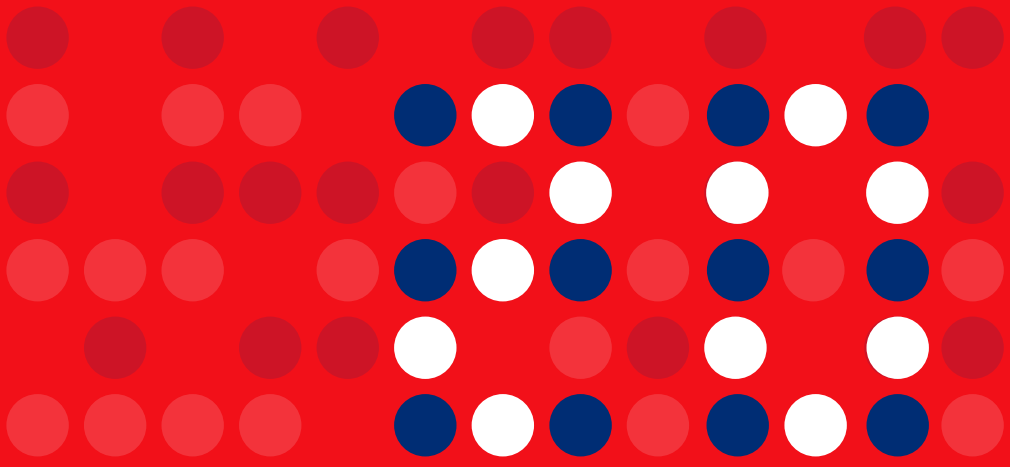
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

# HIV Monitoring Report 2020



## 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.

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HIV Monitoring

# Monitoring Report 2020

## Human Immunodeficiency Virus (HIV) Infection in the Netherlands

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**Reference numbers**

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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 2019 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 2019 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 2020 Monitoring Report on Human Immunodeficiency Virus (HIV) Infection in the Netherlands is the 19th in the series published by Stichting HIV Monitoring (SHM). Based on pseudonymised data from the AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort, the report provides a comprehensive review of trends over time in the HIV epidemic in the Netherlands and the effect of treatment. It also describes quality of care in HIV treatment centres, and includes special reports on HIV in Curaçao and on the Amsterdam Cohort Studies.

SHM has managed the ATHENA cohort since 2001. Today, the cohort's very broad, nationwide coverage and the quality and extensiveness of the data collection affords us a unique insight into the HIV epidemic in the Netherlands and facilitates ongoing improvements in the quality of HIV care provided to people living with HIV. Through this work, SHM makes an important contribution to the ultimate goal (both in the Netherlands and globally) of reducing the number of new HIV infections. The up-to-date, reliable and detailed data generated by SHM and published in this report play an important role in achieving this goal. The data provide a measure of how close we are to realising the goal, but they also provide the evidence-base by which HIV prevention and treatment can, and should, be further optimised.

The Netherlands has already achieved one of the goals set by the UNAIDS and WHO for 2020, namely the 90-90-90 goal (90% of people living with HIV know their HIV status, 90% of people who know they have HIV are receiving treatment, and 90% of people on treatment have an undectable viral load). This year's data show that in 2019, each of the eight public sexual health surveillance regions had reached or surpassed '90-90-90', with the country as a whole standing at '93-93-96'. The Netherlands is on track to achieving another important UNAIDS and WHO 2020 goal, which states that there should be a reduction in the number of new infections of at least 75% between 2010 and 2020. The data reveal that in 2019 the number of estimated newly-acquired infections have dropped by 72 percent, from 960 in 2010 to 270 in 2019. Among men who have sex with men (MSM), there was a drop of 76 percent in the same period, from 690 to 160. These achievements reflect efforts in the Netherlands in recent years to promote the importance of timely diagnosis and treatment initiation, thereby contributing not only to improved health in the individual, but also to the prevention of new infections.

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

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

Finally, I extend my gratitude to the people living with HIV who generously agree to provide data to SHM. It is only through this partnership between both professionals and affected communities that we can further our insight into the many facets of HIV and HIV treatment, and thereby continue to not only improve the care for people living with HIV in the Netherlands, but also provide guidance for prevention.

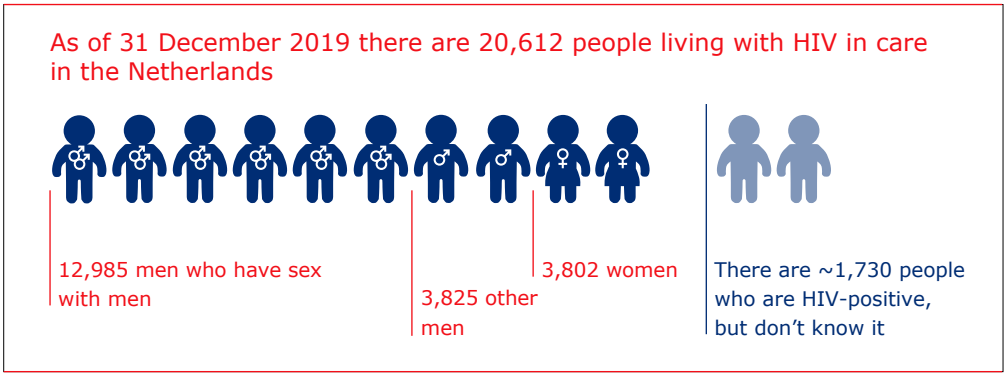
Professor Peter Reiss, MD

**Director, Stichting HIV Monitoring**

# Executive summary

## The HIV epidemic in the Netherlands in 2019

*Figure 1: Number of people living with HIV and in care in the Netherlands in 2019.*




### Number of people with HIV and in care

As of 31 December 2019, 23,700 people were estimated to be living with HIV in the Netherlands (*Figure 1*). Of those, 20,612 were in care in one of the 24 adult or 4 paediatric HIV treatment centres.

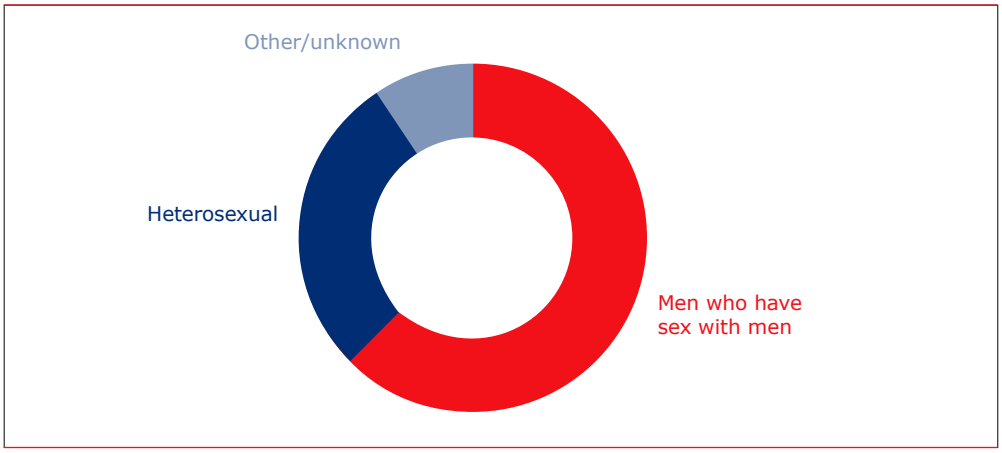
### Trend of fewer new HIV diagnoses continued in 2019

Since 2008, the annual number of newly-diagnosed HIV infections has fallen steadily, and this trend continued in 2019. The projected number of new diagnoses for 2019 is 580, compared with 654 in 2018. This means 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 890). In addition, 217 HIV-positive individuals who were born abroad arrived in the Netherlands in 2019; they were diagnosed prior to arrival.

### Majority of new HIV diagnoses continued to be among men who have sex with men

In 2019, the majority (61%) of newly-diagnosed infections were in men who acquired HIV through having sex with men (MSM), while 28% were acquired through heterosexual contact and 11% through other or unknown modes of transmission (*Figure 2*).

*Figure 2: Mode of HIV acquisition for people living with HIV and in care in the Netherlands in 2019.*




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

The majority of people newly diagnosed with HIV in 2019 (96%), entered specialised HIV care within six 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)

## HIV testing has become more common

Testing rates for HIV appear to be increasing in the Netherlands. This conclusion is based on a number of observations. Firstly, our data show that the proportion of individuals with a known, previously negative HIV test increased in 2019 (73% of MSM, 35% of other men, and 39% of women diagnosed). In addition, the proportion of individuals diagnosed relatively early in their infection (including during primary HIV infection) continued to increase, particularly among MSM. This is reflected in the fact that the CD4 count at diagnosis has gradually risen over time to a median of 361 cells/mm$^3$ in 2019.

## Decline in number of newly-acquired infections continued in 2019

The estimated number of newly-acquired HIV infections has been declining, and reached 270 in 2019; a reduction of 72%, compared with the 2010 figure of 960. This downward trend confirmed that the Netherlands is on track to achieve the UNAIDS fast-track target for 2020 – a 75% reduction in annual, newly-acquired HIV infections since 2010. Among MSM, the number of newly-acquired HIV infections fell by 76%, from 690 in 2010 to 160 in 2019, surpassing the UNAIDS target.

### Late presentation for care remains a problem that needs attention

Despite the observed earlier diagnosis in certain groups, many people still present late for care, in other words, with an already markedly-impaired immune system (CD4 count below 350 cells/mm$^3$) or even AIDS; in 2019, this was the case for 39% of MSM, 64% of other men and 62% of women. Although newly-diagnosed MSM had the lowest proportion of late-stage HIV infections, they accounted for 133 (50%) of all 267 individuals diagnosed with late-stage HIV in 2019.

### Continuum of HIV care in 2019: 93–93–96 – the Netherlands is on course to meet targets

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

The continuum of care for the Netherlands confirms that each of these goals have been reached (93-93-96 in 2019, *see Figure 3*):

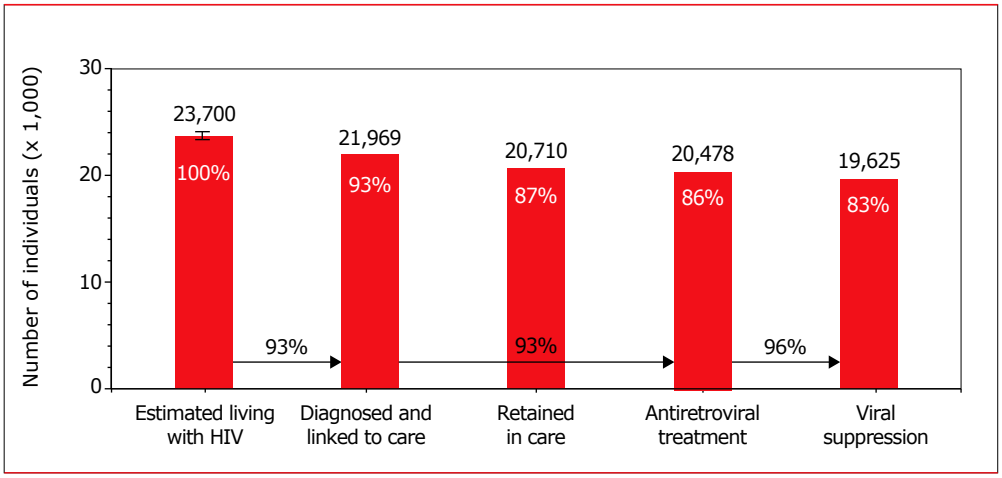
By the end of 2019, 23,700 individuals were estimated to be living with HIV, of whom an estimated 1,730 were still undiagnosed.

In total, 21,969 individuals (93% of the total number estimated to be living with HIV) had been diagnosed, linked to care, and registered by SHM.

Of the individuals who had been diagnosed, linked to care, and registered by SHM, the majority (20,478; 93%), had started antiretroviral treatment, and 19,625 of those (96%) had achieved viral suppression.

The Netherlands is therefore closing in on achieving the national hiv targets of 95-95-95 by 2022. 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 2019.

*Figure 3: Continuum of HIV care for the total estimated HIV-positive population in the Netherlands by the end of 2019, based on UNAIDS 90-90-90 goals for 2020: 93-93-96.*




## All STI surveillance regions reached the 90-90-90 targets

In 2019, all eight STI surveillance regions in the Netherlands reached or surpassed UNAIDS's 90-90-90 targets for 2020. The proportion of HIV-positive people with a suppressed viral load, including those remainding undiagnosed, varied between 80% 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, 10,290 (43%) people with HIV were estimated to be living in the four largest cities (Amsterdam, Rotterdam, Den Haag and Utrecht) in 2019. Of these 10,290 individuals, 610 were estimated to be still undiagnosed.

The figures for the Netherlands are impressive compared with other parts of the world. Nonetheless, in 2019 there were 580 new diagnoses (compared with 654 in 2018, so a 13% reduction) and an estimated 1,730 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 concerning individuals newly-diagnosed with HIV and first entering care from the electronic medical records (EMRs) since July 2019. Up until September 2020, data have been collected from 1,523 such individuals.

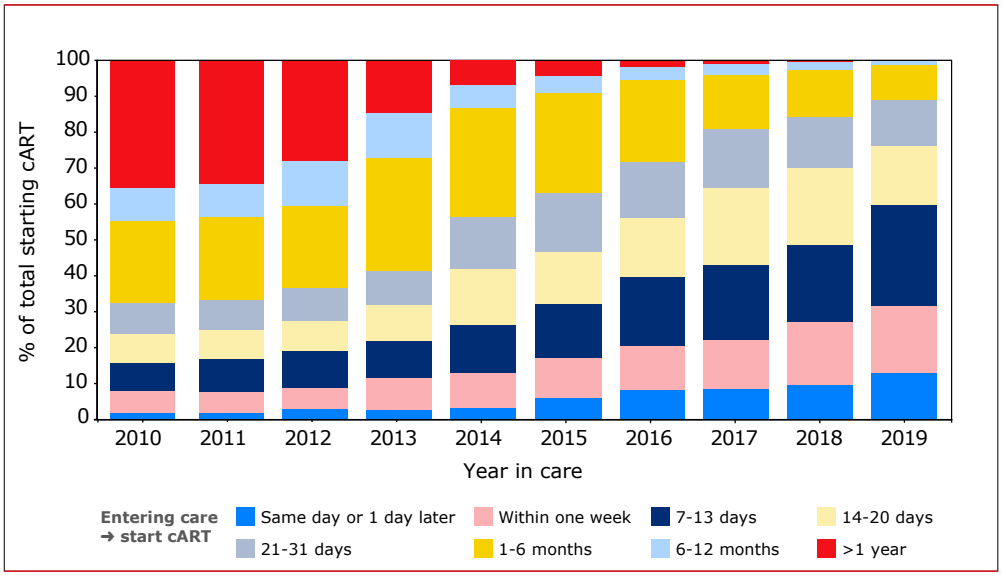
In 1,235 (81.1%) EMRs, no mention was made about prior use of PrEP, whereas in 288 (18.9%) EMRs, information was available on prior use of PrEP. Of the 288 individuals for whom information on prior use of PrEP was available, 38 men (13.2%) had reported prior use of PrEP, and 250 men and women (86.8%) had not. Of the 38 men who reported prior use of PrEP, the most likely route of HIV acquisition was through sexual contact with other men in 33 (86.8%) men. Of the 38 men who reported prior use of PrEP, 18 (47.4%) had obtained PrEP through a healthcare provider in the Netherlands, 9 (23.7%) through a buyers club / internet / store outside of the Netherlands, 3 (7.9%) through a healthcare provider outside of the Netherlands, 1 (2.6%) from an HIV-positive friend who donated some of his own medication, and for 7 men no information was available. Regular periodic medical checkups while using PrEP had been performed in 19 (50.0%) of these 38 men, no checkups were done in 6 (15.8%) and for 13 (34.2%) no information was available. For 25 (65.8%) of the 38 men it was reported that they had used PrEP after the last negative HIV test performed while using PrEP.

For 25 (65.8%) of the men who reported having used PrEP when first entering HIV care a genotypic resistance test was done. Resistance associated mutations possibly associated with the use of the antiretroviral agents that had been used as PrEP were detected in 7 of these 25 men (28%). Six of these seven men had obtained PrEP through a Dutch health care provider, and all seven men had reported that they had continued to use PrEP after their last negative HIV test performed while using PrEP. These data underscore the importance of 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 centers to collect information on prior use of PrEP in all individuals newly entering care.

## Combination antiretroviral therapy in adults

People are increasingly starting combination antiretroviral therapy (cART) sooner after being diagnosed with HIV and entering care. In 2019, 90% of people started cART within one month of entry into care, and 98% did so within 6 months of entry into care. Importantly, this was the case irrespective of the CD4 cell count at entry into care. In addition, in 2019, 13% started cART on the same day or the day after entry into care.

*Figure 4: Time between entry into care and starting combination antiretroviral therapy (cART) for those starting cART between 2008–2019.*




*Legend: cART=combination antiretroviral therapy.*

## Most common cART regimens in 2019

### Initial regimen

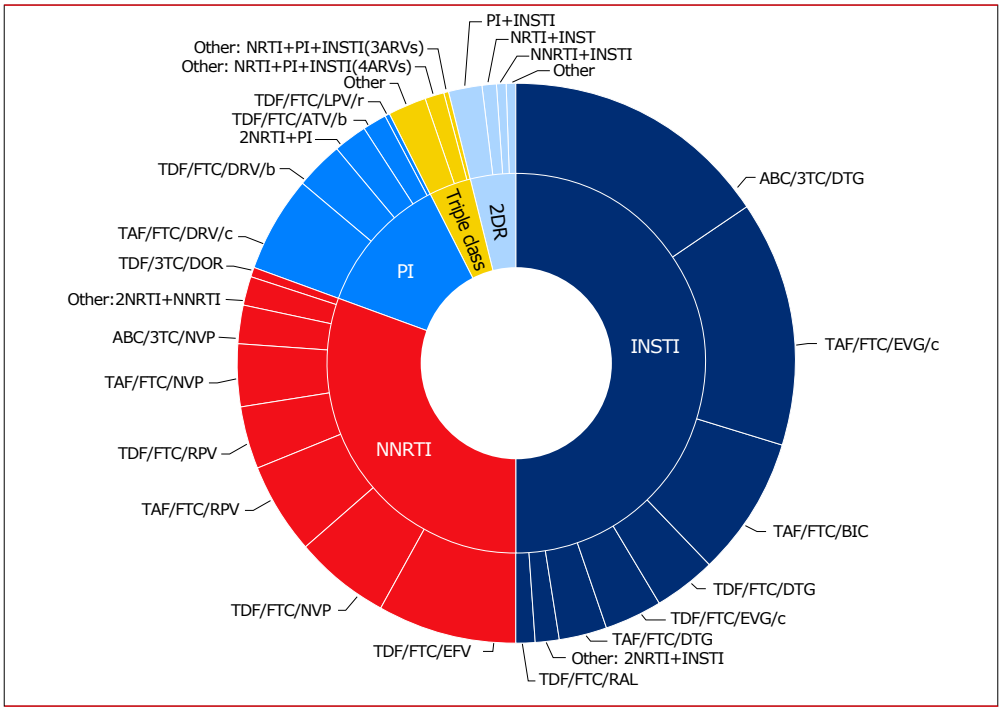
Of the people who started cART in 2019, 81% received a regimen containing an integrase inhibitor; tenofovir alafenamide/emtricitabine/bictegravir and tenofovir disoproxil/emtricitabine/dolutegravir were the most frequently-prescribed.

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

**Use of integrase inhibitor–based cART is on the rise among all HIV–positive individuals**
Integrase inhibitor-based cART continues to be further implemented on a large scale in the Netherlands: in 2019, 50% of all adults in care and on cART received an integrase inhibitor, compared with 39% in 2017 and 46% in 2018. 32% of the population on cART in 2019 received a backbone containing tenofovir disoproxil, new fixed-dose combinations have also led to an increase in the use of tenofovir alafenamide (42%) while the use of abacavir (21%) has decreased.

Among all HIV-positive individuals in care and on treatment in 2019, the majority (92.5%) received a cART regimen based on two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with an integrase inhibitor (50.0%), a non-NRTI (NNRTI, 30.6%), or a protease inhibitor (11.9%) (Figure 5). The most commonly-prescribed regimens in 2019 were abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (15.6%), tenofovir alafenamide (TAF)/FTC/elvitegravir (EVG)/cobicistat (14.3%), and tenofovir disoproxil (TDF)/emtricitabine (FTC)/efavirenz (EFV) (8.0%), tenofovir alafenamide (TAF)/FTC/bictegravir (BIC) (8.0%). Dual regimens mostly consisting of one INSTI plus either one PI, one INSTI or one NNRTI were used by 3.6% all HIV-positive individuals in care and on treatment in 2019.

*Figure 5: Combination antiretroviral therapy (cART) use in 2019.*




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

### Virological response is 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 2019, 98% had achieved viral suppression (viral load <200 copies/ml).

### Changing cART landscape

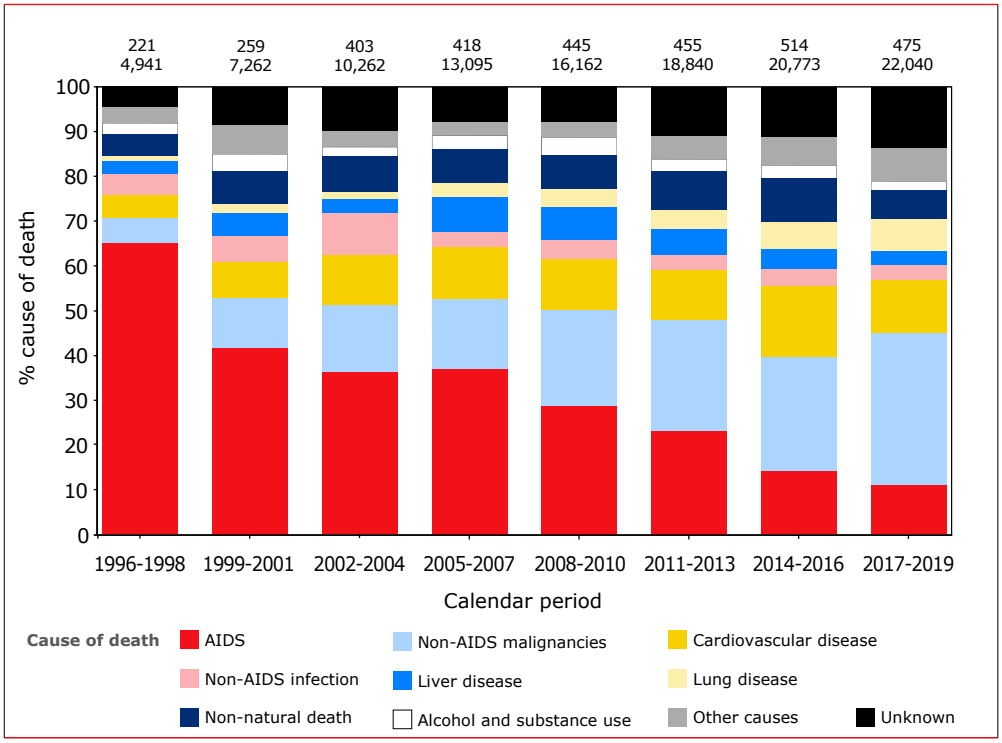
Following revised HIV treatment guidelines, prompt cART initiation has continued to become more common in 2019. In recent years, the introduction of new integrase inhibitor-based once-daily fixed-dose combinations has changed the landscape of cART use in the Netherlands. All currently-recommended regimens are durable.

## Morbidity and mortality

### The downward trend in AIDS-related deaths continued in 2019

Mortality remains low in HIV-positive individuals in care in the Netherlands. Since cART became available in the Netherlands in 1996, there has been a sustained decline in the risk of death from AIDS. Death is now increasingly likely to be caused by non-AIDS comorbidities, including non-AIDS-defining malignancies (NADM), cardiovascular disease (CVD) and chronic liver disease (*Figure 6*).

*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.*



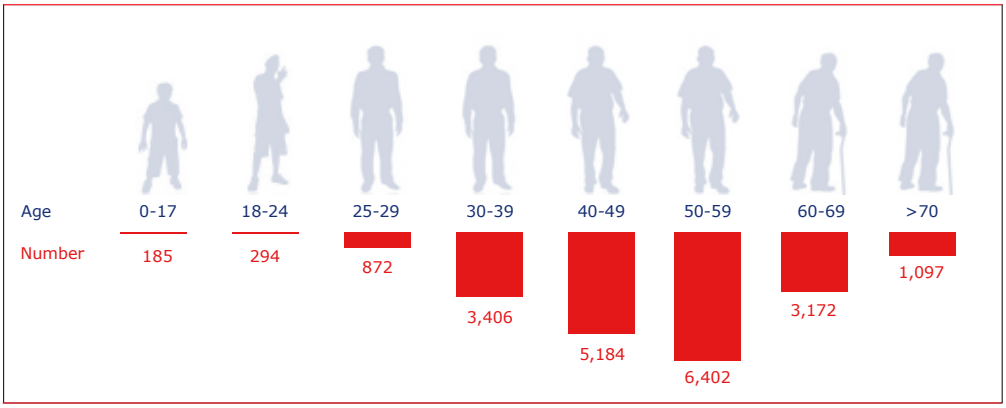

*Legend: cART=combination antiretroviral therapy.*

## Ageing and comorbidities

The number of AIDS-related deaths reported have declined from 24 in 2016 to 18 in 2019. The cases of AIDS-related death that do occur are 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 the infection. Otherwise achieving the national HIV target of zero AIDS-related deaths by 2022 is unlikely to be achieved.

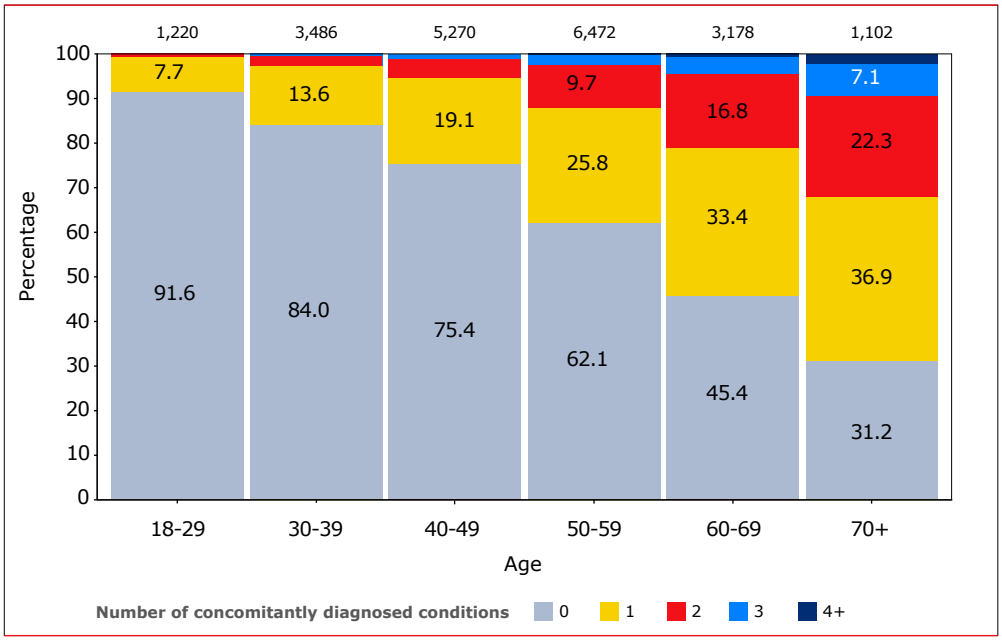
A substantial proportion of people who were newly-diagnosed with HIV and entered HIV care in 2019 were older individuals; 23% were 50 years or older. At the same time, the overall population of people with HIV in care in the Netherlands also continues to age, with 52% currently older than 50 years (*Figure 7*).

***Figure 7:*** *Age distribution of people living with HIV and in care in the Netherlands in 2019.*




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

*Figure 8: Prevalence of non-HIV/AIDS multimorbidity in adults in HIV care in 2019. Numbers on top of the bars represent the number of individuals contributing data to that age category.*




## The data show only a slight increase in cardiovascular risk

Despite the increasing age of the HIV-positive population, the proportion at high cardiovascular risk only increased slightly over the period 2000-2019. 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, anal, and head and neck cancers, as well as Hodgkin's lymphoma. The incidence rate of non-AIDS malignancies in the Netherlands has remained stable over time. However, when the increasing age of the HIV-positive population is taken into account, we observe a decline in the age-adjusted risk of new non-AIDS malignancies in men, including anal cancer. This may be the result of a reduction in risk factors such as smoking,

as well as expanded screening and treatment for early stages of anal cancer, together with a higher proportion of individuals living with higher CD4 cell counts in more recent years. Individuals who initiated ART within 12 months after their last HIV-negative test, had a lower risk of being diagnosed with a non-AIDS-defining malignancy, independent of their current CD4 cell count and other risk factors, suggesting an additional health benefit of early initiation of ART.

**Improved awareness of risk factors may reduce comorbidity**
Resilient ageing in people living with HIV and a lower comorbidity burden can be achieved by increasing awareness of the role of modifiable, lifestyle-related risk factors among both physicians and the people living with HIV themselves. This is particularly relevant for older individuals and those at increased risk of comorbidity.

## 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 HIV-positive individuals than in the general population due to shared routes of transmission. Screening for HCV and HBV co-infection is part of the standard of HIV care in the Netherlands, and the presence or absence of these co-infections is now documented for almost all HIV-positive individuals.

Approximately 12% of all individuals monitored by SHM had evidence of ever having been exposed to HCV, with 5% having documented evidence of chronic infection and 3% having evidence of acute HCV infection at the time of the first diagnosis. Most individuals with HCV infection were male and from the Netherlands or other European countries.

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

### HBV vaccination remains a priority

An estimated 34% of HIV-positive individuals overall had not been exposed to HBV and had not been successfully vaccinated. Of them, 20% were not taking a cART regimen including tenofovir or tenofovir alafenamide and thus remain 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.

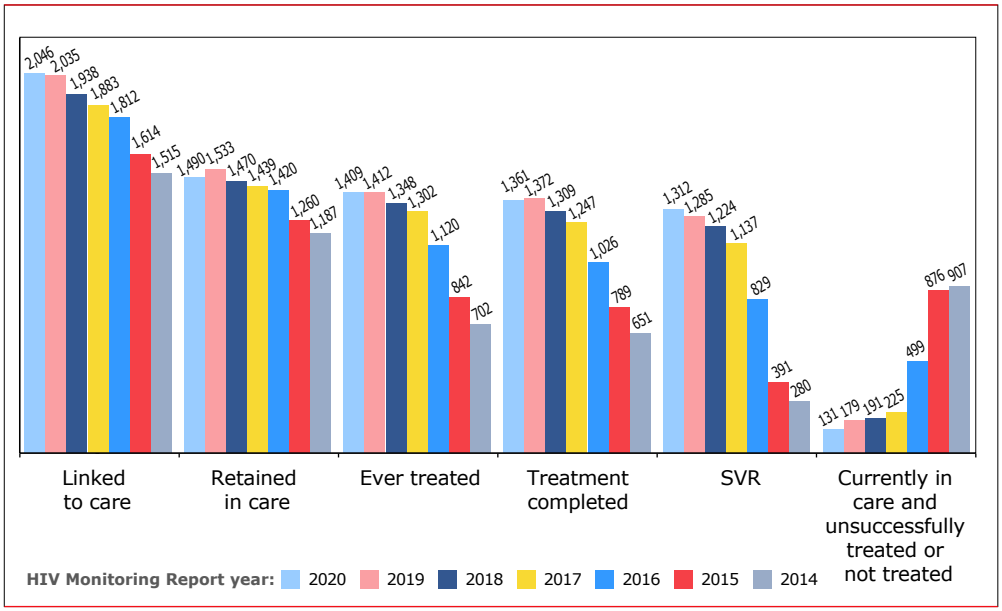
### Risk of dying from HCV or HBV co-infection is decreasing

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

### Successful HCV treatment with direct-acting antivirals has progressed further

Our data clearly show that the large majority of HIV-positive individuals with HCV co-infection have now received effective treatment for HCV. By 31 December 2019, over 1000 individuals had received or were receiving treatment with novel direct-acting antiviral agents (DAAs). Of all people treated with DAAs, 97% achieved a sustained virological response and no longer had evidence of an active HCV infection. These developments have resulted in fewer HCV co-infected individuals remaining in need of treatment than in previous years (*Figure 9*). However, not all individuals in need of treatment have received treatment with DAAs yet; this underlines the need for additional efforts to reach these people.

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




*Legend: SVR=sustained virological response.*

## Successful HCV treatment prevents HCV transmission

Successful treatment of HCV may also prevent onward HCV transmission, as suggested by the lower number of acute HCV infections observed in the past year, together with the rapid decline in prevalence of active HCV infections. In MSM the prevalence of active HCV infections has decreased to 0.5% in 2019. 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 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 from becoming infected with HCV.

### Hepatitis A virus testing and immunity

Fifty-four percent of HIV-positive individuals ever registered in the SHM database have been screened for HAV (hepatitis A). Of those screened, 68% 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, for HIV-positive MSM under the age of 50, only half of those who had been screened had anti-HAV antibodies. Given the European-wide outbreak of HAV among sexually-active MSM in 2017, these individuals should be prioritized for HAV vaccination.

## Pregnancies among women living with HIV in the Netherlands

In total, 387 pregnancies were documented in 303 women receiving HIV care in the Netherlands between 2016-2019. Of these women, 71% were born outside the Netherlands, mainly in sub-Saharan Africa (64%). The most common mode of HIV acquisition was heterosexual contact (92%).

### 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 94% of the deliveries, and between 50-500 copies/ml in a further 4% of deliveries. A number of women however had detectable HIV RNA levels around the time of delivery. Half of them had only been newly-diagnosed with HIV during the course of their pregnancy and therefore also started treatment later during 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 has become rare in the Netherlands, with only one reported case between 2016 and 2019. In the Netherlands, in women who receive treatment, the rate of vertical transmission is 0.42%.

### Viral suppression rates during the post-partum period are suboptimal

Following the change in treatment guidelines in 2015 to recommend cART for all individuals regardless of CD4 count, it is now also recommended for all pregnant women to continue cART after delivery. Nonetheless, of the women who continued using antiretroviral therapy after delivery, 15% had at least one detectable HIV RNA measurement in the year following delivery. Half of these women even had more than one detectable HIV RNA measurement. This may reflect poorer treatment compliance during the post-partum period.

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

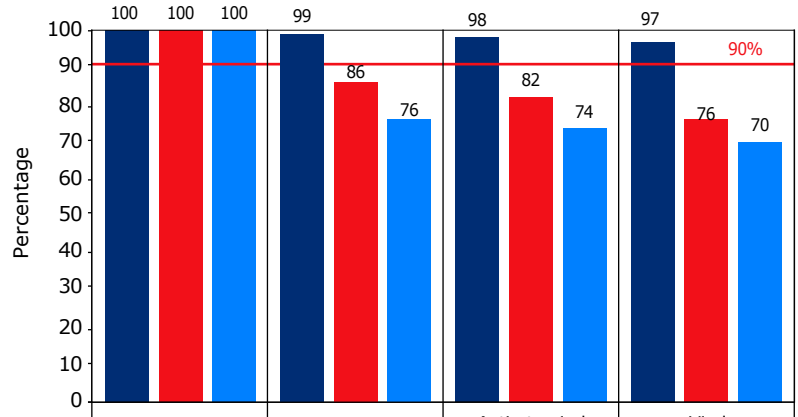
## Children living with HIV

Of 511 children ever registered by SHM since 1998 and who entered into HIV care in the Netherlands, 412 (81%) remain in care and 199 remained under the age of 18 by the end of 2019. Of the children who are currently in care and under 18 years of age, 133 (67%) had been born outside the Netherlands and been adopted by Dutch parents.

### Outcomes for HIV-positive children are generally favourable

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

***Figure 10:*** *Cascade of care by age and mode of HIV acquisition in individuals who acquired HIV in childhood, as of 31 December 2019. The numbers on top of the bars indicate the proportion of individuals.*




| | Linked to care | Retained in care | Antiretroviral treatment | Viral suppression |
|---|---|---|---|---|
| Current age <18 years | 200 | 199 | 197 | 194 |
| Current age ≥18 years vertical transmission | 138 | 118 | 113 | 105 |
| Current age ≥18 years non-vertical transmission | 125 | 95 | 92 | 88 |

### Poorer viral suppression around the time of transition to adult care

Of those individuals who were originally registered as a child, 81% were still in care in 2019, 52% of whom were older than 18 as of 31 December 2019. Of the children who had transitioned from paediatric to adult care, 17% did not have suppressed viraemia at the time of transition, suggesting challenges for these adolescents with respect to adherence to treatment.

### Optimisation of long-term care for adolescents and young adults

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

## Quality of care

### Comparing indicators to the national average

The quality of care provided in Dutch adult HIV treatment centres was explored using indicators based on the national guidelines issued by the Dutch Association of HIV-Treating Physicians. We also compared each centre's indicator to the national average, in a manner that takes into account the diverse mix of patients' geographical origin and modes of HIV transmission that are found across centres.

In all centres the proportion of patients in care in 2019 who had initiated cART and had viral suppression were high and within the expected range of the national average. Overall, retention in care was also found to be high in most HIV treatment centres in the Netherlands.

### Earlier start of cART and high rates of viral suppression

Across most centres, people are starting cART sooner after entering into care, confirming that most centres are following the guideline to offer cART to everyone with newly-diagnosed HIV regardless of CD4 count. In fact, a median of 96% and 98% of all patients who entered care in 2017 and 2018, respectively, and who were retained in care in 2019 had initiated cART, while across all centres, more than 95% of patients in care in 2019 were on cART.

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

## Amsterdam Cohort Studies

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

As of 31 December 2019, 2,899 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 2019, 708 HIV-negative and 53 HIV-positive MSM remained in active follow up at the GGD Amsterdam, with an additional 256 HIV-positive MSM being followed at the MC Jan van Goyen or the DC Klinieken Lairesse-Hiv Focus Centrum in Amsterdam. In 2019, 18 HIV-negative MSM were newly recruited into the ACS. The median age in this group was 29.6 years, while that of the total group of MSM in active follow up was 43.6 years at their last visit. The majority (83.3%) of the total group were born in the Netherlands and 87.9% were residents of Amsterdam. Finally, 77.0% of the participants had a college degree or higher. In 2019, two MSM participating in the ACS seroconverted for HIV. The observed HIV incidence among MSM has remained relatively stable and low in recent years and was 0.11 per 100 person years in 2019.

## HIV in Curaçao in 2019

Over the years, an increasing proportion of individuals with HIV in care at the St Elisabeth Hospital in Willemstad in Curaçao have managed to achieve a suppressed viral load. However, although early start of treatment appears to be possible, data also suggest that long-term retention in care needs to be improved to optimise the sustained effect of treatment. In addition, the proportion of people entering care with late-stage HIV infection remains high, although the proportion with advanced HIV disease appears to be decreasing.

# Monitoring programme report

## 1. The HIV epidemic in the Netherlands

Ard van Sighem, Eline Op de Coul, Ferdinand Wit

**Key findings**

- In 2019, 23,700 people were estimated to be living with HIV in the Netherlands.
- The estimated number of people living with an undiagnosed HIV infection decreased from 4,000 in 2010 to 1,730 in 2019, representing a reduction of 57%.
- The estimated annual number of newly-acquired HIV infections decreased from 960 in 2010 to 270 in 2019, which is a reduction of 72%. During the same period, the number of newly-acquired infections among men who acquired HIV via sex with men (MSM) fell by 76%, from 690 in 2010 to 160 in 2019.
- Of the 525 people who received an HIV diagnosis in 2019, 321 (61%) were MSM and 146 (28%) were men and women who acquired their HIV through heterosexual contact.
- In 2019, 23% of all newly-diagnosed people were aged 50 years or older at the time of diagnosis.
- Of the 20,612 HIV-1-positive people in care by the end of 2019, 52% were 50 years or older; 21% of the people were 60 years or older.
- In total, 27% of the people newly-diagnosed in 2017 or later, were diagnosed within 12 months of HIV infection; in MSM, this proportion was 37%.
- From 2017 onwards, 839 (48%) individuals were diagnosed with late-stage HIV infection: 450 (39%) MSM, 259 (66%) other men, and 139 (58%) women.
- Between 2010 and 2019, the median time from diagnosis to viral suppression decreased from 0.85 to 0.19 years, mainly as a result of treatment starting earlier after entry into care and more rapidly reaching viral suppression after starting treatment.
- The time between acquiring HIV and diagnosis of the infection was estimated to be a median of 2.6 (interquartile range, 1.3-4.8) years in 2019.

## Introduction

As of May 2020, 31,070 HIV-positive individuals had been registered by Stichting HIV Monitoring (SHM). Following registration, further clinical data were collected for 30,353 (97.7%) of the individuals; the remaining 717 (2.3%) people objected to the collection of their data. Among the 30,353 individuals with clinical data, 29,267 were registered with one of the HIV treatment centres in the Netherlands (*Figure 1.1*) and 1,274 were registered with the St. Elisabeth Hospital in Willemstad, Curaçao (see *Chapter 9*); 188 people were registered both in the Netherlands and in Curaçao.

Of the 29,267 people registered in the Netherlands, the majority were diagnosed with HIV-1 (27,916; 95%). A small group of people, 100 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 1,188 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, before briefly considering the HIV-2-positive population. The second part of this chapter discusses the HIV-1-positive individuals who were still in care at the end of 2019.

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

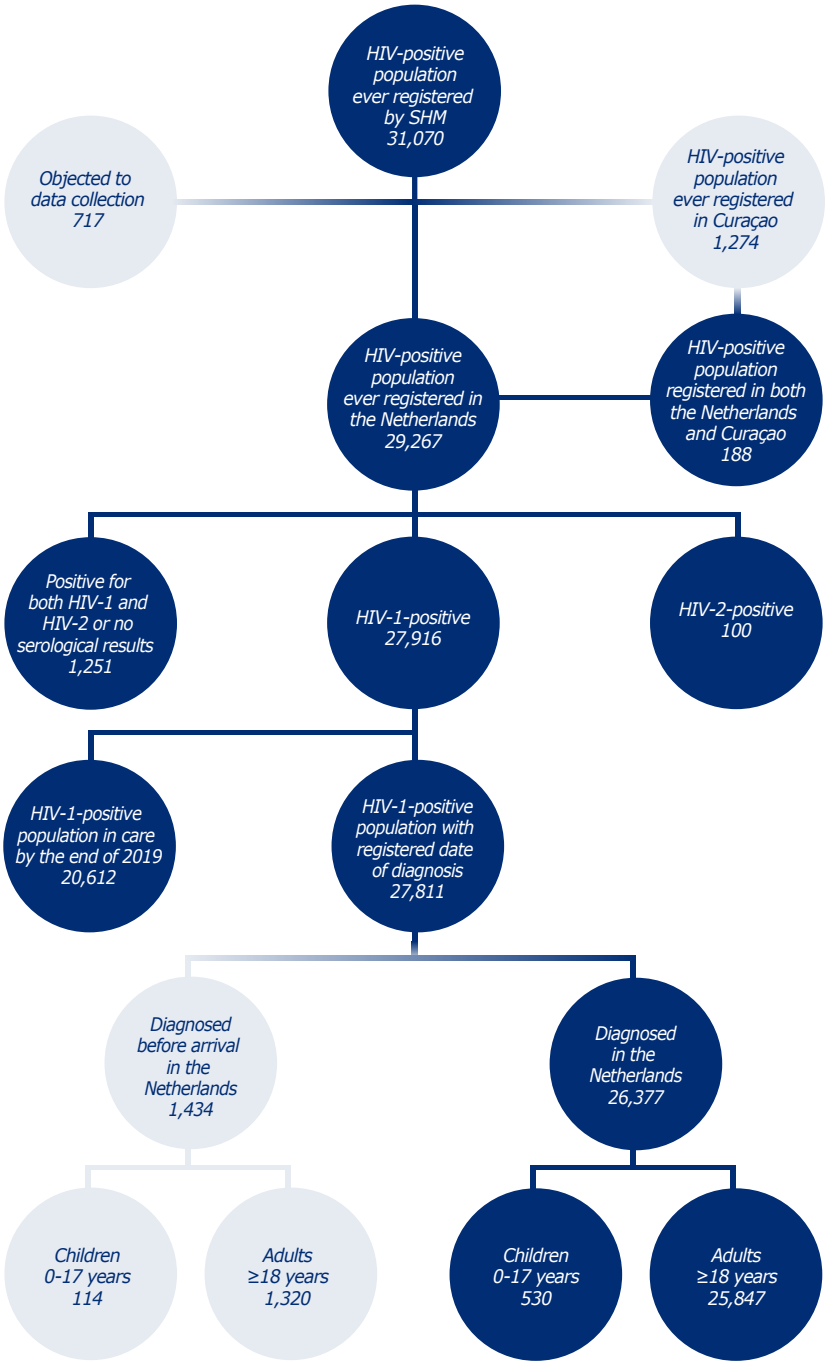
| | |
|---|---|
| **Infection** | The moment an individual acquires an HIV infection. The time of infection is often unknown. |
| **Diagnosis** | The moment an individual is newly diagnosed with an HIV infection. The time of diagnosis can be weeks, months, or years after infection. |
| **Entry into care** | The moment an HIV-positive individual is first seen for care in an HIV treatment centre, which is usually within a few weeks of HIV diagnosis. |
| **Registration** | The moment an HIV-positive individual 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 HIV-positive individual is registered with SHM. |

## Population: HIV-1

### HIV-1-positive individuals

In total, 27,811 individuals were ever diagnosed with HIV-1 and had a recorded date of diagnosis (*Figure 1.1*). Of these individuals, 1,434 (5%) were born abroad and had a documented HIV diagnosis prior to arrival in the Netherlands. These 1,434 individuals were excluded from the analyses on newly-diagnosed individuals further in this section. The remaining 26,377 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 HIV-positive population registered by Stichting HIV Monitoring (SHM) as of the end of 2019.*



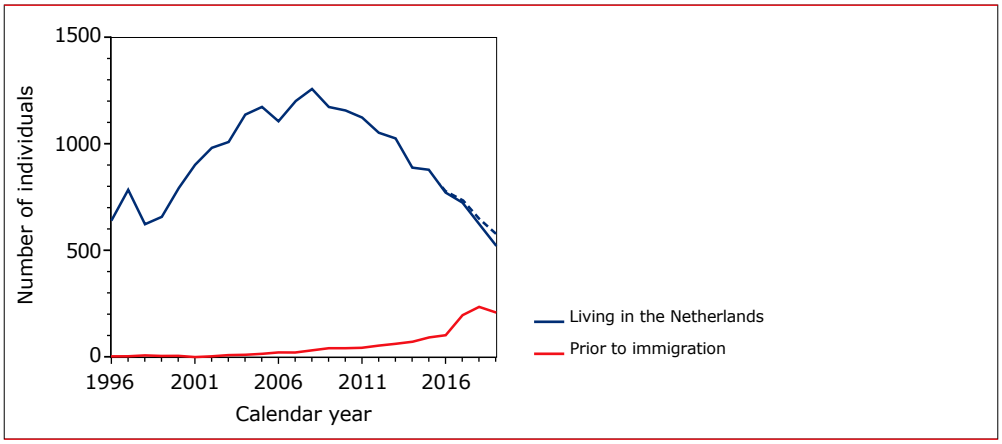
### Individuals diagnosed before arriving in the Netherlands

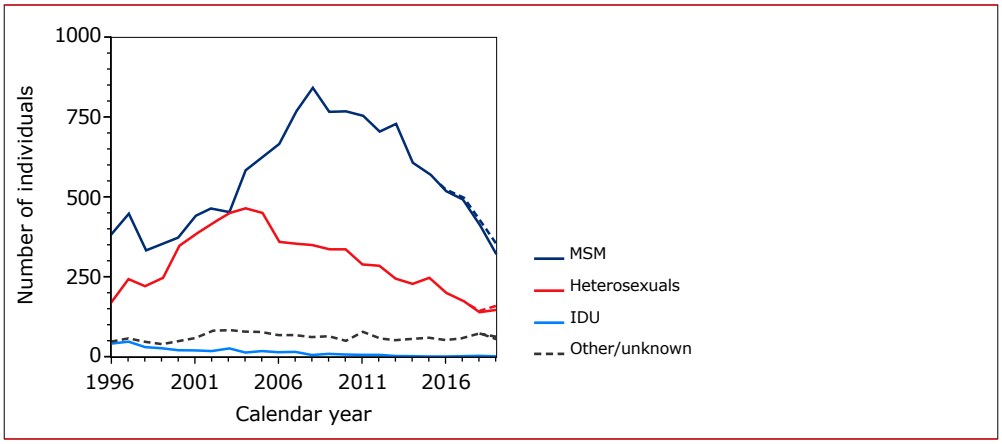
In total, 1,434 individuals who were born abroad, including 1,320 (92%) adults, had a documented HIV-1 diagnosis before arriving in the Netherlands. Of these 1,434 individuals, 211 adults and 6 children aged under 18 years arrived in the Netherlands in 2019; 651 (49%) migrant adults arrived in 2017 or later (*Figure 1.2A*). Information on diagnosis abroad and date of arrival in the Netherlands have been recorded for all individuals newly-registered 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 2,575 (63%) migrant adults diagnosed in 2010 or later; this number falls to 1,415 (18%) migrant adults, for those diagnosed before 2010.

Of the 651 migrant adults who arrived in 2017 or later with a documented pre-arrival HIV diagnosis, 395 (61%) were men who reported sex with men (MSM) as the most likely mode of transmission, 129 (20%) were other men, and 127 (20%) were women. The median age at the time of arrival was 35 (29-41) years; 60 (9%) were young adults below 25 years of age, while 52 (8%) were 50 years of age or older. In total, 120 (18%) migrants originated from sub-Saharan Africa, 111 (17%) from South America, 104 (16%) from western Europe, 68 (10%) from eastern Europe, 60 (9%) from central Europe, and 59 (9%) from the Caribbean. The most commonly reported countries of origin (with at least 20 HIV-positive individuals arriving in the Netherlands) were Brazil (38, 6%), Russian Federation (29, 4%), the United States (25, 4%), Poland (24, 4%), and Trinidad and Tobago (23, 4%).

The majority (553, or 87%) of the 651 individuals had already started antiretroviral treatment before arriving in the Netherlands. The median CD4 count around the time of arrival was 617 (410-810) cells/mm$^3$, although CD4 measurements were available for only 437 (67%) individuals. A viral load measurement around the time of arrival was available for 467 (72%) people, and showed that 386 (83%) had a viral load below 200 copies/ml.

*Figure 1.2: (A) Annual number of adults newly-diagnosed with HIV-1 while living in the Netherlands (by year of diagnosis) or with documented diagnosis abroad prior to moving to the Netherlands (by year of arrival); (B) annual number of adults newly-diagnosed with HIV-1 while living in the Netherlands, according to most likely mode of transmission. In 2019, infections via sex between men (MSM) accounted for 61% of the annual number of new diagnoses, infections via heterosexual sex for 28%, infections via injecting drug use (IDU) for 0%, and infections via other or unknown modes of transmission for 11%. Dashed lines indicate the number of diagnoses after adjusting for a delay in notification to SHM.*




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

## Individuals newly-diagnosed in the Netherlands

Of the 26,377 newly-diagnosed 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, 530 (2%) were diagnosed as minors (under 18 years of age): they are described in more detail in *Chapter 5*. Of the 25,847 individuals diagnosed as adults, 15,605 (60%) were MSM, while 3,569 (14%) other men and 4,176 (16%) women reported having acquired their HIV infection through heterosexual sex (*Table 1.1*). For 742 (3%) individuals, the reported mode of transmission was injecting drug use, while for 321 (1%) individuals, infection occurred through exposure to contaminated blood. Other and unknown modes of transmission accounted for the remaining 1,434 (6%) of HIV diagnoses.

***Table 1.1:*** *Annual number of HIV-1 diagnoses among children and adults per transmission risk group, including individuals who acquired their infections via sex between men (MSM), heterosexual sex, injecting drug use (IDU), contact with contaminated blood, or other or unknown modes of transmission. Numbers reported for 2015-2019 are adjusted for a delay in notification to SHM.*

| Year of | MSM | Heterosexual | | IDU | |
|---|---|---|---|---|---|
| diagnosis | Men | Men | Women | Men | Women |
| ≤1995 | 2,231 | 271 | 391 | 275 | 132 |
| 1996 | 381 | 89 | 82 | 32 | 8 |
| 1997 | 441 | 115 | 125 | 38 | 10 |
| 1998 | 329 | 106 | 112 | 23 | 7 |
| 1999 | 347 | 108 | 137 | 19 | 7 |
| 2000 | 371 | 157 | 190 | 17 | 4 |
| 2001 | 443 | 168 | 215 | 14 | 5 |
| 2002 | 464 | 169 | 250 | 15 | 3 |
| 2003 | 452 | 179 | 270 | 21 | 5 |
| 2004 | 582 | 198 | 266 | 9 | 4 |
| 2005 | 629 | 194 | 256 | 15 | 3 |
| 2006 | 665 | 163 | 196 | 9 | 5 |
| 2007 | 765 | 154 | 199 | 11 | 4 |
| 2008 | 843 | 174 | 175 | 5 | 1 |
| 2009 | 765 | 161 | 175 | 9 | 0 |
| 2010 | 767 | 177 | 158 | 6 | 1 |
| 2011 | 754 | 143 | 145 | 5 | 1 |
| 2012 | 704 | 140 | 144 | 6 | 1 |
| 2013 | 729 | 115 | 128 | 1 | 2 |
| 2014 | 605 | 114 | 113 | 1 | 0 |
| 2015 | 571 | 126 | 122 | 1 | 0 |
| *2015** | *572* | *126* | *122* | *1* | *0* |
| 2016 | 519 | 101 | 99 | 1 | 0 |
| *2016** | *524* | *102* | *100* | *1* | *0* |
| 2017 | 491 | 94 | 80 | 3 | 0 |
| *2017** | *501* | *96* | *82* | *3* | *0* |
| 2018 | 413 | 70 | 68 | 1 | 1 |
| *2018** | *429* | *73* | *71* | *1* | *1* |
| 2019 | 321 | 74 | 72 | 1 | 0 |
| *2019** | *355* | *81* | *79* | *1* | *0* |
| 2020 | 23 | 9 | 8 | 0 | 0 |
| **Total** | **15,605** | **3,569** | **4,176** | **538** | **204** |

**Numbers adjusted for a delay in notification*

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

| Blood or blood products | | Other/unknown | | <18 years of age | | Total |
|---|---|---|---|---|---|---|
| Men | Women | Men | Women | Men | Women | |
| 60 | 22 | 158 | 43 | 49 | 37 | 3,669 |
| 3 | 4 | 36 | 6 | 11 | 2 | 654 |
| 7 | 3 | 40 | 7 | 6 | 9 | 801 |
| 6 | 4 | 30 | 6 | 7 | 8 | 638 |
| 9 | 4 | 21 | 6 | 11 | 12 | 681 |
| 3 | 4 | 38 | 5 | 11 | 28 | 828 |
| 7 | 6 | 41 | 4 | 13 | 34 | 950 |
| 13 | 7 | 59 | 2 | 18 | 18 | 1,018 |
| 9 | 3 | 57 | 13 | 15 | 19 | 1,043 |
| 4 | 3 | 64 | 8 | 13 | 10 | 1,161 |
| 5 | 4 | 60 | 8 | 9 | 9 | 1,192 |
| 5 | 6 | 54 | 3 | 5 | 10 | 1,121 |
| 2 | 6 | 52 | 7 | 9 | 11 | 1,220 |
| 6 | 2 | 48 | 5 | 11 | 13 | 1,283 |
| 3 | 2 | 51 | 8 | 9 | 12 | 1,195 |
| 5 | 0 | 38 | 6 | 16 | 13 | 1,187 |
| 10 | 6 | 57 | 4 | 9 | 8 | 1,142 |
| 4 | 4 | 40 | 10 | 4 | 8 | 1,065 |
| 12 | 0 | 38 | 2 | 5 | 3 | 1,035 |
| 7 | 4 | 36 | 9 | 3 | 7 | 899 |
| 5 | 2 | 47 | 5 | 5 | 5 | 889 |
| *5* | *2* | *47* | *5* | *5* | *5* | *890* |
| 10 | 2 | 36 | 4 | 6 | 3 | 781 |
| *10* | *2* | *36* | *4* | *6* | *3* | *789* |
| 6 | 3 | 45 | 4 | 1 | 1 | 728 |
| *6* | *3* | *46* | *4* | *1* | *1* | *742* |
| 5 | 4 | 59 | 5 | 2 | 1 | 629 |
| *7* | *4* | *61* | *5* | *2* | *1* | *654* |
| 8 | 2 | 41 | 5 | 0 | 1 | 525 |
| *9* | *2* | *45* | *6* | *0* | *1* | *580* |
| 0 | 0 | 3 | 0 | 0 | 0 | 43 |
| **214** | **107** | **1,249** | **185** | **248** | **282** | **26,377** |

## Decreasing number of diagnoses

From the 1990s until 2008, the annual number of new diagnoses in adults increased from approximately 650 to almost 1,300 (*Table 1.1; Figure 1.2A*). From 2009 onwards, the annual number of new diagnoses has steadily declined. In 2019, that downward trend continued and the number of new HIV diagnoses was approximately 580. This number takes into account a projected backlog[a] in registration of HIV cases.

In MSM, the annual number of diagnoses was approximately 400 in 1996 and increased to almost 850 in 2008 (*Figure 1.2B*). Thereafter, the number of diagnoses gradually decreased to approximately 355 in 2019. In individuals who acquired their HIV infection via heterosexual sex, the annual number of new diagnoses has declined to approximately 150 in 2019. As shown later in this chapter, this strong decline in diagnoses in the heterosexual population is largely the result of a reduction in the number of diagnoses in people born abroad. Finally, injecting drug use is now rarely reported as the most likely mode of transmission, which reflects the decreasing popularity of injecting drugs.

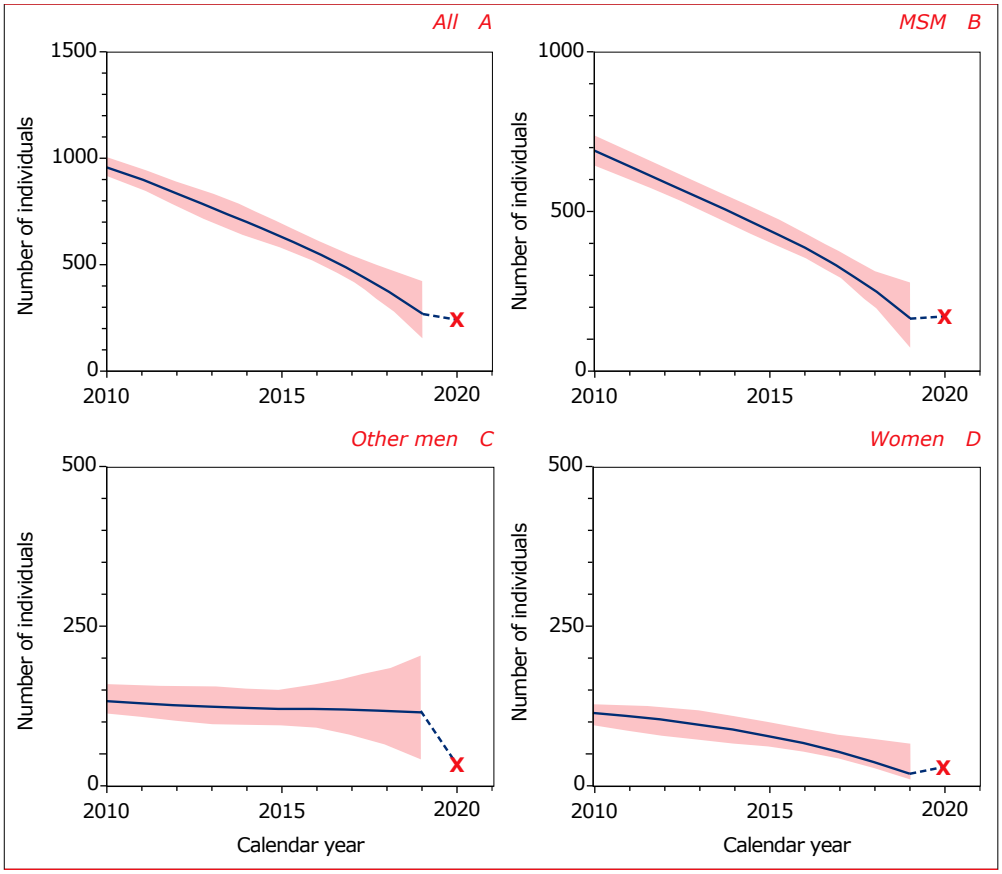
## Decreasing number of newly-acquired infections

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 960 (95% confidence interval [CI], 920-1,010) in 2010 to 270 (150-420) in 2019 (*Figure 1.3A*), which is a reduction of 72% (56-84). This shows that the Netherlands is on course to achieve one of the United Nations 2020 targets: a 75% reduction in the annual number of new infections compared with 2010[1,2]. During the same period, the number of newly-acquired HIV infections among MSM fell by 76% (61-89), from 690 (650-740) in 2010 to 160 (70-280) in 2019, surpassing the United Nations target (*Figure 1.3B*).

In other men, the estimated number of newly-acquired infections in 2010 was 130 (110-160), which was very similar to the estimated number of 110 (100-130) in women. The number of infections in other men has changed very little over time – it was 120 (40-210) in 2019, a decrease of 12% (*Figure 1.3C*). In contrast, the estimated number of infections among women decreased by 83% (38-91) to 20 (10-70) in 2019 (*Figure 1.3D*). It is worth noting, however, that in both other men and women, the uncertainty around the estimates is relatively large. In addition, both groups are characterised by a high proportion of people born abroad and some of the estimated infections may have been acquired while still abroad and only diagnosed as HIV-positive in the Netherlands.

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 2015-2019 were estimated with the European Centre for Disease Prevention and Control (ECDC) HIV Estimates Accuracy Tool* [17].

*Figure 1.3: Estimated annual number of newly-acquired HIV infections in the total population (A), in men who have sex with men (B), in other men (C), and in women (D), according to the European Centre for Disease Prevention and Control (ECDC) HIV Modelling Tool[17]. The cross indicates UNAIDS' target for 2020 of achieving a 75% reduction in the number of newly-acquired HIV infections since 2010.*

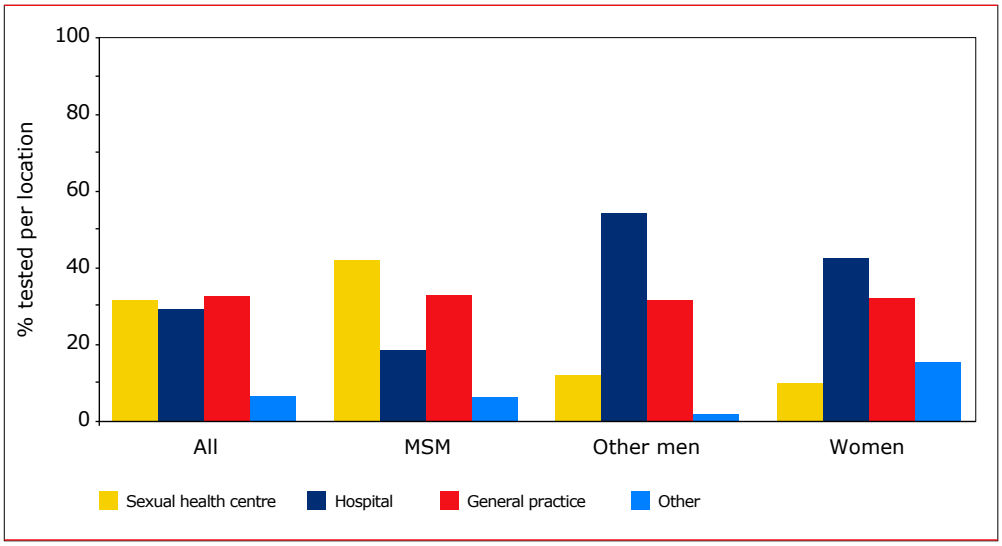



*Legend: MSM=men who have sex with men.*

## Setting in which HIV is diagnosed

Information on the setting in which HIV was diagnosed in the Netherlands was available for 1,822 (90%) of the 1,919 people diagnosed in 2017 or later, while 63 (3%) individuals were known to have been diagnosed abroad. Overall, 31% of these 1,822 individuals received their first HIV-positive test result at a sexual health centre, 29% at a hospital, and 33% at a general practice (*Figure 1.4*). Among those diagnosed at sexual health centres, 88% were MSM, 8% were other men, and 4% were women. These proportions are similar to those directly reported by sexual health centres[3].

*Figure 1.4: Proportion of individuals diagnosed in 2017 or later, stratified by location of testing and transmission risk group.*



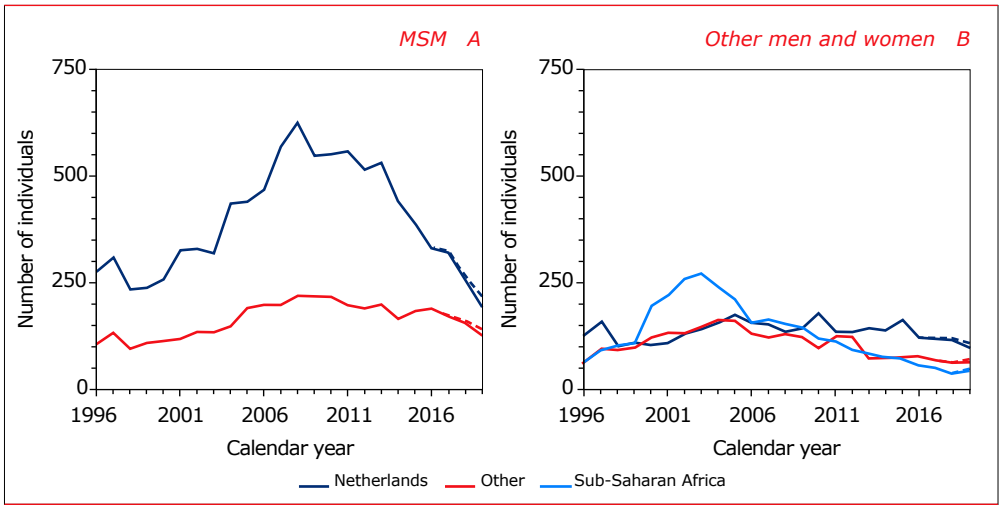

*Legend: MSM=men who have sex with men.*

## Geographical region of origin

In total, 10,810 (42%) people diagnosed with HIV-1 as adults 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, 2017), 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.

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*). However, the number of new diagnoses among sub-Saharan Africans dropped sharply after 2003, probably partly as a result of stricter immigration laws that came into effect in the Netherlands around that time. From 2017 onwards, 51% of the newly-diagnosed women and other men were of Dutch origin, and 20% originated from sub-Saharan Africa.

***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 18 years or older at the time of diagnosis. Of the 1,248 MSM diagnosed in 2017 or later, 786 (63%) originated from the Netherlands, 126 (10%) from other European countries, 109 (9%) from South America, and 88 (7%) from the Caribbean. Of the other 671 people diagnosed in 2017 or later, 339 (51%) originated from the Netherlands, 53 (8%) from other European countries, 134 (20%) from sub-Saharan Africa, 54 (8%) from South America, 36 (5%) from the Caribbean, and 23 (3%) from south and southeast Asia.*




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

Overall, 21% of the people newly diagnosed since 2017, were living in the Amsterdam public health service (PHS) region at the time of diagnosis and 14% were living in the Rotterdam-Rijnmond PHS region. These proportions were 14% and 12%, respectively, for people of Dutch origin and 31% and 17%, respectively, for people originating from other countries. Among MSM, 23% were living in Amsterdam at the time of diagnosis and 14% were living in Rotterdam, while among other

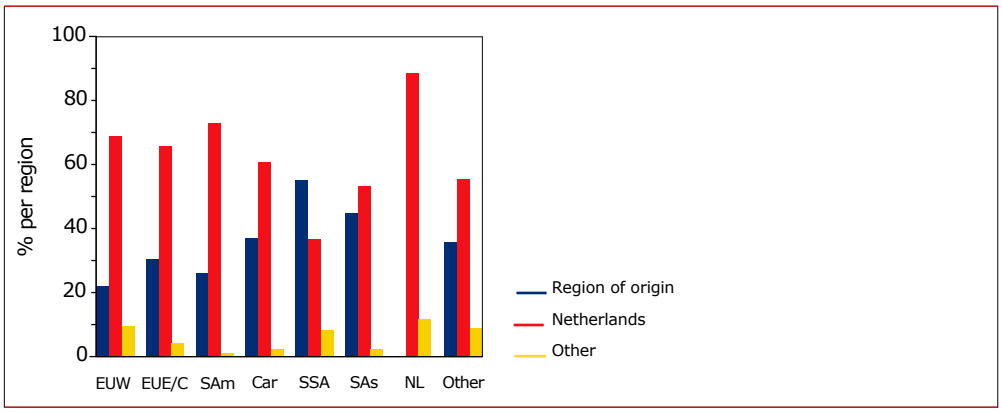
men and among women 17% were living in Amsterdam and 15% in Rotterdam. Other PHS regions with at least 5% of the new diagnoses since 2017 were Utrecht (7%), Haaglanden (6%, including Den Haag), and Hart voor Brabant (5%, including Den Bosch and Tilburg).

### Self-reported geographical region of HIV-1 acquisition

In total, 1,434 (75%) of the adults diagnosed in 2017 or later, 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, 59% of those diagnosed in 2017 or later reported having acquired their HIV infection in the Netherlands.

The majority (85%) of MSM diagnosed in 2017 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, 77% for other men and 93% for women.

***Figure 1.6:*** *Proportion of all HIV-1-positive adults diagnosed in 2017 or later per region of origin who reported to have acquired their HIV infection in their own region of origin, in the Netherlands, or elsewhere.*




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

### Increasingly older age at time of HIV diagnosis

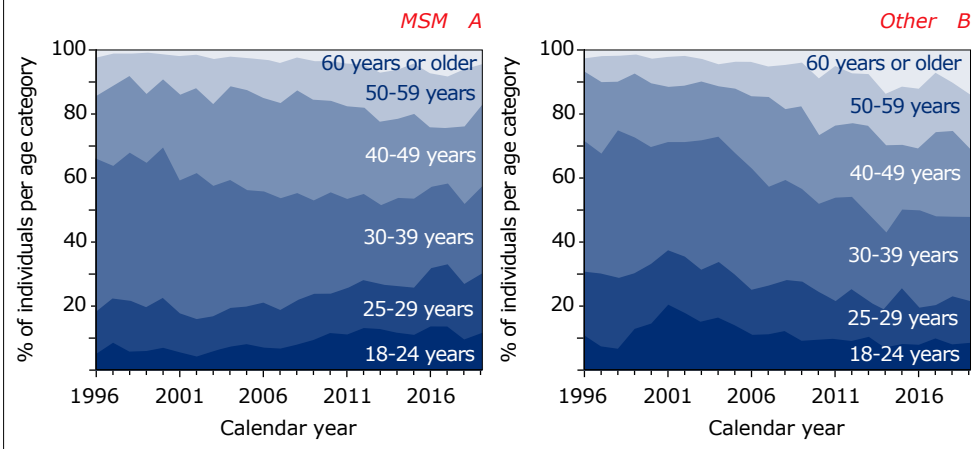
The age at which individuals are diagnosed with HIV has been slowly increasing over time. In 1996, the median age at the time of diagnosis was 36 (interquartile range [IQR], 30-42) years; in 2019, it was 38 (IQR, 30-50) years. Over the entire period from 1996 through 2019, 17% of adults who received an HIV diagnosis were 50 years or older; in 2019, 23% were 50 years or older (*Figure 1.7*).

There were considerable age differences between MSM, other men, and women diagnosed in 2017 or later. MSM born in the Netherlands were diagnosed at a median age of 42 (30-52) years, while MSM of foreign origin were diagnosed at a median age of 33 (27-42) years. Among other people of Dutch origin, the median age at the time of diagnosis was 39 (29-53) years for women and 45 (33-56) years for men. Individuals born in sub-Saharan Africa (women: 35 years; men: 43 years) or elsewhere (women: 37 years; men: 40 years) were younger than their Dutch counterparts. In 2019, 18% of MSM, 34% of other men, and 25% of women were 50 years or older the time of diagnosis.

### Young adults

Between 1996 and 2019, 10% of the individuals who received an HIV diagnosis were young adults under 25 years of age (*Figure 1.7*). In 2019, young adults also accounted for 10% of the new HIV diagnoses; their proportion was 12% among MSM, 6% among other men, and 11% among women.

*Figure 1.7: Age distribution at the time of diagnosis among HIV-1-positive (A) men who have sex with men (MSM), and (B) other men and women. Between 1996 and 2019, the proportion of individuals between 18 and 29 years of age changed from 18% to 30% for MSM and from 31% to 22% for other individuals. During the same period, the proportion of MSM aged 50 years or older at the time of diagnosis changed from 14% to 18%, while these proportions were 7% and 31% for other individuals.*




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

## Entry into care

Of the individuals diagnosed with HIV in 2017 or later for whom the diagnosis setting was known, 94% entered care within 4 weeks of diagnosis and 96% within 6 weeks. The proportion in care within 6 weeks was 96% for individuals who received their first HIV-positive test at a sexual health centre, and similar for those who tested HIV-positive in a hospital (98%), at a general practice (96%), or at other locations (94%). Overall, the proportion in care within 6 weeks was similar for MSM (97%), other men (95%), and women (98%), and did not differ by age at the time of diagnosis. However, the proportion in care within 6 weeks was larger among individuals born in the Netherlands (98%) than among those born abroad (94%).

## Late diagnosis

In total, 30% of the individuals with an HIV diagnosis from 1996 onwards had CD4 counts of 500 cells/mm$^3$ or higher at diagnosis; 20% had CD4 counts between 350 and 499 cells/mm$^3$; 20% had CD4 counts between 200 and 349 cells/mm$^3$; and 30% had CD4 counts below 200 cells/mm$^3$, while 15% had a concurrent AIDS diagnosis. For people newly diagnosed in 2017 or later, these proportions improved somewhat and were 33%, 21%, 19%, and 27%, respectively; 13% had already been diagnosed with AIDS.

Overall, 52% of the individuals diagnosed from 1996 onwards had a late-stage HIV infection at the time of diagnosis, in other words, either a CD4 count below 350 cells/mm$^3$ or an AIDS-defining event regardless of CD4 count[4]. Over time, the proportion of late-stage HIV diagnoses has decreased from 67% in 1996 to 48% in 2019 (*Figure 1.8*). In addition, the proportion of individuals diagnosed with advanced HIV disease (i.e., with a CD4 count below 200 cells/mm$^3$ or AIDS), has likewise decreased over time and was 29% in 2019. Although the downward trends in these *proportions* appear to have halted after 2010, the *number* of individuals diagnosed with late-stage or advanced-stage HIV infection continues 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 450 (54%) of all 839 individuals diagnosed with late-stage HIV in 2017 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 2019, 241 (48%) individuals were diagnosed with late-stage HIV infection: 120 (39%) men who acquired HIV via sex with men (MSM), 73 (63%) other men, and 48 (62%) women; adjusting for reporting delay, 267 (48%) individuals: 133 (39%) MSM, 81 (64%) other men, and 53 (62%) women. During the same year, 148 (29%) individuals were diagnosed with advanced-stage HIV infection: 67 (22%) MSM, 54 (47%) other men, and 27 (35%) women; adjusting for reporting delay, 164 (35%) individuals: 74 (22%) MSM, 60 (47%) other men, and 30 (35%) 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 2017 onwards, the stage of infection was unknown for 153 (8%) individuals.*


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

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

Among individuals diagnosed with HIV in 2017 or later, 450 (39%) MSM, 250 (66%) other men, and 139 (58%) women had a late-stage HIV infection. Late-stage HIV infections, in relative terms, were most common among people originating from sub-Saharan Africa (65%) or south and southeast Asia (54%), and among people originating from the Netherlands (61%) or from South America (57%) 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 56% of MSM, 78% of other men, and 65% of women diagnosed in 2017 or later at 50 years of age or older, compared with 26% of MSM, 52% of other men, and 33% 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 (44%), a sexual health centre (24%), or another testing location (39%).

### 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[5]. As a result, the stage of the infection may inadvertently be classified as late or advanced when individuals are diagnosed with HIV during this early phase of the infection. When people with a known HIV-negative test in the 6 months prior to HIV diagnosis were reclassified as not having a late-stage or advanced-stage HIV infection, the proportion of late-stage HIV infections among individuals diagnosed in 2017 or later changed from 48% to 44%. This decrease was mainly due to a drop in late-stage HIV among MSM (from 39% to 34%) whereas among other men and among women, the proportion decreased by less than a percentage point. The change in the proportion of people diagnosed with advanced-stage HIV infection was more modest: 30% before and 29% after reclassification in people diagnosed in 2017 or later.

*Table 1.2: Characteristics of the 839 individuals with a late-stage HIV infection among the 1,919 individuals diagnosed with HIV in 2017 or later. In total, as a result of missing CD4 cell counts at diagnosis, it was impossible to classify whether 153 (8%) individuals (101 MSM, 38 other men, and 14 women) had a late-stage HIV infection. For each of the four groups (MSM, other men, women, and total), percentages give the proportion of the total number of individuals diagnosed in each category listed in the first column that were found to have a late-stage infection.*

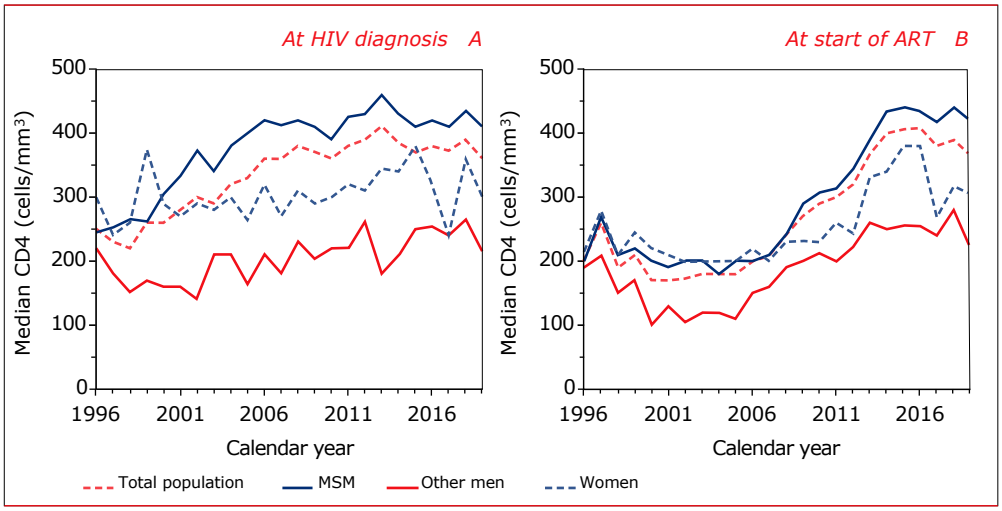
| | Men (n=1,147) | | Other men (n=381) | | Women (n=238) | | Total (n=1,766) | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Overall | 450 | 39 | 250 | 66 | 139 | 58 | 839 | 48 |
| Age at diagnosis (years) | | | | | | | | |
| 18-24 | 37 | 26 | 12 | 52 | 11 | 33 | 60 | 31 |
| 25-29 | 57 | 27 | 17 | 39 | 14 | 41 | 88 | 30 |
| 30-39 | 97 | 34 | 55 | 62 | 53 | 73 | 205 | 45 |
| 40-49 | 115 | 47 | 71 | 69 | 31 | 60 | 217 | 54 |
| 50-59 | 94 | 51 | 57 | 78 | 20 | 63 | 171 | 59 |
| ≥60 | 50 | 66 | 38 | 78 | 10 | 71 | 98 | 71 |
| Region of origin | | | | | | | | |
| The Netherlands | 297 | 41 | 150 | 67 | 44 | 47 | 491 | 47 |
| Sub-Saharan Africa | 11 | 53 | 37 | 70 | 46 | 65 | 94 | 65 |
| Western Europe | 18 | 39 | 5 | 83 | 1 | 100 | 23 | 43 |
| Central Europe | 21 | 38 | 11 | 55 | 10 | 77 | 42 | 47 |
| South America | 34 | 34 | 15 | 54 | 12 | 63 | 61 | 41 |
| Caribbean | 28 | 35 | 7 | 39 | 8 | 62 | 43 | 39 |
| South and southeast Asia | 16 | 39 | 7 | 100 | 11 | 73 | 34 | 54 |
| North Africa and Middle-East | 10 | 25 | 11 | 85 | 2 | 67 | 23 | 41 |
| Other/unknown | 15 | 43 | 7 | 64 | 6 | 60 | 28 | 54 |
| Location of HIV diagnosis | | | | | | | | |
| Sexual health centre | 107 | 23 | 14 | 34 | 10 | 42 | 131 | 24 |
| Hospital | 148 | 72 | 166 | 83 | 83 | 84 | 397 | 79 |
| General practice | 157 | 43 | 58 | 51 | 27 | 37 | 242 | 44 |
| Other/unknown | 38 | 36 | 12 | 43 | 19 | 45 | 69 | 39 |

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

## Earlier diagnosis

Between 1996 and 2019, median CD4 counts in the total adult population at the time of diagnosis increased from 250 to 361 cells/mm$^3$ (*Figure 1.9A*). This overall increase was mainly the result of a rise in CD4 counts in MSM, whereas CD4 counts in women and in other men showed more modest increases.

***Figure 1.9:*** *Changes over calendar time in median CD4 counts (A) at HIV diagnosis and (B) at the start of antiretroviral treatment (ART). (A) Between 1996 and 2019, CD4 counts at the time of diagnosis increased from 250 (interquartile range [IQR], 80-437) to 361 (IQR, 180-554) cells/mm³ in the total adult population. The increase was most apparent for men who acquired their HIV infection through sex with men (MSM): 245 (IQR, 80-450) cells/mm³ in 1996 and 410 (IQR, 250-595) cells/mm³ in 2019. CD4 counts in other men and in women were 220 (IQR, 40-410) and 300 (IQR, 130-450) cells/mm³, respectively, in 1996, and 215 (IQR, 90-460) and 300 (IQR, 150-465) cells/mm³ in 2019. (B) In the total adult population, CD4 counts at the start of ART were approximately 180 cells/mm³ between 2000 and 2005, and increased thereafter. In 2019, CD4 counts were 366 (IQR, 180-560) cells/mm³ in the total population, 420 (IQR, 250-600) cells/mm³ in MSM, 220 (IQR, 89-440) cells/mm³ in other men, and 305 (IQR, 165-515) cells/mm³ in women. The apparent decrease in CD4 counts in women in 2017 is most likely a consequence of the relatively low number of diagnoses in this group.*



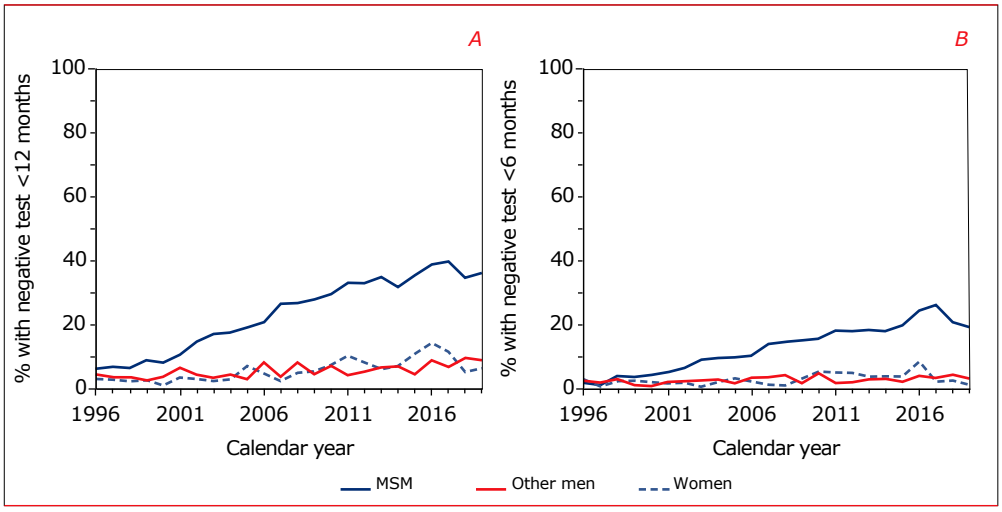

***Legend:*** *MSM=men who have sex with men; ART=antiretroviral treatment.*

## Recent infection

The increase in CD4 counts at diagnosis, in conjunction with a decreasing number of late diagnoses, suggests that, on average, people are being diagnosed increasingly earlier in the course of their HIV infection. Another indication of earlier diagnosis is the increase in the proportion of individuals who were diagnosed with strong evidence of a recent infection, based on a known negative HIV test 6 or 12 months, at most, before their first positive test (*Figure 1.10*). Among MSM, the proportion with a negative test within the 6 or 12 months prior to their HIV diagnosis, increased over time and was 22% and 37%, respectively, for those diagnosed in 2017 or later. For other men and for women, however, the proportions with a recent

infection were considerably lower, and among those diagnosed in 2017 or later, only 8% had a negative test in the 12 months prior to their diagnosis, while 3% had a negative test in the 6 months prior to diagnosis. In total, among the individuals diagnosed in 2017 or later, 27% had a negative test in the 12 months prior to diagnosis, while 16% had a negative test in the 6 months prior to diagnosis.

***Figure 1.10:*** *Proportion of people diagnosed and having (A) a last negative test at most 12 months prior to their diagnosis, or (B) a last negative test at most 6 months prior to their diagnosis. In total, 36% of men who acquired HIV via sex with men (MSM), 9% of other men, 6% of women, and 25% of all individuals diagnosed in 2019 had a last negative test at most 12 months before diagnosis, whereas 19% of MSM, 3% of other men, 1% of women, and 13% of all individuals had a last negative test at most 6 months before diagnosis.*




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

### Amsterdam and Rotterdam vs. rest of the Netherlands

Among MSM diagnosed in 2017 or later, the proportion with a known HIV-negative test in the 6 months before diagnosis was 27% in the Amsterdam public health service region, 25% in Rotterdam-Rijnmond, and 20% in the rest of the Netherlands. Among other men and among women, the proportion of recent infections was 3% and did not differ between Amsterdam, Rotterdam-Rijnmond, and the rest of the country.

### Increasing frequency of testing

Since both CD4 counts at diagnosis and the proportion of recent infections have increased among those diagnosed with HIV, testing for HIV has apparently become more common. An additional indication for this is the increasing proportion of people with a previously negative HIV test recorded (from 22% in 1996 to 59% in 2019). MSM were more likely to have a previously negative HIV test than other men and women. In 2019, 73% of MSM, 35% of other men, and 39% 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 36% of those diagnosed in a hospital, 61% of those tested at a general practice, and 83% of those diagnosed elsewhere.

### Prior use of pre-exposure prophylaxis

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral agents by HIV-negative persons in order 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 health care providers, including as part of the AMPrEP study in Amsterdam, had already started several years earlier. MSM and transgender people at high risk for HIV acquisition are eligible for the official PrEP program.

SHM has started collecting PrEP-related data concerning individuals newly diagnosed with HIV and first entering care from the electronic medical records (EMRs) since July 2019. Up to September 2020, data has been collected from 1,523 such individuals. In 1,235 (81.1%) EMRs, no mention was made about prior use of PrEP, in 288 (18.9%) EMRs, information was available on prior use of PrEP.

There were only minor differences in demographic characteristics of individuals for whom information on prior use of PrEP was available or not. Information on prior use of PrEP was available in: 21.0% of MSM vs. 16.2% of other groups (heterosexual men and women); 19.8% of individuals born in the Netherlands vs. 17.9% of migrants. Individuals for whom information on prior use of PrEP was available were slightly younger (median 36.1, IQR 28.5 – 47.7 years) than individuals without such information (median 39.0, IQR 29.3 – 49.4 years).

Of the 288 individuals for whom information on prior use of PrEP was available, 38 (13.2%) had reported prior use of PrEP, and 250 (86.8%) did not. Prior use of PrEP was reported by none of the 39 women and by 38 (15.3%) of 249 men (18 [12.6%] of 143 men born in the Netherlands, and 20 [18.9%] of migrant men). Of the 38 men

who reported prior use of PrEP, the most likely route of HIV acquisition was through sexual contact with other men in 33 (86.8%) men, tattoo/piercing in 1 (2.6%) man, and was unknown in 4 (10.5%) men. The 38 men who reported prior use of PrEP were much younger (median 29.4, IQR 25.7 – 34.9 years) than the men who did not (median 37.3, IQR 28.9 – 47.8 years).

Of the 38 men who reported prior use of PrEP, 18 (47.4%) had obtained PrEP through a healthcare provider in the Netherlands (10 family practitioner, 6 GGD, 1 HIV treatment center, 1 no information on particular provider), 9 (23.7%) through a buyers club / internet / store outside of the Netherlands, 3 (7.9%) through a healthcare provider outside of the Netherlands, 1 (2.6%) from an HIV-positive friend who donated some of his own medication, and for 7 men no information was available. Co-formulated tenofovir disoproxil/emtricitabine was used by 18 men, for the other 20 information on the specific antiretrovirals used was not available. Daily PrEP use was reported for 11 (29.0%) men, on demand for 8 (21.1%) men, intermittent (i.e. a fixed schedule but not 7 days a week) for 5 (13.2%), and for 14 (36.8%) men no information was available.

Regular periodic medical checkups while using PrEP had been performed at the GGD (8, 21.1%), HIV-treatment center (4, 10.5%), or family practitioner (7, 18.4%), and no checkups were done in 6 (15.8%) men and for 13 (34.2%) men no information was available. In the Dutch PrEP program participants are recommended to undergo 3-monthly HIV testing while on PrEP. For 25 (65.8%) of men it was reported that they had used PrEP after the last negative HIV test performed while using PrEP, 6 (15.8%) men reported having tested HIV-negative within 3 months after discontinuing PrEP, and for 7 (18.4%) no information was available. For 25 (65.8%) of men who reported having used PrEP when first entering HIV care a genotypic resistance test was done. In 8 of these 25 men (32%) resistance associated mutations were detected: 6 men harbored a M184V mutation, 1 man had unspecified RT resistance mutations, and 1 man had V106I in the RT and A71I, V77I, and I93L in the protease gene, which might be naturally occurring polymorphisms and are probably unrelated to the prior use of PrEP.

The high percentage of individuals for whom no information on prior PrEP use could be retrieved from the medical records is noteworthy. To which extent this may partly be driven by clinical staff not yet querying patients about prior use of PrEP as part of the standard medical history, is currently unclear. SHM will continue to work with the HIV treatment centers to collect information on prior use of PrEP in all individuals newly entering care.

### Treated population

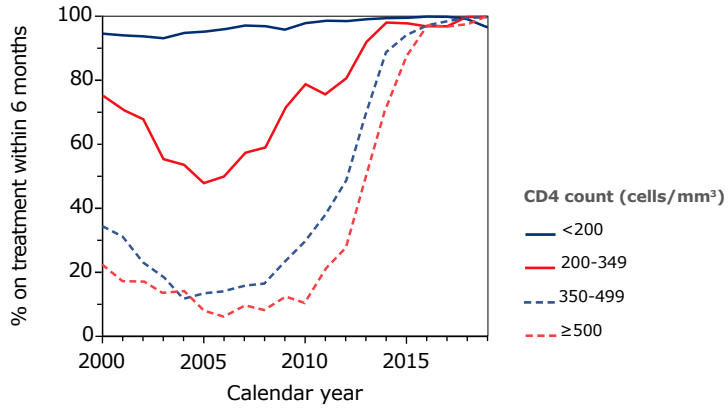
Of the 25,847 adults with a recorded date of diagnosis, including those born abroad with no documented HIV diagnosis prior to arrival in the Netherlands, 24,866 (96%) had started antiretroviral treatment by May 2020. Treatment and treatment outcomes are described in more detail in *Chapter 2*.

### Earlier start

Over the past few years, antiretroviral treatment has been started increasingly earlier in the course of HIV infection, as evidenced by higher CD4 counts at the start of treatment since the mid-2000s (*Figure 1.9B*). In 2019, median CD4 counts at the start of treatment had increased to 366 cells/mm$^3$. Of those starting treatment in 2019, 27% of people started at CD4 counts already below 200 cells/mm$^3$, 20% started at CD4 counts between 200 and 349 cells/mm$^3$, 20% started at CD4 counts between 350 and 499 cells/mm$^3$, and 33% started at CD4 counts of 500 cells/mm$^3$ or above.

The main reason for starting treatment too late (i.e., at low CD4 counts), appears to be a late diagnosis, because most people who are able to start treatment at high CD4 counts now do so. Nearly everyone with fewer than 200 CD4 cells/mm$^3$ at diagnosis had always started treatment within 6 months of diagnosis (*Figure 1.11*). On the other hand, those with higher CD4 counts were less likely in the past to start treatment within 6 months of diagnosis, but this likelihood has rapidly increased in recent years, reflecting the 2015 changes in treatment guidelines towards a universal start of treatment regardless of CD4 count[6]. In 2019, for all CD4 strata, at least 90% of people who were diagnosed with HIV that year started treatment within 6 months.

*Figure 1.11: Proportion of individuals who started antiretroviral treatment (ART) within 6 months of their HIV diagnosis by CD4 count at the time of diagnosis. Individuals were considered only if they had more than 6 months of follow up after diagnosis. Of all individuals diagnosed in 2017 or later, 99% of those with CD4 counts below 200 cells/mm³, 98% of those with CD4 counts between 200 and 349 cells/mm³, 98% of those with CD4 counts between 350 and 499 cells/mm³, and 97% of those with CD4 counts of 500 cells/mm³ or above had started ART within 6 months of diagnosis.*

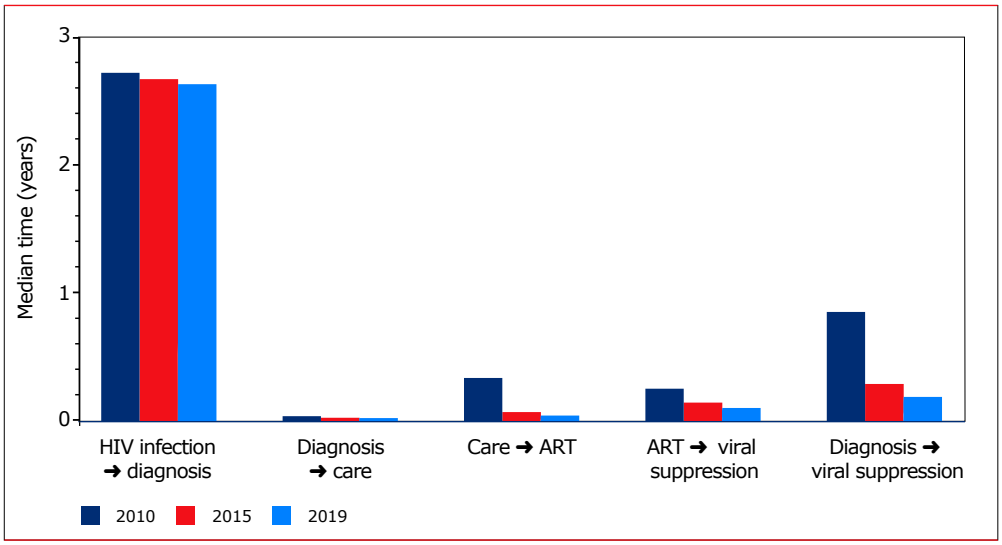



## Time between HIV infection and viral suppression

People with a suppressed viral load do not transmit their virus to uninfected partners ("undetectable equals untransmittable" or "U=U")[7–9]. Therefore, it is of paramount importance, not only for people living with HIV, but also from a public health perspective, to minimise the time between the moment a person acquires HIV and the point at which they achieve viral suppression[10]. However, to reach viral suppression, people with HIV must first be diagnosed, then linked to care, and subsequently start treatment.

Over time, significant improvements have been realised in several of these steps in the HIV care continuum (*Figure 1.12*). Between 2010 and 2019, the median time from diagnosis to viral suppression decreased from 0.85 (IQR, 0.38-2.64) years to 0.19 (0.13-0.30) years, or from 10.2 (4.5-31.7) months to 2.2 (1.6-3.6) months, mainly as a result of 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 2.6 (IQR, 1.3-4.8) years in 2019.

*Figure 1.12: Estimated median time to reach key stages in the HIV care continuum for HIV-1-positive individuals, including time from infection to diagnosis; from diagnosis to entry into care; from entry into care to starting antiretroviral treatment (ART); from starting ART to reaching viral suppression (defined as an RNA measurement below 200 copies/ml); and from diagnosis to viral suppression. Migrants with a documented HIV diagnosis before their arrival in the Netherlands were excluded from all stages.*




## Population: HIV-2

### HIV-2-positive individuals

In total, 100 of the 29,267 registered HIV-positive individuals (45 men and 55 women), acquired an HIV-2 infection; 20 of these were diagnosed in 2008 or later. The majority (79, 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). Only 22 individuals were born in the Netherlands, 15 of whom reported that they acquired their HIV infection in the Netherlands.

For the 83 individuals who were diagnosed in 1996 or later, the median CD4 count at the time of diagnosis was 310 (80-670) cells/mm$^3$. From 1996 onwards, 52% of the people were diagnosed with a late-stage HIV infection, and 42% were diagnosed with advanced HIV disease[4]. The distribution of CD4 counts at diagnosis appeared to be more bimodal than for HIV-1-positive individuals: 41% had CD4 counts below 200 cells/mm$^3$, 37% had CD4 counts of 500 cells/mm$^3$ or higher, while relatively few people (22%) had CD4 counts between 200 and 499 cell/mm$^3$.

### HIV-2-positive people in care

By the end of 2019, a total of 61 people were still in clinical care, 17 had died, 7 had moved abroad, and 15 had had no contact with HIV care in that year. The median age of the people still in care was 61 (IQR, 55-64) years; 52 (85%) individuals were 50 years or older. The majority (80%) of those in care had been living with HIV-2 for more than 10 years, while 31% had been living with it for more than 20 years.

In total, 41 people who were still in care by the end of 2019 had started antiretroviral treatment. The majority used a backbone of tenofovir/emtricitabine (16 individuals) or abacavir/lamivudine (15) in combination with dolutegravir (10) or a boosted protease inhibitor (24).

Of the 61 people still in care by the end of 2019, 47 had a most recent viral load measurement below 500 copies/ml, 2 had a viral load above 500 copies/ml, and 12 people had no available HIV-2 RNA result in 2019. Of the 21 individuals who were still in care and had not started antiretroviral therapy, 17 had a viral load measurement below 500 copies/ml while the other 4 had no RNA result available in 2019. In this group of 21 people, CD4 cell counts were still high, with a median of 700 (550-1030) cells/mm$^3$.

## HIV-1-positive people currently in care

### Population in care

In total, 20,612 (74%) of the 27,916 HIV-1-positive individuals ever registered in the Netherlands (20,427 adults and 185 minors aged under 18 years), were known to be in clinical care by the end of 2019 (*Figure 1.1*; *Table 1.3*). People were considered to be in clinical care if they visited their treating physician in 2019 or had a CD4 count or HIV RNA measurement in that year and were still living in the Netherlands. Of the 7,304 people who, according to this definition, were not in care by the end of 2019, 3,287 (45%) were known to have died, and 1,963 (27%) to have moved abroad. The remainder were either lost to care (1,971), were only diagnosed with HIV in 2020 (48), had only moved to the Netherlands in 2020 (6), or had only entered care in 2020 (29).

*Table 1.3: Characteristics of the 20,612 HIV-1-positive individuals in clinical care by the end of 2019.*

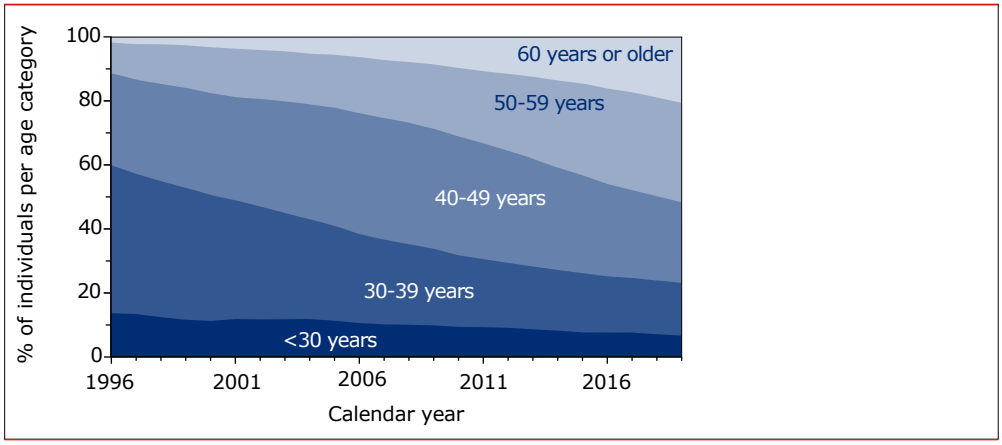
| | Men (n=16,810, 82%) | | Women (n=3,802, 18%) | | Total (n=20,612) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Transmission | | | | | | |
| MSM | 12,985 | 77 | - | - | 12,985 | 63 |
| Heterosexual | 2,496 | 15 | 3,329 | 88 | 5,825 | 28 |
| IDU | 189 | 1 | 82 | 2 | 271 | 1 |
| Blood/blood products | 177 | 1 | 104 | 3 | 281 | 1 |
| Other/unknown | 963 | 6 | 287 | 8 | 1,250 | 6 |
| Current age [years] | | | | | | |
| 0-17 | 86 | 1 | 99 | 3 | 185 | 1 |
| 18-24 | 217 | 1 | 77 | 2 | 294 | 1 |
| 25-29 | 740 | 4 | 132 | 3 | 872 | 4 |
| 30-39 | 2,635 | 16 | 771 | 20 | 3,406 | 17 |
| 40-49 | 3,966 | 24 | 1,218 | 32 | 5,184 | 25 |
| 50-59 | 5,431 | 32 | 971 | 26 | 6,402 | 31 |
| 60-69 | 2,782 | 17 | 390 | 10 | 3,172 | 15 |
| ≥70 | 953 | 6 | 144 | 4 | 1,097 | 5 |
| Region of origin | | | | | | |
| The Netherlands | 10,946 | 65 | 1,157 | 30 | 12,103 | 59 |
| Sub-Saharan Africa | 1,110 | 7 | 1,535 | 40 | 2,645 | 13 |
| Western Europe | 951 | 6 | 122 | 3 | 1,073 | 5 |
| South America | 1,196 | 7 | 343 | 9 | 1,539 | 7 |
| Caribbean | 740 | 4 | 177 | 5 | 917 | 4 |
| South and southeast Asia | 514 | 3 | 252 | 7 | 766 | 4 |
| Other | 1,288 | 8 | 207 | 5 | 1,495 | 7 |
| Unknown | 65 | 0 | 9 | 0 | 74 | 0 |
| Years aware of HIV infection | | | | | | |
| <1 | 442 | 3 | 79 | 2 | 521 | 3 |
| 1-2 | 1,196 | 7 | 181 | 5 | 1,377 | 7 |
| 3-4 | 1,410 | 8 | 239 | 6 | 1,649 | 8 |
| 5-10 | 4,124 | 25 | 693 | 18 | 4,817 | 23 |
| 10-20 | 6,499 | 39 | 1,832 | 48 | 8,331 | 40 |
| >20 | 3,112 | 19 | 756 | 20 | 3,868 | 19 |
| Unknown | 27 | 0 | 22 | 1 | 49 | 0 |

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

## Ageing population

The median age of the population in clinical care by the end of 2019 was 51 (IQR, 41-58) and has been increasing since 1996 (*Figure 1.13*). This increase in age is mainly a result of the improved life expectancy of people with HIV after the introduction of combination antiretroviral treatment (cART). In addition, people are being diagnosed at increasingly older ages, as discussed earlier in this chapter. As a result, approximately half of the people currently in care (52%) are 50 years or older, including 55% of men and 40% of women; 21% of the people are 60 years or older. As the HIV-positive population continues to age, the number of individuals with age-related comorbidities also increases, thereby complicating the management of their HIV infection (see *Chapter 3*).

***Figure 1.13:*** *Increasing age of the HIV-1-positive population in clinical care over calendar time. In 1996, 14% of the individuals in care were younger than 30 years of age, whereas 11% were 50 years or older. In 2019, these proportions were 7% and 52%, respectively, while 21% of individuals in care were 60 years of age or older. The proportion of individuals in clinical care as of 31 December of each calendar year is shown according to age category: <30 years of age, 30 to 39 years, 40 to 49 years, 50 to 59 years, and 60 years or older.*



### Duration of infection

People in clinical care by the end of 2019 were known to be HIV-positive for a median of 11.8 (IQR, 6.7-17.9) years. Therefore, a large group (59%) of those in care have been living with HIV for more than 10 years, while 19% have done so for more than 20 years. The median time since diagnosis was 11.2 years for men who have sex with men (MSM), 12.5 years for other men, and 14.0 years for women. The majority of individuals who acquired their HIV infection via injecting drug use (91%) 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.

### Antiretroviral treatment

In total, 99% of the individuals in care had started antiretroviral treatment, and 95% of them were currently using a once-daily regimen. Of the 219 (1%) individuals who had not yet started antiretroviral treatment by the end of 2019, 14 (6%) were known to have started treatment in 2020, while 98 (45%) other people were diagnosed with HIV in 2019, so their treatment has most likely yet to be recorded in the SHM database. Antiretroviral treatment is discussed in more detail in *Chapter 2*.

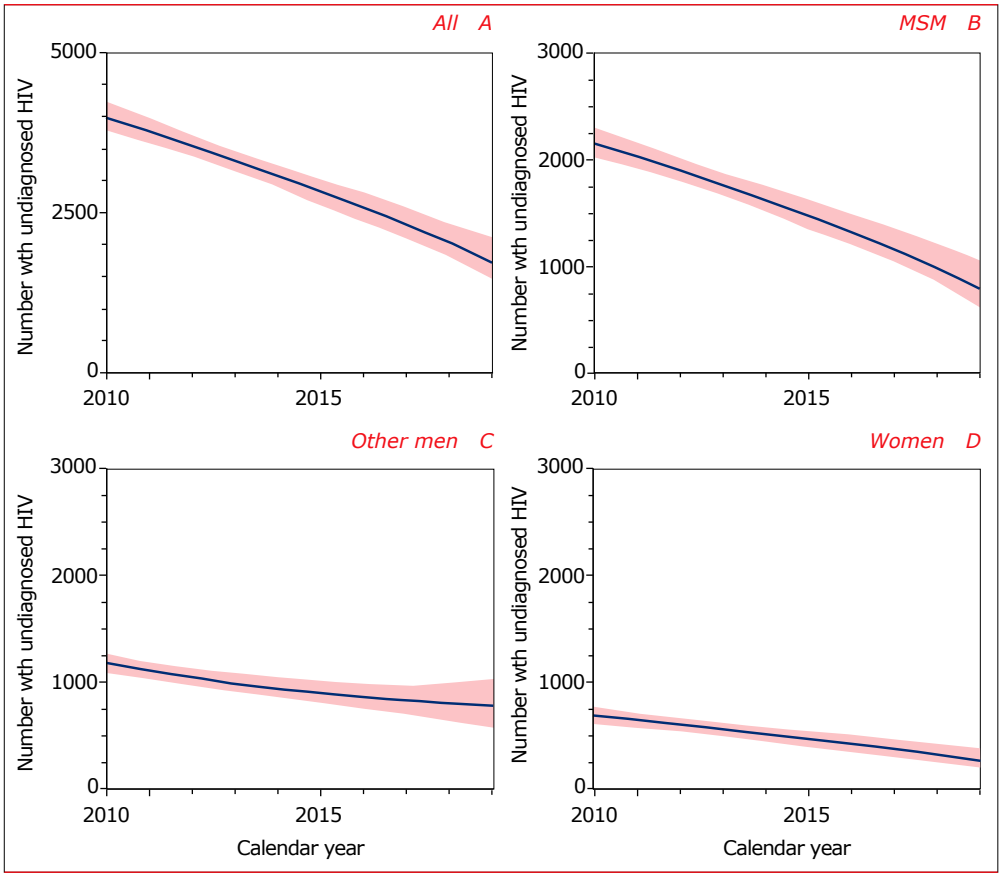
### Clinical condition

The most recent CD4 count in 2019 of the people in care was relatively high at a median of 689 (IQR, 509-900) cells/mm$^3$. This is mainly as a result of treatment, but also partly reflects the earlier diagnoses reported earlier in this chapter. CD4 counts were similar between MSM and women, being 707 (530-910) and 700 (510-926) cells/mm$^3$, respectively, but men who acquired HIV via other modes of transmission had lower CD4 counts at a median of 600 (417-830) cells/mm$^3$. Of the people in care with a viral load measurement in 2019, 97% had a last measurement in that year below 200 copies/ml. More than one fifth (22%) of the individuals had ever been diagnosed with an AIDS-defining disease; 57% of these people had been diagnosed with AIDS concurrently with their HIV diagnosis.

### Undiagnosed population

The estimated number of people living with an undiagnosed HIV infection decreased from 4,000 (95% CI, 3,800-4,200) in 2010 to 1,730 (1,470-2,120) in 2019, representing a reduction of 57% (47-63) (*Figure 1.14A*). This decrease was mostly driven by MSM, among whom the number living with undiagnosed HIV decreased by 63% (51-71) from 2,150 (2,020-2,300) in 2010 to 790 (620-1,060) by the end of 2019 (*Figure 1.14B*). Among other men, the estimated number living with undiagnosed HIV was 1,180 (1,090-1,270) in 2010 and 780 (570-1,030) in 2019, while in women these numbers were 690 (610-770) and 270 (200-380), respectively (*Figure 1.14C* and *1.14D*).

*Figure 1.14: Estimated number of people living with undiagnosed HIV in the Netherlands, overall (A), men who acquired HIV through sex with men (MSM) (B), other men (C), and women (D), according to the European Centre for Disease Prevention and Control (ECDC) HIV Modelling Tool[11].*




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

## Continuum of HIV care – national level

The total number of people living with HIV by the end of 2019 was 23,700 (95% confidence interval [CI] 23,400-24,100), including the estimated 1,730 (1,470-2,120) who remained undiagnosed[11]. Adjusted for registration delay, 21,969 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 20,710 individuals were considered to be retained in care (i.e., they had had at least one documented HIV RNA or CD4 count measurement or a clinic visit in 2019) (*Figure 1.15A*). The majority of these individuals (20,478, or 93% of those diagnosed and linked to care) had started antiretroviral treatment, and 19,625, or 96% of those treated, had a most recent HIV RNA measurement below 200 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 2019, the Netherlands had already reached the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 target for 2020, with the estimate standing at 93-93-96[12]. Of the people still in care by the end of 2019, 14,441 (70%, or 76% of those with a CD4 measurement), had a most recent CD4 count of 500 cells/mm$^3$ or higher measured, at most, two years earlier.

### Viral suppression

In total, 839 individuals (without adjustment for registration delay) had started treatment but did not have a suppressed viral load. On closer inspection, 339 (40%) of these individuals did not have a viral load measurement available in 2019. Of the 500 (60%) people with a viral load measurement and no viral suppression, 78 (16%) had not yet started treatment by the time of their last available viral load measurement in 2019. Another 25 (5%) 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, 1,971 individuals were lost to care, of whom 744 (38%) were lost before the end of 2009, and 1,227 (62%) between 2010 and 2019[b]. The 744 individuals who were lost to care in or before 2009, 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 744 individuals were still living in the Netherlands by the end of 2019 without needing care or antiretroviral treatment. Of the 1,227 individuals lost to care after 2009, 69% were born outside the Netherlands; this proportion was only 41% for those who were still in care by the end of 2019. This suggests that some of those lost to care may actually have moved abroad, in particular back to their country of birth.

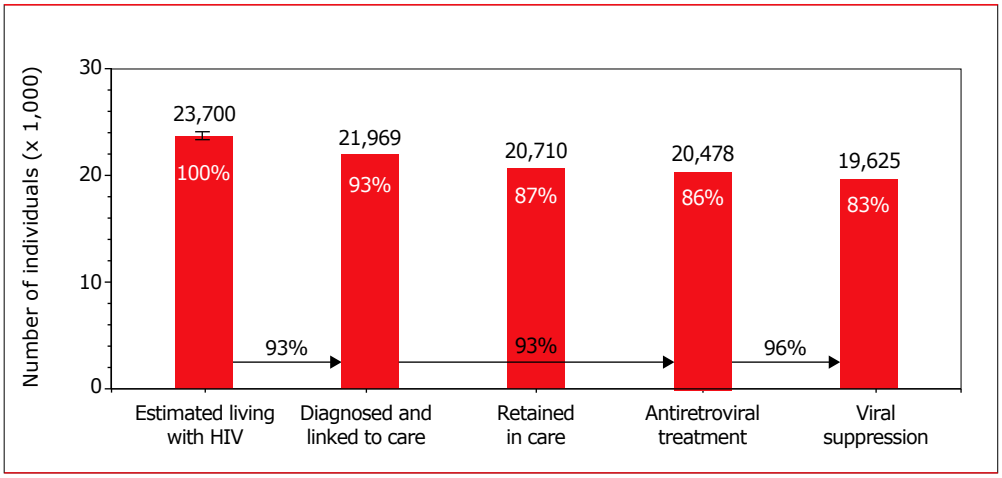
b *In addition to the 1,971 individuals lost to care there were 29 individuals who had already been diagnosed by the end of 2019 and were living in the Netherlands but entered care in 2020. These 29 individuals (31 with adjustment for registration delay), as well as the 1,227 lost to care after 2009 (1,228 with adjustment), are counted in the first and second stage of the continuum but not in the other stages.*

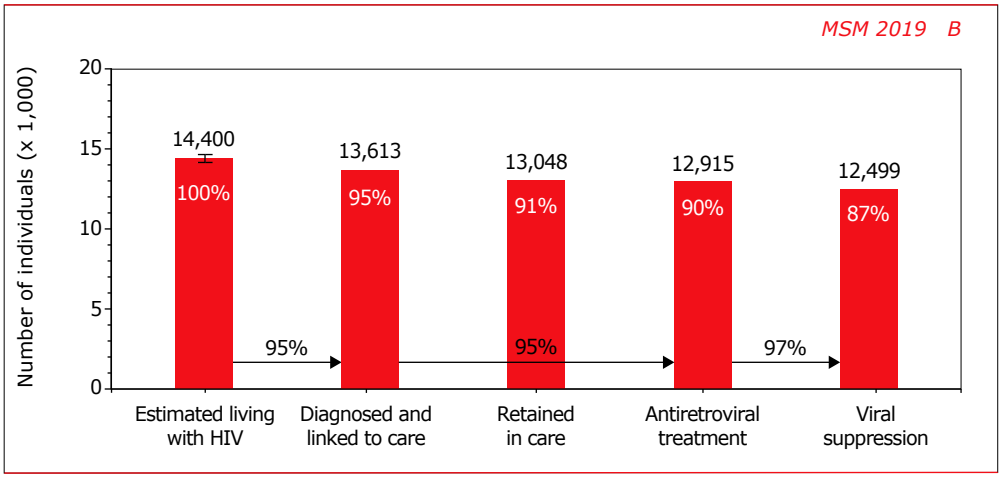
### Continuum of care in MSM, other men, and women

The number of MSM living with HIV at the end of 2019 was estimated to be 14,400 (14,200-14,700), of whom 790 (620-1,060) were yet to be diagnosed. Of these 14,400 MSM, 13,613 (95%) had been diagnosed and linked to care, 13,048 (91%) were still in care, 12,915 (90%) had started antiretroviral treatment, and 12,499 (87%) had a most recent HIV RNA below 200 copies/ml, or 95-95-97 in terms of the UNAIDS 90-90-90 target (*Figure 1.15B*). In total, 9,550 (73%, or 79% of those with a CD4 measurement) of MSM still in care by the end of 2019 had a CD4 count of 500 cells/mm$^3$ or higher at their last measurement in 2018 or 2019.

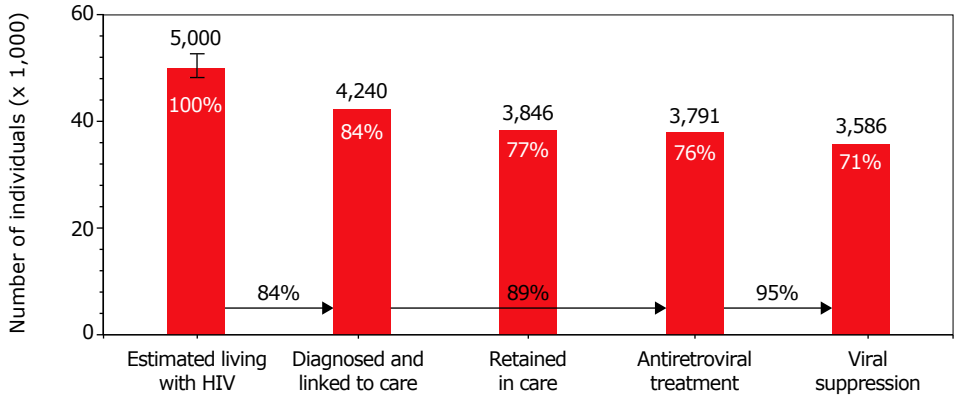
Among other men, the estimated number living with HIV in 2019 was 5,000 (4,800-5,300), including 780 (570-1,030) who were yet to be diagnosed (*Figure 1.15C*). In total, 4,240 (84%) men had been diagnosed and linked to care, 3,846 (77%) were still in care, 3,791 (76%) had started treatment, and 3,586 (71%) had a suppressed viral load below 200 copies/ml. The number of women living with HIV was estimated to be 4,400 (4,300-4,500), of whom 270 (200-380) were yet to be diagnosed (*Figure 1.15D*). Of these women, 4,116 (94%) had been diagnosed and linked to care, 3,816 (87%) were still in care, 3,771 (86%) had started treatment, and 3,539 (81%) had a suppressed viral load. Among women and other men still in care by the end of 2019, the proportion with viral suppression was 93%, which was lower than among MSM (96%).

*Figure 1.15: Continuum of HIV care for people estimated to be living with HIV in the Netherlands by the end of 2019: (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 UNAIDS' 90-90-90 targets for 2020. Numbers were adjusted for reporting delay.*

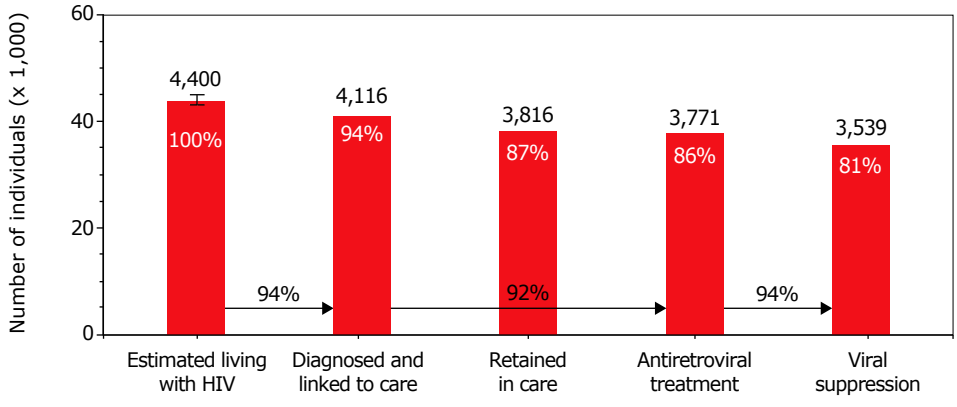


*Other men 2019 C*



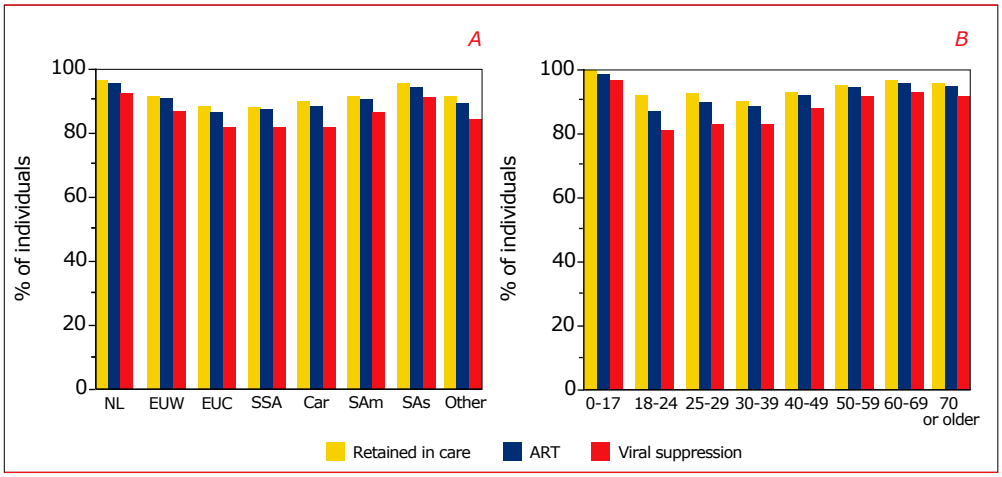

*Women 2019 D*



### Continuum of care by region of origin and age

Individuals of Dutch origin generally reached higher rates of engagement in the various stages of the care continuum than people originating from abroad (*Figure 1.16A*). Engagement in all stages of the care continuum was highest among the youngest age group. Among adults, the proportion of people who were still in care by the end of 2019 exceeded 90% in all age groups. The proportion who had started antiretroviral treatment increased from 87% of those diagnosed and linked to care among 18 to 24-year-olds to more than 95% in the oldest age groups (*Figure 1.16B*). As a consequence, the proportion of people with viral suppression increased with age and was 81% among those aged 18 to 24 years, and above 90% in people 50 years of age 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 2018

We also re-estimated the continuum of HIV care for 2018 and found that, by the end of that year, 23,500 (23,300-23,800) people were living with HIV in the Netherlands, which was similar to the estimated 23,300 (23,000-23,700) reported in last year's Monitoring Report[13]. While the number diagnosed (21,450 compared to 21,360), the number retained in care (20,203 compared to 20,189), and the number of those who started antiretroviral treatment (20,050 compared to 19,913) were

very similar to last year's report, the number with viral suppression (19,278 compared to 19,046) 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 2018, has now been cleared. As a result, the 2018 estimate for the UNAIDS 90-90-90 target has been adjusted and has changed slightly from 92-93-96 in last year's report, to 91-93-96 in this year's report. Similarly, when the 2019 HIV continuum of care is recalculated next year, a comparable change is expected.

### Continuum of HIV care – regional level

New in this year's report, 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 were in Noord-Holland/Flevoland and in Zuid-Holland Zuid, which include the cities of Amsterdam and Rotterdam. In these two regions, 790 (45%) people were estimated to be living with undiagnosed HIV. All eight regions had reached or surpassed UNAIDS' 90-90-90 targets for 2020, and the proportion of all people with HIV, including those with undiagnosed infection, who had a suppressed viral load varied between 80% 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*).

In total, 10,290 (10,180-10,400) people with HIV were estimated to be living in the *four largest cities* in the Netherlands, which is 43% of the total number of people living with HIV in the Netherlands. Of these 10,290 people, 610 (500-720) were estimated to be still undiagnosed (35% of the national estimate of 1,730 individuals with an undiagnosed HIV infection). Of the four cities, Amsterdam had the largest population of people living with HIV; an estimated 6,370 (6,290-6,450) individuals, of whom 320 (250-410) were still undiagnosed (*Table 1.4*). Of the 10,290 people living with HIV in the four largest cities, 9,680 (94%) had been diagnosed and linked to care, 8,999 (87%, or 93% of those diagnosed) had started antiretroviral treatment, and 8,621 (84%, or 96% of those on treatment) had a suppressed viral load. All four cities had reached or surpassed UNAIDS' 90-90-90 targets for 2020 with the current combined estimate for the cities standing at 94-93-96.

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

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 1,770 (1,570-2,030) individuals living with undiagnosed HIV across the eight STI surveillance regions, is very close to the number of 1,730 (1,470-2,120) 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 SHM records.

*Table 1.4: Continuum of care by the end of 2019 for the total HIV-1-positive population living in the Netherlands. Figures are given for each of the eight sexually transmitted infection (STI) surveillance regions, as well as for the four major cities. For 176 individuals diagnosed and linked to care, region of residence was unknown.*

| | Estimated living with HIV | | Diagnosed and linked to care | |
|---|---|---|---|---|
| | Undiagnosed | Total | | |
| | n | % | n | % |
| Region | | | | |
| Noord | 120 | 1,320 | 1,206 | 91 |
| | 90–200 | 1,300–1,400 | | |
| Oost | 280 | 2,690 | 2,406 | 90 |
| | 200–360 | 2,610–2,770 | | |
| Utrecht | 130 | 1,430 | 1,291 | 91 |
| | 90–220 | 1,380–1,510 | | |
| Noord-Holland/Flevoland | 460 | 9,020 | 8,555 | 95 |
| | 360–560 | 8,920–9,110 | | |
| Zuid-Holland Noord | 160 | 1,830 | 1,670 | 91 |
| | 110–250 | 1,780–1,920 | | |
| Zuid-Holland Zuid | 330 | 3,740 | 3,413 | 91 |
| | 250–440 | 3,660–3,860 | | |
| Zeeland/Brabant | 200 | 2,520 | 2,324 | 92 |
| | 140–280 | 2,460–2,600 | | |
| Limburg | 80 | 1,010 | 927 | 92 |
| | 50–150 | 970–1,070 | | |
| Total | 1,770 | 23,560 | 21,793 | 93 |
| | 1,570–2,030 | 23,370–23,820 | | |
| City | | | | |
| Amsterdam | 320 | 6,370 | 6,044 | 95 |
| | 250–410 | 6,290–6,450 | | |
| Rotterdam | 160 | 2,070 | 1,918 | 93 |
| | 110–220 | 2,020–2,140 | | |
| Den Haag | 90 | 1,290 | 1,198 | 93 |
| | 60–150 | 1,250–1,350 | | |
| Utrecht | 40 | 560 | 520 | 92 |
| | 30–90 | 550–610 | | |
| Total | 610 | 10,290 | 9,680 | 94 |
| | 500–720 | 10,180–10,400 | | |

| Retained in care | | Antiretroviral treatment | | Viral suppression | |
|---|---|---|---|---|---|
| n | % | n | % | n | % |
| 1,150 | 87 | 1,145 | 86 | 1,094 | 83 |
| 2,331 | 87 | 2,299 | 86 | 2,218 | 83 |
| 1,217 | 85 | 1,190 | 83 | 1,161 | 81 |
| 8,028 | 89 | 7,957 | 88 | 7,625 | 85 |
| 1,578 | 86 | 1,565 | 85 | 1,486 | 81 |
| 3,207 | 86 | 3,156 | 84 | 3,011 | 80 |
| 2,194 | 87 | 2,172 | 86 | 2,074 | 82 |
| 877 | 87 | 871 | 86 | 843 | 83 |
| 20,583 | 87 | 20,355 | 86 | 19,512 | 83 |
| 5,682 | 89 | 5,632 | 88 | 5,409 | 85 |
| 1,791 | 86 | 1,761 | 85 | 1,675 | 81 |
| 1,131 | 88 | 1,120 | 87 | 1,063 | 83 |
| 493 | 87 | 486 | 86 | 474 | 84 |
| 9,097 | 88 | 8,999 | 87 | 8,621 | 84 |

*Table 1.5: Continuum of HIV care for the total HIV-1-positive population in the Netherlands, stratified by the public health service region in which people were living by the end of 2019. 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 | 581 | 558 | 96 |
| Fryslân | 345 | 335 | 97 |
| Drenthe | 280 | 257 | 92 |
| Oost | | | |
| IJsselland | 353 | 344 | 97 |
| Twente | 431 | 417 | 97 |
| Noord- en Oost-Gelderland | 489 | 477 | 98 |
| Gelderland Midden | 717 | 696 | 97 |
| Gelderland-Zuid | 416 | 397 | 95 |
| Utrecht | | | |
| Regio Utrecht | 1,291 | 1,217 | 94 |
| Noord-Holland/Flevoland | | | |
| Flevoland | 568 | 506 | 89 |
| Gooi & Vechtstreek | 300 | 284 | 95 |
| Hollands Noorden | 452 | 425 | 94 |
| Zaanstreek-Waterland | 375 | 354 | 94 |
| Amsterdam | 6,276 | 5,906 | 94 |
| Kennemerland | 585 | 554 | 95 |
| Zuid-Holland Noord | | | |
| Haaglanden | 1,670 | 1,578 | 95 |
| Zuid-Holland Zuid | | | |
| Hollands Midden | 562 | 529 | 94 |
| Rotterdam-Rijnmond | 2,554 | 2,393 | 94 |
| Dienst Gezondheid & Jeugd ZHZ | 297 | 285 | 96 |
| Zeeland/Brabant | | | |
| Zeeland | 232 | 215 | 93 |
| West-Brabant | 578 | 549 | 95 |
| Hart voor Brabant | 850 | 801 | 94 |
| Brabant-Zuidoost | 665 | 630 | 95 |
| Limburg | | | |
| Limburg-Noord | 399 | 371 | 93 |
| Zuid Limburg | 528 | 506 | 96 |
| Unknown | 176 | 127 | 72 |
| **Total** | **21,969** | **20,710** | **94** |

| | Antiretroviral treatment | | Viral suppression | |
|---|---|---|---|---|
| | n | % | n | % |
| | | | | |
| | 555 | 95 | 537 | 92 |
| | 334 | 97 | 313 | 91 |
| | 256 | 91 | 245 | 87 |
| | | | | |
| | 342 | 97 | 330 | 93 |
| | 413 | 96 | 400 | 93 |
| | 467 | 96 | 451 | 92 |
| | 683 | 95 | 665 | 93 |
| | 394 | 95 | 373 | 90 |
| | | | | |
| | 1,190 | 92 | 1,161 | 90 |
| | | | | |
| | 504 | 89 | 479 | 84 |
| | 279 | 93 | 272 | 91 |
| | 422 | 93 | 401 | 89 |
| | 351 | 94 | 337 | 90 |
| | 5,853 | 93 | 5,622 | 90 |
| | 548 | 94 | 514 | 88 |
| | | | | |
| | 1,565 | 94 | 1,486 | 89 |
| | | | | |
| | 522 | 93 | 502 | 89 |
| | 2,356 | 92 | 2,239 | 88 |
| | 278 | 94 | 269 | 91 |
| | | | | |
| | 213 | 92 | 196 | 84 |
| | 541 | 94 | 521 | 90 |
| | 795 | 94 | 767 | 90 |
| | 623 | 94 | 590 | 89 |
| | | | | |
| | 368 | 92 | 353 | 89 |
| | 504 | 95 | 490 | 93 |
| | 123 | 70 | 113 | 64 |
| | **20,478** | **93** | **19,625** | **89** |

## 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 800. This downward trend continued in 2019 with approximately 580 new diagnoses, although there is some uncertainty concerning this figure because, at the time of writing, not all people diagnosed in 2019 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.

In this year's report, people born abroad who had a documented HIV diagnosis before arrival in the Netherlands, were excluded from the reported annual numbers of newly-diagnosed HIV infections for the first time. So far, 1,434 individuals with a diagnosis prior to their arrival in the Netherlands have been identified. As a result, the decrease in the number of new diagnoses - and in the annual number of newly-acquired HIV infections - compared with 2010 was less pronounced than reported previously[13]. Nevertheless, the estimated annual number of newly-acquired HIV infections has still decreased by more than 70% since 2010.

A significant decrease was observed in the time from infection to diagnosis, and the time of reaching other stages in the HIV care continuum. Over the past few years, more than 1 in 5 MSM were diagnosed with evidence of early HIV infection based on a negative HIV test within the 6 months prior to their first positive test. In the second half of 2019, the successful campaign by the HIV Transmission Elimination Amsterdam Initiative (H-TEAM) aimed at raising awareness of symptoms of acute HIV infection and rapid referral to HIV testing based on reported symptoms was introduced at a national level[14]. As a result, an increase in the proportion of MSM diagnosed with recent HIV infection is likely in the coming years.

Despite 1 in 4 individuals being diagnosed within a year of acquiring HIV, a large proportion (48%) 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 downward trend in the proportion diagnosed with late-stage HIV appears to have halted. This may, however, be a consequence of earlier diagnosis in other groups: by rapidly diagnosing people with early HIV infection, in combination with decreasing numbers of people who newly acquire an HIV infection, the undiagnosed population will mainly comprise people who have been living with HIV for longer durations. 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. As a result of this earlier treatment, in combination with increased testing, earlier diagnosis and a decreasing number of newly-acquired HIV infections, the Netherlands has continued to surpass the UNAIDS 2020 targets of 90-90-90, and close in on achieving the UNAIDS 2030 targets of 95-95-95, with the current figures standing at 93-93-96[15]. In MSM, the 95-95-95 target has already been reached, in part as a consequence of a 76% decrease in annual numbers of newly-acquired HIV infections compared with 2010[1,2].

The data presented in this chapter mainly focus on people diagnosed in 2019. They don't reflect the impact of the COVID-19 pandemic and the partial lockdown in the Netherlands, which came into effect in early 2020 – these are expected to have affected both transmission and diagnosis of HIV. During the lockdown, test services for STIs and HIV at sexual health centres were disrupted and dropped by up to 70%. Figures for testing at other locations, like general practitioners or online services, are not yet available, but it may be expected that testing at these locations decreased as well. The provision of PrEP by STI clinics was near-normal, although between March and June, no new clients could enter the national PrEP programme. Next year's SHM Monitoring Report should be able to provide further insight into the impact of the COVID-19 pandemic on trends in the HIV epidemic in the Netherlands.

**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[16]. In 2019, there were approximately 580 newly-diagnosed infections, which is a reduction of 35% compared to the 890 diagnoses in 2015. With a few more years to go until 2022, reaching this specific goal appears feasible.

A second goal in the National Action Plan is reaching the Joint United Nations Programme on HIV/AIDS (UNAIDS) 95-95-95 target by 2022, 8 years earlier than the UNAIDS' target year of 2030. By the end of 2019, the overall estimate in the Netherlands stood at 93-93-96, while in MSM the National Action Plan target had just been reached (95-95-97). Earlier diagnosis of people with HIV, and retaining people in care will be key in reaching and surpassing this specific goal in all groups affected by HIV.

## Recommendations

A reassessment of the continuum of HIV care for 2018, 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 2030, 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) in the SHM database to all HIV treatment centres in the Netherlands. At present, LabLink is available for 17 of the 24 HIV treatment centres, which together treat approximately 72% of all people followed by SHM.

One of the care continuum indicators which is not performing as well as some others, is the proportion of people who are still in care. In total, 1,971 individuals who were diagnosed in or before 2019, and had been registered with SHM, were marked as lost to care (i.e., they did not visit their HIV physician or nurse in 2019 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. A major step towards achieving this goal would be to reconsider the current restrictions on community-based and home-based HIV testing, and increase awareness of sexual risk behaviour.

Worryingly, a substantial number of individuals are still diagnosed with late-stage or advanced HIV infection. This is even the case among MSM, despite an increase in the proportion that are diagnosed within a year of infection. Clearly, there remain 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 are currently being analysed and 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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# 2. Response to combination antiretroviral therapy

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## Introduction

Since the introduction of combination antiretroviral therapy (cART) in 1996, there have been substantial advances in the use of antiretroviral drugs for the treatment and prevention of HIV infection. The primary goals of cART are to prevent HIV disease progression, improve clinical outcomes, and limit transmission[1,2]. Treatment guidelines across the globe recommend to initiate cART as soon as possible for 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, https://richtlijnhiv.nvhb.nl/index.php/Inhoud) follows the US Department of Health and Human Services guidelines.

Besides preventing clinical events, including tuberculosis and AIDS, the immediate start of cART is also more effective at preventing transmission of HIV than deferral of treatment until the CD4 count has dropped to ≤350 cells/mm$^3$ [8,9]. People living with HIV on cART with an undetectable viral load in their blood have no risk of onward sexual transmission of HIV, (i.e., undetectable equals untransmittable, or U=U[10–15]). 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.

Most guidelines list an unboosted integrase inhibitor as the third agent of preferred first-line cART regimens. Further treatment options, which are recommended in certain clinical situations, include elvitegravir as a boosted integrase inhibitor; darunavir or atazanavir as a boosted protease inhibitor; or doravirine, efavirenz, or rilpivirine as a non-nucleoside reverse transcriptase inhibitor (NNRTI, the latter only if viral load is <100,000 copies/ml). All aforementioned agents are used in combination with a double nucleoside backbone (either tenofovir/emtricitabine

or abacavir/lamivudine)[16]. Additionally, tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are two forms of tenofovir approved by the European Medicines Agency (EMA). TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. TDF use should be avoided in people with reduced renal function and in people with osteoporosis, or a risk of osteoporotic fractures[17,18]. The two-drug regimen of dolutegravir and lamivudine (co-formulated as Dovato®), has also recently been licensed by the US Food and Drug Administration (FDA) and EMA. It is now a recommended regimen for ART-naïve individuals with viral load below 500,000 copies/mL, without chronic HBV co-infection, and for whom a baseline HIV genotype is available to exclude the presence of transmitted resistance to lamivudine. Safety, ease of use, food effects, and potential for significant drug-drug interactions are among the factors to consider when choosing between regimens. Finally, although still frequently used, efavirenz is no longer recommended as the preferred first-line cART regimen in the Netherlands, but remains an alternative[3,7,16].

Treatment with cART generally results in sustained suppression of HIV viral load to levels below the reported threshold. Nevertheless, drug resistance mutations could develop if a given agent, even when combined with other agents, cannot sufficiently prevent the selective pressures driving resistance (i.e., low genetic barrier to resistance). Over time, accumulation of mutations in the HIV genome that are associated with drug resistance can prevent sustained viral suppression, thereby increasing the risk of poor clinical outcomes[19–25].

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. We also analyse the presence of transmitted and acquired HIV drug resistance. *Box 2.1* gives an overview of the number of people included in the various analyses described in this chapter.

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

**There were a cumulative 27,097 adults (≥18 years at the time of diagnosis) registered by SHM as living with HIV-1 in the Netherlands by the end of 2019**

1. **Starting combination antiretroviral therapy**
   25,587 people were known to have initiated cART between January 1996 and December 2019.

2. **In care and on cART in the Netherlands in 2019**
   Of the 25,587 people who initiated cART between January 1996 and December 2019,
   ➔ 19,498 were in care and had a clinical visit in 2019.

3. **Changes in the use of the initial cART regimen**
   Of the 25,587 people who initiated cART between January 1996 and December 2019,
   ➔ 4,581 initiated cART between January 2015 and December 2019.
   ➔ The most frequently used 'common' guideline-recommended initial regimens in 2015-19 were: ABC/3TC/DTG (28.9%), TAF/FTC/EVG/c (13.6%), TDF/FTC/DTG (11.0%), TDF/FTC/EVG/c (8.2%), TAF/FTC/BIC (6.7%), TDF/FTC/EFV (5.0%), TDF/FTC/DRV/b (4.7%), TDF/FTC/RPV (2.7%), TAF/FTC/DTG (2.5%), TAF/FTC/DRV/c (2.4%), TDF/FTC/ATV/b (1.6%), TAF/FTC/RPV (1.2%), and TDF/FTC/RAL (0.9%).

4. **Virological response**
   Of the 25,587 people who initiated cART between January 1996 and December 2019,
   ➔ 21,644 people were ART-naive, not pregnant at cART initiation, and had a viral load result within six months (±three months) of cART initiation.

**5. HIV drug resistance**

*Transmitted HIV drug resistance*

As of January 2020, 7,567 HIV-1 sequences had been obtained from 7,292 ART-naive people before they initiated cART in 2003-19.

➔ 7,559 reverse transcriptase sequences were available from 7,287 individuals.
➔ 7,184 protease sequences were available from 6,918 individuals.
➔ 27 integrase sequences were available from 27 individuals.

*Acquired HIV drug resistance*

As of January 2020, 3,899 HIV-1 sequences had been obtained from 2,402 people who received cART for at least four months in 2000-19.

➔ 2,610 sequences were from 1,691 people who had been ART-naive before initiating cART.
➔ 3,853 reverse transcriptase sequences were available from 2,384 individuals.
➔ 3,732 protease sequences were available from 2,298 individuals.
➔ 167 integrase sequences were available from 138 individuals.

**6. Immunological response**

Of the 25,587 people who initiated cART between January 1996 and December 2019,

➔ 25,088 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).*

## Starting combination antiretroviral therapy

In total, 25,587 adults ever registered by SHM and followed in the ATHENA cohort were 18 years or older at the time of HIV-1 diagnosis, and were known to have initiated cART between January 1996 and December 2019 (*Box 2.1*). Of these, 2,100 (8.1%) had prior exposure to mono or dual nucleoside-analogue antiretroviral therapy (ART) at the start of cART, and 23,487 (91.8%) were ART-naive. The proportion of pre-treated people starting cART has decreased over time to <1%. In *Table 2.1*, we grouped people according to calendar year of cART initiation: 8,475 started in 1996-2004, 5,468 in 2005-09, 7,063 in 2010-14, and 4,581 in 2015-19.

*Table 2.1: Characteristics of people starting combination antiretroviral therapy in 1996–2019.*

| Year of cART initiation | | 1996–2004 | 2005–2009 | 2010–2014 | 2015–2019 | 1996–2019 |
|---|---|---|---|---|---|---|
| Number of individuals | | 8,475 | 5,468 | 7,063 | 4,581 | **25,587** |
| DEMOGRAPHIC | | | | | | |
| Age at cART initiation (years) | Median | 37.6 | 39.9 | 40.0 | 38.0 | **38.7** |
| | Q1 | 31.9 | 33.0 | 31.8 | 29.5 | **31.7** |
| | Q3 | 44.6 | 47.0 | 48.3 | 49.1 | **46.9** |
| Male gender (at birth) | n | 6607 | 4,347 | 6,099 | 3,927 | **20,980** |
| | % | 78.0 | 79.5 | 86.4 | 85.7 | **82.0** |
| Transmission risk group | | | | | | |
| Missing | n | 7 | 5 | 9 | 12 | **33** |
| | % | 0.1 | 0.1 | 0.1 | 0.3 | **0.1** |
| Men who have sex with men | n | 4,576 | 3,157 | 4,859 | 3,041 | **15,633** |
| | % | 54.0 | 57.7 | 68.8 | 66.4 | **61.1** |
| Heterosexual contact | n | 2,799 | 1,827 | 1,767 | 1,157 | **7,550** |
| | % | 33.0 | 33.4 | 25.0 | 25.3 | **29.5** |
| Injecting drug use | n | 495 | 117 | 57 | 27 | **696** |
| | % | 5.8 | 2.1 | 0.8 | 0.6 | **2.7** |
| Blood or blood products | n | 146 | 54 | 62 | 43 | **305** |
| | % | 1.7 | 1.0 | 0.9 | 0.9 | **1.2** |
| Vertical transmission | n | . | . | 4 | 2 | **6** |
| | % | . | . | 0.1 | 0.0 | **0.0** |
| Other/unknown | n | 452 | 308 | 305 | 299 | **1,364** |
| | % | 5.3 | 5.6 | 4.3 | 6.5 | **5.3** |
| Region of origin | | | | | | |
| Missing | n | 41 | 15 | 14 | 31 | 101 |
| | % | 0.5 | 0.3 | 0.2 | 0.7 | 0.4 |
| The Netherlands | n | 4,743 | 2,974 | 4,272 | 2,474 | 14,463 |
| | % | 56.0 | 54.4 | 60.5 | 54.0 | 56.5 |
| Western Europe/North America/Australia | n | 856 | 443 | 478 | 272 | 2,049 |
| | % | 10.1 | 8.1 | 6.8 | 6.0 | 8.0 |
| Eastern/central Europe | n | 140 | 159 | 343 | 345 | 987 |
| | % | 1.7 | 2.9 | 4.9 | 7.5 | 3.9 |
| Latin America and the Caribbean | n | 889 | 669 | 835 | 672 | 3,065 |
| | % | 10.5 | 12.2 | 11.8 | 14.7 | 12.0 |
| Sub-Saharan Africa | n | 1,414 | 900 | 708 | 433 | 3,455 |
| | % | 16.7 | 16.5 | 10.0 | 9.5 | 13.5 |
| Other | n | 392 | 308 | 413 | 354 | 1,467 |
| | % | 4.6 | 5.6 | 5.9 | 7.7 | 5.7 |

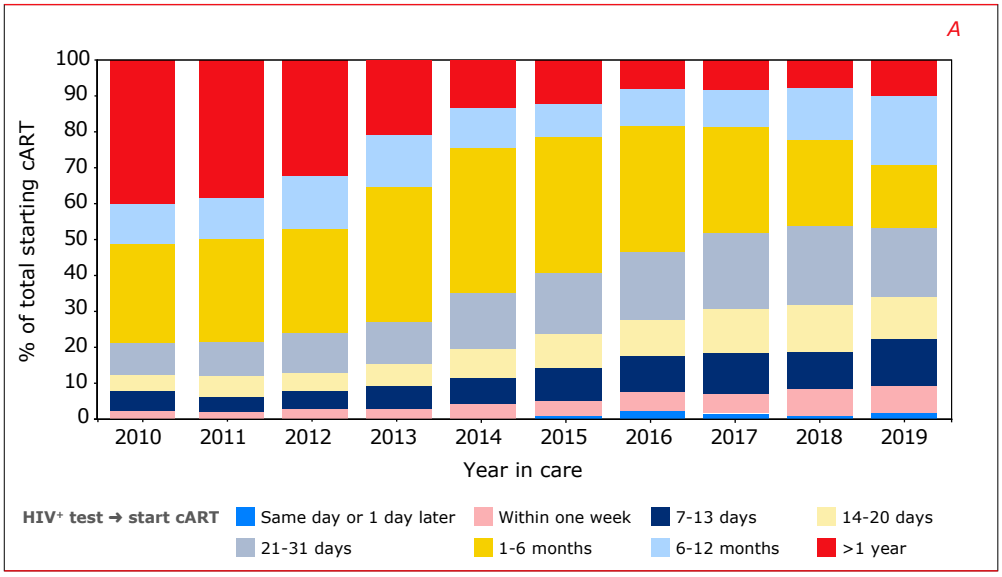
| Year of cART initiation | | 1996–2004 | 2005–2009 | 2010–2014 | 2015–2019 | 1996–2019 |
|---|---|---|---|---|---|---|
| CLINICAL | | | | | | |
| Recent infection | n | 479 | 729 | 1,607 | 1,194 | **4,009** |
| (within 12 months of diagnosis) | % | 5.7 | 13.3 | 22.8 | 26.1 | **15.7** |
| Ever having tested HIV-negative | n | 1,723 | 1,993 | 3,786 | 2,578 | **10,080** |
| | % | 20.3 | 36.5 | 53.6 | 56.3 | **39.4** |
| CD4 cell count at start of cART | Median | 190 | 230 | 330 | 400 | **270** |
| | Q1 | 80 | 120 | 210 | 200 | **130** |
| | Q3 | 320 | 306 | 458 | 585 | **410** |
| HIV RNA ($log_{10}$) at start of cART | Median | 4.9 | 5.0 | 4.9 | 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 | 2,635 | 1,164 | 1,010 | 567 | **5,376** |
| | % | 31.1 | 21.3 | 14.3 | 12.4 | **21.0** |
| Prior mono or dual NRTI treatment | n | 1,987 | 65 | 25 | 23 | **2,100** |
| at start of cART | % | 23.5 | 1.2 | 0.4 | 0.5 | **8.2** |
| Hepatitis B status at start of cART | | | | | | |
| HBV-negative (HBsAg-negative) | n | 7,627 | 5,016 | 6,571 | 4,206 | **23,420** |
| | % | 90.0 | 91.7 | 93.0 | 91.8 | **91.5** |
| HBV-positive (HBsAg-positive) | n | 524 | 312 | 254 | 109 | 1,199 |
| | % | 6.2 | 5.7 | 3.6 | 2.4 | **4.7** |
| Unknown | n | 324 | 140 | 238 | 266 | **968** |
| | % | 3.8 | 2.6 | 3.4 | 5.8 | **3.8** |
| Hepatitis C status at start of cART | | | | | | |
| HCV-negative | n | 7,613 | 5,152 | 6,741 | 4,309 | **23.815** |
| | % | 89.8 | 94.2 | 95.4 | 94.1 | **93.07** |
| HCV RNA-positive | n | 143 | 129 | 117 | 69 | 458 |
| | % | 1.7 | 2.4 | 1.7 | 1.5 | 1.8 |
| HCV Ab seropositive | n | 183 | 44 | 40 | 22 | 289 |
| | % | 2.2 | 0.8 | 0.6 | 0.5 | 1.1 |
| Unknown | n | 536 | 143 | 165 | 181 | 1,025 |
| | % | 6.3 | 2.6 | 2.3 | 4.0 | 4.0 |
| cART started during pregnancy | n | 306 | 255 | 121 | 77 | 759 |
| | % | 3.6 | 4.7 | 1.7 | 1.7 | **3.0** |

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

Of the 25,587 people who had initiated cART since January 1996, 20,980 (82.0%) were men, of whom 15,633 (74.5%) were men who have sex with men (MSM). Overall, 14,433 (56.5%) 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 2009, to 4.9% in 2010-14, and 7.5% in 2015-19. Simultaneously, the number of people from western Europe/North America/Australia decreased slightly from 10.5% in 1996-2004, to 5.9% in 2015-19. This was also true for sub-Saharan Africa; the number declined from 16.7% in 1996-2004, to 9.5% in 2015-19.

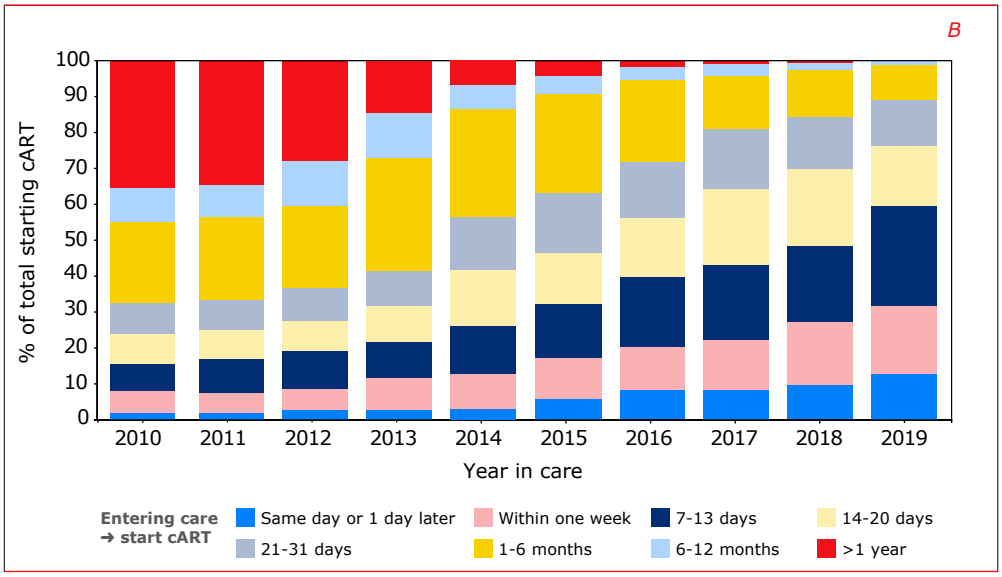
Prompt initiation of cART following an HIV-positive diagnosis has increased over time, reflecting implementation and uptake of evolving HIV treatment guidelines (*Figure 2.1A*). Among people with a known date of HIV diagnosis who started cART in the Netherlands, the median time between an HIV-positive diagnosis and cART initiation shifted from 136 days (interquartile range [IQR] 33-714) for those who entered care in 2011, to 110 days (IQR 30-519) in 2012; 66 days (IQR 27-293) in 2013; 42 days (IQR 21-117) in 2014; 36 days (IQR 17-82) in 2015; 30 days (IQR 14-55) in 2016; 28 days (IQR 14-49) in 2017; 25 days (IQR 11-46) in 2018; and 21 days (IQR 8-44) in 2019. The proportion of subjects initiating cART on the same day they were diagnosed HIV-positive increased from 0.3% in 2010, to 1.0% in 2015, 2.3% in 2016, 1.5% in 2017, 1.1% in 2018, and 1.6% in 2019. Likewise, the time between entering care and starting cART decreased over time (*Figure 2.1B*), with the vast majority of people newly entering care initiating cART within six months. In 2019, 19.0% and 10.2% of individuals initiating cART did so either 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. In 2018 and 2019, of those born outside the Netherlands who initiated cART more than six months after testing HIV-positive, 48.1% first tested HIV-positive after they migrated to the Netherlands, 29.8% tested HIV-positive before they migrated to the Netherlands, and, for 22.1%, the migration date was unknown. Among those who entered care in 2018 and 2019 and who had started ART more than 6 months after HIV diagnosis, 79.4% were migrants, mainly from European countries, North and sub-Saharan Africa and Asia, who were already diagnosed with HIV and on ART before they migrated to the Netherlands. This proportion increased from just 8.5% in 2010, to 40.8% in 2015, to 86.7% in 2019. In recent years, late initiation of ART has become rare in individuals who were first diagnosed with HIV while living in the Netherlands.

*Figure 2.1A: Time between HIV diagnosis and initiation of combination antiretroviral therapy (cART) in people starting cART in 2010–19.*




*Legend: cART=combination antiretroviral therapy.*

*Figure 2.1B: Time between entry into HIV care and initiation of combination antiretroviral therapy (cART) for people starting cART in 2010–19.*




*Legend: cART=combination antiretroviral therapy.*

The proportion of those with a known previous negative HIV test increased over the years, rising from 20.3% in the period 1996-2004, to 36.5% in 2005-09, 53.6% in 2010-14, and 56.3% in 2015-19. In addition, an increasing proportion of those starting cART had evidence of recent infection (i.e., within 12 months of a last negative HIV test); the percentage of 5.7% in 1996-2004, rose to 13.3% in 2005-09, 22.8% in 2010-14, and 26.1% in 2015-19. Over the same time period, there was an increase in the median CD4 cell count at the start of cART, followed by a stabilisation, and then a slight decrease: from 190 cells/mm$^3$ (IQR 80-320) in 1996-2004, to 230 cells/mm$^3$ (IQR 120-306) in 2005-09, 330 cells/mm$^3$ (IQR 210-458) in 2010-14, and 400 cells/mm$^3$ (IQR 200-585) in 2015-19 (p for trend <.0001). In 2019, the median CD4 cell count at the start of cART was 370 cells/mm$^3$ (IQR 180-570). Since 2016, fewer people have initiated cART per calendar year and the median CD4 cell count at cART initiation has continued to decrease. This trend is likely due to the substantial group already in care but not on cART (because of their high CD4 cells counts), which subsequently initiated cART in 2015 and 2016, when the 2015 guideline change recommended ART for all, irrespective of CD4 count.

*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.

## 1. In care and on cART in the Netherlands in 2019

Of the 25,587 people known to have initiated cART between January 1996 and December 2019, 19,489 (76.2%) were alive, receiving cART, and had a recorded visit for HIV care in the Netherlands in 2019. *Table 2.2* shows their treatment and clinical characteristics at their last clinic visit in 2019. Overall, 16,093 (82.6%) were men, and 12,615 (64.7%) were MSM. Their median age on 31 December 2019 was 51 (IQR 42-59) years. The majority (60.0%) originated from the Netherlands, followed by Latin America / the Caribbean (11.8%) and sub-Saharan Africa (11.7%).

*Table 2.2: Characteristics of people receiving combination antiretroviral therapy and known to be in care in 2019.*

| Year of cART initiation | | 1996–2004 | 2005–2009 | 2010–2014 | 2015–2019 | All |
|---|---|---|---|---|---|---|
| Total | n | 5,244 | 4,160 | 5,952 | 4,133 | **19,489** |
| | % | 26.91 | 21.4 | 30.5 | 21.2 | **100** |
| Male sex | n | 4,049 | 3,319 | 5,172 | 3,553 | **16,093** |
| | % | 77.2 | 79.8 | 86.9 | 86.0 | **82.6** |
| Age on 31 December 2019 | Median | 57.0 | 52.2 | 47.7 | 41.3 | **51.0** |
| | Q1 | 51.4 | 45.6 | 39.4 | 32.4 | **41.9** |
| | Q3 | 63.3 | 58.7 | 55.7 | 52.2 | **58.6** |
| Transmission risk group | | | | | | |
| No data | n | 6 | 2 | 7 | 9 | **24** |
| | % | 0.1 | 0.1 | 0.1 | 0.2 | **0.1** |
| Men who have sex with men | n | 3,04 | 2,563 | 4,235 | 2,782 | **12,615** |
| | % | 57.9 | 61.6 | 71.2 | 67.3 | **64.7** |
| Heterosexual contact | n | 1,747 | 1,317 | 1,423 | 1,022 | **5,509** |
| | % | 33.3 | 31.7 | 23.9 | 24.7 | **28.3** |
| Injecting drug use | n | 152 | 56 | 31 | 17 | **256** |
| | % | 2.9 | 1.4 | 0.5 | 0.4 | **1.3** |
| Blood or blood products | n | 95 | 40 | 46 | 41 | **222** |
| | % | 1.8 | 1.0 | 0.8 | 1.0 | **1.1** |
| Vertical transmission | n | . | . | 3 | 2 | **5** |
| | % | . | . | 0.1 | 01 | **0.0** |
| Other/unknown | n | 209 | 182 | 207 | 260 | **858** |
| | % | 4.0 | 4.4 | 3.5 | 63 | **4.4** |
| Region of origin | | | | | | |
| No data | n | 18 | 9 | 14 | 29 | **70** |
| | % | 0.3 | 0.2 | 0.2 | 0.7 | **0.4** |
| The Netherlands | n | 3,126 | 2,470 | 3,802 | 2,308 | **11,706** |
| | % | 59.6 | 59.4 | 63.9 | 55.8 | **60.1** |
| Western Europe/North America/Australia | n | 415 | 251 | 338 | 223 | **1,227** |
| | % | 7.9 | 6.0 | 5.7 | 5.4 | **6.3** |
| Eastern/central Europe | n | 80 | 99 | 258 | 290 | **727** |
| | % | 1.5 | 2.4 | 4.3 | 7.0 | **3.7** |
| Latin America and the Caribbean | n | 543 | 493 | 666 | 588 | **2,290** |
| | % | 10.4 | 11.9 | 11.2 | 14.2 | **11.8** |
| Sub-Saharan Africa | n | 787 | 598 | 520 | 374 | **2,279** |
| | % | 15.0 | 14.4 | 8.7 | 9.1 | **11.7** |
| Other | n | 275 | 240 | 354 | 321 | **1,190** |
| | % | 5.2 | 5.8 | 6.0 | 7.8 | **6.1** |

| Year of cART initiation | | 1996–2004 | 2005–2009 | 2010–2014 | 2015–2019 | All |
|---|---|---|---|---|---|---|
| cART regimen | | | | | | |
| TDF/3TC/DOR | n | 21 | 23 | 49 | 22 | **115** |
| | % | 0.4 | 0.6 | 0.8 | 0.5 | **0.6** |
| TDF/FTC/EFV | n | 368 | 563 | 544 | 91 | **1,566** |
| | % | 7.0 | 13.5 | 9.1 | 2.2 | **8.0** |
| TDF/FTC/NVP | n | 517 | 311 | 284 | 14 | **1,126** |
| | % | 9.9 | 7.5 | 4.8 | 0.3 | **5.8** |
| TDF/FTC/RPV | n | 134 | 130 | 373 | 59 | **696** |
| | % | 2.6 | 3.1 | 6.3 | 1.4 | **3.6** |
| TDF/FTC/ATV/r | n | 68 | 88 | 101 | 17 | **274** |
| | % | 1.3 | 2.1 | 1.7 | 0.4 | **1.4** |
| TDF/FTC/DRV/b | n | 137 | 118 | 227 | 66 | **548** |
| | % | 2.6 | 2.8 | 3.8 | 1.6 | **2.8** |
| TDF/FTC/LPV/r | n | 9 | 9 | 5 | . | **23** |
| | % | 0.2 | 0.2 | 0.1 | . | **0.1** |
| TDF/FTC/DTG | n | 121 | 105 | 170 | 306 | **702** |
| | % | 2.3 | 2.5 | 2.9 | 7.4 | **3.6** |
| TDF/FTC/EVG/c | n | 93 | 92 | 280 | 174 | **639** |
| | % | 1.8 | 2.2 | 4.7 | 4.2 | **3.3** |
| TDF/FTC/RAL | n | 42 | 50 | 77 | 27 | **196** |
| | % | 0.8 | 1.2 | 1.3 | 0.7 | **1.0** |
| ABC/3TC/NVP | n | 26 | 106 | 65 | 2 | **428** |
| | % | 4.9 | 2.6 | 1.1 | 0.1 | **2.2** |
| ABC/3TC/DTG | n | 489 | 551 | 846 | 1,151 | **3,037** |
| | % | 9.3 | 13.3 | 14.2 | 27.9 | **15.6** |
| TAF/FTC/NVP | n | 347 | 183 | 148 | 6 | **684** |
| | % | 6.6 | 4.4 | 2.5 | 0.2 | **3.5** |
| TAF/FTC/RPV | n | 189 | 226 | 463 | 140 | **1,018** |
| | % | 3.6 | 5.4 | 7.8 | 3.4 | **5.2** |
| TAF/FTC/DRV/c | n | 280 | 232 | 337 | 226 | **1,075** |
| | % | 5.3 | 5.6 | 5.7 | 5.5 | **5.5** |
| TAF/FTC/BIC | n | 327 | 257 | 389 | 584 | **1,557** |
| | % | 6.2 | 6.2 | 6.5 | 14.1 | **8.0** |
| TAF/FTC/DTG | n | 116 | 116 | 161 | 179 | **572** |
| | % | 2.2 | 2.8 | 2.7 | 4.3 | **2.9** |
| TAF/FTC/EVG/c | n | 459 | 505 | 984 | 843 | **2,791** |
| | % | 8.8 | 12.1 | 16.5 | 20.4 | **14.3** |
| 2DR: NNRTI+INSTI | n | 52 | 15 | 20 | 9 | **96** |
| | % | 1.0 | 0.4 | 0.3 | 0.2 | **0.5** |
| 2DR: PI+INSTI | n | 204 | 55 | 58 | 29 | **346** |
| | % | 3.9 | 1.3 | 10.0 | 0.7 | **1.8** |

| Year of cART initiation | | 1996–2004 | 2005–2009 | 2010–2014 | 2015–2019 | All |
|---|---|---|---|---|---|---|
| 2DR: NRTI+INSTI | n | 41 | 33 | 55 | 59 | **188** |
| | % | 0.8 | 0.8 | 0.9 | 1.4 | **1.0** |
| Other:2NRTI+NNRTI | n | 184 | 90 | 47 | 13 | **334** |
| | % | 3.5 | 2.2 | 0.8 | 0.3 | **1.7** |
| Other:2NRTI+PI | n | 147 | 133 | 104 | 22 | **406** |
| | % | 2.8 | 3.2 | 1.8 | 0.5 | **2.1** |
| Other:2NRTI+INSTI | n | 85 | 63 | 75 | 35 | **258** |
| | % | 1.6 | 1.5 | 1.3 | 0.9 | **1.3** |
| Other: 2DR | n | 55 | 14 | 15 | 5 | **89** |
| | % | 1.1 | 0.3 | 0.3 | 0.1 | **0.5** |
| Other: NRTI+PI+INSTI (3ARVs) | n | 65 | 9 | 8 | 5 | **87** |
| | % | 1.2 | 0.2 | 0.1 | 0.1 | **0.5** |
| Other: NRTI+PI+INSTI (4ARVs) | n | 132 | 32 | 25 | 30 | **219** |
| | % | 2.5 | 0.8 | 0.4 | 0.7 | **1.1** |
| Other | n | 307 | 51 | 42 | 19 | **419** |
| | % | 5.9 | 1.2 | 0.7 | 0.5 | **2.2** |
| CD4:CD8 ratio | | | | | | |
| No data | n | 636 | 521 | 779 | 603 | **2,539** |
| | % | 12.1 | 12.5 | 13.1 | 14.6 | **13.0** |
| <0.50 | n | 834 | 551 | 699 | 960 | **3,044** |
| | % | 15.9 | 13.3 | 11.7 | 23.2 | **15.6** |
| ≥0.50 <1.00 | n | 2,343 | 2,005 | 2,740 | 1,622 | **8,710** |
| | % | 44.7 | 48.2 | 46.0 | 39.3 | **44.7** |
| ≥1.00 | n | 1,431 | 1,083 | 1,734 | 948 | **5,196** |
| | % | 27.3 | 26.0 | 29.1 | 23.0 | **26.7** |
| CD4 count (cells/mm$^3$) | | | | | | |
| No data | n | 12 | 6 | 14 | 33 | **65** |
| | % | 0.2 | 0.1 | 0.2 | 0.8 | **0.3** |
| <50 | n | 11 | 10 | 4 | 20 | **45** |
| | % | 0.2 | 0.2 | 0.1 | 0.5 | **0.2** |
| 50–199 | n | 98 | 53 | 58 | 154 | **363** |
| | % | 1.9 | 1.3 | 1.0 | 3.7 | **1.9** |
| 200–349 | n | 351 | 241 | 293 | 430 | **1,315** |
| | % | 6.7 | 5.8 | 4.9 | 10.4 | **6.8** |
| 350–499 | n | 817 | 616 | 750 | 578 | **2,761** |
| | % | 15.6 | 14.8 | 12.6 | 14.0 | **14.2** |
| 500–749 | n | 1,817 | 1,584 | 2,121 | 1,235 | **6,757** |
| | % | 34.7 | 38.1 | 35.6 | 29.9 | **34.7** |
| ≥750 | n | 2,138 | 1,650 | 2,712 | 1,683 | **8,183** |
| | % | 40.8 | 39.7 | 45.6 | 40.7 | **42.0** |

| Year of cART initiation | | 1996–2004 | 2005–2009 | 2010–2014 | 2015–2019 | All |
|---|---|---|---|---|---|---|
| Viral load <50 copies/ml | | | | | | |
| No data | n | 5 | 4 | 3 | 9 | **21** |
| | % | 0.1 | 0.1 | 0.1 | 0.2 | **0.1** |
| Yes | n | 4,696 | 3,685 | 5,345 | 3,522 | **17,248** |
| | % | 89.6 | 88.6 | 89.8 | 85.2 | **88.5** |
| No | n | 543 | 471 | 604 | 602 | **2220** |
| | % | 10.4 | 11.3 | 10.2 | 14.6 | **11.4** |
| Viral load <200 copies/ml | | | | | | |
| No data | n | 5 | 4 | 3 | 9 | **21** |
| | % | 0.1 | 0.1 | 0.1 | 0.2 | **0.1** |
| Yes | n | 5,147 | 4,080 | 5,855 | 3,957 | **19,039** |
| | % | 98.2 | 98.1 | 98.4 | 95.7 | **97.7** |
| No | n | 92 | 76 | 94 | 167 | **429** |
| | % | 1.8 | 1.8 | 1.6 | 4.0 | **2.2** |

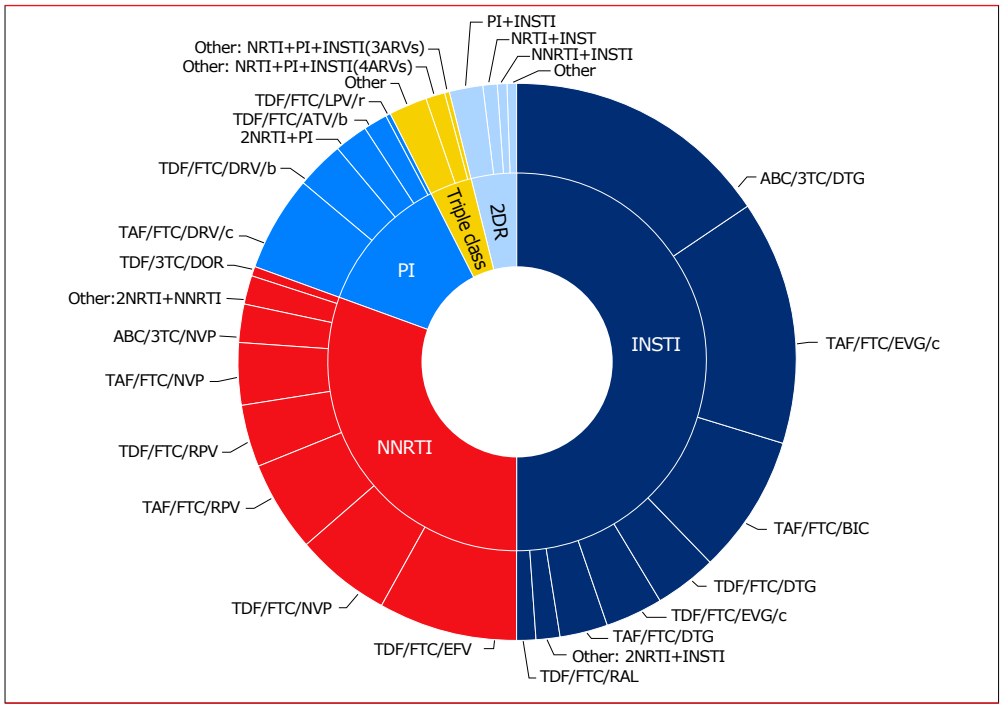
***Legend:*** *3TC=lamivudine; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; ARVs=antiretroviral drugs; BIC=bictegravir; cART=combination antiretroviral therapy; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine;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

Among the 19,720 people in HIV care and on cART in 2019, the vast majority (92.5%) received a regimen based on two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with either an integrase inhibitor (INSTI) (50.0%), an NNRTI (30.6%), or a protease inhibitor (PI) (11.9%). The distribution of cART use among the population in care in 2019 is presented in *Figure 2.2*. The most common regimens were abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (15.6%), tenofovir alafenamide (TAF)/FTC/elvitegravir (EVG)/cobicistat (14.3%), tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/efavirenz (EFV) (8.0%), tenofovir alafenamide (TAF)/FTC/bictegravir (BIC) (8.0%), and tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/nevirapine (NVP) (5.8%). The proportion of the population in care in 2019 using TDF continued to decline (from 46.4% in 2017, to 35.3% in 2018, and 31.9% in 2019), while the proportion using TAF continued to increase (from 24.4% of the population in care in 2017, to 33.2% in 2018, and 42.1% in 2019). Zidovudine was still used by 167 individuals (0.9%, mostly in combination with lamivudine). In total, 606 (3.1%) and 422 (2.2%) individuals used a cART regimen without any NRTI or with just one. There were 719 (3.6%) individuals who used a two-drug regimen (excluding pharmacological boosters): the most common two-drug regimen were a combination of PI+INSTI (346, 48.1%, of which 98.3% used

darunavir plus either dolutegravir (87.6%), or raltegravir (12.4%)); NRTI+INSTI (188, 26.1%, of which 97.3% used lamivudine and 99.5% dolutegravir); NNRTI+INSTI (96, 13.4%, of which 92% used rilpivirine and 93.8% used dolutegravir); and NRTI+PI (57, 7.9%, of which 77.2% used lamivudine, 5.3% used emtricitabine, 10.5% used TDF, 86.0% used darunavir, 7.0% used atazanavir, and 5.3% used lopinavir).

Of those with a plasma HIV RNA measurement in 2019, 88.5% had a viral load <50 copies/ml, and 97.6% had a viral load <200 copies/ml. On the basis of the last available CD4 and CD8 cell count measurements in 2015-19, 76.7% had a CD4 cell count of 500 cells/mm$^3$ or higher, and 26.7% had a CD4:CD8 ratio of 1 or higher.

*Figure 2.2: Combination antiretroviral therapy (cART) use in 2019.*



## 2. Changes in the use of the initial cART regimen

Data from recent clinical trials on new antiretroviral drugs, such as bictegravir, dolutegravir, EVG/c, and TAF, have shown good outcomes in terms of viral suppression, convenience, tolerability, and toxicity. Over the past years, these new antiretroviral drugs and new, once-daily, fixed-dose 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 2013–19.*

| Medicine | Authorisation date |
|---|---|
| TDF/FTC/EVG/cobicistat (Stribild®) | 24 May 2013 |
| Cobicistat (Tybost®) | 19 September 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 |

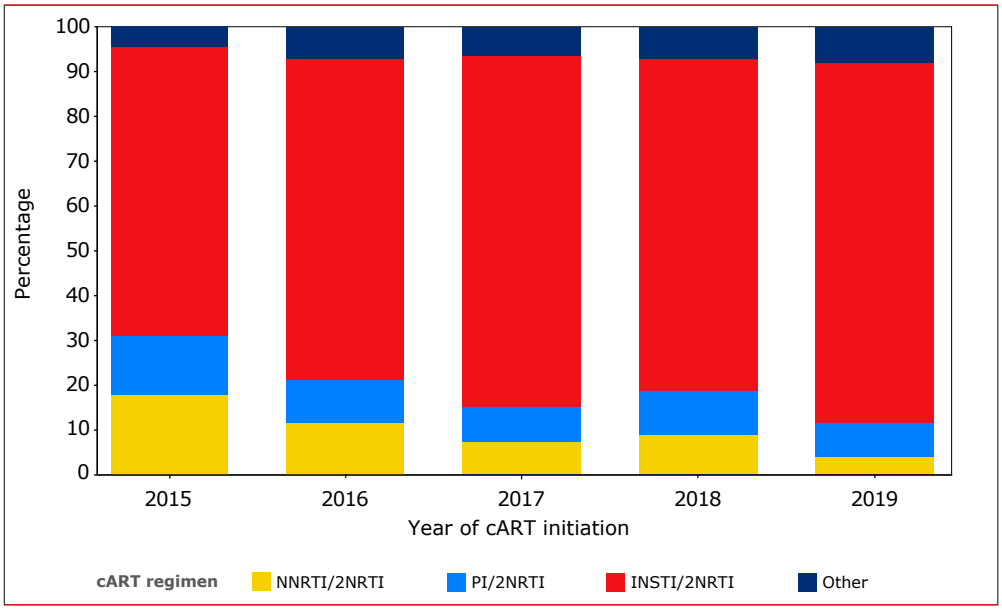
***Legend:** 3TC=lamivudine; ABC=abacavir; BIC = bictegravir; DTG=dolutegravir; DRV=darunavir; EVG=elvitegravir; FTC=emtricitabine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; RPV=rilpivirine.*

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

## Initial cART regimen

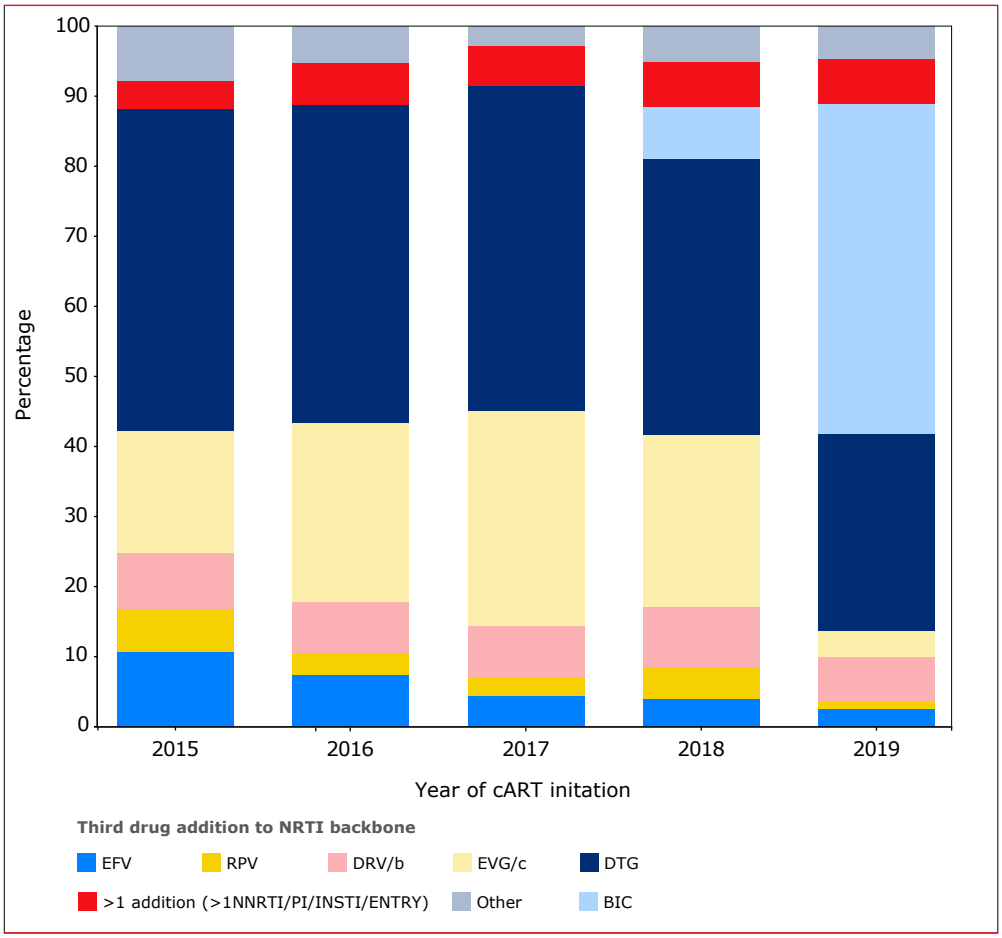
Of the 25,587 people known to have initiated cART between January 1996 and December 2019, 4,581 (17.9%) started cART between January 2015 and December 2019. *Figures 2.3 and 2.4* show the trends over time in third-drug additions to the NRTI backbone used as part of the initial cART regimen in these individuals. The use of integrase inhibitors in combination with an NRTI backbone as initial therapy, continued to rise from 64.4% in 2015, to 71.7% in 2016, 78.4% in 2017, 74.0% in 2018, and 80.7% in 2019. EVG/c was introduced in the Netherlands at the end of 2013 and was used in 17.4%, 25.6%, 31.0%, and 24.4% of the initial regimens in 2015, 2016, 2017, and 2018, respectively, before use dropped sharply to 3.6% in 2019. Dolutegravir was introduced in the Netherlands in 2014 and was used in 46.1%, 45.4%, 46.2%, 39.5%, and 28.2% of the initial regimens in 2015, 2016, 2017, 2018, and 2019, respectively. Bictegravir was introduced in the Netherlands in 2018 and was used in 7.4%, and 47.1% of the initial regimens in 2018 and 2019, respectively. The use of NNRTIs in the initial regimen decreased from 18.0% in 2015 to 11.8% in 2016, 7.4% in 2017, 8.9% in 2018, and 4.2% in 2019. The use of protease inhibitors in the initial regimen decreased from 13.1% in 2015 to 9.4% in 2016, 7.9% in 2017, 10.0% in 2018, and 7.4% in 2019. In 2015-19, 5.4% 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), with or without the addition of NRTI. *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 2015-19. The use of nevirapine, atazanavir, lopinavir, raltegravir, and doravirine as "third additions" to initial regimens did not exceed 5% in any year in the period 2015-19. As a result, those regimens are not shown in figure 2.4. Instead, these agents are categorised in the 'other' group. Dual therapy initial regimens were used too infrequently to be included as a separate category in figure 2.4: in this period, only 60 initial regimens containing fewer than three agents were recorded, 42 of which contained an integrase inhibitor as monotherapy, or combined with either one NRTI or one boosted PI.

*Figure 2.3: Third-drug class additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2015–19.*




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

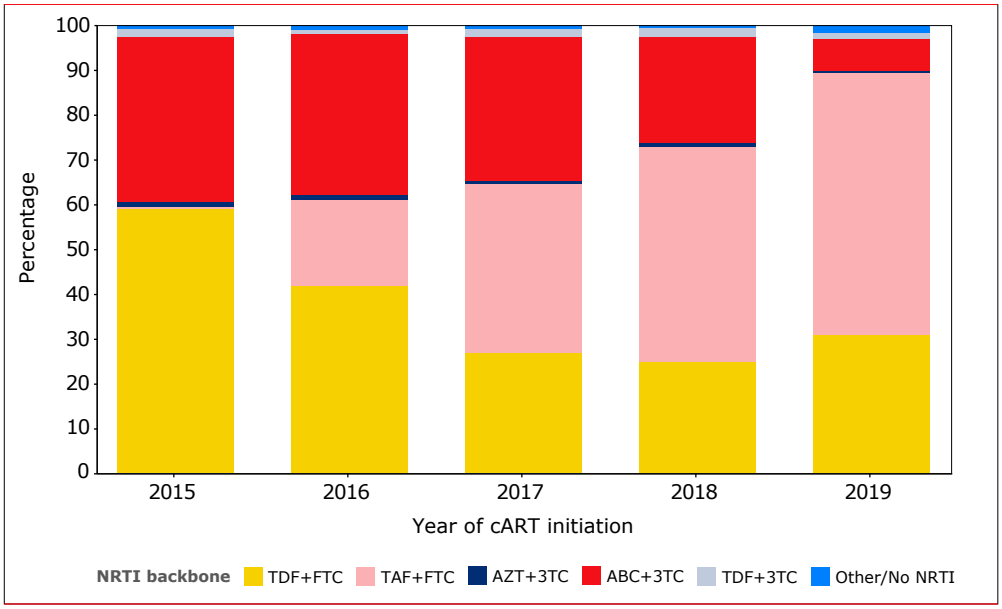
*Figure 2.4: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2015-19.*




*Legend: cART=combination antiretroviral therapy; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /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 between 2015 and 2019. 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 19.3%, 37.8%, 48.2%, and 58.4% of the initial regimens in 2016, 2017, 2018, and 2019, respectively. At the same time, TDF use decreased from 60.9% in 2015 to 26.5% in 2018, and then increased to 32.5% in 2019, probably because of a sharp decrease in the use of abacavir-containing NRTI backbones in 2019. The use of abacavir in combination with lamivudine decreased from 36.8% of all initial regimens in 2015 to 23.7% in 2018, after which there was a sharp decrease to 6.9% in 2019. The combination of zidovudine and lamivudine, often used by migrants who initiated cART before arriving in the Netherlands, has further decreased to <1% since 2016.

***Figure 2.5:*** *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2015–19.*




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

The cART regimens initiated between 2015 and 2019 are presented in *Figure 2.6* and *Table 2.3*. In 2019, the most frequently used initial regimen was TAF/FTC/bictegravir (47.1%). Dolutegravir-containing initial regimens were used in 27.3% of cases: combined with either abacavir and lamivudine as part of the once-daily, fixed-dose combination (6.9%), or provided with emtricitabine and tenofovir separately (TDF 18.5%/TAF 1.9%). Additionally, 3.6% initiated an EVG/c-containing once-daily, fixed-dose combination with emtricitabine and tenofovir (TDF 1.0%/TAF 2.7%). Raltegravir use in an initial regimen was 1.3% in 2019. The combination of ritonavir or cobicistat-boosted darunavir with tenofovir and emtricitabine was used in 6.5% of initial cART regimens in 2019: 1.7% based on TDF and 4.8% on the once-daily, fixed-dose combination with TAF. *Table 2.3* provides more detail on the 'other' initial regimens that are not further specified in *Figures 2.4-2.6*

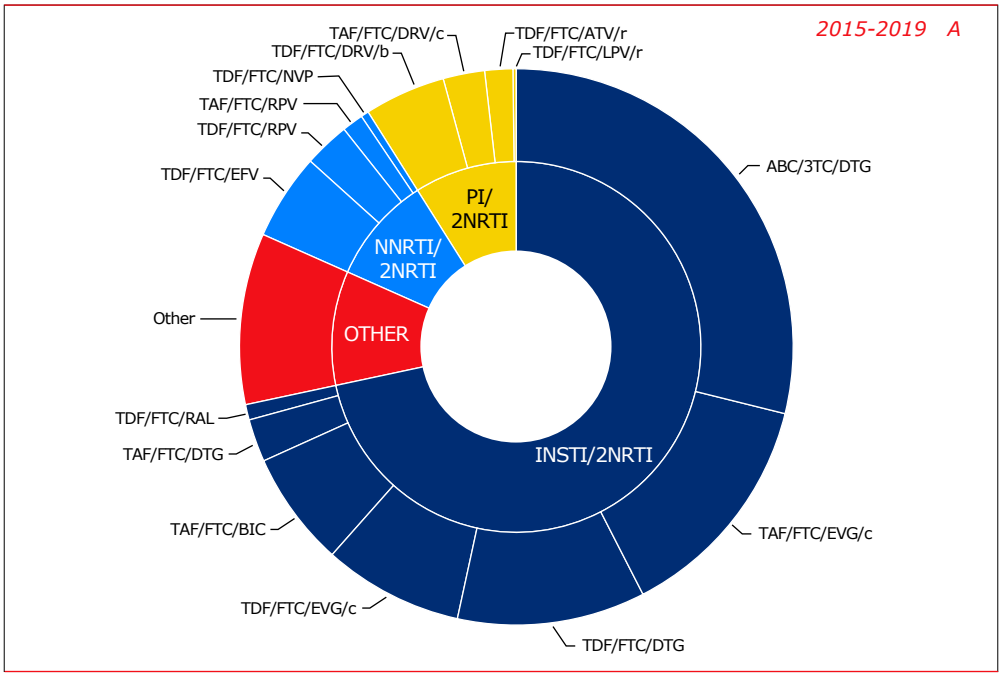
***Table 2.3:** Initial regimen in 2015–19.*

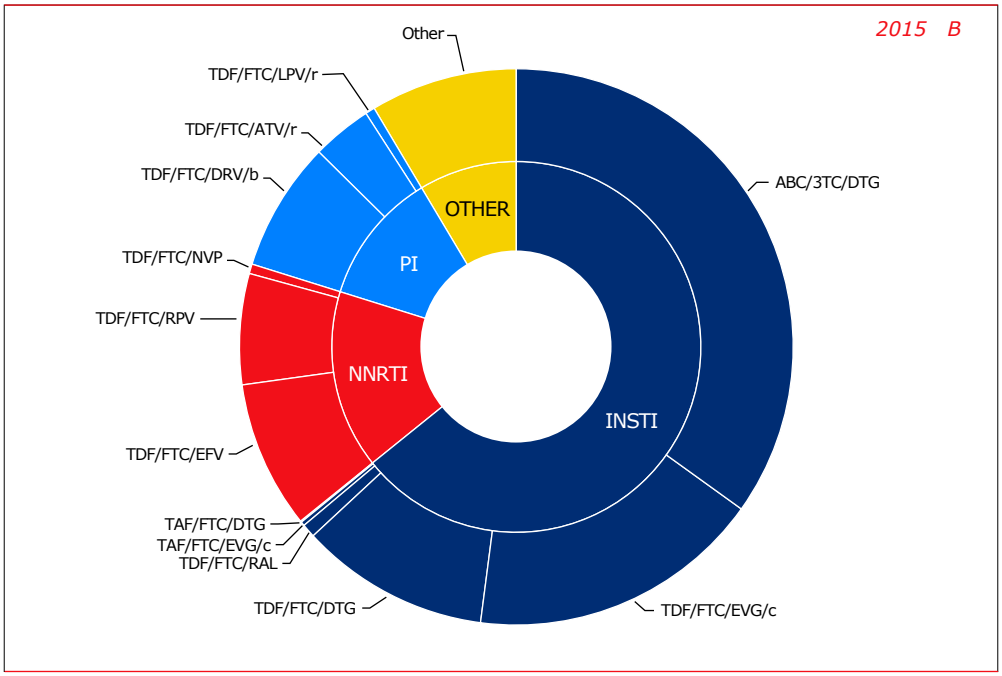
| Regimen | | 2015 | 2016 | 2017 | 2018 | 2019 | 2015–2019 |
|---|---|---|---|---|---|---|---|
| Total | n | 1,258 | 1,065 | 950 | 784 | 524 | **4,581** |
| TDF/FTC/EFV | n | 108 | 65 | 25 | 23 | 9 | 230 |
| | % | 8.6 | 6.1 | 2.6 | 2.9 | 1.7 | 5.0 |
| TDF/FTC/NVP | n | 7 | 9 | 2 | 2 | 1 | 21 |
| | % | 0.6 | 0.9 | 0.2 | 0.3 | 0.2 | 0.5 |
| TDF/FTC/RPV | n | 81 | 30 | 8 | 1 | 2 | 122 |
| | % | 6.4 | 2.8 | 0.8 | 0.1 | 0.4 | 2.7 |
| TDF/FTC/DRV/b | n | 95 | 67 | 35 | 11 | 9 | 217 |
| | % | 7.6 | 6.3 | 3.7 | 1.4 | 1.7 | 4.7 |
| TDF/FTC/ATV/b | n | 44 | 17 | 4 | 6 | 4 | 75 |
| | % | 3.5 | 1.6 | 0.4 | 0.8 | 0.8 | 1.6 |
| TDF/FTC/LPV | n | 7 | 1 | 1 | . | . | 9 |
| | % | 0.6 | 0.1 | 0.1 | . | . | 0.2 |
| TDF/FTC/EVG/c | n | 216 | 85 | 53 | 15 | 5 | 374 |
| | % | 17.2 | 8.0 | 5.6 | 1.9 | 1.0 | 8.2 |
| TDF/FTC/DTG | n | 139 | 103 | 82 | 82 | 97 | 503 |
| | % | 11.1 | 9.7 | 8.6 | 10.5 | 18.5 | 11.0 |
| TDF/FTC/RAL | n | 10 | 7 | 5 | 12 | 7 | 41 |
| | % | 0.8 | 0.7 | 0.5 | 1.5 | 1.3 | 0.9 |
| ABC/3TC/DTG | n | 439 | 370 | 297 | 180 | 36 | 1322 |
| | % | 34.9 | 34.7 | 31.3 | 23.0 | 6.9 | 28.9 |
| TAF/FTC/RPV | n | . | 5 | 16 | 33 | 3 | 57 |
| | % | . | 0.5 | 1.7 | 4.2 | 0.6 | 1.2 |

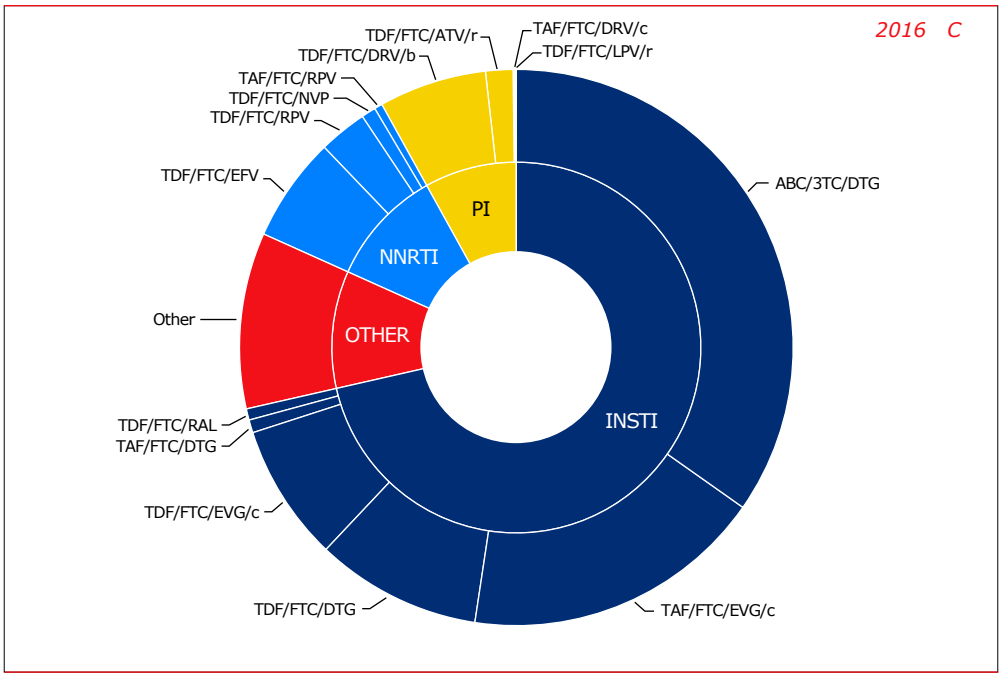
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| TAF/FTC/DRV/c | n | . | 1 | 30 | 55 | 25 | 111 |
| | % | . | 0.1 | 3.2 | 7.0 | 4.8 | 2.4 |
| TAF/FTC/EVG/c | n | 3 | 188 | 241 | 176 | 14 | 622 |
| | % | 0.2 | 17.7 | 25.4 | 22.5 | 2.7 | 13.6 |
| TAF/FTC/DTG | n | 1 | 8 | 54 | 41 | 10 | 114 |
| | % | 0.1 | 0.8 | 5.7 | 5.2 | 1.9 | 2.5 |
| TAF/FTC/BIC | n | . | . | 2 | 58 | 247 | 307 |
| | % | . | . | 0.2 | 7.4 | 47.1 | 6.7 |
| Other: 2NRTI+NNRTI | n | 30 | 17 | 19 | 11 | 7 | 84 |
| | % | 2.4 | 1.6 | 2 | 1.4 | 1.3 | 1.8 |
| Other: 2NRTI+PI | n | 19 | 14 | 5 | 6 | 1 | 45 |
| | % | 1.5 | 1.3 | 0.5 | 0.8 | 0.2 | 1.0 |
| Other: 2NRTI+INST | n | 2 | 3 | 11 | 16 | 7 | 39 |
| | % | 0.2 | 0.23 | 1.2 | 2.0 | 1.3 | 0.9 |
| Other: NNRTI+INST | n | . | . | . | . | 1 | 1 |
| | % | . | . | . | . | 0.2 | 0.0 |
| Other: PI+INSTI | n | 5 | 7 | 7 | 3 | 2 | 24 |
| | % | 0.4 | 0.7 | 0.7 | 0.4 | 0.4 | 0.5 |
| Other: NRTI+PI+INSTI (3ARVs) | n | 2 | . | 1 | 1 | 1 | 5 |
| | % | 0.2 | . | 0.1 | 0.1 | 0.2 | 0.1 |
| Other: NRTI+PI+INSTI (4ARVs) | n | 42 | 58 | 52 | 48 | 32 | 232 |
| | % | 3.3 | 5.5 | 5.5 | 6.1 | 6.1 | 5.1 |
| Other | n | 8 | 10 | . | 4 | 4 | 26 |
| | % | 0.6 | 0.9 | . | 0.5 | 0.8 | 0.6 |

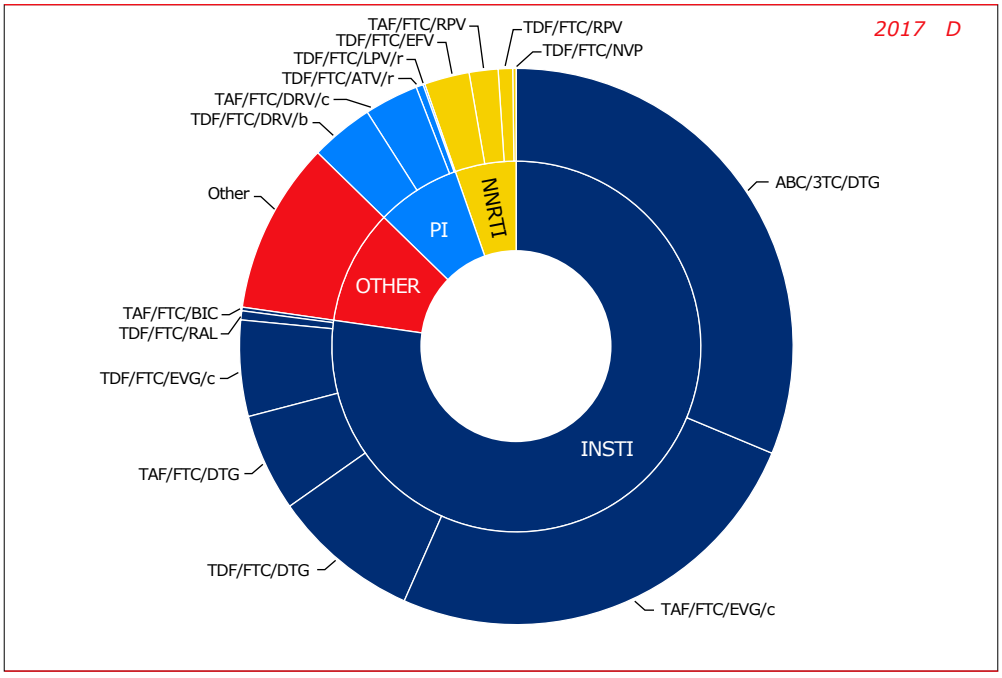
***Legend:*** *ARVs=antiretroviral drugs; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; ATV= atazanavir; BIC=bictegravir; CI=confidence interval; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; LPV=lopinavir;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

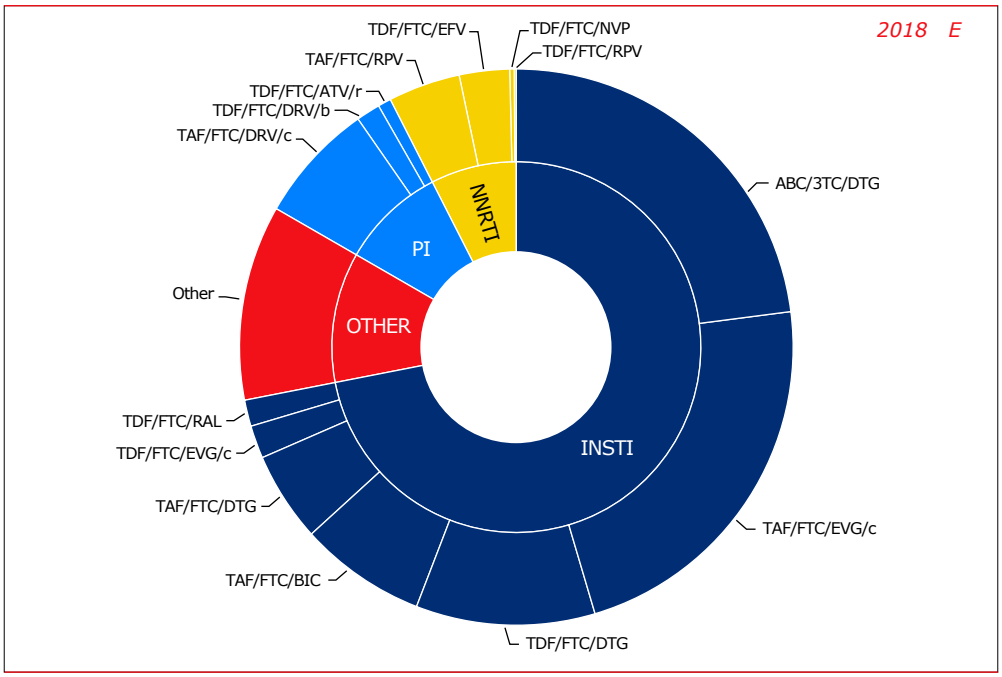
*Figure 2.6A–F: Initial combination antiretroviral therapy regimens in 2015–19.*

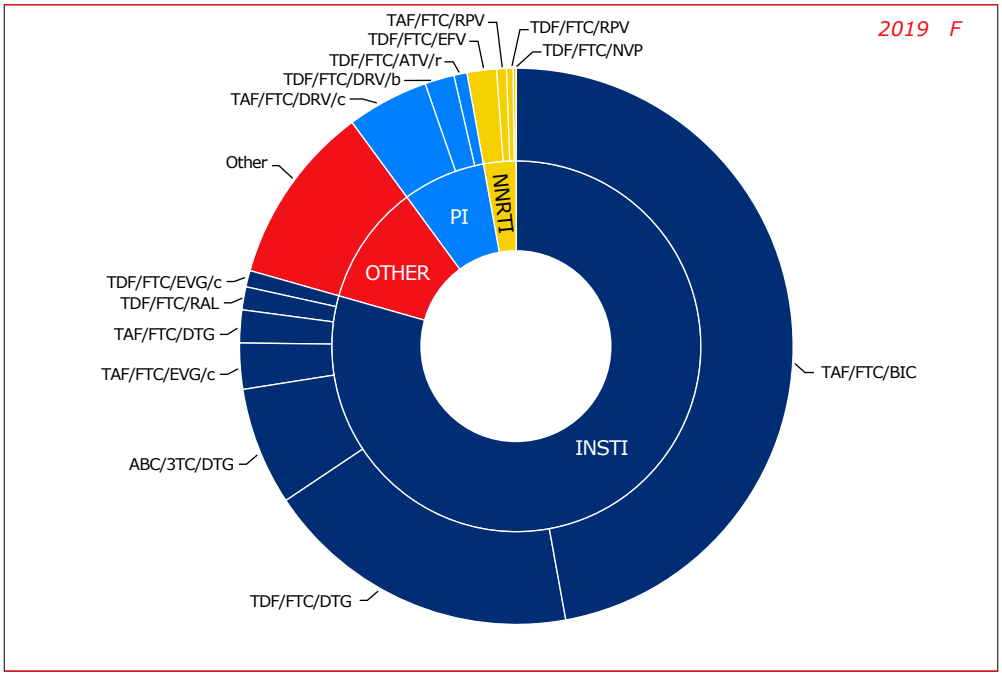



2016 C
TDF/FTC/ATV/r
TAF/FTC/DRV/c
TDF/FTC/DRV/b
TDF/FTC/LPV/r
TAF/FTC/RPV
TDF/FTC/NVP
TDF/FTC/RPV
TDF/FTC/EFV
ABC/3TC/DTG
PI
NNRTI
Other
OTHER
INSTI
TDF/FTC/RAL
TAF/FTC/DTG
TDF/FTC/EVG/c
TDF/FTC/DTG
TAF/FTC/EVG/c


2017 D
TAF/FTC/RPV
TDF/FTC/RPV
TDF/FTC/EFV
TDF/FTC/NVP
TDF/FTC/LPV/r
TDF/FTC/ATV/r
TAF/FTC/DRV/c
TDF/FTC/DRV/b
ABC/3TC/DTG
Other
PI
NNRTI
OTHER
TAF/FTC/BIC
TDF/FTC/RAL
TDF/FTC/EVG/c
INSTI
TAF/FTC/DTG
TDF/FTC/DTG
TAF/FTC/EVG/c



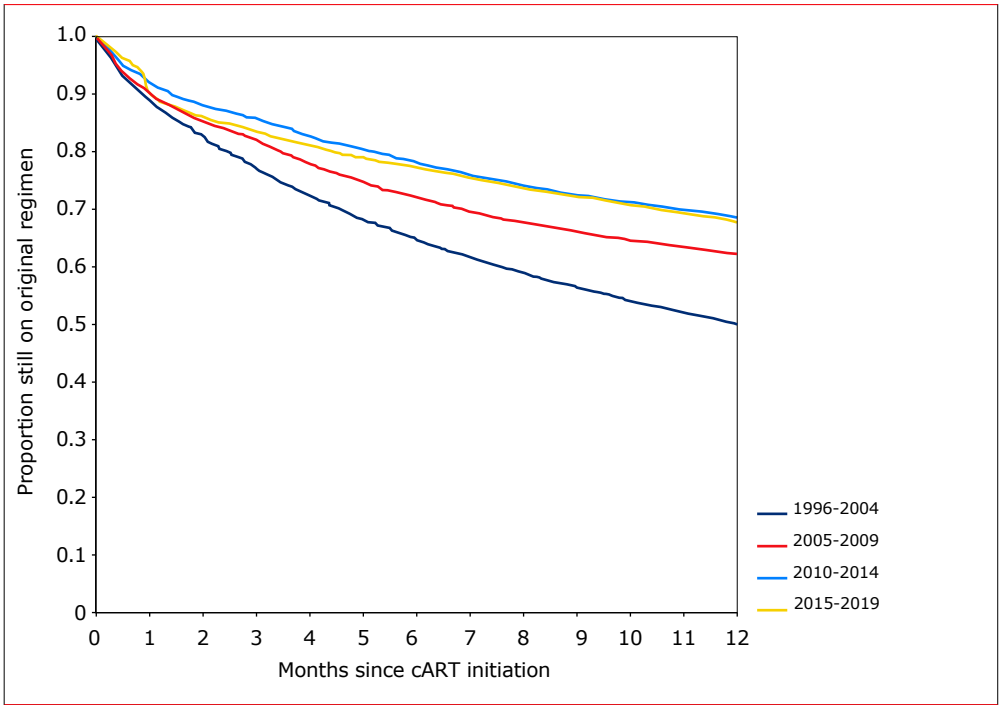

***Legend:*** *3TC=lamivudine; ABC=abacavir; ATV=atazanavir; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; INSTI=integrase inhibitor; LPV=lopinavir; NNRTI=non-nucleoside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

## Discontinuation of the initial cART regimen

For the 25,587 people who started cART between 1996 and 2019, we assessed the time spent on the initial cART regimen. Discontinuation of the initial cART regimen was defined as a change in, or discontinuation of ≥one 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 1996-2019, 38.9% of individuals discontinued their initial regimen within one year. The time remaining on the initial regimen improved over the years: in 1996-2004, 50.0% discontinued their original regimen within a year, compared to approximately a third in 2000-19. The time spent on the initial regimen during the first year of cART stratified by five-year periods is shown in *Figure 2.7*.

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



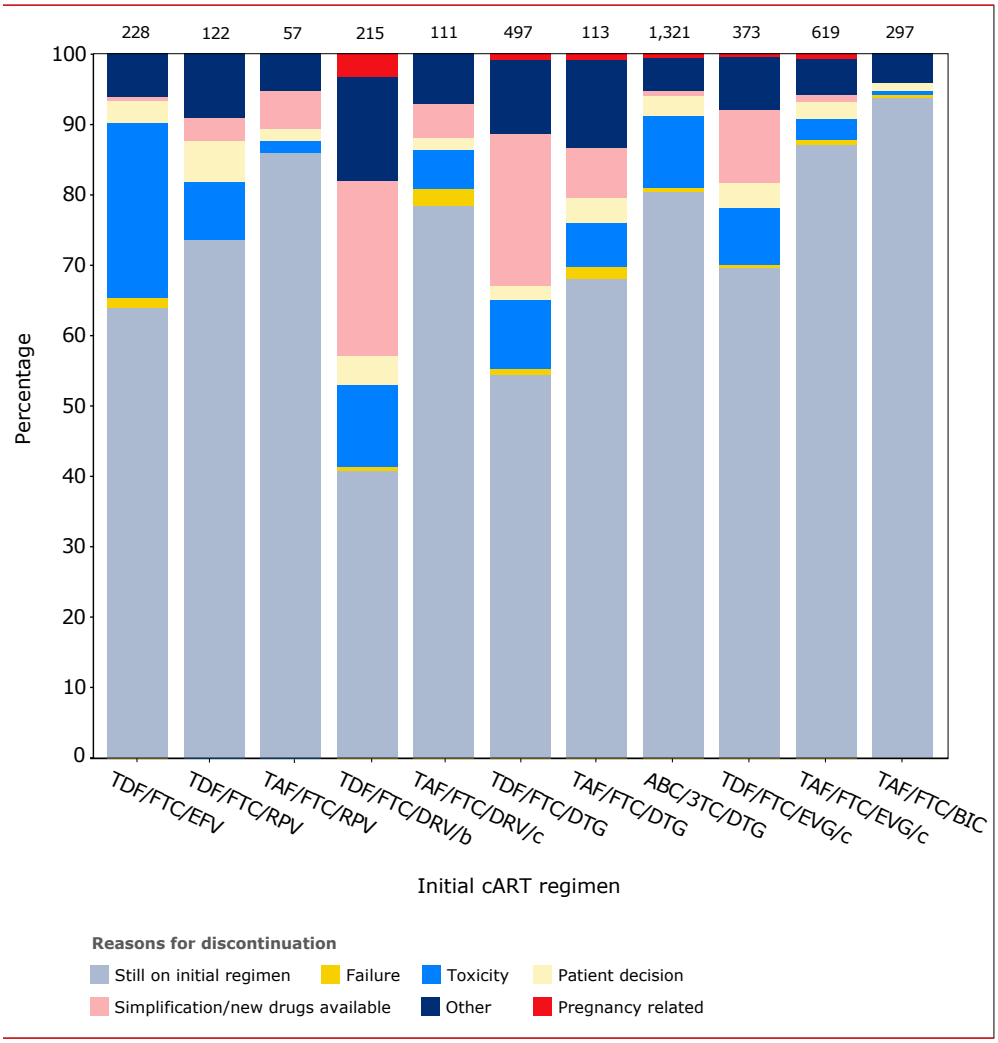

***Legend:*** *cART=combination antiretroviral therapy*

### Discontinuation of the initial cART regimen: 2015–19

We further assessed the time to discontinuation of the initial regimen during the first year of treatment among the 3,953 people who started 'common' and guideline-recommended initial regimens in 2015-19. The regimens considered in this analysis were: tenofovir disoproxil fumarate/emtricitabine combined with efavirenz (TDF/FTC/EFV, 5.7%); rilpivirine (TDF/FTC/RPV, 3.1%); ritonavir-boosted or cobicistat-boosted darunavir (TDF/FTC/DRV/b, 5.4%); cobicistat-boosted elvitegravir (TDF/FTC/EVG/c, 9.4%); dolutegravir (TDF/FTC/DTG, 12.6%); abacavir-lamivudine combined with dolutegravir (ABC/3TC/DTG, 33.4%); tenofovir alafenamide/emtricitabine combined with cobicistat-boosted elvitegravir (TAF/FTC/EVG/c, 15.7%); rilpivirine (TAF/FTC/RPV, 1.4%); dolutegravir (TAF/FTC/DTG, 2.9%); cobicistat-boosted darunavir (TAF/FTC/DRV/c, 2.8%); and bictegravir (TAF/FTC/BIC, 7.5%).

One year after cART initiation, 999 (25.3%) of the 3,953 individuals using one of these initial regimens, had discontinued it. The main reason for this discontinuation was toxicity (342, 34.2%), followed by simplification and/or availability of new drugs (232, 23.2%). 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, 27.9% of all discontinuations were for reasons of simplification and/or availability of new drugs in 2015, 24.0% in 2016, 20.2% in 2017, 18.2% in 2018, and 15.7% in 2019.

*Figure 2.8: Reasons for discontinuation of the initial regimen during the first year of treatment 2015–19, by regimen. Numbers above the bars represent the total number of individuals using that particular regimen.*

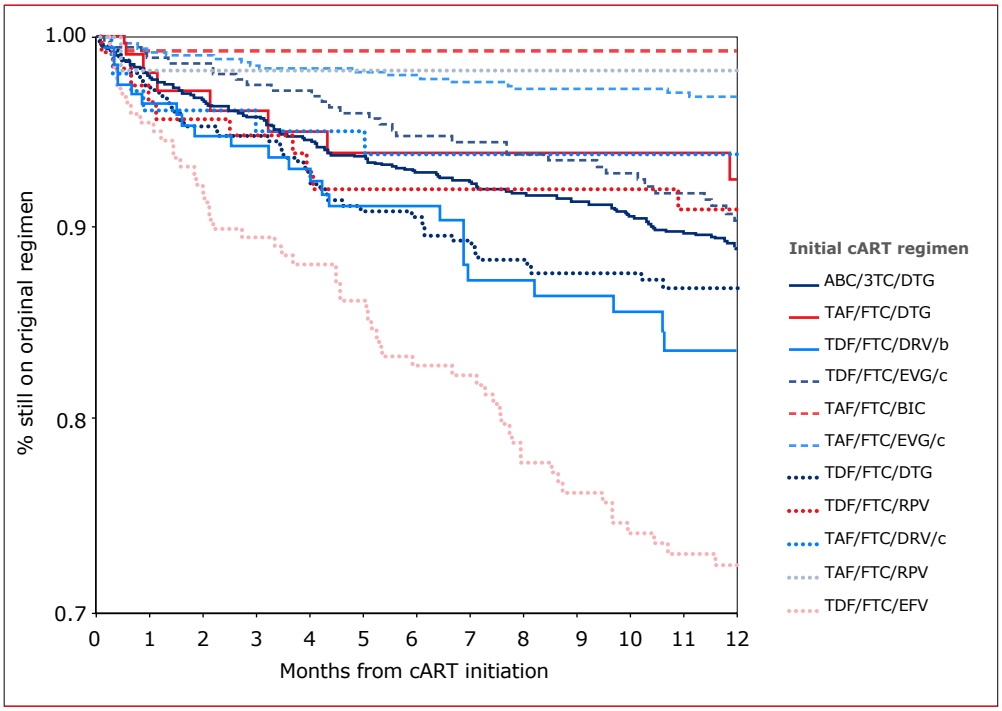



*Legend: cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir 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 2015-19, by regimen. Time was censored when the initial regimen was discontinued due to reasons other than toxicity (log-rank p<0.001).*

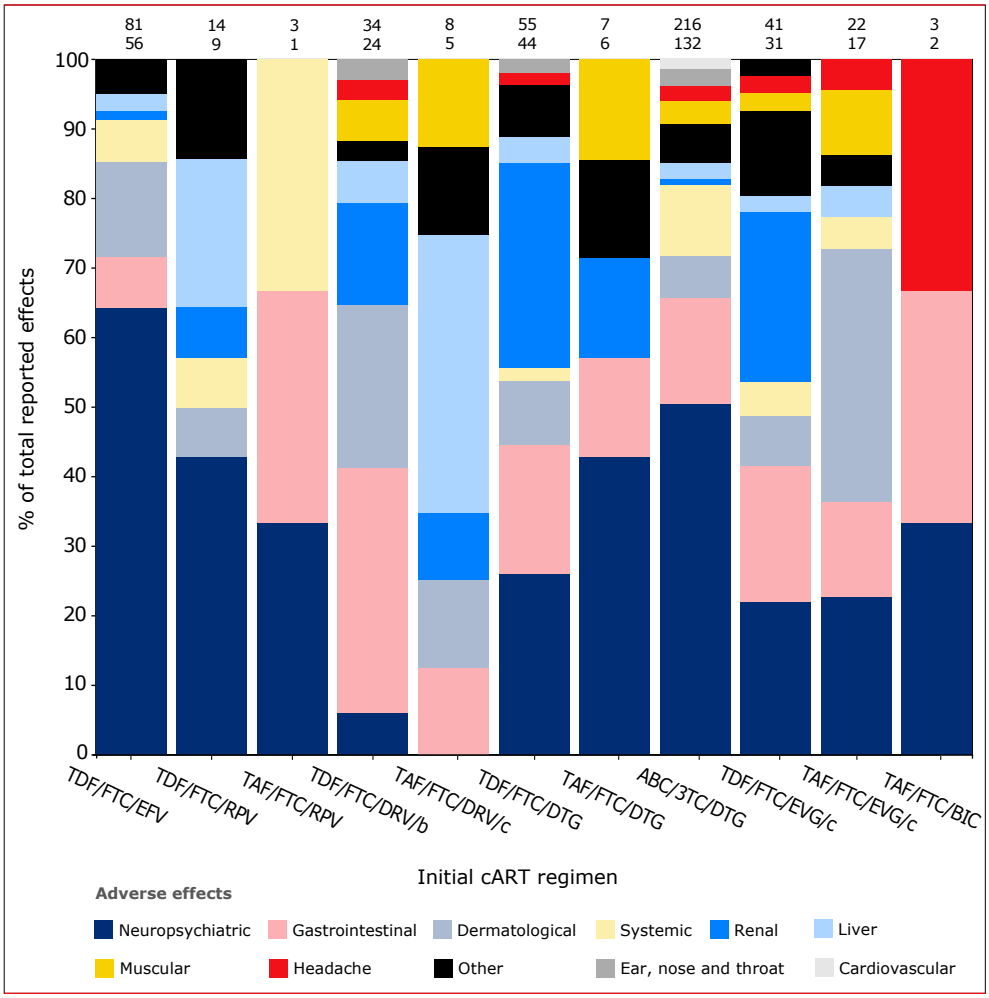



***Legend:*** *cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir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

### Adverse effects

Among the 342 individuals who discontinued their initial cART regimen within a year due to toxicity, 484 adverse effects were recorded. The predominant effects were: 41.7% neuropsychiatric (mainly insomnia, mood changes, dizziness and depression), 15.7% gastrointestinal (mainly diarrhoea and nausea), 10.3% dermatological (rash due to medication, itching), 7.9% systemic (tiredness, apathy, loss of appetite), and 7.0% renal (renal insufficiency and increased serum creatinine). These adverse effects are stratified by cART regimen in *Figure 2.10*. Neuropsychiatric effects were associated with regimens containing efavirenz and dolutegravir, and, to a lesser extent, rilpivirine and elvitegravir. Renal effects were mainly, but not exclusively reported by people who discontinued TDF-based cART.

*Figure 2.10: Adverse effects associated with initial-regimen discontinuation due to toxicity, during the first year of treatment 2015–19. The bars represent the distribution of 484 reported effects among 342 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).*




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

*Note:* The discontinuation rates and reasons for discontinuation are descriptive by nature and should be interpreted with caution. The choice of the initial cART regimen depends on personal characteristics, which might explain differences in discontinuation 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.

## Virological response

In the Netherlands, a total of 25,587 adults started cART between January 1996 and December 2019. For the current analysis of virological outcomes, we have focused on the 22,227 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 in the following section on viral response to cART are therefore restricted to the remaining 21,644 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 <100 copies/ml within six months of starting combination antiretroviral therapy (cART).
The viral load measurement closest to six months (±three months) after cART initiation was included in the analysis, irrespective of the viral load level.

### Viral suppression

Any viral load measurements <200 copies/ml, within 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 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[26].

### Acquired HIV drug resistance

High-level resistance to at least one antiretroviral drug, detected at the time of HIV viral load >500 copies/ml, among people receiving cART for at least 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[27,28].

## Initial virological success

Of the 21,644 individuals with a viral load test result after at least three months of cART initiation, 18,964 (87.6%) had a viral load measurement six months (±three months) after cART initiation. Of these people, 16,031 (84.5%) achieved initial virological success (i.e., a plasma viral load <100 HIV RNA copies/ml (*Box 2.3*)). The percentage of people with initial virological success has improved over time, from 61.1% in those starting cART between 1996 and 2003, to 88.0% in those starting between 2004 and 2010, 92.3% in those starting between 2011 and 2018, and 94.0% in those starting in 2019.

### Initial virological success of common initial cART regimens (2015–19)

We analysed initial virological success among the 4,944 adults who started a common or guideline-recommended cART regimen in 2015-19, 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); described under 'Changes in use of initial antiretroviral therapy 2015-19'), and had a viral load result within six months (±three months) of cART initiation. In total, 94.1% (95% CI 93.5-94.8) 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: 94.3% (95% CI 94.1-95.8) of those on an integrase-inhibitor-based regimen and 94.0% (95% CI 92.6-95.4) on a NNRTI-based regimen had initial virological success, compared to 89.7% (95% CI 87.3-92.1) 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 (</≥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 ≥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 <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.*

| | 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 | 627 | 12.7 | 346 | 11.0 | 97.7 | 96.1 | 99.3 | Ref. |
| TDF/FTC/RPV | 458 | 9.3 | 458 | 14.7 | 95.4 | 93.5 | 97.3 | 0.093 |
| TDF/FTC/DRV/b | 534 | 10.8 | 218 | 7.0 | 95.9 | 93.2 | 98.5 | 0.23 |
| TDF/FTC/DTG | 440 | 8.9 | 220 | 7.0 | 97.3 | 95.1 | 99.4 | 0.75 |
| TDF/FTC/EVG/c | 760 | 15.4 | 524 | 16.8 | 97.3 | 96.0 | 98.7 | 0.74 |
| ABC/3TC/DTG | 1,171 | 23.7 | 787 | 25.2 | 97.2 | 96.1 | 98.4 | 0.64 |
| TAF/FTC/RPV | 43 | 0.9 | 43 | 1.38 | 100 | 100 | 100 | 0.99 |
| TAF/FTC/DRV/c | 87 | 1.8 | 36 | 1.2 | 100 | 100 | 100 | 0.99 |
| TAF/FTC/BIC | 210 | 4.3 | 125 | 4.0 | 96.8 | 93.7 | 99.9 | 0.59 |
| TAF/FTC/DTG | 88 | 1.8 | 42 | 1.3 | 95.2 | 88.8 | 100 | 0.35 |
| TAF/FTC/EVG/c | 526 | 10.6 | 324 | 10.4 | 97.5 | 95.8 | 99.2 | 0.89 |
| Regimen class | | | | | | | | |
| NNRTI/2NRTI | 1,128 | 22.8 | 847 | 27.1 | 96.6 | 95.4 | 97.8 | Ref. |
| PI/2NRTI | 621 | 12.6 | 254 | 8.1 | 96.5 | 94.2 | 98.7 | 0.92 |
| INSTI/2NRTI | 3,195 | 64.6 | 2,022 | 64.9 | 97.2 | 96.5 | 97.9 | 0.35 |
| **All regimens** | **4,944** | **100 .0** | **3,123** | **63.2** | **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; Ref=Reference group.*

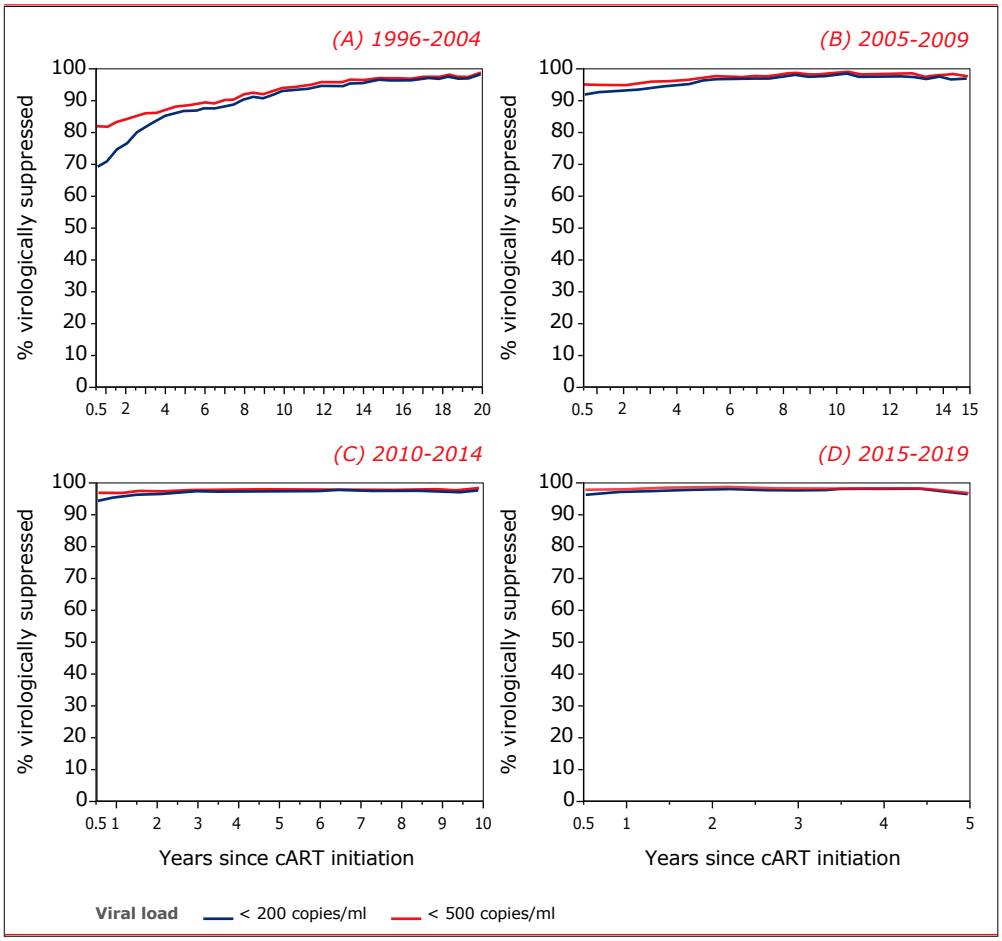
| | | By initial viral load at cART initiation | | | | | |
|---|---|---|---|---|---|---|---|
| | | ≥100,000 copies/ml | | | | | |
| | | n | % | Initial viral success | 95% CI low | 95% CI high | p-value |
| | cART regimen | | | | | | |
| | TDF/FTC/EFV | 281 | 15.4 | 86.1 | 82.1 | 90.2 | Ref. |
| | TDF/FTC/RPV | not recommended | | | | | |
| | TDF/FTC/DRV/b | 316 | 17.4 | 85.4 | 81.6 | 89.3 | 0.81 |
| | TDF/FTC/DTG | 220 | 12.1 | 90.0 | 86.0 | 94.0 | 0.19 |
| | TDF/FTC/EVG/c | 236 | 13.0 | 89.8 | 86.0 | 93.7 | 0.20 |
| | ABC/3TC/DTG | 384 | 21.1 | 92.7 | 90.1 | 95.3 | 0.0061 |
| | TAF/FTC/RPV | not recommended | | | | | |
| | TAF/FTC/DRV/c | 51 | 2.8 | 82.3 | 71.9 | 92.8 | 0.48 |
| | TAF/FTC/BIC | 85 | 4.7 | 90.6 | 84.4 | 96.8 | 0.28 |
| | TAF/FTC/DTG | 46 | 2.5 | 93.5 | 86.3 | 100 | 0.18 |
| | TAF/FTC/EVG/c | 202 | 11.1 | 91.6 | 87.8 | 95.4 | 0.067 |
| | Regimen class | | | | | | |
| | NNRTI/2NRTI | 281 | 15.4 | 86.1 | 82.1 | 90.2 | Ref. |
| | PI/2NRTI | 367 | 20.1 | 85.0 | 81.4 | 88.7 | 0.69 |
| | INSTI/2NRTI | 1,173 | 64.4 | 91.3 | 89.7 | 92.9 | 0.009 |
| | **All regimens** | **1,821** | **36.8** | **89.2** | **87.8** | **90.7** | |

## Viral suppression

We assessed long-term viral suppression rates (i.e., viral load <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 (±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: 1996-2004, 2005-09, 2010-14, and 2015-19. 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 97.3% (95% CI 96.8-97.9) after one year of cART use to 97.9% (95% CI 97.0-98.7) after four years.

***Figure 2.11A–D:*** *Viral suppression following combination antiretroviral therapy (cART) initiation, by calendar period of therapy initiation.*




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

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

## HIV drug resistance

Preventing, monitoring and responding to HIV drug resistance is a key component of comprehensive and effective HIV care. When antiretroviral therapy does not result in complete suppression of viral replication, HIV drug resistance can occur by the selection of mutations in the genetic structure of HIV that detrimentally affects 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[29].

We assessed the occurrence of HIV drug resistance in the Netherlands among adults for whom genotypic test results were available. The genotypic test results presented in this part relate to the HIV-1 reverse transcriptase and protease gene; HIV-1 sequences of the integrase gene were relatively rare. Therefore, results of testing for integrase inhibitor resistance are described in 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 for the full population in care.

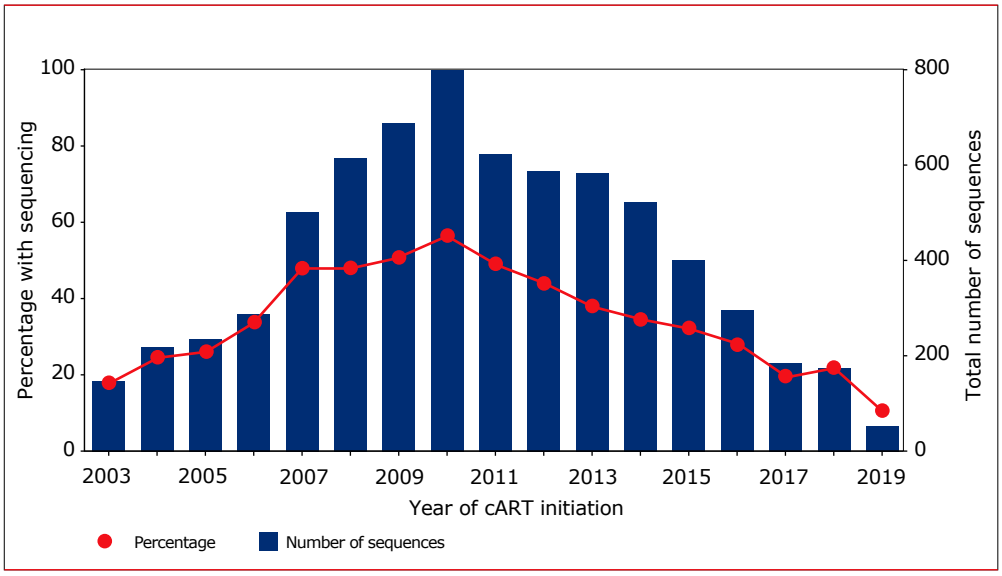
We evaluated the presence of mutations in the HIV genome that are associated with drug resistance. The 2019 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[26]. Furthermore, we assessed the association between these mutations and the susceptibility to 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[27,28]. The definitions of transmitted- and acquired-HIV drug resistance used in our analyses are summarised in *Box 2.3*. The number of sequences and people included in each of the analyses is outlined in *Box 2.1*.

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

In the Netherlands, screening for HIV drug resistance at the time of entry into care has been incorporated in the treatment guidelines since 2003. Transmitted HIV drug resistance occurs when people acquire an HIV strain that harbours drug-resistance mutations. Drug-resistant variants of HIV may remain dormant in resting CD4 cells, awaiting more favourable replication conditions after treatment has started[30–32]. These dormant mutant variants might not be detected, which could make it difficult to distinguish between drug-susceptible versus drug-resistant strains[33]. Therefore, ideally, the presence of transmitted resistance should be identified as close to the moment of infection as possible in people who are antiretroviral (ARV)-naive before initiating cART.

In total, 7,567 HIV-1 sequences were obtained between 2003-19 from 7,292 ARV-naive people before they initiated cART. The number of sequences and proportion of ARV-naive people with sequencing before cART initiation peaked in 2010 and have steadily declined since then (*Figure 2.12*). 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 (68.5%), while (14.4%) were women. Most people with an available pre-treatment sequence originated from the Netherlands (60.5%) or sub-Saharan Africa (11.3%). The main HIV-1 subtype was B (76.2%), followed by non-B subtypes (23.8%), including recombinant form CRF_02AG (6.6%), subtype C (4.8%), and CRF_01AE (3.4%).

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

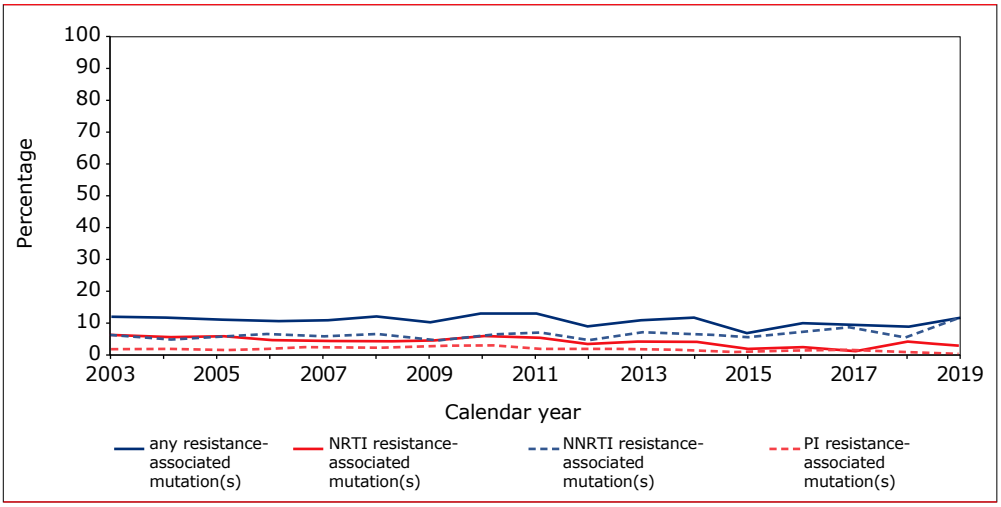



***Legend:*** *cART=combination antiretroviral therapy.*

## Transmitted HIV drug resistance

In total, ≥one resistance-associated major mutation[26] was found in 782 (10.7%) of the people tested for resistance, including 301 (4.1%) with NRTI-associated resistance mutations, 423 (5.8%) with NNRTI-associated resistance mutations, and 131 (1.8%) with PI-associated resistance mutations. The prevalence of transmitted drug resistance was low and remained stable between 2003 and 2019 (*Figure 2.13*).

*Figure 2.13: The annual proportion 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[26].*




*Legend: NRTI=nucleotide/nucleoside reverse transcription inhibitor, NNRTI=non-NRTI, PI=protease inhibitor.*

In total, 195 (2.7%) individuals screened for transmitted drug resistance harboured high-level resistance[27,28] to at least one antiretroviral drug; 37 (0.5%) to at least one NRTI, 143 (2.0%) to at least one NNRTI, and 31 (0.5%) to at least one PI. On the basis of the available resistance data, >97% were fully susceptible to all antiretroviral drugs; 2.3% (166) harboured high-level resistance in one drug class, 0.3% (20) in two drug classes, and <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 often still be constructed.

### Integrase inhibitor resistance before HIV treatment initiation

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

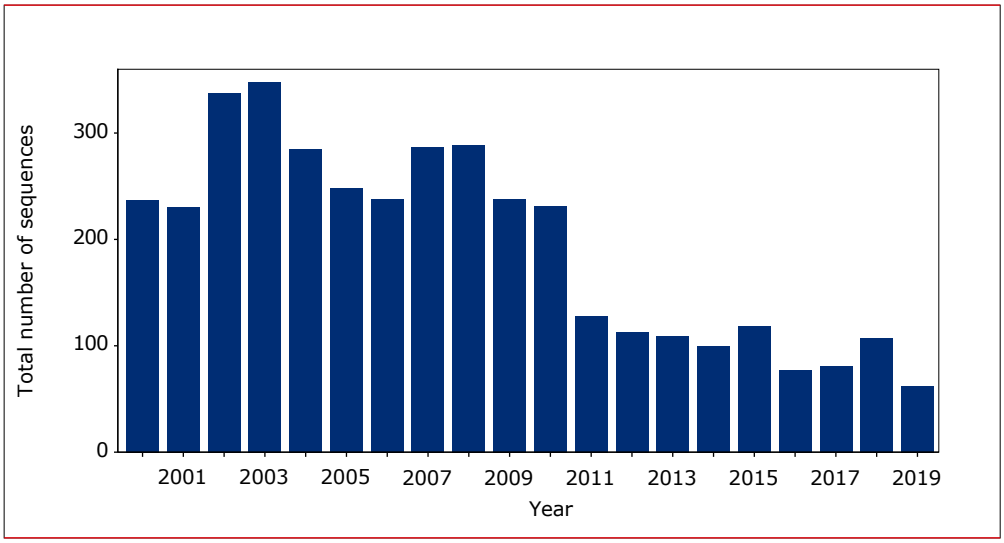
## Acquired HIV drug resistance

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

In this section, we describe the level of acquired drug resistance detected among the treated population with both a viral load >500 copies/ml and resistance test results available after at least four months of cART in 2000-19. If cART had been interrupted >two weeks before the test, the sequence was excluded from the analysis.

In total, 3,899 HIV-1 sequences were obtained from 2,402 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*). The median time between initial start of cART and resistance testing was 5.3 years (IQR 2.9-8.4). The main HIV-1 subtype was B (69.4%), followed by recombinant form CRF_02AG (10.1%), and subtype C (5.8%).

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




***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[27, 28].*

Overall, sequences from people pre-treated with monotherapy or dual therapy were disproportionally represented: 1,289 (33.1%) sequences were obtained from 711 (29.6%) pre-treated people, and 2,610 (66.9%) sequences were obtained from 1,691 (70.4%) ARV-naive people. However, over time this difference became less distinct: in 2000, 73.2% of sequences were obtained from pre-treated people, compared with 36.8% in 2005, and less than 16% from 2010 onwards.

Out of the 3,899 sequences obtained at the time of HIV RNA >500 copies/ml, 2,590 (66.4%) harboured high-level resistance to at least one antiretroviral drug. High-level NRTI resistance was detected in 2,235 (58.0%) sequences; of those, 1,851 (82.8% of 2,235) harboured high-level resistance to emtricitabine or lamivudine. Notably, of the 1,595 individuals ever identified as harbouring the M184V or M184I mutation who were still in care in 2019, 1,055 (66.1%) were still on cART containing lamivudine or emtricitabine, and 834/1055 (79.1%) had undetectable HIV-RNA at their last visit. In addition, 1,549 (40.2%) harboured high-level resistance to at least one NNRTI and 1,002 (26.9%) to at least one PI.

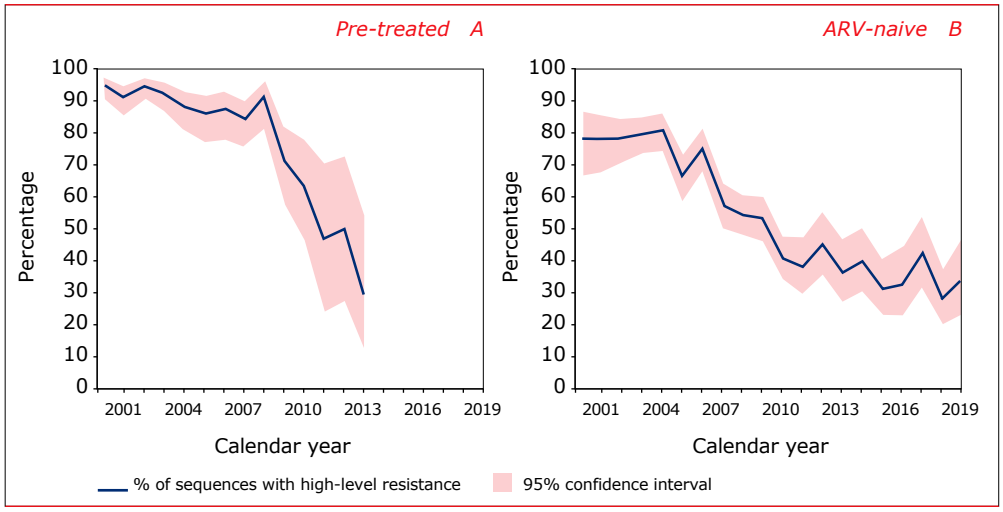
### Previous antiretroviral drug exposure

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

Among pre-treated people, the annual proportion of sequences harbouring high-level resistance to at least one drug was 94.9% (95% CI 90.4-97.3) in 2000, 88.1% (95% CI 80.5-93.0) in 2004, 63.6% (95% CI 46.2-78.1) in 2010, and 29.4% (95% CI 12.8-54.2) in 2013 (*Figure 2.15A*). The availability of new drugs, both in existing and new drug classes, largely explains the decline since 2008[34]. In recent years (2014-19), both the number of pre-treated people, and the number of sequences from pre-treated people, were too low to provide meaningful proportions.

Among previously ARV-naive people, high-level resistance to at least one drug was detected among 78.1% (95% CI 66.4-86.6) of sequences in 2000, 75.3% (95% CI 68.1-81.3) in 2006, 45.5% (95% CI 35.9-55.3) in 2012, and 34.5% (95% CI 23.4-47.5) in 2019 (*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 proportion of sequences with evidence of high-level resistance to any antiretroviral drug, obtained at the time of virological failure when receiving combination antiretroviral therapy (cART), by prior antiretroviral (ARV) drug exposure, among A) people who were pre-treated with mono or dual nucleoside-analogue RT inhibitors (NRTIs), and B) previously antiretroviral drug-naive people. The shaded area represents the 95% confidence interval.*



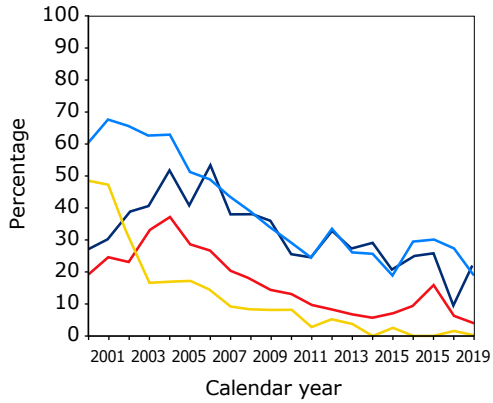

***Note:*** *The number of sequences from pre-treated people in 2014-19 was too low to give meaningful proportions.*

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

In the remainder of our analysis, we focus solely on the 1,691 people who were ARV-naive before cART initiation. Overall, 1,581 (60.6%) of the 2,610 sequences from previously ARV-naive people receiving cART harboured at least one major resistance mutation, associated with resistance to NRTI (1,271, 48.7%), NNRTI (986, 37.8%), or PI (343, 13.1%).

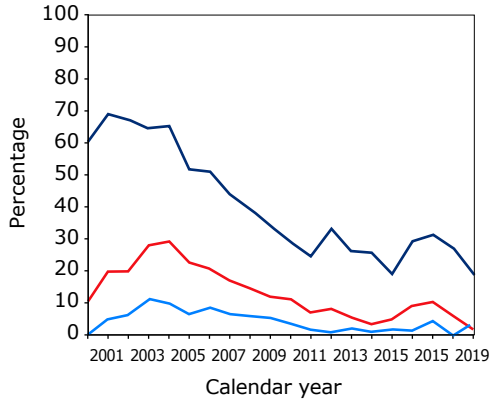
In *Figure 2.16A* and *Table 2.5*, the annual proportion of sequences harbouring high-level resistance is presented for each antiretroviral drug class. In 2000, 68.3% (95% CI 55.8-78.5), 27.0% (95% CI 17.5-39.2), and 48.4% (95% CI 36.5-60.5) of sequences harboured high-level resistance to at least one NRTI, NNRTI, or PI, respectively. The proportion of sequences with high-level of resistance declined over time for all drug classes. In 2009, 35.8% (95% CI 29.3-42.9), 35.8% (95% CI 29.3-42.9), and 7.9% (95% CI 4.8-12.7) of sequences harboured high-level resistance to at least one NRTI, NNRTI, or PI, respectively. In 2019, 20.8% (95% CI 11.9-33.7), 22.6% (95% CI 13.3-35.8), and 0% of sequences harboured high-level resistance to at least one NRTI, NNRTI or PI, respectively. The proportion of sequences with at least one resistance mutation to all three drug classes (i.e., NRTI, NNRTI, and PI) also declined over time: from 7.8% (95% CI 3.3-17.4) in 2000 to 0% in 2014. The annual proportions of sequences harbouring high-level resistance to individual antiretroviral drugs are presented in *Figure 2.16B-D* and *Appendix Table 2.1*, and annual proportions 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 2.16A-E:*** *The annual proportions 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 inhibitor, and protease inhibitors.*



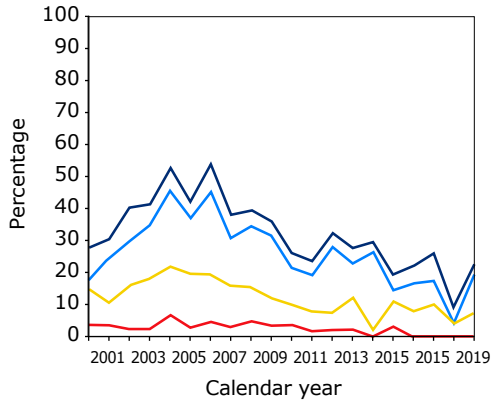

*A*
*By antiretroviral drug class: high-level resistance to at least one drug per class*

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

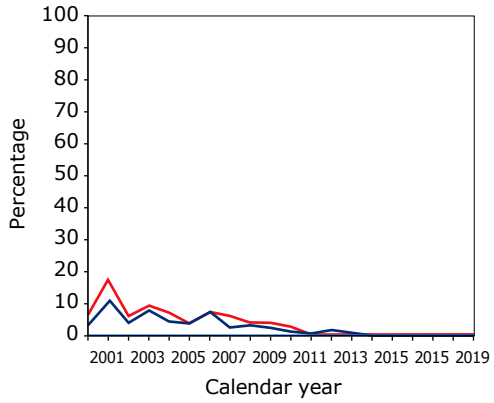



*B*
*By antiretroviral drug: high-level resistance to nucleoside reverse transcriptase inhibitors*

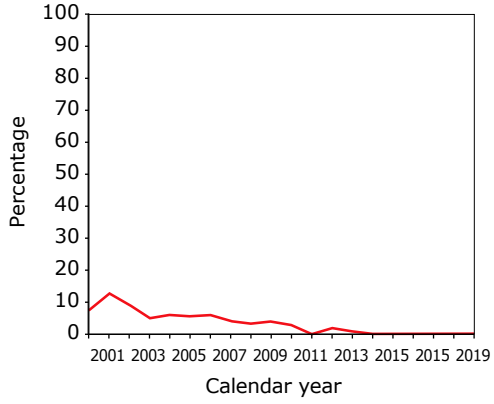
- Lamivudine/emtricitabine resistance
- Abacavir resistance
- Tenofovir resistance




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




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




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

***Legend:*** *ABC=abacavir; ATV=atazanavir; DRV=darunavir; EFV=efavirenz; ETR=etravirine; FTC/3TC=emtricitabine/lamivudine; NRTIs=nucleo(s/t)ide-analogue reverse transcriptase inhibitors; NNRTIs=non-nucleoside reverse transcriptase inhibitors; NVP=nevirapine; LPV=lopinavir; PIs=protease inhibitors; RPV=rilpivirine; TDF=tenofovir disoproxil fumarate.*

***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*[27,28].

***Table 2.5:*** *Acquired drug resistance: the annual proportion of available sequences with evidence of high-level resistance to at least one antiretroviral drug class after virological failure from people who received combination antiretroviral therapy and were previously antiretroviral drug-naive. See Appendix Table 2.2 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 | 68.3 | 55.8 | 78.5 | 27.0 | 17.5 | 39.2 | 48.4 | 36.5 | 60.5 |
| 2001 | 75.6 | 65.4 | 83.5 | 30.2 | 21.5 | 40.7 | 47.1 | 36.7 | 57.6 |
| 2002 | 72.3 | 64.5 | 78.9 | 38.5 | 31.0 | 46.6 | 29.7 | 22.9 | 37.6 |
| 2003 | 70.8 | 64.0 | 76.8 | 40.6 | 33.9 | 47.7 | 16.3 | 11.7 | 22.3 |
| 2004 | 71.9 | 64.9 | 78.0 | 51.7 | 44.4 | 58.9 | 16.9 | 12.0 | 23.1 |
| 2005 | 58.2 | 50.4 | 65.7 | 40.5 | 33.1 | 48.3 | 17.1 | 12.0 | 23.8 |
| 2006 | 58.0 | 50.3 | 65.4 | 53.1 | 45.4 | 60.6 | 14.3 | 9.7 | 20.6 |
| 2007 | 48.7 | 41.6 | 55.8 | 38.0 | 31.3 | 45.1 | 9.1 | 5.7 | 14.1 |
| 2008 | 43.5 | 37.3 | 50.0 | 37.9 | 31.9 | 44.3 | 8.2 | 5.3 | 12.5 |
| 2009 | 35.8 | 29.3 | 42.9 | 35.8 | 29.3 | 42.9 | 7.9 | 4.8 | 12.7 |
| 2010 | 30.5 | 24.5 | 37.2 | 25.5 | 19.9 | 32.0 | 8.0 | 5.0 | 12.7 |
| 2011 | 27.0 | 19.6 | 35.8 | 24.3 | 17.4 | 33.0 | 2.7 | 0.9 | 7.9 |
| 2012 | 33.3 | 24.8 | 43.2 | 32.3 | 23.9 | 42.1 | 5.1 | 2.1 | 11.6 |
| 2013 | 27.2 | 19.1 | 37.1 | 27.2 | 19.1 | 37.1 | 3.4 | 1.1 | 10.2 |
| 2014 | 26.7 | 18.6 | 36.7 | 28.9 | 20.5 | 39.1 | 0 | | |
| 2015 | 21.6 | 14.6 | 30.6 | 20.6 | 13.8 | 29.5 | 2.3 | 0.6 | 8.7 |
| 2016 | 29.2 | 19.5 | 41.4 | 24.6 | 15.7 | 36.5 | 0 | | |
| 2017 | 35.7 | 25.4 | 47.5 | 25.7 | 16.8 | 37.2 | 0 | | |
| 2018 | 27.3 | 19.4 | 36.9 | 9.1 | 4.8 | 16.6 | 1.4 | 0.2 | 9.5 |
| 2019 | 20.8 | 11.9 | 33.7 | 22.6 | 13.3 | 35.8 | 0 | | |

### Acquired integrase inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on cART was relatively rare. The available 167 integrase sequences originated from 138 people who received cART for at least four months; 15 were pre-treated with monotherapy or dual NRTI therapy before initiating cART, and 123 were ARV-naive before initiating cART. Most people had initiated cART years before; the median time between initial cART initiation and testing for integrase inhibitor resistance was 9.4 years (IQR 3.0-13.8). For each person, we used the most recent sequence for further analysis.

At least one acquired major mutation associated with integrase inhibitor resistance was detected in 27 of the 138 individuals, which resulted in high-level resistance to at least one integrase inhibitor[27,35]. Among the 27, the following major INSTI resistance mutations were detected (numbers are given in parentheses): N155H (12) 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, three; T97A, three); T66 (any, three; T66T/A, two; T66T/K, one); and G140S (one). Four of the 27 patients who harboured major INSTI resistance mutations had ever received INSTI-monotherapy.

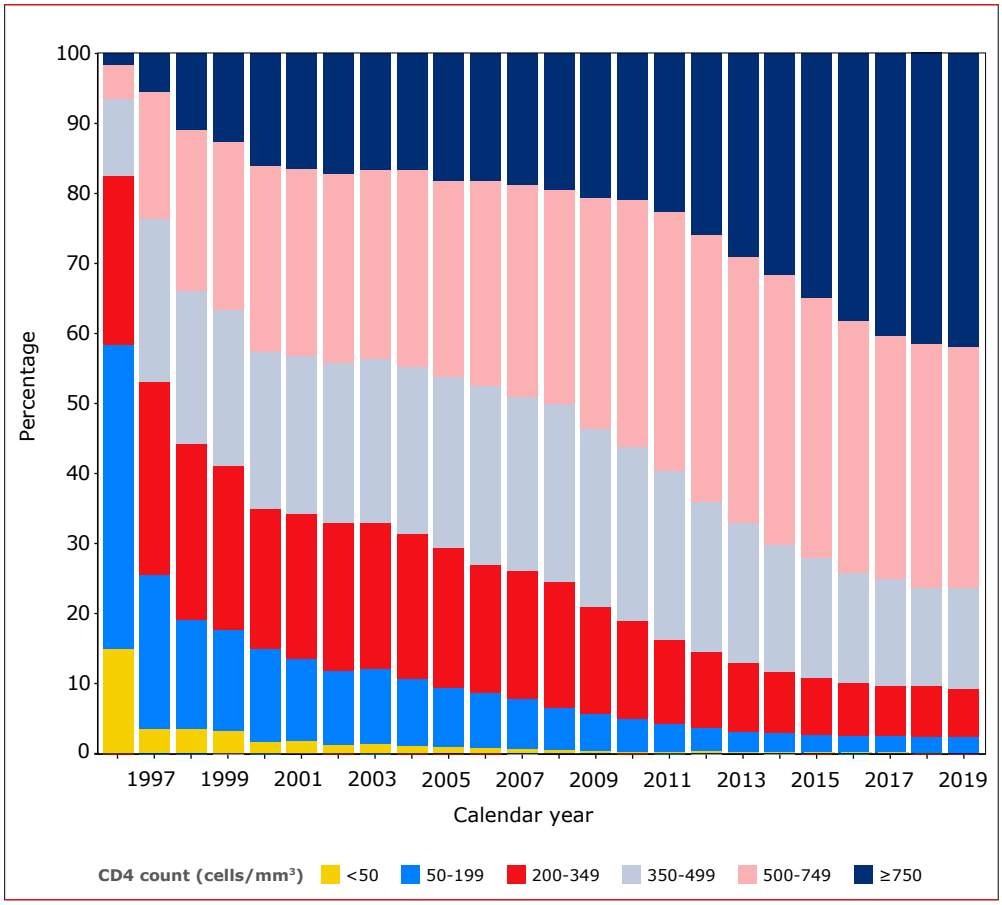
## Immunological response

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 viraemia is associated with poorer recovery of CD4 cell count[36,37]. However, incomplete recovery of CD4 cell count may also occur, despite sustained viral suppression, a situation reported to be associated with an increased risk of progression to AIDS and development of non-AIDS-related diseases[38]. 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[39]. 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[40–45]. The clinical benefit of cART is strongly related to the level of recovery of the immune status (also see *Chapter 3*)[46–50].

## Immunological response – by calendar year

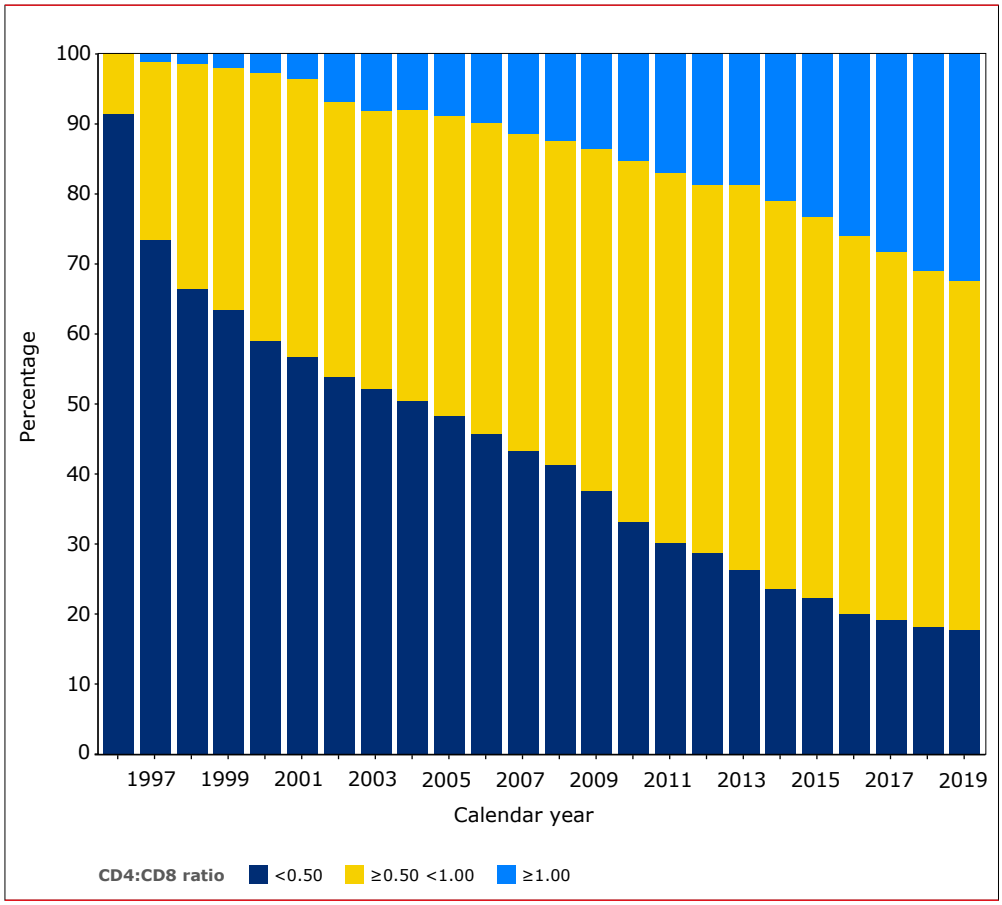
Of the 25,587 people known to have initiated cART between January 1996 and December 2019, CD4 cell count data after cART initiation were available for 25,088 (98.1%). *Figures 2.17* and *2.18* show the last known CD4 cell count and CD4:CD8 ratio of all people in HIV care for each calendar year. After starting cART, the percentage of people with CD4 cell counts <350 cells/mm$^3$ dropped from 53.1% in 1997 to 29.5% in 2005, 19.1% in 2010, 10.9% in 2015, and 9.4% in 2019 (*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 2019 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, 8.9% in 2005, 15.3% in 2010, 23.2% in 2015, and 32.4% in 2019 (*Figure 2.18*). Of all CD4:CD8 ratio measurements ≥one, 10.9% had a CD4 count of less than 500 cells/mm$^3$, 32.6% had a CD4 count between 500-749 cells/mm$^3$, and 56.5% had a CD4 count of ≥750 cells/mm$^3$. When the CD4:CD8 ratio was ≥one, the median CD4 count was 790 cells/mm$^3$ (IQR 620-1,000), and remained fairly stable over time, with a median of 760 cells/mm$^3$ (IQR 590-1,000) in 1996-2004, 750 cells/mm$^3$ (IQR 570-960) in 2005-09, 740 cells/mm$^3$ (IQR 580-940) in 2010-14, and 830 cells/mm$^3$ (IQR 653-1,030) in 2015-19.

***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 (2015–19)

We also assessed the immunological response in people who started cART more recently: 3,627 people started cART in 2015-19, and CD4 cell count data were available at, and after, cART initiation. The level of viral suppression and treatment interruptions after initiating cART were not taken into account in this analysis. Of the 3,627 people who started cART in 2015-19 and had sufficient immunological data available, 9.3% had CD4 counts <50 cells/mm$^3$, 15.7% 50-199 cells/mm$^3$, 18.1% 200-349 cells/mm$^3$, 21.8% 350-499 cells/mm$^3$, and 35.0% ≥500 CD4 cells/mm$^3$ at the time of cART initiation. The CD4 cell count at cART initiation has decreased slightly in recent years (*Appendix Table 2.1*).

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 Therapy Cohort 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[51].

*Figure 2.19: CD4 cell count over time after the start of combination antiretroviral therapy (cART) in 2015–19.*

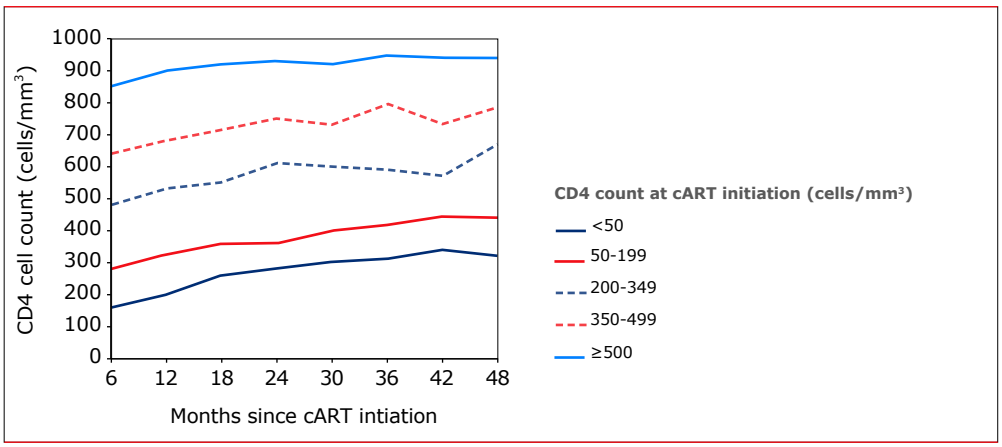
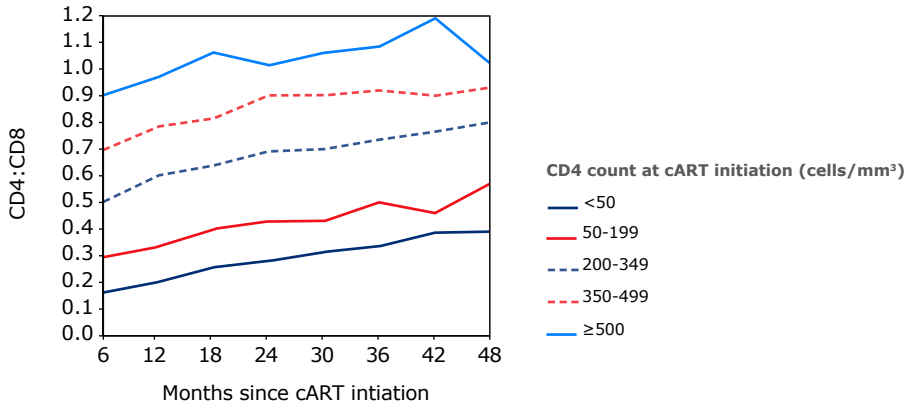


*Figure 2.20: CD4:CD8 ratio over time after the start of combination antiretroviral therapy (cART) in 2015–19.*




*Note:* The presented immunological outcomes are based on available test results. For people with a low to moderate CD4 cell count (<350 cells/mm³), CD4 cell count testing is recommended at least twice a year[52]. When a person has a CD4 cell count >350 cells/mm³, the testing frequency may be reduced. Therefore, CD4 data from people achieving higher CD4 cell counts are disproportionally underrepresented, and their true CD4 responses may be even better.

## Summary and conclusions

### Starting cART 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. However, despite this overall improvement, the proportion of HIV-positive individuals starting cART after six to 12 months, or more than 12 months after HIV diagnosis, increased in 2018 and 2019 to 29.2% of individuals initiating cART more than six months after HIV diagnosis. This increase was caused by a growing proportion of migrants who newly entered into care in the Netherlands while already being diagnosed with HIV and on ART before they migrated to the Netherlands, reflecting the increased availability of ART in their countries of origin. Late initiation of ART has become rare in individuals who were first diagnosed with HIV while living in the Netherlands.

- The CD4 cell count at cART initiation has increased over time, peaking in the year 2015 at a median of 414 cells/mm3 (IQR 220-600). This was when new guidelines came out recommending rapid initiation of cART at any CD4 count, which 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 decreased somewhat. Among HIV-positive individuals starting cART in 2019, the median CD4 cell count was 370 cells/mm3 (IQR 180-570). Immunological recovery was better when cART was started at a higher CD4 cell count.
- In 2019, 80.7% of initial regimens contained an integrase inhibitor. The most frequently used initial regimen was bictegravir/emtricitamine/tenofovir alafenamine (47.1%). Dolutegravir-containing initial regimens were used in 27.3% of cases; combined with either abacavir and lamivudine as part of the once-daily, fixed-dose combination (6.9%), or emtricitabine and tenofovir separately (TDF 18.5%/TAF 1.9%).
- Discontinuation of the initial regimen has become less common over time. Regimen switches were mainly due to intolerance, simplification, or the availability of new drugs.
- Toxicity-associated discontinuations of the initial regimen were often related to neuropsychiatric problems, problems involving the gastrointestinal tract or liver, or a rash due to medication.

### In care and receiving cART in 2019

- Integrase inhibitor-based cART has been implemented on a large scale in the Netherlands and was used by 50.0% of all individuals.
- The nucleoside analogue backbone used by 31.9% contained TDF; 20.7% ABC and 42.1% TAF.
- Only 3.6% used a two-drug regimen.
- Of those receiving cART for at least 12 months, who had a plasma HIV RNA measurement in 2019, 97.5% had a viral load <200 copies/ml, and 95.1% had a viral load ≤50 copies/ml.

### Virological response and drug resistance

- The overall viral suppression rates of the HIV-positive population receiving cART is high and has continued to improve. Among the limited number of individuals who experienced virological failure, the annual proportion of people with acquired drug resistance remained low; this is in line with findings from other high-income settings[53,54].
- Transmitted drug resistance was rare, and the overall prevalence was low and stable over time, in line with reported rates from other European countries[55].

- Integrase inhibitor resistance data remain limited. No transmitted integrase inhibitor resistance was detected amongst 27 people tested by the end of 2019. Detected rates of acquired integrase inhibitor resistance among available sequences continued to remain very low, with almost no significant resistance to dolutegravir.

### Immunological response

- In individuals using cART, the percentage of people with CD4 cell counts <350 cells/mm3 dropped from 53.1% in 1997 to 29.5% in 2005, 19.1% in 2010, 10.9% in 2015, and 9.4% in 2019.
- The percentage of those with a CD4:CD8 ratio of one or above increased from 1.2% in 1997 to 2.8% in 2000, 8.9% in 2005, 15.3% in 2010, 23.2% in 2015, and 32.4% in 2019.

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# Appendix

*Appendix Table 2.1: CD4 cell count at combination antiretroviral therapy (cART) initiation by calendar year 2015–19.*

| Year of cART initiation | 2015 | 2016 | 2017 | 2018 | 2019 | 2015–2019 |
|---|---|---|---|---|---|---|
| CD4 cell count available at cART initiation | 1,088 | 890 | 779 | 598 | 272 | **3,627** |
| CD4 cell count, median cells/mm$^3$ (IQR) | 420 (220–600) | 410 (230–580) | 380 (190–560) | 365 (150–580) | 322 (128–532) | **393 (199–580)** |
| CD4 cell count (cells/mm$^3$) | | | | | | |
| <50 | 87 (8.0) | 80 (9.0) | 66 (8.5) | 72 (12.0) | 33 (12.1) | **338 (12.1)** |
| 50–199 | 163 (15.0) | 110 (12.4) | 130 (16.7) | 107 (17.9) | 59 (21.7) | **569 (21.7)** |
| 200–349 | 181 (16.7) | 162 (18.2) | 155 (19.9) | 106 (17.7) | 54 (19.9) | **658 (18.1)** |
| 350–499 | 252 (23.2) | 209 (23.5) | 170 (21.8) | 111 (18.6) | 50 (18.4) | **792 (18.4)** |
| ≥500 | 405 (37.2) | 329 (37.0) | 258 (33.1) | 202 (33.8) | 76 (27.9) | **1,270 (35.0)** |

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

***Appendix Table 2.2A–C:*** *Acquired drug resistance: annual proportion 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) High-level resistance to nucleoside reverse transcriptase inhibitors.*

| Calendar year | Number of sequences | Emtricitabine/ lamivudine | Zidovudine | Stavudine | Abacavir | Didanosine | Tenofovir |
|---|---|---|---|---|---|---|---|
| 2000 | 63 | 60.3 | 13.6 | 9.3 | 10.3 | 10.9 | 0.0 |
| 2001 | 86 | 69.0 | 16.0 | 18.9 | 20.0 | 17.8 | 5.2 |
| 2002 | 148 | 67.4 | 12.2 | 15.8 | 20.1 | 19.3 | 6.6 |
| 2003 | 192 | 64.5 | 19.4 | 24.9 | 28.2 | 27.9 | 11.2 |
| 2004 | 178 | 65.5 | 19.9 | 23.2 | 29.3 | 29.7 | 10.1 |
| 2005 | 158 | 51.9 | 14.3 | 19.0 | 22.7 | 21.7 | 6.8 |
| 2006 | 162 | 51.0 | 11.3 | 16.8 | 20.9 | 22.6 | 8.8 |
| 2007 | 187 | 44.0 | 10.6 | 13.9 | 17.0 | 14.5 | 6.8 |
| 2008 | 232 | 39.5 | 7.8 | 11.8 | 14.7 | 15.6 | 6.1 |
| 2009 | 190 | 34.0 | 7.3 | 10.1 | 12.2 | 12.0 | 5.5 |
| 2010 | 200 | 29.1 | 5.8 | 8.5 | 11.4 | 11.9 | 3.7 |
| 2011 | 115 | 24.8 | 0.9 | 2.8 | 7.1 | 8.0 | 1.8 |
| 2012 | 99 | 33.3 | 0.0 | 2.1 | 8.3 | 8.2 | 1.1 |
| 2013 | 92 | 26.4 | 0.0 | 2.3 | 5.7 | 5.7 | 2.2 |
| 2014 | 90 | 25.8 | 1.1 | 3.4 | 3.4 | 4.5 | 1.2 |
| 2015 | 102 | 19.2 | 1.0 | 3.1 | 5.1 | 6.9 | 2.0 |
| 2016 | 65 | 29.2 | 1.6 | 3.2 | 9.4 | 6.5 | 1.6 |
| 2017 | 70 | 31.3 | 2.9 | 7.5 | 10.6 | 14.7 | 4.5 |
| 2018 | 99 | 27.3 | 0.0 | 0.0 | 6.1 | 5.1 | 0.0 |
| 2019 | 53 | 19.2 | 0.0 | 3.8 | 1.9 | 3.8 | 3.8 |

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

| Calendar year | Number of sequences | Nevirapine | Efavirenz | Etravirine | Rilpivirine |
|---|---|---|---|---|---|
| 2000 | 63 | 27.9 | 17.9 | 3.8 | 15.0 |
| 2001 | 86 | 30.6 | 25.0 | 3.8 | 10.6 |
| 2002 | 148 | 40.1 | 30.0 | 2.5 | 16.1 |
| 2003 | 192 | 41.3 | 34.9 | 2.5 | 18.2 |
| 2004 | 178 | 52.6 | 45.6 | 6.8 | 21.8 |
| 2005 | 158 | 42.1 | 37.0 | 3.0 | 19.7 |
| 2006 | 162 | 53.8 | 45.0 | 4.8 | 19.6 |
| 2007 | 187 | 38.0 | 30.8 | 3.2 | 15.9 |
| 2008 | 232 | 39.5 | 34.5 | 5.0 | 15.5 |
| 2009 | 190 | 36.0 | 31.5 | 3.6 | 12.1 |
| 2010 | 200 | 26.2 | 21.5 | 3.8 | 10.0 |
| 2011 | 115 | 23.7 | 19.3 | 1.9 | 8.0 |
| 2012 | 99 | 32.3 | 28.0 | 2.2 | 7.6 |
| 2013 | 92 | 27.8 | 23.0 | 2.4 | 12.2 |
| 2014 | 90 | 29.5 | 26.4 | 0.0 | 2.3 |
| 2015 | 102 | 19.4 | 14.4 | 3.2 | 11.1 |
| 2016 | 65 | 22.2 | 16.7 | 0.0 | 8.1 |
| 2017 | 70 | 26.1 | 17.5 | 0.0 | 10.3 |
| 2018 | 99 | 9.1 | 4.3 | 0.0 | 4.2 |
| 2019 | 53 | 22.6 | 19.6 | 0.0 | 7.5 |

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

| Calendar year | Number of sequences | Nelfinavir | Saquinavir | Indinavir | Atazanavir | Fosam-prenavir | Lopinavir | Tipranavir | Darunavir |
|---|---|---|---|---|---|---|---|---|---|
| 2000 | 64 | 48.4 | 8.1 | 5.1 | 6.6 | 6.3 | 3.3 | 1.6 | 0.0 |
| 2001 | 85 | 47.6 | 21.6 | 18.3 | 17.7 | 13.8 | 11.1 | 2.5 | 0.0 |
| 2002 | 148 | 30.1 | 10.6 | 7.4 | 6.5 | 5.8 | 4.2 | 0.0 | 0.0 |
| 2003 | 190 | 17.0 | 9.3 | 9.9 | 9.6 | 7.6 | 8.1 | 1.6 | 0.0 |
| 2004 | 178 | 16.0 | 7.1 | 7.2 | 7.5 | 5.8 | 4.7 | 0.6 | 0.0 |
| 2005 | 158 | 17.1 | 4.2 | 6.8 | 4.0 | 3.4 | 4.0 | 0.7 | 0.0 |
| 2006 | 161 | 13.8 | 6.4 | 8.2 | 7.7 | 5.7 | 7.5 | 2.6 | 0.0 |
| 2007 | 187 | 9.2 | 4.4 | 4.4 | 6.5 | 3.3 | 2.7 | 1.1 | 0.0 |
| 2008 | 232 | 7.0 | 3.5 | 4.9 | 4.4 | 4.8 | 3.6 | 0.4 | 0.0 |
| 2009 | 190 | 7.5 | 3.7 | 4.3 | 4.3 | 4.3 | 2.7 | 1.1 | 0.0 |
| 2010 | 200 | 6.6 | 3.1 | 4.1 | 3.0 | 4.1 | 1.6 | 0.0 | 0.0 |
| 2011 | 113 | 2.7 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.0 | 0.0 |
| 2012 | 99 | 5.1 | 2.1 | 2.1 | 2.0 | 2.0 | 2.0 | 0.0 | 0.0 |
| 2013 | 87 | 3.4 | 0.0 | 1.2 | 1.1 | 2.3 | 1.2 | 0.0 | 0.0 |
| 2014 | 76 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 2015 | 87 | 2.3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 2016 | 54 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 2017 | 56 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 2018 | 70 | 1.4 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 2019 | 19 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |

# 3. Morbidity and mortality

Ferdinand Wit, Marc van der Valk, and Peter Reiss

## Introduction

Since the introduction of cART, the life expectancy of HIV-1-positive individuals has markedly improved; in a subgroup of recently-diagnosed, effectively-treated individuals, it has been shown to be similar to that of the general population in the Netherlands[1]. Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased[2], morbidity and/or mortality associated with non-AIDS-related diseases such as renal and liver disease, diabetes mellitus, myocardial infarction, stroke, osteoporosis, and non-AIDS-defining malignancies, has increased among HIV-1-positive individuals during the cART era[3–8].

Various reports suggest that the risk of non-AIDS morbidity may be higher in HIV-positive individuals treated with antiretroviral therapy (ART), than in HIV-negative individuals of comparable age[9–11]. 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]. Of note, as is the case in HIV-negative individuals, traditional risk factors (e.g., tobacco use[19], alcohol abuse, and viral hepatitis co-infection[20]), also importantly contribute to the increased risk of certain non-AIDS comorbidities in people living with HIV.

One of the most prevalent comorbidities is cardiovascular disease (CVD). In addition to traditional risk factors such as smoking, probable additional risk factors with high prevalence among HIV-1-positive individuals include metabolic abnormalities, such as dyslipidaemia; insulin resistance; hypertension; diabetes; and changes in body 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 adult (18 years and older) HIV-1-positive individuals using updated Stichting HIV Monitoring (SHM) data: a total of 27,622 adult individuals ever registered by SHM – that breaks down as 27,407 adults and an additional 431 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 Centers for Disease Control (CDC) category C condition[23]. In contrast to what is usual in the United States, in our analyses, a CD4 count below 200 cells/mm$^3$ in the absence of an AIDS-defining condition, does not qualify as AIDS.

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 2016-19. We standardised these estimates according to the age distribution of the population during the period 2016-19 (divided into the following age classes: 18-29, 30-39, 40-49, 50-59, 60-69, and ≥70 years) using the indirect method[24]. Indirect standardisation compares the incidence rates in the study and reference (period: 2016-19) 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 <200 cells/mm$^3$, known time spent with plasma HIV RNA >1000 copies/ml while on cART, time on cART, specific antiretroviral drugs used, prior diagnosis of AIDS, presence of chronic active hepatitis B and/or C virus infection, hypertension, smoking, and calendar period.

## Mortality

Mortality was investigated in all 27,622 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 8.0 (95% CI 6.8-9.5) per 1,000 PYFU in 2019 (*Figure 3.1A*). Despite this clear improvement over time, the mortality rate in HIV-1-positive adults remained well above the mortality of the general population in the Netherlands, which was 4.4 per 1,000 PYFU in 2019, when matched in terms of age and gender to our HIV-positive population. In the same group of 27,622 individuals, the incidence of AIDS decreased sharply from 121.0 (95% CI 108.5-134.6) in 1996 to 5.2 (95% CI 4.2-6.4) cases per 1,000 PYFU in 2019 (*Figure 3.1B*). The excess mortality can be partly ascribed to individuals who already had AIDS at the time of their HIV diagnosis, but much less so in recent years. When these individuals were excluded, the mortality rate decreased from 14.1 (95% CI 9.8-19.6) per 1,000 PYFU in 1996 to 7.6 (95% CI 6.3-9.1) per 1,000 PYFU in 2019. *Appendix Figure 3.1* shows the five-year survival curves after diagnosis of the first AIDS-defining condition.

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 high number of individuals who present late for care with immune deficiency that is already advanced. 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[a]. Table 3.1 shows the characteristics of adults who died of AIDS, compared to adults who died of non-AIDS causes in the period 2010 to 2019. 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 nearly 80% qualifying as a late presenter (CD4 count below 350 cells/mm$^3$). In addition, they had much lower nadir CD4 counts, and did not have controlled viremia in 60% of cases, of which 5.7% were 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 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 can also occur at higher 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 other men are overrepresented among those who died of non-AIDS causes, because these three groups have a higher average age compared to migrants, risk groups 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*.

a *Available on https://rivm.openrepository.com/handle/10029/622149, DOI: 10.21945/RIVM-2017-0158*

*Table 3.1: Characteristics of adults who died of AIDS compared to adults who died of non-AIDS causes in the period 2010 to 2019. 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.*

| | Died of non-AIDS causes | Died of AIDS | p-value |
|---|---|---|---|
| Number of subjects | 1120 (81.9%) | 247 (18.1%) | |
| Age, years | 57.3 (49.8-65.6) | 52.6 (44.5-60.5) | <.001 |
| Male gender | 987 (88.1%) | 204 (82.6%) | 0.021 |
| Dutch origin | 798 (71.3%) | 159 (64.4%) | 0.038 |
| MSM | 616 (55.0%) | 109 (44.1%) | 0.002 |
| Heterosexuals | 281 (25.1%) | 80 (32.4%) | 0.021 |
| Other risk groups | 223 (19.9%) | 58 (23.5%) | 0.223 |
| Years since HIV diagnosis | 13 ( 6.8-19.2) | 5.49 (0.51-13.4) | <.001 |
| Years since cART was started | 10.2 (4.74-15.7) | 1.55 (0.26-11.4) | <.001 |
| CD4 at HIV diagnosis | 280 (100-500) | 100 ( 30-310) | <.001 |
| Late presenter (CD4<350 at entry in care) | 646 (57.8%) | 189 (78.4%) | <.001 |
| Very late presenter (CD4<200) | 421 (37.6%) | 158 (64.0%) | <.001 |
| CD4 nadir | 125 ( 50-240) | 45 ( 10-100) | <.001 |
| Last CD4 measured before death | 440 (260-640) | 121 ( 40-270) | <.001 |
| Not undetectable at date of death | 212 (19.1%) | 138 (59.7%) | <.001 |
| Not on cART at date of death | 29 ( 2.6%) | 14 ( 5.7%) | 0.024 |

*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 3.1A-B: (A) Annual mortality and (B) incidence of AIDS in 27,622 HIV-1-positive individuals in the Netherlands after HIV diagnosis from 1996 onwards. Solid lines represent the incidence, while the shaded areas are the 95% confidence intervals. The dashed line is the mortality rate for age-matched and gender-matched individuals from the general population in the Netherlands.*

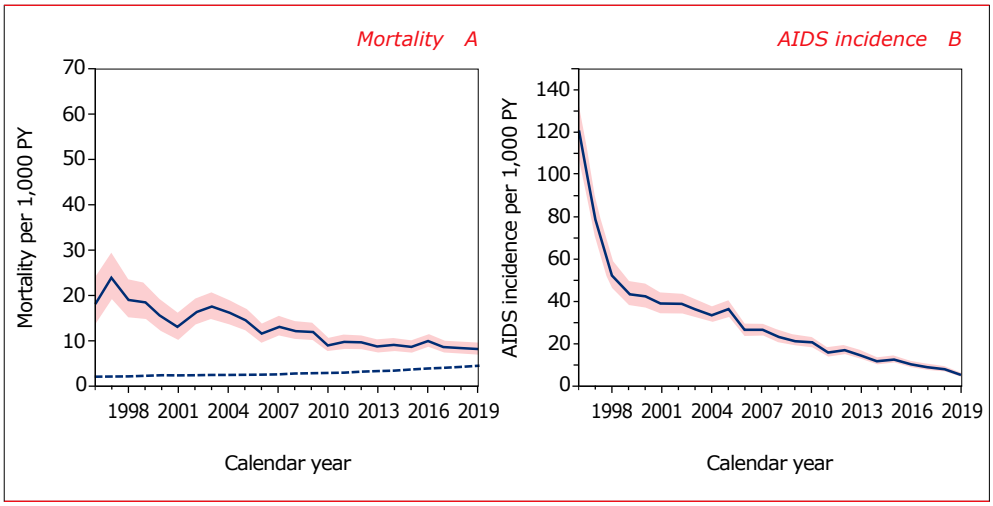
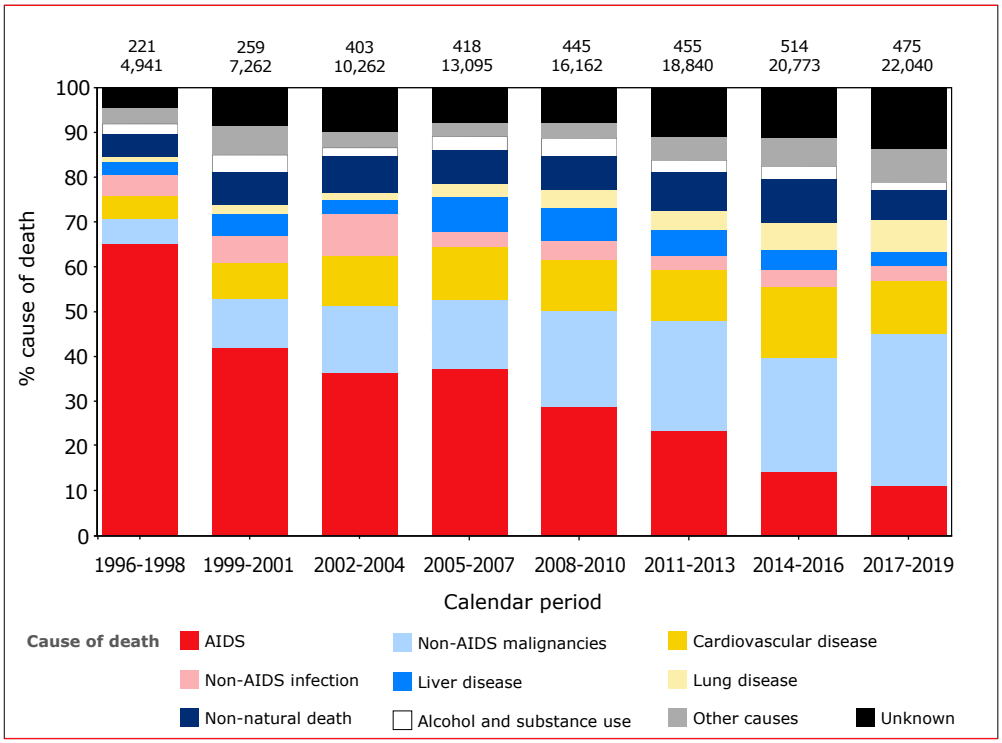


*Figure 3.2: Relative changes in causes of death in different calendar periods since the introduction of combination antiretroviral therapy (cART) in the Netherlands. The numbers at the top of each bar represent the total number of deaths and the total number of individuals that were at risk during that calendar period. Mortality attributed to 'alcohol use' consisted of 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 of starting 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 HBV or HCV; were underweight; were current or past smokers; had spent more time with an HIV RNA level above 1,000 copies/ml while on cART; or had a current CD4 cell count less than 500 cells/mm$^3$, 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 underestimated.

In contrast to previous SHM Monitoring Reports, 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 with HIV in the Netherlands in the period 2011 to 2018 was stable at around ten recorded cases per calendar year; the lower number of three suicides recorded in 2019, appears to be an outlier and might be caused by late reporting of causes of death. For patients with a serious somatic condition who were euthanized 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 2019, a total of 130 cases of euthanasia were recorded; 35% of cases occurred in patients who died of AIDS, 39% in patients who died of non-AIDS-defining malignancies, and the remaining 26% occurred in patients who died of other somatic 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

The incidence of the first occurrence of any AIDS-defining event after entering care was 21.4 events per 1,000 PYFU of follow up. *Appendix Table 3.4* gives an overview of the AIDS events occurring between 1996 and 2019. The most common AIDS events between 2016 and 2019 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 the hepatitis C virus.

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 2019, 23,882 individuals contributed a total of 201.2 thousand PYFU, during which 3,170 CDC-B and/or AIDS-defining events were diagnosed. This resulted in an incidence rate of 15.8 events per 1,000 PYFU (1,924 CDC-B events, 9.6 events/1,000 PYFU; 1,246 CDC-C/AIDS events, 6.2 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 11.4 and 5.7 AIDS-defining illnesses/1000 PYFU, respectively. The incidence rates of AIDS-defining illnesses in the CD4 strata of 500-749 and over 750 cells/mm$^3$ were 3.1 (2.7-3.6) and 1.9 (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 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 in individuals on cART while having an undetectable viral load between 2000 and 2019.*

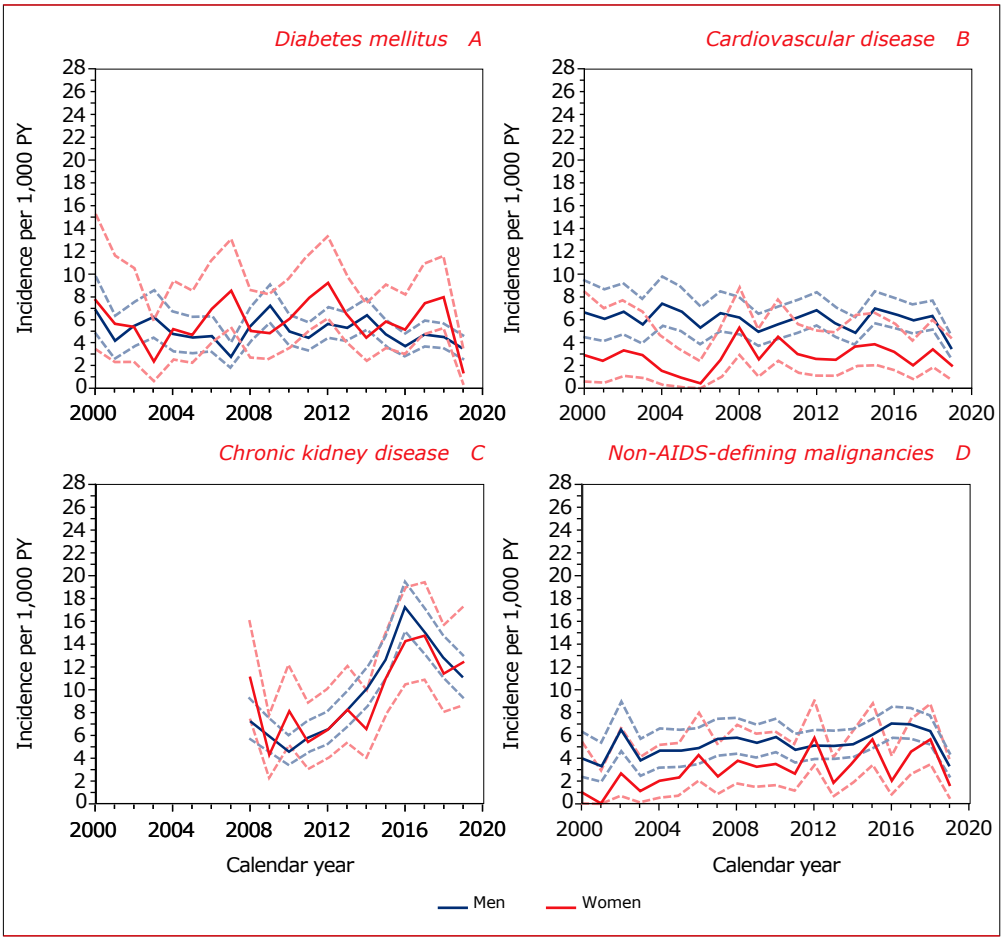
| CD4 category (cells/mm³) | CDC events (n) | CDC B events (n) | CDC C events (n) | PYFU follow-up (x1000) | Incidence rate CDC events (/1000 PY) (95%CI) | Incidence rate CDC-B events (/1000 PY) (95%CI) | Incidence rate CDC-C events (/1000 PY) (95%CI) |
|---|---|---|---|---|---|---|---|
| 0-50 | 244 | 100 | 144 | 0.5 | 513 (451-581) | 210 (171-256) | 303 (255-356) |
| 50-199 | 569 | 317 | 252 | 7.9 | 72.1 (66.3-78.2) | 40.1 (35.9-44.8) | 31.9 (28.1-36.1) |
| 200-349 | 697 | 415 | 282 | 24.7 | 28.2 (26.1-30.4) | 16.8 (15.2-18.5) | 11.4 (10.1-12.8) |
| 350-499 | 607 | 367 | 240 | 42.4 | 14.3 (13.2-15.5) | 8.66 (7.79-9.59) | 5.66 (4.97-6.43) |
| 500-749 | 667 | 444 | 223 | 71.1 | 9.38 (8.68-10.1) | 6.25 (5.68-6.86) | 3.14 (2.74-3.58) |
| 750+ | 386 | 281 | 105 | 54.7 | 7.06 (6.37-7.80) | 5.14 (4.56-5.78) | 1.92 (1.57-2.33) |
| **Total** | **3170** | **1924** | **1246** | **201.2** | **15.8 (15.2-16.3)** | **9.56 (9.14-10.0)** | **6.19 (5.85-6.55)** |

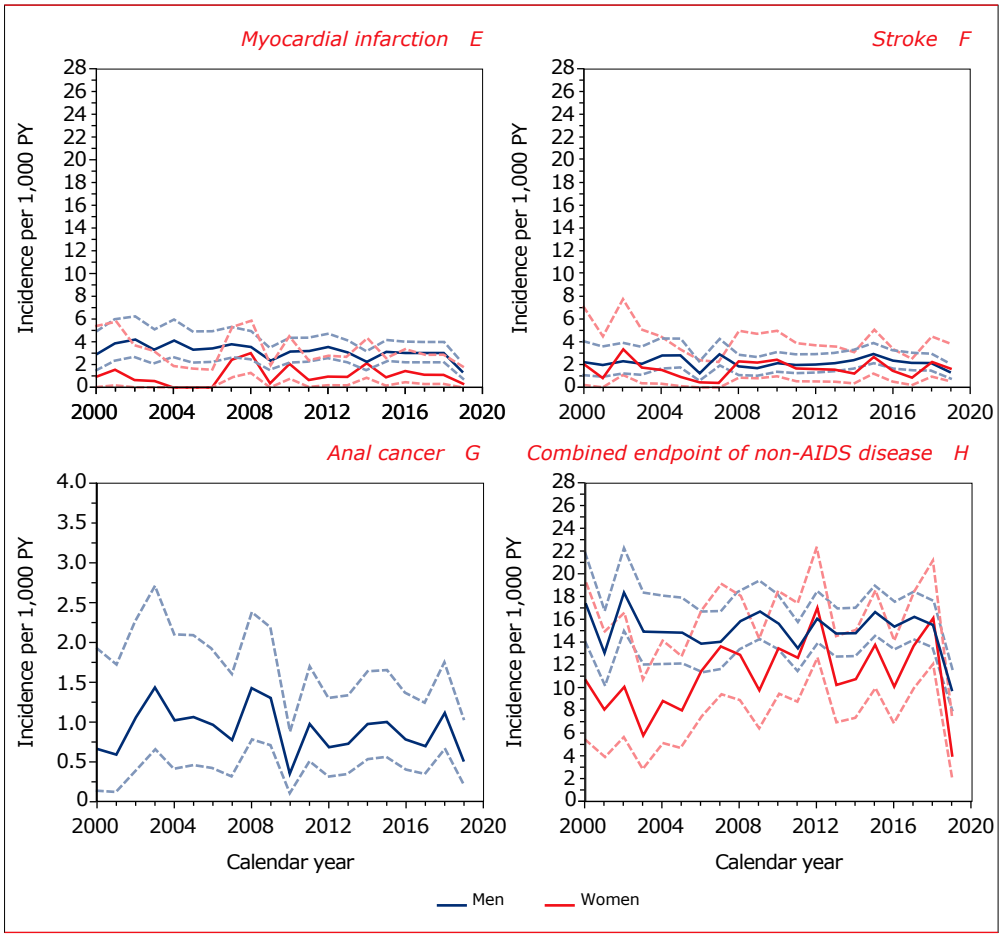
***Legend:** CDC=Centers for Disease Control and Prevention Classification System for HIV Infection; CDC-B=moderately symptomatic HIV disease; CDC-C=AIDS-defining events; cART=combination antiretroviral therapy; PYFU=person years of follow up.*

## Non-AIDS-defining events

Of the 27,622 HIV-1-positive adults ever registered with SHM, 27,064 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 3.3A-H:*** *Crude incidence rates per 1,000 person years of follow up (solid lines) and 95% confidence intervals (dotted lines) of (A) diabetes mellitus, (B) cardiovascular disease, (C) chronic kidney disease, (D) non-AIDS-defining malignancies, (E) myocardial infarction, (F) stroke, (G) anal cancer, and (H) combined endpoint of non-AIDS disease (diabetes mellitus, cardiovascular disease, and non-AIDS-defining malignancies), by gender, with the exception of anal cancer, which is presented for males only. Legend: PYFU=person years of follow up.*






## Diabetes mellitus

Of the 27,064 individuals aged 18 years or older and in follow up in, or after January 2000, a total of 1,346 (1,039 men and 307 women) were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.3A*) and, in 2019, was 3.5 (95% CI 2.6-4.6) per 1,000 PYFU in men and 1.4 (95% CI 0.4-3.6) per 1,000 PYFU in women. In men, the age-standardised incidence ratio declined over time and was significantly lower in 2016-19 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 2016-19 (*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 NRTIs prior to starting cART; and a prior AIDS diagnosis (*Appendix Table 3.6*). Moreover, the risk of new-onset diabetes in the periods 2000-10 and 2011-15 was significantly higher than in the period 2016-19. 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 during 2000–10, 2011–15 and 2016–19 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) | 1.69 (1.53–1.84) | 5.7 (4.8–6.8) | 1.10 (0.91–1.29) |
| 2011–2015 | 5.3 (4.8–5.9) | 1.44 (1.29–1.59) | 6.7 (5.5–8.1) | 1.23 (0.99–1.47) |
| 2016–2019 | 4.2 (3.7–4.7) | 1 (reference) | 5.7 (4.5–7.2) | 1 (reference) |

**Standardised according to the observed age distribution between 2016–19.*

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

## Cardiovascular disease

From January 2000 onwards, 1,399 individuals (1,251 men and 148 women) had a fatal or non-fatal cardiovascular event. Of these, 683 had a myocardial infarction, 514 a stroke, 103 a coronary artery bypass graft, 524 a coronary angioplasty or stenting, and 11 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 <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. Cardiovascular risk was also higher during 2000-10 and 2011-15 than during 2016-19, 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 1.64 to 1.49, p<0.001. Having an eGFR below 90 ml/min was independently associated with a higher risk of CVD; at 60-90 ml/min, the IRR was 1.11 (95% CI 0.96-1.28), p=0.17; at 30-60 ml/min the IRR was 1.74 (1.40-2.17), p<0.001; at 15-30 ml/min, the IRR was 4.66 (3.06-7.09), p<0.001; and at 0-15 ml/min the IRR was 4.45 (2.48-7.99), p<0.001.

From January 2000 onwards, 189 men and 15 women experienced a fatal or non-fatal secondary cardiovascular event (123 had a myocardial infarction, 89 had a stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2019 in men and women with a prior cardiovascular event was 27.9 (95% CI 24.1-32.2) and 16.4 (95% CI 9.2-27.0), 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: 31.2 events per 1,000 PYFU; SIR: 1.33, 95% CI 1.04-1.63), but not during 2011-15 (crude rate: 25.0 events per 1,000 PYFU; SIR: 1.05, 95% CI 0.79-1.31) compared with the reference period 2016-19 (crude rate: 23.8 events per 1,000 PYFU).

***Table 3.4:*** *Crude incidence of cardiovascular disease per 1,000 person years of follow up between 2000–10, 2011–15, and 2016–19 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 | 6.1 (5.6–6.6) | 1.53 (1.39–1.66) | 2.7 (2.1–3.5) | 1.52 (1.14–1.90) |
| 2011–2015 | 6.1 (5.5–6.7) | 1.24 (1.12–1.37) | 3.1 (2.3–4.1) | 1.36 (0.98–1.73) |
| 2016–2019 | 5.6 (5.1–6.3) | 1 (reference) | 2.7 (1.9–3.7) | 1 (reference) |

**Standardised according to the observed age distribution between 2016–2019.*

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

### 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 2019, the proportion of men with available BMI data who were overweight (25-30 kg/m$^2$), or obese (class I: 30-35 and class II: ≥35 kg/m$^2$), was 34%, 8% and 2%, respectively. In women, these respective proportions were 31%, 18% and 11%.

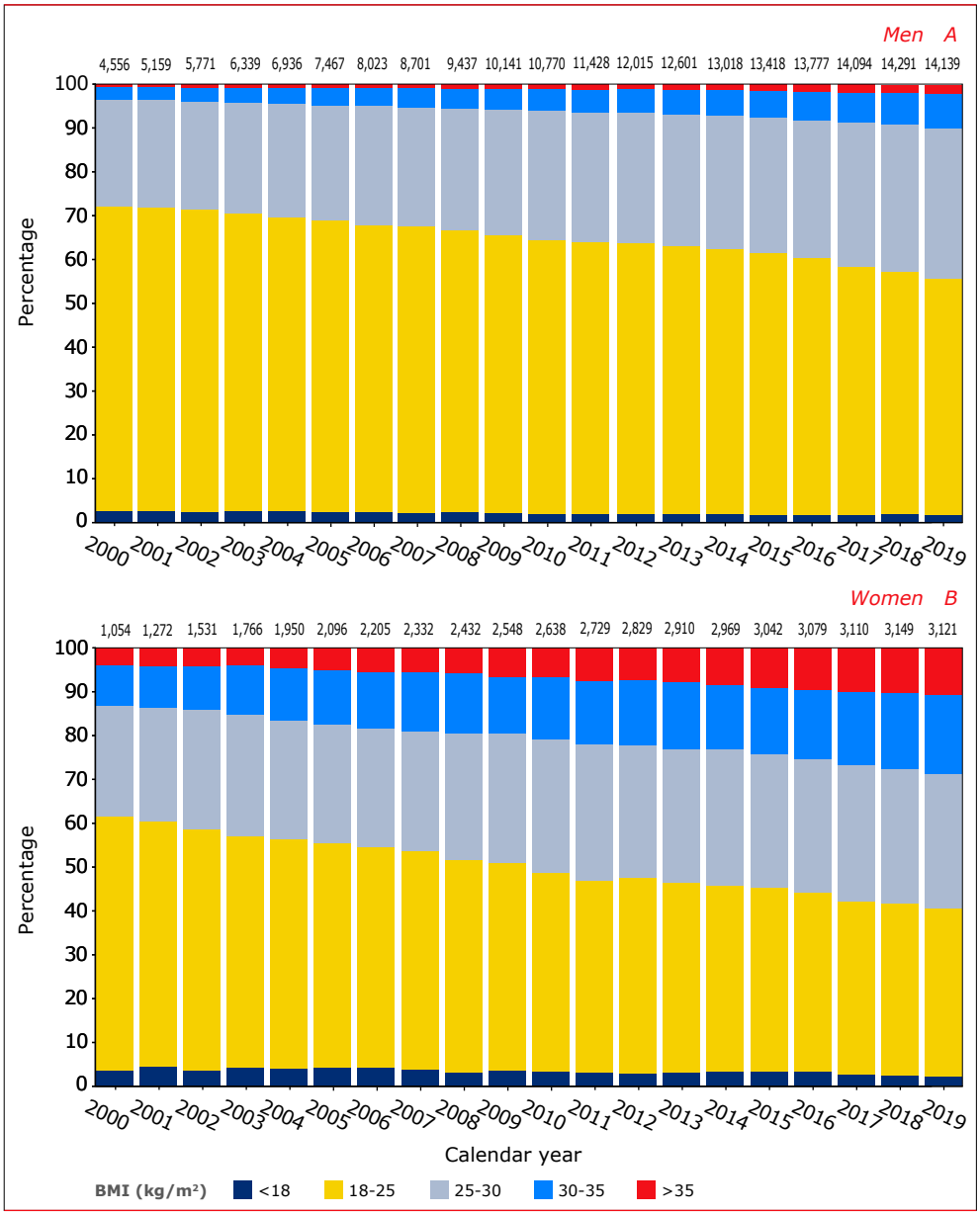
Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the HIV-positive population. This analysis revealed that the increase

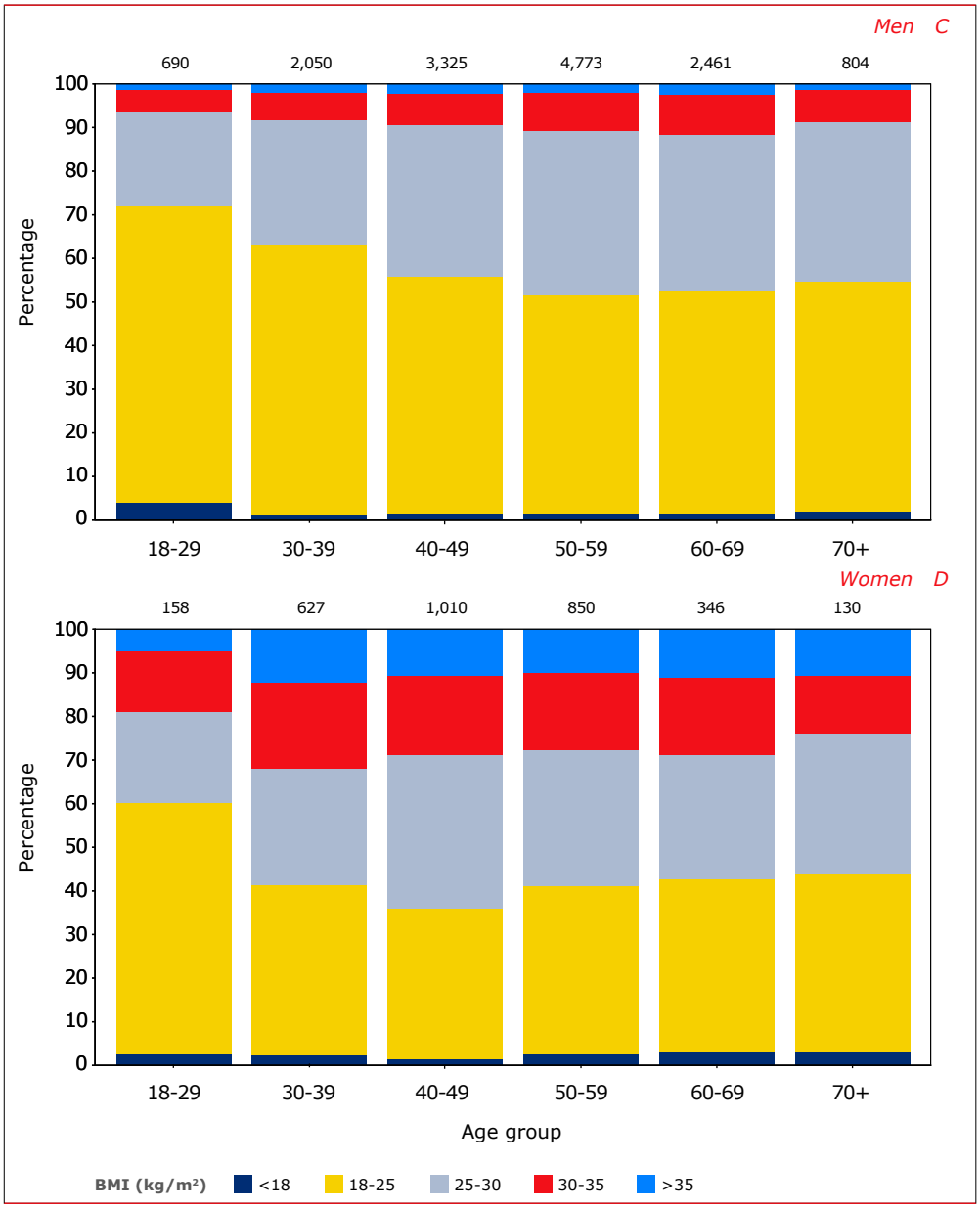
was at least partially driven by changes over time in population demographic characteristics (age, region of origin, transmission risk group) and time since first start of cART, and that this effect was more marked in men than in women.

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 2019 for men and women. Whereas in adult men of all age groups, the proportion classified as obese (10%) was substantially lower than the proportion found in the general Dutch male population (11.3%), in women of all age groups there was more obesity (28%) than in the general Dutch female population (14.0%)[25]. There were substantial differences between native Dutch, Western migrants and non-Western migrants: among males, 9.0% of Dutch, 10.7% of Western migrants and 12.1% of non-Western migrants were obese, whereas in females, those figures were 20.6%, 16.3%, and 34.2%, respectively. Being obese (a BMI over 30) was independently associated with an increased risk of diabetes (IRR 4.82, 95% CI 4.08-5.69, p<0.001) and CKD (IRR 1.19, 95% CI 1.02-1.40, p=0.032), but that was not the case with CVD or non-AIDS-defining malignancies (*Appendix Table 3.7*).

*Figure 3.5A* shows that, in 2019, 48% of those treated with antihypertensives still had grade 1 hypertension or higher. The figures above the bars show that, over time, an increasing number of individuals used antihypertensives. In 2019, 25% (3,890) of individuals not using antihypertensives had grade 1-3 hypertension (*Figure 3.5B*). For 3,588 of these 3,890 individuals, a five-year cardiovascular disease (CVD) risk could be calculated with the recalibrated D:A:D study algorithm[26]. Of the 3,588 individuals, 5.8% 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[27]. *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%) five-year risk were 12% and 5%, respectively, which steadily increased to 20% and 12%, respectively, in 2019. The increase in the percentage of individuals at high or very high risk likely reflects the ageing of the population being studied.

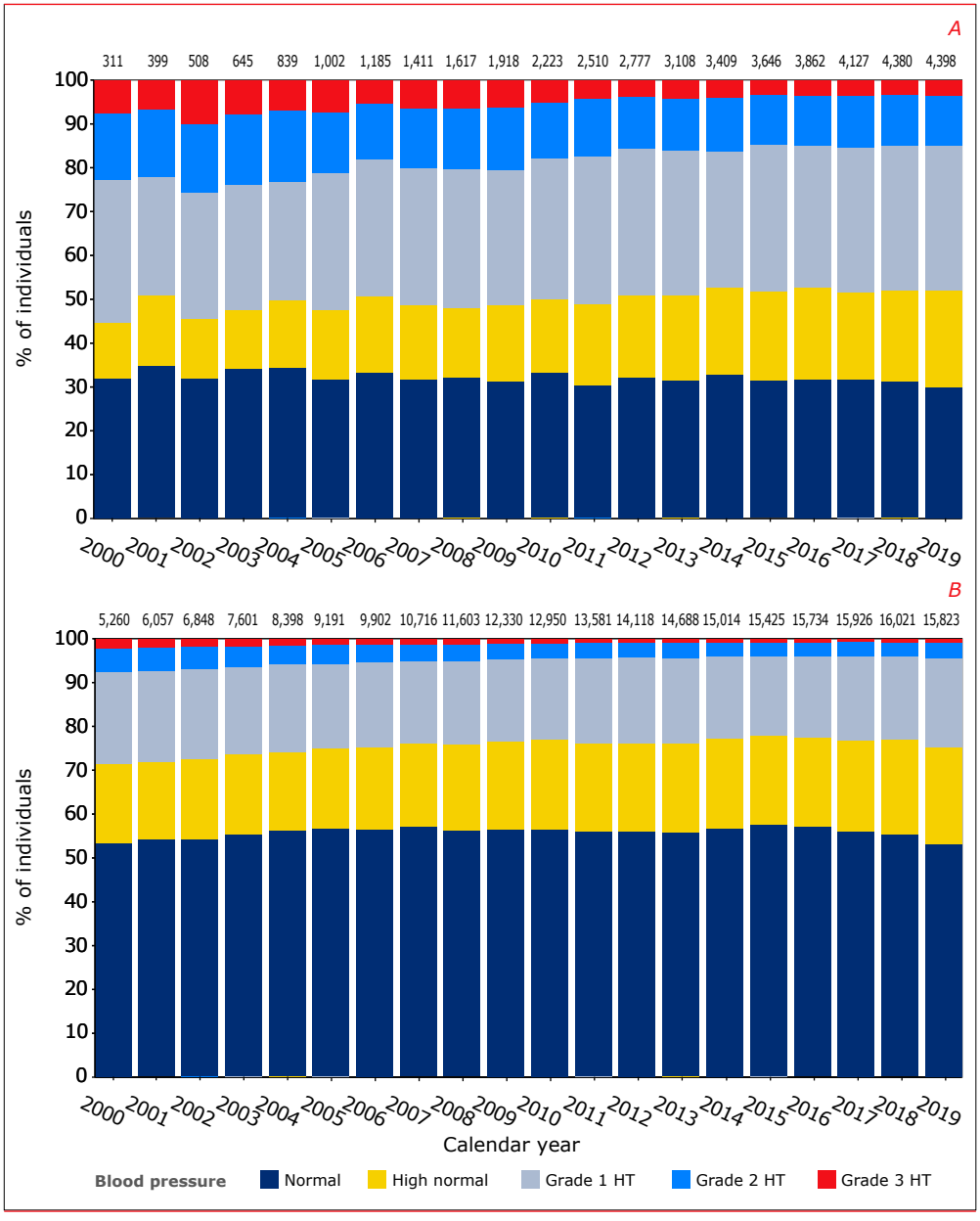
*Figure 3.4A-D: Distribution of the body mass index (BMI) at the end of each calendar year in (A) men, and (B) women, as a percentage of the total number of men and women with a known BMI in each year, and distribution of the BMI over the age groups for (C) men, and (D) women, in 2019. For each individual, 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).*





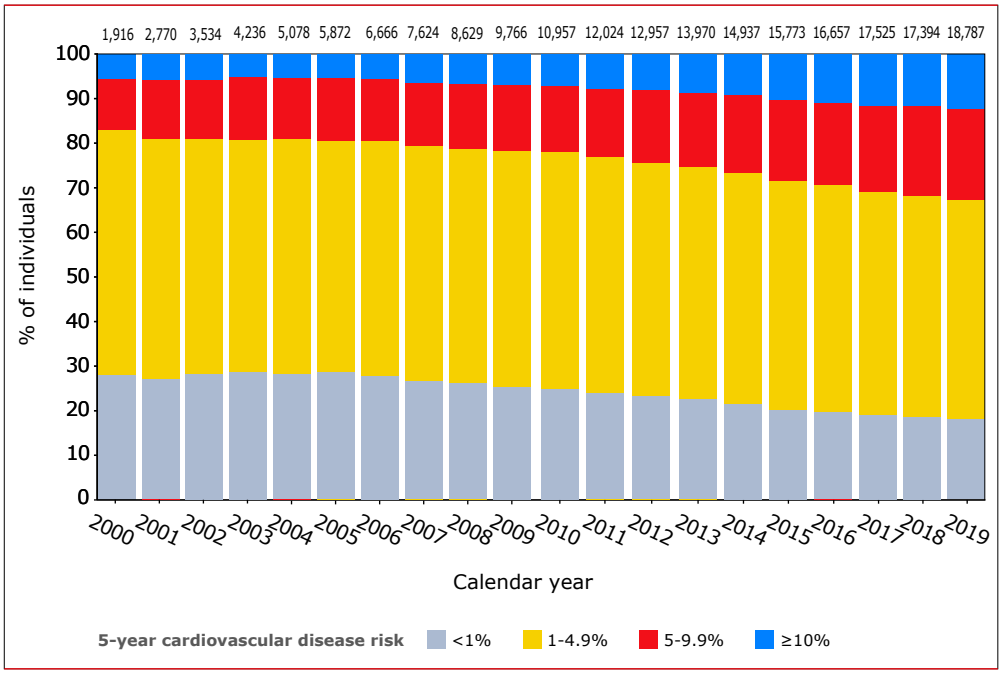

*Legend: BMI=body mass index.*

*Figure 3.5A-B: 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[28]). Normal: systolic blood pressure (SBP) <130 mmHg or diastolic blood pressure (DBP) <85 mmHg; high normal: SBP 130–139 mmHg or DBP 85–89 mmHg; grade 1 hypertension SBP 140–159 mmHg or DBP 90–99 mmHg; grade 2 hypertension SBP 160–179 mmHg or DBP 100–109 mmHg; grade 3 hypertension SBP ≥ 180 mmHg or DBP ≥ 110 mmHg. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.*




*Legend: BP=blood pressure; HT=hypertension.*

*Figure 3.6: 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[26]. Calculation of risk included variables such as total cholesterol, HDL cholesterol, and systolic blood pressure. Values for these variables were estimated on the basis of a 'last observation carried forward' approach. An accurate assessment of an individual's risk requires recent measurements of lipid levels and blood pressure. Recent HDL cholesterol measurements were often lacking or absent. Risk could not be estimated in younger individuals, in particular, because of missing data. Hence, the reported absolute number of individuals is smaller than the number of individuals in active follow up at the end of each calendar year, and older individuals are over-represented. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.*



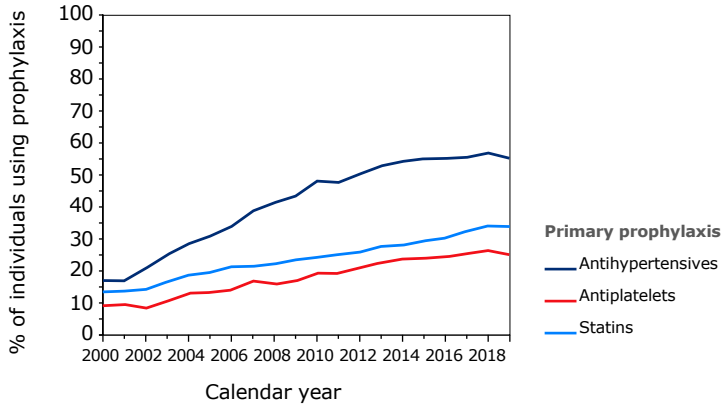

## Use of primary or secondary preventive therapy for myocardial infarction or stroke

### *Primary prevention*

According to EACS guidelines, statin therapy should be offered to individuals with type 2 diabetes or a ten-year CVD risk ≥10%. They also recommend that angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, diuretics, and antihypertensives (verapamil or diltiazem) should be offered to individuals with a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and a ten-year CVD risk ≥20%. For individuals aged 50 years or more with a ten-year CVD risk ≥20%, acetylsalicylic acid is recommended[29]. 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[b] *Figure 3.7* 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 five years.

***Figure 3.7:*** *Percentage of individuals without a previous myocardial infarction, stroke, or cardiovascular surgical procedure who, according to European AIDS Clinical Society (EACS) guidelines, should be offered statin therapy, antiplatelet therapy, or antihypertensives for primary prevention of myocardial infarction or stroke.*



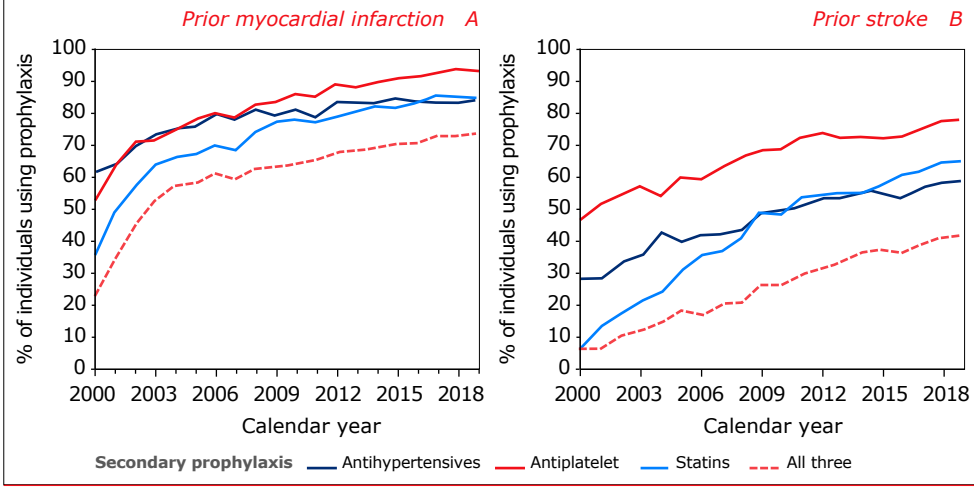

### *Secondary prophylaxis for myocardial infarction or stroke*

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[30,31]. *Figure 3.8A* shows that the percentages of individuals using statins, acetylsalicylic acid/clopidogrel, or antihypertensives after a myocardial infarction increased between 2000 and 2019: in 2019, 85% of individuals with a prior myocardial infarction used statins, 84% used anti-hypertensives, and 93% used acetylsalicylic acid/clopidogrel. Although the use of

b *Richtlijn Cardiovasculair Risicomanagement (CVRM) 2018, https://www.nhg.org/sites/default/files/content/nhg_org/uploads/multidisciplinaire_richtlijn_cardiovaculair_risicomanagement.pdf*

statins and antihypertensives after an ischaemic stroke also increased over time, in 2019 these medications were used less frequently after a stroke than after a myocardial infarction (65% for statins, 78% for acetylsalicylic acid/clopidogrel, and 59% for antihypertensives) (*Figure 3.8B*).

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




## Chronic kidney disease

Glomerular filtration rate (GFR) is a marker of renal function and is commonly estimated by one of three formulae, namely, the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations[32]. As all three equations used to estimate GFR (eGFR) are based on serum creatinine, they may be markedly affected by rapid changes in muscle mass, as is seen in some individuals with advanced HIV disease who commence cART. Of these equations, both the Cockcroft-Gault and the CKD-EPI equations have been validated in HIV-positive individuals[32,33]. However, because the CKD-EPI equation is the one most often used in clinical practice, we have chosen to report eGFR values as estimated by this equation. The distribution of eGFR categories in ml/min/1.73m$^2$ (≥90, normal kidney function; 60-89, mildly reduced; 30-59, moderately reduced; 15-29, severely reduced; and <15, very severely reduced kidney function) is shown in *Figures 3.9A and B* for men and women. The percentage of men with normal kidney function decreased over time from 75% in 2007, to 44% in 2019, 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 >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 <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 7.2 cases per 1,000 PYFU in the period 2008-14 to 12.7 in 2015-19. In women, the incidence rose from 7.3 to 13.1 cases per 1,000 PYFU during the same periods (*Table 3.5*). The standardised incidence ratio in men, but not in women, increased significantly over time (*Table 3.5*).

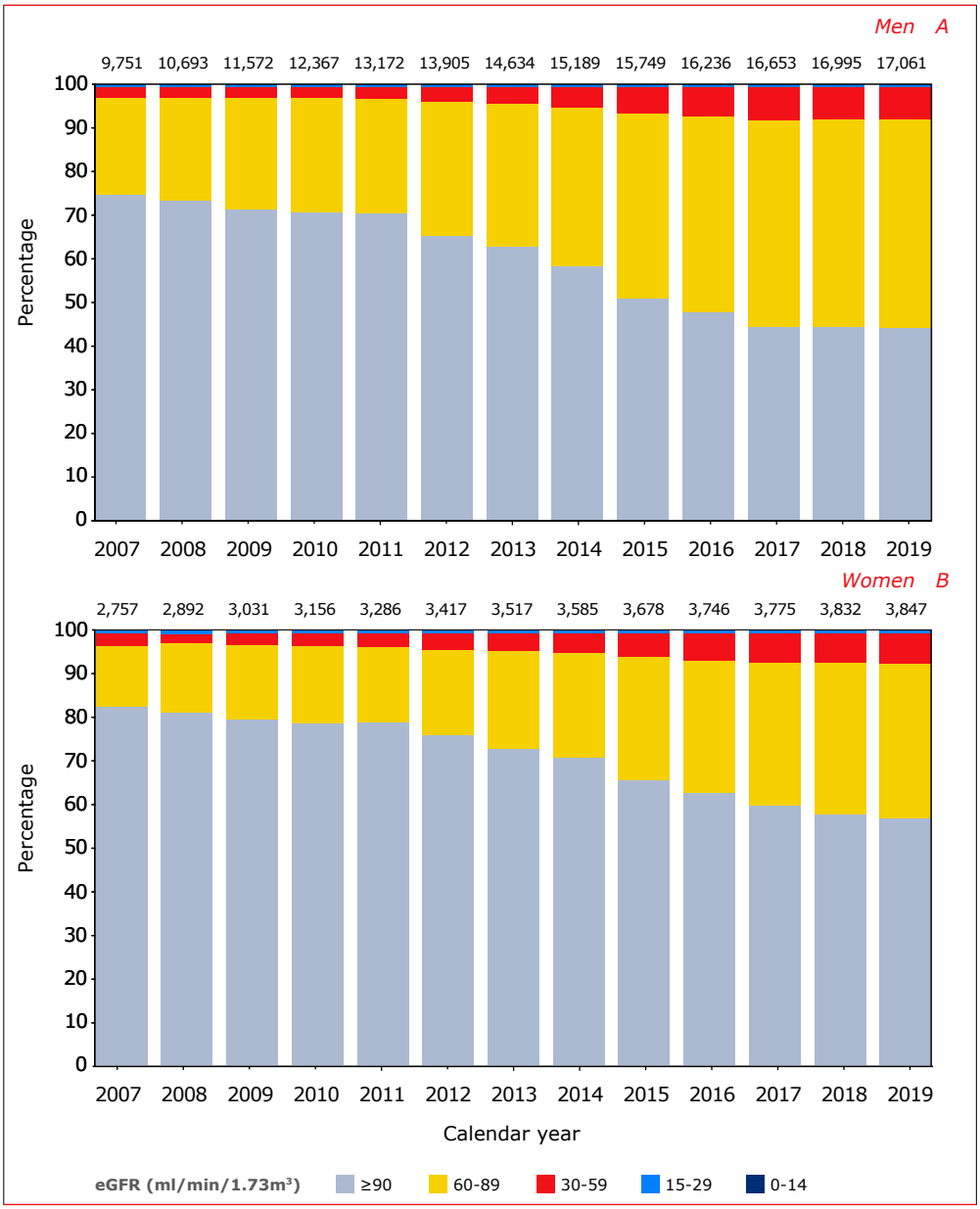
Risk factors for CKD included: female gender; Dutch origin; low current CD4 cell count (<200 cells/mm$^3$); a prior AIDS diagnosis; belonging to the HIV transmission risk group of people who inject drugs; older age group; lower body mass index; hypertension; diabetes mellitus; cardiovascular disease; pre-treatment with monotherapy and dual therapy with nucleoside analogues before the start of cART; and chronic HBV and HCV co-infection (*Appendix Table 3.6*). When current use of cobicistat, rilpivirine, dolutegravir, and bictegravir were added to the model, the increased risk of CKD in the calendar period 2016-19 completely disappeared in comparison to 2008-10 and 2011-15. This suggests that the increase in CKD seen in recent years is largely due to increases in serum creatinine caused by ARV-induced reversible inhibition of two transporters that mediate tubular secretion of creatinine, without affecting the glomerular filtration rate (namely, organic cation transporter 2 (OCT2), and multidrug and toxin extrusion transporter (MATE1)) and 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 (> 12 months) TDF-containing regimen to a TAF-containing regimen. We compared the serum creatinine levels measured within 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 325 subjects fulfilled the above criteria and switched from TDF to TAF because of renal toxicity / elevated serum creatinine. Another 2,637 subjects also fulfilled the above criteria but switched from TDF to TAF for other reasons. The 325 subjects who switched because of renal toxicity, had a median serum creatinine level of 116 (IQR 106-125) micromol/L prior to the switch, and showed a median change of -6 (IQR 0 to -15) micromol/L ≥6 months after the switch. The 2,637 subjects who switched because of other reasons had a median serum creatinine level of 88 (IQR 77-100) micromol/L prior to the switch, and showed a median change of -1 (IQR +5 to -7) micromol/L ≥6 months after the switch.

Using the same approach as for the switch from TDF to TAF, we also looked at changes in serum creatinine in subjects who initiated dolutegravir, bictegravir, rilpivirine, ritonavir or cobicistat, without a concomitant switch (start or stop) of any of the other OCT2 / MATE1 inhibitors, nor of TDF or TAF. In 848 subjects who initiated dolutegravir without concomitant changes in any other OCT2 / MATE1 inhibitor, TDF or TAF, the pre-switch median serum creatinine level was 81 (IQR 71-94) micromol /L and the change in serum creatinine ≥6 months after the switch was +11 (IQR +5 to +18) micromol/L. In 664 subjects switching to rilpivirine with a median baseline creatinine level of 81 (IQR 71-91) micromol/L, the median change was +9 (IQR +3 to +15) micromol/L. In 859 subjects switching to ritonavir (100mg once daily) with a median baseline creatinine level of 75 (IQR 63-85) micromol/L, the median change was +3 (IQR -4 to +10) micromol/L. In 292 subjects switching to cobicistat with a median baseline creatinine level of 82 (IQR 72-92) micromol/L, the median change was +9 (IQR +3 to +18) micromol/L. Not enough subjects switched to bictegravir without a concomitant switch (start or stop) of any of the other OCT2 / MATE1 inhibitors, nor of TDF or TAF, to allow for a reliable estimation of the effect of this switch on serum creatinine levels.

*Figure 3.9A-B: 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.*



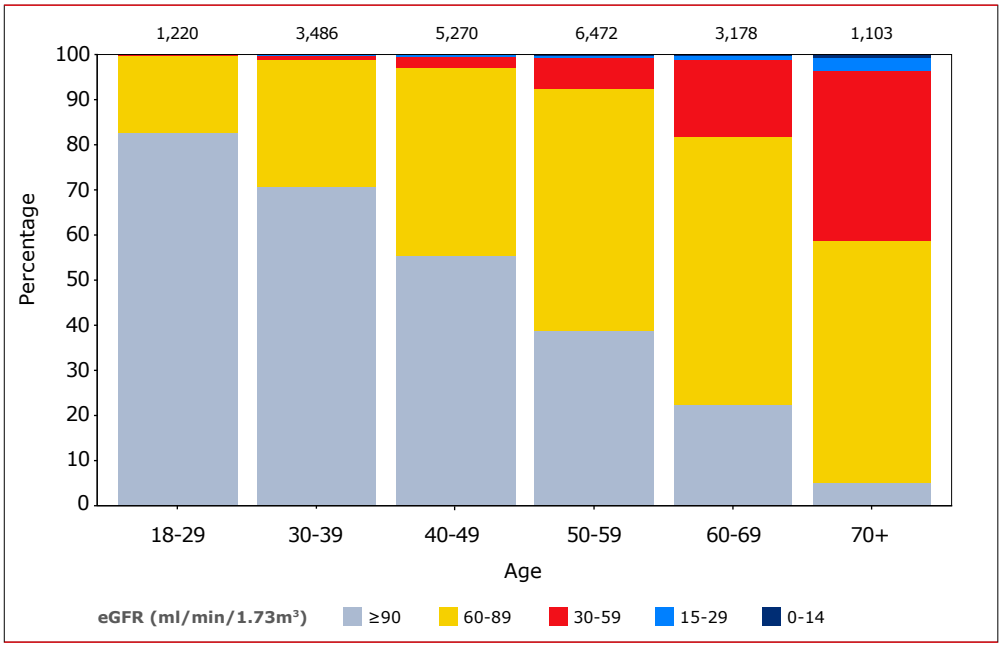

*Legend: eGFR=estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60-89 ml/min/1.73m²: mildly reduced; 30-59 ml/min/1.73m²: moderately reduced; 15-29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

*Table 3.5: Crude chronic kidney disease incidence per 1,000 person years of follow up between 2008-14, and between 2015-19, 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 | 7.2 (6.5-8.1) | 0.70 (0.62-0.77) | 7.3 (5.8-9.0) | 0.79 (0.62-0.97) |
| 2015-2019 | 12.7 (11.7-13.7) | 1 (reference) | 13.1 (11.0-15.5) | 1 (reference) |

**Standardised according to the observed age distribution between 2015-2019.*
***Legend:** CI=confidence interval; PYFU=person years of follow up.*

*Figure 3.10: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2019 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 2019, 1,707 diagnoses of non-AIDS-defining malignancy in 1,585 unique individuals were recorded in SHM's database. An additional 696 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 (17%); haematological malignancies (excluding AIDS-defining non-Hodgkin's lymphoma, 15%); intestinal cancer (excluding liver cancer, 13%); invasive anal cancer (not AIN, 12%); prostate cancer (9%); and head and neck cancers (8%). *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 2016-19, 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 2016-19, than in 2000-10, and to a lesser extent 2011-15 (*Table 3.7*).

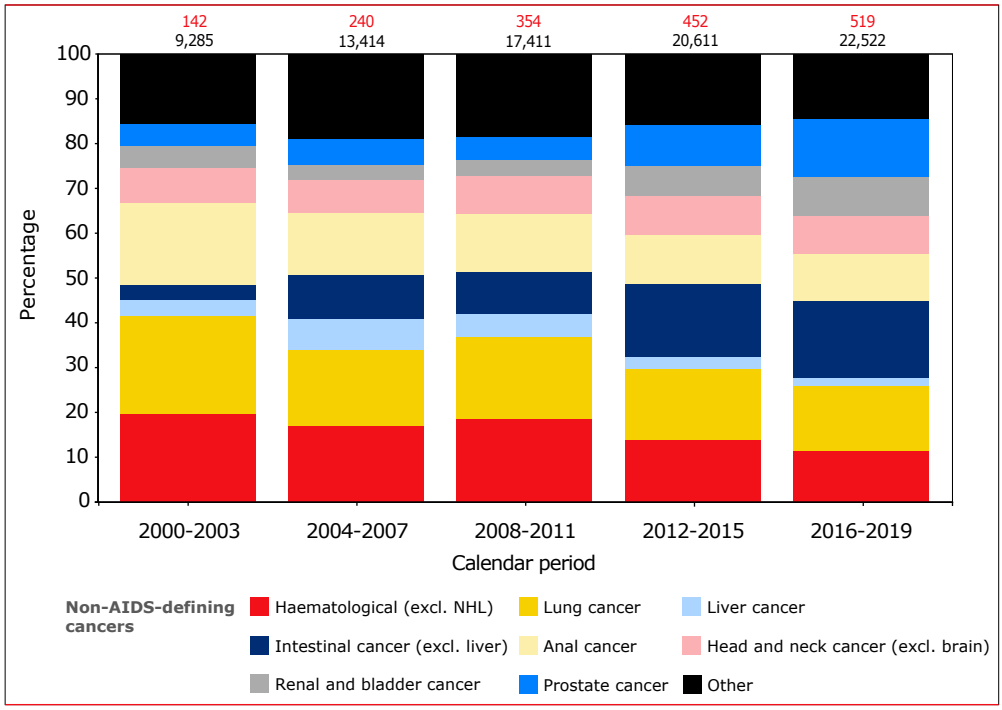
Demographic and clinical factors independently associated with an increased risk of a first non-AIDS-defining malignancy were: older age group; acquiring HIV-1 through injecting drugs or contact with blood or blood products; lower current CD4 cell count (CD4 below 350 cells/mm$^3$); low body mass index; prior AIDS; chronic HBV co-infection; and current or past smoking (*Appendix Table 3.6*). Furthermore, people who had not yet started cART, or 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] 1.25 (95% CI 1.00-1.57) and 1.20 (1.03-1.41) respectively). 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 0.54, 95% CI 0.33-0.86) 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 2019, 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%, compared with 75.7% for CVD, 81.5% for DM, and 86.0% for CKD (*Appendix Figure 3.1*). In the same period, the five-year survival rate of adults newly-entering care in one of the Dutch HIV treatment centres was 95.6%, and 82.2% 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

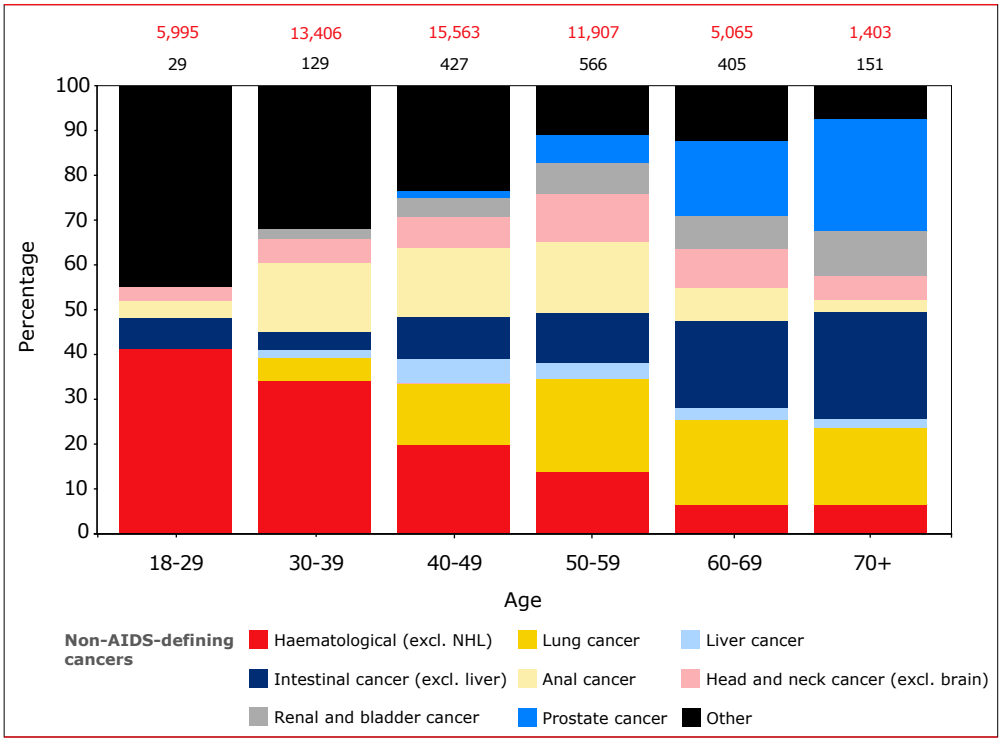
In total, 201 HIV-positive men and seven HIV-positive women were diagnosed with anal cancer. Among HIV-positive men, the incidence of anal cancer fluctuated between 0.5 and 1.4 cases per 1,000 PYFU between 2000 and 2019 (*Figure 3.3G*). A 2015 study exploring the incidence of anal cancer among HIV-1-positive individuals in the Netherlands showed a significantly higher incidence of anal cancer in men who have sex with men (MSM), than in heterosexual men[34]. However, in this chapter, we will not report on the trend in anal cancer among heterosexual men over time, as the number of heterosexual men with anal cancer is too small (n=22) to analyse.

*Figure 3.11: Relative changes in non-AIDS-defining malignancies between 2000 and 2019 in HIV-1-positive individuals in the Netherlands. The numbers at the top of each bar represent the number of non-AIDS-defining cancer diagnoses during that calendar period.*




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

*Figure 3.12: Relative changes in non-AIDS-defining malignancies with increasing age in HIV-1-positive individuals in the Netherlands. The numbers at the top of each bar represent the number of individuals at risk and the number of cancer diagnoses in that age category between 2000 and 2019.*




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

*Table 3.6: Most common non-AIDS-defining malignancies diagnosed between 2000-19, 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 | 284 | 16.6 | 15.1 |
| Haematological cancer (excluding non-Hodgkin's lymphoma) | 258 | 15.1 | 65.1 |
| Anal cancer | 226 | 13.2 | 33.0 |
| Intestinal cancer (excluding liver) | 208 | 12.2 | 63.4 |
| Head and neck cancer (excluding brain) | 149 | 8.7 | 80.0 |
| Prostate cancer | 143 | 8.4 | 58.3 |
| Other cancers | 103 | 6.0 | 67.3 |
| Renal and bladder cancer | 96 | 5.6 | 48.9 |
| Malignant melanoma | 73 | 4.3 | 73.0 |
| Liver cancer | 59 | 3.5 | 14.2 |
| Breast cancer | 44 | 2.6 | 81.7 |
| Testicular cancer | 33 | 1.9 | 86.2 |
| Gynaecological cancer (excluding cervical) | 24 | 1.4 | 64.6 |
| Central nervous system (CNS) cancer | 7 | 0.4 | 57.1 |

*Table 3.7: Crude non-AIDS-defining malignancy incidence per 1,000 person years of follow up between 2000-10, 2011-15, and 2016-19, 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 (6.1-7.1) | 1.36 (1.24-1.47) | 3.1 (2.5-3.9) | 1.28 (0.98-1.57) |
| 2011-2015 | 6.6 (6.0-7.2) | 1.07 (0.97-1.17) | 4.3 (3.3-5.4) | 1.18 (0.90-1.46) |
| 2016-2019 | 7.3 (6.6-8.0) | 1 (reference) | 4.4 (3.4-5.7) | 1 (reference) |

**Standardised according to the observed age distribution between 2011-2019.*

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

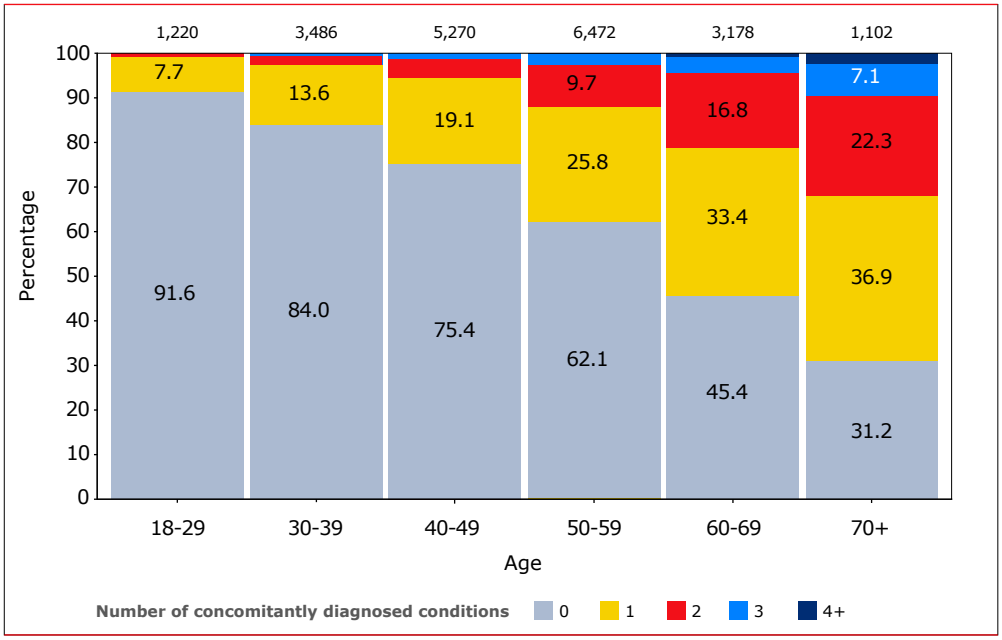
## Multimorbidity

We have also 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 ≥160 mmHg and/or diastolic pressure ≥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 2019. 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 2.17, 95% CI 2.08-2.26, $p<0.001$, per additional comorbidity diagnosed).

*Figure 3.13: Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2019. 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[c]) of the comedications. Note that coformulated combinations, such as cotrimoxazole, have a single ATC code and therefore increase the comedication count by one.

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

In 2019, 23.5% of adults in active follow up had no recorded comedication use, while 32.4%, 15.7%, 9.6%, and 6.2% used one, two, three or four comedications, respectively. A further 12.7% used five or more non-antiretroviral comedications in addition to their cART regimen, which qualifies as polypharmacy. The prevalence of polypharmacy among adults has increased over calendar time (*Figure 3.14*): in 2000, just 3.0% of adults used 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 2007-19, polypharmacy was also associated with an increased risk of death (RR 2.44, 95% CI 2.17-2.74, $p<0.001$) independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities (i.e., multimorbidity). All comedications used by at least 250 adult patients in care in 2019 are listed in *Table 3.8*.

*Table 3.8: Use of comedications in 2019.*

| Comedication use in 2019 | n | % |
|---|---|---|
| ATC group | | |
| Vitamins | 4576 | 11.1 |
| Lipid modifying agents | 3823 | 9.3 |
| Drugs for acid-related disorders | 3281 | 8.0 |
| Agents acting on the renin-angiotensin system | 2926 | 7.1 |
| Antithrombotic agents | 2446 | 6.0 |
| Psychoanaleptics | 2021 | 4.9 |
| Mineral supplements | 1932 | 4.7 |
| Drugs used in diabetes | 1698 | 4.1 |
| Beta blocking agents | 1527 | 3.7 |
| Urological drugs | 1481 | 3.6 |
| Psycholeptics drugs | 1295 | 3.2 |
| Calcium channel blockers | 1258 | 3.1 |
| Antibacterial drugs | 1087 | 2.6 |
| Sex hormones and modulators of the genital system | 996 | 2.4 |
| Drugs for obstructive airway diseases | 985 | 2.4 |
| Diuretic drugs | 976 | 2.4 |
| Antianaemic drugs | 933 | 2.3 |
| Antiepileptic drugs | 751 | 1.8 |
| Analgesic drugs | 736 | 1.8 |
| Antiviral drugs | 670 | 1.6 |
| Corticosteroids systemic | 553 | 1.3 |
| Cardiac therapy | 532 | 1.3 |
| Nasal preparations | 482 | 1.2 |
| Antimycotic drugs | 431 | 1.0 |
| Antidiarrheals, intestinal anti-inflammatory/anti-infective agents | 384 | 0.9 |
| Drugs affecting bone structure and mineralisation | 342 | 0.8 |
| Thyroid therapy | 313 | 0.8 |

*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.*

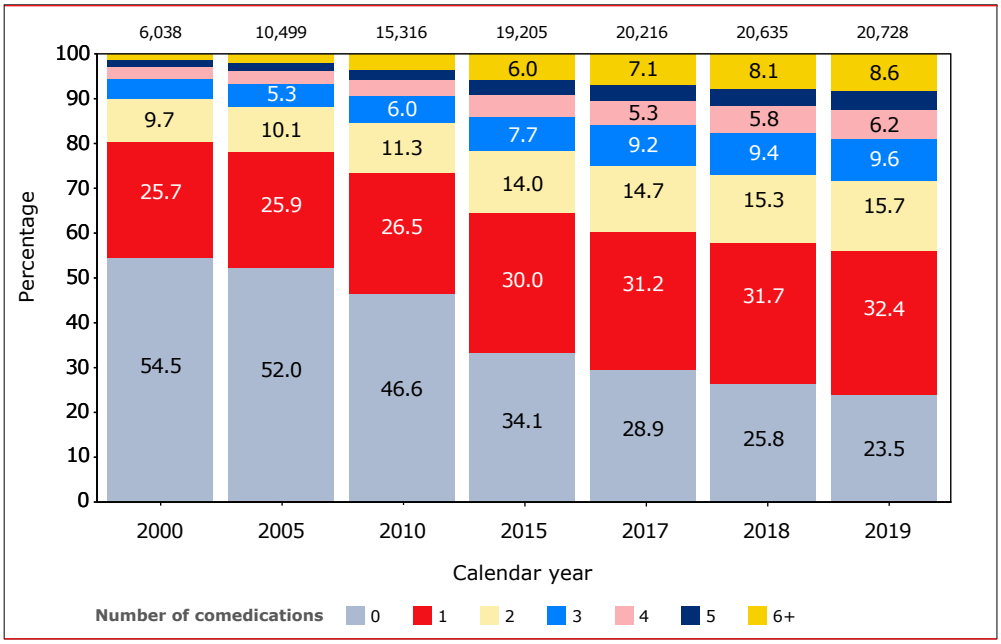
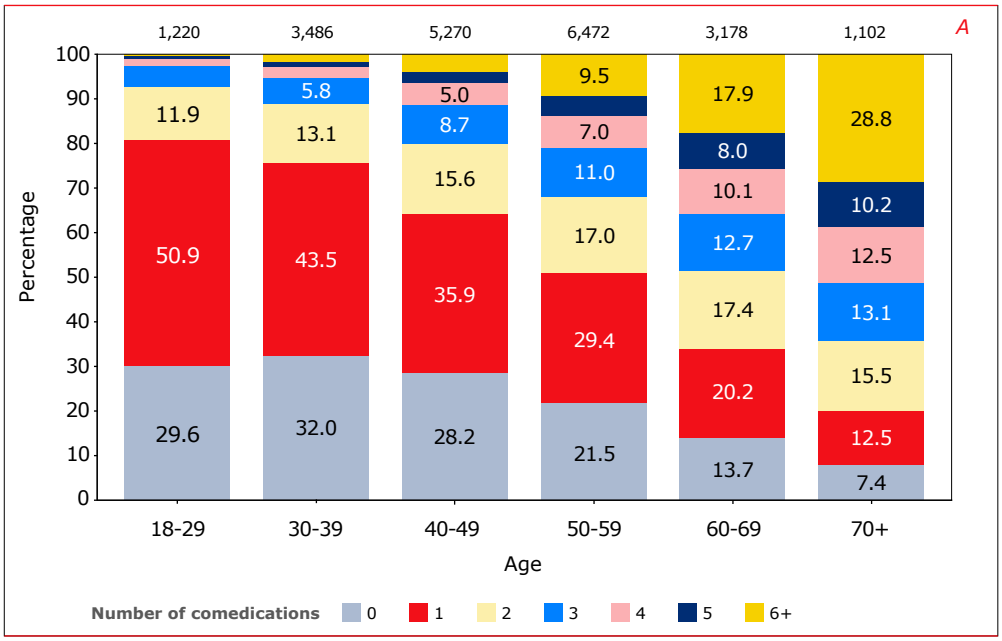


*Figure 3.15A-B: Number of comedications used by (A) age group, and (B) gender. The numbers at the top of each bar represent the number of individuals contributing data to that age/gender category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age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



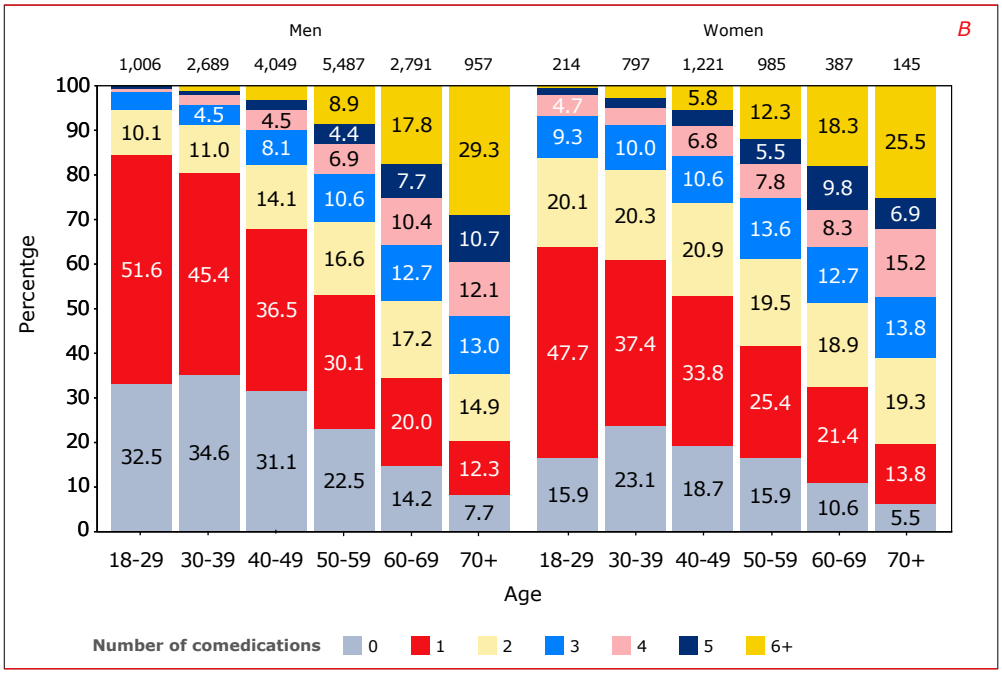
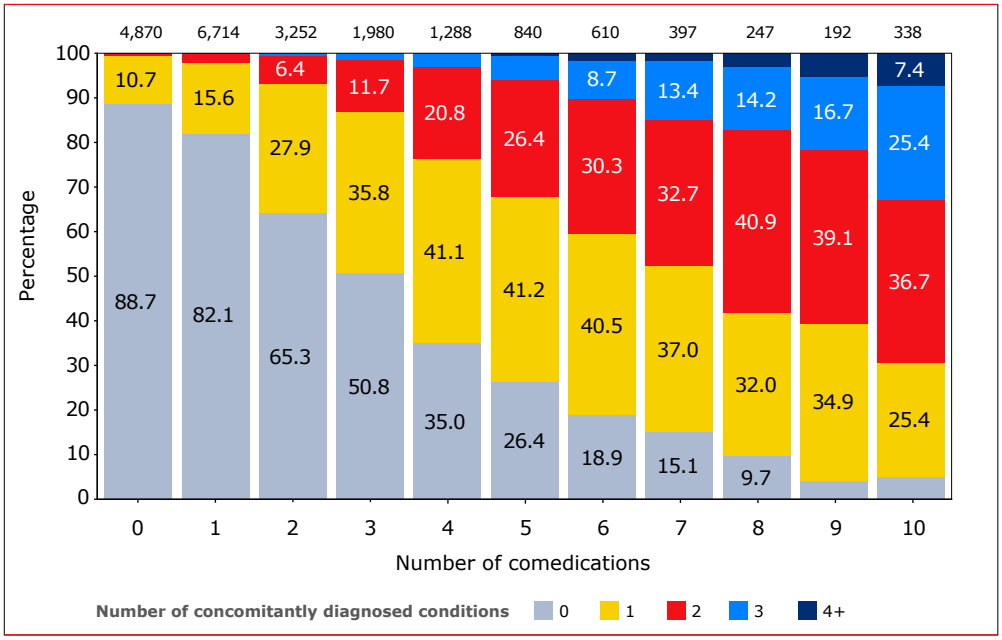



*Figure 3.16: Number of comedications used in relation to the number of prevalent comorbidities. The numbers at the top of each bar represent the number of individuals contributing data to that category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per 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, consistent with reductions reported in studies from Spain[35], Denmark[36], several other European countries[37], and the USA[38]. The limited, but decreasing, number of individuals who still die of AIDS each year, are mainly those who present late for care with already advanced immunodeficiency. Nonetheless, overall, the five-year survival rate after a first AIDS-defining condition was far greater than after a diagnosis of cardiovascular disease (CVD), or a non-AIDS-defining malignancy. Death is increasingly likely to be the result of a non-AIDS cause, with 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, mortality rates among people living with HIV remain higher than in the

general population, although they do approach, or may even drop below, general population rates in individuals who achieve CD4 counts above 500 cells/mm$^3$ on treatment[39,40].

### Diabetes and cardiovascular disease

Whereas the crude incidence of diabetes mellitus and CVD in men and women was found to have remained relatively stable, the age-standardised incidence for both diseases declined over time in men. This decline may suggest improved awareness, prevention (including switching from drugs associated with an increased risk of diabetes mellitus[41] and myocardial infarction[42,43] to those that, to date, have not been associated with such risks), and increased attention to managing traditional risk factors for these conditions. 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 because an increasing proportion of individuals have been using cART long enough to have reached high CD4 cell counts). The observation that the age-standardised incidence ratios do not decline as much in women remains unexplained and needs further study. Finally, the risk factors observed for diabetes mellitus and CVD (including age, hypertension, smoking, and obesity), were similar to those previously reported in other studies[41,44,45]. Several of these risk factors have been reported to be more prevalent among people living with HIV[19].

### Cardiovascular risk factors

Despite the increasing age of the HIV-positive population, the proportion at high, or very high cardiovascular risk increased only slightly over the period 2000-19. This suggests 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[46] (*Chapter 2*). Significant room for further improvement remains, however, particularly given the suboptimal use of statin therapy, antihypertensive therapy, and low-dose acetylsalicylic acid as secondary prevention following a myocardial infarction or ischaemic stroke, and the low, albeit slowly improving, uptake of these medications in the prevention of primary cardiovascular disease.

The clinical significance of the increase in BMI over time, especially in women, requires further study. Recent results have suggested that weight gain after starting cART is associated with lower mortality for normal-weight individuals, but have found no clear benefit for overweight or obese individuals[47]. However, another study found that weight gain after starting cART was associated with an

increased risk of diabetes, and, in those with a pre-antiretroviral therapy BMI in the normal range, with an increased risk of cardiovascular disease[48]. Prospective longitudinal monitoring of lipid levels; smoking status; blood pressure; weight; and other risk factors will be important to further optimise the assessment of cardiovascular risk in our increasingly ageing HIV-1-positive population, and to study the impact of interventions, such as the use of statins and antihypertensive therapy, in modifying disease risk. In our cohort, we found that obesity and overweight were significant risk factors for developing new-onset diabetes 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 for CKD, as were individuals with advanced immunodeficiency. In addition, other studies have also reported hepatitis B and C virus co-infection[49,50], and the use of tenofovir disoproxil fumarate, atazanavir/ritonavir, and lopinavir/ritonavir, to be additional independent predictors of chronic renal impairment[51]. Moreover, renal impairment in the HIV-positive population is associated with an increased risk of cardiovascular disease[52]. 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, anal, and head and neck cancer, as well as Hodgkin's lymphoma. The crude incidence of NADM in the Netherlands has remained stable over time, and we also observed a decline in age-standardised incidence of NADM in men. In addition, our analyses showed that individuals diagnosed with NADM were more likely to be older. This is in line with data from other cohorts, including the Swiss HIV cohort, that have also reported an increased incidence of NADM with increasing age[53–56]. Additional risk factors for NADM identified in our analyses

were: current or past smoking; a CD4 count below 350 cells/mm$^3$; not being on cART, or having been pre-treated with NRTI before the start of cART; and a prior AIDS diagnosis. Other studies have reported that the effect of immunodeficiency may be stronger for infection-related non-AIDS-defining malignancies[57]. 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 independently associated with increased risk of mortality (RR 2.17, 95% CI 2.08-2.26, p<0.001, per additional comorbidity diagnosed).

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 12.7% of adults in active follow up in 2019. 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 2007-19, polypharmacy was also associated with an increased risk of death (RR 2.44, 95% CI 2.17-2.74, p<0.001), 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 in order 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[58–60]. 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 people newly-entering care with an AIDS diagnosis, underlines the importance of primary prevention, early diagnosis and aggressive pursuit of secondary prevention and treatment of non-AIDS comorbidities in the HIV-positive population. Studies such as the ongoing Comorbidity and Aging with HIV ($AGE_nIV$) cohort study have provided further insights into the independent contribution of HIV and HIV-associated factors, such as innate and adaptive immune and coagulation activation and inflammation. This will hopefully guide the development of interventions that target relevant pathophysiological mechanisms[9,61].

It is important to note that the risk of many, if not each, of the comorbidities frequently identified in people living with HIV, is determined by multiple factors. Besides immunodeficiency, additional key contributors for consideration include both well-known traditional unmodifiable risk factors, such as age and genetic predisposition, and modifiable lifestyle-related factors, as well as known, and 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 multimorbidity, 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 concerning 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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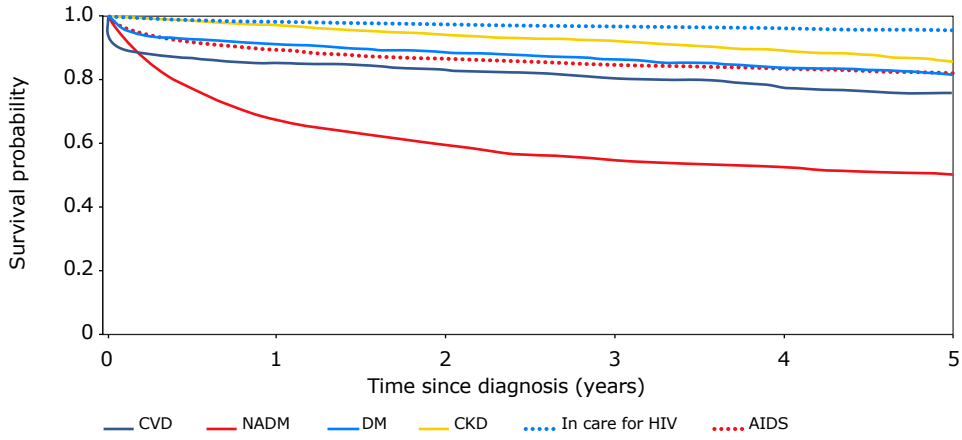
# Appendix

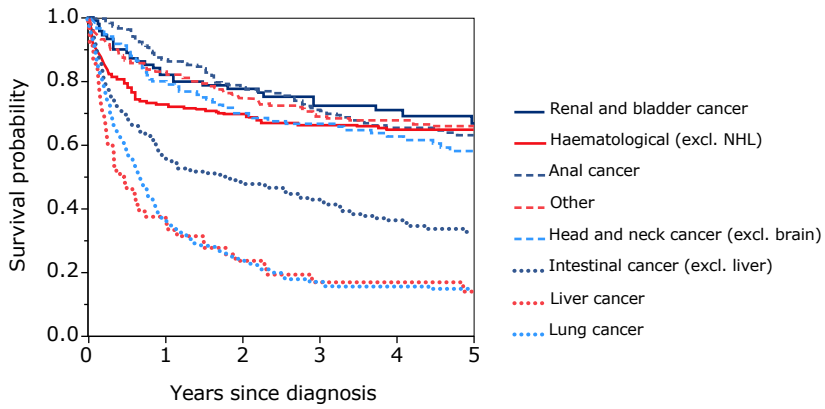
***Appendix Figure 3.1:*** *Estimated five-year survival following the diagnosis of cardiovascular disease, non-AIDS-defining malignancy, diabetes mellitus, and chronic kidney disease. Two reference groups are included: survival from date of entry into HIV care (after 1 January 2000), and from date of 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 | 1,403 | 1,141 | 1,014 | 880 | 765 | 657 |
| NADM | 1,330 | 853 | 665 | 530 | 430 | 353 |
| DM | 1,349 | 1,173 | 1,037 | 916 | 811 | 714 |
| CKD | 2,138 | 1,835 | 1,547 | 1,239 | 957 | 726 |
| In care for HIV | 21,544 | 19,633 | 18,255 | 17,018 | 15,898 | 14,661 |
| AIDS | 3,479 | 2,960 | 2,731 | 2,540 | 2,375 | 2,164 |

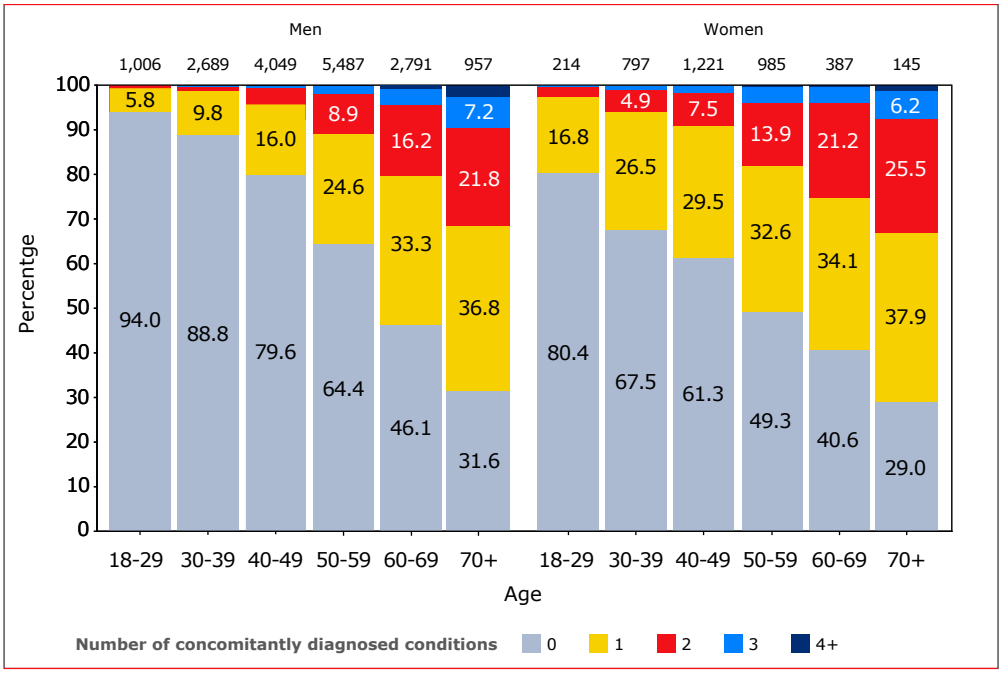
***Legend:*** *CVD=cardiovascular disease; NADM=non-AIDS defining malignancy; DM=diabetes mellitus; CKD=chronic kidney disease.*

***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 2019.*

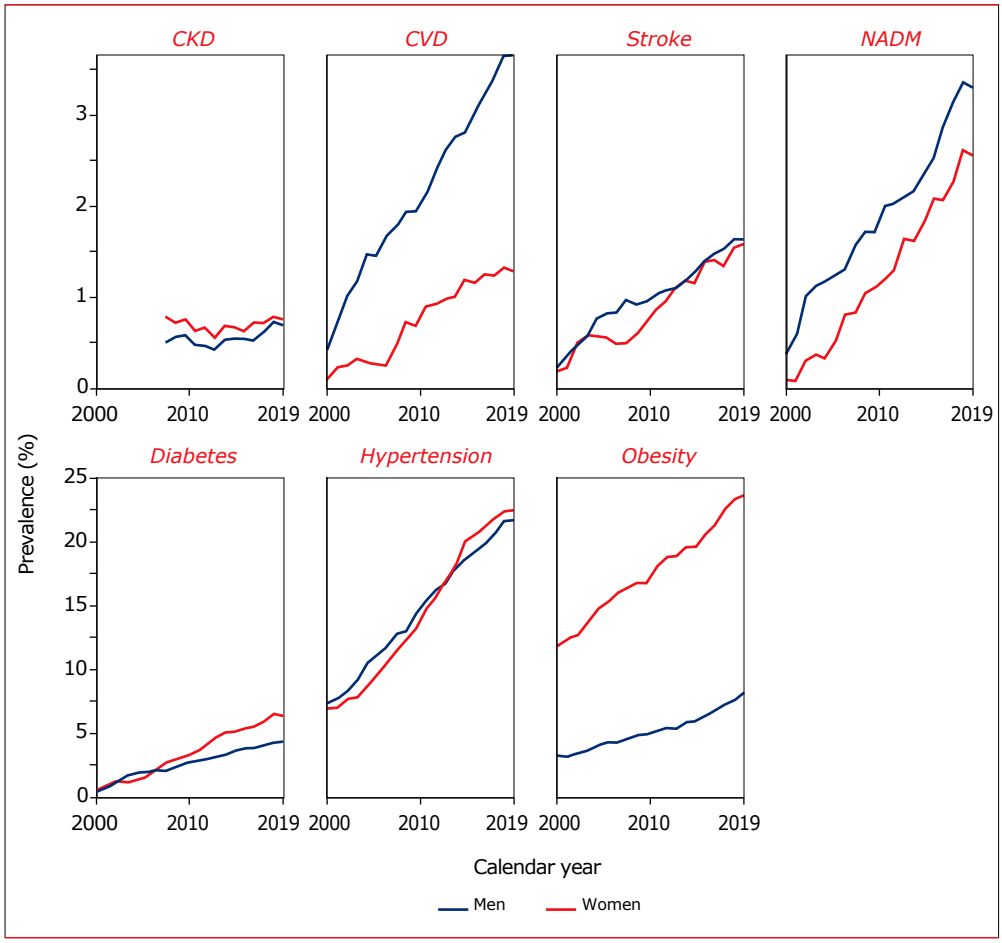



***Legend:*** *excl.=excluding; NHL=non-Hodgkin's lymphoma.*

*Appendix Figure 3.3: Prevalence of non-AIDS multimorbidity by gender in the adult population in 2019. 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.*

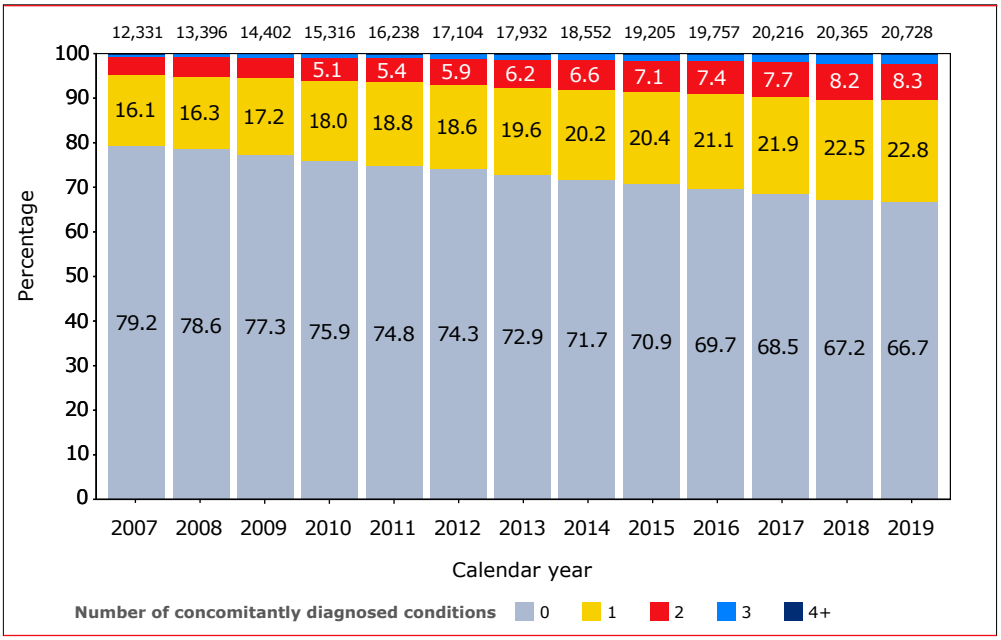


***Appendix Figure 3.4:*** *Prevalence of non-AIDS comorbidities in the adult population between 2000 and 2019.*




***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, 2001-05, 2006-10, and 2011-19.*

| | Calendar period | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Causes of death** | **96-00** | **01-05** | **06-10** | **11-15** | **16-19** | **2016** | **2017** | **2018** | **2019** |
| AIDS | | | | | | | | | |
| AIDS - infection | 69 | 120 | 147 | 103 | 18 | 6 | 4 | 3 | 5 |
| AIDS - malignancy | 60 | 63 | 61 | 43 | 41 | 8 | 13 | 12 | 8 |
| AIDS - unclassifiable | 89 | 63 | 19 | 15 | 21 | 10 | 3 | 3 | 5 |
| *Subtotal* | *218* | *246* | *227* | *161* | *80* | *24* | *20* | *18* | *18* |
| Non-AIDS malignancies | *30* | *95* | *136* | *193* | *210* | *49* | *62* | *48* | *51* |
| Cardiovascular disease | | | | | | | | | |
| Myocardial infarction | 14 | 30 | 46 | 40 | 21 | 8 | 4 | 2 | 7 |
| Stroke | 3 | 11 | 13 | 11 | 15 | 7 | 3 | 3 | 2 |
| Other CVD | 6 | 24 | 26 | 50 | 49 | 16 | 10 | 15 | 8 |
| *Subtotal* | *23* | *65* | *85* | *101* | *85* | *31* | *17* | *20* | *17* |
| Non-AIDS infection | *23* | *42* | *32* | *27* | *24* | *7* | *3* | *10* | *4* |
| Liver disease | *15* | *28* | *55* | *43* | *20* | *6* | *7* | *7* | *.* |
| Lung disease | *7* | *11* | *30* | *38* | *47* | *13* | *14* | *9* | *11* |
| Non-natural death | | | | | | | | | |
| Accident or violence | 6 | 11 | 22 | 16 | 14 | 7 | 2 | 4 | 1 |
| Suicide | 12 | 30 | 30 | 52 | 36 | 10 | 12 | 11 | 3 |
| Euthanasia | 7 | 5 | . | 2 | 1 | 1 | . | . | . |
| *Subtotal* | *25* | *46* | *52* | *70* | *51* | *18* | *14* | *15* | *4* |
| Alcohol and substance abuse | 12 | 15 | 27 | 18 | 19 | 10 | 4 | 4 | 1 |
| Other causes | 21 | 24 | 23 | 43 | 47 | 13 | 8 | 18 | 8 |
| Unknown | 23 | 57 | 53 | 84 | 83 | 20 | 18 | 21 | 24 |
| **Total** | **397** | **629** | **720** | **778** | **666** | **191** | **167** | **170** | **138** |

***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 | 1.32 (1.14-1.52) | <.001 | | 0.97 (0.83-1.14) | 0.750 | |
| Region of birth | | | | | | |
| Netherlands | 1 (reference) | | 0.108 | 1 (reference) | | 0.020 |
| Other | 0.92 (0.83-1.02) | 0.109 | | 1.15 (1.02-1.30) | 0.020 | |
| HIV-1 transmission route | | | | | | |
| Blood contact | 0.71 (0.50-1.01) | 0.054 | | 0.77 (0.53-1.12) | 0.170 | |
| Heterosexual | 1.08 (0.95-1.22) | 0.234 | | 0.86 (0.74-1.00) | 0.057 | |
| IDU | 1.62 (1.33-1.96) | <.001 | | 0.65 (0.50-0.84) | 0.001 | |
| MSM | 1 (reference) | | <.001 | 1 (reference) | | <.001 |
| Age* | | | | | | |
| 18-29 | 0.91 (0.65-1.26) | 0.553 | <.001 | 1.04 (0.84-1.28) | 0.720 | <.001 |
| 30-39 | 1 (reference) | | | 1 (reference) | | |
| 40-49 | 1.53 (1.31-1.78) | <.001 | | 1.12 (0.99-1.28) | 0.079 | |
| 50-59 | 2.65 (2.27-3.09) | <.001 | | 1.38 (1.19-1.61) | <.001 | |
| 60-69 | 4.76 (4.03-5.62) | <.001 | | 1.41 (1.16-1.72) | <.001 | |
| 70+ | 10.24 (8.40-12.48) | <.001 | | 1.89 (1.34-2.67) | <.001 | |
| CD4 cell count** | | | | | | |
| 0-50 | 13.48 (11.16-16.28) | <.001 | <.001 | 6.32 (5.07-7.87) | <.001 | <.001 |
| 50-199 | 5.11 (4.43-5.89) | <.001 | | 2.59 (2.18-3.06) | <.001 | |
| 200-349 | 2.17 (1.89-2.50) | <.001 | | 1.49 (1.26-1.75) | <.001 | |
| 350-499 | 1.43 (1.24-1.65) | <.001 | | 1.22 (1.03-1.44) | 0.021 | |
| 500-749 | 1 (reference) | | | 1 (reference) | | |
| 750+ | 0.88 (0.75-1.03) | 0.101 | | 1.10 (0.90-1.34) | 0.357 | |
| Per year longer on cART with HIV RNA >1,000 copies/ml | 1.05 (1.04-1.07) | <.001 | <.001 | 1.03 (1.01-1.06) | 0.015 | 0.017 |
| Treatment status at start cART | | | | | | |
| Treatment-experienced | 1.00 (0.90-1.11) | 0.956 | | 0.64 (0.56-0.73) | <.001 | |
| Treatment-naive | 1 (reference) | | | 1 (reference) | | |
| Prior AIDS event | 1.74 (1.58-1.91) | <.001 | | | | |
| Hepatitis B virus positive | 1.30 (1.13-1.50) | <.001 | | 1.08 (0.89-1.31) | 0.436 | |
| Hepatitis C virus positive | 1.59 (1.37-1.84) | <.001 | | 1.32 (1.09-1.60) | 0.004 | |

| | Death | | | AIDS | | |
|---|---|---|---|---|---|---|
| | RR (95% CI) | p-value | Overall p-value | RR (95% CI) | p-value | Overall p-value |
| Body mass index* | | | | | | |
| <18 | 3.12 (2.74-3.56) | <.001 | <.001 | | | |
| 18-25 | 1 (reference) | | | | | |
| 25-30 | 0.66 (0.59-0.74) | <.001 | | | | |
| 30+ | 0.82 (0.68-0.98) | 0.028 | | | | |
| Smoking status | | | | | | |
| Current smoker | 1.10 (0.97-1.26) | 0.144 | <.001 | 0.75 (0.66-0.85) | <.001 | <.001 |
| Never smoker | 1 (reference) | | | 1 (reference) | | |
| Past smoker | 2.12 (1.87-2.40) | <.001 | | 0.93 (0.80-1.08) | 0.326 | |
| Early cART*** | 0.85 (0.59-1.23) | 0.390 | | 1.18 (0.89-1.57) | 0.257 | |

**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 2018) by region of origin and time-updated CD4 cell count.*

| | Total | | | Caribbean | | | Western Europe / North America | | |
|---|---|---|---|---|---|---|---|---|---|
| Last CD4 count | n | PY | Incidence/ 1,000 PY (95% CI) | n | PY | Incidence/ 1,000 PY (95% CI) | n | PY | Incidence/ 1,000 PY (95% CI) |
| 0–50 | 45 | 2,645 | 17.0 (12.4–22.8) | 2 | 223 | 9.0 (1.1–32.4) | 9 | 196 | 46.0 (21.0–87.3) |
| 050–199 | 204 | 9,628 | 21.2 (18.4–24.3) | 11 | 642 | 17.1 (8.6–30.7) | 35 | 1,084 | 32.3 (22.5–44.9) |
| 200–349 | 425 | 21,364 | 19.9 (18.0–21.9) | 18 | 876 | 20.5 (12.2–32.5) | 80 | 1,783 | 44.9 (35.6–55.8) |
| 350–499 | 568 | 41,167 | 13.8 (12.7–15.0) | 42 | 1,777 | 23.6 (17.0–31.9) | 115 | 3,475 | 33.1 (27.3–39.7) |
| 500–749 | 789 | 88,137 | 9.0 (8.3–9.6) | 56 | 4,253 | 13.2 (9.9–17.1) | 191 | 7,030 | 27.2 (23.5–31.3) |
| 750+ | 558 | 98,288 | 5.7 (5.2–6.2) | 41 | 4,783 | 8.6 (6.2–11.6) | 164 | 8,822 | 18.6 (15.9–21.7) |

*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 | 1,680 | 2.4 (0.6-6.1) | 24 | 437 | 54.9 (35.2-81.7) | 6 | 109 | 55.1 (20.2-119.9) |
| | 32 | 5,923 | 5.4 (3.7-7.6) | 118 | 1,676 | 70.4 (58.3-84.3) | 8 | 304 | 26.3 (11.4-51.9) |
| | 88 | 13,644 | 6.4 (5.2-7.9) | 213 | 4,315 | 49.4 (43.0-56.5) | 26 | 746 | 34.9 (22.8-51.1) |
| | 128 | 26,514 | 4.8 (4.0-5.7) | 258 | 7,570 | 34.1 (30.0-38.5) | 25 | 1,830 | 13.7 (8.8-20.2) |
| | 249 | 60,068 | 4.1 (3.6-4.7) | 271 | 13,418 | 20.2 (17.9-22.7) | 22 | 3,368 | 6.5 (4.1-9.9) |
| | 209 | 69,513 | 3.0 (2.6-3.4) | 134 | 11,828 | 11.3 (9.5-13.4) | 10 | 3,342 | 3.0 (1.4-5.5) |

***Appendix Table 3.4:*** *Absolute number of first AIDS events among HIV-1-positive individuals during the periods 1996-2000, 2001-05, 2006-10, 2011-15 and 2016-19.*

| CDC event | 1996-2000 | 2001-2005 | 2006-2010 | 2011-2015 | 2016-2019 | Total | |
|---|---|---|---|---|---|---|---|
| | n | n | n | n | n | n | % |
| AIDS dementia complex - HIV encefalopathy | 37 | 47 | 51 | 44 | 14 | 193 | 2.98 |
| Bacterial pneumonia, recurring | 48 | 64 | 65 | 76 | 61 | 314 | 4.85 |
| CMV disease | 27 | 35 | 29 | 34 | 3 | 128 | 1.98 |
| CMV colitis/proctitis | 1 | . | 1 | 1 | 3 | 6 | 0.09 |
| CMV meningo-encefalitis | . | . | . | . | 1 | 1 | 0.02 |
| CMV pneumonitis | . | . | . | . | 7 | 7 | 0.11 |
| CMV retinitis | 30 | 20 | 12 | 12 | 9 | 83 | 1.28 |
| Candidiasis lungs/bronchial/trachea | 7 | 13 | 7 | 6 | 4 | 37 | 0.57 |
| Candidiasis oesophagitis | 260 | 237 | 252 | 222 | 100 | 1071 | 16.55 |
| Cervical cancer, invasive | 3 | 4 | 6 | 5 | 4 | 22 | 0.34 |
| Coccidioimycosis, extrapulmonary / disseminated | . | . | 1 | . | . | 1 | 0.02 |
| Cryptococcosis, extrapulmonary / disseminated | 21 | 31 | 33 | 11 | 10 | 106 | 1.64 |
| Cryptosporidiosis | 22 | 12 | 10 | 12 | 2 | 58 | 0.90 |
| Cystoisosporiasis | 3 | 9 | 6 | . | . | 18 | 0.28 |
| HIV wasting | 50 | 57 | 77 | 77 | 50 | 311 | 4.81 |
| Herpes simplex virus, mucocutaneous, chronic | 33 | 42 | 60 | 40 | 20 | 195 | 3.01 |
| Histoplasmosis, extrapulmonary / disseminated | 9 | 12 | 10 | 7 | 2 | 40 | 0.62 |
| Kaposi sarcoma | 154 | 152 | 186 | 139 | 65 | 696 | 10.75 |
| Leishmaniasis visceral | . | 1 | 2 | 2 | 2 | 7 | 0.11 |
| Microsporidiosis | 11 | 1 | 3 | 1 | . | 16 | 0.25 |
| Mycobacterium other/unspecified, extrapulmo-nary / disseminated | 20 | 13 | 7 | 10 | 3 | 53 | 0.82 |
| Mycobacterium other / unspecified, pulmonary | . | 3 | 4 | 9 | 4 | 20 | 0.31 |
| Mycobacterium avium/kansasii, extrapulmonary / disseminated | 25 | 19 | 28 | 9 | 7 | 88 | 1.36 |
| Mycobacterium avium/kansasii, pulmonary | . | 1 | . | 1 | 6 | 8 | 0.12 |
| Non-Hodgkin's lymphoma (NHL) | 59 | 86 | 80 | 94 | 45 | 364 | 5.62 |
| Penicilliosis | . | . | 1 | . | . | 1 | 0.02 |
| Pneumocystis jirovecii extrapulmonary | 1 | 1 | 3 | . | 1 | 6 | 0.09 |
| Pneumocystis jirovecii pneumonia | 334 | 299 | 326 | 262 | 145 | 1366 | 21.11 |
| Primary CNS lymphoma | 8 | 4 | 9 | 7 | 4 | 32 | 0.49 |
| Progressive multifocal leucoencefalopathy | 18 | 25 | 35 | 24 | 4 | 106 | 1.64 |
| Salmonella sepsis, recurring | 2 | . | . | 1 | . | 3 | 0.05 |

| CDC event | 1996–2000 | 2001–2005 | 2006–2010 | 2011–2015 | 2016–2019 | Total | |
|---|---|---|---|---|---|---|---|
| | n | n | n | n | n | n | % |
| Toxoplasmosis of the brain | 70 | 97 | 55 | 42 | 23 | 287 | 4.43 |
| Tuberculosis, extrapulmonary / disseminated | 78 | 110 | 81 | 52 | 16 | 337 | 5.21 |
| Tuberculosis, pulmonary | 103 | 175 | 114 | 70 | 29 | 491 | 7.59 |
| **Total** | **1434** | **1570** | **1554** | **1270** | **644** | **6472** | **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 (1.12-1.41) | <.001 | . | 1.73 (1.41-2.13) | <.001 | . |
| Region of birth | | | | | | |
| Netherlands | 1 (reference) | . | 0.254 | 1 (reference) | . | 0.090 |
| Other | 1.05 (0.97-1.13) | 0.253 | . | 0.90 (0.79-1.02) | 0.092 | . |
| HIV-1 transmission route | | | | | | |
| MSM | 1 (reference) | . | <.001 | 1 (reference) | . | 0.011 |
| Heterosexual | 1.24 (1.12-1.36) | <.001 | . | 1.24 (1.07-1.44) | 0.004 | . |
| IDU | 1.35 (1.10-1.65) | 0.004 | . | 1.25 (0.90-1.74) | 0.190 | . |
| Blood contact | 1.27 (0.98-1.64) | 0.067 | . | 1.19 (0.79-1.80) | 0.412 | . |
| Age* | | | | | | |
| 18-29 | 0.59 (0.44-0.79) | <.001 | <.001 | 0.56 (0.31-1.05) | 0.069 | <.001 |
| 30-39 | 1 (reference) | . | . | 1 (reference) | . | . |
| 40-49 | 2.03 (1.78-2.31) | <.001 | . | 2.78 (2.15-3.58) | <.001 | . |
| 50-59 | 3.74 (3.28-4.27) | <.001 | . | 5.83 (4.53-7.50) | <.001 | . |
| 60-69 | 6.45 (5.59-7.44) | <.001 | . | 9.81 (7.52-12.81) | <.001 | . |
| 70+ | 10.04 (8.35-12.07) | <.001 | . | 16.69 (12.25-22.75) | <.001 | . |
| CD4 cell count** | | | | | | |
| <50 | 4.13 (3.22-5.28) | <.001 | <.001 | 3.38 (2.16-5.28) | <.001 | <.001 |
| 50-199 | 1.87 (1.59-2.18) | <.001 | . | 1.74 (1.35-2.25) | <.001 | . |
| 200-349 | 1.29 (1.15-1.44) | <.001 | . | 1.38 (1.16-1.66) | <.001 | . |
| 350-499 | 1.08 (0.97-1.19) | 0.155 | . | 1.10 (0.94-1.30) | 0.239 | . |
| 500-749 | 1 (reference) | . | . | 1 (reference) | . | . |
| 750+ | 1.18 (1.07-1.29) | <.001 | . | 1.31 (1.13-1.52) | <.001 | . |
| Per year longer with CD4 <200 cells/mm$^3$ | 0.99 (0.97-1.01) | 0.357 | . | 1.00 (0.97-1.04) | 0.833 | . |
| Prior AIDS event | 1.24 (1.15-1.33) | <.001 | . | 1.13 (1.00-1.27) | 0.052 | . |
| Per year longer on cART while HIV RNA>1000 copies/ml | 1.02 (1.00-1.04) | 0.044 | . | 1.02 (0.99-1.05) | 0.284 | . |
| Treatment status | | | | | | |
| Not (yet) started cART | 1.20 (1.05-1.37) | 0.009 | <.001 | 1.01 (0.79-1.28) | 0.951 | 0.032 |
| Treatment-experienced at start cART | 1.29 (1.17-1.42) | <.001 | . | 1.22 (1.05-1.42) | 0.008 | . |
| Treatment-naive at start | 1 (reference) | . | . | 1 (reference) | . | . |
| Per year longer on cART | 1.01 (1.00-1.02) | 0.035 | . | 1.00 (0.99-1.02) | 0.476 | . |

| | 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 |
| | 1.08 (0.89–1.31) | 0.454 | . | 1.27 (1.07–1.50) | 0.005 | . | 0.63 (0.54–0.74) | <.001 | . |
| | 1 (reference) | . | 0.016 | 1 (reference) | . | <.001 | 1 (reference) | . | <.001 |
| | 0.85 (0.74–0.97) | 0.017 | . | 1.44 (1.27–1.63) | <.001 | . | 0.75 (0.67–0.84) | <.001 | . |
| | 1 (reference) | . | 0.084 | 1 (reference) | . | <.001 | 1 (reference) | . | 0.012 |
| | 1.03 (0.88–1.21) | 0.718 | . | 1.53 (1.32–1.78) | <.001 | . | 1.01 (0.88–1.16) | 0.911 | . |
| | 1.36 (1.00–1.86) | 0.053 | . | 1.62 (1.14–2.28) | 0.006 | . | 1.52 (1.14–2.02) | 0.004 | . |
| | 1.55 (1.07–2.24) | 0.020 | . | 1.56 (1.06–2.31) | 0.024 | . | 1.38 (1.00–1.91) | 0.049 | . |
| | 0.59 (0.34–1.02) | 0.058 | <.001 | 0.62 (0.42–0.93) | 0.019 | <.001 | 0.32 (0.14–0.75) | 0.009 | <.001 |
| | 1 (reference) | . | . | 1 (reference) | . | . | 1 (reference) | . | . |
| | 2.24 (1.76–2.84) | <.001 | . | 1.57 (1.30–1.89) | <.001 | . | 3.18 (2.34–4.30) | <.001 | . |
| | 4.25 (3.35–5.40) | <.001 | . | 2.51 (2.06–3.06) | <.001 | . | 8.51 (6.35–11.41) | <.001 | . |
| | 8.59 (6.68–11.04) | <.001 | . | 4.17 (3.34–5.19) | <.001 | . | 23.60 (17.57–31.70) | <.001 | . |
| | 14.32 (10.65–19.24) | <.001 | . | 4.86 (3.54–6.67) | <.001 | . | 46.09 (33.69–63.05) | <.001 | . |
| | 2.48 (1.50–4.10) | <.001 | <.001 | 6.53 (4.63–9.21) | <.001 | <.001 | 1.27 (0.63–2.59) | 0.502 | 0.001 |
| | 1.95 (1.52–2.52) | <.001 | . | 1.85 (1.43–2.39) | <.001 | . | 1.66 (1.31–2.11) | <.001 | . |
| | 1.34 (1.12–1.61) | 0.002 | . | 1.16 (0.96–1.41) | 0.135 | . | 1.22 (1.04–1.43) | 0.015 | . |
| | 1.11 (0.95–1.30) | 0.190 | . | 1.01 (0.85–1.19) | 0.939 | . | 1.03 (0.91–1.18) | 0.621 | . |
| | 1 (reference) | . | . | 1 (reference) | . | . | 1 (reference) | . | . |
| | 0.93 (0.79–1.09) | 0.354 | . | 1.30 (1.12–1.51) | <.001 | . | 0.96 (0.86–1.08) | 0.530 | . |
| | 0.98 (0.94–1.01) | 0.209 | . | 0.99 (0.95–1.02) | 0.508 | . | 0.99 (0.96–1.02) | 0.335 | . |
| | 1.23 (1.09–1.39) | 0.001 | . | 1.33 (1.17–1.50) | <.001 | . | 1.14 (1.03–1.26) | 0.012 | . |
| | 1.01 (0.97–1.04) | 0.771 | . | 1.02 (0.98–1.05) | 0.382 | . | 0.98 (0.95–1.01) | 0.163 | . |
| | 1.25 (1.00–1.57) | 0.055 | 0.014 | 1.45 (1.17–1.80) | <.001 | <.001 | 0.40 (0.28–0.58) | <.001 | <.001 |
| | 1.20 (1.03–1.41) | 0.021 | . | 1.30 (1.11–1.54) | 0.002 | . | 1.13 (0.98–1.30) | 0.093 | . |
| | 1 (reference) | . | . | 1 (reference) | . | . | 1 (reference) | . | . |
| | 1.00 (0.99–1.02) | 0.614 | . | 1.01 (0.99–1.03) | 0.254 | . | 0.99 (0.98–1.00) | 0.025 | . |

| | Non-AIDS-defining disease | | | Cardiovascular disease | | |
|---|---|---|---|---|---|---|
| | IRR (95% CI) | p-value | Overall p-value | IRR (95% CI) | p-value | Overall p-value |
| Early cART within 12 months after last HIV-negative | 0.85 (0.67-1.08) | 0.177 | . | 1.20 (0.86-1.66) | 0.283 | . |
| Body mass index* | | | | | | |
| 0-18 | 1.45 (1.18-1.77) | <.001 | <.001 | 1.11 (0.79-1.56) | 0.547 | 0.160 |
| 18-25 | 1 (reference) | . | . | 1 (reference) | . | . |
| 25-30 | 1.20 (1.11-1.31) | <.001 | . | 0.99 (0.87-1.13) | 0.886 | . |
| 30+ | 1.91 (1.71-2.14) | <.001 | . | 1.12 (0.91-1.38) | 0.281 | . |
| Hepatitis B virus positive | 1.20 (1.06-1.37) | 0.004 | . | 1.03 (0.83-1.28) | 0.808 | . |
| Hepatitis C virus positive | 1.04 (0.91-1.18) | 0.599 | . | 0.96 (0.77-1.18) | 0.679 | . |
| Hypertension | 1.14 (1.06-1.23) | <.001 | . | 1.23 (1.10-1.38) | <.001 | . |
| Smoking status | | | | | | |
| Current smoker | 1.38 (1.27-1.51) | <.001 | <.001 | 1.92 (1.67-2.21) | <.001 | <.001 |
| Never smoker | 1 (reference) | . | . | 1 (reference) | . | . |
| Past smoker | 1.45 (1.32-1.59) | <.001 | . | 1.57 (1.35-1.84) | <.001 | . |
| Calendar year period | | | | | | |
| 2000-2010 | 1.37 (1.23-1.52) | <.001 | <.001 | 1.56 (1.32-1.84) | <.001 | <.001 |
| 2011-2015 | 1.23 (1.12-1.35) | <.001 | . | 1.33 (1.15-1.54) | <.001 | . |
| 2016-2019 | 1 (reference) | . | . | 1 (reference) | . | . |
| Recent use of ABC*** | | . | . | 1.64 (1.45-1.85) | <.001 | . |
| Per year longer on LOP/r | | . | . | 1.01 (0.99-1.02) | 0.265 | . |
| Per year longer on IDV | | . | . | 1.00 (0.99-1.01) | 0.769 | . |
| 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 | | . | . | | . | . |
| RPVnow | | . | . | | . | . |
| BICnow | | . | . | | . | . |

**Time-updated.*

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

****Current use or recently used in the past six 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 |
| | 0.54 (0.33-0.86) | 0.009 | . | 0.79 (0.50-1.23) | 0.295 | . | 1.05 (0.83-1.33) | 0.700 | . |
| | | | | | | | | | |
| | 1.97 (1.50-2.58) | <.001 | <.001 | 1.38 (0.94-2.03) | 0.102 | <.001 | 1.51 (1.14-2.01) | 0.004 | 0.015 |
| | 1 (reference) | . | . | 1 (reference) | . | . | 1 (reference) | . | . |
| | 0.84 (0.73-0.97) | 0.015 | . | 2.18 (1.89-2.52) | <.001 | . | 1.12 (1.00-1.25) | 0.046 | . |
| | 0.94 (0.75-1.19) | 0.620 | . | 4.82 (4.08-5.69) | <.001 | . | 1.19 (1.02-1.40) | 0.032 | . |
| | 1.64 (1.36-1.97) | <.001 | . | 1.06 (0.85-1.32) | 0.603 | . | 1.44 (1.21-1.71) | <.001 | . |
| | 1.10 (0.89-1.35) | 0.380 | . | 1.02 (0.82-1.28) | 0.852 | . | 1.31 (1.12-1.53) | <.001 | . |
| | 0.97 (0.86-1.09) | 0.599 | . | 1.16 (1.03-1.30) | 0.015 | . | 1.15 (1.04-1.26) | 0.005 | . |
| | | | | | | | | | |
| | 1.49 (1.28-1.73) | <.001 | <.001 | 0.97 (0.84-1.12) | 0.665 | <.001 | 0.84 (0.74-0.94) | 0.003 | 0.011 |
| | 1 (reference) | . | . | 1 (reference) | . | . | 1 (reference) | . | . |
| | 1.81 (1.55-2.11) | <.001 | . | 1.26 (1.09-1.47) | 0.002 | . | 1.00 (0.89-1.12) | 0.975 | . |
| | | | | | | | | | |
| | 1.03 (0.87-1.22) | 0.702 | 0.929 | 1.55 (1.29-1.86) | <.001 | <.001 | 1.19 (1.00-1.41) | 0.051 | 0.009 |
| | 1.02 (0.88-1.18) | 0.832 | . | 1.45 (1.24-1.69) | <.001 | . | 1.20 (1.07-1.36) | 0.002 | . |
| | 1 (reference) | . | . | 1 (reference) | . | . | 1 (reference) | . | . |
| | | . | . | | . | . | | . | . |
| | | . | . | | . | . | | . | . |
| | | . | . | | . | . | | . | . |
| | | . | . | 1.01 (1.00-1.02) | 0.110 | . | | . | . |
| | | . | . | 1.02 (0.99-1.05) | 0.175 | . | | . | . |
| | | . | . | 1.06 (1.03-1.09) | <.001 | . | | . | . |
| | | . | . | | . | . | 1.00 (0.98-1.02) | 0.683 | . |
| | | . | . | | . | . | 1.01 (1.00-1.02) | 0.105 | . |
| | | . | . | | . | . | 1.59 (1.36-1.86) | <.001 | . |
| | | . | . | | . | . | 1.26 (1.06-1.50) | 0.007 | . |
| | | . | . | | . | . | 1.71 (1.47-1.98) | <.001 | . |
| | | . | . | | . | . | 3.39 (3.00-3.82) | <.001 | . |
| | | . | . | | . | . | 1.39 (1.15-1.68) | <.001 | <.001 |
| | | . | . | | . | . | 2.35 (1.52-3.64) | <.001 | <.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 2019.*

| | | All events | | 0–50 | |
|---|---|---|---|---|---|
| | **CDC event** | **n** | **%** | **n** | **%** |
| CDC-B events | Aspergillosis, invasive pulmonary | 6 | 0.2% | 1 | 0.4% |
| | Bacillary angiomatosis | 1 | 0.0% | 0 | 0.0% |
| | Candidiasis oropharyngeal | 719 | 22.1% | 67 | 26.8% |
| | Candidiasis vulvovaginal, frequent/persistent | 53 | 1.6% | 1 | 0.4% |
| | Cardiomyopathy, HIV-related | 3 | 0.1% | 0 | 0.0% |
| | Cardiomyopathy, with HIV-related component | 12 | 0.4% | 1 | 0.4% |
| | Cervical dysplasia | 525 | 16.1% | 8 | 3.2% |
| | Diarrhoea, HIV-related ≥30 days | 64 | 2.0% | 1 | 0.4% |
| | Fever e.c.i. / HIV-related | 6 | 0.2% | 0 | 0.0% |
| | HIV-associated nephropathy (HIVAN) | 20 | 0.6% | 2 | 0.8% |
| | Herpes zoster, multidermatomal | 11 | 0.3% | 0 | 0.0% |
| | Herpes zoster, recurring / multidermatomal unspecified | 217 | 6.7% | 9 | 3.6% |
| | Herpes zoster, unidermatomal recurrent | 6 | 0.2% | 2 | 0.8% |
| | Myelopathy, HIV-related | 10 | 0.3% | 0 | 0.0% |
| | Neuropathy, HIV-related | 92 | 2.8% | 2 | 0.8% |
| | Neuropathy, with HIV-related component | 59 | 1.8% | 1 | 0.4% |
| | Nocardiosis | 2 | 0.1% | 1 | 0.4% |
| | Oral Hairy Leucoplakia (OHL) | 52 | 1.6% | 2 | 0.8% |
| | Pelvic inflammatory disease | 5 | 0.2% | 0 | 0.0% |
| | Thrombocytopenia, HIV-related | 100 | 3.1% | 3 | 1.2% |
| | Thrombocytopenia, with HIV-related compo-nent | 7 | 0.2% | 3 | 1.2% |
| | Weight loss >10kg, HIV-related / unknown cause | 38 | 1.2% | 2 | 0.8% |
| **Subtotal** | | **2008** | **61.7%** | **106** | **42.4%** |
| CDC-C events | AIDS dementia complex - HIV encephalopathy | 44 | 1.4% | 5 | 2.0% |
| | Bacterial pneumonia, recurring | 299 | 9.2% | 13 | 5.2% |
| | CMV disease | 19 | 0.6% | 5 | 2.0% |
| | CMV esophagitis | 1 | 0.0% | 1 | 0.4% |
| | CMV retinitis | 18 | 0.6% | 4 | 1.6% |
| | Candidiasis lungs/bronchial/trachea | 10 | 0.3% | 2 | 0.8% |
| | Candidiasis esophagitis | 221 | 6.8% | 24 | 9.6% |
| | Cervical cancer, invasive | 8 | 0.2% | 1 | 0.4% |
| | Coccidioimycosis, extrapulmonary / disseminated | 1 | 0.0% | 0 | 0.0% |
| | Cryptococcosis, extrapulmonary / disseminated | 16 | 0.5% | 5 | 2.0% |

| CD4 category | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 50–199 | | 200–349 | | 350–499 | | 500–749 | | 750+ | |
| n | % | n | % | n | % | n | % | n | % |
| 2 | 0.3% | 0 | 0.0% | 0 | 0.0% | 2 | 0.3% | 1 | 0.3% |
| 1 | 0.2% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| 174 | 29.9% | 145 | 20.4% | 118 | 18.9% | 133 | 19.2% | 82 | 20.6% |
| 5 | 0.9% | 9 | 1.3% | 17 | 2.7% | 16 | 2.3% | 5 | 1.3% |
| 0 | 0.0% | 0 | 0.0% | 2 | 0.3% | 0 | 0.0% | 1 | 0.3% |
| 3 | 0.5% | 1 | 0.1% | 2 | 0.3% | 3 | 0.4% | 2 | 0.5% |
| 55 | 9.5% | 120 | 16.9% | 106 | 17.0% | 141 | 20.4% | 95 | 23.8% |
| 5 | 0.9% | 17 | 2.4% | 11 | 1.8% | 22 | 3.2% | 8 | 2.0% |
| 1 | 0.2% | 2 | 0.3% | 0 | 0.0% | 1 | 0.1% | 2 | 0.5% |
| 3 | 0.5% | 3 | 0.4% | 4 | 0.6% | 4 | 0.6% | 4 | 1.0% |
| 2 | 0.3% | 3 | 0.4% | 2 | 0.3% | 1 | 0.1% | 3 | 0.8% |
| 24 | 4.1% | 54 | 7.6% | 43 | 6.9% | 56 | 8.1% | 31 | 7.8% |
| | | | | | | | | | |
| 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 0.1% | 3 | 0.8% |
| 4 | 0.7% | 2 | 0.3% | 0 | 0.0% | 1 | 0.1% | 3 | 0.8% |
| 7 | 1.2% | 18 | 2.5% | 25 | 4.0% | 23 | 3.3% | 17 | 4.3% |
| 7 | 1.2% | 9 | 1.3% | 14 | 2.2% | 18 | 2.6% | 10 | 2.5% |
| 0 | 0.0% | 1 | 0.1% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| 12 | 2.1% | 10 | 1.4% | 9 | 1.4% | 11 | 1.6% | 8 | 2.0% |
| 0 | 0.0% | 1 | 0.1% | 0 | 0.0% | 3 | 0.4% | 1 | 0.3% |
| 19 | 3.3% | 21 | 3.0% | 23 | 3.7% | 22 | 3.2% | 12 | 3.0% |
| 0 | 0.0% | 3 | 0.4% | 0 | 0.0% | 1 | 0.1% | 0 | 0.0% |
| 5 | 0.9% | 9 | 1.3% | 7 | 1.1% | 9 | 1.3% | 6 | 1.5% |
| **329** | **56.6%** | **428** | **60.3%** | **383** | **61.5%** | **468** | **67.7%** | **294** | **73.7%** |
| 6 | 1.0% | 8 | 1.1% | 11 | 1.8% | 7 | 1.0% | 7 | 1.8% |
| 50 | 8.6% | 77 | 10.8% | 73 | 11.7% | 61 | 8.8% | 25 | 6.3% |
| 2 | 0.3% | 3 | 0.4% | 5 | 0.8% | 1 | 0.1% | 3 | 0.8% |
| 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| 5 | 0.9% | 2 | 0.3% | 6 | 1.0% | 1 | 0.1% | 0 | 0.0% |
| 2 | 0.3% | 3 | 0.4% | 1 | 0.2% | 1 | 0.1% | 1 | 0.3% |
| 55 | 9.5% | 50 | 7.0% | 35 | 5.6% | 35 | 5.1% | 22 | 5.5% |
| 1 | 0.2% | 1 | 0.1% | 2 | 0.3% | 3 | 0.4% | 0 | 0.0% |
| 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 0.1% | 0 | 0.0% |
| 7 | 1.2% | 3 | 0.4% | 0 | 0.0% | 1 | 0.1% | 0 | 0.0% |

| | | All events | | 0–50 | |
|---|---|---|---|---|---|
| | **CDC event** | **n** | **%** | **n** | **%** |
| | Cryptosporidiosis | 10 | 0.3% | 4 | 1.6% |
| | Cystoisosporiasis | 1 | 0.0% | 0 | 0.0% |
| | HIV wasting | 16 | 0.5% | 6 | 2.4% |
| | Herpes simplex virus, chronic ulcer | 76 | 2.3% | 7 | 2.8% |
| | Histoplasmosis, extrapulmonary / disseminated | 4 | 0.1% | 3 | 1.2% |
| | Kaposi sarcoma | 104 | 3.2% | 7 | 2.8% |
| | Leishmaniasis visceral | 5 | 0.2% | 1 | 0.4% |
| | Microsporidiosis | 5 | 0.2% | 2 | 0.8% |
| | Mycobacterium avium/kansasii, extrapulmonary / disseminated | 21 | 0.6% | 5 | 2.0% |
| | Mycobacterium avium/kansasii, pulmonary | 3 | 0.1% | 0 | 0.0% |
| | Mycobacterium other/unspecified, extrapulmonary / disseminated | 7 | 0.2% | 2 | 0.8% |
| | Mycobacterium other / unspecified, pulmonary | 5 | 0.2% | 0 | 0.0% |
| | Non-Hodgkin's lymphoma (NHL) | 140 | 4.3% | 7 | 2.8% |
| | Pneumocystis jirovecii extrapulmonary | 1 | 0.0% | 0 | 0.0% |
| | Pneumocystis jirovecii pneumonia | 65 | 2.0% | 20 | 8.0% |
| | Primary CNS lymphoma | 5 | 0.2% | 1 | 0.4% |
| | Progressive multifocal leucoencephalopathy | 17 | 0.5% | 5 | 2.0% |
| | Toxoplasmosis of the brain | 18 | 0.6% | 8 | 3.2% |
| | Tuberculosis, extrapulmonary / disseminated | 38 | 1.2% | 3 | 1.2% |
| | Tuberculosis, pulmonary | 68 | 2.1% | 3 | 1.2% |
| **Subtotal** | | **1246** | **38.3%** | **144** | **57.6%** |
| **Total** | | **3254** | **100.0%** | **250** | **100.0%** |

| CD4 category | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 50–199 | | 200–349 | | 350–499 | | 500–749 | | 750+ | |
| | n | % | n | % | n | % | n | % | n | % |
| | 0 | 0.0% | 1 | 0.1% | 3 | 0.5% | 1 | 0.1% | 1 | 0.3% |
| | 0 | 0.0% | 1 | 0.1% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | 6 | 1.0% | 1 | 0.1% | 2 | 0.3% | 1 | 0.1% | 0 | 0.0% |
| | 7 | 1.2% | 13 | 1.8% | 18 | 2.9% | 25 | 3.6% | 6 | 1.5% |
| | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 0.1% | 0 | 0.0% |
| | 11 | 1.9% | 23 | 3.2% | 22 | 3.5% | 29 | 4.2% | 12 | 3.0% |
| | 3 | 0.5% | 1 | 0.1% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | 2 | 0.3% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 0.3% |
| | 7 | 1.2% | 5 | 0.7% | 2 | 0.3% | 1 | 0.1% | 1 | 0.3% |
| | 0 | 0.0% | 1 | 0.1% | 0 | 0.0% | 1 | 0.1% | 1 | 0.3% |
| | 1 | 0.2% | 3 | 0.4% | 0 | 0.0% | 1 | 0.1% | 0 | 0.0% |
| | 2 | 0.3% | 0 | 0.0% | 2 | 0.3% | 1 | 0.1% | 0 | 0.0% |
| | 34 | 5.9% | 38 | 5.4% | 28 | 4.5% | 24 | 3.5% | 9 | 2.3% |
| | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 0.3% |
| | 19 | 3.3% | 12 | 1.7% | 8 | 1.3% | 4 | 0.6% | 2 | 0.5% |
| | 1 | 0.2% | 2 | 0.3% | 1 | 0.2% | 0 | 0.0% | 0 | 0.0% |
| | 5 | 0.9% | 4 | 0.6% | 2 | 0.3% | 1 | 0.1% | 0 | 0.0% |
| | 5 | 0.9% | 2 | 0.3% | 2 | 0.3% | 1 | 0.1% | 0 | 0.0% |
| | 8 | 1.4% | 6 | 0.8% | 4 | 0.6% | 10 | 1.4% | 7 | 1.8% |
| | 13 | 2.2% | 22 | 3.1% | 13 | 2.1% | 11 | 1.6% | 6 | 1.5% |
| | **252** | **43.4%** | **282** | **39.7%** | **240** | **38.5%** | **223** | **32.3%** | **105** | **26.3%** |
| | **581** | **100.0%** | **710** | **100.0%** | **623** | **100.0%** | **691** | **100.0%** | **399** | **100.0%** |

# 4. Viral hepatitis

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*Box 4.1: Viral hepatitis data in the ATHENA cohort in the Netherlands.*

**Population described in this chapter**
All individuals ever registered with Stichting HIV Monitoring (SHM) by 1 May 2020 – the date the SHM database was locked for the purposes of this report.

## 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 ever having been exposed 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 HIV-positive individuals 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 can ultimately result in end-stage liver disease and/or hepatocellular carcinoma (HCC)[6,7]. Progression to severe liver disease takes, on average, 20 to 30 years in individuals mono-infected with HCV or HBV[8,9]. While liver fibrosis progression 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[10,11]. Meanwhile, co-infection with HBV/HDV is known to be highly associated with severe liver-related outcomes compared to HBV mono-infection[12], with accelerated progression to end-stage liver disease in HIV-positive individuals, despite effective cART[13].

Infection with hepatitis A virus (HAV) and hepatitis E virus (HEV) is more frequent in the Netherlands compared to HBV and HCV. Both are enterically transmitted and can cause acute, self-limited inflammatory liver disease[14,15]. 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[16], whereas markers of previous HEV infection can be detected in roughly 10% of the general population[17]. HAV and HEV infection 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)[18]. HEV infection more commonly persists and develops into chronic infection in immunocompromised individuals, who are then at increased risk of developing ongoing symptoms[15].

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.

## HCV

*Box 4.2: Definitions of hepatitis C infection.*

**Chronic hepatitis C virus (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**[19,20]

1. Case definition of acute hepatitis C virus according to preferred criteria[19]
   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 sero-conversion within the past 12 months.
2. Case definition of acute hepatitis C virus according to alternative criteria[19]
   Detectable HCV RNA in association with a rise in alanine aminotransferase (ALT) (>200 IU/l) with a documented normal ALT within the past 12 months.

**Spontaneously cleared HCV infection**
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.

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

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

**Hepatitis C re-infection**
Detectable HCV RNA after an earlier achieved SVR12 or SVR24, or 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- or endoscopically-documented evidence of the presence of portal hypertension in terms of oesophageal varices, ascites, splenomegaly, and reversal of portal blood flow and/or cirrhosis.

*Definitive* if:
- liver transplantation
- or presumptive 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).

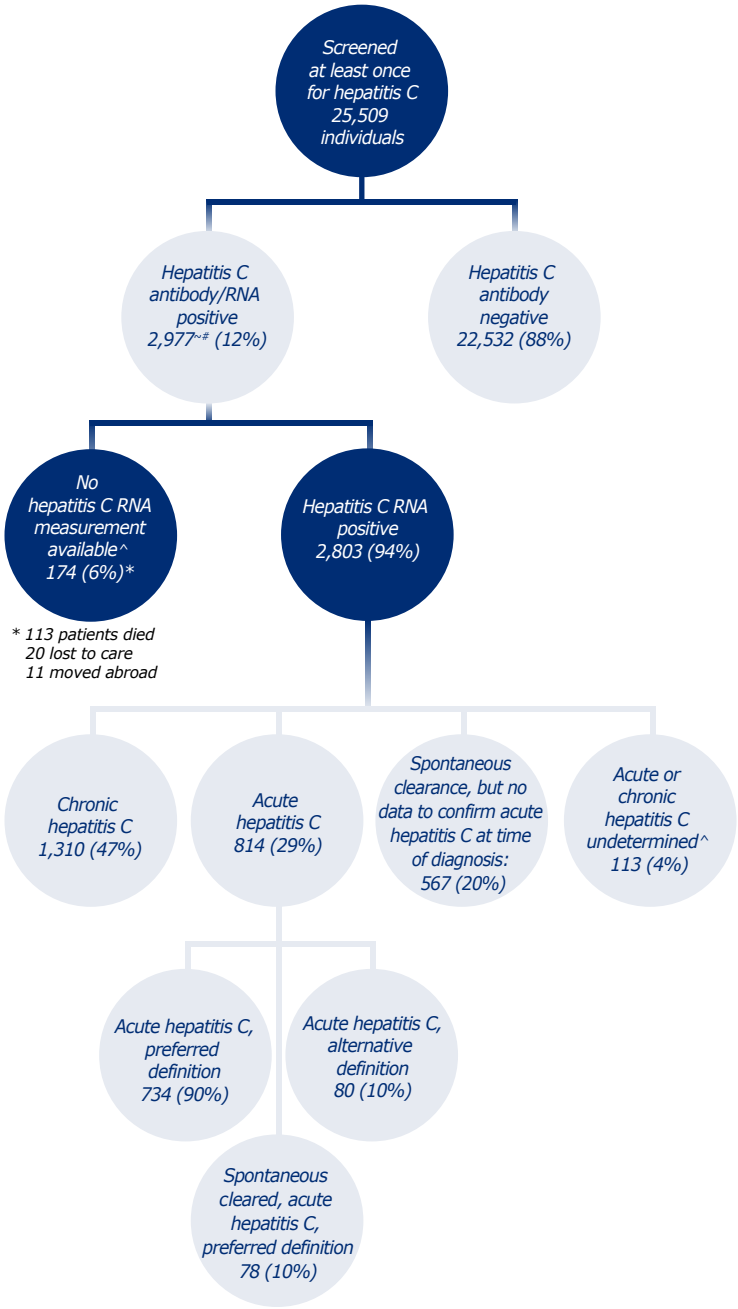
## HCV positive individuals

As of May 2020, 27,093[a] HIV-1-positive adults (≥18 years of age at time of HIV-1 diagnosis) had ever been registered by Stichting HIV Monitoring (SHM) and in care in one of the HIV treatment centres in the Netherlands. Of those individuals, 25,509 (94%) were ever screened for HCV co-infection and 2,977 (12%) had a positive result with an HCV antibody test and/or HCV RNA test. This confirms that HCV is far more prevalent among the HIV-positive population, than is estimated for the general Dutch population (*Figure 4.1*). HCV RNA data were not documented in 174 of the 2,977 cases (6%). Of these 174 individuals, 113 have died, 20 have been lost to care, and 11 have moved abroad; the reason for an undocumented HCV RNA in the remaining 30 individuals is unknown. Of the 2,803 individuals with documented HCV RNA data, 814 (29%) were initially diagnosed with acute HCV infection; 78 spontaneously cleared their infection; and 736 became chronic HCV infections, or were treated within six months of diagnosis. Another 1,310 (47%) individuals were classified as having chronic HCV infection at the time of diagnosis. In total,

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

567 (20%) individuals had evidence of spontaneous clearance of HCV, but could not be classified as acute HCV infection at the time of HCV diagnosis. The remaining 113 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 have therefore been excluded from the analysis.

*Figure 4.1: Flowchart of HIV-positive individuals 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, 645 individuals spontaneously cleared their HCV infection. Among the 814 individuals with primary acute hepatitis, 78 cases of spontaneous clearance were observed (10%). Another 567 cases of spontaneous clearance were observed among individuals who could not be classified as having a primary acute infection: 258 infections were classified as a definitive spontaneous clearance (i.e., two negative HCV RNA test results after a positive HCV test result), and 309 as possible spontaneous clearance (i.e., one negative HCV RNA test). 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 (*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, 1998-2019.*

| | Total HCV co-infected | Spontaneous clearance |
|---|---|---|
| Total number of individuals | 2,691 | 645 (24%) |
| Age at HCV diagnosis (median, IQR) | 40 (34-47) | 40 (35-47) |
| HCV status | | |
| Chronic HCV | 1,310 | |
| Acute HCV | 736 | |
| Definitive clearance | 258 | 258 |
| Possible clearance | 309 | 309 |
| Spontaneous clearance after confirmed primary acute infection | 78 | 78 |
| Male gender, n (%) | 2,318 (86) | 525 (81) |
| Region, n (%) | | |
| Netherlands | 1,657 (62) | 337 (52) |
| Europe | 350 (13) | 86 (13) |
| Sub-Saharan Africa | 116 (4) | 59 (9) |
| Caribbean/South America | 202 (8) | 72 (11) |
| Southeast Asia | 87 (3) | 22 (3) |
| Other | 279 (10) | 69 (11) |
| HIV transmission route, n (%) | | |
| Men who have sex with men | 1,581 (59) | 350 (54) |
| Heterosexual | 303 (11) | 111 (17) |
| People who use/used injecting drugs | 565 (21) | 116 (18) |
| Other | 242 (9) | 68 (11) |
| cART, n (%) | 2,606 (97%) | 617 (96) |
| Deaths, n (%) | 454 (22%) | 98 (15) |

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

The analyses described in the remainder of this section on HCV are limited to the individuals who could be definitively classified as having either chronic (n=1,310), or acute (n=814) HCV infection at the time of their primary HCV diagnosis (*Appendix Figure 4.1*). Most of these were male (81% and 99%, respectively), and the majority originated from the Netherlands (chronic: 753/1,310 [57%]; acute: 621/814 [76%]) (*Table 4.2*). Fifty-nine percent of the registered individuals who had acquired HIV through injecting drug use (IDU), had a chronic HCV infection (442 of the total 752 people who use/used injecting drugs [PWID]). In the MSM HIV transmission group (15,602), 3% (541) had a chronic HCV infection and 5% (765) had a documented acute HCV infection.

The HCV genotype was determined and documented in the clinical records of 1,176 of the 1,310 (89%) individuals with a chronic HCV infection. Of the individuals with a genotype determination, the majority (61%, n=725) were infected with HCV genotype 1; 61% (n=441) with genotype 1a, and 13% (n=94) with genotype 1b. For 26% of the people infected with genotype 1, the subtype was not further specified. Five percent (n=57) were infected with HCV genotype 2, 18% (n=206) 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 714 of the 814 (88%) individuals with an acute HCV infection. They were most likely to be infected with either genotype 1 (71%, n=514) or genotype 4 (20%, n=146). Of the 514 infected with genotype 1, 84% (n=430) were infected with genotype 1a and 5% (n=24) with genotype 1b. For 12% 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, 1998-2019.*

| | Total | Chronic HCV | Acute HCV |
|---|---|---|---|
| Total number of individuals screened for HCV | 25,509 | 1,310 | 814 |
| Age at baseline (median, IQR) | 40 (34-47) | 39 (32-45) | 43 (36-49) |
| Male gender, n (%) | 20,985 (82) | 1,063 (81) | 806 (99) |
| Region of origin, n (%) | | | |
| Netherlands | 14,199 (55) | 753 (57) | 621 (76) |
| Europe | 1,709 (7) | 204 (16) | 68 (9) |
| Sub-Saharan Africa | 3,456 (14) | 47 (4) | 11 (1) |
| Caribbean/South America | 3,144 (12) | 87 (7) | 49 (6) |
| Southeast Asia | 912 (4) | 43 (3) | 24 (3) |
| Other | 2,089 (8) | 176 (13) | 41 (5) |
| HIV transmission route, n (%) | | | |
| Men who have sex with men | 15,602 (61) | 541 (41) | 765 (94) |
| Heterosexual | 7,517 (30) | 66 (13) | 28 (3) |
| People who use/used injecting drugs | 752 (3) | 442 (34) | 8 (1) |
| Other | 609 (6) | 159 (12) | 13 (2) |
| cART, n (%) | 24,554 (96) | 1,256 (96) | 809 (99) |
| HCV genotype (GT), n (%*) | | | |
| Total determined | | 1,176 (90) | 714 (88) |
| GT 1 | | 725 (62) | 514 (71) |
| 1a | | 441 | 430 |
| 1b | | 94 | 24 |
| 1c, 1a/b or not further specified | | 190 | 60 |
| GT 2 | | 57 (5) | 37 (5) |
| GT 3 | | 206 (18) | 16 (2) |
| GT 4 | | 186 (16) | 146 (20) |
| GT 5&6 | | 2 (0.1) | 1 (<1) |
| Deaths, n (%) | 2,833 (11) | 320 (24) | 39 (5) |

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

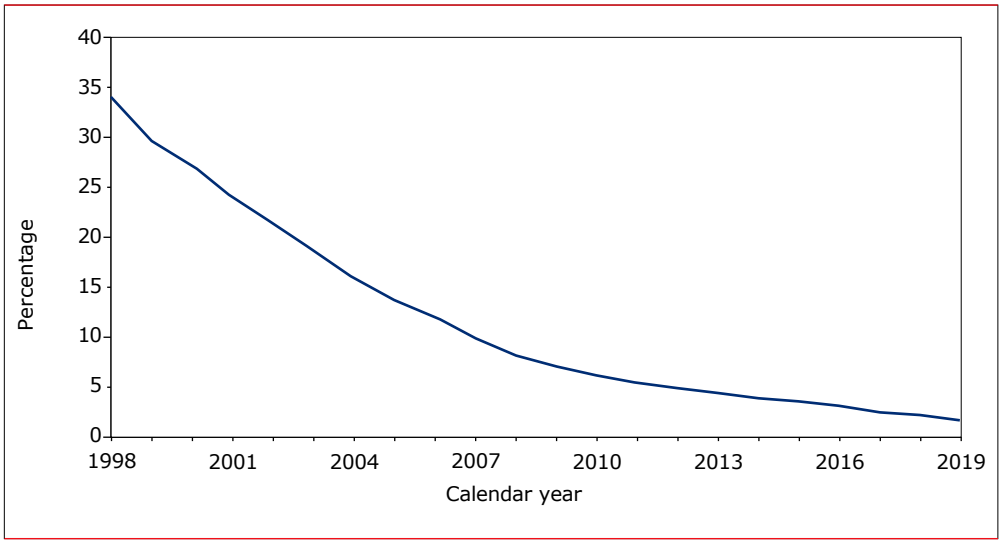
***Legend:** n=total for each category; (%)=percentage of the total for each column; HCV=hepatitis C virus; cART= combination antiretroviral therapy; GT= genotype.*

## Changes over time

### Testing for HCV over time

In the Netherlands, the national guidelines for the treatment and monitoring of HIV recommend HCV screening at first clinical visit after HIV diagnosis, and additional annual HCV screening for MSM who report HCV-related risk-taking behaviour[21]. Screening for HCV infection among the HIV-positive individuals ever registered with SHM has increased over calendar time. In 1998, 34% of the HIV-positive individuals in care had never been screened for the presence of HCV infection in that specific calendar year. However, over time, a strong and steady increase in the percentage of individuals with a known HCV status was observed, and, in 2019, only 1.8% of the individuals in care had never been screened for HCV co-infection (*Figure 4.2*). In 2019, unknown HCV status was relatively more common among individuals with heterosexually-acquired HIV (n=187/5,821, 3.2%) or with another or unknown mode of HIV acquisition (n=36/853, 4.2%), and relatively less common among MSM (0.9%) and PWID or former PWID (0.7%).

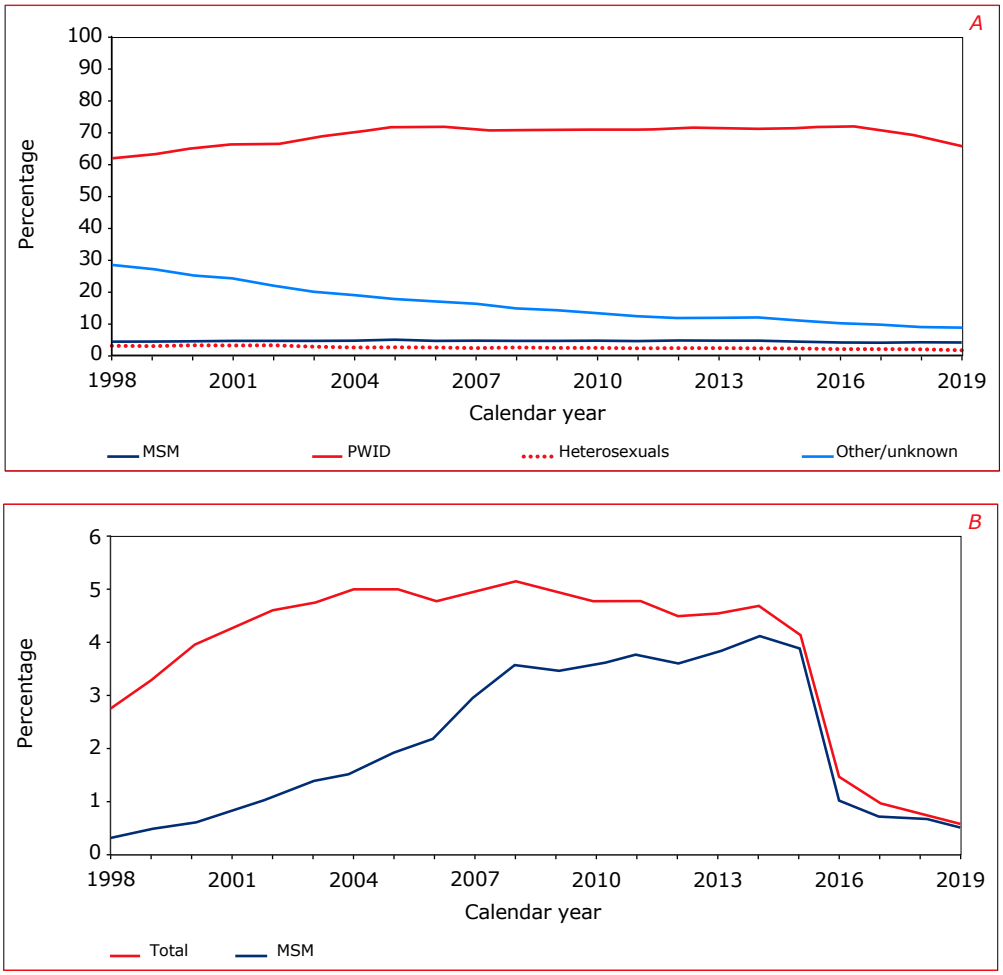
*Figure 4.2: Percentage of individuals in care with an unknown hepatitis C status per calendar year of care.*



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

The overall prevalence of ever being diagnosed with a chronic HCV co-infection among HIV-positive individuals ever registered, decreased from 11.2% in 1998 to 4.6% in 2019, but was not equally distributed across HIV transmission categories. The highest prevalence was found among individuals who had acquired HIV by injecting drug use, and this number varied between 62% 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 2.8% in 1998 and 5.1% in 2008, before dropping to 0.6% in 2019. In MSM, the highest percentage of HCV RNA positivity was 4% in 2014; by 2019, the percentage of positive HCV RNA tests in this group decreased sharply to 0.5%.

### Incidence of acute HCV infection over time

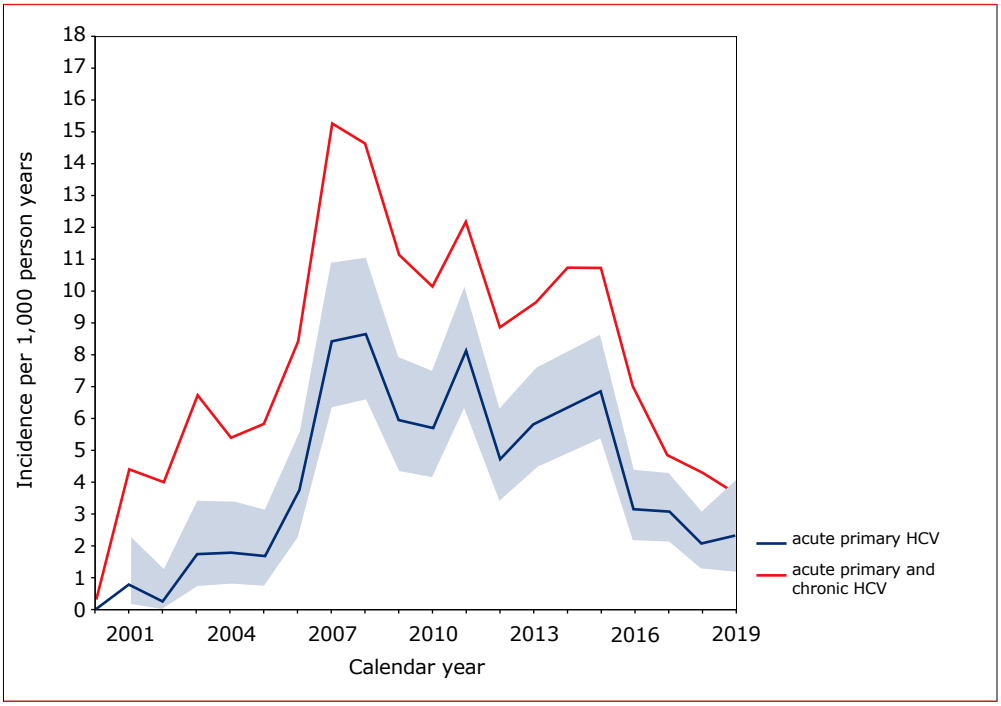
For the purpose of this analysis, the definition of acute HCV infection includes only cases of primary acute HCV infection (first diagnosis of HCV). This definition is consistent with the one given in the European AIDS Treatment Network (NEAT) preferred criteria[19]. In addition, we have expanded this definition to include alternative criteria[19,20]. This alternative definition is based on detectable HCV RNA associated with an acute rise in alanine aminotransferase (ALT) greater than five times the upper limit of normal (>200 U/l), and 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=765/814 [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 programs implemented in addictive care centres in the Netherlands. Twenty-eight cases occurred among individuals who had acquired HIV heterosexually.

*Figure 4.4* shows both the incidence of acute primary HCV infection and all newly-diagnosed acute primary and chronic HCV diagnoses among MSM over time. The overall rate of acute HCV infection in this group was 4.5 per 1,000 person years (PY) (95% CI, 4.2-4.9). When the preferred NEAT acute HCV definition was used, the incidence increased from 0 diagnoses per 1,000 PY in 2000 to a peak of 8.4 and 8.7 per 1,000 PY in 2007 and 2008, respectively. The incidence, which was 6.9 diagnoses per 1,000 PY in 2015, declined to 3.2 in 2016, before stabilising at 2.3 diagnoses per 1,000 PY in 2019.

As expected, incidence rates among MSM were higher when the preferred and alternative case definitions of acute HCV were combined, with incidence rates of 7.9 diagnoses per 1,000 PY in 2015, 4.2 in 2016, and 2.7 in 2019.

*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; shaded area represents the 95% confidence interval.*

## Treatment for HCV infection

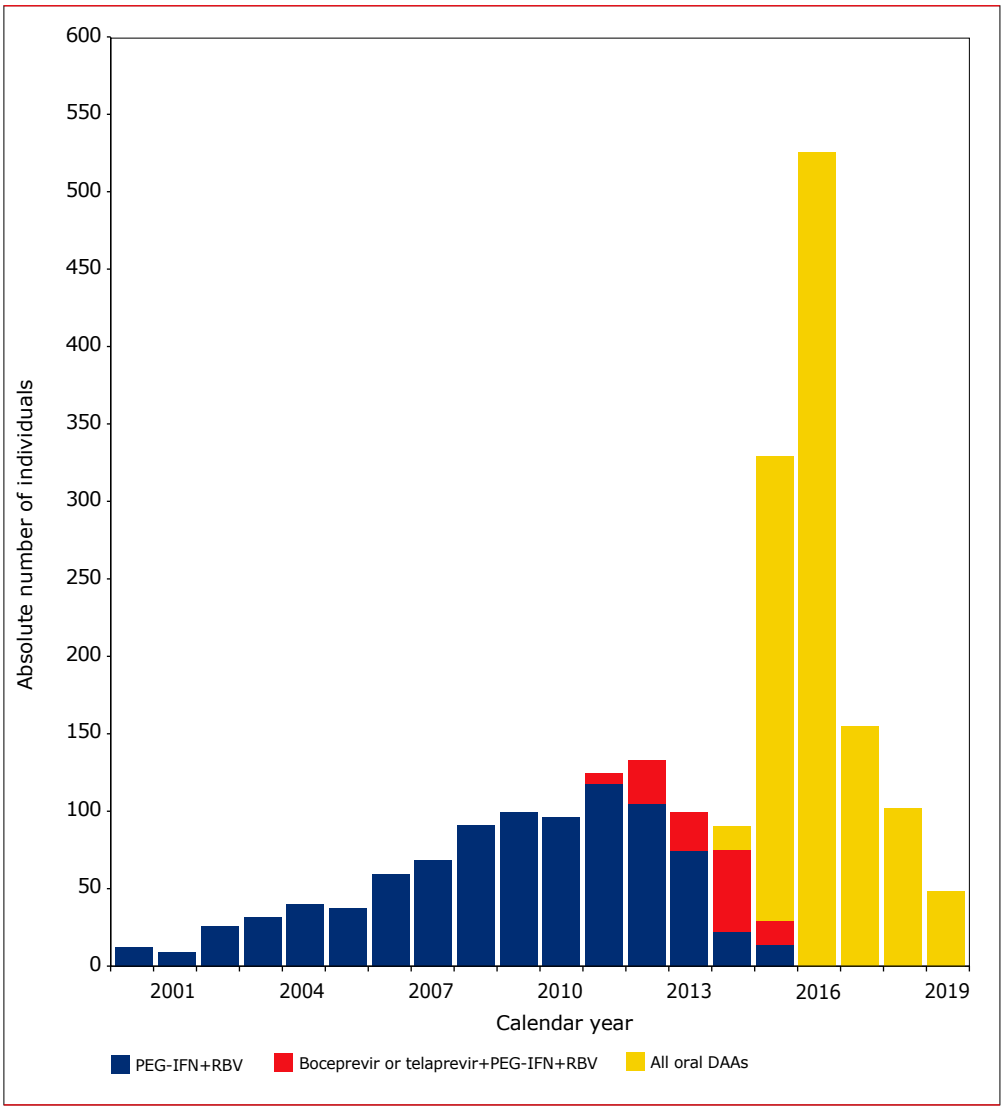
The primary aim of HCV treatment is to achieve a sustained virological response (SVR)[22] and the treatment used have changed markedly in recent years. In the past, treatment consisted of interferon alpha (IFN alpha), and subsequently pegylated interferon alpha (PEG-IFN alpha) in combination with ribavirin (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. Among the 2,046 individuals ever diagnosed with chronic or acute HCV, 1,707 have ever received HCV treatment; of those, 415 have received HCV treatment more than once (this includes people who were unsuccessfully treated and those who re-acquired HCV after prior successful treatment).

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




***Note:*** *numbers in 2019 may be underreported, due to a delay in data collection.*

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

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

The outcome for people treated with 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 2020, 1,060 individuals were known to have started a DAA regimen; 86 of those had been treated more than once with a DAA regimen. The most common reasons for receiving DAA treatment more than once were: re-infection after earlier DAA treatment-induced clearance (n=40); no SVR or discontinuation of first treatment episode due to lack of early virological response during the first episode of DAA treatment (n=24), or toxicity (n=5). Of the total 1,156 DAA treatment episodes, 15 occurred in 2014, 299 in 2015, and 526 in 2016. The number of treatment episodes has subsequently decreased to 155 in 2017, 104 in 2018, and 51 in 2019 (*Figure 4.5*).

The most frequently used DAA regimens were 1) sofosbuvir plus ledipasvir +/- RBV (n=568); 2) sofosbuvir plus daclatasvir +/- RBV (n=247); and 3) pibrentasvir/glecaprevir (n=75). Thirty seven individuals who had previously been treated with DAAs are known to have died. The causes of death were liver disease (n=6), non-AIDS-defining malignancies (n=7), cardiovascular disease (n=4), non-AIDS-defining infection (n=3), and non-natural death (n=3); the remaining deaths (n=14) were related to alcohol and substance use, AIDS, lung disease, or the cause was unknown.

### Treatment outcomes

HCV RNA data were collected up to 1 May 2020. At that point, 1,100 out of 1,156 treatment episodes had been completed with one of the DAA regimens, and sufficient time had elapsed since discontinuation of treatment to enable calculation of the SVR12 rate. In total:

- In 1,065 of the 1,100 treatment episodes SVR12 (97%) was achieved.
- No SVR was achieved in 30 treatment episodes.
- For the remaining five treatment episodes, no follow-up data on SVR was available; because persons had died shortly after being treated (n=4) or no reported HCV RNA tests were available to assess treatment outcome (n=1).

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 (92%). 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:
- 15 were successfully retreated with a DAA regimen
- Nine were not retreated
- Three were unsuccessfully retreated

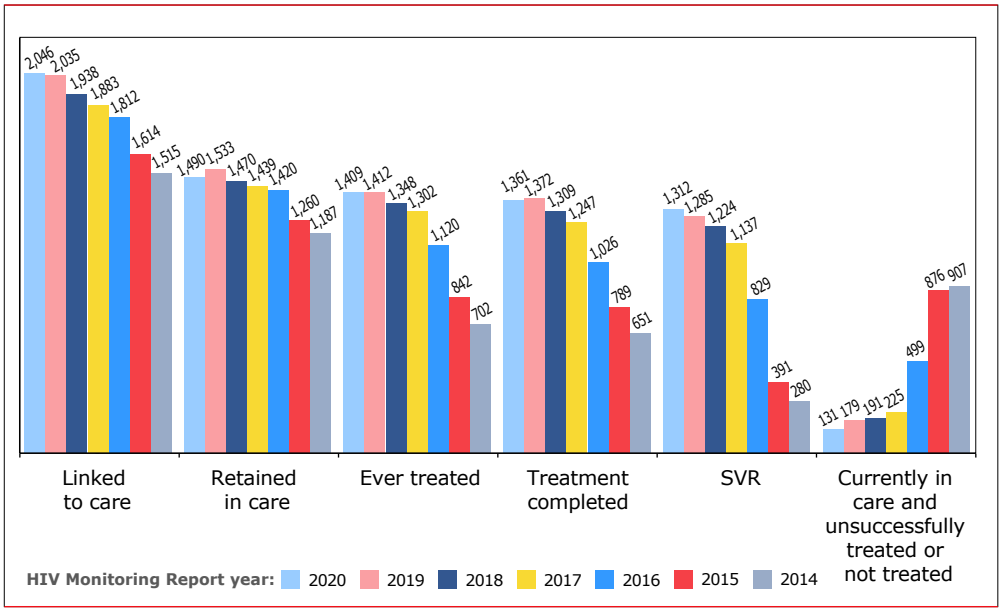
### Continuum of care for those with diagnosed HCV co-infection

*Figure 4.6* shows the HCV continuum of care, based on the number of people known to be in HIV care as of 31 December 2019, with data from previous monitoring reports for 2014-18 shown for comparison. A total of 2,046 individuals linked to HIV care were diagnosed with HCV (1,310 with a chronic HCV infection and 736 with an acute HCV infection [814 minus 78 with spontaneous clearance] at diagnosis). Of these, 1,490 (73%) were retained in care, while 556 individuals were no longer in care (356 had died, 106 had moved abroad, and 94 were lost to care). Of those still alive and in care, 1,409 (95%) had received treatment for HCV (with DAAs or a pegylated interferon-containing regimen) and 1,361 (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, 1,312 of the 1,361 people who completed treatment (96%) achieved an SVR, including those who achieved an SVR on a pegylated interferon-containing regimen.

As a result, 178 (11%) of the 1,490 individuals known to be alive and in care in one of the Dutch HIV treatment centres on 31 December 2019, were still in need of HCV treatment:
- 81 individuals had never been treated for HCV; 75 of these were receiving cART for HIV during their last clinical visit, and 71 of these 81 individuals had an HIV RNA <100 copies/ml; the percentage untreated was higher among PWID (11%) and people with an unknown HIV transmission mode (6%), compared to MSM (4%) (P=0.01).
- 49 had been unsuccessfully treated for HCV, including those who had not achieved an SVR on a pegylated interferon-containing regimen; eight of these individuals had documented evidence of severe liver disease.
- 48 were still being treated or had insufficient time after treatment discontinuation to allow SVR calculation.

Of the 48 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 of 97% to these individuals and assumed that 47 of the 48 will achieve SVR. This results in a more realistic estimate of individuals (178-47=131) who remained untreated or unsuccessfully treated.

*Figure 4.6: Hepatitis C continuum of care.*




*Legend: SVR=sustained virological response.*

## HCV re-infection

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

To identify possible HCV re-infection among HCV co-infected individuals, we selected people who had initially achieved an SVR after having received any type of HCV treatment, and individuals with spontaneous clearance of HCV.

In total 1,866 individuals were susceptible for HCV re-infection (1,329 after SVR, 537 after spontaneous clearance).

Of these 1,866 individuals, 271 re-infections among 240 individuals (13%) were documented (*Appendix Figure 4.1*): 144 after SVR and 127 after spontaneous clearance. The median time between SVR and HCV re-infection was 1.6 years (IQR: 0.9-3.0) and between spontaneous clearance and re-infection it was 1.2 years (IQR: 0.5-3.2).

Most individuals who became re-infected were MSM (210/240, 88%). Another 21 were PWID or former PWID (21/240, 9%). For the remaining nine individuals, documented HIV transmission routes were heterosexual contact (three), blood-blood contact (two) and unknown (four).

Out of the 271 re-infections, 228 (84%) were re-treated (171 with DAA, 57 with interferon+/-boceprevir/telaprevir) The median time to re-treatment after re-infection diagnosis, stratified by calendar year of treatment initiation, was:

- <2014: 3.1 months (IQR: 1.2-7.1)
- 2014-18: 11.6 months (IQR: 3.2-34.8)
- ≥2018: 3.6 months (IQR: 2.0-15.3).

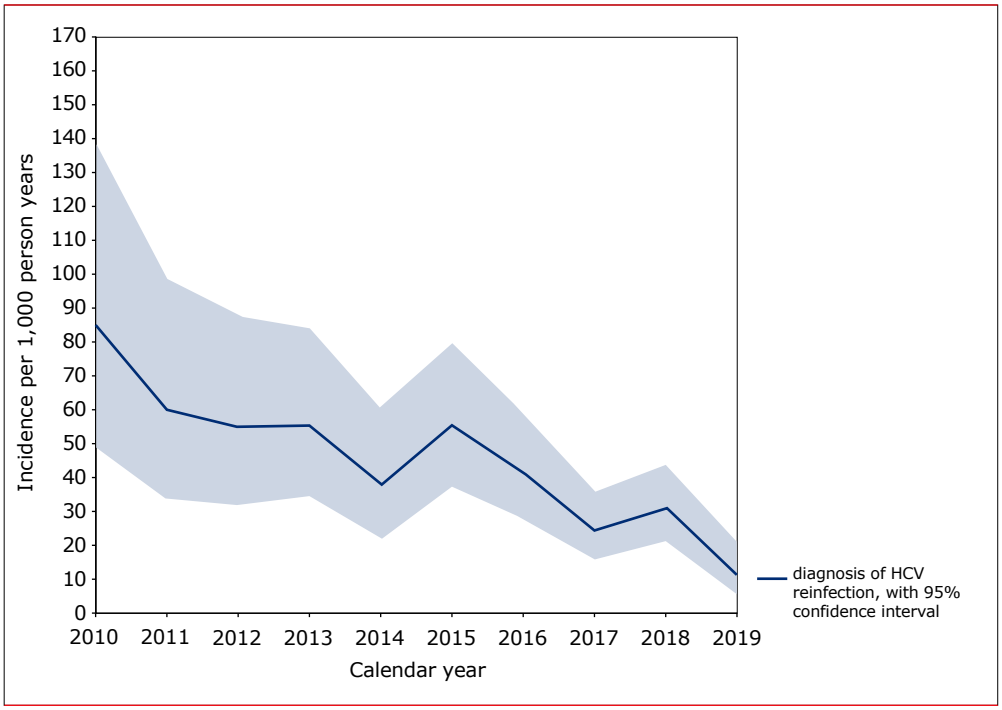
We calculated the incidence of re-infection between 2010 and 2019 for these 1,866 individuals. Follow-up time was from the date of SVR, date of spontaneous clearance, or from 1 January 2010 onward, until the earliest date of HCV re-infection, death, or last known contact.

The incidence of HCV re-infection for the total population was 20 re-infections per 1,000 PY (95% CI: 17-23), and for MSM it was 29 re-infections per 1,000 PY (95% CI: 25-33).

Because most re-infections occurred among MSM, the incidence of HCV re-infection after achieving an SVR over time is shown only for MSM (*Figure 4.7*). This incidence increased from 35 re-infections per 1,000 PY in 2010 to 49 in 2015, and then declined to 27 re-infections per 1,000 PY in 2018, and 11 in 2019.

Screening for HCV RNA among those at risk for HCV re-infection is an important factor in identifying HCV re-infection. The national guidelines for the treatment and monitoring of HIV recommend annual HCV screening for MSM who report HCV-related risk-taking behaviour[21]. In the Netherlands, among HIV-positive MSM at risk of re-infection, the percentage of men with an HCV RNA test during a calendar year varied between 55% and 65% for 2010-16, but showed a decline to 45% in 2018, and 40% in 2019. It is worth noting that these data might include MSM who are not considered at risk for HCV re-infection by the treating physician, as data on HCV-related risk-taking behaviour are not available to SHM.

*Figure 4.7: Incidence of hepatitis C re-infection after earlier treatment-induced clearance or spontaneous clearance among men who have sex with men, per calendar year. Note, numbers in 2019 may be affected by a delay in data collection.*




## Liver-related morbidity

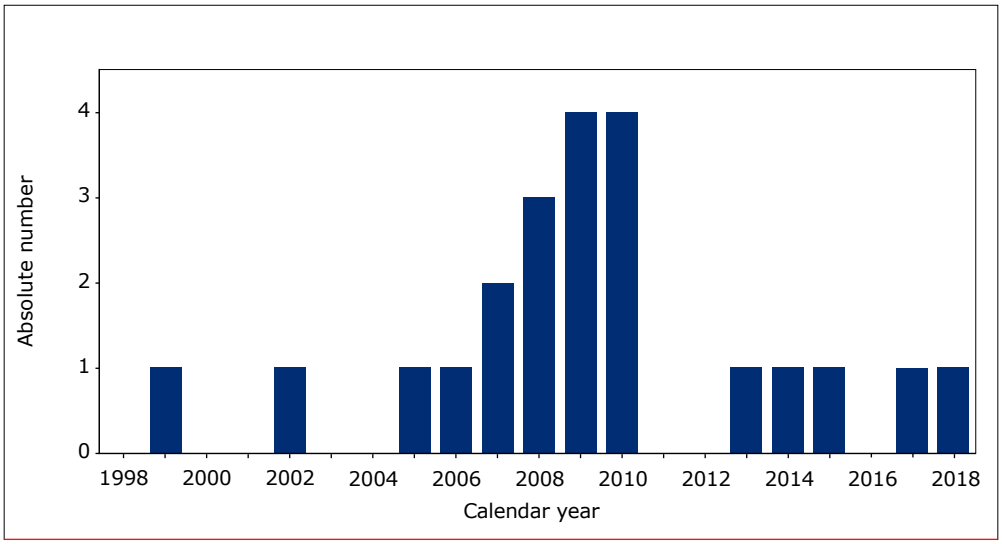
Data on liver-related morbidity are collected for all HIV-positive individuals in follow up in the ATHENA cohort. In total 1,112 cases of severe liver disease according to our definition were considered to be present (presumptive and definitive categories combined); 502 among individuals with HCV co-infection, 265 among individuals with HBV co-infection, and 345 among HIV-positive individuals 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 are limited to those with viral hepatitis. Findings are first discussed for HCV infection, and then for HBV infection in the corresponding section of this chapter.

### 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 1,702 of the 2,046 individuals with HCV co-infection. Review of these additional data showed that severe chronic liver disease was considered to be present (presumptive and definitive categories combined) in 502 (25%) of the individuals with HCV co-infection. Definitive severe chronic liver disease was documented for 120 individuals with an HCV co-infection (6%).

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. Between 1998-2019, HCC was diagnosed in 22 out of 2,046 individuals (1.1%) with an HCV co-infection, 16 of whom were born in the Netherlands.

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



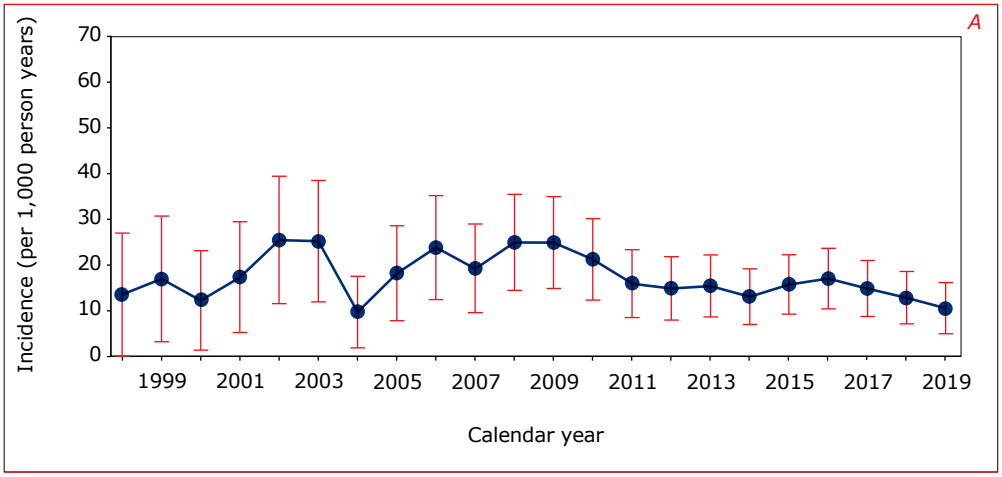

## Mortality

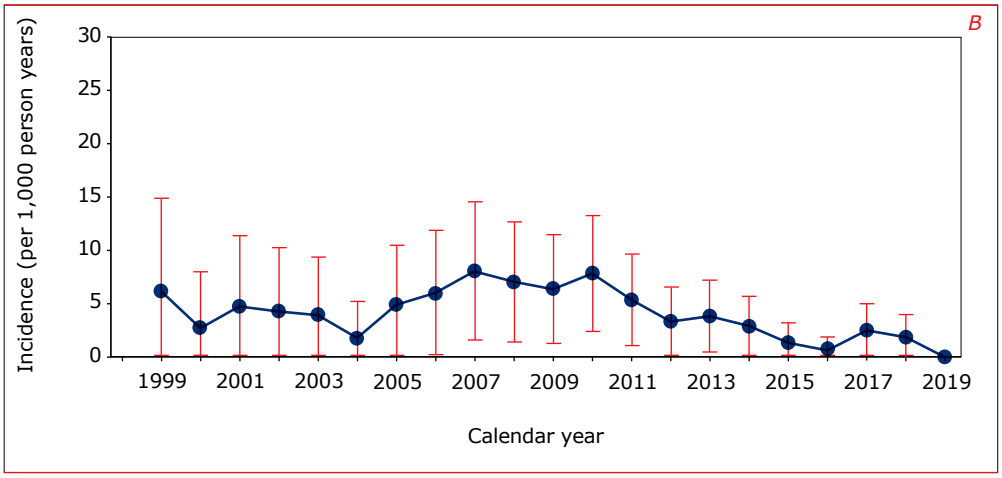
### All-cause mortality

The percentage of the 2,046 individuals with an HCV infection who died from any cause was 17%. For individuals with HCV infection, the incidence-rate of death from any cause, adjusted for age and gender of the SHM population, was 17.8/1000

person years in 1998-2002, 20.5 in 2003-11 and 14.4 from 2012 onwards (*Figure 4.9A*). In MSM with HCV infection, these incidence rates were 5.3/1000 person years in 1998-2002, 8.9 in 2003-11, and 4.7 from 2012 onwards. In PWID with HCV infection, these incidence rates were 20.3/1000 person years in 1998-2002, 38.0 in 2003-11, and 46.2 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 2,046 HIV-1-positive individuals who were ever diagnosed with an acute or chronic HCV infection.*



### Liver-related mortality

In total, 72 individuals co-infected with HCV died of a liver-related cause between 1998 and 2019. Other important causes of death among individuals with an HCV co-infection were non-AIDS malignancies (2%), 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 3.8/1000 person years 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 0/1000 person years in 1998-2002, 2.5 in 2003-11, and 0.7 from 2012 onwards. In PWID with HCV infection, these incidence rates were 2.6/1000 person years in 1998-2002, 8.5 in 2003-11, and 4.6 from 2012 onwards.

## HBV

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

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

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

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

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

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

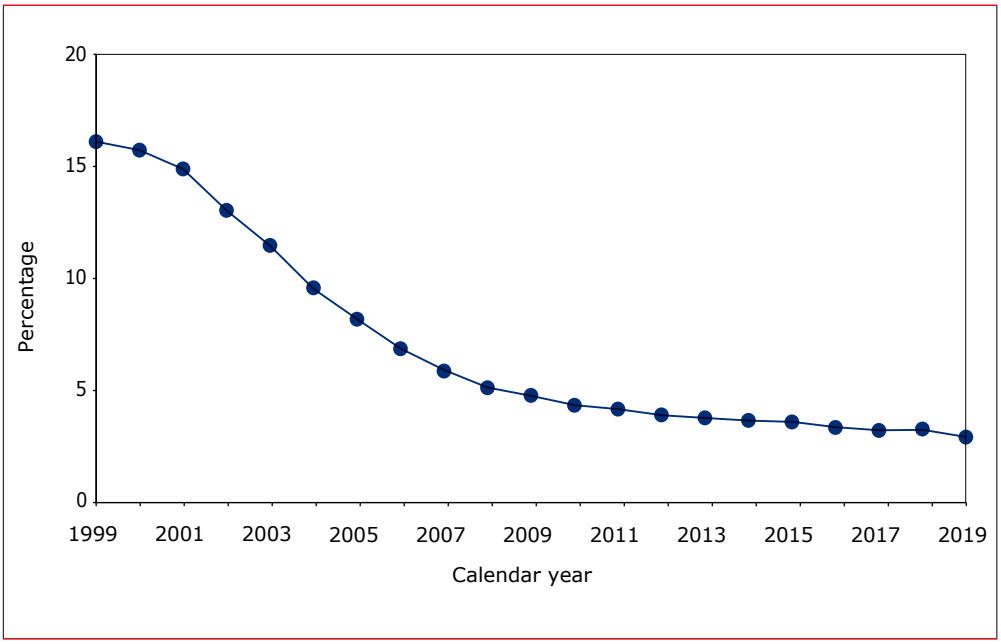
### HBV screening

Ninety-six percent of the 27,167[b] HIV-positive individuals 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 HIV-positive individuals in care has improved over calendar time. In 1999, 16% of individuals had not been screened for HBV infection (*Figure 4.10*). Since then,

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

the percentage of HIV-positive individuals without HBV screening has decreased markedly, with just under 3% of all HIV-positive individuals in care having no measured HBV serological markers in 2019 (*Figure 4.10*).

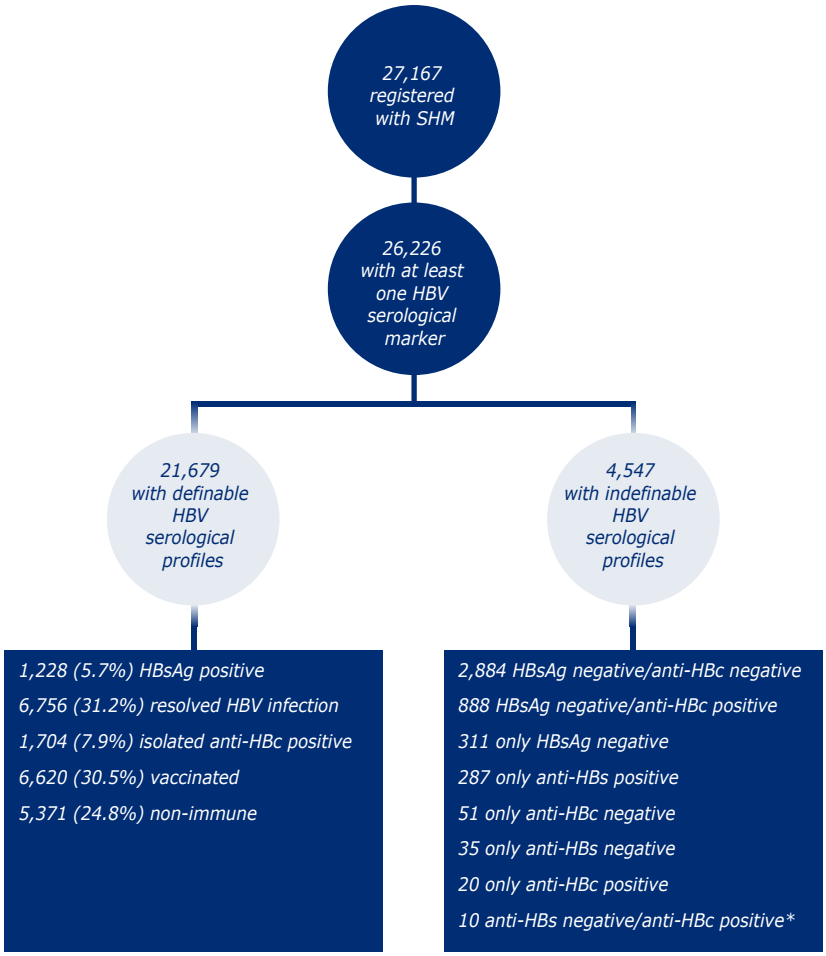
***Figure 4.10:*** *Percentage of individuals in care without any hepatitis B virus serological test per calendar year of care.*




## HBV serological profiles

HBV serological profiles could be defined for 21,680 (83%) of the 26,226 screened individuals (*Figure 4.10*). A full HBV serological battery is not routinely performed in HIV-positive individuals; therefore, any results from an HBV serological test were assumed to remain the same over time until the performance of a new serological test. The distribution of HBV serological profiles at the last visit are given in *Figure 4.11*. The remaining 4,546 (17%) individuals either had insufficient information to establish HBV serological profile (n=4,485) or were previously HBsAg-positive, no longer had anti-HBc antibodies and did not have anti-HBs antibodies (n=61). The demographic characteristics of people with definable HBV serological profiles are compared in *Table 4.3*.

***Figure 4.11:*** *Flowchart of HIV-positive individuals registered in the SHM database, 1999-2019, with testing for hepatitis B virus (HBV).*




*Information obtained from the most recent serological result.*

**The 61 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 HIV-positive individuals in care, according to their hepatitis B virus (HBV) serological profile as registered in the SHM database, 1998-2019.*

| | HBV serological profile*, n (%) | | | | |
|---|---|---|---|---|---|
| | Active HBV infection | Resolved HBV infection | Isolated anti-HBc positive | Vaccinated | Non-immune |
| Total number | 1,228 | 6,756 | 1,704 | 6,620 | 5,371 |
| Male gender | 1,056 (86%) | 5,832 (86%) | 1,305 (77%) | 5,724 (86%) | 3,981 (74%) |
| Region of origin | | | | | |
| Netherlands | 534 (43%) | 3,676 (54%) | 676 (40%) | 4,037 (61%) | 3,095 (58%) |
| Europe | 79 (6%) | 479 (7%) | 117 (7%) | 497 (8%) | 293 (5%) |
| Sub-Saharan Africa | 315 (26%) | 1,020 (15%) | 545 (32%) | 487 (7%) | 640 (12%) |
| Caribbean/South America | 133 (11%) | 824 (12%) | 166 (10%) | 797 (12%) | 800 (15%) |
| Southeast Asia | 65 (5%) | 281 (4%) | 66 (4%) | 206 (3%) | 143 (3%) |
| Other | 102 (8%) | 476 (7%) | 134 (8%) | 596 (9%) | 400 (7%) |
| HIV transmission group | | | | | |
| Men who have sex with men | 704 (57%) | 4,692 (69%) | 755 (44%) | 4,856 (73%) | 2,491 (46%) |
| Heterosexual | 377 (31%) | 1,442 (21%) | 605 (36%) | 1,412 (21%) | 2,382 (44%) |
| Injecting drug use | 50 (4%) | 229 (3%) | 190 (11%) | 61 (1%) | 105 (2%) |
| Other | 97 (8%) | 393 (6%) | 154 (9%) | 291 (4%) | 393 (7%) |
| cART | 1,176 (96%) | 6,537 (97%) | 1,629 (96%) | 6,477 (98%) | 5,186 (97%) |
| Deaths | 247 (20%) | 962 (14%) | 298 (17%) | 311 (5%) | 626 (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 active HBV infection

### Prevalence of active HBV infection

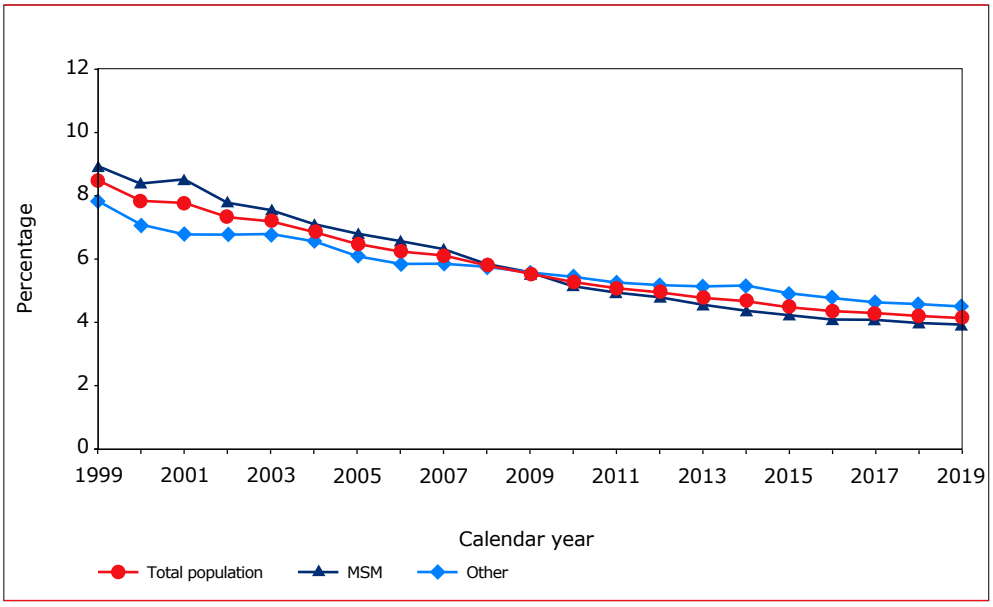
Of the 26,226 individuals ever screened for at least one HBV serological marker, a total of 1,597 (6%) received a positive HBsAg test result. Over time, 190 (12%) of these individuals resolved their HBV infection (i.e., they became HBsAg-negative and acquired anti-HBs antibodies); an additional 178 (11%) became HBsAg-negative without acquiring anti-HBs antibodies. The remaining 1,229 (77%) individuals continued clinical care with HBsAg-positive serology.

The prevalence of HBsAg-positive serology was 8.5% in 1999, and it slowly decreased to 4.2% in 2019 (*Figure 4.12*). This decreasing prevalence could be the result of several factors, including lower numbers of individuals with incident HBV infection (as a result of increased vaccination coverage among MSM[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 HIV-positive individuals with HBsAg-positive serology[31].

As is the case for HCV co-infection, the percentage of HIV-positive individuals in care and chronically co-infected with HBV is considerably higher than the percentage found in the general Dutch population. Individuals co-infected with HBV were predominantly male (1,057/1,229; 86%), 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. Finally, HBV co-infection was less common than HCV co-infection among PWID.

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



### Presence of HBV/HDV infection

By 2019, 190/1,597 (11.9%) 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 (12%) were identified with either past or current HDV infection; nine of which were tested for HDV RNA, which found that six had detectable HDV RNA, indicating active HDV infection.

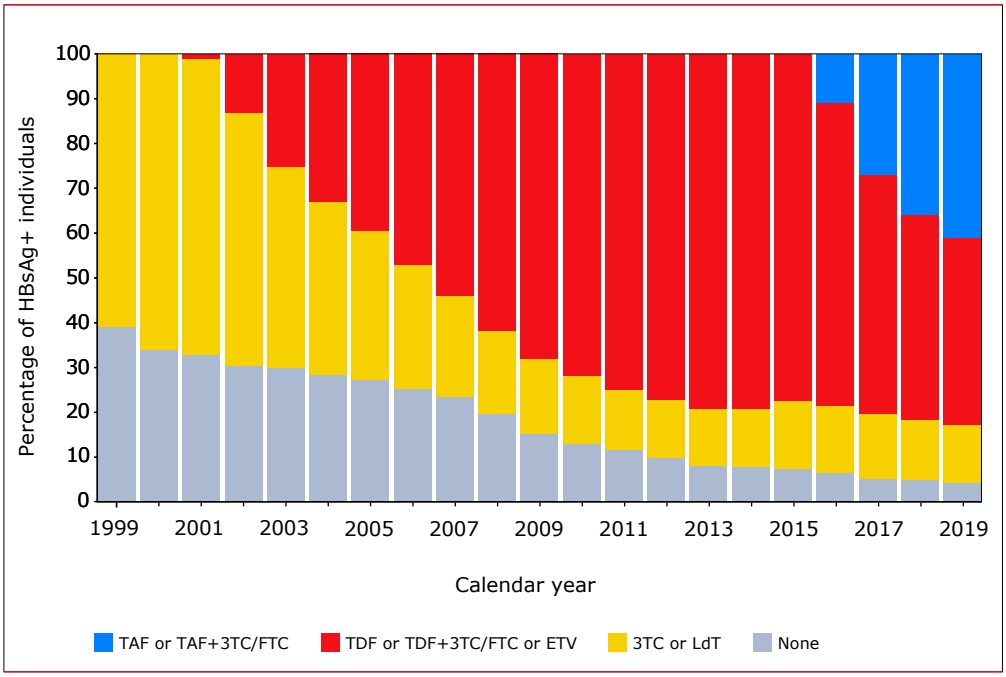
### Treatment for chronic HBV infection

The treatment for chronic HBV infection aims to reduce viral replication. As HBV DNA is the parameter most directly influenced by therapy with either nucleoside or nucleotide analogues, HBV DNA undetectability is an appropriate surrogate marker for treatment response. Persistent lowering of HBV DNA levels to less than 20 IU/ml has also been shown to delay progression of liver fibrosis to cirrhosis[32]. Lowering HBV DNA levels may result in HBsAg negativity in a small subgroup of individuals. Persistent HBsAg negativity, together with the development of anti-HBs antibodies, is known as HBs Ag- seroconversion and is the penultimate goal of HBV therapy. In those individuals who are also e-antigen positive (HBeAg+), a similar seroconversion from HBeAg positivity to negativity can occur, with subsequent development of anti-hepatitis B e-antigen (anti-HBe) antibodies. This so-called HBeAg-seroconversion is an important secondary treatment parameter, since studies have shown that it is associated with reduced viral activity in the liver, thereby decreasing the risk of progression of liver fibrosis. A few antiviral agents used for treatment of HIV, such as lamivudine, and particularly TDF/TAF, are also active against HBV.

Of the 1,597 individuals with HIV in the SHM database who have ever had an HBsAg-positive serological test result, 1,529 (96%) received a cART regimen that included one or more agents with activity against both HIV and HBV. The reasons for the remaining 68 individuals not receiving anti-HBV treatment included: death before being able to start treatment (n=16), recent entry into care (n=3), loss to follow up (n=44), and lack of sufficient information (n=5).

Most people with active HBV infection 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=83/634, 13%) and became more commonly used than lamivudine in 2006. TAF-based cART (with or without lamivudine or emtricitabine) was first used in 2016 (n=132/1,214, 11%). In 2019, most HBV co-infected individuals were receiving TDF-based cART (n=522/1,247, 42%), closely followed by TAF-based cART (n=513/1,247, 41%), and lamivudine-based cART (n=159/1,247, 13%), or no anti-HBV-containing cART (n=53/1,247, 4%)

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



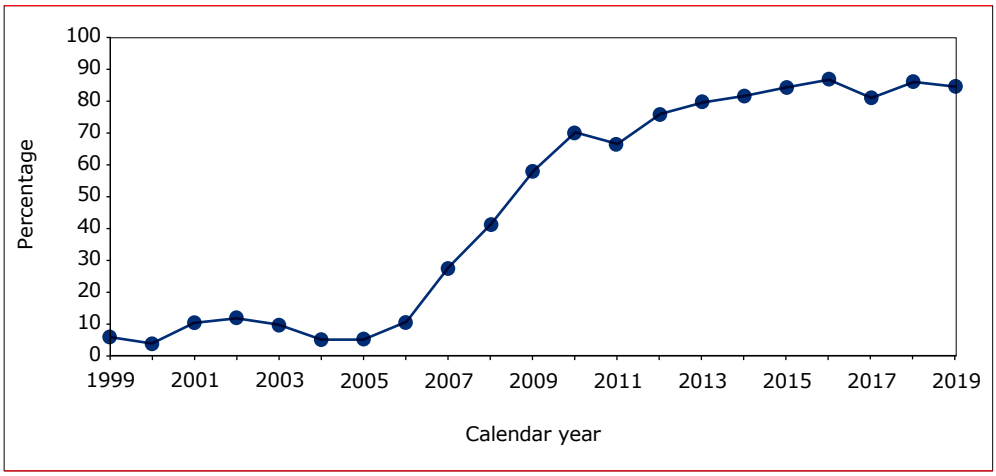

***Legend:*** *TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; ETV=entecavir; 3TC=lamivudine; LdT=telbuvidine; FTC=emtricitabine.*

***Note:*** *Anti-HBV agents were divided as none, 3TC or LdT, TDF or TDF+3TC/FTC or ETV, and TAF or TAF+3TC/FTC. 3TC and LdT should not be combined and TDF and ETV can be combined under special circumstances[33].*

In most individuals mono-infected with HBV, a persistently HBeAg-negative chronic HBV infection with undetectable HBV DNA confers a favourable long-term outcome, with low risk of cirrhosis and HCC[34]. We therefore examined the HBV DNA levels per calendar year in the population of individuals co-infected with HIV and HBV. In many treatment centres, HBV DNA is not routinely collected after the first negative HBV DNA result during treatment with TDF/TAF, provided that HIV RNA is undetectable. Therefore, for each year, HBV DNA measurements were available on average in 24% of individuals co-infected with HBV. *Figure 4.14* shows the percentage of those over time with an undetectable HBV DNA level less than 20 IU/ml, as a percentage of the total number of individuals with an HBV DNA measurement. For HBV DNA measurements with a detection limit other than 20 IU/ml, we used the detection limit of the specific assay (<100, <200, <400, <1000

or <2000 IU/ml). In 1999-2005, at most, 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, and reached 80% in 2013. In 2019, 85% of individuals co-infected with HIV and HBV had an undetectable HBV DNA level (*Figure 4.14*).

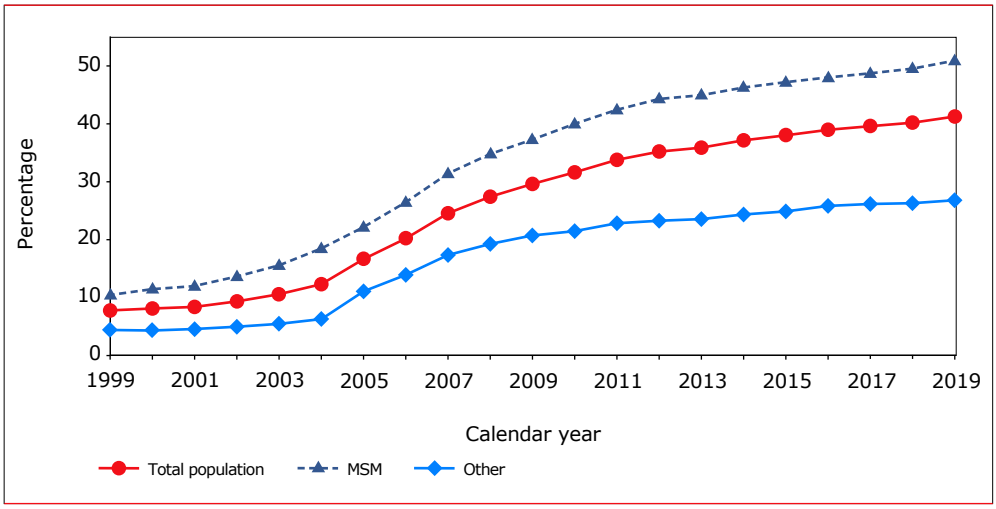
***Figure 4.14:*** *Percentage of individuals with undetectable hepatitis B virus (HBV) DNA levels by assay, with a detection limit of <20, <100, <200 or <2000 IU/ml HBV DNA per calendar year, regardless of HBeAg status.*




## HBV vaccination in HIV-positive individuals

Of the 21,680 individuals with definable HBV serological profiles, 6,619 (31%) 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 41% in 2019 (*Figure 4.15*). 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 4.15: Prevalence of hepatitis B vaccination per calendar year.*




## HBV non-immune status in HIV-positive individuals

Of the 21,680 individuals with definable HBV serological profiles, 5,371 (25%) had serological evidence of being non-immune and non-exposed to HBV at their last visit. When the 4,546 individuals with undefinable HBV serological profiles were considered, 72 out of 391 with an anti-HBs antibody test did not have detectable anti-HBs antibodies, and 3,810 out of 4,155 without an anti-HBs antibody test were not reported to have been vaccinated by their treating physician. Therefore, at most, 9,253 of 27,167 (34%) individuals screened for HBV remained susceptible to infection at the time of their last visit [5,371 non-immune *plus* 72 with undefinable HBV profile and anti-HBs antibody negative *plus* 3,810 with undefinable HBV profile and missing data on anti-HBs antibody status and no physician-reported vaccination].

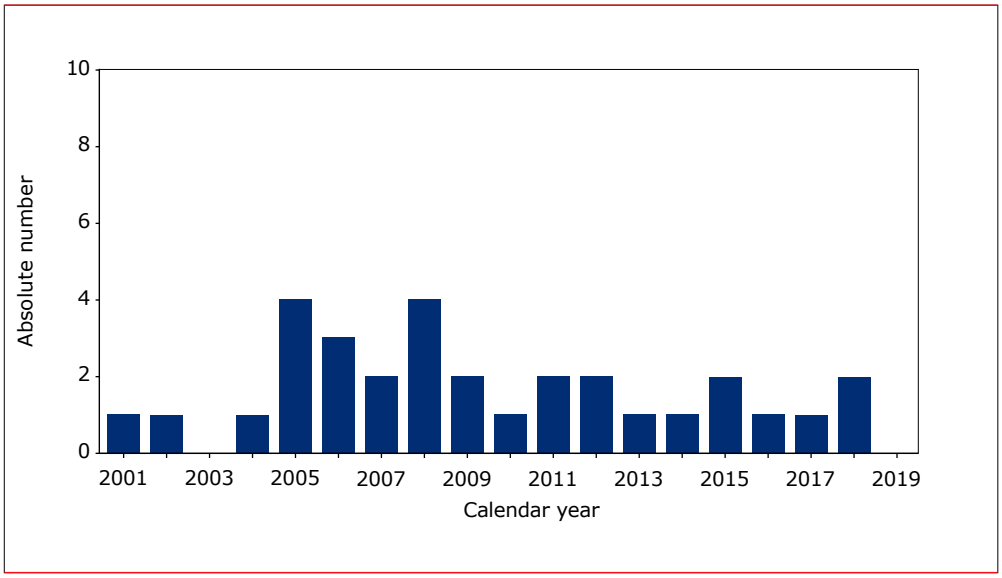
Individuals at risk, and MSM in particular, should be actively counselled about HBV vaccination, although they may be protected from HBV infection by the use of TDF or TAF as part of their cART regimen, according to the findings reported by an international study and by one of the Dutch HIV treatment centres[35,36]. Data from SHM show that, of those people who remain at risk of acquiring HBV, 80% are currently being treated with a cART regimen that includes TDF or TAF; for MSM, this percentage is 82%.

## Liver-related morbidity

Additional data from liver biopsy pathology reports, transient elastography, radiology reports, or a combination of those sources, were available for 1,223 of the 1,597 individuals with an HBV co-infection. Review of these additional data showed that severe chronic liver disease, according to our definition, was considered to be present (presumptive and definitive categories combined) in 265 (22%) of those with HBV co-infection. Definitive severe chronic liver disease was documented for 72 (6%) with an HBV co-infection. Of the 256 individuals with severe chronic liver disease, nine (3%) had past or current HDV infection.

*Figure 4.16* shows that the annual number of new HCC diagnoses declined from 2010 onwards. HCC was found in 33 (2.1%) individuals with a chronic HBV co-infection, 18 of whom were born in the Netherlands, nine in sub-Saharan Africa, two in Asia, and one each in South America, the United States, Australia, and western Europe. One individual with newly diagnosed HCC had either past or current HDV infection.

***Figure 4.16:*** *Absolute number of annually-reported HCC cases among HBV co-infected individuals over time.*



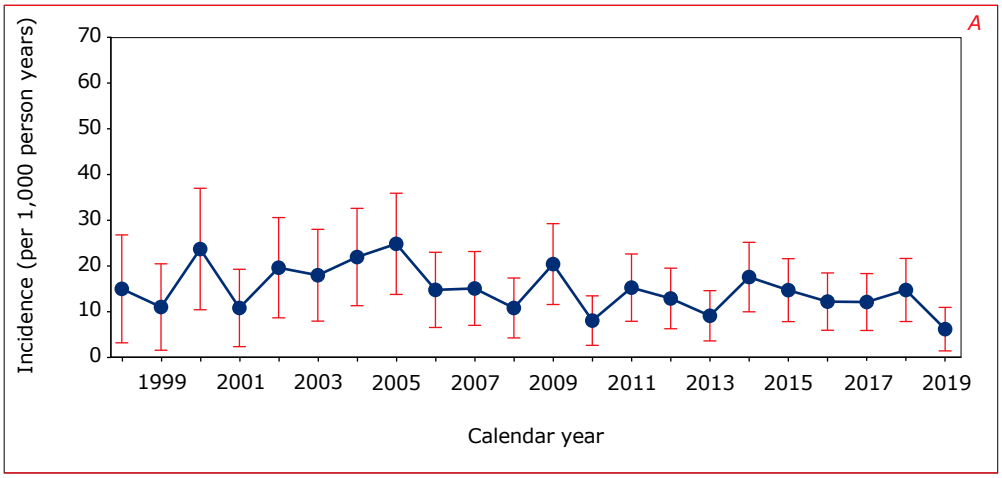
## Mortality

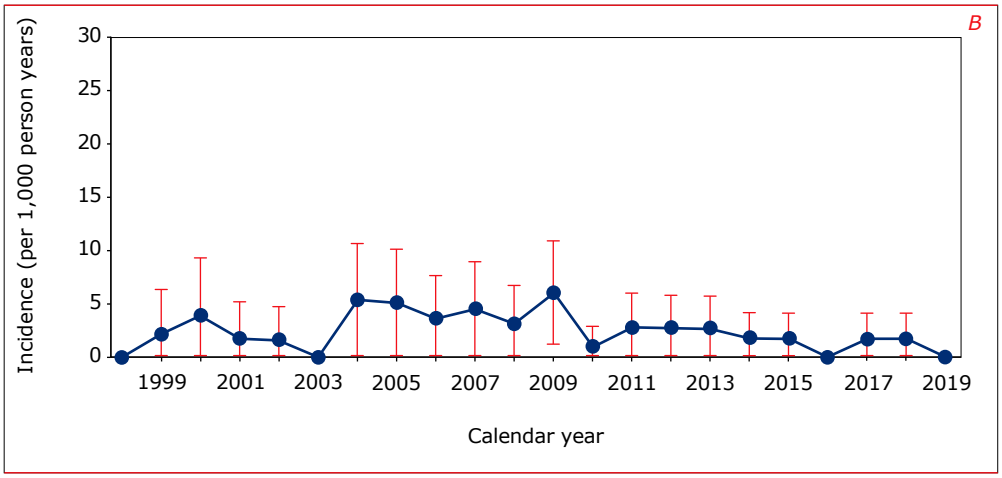
### All-cause mortality

Nineteen percent (n=298) of the 1,597 individuals with an HBV infection died of any cause (*Table 4.3*). For individuals with HBV infection, the incidence rate of death from any cause, adjusted for age and gender of the SHM population, was 16.1/1000 person years in 1998-2002, 16.0 in 2003-11 and 12.4 from 2012 onwards (*Figure 4.17A*). In MSM with HBV infection, these incidence rates were 11.7/1000 person years in 1998-2002, 13.3 in 2003-11, and 10.0 from 2012 onwards. In PWID with HCV infection, these incidence rates were 52.4/1000 person years in 1998-2002, 60.6 in 2003-11, and 89.2 from 2012 onwards.

Of the 298 individuals with an HBV infection who died from any cause, five (1.7%) had either past or current HDV infection.

*Figure 4.17: 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 individuals positive for HIV-1 who were ever diagnosed with an acute or chronic HBV infection.*



### Liver-related mortality

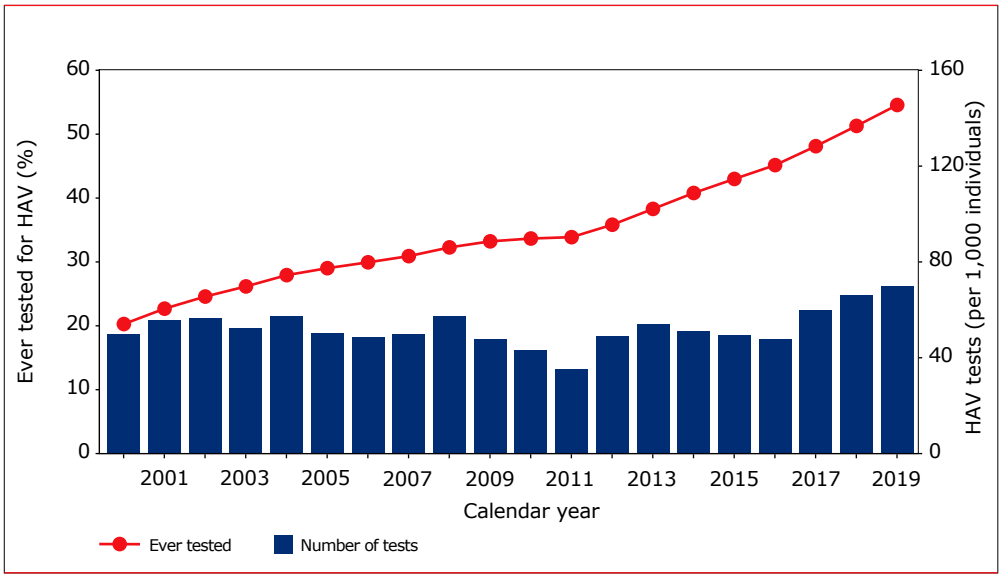
In total, 48 individuals co-infected with HBV died of a liver-related cause, only one of whom had either past or current HDV infection. For individuals with HBV infection, the incidence rate of liver-related death, adjusted for age and gender of the SHM population, was 1.9/1000 person years in 1998-2002, increasing to 3.5 in 2003-11, and decreasing to 1.6 from 2012 onwards (*Figure 4.17B*). In MSM with HBV infection, these incidence rates were 2.4/1000 person years in 1998-2002, 3.2 in 2003-11, and 1.4 from 2012 onwards. In PWID with HBV infection, these incidence rates were 0.4/1000 person years in 1998-2002, 1.4 in 2003-11, and 1.3 in 2012 onwards.

## 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-four percent (n=14,777) of the 27,167 HIV-positive individuals ever registered in the SHM database have been screened for HAV. The frequency of screening for HAV in HIV-positive individuals has been consistent over the past two decades (*Figure 4.18*). Between 2000 and 2017, roughly four to six HAV tests per 1000 individuals were conducted each year. Between 2018 and 2019, screening frequency increased to almost seven HAV tests per 1000 individuals per year. Accordingly, the percentage of individuals who have ever been tested for HAV was 20% in 2000 and steadily increased to 55% in 2019 (*Figure 4.18*).

*Figure 4.18: Percentage ever tested for anti-HAV antibodies and anti-HAV antibody testing, frequency per calendar year.*

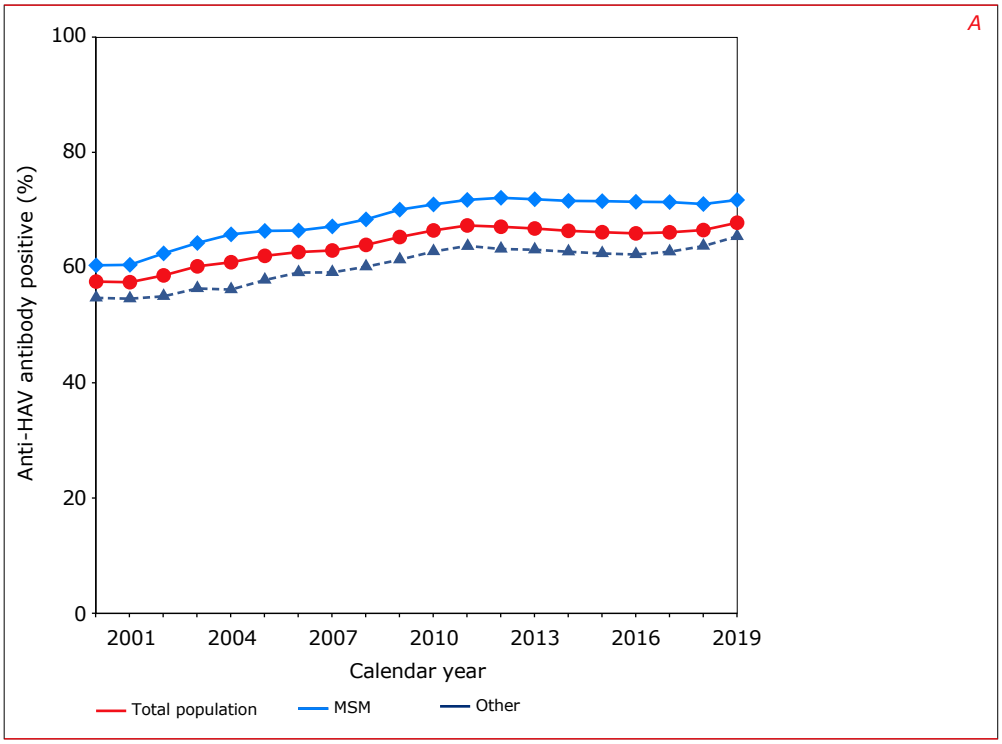


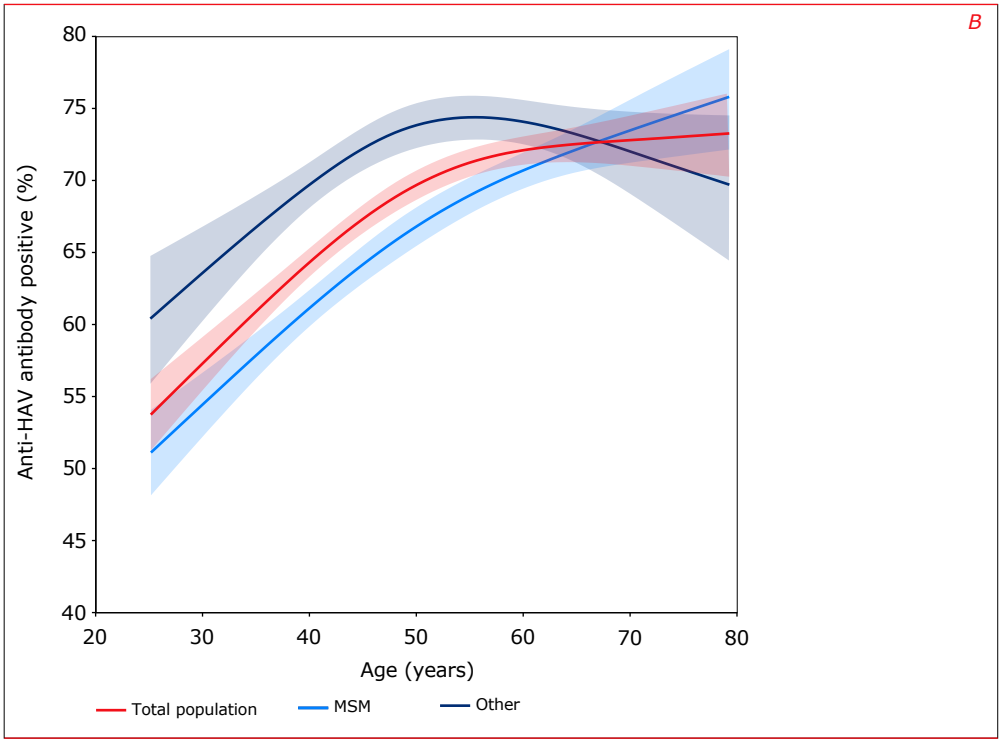

*Legend: HAV=hepatitis A virus.*

## HAV seropositivity

Of the 14,777 individuals ever screened for HAV, a total of 10,002 (68%) had a positive anti-HAV antibody test result; 65% were observed in MSM, 67% in PWID, 72% in heterosexuals, and 73% in people from other transmission groups. The prevalence of anti-HAV antibody positivity was 57% in 1999 and it slowly increased to 68% in 2019 (*Figure 4.19A*). For MSM, the prevalence of anti-HAV antibody positivity was 55% in 1999 and it also slowly increased to 65% in 2019. For all other transmission groups, the prevalence of anti-HAV antibody positivity was 60% in 1999 and it slowly increased to 72% in 2019.

*Figure 4.19: 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.*

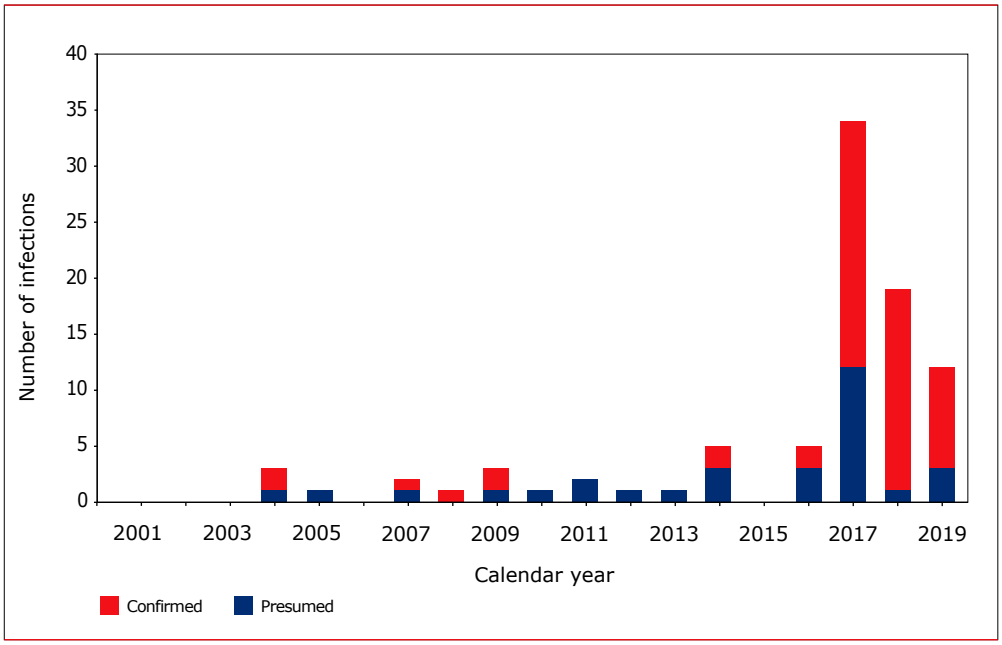
Epidemiological studies have highlighted the strong relationship between increasing anti-HAV antibody positivity and increasing age[37]. This age-dependent relationship was also observed in the 14,777 individuals ever screened for HAV (*Figure 4.19B*). Overall, anti-HAV antibody positivity was 60% for individuals below the age of 40, and 70% for those aged 40 or older. For MSM, anti-HAV antibody positivity was 56% for individuals below the age of 40, and 68% for those aged 40 or older. For all other transmission categories, anti-HAV seropositivity was 65% 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 2019, there were 90 reported cases of acute HAV infection ($n$=59, presumed; $n$=31, confirmed), of which 72 (80%) were observed in MSM, 17 (19%) in heterosexuals,

and one (1%) in PWIDs. Cases of acute HAV were first documented in 2004 and the number of acute HAV cases remained between 0 to 5 cases per year until 2016 (*Figure 4.20*). In 2017, 34 cases of acute HAV infection were documented (*n*=22, presumed; *n*=12, confirmed). The number of cases of acute HAV infection decreased to 19 in 2018 and 12 in 2019. Of the 65 documented cases occurring between 2017 and 2019, 55 (85%) were observed in MSM. This increase in HAV infections was part of a European-wide outbreak of HAV among sexually-active MSM in 2017[38].

***Figure 4.20:*** *Number of reported cases of confirmed and presumed acute HAV infection per calendar year.*

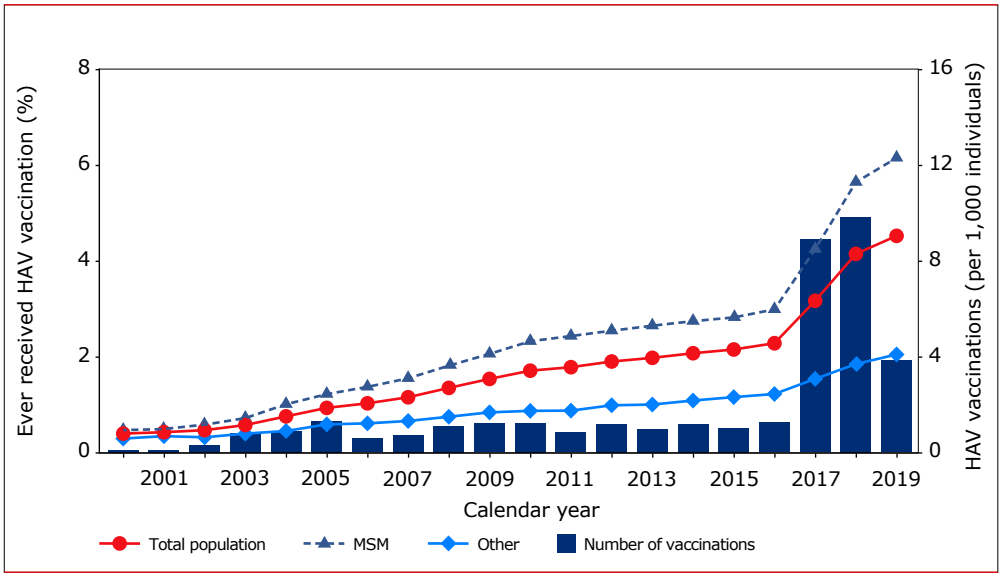



Of the 90 reported cases of acute HAV infection, 47 (52%) reported having severe clinical symptoms due to infection. Severe chronic liver disease, according to our definition, was considered to be present (presumptive and definitive categories combined) in 14 (16%) of those with a reported acute HAV infection. Definitive severe chronic liver disease was documented for three (3%) with a reported HAV infection. No deaths due to acute HAV infection were reported.

## HAV vaccination in HIV-positive individuals

Information on HAV vaccination status was obtained from clinical files and was unknown for the majority of individuals ever registered by SHM. Of the 27,167 HIV-positive individuals ever registered in the SHM database, 1,231 (5%) 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)[39]. HAV vaccination frequency was consistently lower than two vaccinations per 1000 HIV-positive individuals from 2000 to 2016, and it increased substantially to 9 and 10 vaccinations per 1000 individuals in 2017 and 2018, respectively (*Figure 4.21*). Accordingly, the percentage reported to have ever received an HAV vaccination was 1.3% in 2000, increasing to 2.5% in 2016, and then 4.5% in 2019. In MSM, this percentage was 1.7% in 2000, 3.3% in 2016, and 6.2% in 2019.

***Figure 4.21:*** *Percentage that ever received an HAV vaccination and HAV vaccination frequency per calendar year.*



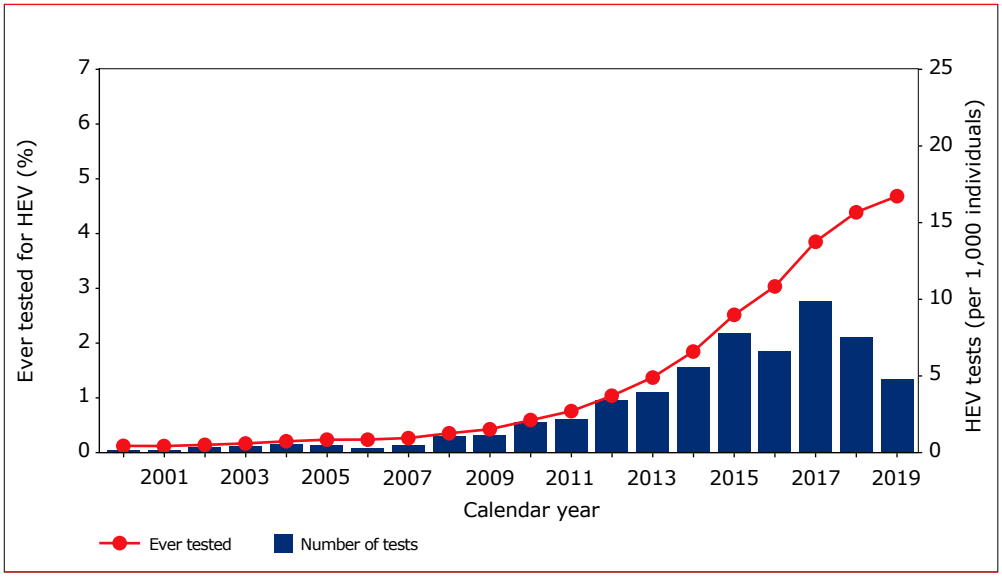

***Legend:*** *HAV=hepatitis A virus; MSM=men who have sex with men.*

# 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 27,167 HIV-positive individuals ever registered in the SHM database have been screened for HEV. The screening frequency for HEV infection in HIV-positive individuals in care was low between 2000 and 2010, ranging between fewer than one and two tests per 1000 individuals (*Figure 4.22*). HEV testing frequency rapidly increased from two tests per 1000 individuals in 2011, to 10 tests per 1000 individuals in 2017. In 2019, this frequency was five tests per 1000 individuals.

***Figure 4.22:** 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 1,268 individuals who were in care between 2000 and 2019 and who were ever screened for HEV, 181 (14%) were newly diagnosed as having past or current HEV infection. Of these individuals, 122 (67%) were MSM, 48 (27%) heterosexuals, six (3%) PWID, and five (3%) were from other transmission groups. The largest number of new diagnoses were observed between 2013 and 2019 (*Figure 4.23*), mainly due to the higher frequency of HEV testing among HIV-positive individuals. The percentage of individuals newly diagnosed with past or current HEV infection ranged from 9% to 15% between 2004 and 2019 (*Figure 4.24*).

Of all individuals tested for HEV and in care between 2000 and 2019, there were 43 individuals diagnosed with acute HEV infection, of whom 33 were MSM and 10 heterosexuals. Only one of these cases was confirmed to have progressed to chronic infection (i.e., positive HEV RNA lasting more than three months).

***Figure 4.23:*** *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.*

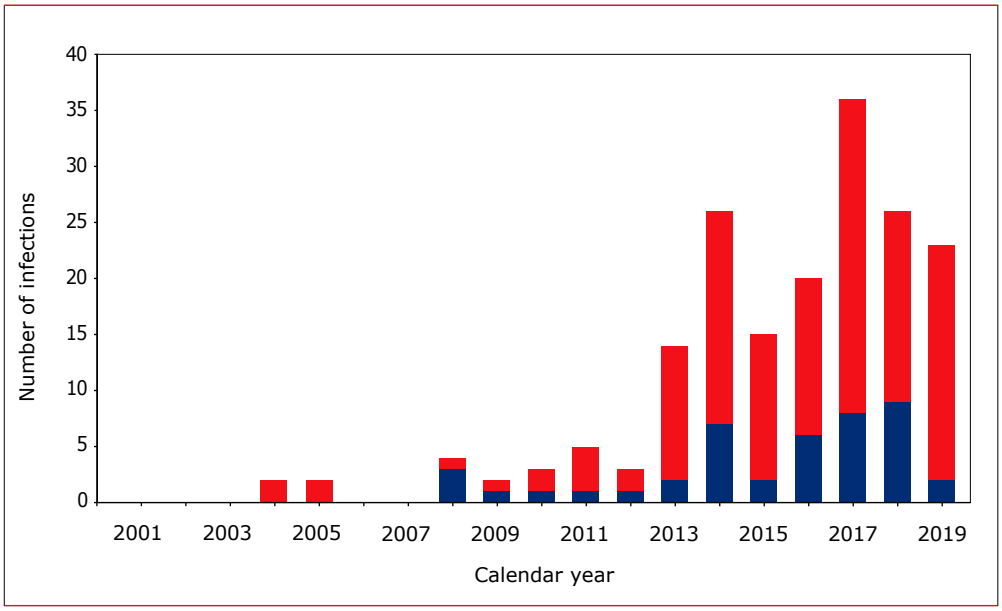
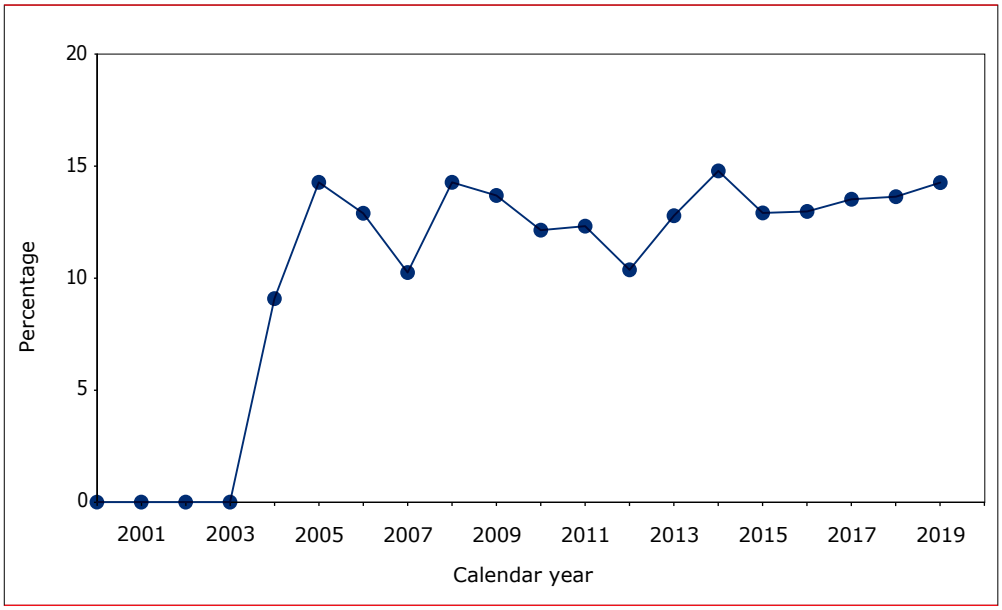


*Figure 4.24: Percentage ever infected with HEV per calendar year.*




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 HIV-positive population in the Netherlands has continued to improve over time and nowadays is documented almost universally. Five percent of HIV-positive individuals ever registered between 1998 and 2019 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, with 5% of the MSM ever being diagnosed with an acute HCV infection.

Our data clearly show that since the arrival of novel DAAs in 2014, they have entirely replaced PEG-IFN-containing regimens. The number of HIV-positive individuals treated for HCV has rapidly increased. More than 1,000 individuals have received, or are currently receiving, treatment with novel DAAs. Overall, 97% of all individuals with sufficient follow-up data to calculate an SVR were found to have been cured. This high cure rate has seen the number of HCV co-infected individuals remaining in need of HCV treatment fall to 131. Overall, a rapid reduction

in the prevalence of active HCV infections has been achieved, with prevalence in MSM having declined to 0.5% in 2019. The rapidly increasing availability of novel interferon-free, highly-effective combination antiviral regimens for HCV, together with optimised screening for HCV co-infection, will also limit the impact of HCV co-infection on liver-related morbidity and mortality. Successful treatment of HCV will also prevent onward transmission of HCV, which is possibly reflected in a lower incidence of acute HCV infections in recent years. However, in line with earlier reports[26,29], HCV re-infection after successful treatment has been observed. Although the rate of re-infection has declined in the most recent years, ongoing transmission of HCV persists.

Six percent of the HIV-positive individuals ever in care 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 34% of all HIV-positive individuals, and 27% of MSM, have either not been exposed to HBV, or have not been successfully vaccinated, and may remain at risk of acquiring HBV. Since 80% of all individuals, and 82% of MSM, still at risk of acquiring HBV infection use a cART regimen that includes TDF/TAF, their risk could be essentially nil due to sustained chemoprophylaxis. The remaining 20% of the HIV-positive individuals ever registered, and 18% of the MSM, remain unprotected against HBV, which represents an estimated 7.0% of the total population of HIV-positive individuals 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 HIV-positive individuals ever registered by SHM, 25% of the individuals chronically co-infected with HCV, and 22% of the individuals chronically co-infected with HBV, had evidence of severe chronic liver disease. However, the absolute number of HCC diagnoses has been decreasing since 2010, which can likely be attributed to the use of effective antiviral treatment for HBV and HCV co-infections. Overall, people with chronic HCV or HBV co-infection remain at increased risk of having a liver-related cause of death, although this risk has declined substantially since 2012. The overall mortality rate has decreased in individuals with HCV and HBV co-infections since 2012, yet the rate remains 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 and testing frequency of anti-HAV antibodies was consistent across calendar years. The percentage of tested individuals found to have anti-HAV

antibodies is no different between MSM and other transmission groups, and it is over twice as high as that of the general Dutch population[40]. The percentage with anti-HAV antibodies was also higher with increasing age, as would be expected from the general epidemiology of HAV infection[37]. Among the individuals diagnosed with HAV, almost half reported having severe symptoms during their infection, while one patient 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 5%. This low percentage of vaccine uptake 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 were tested for anti-HAV immunity, and vaccine uptake was low, could signal a substantial percentage of individuals who 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. This increase was likely due to awareness of HEV infection in Europe and its recognised role in hepatitis and liver-related disease[18]. With increased testing, the number of individuals newly diagnosed with past or current HEV infection, or who had acute HEV infection, also increased from 2014. 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 what would be expected in the Dutch general population[17]. 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 re-infection. In particular, efforts should continue to increase HBV vaccination rates among HIV-positive individuals who remain at increased risk of acquiring HBV, particularly those who are not receiving an antiretroviral regimen containing TDF or TAF, or those previously not responding to vaccination[41]. In the long term, provision of highly-effective DAA regimens for all known HCV co-infected HIV-positive individuals is expected to further contribute to reducing the burden of severe chronic liver disease, hepatocellular carcinoma, and mortality related to liver disease among people living with HIV. In addition, these novel regimens may

have a beneficial impact on the risk of ongoing HCV transmission. The fact that DAA treatment uptake is lagging behind for a small group of individuals, shows that additional research is required to establish the underlying reasons why treatment may be delayed in some individuals. Importantly, regular HCV RNA screening among individuals who have been successfully treated for HCV infection, and remain at risk of re-infection, is recommended to ensure early detection of new HCV infections; this is in combination with behavioural interventions aimed at MSM to prevent HCV re-infection after successful treatment of HCV.

HBV clinical practice guidelines from the European Association for the Study of the Liver suggest that HDV should be tested at least once for all individuals with chronic hepatitis B infection[42]. In the Netherlands, roughly 12% 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 of liver-related morbidity and mortality in HIV-positive individuals with HBV infection, as found in other settings[13].

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 reports of HAV infections were uncommon in the last two decades, the recent HAV outbreak in MSM 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[43]. However, data from SHM and data from a recent meta-analysis, support no noteworthy increase in HEV prevalence among HIV-positive individuals[44], and only one patient in the database was diagnosed with chronic HEV infection. We recommend following current European guidance, which recommends that individuals with persistently elevated transaminase levels should be screened for HEV-RNA[18]. Further data are needed to determine to what extent liver-related and non-liver-related disease occurs as a result of HEV infection in HIV-positive individuals.

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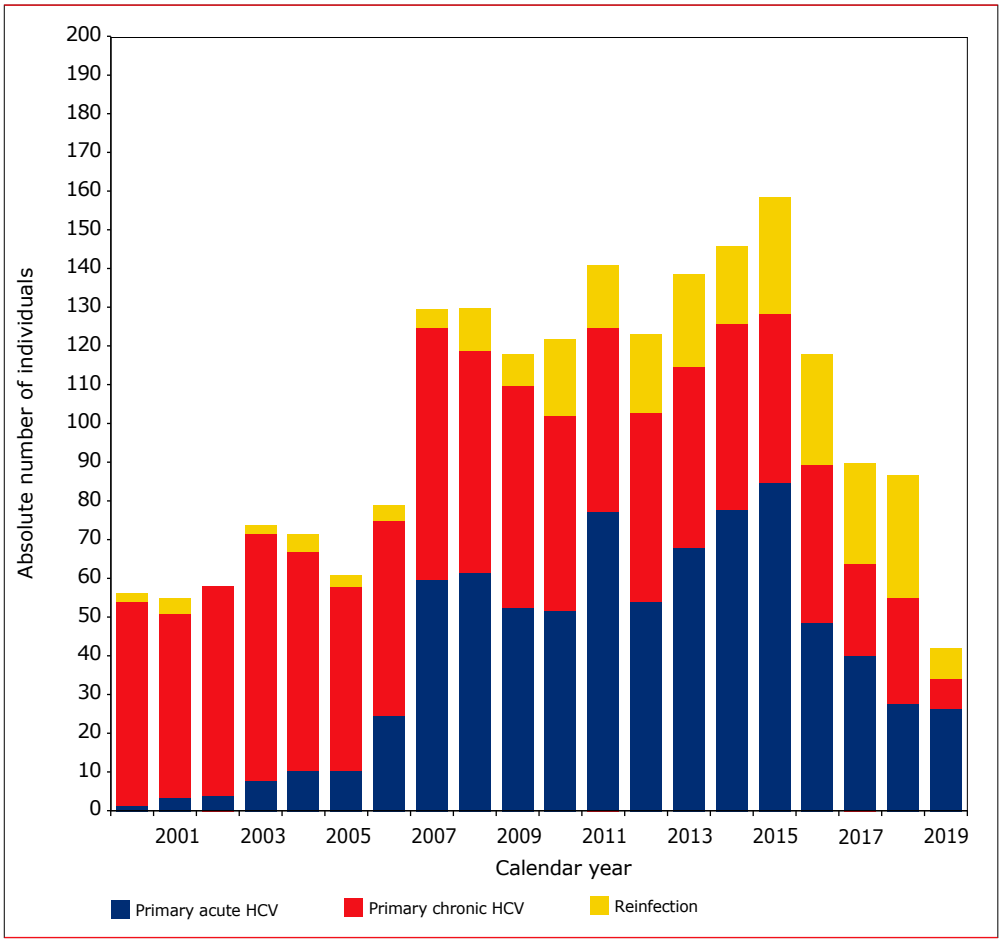
# Appendix:

*Appendix Figure 4.1: Total number of primary and chronic infections, and re-infections with hepatitis C among HIV-positive individuals in care from 2000-2019, by year of HCV diagnosis.*




*Legend: HCV=hepatitis C virus*

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

Colette Smit, Tom Wolfs, Annemarie van Rossum

*Box 5.1: Chapter definitions*

| | |
|---|---|
| **Child** | An individual diagnosed with HIV and who made the first visit to a Dutch HIV treatment centre before the age of 18. |
| **Infection** | The moment a child acquires an HIV infection. |
| **Diagnosis** | The moment a child is newly diagnosed with HIV. |
| **Registration** | The moment an HIV-positive child in care is notified to SHM by their treating physician or nurse and registered in the SHM database. |
| **In care in 2019** | Clinic visit or lab measurement in 2019. |
| **ART** | Antiretroviral therapy. |
| **cART** | Combination antiretroviral therapy: a combination of at least three antiretroviral drugs from two different antiretroviral drugs classes or at least three nucleoside reverse transcriptase inhibitors. |
| **Viral suppression** | Any viral load measurements <200 copies/ml, except for time points in the past where tests were used with quantification limits higher than 200 copies/ml. |

## Populations described in this chapter

Vertical transmission rates of HIV remain very low in the Netherlands. Together with a decrease in the number of children with HIV being adopted by Dutch parents, this has resulted in only nine new children being registered with SHM in 2019. This chapter provides an update on the population of children in HIV care in the Netherlands, including those nine children.

*Box 5.2: Outline of the paediatric ATHENA cohort in the Netherlands: HIV-positive children ever registered in the ATHENA cohort by 31 December 2019. (Children = individuals aged <18 years at the time of diagnosis who have made a first visit to a Dutch HIV treatment centre before the age of 18 years.)*

1. Children who entered care in the Netherlands whilst less than 18 years of age (n=511)
2. Population in care in 2019:
   - aged <18 years in 2019 (n=199): 193 with vertically-acquired HIV, 3 with non-vertically acquired HIV, and 3 with an unknown route of transmission;
   - aged ≥ 18 years in 2019 (n=213); 118 with vertically-acquired HIV, 88 with non-vertically acquired HIV, and 7 with an unknown route of transmission.
3. Specific populations:
   - adopted children (n=140)
   - children who have transferred to adult care (n=158)

## Background

Combination antiretroviral therapy (cART) has dramatically decreased morbidity and mortality in HIV-positive children worldwide[1,2,3,4,5]. Immediate initiation of cART, regardless of CD4 cell count or percentage, is associated with a higher survival rate when compared with delayed cART initiation guided by CD4 cell count[6,7,8,9]. 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, irrespective of CD4 cell count, including in all children[10].

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. Diagnosis, treatment and follow up of all these children is monitored by Stichting HIV Monitoring (SHM).

Here we report on the demographics, clinical characteristics, and long-term virological and immunological responses to treatment of HIV-positive children ever cared for in one of the paediatric and/or adult HIV treatment centres in the Netherlands, while under the age of 18 (*Box 5.2*).

## Ever registered

As of 31 December 2019, SHM registered 657 individuals ever diagnosed with HIV whilst less than 18 years of age. Of these 657 children, 511 entered care in the Netherlands before 18 years of age. Those who first entered Dutch HIV care while 18 years or older (n=146) are not included in this chapter. Nine children were newly registered in 2019, and two children who had been included in the Monitoring report of 2019 were subsequently excluded from the database as they objected to further collection of their data.

Of the 511 children we report on, 393 first entered care at a paediatric HIV treatment centre and 118 at an adult treatment centre. Those who entered care at an adult HIV treatment centre were predominantly diagnosed with HIV at an older age, and had mostly acquired HIV through non-vertical transmission (*Table 5.1*).

***Table 5.1:** Demographic and HIV-related characteristics of 511 HIV-positive children ever registered by SHM and who entered care in the Netherlands below the age of 18, as of 31 December 2019.*

| Characteristics | Vertically-acquired HIV infection* | Non-vertically-acquired HIV infection* | Route of transmission unknown* |
|---|---|---|---|
| Total | 360 | 139 | 12 |
| HIV treatment centre | | | |
| Paediatric care | 352 (98) | 31(22) | 10 (83) |
| Adult care | 8 (2) | 108 (78) | 2 (17) |
| Gender | | | |
| Male | 174 (48) | 50 (36) | 8 (67) |
| Female | 186 (52) | 89 (64) | 4 (33) |
| Country of origin child | | | |
| The Netherlands | 111 (31) | 32 (23) | 0 |
| Sub-Saharan Africa | 206 (57) | 81 (58) | 10 (83) |
| Other | 4 (12) | 26 (19) | 2(17) |
| Country of origin mother | | | |
| The Netherlands | 32 (9) | 3 (2) | 1 (8) |
| Sub-Saharan Africa | 190 (53) | 13 (9) | 6 (50) |
| Other/unknown | 138 (38) | 123 (8) | 5 (42) |
| Age at HIV diagnosis | 1.1 (0.2-4.0) | 16.9 (16-17) | 11.3 (6-14) |
| Adopted^ | 137 (38) | 1 (0.7) | 2 (17) |
| cART-treated | 356 (99) | 131 (94) | 11 (92) |
| Therapy-naive at cART initiation | 305(85) | 124 (89) | 11 (92) |
| CD4 at cART initiation | 540 (270-1170) | 310 (200-430) | 315 (150-522) |
| CD4 Z-score at cART initiation | -0.63 (-1.04--0.15) | -0.56 (-0.96-- 0.28) | -0.60 (-0.99- -0.29) |
| VL (log copies/ml) at cART initiation | 5.2 (4.5-5.8) | 4.5 (4.0-5.2) | 4.8 (4.5-5.3) |

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

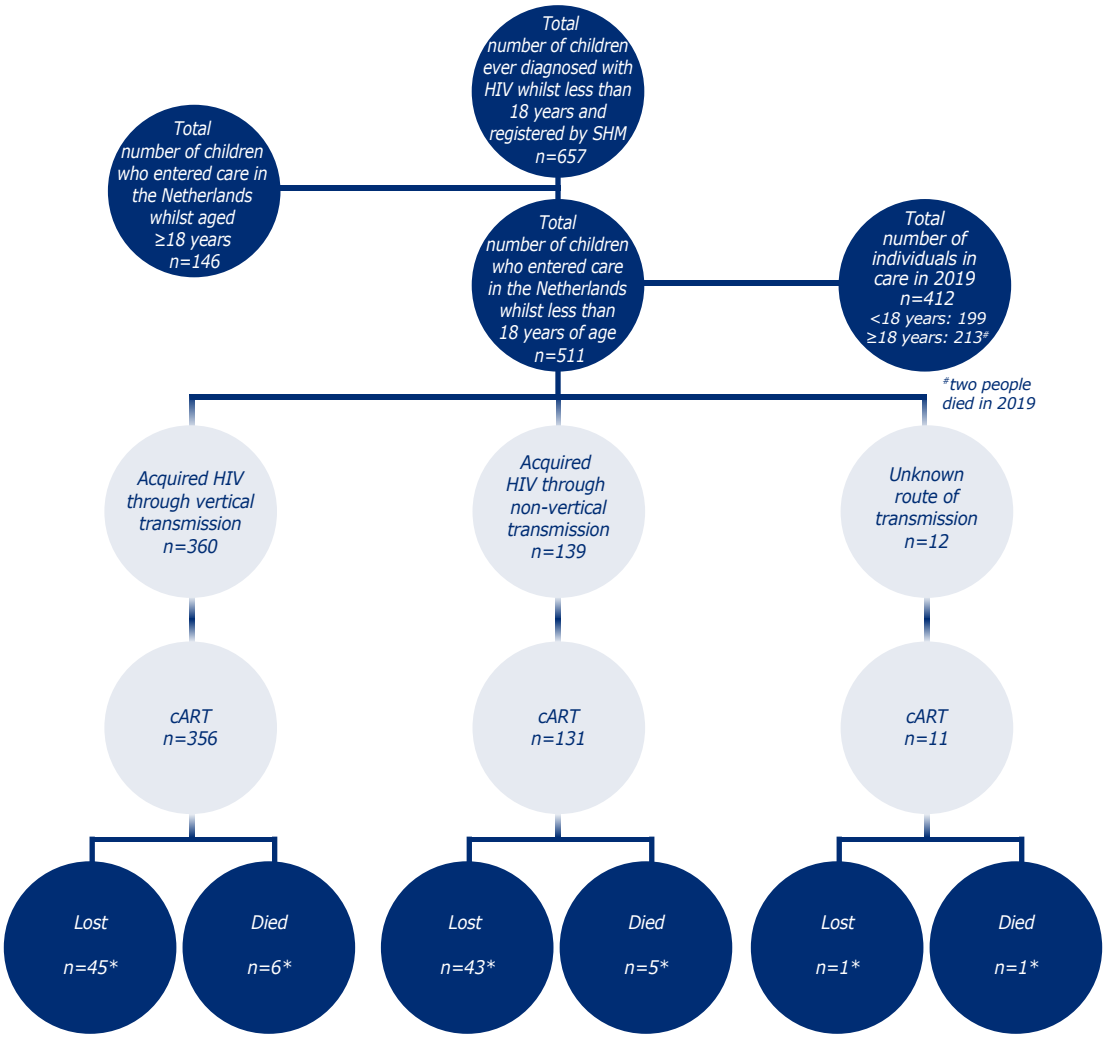
*^ All adopted children were born outside the Netherlands*

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

## Mode of transmission

The majority of the children registered had acquired HIV through vertical transmission or, in the absence of vertical transmission, through sexual contact (*Figure 5.1*). *Figure 5.2* shows the number of newly-registered children by year of entering care in the Netherlands and the mode of HIV transmission. In addition, for those with vertically-acquired HIV, it shows whether or not they were adopted at the time of registration.

***Figure 5.1:*** *Overview of HIV-positive children registered by Stichting HIV Monitoring as of 31 December 2019.*



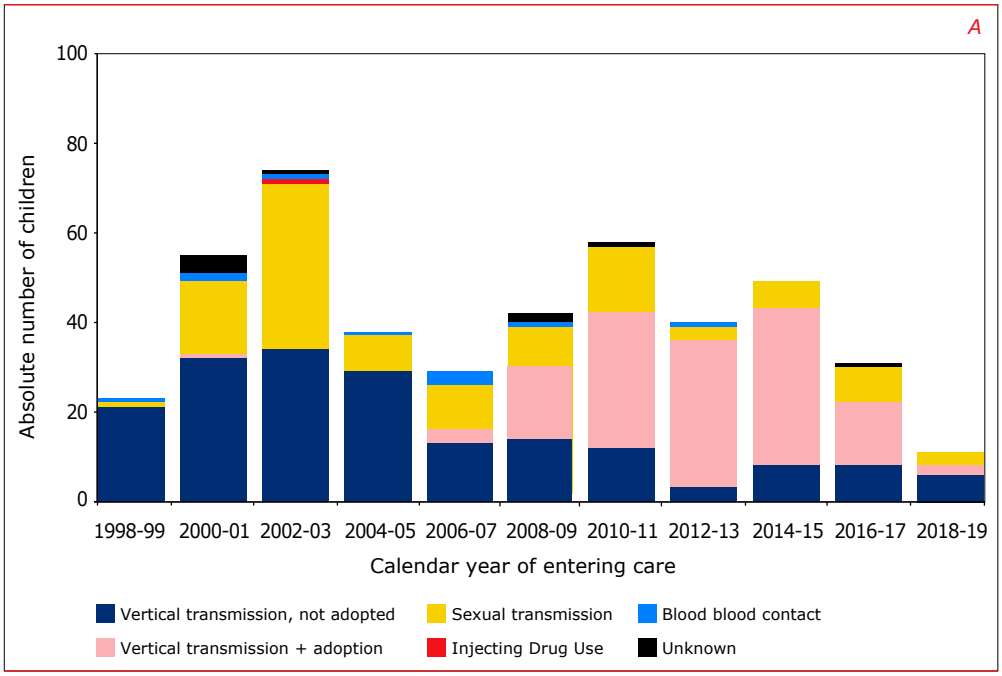

** of the total number of children who acquired HIV through a vertical, non-vertical or an unknown route of transmission.*

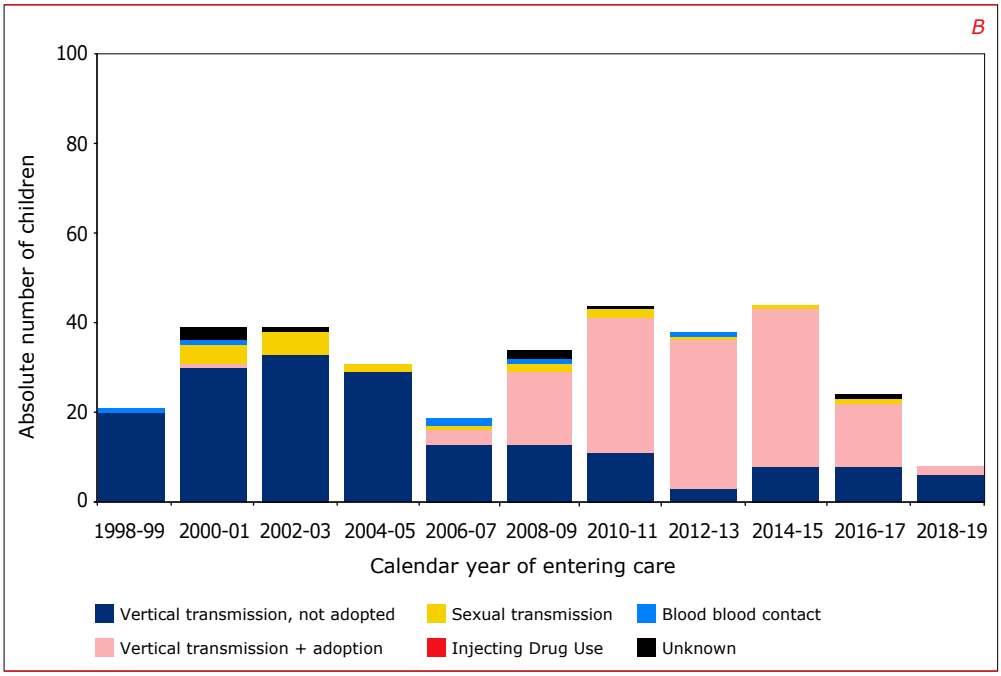
***Legend:*** *cART=combination antiretroviral therapy.*

## Children with vertically-acquired HIV

- Between 1998 and 2019, 360 children acquired 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] 0.2-4.0 years).
- 57% (n=206) of the children were born in sub-Saharan Africa.
- 31% (n=111) of the children were born in the Netherlands.
- 9% of the children born in the Netherlands (10 out of 111), had two Dutch parents.
- 98% received care in a paediatric HIV treatment centre in the Netherlands and the remaining 2% were seen in adult care.
- For 99% of the children, the date on which they started cART was documented.

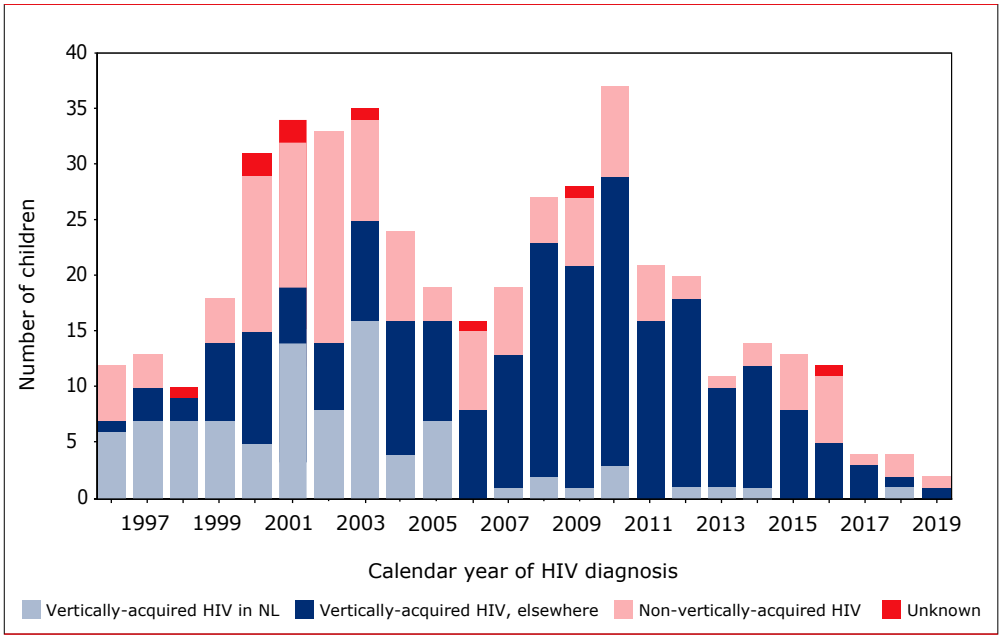
*Figure 5.2: Number of HIV-positive children by year of entering care in the Netherlands, stratified by HIV transmission mode and, for those who acquired HIV through vertical transmission, by whether or not they were adopted during the period 1998-2019. Total population (A), HIV paediatric care only (B).*






***Note:*** *Low numbers in 2019 may be due to a delay in registration.*

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




*Note: Registration for 2019 is not yet complete.*

## Vertical transmission of HIV in the Netherlands has become a rare event since 2015

*Figure 5.3* shows the number of registered HIV diagnoses among children by year of diagnosis, mode of transmission, and region of origin. As shown in the figure, vertical transmission of HIV occurring in the Netherlands declined markedly after 2004 and 2005; in fact, the most recent registered case of vertical transmission in the Netherlands was in 2018. However, as reported in chapter 6 of this report - Pregnancies in HIV-infected women - a single vertical transmission did occur in 2019. The mother was newly registered in the SHM database, but as her child had yet to be formally registered at the time of database closure, it was not included in the analysis for this chapter on Children living with HIV in the Netherlands. The standard HIV screening among pregnant women, introduced nationally in 2004[11,12] is responsible for the decline in vertical transmission in the Netherlands.

Since the introduction of this screening programme, only ten children born with HIV in the Netherlands have been registered with SHM. These ten children are described briefly below:

- Seven children were born to mothers who only first tested HIV positive themselves after giving birth: the mothers of five of these seven children had had a negative test result during the first trimester pregnancy screening; they acquired HIV later during their pregnancy.
- Two children were born to mothers known to be HIV-positive; one mother did not receive treatment during her pregnancy for an unknown reason; the other mother was newly diagnosed with HIV and did start cART during pregnancy, 22 weeks after conception. Prior to initiating cART, the mother had detectable HIV RNA levels, but the last available HIV RNA measurement before delivery was undetectable (<50 copies/ml). This makes peripartum transmission highly unlikely and may suggest *in utero* transmission of HIV.
- The remaining child was born to a mother whose HIV status during pregnancy, and results of any HIV screening, remain unknown.

### Children with non-vertically-acquired HIV

- Between 1998 and 2019, 139 children were registered with HIV infection acquired through non-vertical transmission.
- The median age at which they received their first reported HIV-positive test result was 16.9 years (IQR, 16-17).
- The main route of HIV transmission was sexual contact (*Figure 5.2*):
  - 92 children acquired HIV through heterosexual contact, and
  - 28 children acquired HIV through homosexual contact.
- Eighteen children acquired HIV through contaminated blood or blood products. This mode of transmission was no longer reported from 1997 onwards among children born in the Netherland, and from 2009 onwards among all children, regardless of country of birth.
- The remaining child acquired HIV either through injecting drug use or accidental contact with contaminated needles.
- 5% were born in sub-Saharan Africa.
- 78% received care in an adult HIV treatment centre.
- In total, 94% of these children had started cART.

### Unknown route of HIV transmission

- For 12 HIV-positive children, the route of transmission was unknown.
- Their median age at diagnosis was 11.3 years (IQR, 6-14).
- Ten children were in care at a paediatric HIV treatment centre.
- In total, 92% of these children had started cART.

### Children with HIV who were newly registered with SHM in 2019

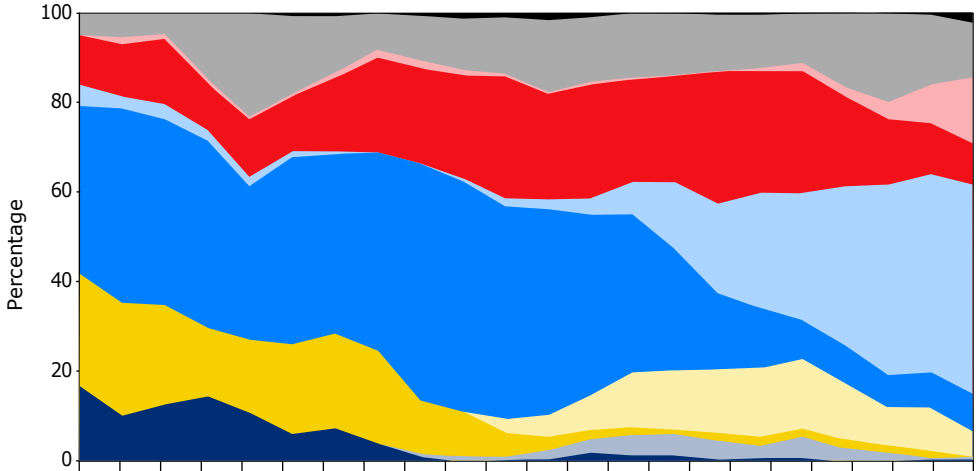
Nine children were newly registered in 2019. Two children included in earlier reports were subsequently excluded from the database as they objected to further collection of their data.

- Seven children had vertically-acquired HIV and two children acquired HIV through sexual contact.
- One child with non-vertically acquired HIV was born in the Netherlands.
- Four children were born in Sub-Sahara Africa and all had vertically-acquired HIV.
- The remaining four children were born in Europe or Latin America. All four had recently migrated to the Netherlands and had their first visit to one of the Dutch HIV treatment centres within 3.5 months of their reported date of migration.
- Eight children entered paediatric care and the remaining child entered care in an adult HIV treatment centre.

### Age distribution

The age distribution of children receiving HIV care shifted between 1998 and 2008 (*Figure 5.4*). From 2008 onwards, there has been an increase in the proportion of children aged 0 to 5 years. This is due to an increase in the rate of adoption of HIV-positive children in these age groups, as illustrated by the shaded areas in *Figure 5.4*. In 2019, about 86% of the children aged 12 years or younger living with HIV were adopted.

*Figure 5.4: Time-dependent age distribution of HIV-positive children in care over time.*




| | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 16-18*, adopted | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 2 | 2 | 3 | 2 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 4 |
| 16-18* | 3 | 4 | 4 | 18 | 35 | 28 | 20 | 13 | 16 | 20 | 22 | 30 | 27 | 29 | 28 | 26 | 25 | 25 | 38 | 45 | 32 | 23 |
| 12-16*, adopted | 0 | 1 | 1 | 1 | 1 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 4 | 5 | 9 | 18 | 28 |
| 12-16* | 7 | 9 | 14 | 13 | 20 | 20 | 27 | 35 | 36 | 41 | 49 | 45 | 49 | 47 | 49 | 63 | 59 | 63 | 47 | 34 | 24 | 18 |
| 5-12*, adopted | 3 | 2 | 3 | 3 | 3 | 2 | 1 | 0 | 0 | 1 | 3 | 4 | 7 | 15 | 31 | 43 | 56 | 66 | 84 | 98 | 93 | 89 |
| 5-12* | 24 | 33 | 39 | 52 | 53 | 68 | 66 | 73 | 89 | 91 | 86 | 88 | 78 | 73 | 56 | 36 | 29 | 20 | 18 | 17 | 17 | 16 |
| 2-5*, adopted | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 9 | 15 | 25 | 28 | 30 | 33 | 36 | 31 | 19 | 20 | 11 |
| 2-5* | 16 | 19 | 22 | 19 | 25 | 33 | 35 | 34 | 20 | 18 | 10 | 6 | 4 | 4 | 2 | 4 | 4 | 4 | 5 | 4 | 3 | 0 |
| 0-2*, adopted | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 4 | 6 | 9 | 10 | 9 | 6 | 11 | 7 | 5 | 1 | 1 |
| 0-2* | 11 | 8 | 13 | 18 | 17 | 10 | 12 | 7 | 2 | 0 | 1 | 1 | 5 | 3 | 3 | 1 | 2 | 2 | 0 | 1 | 1 | 1 |

** age in years*

### Low mortality rates

The mortality rate among children registered with SHM between 1998 and 2019 is very low. Three children (0.5%) under the age of 18 years have died since the start of registration. These three boys were born outside the Netherlands and died before 2010. AIDS was the reported cause of death for each of them, despite the fact that two of the boys were receiving cART. One boy had very low CD4 cell counts while using cART, and the other boy died shortly after the start of cART; he had a high HIV RNA and low CD4 cell count.

### Antiretroviral treatment

Of the 511 children who entered care in the Netherlands before 18 years of age, 498 (97%) started cART. Of these 498 children, 440 (88%) were treatment-naive at the start of cART and 58 (12%) had previously been exposed to monotherapy or dual therapy (i.e., were pre-treated).

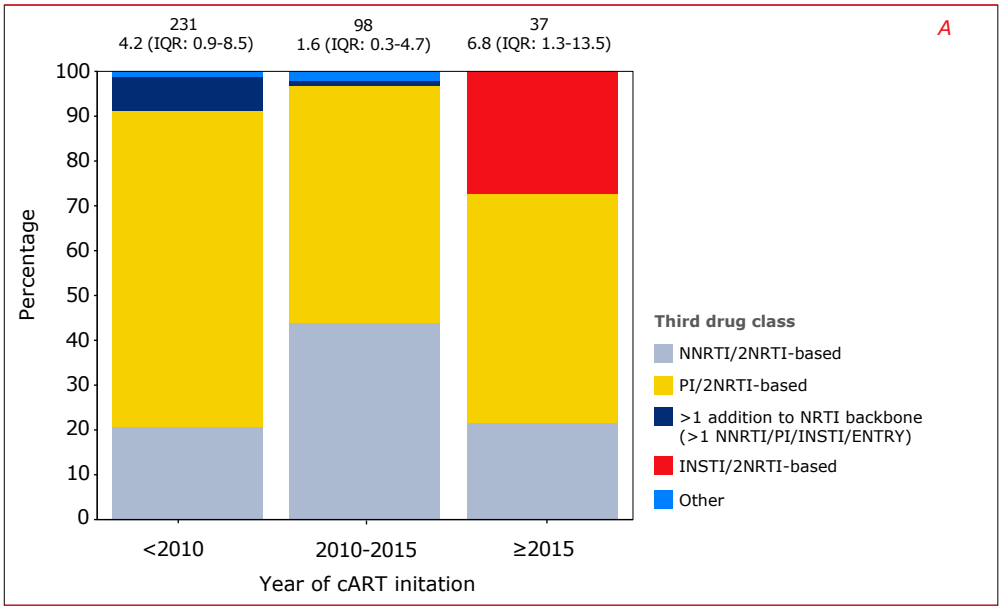
For the purposes of this analysis, we included both pre-treated and treatment-naive children, and grouped them according to calendar year of starting cART: 311 children started a cART regimen before 2010, 134 between 2010 and 2015, and 53 children from 2015 onwards.

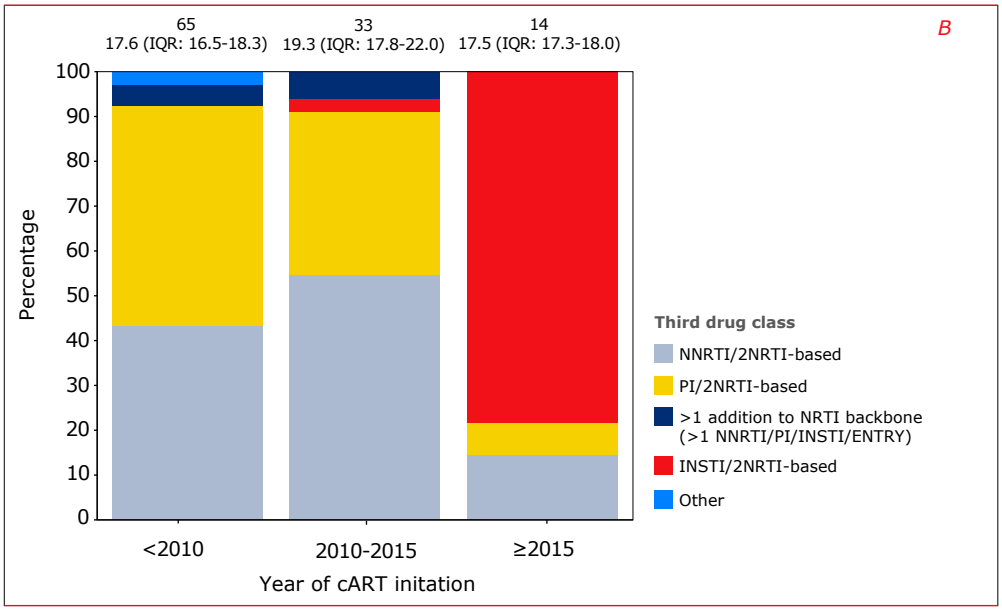
Of the 13 children not treated with cART, one died shortly after entering care, eight were lost to follow up, and another two moved abroad. The reason the remaining two children did not start cART was recorded as 'own decision', and in the second child, cART initiation was delayed because of persistent low HIV RNA levels and high CD4 cell counts in the absence of treatment.

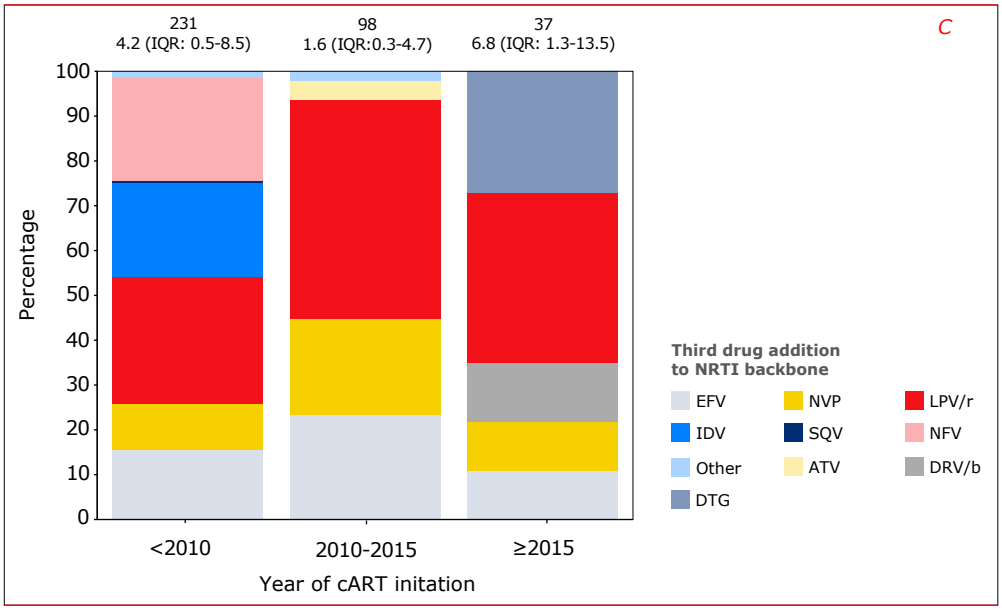
### Initial combination antiretroviral regimen

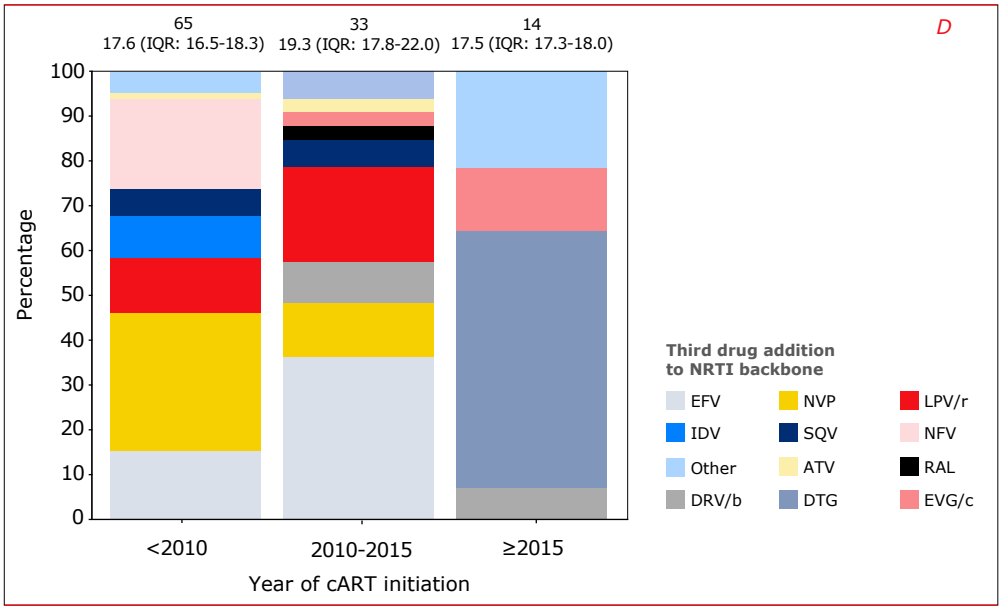
Of the 498 registered children known to have initiated cART, 58% were treated with a first-line regimen that included a protease inhibitor (PI) and two or more nucleoside reverse transcriptase inhibitors (NRTIs). Another 31% were treated with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimen with two or more NRTIs. *Figure 5.5* show the trends over time for the third-drug additions to the NRTI backbone as part of the initial cART regimens, stratified by calendar year of starting cART, and by being in care in a paediatric or adult HIV treatment centre. Among children in paediatric care, lopinavir was the most commonly-used protease inhibitor. Following their introduction in 2013 and 2014, the integrase inhibitors dolutegravir and elvitegravir have also become part of an initial cART regimen in children, but were mainly prescribed to children older than 12 years of age and to only one child younger than 12.

*Figure 5.5: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial cART regimen, stratified by calendar year period, according to (A) antiretroviral class among children in paediatric care, (B) antiretroviral class among children in adult care and (C) specific third drugs among children in paediatric care and (D) specific third drugs among children in adult care. Numbers above the bars represent the total number of individuals initiating cART in that particular calendar year period. Median age and interquartile range above the bars represents the age of individuals at 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 498 children who had ever started cART spent on an initial regimen was 19.4 months (IQR, 5-50). Discounting weight-related dose changes, 423 children (90%) discontinued their first-line treatment regimen. The most important reasons for changing first-line cART included toxicity (18%) and simplification (23%). Virological failure accounted for changing first-line cART therapy in 9% of cases. Other reasons were low drug concentrations, decision by parents and/or child, research protocol-driven reasons, or unknown.

### Immunological response

Earlier reports have shown that the clinical benefit of cART is strongly related to the degree to which the CD4 cell count recovers[13]. Long-term CD4 cell count changes were assessed among the 498 children who had ever started cART. Children with vertically-acquired HIV were stratified according to age at the time of cART initiation, resulting in the following categories:
(1) vertically-acquired, 0-1 year,
(2) vertically-acquired, 2-5 years,
(3) vertically-acquired, 5-18 years,
(4) non-vertically-acquired or unknown mode of HIV transmission[a], 5-18 years.

Given that normal CD4 cell counts in younger children are highly age-dependent[14], it is more appropriate to analyse time-dependent CD4 count trajectories, expressing CD4 counts as Z-scores, in which counts are standardised in relation to age. CD4 Z-scores, which represent the standard deviation from the reference values for HIV-negative children, were calculated for CD4 cell counts to correct for age-related differences. All absolute CD4 T-cell counts were transformed into Z-scores by subtracting the age-related reference value for the age at the time of the CD4 measurement[15] and dividing the outcome by the age-related standard deviation. A Z-score of zero represents the age-appropriate median. A CD4 Z-score of minus 1 indicates that a child's CD4 cell count is 1 standard deviation below the age-specific median of the HIV-negative population.

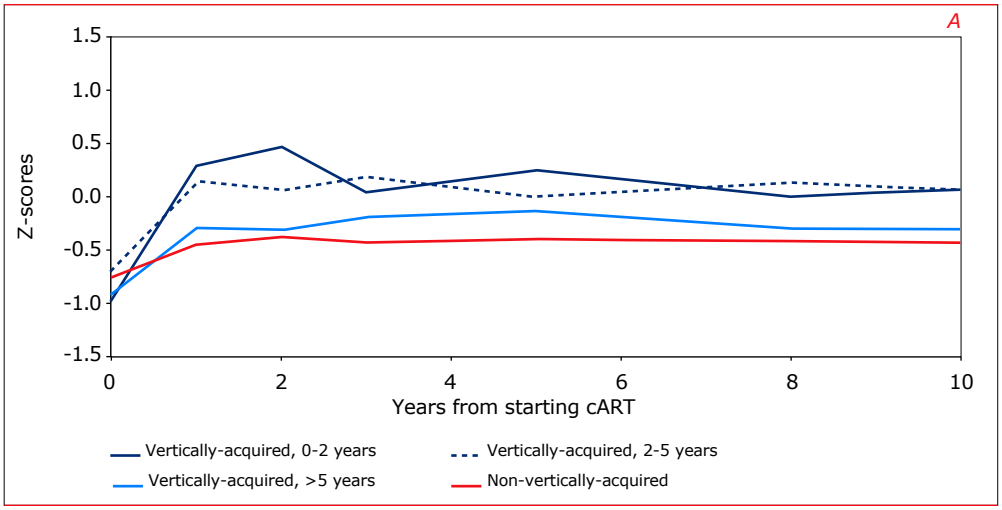
*Figures 5.6A and 5.6B* show the changes in CD4 T-cell Z-scores among HIV-positive children stratifying those with vertically-acquired HIV by age at initiation of cART, and by calendar year of cART initiation. The youngest children (less than two years of age at cART initiation), as expected, had the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

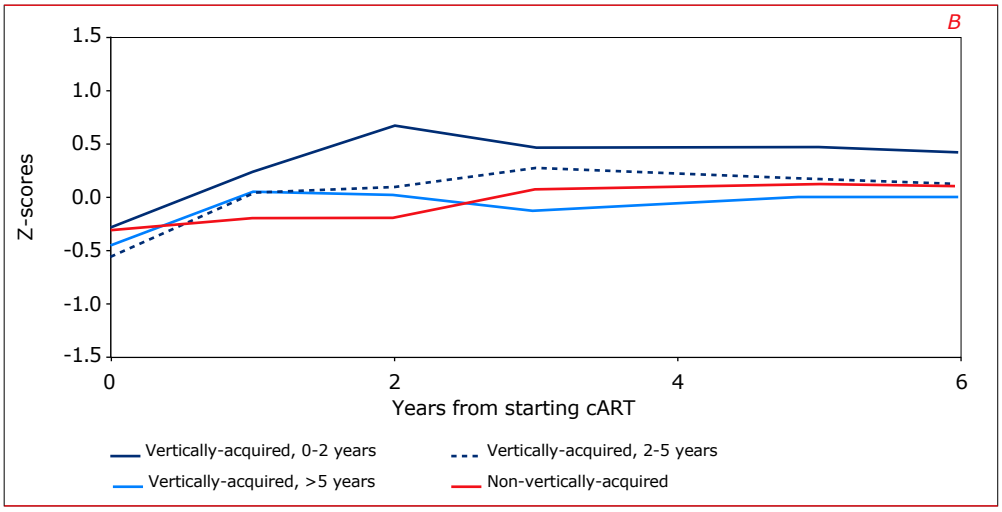
a *The number of children with an unknown route of HIV transmission is too small to include as a separate category in this analysis. As these children had the same age distribution as those with non-vertically-acquired HIV, these two groups were jointly analysed in a shared category.*

Among those initiating cART between 1998 and 2009, CD4 Z-scores increased significantly in the year following cART initiation in all children with vertically-acquired HIV. The increase in CD4 Z-scores was less strong among children with non-vertically-acquired HIV. However, the youngest children (below 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 with vertically-acquired HIV. During the first two years, increases in CD4 Z-scores were slowest in children with non-vertically-acquired HIV. CD4 Z-cores remained consistently highest among the youngest children (aged below 2 years at the time of cART initiation) (*Figure 5.6B*).

*Figure 5.6: Changes in Z-scores for CD4 T-cell counts among HIV-positive children, stratified by age at initiation of combination antiretroviral therapy (cART: (A) cART initiation between 1998 and 2009 and (B) cART initiation between 2010 and 2019.*




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

## Virological response

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

The current analysis uses data from the 498 children who were registered with SHM and had ever started cART. Children with vertically-acquired infection were stratified by age at cART initiation, as described earlier in this chapter.

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

*Figure 5.7* shows viral suppression rates by calendar period of cART initiation: 1998-2009 and 2010-2019.

cART initiation between 1998 and 2009:

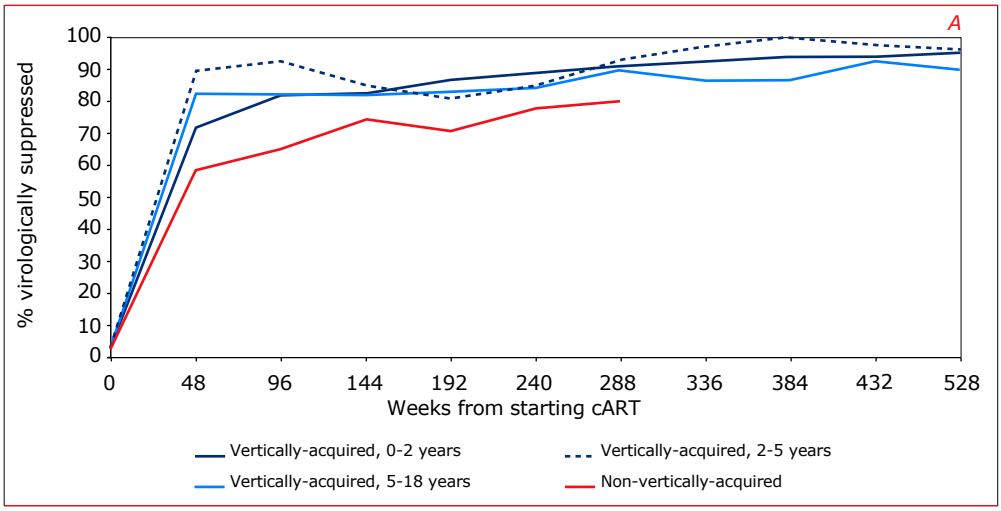
- Among children with vertically-acquired HIV who were aged 0-2 years at time of cART initiation, viral suppression rates increased from 72% after one year of cART, to 88% and 95% after five and ten years, respectively.
- Among children with vertically-acquired HIV who were aged 2-5 years at cART initiation, viral suppression rates increased from 90% after one year of cART, to 85% and 97% after five and ten years, respectively.
- Among children with vertically-acquired HIV who were aged over 5 years at cART initiation, viral suppression rates increased to 82% after one year of cART use. However, ten-year viral suppression rates were somewhat lower (90%) compared with children who were aged under 5 years of age at the time of cART initiation.
- Among children with non-vertically-acquired HIV, the five-year viral suppression rate was 78%. The ten-year viral suppression rate is not shown, due to the small number of children for whom such long-term data could be calculated [*Figure 5.7A*].

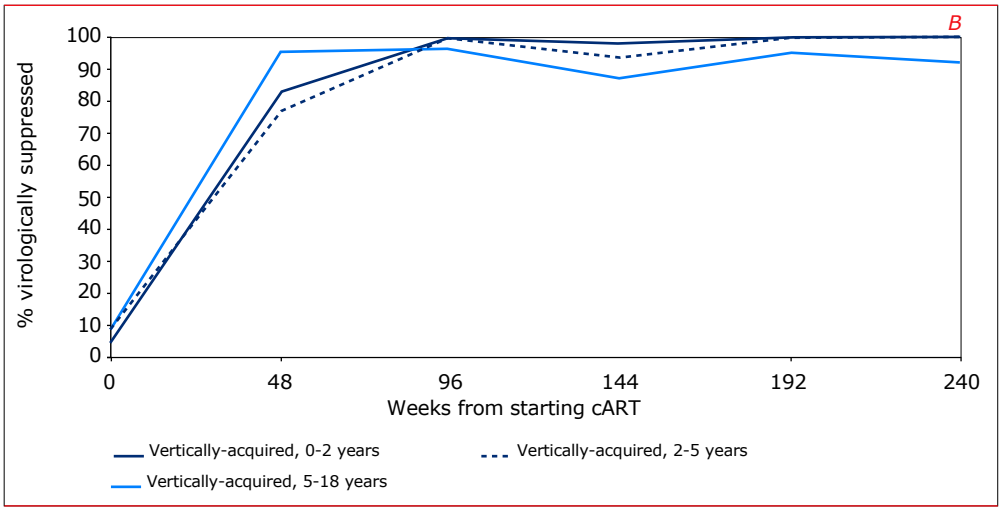
cART initiation in or after 2010:

- The viral suppression rates were 100% in children with vertically-acquired HIV who initiated cART before the age of 5 years. However, among children with vertically-acquired HIV who were aged over 5 years at the time of cART initiation, the viral suppression rate was 92% after five years of cART use. 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 5.7B*).

***Figure 5.7:*** *Viral suppression since combination antiretroviral therapy initiation, by calendar period of therapy initiation: (A) 1998-2010 and (B) 2010-2019. Viral suppression is defined as any viral load measurements <200 copies/ml, except for time points in the past where tests were used with quantification limits higher than 200 copies/ml.*




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

### Currently in clinical care

Of the 511 HIV-positive children ever registered by SHM who entered care in the Netherlands before the age of 18 years, 412 (81%) were still in care in 2019 (*Figure 5.1*). Of the remaining 99 children no longer in care, ten had died, 39 had moved abroad, and a substantial number of children (50 children) were lost to follow up.

### Currently in care and less than 18-years-old

- Of the 511 individuals with HIV who entered care before the age of 18 years, 199 were still aged under 18 at the end of 2019.
- 196 of these 199 children were in care in one of the paediatric HIV treatment centres, and the remaining three children were in care in one of the adult HIV treatment centres. As of 31 December 2019, their median age was 11 years (IQR, 8-14).

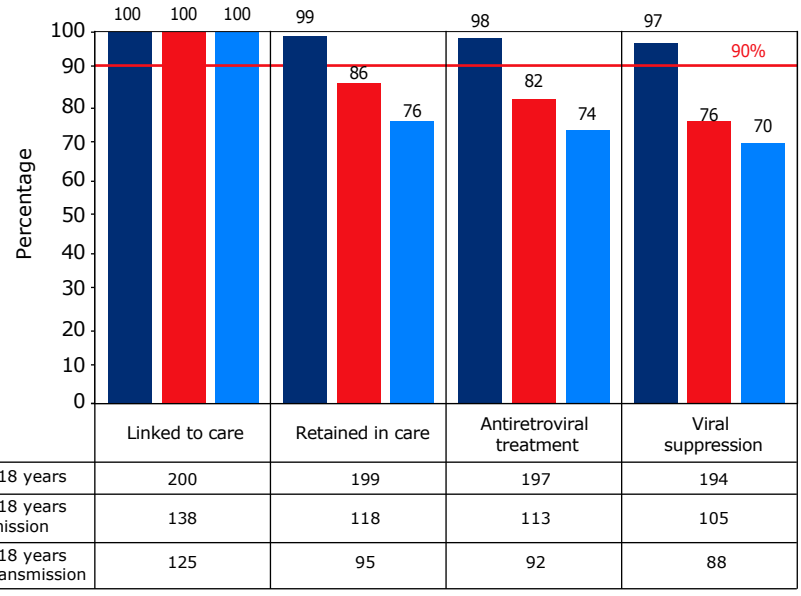
### Currently in clinical care and 18 years or older

- The remaining 213 HIV-positive individuals who were first registered when still a child, were in care and older than 18 at the end of 2019.
- Their median age was 23 years (IQR, 20-28) for those who had vertically-acquired HIV, and 33 years (IQR, 26-36) for those with non-vertically-acquired HIV.

### Continuum of care

A 'continuum of care' was constructed, based on the total number of HIV-positive children ever registered by SHM that were still alive on 31 December 2019, and not reported to have moved abroad or to have 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 2019, and by mode of HIV acquisition. The numbers above the bars indicate the proportion of individuals.*




Individuals were stratified by age on 31 December 2019 and categorised as:

I. current age <18 years; in this age group, the number of children with non-vertically-acquired HIV was too small (n=6) for stratification by mode of acquisition;
II. current age ≥18 years with vertically-acquired HIV;
III. current age ≥18 years with non-vertically-acquired HIV.

**I Continuum of care: current age <18 years**

- In total, 200 children under 18 years of age on 31 December 2019 were linked to care, registered by SHM, still alive, and not reported as having moved abroad.
- Of these children, 99.5% were retained in care (199/200); 196 children were receiving paediatric care. The single child lost to follow up was born outside the Netherlands.
- During their last clinical visit in 2019, 98% (197/200) were using antiretroviral therapy.
- Overall, 97% had a most recent HIV RNA measurement below 200 copies/ml (194/200).

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

- 138 individuals who acquired HIV through vertical transmission and were over 18 years of age on 31 December 2019 were linked to care.
- Of these 138 individuals, 86% (118) were still in care as of 31 December 2019. The remaining 20 individuals were lost to follow up - 11 of these were born in the Netherlands.
- 82% (113/138) were using antiretroviral therapy during their last registered clinical visit.
- Overall, 76% (105/138) had a most recent HIV RNA measurement below 200 copies/ml.

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

- 125 individuals were older than 18 by 31 December 2019 and acquired HIV through non-vertical-transmission.
- Of these, 95 (76%) were still in care as of 31 December 2019; 30 individuals were lost to follow up, including 18 women originating from sub-Saharan Africa.
- 74% (92/125) were using antiretroviral therapy during their last registered clinical visit.
- Overall, 70% (88/125) had a most recent HIV RNA measurement below 200 copies/ml.

### In care and on cART in 2019

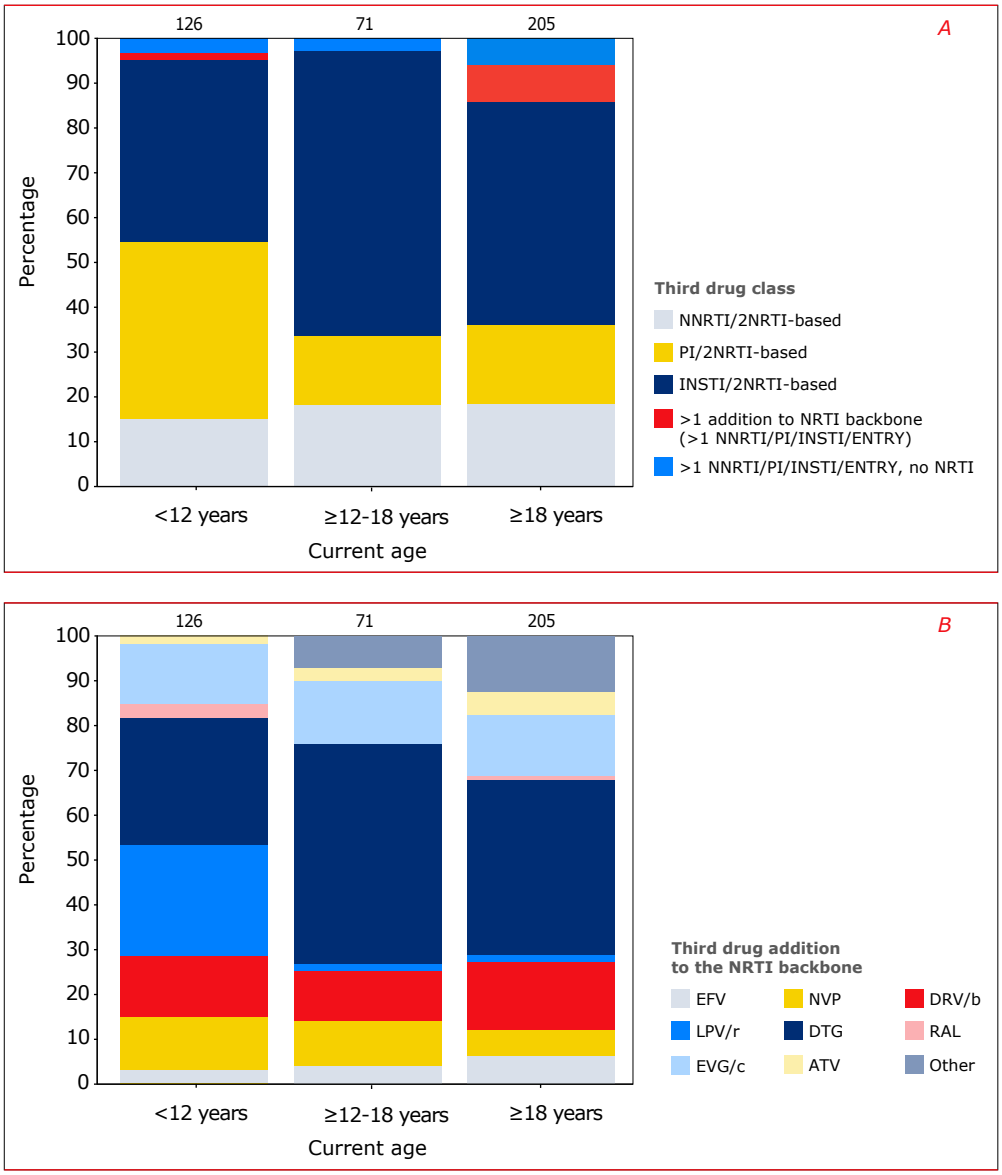
Of the 199 children known to be in care in 2019 and under 18 years of age, 197 (97%) were on cART during their last reported clinical visit. The distribution of current cART use is shown in *Figure 5.9*, according to age on 31 December 2019.

Among those aged <12 years, PI-containing and INSTI-based regimens were currently most often used (both categories are 40%), with dolutegravir (29%) and lopinavir/ritonavir (25%) the most common individual third agents.

In children aged between 12 and 18 years, 18% were using an NNRTI-based regimen, 15% a PI-based regimen, and 63% an INSTI-based regimen. Among those using an INSTI-based regimen, dolutegravir was the most commonly used (49%).

Among individuals diagnosed with HIV during childhood who are currently over 18 years of age, 50% were using an INSTI-based regimen, mainly dolutegravir.

*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.*

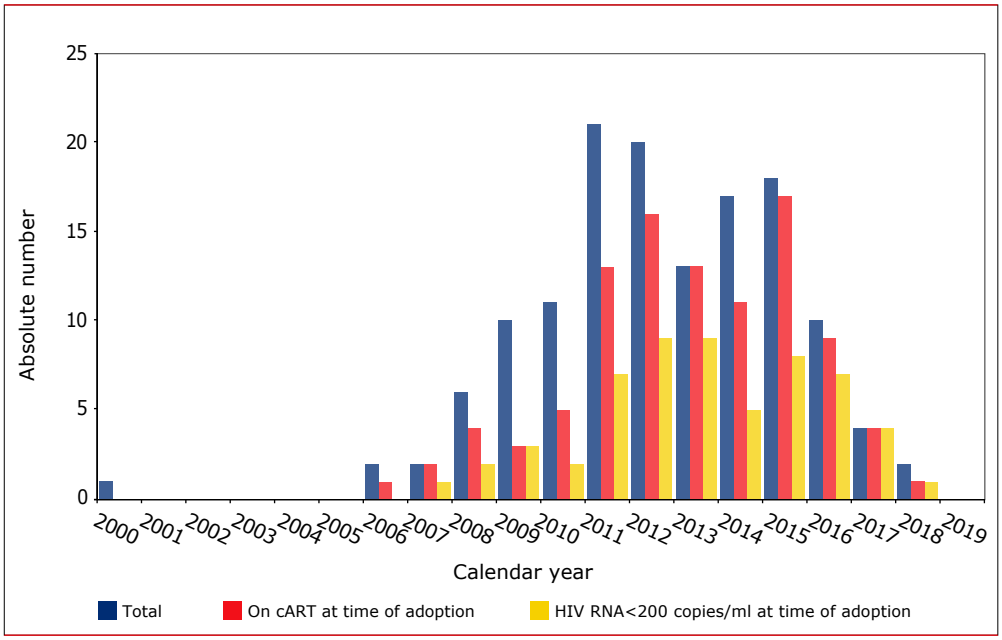
## Special Populations

### Adopted children

Of the 511 children ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 140 (27%) had been adopted by Dutch parents. The absolute number of child adoptions varied between two in 2006 and a maximum of 21 in 2011, with a decrease from 2016 onwards to four children in 2017, two children in 2018 and no adopted children being registered in 2019(*Figure 5.10*):

- Their median age at the time of entering care in the Netherlands was 2.7 years (IQR, 1.5-5.1).
- All children used cART during follow up in clinical care in one of the Dutch HIV treatment centres.
- In total, 99 (71%) children were already receiving cART before they were adopted.
- 18 (13%) children had been treated with monotherapy or dual therapy before the start of cART.
- The proportion of children already receiving HIV treatment prior to adoption varied over time, and was 100% for children adopted in 2017 and 2018. At the moment of entering care in the Netherlands, only 58 (41%) of the 140 children had a viral load <200 copies/ml, and this proportion did not increase substantially over time.
- As of 31 December 2019, all children were currently alive and in care, and their median current age was 9.3 years (IQR, 7.1-11.7).
- All children who started cART were still receiving treatment in 2019, and all (100%) had an undetectable viral load (≤200 copies/ml) at the last known time point.

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




*Legend: cART=combination antiretroviral therapy.*

## Transfer to adult care

Of the 511 children ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 393 initially received that care in one of the paediatric HIV treatment centres. As of 31 December 2019, 158 (40%) of these 393 children were aged over 18 years and had transferred to adult care

The number of adolescents who transferred to an adult centre each year varied; it was one in 2000, 20 in 2011, 11 in 2016, and 16 in 2019. The median age at the time of transfer was 19.0 years (IQR, 18.4-19.8). The median time in care after transfer until last documented visit is 5.6 years (IQR, 1.3-8.0). Of the 158 individuals who transferred to adult care, 11 (7%) have been lost to follow up, six (4%) have moved abroad, and five (3%) have died. The remaining 136 are alive and in care.

At the time of their last clinical visit in 2019, eight of the 136 individuals still in care (6%) had a last known HIV RNA level >200 copies/ml (median 4501; IQR 3957-162,869), a decline from the 12% described in the 2019 SHM Monitoring report.

At the time of transfer to an adult HIV treatment centre, 139 out of the 158 adolescents had a documented HIV RNA level; 24(17%) had an HIV RNA level >200 copies/ml and 115 (83%) of these 139 adolescents with an available HIV RNA measurement had an HIV RNA ≤200 copies/ml. These rates are comparable to results from the UK, which found that three quarters of the adolescents were virologically suppressed at the time of transition[16]. We also observed comparable proportions of undetectable HIV RNA levels in the year before and after transfer to adult care: one year before transfer to adult care, 84% of the adolescents had an HIV RNA level ≤200 copies/ml, compared to 79% of the young adults one year after their transfer.

Of the 24 adolescents without viral suppression at the time of transfer, three have died, seven are no longer in care, and three had a most recent HIV RNA >200 copies/ml. The remaining 11 adolescents are virally suppressed, according to their last available HIV RNA measurement.

Weijsenfeld *et al.* explored the data on transition to adult care in our registry in more detail[17], and reported an increased risk of virological failure between 18-19 years of age, with this risk being concentrated around the time of transitioning to adult care. Virological failure was associated with a low level of education and a lack of autonomy regarding medication adherence at the time of transitioning to adult care.

## Summary

Of the 511 children with HIV ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 81% remain in care in the Netherlands. A substantial proportion of the children newly registered since 2010 are children who have been adopted by Dutch parents. This has driven the observed increase in the proportion of children in care aged between 0 and 12 years old. It is worth noting that the annual number of newly-registered children who were adopted by Dutch parents has been decreasing since 2016. 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 extremely rare, with two cases reported since 2015. This reflects the success of standardised HIV screening during the first trimester of pregnancy[11]. 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 HIV-positive children in care in the Netherlands. In total,

97% of HIV-positive children ever in care in the Netherlands have received cART. The cART regimens have changed over time and, in more recent years, mostly include the protease inhibitors lopinavir/ritonavir and darunavir in the younger children, as well as 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, the viral suppression rate after five years of cART in HIV-positive children who initiated cART in or after 2010, was high (97% HIV-RNA < 200 copies/ml), including among the youngest children.

The continuum of care shows a high retention-in-care rate among children currently aged less than 18 years. However, once young people reach the age of 18 they become more likely to be lost to follow up. 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 2019 (97% versus 73%). Another important point is that all children who were adopted by Dutch parents have suppressed HIV RNA levels, based on their last available HIV RNA measurement.

Of those individuals originally registered as a child who were still in care in 2019, 52% were older than 18 on 31 December 2019. The high rate of detectable HIV viral load in HIV-positive individuals around the time of transitioning to adult care is of concern. Viral suppression rates have improved over time, resulting in relatively more young people being virally suppressed during their most recent clinical visit. However, there remains a group of young people who are unable to achieve HIV RNA suppression, despite cART use.

### Recommendations

The provision of care for children living with HIV in the Netherlands has resulted in generally favourable outcomes, with a low mortality rate and good long-term virological and immunological responses to treatment. An increasing proportion of the children 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.

Although the occurrence of vertical transmission of HIV in the Netherlands has become very rare due to universal HIV screening during the first trimester of pregnancy, healthcare providers should remain vigilant for the occasional incident maternal HIV infection later during pregnancy, which, if unnoticed, can result in vertical transmission.

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# 6. Pregnancies in women living with HIV in the Netherlands

Colette Smit, Jeannine Nellen, Liesbeth van Leeuwen

## Introduction

The most common mode of HIV acquisition for children aged 0 to 15 years worldwide is transmission from an HIV-positive mother to her child[1]. Mother-to-child transmission (MTCT) of HIV mostly occurs perinatally during labour and delivery, less commonly *in utero*, or postnatally during breastfeeding. 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 combination antiretroviral therapy (cART) was based on the maternal CD4 cell count. As a result, a substantial proportion of women who did not need to start cART according to these early guidelines, started it for the first time during pregnancy, with the sole purpose of reducing maternal HIV RNA to limit the MTCT risk. In many of these cases, cART was discontinued after delivery. After 2015, general treatment guidelines were revised, and treatment for all individuals was recommended, regardless of CD4 cell count[6]. As a result, these days pregnant women are advised to continue cART postpartum.

To ensure timely initiation of cART, and reduce the risk of MTCT, it is important to ascertain pregnant women'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.

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].

For the purpose of this year's report, we have decided to focus on the women who were pregnant during the years 2016 to 2019, as this population better reflects current treatment guidelines.

# Demographics

## Maternal characteristics

*Table 6.1: Characteristics of HIV-positive pregnant women registered and monitored by Stichting HIV Monitoring between 2016-2019. It should be noted that data on the number of registered pregnancies in 2019 may be incomplete due to a delay in data collection.*

| | Total n (%) | Dutch n (%) | Non-Dutch n (%) |
|---|---|---|---|
| Maternal characteristics | 303 | 87 (29) | 216 (71) |
| HIV diagnosis before pregnancy (%) | 264 (87) | 11 (13) | 28 (13) |
| Age at start of first pregnancy occurring in HIV infection (years*) | 32 (28-36) | 30 (25-35) | 33 (28-37) |
| HIV transmission route | | | |
| Heterosexual contact (%) | 278 (92) | 80 (92) | 198 (92) |
| Other (%) | 25 (8) | 7 (8) | 18 (8) |
| Total number of pregnancies | 387 | 112 | 275 |
| Number of pregnancies among women registered between 2016-2019 | | | |
| 1 | 105 (35) | 31 (36) | 74 (34) |
| 2 | 84 (28) | 27 (31) | 57 (27) |
| ≥3 | 114 (37) | 29 (33) | 85 (39) |
| Pregnancy outcome | | | |
| Partus (%) | 237 (64) | 74 (66) | 163 (59) |
| Miscarriage (%) | 92 (24) | 22 (20) | 70 (26) |
| Abortion (%) | 55 (14) | 16 (14) | 39 (14) |
| Unknown (%) | 3 (1) | | 1 (1) |
| Total number of partus | 237 | 74 | 163 |
| Mode of delivery | | | |
| Vaginal | 165 (70) | 55 (74) | 110 (67) |
| Caesarean | 70 (30) | 19 (36) | 51 (31) |
| Unknown | 2 (1) | 0 | 2 (1) |
| Pregnancy duration | | | |
| ≥37 weeks | 195 (82) | 59 (80) | 136 (83) |
| 32-37 weeks | 27 (11) | 13 (18) | 14 (9) |
| <32 weeks | 14 (6) | 2 (3) | 12(7) |
| Unknown | 1 (<0.5) | 0 | 1 (<1) |
| Birth weight (grammes, IQR*) | 3,042 (2,743-3,357) | 3,137 (2,625-3,335) | 3,024 (2,776-3,405) |

| | Total<br>n (%) | Dutch<br>n (%) | Non-Dutch<br>n (%) |
|---|---|---|---|
| Perinatal deaths | 3 (1) | 0 | 3(2) |
| Combination antiretroviral therapy started | | | |
| Before pregnancy | 194 (82) | 61 (82) | 133 (82) |
| During pregnancy | 43 (18) | 13 (18) | 30 (18) |
| No combination antiretroviral therapy during pregnancy | 0 | 0 | 0 |
| HIV RNA plasma levels before delivery HIV | | | |
| HIV RNA available | 235/237^(98) | 73/74^(99) | 162/163 (99) |
| Undetectable | 217 (92) | 69 (95) | 148 (91) |
| Detectable# | 18 (8) | 4 (5) | 14 (9) |

** Median, Interquartile Range (IQR)*

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

*# based on the detection limit of the assay*

*Table 6.1* shows the characteristics of the 303 HIV-positive women who had a registered pregnancy in the Netherlands between 2016 and 2019. Of these women, 216 (71%) were of non-Dutch origin and 87 (29%) originated from the Netherlands. The majority of women of non-Dutch origin were born in sub-Saharan Africa (n=139, 64%) or the Caribbean/Latin America region (n=42, 20%).

The majority of the 303 women (264 women, 87%) were aware of their HIV infection before becoming pregnant and this proportion did not differ between women of Dutch and non-Dutch origin. Their median age at the time of the first registered pregnancy was 32 years (interquartile range [IQR] 28-36).

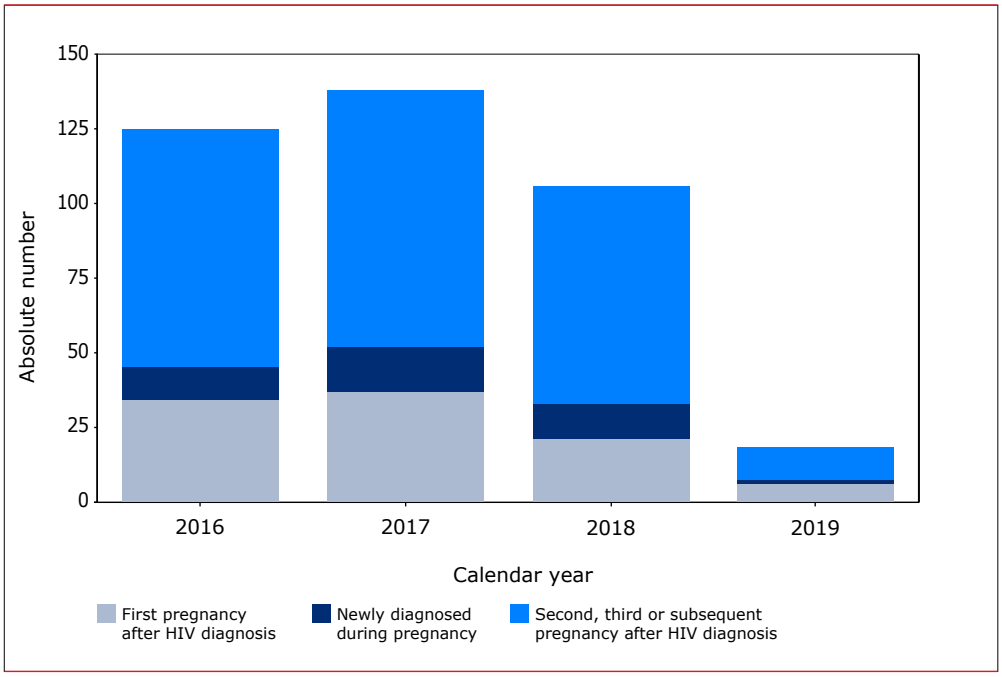
Looking at the 303 women, we see that in women of both Dutch and non-Dutch origin, heterosexual contact was the most common mode of HIV acquisition (92%). Injecting drug use (IDU) was not a reported mode of HIV acquisition. Eleven pregnant women acquired HIV through MTCT themselves.

Between 2016 and 2019, none of the mothers were documented to have died during follow up. A total of 20 women were no longer in care; of these, seven were known to have moved abroad and 13 were lost to follow up. Being lost to follow up was relatively somewhat more common in women of non-Dutch origin (5%) than in those of Dutch origin (3%).

## Trends in number of pregnancies in HIV-positive women

The absolute annual number of pregnancies in women in care in the Netherlands varied between 125 pregnancies in 2016, a maximum of 137 pregnancies in 2017, 106 pregnancies in 2018, and, to date, 18 reported pregnancies in 2019[a] (*Figure 6.1*). The number of women newly diagnosed with HIV during pregnancy varied between 11 in 2016 and 15 in 2019. The number of second, third or subsequent pregnancies in women already known to be HIV positive was approximately 80 annually (*Figure 6.1*).

***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. It should be noted that our data on the number of registered pregnancies in 2019 may be incomplete due to a delay in data collection.*




a *It should be noted that data of the number of registered pregnancies in 2019 may be incomplete due to a delay in data collection.*

## Pregnancy-related characteristics

Overall, 303 women accounted for 387 registered pregnancies: 34% of the women had one registered pregnancy, 28% had two registered pregnancies, and 38% of the women had three or more registered pregnancies (*Table 6.1*).

### Pregnancy outcome

The 387 pregnancies resulted in 237 (71%) births (including both live and stillbirths). A total of 92 pregnancies (24%) ended in a miscarriage, and 54 (14%) were ended by abortion. However, this may be an underestimation as not all miscarriages or pregnancy terminations may have been reported. For the remaining three (1%) pregnancies, the outcome was unknown.

### Pregnancy duration, preterm birth and perinatal death

A total of 237 pregnancies lasted at least 24 weeks and were therefore counted as a birth. The duration of pregnancy is known for 236 of these pregnancies. Overall, 195 (82%) pregnancies lasted at least 37 weeks, whereas 41 (15%) pregnancies resulted in preterm birth (defined as a pregnancy duration between 24 and 37 weeks). This preterm birth rate of 15% is higher than would be expected, based on figures from the general Dutch population, where preterm birth is reported in 7% of pregnancies[9].

Perinatal death, including antepartum death, occurred in three (1%) births. Congenital disorders were registered for five infants and none of these were fatal.

### Mode of delivery

If viral suppression during pregnancy can be achieved with cART, vaginal delivery is recommended for HIV-positive women[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; 74% of the women of Dutch origin delivered vaginally compared to 67% of women of non-Dutch origin. Thirty percent of newborns were delivered by Caesarean section, which was elective in 51% of cases.

Looking at the mode of delivery, we see that 98% of the women who delivered vaginally had an HIV RNA <50 copies/ml. This figure was 88% for women who delivered by elective section.

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

From 2016 onwards, cART was used during all 237 pregnancies that lasted at least 24 weeks: in 194 (82%) pregnancies, women were already using cART at the time of conception, while in 43 (18%) pregnancies, use of cART began during pregnancy.

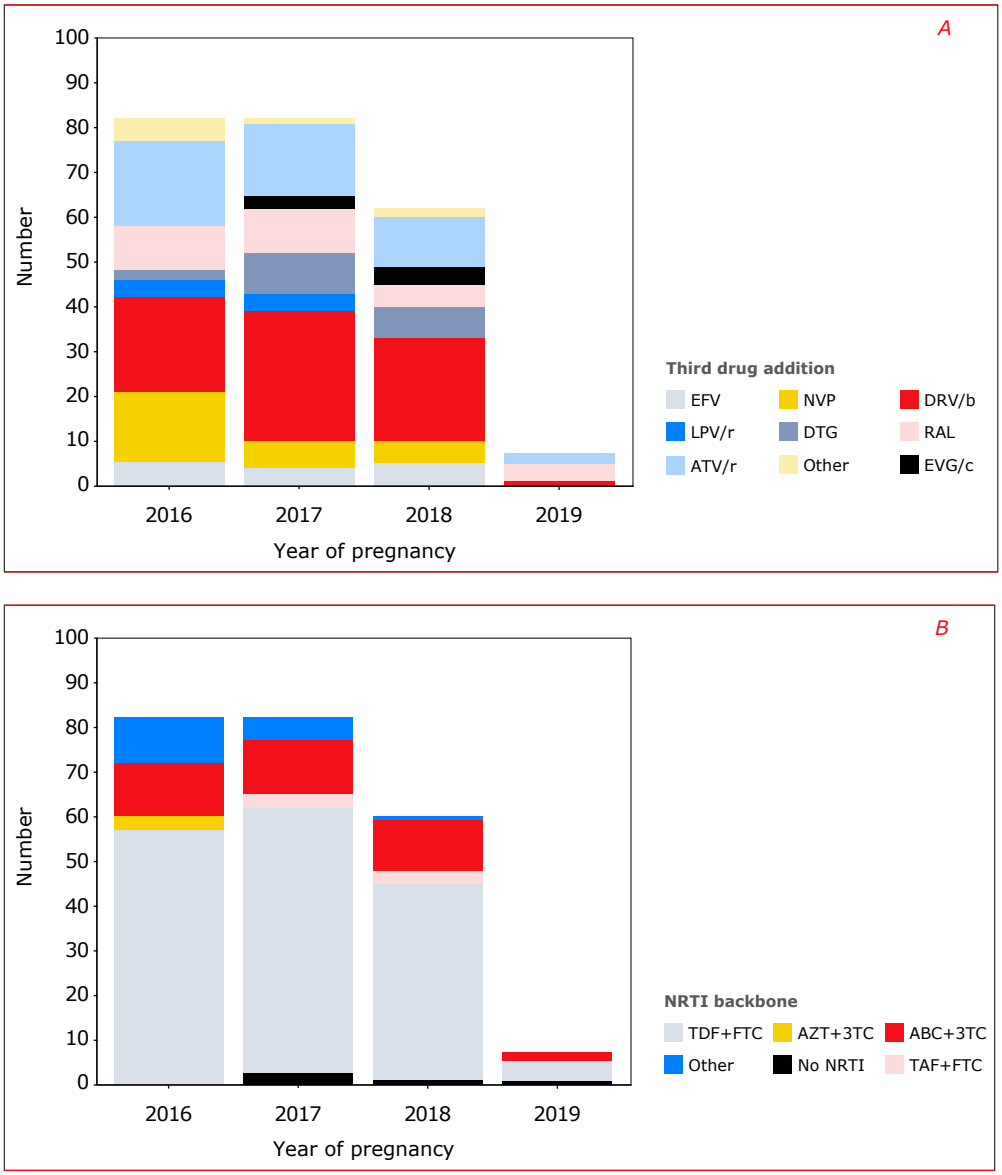
*Figure 6.2A* shows the most commonly used third-drug additions to the nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone as part of cART in pregnant women between 2016 and 2019. The most commonly used regimens were darunavir-containing (32%) and atazanavir-containing regimens (21%).

In May 2018, a potential safety signal was reported regarding dolutegravir and a possible relation with neural tube defects[13]. Between 2016 and 2019, dolutegravir was used *around the time of conception* by 29 women in the Netherlands, 17 of whom switched to another regimen during pregnancy (median time between conception and the switch was seven weeks [IQR 5-9]). The remaining 12 women continued with dolutegravir for the duration of their pregnancies. These 29 pregnancies resulted in 28 live births and one stillbirth. An additional six women initiated dolutegravir *during pregnancy* at a median of 27 weeks pregancy duration (IQR 19-31). These six pregnancies resulted in six live births. No neural tube defects were documented in any of the infants, including the one stillborn.

*Figure 6.2B* provides an overview of the components of the NRTI backbone used during pregnancy between 2016 and 2019. The most commonly prescribed backbone was the combination of tenofovir and emtricitabine (TDF+FTC) (70%), followed by a combination of abacavir and lamivudine (ABC+3TC) (16%).

Because of reduced serum levels of cobicistat during the second 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[14]. In the Netherlands, cobicistat at the time of delivery was used in in eight pregnancies between 2016 and 2019, all women had an HIV RNA <50 copies/ml at time of delivery.

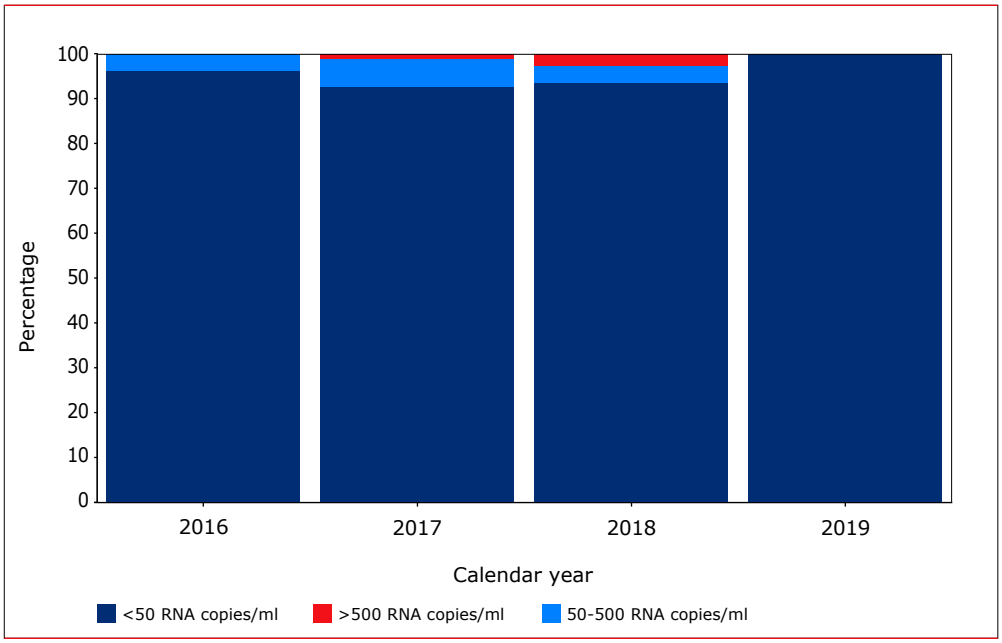
*Figure 6.2: A) Third-drug additions and B) the nucleoside reverse transcriptase backbone used as part of the cART regimens during pregnancy in 2016-19.*




*Legend: 3TC=lamivudine; /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; AZT=zidovudine; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; IDV=indinavir; LPV=lopinavir; NFV=nelfinavir; NVP=nevirapine; RAL=raltegravir; SQV=saquinavir; TDF=tenofovir disoproxil fumarate; 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 <50 copies/ml, 50-500 copies/ml, and >500 copies/ml. In 94% of the overall births, the mothers had an HIV RNA level <50 copies/ml at the time of delivery, and 4% had an HIV RNA level between 50 and 500 copies/ml. The proportion of women with an HIV RNA <500 copies/ml at the time of delivery was 100% in 2016 and 2019, but it was 99% in 2017 and 97% in 2018. These lower proportions were driven by three women with HIV RNA > 500 copies/ml. One of these women had been diagnosed with HIV after 36 weeks of pregnancy. The remaining two women had initiated cART in the past, but both had previously reported treatment interruptions and one of them briefly interrupted cART during pregnancy. Another ten women had HIV RNA levels between 50 and 500 copies/ml (median RNA=94 copies/ml, minimum: 53, maximum= 491). Five of these ten women had first been diagnosed with HIV during their pregnancy, three other women initiated cART in the second trimester, and the remaining two women in the third trimester of pregnancy. No MTCT was reported among the infants born to mothers who had HIV RNA levels >50 copies/ml at time of delivery

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




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

Between 2016 and 2019, 237 births were registered among mothers in whom HIV was known either prior to conception or was first diagnosed during pregnancy. Vertical transmission occurred in a single infant, resulting in a MTCT transmission rate in pregnant women using cART in the Netherlands of 0.42% (1/237), which is in line with low reported MTCT rates in other countries[15,16,17,18]. Further investigation of this case of MTCT revealed that the mother was not screened for HIV as part of the national pregnancy screening and was newly diagnosed with HIV during the 35th week of the pregnancy. The mother started cART in the 36th week. At time of cART initiation, the mother had a detectable HIV RNA level, but the last available HIV RNA measurement one day before delivery was undetectable (<40 copies/ml).

## 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 237 pregnancies lasting 24 weeks or longer, 52 were excluded from this analysis: 44 because of insufficient follow up between delivery and the time of database closure, and eight because they were no longer in care (two had moved abroad and six were reported as lost to follow up during the postpartum period). For the remaining 185 pregnancies in 173 women, cART was initiated before conception or during pregnancy in 83% and 17% of cases, respectively. In 15 of these 185 pregnancies, treatment was discontinued postpartum. In five of these 15 pregnancies, treatment was restarted after a median of nine weeks (IQR 3-11 weeks). In the remaining ten pregnancies, the women did not restart cART postpartum; four women restarted cART after the postpartum period and six women did not have any documented restart.

### Virological outcome

Detectable viraemia postpartum was defined as at least one HIV RNA measurement above 50 copies/ml during the postpartum period. On the basis of this definition, detectable HIV RNA was observed in 19% of the 185 pregnancies we analysed. For the subset of women with documented continued postpartum use of cART, 25 women (15%) had at least one HIV RNA level above 50 copies/ml (median HIV RNA=250 copies/ml, minimum 65 and maximum 85900 copies/ml). 12 out of the 25 women had one HIV RNA level above 50 copies/ml and 13 had more than one HIV RNA level above 50 copies/ml. In the 15 women who discontinued the use of cART postpartum, 11 experienced viral rebound (median HIV RNA=19800 copies/ml, minimum 617 and maximum 118579 copies/ml), but 4 remained suppressed. These four women had ongoing high CD4 cell counts, although for two women low compliance to treatment was reported.

### Breastfeeding

For the above-mentioned 185 pregnancies, data on breastfeeding were available for 163 of them. Breastfeeding was reported in nine women, all of whom were on cART with an undetectable HIV RNA level postpartum. 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, and more than 90% had an undetectable HIV RNA level around the time of delivery. The MTCT rate in pregnant women using cART was 0.42% during the period 2016 to 2019, which is comparable to the low figures reported in other western European countries[15,16,17,19].

Despite the high proportion of women with undetectable viraemia near the time of delivery, we did observe a somewhat increased proportion with detectable HIV RNA levels in 2017 and 2018. To ensure continued zero vertical transmissions of HIV, this increase needs to be closely monitored, particularly in women who are newly diagnosed with HIV after conception, and therefore start cART only during pregnancy.

Results of earlier studies analysing exposure to cART as an increased risk factor for preterm birth were conflicting[20]. However, more recent studies have reported declines in preterm births in women living with HIV, attributed partly to the reduction in Caesarean sections to prevent vertical transmission of HIV[21,22]. Nevertheless, the proportion of preterm births in HIV-positive women in the Netherlands remains higher than that seen in the general population[9]. Because of the safety signal regarding dolutegravir and a possible relation with neural tube defects, we looked at women who used dolutegravir around time of conception and during pregnancy and no neural tube defects were reported among their infants.

Finally, since 2015, cART has been recommended for all individuals, regardless of CD4 cell count and, as such, is also recommended for women postpartum. From 2016 onwards, 15% of women who continued to use cART postpartum had at least one episode of viraemia, of whom half of them had more than one HIV RNA level above 50 copies/ml . This is possibly due to poorer adherence, which has previously been reported to deteriorate during the postpartum period[23,24,25,26,27,28].

## Recommendations

As a result of changes to guidelines concerning HIV and pregnancy, cART is more likely to be started earlier in pregnancy. This is expected to result in a greater number of women becoming virally suppressed earlier in their pregnancy and around the time of delivery. Women with HIV who first 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 after delivery to maintain adherence to cART. Finally, although breastfeeding should not be actively recommended, women who decide to breastfeed need to be closely monitored clinically and virologically, along with their infants[29,30]. They need continuous adherence support in order to ensure sustained viral suppression and prevention of MTCT of HIV while breastfeeding.

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# 7. Quality of care

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## Introduction

One of SHM's missions is to contribute to the quality of HIV care in the Netherlands. With the collection of pseudonymised data from HIV-positive individuals in outpatient care in HIV treatment centres, SHM provides a nationwide overview of the outcome of care for individuals living with HIV. There were 26 officially-acknowledged HIV treatment centres for most of 2018 and 24 centres in 2019. This unique overview allows SHM to facilitate assessment of the quality of HIV care in the Netherlands.

In general, HIV treatment guidelines are intended to not only support physicians in providing optimal health care, but also to reduce the variation in care between different treatment centres. The Dutch Association of HIV-Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) has issued national guidelines for the treatment and monitoring of HIV-positive people in the Netherlands[1]. Using these guidelines as a basis, we have defined a set of indicators, which are used to explore the quality of care in Dutch HIV treatment centres, and gain insight into potential variation in outpatient care between HIV treatment centres.

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

| | |
|---|---|
| **Diagnosis** | The moment an individual is newly diagnosed with an HIV infection. The time of diagnosis can be weeks, months, or years after infection. |
| **Entry into care** | The moment an HIV-positive individual is first seen for care in an HIV treatment centre, which is usually within a few weeks of HIV diagnosis. |
| **Registration** | The moment an HIV-positive individual in care is notified to SHM by their treating 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 HIV-positive individual 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 has been specifically used in Chapter 7 to denote the role of the individual in a medical context. |

| | |
|---|---|
| **Volume indicator** | The number of people newly entering care for the first time in 2018 and 2019 for each treatment centre. |
| **Outcome indicators**<br>*Retention in care* | I. Short-term retention: The percentage of people who entered care for the first time after being diagnosed with HIV in one of the HIV treatment centres in 2016 and 2017, and who were still alive and in care at least 18 months after entering care. Patients who died or moved abroad were excluded from this indicator.<br>II. Long-term retention in care in 2019: the percentage of all individuals who entered care during the period 2014-2017, did not move abroad or die, and had a documented clinical visit in 2019. |
| *Initiation of cART* | I. Start of combination antiretroviral therapy (cART) within six months of entry into care in 2017 and 2018.<br>II. The percentage of people who initiated cART and were still in care in 2019. |
| *Viral suppression* | I. The percentage of treatment-naive people with a plasma HIV RNA level <400 copies/ml at six months after starting cART in 2018 (this definition of viral suppression is a requirement of the national certification process for HIV treatment centres in the Netherlands[2]).<br>II. The percentage of all HIV-positive people on cART for at least six months, in care in 2018 and 2019, with a plasma HIV RNA level <100 copies/ml.<br>III. The percentage of all HIV-positive people in care in 2018 and 2019 with a plasma HIV RNA level <100 copies/ml. |
| **Process indicators**<br>*Prior to cART initiation* | The percentage of people newly entering HIV care in 2017 and 2018 for whom data were available on CD4 count and plasma HIV RNA within six months of entering care. |
| *Following cART initiation* | The percentage of people initiating cART in 2017 and 2018 for whom CD4 cell count and plasma HIV RNA were measured at least once within 13 months of cART initiation. |

*Box 7.2: 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?**<br>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 entering care in 2017, the total number of patients in care in 2019, 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. |
| *Is it possible to determine a difference with so few patients?* | Much like any statistical test, inference can be difficult when patient sizes are too small. If a centre size is small, the difference needed to find a statistically lower indicator would be very large. This means that the "lower" boundary could reach below 50%, which is far from a clinically meaningful indicator. In this report, we do not state if a centre's indicator is below the national average when there are fewer than 40 patients included. |

## Methods

The indicators selected for this analysis are classified as volume, outcome, or process indicators (*Box 7.1*). They were derived from formal NVHB recommendations that, in general, follow the United States Department of Health and Human Services (DHHS) HIV/AIDS practice guidelines[1].

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

### Volume indicator

To meet the requirements of the national certification process for HIV treatment centres in the Netherlands (*Harmonisatie Kwaliteitsbeoordeling in de Zorgsector*, HKZ), HIV treatment centres are expected to enrol a minimum of approximately 20 new patients each year. Therefore, as a volume indicator, we have quantified the number of patients newly entering care for the first time each year in 2018 and 2019 for each 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 long-term retention in care as follows:

*Short-term retention in care*: The percentage of those patients who, after being diagnosed with HIV, entered care for the first time in one of the Dutch HIV treatment centres in 2016 and 2017, and who were still alive and in care at least 18 months after entering care. Patients who were known to have died or moved abroad were excluded from this retention-in-care indicator. During the observation

period, approximately 12% of patients switched treatment centres (mainly because of the closure of two treatment centres during 2018); these patients were considered to be retained in care, since they were documented as having remained in care elsewhere, and were not lost to follow up. However, to avoid double counting, they were assigned to their most recent treatment centre.

*Long-term retention in care*: The percentage of all patients who entered care during the period 2014-17, did not move abroad or die, *and* had a documented clinical visit in 2019. 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 patients who entered care in 2017 and 2018 and started cART within six months of entry; and 2) the percentage of patients still in care in 2019 who had ever initiated cART.

*Viral suppression* was assessed by three indicators:
The *first* indicator was defined as the percentage of treatment-naive patients with a plasma HIV RNA level <400 copies/ml at six months after starting cART in 2018. The HIV RNA measurement closest to six months (±three months) after the start of cART was chosen. The target percentage of viral suppression was set at ≥90%. This indicator, developed using the Delphi method, is part of the HKZ certification process and was defined jointly with the NVHB[2] during the development of *Zichtbare Zorg* (Visible Healthcare; ZiZo) indicators and HKZ.

The *second* indicator was the percentage of all HIV-positive patients on cART for at least six months with a plasma HIV RNA level <100 copies/ml. This indicator was calculated for the calendar years 2018 and 2019.

The *third* indicator was the percentage of all HIV-positive patients in care who had a last available HIV RNA level <100 copies/ml. This indicator was also calculated for the calendar years 2018 and 2019.

### Process indicators

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

To calculate the process indicators *prior to cART initiation*, we included all patients who entered care in 2017 and 2018. Only patients who entered care for the first time and were in care for at least 12 months were included; patients who switched treatment centres were not counted as newly entering care, as they had already been in care elsewhere. The indicators were defined as the percentage of patients newly entering care in 2017 and 2018 for whom the following measurements were available in the six months after entry into care: CD4 and plasma HIV RNA.

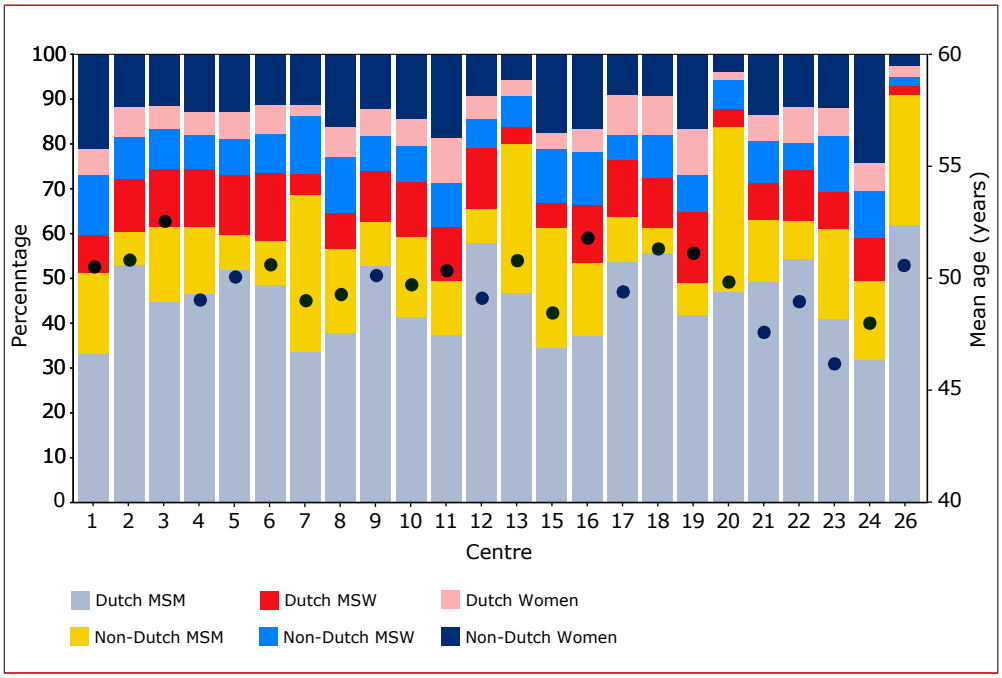
To calculate the process indicators *following cART initiation*, we included patients who had started cART in 2017 and 2018. Of note, patients who had been in care and started cART outside the Netherlands were excluded. The indicators were defined as the percentage of patients for whom the following measurements were recorded at least once within 13 months of their cART initiation: CD4 cell count and plasma HIV RNA.

## Results

### Patient mix across centres

The characteristics of patients in care in 2019 are described per HIV treatment centre in *Figure 7.1* (patient 'mix'). The largest geographical origin/mode of transmission/gender group observed for almost all centres was Dutch MSM, ranging from 32% to 62% (median = 47%) of patients within centres. There was substantial variation across centres in the other geographical origin/mode of transmission/gender groups: Non-Dutch MSM (median: 16%, range: 6-37%), Dutch MSW (median: 11%, range: 2–16%), Non-Dutch MSW (median: 9%, range: 2–13%), Dutch women (median: 6%, range: 2–10%), and Non-Dutch women (median: 12%, range: 3–24%). The mean within-centre age ranged between 46 to 53 years (median = 50 years).

*Figure 7.1: Description of the patient 'mix' for HIV-positive individuals in care in 2019 in the Netherlands.*




***Note:*** *Percentage of individuals per centre is given in the bar chart according to geographical origin/mode of transmission/gender group. Mean age of patients in care at each centre is given in black dots. Since centres 14 and 25 were closed in 2018, they are not depicted in this figure*

***Legend:*** *MSM=men who have sex with men; MSW=men who exclusively have sex with women.*

## Volume indicator

The numbers of patients who newly entered care in 2018 and 2019 across the HIV treatment centres are shown in *Figure 7.2*. The median number was 29 in 2018 and 2019, with a minimum number of five patients in 2018 and three in 2019. In 2019, eight HIV treatment centres had fewer than 20 newly-entering patients and these centres were of small (two), medium (three) and large (three) patient size.

***Figure 7.2:** Annual number of patients newly entering care per HIV treatment centre in the Netherlands in 2018–2019.*

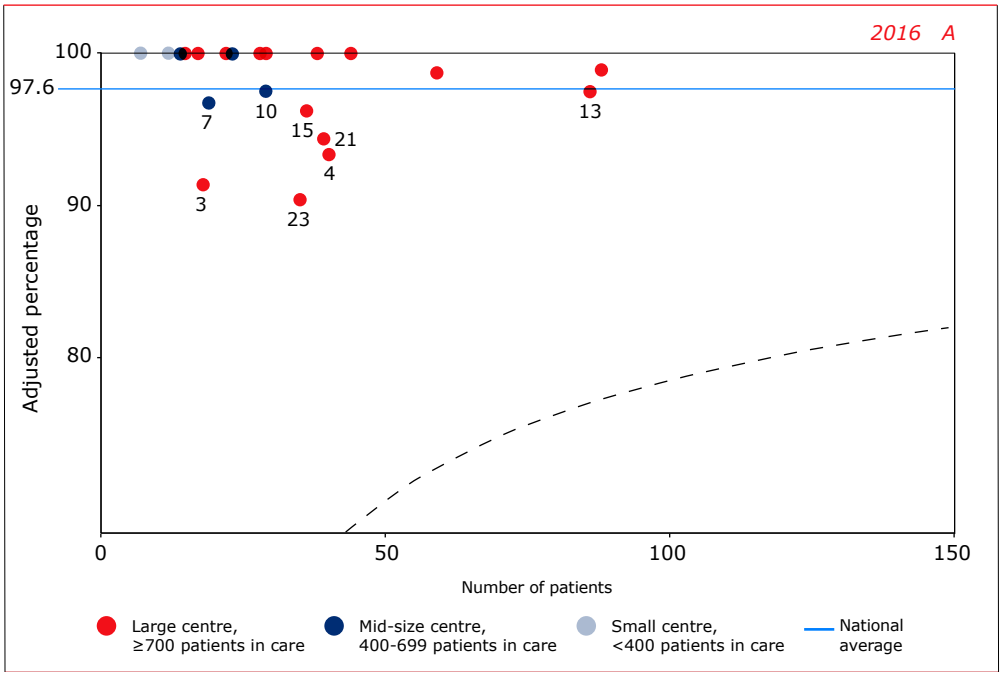
## Outcome indicators

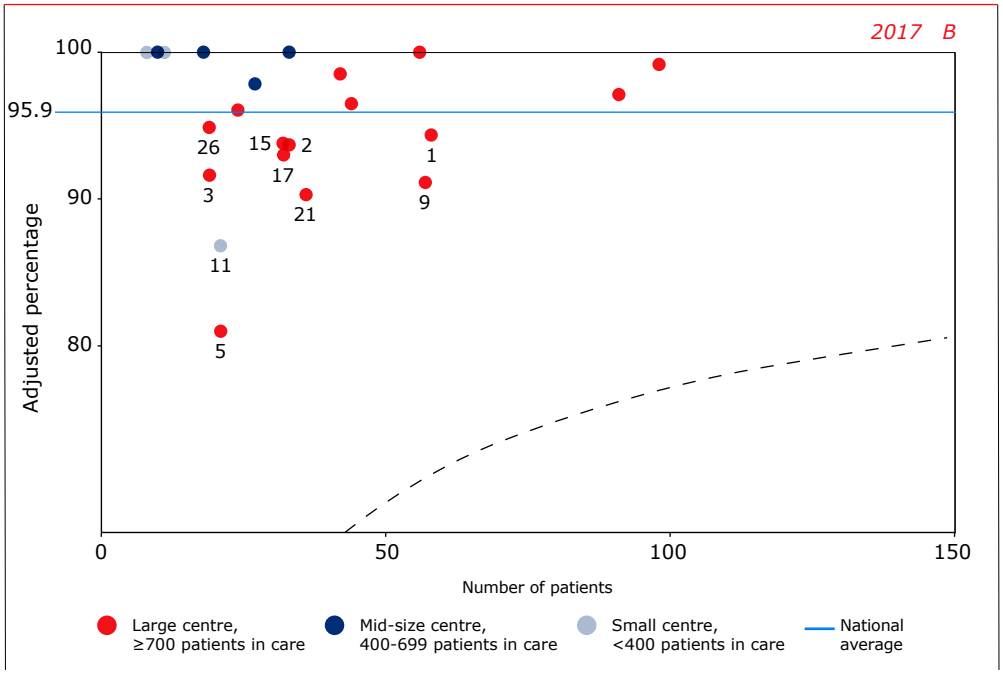
### Retention in care

Across centres, the median adjusted percentage of individuals with short-term retention was 100% (range = 90–100%) for patients entering care in 2016, and 97% (range = 81–100%) for those entering care in 2017. *Figure 7.3* shows the variation in adjusted percentages of short-term retention in care across treatment centres for patients who entered care in 2016 (*Figure 7.3A*) and 2017 (*Figure 7.3B*). This figure demonstrates that all centres with at least 40 patients entering care during these years had adjusted percentages of short-term retention within the expected range, when compared to the national level.

For all individuals in care as of 2019, the median adjusted percentage of individuals with long-term retention was 92% (range = 76–100%) across centres for patients entering care in 2014. This percentage has increased in subsequent years, with a median percentage retained of 96% (range = 82–100%) for those entering care in 2017. *Figure 7.4* shows the adjusted percentage of individuals in long-term retention in care per centre, by year of entry. Once again, all centres with at least 40 patients entering care in 2014 (*Figure 7.4A*), 2015 (*Figure 7.4B*), 2016 (*Figure 7.4C*), and 2017 (*Figure 7.4D*), had adjusted percentages of long-term retention within the expected range, when compared to the national level.

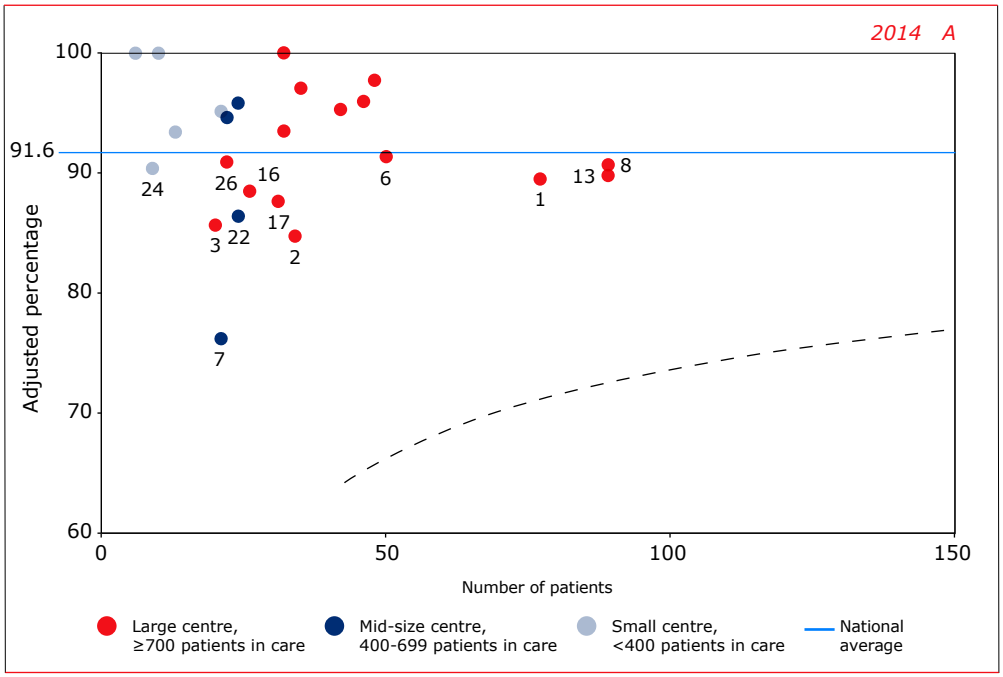
*Figure 7.3: Short-term retention in care, in other words, 18 months after entering care for those who entered care in A) 2016 and B) 2017. The percentage of individuals retained in care has been adjusted for patient mix and is plotted as a function of the number of patients entered into care.*

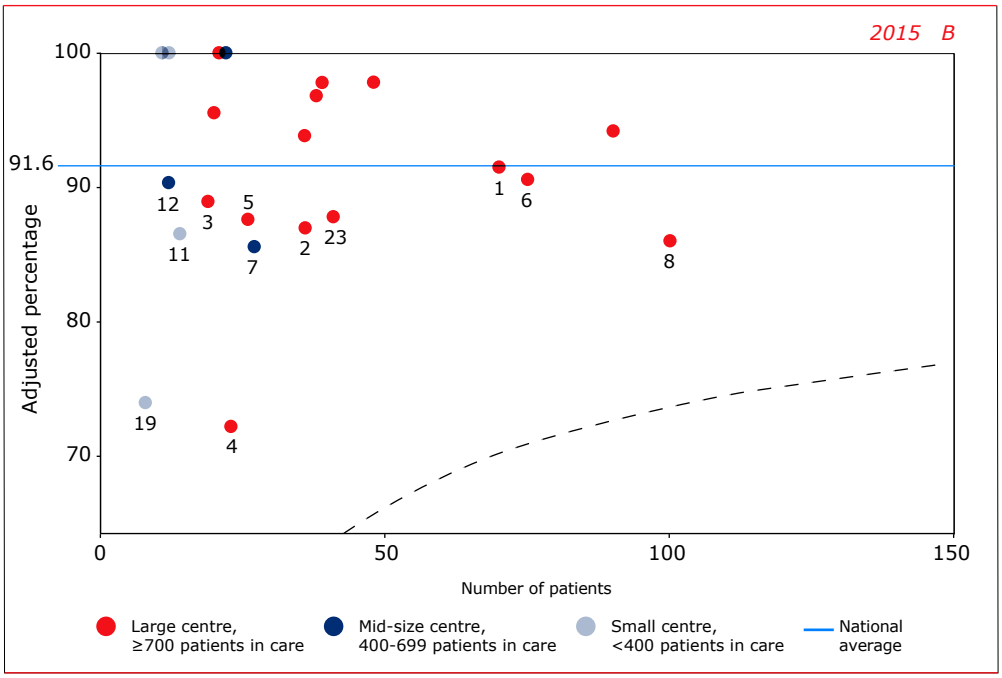


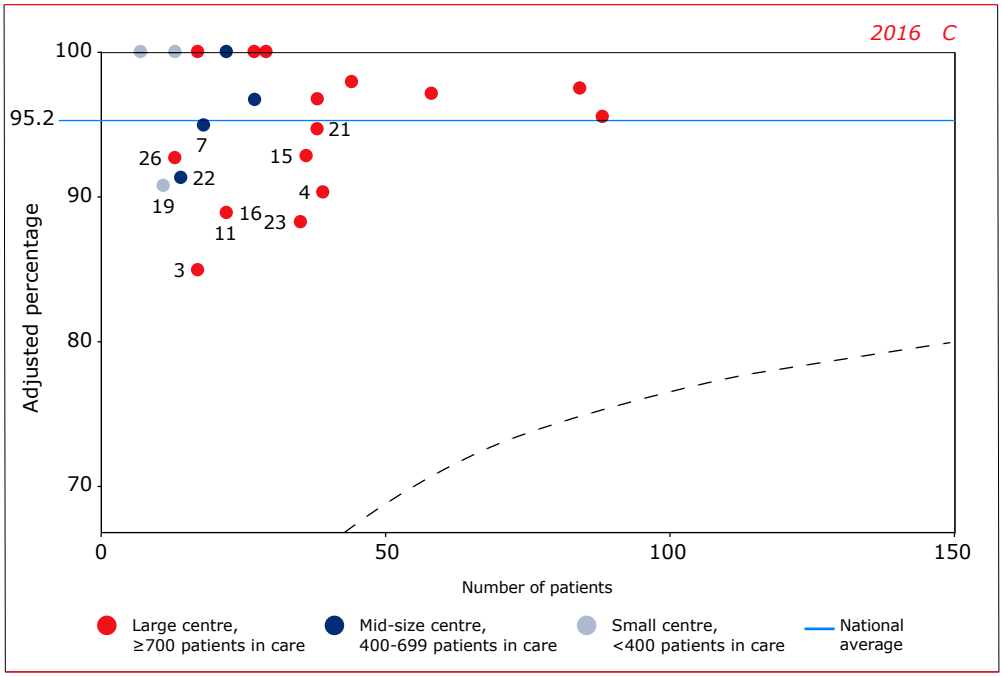


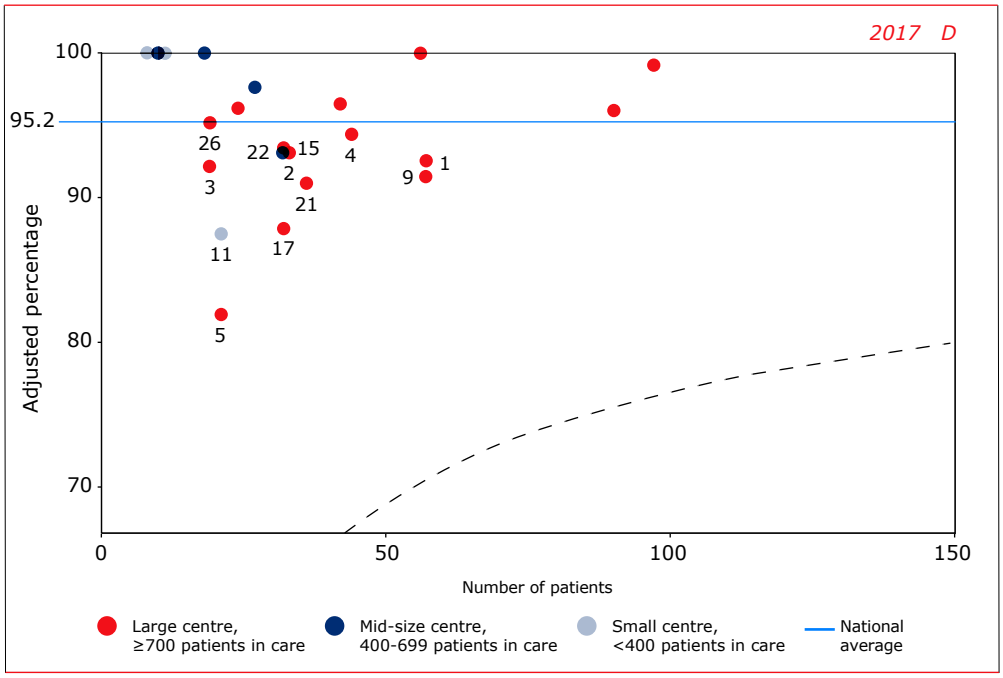

***Legend:*** *Data points with centre numbers below the national average are labelled and correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line.*

*Figure 7.4: Long-term retention in care, in other words, the status in 2019 for those who entered care between (A–D) 2014–17. The percentage of individuals retained in care has been adjusted for patient mix and is plotted as a function of the number of patients entered into care.*





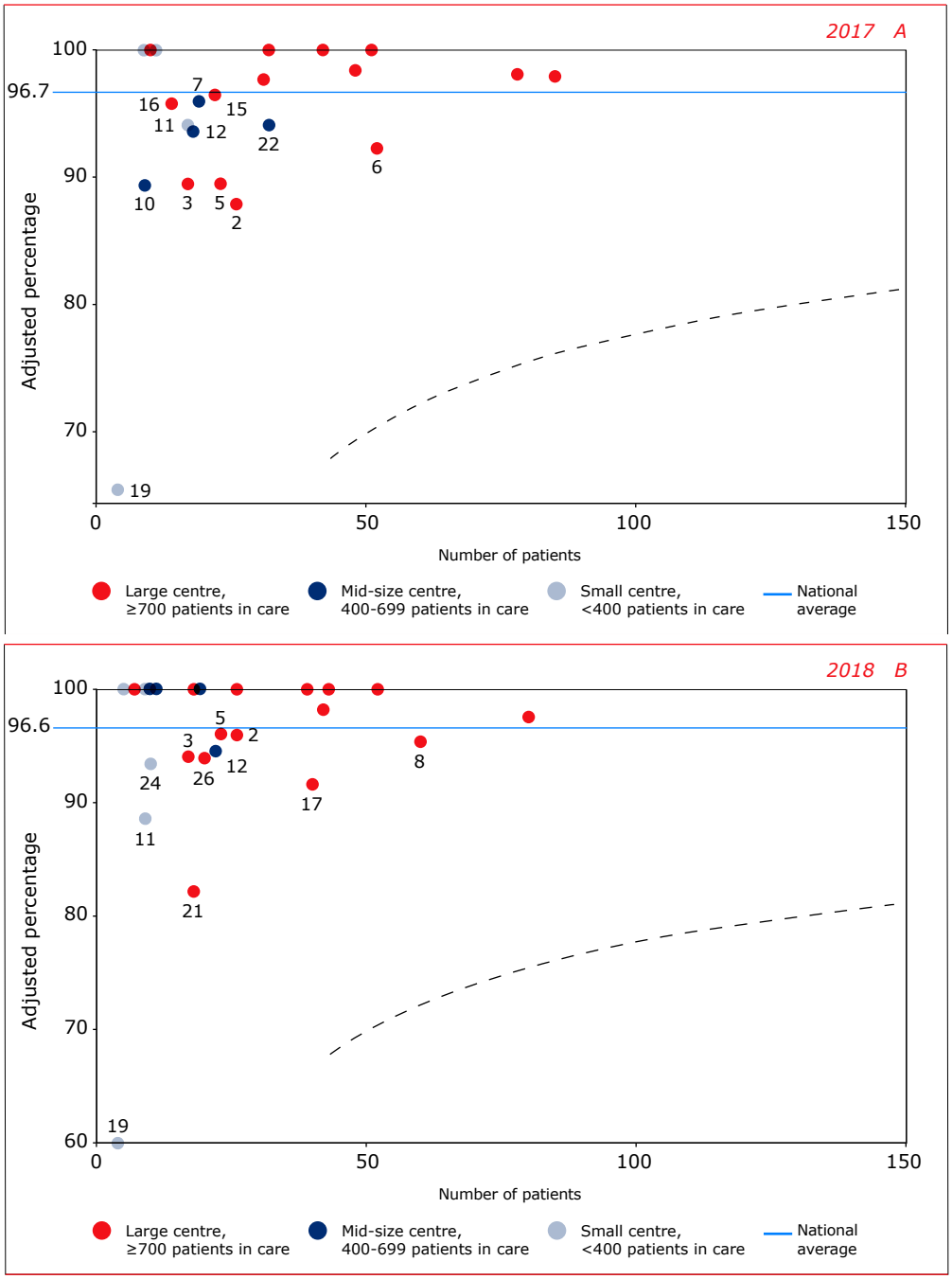

***Legend:*** *Data points with centre numbers below the national average are labelled and correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line.*

### Initiation of cART

Across centres, the median adjusted percentage of patients who started cART within six months of entering care, was 96% for those entering care in 2017, and 98% for those entering care in 2018. In terms of variation across HIV treatment centres, this percentage ranged between 65–100% in 2017, and 60–100% in 2018. *Figure 7.5* shows the adjusted percentages of patients starting cART within six months of entering care per centre, according to the year in which they entered care. This figure demonstrates that all centres with at least 40 patients entering care in 2017 (*Figure 7.5A*) and in 2018 (*Figure 7.5B*), had adjusted percentages of patients starting cART within the expected range, when compared to the national average.

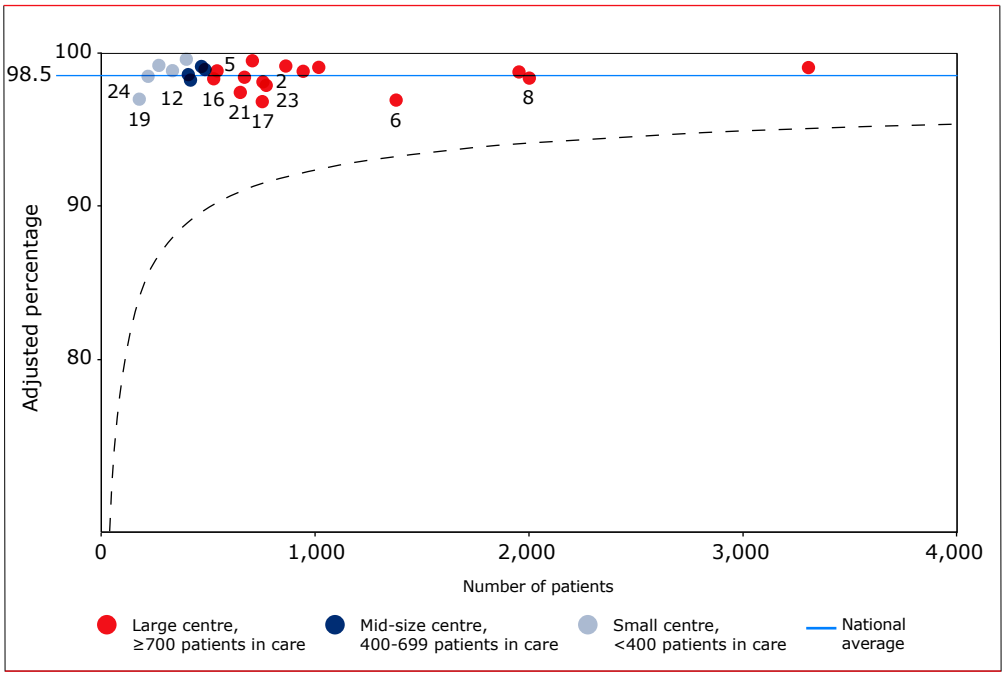
Among those who remained in care in 2019, the vast majority had initiated cART (across-centre median = 99%). This percentage was greater than 95% in all centres. *Figure 7.6* shows the adjusted percentages of patients in care in 2019 who had started cART, per centre. All percentages were within the expected range, when compared to the national average.

*Figure 7.5: The overall percentage of patients who entered care in A) 2017 and B) 2018, and started combination antiretroviral therapy (cART) within six months of entry. The percentage of individuals starting cART has been adjusted for patient mix and is plotted as a function of the number of patients entered into care.*




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

*Figure 7.6: The percentage of patients who entered care and who ever initiated cART and were still in care in 2019. The percentage of individuals starting cART has been adjusted for patient mix and is plotted as a function of the number of patients still in care in 2019.*



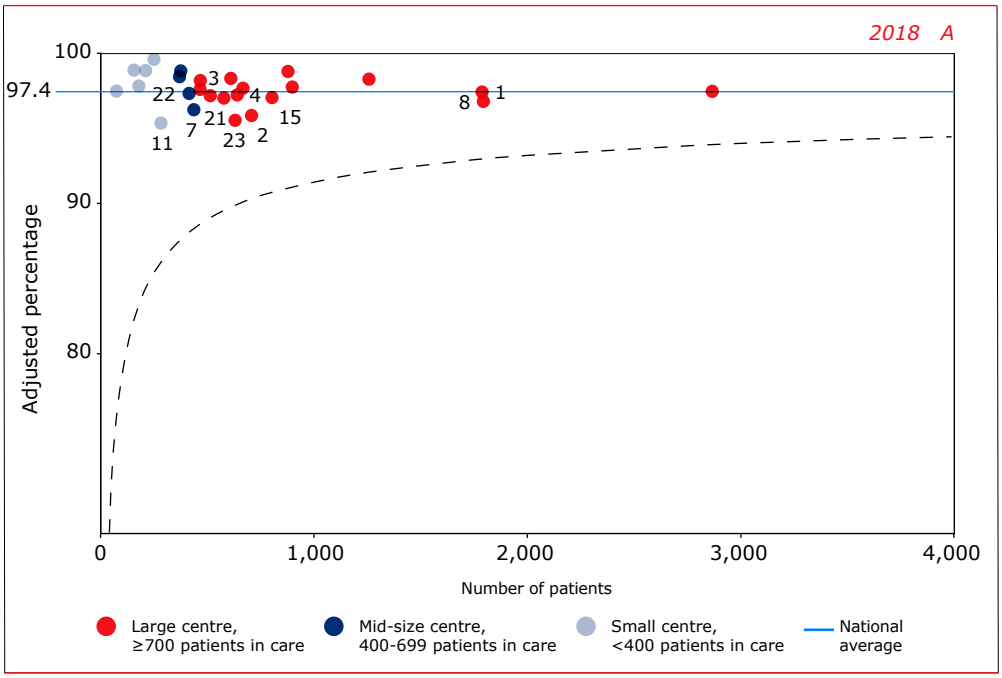

*Legend: Data points with centre numbers below the national average are labelled and correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line.*

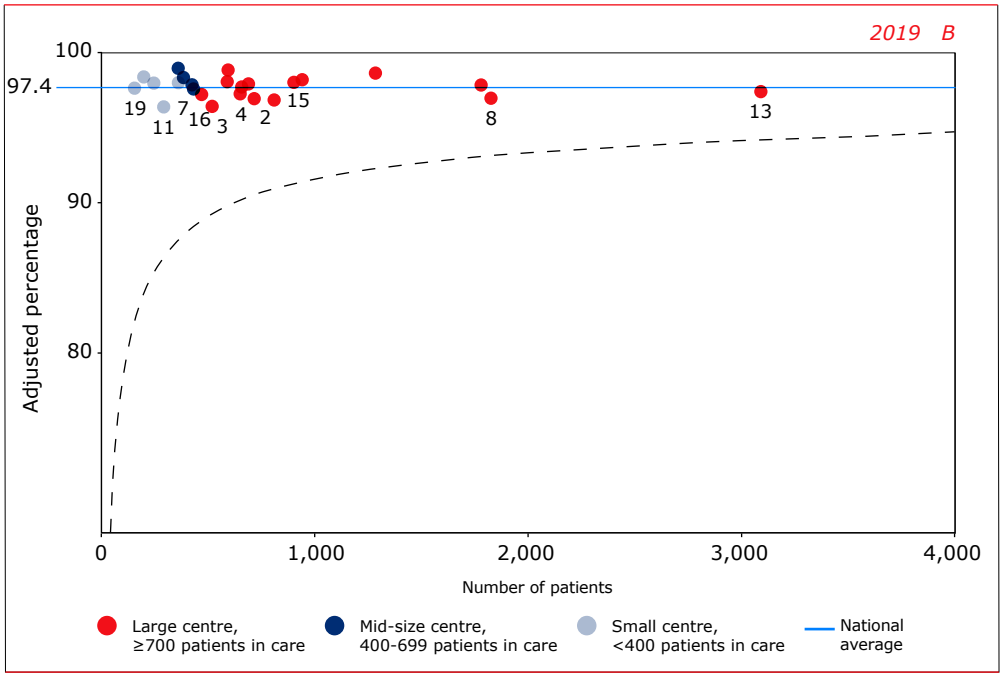
### Viral suppression

Viral suppression was assessed with *three* indicators. The *first* indicator is the percentage of treatment-naive patients with an HIV RNA level <400 copies/ml six months (± three months) after the start of cART of patients newly initiating treatment in 2018, with follow up in 2019. The unadjusted percentage was 100% for all treatment centres. Since there was no across-centre variation in the percentage of patients who achieved viral suppression, we did not perform a funnel plot for this indicator.

The *second* viral suppression indicator is the percentage of all HIV-positive patients in care who have been on cART for at least six months and have a last available HIV RNA level <100 copies/ml. This indicator was calculated for the calendar years 2018 and 2019. In both calendar years, the median adjusted percentage was more than 90% (the minimum target of this indicator) across centres. *Figure 7.7* shows the adjusted percentage of this viral suppression indicator per treatment centre, illustrating the limited variation across centres of different patient volume in 2018 (*Figure 7.7A*) and in 2019 (*Figure 7.7B*). All centres had adjusted percentages within the expected range, when compared to the national level.

*Figure 7.7: The percentage of all HIV-positive patients in care in A) 2018 and B) 2019, respectively, who had been on combination antiretroviral therapy (cART) for at least six months and who had an HIV RNA level <100 copies/ml. The percentage of individuals with viral suppression has been adjusted for patient mix and is plotted as a function of the number of patients in care in 2018 and 2019 who had been on cART for at least six months.*

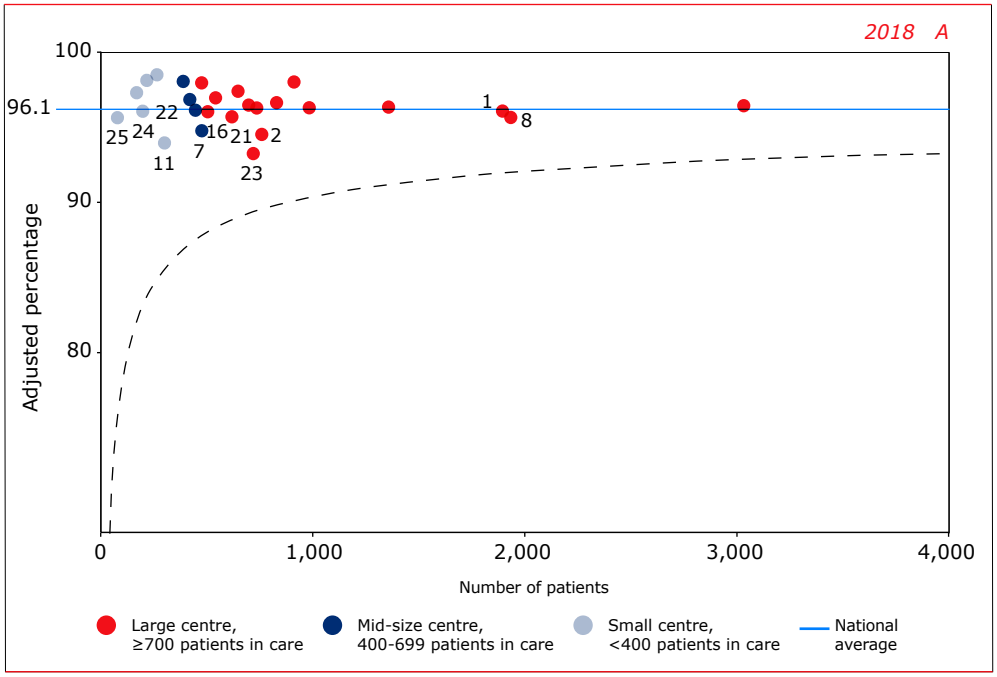


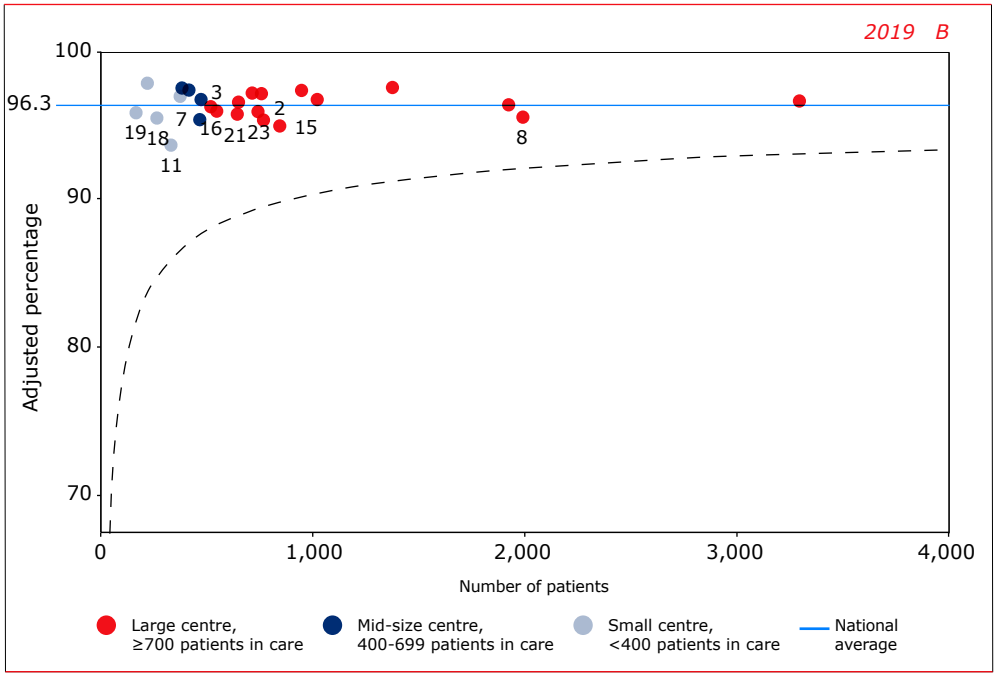



***Legend:*** *Data points with centre numbers below the national average are labelled and correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line.*

The *third* viral suppression indicator is the percentage of all HIV-positive patients in care who have a last available HIV RNA level <100 copies/ml. This indicator was calculated for the calendar years 2018 and 2019, for all individuals with an HIV RNA measurement (the percentage without HIV RNA measurements was 1.6% in 2018 and 1.9% in 2019). Across centres, the median adjusted percentage was 96% (range = 93–98%) in 2018 and 96% (range = 94–98%) in 2019. *Figure 7.8* shows the adjusted percentage of this viral suppression indicator per treatment centre in 2018 (*Figure 7.8A*) and in 2019 (*Figure 7.8B*). All centres had adjusted percentages within the expected range, when compared to the national level.

*Figure 7.8: The percentage of all HIV-positive patients in care in A) 2018 and B) 2019, respectively, 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 2018 and 2019.*



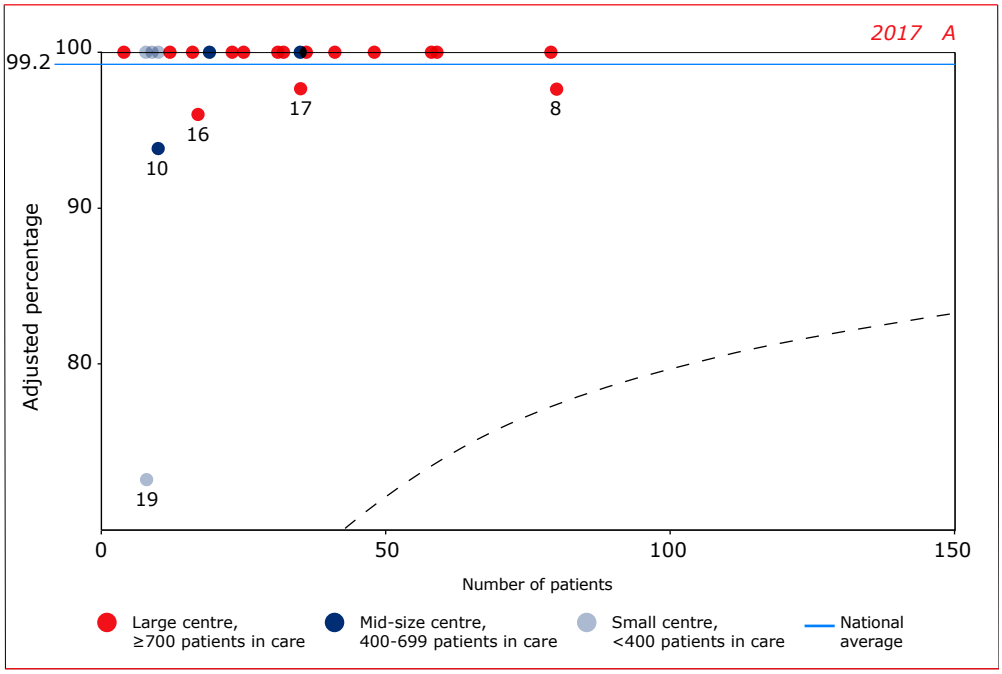

*Legend: Data points with centre numbers below the national average are labelled and correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line.*

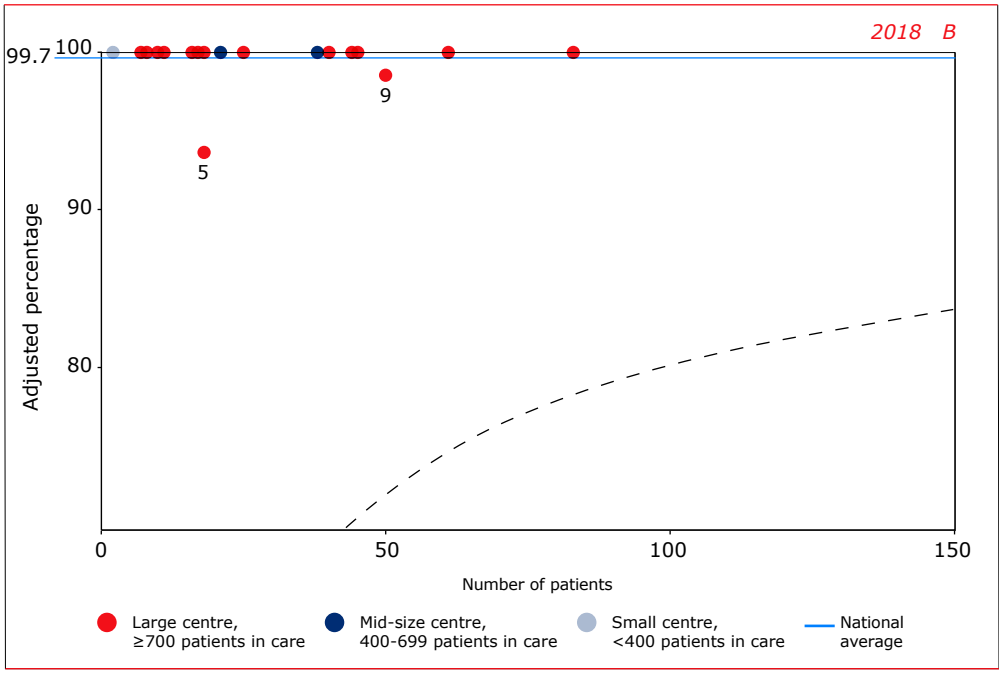
## Process indicators

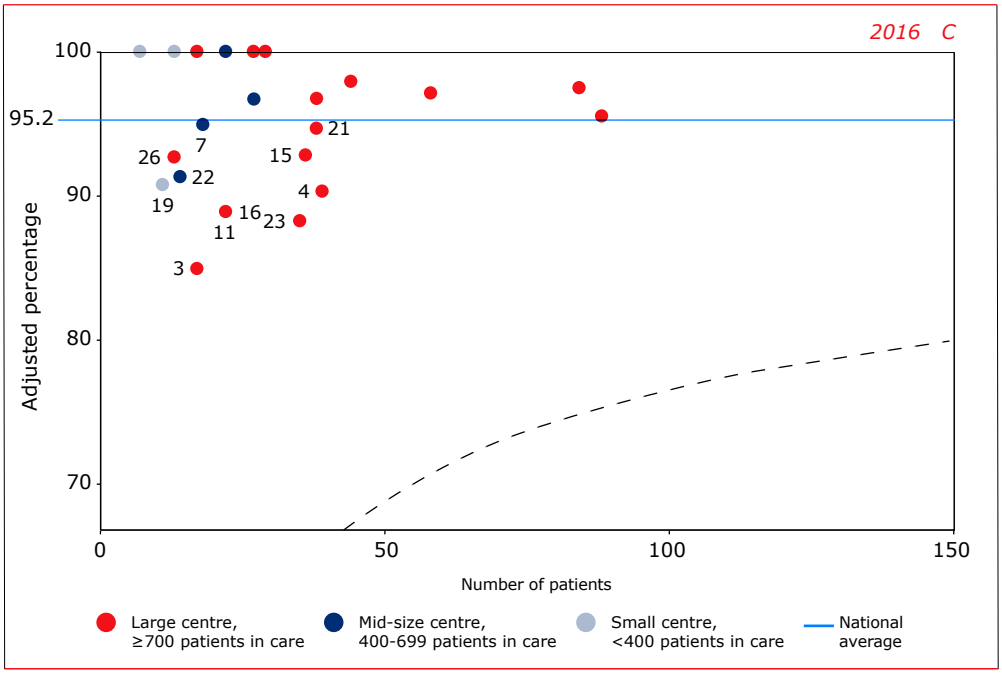
### Prior to starting cART

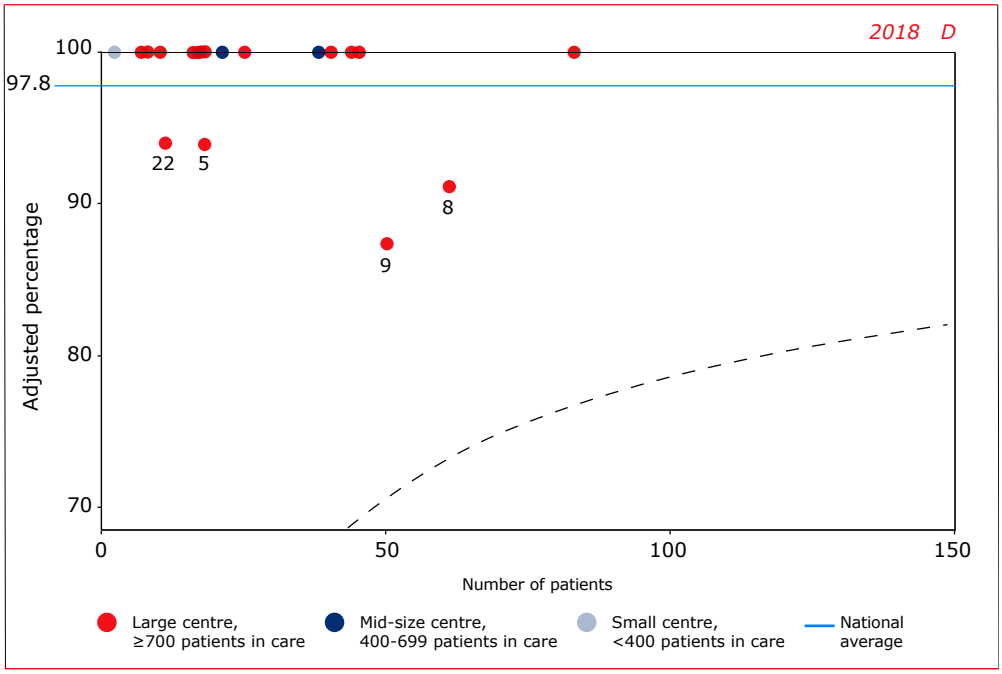
Process indicators were evaluated in patients who newly entered care in 2017 and 2018. Across centres, the median adjusted percentage of individuals tested for plasma HIV RNA and CD4 cell count within six months of entering care were respectively 100% (range = 73–100%) and 100% (range = 87–100%) in 2017, and 100% (range = 94–100%) and 100% (range = 87–100%) in 2018. *Figure 7.9* shows the across-centre variation in adjusted percentages of individuals who had plasma HIV RNA (*Figures 7.9A and 7.9B*), and CD4 cell count measurements (*Figures 7.9C and 7.9D*). This figure demonstrates that all centres with at least 40 patients entering care in 2017 and 2018 had adjusted percentages within the expected range, when compared to the national level.

*Figure 7.9: The percentage of patients who newly entered care in Dutch HIV treatment centres in 2017 and 2018, respectively, with assessment within six months of (A, B) plasma HIV RNA and (C, D) CD4 cell count. The percentage of individuals with plasma HIV RNA and CD4 cell count measurements has been adjusted for patient mix and is plotted as a function of the number of patients entered into care.*





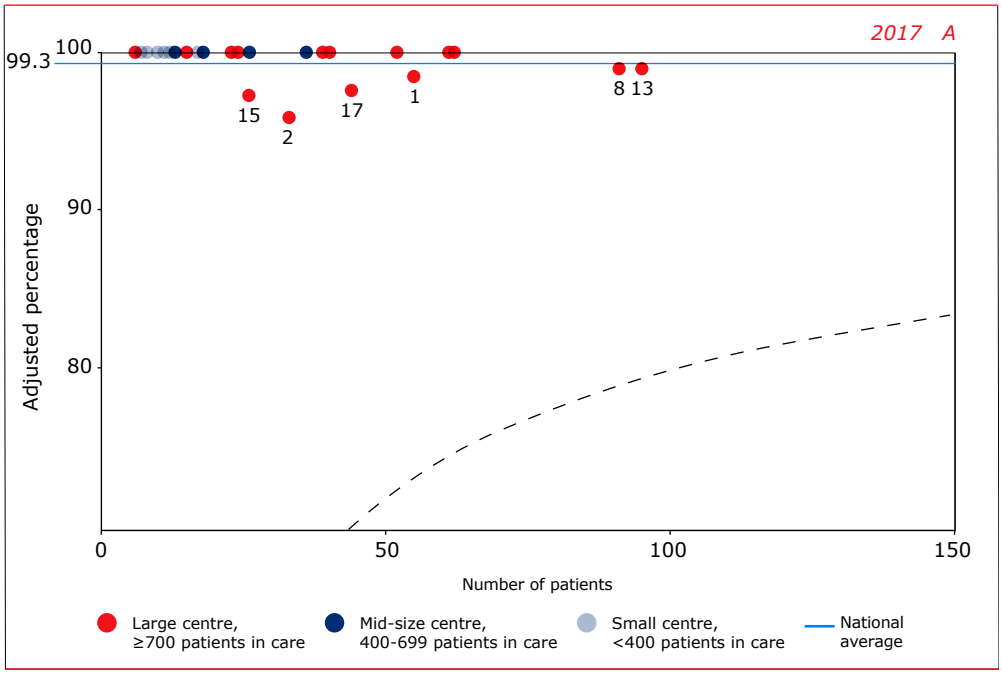



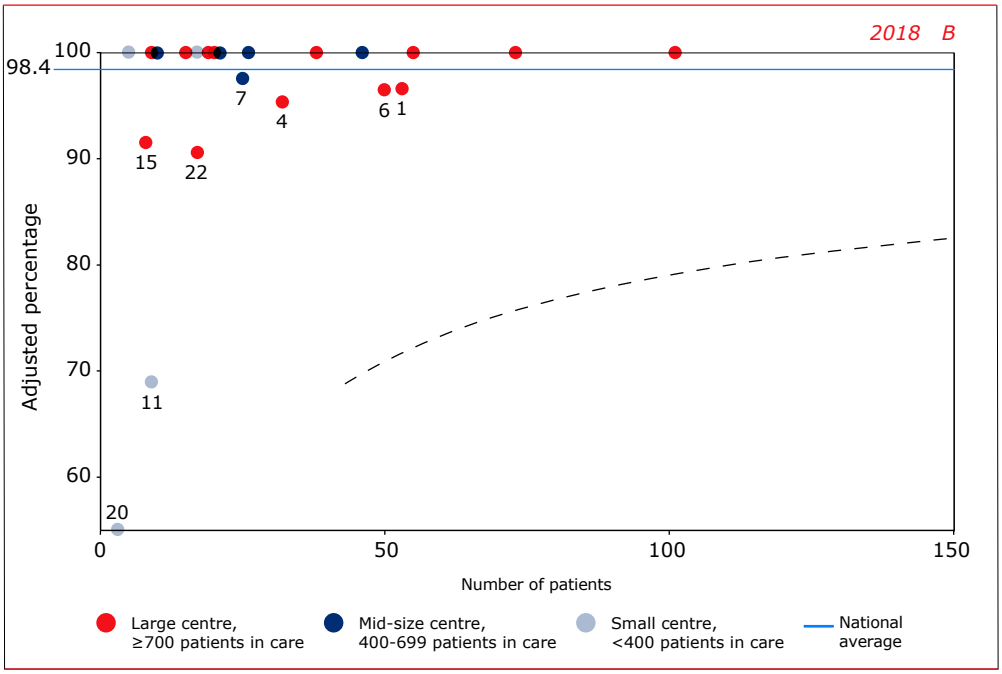

***Legend:*** *Data points with centre numbers below the national average are labelled and correspond to Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.2); no centre falls below this line.*

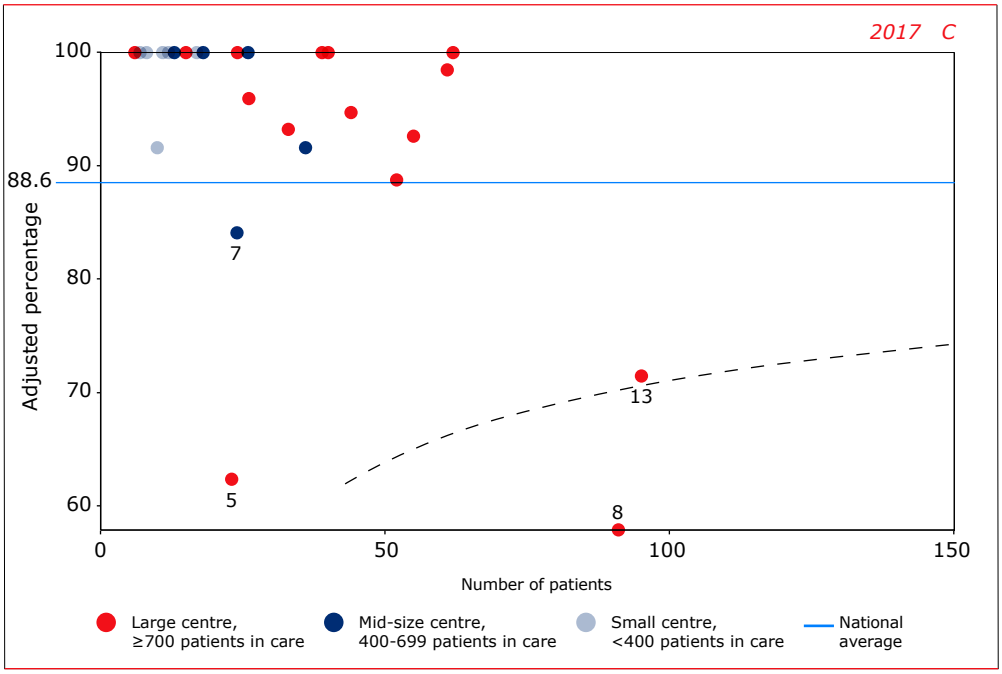
### Following the start of cART

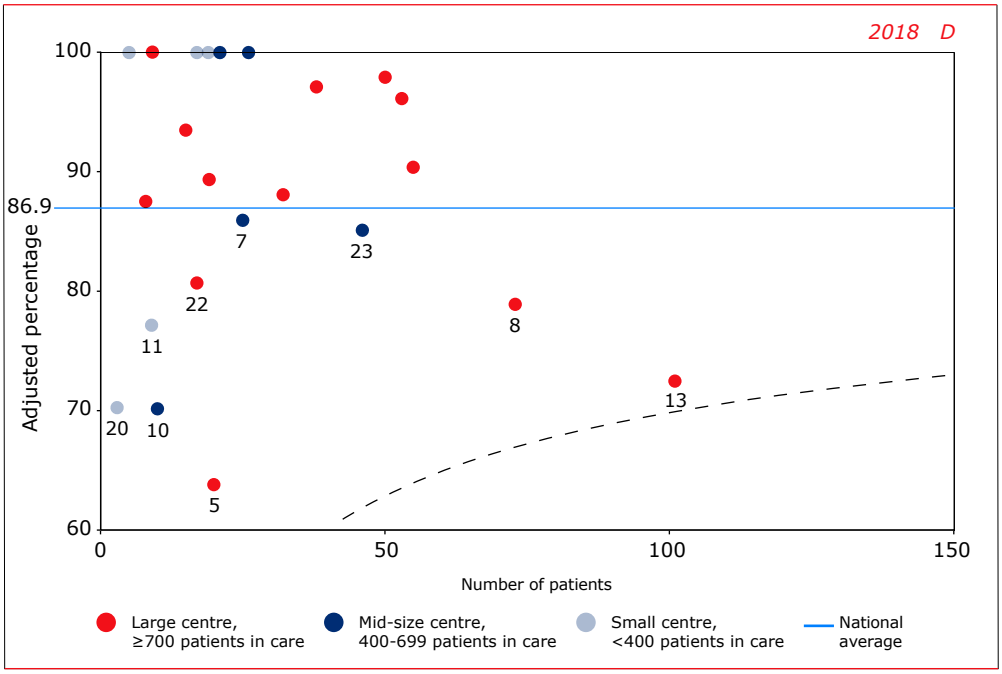
Process indicators were evaluated in patients who initiated cART in 2017 and 2018. Across centres, the median adjusted percentage of individuals tested for plasma HIV RNA and CD4 cell count within 13 months of initiating cART were respectively 98% (range = 83–100%) and 90% (64–100%) in 2017, and 95% (range = 52–100%) and 90% (64–100%) in 2018. *Figure 7.10* shows the across-centre variation in adjusted percentages who had plasma HIV RNA (*Figures 7.10A and 7.10B*), and CD4 cell count measurements (*Figures 7.10C and 7.10D*). This figure demonstrates that almost all centres with at least 40 patients entering care in 2017 and 2018 had adjusted percentages within the expected range when compared to the national level. One large-volume centre had a lower-than-expected percentage of individuals measured for CD4 cell count within 13 months of initiating cART in 2017. However, some of the variation in this indicator could be due to differences in the CD4 measurement protocols between centres.

*Figure 7.10: The percentage of patients in HIV treatment centres in the Netherlands who initiated combination antiretroviral therapy (cART) in 2017 and 2018, respectively, with assessment of (A, B) plasma HIV RNA and (C, D) CD4 cell count within 13 months of cART initiation. The percentage of individuals with plasma HIV RNA and CD4 cell count measurements has been adjusted for patient mix and is plotted as a function of the number of patients who initiated cART in 2017 and 2018.*






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

### Indicators for patients who were in care in the two centres that closed in 2018

In 2018, two officially-acknowledged HIV treatment centres closed (MC Slotervaart, Amsterdam and MC Zuiderzee, Lelystad). During 2018, 778 patients were still in care in these two centres. Of these patients, 536 (69%) transferred to the care of another HIV treatment centre in the Netherlands (of whom 485 had a clinical visit in 2019); 59 (8%) moved abroad; 57 (7%) were lost to care; and 15 (2%) died. For 111 (14%) patients, care status was unknown at the time of this analysis (i.e., their current status was not relayed to the database). The percentage who moved abroad, were lost to care, or died are similar to those of the entire adult HIV-1 positive population in SHM in 2019 (Chapter 1). The high percentage with unknown care status is likely due to an administrative backlog; more information on these 111 patients is expected to become available in 2020.

The indicators most relevant to the group of patients who transferred care to another HIV treatment centre are as follows: the percentage of all HIV-positive people who had initiated cART and were still in care in 2019; the percentage of people on cART for at least six months in 2019 with a plasma HIV RNA level <100 copies/ml; and the percentage of all HIV-positive people in care in 2019 with a plasma HIV RNA level <100 copies/ml. *Table 7.1* summarises these indicators for individuals who were in care at a closed centre before transferring to another centre, and compares them to the median adjusted indicators across centres. This table shows that all indicators for the individuals who were transferred to a different centre were within the range of adjusted indicators across centres.

***Table 7.1:** Indicators in individuals who were in care at a closed centre before transferring to another HIV treatment centre.*

| Indicator (Box 7.1) | Individuals transferred from a closed centre (n=485) | Median adjusted* indicators (range) across all centres in the Netherlands |
|---|---|---|
| Initiated cART and still in care in 2019 | 99% | 99% (97–100%) |
| On cART for at least six months in 2019 with a plasma HIV RNA level <100 copies/mL | 98% | 98% (95–100%) |
| In care in 2019 with a plasma HIV RNA level <100 copies/mL | 97% | 98% (93–100%) |

**Adjusted for patient mix.*

### Comparison between treatment centres and benchmarking

SHM has provided HIV treatment centres with the outcomes of centre-specific, ZiZo and HKZ-approved indicators since 2011. However, in 2017 and 2019, SHM also provided each centre with a number of the indicators described in this chapter, in a manner that allowed the centres to compare their indicators with the blinded scores of other centres. Subsequently, several centres approached SHM for more specific data regarding their scores.

In the context of quality of HIV care in the Netherlands, the data presented in this chapter may serve as a useful benchmark that centres can use to identify potential aspects for improvement. It is likely too early to observe an effect of this benchmarking, as most of the recent indicator scores are only reported through 2018; although performance in terms of the HKZ indicator "short-term viral suppression" is generally very high.

This year, each treatment centre will again be provided with 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.

## Key findings and conclusions

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

- In 2019, eight HIV treatment centres of various patient sizes did not meet the criterion of seeing a minimum of 20 new patients per year, as required by the current HKZ standards for HIV treatment centres in the Netherlands. Five of these eight centres had already failed to meet this particular criterion in 2018. Further discussion about the appropriateness of this standard seems warranted.
- After exclusion of patients who either died or moved abroad, both short-term and long-term retention-in-care rates are generally high. This is also the case when adjusting for patient mix.
- The percentage of patients initiating cART within six months of entering care, remained high for those who entered care in 2017 and 2018, maintaining a median of 100%. The overall coverage of cART in 2019, regardless of time since entering care, was high across all centres, despite variations in centre volume and patient mix.
- Viral suppression rates in the first six months on cART, and during longer-term use of cART, were 100% across all HIV treatment centres in the Netherlands in 2019.

- Across centres, the median adjusted percentage of all patients in care with an HIV RNA level <100 copies/ml was 96% in 2018 and 98% in 2019. There was little variation in this percentage across centres after adjusting for patient mix.
- With only one exception, for every indicator, all centres were within the statistically-expected range, based on the national average and accounting for centre volume and patient mix.
- The cART and viral suppression indicators for individuals who were originally in care in one of the two centres that closed, do not appear to have been affected by the transfer of care to another HIV treatment centre. However, more information is needed on individuals whose current care status is unknown.
- The funnel plots provide a statistical interpretation of whether a centre performs within the expected range of the national average. Unfortunately, this interpretation becomes less reliable when a centre is treating only a limited number of patients (i.e., fewer than 40, for the purpose of this report). As many centres had fewer than 40 patients newly entering care in 2016-19, they could not be feasibly compared to the national average. We therefore urge caution when comparing indicators of these small centres to the national average, or even to fixed levels (e.g., 90%). Understanding the reasons for not achieving higher percentages would require more in-depth analysis at the centre level, which cannot be readily performed by the SHM.
- 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 will be met at the centre level. Nonetheless, data reliability remains an important issue, and it should be recognised that some of the reported variation 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.

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# 8. The Amsterdam Cohort Studies on HIV infection: annual report 2019

Amy Matser, Ward van Bilsen, 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 under 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 and human papillomavirus (HPV). This expertise, in turn, has contributed directly to advances in prevention, diagnosis, and management of these infection.

### 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 have 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 Amsterdam Cohort Studies in 2019

### The cohort of men who have sex with men (MSM)

As of 31 December 2019, 2,899 MSM were included in the ACS. Every three to six months, participants complete a standardized questionnaire designed to obtain information regarding medical history, sexual and drug use behavior, underlying psychosocial determinants, healthcare use, depression, psychological disorders, and demographics. Blood is also collected for diagnostic tests and storage. Of the 2,899 MSM, 607 were HIV-positive at entry into the study, and 263 seroconverted for HIV during follow up. In total, the GGD Amsterdam was visited 61,172 times by MSM.

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. From 1988 to 1998, the cohort was also open for HIV-positive MSM. During the period 1995–2004, only men aged ≤30 years with at least one male sexual partner in the previous six months, could enter the study. 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 with the city of Amsterdam, and have had at least one male sexual partner in the preceding six months. In line with the advice issued by the international scientific advisory committee in 2013, the cohort now makes additional efforts to recruit young HIV-negative MSM (age ≤30 years).

HIV-seroconverters within the ACS remained in the cohort until 1999, when follow up of a selection of HIV-positive MSM was transferred to the MC Jan van Goyen. In 2003, the *Hiv Onderzoek onder Positieven* (HOP) protocol (*HIV Research in Positive Individuals*) was initiated. Individuals with a recent HIV infection 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 2019, 708 HIV-negative and 53 HIV-positive MSM were in active participation at the GGD Amsterdam; in other words, these men visited the cohort at least once in 2019 or 2018. All 53 HIV-positive MSM filled out behavioural questionnaires. In addition to the HIV-positive MSM visiting the GGD Amsterdam, 256 HIV-positive MSM participated at the MC Jan van Goyen, or the DC Klinieken Lairesse-HIV Focus Centrum in Amsterdam. Behavioural questionnaires were not filled out by these men. In 2019, 18 new HIV-negative MSM were recruited. The median age of this group was 29.6 years (interquartile range [IQR] 26.9-31.7), while that of the total group of MSM in active follow up was 43.6 years at their last visit (IQR 33.2-51.0). The majority (83.3%) of the total group was born in the Netherlands and 87.9% were residents of Amsterdam. In total, 77.0% 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), 8.1% had attained a high level of education, and 63.4% were born in the Netherlands.

## The Amsterdam Cohort Studies biobank

The ACS visits, together with data collection from several subgroup studies and affiliated studies embedded in the ACS, have resulted in a large collection of stored samples. The ACS biobank includes plasma/serum and PBMC samples collected within the context of the ACS cohorts and the Primo-SHM study (a national randomised study comparing the effects of early temporary antiviral therapy with that of no therapy among patients who presented with primary HIV-1 infection at the AMC HIV outpatient clinic, and ACS seroconverters). These samples are stored at the 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 includes plasma and PBMC samples that were collected from HIV-positive and HIV-exposed children at the Emma Kinderziekenhuis in the AUMC, location AMC until 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 HIV-positive individuals aged ≥45 years, and to determine the extent to which comorbidities, their risk factors and their relation to quality of life differ between HIV-positive and HIV-negative groups.

Participants undergo a comprehensive assessment for comorbidities and complete a questionnaire at intake, 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 and were as comparable as possible with respect to age, gender, ethnicity, and risk behaviour. In the fourth round (2016-18), 420 HIV-positive and 457 HIV-negative participants had a fourth visit. In 2019, visits for the fifth round started and this round is expected to be completed in 2021.

## 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) participants of the ACS who were in active participation, 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, collection of anal and genital swabs has been resumed in all consenting ACS participants. The key aim of this second new study (the H2M3 study), which builds on the H2M study, is to examine long-term incidence and clearance of anal and penile hrHPV infections. Between September 2014 and November 2015, 700 men provided samples for HPV testing during ACS cohort visits. Of these, 434 (62%) were already participating in the H2M study (recruited 2010-11), and 266 (38%) were new participants who joined the ACS after the H2M study had ended. Samples at two time points (six months apart) were tested in the laboratory for HPV DNA, and analyses of anal samples were conducted. This study, supported by Crucell (Leiden), found that a quarter of MSM did not clear an anal HPV-16 infection after three years; therefore, persistence of anal HPV is common. Twenty-two percent of men who were not infected with HPV-16 at baseline, acquired an anal HPV-16 infection over a four-year period. Therefore, even in highly pre-exposed men, the incidence rate of hrHPV infections is high. Analysis of penile HPV infections showed that HPV-16 had the highest incidence rate of all high-risk HPV types, and the lowest clearance rate. In 2019, collection of anal and penile swabs from ACS participants continued and these are 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 is a prospective, longitudinal, open-label demonstration study. Its aim is to assess the uptake and acceptability of daily, versus event-driven, pre-exposure prophylaxis (PrEP) among MSM and transgender people (TGP) at increased risk for HIV infection, as part of a comprehensive HIV-reduction package offered at a large STI clinic.

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

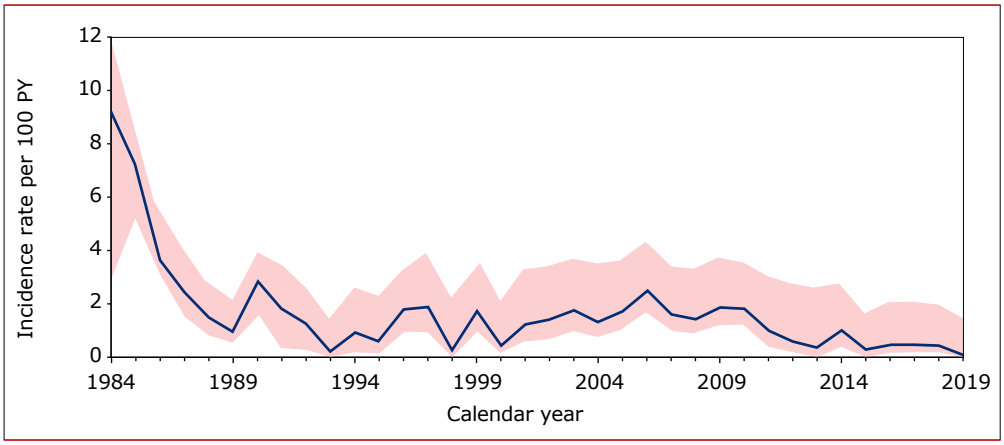
The AMPrEP project is part of the HIV Transmission Elimination Amsterdam (H-TEAM) initiative, a multidisciplinary and integrative approach to stop the epidemic (www.hteam.nl).

## The HIV epidemic

### HIV incidence

The observed HIV incidence among MSM participating in the ACS has changed over time. Between 1985-1993, the HIV incidence rate declined significantly, which was followed by a stable incidence between 1993 and 1996, and a rising incidence in 1996-2009. From 2009 onwards, the HIV incidence decreased significantly. In 2019, two MSM participating in the ACS seroconverted for HIV. The HIV incidence rate was 0.11 per 100 person years (95%-confidence interval (CI) 0.02-0.81) in 2019. *Figure 8.1* shows the yearly-observed HIV incidence rate for MSM from the start of the ACS through 2019.

***Figure 8.1:*** *HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984–2019.*



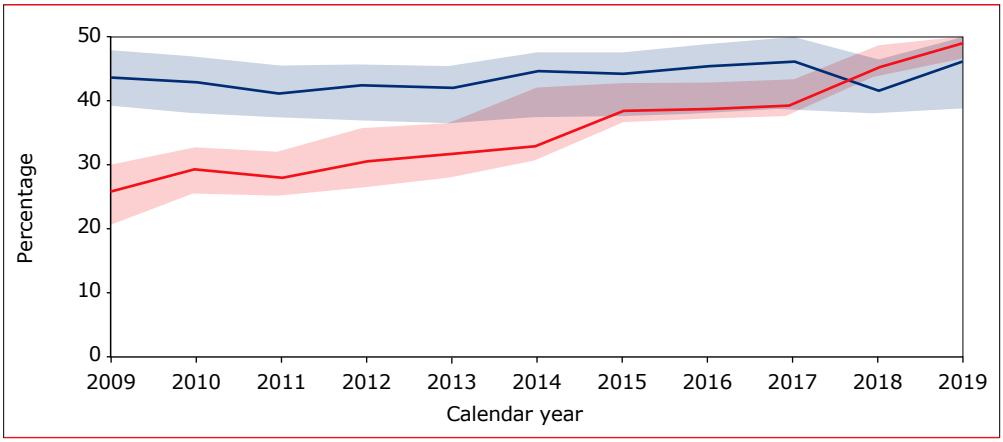
## Transmission of therapy-resistant HIV strains

In 2019, no surveillance of transmitted drug-resistant HIV-1 strains was conducted.

## Risk behaviour of MSM in ACS

Condomless anal sex (CAS) with a steady partner was reported by 295/639 (46.2%) HIV-negative MSM at their last cohort visit, compared with 314/639 (49.1%) who reported CAS with a casual partner. Trends in CAS among HIV-negative MSM participating in the ACS, especially CAS with casual partners, continued to show a gradual increase from 2009 onwards (*Figure 8.2*). The use of PrEP has also increased over time since 2015. In 2019, 185/662 (27.9%) HIV-negative MSM in active participation reported PrEP use in the preceding six months. CAS with a steady partner was reported by 77/173 (44.5%) MSM who used PrEP, and 180/441 (40.8%) MSM who did not use PrEP. CAS with a casual partner was reported by 140/173 (80.9%) MSM who used PrEP, and 96/441 (21.7%) MSM who did not use PrEP.

*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), 2009-19.*

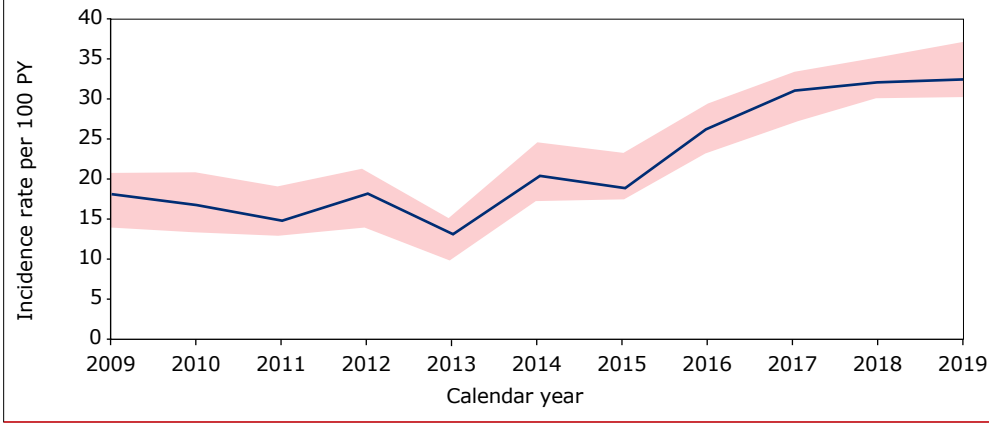



## STI screening among MSM in ACS

Since October 2008, all MSM in the ACS have been routinely screened for chlamydia and gonorrhoea by polymerase chain reaction (PCR) techniques using urine samples and pharyngeal and rectal swabs. Cases of syphilis are detected by *Treponema pallidum* haemagglutination assay (TPHA). In 2019, 731 MSM from the ACS were screened for STIs. The incidence rate of any STI (i.e., chlamydia, gonorrhoea, or syphilis) was 30.2/100 person-years in 2019 (95%-CI 25.6-35.6) among HIV-negative MSM. The incidence rate of any STI significantly increased

between 2009-19 (*Figure 8.3*). The incidence rate of any STI was 37.6/100 PY (95%-CI 27.5-51.5) among HIV-negative MSM who used PrEP, and 24.8/100 PY (95%-CI 20.4-30.0) among HIV-negative MSM who did not report use of PrEP.

***Figure 8.3:*** *The incidence of any STI (i.e., chlamydia, gonorrhoea, or syphilis) among HIV-negative MSM in the Amsterdam Cohort Studies (ACS), 2009-19.*




## The Amsterdam Cohort Studies research highlights

### Cross-genotype AR3-specific neutralizing antibodies confer long-term protection in injecting drug users after HCV clearance

Although effective treatments against HCV are available, each year, 500,000 people die from liver disease caused by HCV, and approximately 1.75 million people are newly infected. These infections could be prevented if there was a vaccine available against HCV. To design such a vaccine, more insight into the role of antibodies in protection against HCV infection is needed. In the ACS cohort of PWID, antibodies interfering with HCV cell entry were found. A strong B cell response, producing cross-genotype and neutralizing antibodies, especially targeting antigenic region 3 of HCV, contributed to clearance and long-term immune protection against HCV. In addition, three individuals developed antibodies recognizing antigenic region 4, of which one monoclonal antibody showed cross-neutralizing capacity. These observations permit cautious optimism that development of an effective preventive vaccine is feasible. Published by: Merat SJ, Bru C, van de Berg D, et al. *J Hepatol. 2019;71(1):14-24. doi:10.1016/j.jhep.2019.02.013*

### Infection Pressure in Men Who Have Sex With Men and Their Suitability to Donate Blood

Deferral of men who have sex with men (MSM) from blood donation is highly debated. To assist in defining MSM donor deferral policies, we have investigated their suitability to donate blood by comparing the antibody prevalence of 10 sexually-transmissible and transfusion-transmissible infections (TTI) among 583 MSM from the Amsterdam Cohort Studies, and 583 age-matched repeat male blood donors. MSM were classified as low-risk (lr) or medium-to-high-risk (hr) based on self-reported sexual behaviour, and as qualified or unqualified using Dutch donor deferral criteria other than male-to-male sex. Infection pressure was defined as the number of antibody-reactive infections, with class A infections (HIV-1/2, HBV, HCV, HTLV-1/2, syphilis), given double weight compared to class B infections (CMV, HSV-1/2, HHV-8, HEV, Parvovirus B19). We found that donors had a lower infection pressure than qualified lr-MSM and qualified hr-MSM. A low infection pressure was found in 76% of donors, 39% of qualified lr-MSM, and 27% of qualified hr-MSM. The prevalence of class A infections did not differ between donors and qualified lr-MSM, but was significantly higher in qualified hr-MSM and unqualified MSM. Recently-acquired class A infections were detected in hr-MSM only. Compared to blood donors, human herpes viruses were more prevalent in all MSM groups, and prevalence increased with self-reported risk behaviour. In conclusion, infection pressure correlated with self-reported risk behaviour among MSM. Although lr-MSM might form a low threat for blood safety with regards to class A infections, the high seroprevalence of human herpes viruses in lr-MSM warrants further investigation. Published by: van Bilsen WPH, Zaaijer HL, Matser A, et al. *Clin Infect Dis. 2019;68(6):1001-1008. doi:10.1093/cid/ciy596*

### Steering committee

In 2019, the steering committee met five times. Eight proposals for use of data and/or samples (serum/PBMC) were submitted to the committee: one from the AUMC, location AMC Experimental Immunology, four from the Amsterdam UMC, location AMC laboratory of Experimental Virology, and three from the GGD Amsterdam. Three of the proposals were collaborations with groups outside the ACS: two proposals from the the RIVM, and one proposal from Erasmus MC, all three in collaboration with GGD Amsterdam. All eight requests were approved, of which three were approved following revisions recommended by the ACS steering committee.

## Publications in 2019 that include ACS data

**Genomic characterization of hepatitis C virus transmitted founder variants with deep sequencing**
Abayasingam A, Leung P, Eltahla A, Bull RA, Luciani F, Grebely J, Dore GJ, Applegate T, Page K, Bruneau J, Cox AL, Kim AY, Schinkel J, Shoukry NH, Lauer GM, Maher L, Hellard M, Prins M, Lloyd A, Rodrigo C; InC3 Study Group.
*Infect Genet Evol. 2019 Jul;71:36-41.*
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6487228/

**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**
Achterbergh RCA, de Vries HJC, Boyd A, et al.
*Addiction. 2020;115(1):121-133. doi:10.1111/add.14774*
https://pubmed.ncbi.nlm.nih.gov/31400174/

Potential effectiveness of prophylactic HPV immunization for men who have sex with men in the Netherlands: A multi-model approach
Bogaards JA, Mooij SH, Xiridou M, Schim van der Loeff MF.
*PLoS Med. 2019 Mar 4;16(3):e1002756. doi: 10.1371/journal.pmed.1002756. PMID: 30830901; PMCID: PMC6398832.*
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6398832/

**Lower Broadly Neutralizing Antibody Responses in Female Versus Male HIV-1 Infected Injecting Drug Users**
Euler Z, van den Kerkhof TL, Kouyos RD, Tully DC, Allen TM, Trkola A, Sanders RW, Schuitemaker H, van Gils MJ.
*Viruses. 2019 Apr 25;11(4):384. doi: 10.3390/v11040384.*
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6521154/

**Estimating incidence rates of grouped HPV types: A systematic review and comparison of the impact of different epidemiological assumptions**
Jongen VW, van Santen DK, Alberts CJ, Schim van der Loeff MF.
*Papillomavirus Res. 2019 Dec;8:100187. doi: 10.1016/j.pvr.2019.100187. Epub 2019 Oct 7. PMID: 31600572; PMCID: PMC6804437.*
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6804437/

**Incidence and Clearance of Anal High-risk Human Papillomavirus Infections and Their Determinants Over 5 Years Among Human Immunodeficiency Virus–negative Men Who Have Sex With Men**
Marra E, Kovaleva A, Bruisten SM, Vermeulen W, Boyd A, Schim van der Loeff MF.
*Clin Infect Dis. 2019;68(9):1556-1565. doi:10.1093/cid/ciy738*
https://pubmed.ncbi.nlm.nih.gov/30169621/

**Virological and Serological Predictors of Anal High-grade Squamous Intraepithelial Lesions Among Human Immunodeficiency Virus-positive Men Who Have Sex With Men**
Marra E, Siegenbeek van Heukelom ML, Leeman A, et al.
*Clin Infect Dis. 2019;68(8):1377-1387. doi:10.1093/cid/ciy719*
https://pubmed.ncbi.nlm.nih.gov/30165551/

**Cross-genotype AR3-specific neutralizing antibodies confer long-term protection in injecting drug users after HCV clearance**
Merat SJ, Bru C, van de Berg D, Molenkamp R, Tarr AW, Koekkoek S, Kootstra NA, Prins M, Ball JK, Bakker AQ, de Jong MD, Spits H, Beaumont T, Schinkel J. J Hepatol.
*2019 Jul;71(1):14-24. doi: 10.1016/j.jhep.2019.02.013.*
https://pubmed.ncbi.nlm.nih.gov/30797052/

**Cross-genotype AR3-specific neutralizing antibodies confer long-term protection in injecting drug users after HCV clearance**
Merat SJ, Bru C, van de Berg D, Molenkamp R, Tarr AW, Koekkoek S, Kootstra NA, Prins M, Ball JK, Bakker AQ, de Jong MD, Spits H, Beaumont T, Schinkel J. J Hepatol.
*2019 Jul;71(1):14-24. doi: 10.1016/j.jhep.2019.02.013. Epub 2019 Feb 21. Erratum in: J Hepatol. 2020 Aug 1;: PMID: 30797052.*
https://pubmed.ncbi.nlm.nih.gov/32753312/

**HIV-1 molecular transmission clusters in nine European countries and Canada: association with demographic and clinical factors**
Paraskevis D, Beloukas A, Stasinos K, Pantazis N, de Mendoza C, Bannert N, Meyer L, Zangerle R, Gill J, Prins M, d'Arminio Montforte A, Kran AB, Porter K, Touloumi G; CASCADE collaboration of EuroCoord.
*BMC Med. 2019 Jan 8;17(1):4. doi: 10.1186/s12916-018-1241-1.PubMed PMID: 30616632*
https://pubmed.ncbi.nlm.nih.gov/30616632/

**Cost-effectiveness of increased HIV testing among MSM in The Netherlands**
Reitsema M, Steffers L, Visser M, Heijne J, van Hoek AJ, Schim van der Loeff M, van Sighem A, van Benthem B, Wallinga J, Xiridou M, Mangen MJ.
*AIDS. 2019 Oct 1;33(12):1807-1817. doi: 10.1097/QAD.0000000000002199. PMID: 30889012.*
https://pubmed.ncbi.nlm.nih.gov/30889012/

**Genomic variability of within-host hepatitis C variants in acute infection**
Rodrigo C, Leung P, Lloyd AR, Bull RA, Luciani F, Grebely J, Dore GJ, Applegate T, Page K, Bruneau J, Cox AL, Osburn W, Kim AY, Shoukry NH, Lauer GM, Maher L, Schinkel J, Prins M, Hellard M, Eltahla AA; InC3 Collaborative.
*J Viral Hepat. 2019 Apr;26(4):476-484. doi: 10.1111/jvh.13051. Epub 2019 Jan 22. PMID: 30578702; PMCID: PMC6417964.*
https://pubmed.ncbi.nlm.nih.gov/30578702/

**SNP rs688 within the low-density lipoprotein receptor (LDL-R) gene associates with HCV susceptibility**
Steba GS, Koekkoek SM, Tanck MWT, Vanhommerig JW, van der Meer JTM, Kwa D, Brinkman K, Prins M, Berkhout B, Pollakis G, Molenkamp R, Schinkel J, Paxton WA; MOSAIC (MSM observational Study of Acute infection with Hepatitis C) Study Group and the ACS (Amsterdam Cohort Studies).
*Liver Int. 2019 Mar;39(3):463-469.*
https://pubmed.ncbi.nlm.nih.gov/30260075/

**Similarities and differences between native HIV-1 envelope glycoprotein trimers and stabilized soluble trimer mimetics**
Torrents de la Peña A, Rantalainen K, Cottrell CA, Allen JD, van Gils MJ, Torres JL, Crispin M, Sanders RW, Ward AB.
*PLoS Pathog. 2019 Jul 15;15(7):e1007920. doi: 10.1371/journal.ppat.1007920.*
https://pubmed.ncbi.nlm.nih.gov/31306470/

**HPV infections and flat penile lesions of the penis in men who have sex with men**
van Bilsen WPH, Kovaleva A, Bleeker MCG, et al.
*Papillomavirus Res. 2019;8:100173. doi:10.1016/j.pvr.2019.100173*
https://pubmed.ncbi.nlm.nih.gov/31226447/

**Infection Pressure in Men Who Have Sex With Men and Their Suitability to Donate Blood**
van Bilsen WPH, Zaaijer HL, Matser A, et al.
*Clin Infect Dis. 2019;68(6):1001-1008. doi:10.1093/cid/ciy596*
https://pubmed.ncbi.nlm.nih.gov/30052873/

**Effect of incident hepatitis C infection on CD4+ cell count and HIV RNA trajectories based on a multinational HIV seroconversion cohort**
van Santen DK, van der Helm JJ, Touloumi G, Pantazis N, Muga R, Gunsenheimer-Bartmeyer B, Gill MJ, Sanders E, Kelleher A, Zangerle R, Porter K, Prins M, Geskus RB; CASCADE Collaboration within EuroCoord.
*AIDS. 2019 Feb 1;33(2):327-337. doi: 10.1097/QAD.0000000000002040. PubMed PMID: 30325767.*
https://pubmed.ncbi.nlm.nih.gov/30325767/

## Theses in 2019 that include ACS data

Janneke Bil – HIV, hepatitis B & C, and sexually transmitted infections: innovations in prevention and testing
https://dare.uva.nl/search?identifier=de4029ab-e910-4b89-b2a5-c80757ff321b

Sabrina Merat - Protective antibody responses against HCV E1E2 in high-risk populations
https://dare.uva.nl/search?field1=keyword;value1=merat;docsPerPage=1;startDoc=1

# Special report

## 9. Curaçao

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

### Introduction

Since 2005, Stichting HIV Monitoring (SHM) has assisted in collecting demographic and clinical data about HIV-positive individuals receiving care at the St. Elisabeth Hospital in Willemstad in Curaçao. As a result of this registration and monitoring, an extensive database has been established. Such a database is unique for the region and gives a clear picture of the HIV-positive population, the effectiveness of HIV care, and the challenges that exist in this relatively small Caribbean setting. This special report presents a concise overview of the current state of the HIV epidemic in Curaçao.

### Population

In total, 1,274 HIV-positive individuals registered by SHM have been followed in the St. Elisabeth Hospital in Curaçao. Of these people, the majority were diagnosed with HIV-1 (1,260; 99%), while two individuals were diagnosed with HIV-2, and two had antibodies against both HIV-1 and HIV-2. For ten individuals, serological results on HIV type were not available in the SHM database.

#### People newly diagnosed with HIV-1

At the time of writing, 1,244 individuals were diagnosed with HIV-1 and had a recorded date of diagnosis (*Table 9.1*). Of these 1,244 individuals, five were born abroad and had a documented HIV diagnosis prior to arrival in Curaçao. The remaining 1,239 individuals, including 321 (26%) individuals born in the former Netherlands Antilles, were newly diagnosed while living in Curaçao, or information on where they lived at the time of diagnosis was not yet available. Of these 1,239 people, 44 (4%) were diagnosed before the age of 18 years. The 1,195 individuals who were diagnosed as adults comprised 277 (23%) men who reported sex with men (MSM) as the most likely mode of transmission, 492 (41%) other men, and 426 (36%) women (*Table 9.1*). Between 2000 and 2018, the annual number of newly-diagnosed infections hovered around 50, and decreased to 17 in 2019. However, at the time of writing, there may have been some backlog in reporting HIV infections newly diagnosed in 2019, due to the transition to a new hospital at the end of that year.

## People in clinical care

In total, 683 (54%) of the 1,260 registered HIV-1-positive individuals were known to be in clinical care in Curaçao by the end of 2019. People were considered to be in clinical care if they had visited their treating physician in 2019, or had a CD4 count or HIV RNA measurement during that year and had not moved abroad. Of the 577 individuals who, according to this definition, were not in care by the end of 2019, 191 (33%) are known to have died, and 122 (21%) to have moved abroad, while 257 were lost to care. Another three were only diagnosed with HIV in 2020, three moved to Curaçao in 2020, and one entered care in 2020. Of the 257 people lost to care, 59 (23%) had their last visit within a year of entering care; another 32 (12%) had no follow-up visit after entering care.

*Table 9.1: Annual number of newly-diagnosed HIV-1 infections in Curaçao among minors less than 18 years of age, and among adult men who acquired HIV via sex with men (MSM), other men, and women.*

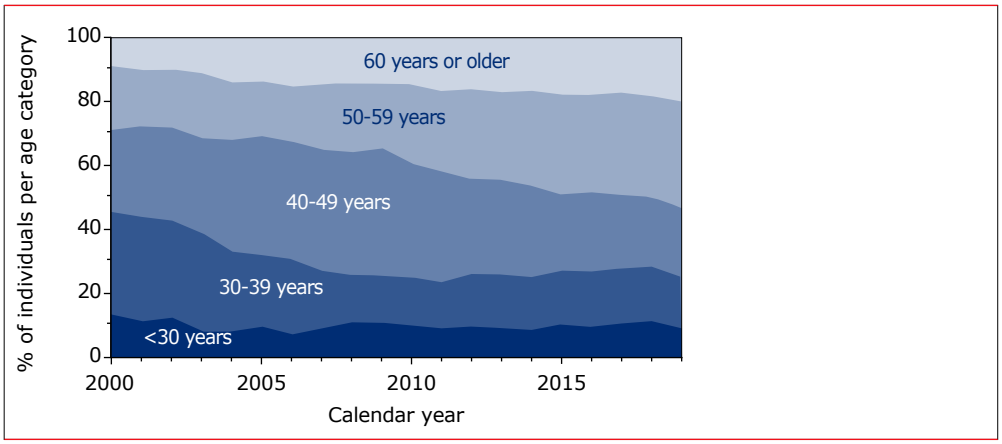
| Year of diagnosis | MSM | Other men | Women | <18 years of age | Total |
|---|---|---|---|---|---|
| ≤1999 | 37 | 112 | 82 | 23 | 254 |
| 2000 | 9 | 17 | 17 | 3 | 46 |
| 2001 | 5 | 13 | 16 | 2 | 36 |
| 2002 | 11 | 19 | 17 | 2 | 49 |
| 2003 | 9 | 29 | 21 | 0 | 59 |
| 2004 | 7 | 24 | 19 | 0 | 50 |
| 2005 | 14 | 20 | 19 | 0 | 53 |
| 2006 | 8 | 23 | 17 | 1 | 49 |
| 2007 | 15 | 16 | 10 | 2 | 43 |
| 2008 | 14 | 16 | 20 | 2 | 52 |
| 2009 | 11 | 19 | 21 | 1 | 52 |
| 2010 | 5 | 20 | 19 | 2 | 46 |
| 2011 | 14 | 19 | 24 | 1 | 58 |
| 2012 | 16 | 18 | 25 | 1 | 60 |
| 2013 | 22 | 31 | 23 | 0 | 76 |
| 2014 | 15 | 15 | 13 | 1 | 44 |
| 2015 | 17 | 21 | 12 | 1 | 51 |
| 2016 | 13 | 23 | 15 | 0 | 51 |
| 2017 | 15 | 15 | 13 | 0 | 43 |
| 2018 | 15 | 12 | 19 | 1 | 47 |
| 2019 | 4 | 9 | 3 | 1 | 17 |
| 2020 | 1 | 1 | 1 | 0 | 3 |
| **Total** | **277** | **492** | **426** | **44** | **1,239** |

***Note:** data collection for 2019 may not have been finalised at the time of writing.*

## Ageing population

The median age of the population in care by the end of 2019 was 51 (interquartile range [IQR], 40-58) years and has been increasing since 2000 (*Figure 9.1*). This increase in age is mainly a result of the improved life expectancy of HIV-positive individuals after the introduction of combination antiretroviral treatment (cART). As a result, more than half of all people currently in care (53%) are 50 years or older, including 52% of men and 54% of women; 20% of the individuals are 60 years or older. Among the 110 individuals diagnosed in 2017 or later, the median age at diagnosis was 33 (26-45) years with no differences between men and women. Of these 110 individuals, 18 (16%) were 50 years or older at the time of their diagnosis, while 40 (36%) were younger than 30 years of age.

***Figure 9.1:*** *Increasing age of the HIV-1-positive population in clinical care in Curaçao over calendar time. In 2000, 13% of the people in care were younger than 30 years of age, whereas 29% were 50 years or older. In 2019, these proportions were 9% and 53%, respectively, while 20% of people in care were 60 years of age or older. The proportion of people in clinical care as of 31 December of each calendar year is shown according to those who were <30 years of age, 30 to 39 years, 40 to 49 years, 50 to 59 years, and 60 years or older.*




## Duration of infection

People in care by the end of 2019 had been diagnosed with HIV a median of 9.5 (IQR, 4.9-15.9) years previously. Therefore, a large group (47%) have lived with HIV for more than 10 years; 14% for more than 20 years (*Table 9.2*). The median time since diagnosis was 8.3 years for MSM, 9.5 years for other men, and 10.1 years for women.

*Table 9.2: Characteristics of the 683 HIV-1-positive individuals in clinical care in Curaçao by the end of 2019.*

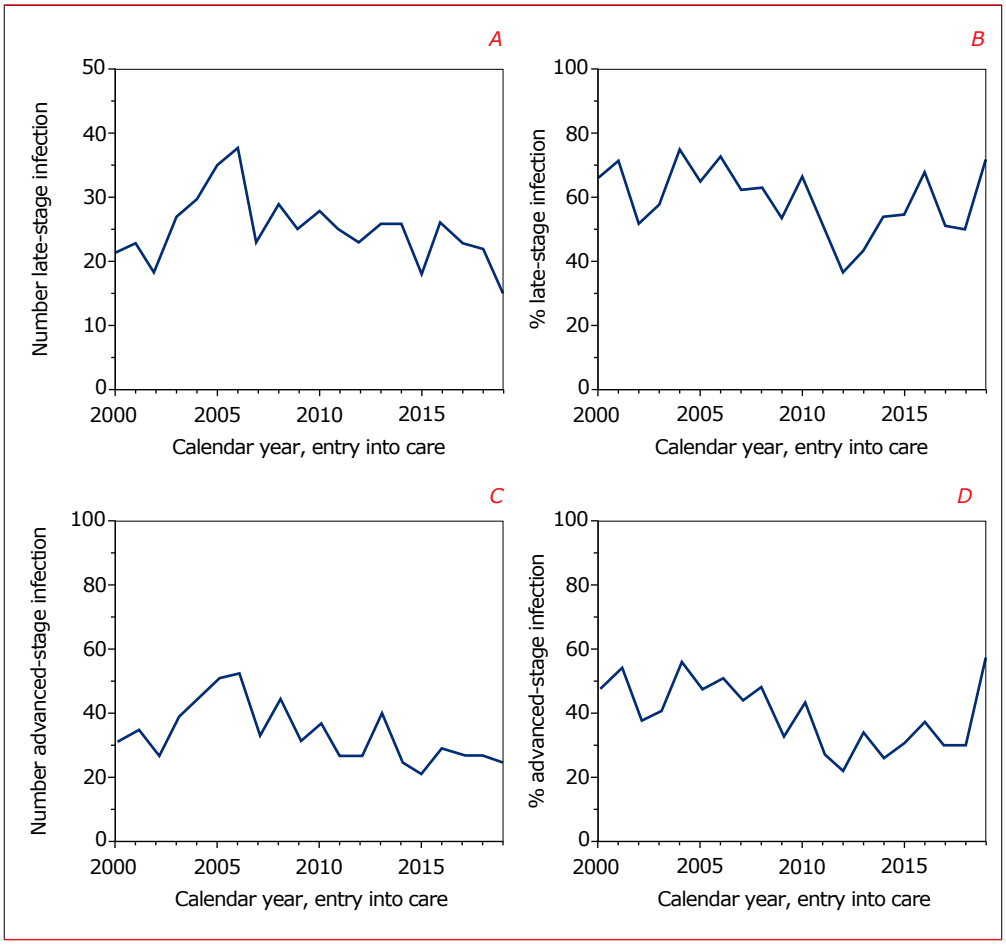
| | Men (n=429, 63%) | | Women (n=254, 37%) | | Total (n=683) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Transmission | | | | | | |
| MSM | 171 | 40 | – | – | 171 | 25 |
| Heterosexual | 180 | 42 | 238 | 94 | 418 | 61 |
| Other/unknown | 78 | 18 | 16 | 6 | 94 | 14 |
| Current age (years) | | | | | | |
| 0–17* | – | – | 1 | – | 1 | – |
| 18–24 | 10 | 2 | 6 | 2 | 16 | 2 |
| 25–29 | 35 | 8 | 9 | 4 | 44 | 6 |
| 30–39 | 72 | 17 | 39 | 15 | 111 | 16 |
| 40–49 | 87 | 20 | 61 | 24 | 148 | 22 |
| 50–59 | 138 | 32 | 90 | 35 | 228 | 33 |
| 60–69 | 61 | 14 | 31 | 12 | 92 | 13 |
| ≥70 | 26 | 6 | 17 | 7 | 43 | 6 |
| Country of origin | | | | | | |
| Former Netherlands Antilles | 356 | 83 | 165 | 65 | 521 | 76 |
| Dominican Republic | 10 | 2 | 40 | 16 | 50 | 7 |
| Haiti | 23 | 5 | 27 | 11 | 50 | 7 |
| The Netherlands | 11 | 3 | 1 | 0 | 12 | 2 |
| Other | 29 | 7 | 21 | 8 | 50 | 7 |
| Years aware of HIV infection | | | | | | |
| <1 | 13 | 3 | 4 | 2 | 17 | 2 |
| 1–2 | 47 | 11 | 26 | 10 | 73 | 11 |
| 3–4 | 59 | 14 | 23 | 9 | 82 | 12 |
| 5–10 | 111 | 26 | 72 | 28 | 183 | 27 |
| 10–20 | 139 | 32 | 88 | 35 | 227 | 33 |
| >20 | 57 | 13 | 40 | 16 | 97 | 14 |
| Unknown | 3 | 1 | 1 | 0 | 4 | 1 |

***Legend:** MSM=men who have sex with men; *data on children and adolescents are not yet collected.*

## Late presentation

A large proportion of people who have entered care since 2000 were late presenters; in other words, individuals who presented for care with a CD4 count below 350 cells/mm$^3$, or presented with an AIDS-defining event regardless of CD4 count[1]. The proportion of late presenters was 58% among individuals entering care between 2000 and 2016, and remained at a high level (54%, or 20 individuals on average each year) among those entering care in 2017 or later (*Figures 9.2A and 9.2B*). In contrast, there appears to have been a decrease in the proportion of people presenting for care with advanced HIV infection (i.e., with a CD4 count less than 200 cells/mm$^3$ or AIDS). In 2000, 15 (47%) individuals presented with advanced HIV infection, while this proportion was 34% among those presenting for care in 2017 or later (*Figures 9.2C and 9.2D*). In 2019, however, more than half of the people entering care had advanced-stage HIV infection, although the absolute number was similar to the years before. In total, 11% of the individuals who have entered care since 2000 have presented with an AIDS-defining disease.

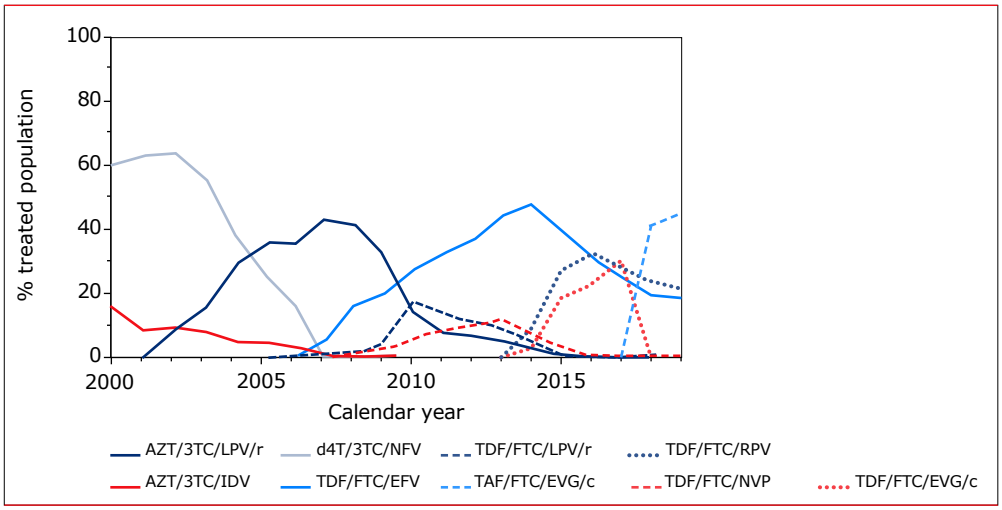
*Figure 9.2: Number and proportion of people classified as presenting with (A, B) late-stage or (C, D) advanced-stage HIV infection at the time of entry into care. From 2017 onwards, 61 (54%) individuals presented with late HIV disease while 38 (33%) were advanced presenters. Late-stage HIV infection: 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 2017 onwards, the stage of infection was unknown for 21 (16%) individuals.*



## Antiretroviral treatment

In total, 1,159 (92%) of the 1,260 registered HIV-1-positive individuals had started antiretroviral treatment by May 2020. Over time, there have been clear shifts in the treatment regimens prescribed in Curaçao (*Figure 9.3*). Of the people who started antiretroviral treatment and were still in care by the end of 2019, 45% were being treated with a combination of tenofovir alafenamide, emtricitabine, and cobicistat-boosted elvitegravir; 21% with tenofovir disoproxil/emtricitabine/rilpivirine; and 19% with tenofovir disoproxil/emtricitabine/efavirenz. The majority (97%) used a once-daily regimen, with 86% being treated with a fixed-dose single tablet regimen.

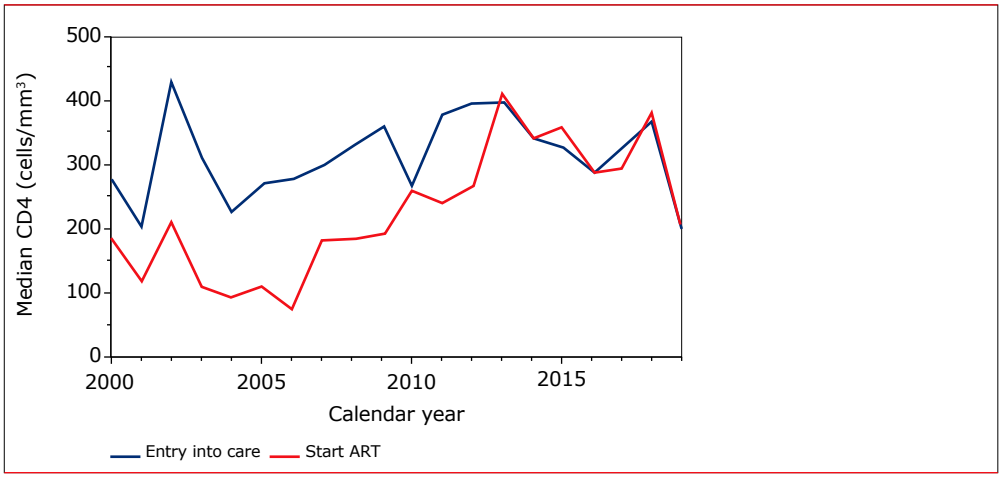
***Figure 9.3:*** *Percentage of individuals treated with antiretroviral therapy (ART) by specific regimens over calendar time. At the end of 2019, 45% of the people were receiving TAF/FTC/EVG/c, 21% RPV/TDF/FTC, and 19% TDF/FTC/EFV.*




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

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 9.4*). Between 2017 and 2019, 33% of those for whom a CD4 count was available at the start of treatment had less than 200 CD4 cells/mm$^3$; 22% had CD4 counts between 200 and 349 cells/mm$^3$; 25% had CD4 counts between 350 and 499 cells/mm$^3$; and 19% had CD4 counts of 500 cells/mm$^3$ or higher. During the same period, 95% of the people entering care received treatment within six months, irrespective of their CD4 count.

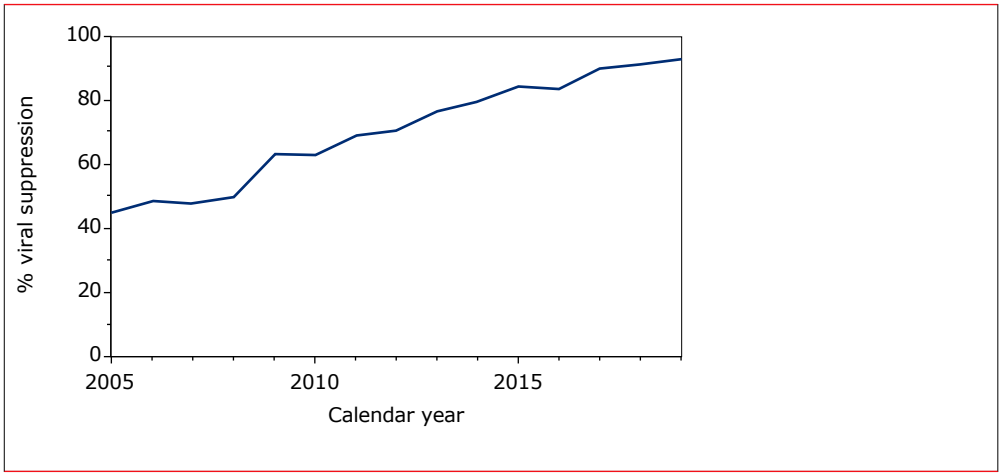
*Figure 9.4: Changes over calendar time in median CD4 counts at entry into care and at the start of antiretroviral treatment (ART). In 2000, median CD4 counts were 275 (interquartile range [IQR], 144-449) cells/mm³ at entry into care and 186 (69-313) cells/mm³ at start of treatment. Between 2017 and 2019, CD4 counts at entry into care were 332 (169-465) cells/mm³ and were very similar, 309 (155-459) cells/mm³, at start of treatment.*




## Treatment outcome

In the total population still in care by the end of 2019, the median current CD4 count was 480 (IQR, 335-678) cells/mm³. CD4 counts were similar between MSM (504 [IQR, 364-723] cells/mm³) and women (516 [366-729] cells/mm³), but men who acquired their infection via other or unknown modes of transmission had lower CD4 counts (426 [265-627] cells/mm³). Among individuals with a viral load measurement, the proportion with HIV RNA levels less than 200 copies/ml, increased from 45% in 2005 to 93% in 2019 (*Figure 9.5*).

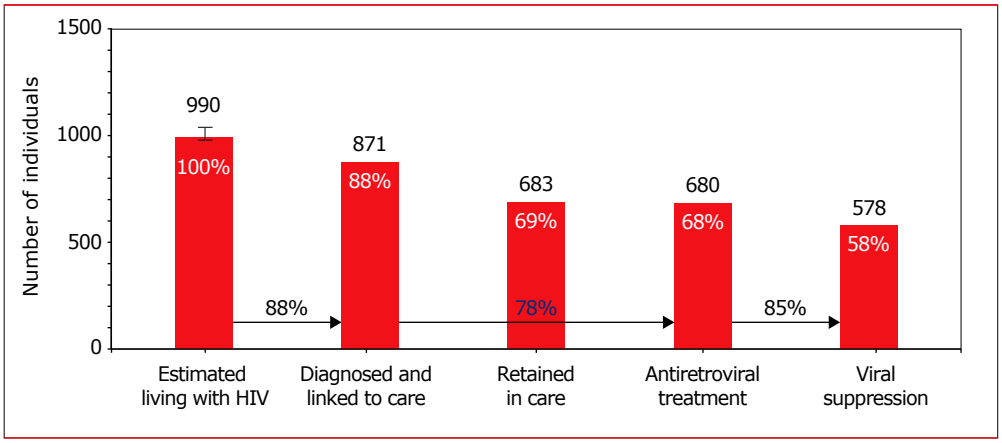
*Figure 9.5: Proportion of people in care with HIV RNA <200 copies/ml at their last viral load measurement in each calendar year.*




## Continuum of HIV care

The total number of people living with HIV by the end of 2019, including those not yet diagnosed, was estimated to be 990 (95% confidence interval [CI] 980-1,030), of whom 122 (110-160) were still undiagnosed (*Figure 9.6*)[2]. In total, 871 individuals, or 88% 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, 683 (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 2019. The majority of these 683 individuals (680, or 78% of those diagnosed and linked to care) had started antiretroviral treatment; 623 (92% of those who started treatment) had an HIV RNA measurement available in 2019 and 578 (93%, or 85% of those treated) had a most recent HIV RNA below 200 copies/ml. Overall, 58% of the total estimated population living with HIV, and 66% of the 871 individuals diagnosed and ever linked to care, had a suppressed viral load. In terms of the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 target for 2020, the current estimate for Curaçao stands at 88-78-85: 88% of people living with HIV know their HIV status, 78% of all people diagnosed receive antiretroviral treatment, and 85% of people receiving treatment have a suppressed viral load[3].

*Figure 9.6: Continuum of HIV care for the total estimated HIV-1-positive population estimated to be living with HIV in Curaçao by the end of 2019. Percentages at the top of the bars are calculated relative to the number living with HIV, while percentages at the bottom correspond to UNAIDS' 90-90-90 targets.*




## Viral suppression

Of the 680 individuals who had started antiretroviral treatment, 102 (15%) did not have a suppressed viral load. On closer inspection, 57 (56%) of these individuals were found to have no documented RNA measurement in 2019. The remaining 45 (44%) people had a viral load measurement in 2019, but with RNA levels exceeding 200 copies/ml. Of these 45 individuals, five had not yet started treatment by the time of their last available viral load measurement in 2019, and five had 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 35 individuals with RNA levels above 200 copies/ml, had been on antiretroviral treatment for longer than six months.

## Lost to care

In total, 257 individuals were lost to care; 69 (27%) before the end of 2009, and 188 (73%) after 2009. The 69 individuals who were lost to care before 2009, 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 69 individuals are still living in Curaçao without needing care or antiretroviral treatment. Of the 188 individuals lost to care after 2009 (i.e., the difference between the second stage (871) and third stage (683) in the care continuum), 32 (12%) were last seen for care in 2018. In total, 59 (31%) of the 188 individuals were born outside the former Netherlands Antilles, including 24 in Haiti and 12 in the Dominican Republic:

for those still in care by the end of 2019, this percentage falls to 24%. 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 HIV-positive individuals 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 the progress towards achieving UNAIDS' 90-90-90 goals for 2020. However, the relatively high proportion of people lost to care is worrisome and may affect underreporting of death and/or outmigration. In addition, the proportion of people entering care with late-stage HIV infection remains high, although the proportion with advanced HIV disease appears to be decreasing.

Of note, data reported for 2019 may not yet be complete. As mentioned above, the hospital moved to a new building at the end of last year, which may have delayed notification to SHM of individuals newly diagnosed and enrolled in care around that time. Also, data collection for 2019, which normally would have been carried out in the first months of 2020, was hampered by a lack of access to electronic patient records for the data collector, as well as by 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 HIV-positive individuals 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 HIV-positive children. 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 also 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 recently been 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, albeit decreasing, 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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3. Joint United Nations Programme on HIV/AIDS (UNAIDS). *90-90-90 An Ambitious Treatment Target to Help End the AIDS Epidemic*.; 2014. http://www.unaids.org/en/resources/documents/2017/90-90-90

# Acknowledgements

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| *Deputy director* | S. Zaheri MSc |

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

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| | T.J. Woudstra |
| *Data quality staff* | D. Bergsma MSc (coordinator) |
| | T. Rutkens |
| | L. van de Sande MA |
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| | K.J. Lelivelt MSc |
| | A. Scheijgrond MSc |
| *Data protection officer* | J.P. Feijt |
| *Patient registration & data collection* | L.G.M. de Groot-Berndsen (coordinator) |

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|---|---|
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| **Communications** | S.F. Boucherie MSc (manager)<br>Y. de Waart |
| *Human resources, finance & administration* | I. Bartels (HR advisor)<br>Y. de Waart (HR assistant)<br>R.P. Geerling (Qualified Controller)<br>H.J.M. van Noort MSc (financial administrator)<br>M.M.T. Koenen (office manager) |

# Publications & presentations

The publications and presentations listed below are those available since the publication of HIV Monitoring Report 2019

## Publications

**Incidence of switching to second-line antiretroviral therapy and associated factors in children with HIV: an international cohort collaboration**
The Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration
*Lancet HIV. Author manuscript; available in PMC 2020 Mar 25.Published in final edited form as: Lancet HIV. 2019 Feb; 6(2): e105–e115. doi: 10.1016/S2352-3018(18)30319-9Correction in: Lancet HIV. 2020 Jan 28*
*https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(18)30319-9/fulltext*

**Cessation of Cigarette Smoking and the Impact on Cancer Incidence in Human Immunodeficiency Virus-infected Persons: The Data Collection on Adverse Events of Anti-HIV Drugs Study**
Shepherd L, Ryom L, Law M, Petoumenos K, Hatleberg CI, d'Arminio Monforte A, Sabin C, Bower M, Bonnet F, Reiss P, de Wit S, Pradier C, Weber R, El-Sadr W, Lundgren J, Mocroft A; Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group
*Clin Infect Dis. 2019 Feb 1;68(4):650-657. doi: 10.1093/cid/ciy508.PMID: 29912335*
*https://academic.oup.com/cid/article/68/4/650/5038118*

**Validation of a Novel Multivariate Method of Defining HIV-Associated Cognitive Impairment**
Underwood J, De Francesco D, Cole JH, Caan MWA, van Zoest RA, Schmand BA, Sharp DJ, Sabin CA, Reiss P, Winston A; COmorBidity in Relation to AIDS (COBRA) Collaboration and the Pharmacokinetic and clinical Observations in PePle over fiftY (POPPY) Study Group
*Open Forum Infect Dis. 2019 May 3;6(6):ofz198. doi: 10.1093/ofid/ofz198. eCollection 2019 Jun*
*https://academic.oup.com/ofid/article/6/6/ofz198/5485702*

**Impact of the M184V/I Mutation on the Efficacy of Abacavir/Lamivudine/Dolutegravir Therapy in HIV Treatment-Experienced Patients**
Olearo F, Nguyen H, Bonnet F, Yerly S, Wandeler G, Stoeckle M, Cavassini M, Scherrer A, Costagiola D, Schmid P, Günthard HF, Bernasconi E, Boeni J, D'arminio Monforte A, Zazzi M, Rossetti B, Neau D, Bellecave P, Rijnders B, Reiss P, Wit F, Kouyos R, Calmy A
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*https://academic.oup.com/ofid/article/6/10/ofz330/5532016*

**Disparities in access to and use of HIV-related health services in the Netherlands by migrant status and sexual orientation: a cross-sectional study among people recently diagnosed with HIV infection**
Bil JP, Zuure FR, Alvarez-Del Arco D, Prins JM, Brinkman K, Leyten E, van Sighem A, Burns F, Prins M.
*BMC Infect Dis. 2019 Oct 29;19(1):906. doi: 10.1186/s12879-019-4477-2. PMID: 31664925*
*https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-019-4477-2*

**Effectiveness of Transmitted Drug Resistance Testing Before Initiation of Antiretroviral Therapy in HIV-Positive Individuals**
Lodi S, Günthard HF, Gill J, Phillips AN, Dunn D, Vu Q, Siemieniuk R, Garcia F, Logan R, Jose S, Bucher HC, Scherrer AU, Reiss P, van Sighem A, Boender TS, Porter K, Gilson R, Paraskevis D, Simeon M, Vourli G, Moreno S, Jarrin I, Sabin C, Hernán MA.
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*https://journals.lww.com/jaids/Fulltext/2019/11010/Effectiveness_of_Transmitted_Drug_Resistance.12.aspx*

**Is reaching 90-90-90 enough to end AIDS? Lessons from Amsterdam**
de Bree GJ, van Sighem A, Zuilhof W, van Bergen JEAM, Prins M, Heidenrijk M, van der Valk M, Brokx P, Reiss P; HIV Transmission Elimination AMsterdam (H-TEAM) Initiative
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**Effectiveness of Transmitted Drug Resistance Testing Before Initiation of Antiretroviral Therapy in HIV-Positive Individuals**
Lodi S, Günthard HF, Gill J, Phillips AN, Dunn D, Vu Q, Siemieniuk R, Garcia F, Logan R, Jose S, Bucher HC, Scherrer AU, Reiss P, van Sighem A, Boender TS, Porter K, Gilson R, Paraskevis D, Simeon M, Vourli G, Moreno S, Jarrin I, Sabin C, Hernán MA
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*https://journals.lww.com/jaids/FullText/2019/11010/Effectiveness_of_Transmitted_Drug_Resistance.12.aspx/*

**Immune reconstitution inflammatory syndrome in HIV late presenters starting integrase inhibitor containing antiretroviral therapy**
Wijting IEA, Wit FWNM, Rokx C, Leyten EMS, Lowe SH, Brinkman K, Bierman WFW, van Kasteren MEE, Postma AM, Bloemen VCM, Bouchtoubi G, Hoepelman AIM, van der Ende ME, Reiss P, Rijnders BJA; ATHENA national observational HIV cohort
*EClinicalMedicine. 2019 Dec 13;17:100210. doi: 10.1016/j.eclinm.2019.11.003. eCollection 2019 Dec. https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30209-3/fulltext*

**Parameter estimates for trends and patterns of excess mortality among persons on antiretroviral therapy in high-income European settings**
Trickey A, van Sighem A, Stover J, Abgrall S, Grabar S, Bonnet F, Berenguer J, Wyen C, Casabona J, d'Arminio Monforte A, Cavassini M, Del Amo J, Zangerle R, Gill MJ, Obel N, Sterne JAC, May MT.
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**Pre-exposure prophylaxis for MSM in the Netherlands: impact on HIV and N. gonorrhoeae transmission and cost-effectiveness**
Reitsema M, Van Hoek AJ, Van Der Loeff MS, Hoornenborg E, Van Sighem A, Wallinga J, Van Benthem B, Xiridou M.
*AIDS. 2019 Dec 27. doi: 10.1097/QAD.0000000000002469. [Epub ahead of print] https://journals.lww.com/aidsonline/Abstract/2020/03150/Preexposure_prophylaxis_for_men_who_have_sex_with.14.aspx*

**Frailty is associated with mortality and incident comorbidity among middle-aged HIV-positive andHIV-negative participants**
Verheij E, Kirk GD, Wit FW, van Zoest RA, Verboeket SO, Lemkes BA, Schim van der Loeff MF, Reiss P.
*J Infect Dis. 2020 Jan 20. pii: jiaa010. doi: 10.1093/infdis/jiaa010. [Epub ahead of print] https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa010/5709696*

**Acute hepatitis C infection among adults with HIV in the Netherlands between 2003 and 2016: a capture–recapture analysis for the 2013 to 2016 period**
Boender TS, Op de Coul E, Arends J, Prins M, van der Valk M, van der Meer JTM, van Benthem B, Reiss P, Smit C.
*Euro Surveill. 2020 Feb;25(7). doi: 10.2807/1560-7917.ES.2020.25.7.1900450. https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.7.1900450*

**The EuroSIDA study: 25 years of scientific achievements**
Laut K, Kirk O, Rockstroh J, Phillips A, Ledergerber B, Gatell J, Gazzard B, Horban A, Karpov I, Losso M, d'Arminio Monforte A, Pedersen C, Ristola M, Reiss P, Scherrer AU, de Wit S, Aho I, Rasmussen LD, Svedhem V, Wandeler G, Pradier C, Chkhartishvili N, Matulionyte R, Oprea C, Kowalska JD, Begovac J, Miró JM, Guaraldi G, Paredes R, Raben D, Podlekareva D, Peters L, Lundgren JD, Mocroft A
*HIV Med. 2020 Feb;21(2):71-83. doi: 10.1111/hiv.12810. Epub 2019 Oct 24 https://onlinelibrary.wiley.com/doi/abs/10.1111/hiv.12810*

**Outcomes of second-line antiretroviral therapy among children living with HIV: a global cohort analysis**
The Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration
*J Int AIDS Soc. 2020 Apr; 23(4): e25477. Published online 2020 Apr 15. doi: 10.1002/jia2.25477 https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25477*

**Risk of recurrent venous thromboembolism in patients with HIV infection: A nationwide cohort study**
*Rokx C, Borjas Howard JF, Smit C, Wit FW, Pieterman ED, Reiss P, Cannegieter SC, Lijfering WM, Meijer K, Bierman W, Tichelaar V, Rijnders BJA, on behalf of the ATHENA observational HIV cohort PLoS Med. 2020 May; 17(5): e1003101.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7224453/

**Decreased time to viral suppression after implementation of targeted testing and immediate initiation of treatment of acute HIV infection among men who have sex with men in Amsterdam**
Dijkstra M, van Rooijen MS, Hillebregt MM, van Sighem A, Smit C, Hogewoning A, Davidovich U, Heijman T, Hoornenborg E, Reiss P, van der Valk M, Prins M, Prins JM, Schim van der Loeff MF, de Bree G
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**Cause-specific mortality after diagnosis of cancer among HIV-positive patients: A collaborative analysis of cohort studies**
Trickey A, May MT, Gill MJ, Grabar S, Vehreschild J, Wit FWNM, Bonnet F, Cavassini M, Abgrall S, Berenguer J, Wyen C, Reiss P, Grabmeier-Pfistershammer K, Guest JL, Shepherd L, Teira R, d'Arminio Monforte A, Del Amo J, Justice A, Costagliola D, Sterne JAC.
*Int J Cancer. 2020 Jun 1;146(11):3134-3146. doi: 10.1002/ijc.32895. Epub 2020 Mar 12. https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.32895*

**Monitoring progress towards the first UNAIDS 90-90-90 target in key populations living with HIV in Norway**
Whittaker R, Case KK, Nilsen Ø, Blystad H, Cowan S, Kløvstad H, van Sighem A
*BMC Infectious Diseases volume 20, Article number: 451 (2020) https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-020-05178-1*

**Impact of frequent testing on the transmission of HIV and N. gonorrhoeae among men who have sex with men: a mathematical modelling study**
Reitsema M, Heijne J, Visser M, van Sighem A, Schim van der Loeff M, Op de Coul ELM, Bezemer D, Wallinga J, van Benthem BHB, Xiridou M.
*Sex Transm Infect. 2020 Aug;96(5):361-367. doi: 10.1136/sextrans-2018-053943. Epub 2019 Dec 4. PMID: 31801895 https://sti.bmj.com/content/96/5/361*

**Human Immunodeficiency Virus Continuum of Care in 11 European Union Countries at the End of 2016 Overall and by Key Population: Have We Made Progress?**
Vourli G, Noori T, Pharris A, Porter K, Axelsson M, Begovac J, Cazein F, Costagliola D, Cowan S, Croxford S, d'Arminio Monforte A, Delpech V, Díaz A, Girardi E, Gunsenheimer-Bartmeyer B, Hernando V, Leierer G, Lot F, Nunez O, Obel N, Op de Coul E, Paraskeva D, Patrinos S, Reiss P, Schmid D, Sonnerborg A, Suligoi B, Supervie V, van Sighem A, Zangerle R, Touloumi G; European HIV Continuum of Care Working Group.
*Clin Infect Dis. 2020 Sep 22:ciaa696. doi: 10.1093/cid/ciaa696. Online ahead of print. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa696/5910027*

**Monocyte and T cell immune phenotypic profiles associated with age advancement differ between people with HIV, lifestyle-comparable controls and blood donors**
De Francesco D, Sabin C, Reiss P, Kootstra N, on behalf of The Co-morBidity in Relation to Aids (COBRA) Collaboration
*Front. Immunol., October 2020, Volume 11, Article 581616 https://doi.org/10.3389/fimmu.2020.581616 https://www.frontiersin.org/articles/10.3389/fimmu.2020.581616/full*

**Estimating the burden of HIV late presentation and its attributable morbidity and mortality across Europe 2010–2016**
The Late Presentation Working Groups in EuroSIDA and COHERE
*BMC Infect Dis 20, 728 (2020). https://doi.org/10.1186/s12879-020-05261-7 https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-020-05261-7#citeas*

**Use of Contemporary Protease Inhibitors and Risk of Incident Chronic Kidney Disease in Persons With Human Immunodeficiency Virus: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study**
Ryom L, Dilling Lundgren J, Reiss P, Kirk O, Law M, Ross M, Morlat P, Andreas Fux C, Fontas E, De Wit S, D'Arminio Monforte A, El-Sadr W, Phillips A, Ingrid Hatleberg C, Sabin C, Mocroft A; Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group
*J Infect Dis. 2019 Oct 8;220(10):1629-1634. doi: 10.1093/infdis/jiz369.PMID: 31504669 https://academic.oup.com/jid/article-abstract/220/10/1629/5532715?redirectedFrom=fulltext*

**Compliance with laboratory monitoring guidelines in outpatient HIV care: a qualitative study in the Netherlands**
Toxopeus DCM, Pell CL, Westrhenen NB, Smit C, Wit FWNM, Ondoa P, Reiss P, Boender TS
*AIDS Care. 2019 Jul;31(7):840-847. doi: 10.1080/09540121.2018.1563280. Epub 2019 Jan 2.PMID: 30602294 https://www.tandfonline.com/doi/full/10.1080/09540121.2018.1563280*

**Lower IQ and poorer cognitive profiles in treated perinatally HIV-infected children is irrespective of having a background of international adoption**
Van den Hof M, Ter Haar AM, Scherpbier HJ, Reiss P, Wit FWNM, Oostrom KJ, Pajkrt D.
*PLoS One. 2019 Dec 5;14(12):e0224930. doi: 10.1371/journal.pone.0224930. eCollection 2019.PMID: 31805059 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0224930*

**HIV-negative Men Who Have Sex with Men have higher CD8+ T-cell Counts and Lower CD4+/CD8+ T-cell Ratios compared to HIV-negative Heterosexual Men**
Verboeket SO, Wit FW, Verheij E, van Zoest RA, Kootstra NA, van der Valk M, Prins JM, Schim van der Loeff MF, Reiss P.
*J Infect Dis. 2020 Jan 31:jiaa048. doi: 10.1093/infdis/jiaa048. Online ahead of print. PMID: 32003801 https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa048/5718997*

**Cognitive function and drivers of cognitive impairment in a European and a Korean cohort of people living with HIV**
De Francesco D, Choi JP, Choi JY, van Zoest RA, Underwood J, Schouten J, Ku NS, Kim WJ, Reiss P, Sabin CA, Winston A; ComorBidity in Relation to AIDS (COBRA) Collaboration and the Korean NeuroAIDS Project
*Int J STD AIDS. 2020 Jan;31(1):30-37. doi: 10.1177/0956462419881080. Epub 2019 Dec 4.PMID: 31801030*
*https://journals.sagepub.com/doi/10.1177/0956462419881080*

**HIV-associated gut dysbiosis is independent of sexual practice and correlates with noncommunicable diseases**
Vujkovic-Cvijin I, Sortino O, Verheij E, Sklar J, Wit FW, Kootstra NA, Sellers B, Brenchley JM, Ananworanich J, Loeff MSV, Belkaid Y, Reiss P, Sereti I.
*Nat Commun. 2020 May 15;11(1):2448. doi: 10.1038/s41467-020-16222-8.PMID: 32415070*
*https://www.nature.com/articles/s41467-020-16222-8*

**Prevalence and Clinical Outcomes of Poor Immune Response Despite Virologically Suppressive Antiretroviral Therapy Among Children and Adolescents With Human Immunodeficiency Virus in Europe and Thailand: Cohort Study**
European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) Study Group in EuroCoord.Clin Infect Dis. 2020 Jan 16;70(3):404-415. doi: 10.1093/cid/ciz253.PMID: 30919882
*https://academic.oup.com/cid/article/70/3/404/5421269*

**Withholding primary PcP prophylaxis in virologically suppressed HIV patients: An emulation of a pragmatic trial in COHERE**
Atkinson A, Zwahlen M, Barger D, d'Arminio Monforte A, De Wit S, Ghosn J, Girardi E, Svedhem-Johansson V, Morlat P, Mussini C, Noguera-Julian A, Stephan C, Touloumi G, Kirk O, Mocroft A, Reiss P, Miro JM, Carpenter JR, Furrer H; Opportunistic Infections Project Working Group of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord
*Clin Infect Dis. 2020 May 25:ciaa615. doi: 10.1093/cid/ciaa615. Online ahead of print.PMID: 32448894*
*https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa615/5843639*

**Decreased All-Cause and Liver-Related Mortality Risk in HIV/Hepatitis B Virus Coinfection Coinciding With the Introduction of Tenofovir-Containing Combination Antiretroviral Therapy**
van Welzen BJ, Smit C, Boyd A, Lieveld FI, Mudrikova T, Reiss P, Brouwer AE, Hoepelman AIM, Arends JE.
*Open Forum Infect Dis. 2020 Jun 25;7(7): ofaa226. doi: 10.1093/ofid/ofaa226. eCollection 2020 Jul.PMID: 32665961*
*https://academic.oup.com/ofid/article/7/7/ofaa226/5862425*

**The impact of immunosuppression on chronic kidney disease in people living with HIV; the D:A:D study**
Ryom L, Lundgren JD, Reiss P, Ross M, Kirk O, Fux CA, Morlat P, Fontas E, Smith C, De Wit S, d'Arminio Monforte A, El Sadr W, Hatleberg C, Phillips A, Sabin C, Law M, Mocroft A; D:A:D Study Group.
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**Human Immunodeficiency Virus Continuum of Care in 11 European Union Countries at the End of 2016 Overall and by Key Population: Have We Made Progress?**
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### Presentations – Orals

**Highlights from the 2019 HIV Monitoring Report**
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**Offering a choice of daily and event-driven PrEP for MSM: a cost-effectiveness analysis**
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**Morbiditeit en mortaliteit bij mensen met hiv in Nederland [Morbidity and mortality among people with hiv in the Netherlands]**
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**Ken je epidemide: hiv in de regio [Know your epidemic: HIV in the region]**
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## Presentations – Posters

**Excellent quality of life among people living with HIV in the Netherlands**
Popping S, Stempher E, Nichols BE, Versteegh L, van de Vijver DAMC, van Sighem A, Boucher CAB, Verbon A.
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**A major reduction in estimated newly-acquired HIV infections shows the Netherlands is on track to achieve the United Nations 2020 incidence target**
van Sighem A,
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# Terminology

**Acute infection**
Any infection that begins suddenly, with intense or severe symptoms, is called acute (or primary). If the illness lasts more than a couple of weeks, it is called chronic.

**Adherence**
Adherence measures how faithfully a person takes all antiretroviral medications at the right time. Poor adherence is one of the main reasons antiretroviral combinations fail.

**AIDS**
Acquired Immunodeficiency Syndrome. A disease caused by a retrovirus, HIV (human immunodeficiency virus), and characterised by failure of the immune system to protect against infections and certain cancers.

**AIGHD**
Amsterdam Institute for Global Health and Development.

**Antibody**
An immune system protein formed in response to invading disease agents such as viruses, fungi, bacteria, and parasites. Usually antibodies defend the body against invading disease agents, however, the HIV antibody does not give such protection.

**Antigen**
An invading substance that may be the target of antibodies.

**Antiretroviral therapy (ART)**
A treatment that may prevent HIV from further damaging the immune system by blocking or hampering the reproduction of the virus.

**Antiviral**
A substance that stops or suppresses the reproduction of a virus.

**ATHENA**
AIDS Therapy Evaluation in the Netherlands project (ATHENA). Stichting HIV Monitoring was founded in 2001 as a result of the successful ATHENA project.

**Baseline**
An initial measurement used as the basis for future comparison. For people infected with HIV, baseline testing includes CD4 count, viral load (HIV RNA), and resistance testing. Baseline test results are used to guide HIV treatment choices and monitor effectiveness of antiretroviral therapy (ART).

**cART**
Combination antiretroviral treatment.

**CD4 (T4) cell**
CD4+ T-lymphocyte, or T4 cell or T-helper cell. A white blood cell that plays a vital role within the immune system and can be infected by HIV. In the course of the HIV infection the number of CD4 cells may drop from normal levels (>500 per $mm^3$) to dangerously low levels (<200 CD4 cells per $mm^3$ blood).

**CDC**
US Centers for Disease Control and Prevention.

**CIb**
Centre for Infectious Disease Control Netherlands, National Institute for Public Health and Environment (www.rivm.nl/cib).

**Co-infection**
When a person has two or more infections at the same time. For example, a person infected with HIV may be co-infected with hepatitis C (HCV) or tuberculosis (TB) or both.

**Comorbidity**
When a person has two or more diseases or conditions at the same time. For example, a person with high blood pressure may also have heart disease.

**DAAs**
Direct-acting antivirals (DAAs) are new-generation drugs that treat hepatitis C virus infection by targeting specific steps in the hepatitis C virus life cycle. There are different classes of DAAs, defined by their mechanism of action and therapeutic target.

**DNA**
Deoxyribonucleic acid. A complex protein that carries genetic information. HIV can insert its own genetic material into the DNA molecules inside human cells and establish dormant infection.

**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 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 the Acquired Immunodeficiency Syndrome (AIDS). HIV attacks and destroys the immune system by entering and destroying the cells that control and support the immune response system.

**HIV type 1 (HIV-1)**
The HIV type responsible for the majority of HIV infections worldwide.

**HIV Vereniging**
Dutch HIV association.

**Immunological failure**
A type of HIV treatment failure. There is no consensus on the definition of immunological failure. However, some experts define immunological failure as the failure to achieve and maintain adequate CD4 counts despite viral suppression.

**Interferon**
Interferons are naturally-occurring proteins (cytokines) produced by immune cells in response to an antigen, usually a virus. Although they don't directly kill viral cells, they boost the immune response by signalling neighbouring cells into action and inhibiting the growth of malignant cells. There are three types of interferons: alpha, beta, and gamma. Laboratory-made interferons are used to treat certain cancers and opportunistic infections. Addition of polyethylene glycol to interferons prolongs the half-life of interferon. Pegylated interferon alpha is used to treat chronic hepatitis C infection.

**Mono-infection**
When a person has only one infection.

**Mortality**
Mortality rate is a measure of the frequency of occurrence of death among a defined population during a specified time period.

**MSM**
Men who have sex with men.

**Nederlandse Federatie Universitair Medische Centra (NFU)**
Netherlands Federation of University Medical Centres.

**Non-AIDS events**
Diseases and clinical events that are not related to AIDS (i.e., that are not listed as being associated with AIDS by the Centers for Disease Control and Prevention) and include conditions such as malignancies, end-stage renal disease, liver failure, pancreatitis, cardiovascular disease.

**Non-nucleoside reverse transcriptase inhibitor (NNRTI)**
Antiretroviral HIV drug class. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind to and block HIV reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

**Nucleoside reverse transcriptase inhibitor (NRTI)**
Antiretroviral HIV drug class. Nucleoside reverse transcriptase inhibitors (NRTIs) block reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

**Nucleotide**
A building block of nucleic acids. DNA and RNA are nucleic acids.

**Nucleotide reverse transcriptase inhibitor (NRTI)**
A type of antiretroviral (ARV) HIV drug. Nucleotide reverse transcriptase inhibitors (NtRTIs) interfere with the HIV life cycle in the same way as NRTIs. Both block reverse transcription. NtRTIs are included in the NRTI drug class.

**NVHB**
Dutch Association of HIV-Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*).

**Person year**
A measure of time used in medical studies that combines the number of persons and their time contribution (e.g., in years) to the study. In the ATHENA cohort, person years generally refer to the cumulative number of years that individuals were followed by SHM.

**Perinatal transmission**
Perinatal transmission of HIV refers to the passage of HIV from an infected mother to her child during pregnancy, labour and delivery, or breastfeeding (through breast milk).

**Protease**
A type of enzyme that breaks down proteins into smaller proteins or smaller protein units, such as peptides or amino acids. HIV protease cuts up large precursor proteins into smaller proteins. These smaller proteins combine with HIV's genetic material

to form a new HIV virus. Protease inhibitors (PIs) prevent HIV from replicating by blocking protease.

**Protease inhibitor (PI)**
Antiretroviral HIV drug class. Protease inhibitors (PIs) block protease (an HIV enzyme). This prevents new HIV from forming.

**Pseudonymisation**
Pseudonymisation is a privacy-enhancing technique that replaces personal identifiers with coded data. Certain identifiers (such as gender and age) are included in the record, but personal information is removed or replaced by a randomised string of characters. The data collected from people living with HIV are stored in SHM's database in a pseudonymised form. Pseudonymisation takes place within the HIV treatment centre and the key to the code is only available to the HIV treating physician.

**Retrovirus**
A class of viruses which includes HIV. Retroviruses are so named because they carry their genetic information in RNA rather than DNA, and the RNA information must be translated "backwards" into DNA.

**Reverse transcriptase**
After infecting a cell, HIV uses an enzyme called reverse transcriptase to convert its RNA into DNA and then replicates itself using the cell's machinery.

**RIVM**
The Netherlands' National Institute for Public Health and the Environment (*Rijksinstituut voor Volksgezondheid en Milieu*).

**Seroconversion**
The change from an absence of HIV antibodies in the blood to the presence of those antibodies.

**SHM**
Stichting HIV Monitoring, the Dutch HIV Monitoring Foundation.

**Sustained virologic response (SVR12 or SVR24)**
A measure of the response to hepatitis C virus (HCV) treatment. SVR12 or SVR24 indicates an undetectable level of HCV in blood 12 or 24 weeks, respectively, after completion of antiviral therapy for chronic HVC infection.

**Sustained viral suppression**
The continuous, long-term suppression of a person's viral load (HIV RNA), generally to undetectable levels, as the result of treatment with antiretroviral drugs.

**Tolerability**
The extent to which a drug's side effects can be tolerated by the patient.

**Viraemia**
The presence of a virus in the blood.

**Virological failure**
A type of HIV treatment failure. Virological failure occurs when antiretroviral therapy (ART) fails to suppress and sustain a person's viral load to less than 200 copies/ml. Factors that can contribute to virological failure include drug resistance, drug toxicity, and poor treatment adherence.

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

**Viral suppression or virological control**
When antiretroviral therapy (ART) reduces a person's viral load (HIV RNA) to an undetectable level. Viral suppression does not mean a person is cured; HIV still remains in the body.

**VWS**
Dutch ministry of Health, Welfare and Sport.

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