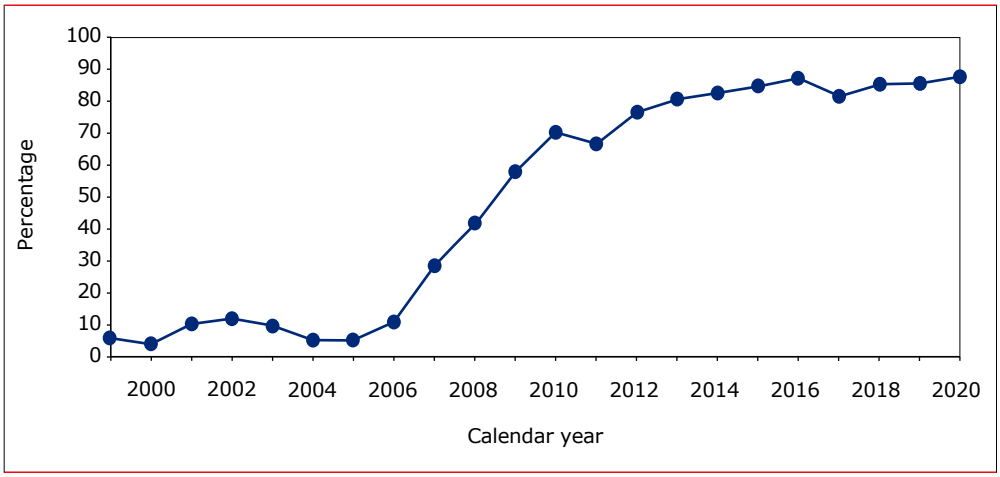
Note: *The categories of anti-HBV agents were: none, 3TC or LdT, TDF or TDF+3TC/FTC or ETV, and TAF or TAF+3TC/FTC. 3TC and LdT should not be combined and TDF and ETV can be combined under special circumstances[34].*

Legend: *TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; ETV=entecavir; 3TC=lamivudine; LdT=telbuvidine; FTC=emtricitabine; HBsAg+=hepatitis B surface antigen positive.*

We 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, so long as HIV RNA is undetectable. Therefore, for each year, HBV DNA measurements were available, on average, in 24% of individuals co-infected with HBV. *Figure 4.14* shows the percentage of those over time with an undetectable HBV DNA level below 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 (below 20, below 100, below 200, below 400, below 1,000; or below 2,000 IU/ml). In 1999-2005, at most, 12% 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, reaching 81% in 2013. In 2020, 88% of individuals co-infected with HIV and HBV had an undetectable HBV DNA level (*Figure 4.14*).

Figure 4.14: *Percentage of co-infected individuals with undetectable hepatitis B virus (HBV) DNA levels by assay, with a detection limit of <20, <100, <200, <400, <1,000, or <2,000 IU/ml HBV DNA per calendar year, regardless of HBeAg status.*

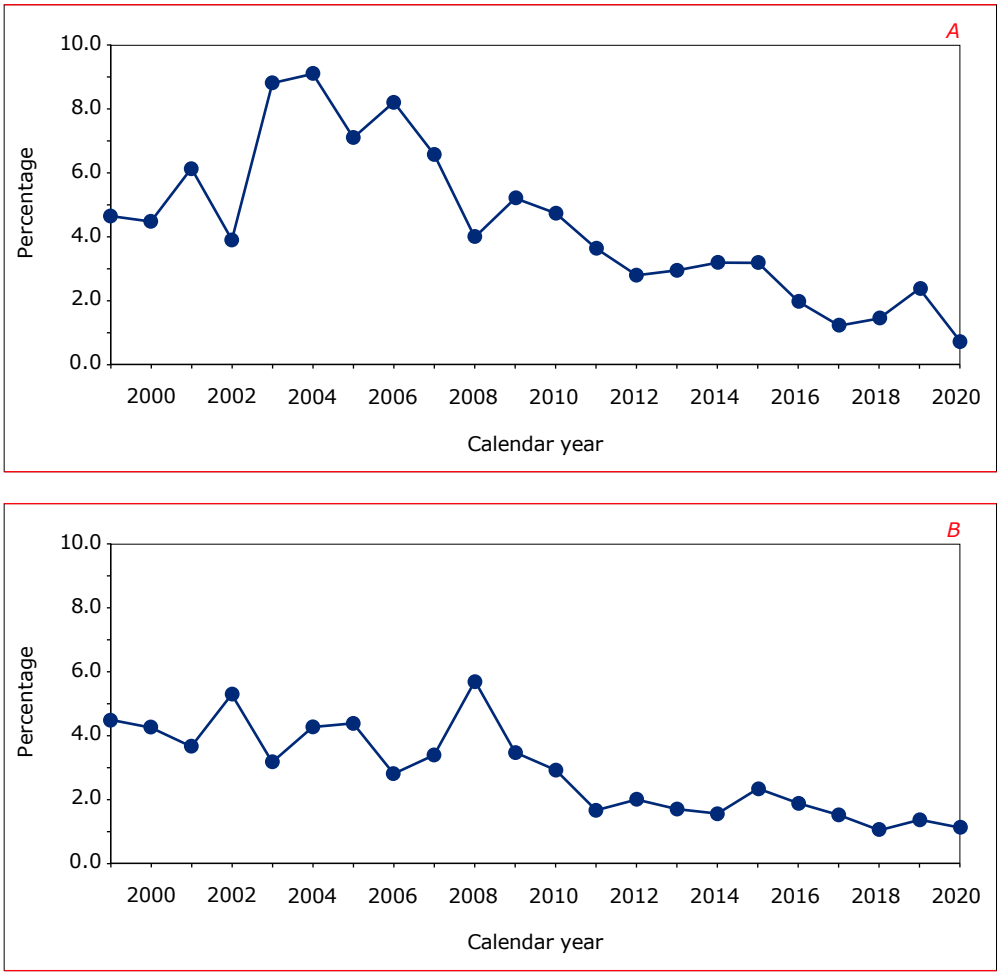


There are other serological outcomes associated with a more favourable prognosis in individuals with HBV infection[35]. Persistently negative hepatitis B "e" antigen (HBeAg) is associated with lower levels of HBV DNA replication. It also confers a favourable long-term outcome with low risk of cirrhosis and HCC, so long as transaminase and HBV DNA levels are low[36]. In those individuals with HBeAg-positive status, the loss of HBeAg, known as HBeAg seroclearance, is therefore a desired endpoint. Persistently negative hepatitis B surface antigen (HBsAg) is associated with reduced viral activity, very low risk of developing HCC, and improved survival. For all individuals with HBV infection, the loss of HBsAg, known as HBsAg seroclearance, is the penultimate goal of HBV therapy.

The percentage of individuals with HBeAg seroclearance ranged from 3.9% to 9.1% between 1999 and 2010, and slowly declined to 0.7% in 2020 (*Figure 4.15A*). Similarly, the percentage of individuals with HBsAg seroclearance was higher between 1999 and 2010, ranging from 2.8% to 5.7%, and slowly declined to 1.1% in 2020 (*Figure 4.15B*). Individuals with HIV-HBV co-infection, who initiate cART at very low CD4+ cell counts, are more likely to have seroclearance due to an immuno-inflammatory

reaction with accelerated CD4+ cell increases[37]. The higher percentages with seroclearance before 2010 could be due, in part, to the higher percentage of co-infected individuals initiating cART with severe immunosuppression during this period. Furthermore, the number of HBeAg tests peaked in 2004 at 116, before slowly declining to 23 tests in 2020. The number of HBsAg tests peaked in 2008 at 214, before less dramatically decreasing to 144 tests in 2019, and 105 tests in 2020. The lower percentage with seroclearance after 2010 might also be due to the lower testing rates in co-infected individuals.

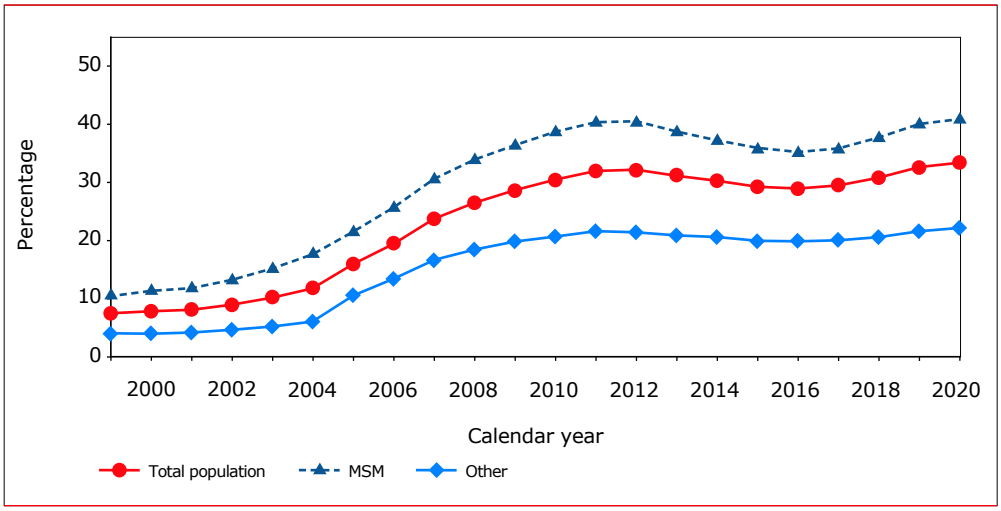
Figure 4.15: *(A) Percentage of hepatitis B "e" positive (HBeAg) co-infected individuals with HBeAg-seroclearance, and (B) percentage of all co-infected individuals with hepatitis B surface antigen-seroclearance. Both are shown by calendar year.*



HBV vaccination in individuals living with HIV

Of the 20,596 individuals with definable HBV serological profiles, 5,618 (27%) 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 33% in 2020 (*Figure 4.16*). The largest increase in HBV vaccination was observed in MSM, likely due to the national vaccination campaign targeting these individuals from 2002 onwards[30].

Figure 4.16: *Prevalence of hepatitis B vaccination per calendar year.*



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

HBV non-immune status in individuals living with HIV

Of the 20,596 individuals with definable HBV serological profiles, 5,752 (28%) had serological evidence of being non-immune and non-exposed to HBV at their last visit. When the 6,596 individuals with undefinable HBV serological profiles were considered, 84 of the 439 with an anti-HBs antibody test did not have detectable anti-HBs antibodies, and 5,528 of the 6,157 without an anti-HBs antibody test were not reported to have been vaccinated by their treating physician. Therefore, at most, 11,364 (42%) of the 27,192 individuals screened for HBV remained susceptible to infection at the time of their last visit (5,752 non-immune, 84 with an undefinable HBV profile and anti-HBs antibody negative, and 5,528 with an undefinable HBV profile and missing data on anti-HBs antibody status, and no physician-reported vaccination).

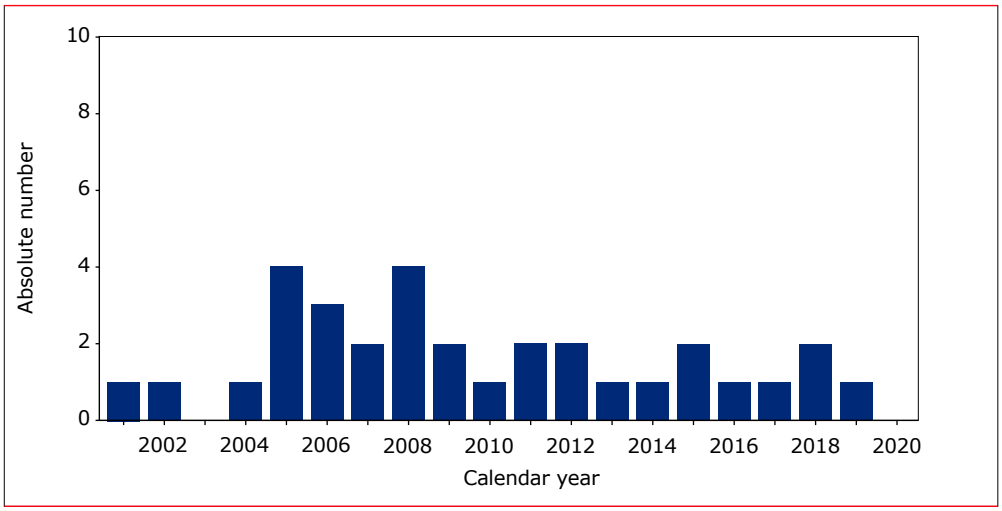
Individuals at risk, and MSM in particular, should be actively counselled about HBV vaccination. However, they may be protected from HBV infection by the use of tenofovir (TDF), or tenofovir alafenamide (TAF), as part of their cART regimen, according to findings reported by an international study, and one of the Dutch HIV treatment centres[38,39]. Data from SHM show that, of those people who remained at risk of acquiring HBV, 82% were being treated with a cART regimen that included TDF or TAF; for MSM, this percentage was 84%.

Liver-related morbidity in HBV

Additional data from liver biopsy pathology reports, transient elastography, radiology reports, or a combination of those sources, were available for 1,260 of the 1,621 individuals with an HBV co-infection. Review of these additional data show that severe chronic liver disease, according to our definition, was considered to be present (presumptive and definitive categories combined) in 273 (22%) of those with HBV co-infection. Definitive severe chronic liver disease was documented for 76 (6%) with an HBV co-infection. Of the 273 individuals with severe chronic liver disease, nine (3%) had past or current HDV infection.

Figure 4.17 shows that the annual number of new HCC diagnoses declined from 2010 onwards. HCC was found in 32 (2.1%) individuals with a chronic HBV co-infection, 18 of whom were born in the Netherlands, nine in sub-Saharan Africa, and one each in Asia, South America, the United States, Australia, and western Europe. One individual with newly-diagnosed HCC had either past or current HDV infection.

Figure 4.17: Absolute number of annually-reported HCC cases among HBV co-infected individuals over time.



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

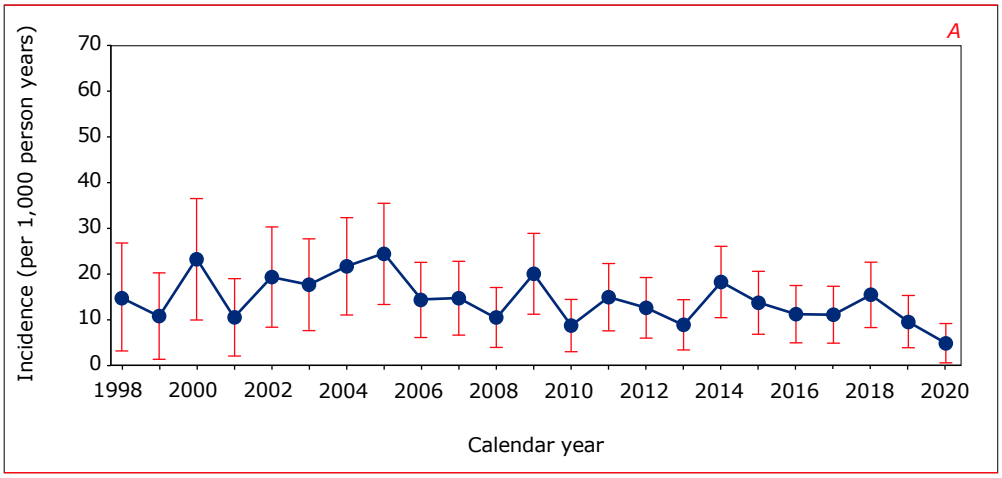
Mortality

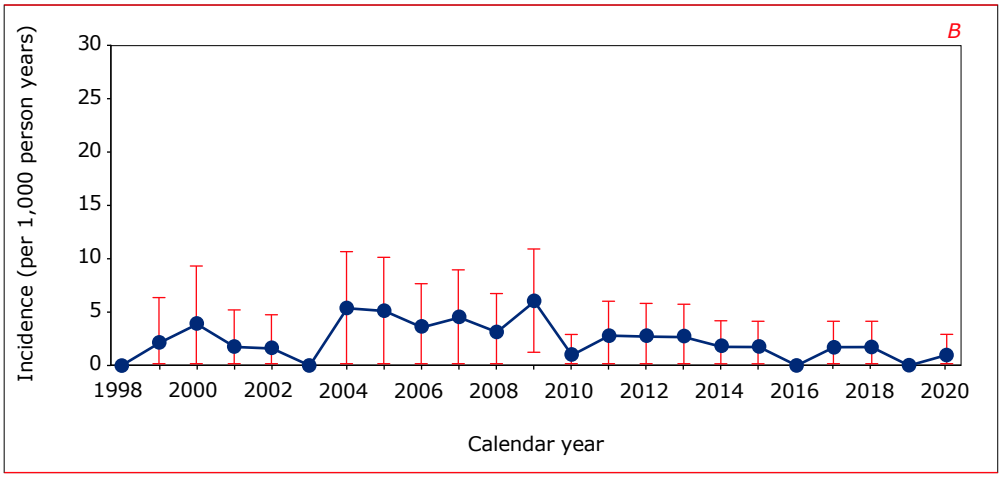
All-cause mortality

Nineteen percent (n=308) of the 1,621 individuals with an HBV infection died of any cause. For individuals with HBV infection, the incidence rate of death from any cause, adjusted for age and gender of the SHM population, was 16.0/1,000 PY in 1998-2002, 16.0 in 2003-11, and 11.9 from 2012 onwards (*Figure 4.18A*). In MSM with HBV infection, these incidence rates were 11.7/1,000 PY in 1998-2002, 13.5 in 2003-11, and 10.1 from 2012 onwards. In PWID with HBV infection, these incidence rates were 52.5/1,000 PY in 1998-2002, 60.4 in 2003-11, and 94.4 from 2012 onwards.

Of the 308 individuals with an HBV infection who died from any cause, five (1.6%) had either past or current HDV infection.

Figure 4.18: Annual: (A) all-cause mortality rate, and (B) mortality related to liver disease (adjusted for age and gender of the SHM population), in 1,597 HIV-1-positive individuals who were ever diagnosed with HBV infection.





***Note:** Individuals who were diagnosed with HBV infection could be co-infected with HCV.*

Liver-related mortality

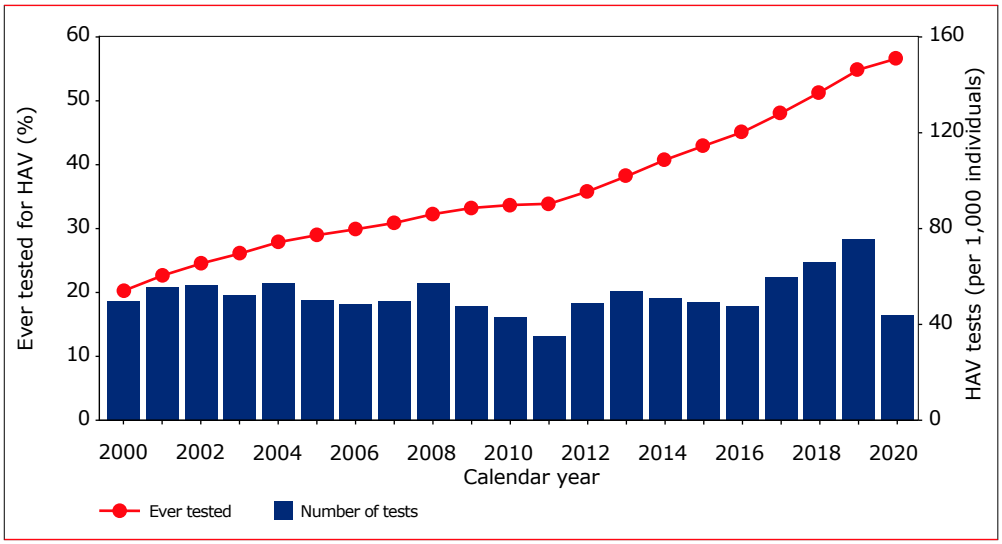
In total, 49 individuals co-infected with HBV died of a liver-related cause, only one of whom had either past or current HDV infection. For individuals with HBV infection, the incidence rate of liver-related death, adjusted for age and gender of the SHM population, was 1.9/1,000 PY in 1998-2002, increasing to 3.5 in 2003-11, and decreasing to 1.5 from 2012 onwards (*Figure 4.18B*). In MSM with HBV infection, these incidence rates were 2.4/1,000 PY in 1998-2002, 3.2 in 2003-11, and 1.4 from 2012 onwards. In PWID with HBV infection, these incidence rates were 3.4/1,000 PY in 1998-2002, 13.5 in 2003-11, and 11.9 from 2012 onwards.

Hepatitis A virus (HAV)

HAV screening

Screening for HAV involves testing for IgG anti-HAV antibodies (to establish past or current HAV infection, or HAV vaccination response) and/or IgM anti-HAV antibodies (to establish acute HAV infection). Fifty-six percent (n=15,918) of the 28,223 individuals living with HIV ever registered in the SHM database have been screened for HAV. The frequency of screening for HAV in individuals living with HIV has been consistent over the past two decades (*Figure 4.19*). Between 2000 and 2017, roughly 40 to 60 HAV tests per 1,000 individuals were conducted each year. Between 2018 and 2019, screening frequency increased to 68 and 76 HAV tests per 1,000 individuals per year, respectively. In 2020, screening frequency returned to 44 HAV tests per 1,000 individuals. The percentage of individuals who have ever been tested for HAV was 20% in 2000, and steadily increased to 57% in 2020 (*Figure 4.19*).

Figure 4.19: Percentage ever tested for anti-HAV antibodies and anti-HAV antibody testing frequency per calendar year.

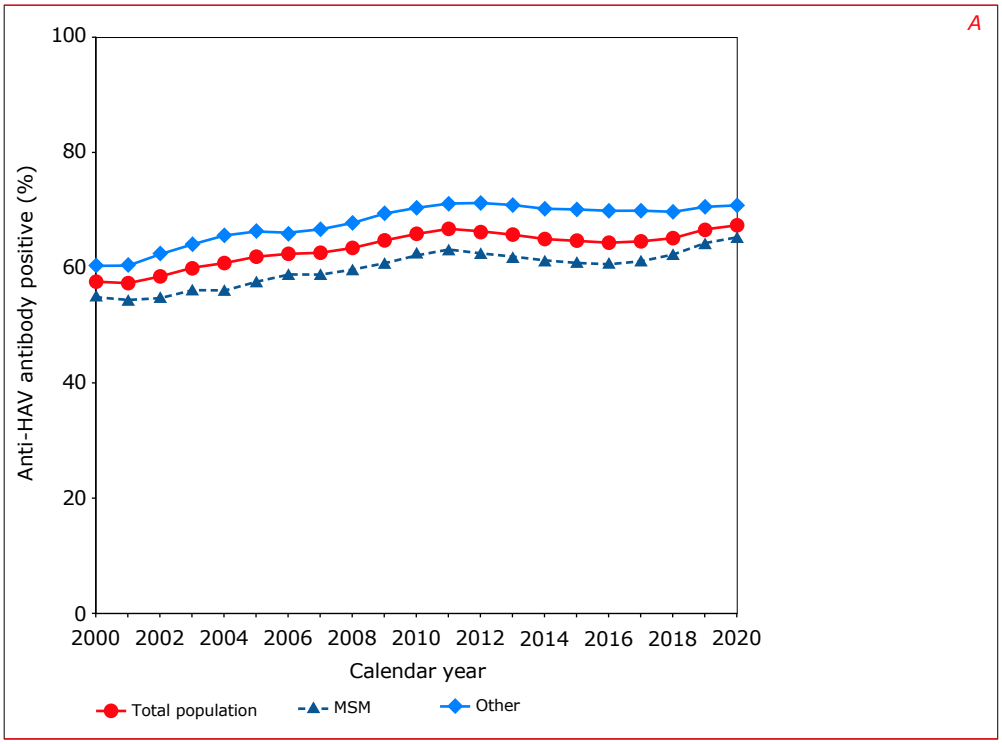


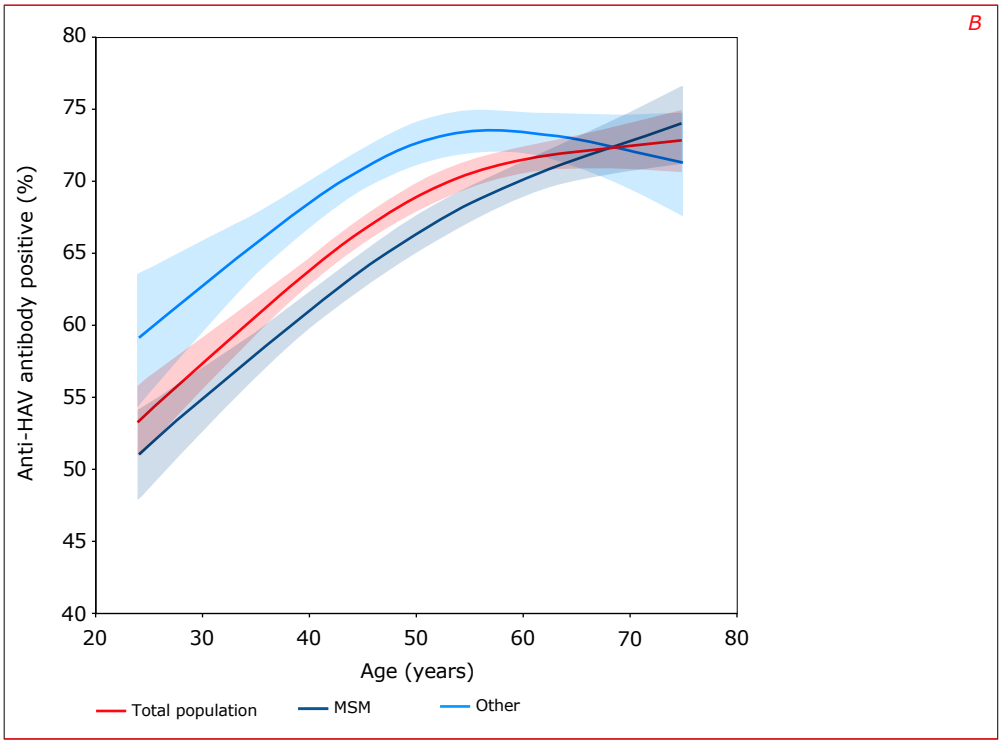
Legend: HAV=hepatitis A virus.

HAV seropositivity

Of the 15,918 individuals ever screened for HAV, a total of 10,711 (67%) had a positive anti-HAV antibody test result; 60% were observed in MSM, 3% in PWID, 35% in heterosexuals, and 2% in people from other transmission groups. The prevalence of anti-HAV antibody positivity was 58% in 2000 and then slowly increased to 67% in 2020 (*Figure 4.20A*). For MSM, the prevalence of anti-HAV antibody positivity was 55% in 2000, and it also slowly increased, reaching 65% in 2020. For all other transmission groups, the prevalence of anti-HAV antibody positivity was 60% in 2000 and 71% in 2020.

Figure 4.20: Percentage with anti-HAV antibodies per: A) calendar year, and B) age in years.





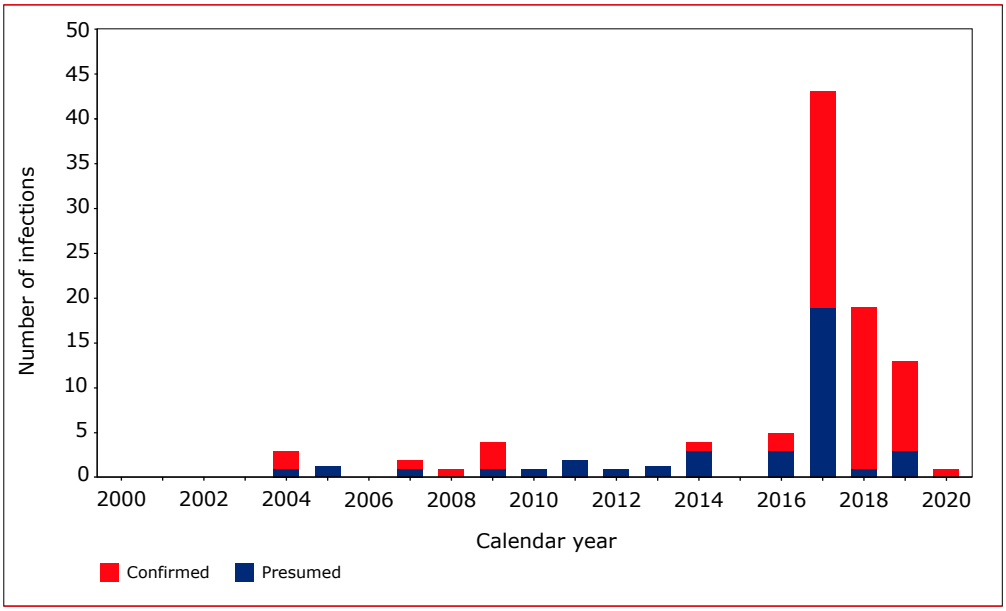
Legend: HAV=hepatitis A virus; MSM=men who have sex with men.

Epidemiological studies have highlighted the strong relationship between increasing anti-HAV antibody positivity and increasing age[40]. This age-dependent relationship was also observed in the 15,918 individuals ever screened for HAV (*Figure 4.20B*). Overall, anti-HAV antibody positivity was 59% for individuals below the age of 40, and 70% for those aged 40 or older. For MSM, anti-HAV antibody positivity was 57% for individuals below the age of 40, and 68% for those aged 40 or older. For all other transmission categories, anti-HAV antibody seropositivity was 64% for individuals below the age of 40, and 73% for those aged 40 or older.

Individuals with acute HAV diagnoses

Diagnoses of acute HAV infection were determined as either presumed (i.e., reported in the clinical file), or confirmed (i.e., detection of IgM anti-HAV antibodies or HAV RNA). Among the individuals who were in care between 2000 and 2020, there were 105 reported cases of acute HAV infection (n=65, presumed; n=40, confirmed), of which 85 (81%) were observed in MSM, 19 (18%) in heterosexuals, and one (1%) in PWIDs. Cases of acute HAV were first documented in 2000, and the number of acute HAV cases were lower than five per year until 2017, when 43 cases of acute HAV infection were documented (n=24, presumed; n=19, confirmed) (*Figure 4.21*). This figure decreased to 19 in 2018 and 13 in 2019. Of the 76 documented cases occurring between 2017 and 2020, 66 (87%) were observed in MSM. This increase in HAV infections was part of a European-wide outbreak of HAV among sexually-active MSM in 2017[41]. In 2020, there was only one presumed case of acute HAV infection.

Figure 4.21: *Number of reported cases of confirmed and presumed acute HAV infection per calendar year.*

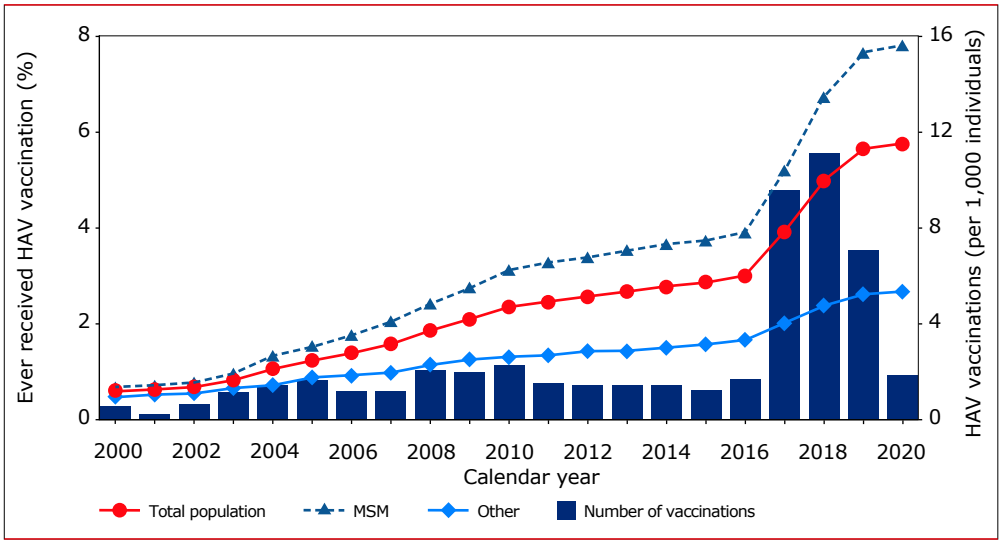


Of the 105 reported cases of acute HAV infection, 54 (51%) were recorded to have severe clinical symptoms. Severe chronic liver disease, according to our definition, was considered to be present (presumptive and definitive categories combined) in 16 (15%) of those with a reported acute HAV infection. Definitive severe chronic liver disease was documented for four (4%) with a reported HAV infection. No deaths due to acute HAV infection were reported.

HAV vaccination in individuals living with HIV

Information on HAV vaccination status was obtained from clinical files and was unknown for the majority of individuals ever registered by SHM. Of the 28,223 individuals living with HIV ever registered in the SHM database, 1,668 (6%) had received at least one HAV vaccination, according to their clinical file. The Netherlands has recommended HAV vaccination for any individual at risk of acquiring HAV infection (e.g., travellers to high-HAV endemic regions, professionals with potential exposure to HAV, and people with chronic hepatitis B or C)[42]. HAV vaccination frequency was consistently lower than, or equal to two vaccinations per 1,000 individuals living with HIV from 2000 to 2016, and it increased substantially to nine and 11 vaccinations per 1,000 individuals in 2017 and 2018, respectively (*Figure 4.22*). Accordingly, the percentage reported to have ever received an HAV vaccination was 1.5% in 2000, 3.1% in 2016, and 5.9% in 2020. In MSM, this percentage was 2.0% in 2000, 4.1% in 2016, and 8.0% in 2020.

Figure 4.22: *Percentage that ever received an HAV vaccination and HAV vaccination frequency per calendar year.*



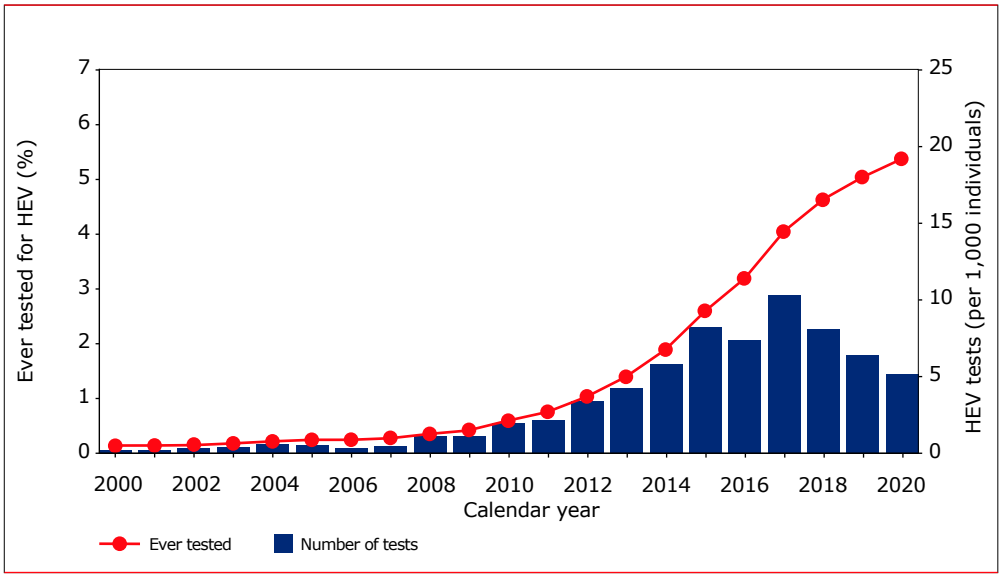
Legend: *HAV=hepatitis A virus; MSM=men who have sex with men.*

Hepatitis E virus (HEV)

HEV screening and seropositivity

Screening for HEV involves testing for IgG anti-HEV antibodies or HEV antigen (to establish past or current infection), or a combination of HEV RNA and/or IgM anti-HEV antibodies (to establish acute HEV infection). Five percent of the 28,223 individuals living with HIV ever registered in the SHM database have been screened for HEV. The screening frequency for HEV infection in individuals living with HIV in care was low between 2000 and 2010, reaching a maximum of two tests per 1,000 individuals (*Figure 4.23*). HEV testing frequency rapidly increased from two tests per 1,000 individuals in 2011 to 10 tests per 1,000 individuals in 2017. In 2020, this frequency was five tests per 1,000 individuals.

Figure 4.23: *Percentage ever tested for anti-HEV antibodies and anti-HEV antibody testing frequency per calendar year.*



Legend: *HEV=hepatitis E virus.*

Individuals with acute HEV diagnoses

Of the 1,510 individuals who were in care between 2000 and 2020, and who were ever screened for HEV, 207 (14%) were newly diagnosed as having past or current HEV infection. Of these individuals, 136 (66%) were MSM, 59 (29%) heterosexuals, six (3%) PWID, and six (3%) were from other transmission groups. The largest

number of new diagnoses were observed between 2013 and 2020 (*Figure 4.24*), mainly due to the higher frequency of HEV testing among individuals living with HIV. The percentage of individuals newly diagnosed with past or current HEV infection ranged from 9% in 2004 to 14% in 2020 (*Figure 4.25*).

Of all individuals tested for HEV and in care between 2000 and 2020, there were 49 individuals diagnosed with acute HEV infection, of whom 36 were MSM and 13 heterosexuals. Only two of these cases were confirmed to have progressed to chronic infection (i.e., positive HEV RNA lasting more than three months). One of these individuals was treated with ribavirin and both were able to resolve their infection (i.e., achieve undetectable HEV RNA after chronic infection had been established).

Figure 4.24: *Number of individuals newly identified with past or current HEV infection and with acute HEV infection per calendar year. Blue bars represent the percentage of newly-identified HEV infections that were confirmed as acute HEV infections.*

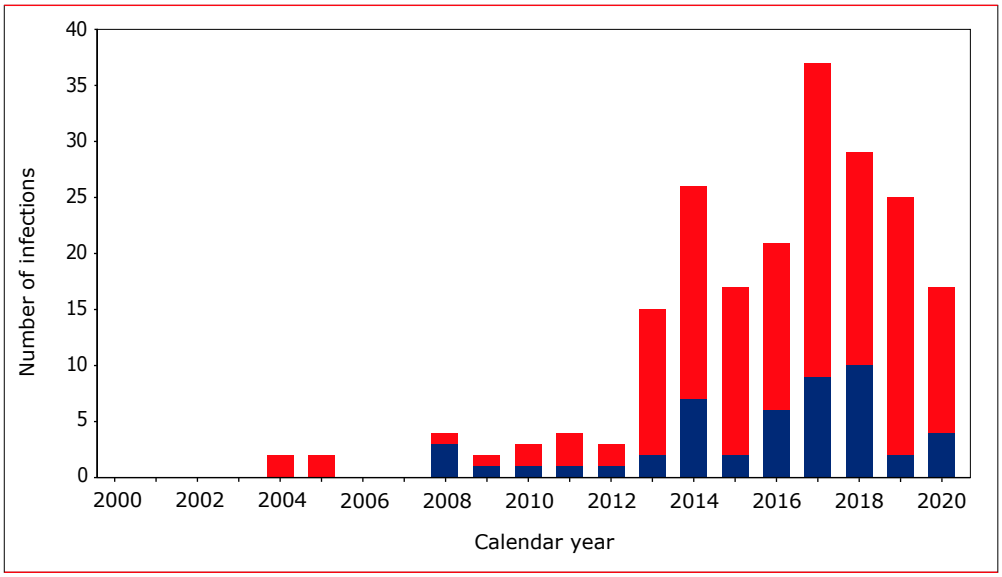
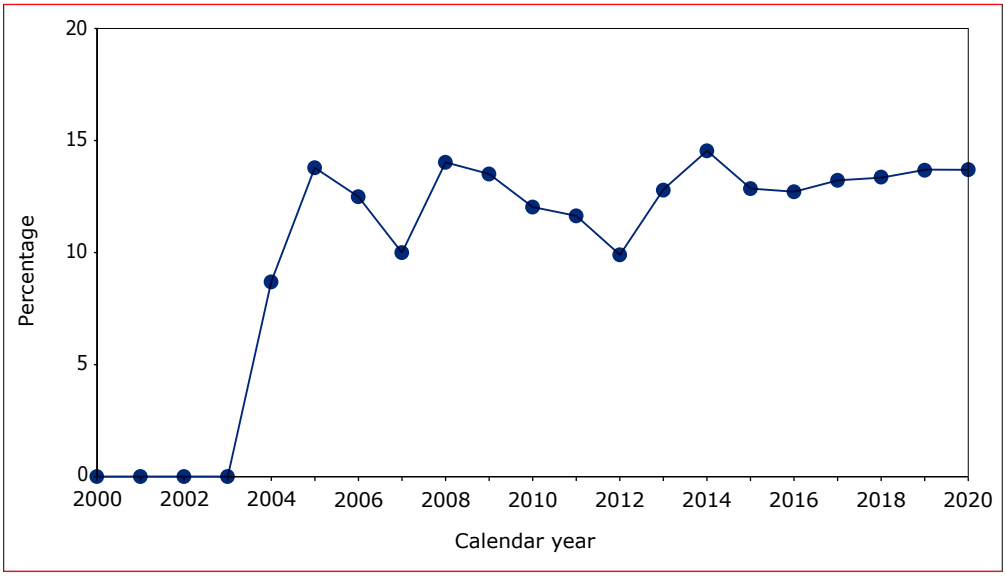


Figure 4.25: Percentage ever infected with HEV per calendar year.



Data on liver-related morbidity and mortality, and extra-hepatic complications associated with HEV infection, are not collected in the SHM database.

Conclusions

Screening for HCV and HBV co-infection in the population living with HIV in the Netherlands has continued to improve over time and is now almost universally documented. Five percent of individuals living with HIV ever registered between 1998 and 2020 in the SHM database, have been documented as chronically infected with HCV at some stage, and 3% have been documented as having had an acute HCV infection. Acute HCV infection occurred more often among MSM (5%), while reinfection of HCV was documented in 17% of the MSM ever diagnosed with a primary HCV infection.

Our data clearly show that novel DAAs, which arrived in 2014, have entirely replaced PEG-IFN-containing regimens. In addition, the number of individuals living with HIV treated for HCV has rapidly increased. More than 1,100 individuals have now 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. When retreatment was taken into account, the SVR for the last course of treatment was 99%. This high cure rate has reduced the

number of HCV co-infected individuals remaining in need of HCV treatment to 55 in 2020. Overall, a rapid reduction in the prevalence of active HCV infections was achieved, with prevalence in MSM having declined to 0.29% in 2020. Successful treatment of HCV will also prevent onward transmission of HCV, which is possibly reflected in the lower incidence of acute HCV infections in recent years[21]. However, in line with earlier reports[26,29,43], HCV reinfection after successful treatment has been observed. Although the rate of reinfection has declined over the past few years, ongoing transmission of HCV persists.

Six percent of the individuals living with HIV ever in care have 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[30], together with the HBV-prophylactic effect of TDF/TAF in cART-treated individuals. Nonetheless, an estimated 28% of all individuals living with HIV have either not been exposed to HBV, or have not been successfully vaccinated, and may remain at risk of acquiring HBV. Since 82% of all individuals 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 18% of the individuals living with HIV ever registered remain unprotected against HBV, which represents an estimated 7.0% of the total population of individuals living with HIV screened for hepatitis B. Very few individuals were tested for HDV infection and, of those who were tested, a small percentage had evidence of active HDV infection.

Among the individuals living with HIV ever registered by SHM, 29% of the individuals chronically co-infected with HCV, and 17% 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 remained 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 since 2012, yet the rate remained much higher for co-infected PWIDs, compared to other transmission groups.

Almost half of the individuals ever registered by SHM have been tested for anti-HAV antibodies, with testing frequency consistent across calendar years. The percentage of tested individuals found to have anti-HAV antibodies was no different between MSM and other transmission groups, but it was more than double the percentage found in the general Dutch population[44]. The percentage of people living with HIV with anti-HAV antibodies was higher in older age groups, as would be expected from the general

epidemiology of HAV infection[40]. Among the individuals diagnosed with HAV, almost half reported having severe symptoms during their infection, while four patients developed definitive severe chronic liver disease. Nevertheless, no individual died due to HAV infection.

The percentage of individuals reported to have received at least one HAV vaccination was low at 6%; this could be due to incomplete data on HAV vaccination. Despite the high prevalence of anti-HAV antibodies, the fact that only half of the individuals ever registered by SHM were tested for anti-HAV immunity, and vaccine uptake was low, could signal that a substantial percentage of individuals remain at risk of HAV infection. Indeed, the majority of HAV diagnoses that were registered in the SHM database were observed in HAV-susceptible MSM between 2017 and 2019.

Almost one in 20 individuals ever registered by SHM have been screened for HEV. Testing frequency of HEV has increased substantially since 2014, probably due to awareness of HEV infection in Europe and its recognised role in hepatitis and liver-related disease[17]. With increased testing, the number of individuals newly diagnosed with past or current HEV infection, or with acute HEV infection, also increased from 2014 onwards. Nevertheless, the percentage of individuals ever identified as having an HEV infection has remained stable at between 9% and 15% over the past decade. This percentage is similar to figures found in the Dutch general population[16]. We were unable to determine whether any liver-related morbidity and mortality, or any extra-hepatic disease was associated with HEV infection.

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 reinfection. In particular, efforts should continue to increase HBV vaccination rates among individuals living with HIV who remain at increased risk of acquiring HBV, particularly those who are not receiving an antiretroviral regimen containing TDF or TAF, and those who previously failed to respond to vaccination[45]. Already, the provision of highly-effective DAA regimens for all known HCV co-infected individuals living with HIV has coincided with reductions in the burden of severe chronic liver disease, hepatocellular carcinoma, and mortality related to liver disease. In addition, these novel regimens may have a beneficial impact on the risk of ongoing HCV transmission. Importantly, regular HCV RNA screening among individuals who have been successfully treated for HCV infection, and who remain at risk of reinfection, is recommended to ensure early detection of new HCV infections, combined with behavioural interventions aimed at MSM to prevent HCV reinfection after successful treatment of HCV.

HBV clinical practice guidelines from the European Association for the Study of the Liver suggest that individuals with chronic hepatitis B infection should be tested at least once for HDV[35]. In the Netherlands, 13% of individuals who were ever infected with HBV had been tested for HDV infection; the reasons for this low percentage need to be elucidated. This information could help to establish whether HDV infection in the Netherlands is a substantial contributor to liver-related morbidity and mortality in individuals living with HIV with HBV infection, as found in other settings[12].

Only half of the individuals ever registered by SHM have been screened for HAV and, among those tested, almost two-thirds had anti-HAV antibodies from either vaccination or cleared infection. Even though HAV infection reports have been uncommon over the last two decades, the recent HAV outbreak in MSM[40] brings strong evidence that clinicians need to assess HAV risk and, if present, recommend vaccination. Given that anti-HAV antibodies were less commonly detected in younger individuals, they should be particularly targeted for HAV vaccination.

Studies have suggested that individuals who are immunosuppressed should be tested yearly for HEV[46]. However, data from SHM and a meta-analysis found no noteworthy increase in HEV prevalence among individuals living with HIV[47], and only two patients in the SHM database were diagnosed with chronic HEV infection. We recommend following current European guidance, which states that individuals with persistently-elevated transaminase levels should be screened for HEV RNA[17]. Further data are needed to determine to what extent liver-related, and non-liver-related disease occurs as a result of HEV infection in individuals living with HIV.

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

Colette Smit, Tom Wolfs, Annemarie van Rossum

Box 5.1: Chapter definitions.

Child living with HIV	A child diagnosed with HIV before the age of 15[1,2], whose first visit to a Dutch HIV treatment centre was before the age of 18 years.
Infection	The moment a child acquires an HIV infection.
Diagnosis	The moment a child is first diagnosed with HIV.
Registration	The moment that SHM is notified of a child living with HIV in care by their treating physician or nurse and the child is registered in the SHM database. Registration is usually within a few months of entering care, but can take longer.
In care in 2020	People are considered to be in care if they had a documented clinic visit or lab measurement in 2020.
Vertically-acquired HIV	Transmission of HIV from a woman living with the virus to a child during pregnancy, delivery, or breastfeeding.
Non-vertically-acquired HIV	Transmission of HIV through sexual contact or contact with contaminated blood or blood products.
cART	Combination antiretroviral therapy: a combination of at least three antiretroviral drugs from two different antiretroviral drug classes, or at least three nucleoside reverse transcriptase inhibitors.
Viral suppression	Any viral load measurements below 200 copies/ml, except for time points in the past where tests had quantification limits higher than 200 copies/ml.

Box 5.2: Outline of the paediatric ATHENA cohort in the Netherlands: all children living with HIV registered in the ATHENA cohort before 31 December 2020. (Children=individuals under 15 years of age at the time of diagnosis who made a first visit to a Dutch HIV treatment centre before the age of 18 years.)

1. Children who were diagnosed when younger than 15 years of age and who entered care in the Netherlands before they were 18 years (n=393).
2. Population of those who were diagnosed as a child and in care in 2020:
   - aged under 15 years in 2020 (n=152).
   - aged 15-18 years in 2020 (n=26).
   - aged 18 years or over in 2020 (n=160). Of the 160 children, 136 transferred to adult care (sometimes within the same treatment centre), five started care in an adult HIV treatment centre, and 19 were still registered as being in care at one of the paediatric HIV treatment centres.

Background

Combination antiretroviral therapy (cART) has dramatically decreased morbidity and mortality in children living with HIV worldwide[3-7]. Immediate initiation of cART, regardless of CD4 cell count or percentage, is associated with a higher survival rate when compared with delayed cART initiation guided by CD4 cell count[8-11]. Studies showing a clinical benefit of early cART initiation led to a 2015 revision of the World Health Organization (WHO) guidelines on when to start cART; they now recommend initiation in everyone living with HIV (including children), irrespective of CD4 cell count[12].

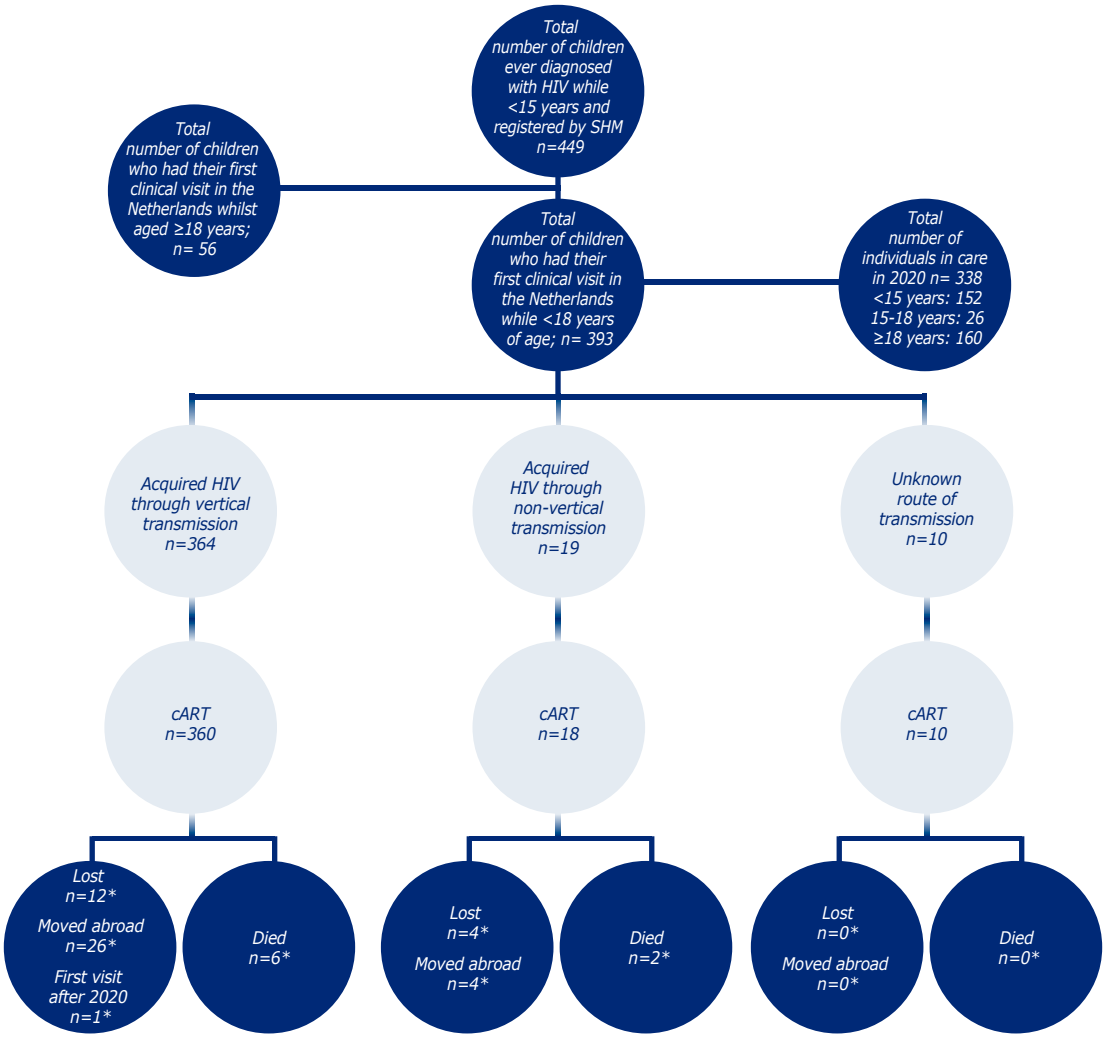
In the Netherlands, children living with HIV generally receive health care at one of four paediatric HIV treatment centres. These children transition to adult HIV care when they reach the age of 18. However, children who acquire HIV at an older age through non-vertical transmission are more likely to enter care at an adult HIV treatment centre. Accordingly, those who are diagnosed with HIV over 15 years of age are described in *Chapter 1* as part of the adult population.

Here we report on the demographics, clinical characteristics, and long-term virological and immunological responses to treatment of children diagnosed with HIV before 15 years of age and 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*). The criteria for the age group before 15 years is aligned with the definition of children used by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO)[1,2].

Ever registered

As of 31 December 2020, the number of individuals that SHM had registered as ever being diagnosed with HIV while under 15 years of age was 449 (*Figure 5.1*). Of these, 124 were diagnosed with HIV before arrival in the Netherlands and 325 were newly diagnosed in the Netherlands. In total, 393 of the 449 children entered care in the Netherlands before 18 years of age.

Figure 5.1: *Overview of children living with HIV registered by stichting hiv monitoring as of 31 December 2020.*



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

Legend: *cART=combination antiretroviral therapy.*

The majority (98%) of the children reported on, entered care at a paediatric HIV treatment centre. Nine entered care at an adult HIV treatment centre at a median age of 16.7 years (IQR 16.2-17.6) (*Table 5.1*).

Table 5.1: *Demographic and HIV-related characteristics of 393 children living with HIV ever registered by SHM who were diagnosed before 15 years of age and entered care in the Netherlands below the age of 18.*

Characteristics	Vertical transmission*	Non-vertical transmission*	Route of transmission unknown*
Total	364 (93)	19 (5)	10 (3)
HIV treatment centre			
Paediatric care	361 (99)	14(74)	9 (90)
Adult care	3 (1)	5 (26)	1 (10)
Gender			
Male	173 (48)	8 (42)	7 (70)
Female	191 (52)	11 (58)	3 (30)
Child's country of origin			
The Netherlands	113 (31)	2 (11)	0
Sub-Saharan Africa	208 (57)	15 (80)	9 (90)
Other	43 (12)	2 (11)	1 (10)
Mother's country of origin			
The Netherlands	32 (9)	1 (5)	1 (10)
Sub-Saharan Africa	189 (52)	7 (37)	6 (60)
Other/unknown	143 (39)	11 (58)	3 (30)
Adopted	146 (40)	0	3 (30)
Age at HIV diagnosis	1.1 (0.25-3.6)	10.9 (6.5-14.6)	10.5 (6.3-11.8)
cART-treated	360 (99)	18 (95)	10 (100)
Therapy-naive at cART initiation	312(86)	15 (80)	10 (100)
CD4 at cART initiation	560 (286-1220)	324 (171-508)	325 (250-522)
CD4 Z-score at cART initiation	-0.58 (-1.00- -0.10)	-0.63 (-1.13- -0.08)	-0.50 (-0.91— -0.28)
VL (log copies/ml) at cART initiation	5.2 (4.5-5.8)	4.3 (4.0-5.5)	4.8 (4.3-4.9)

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

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

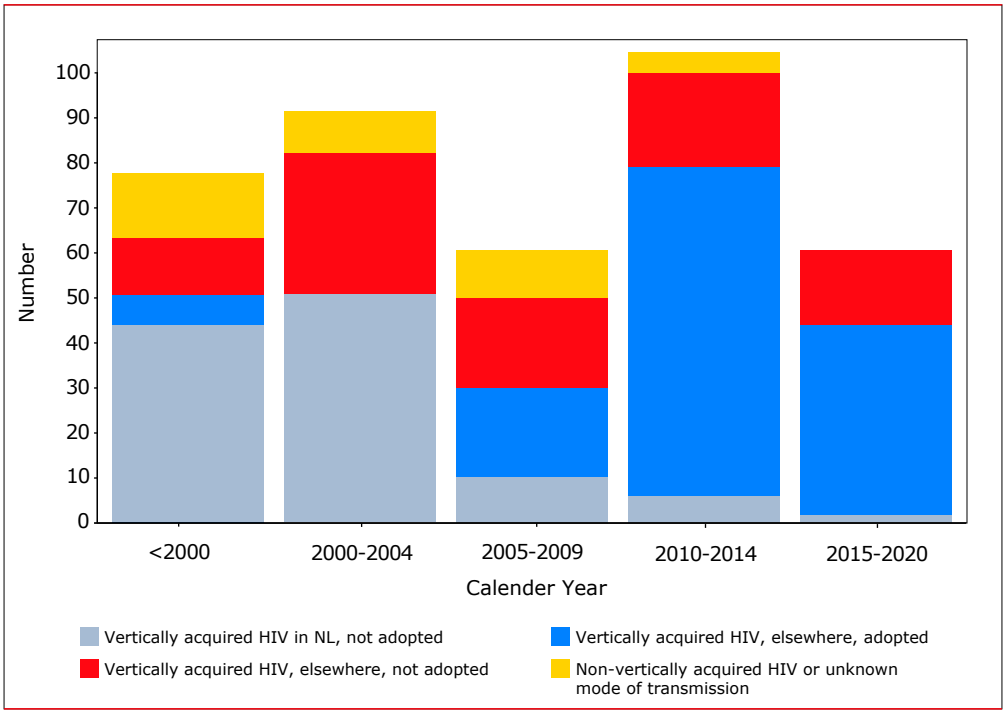
Mode of transmission

The majority (93%) of the children registered acquired HIV through vertical transmission (*Figure 5.1*).

Vertical transmission

- Between 1998 and 2020, 364 children entered care after acquiring HIV through vertical transmission.
- The median age at which they received their first reported HIV-positive test result (including self-reported tests performed in their country of origin), was 1.1 years (interquartile range [IQR] 0.3-3.6 years).
- 99% received care in a paediatric HIV treatment centre in the Netherlands.
- cART initiation was documented for 99% of the children.
- 57% (n=208) of the children were born in sub-Saharan Africa.
- 31% (n=113) of the children were born in the Netherlands.
- 9% of the children born in the Netherlands (10 out of 113), had two Dutch parents.

Figure 5.2: Number of children living with HIV by year of entering care in the Netherlands, stratified by mode of HIV transmission and adoption status.



Decline in vertical transmission of HIV in the Netherlands since 2005

Figure 5.2 shows the number of registered children by year of entering care, mode of transmission, and region of origin. The number newly entering care in the Netherlands has fallen over time from 104 in 2010-14 to 61 in 2015-20. This drop is likely linked to the declining number of adopted children newly entering care over time. Standard HIV screening among pregnant women, introduced nationally in 2004[13,14], is responsible for the strong decline in vertical transmission in the Netherlands from 2005 onwards.

Non-vertical transmission

- Between 1998 and 2020, 19 children were registered as having acquired HIV through non-vertical transmission; the reported modes were heterosexual transmission and contact with contaminated blood and blood products. Of note, contact with contaminated blood or blood products was no longer reported from 1997 onwards for children born in the Netherlands, and from 2009 onwards for all children, regardless of country of birth.
- The median age at which they received their first reported HIV-positive test result was 10.9 years (IQR 6.5-14.6). However, the median age of HIV diagnosis for those who acquired HIV by sexual transmission was higher at 14.8 years (IQR 14.1-14.8).
- In total, 95% of these children had started cART.
- 37% of children acquired HIV through heterosexual contact.
- 80% were born in sub-Saharan Africa.
- 26% received care in an adult HIV treatment centre.

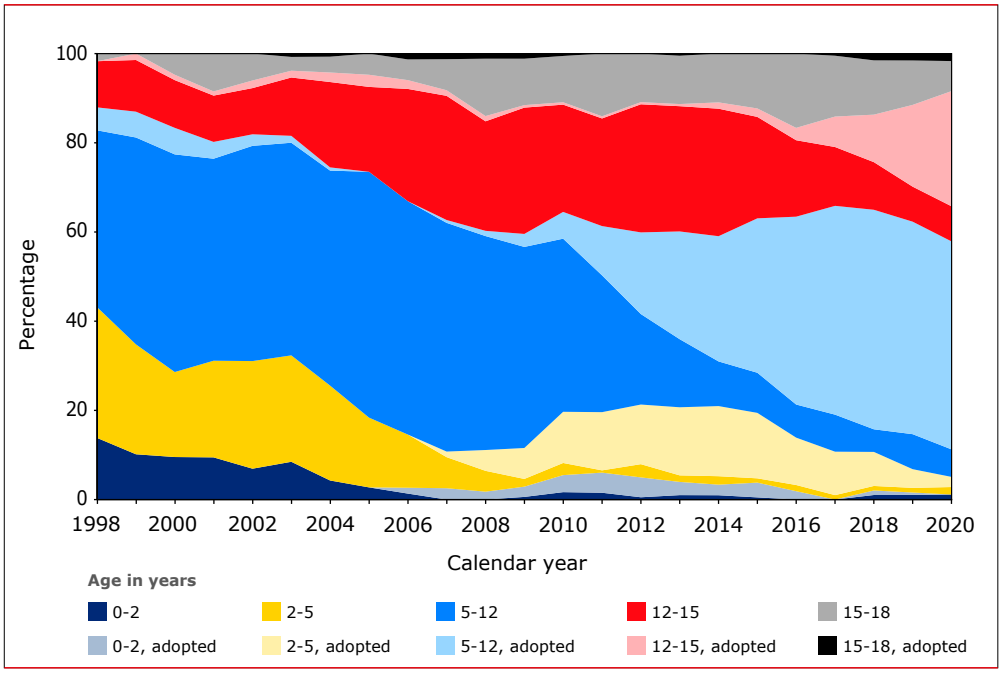
Unknown route of HIV transmission

- For 10 children living with HIV, the route of transmission remains unknown.
- Their median age at diagnosis was 10.5 years (IQR 6-12).
- All children had started cART.

Age distribution

The age distribution of children receiving HIV care shifted between 1998 and 2009 (*Figure 5.3*). From 2009 onwards, there was an increase in the proportion of children aged 0 to 5 years. This was due to a rise in adoption rates of children living with HIV in those age groups. In 2020, about 82% of children living with HIV aged 15 years or younger were adopted.

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



Low mortality rates

The mortality rate between 1998 and 2020 for children registered with SHM was very low. In total, two children (0.5%) under the age of 18 years have died since the start of registration. Both children died from AIDS before 2010. Another six (1.5%) young adults diagnosed with HIV as children died when over the age of 18 years; their median age of death was 27 years (IQR 24-30) and all died before the age of 35 years. Four of these young adults died from AIDS and two of a non-AIDS related cause.

Antiretroviral treatment

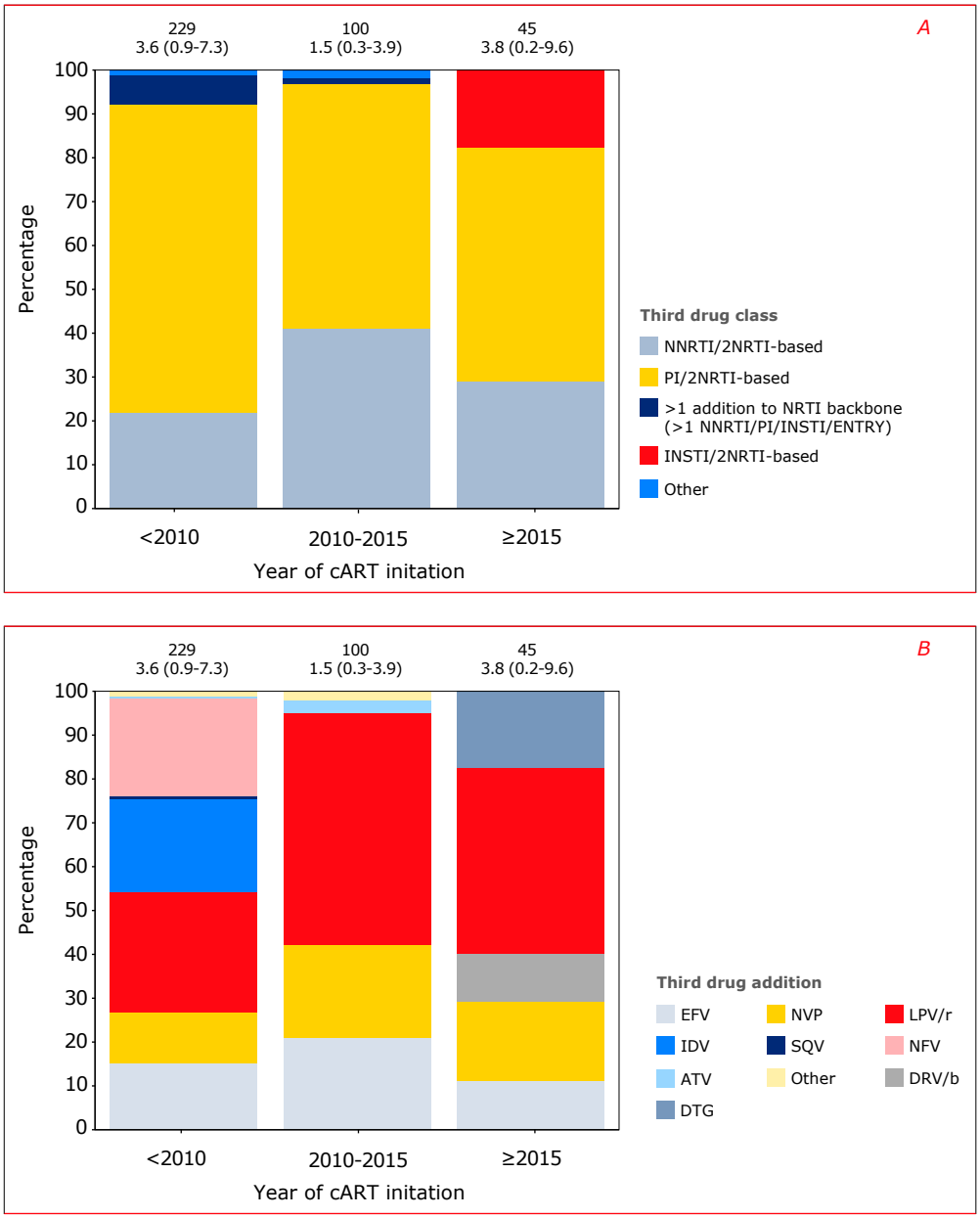
Of the 393 children who entered care in the Netherlands before 18 years of age, 388 (99%) started cART; 337 (87%) of them were treatment-naive at the start of cART and 51 (14%) had previously been exposed to monotherapy or dual therapy (i.e., were pre-treated).

For the purposes of this analysis, we have included both pre-treated and treatment-naive children, and grouped them by calendar year of cART initiation: 229 children started a cART regimen before 2010, 100 in 2010-15, and 45 children after 2015. For 14 children, the year of cART initiation is not known. In total, five children were not treated with cART, of whom four are no longer in care.

Initial combination antiretroviral regimen

Of the 388 registered children known to have initiated cART, 64% were treated with a first-line regimen that included a protease inhibitor (PI) and two or more nucleoside reverse transcriptase inhibitors (NRTIs). Another 28% were treated with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimen with two or more NRTIs. *Figure 5.4* shows the trends over time for the third-drug additions to the NRTI backbone as part of the initial cART regimens, stratified by calendar period of starting cART. Among children, lopinavir was the most commonly-used PI (36%). Following its introduction in 2014, the integrase inhibitor dolutegravir was included in the initial cART regimen given to 18% of the children; only one of those children was under 12 years of age.

Figure 5.4: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial cART regimen, stratified by calendar year period, according to (A) antiretroviral class, and (B) specific third drugs. Numbers above the bars represent the total number of individuals initiating cART in that calendar year period. Median ages and interquartile ranges above the bars represent the ages of individuals at the time of cART initiation.



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 the 388 children who had ever started cART spent on an initial regimen was 22.6 months (IQR 7-56). Discounting weight-related dose changes, 327 children (84%) discontinued their first-line treatment regimen. The most important reasons for changing included simplification (38%) and toxicity (15%). Virological failure was the reason given in 14% of cases, and lack of adherence in 4%. Other reasons included decision by parents or child, blood level-related, or difficulties taking medication.

Virological response

Virological response to cART was assessed based on viral suppression (i.e., viral load below 200 copies/ml, [*Box 5.1*]). Initial virological response is reported for the first two years after starting cART and stratified by calendar year of cART initiation. Long-term virological response is reported by time-updated age for those who used cART for at least 24 months.

Initial response to cART

This analysis used data from the 388 children who were registered with SHM and had ever started cART. Children who acquired HIV through vertical transmission were stratified by age at cART initiation, resulting in the following categories:
(1) vertical transmission, 0-1 year
(2) vertical transmission, 2-5 years
(3) vertical transmission, 5-18 years
(4) non-vertical transmission or unknown mode of HIV transmission[a], 5-18 years

Among the children who ever started cART, we assessed their viral suppression rates at 24-week intervals while they were on cART. Viral load measurements closest to each 24-week time point (plus or minus 8 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.
Figures 5.5A and *5.5B* shows viral suppression rates by calendar period of cART initiation: 1998-2009 and 2010-20.

cART initiation between 1998 and 2009:

- Among children with vertically-acquired HIV who were aged 0-2 years at the time of cART initiation, viral suppression rates increased from 78% after one year of cART, to 81% after two years.
- Among children with vertically-acquired HIV who were aged 2-5 years at cART initiation, viral suppression rates increased from 95% after one year of cART, to 93% after two years.

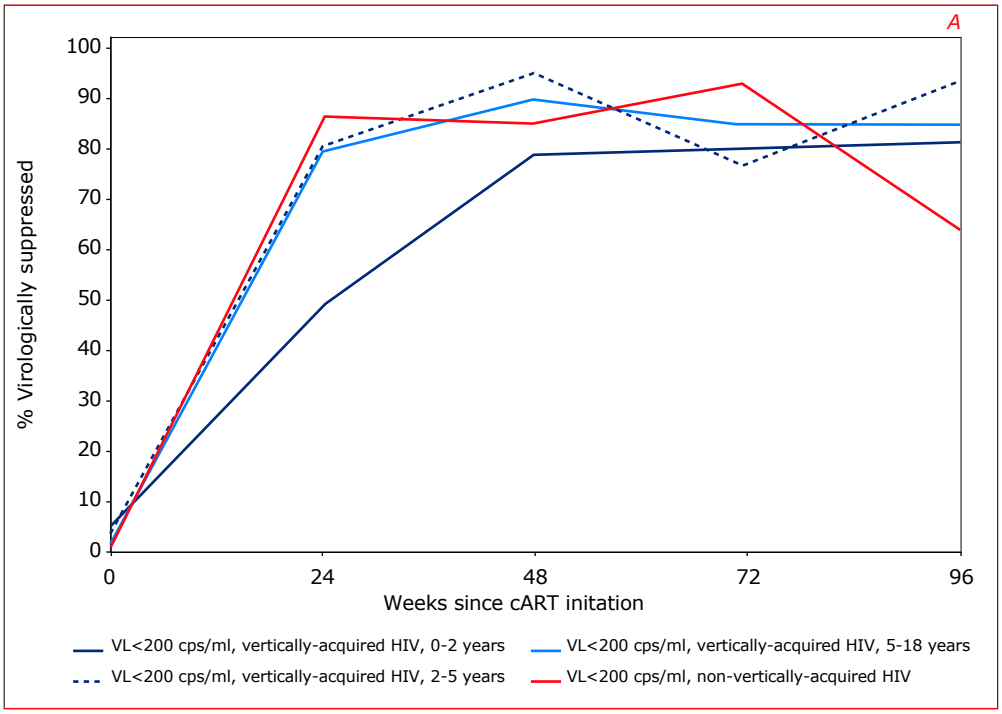
a *The number of children with an unknown route of HIV transmission is too small to include as a separate category in this analysis. As these children had the same age distribution as those with non-vertically-acquired HIV, these two groups were jointly analysed in a shared category.*

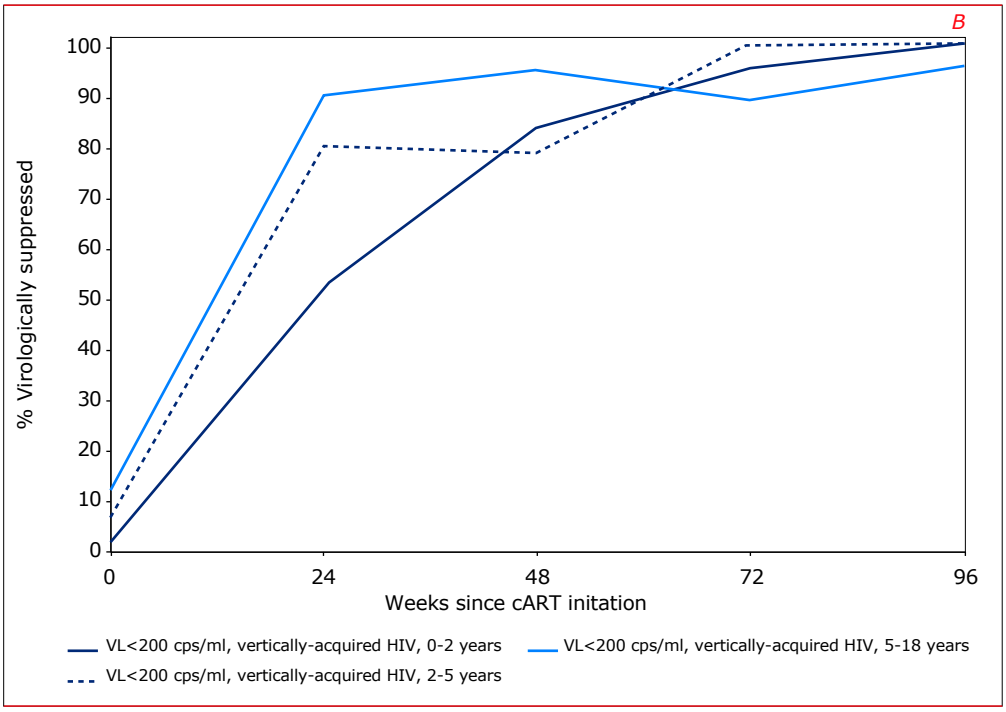
- Among children with vertically-acquired HIV who were over 5 years of age at cART initiation, viral suppression rates increased to 89% after one year of cART use. However, two-year viral suppression rates (85%) were lower than those seen among children aged 2-5 years of age at the time of cART initiation.
- Among children with non-vertically-acquired HIV, the one-year viral suppression rate was 80% and the two-year viral suppression rate was the lowest seen among all groups at 64% (*Figure 5.5A*).

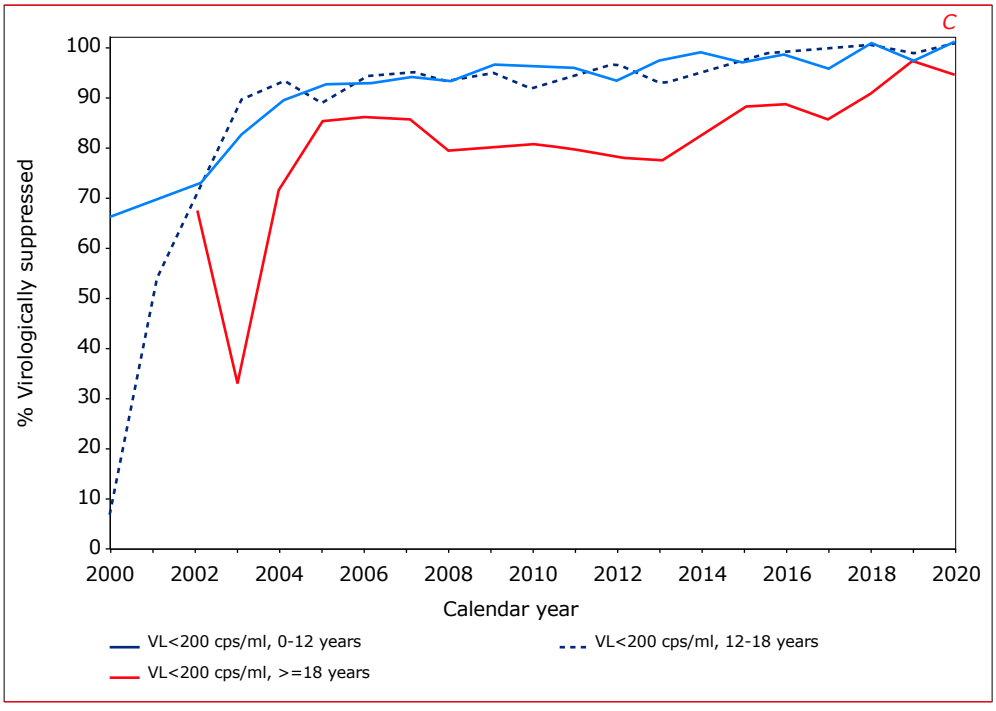
cART initiation in or after 2010:

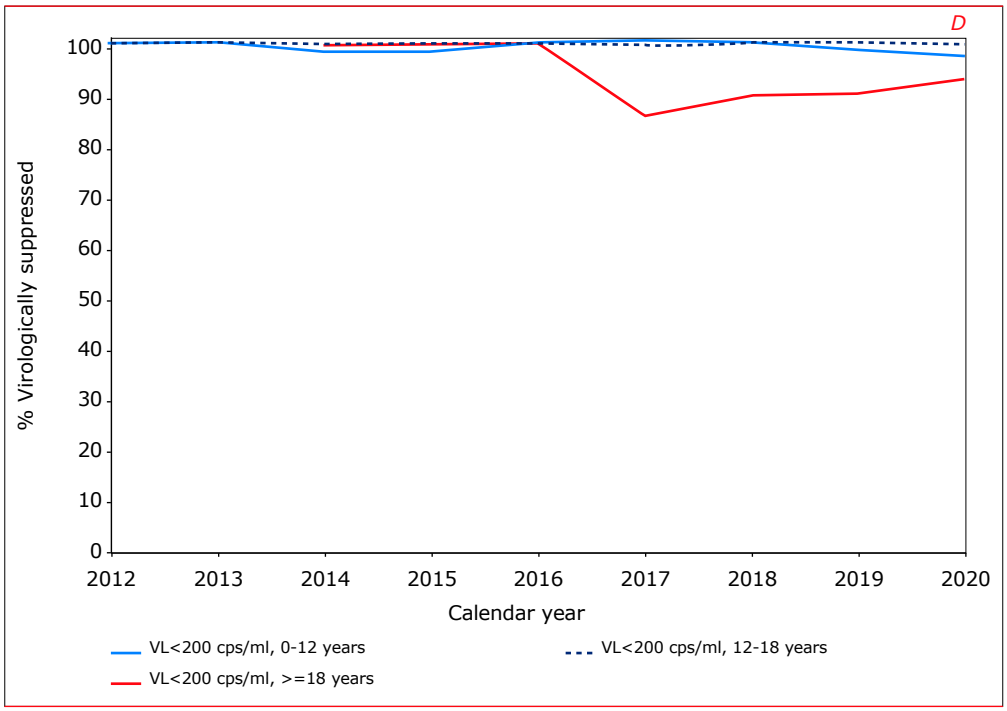
- Two years after treatment initiation, the viral suppression rates were 100% in all children who acquired HIV through vertical transmission below the age of 5 years. However, children with vertically-acquired HIV who were aged over 5 years at the time of cART initiation, reached a somewhat lower viral suppression rate of 96% over the same period. Note: Viral suppression rates are not presented for those with non-vertically-acquired HIV, due to the limited follow-up time between age at cART initiation and reaching 18 years of age (*Figure 5.5B*).

Figure 5.5: *Viral suppression following combination antiretroviral therapy (cART) initiation, by calendar period of therapy initiation: (A) during the first two years of cART 1998–2009, (B) during the first two years of cART 2010–2020, (C) time-dependent and age-dependent viral suppression rates after two years of cART for children who initiated cART in 1998–2010, and (D) time-dependent and age-dependent viral suppression rates for children after two years of cART who initiated cART in 2010–2020.*
Viral suppression is defined as any viral load measurements below 200 copies/ml, except for time points in the past where tests were used with quantification limits above 200 copies/ml.




B
% Virologically suppressed
100
90
80
70
60
50
40
30
20
10
0
0
24
48
72
96
Weeks since cART initation
VL<200 cps/ml, vertically-acquired HIV, 0-2 years
VL<200 cps/ml, vertically-acquired HIV, 5-18 years
VL<200 cps/ml, vertically-acquired HIV, 2-5 years


C
% Virologically suppressed
100
90
80
70
60
50
40
30
20
10
0
2000
2002
2004
2006
2008
2010
2012
2014
2016
2018
2020
Calendar year
VL<200 cps/ml, 0-12 years
VL<200 cps/ml, 12-18 years
VL<200 cps/ml, >=18 years



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

Long term virological response

Among the children who were using cART for more than 24 months, we assessed viral suppression rates by calendar year of follow-up. The latest viral load measurement in each calendar year was 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.

Time-updated age of HIV RNA measurements was calculated, and children were stratified by the following time-updated age ranges:
(1) 0-12 years
(2) 12-18 years
(3) 18 years or older

Age and time-updated HIV RNA viral suppression rates slightly improved over calendar time among those who initiated cART before 2010. However, viral suppression was lowest among those aged 18 years or older (*Figure 5.5C*). Consistently high viral suppression rates over calendar time were seen among children who initiated cART after 2010. Still, viral suppression rates decreased when the age of 18 years was reached (*Figure 5.5D*).

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[15]. Long-term CD4 cell count changes were assessed among the 388 children who had ever started cART. Children with vertically-acquired HIV were stratified according to their age at the time of cART initiation, as described earlier in this chapter.

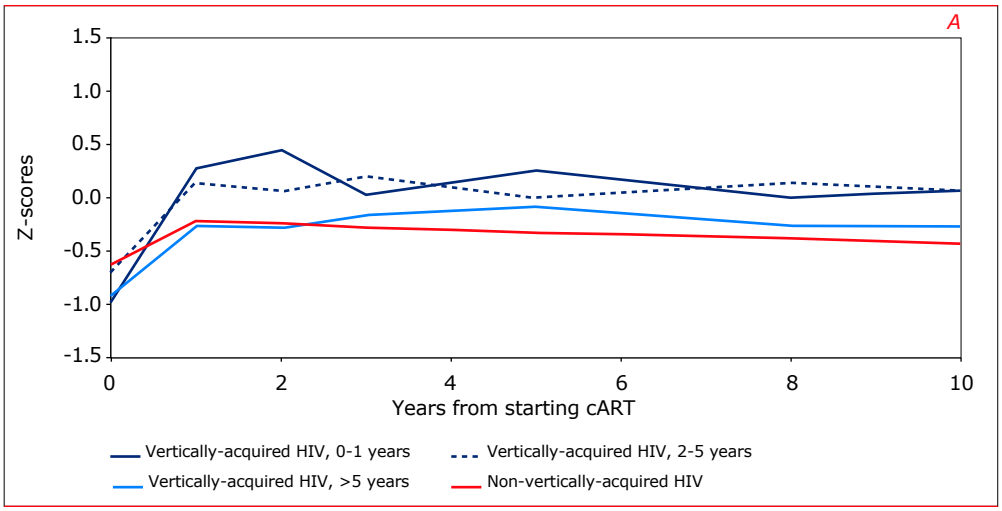
Given that normal CD4 cell counts in younger children are highly age-dependent[16], it is more appropriate to analyse time-dependent CD4 count trajectories, expressing CD4 counts as Z-scores, in which counts are standardised in relation to age. CD4 Z-scores, which represent the standard deviation from 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[17] 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.

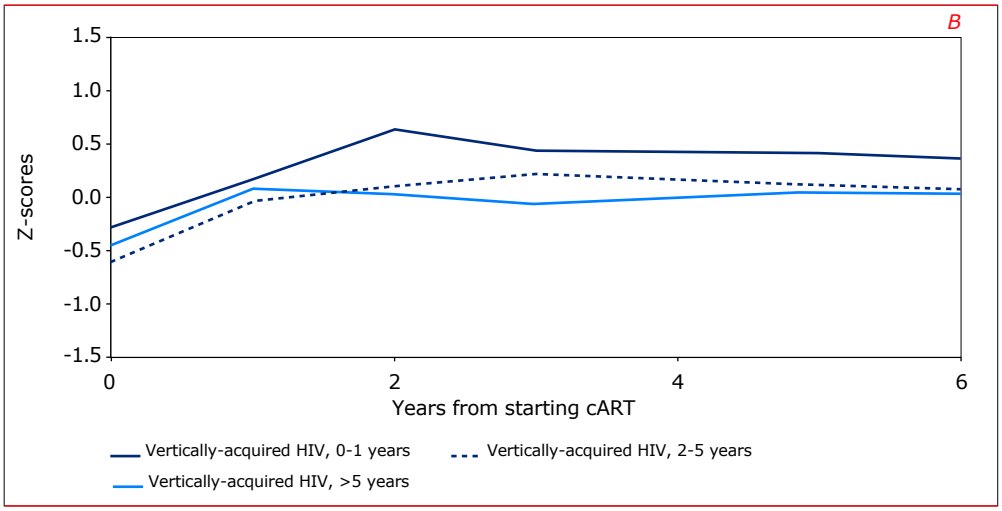
Figures 5.6A and *5.6B* show the changes in CD4 T-cell Z-scores among children living with HIV stratifying those with vertically-acquired HIV by age at initiation of cART, and by calendar year of cART initiation. As expected, the youngest children (under two years of age at cART initiation), had the highest absolute CD4 cell counts at cART initiation (*Table 5.1*), but the age-adjusted CD4 Z-scores did not differ between groups.

For those who initiated cART between 1998 and 2009, CD4 Z-scores increased significantly in the year following cART initiation, whether HIV transmission was non-vertical or vertical. However, the increase in CD4 Z-scores was less strong among children with non-vertical transmission. The youngest children (under 5 years of age at the time of cART initiation), had higher CD4 Z-scores compared to children who were over 5 years of age at the time of cART initiation, and CD4 Z-scores remained consistently higher among the youngest children (*Figure 5.6A*).

In those who initiated cART in or after 2010, the youngest children (below two years of age at cART initiation) had the highest CD4 Z-scores at the time of cART initiation. In the first year following cART initiation, CD4 Z-scores increased significantly in all children in the vertical transmission group. CD4 Z-scores remained consistently higher among the youngest age group (below 2 years of age at cART initiation) (*Figure 5.6B*). Note: CD4 Z-scores are not presented for those in the non-vertical transmission group, due to the low number of children who started cART after 2010.

Figure 5.6: *Changes in Z-scores for CD4 T-cell counts among children living with HIV, stratified by age at initiation of combination antiretroviral therapy (cART): (A) cART initiation between 1998 and 2009, and (B) cART initiation between 2010 and 2020.*





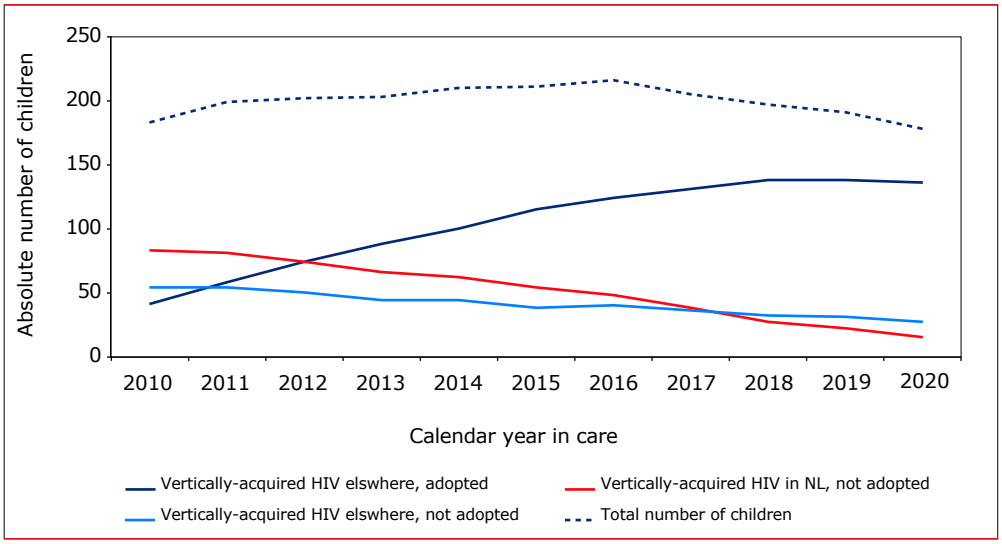
Legend: *cART=combination antiretroviral therapy.*

Currently in clinical care

Of the 393 children living with HIV ever registered by SHM who entered care in the Netherlands before the age of 18 years, 338[b] (86%) were still in care in 2020, 178 of whom were under 18 years of age (*Figure 5.1*). Of the 54 children no longer in care, eight had died, 30 had moved abroad, and 16 children, a substantial number, were lost to follow up.

Figure 5.7 shows the number of children under 18 years of age in care in each calendar year; the number was highest in 2016, with 216 children. However, by 2020, this figure had declined to 178, mainly due to the fact that more children with vertically-acquired HIV who are not adopted are reaching the age of 18 years and, at the same time, fewer children are newly entering care. The number of adopted children in care increased from 41 in 2010 to 138 in 2018, a figure that has remained more or less stable over the last three years.

Figure 5.7: *Number of children aged <18 years known to be in care at the end of each calendar year shown by mode of HIV transmission and adoption status.*



Note: *Children with non-vertically-acquired HIV are not reported as a separate category due to their small numbers, but they are included in the total number of children in care.*

b *One child had a first clinical visit after 2020.*

Currently in care and under 18 years of age

- Of the 393 individuals with HIV who entered care before the age of 18 years, 178 were still aged under 18 at the end of 2020 and 152 were younger than 15 years.
- As of 31 December 2020, their median age was 11 years (IQR 8-14).

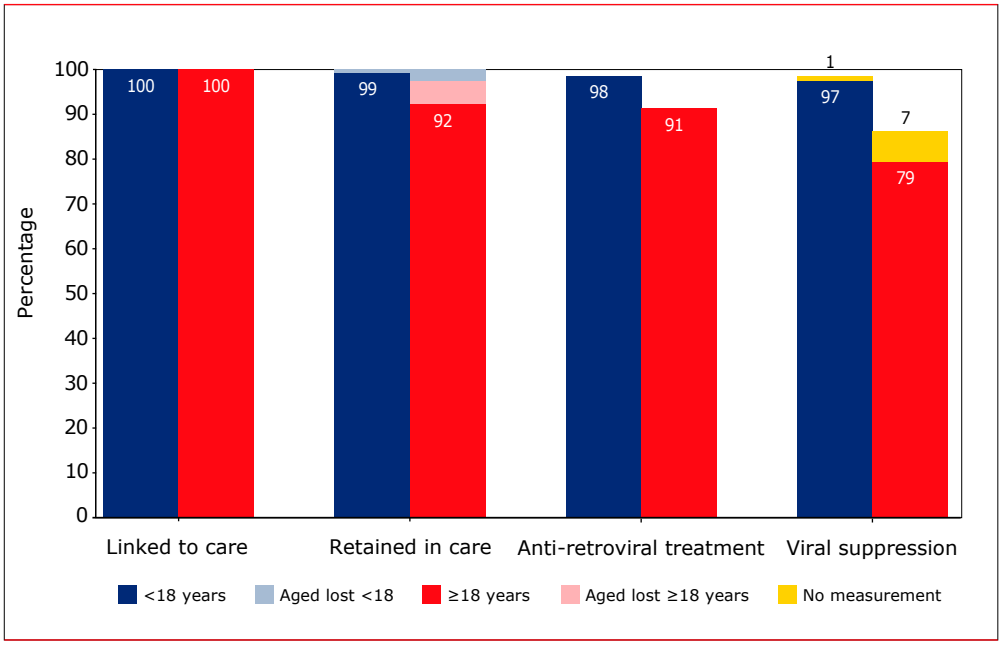
Currently in clinical care and 18 years or older

- The remaining 160 individuals living with HIV who were first registered when still a child, were in care and older than 18 years at the end of 2020.
- As of 31 December 2020, their median age was 24 years (IQR 21-28).

Continuum of care

A 'continuum of care' was constructed, based on the total number of children living with HIV ever registered by SHM that were still alive on 31 December 2020, and not reported to have moved abroad or died. This continuum of care depicts engagement in HIV care across a number of key indicators, the last one being the number of children whose most recent HIV RNA measurement was below 200 copies/ml (*Figure 5.8*).

Figure 5.8: *Continuum of care by age, as of 31 December 2020. The numbers in and above the bars indicate the proportion of individuals.*



Individuals were stratified by age on 31 December 2020 and categorised as:
I. current age, under 18 years
II. current age, 18 years or older

Note: The numbers of children with non-vertically-acquired HIV or unknown mode of HIV transmission in care in 2020 were too small (n=19) for stratification by mode of acquisition.

I Continuum of care: current age under 18 years:
- In total, 180 children under 18 years of age on 31 December 2020 were linked to care, registered by SHM, still alive, and not reported as having moved abroad.
- Of these children, 99% (178/180) were retained in care. Two children, both born outside the Netherlands, were lost to follow up.
- During their last clinical visit in 2020, 98% (177/180) were using antiretroviral therapy.
- Overall, 97% (164/180) had a most recent HIV RNA measurement below 200 copies/ml. Note: one child did not have an HIV RNA measurement in 2020, however, the last HIV RNA measurement in 2019 was below 200 copies/ml.

II Continuum of care: current age 18 years or older:
- 174 individuals over 18 years of age on 31 December 2020 were linked to care.
- 92% (160/174) were still in care as of 31 December 2020. The remaining 14 individuals (six of whom were born outside the Netherlands), were lost to follow up; six before they were 18 years and the remaining eight when they were older than 18 years. Four of these 14 adolescents, who were aged between 17 and 19 years at the time of their last clinical contact at a paediatric HIV treatment centre, were signed off in the registration; they may have been lost during transition to adult care or may be waiting to be re-registered by the adult treatment centre.
- 91% (159/174) were using antiretroviral therapy during their last registered clinical visit.
- Overall, 79% (138/174) had a most recent HIV RNA measurement below 200 copies/ml. Note: 12 young adults did not have an HIV RNA measurement in 2020. For this group, a non-physical consultation was often reported (i.e., via web camera or telephone). The COVID-19 pandemic has shifted how consultations are conducted for adults in care in an HIV treatment centre (see *Chapter 7: Quality of care*). For ten of these 12 young adults, there was a 2019 HIV RNA measurement available; all were below 200 copies/ml.

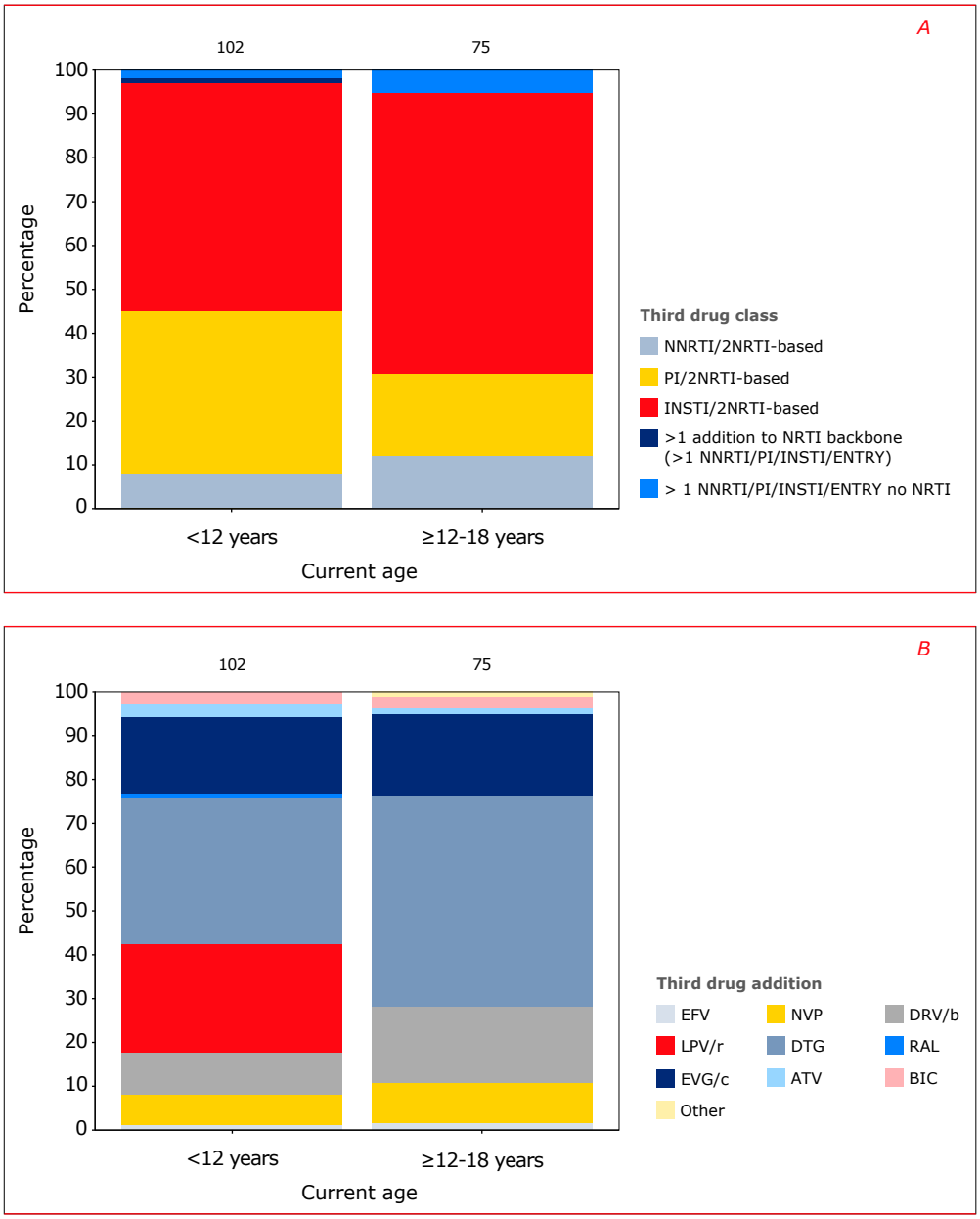
In care and on cART in 2020

Of the 178 children known to be in care in 2020 and under 18 years of age, 177 (99%) were on cART during their last reported clinical visit. The distribution of current cART use is shown in *Figure 5.9*, according to age on 31 December 2020.

Among those under 12 years of age, PI-containing and INSTI-based regimens were the most commonly-used (37% and 52%), with dolutegravir (33%) and lopinavir/ritonavir (25%) the most common individual third agents.

In children aged between 12 and 18 years, 12% were using an NNRTI-based regimen, 19% a PI-based regimen, and 64% an INSTI-based regimen. Among those using an INSTI-based regimen, dolutegravir was most common (48%), followed by elvitegravir (19%). Overall, five children used bictegravir.

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. Numbers above the bars represent the total number of individuals initiating cART in that particular calendar year period.



***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; BIC=bictegravir.*

Special Populations

Adopted children

Of the 393 children ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 149 (38%) had been adopted by Dutch parents. The percentage of adopted children newly entering care increased from 3% in 2000 and 2001 to 89% in 2012 and 2013:

- Their median age at the time of entering care in the Netherlands was 2.7 years (IQR 1.5-5.0).
- All children used cART during follow up in clinical care in one of the Dutch HIV treatment centres.
- In total, 104 (70%) children were already receiving cART before they were adopted.
- 19 (13%) had been treated with monotherapy or dual therapy before the start of cART.
- At the moment of entering care in the Netherlands, only 64 (43%) of the 149 children had a viral load below 200 copies/ml.
- *Figure 5.7* shows the number of adopted children still in care and under 18 years of age. As of 31 December 2020, 146 children were alive and in care and 136 of them were aged below 18 years. Their median age was 10.5 years (IQR 8.7-13.1).
- Three adopted children are no longer in care.
- All children who started cART and who are known to be in care, were still receiving treatment in 2020, and 99% had an undetectable viral load (equal to or below 200 copies/ml) at the last known time point.

Transfer to adult care

Of the 393 children ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 150 children were aged over 18 years and had transferred from paediatric care to adult care by 31 December 2020.

The number of adolescents transferring to an adult centre each year varied between one and 20. The median age for their last visit in paediatric care was 18.3 years (IQR 18.0-19.0). The median time between their last visit in paediatric care and their first visit in adult care was 3.7 months (IQR 2.5-5.2). Time in care after transfer until last documented visit was 6.0 years (IQR 2.7-9.3). Of the 150 individuals who transferred to adult care, four (3%) were lost to follow up, two were signed off registration in the paediatric centre but have not yet been re-registered in an adult treatment centre (which could be down to an administrative delay in re-registration), two (3%) moved abroad, and five (3%) died. The remaining 137 are alive and in care.

At the time of their last clinical visit in paediatric care, 30/150 (20%) had an HIV RNA level above 200 copies/ml (median 3443; IQR 1220-27065). These rates are comparable to results from the UK, which found that three quarters of adolescents were virologically suppressed at the time of transition[18]. We also observed lower proportions of undetectable HIV RNA levels in the year before transfer to adult care, but higher levels one year after transfer: one year before transfer to adult care, 14% of the adolescents had a detectable HIV RNA level, compared to 25% one year after their transfer.

In 2020, 126 of the 137 young adults who were still in care after transfer had an HIV RNA measurement; in 6% of cases it was above 200 copies/ml.

During their last visit in paediatric care, 91% of the adolescents were using cART, while nine percent had discontinued cART: reported reasons for discontinuation were decision by adolescents or parents, low adherence, or decision by physician or nurse. Among adolescents using cART, 29% used a NNRTI-based regimen, 24% a PI-based regimen and 22% an integrase-containing regimen. Of the 137 children who transferred to adult care and who were still in care in 2020, 99% used cART. The majority of them used an integrase inhibitor-based regimen (53%).

Summary

Of the 393 children with HIV ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 86% remain in care in the Netherlands. A substantial proportion of the children newly registered since 2010 are children who were adopted by Dutch parents. This has driven the observed increase in the proportion of children in care who are aged 0-12 years. It is worth noting that the annual number of newly-registered children, who were adopted by Dutch parents, has been decreasing since 2016. This decrease contributes to the drop in the overall number of newly-registered children with HIV in the Netherlands since 2016.

The majority of children with vertically-acquired HIV were born outside the Netherlands. Vertical transmission of HIV within the Netherlands has become rare. This reflects the success of standardised HIV screening during the first trimester of pregnancy[13]. This screening does not, however, completely prevent vertical transmission from occurring. Physicians should therefore remain alert to the possibility of HIV acquisition later during pregnancy in women who tested HIV-negative during the first trimester. They should also be aware of possible signs of primary HIV infection.

We observed low mortality rates in children living with HIV in care in the Netherlands, however the mortality rate was higher among young adults who were diagnosed with HIV as a child, and it included AIDS-related causes of death.

In total, 99% of children living with HIV ever in care in the Netherlands have received cART. The cART regimens have changed over time. Current regimens in use include dolutegravir and lopinavir/ritonavir for younger children, and the integrase inhibitors dolutegravir and elvitegravir in children 12 years of age or older.

Although a less favourable initial virological response was seen in the youngest children, long-term viral suppression rates in children living with HIV who initiated cART in or after 2010, have improved over time, including among that young age group. However, those response rates are lower when children reach the age of 18 years; for example, detectable HIV RNA rates were 20% at the time of transition to adult care, which generally happens around the age of 18.

The continuum of care showed a high retention-in-care rate among children under 18 years of age. Moreover, compared with children younger than 18, a substantially lower proportion of those aged 18 years or older had suppressed HIV RNA levels by the end of 2020 (97% versus 79%). A small number of young adults had no available HIV RNA measurement in 2020 after the start of the COVID-19 pandemic, but most of them had suppressed HIV RNA levels in 2019.

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 among those under 18 years of age. An increasing proportion of the children registered with SHM have now reached the age of 18 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 and treatment interruptions.

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

Colette Smit, Liesbeth van Leeuwen, Tania Mudrikova, Jeannine Nellen

Introduction

The most common mode of HIV acquisition for children aged 0 to 15 years worldwide is transmission from an mother living with HIV[1]. Mother-to-child transmission (MTCT) of HIV mostly occurs perinatally during labour and delivery, or postnatally during breastfeeding. Less common is in utero. Without intervention, the risk of MTCT varies between 15% and 45%[2,3]. 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].

Recommendations for the treatment of HIV during pregnancy 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 based on their CD4 cell count, started it for the first time during pregnancy, with the sole purpose of reducing maternal HIV RNA and limiting the MTCT risk. In many of these cases, cART was discontinued after delivery. In 2015, general treatment guidelines were revised, and treatment for all individuals was recommended, regardless of their CD4 cell count[6]. As a result, most women living with HIV are already being treated with cART at the point they conceive and are advised to continue treatment during pregnancy and postpartum.

To ensure timely initiation of cART, and reduce the risk of MTCT, it is important to ascertain a pregnant woman's HIV status. In January 2004, the Netherlands introduced standardised, voluntary HIV antibody testing for pregnant women during the first trimester of pregnancy[7]. This has resulted in a sharp decline of MTCT of HIV in the Netherlands, as described in further detail in *Chapter 5: Children living with HIV in the Netherlands*.

For the purpose of this year's report, we have decided to focus on women who were pregnant during the years 2016 to 2020, as this population reflects current treatment guidelines. The follow-up and treatment outcomes of all pregnant women in care during the period 1996 to 2018 were described in detail in the 2019 SHM Monitoring report[8].

Demographics

Maternal characteristics

Table 6.1 shows the characteristics of the 429 HIV-1-positive women who had a registered pregnancy in the Netherlands between 2016 and 2020. Of these women, 307 (72%) were non-Dutch in origin and 122 (28%) were born in the Netherlands. The majority of women of non-Dutch origin were born in sub-Saharan Africa (n=192, 63%) or the Caribbean/Latin America region (n=61, 20%).

The majority of the 429 women (367 women, 86%) were aware of their HIV infection before becoming pregnant; the proportion did not differ between women of Dutch and non-Dutch origin. In total, 62 women were diagnosed during their pregnancy; 76% of them as part of the national pregnancy screening. Of the total, 56% received their diagnosis during the first trimester of their pregnancy, 36% in their second trimester, and 8% in their third trimester. Thirty-eight of the 62 newly-diagnosed women reported an earlier negative HIV antibody test. The median time between the date of the HIV test and first contact with one of the HIV treatment centres was eight days (interquartile range [IQR] 6-16). The median time between their first visit to a treatment centre and receiving antiretroviral treatment was also eight days (IQR 1-16). While the database captures the date that blood was drawn for the HIV antibody test, the moment the woman received her HIV diagnosis and was referred to a HIV treatment centre is not recorded.

Based on the first CD4 cell measurement after conception, median CD4 cell count was 570 cells/mm^3 (IQR 390-769) for all women. A lower median CD4 cell count was seen among women who were newly diagnosed with HIV (and started cART) during pregnancy (340 cells/mms, IQR 225-470). However, as CD4 cell counts during pregnancy can be affected by hemodilution, resulting in lower CD4 cell counts[9], CD4 cell percentages may be a more reliable measurement; these were also found to be lower than average among the group of women newly diagnosed during pregnancy (*Table 6.1*).

Among the 429 women, heterosexual contact was found to be the most common mode of HIV acquisition (90%). For eight women, the reported mode of HIV transmission was exposure to contaminated blood, while, for two women of non-Dutch origin, infection occurred through injecting drug use. Seventeen pregnant women acquired HIV through MTCT themselves. For the remaining 15 women, the mode of transmission remains unknown.

Between 2016 and 2020, none of the mothers were documented to have died during follow up. A total of 20 (5%) were no longer in care; of these, nine (9%) were known to have moved abroad and 11 were lost to follow up (3%). No significant differences in lost to follow up were observed between women of Dutch and non-Dutch origin.

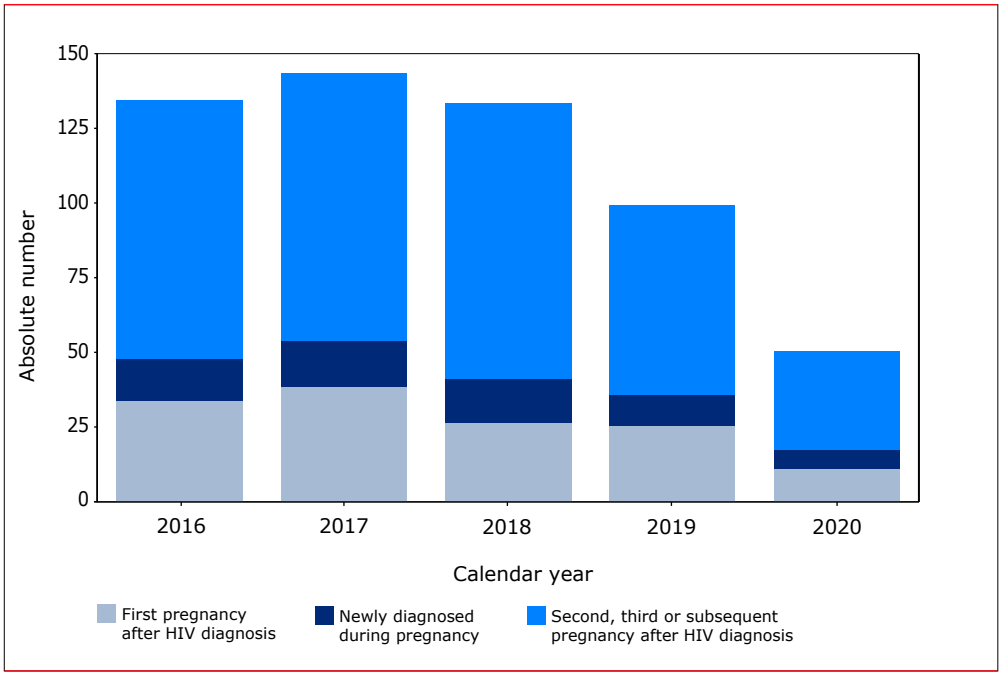
Of the 11 women lost to care, four started cART during their pregnancy, of whom three were newly diagnosed with HIV. All but one had a documented cART regimen, while two women had a detectable HIV RNA during their last clinical visit. In total, nine pregnancies resulted in a live-birth and two in an abortion between 2016 and 2019. All were singleton pregnancies. The median time between delivery of the nine infants and last contact was 2.4 months (IQR 0.3-8.7). Vertical transmission or breastfeeding was not reported in any of the pregnancies.

Trends in number of pregnancies in women living with HIV

In total, 562 pregnancies among the 429 women were reported between 2016 and 2020. The absolute annual number of pregnancies in women living with HIV in care in the Netherlands varied between 144 in 2017 and 50 in 2020[a] (*Figure 6.1*). The number of women newly diagnosed with HIV during pregnancy varied between 16 in 2017 and six in 2020, but remained relatively stable as a proportion of the total number of pregnancies per year at 10-12%. The number of second, third or subsequent pregnancies in women already known to be HIV positive was approximately 73 annually (*Figure 6.1*).

a *It should be noted that data on the number of registered pregnancies in 2020 may be incomplete due to a delay in data collection. Furthermore, the number of reported pregnancies for 2016-19 is higher in this year's report than in the Monitoring Report of 2020; this is due to the clearance of a backlog of retrospective data following a major revision of the data collection protocol in 2018.*

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



Pregnancy-related characteristics

Overall, 429 women accounted for 562 registered pregnancies: 34% of the women had one registered pregnancy, 30% had two registered pregnancies, and 36% of the women had three or more registered pregnancies (*Table 6.1*).

Table 6.1: Characteristics of pregnant women living with HIV registered and monitored by stichting hiv monitoring in 2016-2020.

	Total n (%)	Dutch n (%)	Non-Dutch n (%)
Maternal characteristics	429	122 (28)	307 (72)
HIV diagnosis prior to pregnancy (%)	367 (86)	105 (86)	262 (85)
First CD4 cell count in pregnancy for all women (cell/mm3)*	570 (390-769)	642 (440-860)	550 (370-750)
CD4 percentage**	32 (23-39)	37 (28-40)	30 (22-37)
First CD4 cell count for women newly diagnosed during pregnancy (cell/mm3)*	340 (225-470)	350 (210-520)	330 (230-470)
CD4 percentage**	23 (17-25)	24 (21-32)	21 (16-24)
Age at start of first pregnancy following HIV diagnosis (years*)	34 (30-37)	32 (29-36)	34 (30-37)
HIV transmission route			
Heterosexual contact (%)	387 (90)	112 (92)	275 (90)
Vertical transmission (%)	17 (4)	7 (6)	10 (3)
Other~ (%)	25 (6)	3 (2)	22 (7)
HBsAg positive§			
Yes	19 (5)	2 (2)	17 (6)
No	404 (94)	119 (97)	285 (93)
Unknown	6 (1)	1 (1)	5 (1)
HCV# Ab positive			
Yes	8 (2)	1 (1)	7 (2)
No	408 (95)	117 (96)	291 (95)
Unknown	13 (3)	4 (3)	9 (3)
Total number of pregnancies	562	157	405
Number of pregnancies among women registered in 2016-2020			
1	146 (34)	47 (39)	99 (32)
2	129 (30)	35 (29)	94 (31)
≥3	154 (36)	40 (33)	114 (37)
Pregnancy outcome			
Partus, after at least 24 weeks (%)	367 (65)	107 (68)	260 (64)
Spontaneously or induced abortion, <24 weeks (%)	192 (34)	49 (31)	143 (35)
Unknown (%)	3 (<1)	1 (<1)	2 (<1)

	Total n (%)	Dutch n (%)	Non-Dutch n (%)
Total number of partus	367	107	260
Mode of delivery			
Vaginal	256 (70)	82 (77)	174 (67)
Caesarean	108 (29)	24 (22)	84 (32)
Unknown	3 (<1)	1 (<1)	2 (<1)
Pregnancy duration			
≥37 weeks	314 (86)	88 (82)	226 (7)
32–37 weeks	40 (11)	15 (14)	25 (10)
<32 weeks	10 (3)	3 (3)	7 (3)
Unknown	3 (<1)	1 (1)	2 (1)
Birth weight (grams, IQR*)	3,110 (2,773–3,421)	3,130 (2,665–3,360)	3,100 (2,790–3,455)
Perinatal deaths	4 (1)	1 (1)	3 (1)
Combination antiretroviral therapy started			
Before pregnancy	303 (83)	91 (85)	212 (82)
During pregnancy	64 (17)	16 (15)	48 (18)
No combination antiretroviral therapy during pregnancy	0	0	0
Latest available plasma HIV RNA level prior to delivery			
<50 copies/ml	351 (96)	104 (97)	247 (95)
50–500 copies/ml	12 (3)	3 (3)	9 (3)
>500 copies/ml	4 (1)	0 (0)	4 (2)
Time between delivery and latest HIV RNA measurement (weeks)*	3 (1–4)	3 (1–5)	3 (1–4)

** Median, interquartile range (IQR).*

*** Percentage of total lymphocytes, with IQR.*

$ HBsAg=hepatitis B surface antigen.

 # HCV ab=hepatitis C virus antibodies.

~ Including blood or blood contact (n=8), injecting drug use (n=2) or unknown mode (n=15).

***Legend:** n=total for each category; (%)=percentage of the total for each column.*

Pregnancy outcome

The 562 pregnancies resulted in 367 (65%) births (including both live and stillbirths). A total of 192 (34%) pregnancies ended in miscarriage or abortion. For the remaining three (1%) pregnancies, the outcome is unknown due to missing data.

Pregnancy duration, preterm birth and perinatal death

A total of 367 pregnancies lasted at least 24 weeks and are therefore counted as a birth. The duration of these pregnancies is known in 366 cases. Overall, 314 (86%) pregnancies lasted at least 37 weeks, whereas 50 (14%) pregnancies resulted in preterm birth (defined as a pregnancy duration of 24-37 weeks). It is worth noting that almost half of the preterm births had a pregnancy duration of 36 weeks, and preterm births were often linked to twins or Caesarean sections ($p<0.001$).

Perinatal death, including antepartum death, occurred in four (1%) births. Congenital disorders were registered for nine infants.

Mode of delivery

If viral suppression during pregnancy can be achieved with cART, vaginal delivery is recommended for women living with HIV[10,11]. 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[12].

Overall, 70% of newborns were delivered vaginally; 77% of the women of Dutch origin delivered vaginally, compared to 67% of women of non-Dutch origin. Twenty-nine percent of newborns were delivered by Caesarean section, which was elective in 48% of cases.

Looking at the mode of delivery, we see that 98% of the women who delivered vaginally had an HIV RNA below 50 copies/ml. This figure was 92% for women who delivered by elective Caesarean section, and 89% for those with a secondary (unplanned) section ($p<0.001$).

Combination antiretroviral therapy (cART) use and response to treatment in pregnant women

From 2016 onwards, during the 367 pregnancies that lasted at least 24 weeks, cART was taken by the women involved in all cases: in 303 (83%) pregnancies, women were already using cART at the time of conception, while in 64 (17%) pregnancies, use of cART began during pregnancy. In nine out these 64 pregnancies, cART was started during the first trimester.

Figure 6.2A 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 2016 and 2020. The most commonly used regimens contained darunavir (34%), atazanavir (19%) and raltegravir (13%).

During 107 pregnancies, a switch in cART regimen was reported. The most common documented reason for the switch was pregnancy-related (n=70); toxicity-related was reported in 14 switches. In 28 pregnancies, cART was switched from an integrase-containing regimen to a protease inhibitor (PI, mostly darunavir or atazanavir). Other common switches were within the class of integrase inhibitors, particularly from dolutegravir or elvitegravir to raltegravir. After switching, 4% of the women used a regimen that included a non-preferred antiretroviral (ARV) agent, except in the special circumstances outlined in the most recent guidelines[13].

In May 2018, a potential safety signal was reported regarding dolutegravir and a possible link to neural tube defects[14]; however results from recent studies show the risk is very small. Given those findings and the advantages of dolutegravir, such as its high efficacy and high genetic barrier to drug resistance, dolutegravir is now recommended as the preferred ARV agent during pregnancy; although counselling and informed decision making regarding dolutegravir is still advised by the guidelines[13]. Between 2016 and 2020, dolutegravir was used during 79 pregnancies. No neural tube defects were documented in any of these pregnancies.

Figure 6.2B provides an overview of the components of the NRTI backbone used during pregnancy between 2016 and 2020. The most commonly prescribed backbone was the combination of tenofovir disoproxil fumarate and emtricitabine (TDF+FTC) (72%), followed by a combination of abacavir and lamivudine (ABC+3TC) (14%).

Due to reduced serum levels of cobicistat during the second and third trimesters of pregnancy, and thereby also reduced levels of darunavir and elvitegravir when boosted with cobicistat, from 2018 onwards, cobicistat-containing regimens were no longer recommended during pregnancy[15]. In the Netherlands, cobicistat at the time of delivery was used in two pregnancies after 2018, and another two women used cobicistat during the second or third trimester. All but one of these women had an HIV RNA below 50 copies/ml at the time of delivery.

Figure 6.2A: The most commonly used third-drug additions to the nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone used as part of cART regimens during pregnancies in 2016-2020.

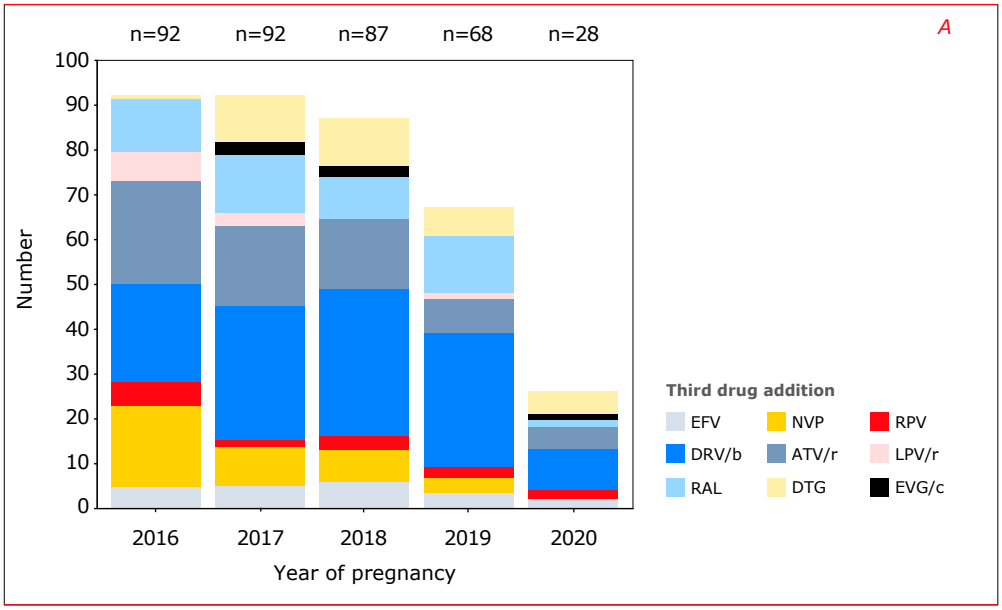
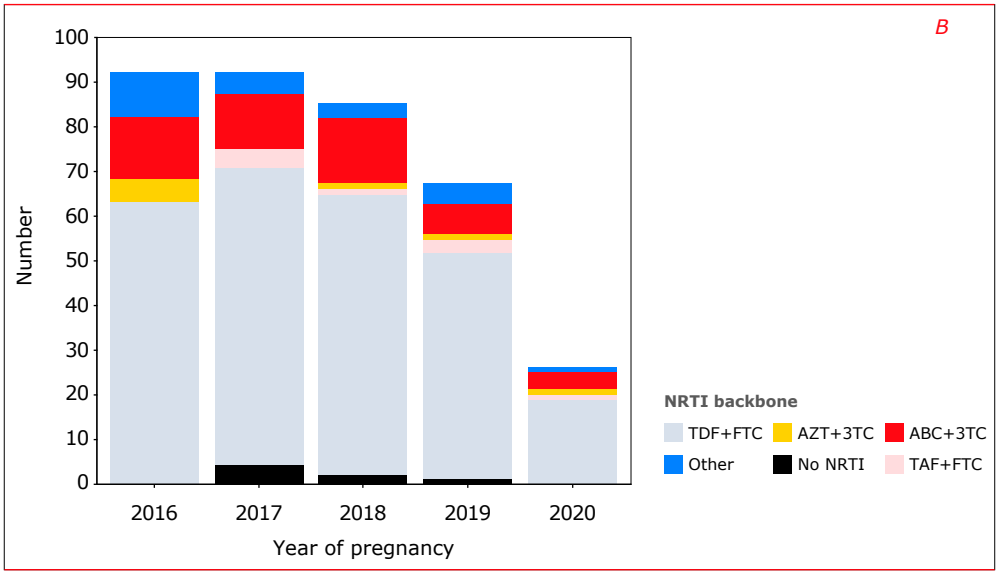


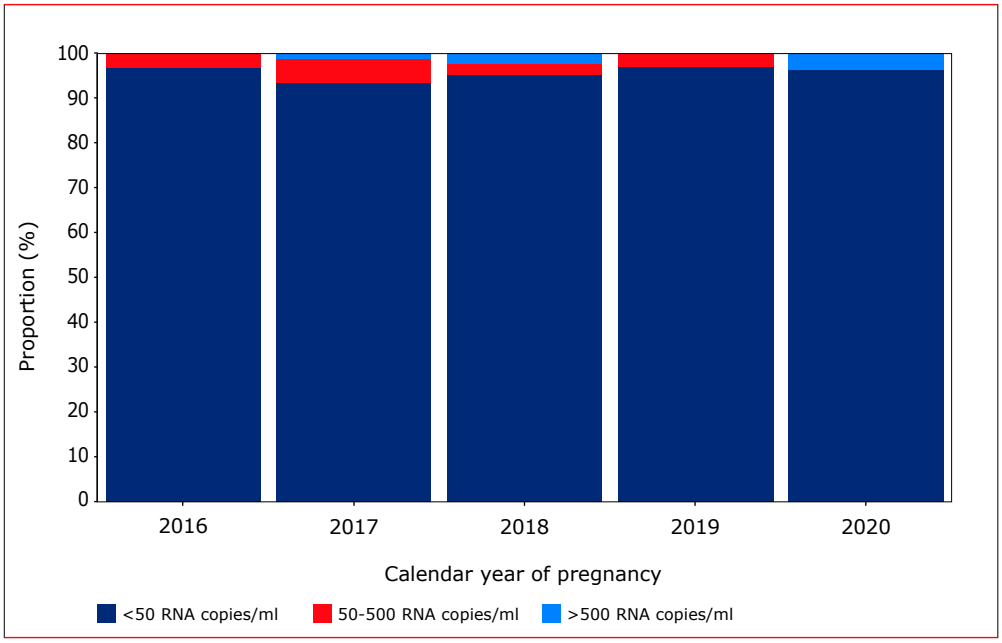
Figure 6.2B: The nucleoside reverse transcriptase (NRTI) backbone used as part of cART regimens during pregnancies in 2016-2020.



Legend: *3TC=lamivudine; /b=boosted (cobicistat or ritonavir); /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; RPV=rilpivirine; SQV=saquinavir; TDF=tenofovir disoproxil fumarate; TAF=tenofovir alafenamide; NRTI=nucleoside analogue reverse transcriptase inhibitor.*

Figure 6.3 shows the percentage of women on cART and their latest available plasma HIV RNA level prior to delivery; HIV RNA levels were categorised as below 50 copies/ml, 50-500 copies/ml, and above 500 copies/ml. In 96% of the overall births, the mothers had an HIV RNA level below 50 copies/ml at the time of delivery, and 3% had an HIV RNA level between 50 and 500 copies/ml. The proportion of women with an HIV RNA below 500 copies/ml at the time of delivery was 100% in 2016 and 2019, but it was 99% in 2017, 98% in 2018 and 96% in 2020. These lower proportions were driven by four women with HIV RNA above 500 copies/ml. Two women began cART treatment during pregnancy at weeks 15 and 37; one of these women had been diagnosed with HIV after 36 weeks of pregnancy. Another 12 women had HIV RNA levels between 50 and 500 copies/ml (median RNA=100 copies/ml, minimum=53, maximum=491). Six of these 12 women were first diagnosed with HIV during their pregnancy. No MTCT was reported among the infants born to mothers who had HIV RNA levels above 50 copies/ml at the time of delivery. In total, eight women with a detectable HIV RNA were already using cART at the time of conception; six of them had failed on cART in the past, before this pregnancy.

Figure 6.3: *Distribution of women using cART with their latest HIV RNA levels prior to delivery: <50 copies/ml, 50-500 copies/ml, or >500 copies/ml.*



Mother-to-child transmission rate in the Netherlands

Between 2016 and 2020, 367 births were registered in the Netherlands among mothers who knew they had HIV prior to conception, or were first diagnosed during pregnancy. All mothers used cART during their pregnancy, which resulted in an MTCT transmission rate in pregnant women using cART in the Netherlands of 0.27%, with a single transmission, which is in line with low reported MTCT rates in other countries[16-19]. That single transmission occurred after the woman was diagnosed in the third trimester of her pregnancy, and, despite the fact that cART was initiated late in the pregnancy, the last measured HIV RNA level before delivery was undetectable.

Postpartum follow up

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 367 pregnancies lasting 24 weeks or longer, 70 were excluded from this analysis: 60 because of insufficient follow up between delivery and the time of database closure; one because data was missing on ARV use during the postpartum period; and nine because the women were no longer in care (two had moved abroad and seven were reported as lost to follow up during the postpartum period). For the remaining 297 pregnancies in 271 women, cART was initiated before conception or during pregnancy in 82% and 18% of cases, respectively. In 35 of these 297 pregnancies, treatment was discontinued postpartum; in 21 cases, the documented reason was a decision by the patient and in two cases by the treating physician. In 20 of these 35 pregnancies, treatment was restarted after a median of nine weeks (IQR 3-13). In the remaining 15 pregnancies, the women did not restart cART postpartum; seven women restarted cART after the postpartum period ended, and eight women did not have any documented restart at the time of database closure.

Virological outcome

Detectable viremia 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 16% of the 297 pregnancies we analysed. For the subset of women with documented continued postpartum use of cART, 29 (11%) women had a HIV RNA level above 50 copies/ml (median HIV RNA=171 copies/ml, minimum=52 and maximum=450,000 copies/ml), ten of the women

had more than one HIV RNA level above 50 copies/ml during the postpartum period. In the 35 women who discontinued the use of cART postpartum, 18 (51%) experienced viral rebound (median HIV RNA=11,706 copies/ml, minimum 617 and maximum 118,579 copies/ml). In addition, 17 women had an undetectable HIV RNA, despite no cART use after their discontinuation during the postpartum period. For two of these women, it was reported that their high CD4 cells counts and undetectable HIV RNA continued despite no cART use; five experienced a viral rebound after the postpartum period and eight remained virally suppressed (six of them eventually restarted cART). No follow-up data are available for the remaining women, due to the short period of time between the postpartum period ending and the closure of the SHM database.

Breastfeeding

Breastfeeding data were available for 256 of the 297 pregnancies. Breastfeeding was reported in 14 women, however, the duration of breastfeeding was not documented. Importantly, all 14 had HIV RNA levels below 100 copies/ml during the postpartum period. No cases of vertical transmission were documented in any of these breastfeeding women.

Summary and conclusions

All women with a registered pregnancy since 2016 have received cART during their pregnancy. More than 96% had an HIV RNA level below 50 copies/ml around the time of delivery and 99% below 500 copies/ml. The MTCT rate in pregnant women using cART was 0.27% during the period 2016 to 2020, which is comparable to the low figures reported in other western European countries[16-19].

Despite the high proportion of women with undetectable viremia near the time of delivery, we did observe a somewhat higher proportion with detectable HIV RNA levels in 2017 and 2018. Half of the women with a detectable HIV RNA started cART during their pregnancy and the other half were already using cART, but the majority of these women had earlier episodes of virological failure. To maintain a low rate of vertical transmission of HIV, it will be important to closely monitor women who are newly diagnosed with HIV after conception, and therefore only start cART during pregnancy, and those with a history of virological failure.

Although most women were aware of their HIV infection prior to their pregnancy, 14% were not and were newly diagnosed during pregnancy. In most of these cases, their diagnosis was a result of the national HIV pregnancy screening during the first trimester of the pregnancy. However, some women received their HIV diagnosis during the second or third trimester of their pregnancy, which could complicate the timely start of cART.

Finally, since 2015, cART has been recommended for all individuals, regardless of CD4 cell count, including continued use of cART for women postpartum. From 2016 onwards, 11% of women who continued to use cART postpartum had at least one episode of viraemia, of whom one third had more than one HIV RNA level above 50 copies/ml. This could be due to the fact that adherence to treatment has been reported to deteriorate during the postpartum period[20-25].

The proportion of preterm births and Caesarean sections among women living with HIV were higher than those observed in the general population of women (14% and 29% vs 7% and 15%[26]). During labour, a cardiotocogram is performed to monitor fetal condition. If the results are unclear, fetal blood sampling is often carried out. However, as fetal blood sampling is contraindicated in cases of HIV infection, the threshold for Caesarean section is generally lower. It is not clear whether this lower threshold contributed to the higher Caesarean numbers observed. Premature delivery has been linked to cART use, especially in the first 12 weeks of pregnancy[27,28]. As the etiology of preterm delivery is complex and multifactorial, it is unclear whether this can explain the high proportion of preterm births. The association between various ARVs and adverse pregnancy outcomes, including low birthweight, has been evaluated in different studies with conflicting results[29]. The effect of ARVs on pregnancy outcomes might be influenced by duration of exposure, whether ARV was used during conception or in the first trimester, and the effect may also vary between ARVs within the same ARV drug class.

Recommendations

As a result of changes to guidelines concerning HIV and pregnancy in 2015, cART is more likely to be used at conception and continued post delivery. This is expected to result in a greater number of women with virally-suppressed HIV RNA levels earlier in their pregnancy and around the time of delivery.

Women with HIV who start cART when already pregnant, require a higher degree of support; not only during pregnancy to ensure suppressed HIV RNA levels at the time of delivery, but also post delivery to maintain adherence to cART. Some hospitals now discuss the option of breastfeeding, opposed to formula feeding, with women with sustained undetectable viral loads who do not have treatment adherence issues, based on shared decision making. However, this is not common practise throughout the Netherlands. Women who decide to exclusively breastfeed should be closely monitored clinically and virologically, along with their infants[30,31]. In the Netherlands, this monitoring is described in the HIV exposure follow up protocol for newborns[32]. They need continuous support to ensure sustained viral suppression and prevention of MTCT of HIV while breastfeeding.

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7. Quality of care

Anders Boyd, Colette Smit, Kees Brinkman, Suzanne Geerlings, Judith Branger, Marc van der Valk

Introduction

One of the missions of stichting hiv monitoring (SHM) is to contribute to the quality of HIV care in the Netherlands. In 2018, there were 26 official HIV treatment centres in the Netherlands. In 2019, this number changed to 24. Via the collection of pseudonymised data from patients in outpatient care at these centres, SHM can provide a nationwide overview of the outcome of care for patients. This unique overview allows SHM to facilitate assessment of the quality of HIV care in the Netherlands.

HIV treatment guidelines are not only intended to help physicians provide 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 people living with HIV in the Netherlands[1]. In general, these guidelines follow the United States Department of Health and Human Services (DHHS) HIV/AIDS practice guidelines[1]. Using these guidelines as a basis, we defined a set of indicators that have been used in this analysis to explore the quality of care in Dutch HIV treatment centres, and provide insight into any potential variation between HIV treatment centres.

Our analysis is based on the data of individuals who were diagnosed with an HIV infection, entered care and were registered with the SHM (*Box 7.1*). The indicators selected for this analysis fall into three categories: volume, outcome, or process. Each category contains a host of specific indicators, which are applicable to different focus populations. The details of the indicators used in this chapter, along with the focus populations to which they were applied, are defined in *Box 7.2*. Indicators are only reported for the 24 HIV treatment centres that are currently in use. Each HIV treatment centre is referenced by a number, which is used consistently across all figures in this chapter.

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 a patient is first seen for care in a Dutch HIV treatment centre, which is usually within a few weeks of HIV diagnosis.
Registration	The moment the details of a patient in care are reported to SHM by their treating physician or nurse, and they are 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 a patient is registered with SHM.
Patient	An individual living with HIV who is receiving, or has received, medical care at an HIV treatment centre. This term is specifically used in this chapter to denote the role of the individual in a medical context.

Box 7.2: Definitions of specific indicators and focus populations.

Specific indicator	Definition	Focus population
Volume indicator		
Newly entering care	The number of patients who entered care at one of the Dutch HIV treatment centres for the first time.	Entered care
Outcome indicators		
Retention in care		
Short-term retention	The percentage of patients who were still in care at least 18 months after entering care.	Entered care[1]
Overall retention	The percentage of patients who have a documented clinical visit.	In care
Initiation of cART		
Early cART initiation	The percentage of patients who initiated cART within six months of entry into care.	Entered care[2]
Overall cART initiation	The percentage of patients who have initiated cART.	In care

Specific indicator	Definition	Focus population
Viral suppression		
Suppression after cART initiation	The percentage of patients with a plasma HIV RNA level <400 copies/ml within nine months of cART initiation.	Starting cART[3]
Suppression while on cART	The percentage of patients with a plasma HIV RNA level <100 copies/ml.	On cART[4]
Suppression while in care	The percentage of patients with a plasma HIV RNA level <100 copies/ml.	In care
Process indicators		
Lab measurements prior to cART	The percentage of patients for whom data were available on plasma HIV RNA or CD4 count within the six months prior to or the one month following cART initiation.	Starting cART[3]
Lab measurements while in care	The percentage of patients for whom data were available on plasma HIV RNA or CD4 count.	In care

All indicators are reported for a given year.

Abbreviations: cART, combination antiretroviral therapy.

[1] *This indicator is calculated for patients who entered care in the two years prior to a given year. It does not include individuals who moved abroad or died.*

[2] *Entered care and did not move abroad or die.*

[3] *Treatment-naive people who started cART in a given calendar year.*

[4] *On cART for at least six months and still in care in a given calendar year.*

Volume indicator

As a volume indicator, we quantified the number of patients *newly entering care* each year per treatment centre.

Outcome indicators

The outcome indicators include *retention in care*, *initiation of cART* and achievement of *viral suppression*.

For the purpose of the current analysis, we have defined short-term and overall retention in care as follows:

- *Short-term retention in care*: The percentage of patients who entered care for the first time at one of the Dutch HIV treatment centres, after being diagnosed with HIV, who were still alive and in care at least 18 months after entering care. Patients known to have died or moved abroad were excluded from this retention-in-care indicator. Approximately 10% and 9% of patients who entered care in 2017 and 2018, respectively, switched treatment centres (mainly due to the closure of two treatment centres in 2018); we considered these to be retained in care, since they were not lost to follow up. However, to avoid double counting, they were assigned to their most recent treatment centre.
- *Overall retention in care*: The percentage of all patients in care who did not move abroad or die, *and* had a documented clinical visit for a given year. 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) the percentage of patients entering care who started cART within six months of entry; and 2) the percentage of patients still in care who had ever initiated cART.

Viral suppression was assessed by three indicators: 1) the percentage of treatment-naive patients, who started cART, with a plasma HIV RNA level below 400 copies/ml within nine months of starting cART; 2) the percentage of all patients on cART for at least six months who had a plasma HIV RNA level below 100 copies/ml; and 3) the percentage of all patients in care who had a last available HIV RNA level below 100 copies/ml.

Process indicators

Process indicators were calculated for two scenarios: prior to starting cART and while in care.

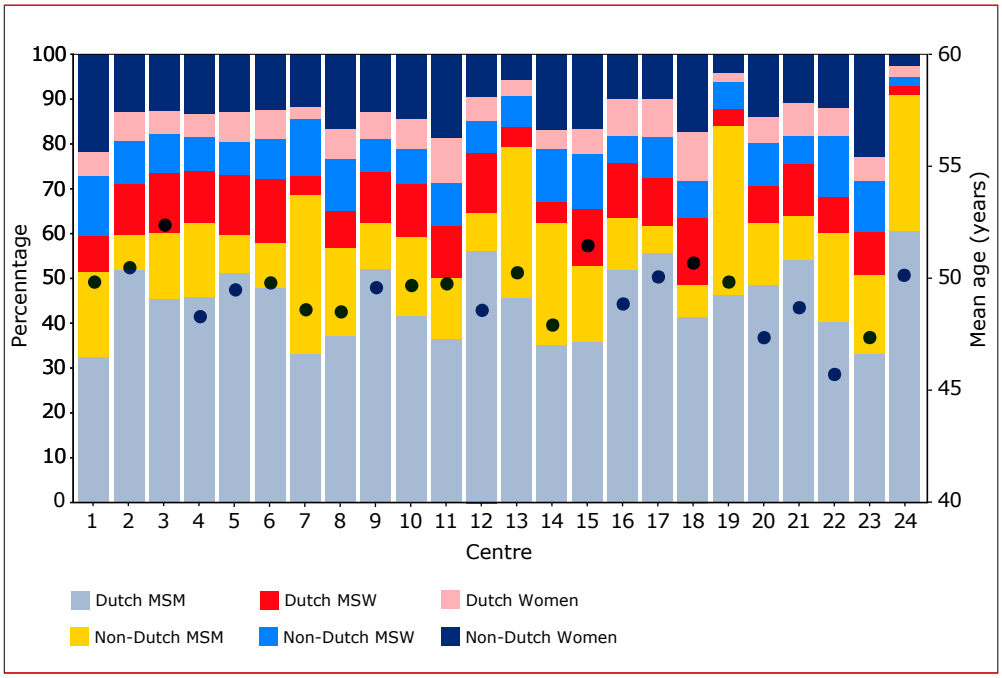
To calculate indicators *prior to cART initiation,* we included all patients who had newly entered care in a given year. Patients who switched treatment centres were not counted as newly entering care, as they had already been in care elsewhere. Two separate indicators were defined as the percentage of individuals initiating cART for whom 1) plasma HIV RNA or 2) CD4 count measurements were available in the six months prior to or one month following cART initiation. This period was selected as some patients may have initiated cART directly after entering care, in which case HIV RNA or CD4 count measurements will have been measured on the same day or directly after cART initiation.

To calculate indicators *while in care*, we included all individuals who were in care and did not move abroad or die. Two sperate indicators were defined as the percentage of patients in care for whom 1) plasma HIV RNA or 2) CD4 count measurements were recorded at least once during a given calendar year.

Centre overview

The characteristics of patients in care in 2020 are described per HIV treatment centre in *Figure 7.1* (i.e., patient 'mix'). The largest geographical origin/mode of transmission/gender group observed for almost all centres was Dutch men who have sex with men (MSM), ranging from 32% to 60% (median 46%) of patients per centre. Most individuals in the non-Dutch groups originated from the Caribbean/South America (30%), sub-Saharan Africa (28%), other countries in Europe (13%), or southeast Asia (9%). The distribution of regions of birth for non-Dutch patients in care in 2020 are described per centre in *Appendix Figure 7.1*. There was substantial variation across centres in the other geographical origin/mode of transmission/gender groups: non-Dutch MSM (median 16%, range 6-38%), Dutch men who exclusively have sex with women (MSW) (median 11%, range 2-15%), non-Dutch MSW (median 9%, range 2-13%), Dutch women (median 6%, range 2-11%), and non-Dutch women (median 13%, range 2-23%). The mean within-centre age range was 46 to 52 years (median 50 years).

Figure 7.1: Description of the patient 'mix' for patients in care in 2020 in the Netherlands.



***Note:** The bars in this chart show the percentage of individuals per centre according to geographical origin/ mode of transmission/gender group. Black dots represent the mean age of patients in care at each centre.*
***Legend:** MSM=men who have sex with men; MSW=men who exclusively have sex with women.*

Evolution of indicators over time

HIV testing and treatment guidelines have remained unchanged in the Netherlands since 2015. The distribution of patient 'mix' in care has also remained rather stable over the past five years. As a result, increases in indicators over time are likely to indicate organisational improvement in providing care to patients living with HIV, while decreases might indicate potential issues that require further assessment. To provide an understanding of how indicators have evolved, each indicator in *Box 7.2* has been reported for its corresponding focus population on an annual basis between 2016 and 2020. For example, the indicator 'overall cART initiation' has been provided for individuals who were in care in 2016, 2017, 2018, 2019, and 2020.

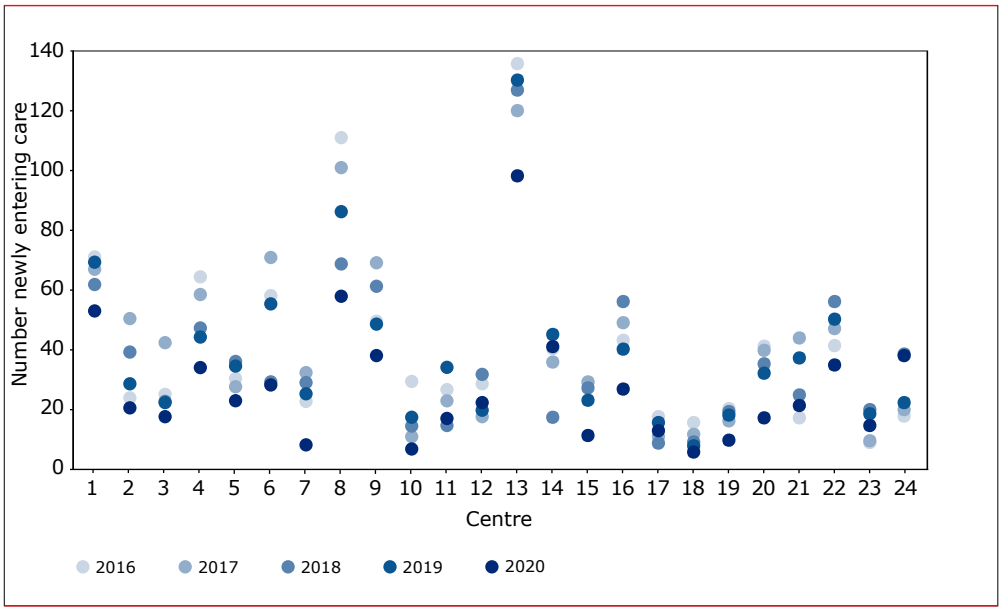
The first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the disease known as COVID-19, was detected in the Netherlands on 27 February 2020[2]. The rapidly evolving SARS-CoV-2 pandemic forced HIV treatment

centres to reorganise their services at the end of March 2020. Visits that usually took place physically at the HIV treatment centres were, for the most part, replaced with other types of consultations, such as virtual consultations via telephone or a web camera, and blood had to be drawn at other locations. These reduced services may have affected many of the indicators for quality of care, thus particular attention has been given to the changes in indicators between 2019 and 2020.

Volume indicator

The numbers of patients who newly entered care across the HIV treatment centres each year are shown in *Figure 7.2*; this number has steadily decreased for most centres over the past five years. The median number who newly entered care across centres was 33 in 2019 and 22 in 2020, with a minimum number of six patients in 2019 and five in 2020. In 2020, ten HIV treatment centres had fewer than 20 patients newly entering care; two of these were of small patient size (i.e., fewer than 400 in care), and eight were of medium patient size (i.e., 400-700 in care).

Figure 7.2: *Annual number of patients newly entering care per HIV treatment centre in the Netherlands between 2016 and 2020.*

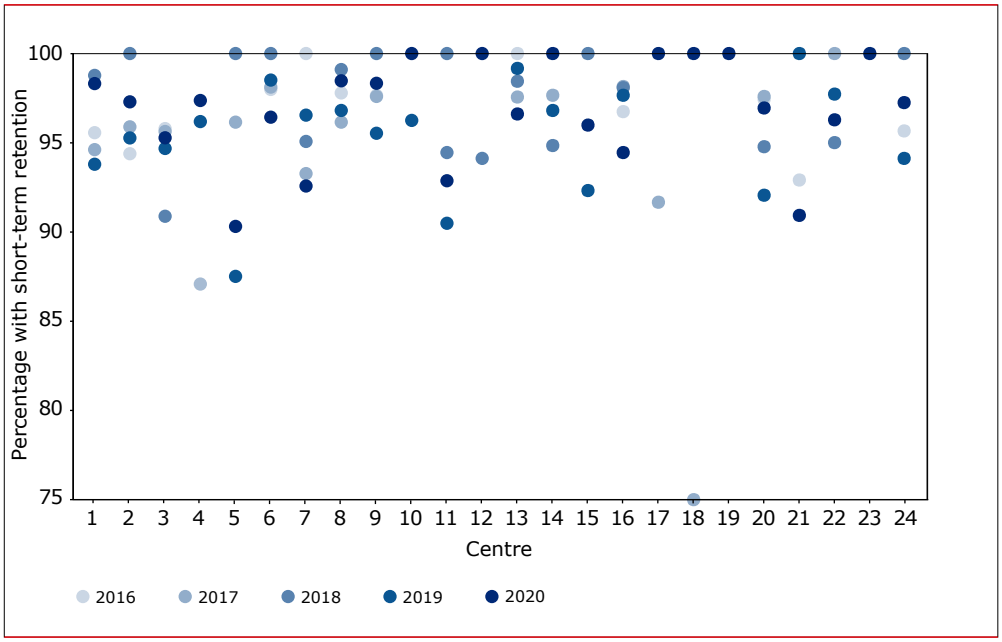


Outcome indicators

Retention in care

The annual percentage of patients with short-term retention has remained stable over the past five years and can be viewed per centre in *Figure 7.3*. The median percentage across centres was 97% (range 88-100%) in 2019, for patients entering care in 2017, and 97% (range 90-100%) in 2020, for those entering care in 2018. For most centres, the difference between 2020 and 2019 was within a margin of ±2%. A decrease of more than 5% was observed in only one centre, which was of medium size.

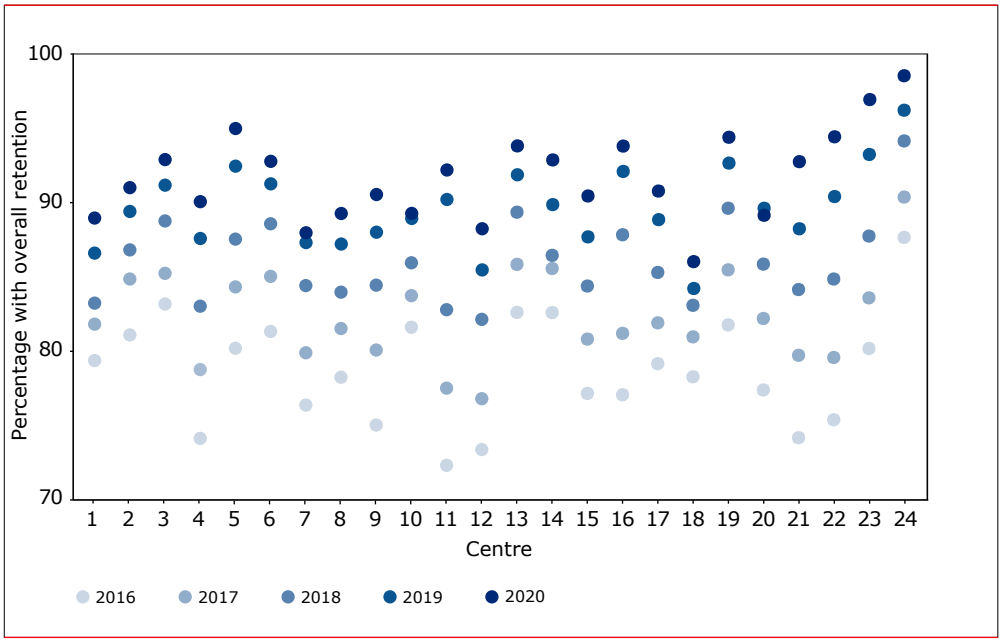
Figure 7.3: *Short-term retention in care; in other words, patients who entered care two years prior to 2016, 2017, 2018, 2019, or 2020, and were still in care 18 months later.*



Legend: *Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

The annual percentage of patients per centre with overall retention is given in *Figure 7.4*. This percentage has steadily increased for most centres over the past five years. The median increase from 2016 to 2020 across centres was 12% (range 8-20). Of note, the median percentage with overall retention across centres was 89% (range 84-96%) in 2019 and 92% (range 86-99%) in 2020. No centre saw a decrease of more than 2% between 2020 and 2019.

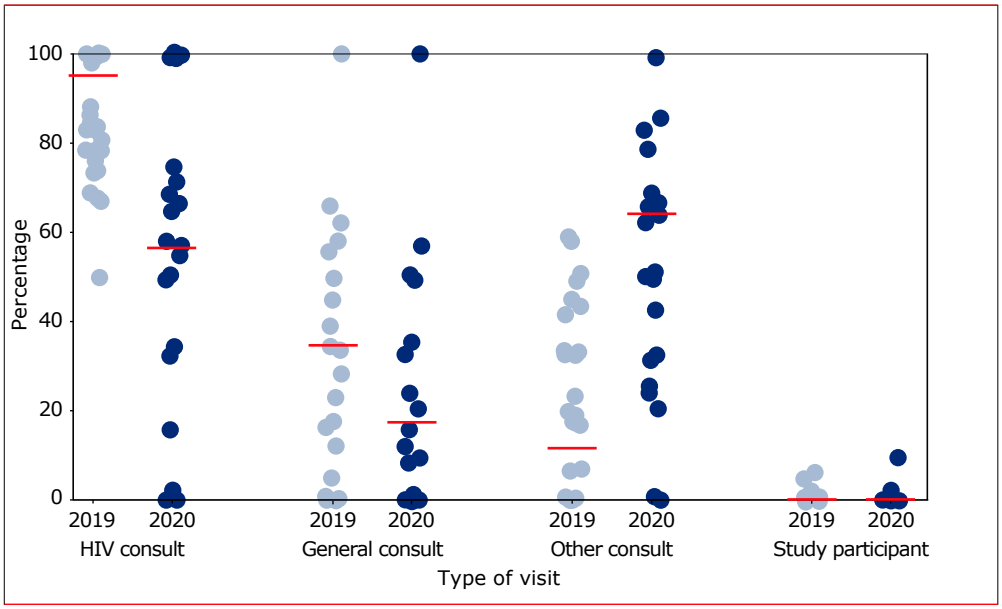
Figure 7.4: Overall retention in care; in other words, patients in care who had a documented visit per calendar year between 2016 and 2020.



Legend: Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.

Overall retention is defined by whether a visit occurred during a given year. Since services at many of the HIV treatment centres were greatly reduced during the COVID-19 pandemic, alternative consultation options were required. *Figure 7.5* illustrates the change in visit types between 2019 and 2020 for those in care. The median percentage of patients who had a physical consultation with an HIV specialist decreased from 95% (range 71-100%) in 2019 to 56% (range 28-81%) in 2020. Similarly, the median percentage of patients who had a physical consultation with another specialist, consultant, or nurse consultant/specialist decreased from 35% (range 0-91%) in 2019 to 17% (range 0-57%) in 2020. In contrast, the percentage of patients who had a non-physical consultation with any type of healthcare professional increased from a median 12% (range 2-33%) in 2019 to 64% (range 42-90%) in 2020. Most of these consultations occurred over the telephone or via email (94%) and few occurred virtually using video consultation (2%) or other means (5%). The percentage of patients who had a consultation as part of participating in a study remained comparable between 2019 and 2020.

Figure 7.5: Distribution of visit types for patients in care in 2019 and 2020.

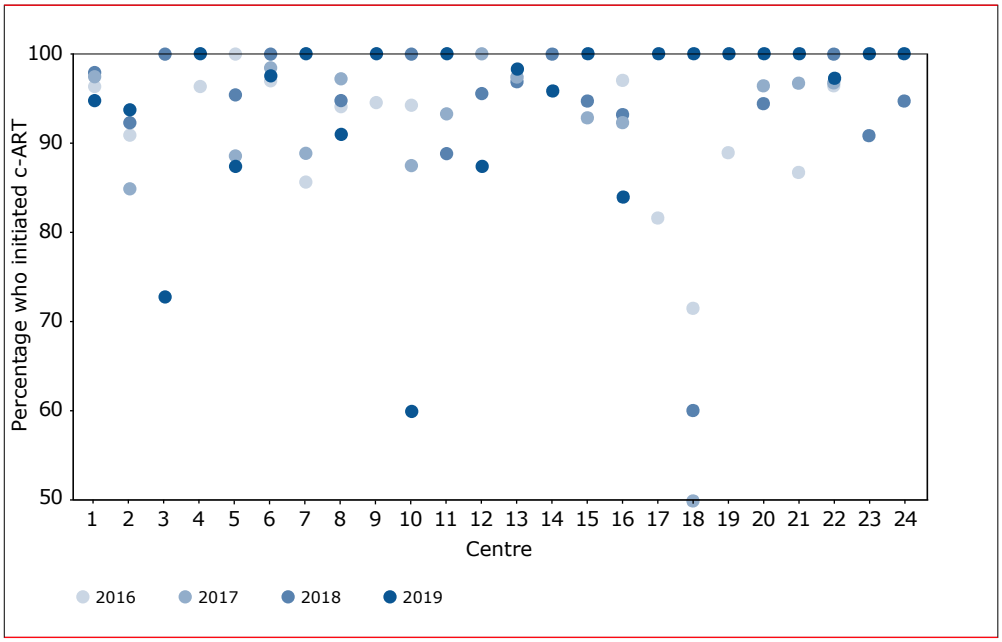


Legend: Grey-blue and dark blue circles represent 2019 and 2020, respectively. 'HIV consult' refers to a physical consultation with an HIV specialist. 'General consult' refers to a physical consultation with another specialist, consultant, or nurse. 'Other consult' refers to a consultation with any type of healthcare professional, which replaced what would have been a physical consultation. 'Study participant' refers to a visit as part of participating in a biomedical study.

Initiation of cART

The annual percentage of patients per centre who started cART within six months of entering care is given in *Figure 7.6*. This percentage varied only slightly at most centres over calendar years. Across centres, the median percentage was 97% (range 60-100%) in 2018 and 99% (range 60-100%) in 2019. Five centres had a percentage lower than 90%, of which one was of medium size and four were of large patient size (i.e., more than 700 in care). For individuals who started cART, the time between entering care in 2018 to starting their treatment, averaged within centres, was a median 12 days (range 3-38). No data are given for 2020 as there has not been enough follow-up time to calculate this indicator for patients who entered care in the latter half of 2020.

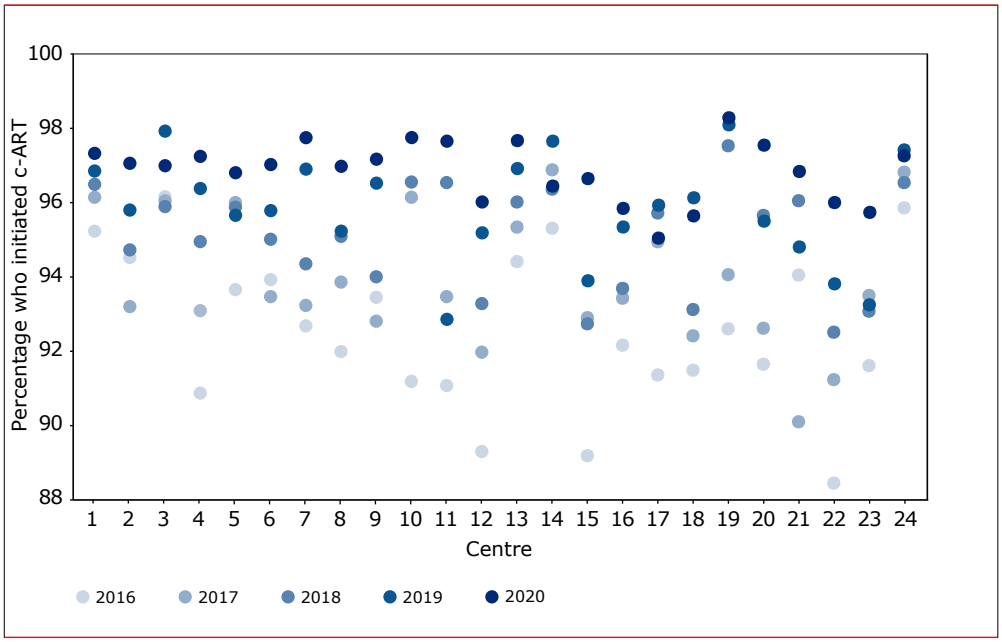
Figure 7.6: *The annual percentage of patients entering care between 2016 and 2019 who started combination antiretroviral therapy (cART) within six months of entry.*



Legend: *Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

The annual percentage of patients per centre remaining in care who ever initiated cART is given in *Figure 7.7*. This percentage has been steadily increasing for most centres over the past five years. The vast majority of patients in care in 2019 and 2020 initiated cART (across-centre median 96% and 97%, respectively). This percentage exceeded 95% in all centres in 2020.

Figure 7.7: The annual percentage of patients in care between 2016 and 2020 who ever initiated combination antiretroviral therapy (cART).

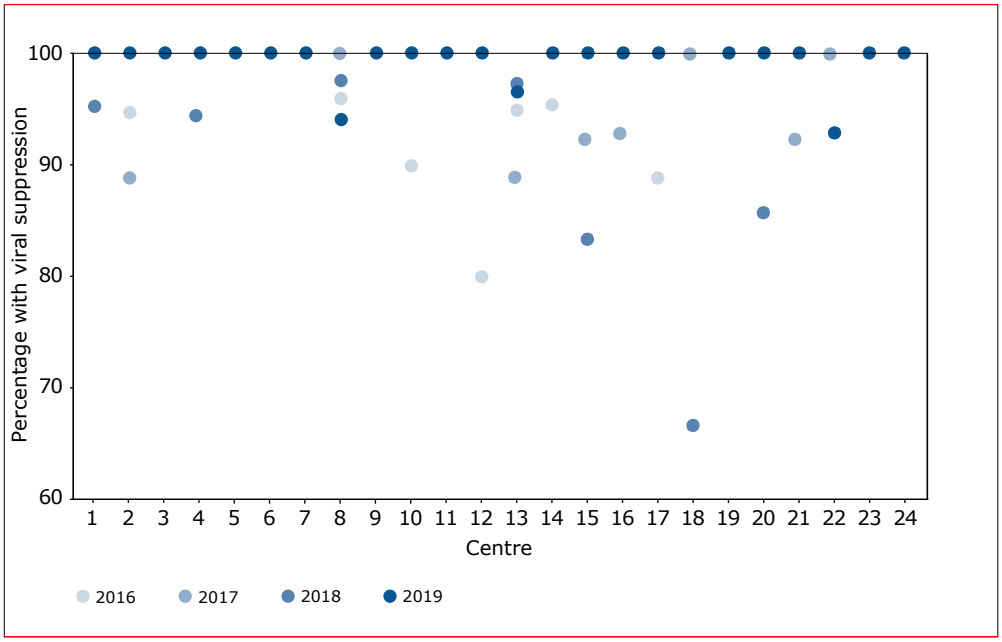


Legend: Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.

Viral suppression

Viral suppression was assessed using *three* indicators. The *first* indicator is the percentage of treatment-naive patients newly initiating treatment who had an HIV RNA level below 400 copies/ml within nine months of starting cART. The annual percentage per centre is given in *Figure 7.8*, which shows consistently high percentages at most centres for individuals initiating cART between 2016 and 2019. The median percentage with viral suppression after cART initiation was 100% (range 89-100%) in 2018 and 100% (range 93-100%) in 2019; two centres with fewer than three patients were excluded from the calculation. No data are given for 2020 as there has not been enough follow-up time to calculate this indicator for patients who initiated cART in the latter half of 2020.

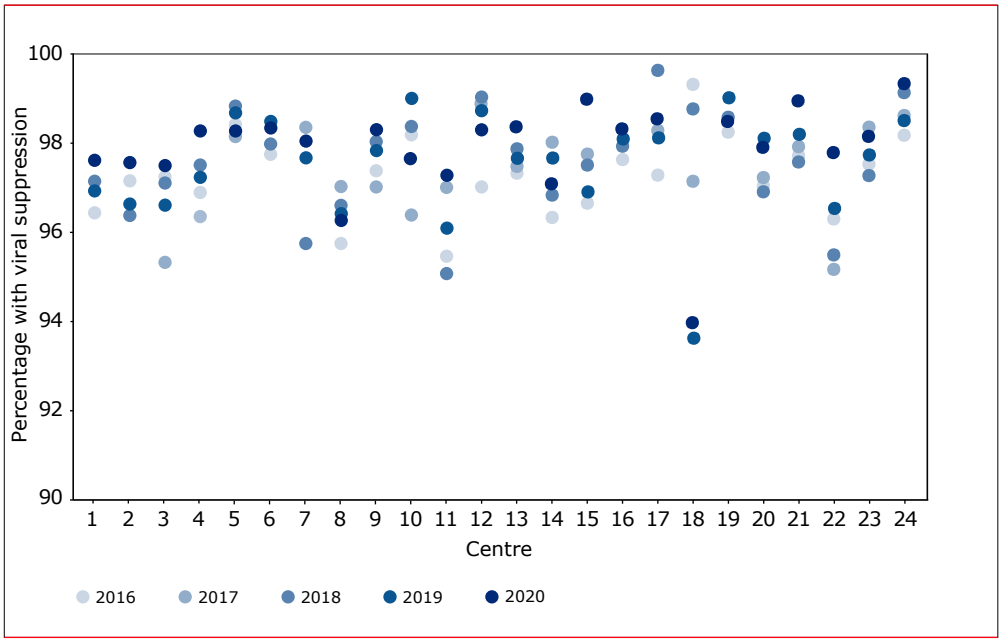
Figure 7.8: The annual percentage of all patients who initiated combination antiretroviral therapy (cART) and stayed on it at least six months between 2016 and 2019, and who had an HIV RNA level <100 copies/ml within nine months of initiating treatment.



Legend: Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1. Two centres were excluded – one in 2018 (centre 19) and one in 2019 (centre 18) – as they had fewer than three patients included in the indicator.

The *second* viral suppression indicator is the percentage of all patients in care who have been on cART for at least six months and have a last available HIV RNA level below 100 copies/ml. This annual percentage is given per centre in *Figure 7.9*, which shows rather high percentages with little variation over the past five years. The median percentage was 98% (range 93-99%) in 2019 and 98% (range 94-99%) in 2020.

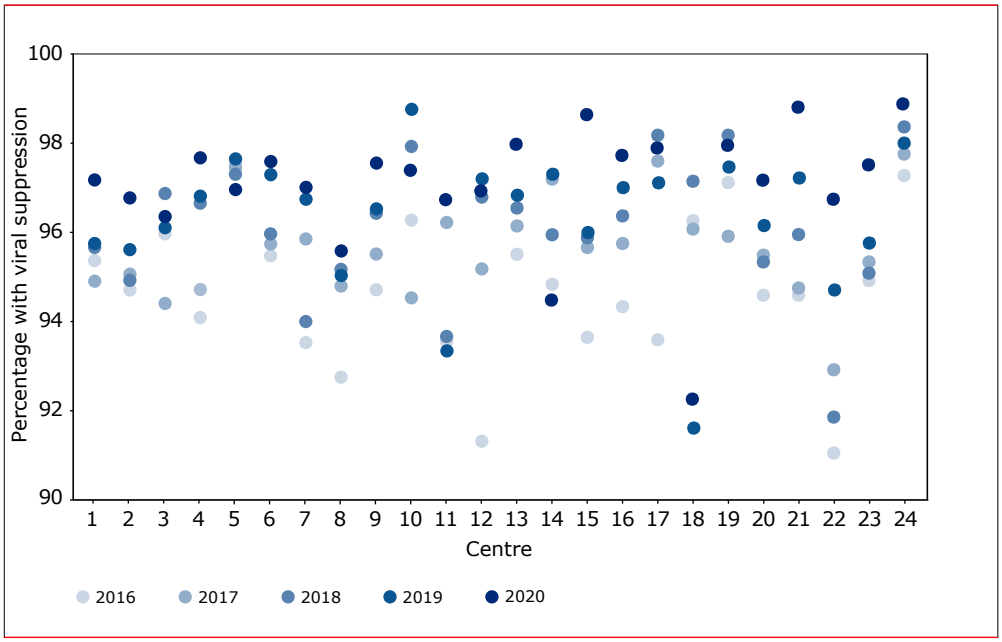
Figure 7.9: *The annual percentage of all patients on combination antiretroviral therapy (cART) for at least six months between 2016 and 2020 who had an HIV RNA level <100 copies/ml.*



Legend: *Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

The *third* viral suppression indicator is the percentage of all patients in care between 2016 and 2020 whose last available HIV RNA level was below 100 copies/ml (the percentage without HIV RNA measurements was 1.4% in 2016, 1.4% in 2017, 1.1% in 2018, 1.1% in 2019, and 3.3% in 2020). This annual percentage per centre is given in *Figure 7.10*, which shows again rather high percentages of this indicator with little variation over the past five years. The median percentage was 97% (range 92-99%) in 2019 and 97% (range 92-99%) in 2020.

Figure 7.10: The annual percentage of all patients living with HIV in care between 2016 and 2020 who had an HIV RNA level <100 copies/ml.



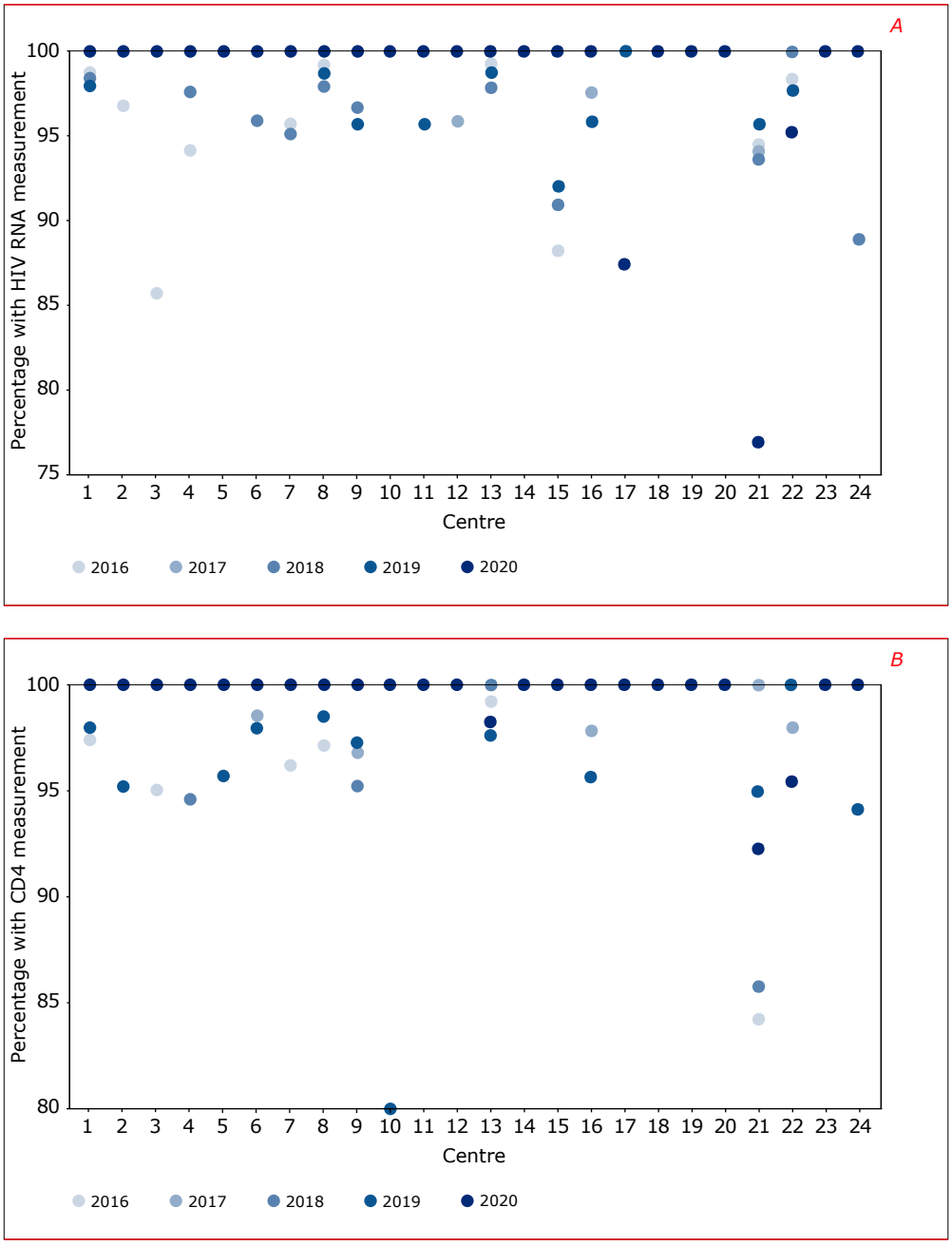
Legend: Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.

Process indicators

Prior to starting cART

Process indicators were evaluated in treatment-naïve patients who newly started cART. The annual percentages of patients who were tested for plasma HIV RNA or CD4 cell count within the six months prior to or one month following cART initiation are given per centre in *Figure 7.11A* (for plasma HIV RNA) and *Figure 7.11B* (for CD4 cell count). These percentages have been above 95% for most centres over the past five years. The percentages tested for plasma HIV RNA were 100% (range 96-100%) in 2019 and 100% (range 77-100%) in 2020, and the percentages tested for CD4 cell count were 100% (range 80-100%) in 2019 and 100% (range 92-100%) in 2020. For most centres, the difference in percentages between 2020 and 2019 was negligible. However, a decrease of more than 5% in plasma HIV RNA testing was observed in two centres, of which the total numbers of patients included in this indicator were eight and 13.

Figure 7.11: The annual percentage of patients newly initiating combination antiretroviral therapy (cART) between 2016 and 2020 who had (A) a measurement of plasma HIV RNA or (B) CD4 cell count within the six months prior to initiating cART or the one month following cART initiation.

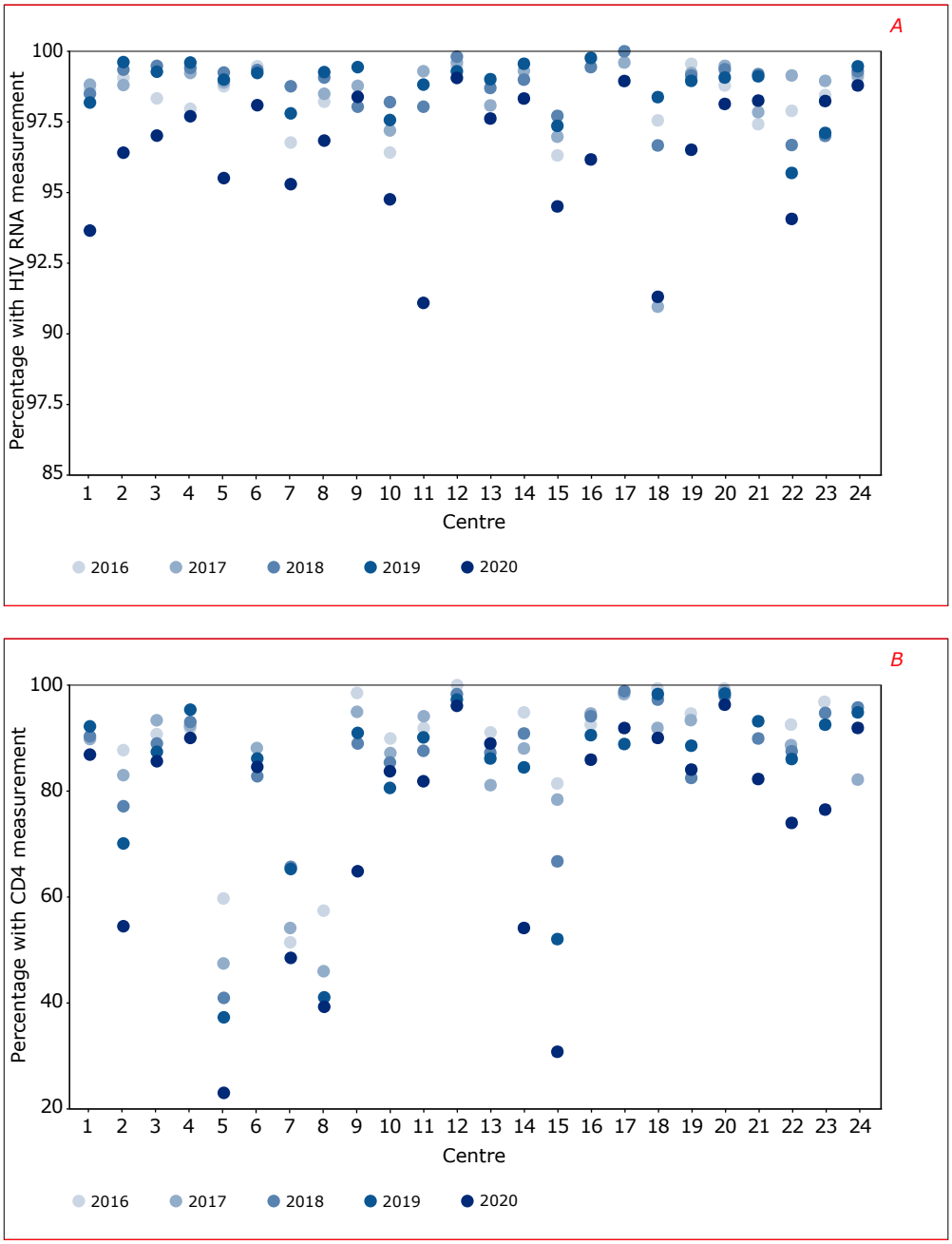


Legend: Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.

While in care

Process indicators were also evaluated for all patients who were in care. The annual percentages of patients who were tested for plasma HIV RNA or CD4 cell count while in care are given per centre in *Figure 7.12A* (for plasma HIV RNA) and *Figure 7.12B* (for CD4 cell count). These percentages have varied widely for some centres over the past five years, particularly in relation to CD4 cell count testing. The percentages tested for plasma HIV RNA were 96% (range 96-100%) in 2019 and 97% (range 91-99%) in 2020, and the percentages tested for CD4 cell count were 89% (range 37-98%) in 2019 and 84% (range 23-96%) in 2020. For many centres, the difference in percentages between 2020 and 2019 was negligible. However, a decrease of more than 5% in plasma HIV RNA testing was observed in two centres and a decrease of more than 5% in CD4 cell count testing was observed in 13 centres.

Figure 7.12: The annual percentage of all patients in care between 2016 and 2020 who had (A) a measurement of plasma HIV RNA or (B) CD4 cell count.



Legend: Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.

Centre performance

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[3-6].

Regarding centre volume, a smaller number of patients in an HIV treatment centre increases the chance that an indicator is more variable. When this occurs, it is difficult to distinguish whether a low-level indicator is the result of performing below expectations or having excessive variation. 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 7.3*). Given that statistical interpretation is unreliable when centre sizes are small, only indicators whose focus population contains more than 40 patients have been considered in this analysis.

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 the characteristics of patients attending those centres is driving these differences. We have therefore adjusted all indicators by year of birth and geographical origin/mode of transmission/gender (*Box 7.3*).

For this section, the indicators that we have used (defined in *Box 7.2*), while accounting for the issues described above, are: overall retention for patients in care, overall cART initiation for patients in care, viral suppression while on cART and while in care, and HIV RNA and CD4 cell counts while in care. Only indicators from 2020 were considered in this analysis.

Box 7.3: Funnel plots to compare centres to the national average.

What types of problems occur when evaluating indicators?	
Centres treating 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 expected.
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 is 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/gender (Dutch men who have sex with men [MSM], non-Dutch MSM, Dutch men who exclusively have sex with women [MSW], non-Dutch MSW, Dutch women, and non-Dutch women).

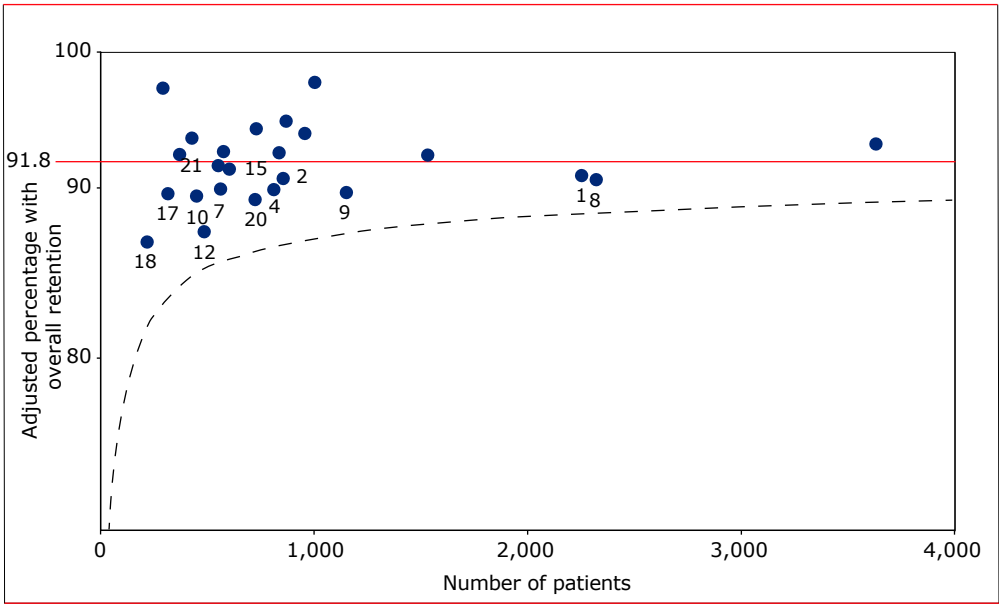
What is a funnel plot? A funnel plot is a graphical depiction that allows us to compare a centre's indicator to the national average. It can help account for the problems listed above. The following are key components of this plot:	
Patient size	The *x*-axis depicts the number of patients considered in a given indicator. For example, this number could be the total number of patients in care in 2020, 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 this 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.

Outcome indicators

Overall retention in care

Figure 7.13 shows the adjusted percentage of patients in care in 2020 with overall retention in care per centre. The median adjusted percentage across centres was 91% (range 86-98%). All centres had adjusted percentages of overall retention within the expected range, when compared to the national level.

Figure 7.13: *Overall retention in care; in other words, patients in care who had a documented visit in 2020. The percentage with overall retention in care has been adjusted for patient mix and is plotted as a function of the number of patients who were still in care in 2020.*

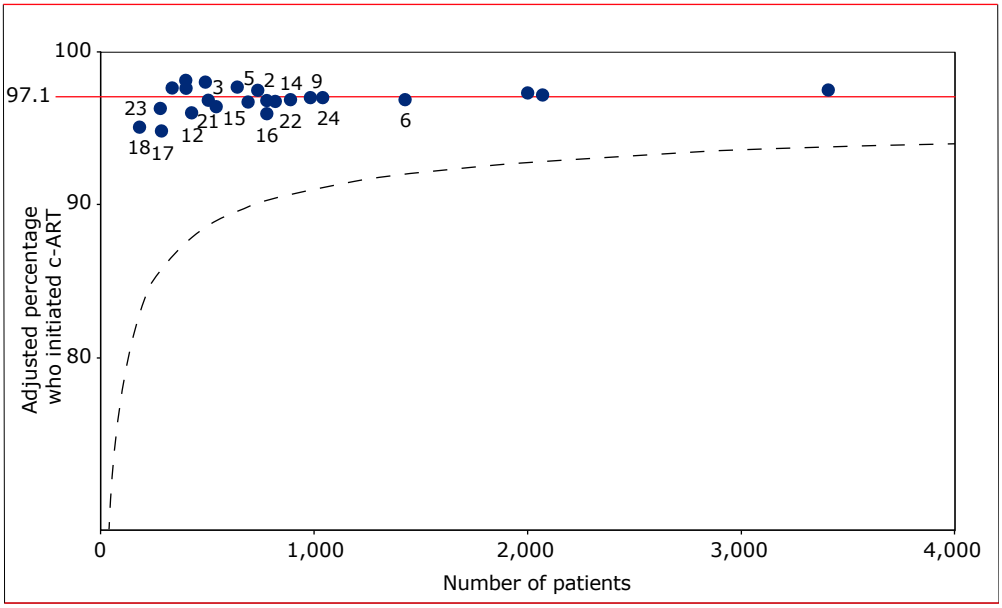


Legend: *Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The 'lower' boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.3).*

Overall initiation of cART in care

Figure 7.14 shows, per centre, the adjusted percentage of patients in care in 2020 who had ever initiated cART. The median adjusted percentage across centres was 97% (range 95-98%). All centres had adjusted percentages of overall cART initiation within the expected range, when compared to the national level.

Figure 7.14: The percentage of patients in care in 2020 who ever initiated combination antiretroviral therapy (cART). The percentage of overall cART initiation has been adjusted for patient mix and is plotted as a function of the number of patients still in care in 2020.

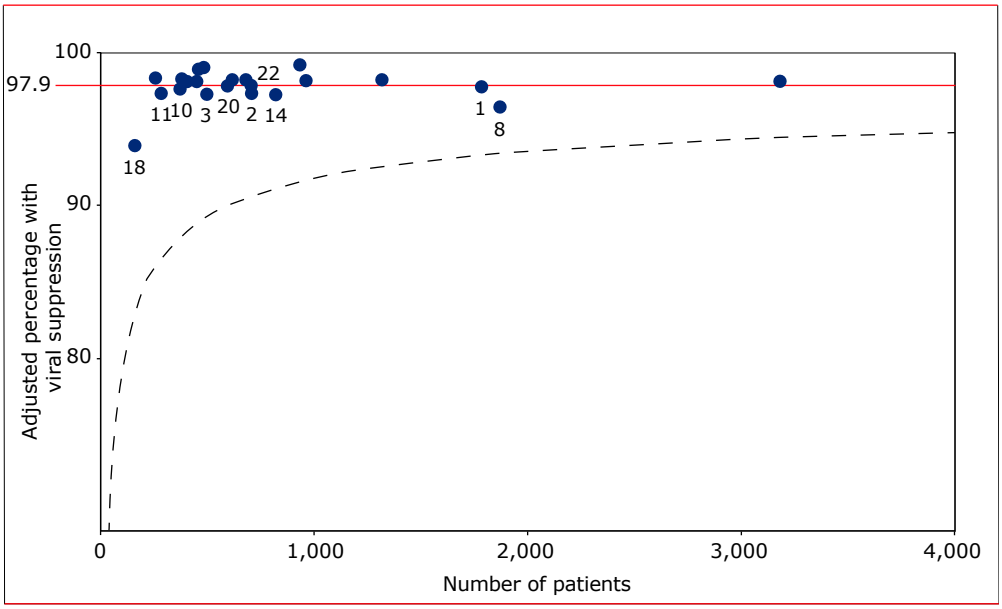


Legend: Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The 'lower' boundary of expected percentage initiating cART (as compared to the national average) is indicated with a dashed line (Box 7.3).

Viral suppression

Figure 7.15 shows, per treatment centre, the adjusted percentage of patients on cART in 2020 who had a plasma HIV RNA viral load below 100 copies/ml (i.e., viral suppression while on cART). It illustrates the limited variation across centres of different patient volume in 2020. The median adjusted percentage across centres was 98% (range 94-99%). All centres had adjusted percentages within the expected range when compared to the national level.

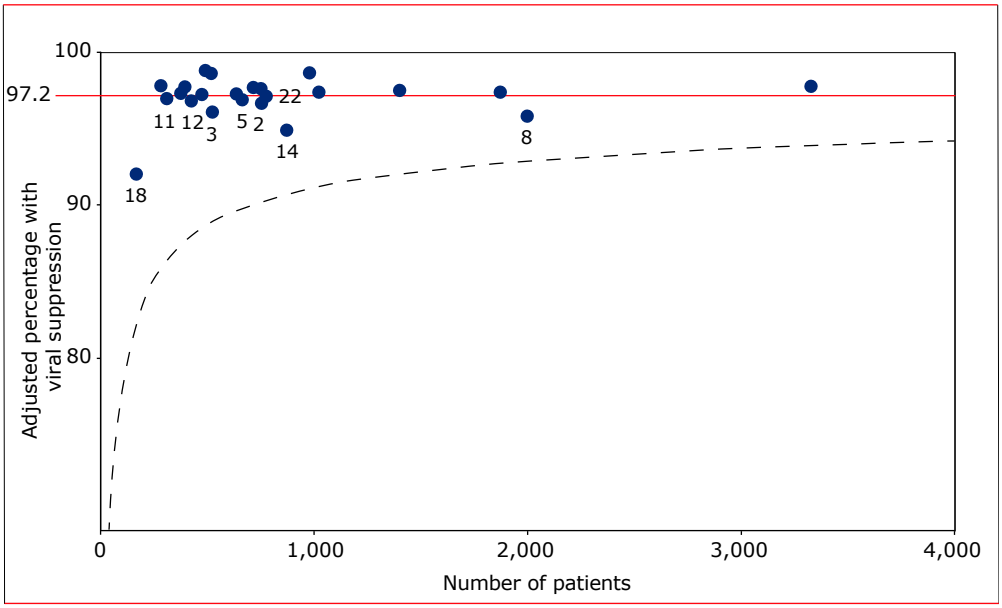
Figure 7.15: *The percentage of all patients living with HIV on combination antiretroviral therapy (cART) for at least six months in 2020 who had an HIV RNA level <100 copies/ml. The percentage of individuals with viral suppression has been adjusted for patient mix and is plotted as a function of the number of patients in care in 2020 who had been on cART for at least six months.*



Legend: *Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The 'lower' boundary of expected percentage with viral suppression (as compared to the national average) is indicated with a dashed line (Box 7.3).*

Figure 7.16 shows, per treatment centre, the adjusted percentage of patients in care in 2020 who had a plasma HIV RNA viral load below 100 copies/ml (i.e., viral suppression while in care). The median adjusted percentage across centres was 97% (range 92-99%), with slightly more variation across centres of different patient volume than for the indicator, viral suppression while on cART. All centres had adjusted percentages within the expected range when compared to the national level.

Figure 7.16: The percentage of all patients living with HIV in care in 2020 who had an HIV RNA level <100 copies/ml. The percentage of individuals with viral suppression has been adjusted for patient mix and is plotted as a function of the number of patients in care in 2020.



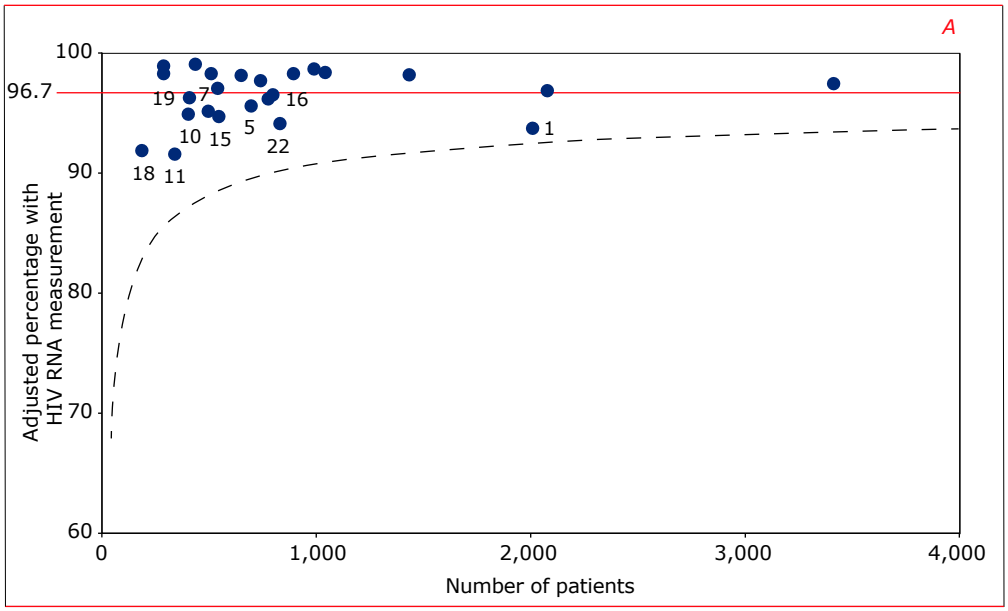
Legend: Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The 'lower' boundary of expected percentage with viral suppression (as compared to the national average) is indicated with a dashed line (Box 7.3).

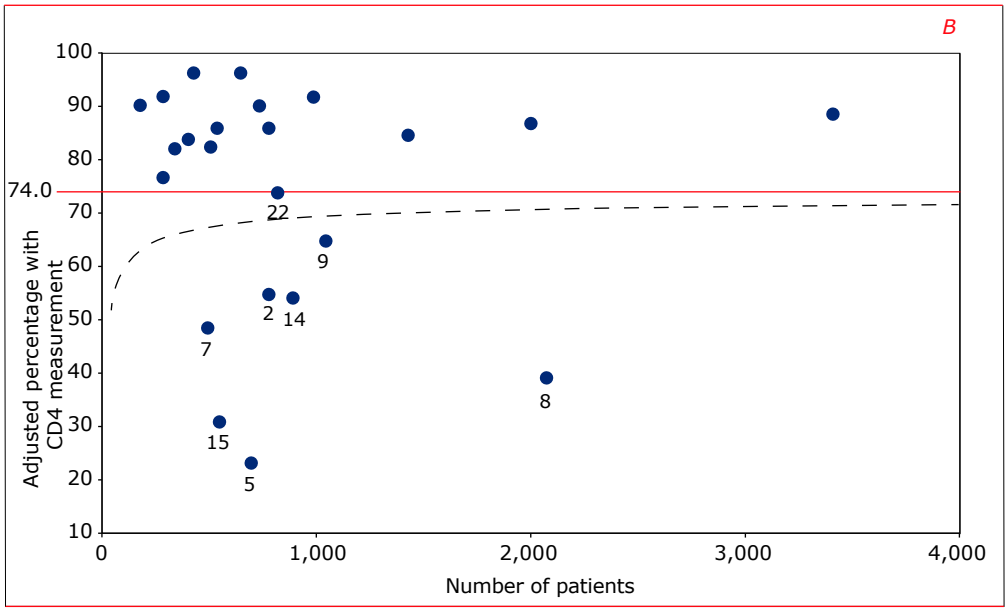
Process indicators

While in care

Process indicators were evaluated in patients who were in care in 2020. *Figure 7.17A* and *Figure 7.17B* show the across-centre variation in adjusted percentages of patients who had plasma HIV RNA or CD4 cell count measurements, respectively. Across centres, the median adjusted percentage of individuals tested for plasma HIV RNA was 97% (range 92-99%), with only slight variation observed across centres of different patient volume. All centres had adjusted percentages of plasma HIV RNA tested within the expected range when compared to the national level (*Figure 7.17A*). Across centres, the median adjusted percentage of individuals tested for CD4 cell count was 84% (range 23-96%), with large variation observed across centres of different patient volume. Seven centres of varying patient volume had a lower-than-expected percentage of patients in care measured for CD4 cell count in 2020. However, some of the variation in this indicator could be due to differences in the CD4 measurement protocols between centres. Of note, there is no specific recommended frequency for CD4 cell count monitoring among patients with a CD4 level above 350 cells/mm^3 in the national guidelines[1].

Figure 7.17: The percentage of all patients in care in 2020 who had (A) a measurement of plasma HIV RNA or (B) a CD4 cell count. The percentages have been adjusted for patient mix and are plotted as a function of the number of patients in care in 2020.





***Legend:** Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The 'lower' boundary of expected percentage with measurements (as compared to the national average) is indicated with a dashed line (Box 7.3).*

Indicators according to patient mix

In the previous analysis on centre performance, we accounted for the patient mix by adjusting each indicator using the six geographical origin/mode of transmission/gender groups. However, it remains difficult to determine whether indicators per centre are different across groups. We therefore explored centre-level differences for several indicators while stratifying on patient mix and accounting for age differences between groups.

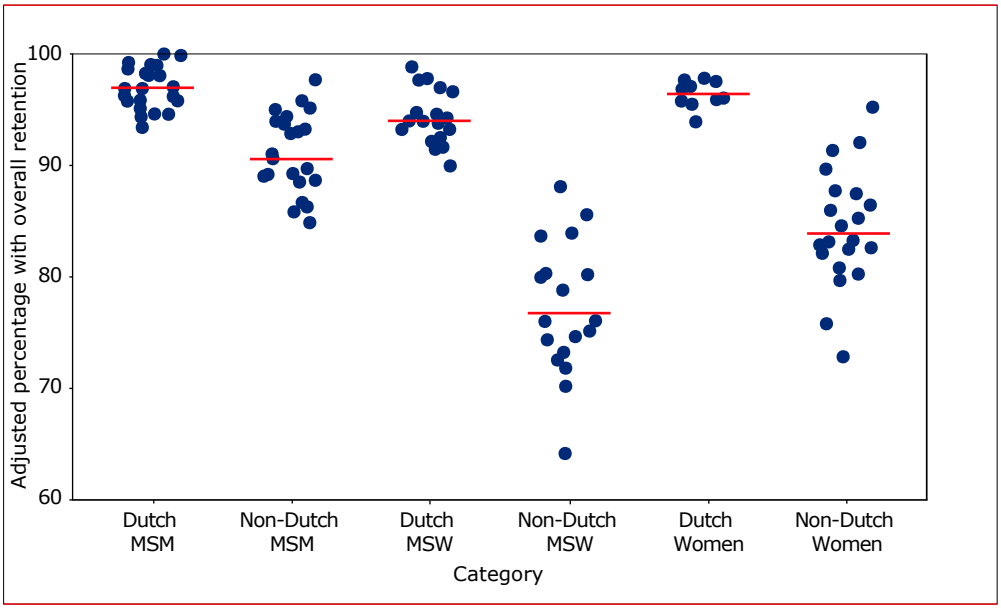
For this section, the indicators that we have used (defined in *Box 7.2*) are: overall retention for patients in care, overall cART initiation for patients in care, viral suppression while on cART and while in care, and HIV RNA and CD4 cell counts while in care. Given that interpretation of differences is unreliable when centre sizes are small, only indicators whose focus population contains more than 40 patients have been considered in this analysis. In addition, only indicators from 2020 are considered.

Outcome indicators

Overall retention in care

Figure 7.18 shows the adjusted percentage of patients in care in 2020 with overall retention in care per centre, according to patient mix groups. The highest median percentages across centres were observed in Dutch MSM (97%, range 95-99%) followed by Dutch women (97%, range 96-98%), Dutch MSW (94%, range 90-97%), and non-Dutch MSM (91%, range 84-97%). Two groups had median percentages below 90%: non-Dutch women (median 84%, range 75-95%) and non-Dutch MSW (median 77%, range 67-86%).

Figure 7.18: Overall retention in care; in other words, patients in care who had a documented visit in 2020. The percentage has been adjusted for patient age.

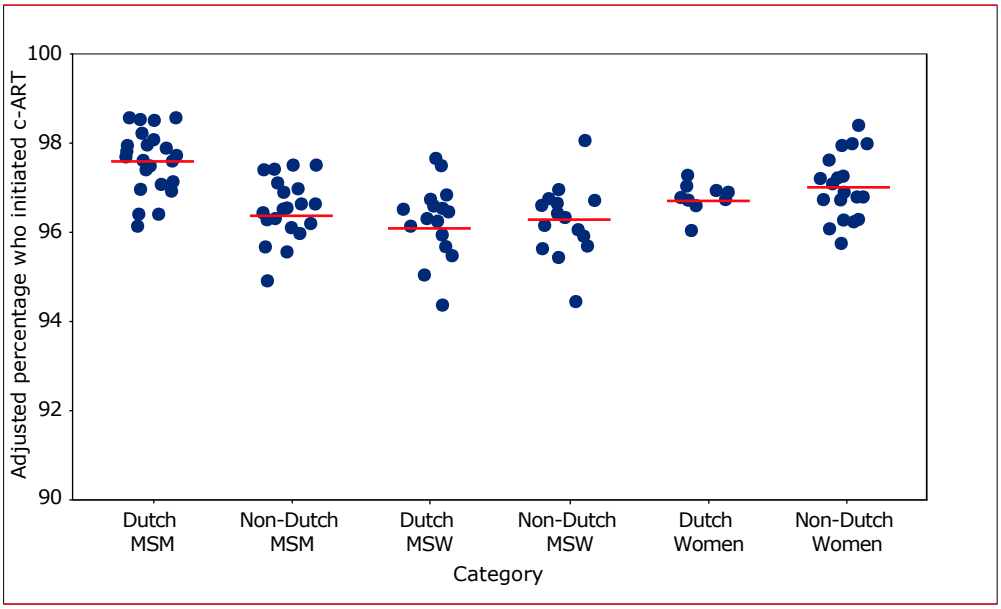


Legend: The median adjusted percentage across centres is indicated with a solid line for each patient mix group. MSM=men who have sex with men; MSW=men who exclusively have sex with women.

Overall initiation of cART in care

Figure 7.19 shows the adjusted percentage of patients in care in 2020 who ever initiated cART per centre, according to patient mix groups. All median percentages were above 95% for each of the patient mix groups. The highest median percentages were 98% in Dutch MSM (range 96-99%), 96% (range 95-98%) in non-Dutch MSM, 96% (range 95-97%) in Dutch MSW, 96% (range 95-98%) in non-Dutch MSW, 97% (range 96-97%) in Dutch women, and 97% (range 96-98%) in non-Dutch women.

Figure 7.19: The percentage of patients in care in 2020 who ever initiated combination antiretroviral therapy (cART). The percentage has been adjusted for patient age.

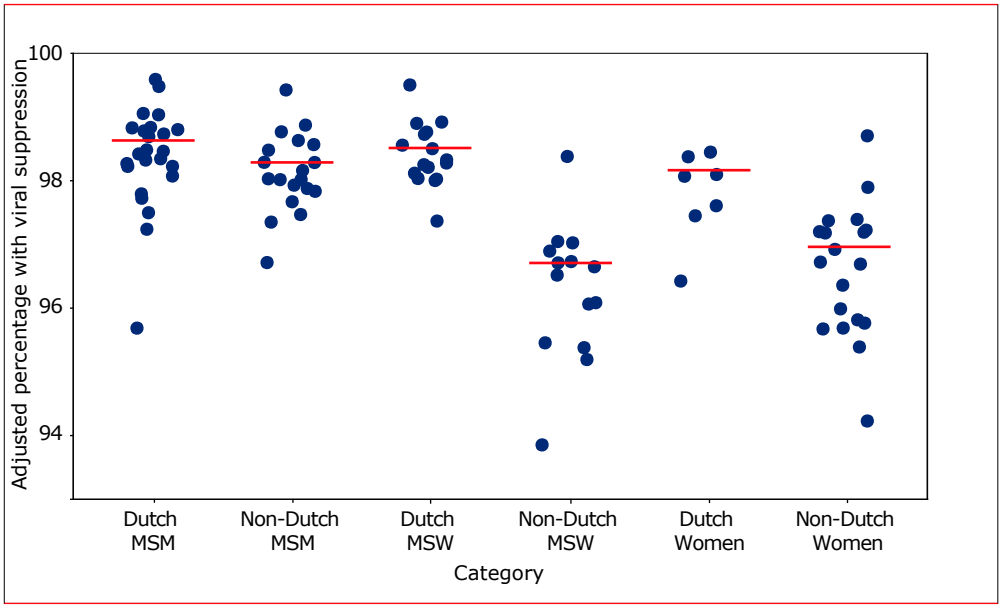


Legend: The median adjusted percentage across centres is indicated with a solid line for each patient mix group. MSM=men who have sex with men; MSW=men who exclusively have sex with women.

Viral suppression

Figure 7.20 shows the adjusted percentage of patients on cART in 2020 who had a plasma HIV RNA viral load below 100 copies/ml (i.e., viral suppression while on cART) per treatment centre, according to patient mix groups. All median percentages were above 95% for each of the patient mix groups. The highest median percentages were 99% in Dutch MSM (range 95-99%), 98% (range 97-99%) in non-Dutch MSM, 99% (range 97-99%) in Dutch MSW, 97% (range 94-98%) in non-Dutch MSW, 98% (range 96-98%) in Dutch women, and 97% (range 94-98%) in non-Dutch women.

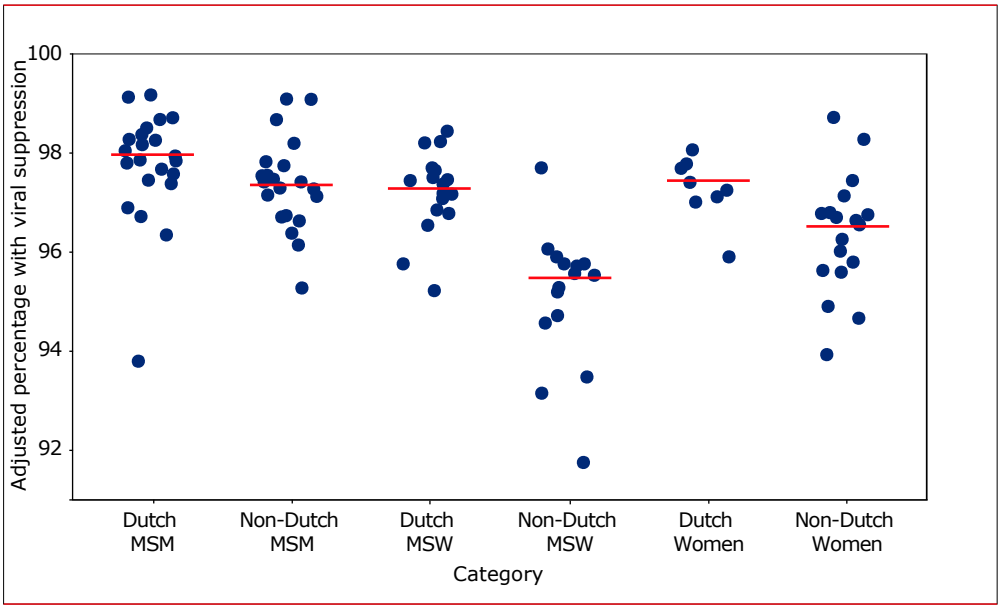
Figure 7.20: *The percentage of all patients living with HIV on combination antiretroviral therapy (cART) for at least six months in 2020 who had an HIV RNA level below 100 copies/ml. The percentage has been adjusted for patient age.*



Legend: *The median adjusted percentage across centres is indicated with a solid line for each patient mix group. MSM=men who have sex with men; MSW=men who exclusively have sex with women.*

Figure 7.21 shows the adjusted percentage of patients in care in 2020 who had a plasma HIV RNA viral load below 100 copies/ml (i.e., viral suppression while in care) per treatment centre, according to patient mix groups. All median percentages were again above 95% for each of the patient mix groups. The highest median percentages were 98% in Dutch MSM (range 94-99%), 97% (range 95-99%) in non-Dutch MSM, 97% (range 95-99%) in Dutch MSW, 95% (range 92-98%) in non-Dutch MSW, 97% (range 96-98%) in Dutch women, and 97% (range 94-98%) in non-Dutch women.

Figure 7.21: The percentage of all patients living with HIV in care in 2020 who had an HIV RNA level <100 copies/ml. The percentage has been adjusted for patient age.



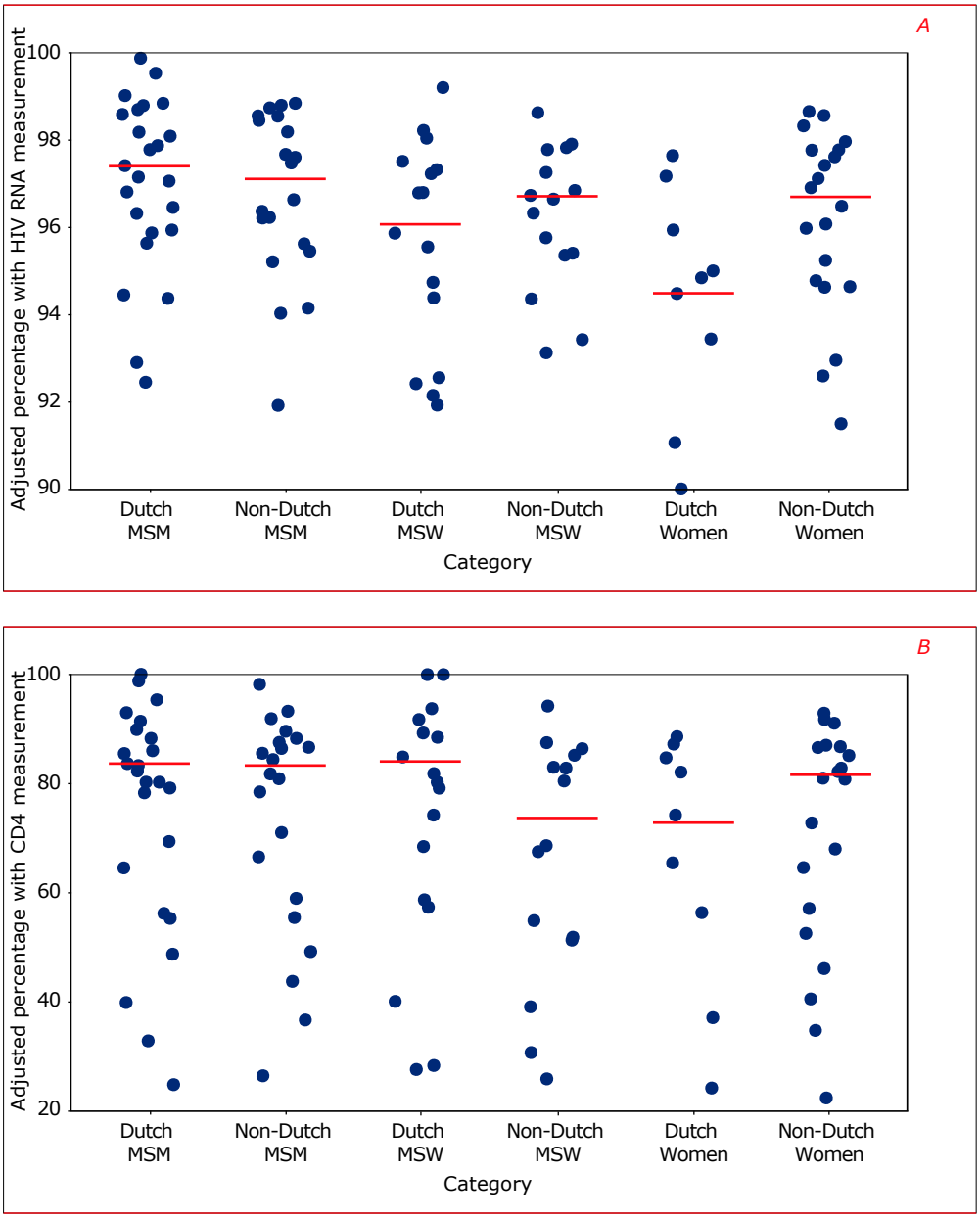
Legend: The median adjusted percentage across centres is indicated with a solid line for each patient mix group. MSM=men who have sex with men; MSW=men who exclusively have sex with women.

Process indicators

While in care

Process indicators were evaluated for patients who were in care in 2020. *Figure 7.22A* and *Figure 7.22B* show the across-centre variation, in adjusted percentages, of those who had plasma HIV RNA and CD4 cell count measurements, respectively, according to patient mix groups. All median adjusted percentages for HIV RNA measurements were high across patient mix groups, with the highest in Dutch MSM (97%, range 93-99%) and the lowest in Dutch women (95%, range 90-97%). All adjusted percentages for CD4 cell count measurements were highly variable across patient mix groups, with slightly lower percentages in non-Dutch MSW (74%, range 23-96%) and Dutch women (73%, range 22-88%).

Figure 7.22: The percentage of all patients in care in 2020 who had (A) a measurement of plasma HIV RNA or (B) CD4 cell count. The percentage has been adjusted for patient age.



Legend: The median adjusted percentage across centres is indicated with a solid line for each patient mix group. MSM=men who have sex with men; MSW=men who exclusively have sex with women.

Indicators after centre closure

In 2018, two official HIV treatment centres closed (MC Slotervaart, Amsterdam, and MC Zuiderzee, Lelystad). At the time of closure, 663 patients were still in care at these centres. Of these patients, 578 (87%) transferred to another HIV treatment centre in the Netherlands: 485 had a clinical visit in 2020; 12 (2%) moved abroad; 14 (2%) were lost to care; and 25 (4%) died. For 34 (5%) patients, care status was unknown at the time of this analysis (i.e., their current status was not in the database). The percentages who moved abroad or died are comparable to those recorded for the entire adult HIV-1 positive population in SHM in 2020 (*Chapter 1*).

The indicators most relevant to the group of patients who transferred care from a closed centre to another HIV treatment centre are: the percentage of all people living with HIV who ever initiated cART and were still in care in 2020; the percentage of people on cART for at least six months in 2020 with a plasma HIV RNA level below 100 copies/ml; and the percentage of all people living with HIV in care in 2020 with a plasma HIV RNA level below 100 copies/ml. *Table 7.1* summarises these indicators for individuals whose care was transferred from a closed centre, and compares them to the unadjusted median indicators across centres: all were within range.

Table 7.1: *Indicators in individuals whose care was transferred from a closed centre to another HIV treatment centre.*

Indicator *(Box 7.2)*	**Individuals transferred from a closed centre (n=578)**	**Median indicators (range) across all centres in the Netherlands in 2020**
Overall cART initiation and still in care in 2020	99%	97% (95-99%)
Viral suppression while on cART in 2020	99%	98% (94-99%)
Viral suppression while in care in 2020	99%	97% (92-99%)

Key findings and conclusions

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

- The number of newly HIV-diagnosed individuals entering care has been slowly decreasing for the vast majority of centres, which is in line with the national trend of fewer, newly diagnosed HIV infections.
- After exclusion of patients who either died or moved abroad, short-term retention has been high for individuals entering care, and the overall retention has witnessed a median increase of 12% over the past five years. No centre had an overall retention rate lower than the national average when adjusting for patient mix. Nevertheless, the overall retention rate for non-Dutch MSW and non-Dutch women was considerably lower than other groups after adjusting for age. The reasons for this finding need to be explored in future research.
- The COVID-19 pandemic drastically shifted how consultations were conducted at HIV treatment centres, with all centres opting for consultations via telephone or email over physical consultations.
- The percentage of patients initiating cART within six months of newly entering care remained high for those who entered care between 2016 and 2019. Nevertheless, some centres saw a considerable decline in this indicator for individuals entering care in 2019. The overall percentage of patients in care who ever initiated cART has been slowly increasing over the past five years. In fact, no centre had an overall cART initiation figure lower than expected from the national average when adjusting for patient mix.
- Viral suppression rates in the first six months on cART, during longer-term use of cART, and while in care have been high across all HIV treatment centres in the Netherlands over the past five years. There was little variation in the percentage with viral suppression while on cART and in care across centres after adjusting for patient mix.
- The percentage of individuals with HIV RNA measurements prior to cART, or while in care, has been high across centres over the past five years, even during the COVID-19 pandemic in 2020. However, several centres had a much lower-than-expected percentage with CD4 measurements while in care in 2020, as compared to the national average and after adjusting for patient mix.
- The cART and viral suppression indicators for individuals who were originally registered with the two HIV treatment centres that closed do not appear to have been affected by the transfer of their care to another HIV treatment centre. However, more information might be needed for individuals who were lost to care.

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. These analyses also provide information on whether some of the 2022 targets of the Dutch National Action Plan for STIs, HIV and Sexual Health (*Nationaal Actieplan soa, hiv en seksuele gezondheid: 2017-2022*) will be met at the centre level. Nonetheless, data reliability remains an important issue, and it should be recognised that some of the reported variations may be due to missing data. Other important indicators reflecting the quality of care, such as quality of life, reduction in stigma, and discrimination, are difficult to obtain from patient files, and are therefore not collected in the SHM database.

The data presented in this chapter may additionally serve as a useful benchmark that centres can use to identify potential aspects for improvement. As in previous years, each treatment centre will be provided with a selection of their unadjusted, centre-specific indicators, benchmarked against the blinded scores of all other centres. These scores will be available through online centre-specific reports: https://shm.amc.nl.

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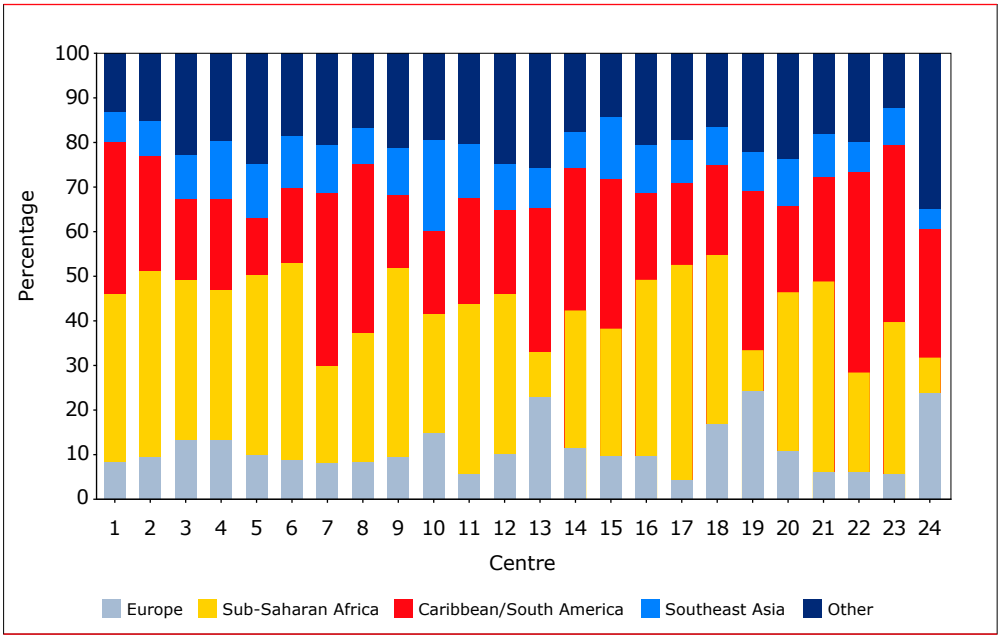
Appendix Figure 7.1: *Distribution of region of origin for non-Dutch individuals living with HIV in care in 2020 in the Netherlands.*



Note: *Percentage of individuals per centre is given in the bar chart according to region of origin.*

8. The Amsterdam Cohort Studies (ACS) on HIV infection: annual report 2020

Amy Matser, Jeffrey Koole, Neeltje Kootstra, Lia van der Hoek, Maria Prins

Introduction

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS 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/used injecting drugs (PWID) was initiated in 1985. In 2019, the cohorts reached 35 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 35 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 (STIs), 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, and other infections such as viral hepatitis B and C (HBV and HCV) and human papillomavirus (HPV). This expertise, in turn, has contributed directly to advances in prevention, diagnosis, and management of these infections.

Collaborating institutes and funding

Within the ACS, different institutes collaborate to bring together 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 Centres (Academic Medical Centre [AMC] site): Departments of Medical Microbiology, Experimental Immunology, and Internal Medicine (Division of Infectious Disease); the Emma Kinderziekenhuis (paediatric

HIV treatment centre); stichting hiv monitoring (SHM); MC Jan van Goyen: Department of Internal Medicine; and the HIV Focus Centrum (DC Klinieken Lairesse). From the start, Sanquin Blood Supply Foundation has been involved in the ACS and, since 2007, has provided financial support for the biobank of viable peripheral blood mononuclear cells (PBMC) at the AMC's Department of Experimental Immunology. In addition, there are numerous collaborations between the ACS and other research groups, both within and outside the Netherlands. The ACS is financially supported by the Centre for Infectious Disease Control Netherlands of the National Institute for Public Health and the Environment (*Centrum voor Infectieziektenbestrijding-Rijksinstituut voor Volksgezondheid en Milieu*, RIVM-CIb).

Ethics statement

The ACS has been conducted in accordance with the ethical principles set out in the Helsinki declaration. 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 PWID cohort.

The ACS in 2020

The cohort of men who have sex with men (MSM)

As of 31 December 2020, 2,901 MSM were included in the ACS. Every three to six months, participants complete a standardised questionnaire designed to obtain data regarding medical history, sexual behaviour and drug use, underlying psychosocial determinants, health care use, signs of depression and other psychological disorders, and demographics. Moreover, blood is collected for diagnostic tests and storage at the ACS biobank. Of the 2,901 MSM, 607 were HIV-positive at entry into the study and 263 seroconverted for HIV during follow up. In total, the GGD Amsterdam has been visited 63,154 times by MSM since 1984.

In 1984-85, men who had had sexual contact with a man in the preceding six months were enrolled, independent of their HIV status. In the period 1985-88, 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. In 1988-98, the cohort also included MSM living with HIV. In 1995–2004, only men aged 30 years or younger, with at least one male sexual partner in the previous six months, could be included the study. Since 2005, HIV-negative men of all age groups have been eligible to participate in the ACS if they live in, or are closely connected to 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 continues additional efforts to recruit young HIV-negative MSM (aged 30 years or younger).

HIV-seroconverters within the ACS remained in the cohort until 1999, when follow up of a selection of MSM living with HIV was transferred to the MC Jan van Goyen. In 2003, the HIV Research in Positive Individuals (*Hiv Onderzoek onder Positieven*, HOP) protocol was initiated. Individuals with a recent HIV infection when entering the study at the GGD Amsterdam, and those who seroconverted for HIV during follow up within the cohort, continue to return for study visits at the GGD Amsterdam, or at an HIV treatment centre. Blood samples from these participants are stored. All behavioural data are collected on a six-monthly basis by questionnaires, coordinated by the GGD Amsterdam, and clinical data are provided by SHM.

In 2020, which was affected by the COVID-19 pandemic, 699 HIV-negative and 50 MSM living with HIV were active participants at the GGD Amsterdam; in other words, they visited the cohort at least once in 2019 or 2020. All 50 MSM living with HIV filled out behavioural questionnaires. In 2020, two new HIV-negative MSM, who were 28.7 and 48.4 years of age at inclusion, were recruited. The median age of the total group of MSM in active follow up was 44.5 (interquartile range [IQR] 34.0-55.9) years at their last cohort visit. The majority were born in the Netherlands and were residents of Amsterdam (83.4% and 88.8%, respectively). In total, 77.2% of the participants had a college degree or higher.

The cohort of people who use/used injecting drugs (PWID)

As of 31 December 2016, 1,680 PWID were included in the ACS and contributed 28,194 visits. In 2014, the cohort was closed to new participants. Regular follow up of PWID continued until February 2016. All PWID who had ever participated in the ACS were then invited for an end-of-study interview and follow up was successfully ended in July 2016. Of the 1,680 PWID, 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 PWID. The median age of the PWID who visited the ACS in 2016 was 55 (IQR 49-59) years, 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 collected 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 ACS cohorts. It also contains samples collected during the Primo-SHM study (a national randomised study, which started in 2003, comparing the effects of early, temporary antiviral therapy with that of no therapy among patients who presented with primary HIV-1 infection at the AMC HIV outpatient clinic, and ACS seroconverters). These samples are stored at the Amsterdam University Medical Centres (AUMC), location AMC. At present, biological samples are still being collected prospectively for Primo-SHM participants visiting the AUMC, location AMC clinic, until one year after they have recommenced therapy. The ACS biobank also contains plasma and PBMC samples that were collected from HIV-positive and HIV-exposed children at the Emma Kinderziekenhuis in the AUMC, location AMC, before 2008. All stored samples are available for ACS research.

Subgroup studies and affiliated studies

AGE$_h$IV cohort study

The AGE$_h$IV cohort study (a collaboration between the Amsterdam UMC, location 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, along with known risk factors for these comorbidities, in individuals living with HIV aged 45 years and older, 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, as well as research follow-up questionnaires every subsequent two years. 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 AUMC, location AMC, HIV outpatient clinic, and HIV-negative participants from similar risk groups through the STI clinic at the GGD Amsterdam (486), or the ACS (64). All participants were aged 45 years or older and were as comparable as possible with respect to age, gender, ethnicity, and risk behaviour. In 2020, the fifth round (2019-20) was concluded; 376 HIV-positive and 437 HIV-negative participants had a fifth visit. Due to the COVID-19 pandemic, the sixth round of the AGE$_h$IV study did not start in 2020.

In 2020, a two-year COVID-19 sub-study was started in this cohort. Participants were invited to complete a short online questionnaire and provide a blood sample for the measurement of SAR-CoV-2 antibodies. The first round of this sub-study

took place in September-October 2020, and the next rounds are scheduled for 2021 and 2022. In the first round of the sub-study 548 people participated (312 HIV-negative and 236 HIV-positive participants). Analyses are underway.

H2M cohort studies

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) active participants in the ACS, and also among patients of the STI clinic of GGD Amsterdam and MC Jan van Goyen. The aim of the Aidsfonds-supported study was to compare the prevalence, incidence, and clearance of HPV infections associated with high-risk (hr) of anal cancer between HIV-negative and HIV-positive MSM.

Since September 2014, the collection of anal and genital swabs has been resumed in all consenting ACS participants. The key aim of this second study (the H2M3 study), which builds on the H2M study, is to examine long-term incidence and clearance of anal and penile hrHPV infections. As assays to determine HPV infection status are very costly, samples have been collected and stored, but not yet analysed. In 2020, collection of anal and penile swabs from ACS participants continued. Swabs have been stored at the laboratory of the Public Health Service of Amsterdam for future studies.

AMPrEP project in H-TEAM

The Amsterdam pre-exposure prophylaxis (AMPrEP) project was a prospective, longitudinal, open-label demonstration study, conducted in 2015-20. The aim was to assess the uptake and acceptability of daily, versus event-driven, pre-exposure prophylaxis (PrEP) among MSM and trans people at increased risk of HIV infection, as part of a comprehensive HIV-reduction package offered at a large centre for sexual health.

In total, 374 MSM and two trans persons were enrolled between August 2015 and May 2016 at GGD Amsterdam's centre of sexual health, including 35 ACS participants who chose to participate in the AMPrEP project. Participants were asked to attend a follow-up visit one month after their PrEP initiation visit, and return every three months thereafter. At every visit, participants filled out questionnaires on risk behaviour, adherence, and general wellbeing, and were screened for STIs and HIV. AMPrEP follow-up was completed on 1 December 2020. By then, all participants still in care and willing to continue PrEP were included in the national PrEP pilot at a centre for sexual health of their choice.

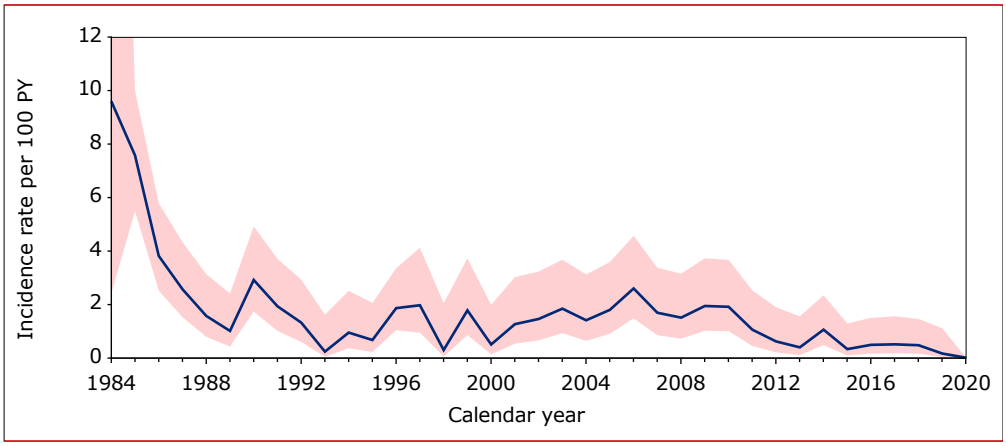
The AMPrEP project was part of the HIV Transmission Elimination Amsterdam (H-TEAM) initiative, a multidisciplinary and integrative approach to stop the epidemic[a].

The HIV epidemic

HIV incidence

The observed HIV incidence rate among MSM participating in the ACS has changed over time. In 1985-93, it declined significantly, it then stabilised in 1993-96, before rising in 1996-2009. From 2009 onwards, the HIV incidence decreased significantly. In 2020, none of the MSM participating in the ACS seroconverted for HIV. *Figure 8.1* shows the yearly-observed HIV incidence rate for MSM from the start of the ACS through 2020.

Figure 8.1: *HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984-2020.*



Transmission of therapy-resistant HIV strains

In 2020, there was no surveillance conducted of transmitted, drug-resistant HIV-1 strains.

Risk behaviour of MSM in ACS

Condomless anal sex (CAS) with a steady or casual partner was reported by 207/453 (45.7%) and 150/453 (33.1%) HIV-negative MSM, respectively, during their cohort visit in 2020. Trends in CAS among HIV-negative MSM participating in the ACS, continued to show a gradual increase from 2009 onwards (*Figure 8.2*). Use of PrEP

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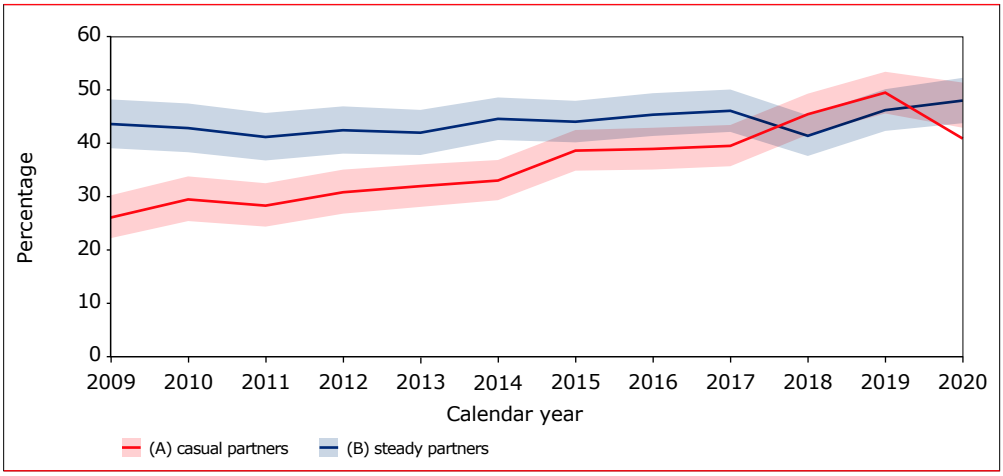
has also increased since 2015. In 2020, 210/684 (30.7%) HIV-negative MSM actively participating in the ACS reported PrEP use in the preceding six months. CAS with a steady or casual partner was reported by 95 (45.2%) and 170 (81.0%) PrEP-using MSM, respectively. Among non-PrEP-using MSM, those figures were 166 (48.1%) and 98 (26.8%), respectively.

Figure 8.2: Trend in the proportion of condomless anal sex (CAS) with: (A) casual partners, and (B) steady partners, among HIV-negative men who have sex with men (MSM) in the Amsterdam Cohort Studies (ACS), 2009-2020.



STI screening among MSM in ACS

Since October 2008, all MSM participating in the ACS have been routinely screened for bacterial STIs during their cohort visits. This conforms with the standard care offered by the GGD STI clinics. Chlamydia and gonorrhoea were detected by polymerase chain reaction (PCR) techniques using urine samples and pharyngeal and rectal swabs. Syphilis was detected by Treponema pallidum haemagglutination assay (TPHA). In 2020, 42/533 (7.8%) MSM in the ACS tested positive for one of the bacterial STIs at least once during a cohort visit. For HIV-negative and HIV-positive MSM, these figures were 36/498 (7.2%) and 6/35 (17.1%), respectively. Since the STI testing frequency differs between PrEP-using (quarter-annually) and non-PrEP-using participants (semi-annually), STI incidence rates of these groups cannot be compared and, therefore, are not reported. In general, the incidence rate of a bacterial STI significantly increased between 2009-20.

Impact of COVID-19 on ACS

In 2020, the COVID-19 pandemic was a global public health threat. It also affected ACS data collection. In line with government measures to reduce the spread of COVID-19, the ACS was closed during periods of lockdown, from March to May 2020 and after December 15 2020. The only participants allowed to visit the cohort were those who a) had been warned by a partner that they may have contracted an STI, b) had run out of PrEP pills, or c) had STD symptoms. These criteria have led to selection bias. Moreover, sexual behaviour changed during the COVID-19 restrictions; the majority of participants (73%) reported fewer casual sex partners and 11% stopped using PrEP. Before the COVID-19 pandemic, 78% reported sexual contact with a casual sex partner; this figure dropped to 38% during the pandemic[1]. These behavioural changes may have affected STI transmission.

ACS 2020 research highlight

HIV-negative men who have sex with men (MSM) have an altered T-cell phenotype and bioenergy metabolism

CD8+ T-cell responses are crucial for our immune defence against viruses. However, continued antigen exposure, due to recurrent or chronic infections, induces T-cell exhaustion and senescence, affecting T-cell functionality. We have previously reported that higher levels of T-cell activation, exhaustion, and terminal differentiation are found in MSM, compared to blood donors. In Kruize et al., the bioenergy metabolism of T-cells in MSM was also impaired. Immunological and metabolic changes are associated with high-risk behaviour and cytomegalovirus (CMV) infection. This indicates that the higher antigen exposure in this group of MSM is likely to induce immunological changes in the T-cell population[2].

Immune activation correlates with, and predicts CXCR4 coreceptor tropism switch in HIV-1 infection

Coreceptor switching of HIV (from CCR5 to CXCR4 using HIV) is strongly associated with accelerated disease progression. We investigated the relationship between immunological factors and HIV coreceptor switching in a) a cross-sectional study in HIV-1 subtype C (HIV-1C)-infected patients, and b) in a longitudinal HIV-1 subtype B (HIV-1B) seroconverter cohort (ACS). In Connell et al., T-cell activation preceded and independently predicted X4-coreceptor switching providing novel insights into HIV-1 pathogenesis[3].

SARS-CoV-2 research within the ACS

Seasonal coronavirus protective immunity is short-lasting

A key unsolved question in the current coronavirus disease 2019 (COVID-19) pandemic is the duration of acquired immunity. Insights from infections with the four seasonal human coronaviruses might reveal common characteristics applicable to all human coronaviruses. We monitored healthy individuals for more than 35 years. Edridge et al. found that reinfection with the same seasonal coronavirus occurred frequently at 12 months after infection[4].

Sexual behaviour and its determinants during COVID-19 restrictions among men who have sex with men (MSM) in Amsterdam

We investigated the impact of Dutch COVID-19 restrictions on sexual behaviour and HIV/sexually-transmitted infection (STI) rates among MSM participating in the ACS. ACS participants complete a questionnaire on sexual behaviour and are tested for HIV/STI biannually. They may also be tested at the STI clinic between study visits. On 29 May 2020, ACS participants were invited to complete an online questionnaire on health, COVID-19 risk perceptions, and sexual behaviour. Determinants of reporting casual sex partners (CSP) during COVID-19 restrictions were examined using logistic regression. Of 683 MSM, 353 (52%; median age 47 years; IQR 38-53 years) completed the questionnaire. The majority (73%) reported a reduction in the number of their CSP during COVID-19 restrictions. In total, 133 MSM (38%), reported CSP during COVID-19. In multivariable analysis, these men were associated with not having a college/university degree, being single, lower perceived importance of avoiding COVID-19, number of CSP before COVID-19, and current preexposure prophylaxis use (P, 0.05 for all). During COVID-19 restrictions, no HIV infections were diagnosed, and the STI positivity rate was 8%. Since COVID-19, the number of CSP has decreased among MSM, and there may have been a temporary reduction in HIV/STI transmission. Some MSM were not fully compliant to social distancing regulations and reported CSP, which was related to prior sexual behaviour and low perceived importance of avoiding COVID-19. For these men, it is important to maintain accessible HIV/STI-related testing and care during times of lockdown[1].

Current and upcoming ACS research projects

Currently, data collected within the ACS are used for multiple research projects. HCV-infection incidence and spontaneous-clearance rates, along with associated factors, are in the process of being estimated and identified.

Blood samples of ACS participants are among others being analysed for SARS-CoV-2 antibodies. Seroprevalence of SARS-CoV-2 antibodies and their determinants are to be determined.

Since 2019, PrEP has been widely available for eligible individuals. To optimise current PrEP eligibility criteria, uptake, and retention, data from ACS is being used. Previously, trials on prophylactic use of antibiotics before or after sex to prevent bacterial STIs have been conducted outside the ACS cohort. Currently, within the Netherlands, the option to take antibiotics in this way is not offered due to insufficient evidence on its efficacy and safety. Current informal use, intentions, and beliefs regarding prophylactic antibiotics among ACS participants are to be determined.

In trials, long-acting oral and injectable PrEP were found to be as safe and effective as the (short-acting oral) PrEP that is currently available in the Netherlands. Attitudes towards and intentions to switch to long-acting PrEP among ACS participants are to be determined.

Using qualitative research methods, the definition and aspects of sexual wellbeing are to be determined using data of, among others, ACS participants.

Steering committee

In 2020, the steering committee met five times (since April 2020, these have been online meetings). Seven proposals for use of data and/or samples (serum/PBMC) were submitted to the committee: one from Experimental Immunology (AUMC), four from Laboratory of Experimental Virology (AUMC), and two from the GGD Amsterdam. Three of the proposals were collaborations with groups outside the ACS: one proposal from the RIVM, and one from Medical Microbiology (AUMC), both in collaboration with the GGD Amsterdam, and one was a collaboration with a diagnostic company. Six requests were approved after minor revisions recommended by the ACS steering committee. One proposal was initially rejected, but, following major revisions, the proposal was eventually approved (in 2021).

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Identification and characterization of latent classes based on drug use among men who have sex with men at risk of sexually transmitted infections in Amsterdam, the Netherlands.
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CD32+CD4+ T Cells Are Highly Enriched for HIV DNA and Can Support Transcriptional Latency.
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Shoukry NH, Lloyd AR, Kim AY, Lauer G, Cox AL, Page K, Maher L.
Clin Infect Dis. 2020 Jan 1;70(1):123-131. https://doi.org/10.1093/cid/ciz162

Anal Squamous Intraepithelial Lesions (SILs) in Human Immunodeficiency Virus–Positive Men Who Have Sex With Men: Incidence and Risk Factors of SIL and of Progression and Clearance of Low-Grade SILs.
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J Infect Dis. 2020 Jun 16;222(1):62-73. doi:10.1093/infdis/jiz614. PMID: 31755920.

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Arch Sex Behav. 2020 Aug; 49(6):1995-2003. doi: 10.1007/s10508-020-01744-5

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9. Curaçao

Diederik van de Wetering, Esther Rooijakkers, Gonneke Hermanides, Marije Hofstra, Ashley Duits, Ard van Sighem

Introduction

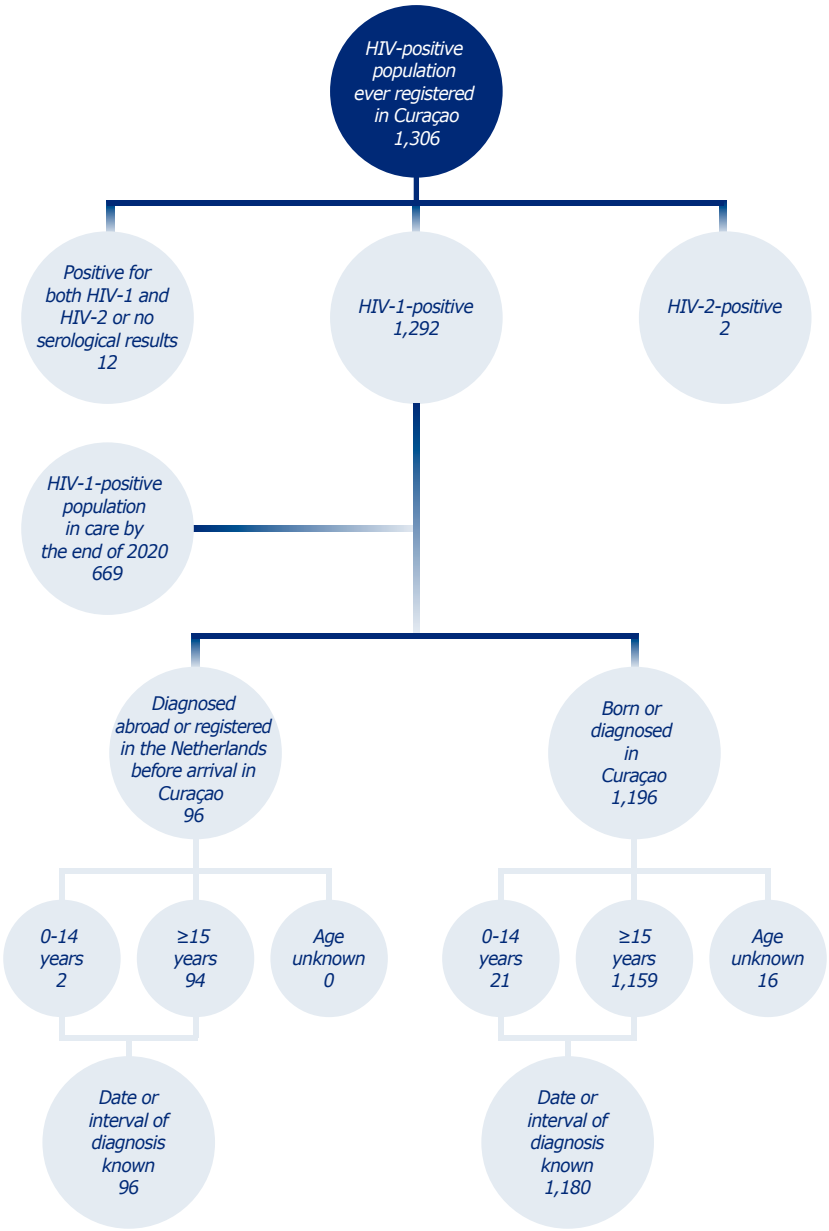
Since 2005, stichting hiv monitoring (SHM) has assisted in collecting demographic and clinical data about individuals living with HIV receiving care at the Curaçao Medical Center in Willemstad, Curaçao. As a result of this registration and monitoring, an extensive database has been established. Such a database is unique for the region and gives a clear picture of the population living with HIV, 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 the HIV epidemic in Curaçao.

In total, 1,306 individuals with HIV registered by SHM have been followed in the Curaçao Medical Center. Of these people, the majority were diagnosed with HIV-1 (1,292; 99%), while two individuals were diagnosed with HIV-2, and two had antibodies against both HIV-1 and HIV-2 (*Figure 9.1*). For ten individuals, serological results on HIV type were not available in the SHM database.

People newly diagnosed with HIV-1

Of the 1,292 individuals diagnosed with HIV-1, 91 (7%) were registered with an HIV treatment centre in the Netherlands prior to moving to Curaçao (*Figure 9.1*). The majority of these 91 individuals (66; 73%) originated from the former Netherlands Antilles, while 21 (23%) were born in the Netherlands and four (4%) were born elsewhere. Another five individuals were also born abroad (four in Venezuela, one in the Dominican Republic), and had a documented HIV diagnosis prior to migrating to Curaçao. The remaining 1,196 individuals were newly diagnosed while living in Curaçao, or information on where they lived at the time of diagnosis was not yet available (*Figure 9.1*). Of these 1,196 individuals, 887 (74%) were born in the former Netherlands Antilles, 112 (9%) originated from Haiti, and 90 (8%) from the Dominican Republic.

Figure 9.1: Overview of the population with HIV registered in Curaçao by the end of 2020.



For 16 (1%) of the 1,196 individuals diagnosed while living in Curaçao, the date or interval of diagnosis was not recorded in the SHM database. Among the remaining 1,180 individuals, 21 (2%) were diagnosed before the age of 15 years. The 1,159 individuals who were diagnosed at 15 years or older, comprised 243 (21%) men who reported sex with men (MSM) as the most likely mode of transmission, 492 (42%) other men, and 424 (37%) women (*Table 9.1*). Among the 492 other men, 322 (65%) most likely acquired their infection via sex with women, while the remaining 170 (35%) acquired their infection via other or unknown modes of transmission. Among the 424 women, 404 (95%) reported sex with men as the most likely mode of transmission, while the remaining 20 women reported other or unknown modes of transmission. Between 2000 and 2018, the annual number of newly-diagnosed infections hovered around 50, before decreasing to 20 in 2019 and 22 in 2020. However, at the time of writing, there may have been some backlog in reporting HIV infections newly diagnosed in 2019 and 2020, due to the transition to a new hospital at the end of 2019, and a disruption in data collection caused by the COVID-19 pandemic.

Table 9.1: Annual number of HIV-1 diagnoses in Curaçao among children under 15 years of age, and among men who acquired HIV via sex with men (MSM), other men, and women diagnosed at 15 years or older.

Year of diagnosis	MSM	Other men	Women	<15 years of age	Total
≤1999	31	105	77	17	230
2000	7	18	18	1	44
2001	3	13	14	1	31
2002	7	19	17	0	43
2003	8	28	19	0	55
2004	3	23	16	0	42
2005	12	19	17	0	48
2006	6	23	17	0	46
2007	12	17	10	0	39
2008	11	17	20	1	49
2009	9	17	21	1	48
2010	4	19	21	0	44
2011	12	19	24	0	55
2012	13	16	26	0	55
2013	19	31	22	0	72
2014	16	14	14	0	44
2015	16	22	12	0	50
2016	12	22	15	0	49
2017	14	17	13	0	44
2018	17	12	18	0	47
2019	6	10	4	0	20
2020	4	9	9	0	22
2021	1	2	0	0	3
Total	**243**	**492**	**424**	**21**	**1,180**

Note: *Data collection for 2020 may not have been finalised at the time of writing.*

Note: *Data on children are not yet collected.*

Legend: *MSM=sex between men.*

People in clinical care

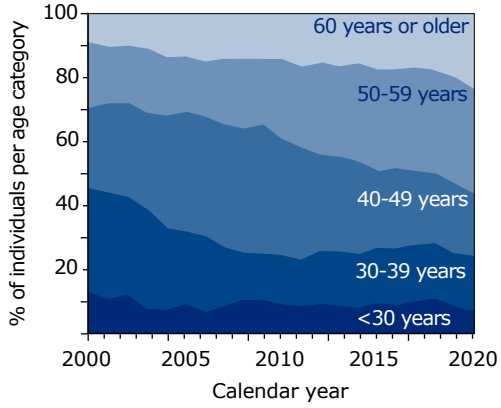
In total, 669 (52%) of the 1,292 registered HIV-1-positive individuals were known to be in clinical care in Curaçao by the end of 2020. People were considered to be in clinical care if they had visited their treating physician in 2020, or had a CD4 count or HIV RNA measurement during that year, and had not moved abroad. Of the 623 individuals who, according to this definition, were not in care by the end of 2020, 194 (31%) were known to have died, 140 (22%) to have moved abroad, and 280

(45%) were lost to care. Another three were only diagnosed with HIV in 2021 and six entered care in 2021. Of the 280 people lost to care, 60 (21%) had their last visit within a year of entering care, while another 33 (12%) had no follow-up visit after entering care. The 669 people in clinical care in 2020 included ten individuals who did not have a visit or a CD4 count or HIV RNA measurement in 2019, but had previously received care for their HIV infection. Five of these individuals had not been in care for more than three years.

Ageing population

The median age of the population in care by the end of 2020 was 52 years (interquartile range [IQR] 40-59) and has been increasing since 2000 (*Figure 9.2*). This increase in age is mainly a result of the improved life expectancy of individuals living with HIV following the introduction of combination antiretroviral treatment (cART). As a result, more than half of all people currently in care (56%) are 50 years or older, including 54% of men and 59% of women; 24% are 60 years or older. Among the 92 individuals diagnosed in 2018 or later, the median age at diagnosis was 34 years (IQR 28-46), with no differences between men and women. Of these 92 individuals, 19 (21%) were 50 years or older at the time of their diagnosis, while 30 (33%) were younger than 30 years of age.

Figure 9.2: *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 2020, these proportions were 8% and 56%, respectively, while 24% 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, 30-39 years, 40-49 years, 50-59 years, and 60 years or older.*



Duration of infection

People in care by the end of 2020 had been diagnosed with HIV a median of 10.5 years (IQR 5.6-16.8) previously. Therefore, a large group (52%) has lived with HIV for more than 10 years; 17% for more than 20 years (*Table 9.2*). The median time since diagnosis was 9.4 years for MSM, 10.4 years for other men, and 10.8 years for women.

Table 9.2: *Characteristics of the 669 HIV-1-positive individuals in clinical care in Curaçao by the end of 2020.*

	Men (n=415, 62%)		Women (n=254, 38%)		Total (n=669)	
	n	%	n	%	n	%
Transmission						
MSM	162	39	–	–	162	24
Heterosexual	171	41	240	94	411	61
Other/unknown	82	20	14	6	96	14
Current age (years)						
0–15*	1	0	–	–	1	0
15–24	9	2	7	3	16	2
25–29	26	6	10	4	36	5
30–39	72	17	40	16	112	17
40–49	82	20	47	19	129	19
50–59	127	31	90	35	217	32
60–69	70	17	42	17	112	17
≥70	28	7	18	7	46	7
Country of origin						
Former Netherlands Antilles	344	83	168	66	512	77
The Dominican Republic	10	2	40	16	50	7
Haiti	21	5	26	10	47	7
The Netherlands	11	3	0	0	11	2
Other	29	7	20	8	49	7
Years aware of HIV infection						
<1	11	3	5	2	16	2
1–2	38	9	19	7	57	9
3–4	47	11	19	7	66	10
5–10	112	27	68	27	180	27
10–20	139	33	96	38	235	35
>20	65	16	46	18	111	17
Unknown	3	1	1	0	4	1

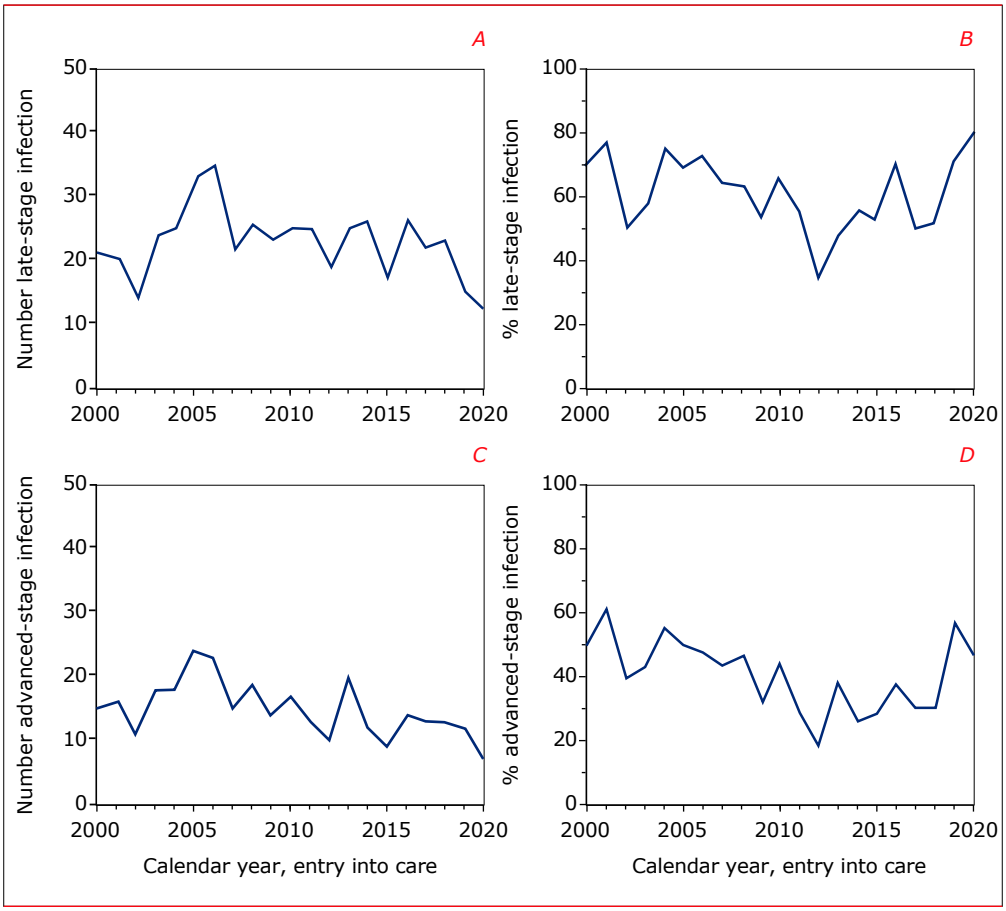
** Data on children are not yet collected.*

Legend: *MSM=sex between men.*

Late presentation

Among the 1,180 people diagnosed with HIV-1 while living in Curaçao, a large proportion of those who have entered care since 2000 were late presenters; in other words, individuals who entered care with a CD4 count below 350 cells/mm^3, or with an AIDS-defining event, regardless of CD4 count[1]. The proportion of late presenters was 59% among individuals entering care in 2000-17, and remained at a high level of 64% among those entering care in 2018 or later (*Figures 9.3A* and *9.3B*). In 2019 and 2020, late presentation among those entering care appeared to be more common, but this most likely reflects underreporting of people entering care, rather than an increase in the absolute number with late presentation. In contrast, there appears to have been a decrease in the proportion of people entering care with advanced HIV infection (i.e., with a CD4 count below 200 cells/mm^3 or AIDS), from 50% in 2000 to 30% in 2017 (*Figures 9.3C* and *9.3D*). From 2018 onwards, 41% among those entering care had advanced-stage HIV. In total, 12% of the individuals who have entered care since 2000 have presented with an AIDS-defining disease. There were no significant differences in late presentation in 2018 or later between MSM (53%), other men (72%), and women (67%), but advanced presentation appeared to be less common in MSM (25%) than in other men (56%) and women (41%).

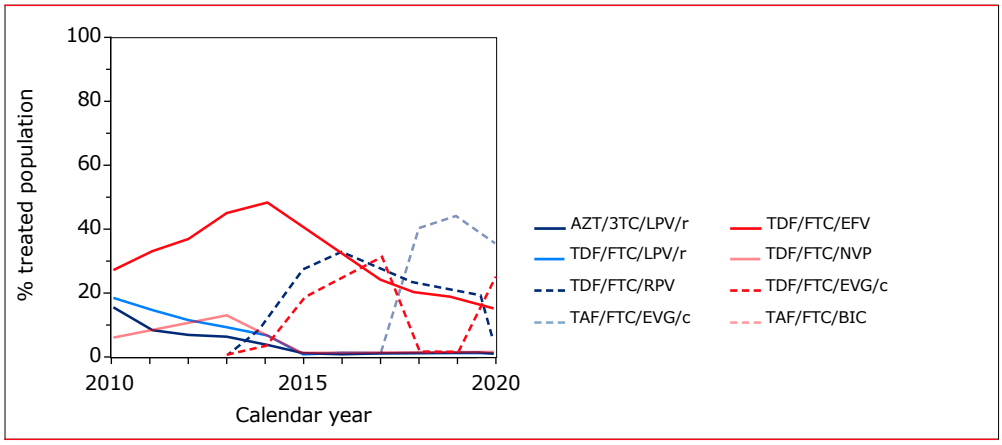
Figure 9.3: *Number and proportion of people classified as presenting with (A, B) late-stage, or (C, D) advanced-stage HIV infection at the time of entry into care. From 2018 onwards, 56 (64%) individuals presented with late HIV disease while 36 (41%) were advanced presenters. Late-stage HIV infection: 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 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 all individuals. From 2018 onwards, the stage of infection was unknown for 24 (22%) individuals.*



Antiretroviral treatment

In total, 1,194 (92%) of the 1,292 registered HIV-1-positive individuals had started antiretroviral treatment by May 2021. Of the 98 people who never received treatment, 96 were not in care anymore, including 35 who had died, while two managed to achieve HIV RNA levels below the lower limit of quantification without treatment. Over time, there have been clear shifts in the treatment regimens prescribed in Curaçao (*Figure 9.4*). Of the 663 people who were still in care by the end of 2020 and had started antiretroviral treatment, 35% were being treated with a combination of tenofovir alafenamide, emtricitabine, and cobicistat-boosted elvitegravir; 24% with tenofovir alafenamide, emtricitabine, and bictegravir; 28% with tenofovir disoproxil, emtricitabine and rilpivirine; and 16% with tenofovir disoproxil, emtricitabine and efavirenz. The majority (98%) used a once-daily regimen, with 93% being treated with a fixed-dose, single tablet regimen.

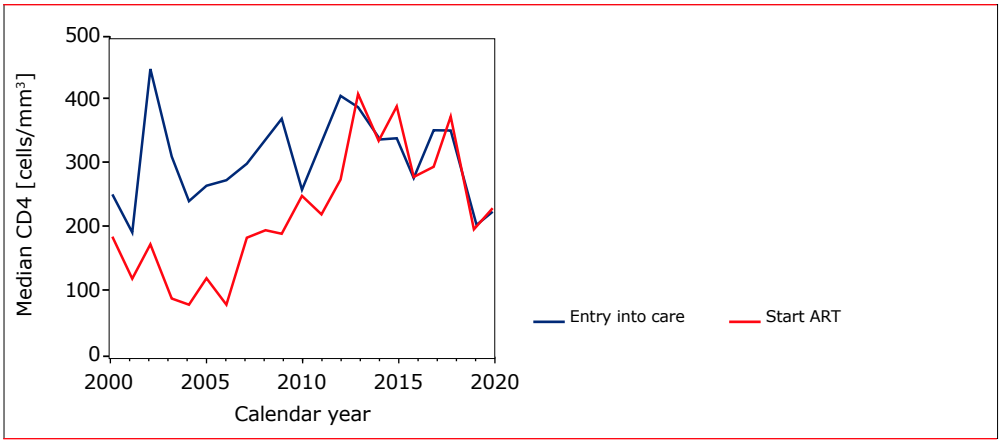
Figure 9.4: *Percentage of individuals treated with antiretroviral therapy by specific regimens over calendar time. At the end of 2020, 35% were receiving TAF/FTC/EVG/c, 24% TAF/FTC/BIC, 18% TDF/FTC/RPV, and 16% TDF/FTC/EFV.*



Legend: *AZT=zidovudine; 3TC=lamivudine; LPV/r=ritonavir-boosted lopinavir; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; FTC=emtricitabine; RPV=rilpivirine; EFV=efavirenz; NVP=nevirapine; EVG/c=cobicistat-boosted elvitegravir; BIC=bictegravir.*

Since the mid-2000s, there has been an increase in CD4 cell counts at the start of treatment, reflecting changes in guidelines on when to start (*Figure 9.5*). CD4 counts at entry into care and at the start of treatment are now almost identical, which implies that people rapidly start treatment after entry into care. In 2018-20, 96% of people received treatment within six months of entering care, irrespective of their CD4 count. During the same period, 36% of those for whom a CD4 count was available at the start of treatment had a CD4 count lower than 200 CD4 cells/mm^3; 23% had between 200 and 349 cells/mm^3; 24% had between 350 and 499 cells/mm^3; and 17% had CD4 counts of 500 cells/mm^3 or higher.

Figure 9.5: *Changes over calendar time in median CD4 counts at entry into care and at the start of antiretroviral treatment (ART). In 2018–2020, CD4 counts at entry into care were 275 cells/mm^3 (interquartile range [IQR] 155–457) and were very similar, 280 cells/mm^3 (IQR 153–454), at the start of treatment.*

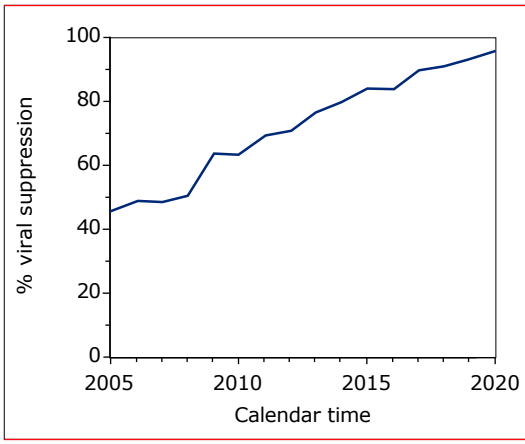


Legend: *ART=antiretroviral treatment.*

Treatment outcome

In the total population still in care by the end of 2020, the median current CD4 count was 487 cells/mm^3 (IQR 320-726). CD4 counts were similar between MSM (503 cells/mm^3; IQR 356-741) and women (607 cells/mm^3; IQR 376-789). Men who acquired their infection via other or unknown modes of transmission had lower CD4 counts (389 cells/mm^3; IQR 228-624). Among individuals with a viral load measurement, the proportion with HIV RNA levels lower than 200 copies/ml, increased from 45% in 2005 to 95% in 2020 (*Figure 9.6*).

Figure 9.6: Proportion of people in care with HIV RNA <200 copies/ml at their last viral load measurement in each calendar year.



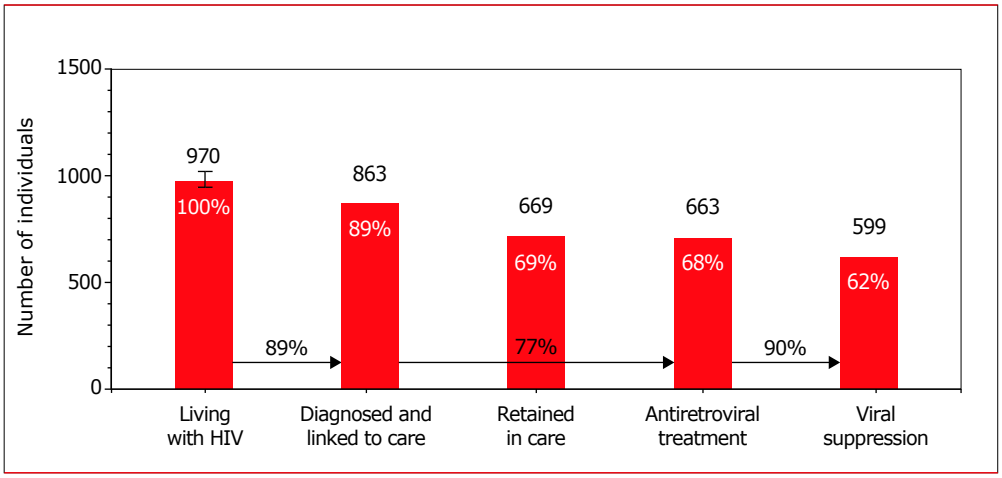
Continuum of HIV care

The total number of people living with HIV by the end of 2020, including those not yet diagnosed, was estimated to be 970 (95% confidence interval [CI] 950-1,010), of whom 110 (95% CI 90-150) were still undiagnosed (*Figure 9.7*). Of note, estimation of the undiagnosed population was based on trends over calendar time in observed diagnoses and CD4 counts at the time of diagnosis[2]. As a result of the likely underreporting in 2019 and 2020, the estimated number of 110 may be lower than the true number. Also, the estimated number of people with undiagnosed HIV does not include populations of undocumented migrants, who are less likely to reach HIV care.

In total, 863 individuals, or 89% 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, 669 (69%) people were still in care; in other words, they had had at least one HIV RNA or CD4 count measurement, or a clinic visit in 2020. The majority of those 669 individuals (663, or 77% of those diagnosed and linked to care), had started antiretroviral treatment; 625 (94% of those who started treatment) had an HIV RNA measurement available in 2020 and 599 (96%, or 90% of those treated) had a most recent HIV RNA below 200 copies/ml. Overall, 62% of the total estimated population living with HIV, and 69% of the 863 individuals diagnosed and ever linked to care, had a suppressed viral load. In terms of the Joint United Nations Programme on HIV/AIDS' (UNAIDS) 95-95-95

target for 2025, the current estimate for Curaçao stands at 89-77-90: 89% 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 9.7: Continuum of HIV care for the total estimated HIV-1-positive population in Curaçao by the end of 2020. Percentages at the top of the bars are calculated relative to the number living with HIV, while percentages at the bottom correspond to UNAIDS' 95-95-95 targets.



Viral suppression

Of the 663 individuals who had started antiretroviral treatment, 64 (10%) did not have a suppressed viral load. On closer inspection, 38 (59%) of these individuals were found to have no documented RNA measurement in 2020. The remaining 26 (41%) had a viral load measurement in 2020, but with RNA levels exceeding 200 copies/ml. Of these 26 individuals, one had not yet started treatment at the time of their last available viral load measurement in 2020, and one only started treatment within the six month-period prior to their last measurement and may not have had sufficient follow up to achieve a documented suppressed viral load. The remaining 24 individuals with RNA levels above 200 copies/ml, had been on antiretroviral treatment for longer than six months.

Lost to care

In total, 280 individuals were lost to care; 86 (31%) before the end of 2010, and 194 (69%) after 2010. The 86 individuals who were lost to care before 2010, 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 86 individuals are still living in Curaçao without needing care or antiretroviral treatment. Of the 194 individuals lost to care after 2010 (i.e., the difference between the second stage (863) and third stage (669) in the care continuum), 40 (21%) were last seen for care in 2019 and 24 (12%) in 2018. In total, 63 (32%) of the 194 individuals were born outside the former Netherlands Antilles, including 25 in Haiti and 11 in the Dominican Republic; for those still in care by the end of 2020, this percentage falls to 23%. This suggests that some of those lost to care may have moved abroad; in particular, back to their country of birth. It also shows that, overall, a considerable proportion was not retained in care.

Conclusion

Over the years, the quality of treatment offered to individuals living with HIV in Curaçao has improved considerably, as evidenced by the 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 progress towards achieving UNAIDS' 95-95-95 goals for 2025. However, the relatively high proportion of people lost to care is worrisome and may result in underreporting of death and/or outmigration. In addition, the proportion of people entering care with late-stage HIV infection remained high, and may even have been rising in recent years.

Of note, data reported for 2019 and 2020 may not yet be complete. As mentioned above, the hospital moved to a new building at the end of 2019, which may have delayed notification to SHM of individuals newly diagnosed and enrolled in care around that time. Also, data collection for 2019 and 2020 was hampered by the data collector's lack of access to electronic patient records, as well as the partial lockdown in Curaçao in response to the COVID-19 pandemic. Access to patient records has now been restored and data are expected to be complete in next year's monitoring report.

Recommendations

Curaçao is in a unique position in the Caribbean, in that data from individuals living with HIV in care are regularly collected and monitored. However, it is important that the quality of these data is maintained. Moreover, currently there is no regular data collection for children living with HIV. As a result, data on children living with HIV in Curaçao are of unknown quality and are unsuitable for use in strategic planning of HIV care for this specific population. Therefore, data collection needs to be extended to include children.

Early start of ART in adults appears possible, but long-term, continuous follow up should be guaranteed to optimise the effect of ART. 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 been recently stepped up to trace people who miss their scheduled appointment in the hospital. As a result, retention in care will hopefully improve in the near future.

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

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Acknowledgements

Clinical centres

** denotes site coordinating physician*

Amsterdam UMC, AMC site, Amsterdam:
HIV treating physicians: M. van der Valk*, S.E. Geerlings, A. Goorhuis, V.C. Harris, J.W. Hovius, B. Lempkes, F.J.B. Nellen, T. van der Poll, J.M. Prins, P. Reiss, V. Spoorenberg, M. van Vugt, W.J. Wiersinga, F.W.M.N. Wit.
HIV nurse consultants: C. Bruins, M. van Duinen, J. van Eden, A.M.H. van Hes, F.J.J. Pijnappel, S.Y. Smalhout, A.M. Weijsenfeld.
HIV clinical virologists/chemists: N.K.T. Back, B. Berkhout, M.T.E. Cornelissen, R. van Houdt, M. Jonges, S. Jurriaans, C.J. Schinkel, K.C. Wolthers, H.L. Zaaijer.

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, J. Steiner.
HIV clinical virologists/chemists: N.K.T. Back, B. Berkhout, M.T.E. Cornelissen, R. van Houdt, M. Jonges, S. Jurriaans, C.J. Schinkel, K.C. Wolthers, H.L. Zaaijer.

Emma Kinderziekenhuis (Amsterdam UMC, AMC site), Amsterdam:
HIV treating physicians: M. van der Kuip, D. Pajkrt.
HIV nurse consultants: C. de Boer, 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: P. van Keulen, J. Stohr, B. Wintermans.

Catharina Ziekenhuis, Eindhoven:
HIV treating physicians: M.J.H. Pronk*, H.S.M. Ammerlaan.
HIV nurse consultants: 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, Amsterdam:
HIV treating physicians: M. van der Valk*, A. van Eeden, E. Hoornenborg, J. Nellen.
HIV nurse consultants: W. Brokking, L.J.M. Elsenburg, H. Nobel.
HIV clinical virologists/chemists: C.J. Schinkel.

ETZ (Elisabeth-TweeSteden Ziekenhuis), Tilburg:
HIV treating physicians: M.E.E. van Kasteren*, M.A.H. Berrevoets, A.E. Brouwer.
HIV nurse specialist: B.A.F.M. de Kruijf-van de Wiel.
HIV nurse consultants: A. Adams, A. Dievelaar-Oomen, R. van Erve, S. Phaf, B. van de Ven.
HIV data collection: B.A.F.M. de Kruijf-van de Wiel.
HIV clinical virologists/chemists: A.G.M. Buiting, J.L. Murck.

Erasmus MC, Rotterdam:
HIV treating physicians: C. Rokx*, A.A. Anas, H.I. Bax, E.C.M. van Gorp, M. de Mendonça Melo, E. van Nood, J.L. Nouwen, B.J.A. Rijnders, C.A.M. Schurink, L. Slobbe, T.E.M.S. de Vries-Sluijs.
HIV nurse consultants: N. Bassant, J.E.A. van Beek, M. Vriesde, L.M. van Zonneveld.
HIV data collection: J. de Groot.
HIV clinical virologists/chemists: J.J.A. van Kampen, M.P.G Koopmans.

Erasmus MC Sophia Kinderziekenhuis, 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, L. Smit.
HIV nurse consultants: J. Geilings, S. van Winden.
HIV data collection: G. van der Hut.
HIV clinical virologists/chemists: 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: A.G.W. van Hulzen, S. Kraan, M.S.M. Kruiper.
HIV 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: A.H.E. Roukens*, M.G.J. de Boer, H. Jolink, M.M.C. Lambregts, 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, D. Heida-Peters, E. Mulder, J.V. Smit, D. Struik-Kalkman.
HIV data collection: T. van Niekerk.
HIV clinical virologists/chemists: O. Pontesilli, C. van Tienen.

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.
HIV data collection: B. Weijenberg-Maes.
HIV clinical virologists/chemists: T.R.A. Havenith, M. van Loo.

Medisch Centrum Leeuwarden, Leeuwarden:
HIV treating physicians: M.G.A. van Vonderen*, L.M. Kampschreur.
HIV nurse consultants: M.C. van Broekhuizen, S. Faber.
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, J. Wagenaar.
HIV nurse consultants & HIV data collection: D. Ruiter-Pronk, F.A. van Truijen-Oud.
HIV clinical virologists/chemists: J.W.T. Cohen Stuart, M. Hoogewerf, W. Rozemeijer, J.C. Sinnige.

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

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, O. Richel.
HIV nurse consultants: M. Albers, K.J.T. Grintjes-Huisman, M. de Haan, M. Marneef.
HIV clinical virologists/chemists: J. Rahamat-Langendoen, F.F. Stelma.
HIV clinical pharmacology consultant: D. Burger.

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

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.
HIV clinical virologists/chemists: J.S. Kalpoe, A. Vahidnia, A. Wagemakers.

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

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

Beatrix Kinderziekenhuis (Universitair Medisch Centrum Groningen), Groningen:
HIV treating physicians:
E.H. Schölvinck, A.R. Verhage.
HIV nurse consultants: H. de Groot-de Jonge.
HIV clinical virologists/chemists:
M. Knoester, C.C. van Leer-Buter, H.G.M. Niesters.

Universitair Medisch Centrum Utrecht, Utrecht:
HIV treating physicians:
A.I.M. Hoepelman*, R.E. Barth, A.H.W. Bruns, P.M. Ellerbroek, M.P.M. Hensgens, T. Mudrikova, J.J. Oosterheert, E.M. Schadd, A. Verbon, B.J. van Welzen.
HIV nurse consultants:
B.M.G. Griffioen-van Santen, I. de Kroon.
HIV data collection: M. van Berkel, C.S.A.M. van Rooijen.
HIV clinical virologists/chemists:
L.M. Hofstra, R. Schuurman, A.M.J. Wensing.

Wilhelmina Kinderziekenhuis, UMC Utrecht, Utrecht:
HIV treating physicians: S.P.M. Geelen, Y.G.T. Loeffen, T.F.W. Wolfs.
HIV nurse consultants: N. Nauta.

Curaçao Medical Center, Willemstad (Curaçao):
HIV treating physicians:
E.O.W. Rooijakkers, D. van de Wetering.
HIV nurse consultants: A. Alberto.
Data collection: I. der Meer.

Composition of stichting hiv monitoring

SHM Board of Directors (since 1 April 2021)

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S. Zaheri MSc

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Reviewers

Name	Affiliation
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D.r G. Hermanides	Rode Kruis Ziekenhuis, Beverwijk
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Dr. J. Schinkel	Amsterdam UMC, AMC location, Amsterdam
Dr. E.F. Schippers	HagaZiekenhuis, Den Haag
Dr. R. Schuurman	UMC Utrecht, Utrecht
Dr. K. Sigaloff	Amsterdam UMC, VUmc location, Amsterdam
Dr. J. Schouten	Rijnstate, Arnhem
Dr. T.E.M.S. de Vries-Sluys	Erasmus MC, Rotterdam

External authors and co-authors

Name	Affiliation
Dr J. Branger	Flevoziekenhuis, Almere
Prof. K. Brinkman	OLVG, Amsterdam
Dr M.A.A. Claassen	Rijstate, Arnhem
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 C.M. van der Hoek	Amsterdam UMC, AMC location, Amsterdam
Dr L.M. Hofstra	UMC Utrecht, Utrecht
J. Koole	GGD Amsterdam, Amsterdam
Dr N.A. Kootstra	Amsterdam UMC, AMC location, Amsterdam
Dr L. van Leeuwen	Amsterdam UMC, AMC location, Amsterdam
Dr A. Matser	GGD Amsterdam, Amsterdam
Dr T. Mudrikova	UMS Utrecht, Utrecht
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
Prof. P. Reiss	Amsterdam UMC, AMC location, Amsterdam
Dr B.J.A. Rijnders	Erasmus MC, Rotterdam
E. Rooijakkers	Curaçao Medical Center, Willemstad, Curaçao
Prof. A.M.C. van Rossum	Erasmus MC, Rotterdam
Dr B.J. van Welzen	UMC Utrecht, Utrecht
Prof. A.M.J. Wensing	UMC Utrecht, Utrecht
Dr D. van de Wetering	Curaçao Medical Center, Willemstad, Curaçao
Dr T. Wolfs	Wilhelmina Kinderziekenhuis, Utrecht

SHM personnel

Data analysis, reporting & research unit

Researchers	D.O. Bezemer PhD A.C. 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) T. Rutkens T.J. Woudstra
Data quality staff	D. Bergsma MSc (coordinator) N.M. Brétin K.J. Lelivelt MSc L. van de Sande MA K.M. Visser S.T. 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 R. Alexander Y.M. Bakker A. el Berkaoui M. Bezemer-Goedhart E.A. Djoechro MSc M. Groters MSc L.E. Koster MSc C.R.E. Lodewijk R.J. Loenen MSc E.G.A. Lucas S. van Meerveld L. Munjishvili MA F. Paling MSc B.M. Peeck MSc C.M.J. Ree R. Regtop A.F. van Rijk PhD 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	S.F. Boucherie MSc (manager) C.W. Don (a.i.) Y. de Waart
Human resources, finance & administration	I. Bartels (HR advisor) Y. de Waart (HR assistant) R.P. Geerling (Qualified 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 HIV Monitoring Report 2020

Publications

Rationale, design and initial results of an educational intervention to improve provider-initiated HIV testing in primary care
Bogers S, Schim van der Loeff M, van Dijk N, Groen K, Groot Bruinderink M, de Bree G, Reiss P, Geerlings S, van Bergen J
Fam Pract, DOI: 10.1093/fampra/cmaa139

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Pasternak AO, Grijsen ML, Wit FW, Bakker M, Jurriaans S, Prins JM, Berkhout B
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Neesgaard B, Mocroft A, Zangerle R, Wit F, Lampe F, Günthard HF, Necsoi C, Law M, Mussini C, Castagna A, d'Arminio Monforte A, Pradier C, Chkhartisvilli N, Reyes-Uruena J, Vehreschild J, Wasmuth JC, Sönnerborg A, Stephan C, Greenberg L, Llibre JM, Volny-Anne A, Peters L, Pelchen-Matthews A, Vannappagari V, Gallant J, Rieger A, Youle M, Braun D, de Wit S, Petoumenos K, Borghi V, Spagnuolo V, Tsertsvadze T, Lundgren J, Ryom L, RESPOND study group
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HCV micro-elimination in HIV-positive individuals in the Netherlands: four years after universal access to direct-acting antivirals
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Terminology

Acute infection
Any infection that begins suddenly, with intense or severe symptoms, is called acute (or primary). If the illness lasts longer, such as more than a couple of weeks, it is called chronic.

Adherence
Adherence measures how regularly a person takes all their antiretroviral medications at the right time. Poor adherence is one of the main reasons that antiretroviral combinations fail.

AIDS
Acquired Immunodeficiency Syndrome. A disease caused by a retrovirus, HIV (human immunodeficiency virus), and characterised by the immune system's failure 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 comparisons. 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 to monitor the 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 (above 500 per mm^3) to dangerously low levels (below 200 CD4 cells per mm^3 blood).

CDC
US Centres 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), tuberculosis (TBn), 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.

COVID-19
COVID-19 is an infectious disease caused by the SARS-CoV-2 virus (coronavirus).

DAAs
Direct-acting antivirals (DAAs) are new-generation drugs that treat hepatitis C virus infection by targeting specific steps in the hepatitis C virus lifecycle. 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.

EASL
European Association for the Study of the Liver.

ECDC
European Centre for Disease Prevention and Control.

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 A virus (HAV)
A viral infection that affects the liver and is acquired predominately through faecal-oral transmission.

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 injecting drug use – and sometimes through sexual contact.

Hepatitis D virus (HDV)
A viral infection that affects the liver and requires infection with hepatitis B virus (HBV). It is transmitted by the same routes as HBV.

Hepatitis E virus (HEV)
A viral infection that affects the liver and is transmitted by indirect, or direct contact with animals.

HIV
Human Immunodeficiency Virus; the virus that causes Acquired Immunodeficiency Syndrome (AIDS). HIV enters and destroys the cells that control and support the immune response system.

HIV type 1 (HIV-1)
The HIV type responsible for the majority of HIV infections worldwide.

HIV type 2 (HIV-2)
An HIV type endemic to West Africa. HIV-2 infections generally take longer to progress to AIDS than HIV-1.

HIV Vereniging
Dutch HIV association.

HIVdb genotypic resistance interpretation algorithm
A tool developed by Stanford University to determine the level of treatment resistance that is found in HIV circulating in the blood.

IAS
International AIDS Society

Immunoglobulin G (IgG)
A type of antibody molecule that develops as a result of an infection and is often continuously produced in the body well after infection.

Immunoglobulin M (IgM)
A type of antibody molecule that often develops immediately as a result of an infection and is no longer produced within a short time after infection.

Immunological failure
A type of HIV treatment failure. There is no consensus on the definition of immunological failure; however, some experts define it as the failure to achieve and maintain adequate CD4 counts, despite viral suppression.

Integrase
A type of enzyme that helps the virus insert its viral genome into the genome of a cell (integration). HIV inserts a double-stranded DNA copy of its viral genome using this enzyme. Blocking integrase activity helps decrease HIV replication.

Interferon
Interferons are naturally-occurring proteins (cytokines) produced by immune cells in response to an antigen, usually a virus. Although they do not directly kill viral cells, they boost the immune response by signalling neighbouring cells into action and inhibiting the growth of malignant cells. There are three types of interferons: alpha, beta, and gamma. Laboratory-made interferons are used to treat certain cancers and opportunistic infections. Addition of polyethylene glycol to interferons prolongs their half-life. Pegylated interferon alpha was formally 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)
Dutch Federation of University Medical Centres.

Non-AIDS event
Diseases and clinical events that are not related to AIDS (i.e., they are not listed as being associated with AIDS by the Centres for Disease Control and Prevention). These include conditions such as malignancies, end-stage renal disease, liver failure, pancreatitis, and cardiovascular disease.

Non-nucleoside reverse transcriptase inhibitor (NNRTI)
An antiretroviral HIV drug class. NNRTIs bind to and block HIV reverse transcriptase; an enzyme that HIV uses to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

Nucleoside reverse transcriptase inhibitor (NRTI)
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Nucleotide
A building block of nucleic acids. DNA and RNA are nucleic acids.

Nucleotide reverse transcriptase inhibitor (NtRTI)
A type of antiretroviral (ARV) HIV drug included in the NRTI drug class. NtRTIs interfere with the HIV lifecycle in the same way as NRTIs; both block reverse transcription.

NVHB
Dutch Association of HIV-Treating Physicians (Nederlandse Vereniging van HIV Behandelaren).

Person year
A measure of time used in medical studies. It combines the number of people 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 transfer of HIV from a pregnant person with HIV to their child during pregnancy, labour and delivery, or via breastfeeding (through breast milk).

PrEP
Pre-Exposure Profylaxis. A treatment to avoid an infection with hiv.

Protease
A type of enzyme that breaks proteins down into smaller proteins or protein units, such as peptides or amino acids. In the case of HIV, 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)
An antiretroviral HIV drug class. In people with HIV, PIs block protease from forming new HIV viruses (see Protease definition).

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 that includes HIV. Retroviruses are so named because they carry their genetic information in RNA, rather than DNA, and then translate that RNA information "backwards" into DNA.

Reverse transcriptase
After infecting a cell, HIV uses an enzyme called reverse transcriptase to convert its RNA into DNA. It then replicates itself using the cell's machinery.

RIVM
The Netherlands' National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu).

RNA
Ribonucleic acid. A complex protein that carries genetic information.

Seroconversion
The change from an absence of HIV antibodies in the blood to the presence of those antibodies.

SHM
The Dutch HIV Monitoring Foundation (stichting hiv monitoring).

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 in the 12 or 24 weeks, respectively, following 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.

UNAIDS
The Joint United Nations Programme on HIV/AIDS

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 other bodily 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.

V&VN VCH
Dutch Association for HIV nursing consultants (Verpleegkundigen & Verzorgenden Nederland Verpleegkundig Consulenten HIV).

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

Some of the above definitions were taken from hivinfo.nih.gov