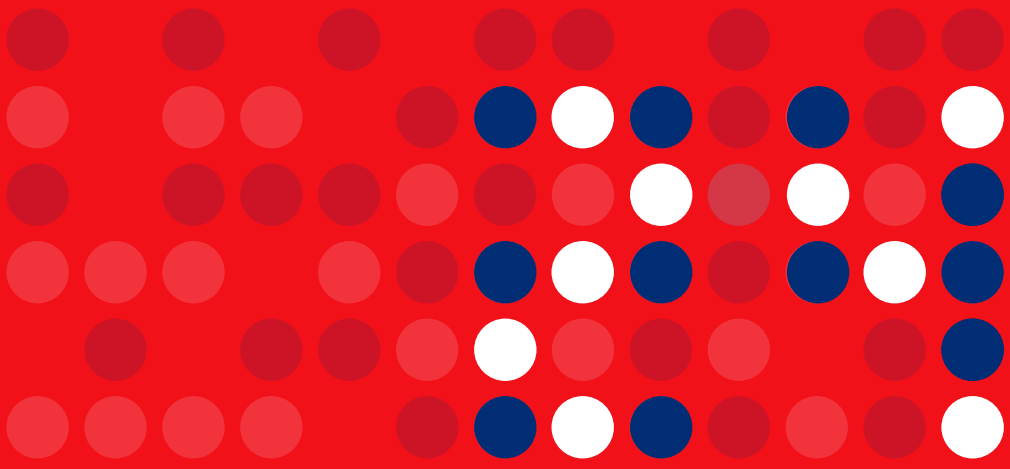
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2024



About stichting hiv monitoring

Stichting hiv monitoring (SHM) is tasked by the Dutch Ministry of Healthcare, Welfare and Sports to continually monitor and report on all aspects of HIV infection and treatment across the population of people with HIV in the Netherlands.

In collaboration with all HIV treatment centres across the Netherlands, SHM has developed a framework for systematically collecting long-term HIV data 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 HIV infection and the effect of treatment. Patient data are collected and entered into the database in a pseudonymised form for analyses and reporting purposes. In this way SHM is able to comprehensively map the population of people with HIV and 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, in people with HIV in care in the Netherlands.

www.hiv-monitoring.nl

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Human Immunodeficiency Virus (HIV) Infection in the Netherlands

Interactive PDF user guide

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

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

Reference numbers

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Monitoring the HIV population in the Netherlands is a collaborative effort between stichting hiv monitoring (SHM) and 23 health insitutes acknoledged by the Dutch Minister of Health, Welfare and Sport as HIV treatment centres or subcentres. In addition, children and adolescents with HIV are monitored in four institutes recognised as paediatric HIV treatment centres.

The following health institutions are recognized as centres for adult HIV care (in alphabetical order of city):

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

The following health institutions are recognized as centers for paediatric HIV care:

	Emma Kinderziekenhuis (EKZ), Amsterdam UMC, locatie AMC	Amsterdam
A	Beatrix Kinderziekenhuis (BKZ), UMCG	Groningen
B	Erasmus MC Sophia Kinderziekenhuis	Rotterdam
C	Wilhelmina Kinderziekenhuis (WKZ), UMC	Utrecht
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1. HIV in the Netherlands

Ard van Sighem, Casper Rokx, Eline Op de Coul, Marc van der Valk

Key findings

2023 at a glance

By the end of 2023, there were an estimated 25,240 people with HIV in the Netherlands, including 1,470 with an undiagnosed HIV infection. Altogether, 86% of this total, and 92% of those diagnosed and ever linked to care, had a suppressed viral load.

Of the 424 people with a new HIV diagnosis, 242 (57%) were men who have sex with men (MSM), 103 (24%) were other men, 66 (16%) were women, and 13 (3%) were trans men and women.

In total, 26% of all people newly diagnosed with HIV were aged 50 years or older at the time of diagnosis.

Of the 22,513 people with HIV-1 in care by the end of 2023, 57% were 50 years or older and 28% were 60 years or older. In total, 70% of people who are still in care have lived with HIV for more than 10 years.

Trends

2010–2023

The registered number of newly diagnosed HIV infections fell by 63% from 1,157 to 424, while among MSM this dropped by 68%, from 760 to 242. The decrease in number of new HIV diagnoses appears to be levelling off after 2020.

2002–2023

The proportion of MSM under the age of 30 at the time of diagnosis increased from 15% to 29%. For those aged 50 or older in this group, this figure rose from 12% to 25%.

2021–2023

Of all people newly diagnosed, 22% were diagnosed within 12 months of HIV infection; in MSM, this proportion was 31%.

In focus: PrEP

In 2023, 15% of MSM and trans men and women with a new HIV diagnosis reported prior use of PrEP, while 51% had not used PrEP. Information on prior use of PrEP was not available for the remaining 35%.

In focus: late-stage HIV 2021-2023

In 2021-2023, 567 (46%) individuals have been diagnosed with late-stage HIV infection. This figure comprises 251 MSM, 187 other men, 118 women, and 11 trans men and women, which is 37%, 64%, 57%, and 29%, respectively, of the total number diagnosed in each group.

In the under-30 years of age category, 25% of MSM, 34% of other men, and 36% of women were diagnosed with late-stage HIV infection. The proportion of individuals with late-stage HIV increased with age: it was found in 54% of MSM, 78% of other men and 44% of women diagnosed at 60 years of age or older.

Introduction

By May 2024, stichting hiv monitoring (SHM) had registered 35,017 individuals with HIV. The vast majority of these (34,044, or 97.2%) agreed to the collection of further clinical data once registered, whereas 973 (2.8%) declined to take part. Among those whose clinical data is collected, most (32,821) are registered with one of the HIV treatment centres in the Netherlands (*Figure 1.1*) while 1,458 are registered with the Curaçao Medical Center in Willemstad, Curaçao (see *Chapter 11*) and 22 with the Horacio Oduber Hospital in Oranjestad, Aruba.

Of those registered in the Netherlands, the vast majority were diagnosed with HIV-1 (31,535, or 96%). Only 102 people were diagnosed with HIV-2, while 61 individuals were found to carry antibodies against both HIV-1 and HIV-2. Data is limited for individuals registered before the start of the AIDS Therapy Evaluation in the Netherlands (ATHENA) study, which accounts for the absence of serological information for most of the remaining 1,123.

The first part of this chapter focuses on the characteristics of people with HIV-1 at the time of diagnosis, and individuals with HIV-1 still in care at the end of 2023. This is followed by a brief overview of trans people with HIV-1. The chapter concludes with an outline of the population with an HIV-2 infection.

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

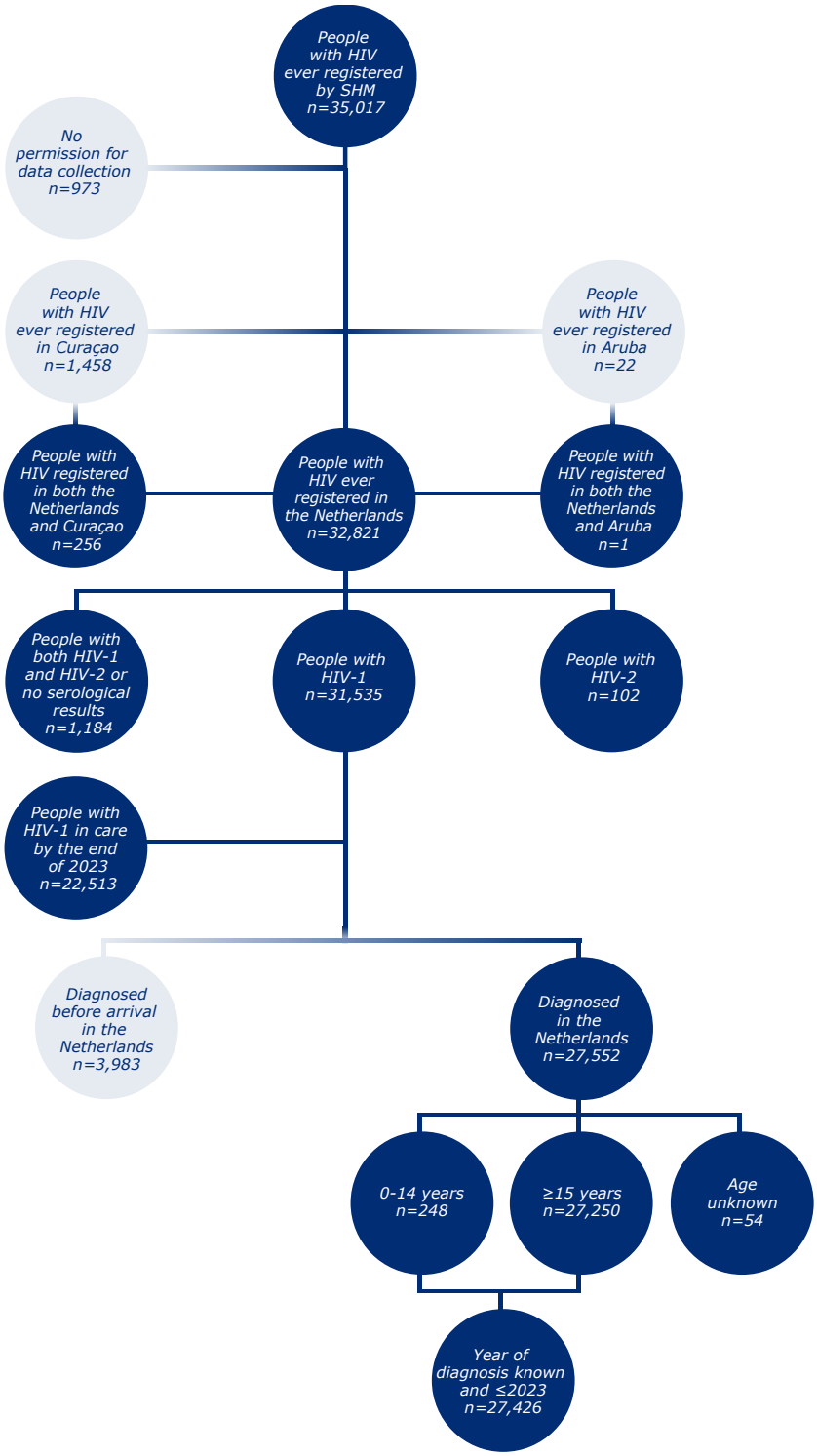
Infection	The moment an individual acquires HIV. The time of infection is often unknown.
Diagnosis	The moment an HIV infection in an individual is confirmed by blood tests. The time of diagnosis can be weeks, months, or years after infection.
Entry into care	The moment an individual with HIV first receives care at an HIV treatment centre. This usually takes place within a few weeks of HIV diagnosis.
Registration	The moment an HIV physician or nurse notifies SHM of an individual with HIV (in care) and the individual's details are recorded in the SHM database. Registration usually takes place within a few months of entering care, but can take longer. Demographic and clinical data from the time of HIV diagnosis can only be collected after registration.

HIV-1

Individuals with HIV-1

Of the 31,535 individuals in the Netherlands who were ever diagnosed with HIV-1, 3,983 (13%) were born abroad and had a documented HIV diagnosis prior to arrival in the Netherlands (*Figure 1.1*). These 3,983 individuals have been excluded from the analyses on newly diagnosed individuals later in this section. The remaining 27,552 individuals were newly diagnosed while living in the Netherlands, or their date of arrival in the country has not yet been recorded in the SHM database.

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



Individuals diagnosed before arriving in the Netherlands

Of the 3,983 individuals who were born abroad and had a documented HIV-1 diagnosis before arriving in the Netherlands, 1,198 (30%) arrived in the Netherlands in 2021-2023, including 314 in 2023 (*Figure 1.2A*). So far, SHM has registered 589 migrants who arrived in 2022, which is an increase of 92% compared with the average annual number of 307 migrants in the other years in the period 2018-2023. Information on diagnosis abroad and date of arrival in the Netherlands has been recorded for all newly registered individuals since early 2018, but is not yet available for everyone included in the SHM database.

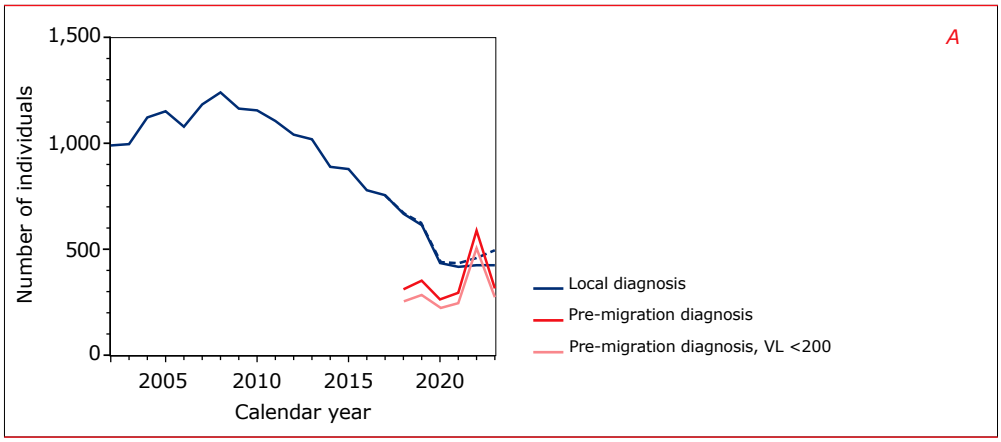
Of the 1,198 migrants who arrived in 2021-2023 with a documented pre-arrival HIV diagnosis, 607 (51%) were men who have sex with men (MSM), 260 (22%) were other men, 295 (25%) were women, and 36 (3%) were trans people. The median age at the time of arrival was 36 years (interquartile range [IQR] 30-43); 103 (9%) were below 25 years of age, including 12 children under the age of 15, while 122 (10%) were 50 years of age or older. In terms of geographic origins, migrants arrived from:

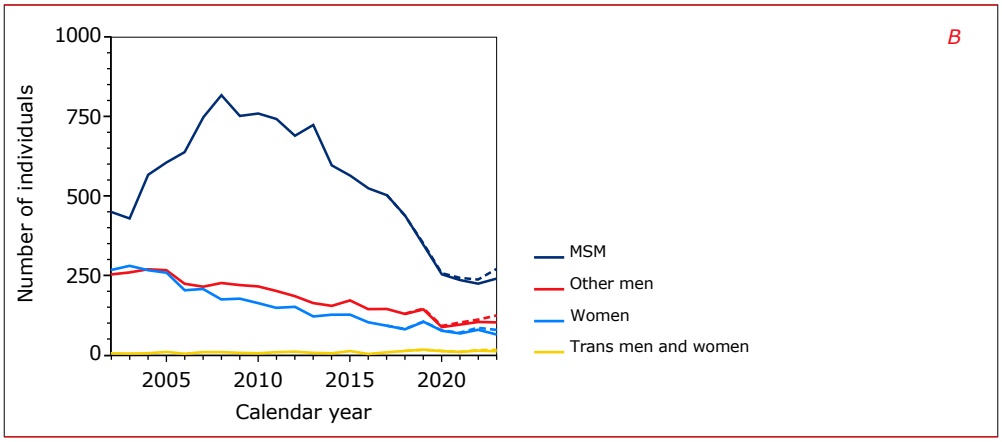
- eastern Europe (385, 32%);
- South America (212, 18%);
- sub-Saharan Africa (138, 12%);
- central Europe (103, 9%);
- western Europe (90, 8%);
- Caribbean (88, 7%);
- north Africa and Middle East (63, 5%);
- south and southeast Asia (61, 5%); and
- other regions (58, 5%).

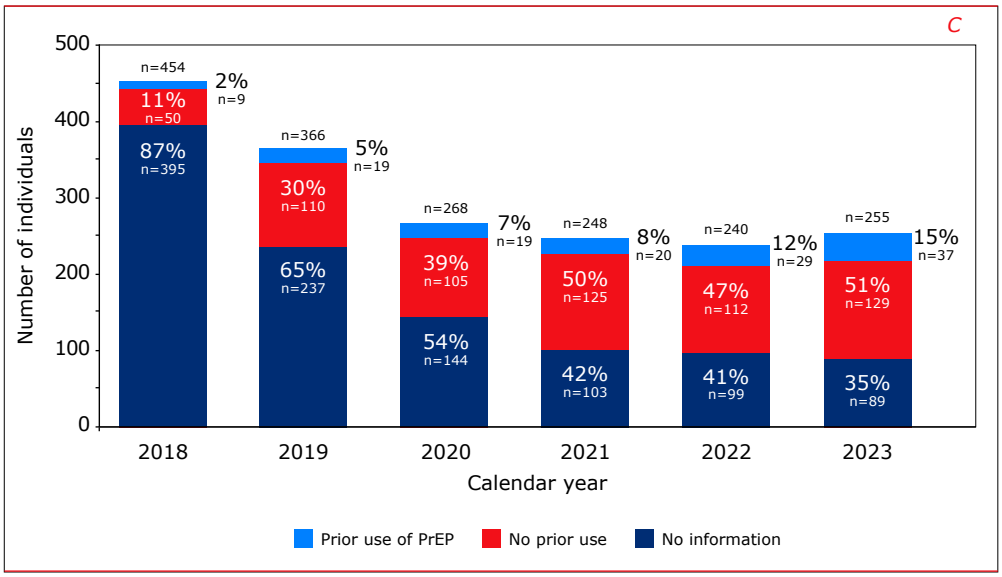
The most commonly reported countries of origin (from where at least 25 individuals with HIV arrived in the Netherlands) were Ukraine (285, 24%), Brazil (68, 6%), Russian Federation (63, 5%), Colombia (53, 4%), Poland (50, 4%), Curaçao (45, 4%), and Turkey (31, 3%). Individuals from Ukraine and the Russian Federation accounted for 237 (40%) and 36 (6%), respectively, of the 589 migrants arriving in 2022; these numbers decreased to 44 (14%) and 12 (4%), respectively, in 2023.

The majority (1,079, or 90%) of the 1,198 migrants had already started antiretroviral therapy (ART) before arriving in the Netherlands. By the time they entered HIV care in the Netherlands, their median CD4 counts were 655 (IQR 440-870) cells/mm^3, while 1,046 individuals had HIV RNA levels below 1,000 copies/ml (88% of the 1,188 who had an available viral load measurement), including 1,024 individuals with RNA levels below 200 copies/ml (86% of the 1,188 with a viral load measurement).

Figure 1.2: *(A) Annual number of individuals newly diagnosed with HIV-1 in the Netherlands (by year of diagnosis) or with documented diagnosis abroad before moving to the Netherlands (by year of arrival), (B) annual number of individuals newly diagnosed with HIV-1 in the Netherlands and aged 15 years or older at the time of diagnosis, according to key population, and (C) annual number of new diagnoses in men who have sex with men (MSM) and trans men and women stratified by whether or not prior use of PrEP was reported. In 2023, MSM accounted for 57% of the annual number of new diagnoses, other men for 24%, women for 16%, and trans men and women for 3%. Dashed lines indicate the number of diagnoses after adjusting for a delay in notification to SHM. VL <200: individuals with documented diagnosis abroad before moving to the Netherlands who already had a suppressed viral load below 200 copies/ml by the time they entered HIV care in the Netherlands.*







Legend: *MSM = men who have sex with men; VL = viral load; PrEP = pre-exposure prophylaxis.*

Individuals newly diagnosed in the Netherlands

Of the 27,552 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, 248 (1%) were diagnosed as children under 15 years of age: they are described in more detail in *Chapter 7*. Among the 27,426 individuals for whom the date or period of diagnosis was known, 27,181 (99%) were diagnosed at 15 years of age or older. Of these 27,181 individuals, 16,211 (60%) were men who have sex with men, 5,804 (21%) were other men, 4,898 (18%) were women, and 268 (1%) were trans men and women (*Table 1.1*).

Table 1.1: *Annual number of HIV-1 diagnoses among who men who have sex with men (MSM), other men, women, trans men and women, and children below 15 years of age. Numbers in the second column for each group are adjusted to reflect a delay in notification to SHM and due to rounding may not add up to the total number reported in the last column.*

Year of diagnosis	MSM		Other men		Women		Trans men and women		<15 years of age		Total	
≤1995	2,112		729		565		15		56		3,477	
1996	367		160		100		3		10		640	
1997	425		190		139		5		11		770	
1998	319		156		125		1		11		612	
1999	335		159		150		5		14		663	
2000	361		206		203		5		15		790	
2001	426		230		241		7		18		922	
2002	450		252		268		6		15		991	
2003	430		257		282		7		21		997	
2004	566		266		269		7		14		1,122	
2005	606		266		260		11		11		1,154	
2006	639		223		206		6		4		1,078	
2007	747		215		209		10		4		1,185	
2008	817		222		177		11		11		1,238	
2009	753		221		178		8		6		1,166	
2010	760		215		165		7		10		1,157	
2011	744		202		150		11		1		1,108	
2012	690		185		153		12		3		1,043	
2013	724		164		123		9		1		1,021	
2014	599		154		128		7		2		890	
2015	566		172		128		14		1		881	
2016	526	526	145	145	104	104	5	5	2	2	782	783
2017	504	505	146	146	94	94	10	10	1	1	755	756
2018	439	440	131	133	82	83	15	15	1	1	668	672
2019	348	351	144	147	106	108	18	18	1	1	617	626
2020	254	259	89	92	77	80	14	14	0	0	434	445
2021	237	245	97	102	69	73	11	12	1	1	415	432
2022	225	237	105	115	81	89	15	16	0	0	426	458
2023	242	273	103	125	66	81	13	16	0	0	424	494
Total	**16,211**	**16,272**	**5,804**	**5,849**	**4,898**	**4,930**	**268**	**274**	**245**	**245**	**27,426**	**27,571**

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

Number of new diagnoses

The annual registered number of new HIV diagnoses steadily fell from approximately 1,200 in 2008 to 434 in 2020 (*Table 1.1; Figure 1.2A*). Thereafter, the decrease appeared to be levelling off and, so far, 424 new HIV diagnoses have been registered for 2023. However, taking into account the backlog[a] in registration of HIV cases, the projected number of new HIV diagnoses in 2023 after adjustment may be as high as 494.

In MSM, the annual number of diagnoses rose to 817 in 2008 and gradually fell to 242 (adjusted 273) in 2023 (*Figure 1.2B*). Among other men and among women, the annual number of new diagnoses has decreased to 103 (adjusted 125) and 66 (adjusted 81), respectively, in 2023. Finally, the number of new diagnoses among trans men and women varied between approximately ten and fifteen in most recent calendar years.

SHM collects data on prior use of pre-exposure prophylaxis (PrEP) in all individuals newly diagnosed with HIV since 2018 (see for more details *Special Report 1.2*). Among MSM and trans individuals, who are the primary target groups of the national PrEP programme, the proportion of people reporting prior use of PrEP has steadily increased over calendar time (*Figure 1.2C*). In 2023, 37 (15%) of the 255 observed new diagnoses in MSM and trans individuals were in people who reported prior use of PrEP, while 129 (51%) people reported never to have used PrEP. For 89 (35%) individuals, information on prior use of PrEP was not available.

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 in people living in the Netherlands at the time they acquired HIV decreased from 905 (95% confidence interval [CI] 870-940) in 2010 to 270 (245-300) in 2020. Thereafter, the number of infections appeared to rise, albeit with considerable uncertainty, to 310 (225-385) in 2023 (*Figure 1.3A*). During the same period, the number of newly acquired HIV infections among MSM fell from 690 (660-725) in 2010 to 155 (135-170), and was 200 (145-260) in 2023 (*Figure 1.3B*).

In other men and in women, the estimated numbers of newly acquired infections in 2010 were 125 (95% CI 110-135) and 90 (80-100), respectively. By 2023 this had dropped in both groups, reaching 80 (35-125) in other men and 25 (5-55) in women (*Figure 1.3C* and *1.3D*).

a As it may take some time before people with HIV are registered in the SHM database by their treating physician, there is a backlog for the most recent calendar years. Based on past trends in registration, adjustment factors for 2016-2023 were estimated using the European Centre for Disease Prevention and Control (ECDC) HIV Platform Tool[1].

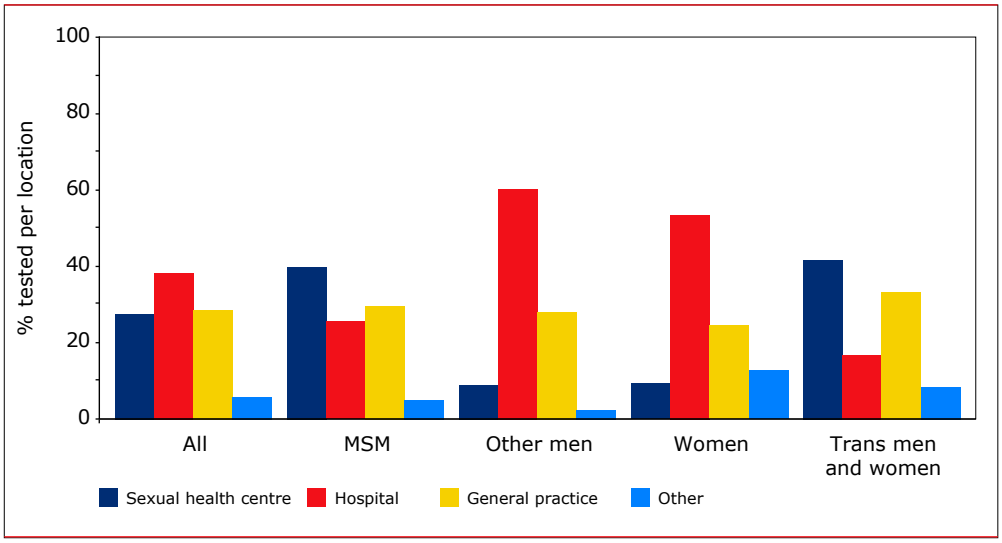
Figure 1.3: *Observed annual number of HIV diagnoses (red) and estimated annual number of newly acquired HIV infections (blue) in: the total population (A), in men who have sex with men (B), in other men (C), in women (D), according to the European Centre for Disease Prevention and Control (ECDC) HIV Platform Tool[1]. The red dashed lines represent the number of diagnoses after adjusting for the delay in notification to SHM, while the pink bands are the uncertainty bounds. The blue dashed lines indicate that estimates in 2020 and later are still uncertain, as these are quite sensitive to the observed number of diagnoses in those years. Estimates are based on adjusted numbers of diagnoses excluding migrants with a documented pre-arrival diagnosis and other migrants who were likely to have acquired their HIV infection before arrival in the Netherlands.*

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 1,202 (95%) of the 1,264 people diagnosed in 2021-2023, while 44 (3%) individuals were known to have been diagnosed abroad. Overall, 331 (27%) of these 1,202 individuals received their first HIV-positive test result at a sexual health centre, 459 (38%) at a hospital, 342 (28%) at a general practice, and 70 (6%) at another location (*Figure 1.4*). Among the 331 individuals diagnosed at sexual health centres, 272 (82%) were MSM, 25 (8%) were other men, 19 (6%) were women, and 15 (5%) were trans men and women, which was similar to the proportions directly reported by sexual health centres for 2023[2]. Among the 459 individuals diagnosed in a hospital, 175 (38%) were MSM, 169 (37%) were other men, 109 (24%) were women, and 6 (1%) were trans men and women, while among the 342 people diagnosed at a general practice 201 (59%) were MSM, 79 (23%) were other men, 50 (15%) were women, and 12 (4%) were trans men and women.

Figure 1.4: *Proportion of individuals diagnosed in 2021–2023, stratified by location of testing and key population. Location of testing in the Netherlands is known for 1,202 (95%) of 1,264 individuals diagnosed, of whom 682 (57%) MSM, 280 (23%) other men, 204 (17%) women, and 36 (3%) trans men and women, while 44 (3%) individuals were diagnosed abroad.*



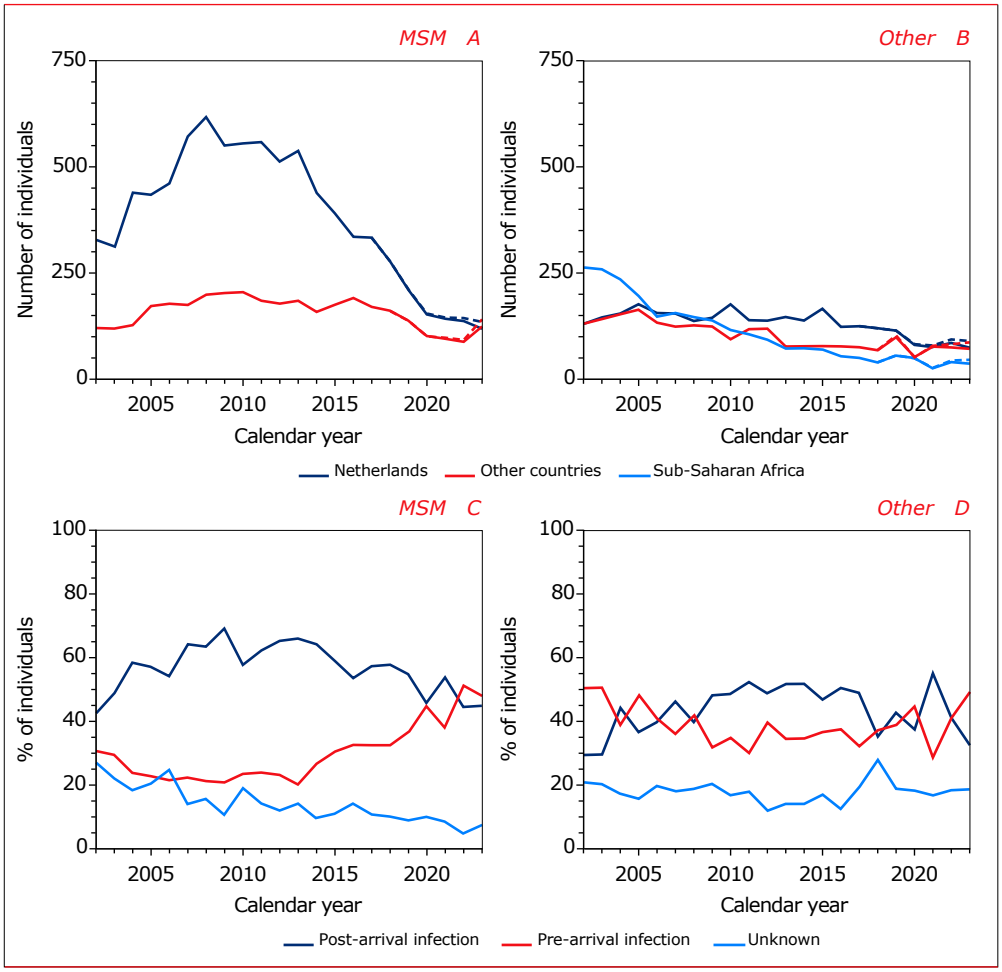
Legend: *MSM = men who have sex with men.*

Geographical region of origin

Of the 19,442 people diagnosed with HIV-1 in 2002-2023 at 15 years of age or older, 11,321 (58%) were born in the Netherlands and 8,121 (42%) outside the Netherlands. Of the 11,866 MSM, 71% originated from the Netherlands, 10% from other European countries, 6% from South America, 4% from the Caribbean, and 3% from south and southeast Asia (*Figure 1.5A*). In recent years (i.e. for diagnoses in 2021-2023), the proportion of MSM of Dutch origin was 57%, down from 72% before 2021, while the proportion of MSM from central Europe was 11%, up from 3% before 2021.

Among the 7,576 individuals other than MSM diagnosed in 2002-2023, 38% originated from the Netherlands, while 32% originated from sub-Saharan Africa, 9% from South America, 8% from other European countries, 5% from the Caribbean, and 4% from south and southeast Asia (*Figure 1.5B*). Between 2021 and 2023, 42% were of Dutch origin (38% before 2021), and 18% originated from sub-Saharan Africa (33% before 2021), while 8% were from central Europe (3% before 2021), and 6% from Eastern Europe (1% before 2021).

Figure 1.5: *Annual number of diagnoses by region of origin and, for individuals born outside the Netherlands, proportion of pre- and post-arrival infections among: (A, C) men who have sex with men (MSM), and (B, D) other people aged 15 years or older at the time of diagnosis. Of the 704 MSM diagnosed in 2021-2023, 398 (57%) originated from the Netherlands, 129 (18%) from other European countries, 60 (9%) from South America, 35 (5%) from the Caribbean, and 31 (4%) from south and southeast Asia. Of the other 560 people diagnosed in 2021-2023, 235 (42%) originated from the Netherlands, 89 (16%) from other European countries, 103 (18%) from sub-Saharan Africa, 48 (9%) from South America, 28 (5%) from the Caribbean, and 27 (5%) from south and southeast Asia.*



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

Overall, 15% of individuals newly diagnosed in 2021-2023 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. Of the people of Dutch origin diagnosed in these years, 9% and 14%, respectively, were living in each of the above PHS regions, while these proportions were 20% and 14%, respectively, for the people born outside the Netherlands. Among MSM, 17% were living in Amsterdam at the time of diagnosis and 14% were living in Rotterdam-Rijnmond, while among other individuals, 12% were living in Amsterdam and 15% in Rotterdam-Rijnmond. Other PHS regions with at least 5% of the new diagnoses in 2021-2023 were Haaglanden (9%, including Den Haag), Hart voor Brabant (7%, including Den Bosch and Tilburg), and Utrecht (5%).

HIV infections acquired before arrival in the Netherlands

Among the 1,264 individuals with an HIV diagnosis in the Netherlands in 2021-2023, 631 (50%) were born outside the Netherlands, of whom 306 MSM and 325 other men, women, or trans individuals. Overall, 269 (43%) most likely acquired their HIV infection before arrival in the Netherlands and 283 (45%) after arrival. The likelihood of pre- or post-migration infection was mainly based on whether an individual was diagnosed with a recent HIV infection, on the CD4 cell count at the time of diagnosis, on the time of arrival in the Netherlands, and on the rate of decline in CD4 cell counts after acquiring HIV[3,4]. For 79 (13%) individuals, there was not enough information to determine this likelihood.

In MSM born outside the Netherlands, the proportion with likely pre-migration infection appears to have increased since 2010 (*Figure 1.5C*). Of the 306 MSM born outside the Netherlands and diagnosed in 2021-2023, 140 (46%) most likely acquired their HIV infection before moving to the Netherlands, 145 (47%) most likely acquired their infection after arrival, while for 21 (7%) the likelihood of pre- or post-migration could not be determined. Among individuals other than MSM, there were no changes over calendar time and in 2021-2023, 129 (40%) most likely acquired HIV before arrival in the Netherlands, 138 (42%) after arrival, and for 58 (18%) the likelihood could not be determined (*Figure 1.5D*).

Age at time of HIV diagnosis

The age at which individuals are diagnosed with HIV has been slowly increasing over time. In 2002, the median age at the time of diagnosis was 36 years (interquartile range [IQR] 29-43); in 2023, it was 39 years (IQR 30-50). In 2002-2023, 19% of individuals who received an HIV diagnosis were aged 50 years or older; in 2023, 26% were 50 years or older (*Figure 1.6*)[5].

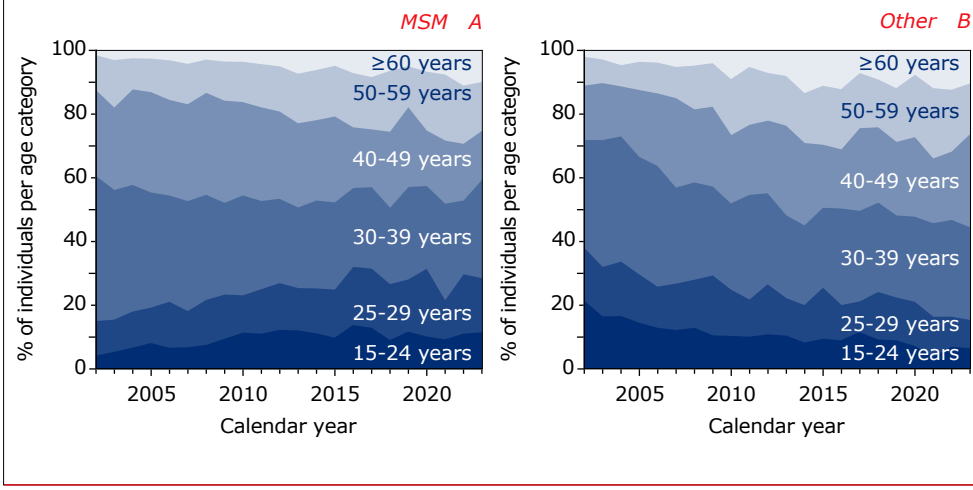
It is worth noting that although the median age at diagnosis in MSM (39 years) did not change between 2002 and 2023, both the proportion diagnosed below 30 years of age and the proportion diagnosed above 50 years of age increased during this period. In 2002, 15% of MSM were younger than 30 years at the time of their diagnosis while 12% were 50 years of age or older; these proportions were 29% and 25%, respectively, in 2023. The increases in the proportions do, however, not reflect increases in the annual number of HIV diagnoses but rather a steeper decrease in diagnoses in the group between 30 and 50 years of age. Between 2010 and 2023, the annual number of diagnoses among MSM 30 to 50 years of age decreased by 76%, from 461 to 112. During the same period, the number of diagnoses decreased from 176 to 69, or 61%, in MSM younger than 30 years, and from 123 to 61, or 50%, in MSM 50 years of age or older.

There were some age differences between MSM, other men, and women diagnosed in 2021-2023. MSM born in the Netherlands were diagnosed at a median age of 46 years (IQR 32-57), while MSM of foreign origin were diagnosed at a much younger median age of 33 years (28-40). Men other than MSM were 44 years (36-55) of age at the time diagnosis, which was somewhat older than the median age of 40 years (31-51) for women. In 2023, 25% of MSM, 28% of other men, and 27% of women were 50 years or older at the time of diagnosis.

HIV diagnoses in people under 25 years of age

Between 2002 and 2023, 2,062 (11%) individuals who received an HIV diagnosis at 15 years of age or older were under 25 years of age (*Figure 1.6*). In 2023, 40 people under 25 years of age (all aged 18 or older) were diagnosed with HIV, which amounted to 9% of all people diagnosed with HIV that year. The number of individuals under 25 years of age diagnosed in 2023 was 28 (12%) among MSM, 5 (5%) among other men, and 5 (8%) among women. Of the 40 young people, 18 (45%) were born in the Netherlands, while six originated from South America, five from central Europe, four from sub-Saharan Africa, and seven from elsewhere.

Figure 1.6: *Age distribution at the time of diagnosis among: (A) men who have sex with men (MSM), and (B) other men and women with HIV-1. In 2002-2023, the proportion of individuals between 15 and 29 years of age changed from 15% to 29% for MSM, and from 38% to 15% for other individuals. During the same period, the proportion of MSM aged 50 years or older at the time of diagnosis changed from 12% to 25%, while these proportions were 11% and 26% for other individuals.*



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

Entry into care

Of the 1,202 individuals diagnosed with HIV in 2021-2023 for whom the diagnosis setting was known, 59% entered HIV care within a week of diagnosis, 83% within two weeks, 95% within four weeks, and 98% within six weeks. For individuals diagnosed in 2023, these proportions were 60%, 83%, 95%, and 99%, respectively. The proportion in care within four weeks was 95% for individuals who received their first HIV-positive test at a sexual health centre, and similar for those who tested HIV-positive in a hospital (97%), at a general practice (94%), or at other locations (90%). The proportion in care within four weeks did neither differ between MSM, other men, and women, nor by age at the time of diagnosis. The proportion in care within four weeks of diagnosis was larger among individuals born in the Netherlands (97%) than among those born abroad (94%).

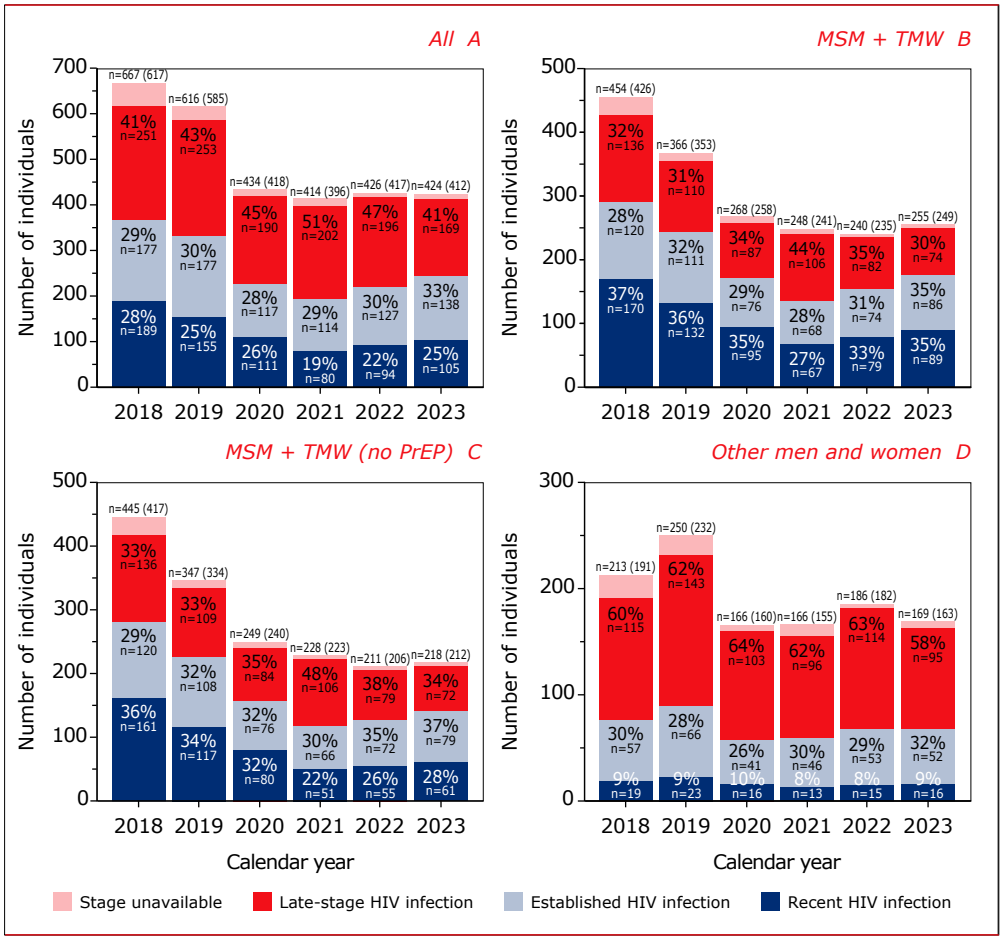
Stage at time of HIV diagnosis

Individuals newly diagnosed with HIV were classified into the following four mutually exclusive stages:

- recent HIV infection: evidence of having acquired HIV in the 12 months prior to diagnosis, based on having (i) a negative or indeterminate blot at the time of diagnosis, or (ii) a last negative test at most 12 months prior to diagnosis.
- established HIV infection: diagnosed with a CD4 count above 350 cells/mm^3, no AIDS-defining event at the time of diagnosis, and no evidence of having acquired HIV in the previous 12 months.
- late-stage HIV infection: diagnosed with a CD4 count below 350 cells/mm^3 or an AIDS-defining event regardless of CD4 count, and no evidence of having acquired HIV in the previous 12 months[6].
- stage unavailable: no evidence of having acquired HIV in the previous 12 months, no AIDS-defining event at the time of diagnosis, and no CD4 count available at the time of diagnosis.

The proportion of individuals diagnosed with recent HIV infection decreased from 28% in 2018 to 19% in 2021 and then increased to 25%, while the proportion with late-stage HIV was 41% in 2018, increased to 51% in 2021 and was 41% in 2023 (*Figure 1.7A*). Meanwhile, there were only minor changes in the proportion with established HIV infection. On closer inspection, these changes were to some extent the result of a decreasing number of MSM and trans men and women relative to the total annual number of newly diagnosed HIV infections, from 68% in 2018 to 60% in 2023. Besides, changes in the number and proportion of MSM and trans men and women diagnosed with recent, established, or late-stage HIV were also the result of the increasing share of people reporting prior use of PrEP among the annual number of new HIV diagnoses (*Figure 1.7B* and *1.7C*). In other men and women, changes in the proportion diagnosed in each of these three stages were less pronounced (*Figure 1.7D*).

Figure 1.7: *Annual number and proportion of individuals diagnosed with recent, established, or late-stage HIV infection in 2018–2023 (A) in the total population aged 15 years or older at the time of diagnosis, (B) in men who have sex with men (MSM) and trans men and women, (C) in MSM and trans men and women excluding those who reported prior use of pre-exposure prophylaxis, and (D) in other men and women. Recent HIV infection was (i) a negative or indeterminate blot at the time of diagnosis, or (ii) a last negative test at most 12 months or 6 months prior to diagnosis; established HIV infection: no recent HIV infection, CD4 counts above 350 cells/mm³, and not having AIDS at the time of diagnosis; late-stage HIV infection: no recent HIV infection, CD4 counts below 350 cells/mm³ or having AIDS, regardless of CD4 count. Numbers above the bars are the total number of diagnoses in each year, while numbers in brackets are the number of diagnoses excluding individuals whose stage at diagnosis is unavailable. Percentages inside the bars are relative to the number in brackets for late-stage and established infection, and relative to the total number of diagnoses for recent HIV infection.*

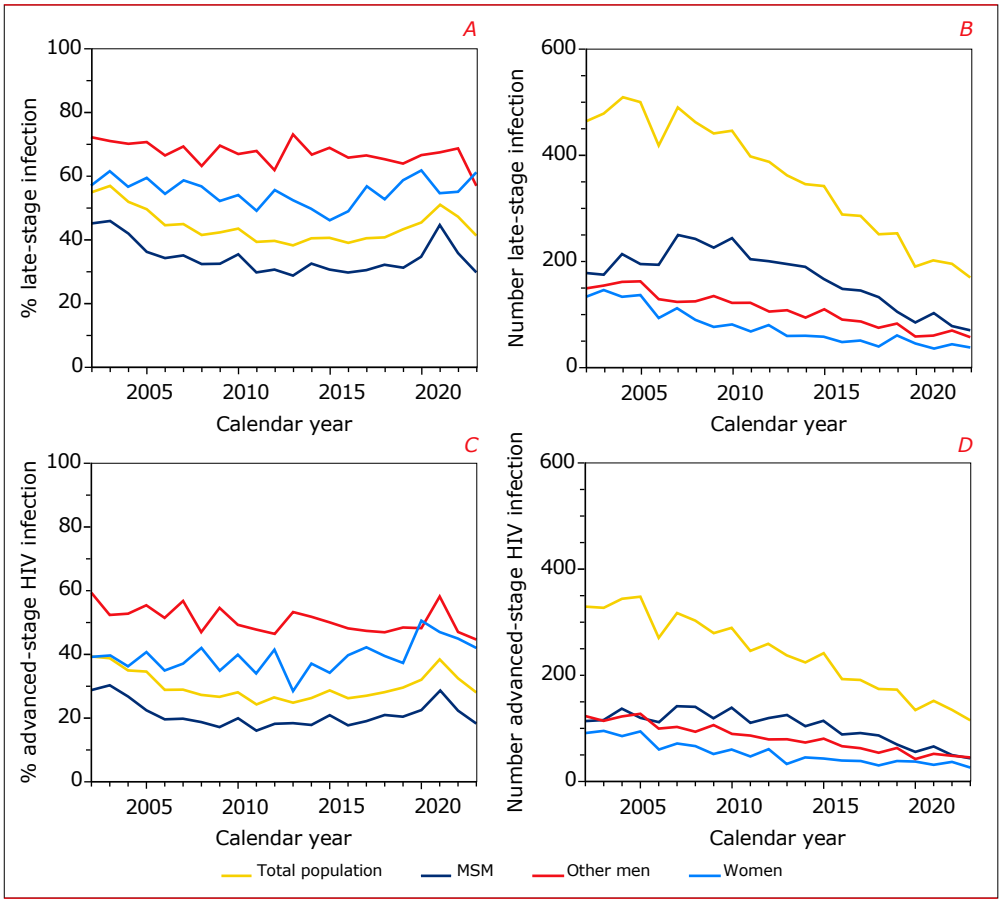


Legend: *MSM = men who have sex with men; TMW = trans men and women; PrEP = pre-exposure prophylaxis.*

Late diagnosis

Overall, 46% of the individuals diagnosed in 2021-2023 had a late-stage HIV infection at the time of diagnosis. Over time, the proportion of late-stage HIV diagnoses decreased from 55% in 2002 to a nadir of 38% in 2013, increased to 51% in 2021, and then again decreased to 47% in 2022, and 41% in 2023 (*Figure 1.8A*). This increase between 2013 and 2021 was mainly due to changes in the proportion of MSM diagnosed with late-stage HIV (see also *Figure 1.7B*). The proportion of individuals diagnosed with advanced HIV disease (i.e. with a CD4 count below 200 cells/mm^3 or AIDS-defining event, and no evidence of having acquired HIV in the previous 12 months), has followed a similar pattern, and reached 28% in 2023 (*Figure 1.8C*). Although the downward trend in these *proportions* appears to have halted after 2013, the *number* of individuals diagnosed with late-stage or advanced-stage HIV infection continued to decrease, albeit gradually (*Figure 1.8B* and *1.8D*). It is worth noting that although newly diagnosed MSM had the lowest proportion of late-stage HIV infections, they accounted for 251 (44%) of all 567 individuals diagnosed with late-stage HIV in 2021-2023.

Figure 1.8: *Proportion and number of individuals classified as having: (A, B) late-stage, or (C, D) advanced-stage HIV infection at the time of diagnosis. In 2023, 169 (41%) individuals were diagnosed with late-stage HIV infection: 70 (30%) men who have sex with men (MSM), 57 (56%) other men, 38 (61%) women, and 4 (33%) trans men and women. During the same year, 115 (28%) individuals were diagnosed with advanced-stage HIV infection: 43 (18%) MSM, 45 (45%) other men, 26 (42%) women, and 1 (8%) trans individual. 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 therapy was sometimes missing, the stage of the HIV infection could not be determined for all individuals. In 2021–2023, the stage of infection was unknown for 39 (3%) 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 2021-2023, 251 (37%) MSM, 187 (64%) other men, 118 (57%) women and 11 (29%) trans men and women had a late-stage HIV infection. Late-stage HIV infections, in relative terms, were most common among people originating from sub-Saharan Africa (62%, or 71 individuals), from south and southeast Asia (59%, 33 individuals), or from central Europe (50%, or 59 individuals) (*Table 1.2*).

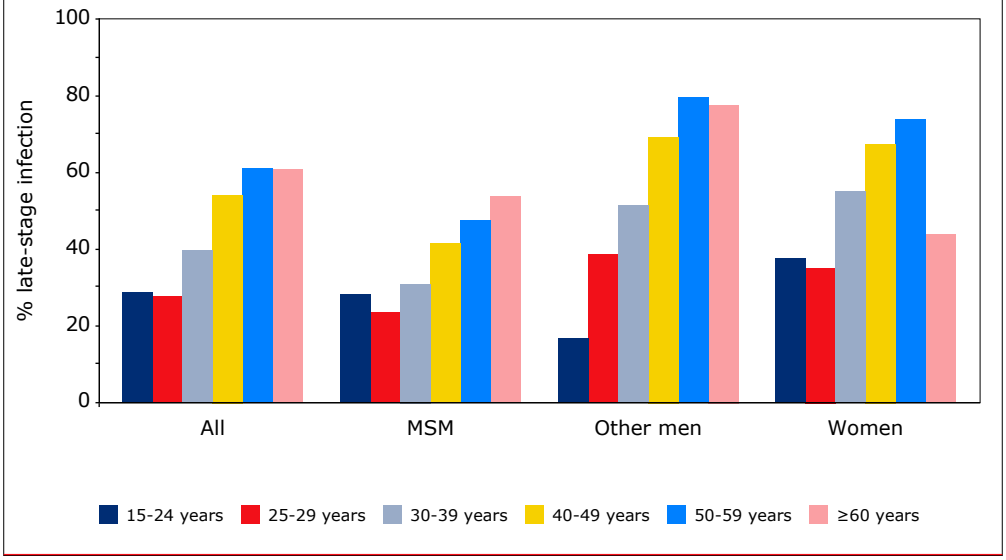
Older age at the time of diagnosis was also associated with a higher proportion of late-stage HIV infection. Of those diagnosed in 2021-2023, late-stage HIV was seen in 54% of MSM, 78% of other men, and 44% of women aged 60 years or older, compared with 25% of MSM, 34% of other men, and 36% of women diagnosed below the age of 30 years (*Table 1.2; Figure 1.9*).

Table 1.2: *Characteristics of the 567 individuals with a late-stage HIV infection among the 1,264 individuals diagnosed with HIV in 2021–2023. In total, as a result of missing CD4 cell counts at diagnosis, it was not possible to classify whether 39 (3%) individuals (17 MSM, 13 other men, 8 women, and 1 trans individual) had a late-stage HIV infection. For each of the five groups (MSM, other men, women, trans men and women, and total), percentages represent the proportion with late-stage infection of the total number of individuals diagnosed in each category listed in the first column.*

	MSM (n=687)		Other men (n=292)		Women (n=208)		Trans men and women (n=38)		Total (n=1,225)	
	n	%	n	%	n	%	n	%	n	%
Overall	251	37	187	64	118	57	11	29	567	46
Age at diagnosis (years)										
15–24	20	28	1	17	9	38	0	0	30	29
25–29	26	24	10	38	7	35	3	33	46	28
30–39	60	31	40	51	33	55	6	32	139	40
40–49	51	41	54	69	31	67	0	0	136	54
50–59	58	48	47	80	31	74	2	67	138	61
60–69	24	45	23	77	5	36	0	0	52	54
≥70	12	86	12	80	2	100	0	0	26	84
Region of origin										
Western	*156*	*37*	*101*	*66*	*35*	*45*	*2*	*33*	*294*	*44*
The Netherlands	146	37	99	67	32	44	2	33	279	45
Other western*	10	29	2	33	3	60	0	0	15	33
Non-Western	*95*	*36*	*86*	*62*	*83*	*64*	*9*	*28*	*273*	*48*
Sub-Saharan Africa	2	12	27	77	42	67	0	0	71	62
Central Europe	31	41	20	69	7	58	1	100	59	50
South America	19	33	9	64	7	44	4	24	39	38
Caribbean	15	44	5	38	2	25	2	33	24	39
South and southeast Asia	16	53	8	57	7	88	2	50	33	59
North Africa and the Middle-East	5	29	8	53	3	75	0	0	16	43
Other/unknown	7	22	9	50	15	79	0	0	31	43
Location of HIV diagnosis										
Sexual health centre	52	19	13	54	4	21	4	27	73	22
Hospital	118	69	126	77	83	77	3	50	330	73
General practice	62	31	38	49	20	42	2	18	122	36
Other/unknown	19	39	10	37	11	33	2	33	42	37
Last negative test†										
(1,2] years	26	35	4	27	3	27	1	17	34	32
(2–4] years	20	33	10	59	10	63	4	67	44	44
>4 years	69	65	25	69	28	65	0	0	122	65
Never tested / not available	136	60	148	76	77	63	6	60	367	66

Legend: *MSM = men who have sex with men; *includes western Europe, North America, Australia and New Zealand; †all individuals with a negative test within 1 year prior to diagnosis are classified as recent HIV infection.*

Figure 1.9: Proportion of individuals diagnosed with late-stage HIV infection stratified by age category at the time of diagnosis for those diagnosed in 2021-2023 or later.



Legend: MSM = men who have sex with men.

Late-stage HIV was also observed more frequently in people who received their HIV diagnosis at a hospital (73%) than among those who were tested at a general practice (36%), a sexual health centre (22%), or another testing location (37%). These proportions did not change over time except for individuals diagnosed at a hospital, in whom the proportion with late-stage HIV increased from 64% in 2010 to 77% in 2021 and was 68% in 2023. Late diagnosis was less common (38%) among people who had a most recent negative HIV test one to four years prior to their diagnosis than among individuals whose last negative test was more than four years previously (65%) or who did not report ever having tested for HIV before (66%).

Late diagnosis and hospitalisation

Hospitalisation around the time of HIV diagnosis was more frequently reported for individuals diagnosed with late-stage HIV infection than for those with recent or established HIV infection (*Table 1.3*). Among the 567 people diagnosed with late-stage HIV infection in 2021-2023, 243 (43%) were hospitalised within a year of diagnosis, including 203 (36%) as a direct result of their HIV infection. In contrast, only 64 (10%) of the 658 individuals diagnosed with recent or established HIV infection were hospitalised within a year of diagnosis, including

21 (3%) hospitalisations due to HIV. Within the group of people with late-stage HIV infection, hospitalisation was most frequently recorded among those who were diagnosed with AIDS (*Table 1.3*).

Late diagnosis and mortality

Of the 567 individuals diagnosed with late-stage HIV infection in 2021-2023, 20 (4%) died within a year of diagnosis, including 13 (2%) who died of AIDS (*Table 1.3*). Among the 658 people diagnosed with recent or established HIV infection, 4 (1%) died with a year of diagnosis, including no one who died of AIDS.

***Table 1.3:** Number and proportion of individuals diagnosed in 2021–2023 who were hospitalised or who died within a year of diagnosis, stratified by stage of infection.*

		Hospitalisation				Death			
		Total		HIV-related		Total		AIDS-related	
Stage	**n**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Recent or established HIV infection	658	64	10	21	3	4	1	0	0
Late-stage HIV infection	567	243	43	203	36	20	4	13	2
CD4 200–349, no AIDS	165	20	12	10	6	0	0	0	0
CD4 <200, no AIDS	188	53	28	30	16	5	3	3	2
AIDS	214	170	79	163	76	15	7	10	5

***Note:** AIDS = AIDS-defining event.*

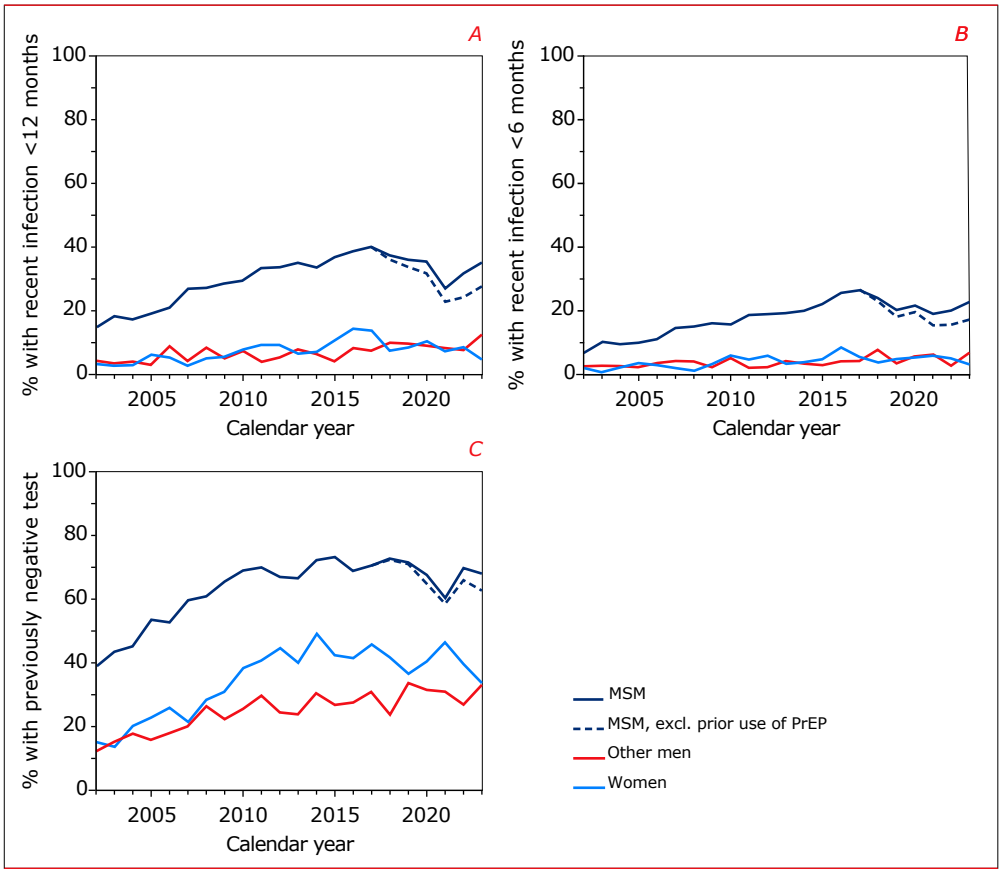
Late diagnosis and prior use of PrEP

Among MSM and trans men and women diagnosed in 2021-2023, 262 (36%) were diagnosed with a late-stage HIV infection (*Figure 1.7B*). When people who reported prior use of PrEP were excluded, the number diagnosed with late-stage HIV reduced to 257, but this represented a slightly higher proportion, 40%, of those diagnosed (*Figure 1.7C*).

Recent infection

Although many individuals are diagnosed with a late-stage HIV infection, a considerable proportion of people receive their HIV diagnosis early in the course of their infection. In total, among the individuals diagnosed in 2021-2023, 22% had evidence of having acquired their HIV infection in the 12 months prior to diagnosis, while 14% had evidence of having acquired HIV in the six months prior to diagnosis (Figure 1.10A and *1.10B*). For MSM, these proportions were 31% and 21%, respectively, while they were similar for trans men and women, 36% and 15%, respectively. Among other men and among women these proportions were considerably lower (8% and 5%, respectively).

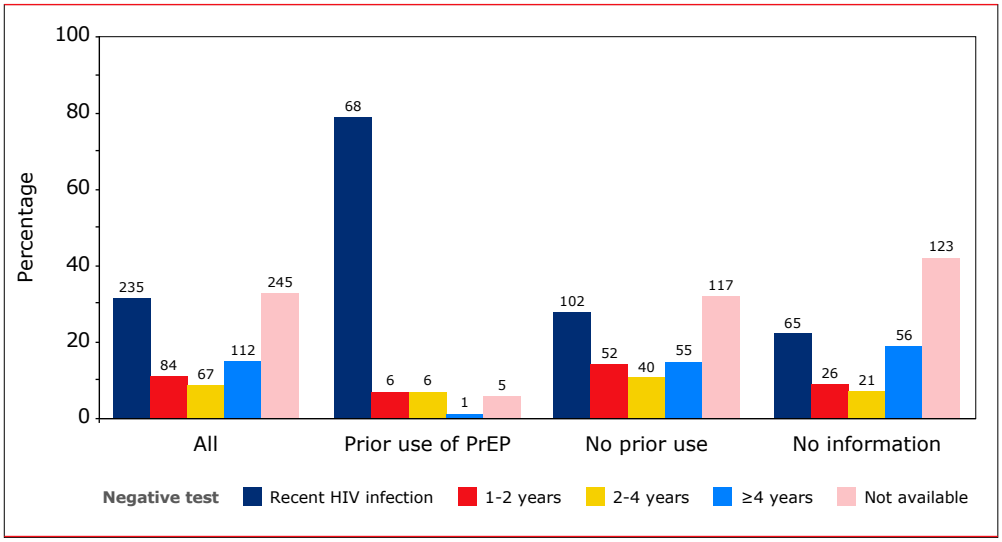
Figure 1.10: *Proportion of people diagnosed (A) with evidence of having acquired their HIV infection at most 12 months prior to their diagnosis, (B) at most 6 months prior to their diagnosis, (C) with a previously negative test at any time prior to their diagnosis. Evidence of a recent infection was (i) a negative or indeterminate blot at the time of diagnosis, or (ii) a last negative test at most 12 months or 6 months prior to diagnosis. In total, 85 (35%) men who have sex with men (MSM), or 57 (28%) MSM when excluding those who reported prior use of pre-exposure prophylaxis (PrEP), 13 (13%) other men, 3 (5%) women, 4 (31%) trans men and women, and 105 (25%) of all 424 individuals diagnosed in 2023 had evidence of having acquired HIV at most 12 months before diagnosis. In the same year, 55 (23%) MSM, or 35 (17%) MSM when excluding those who reported prior use of PrEP, 7 (7%) other men, 2 (3%) women, 2 (14%) trans men and women, and 65 (15%) of all 424 individuals had evidence of having acquired HIV at most six months before diagnosis.*



Legend: *MSM = men who have sex men; PrEP = pre-exposure prophylaxis.*

It is worth noting that the proportion of MSM with evidence of having acquired their HIV infection in the 12 months prior to diagnosis was 37% in 2018-2020, appeared to be lower, 27%, in 2021, and then increased to 32% in 2022 and 35% in 2023 (*Figure 1.10A*). This increase after 2021 appeared to be to a large extent due to the growing proportion of MSM reporting prior use of PrEP. When these MSM were excluded the proportions with a recent HIV infection were considerably lower, 22% in 2021, 24% in 2022, and 28% in 2023. A similar reduction in the proportion with recent HIV infection after excluding individuals reporting prior use of PrEP was seen in the combined population of MSM and trans men and women (*Figure 1.7B* and *1.7C*). The reason that the proportion with recent HIV infection decreased after excluding people reporting prior use of PrEP is that in this group of former PrEP users, the proportion diagnosed with recent HIV infection was much higher, 79%, than in people who never used PrEP or for whom no information on PrEP use was available (*Figure 1.11*).

Figure 1.11: *Proportion of men who have sex with men (MSM) and trans men and women diagnosed in 2021–2023 whose most recent negative HIV test was less than 1 year (i.e. recent HIV infection, including those with negative or indeterminate blot at the time of diagnosis), 1 to 2 years, 2 to 4 years, or more than 4 years prior to their HIV diagnosis, or who reported never having tested for HIV, overall and stratified by whether or not they reported prior use of PrEP. Numbers above the bars are the number of individuals diagnosed in each category and represented by each bar.*

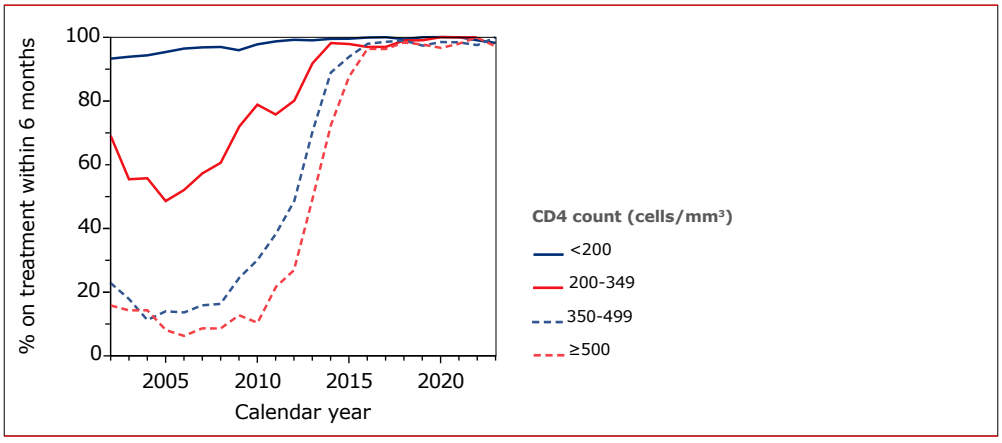


The proportion of people with a recorded previously negative HIV test any time before their HIV diagnosis increased from 25% in 2002 to 54% in 2023. MSM were more likely to have a previously negative HIV test than other men and women. In 2023, 68% of MSM newly diagnosed with HIV had a previously negative test, while this proportion was 33% both in other men and in women (*Figure 1.10C*). Overall, of MSM diagnosed in 2021-2023, 66% reported a previously negative test, meaning that a third (34%) never had an HIV test before their HIV diagnosis (see also *Figure 1.11*). The proportion with a known previously negative test was highest among those diagnosed at a sexual health centre (81%), compared with 37% of those diagnosed in a hospital, and 51% of those diagnosed at a general practice.

Antiretroviral therapy

Of the 27,181 individuals diagnosed at 15 years of age or older, 26,332 (97%) had started antiretroviral therapy (ART) by the end of 2023. Over the past two decades, ART has increasingly been initiated earlier in the course of an HIV infection (*Figure 1.12*). This is a consequence of people being diagnosed sooner, on average, after acquiring their HIV infection, and treatment guidelines recommending immediate initiation of ART, regardless of CD4 count[7]. Prior to 2015, individuals with higher CD4 counts were less likely to start therapy shortly after an HIV diagnosis, but after the treatment guidelines changed that year, there is now almost no delay between diagnosis and start of therapy. In 2021-2023, 98% of people who were diagnosed with HIV that year started ART within six months.

Figure 1.12: *Proportion of individuals who started antiretroviral therapy (ART) within six months of their HIV diagnosis by CD4 count at the time of diagnosis. Of all individuals diagnosed in 2021-2023, 98% had started ART within six months of diagnosis.*



Time between HIV infection and viral suppression

Individuals with a suppressed viral load below 1,000 copies/ml cannot transmit HIV to other people (undetectable equals untransmittable, or U=U)[8–11]. Hence it is crucial to minimise the time between the moment a person acquires HIV and the point at which they achieve this threshold[12], not only for people with HIV, but also from a public health perspective. However people with HIV must first be diagnosed, then linked to care, and subsequently start therapy in order to be able to reach viral suppression.

Over time there have been significant improvements in several of these steps in the HIV care continuum. Between 2010 and 2023, the median time from diagnosis to reaching a viral load level below 200 copies/ml decreased from 0.84 years (IQR 0.37-2.59) to 0.18 years (IQR 0.13-0.29), or from 10.0 months (IQR 4.5-31.1) to 2.1 months (IQR 1.5-3.5). The median time to reaching a viral load level below 1,000 copies/ml was somewhat shorter, being 0.54 years (IQR 0.24-2.07) years, or 6.5 months (IQR 2.9-24.8), in 2010, and 0.15 years (IQR 0.11-0.23), or 1.8 months (IQR 1.3-2.7) in 2023. This decrease in time to viral suppression was achieved mainly as a result of starting therapy sooner after entry into care, and individuals with HIV reaching viral suppression faster once therapy had begun. The time from infection to diagnosis was the greatest contributing factor to the delay between acquiring HIV and achieving viral suppression. In 2023, this was estimated to be a median of 2.7 years (IQR 1.3-5.1).

Population in care

In total, 22,513 (71%) of the 31,535 individuals with HIV-1 ever registered in the Netherlands were known to be in clinical care by the end of 2023 (*Figure 1.1*; *Table 1.4*). People were considered to be in clinical care if they had visited their treating physician in 2023, or had a CD4 count or HIV RNA measurement in that year, and were still living in the Netherlands. Of the 9,022 people who were not in care by the end of 2023, 4,201 (47%) had died, of whom 2,296 (55%) died before the end of 2013. Another 2,577 (29%) had moved abroad, including 1,077 (42%) who did so before the end of 2013. The remaining 2,244 (25%) individuals:

- were lost to care (2,106, 94%);
- were only diagnosed with HIV in 2024 (68, 3%);
- had only moved to the Netherlands in 2024 (19, 1%); or
- had newly entered care in 2024 (51, 2%).

Of the people who moved abroad, 2,065 (80%) had RNA levels below 200 copies/ml at their last viral load measurement; in those lost to care, that figure was 1,368 (65%).

Table 1.4: Characteristics of the 22,513 people with HIV-1 in clinical care by the end of 2023.

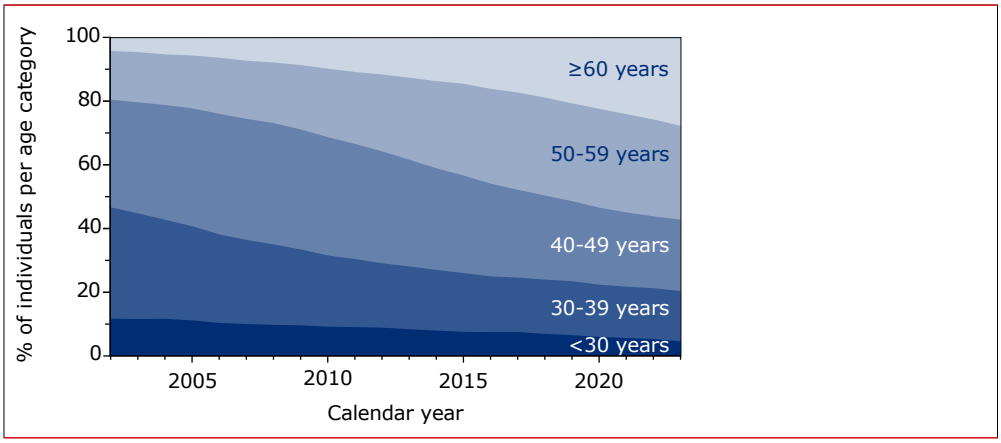
	MSM (n=13,855, 62%)		Other men (n=4,092, 18%)		Women (n=4,242, 19%)		Trans men and women (n=324, 1%)		Total (n=22,513)	
	n	%	n	%	n	%	n	%	n	%
Transmission										
Sex with men	12,803	92	0	0	3,682	87	256	79	16,741	74
Sex with women	11	0	2,632	64	1	0	7	2	2,651	12
Sex, unspecified	952	7	107	3	0	0	29	9	1,088	5
IDU	11	0	200	5	82	2	1	0	294	1
Blood/blood products	18	0	194	5	120	3	4	1	336	1
Other/unknown	60	0	959	23	357	8	27	8	1,403	6
Current age (years)										
0–14	0	0	57	1	54	1	0	0	111	0
15–24	109	1	72	2	99	2	8	2	288	1
25–29	412	3	94	2	131	3	22	7	659	3
30–39	2,238	16	507	12	659	16	136	42	3,540	16
40–49	2,888	21	854	21	1,240	29	78	24	5,060	22
50–59	4,080	29	1,232	30	1,245	29	64	20	6,621	29
60–69	2,967	21	914	22	610	14	15	5	4,506	20
≥70	1,161	8	362	9	204	5	1	0	1,728	8
Region of origin										
The Netherlands	9,172	66	1,869	46	1,216	29	56	17	12,313	55
Sub-Saharan Africa	230	2	943	23	1,649	39	9	3	2,831	13
Western Europe	864	6	142	3	115	3	11	3	1,132	5
Central Europe	543	4	166	4	99	2	6	2	814	4
Eastern Europe and Central Asia	239	2	168	4	223	5	5	2	635	3
South America	1,056	8	289	7	365	9	125	39	1,835	8
Caribbean	624	5	181	4	199	5	67	21	1,071	5
South and southeast Asia	480	3	104	3	265	6	32	10	881	4
North Africa and Middle East	256	2	168	4	74	2	12	4	510	2
Other	311	2	35	1	25	1	0	0	371	2
Unknown	80	1	27	1	12	0	1	0	120	1
Years aware of HIV infection										
<1	239	2	107	3	69	2	13	4	428	2
1–2	503	4	219	5	162	4	28	9	912	4
3–4	652	5	236	6	206	5	34	10	1,128	5
5–9	2,838	20	715	17	636	15	66	20	4,255	19
10–19	6,178	45	1,604	39	1,706	40	124	38	9,612	43
20–29	2,610	19	1,005	25	1,219	29	50	15	4,884	22
≥30	822	6	193	5	226	5	7	2	1,248	6
Unknown	13	0	13	0	18	0	2	1	46	0

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

Ageing population

The median age of the population in clinical care by the end of 2023 was 53 years (IQR 42-61). This figure has been increasing since 2002 (*Figure 1.13*), which is mainly a result of the improved life expectancy of people with HIV following the introduction of combination antiretroviral therapy (ART). Moreover, individuals are being diagnosed at an increasingly older age, as discussed earlier in this chapter. Consequently, approximately half of those currently in care (57%) are 50 years or older (59% of MSM, 61% of other men, 49% of women, and 25% of trans men and women), and 28% are 60 years or older. As the population with HIV continues to age, the number of individuals with age-related comorbidities also increases. These conditions are known to complicate HIV infection management (see *Chapter 5*).

Figure 1.13: *Increasing age of the population with HIV-1 in clinical care over calendar time. In 2002, 12% of the individuals in care were younger than 30 years of age, whereas 20% were 50 years or older. In 2022, these proportions were 5% and 57%, respectively, while 28% of individuals in care were 60 years of age or older. The proportion of individuals in clinical care as of 31 December each calendar year is shown according to age category: <30 years of age, 30-39 years, 40-49 years, 50-59 years, and 60 years or older.*



Duration of infection

People in clinical care by the end of 2023 were known with HIV for a median of 14.5 years (IQR 8.7-20.7). Therefore, a large group (70%) of those in care have been living with HIV for more than 10 years, including 27% who have done so for more than 20 years. The median time since diagnosis was 13.9 years for men who have sex with men (MSM), 14.7 years for other men, 16.5 years for women, and 11.5 years for trans men and women.

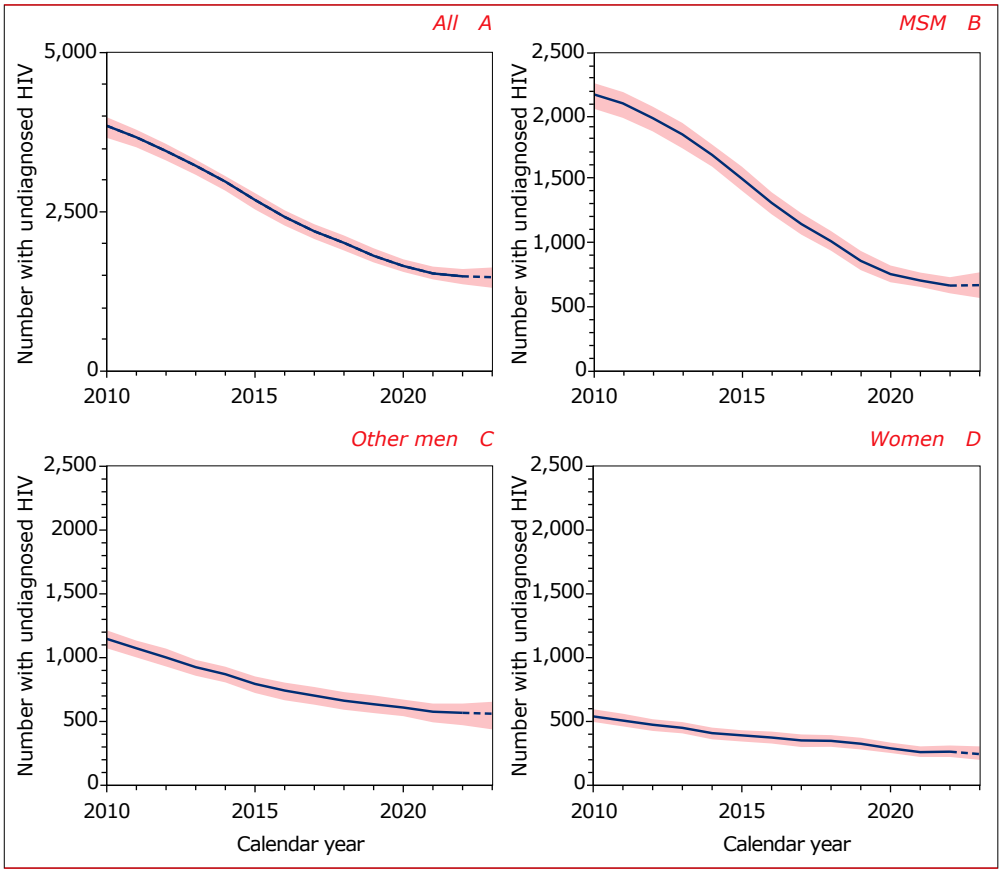
Treated population

By the end of 2023, almost all individuals in care had started ART, and 97% of them were using a once-daily regimen. Of the 84 individuals who had not yet started ART by the end of 2023, 5 (6%) were known to have started therapy in 2024, while another 29 (35%) individuals were diagnosed with HIV in 2023, so it is likely that their therapy has yet to be recorded in the SHM database. ART is discussed in more detail in *Chapter 4*.

Undiagnosed population

The estimated number of people with an undiagnosed HIV infection decreased from 3,850 (95% CI 3,660-3,980) in 2010 to 1,470 (1,305-1,620) in 2023 (*Figure 1.14A*). The 1,470 individuals with an undiagnosed HIV infection comprised 1,220 (1,050-1,370) who most likely acquired their HIV infection in the Netherlands and an estimated 250 individuals who acquired their HIV infection before migrating to the Netherlands. This decrease was mostly driven by MSM, among whom the number of undiagnosed HIV cases fell from 2,170 (2,055-2,260) in 2010 to 675 (575-780) by the end of 2023 (*Figure 1.14B*). Among other men, the estimated number with undiagnosed HIV was 1,145 (1,070-1,210) in 2010 and 555 (435-650) in 2023, while in women these numbers were 535 (485-590) and 240 (195-305), respectively (*Figures 1.14C* and *1.14D*).

Figure 1.14: *Estimated number of people with undiagnosed HIV in the Netherlands: (A) overall, (B) men who have sex with men (MSM), (C) other men, and (D) women, according to the European Centre for Disease Prevention and Control (ECDC) HIV Platform Tool[1]. Estimates for the overall population do not include trans individuals and children.*



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

Continuum of HIV care – national level

The total number of people with HIV by the end of 2023 was 25,240 (95% CI 25,075-25,390), including the estimated 1,470 (1,305-1,620) who remained undiagnosed[1]. Adjusted for registration delays, of this total:

- 23,770 individuals (94% of the total number of people with HIV) had been diagnosed, linked to care, and registered by SHM;
- 22,649 (90%, or 95% of those diagnosed and linked to care) were retained in care (i.e. they had at least one documented HIV RNA or CD4 count measurement, or a clinic visit in 2023) (*Figure 1.15A*);
- 22,557 (89%, or 95% of those diagnosed and linked to care) had started ART;
- 21,912 (87%, or 97% of those treated) had a most recent HIV RNA measurement below 1,000 copies/ml;
- 21,753 (86%, or 96% of those treated) had a most recent HIV RNA measurement below 200 copies/ml; and
- 21,288 (84%, or 94% of those treated) had a most recent measurement below 50 copies/ml.

Overall, 86% of the total estimated population with HIV and 92% of those diagnosed and ever linked to care had a suppressed viral load below 200 copies/ml. This means that by 2023 the Netherlands had almost reached the Joint United Nations Programme on HIV/AIDS (UNAIDS) 95-95-95 target for 2025; with the estimate standing at 94-95-96, or 94-95-97 if 1,000 copies/ml, and 94-95-94 if 50 copies/ml is used as a threshold of viral suppression[13]. Of the people still in care by the end of 2023, 16,707 (74%, or 79% of those with a CD4 measurement) had a most recent CD4 count of 500 cells/mm^3 or higher, which was measured, at most, three years earlier.

Viral suppression

In total, 783 individuals (without adjusting for registration delays) had started therapy but did not have a suppressed viral load below 200 copies/ml by the end of 2023. On closer inspection, 320 (41%) of these individuals did not have an HIV RNA measurement available in 2023; 252 (79%) of these 320 individuals had an RNA level below 200 copies/ml at their last measurement in 2022, 16 (5%) had an RNA level of 200 copies/ml or above, and 52 (16%) also had no RNA measurement in 2022.

Of the 463 (59%) people with a viral load measurement and a viral load level above 200 copies/ml, 61 (13%) started therapy after their last available viral load measurement in 2023. Another 32 (7%) had only started therapy 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

Based on SHM data only, 2,106 individuals were lost to care by the end of 2023, and of these:

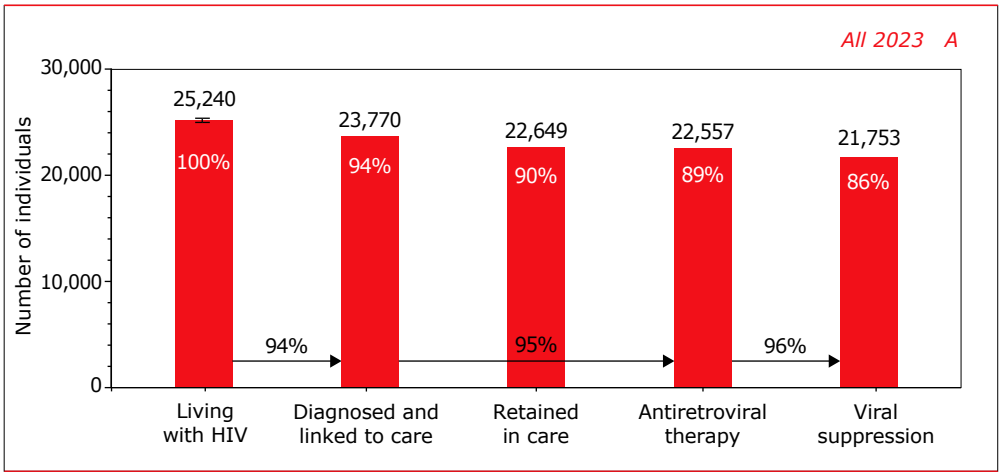
- 1,039 (49%) were last seen for care before the end of 2013;
- 514 (24%) in 2013-2018;
- 101 (5%) in 2020;
- 147 (7%) in 2021; and
- 305 (14%) in 2022[b].

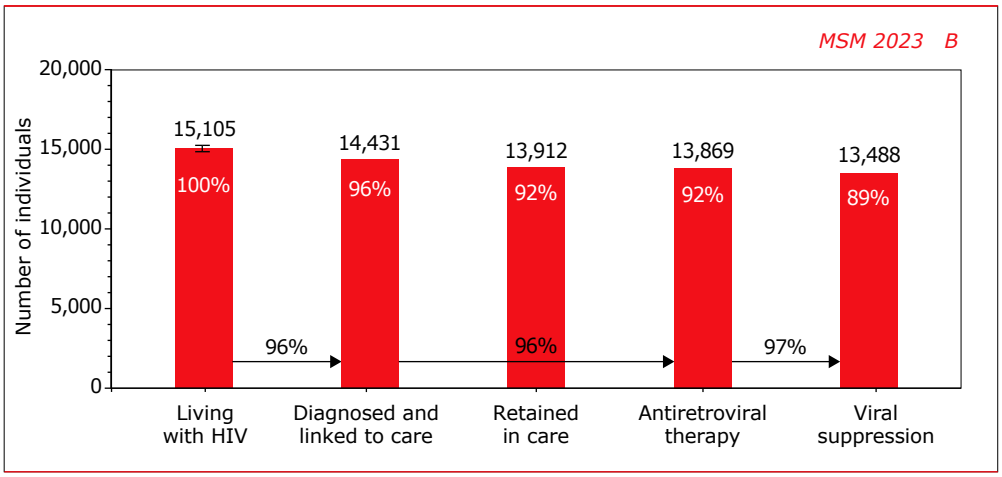
The 1,039 individuals who were lost to care in or before 2013, were excluded from the estimated number of people with HIV and the number of people diagnosed and linked to care. It was assumed to be unlikely that these 1,039 individuals were still living in the Netherlands by the end of 2023 without requiring care or ART during that ten-year period.

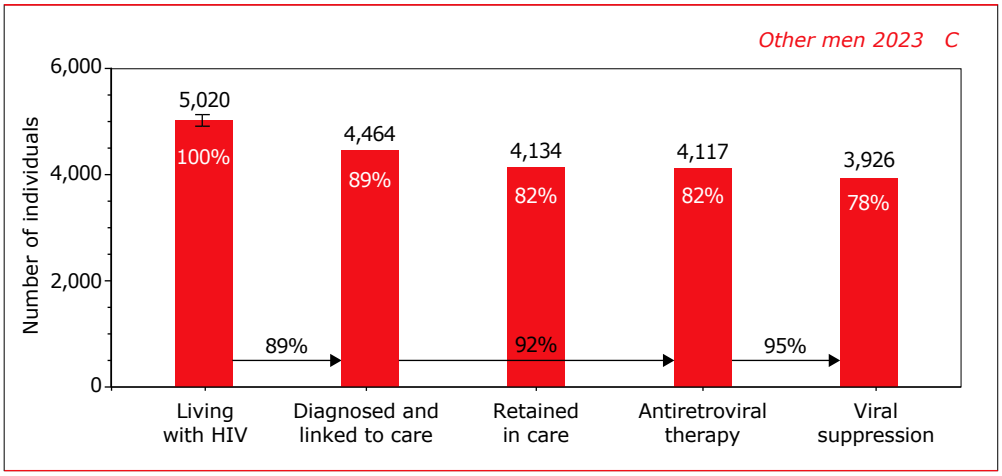
Of the 1,067 individuals lost to care after 2013, 68% were born outside the Netherlands; this proportion was only 45% for those who were still in care by the end of 2023. This suggests that some of those lost to care may have moved abroad; in particular, back to their country of birth. It should be pointed out that 93 (9%) individuals were lost to care because they had planned transfer of care to another treatment centre, but there was no confirmation that they did indeed register at a new centre. Of the 452 individuals last seen for care in 2021 or 2022, 336 (74%) had a suppressed viral load below 200 copies/ml, 63 (14%) had a viral load level above 200 copies/ml, and 53 (12%) had no measurement available.

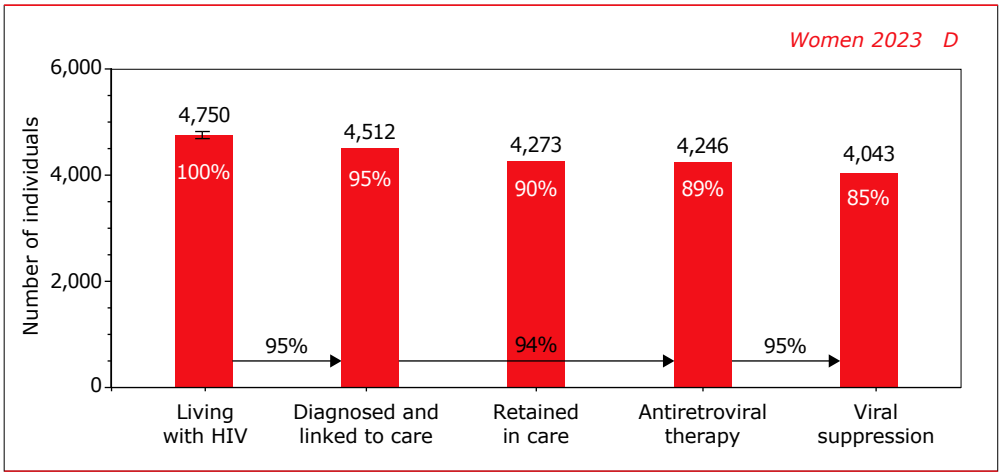
b In addition to the 2,106 individuals lost to care there were 51 individuals who had already been diagnosed by the end of 2023 and were living in the Netherlands but entered care in 2024. These 51 individuals (53 with adjustment for registration delay), as well as the 853 (1,067 minus 307) lost to care after 2013 (854 with adjustment), are counted in the first and second stage of the continuum but not in the other stages.

Figure 1.15: *Continuum of HIV care for people with HIV in the Netherlands by the end of 2023: (A) the total population with HIV-1, (B) men who have sex with men (MSM), (C) other men, and (D) women. Percentages at the top of the bars are calculated relative to the number with HIV, while percentages at the bottom correspond to the UNAIDS' 95-95-95 targets for 2025. Numbers were adjusted to reflect reporting delays.*









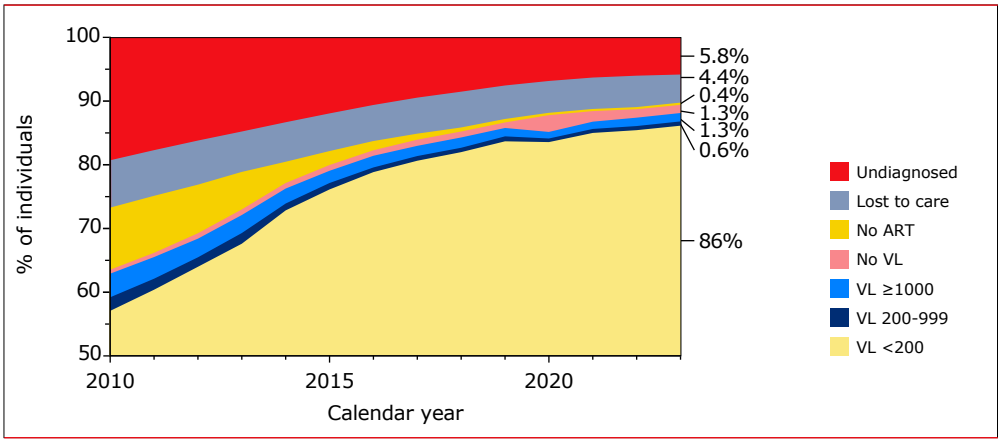
Legend: *MSM = men who have sex with men.*

Transmittable levels of virus

The proportion of people with HIV living in the Netherlands (at the end of each calendar year) who were using ART and had a confirmed viral load level below 200 copies/ml, grew steadily between 2010 and 2023 (*Figure 1.16*). In 2010, 57% of the estimated 19,980 (95% CI 19,785-20,110) people with HIV had a suppressed viral load below 200 copies/ml, while this proportion was 86% in 2023. During the same period, the proportion using ART with a viral load below 1,000 copies/ml grew from 59% in 2010 to 87% in 2023. This increase was mainly the result of a reduction in the proportion of people unaware of their infection, from 19% in 2010 to 6% in 2023, and, to a lesser extent, of a smaller proportion not yet on ART (10% in 2010, 0.4% in 2023).

The number of individuals with HIV who were likely to have an unsuppressed viral load of 1,000 copies/ml or higher by the end of 2023 was estimated to be 3,330, or 13% of all people with HIV, which is the difference between the first and the last stage in the HIV care continuum. These individuals could still pass HIV onto individuals without HIV. The number of 3,330 individuals includes the 1,470 (44%) people who were not yet diagnosed by the end of 2023. The remaining 1,860 (diagnosed) individuals are likely to be an overestimate of the true number with an unsuppressed viral load in the Netherlands because, as discussed above, some of the people who were lost to care may have moved abroad and may be receiving HIV care outside the Netherlands. Additionally, 1% of all people with HIV had no viral load measurement in 2023 but it is likely that many now have a suppressed viral load, as they all started ART.

Figure 1.16: *Estimated proportions of people with HIV across the various stages in the HIV care continuum. The numbers to the right of the graph are the proportions in 2023.*



Legend: *ART = antiretroviral therapy; VL = viral load.*

Continuum of care in MSM, other men, and women

The number of MSM with HIV at the end of 2023 was estimated at 15,105 (95% CI 15,005-15,210), of whom 675 (575-780) had yet to be diagnosed. Of these:

- 14,431 (96%) had been diagnosed and linked to care;
- 13,912 (92%) were still in care;
- 13,869 (92%) had started ART; and
- 13,488 (89%) had a most recent HIV RNA below 200 copies/ml, while 13,558 (90%) had a viral load below 1,000 copies/ml.

In terms of the 2025 UNAIDS 95-95-95 target, this translates to 96-96-97, meaning that in MSM, the UNAIDS targets have already been met (*Figure 1.15B*). In total, 10,673 (77%, or 82% of those with a CD4 measurement) of MSM still in care by the end of 2023 had a CD4 count of 500 cells/mm^3 or higher at their last measurement in 2021-2023.

Among other men, the estimated number with HIV in 2023 was 5,020 (95% CI 4,895-5,110), including 555 (435-650) who were not yet diagnosed (*Figure 1.15C*). Of these:

- 4,464 (89%) men had been diagnosed and linked to care;
- 4,134 (82%) were still in care;
- 4,117 (82%) had started ART; and
- 3,926 (78%) had a suppressed viral load below 200 copies/ml, while 3,964 (79%) had a viral load below 1,000 copies/ml.

The number of women with HIV was estimated to be 4,750 (95% CI 4,710-4,815), of whom 240 (195-305) were not yet diagnosed (*Figure 1.15D*). Of these women:

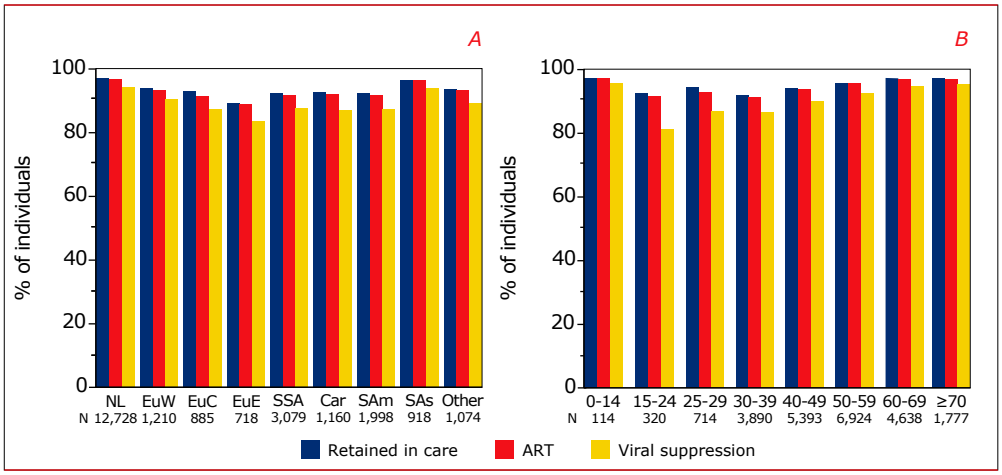
- 4,512 (95%) had been diagnosed and linked to care;
- 4,273 (90%) were still in care;
- 4,246 (89%) had started ART; and
- 4,043 (85%) had a suppressed viral load below 200 copies/ml, while 4,088 (86%) had a viral load below 1,000 copies/ml.

Among women and other men still in care by the end of 2023, the proportion with viral suppression was 95%, which was somewhat lower than among MSM (97%).

Continuum of care by region of origin and age

Individuals originating from the Netherlands and south and southeast Asia generally engaged more with the various stages of the care continuum than people from other countries (*Figure 1.17A*). Engagement with all stages of the care continuum was highest among the youngest and the oldest age group. Levels of engagement were generally lower in the other age groups, but both the proportion of people who were still in care and the proportion who had started ART by the end of 2023, increased with age, and exceeded 95% in people aged 50 years or older (*Figure 1.17B*). As a consequence, the proportion of people with viral suppression also increased with age; rising from 81% among those aged 15 to 24 years, to more than 90% for people aged 40 years or older.

Figure 1.17: *Continuum of HIV care: (A) by region of origin, and (B) by age group (in years) for the total population with HIV-1. Proportions are given relative to the number of people diagnosed and linked to care, which are shown below the figures.*



Legend: *NL = the Netherlands; EuW = western Europe; EuC = central Europe; EuE = eastern Europe and Central Asia; SSA = sub-Saharan Africa; Car = Caribbean; Sam = South America; SAs = south and southeast Asia; Other = other regions of origin; ART = antiretroviral therapy.*

Continuum of HIV care – regional level

We also determined the continuum of care (including the first stage: estimated number of people with HIV) for the eight STI surveillance regions[c] in the Netherlands, and for the four largest cities in the country (*Table 1.5*). By the end of 2023, more than half (53%) of all estimated people with HIV were living in Noord-Holland/Flevoland and in Zuid-Holland Zuid, which include the cities of Amsterdam and Rotterdam. In total an estimated 525 (36%) people with undiagnosed HIV were living in these two regions. All eight regions had reached or were close to reaching most of the UNAIDS' 95-95-95 targets for 2025, and the proportion of all people with HIV who had a suppressed viral load below 200 copies/ml varied between 82% and 89%, or between 83% and 89% when considering a viral load below 1,000 copies/ml. Those diagnosed and linked to care showed similar levels of engagement in the various stages of the care continuum across all 25 public health service regions in the Netherlands (*Table 1.6*).

c Reporting to the national STI surveillance system is organised in eight regions, which each consist of one or more public health service regions (see also *Table 1.6*).

Table 1.5: Continuum of care by the end of 2023 for the total population with HIV-1 living in the Netherlands in each of the eight sexually-transmitted infection (STI) surveillance regions, or in one of the four major cities. For each region or city, percentages on the first row are relative to the estimated number of people with HIV, while those on the second row correspond to UNAIDS' 95-95-95 targets. For 188 individuals diagnosed and linked to care, region of residence was unknown.

	Estimated population with HIV		Diagnosed and linked to care	
	Undiagnosed	Total		
	n	n	n	%
Region				
Noord	170	1,605	1,435	89
	120–230	1,555–1,665		*89*
Oost	180	2,870	2,691	94
	130–235	2,820–2,925		*94*
Noord-Holland/Flevoland	295	9,305	9,012	97
	230–360	9,245–9,370		*97*
Utrecht	75	1,435	1,360	95
	50–110	1,410–1,470		*95*
Zuid-Holland Noord	170	1,925	1,756	91
	110–230	1,865–1,985		*91*
Zuid-Holland Zuid	230	3,960	3,726	94
	175–300	3,900–4,025		*94*
Zeeland/Brabant	255	2,820	2,566	91
	200–325	2,765–2,890		*91*
Limburg	70	1,105	1,036	94
	40–95	1,080–1,135		*94*
Total	1,445	25,030	23,582	94
	1,300–1,605	24,880–25,185		*94*
City				
Amsterdam	155	6,460	6,302	98
	115–200	6,420–6,505		*98*
Rotterdam	80	2,140	2,058	96
	65–120	2,120–2,180		*96*
Den Haag	100	1,355	1,252	92
	60–150	1,310–1,405		*92*
Utrecht	25	590	564	96
	20–35	580–595		*96*
Total	365	10,540	10,176	97
	305–440	10,480–10,620		*97*

	Retained in care		Antiretroviral therapy		Viral suppression	
	n	%	n	%	n	%
	1,364	85	1,357	84	1,321	82
				95		*97*
	2,624	91	2,616	91	2,508	87
				97		*96*
	8,545	92	8,518	92	8,232	88
				95		*97*
	1,315	92	1,310	91	1,274	89
				96		*97*
	1,694	88	1,678	87	1,617	84
				96		*96*
	3,560	90	3,544	90	3,402	86
				95		*96*
	2,457	87	2,449	87	2,353	83
				95		*96*
	975	88	971	88	932	84
				94		*96*
	22,534	90	22,442	90	21,639	86
				95		*96*
	5,981	93	5,962	92	5,782	90
				95		*97*
	1,966	92	1,954	91	1,867	87
				95		*96*
	1,210	89	1,195	88	1,152	85
				95		*96*
	549	93	545	93	529	90
				97		*97*
	9,705	92	9,657	92	9,331	89
				95		*97*

In total, 10,540 (95% CI 10,480-10,620) people with HIV were estimated to be living in the four largest cities in the Netherlands, which amounts to 42% of the total number of people in the country with HIV. Of these 10,540 people, 365 (305-440) were estimated to be undiagnosed (25% of the national estimate of 1,470 individuals with an undiagnosed HIV infection). Of the four cities, Amsterdam had the largest population of people with HIV; an estimated 6,460 (6,420-6,505) individuals, of whom 155 (115-200) were still undiagnosed (*Table 1.5*). Of the 10,540 people with HIV in the four largest cities:

- 10,176 (97%) had been diagnosed and linked to care;
- 9,656 (92%, or 95% of those diagnosed) had started ART; and
- 9,331 (89%, or 97% of those on therapy) had a suppressed viral load below 200 copies/ml.

All four cities had reached or were close to reaching the UNAIDS' 95-95-95 targets for 2025 with the current combined estimate for the cities standing at 97-95-97.

As shown in *Tables 1.5* and *1.6*, some of the regions have relatively small numbers of people 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 1,445 (95% CI 1,300-1,605) individuals living with undiagnosed HIV across the eight STI surveillance regions, is reasonably close to the number of 1,470 (1,305-1,620) we have estimated for the total nationwide population.

Table 1.6: Continuum of HIV care for the total population with HIV-1 in the Netherlands diagnosed and linked to care, stratified by the public health service region in which people were living at the end of 2023. Proportions are given relative to the number of people diagnosed and linked to care.

	Diagnosed and linked to care	Retained in care		Antiretroviral therapy		Viral suppression	
Public health service region	**n**	**n**	**%**	**n**	**%**	**n**	**%**
Noord							
Groningen	685	648	95	647	94	629	92
Fryslân	417	399	96	397	95	387	93
Drenthe	332	316	95	313	94	305	92
Oost							
IJsselland	404	397	98	394	98	370	92
Twente	491	478	97	476	97	460	94
Noord- en Oost-Gelderland	546	534	98	533	98	512	94
Gelderland Midden	805	783	97	781	97	757	94
Gelderland-Zuid	445	432	97	432	97	410	92
Utrecht							
Regio Utrecht	1,360	1,315	97	1,310	96	1,274	94
Noord-Holland/Flevoland							
Flevoland	619	586	95	581	94	552	89
Gooi & Vechtstreek	284	268	94	267	94	263	93
Hollands Noorden	482	457	95	456	95	433	90
Zaanstreek-Waterland	415	389	94	389	94	374	90
Amsterdam	6,598	6,267	95	6,246	95	6,060	92
Kennemerland	614	579	94	579	94	550	90
Zuid-Holland Noord							
Haaglanden	1,756	1,694	96	1,678	96	1,617	92
Zuid-Holland Zuid							
Hollands Midden	607	579	95	577	95	560	92
Rotterdam-Rijnmond	2,772	2,651	96	2,638	95	2,526	91
Dienst Gezondheid & Jeugd ZHZ	347	330	95	329	95	315	91
Zeeland/Brabant							
Zeeland	258	241	93	241	93	228	89
West-Brabant	624	610	98	605	97	582	93
Hart voor Brabant	925	891	96	891	96	864	93
Brabant-Zuidoost	759	715	94	712	94	679	89
Limburg							
Limburg-Noord	440	412	94	411	93	393	89
Zuid Limburg	596	563	94	561	94	539	91
Unknown	188	115	61	115	61	114	61
Total	**23,770**	**22,649**	**95**	**22,557**	**95**	**21,753**	**92**

Trans people

Geographical region of origin

Of the 31,535 individuals with an HIV-1 infection, 398 were trans people; 380 (95%) trans women and 18 (5%) trans men. In this group of 398 individuals, the most commonly-reported regions of origin were South America (155, 39%), the Caribbean (81, 20%), the Netherlands (71, 18%), and south and southeast Asia (37, 9%). Interestingly, many of the trans people originated from only a few specific countries. Among the 155 individuals from South America, there were 33 people from Colombia, 33 from Ecuador, 30 from Brazil, 19 from Suriname, and 16 from Venezuela. Most frequently reported countries of origin in the Caribbean were the former Netherlands Antilles (33) and Cuba (18), while 20 people from south and southeast Asia originated from Thailand.

In total, 123 trans people, or 38% of those born abroad, had a documented HIV-1 diagnosis before moving to the Netherlands. The majority (85) of these 123 people had already started ART before arrival. By the time these 85 people entered HIV care in the Netherlands, 66 (78%) had HIV RNA levels below 200 copies/ml, which was similar to cis people of whom 84%, or 2,509 out of 2,999, had RNA levels below 200 copies/ml.

Diagnosis

In 2021-2023, 39 trans individuals were newly diagnosed with HIV while living in the Netherlands. These 39 people were relatively young, with a median age of 33 years (IQR 30-37) at the time of their HIV diagnosis, and most of them (33) were born abroad. Similar to MSM, the majority of the trans men and women, 42%, received their HIV diagnosis at a sexual health centre (*Figure 1.4*). Among the 39 trans individuals, 14 were diagnosed with a recent HIV infection, 13 with established, and 11 with late-stage HIV infection, which was comparable to the distribution across these stages among MSM; for 1 individual the stage of infection could not be determined.

Population in care

In total, 324 (81%) of the 398 trans individuals with HIV-1 were known to be in clinical care by the end of 2023. Of the 74 people who were not in care anymore, 19 had died, including six who died of AIDS and three individuals whose cause of death was recorded as suicide. Another 18 had moved abroad. The remainder were either lost to care (30), were only diagnosed in 2024 (three), or only entered HIV care in 2024 (four). In total, 13 of the people who moved abroad and 20 of those lost to care had RNA levels below 200 copies/ml at their last viral load measurement.

Clinical condition

The majority of trans people in clinical care (321, or 99%), had started ART by the end of 2023. Of the 312 people in care with a viral load measurement in 2023, 292 (94%) had a last measurement in that year below 200 copies/m. The most recent CD4 count in 2021-2023 of those in care stood at a median of 760 (IQR 530-997) cells/mm^3, which was comparable to the CD4 counts in the total population in care.

HIV-2

In total, 102 of the 32,821 registered individuals with HIV acquired an HIV-2 infection (12 MSM, 34 other men, and 56 women); 10 of these were diagnosed in 2013 or later. HIV-2 is endemic in West Africa, and 65 people originated from this region, mostly from Ghana (25 people) or Cape Verde (24 people). Twenty-two individuals were born in the Netherlands.

Population in care

By the end of 2023, a total of 59 people were still in clinical care, 23 had died, seven had moved abroad, and 13 had no contact with HIV care during that year. The median age of those still in care was 64 years (IQR 56-68); 52 (88%) individuals were 50 years or older. The majority (92%) of those in care had been living with HIV-2 for more than 10 years, while 49% had been living with it for more than 20 years.

Clinical condition

Of the 59 people still in care, 50 had a most recent viral load measurement below 200 copies/ml, and 8 people had no available HIV-2 RNA result in 2023; there was one individual with a viral load above 200 copies/ml. Most people in care (41, 69%) had started ART. Of the 18 individuals who were still in care but had not started therapy, 14 had a viral load measurement below 200 copies/ml, while the other 4 people had no RNA measurement in 2023. CD4 counts in the group of 59 people in care were a median of 700 (IQR 495-843) cells/mm^3.

Conclusions

Since 2008 there has been a steady decrease in the annual number of new HIV diagnoses. This decrease in HIV diagnoses can, in part, be attributed to a fall in the estimated annual number of newly acquired HIV infections. Nonetheless, it is worrisome that the downward trend in new HIV diagnoses appears to have levelled off since 2020. Almost half of the people with a new HIV diagnosis have a late-stage HIV infection (37% MSM; 64% other men; 57% women) resulting in hospitalisation in 43% and a mortality of 4% within one year of diagnosis.

In 2023, 15% of the new HIV diagnoses among MSM and trans men and women were in people who reported prior use of PrEP. This proportion of people with previous PrEP use is rising. People with prior use of PrEP accounted for a large share of the rebound in the proportion of individuals diagnosed with a recent HIV infection compared with 2021.

Apart from the 424 new HIV diagnoses in 2023, there were 314 people born abroad who arrived in the Netherlands in 2023 and had a documented HIV-1 diagnosis prior to arrival. The large majority of this group had already started antiretroviral therapy before arriving in the Netherlands and had a suppressed viral load.

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2. Prior use of pre-exposure prophylaxis

Ferdinand Wit, Casper Rokx, Eline Op de Coul, Marc van der Valk

Summary

The number and proportion of men who have sex with men (MSM) and transgender persons newly diagnosed with HIV in the Netherlands who report prior use of PrEP continued to increase from 7.3% (18 out of 248 individuals) in 2021, to 11.3% (27 of 240) in 2022 and 13.3% (34 of 255) in 2023. However, these are conservative estimates because individuals for whom no information about prior PrEP use was recorded in their electronic medical records (36.2% in 2023) were considered not to have used PrEP.

Of the individuals who reported prior use of PrEP and who received a genotypic resistance test prior to initiation of antiretroviral therapy (ART), 13.5% harboured resistance-associated mutations (RAMs) in the reverse transcriptase (RT) that are associated with the use of PrEP (M184VI with or without K65R RT RAMs). All individuals in whom PrEP-associated RT RAMs had been detected, were still using PrEP at the moment they tested HIV positive, or they had discontinued PrEP only a few months earlier. When limiting this analysis to individuals who had tested HIV-positive while still using PrEP or within 3 months of discontinuing PrEP, 13 (25.5%) out of 51 tested individuals harboured PrEP-associated RT RAMs. Reassuringly, the virological treatment response after initiation of ART appears to be largely unaffected by the prior use of PrEP, also in those individuals where PrEP-associated RT RAMs had been detected.

A substantial proportion (40.1%) of MSM and transgender people who reported they did not use PrEP, had indicated they would have wanted to do so, but either had no access to PrEP (22.3%), were on a PrEP waiting list when they seroconverted (2.1%), or tested HIV positive while being screened for HIV before initiating PrEP (16.8%). A further 19.3% of MSM and transgender people indicated they did not knew that PrEP existed. These proportions were fairly stable over time.

Aims

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs by people without HIV, to prevent HIV acquisition. In the Netherlands, individuals at high risk of HIV acquisition are eligible for the national PrEP programme at the Sexual Health Centers (SHC) of the municipal Public Health Services (GGD), which was launched in September 2019. The primary target groups of this programme are men who have sex with men (MSM) and transgender persons. Prior to this programme, PrEP use prescribed by other healthcare providers (mainly general practitioners) or accessed via informal routes like buyers' clubs, was monitored through demonstration programmes such as the AMPrEP study in Amsterdam.

In this section we describe time trends in the proportion of people newly diagnosed with HIV since 2018 who reported prior use of PrEP at the moment they enter into HIV care in the Netherlands. The primary population of interest consisted of MSM and transgender persons, who constitute the main target populations for PrEP in the Netherlands. We compared demographic and other characteristics of MSM and transgender persons who reported prior use of PrEP with those who did not.
In the group of MSM and transgender persons who did not report prior use of PrEP, we investigated their reasons and barriers for not having used PrEP.

In the group of MSM and transgender persons who did report prior use of PrEP, we evaluated if the acquisition of HIV took place while using PrEP or after discontinuation of PrEP. Furthermore, we report on acquired HIV drug resistance as a potential consequence of acquiring HIV while still using PrEP, and investigate possible impairment of the initial treatment response after start of first-line ART in this group.

Data collection

SHM collects data on prior use of PrEP in all people diagnosed with HIV from 1 January 2018 onwards who are entering care in one of the 24 Dutch HIV treatment centers. SHM has prospectively collected PrEP-related data from the electronic medical records (EMRs) of individuals with HIV first entering care, since July 2019. This is carried out in consultation and collaboration with the Dutch Association of HIV-Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB), and the Dutch Nurses Association's HIV/AIDS nurse consultants unit ('*Verpleegkundigen & Verzorgenden Nederland – Verpleegkundig Consulenten Hiv*', V&VN VCH). Additionally, SHM retrospectively gathered information from the EMRs on prior use of PrEP by individuals who first entered into care between January 2018 and June 2019.

The population of interest for this report consists of the primary target groups for PrEP in the Netherlands: MSM and transgender men and women. In this report, cisgender men were classified as MSM when the recorded mode of HIV acquisition was 'sexual contact with other men' or 'sexual contact with men and women'. Whenever a cisgender man had another or unknown mode of HIV acquisition recorded but that man was known to have male sex partners, that individual was also grouped among the MSM.

A substantial proportion of individuals who enter into HIV care in the Netherlands, have not been born in the Netherlands, and some of them were already diagnosed with HIV before migrating to the Netherlands. Furthermore, some had used PrEP prior to migrating to the Netherlands, while others used PrEP while living in the Netherlands. When appropriate, the analyses take these factors into account.

Of note, SHM does not record data about a person's race / ethnicity, nor can we identify second or third generation migrants. In our analyses, we make a distinction between those who are born in the Netherlands versus those who were born in another country, irrespective of race / ethnicity and migrant status of their (grand)parents.

Population of interest

Between 1 January 2018 and 31 December 2023 3,566 adults were diagnosed with HIV and entered into HIV care in one of the 24 Dutch HIV treatment centers. In the EMR of 1,291 (36.2%) individuals, information was recorded on prior use of PrEP. The proportion of individuals for whom this information was available in the EMR increased from 15.4% in 2018, to 50.2% in 2023 (Figure 21, blue bars).

Of the 3,566 individuals diagnosed with HIV between 2018 and 2023 and entering HIV care, 2,203 were from the primary target groups of the Dutch PrEP programme: 2,090 cisgender MSM and 113 transgender persons. In the PrEP target groups, 911 (41.4%) out of 2,203 individuals had information about prior PrEP use available in the EMR: increasing from 16.6% in 2018, to 63.8% in 2023 (Figure 21, red bars).

The proportion of individuals newly entering in HIV care in the Netherlands, who were not born in the Netherlands, has been increasing over time. Of the 3,566 individuals, 1,586 (44.5%) were born in the Netherlands, and the remaining 1,980 (55.5%) individuals were migrants. Of these 1,980 migrants, 589 (29.8%) individuals were already diagnosed with HIV before migrating to the Netherlands, and 351 (17.7%) individuals had a negative HIV-test after they migrated to the Netherlands and hence are known to have acquired HIV after migrating to the Netherlands. For the remaining 1,040 (52.5%) migrants, we could not ascertain the country were they acquired HIV, because although these individuals first tested HIV positive while living in the Netherlands, they had no documented negative HIV test in the Netherlands. In the PrEP target groups of MSM and transgender persons, 1,828 (83.0%) out of 2,203 individuals had been diagnosed with HIV in the Netherlands, and 375 (17.0%) had been diagnosed with HIV prior to migrating to the Netherlands.

The demographic characteristics of individuals from the PrEP target groups for whom EMR information on prior PrEP use was available were largely similar to those for whom it was not (see *Table 21*).

PrEP awareness and uptake

For 322 (51.2%) of the 629 MSM and transgender people who reported no prior PrEP use and who had been newly diagnosed with HIV in the Netherlands, information was available on why they had not done so. 'Presumed to be at low risk for HIV' (25.5%), 'Not knowing PrEP existed' (19.3%), and 'Wanted to use PrEP but had no access' (18.3%) were the most commonly reported reasons. In total, 60 (18.6%) individuals had wanted to start using PrEP but tested HIV-positive at screening before entry into a PrEP programme. Eight individuals (2.5%, of whom 6 were born in the Netherlands, 2 were migrants newly diagnosed with HIV in the Netherlands) reported that they seroconverted while on a PrEP programme waiting list.

Figure 2.2A shows time trends in the reported reasons for not having used PrEP in MSM and transgender persons.

We compared the reasons for not having used PrEP between people born in the Netherlands, and those originating from western or non-western countries (Figure 2.2B). People born in the Netherlands were most likely to report 'Presumed to be at low risk for HIV' and they were least likely to report 'Not knowing PrEP existed'. People originating from non-western countries most often reported they 'Tested HIV-positive at screening before entry into a PrEP programme' or 'Not knowing PrEP existed', and they were least likely to report they 'Knew about PrEP but did not want to use it'.

Prior use of PrEP

Of the 1,291 individuals for whom information on prior use of PrEP was available in the EMR, the majority (1,142, 88.5%) reported no such use, whereas 149 (11.5%) reported prior PrEP use (*Table 2.2*).

Of the 149 people who reported prior use of PrEP, 142 were from the primary target groups for PrEP in the Netherlands: 140 MSM and 2 transgender persons. The remaining 7 individuals were 6 cisgender men and 1 cisgender woman, who were all migrants who had used PrEP prior to migrating to the Netherlands. Of the 149 individuals who reported prior PrEP use, 81 (54.4%) were migrants, 57 of which had used PrEP in the Netherlands, and 24 had used PrEP prior to migrating to the Netherlands, of whom 12 had already been diagnosed with HIV prior to migrating to the Netherlands.

The 149 individuals who reported prior use of PrEP were younger and had higher CD4 counts at diagnosis compared to those who did not use PrEP.

We calculated percentages of prior PrEP use of all 1,828 MSM and transgender people who were newly diagnosed with HIV in the Netherlands between 2018 and 2023. We conservatively assumed that when no explicit mention was made in the EMR about prior use of PrEP, the individuals had not used it. The percentage of MSM and transgender people newly diagnosed with HIV in the Netherlands for which prior PrEP use was recorded in the EMR has increased since 2019 (P_{trend}<0.0001, see Figure 2.3, red bars), with 2.0% in 2018, 4.7% in 2019, 6.7% in 2020, 7.3% in 2021, 11.3% in 2022, and 13.3% in 2023. When also including those MSM and transgender people who were diagnosed with HIV prior to migrating to the Netherlands (n=2,203), the proportions remained similar: 1.6% in 2018, 4.4% in 2019, 7.3% in 2020, 7.2% in 2021, 10.8% in 2022, and 14.2% in 2023 (see Figure 2.3, blue bars).

Access to PrEP and usage patterns

The characteristics of all 149 individuals who reported prior use of PrEP are shown in *Table 2.3*, with a stratification by those who used PrEP in the Netherlands and those who used it while still living abroad, with migrants who initiated PrEP before they migrated to the Netherlands but who continued using PrEP after they migrated to the Netherlands being included into the former group.

Of the 149 individuals who reported prior PrEP use, 24 (16.1%) were migrants who had used PrEP before moving to the Netherlands. There were 125 individuals who had used PrEP in the Netherlands, 3 of these had started PrEP before migrating to the Netherlands but continued using it until after they migrated to the Netherlands. In the remainder of this chapter we will report on these 125 individuals who had used PrEP while living in the Netherlands.

Of the 125 individuals who had used PrEP in the Netherlands, 76 (60.8%) obtained it from a healthcare provider in the Netherlands (see Table 2.3), comprising the Municipal Public Health Service (n=41), family practitioner (26), HIV treatment center (5), and other medical specialist (1). There was no further detailed information available for 3 individuals. The remaining individuals for whom this information was recorded, obtained their PrEP:

- through informal routes: buyers' club/internet/store outside of the Netherlands (15);
- from a healthcare provider outside of the Netherlands (4); or
- from a friend living with HIV who had donated some of their own medication (3).

There was no information available about the PrEP provider for the remaining 27 individuals.

Dosage schedule information was available for 78 individuals:

- 45 individuals (36.0%) reported on-demand use
- 30 individuals (24.0%) reported daily use
- 3 individuals (2.4%) reported having used PrEP less than a week

For the remaining 46 individuals (36.8%), no dosage schedule information was available.

Of the 125 individuals who reported prior PrEP use, 41 (32.8%) had regular medical check-ups at the Municipal Public Health Service during that period, 7 individuals (5.6%) attended an HIV treatment center, 17 (13.6%) were seen by a family practitioner, and 2 individuals (1.6%) were checked by a medical specialist other than HIV treatment center staff. Seventeen individuals (13.6%) reported that they did not have any medical check-ups, and there was no information available for the remaining 41 individuals (32.8%). Most of the 17 individuals who reported they had received no medical check-ups had obtained PrEP via informal means, only 4 of them had received their PrEP from a healthcare provider in the Netherlands (2 of these 4 had used PrEP for less than 1 month). Figure 2.4 shows the time trends in the PrEP providers of the MSM and transgender people who had used PrEP while living in the Netherlands.

Of the 24 individuals who had used PrEP before migrating to the Netherlands, 2 were known to have seroconverted in the Netherlands (they both had an earlier negative HIV test performed after migration to the Netherlands). Twelve of those 24 individuals had already tested HIV positive before migrating to the Netherlands, and for 10 individuals it is uncertain if they seroconverted before or after migrating to the Netherlands.

The median (IQR) number of days between the last dose of PrEP and testing HIV-positive was calculated only for those individuals for which the relevant dates were known with sufficient precision (to within a month) and was 26 (0-132) days. A total of 37 (29.6%) individuals tested HIV-positive while still using PrEP. Of the 88 individuals who did not test HIV-positive while taking PrEP, 32 reported having tested HIV-seronegative after their last use of PrEP, while 35 did not have an HIV-test shortly after discontinuing the use of PrEP. There was no information available for 21 individuals.

PrEP and possible drug resistance

Genotypic resistance test results were available for 101 (80.8%) of the 125 individuals who reported having used PrEP in the Netherlands when first entering HIV care. Reverse transcriptase (RT) resistance-associated mutations (RAM)[a], associated with the use of PrEP, were detected in 13 individuals (12.9%). All 13 individuals harboured an M184VI RT RAM (which decreases susceptibility to lamivudine and emtricitabine), and 2 of these also harboured a K65R RT RAM (which is selected for by tenofovir and decreases susceptibility to tenofovir, abacavir, lamivudine and emtricitabine).

All 13 individuals in whom M184VI RT RAM (with or without K65R RT RAM) had been detected, were still using PrEP at the moment they tested HIV positive, or they had last used PrEP only a few months before testing positive. There were 62 individuals who had tested HIV-positive while still using PrEP or within 3 months of discontinuing PrEP, 51 of these 62 individuals had received a genotypic resistance test, and 13 (25.5%) harboured PrEP-associated RAMs.

In the 24 individuals who had used PrEP prior to migrating to the Netherlands, 10 (41.7%) had genotypic resistance test results available, 2 of which showed M184VI RT resistance-associated mutations.

Prior use of PrEP and antiretroviral therapy (ART)

We investigated the virological treatment response to first-line antiretroviral therapy in the 134 people who had reported prior use of PrEP and who had been diagnosed with HIV in the Netherlands and subsequently initiated ART. Data on the subsequent virological treatment response was available for 132 of these 134 individuals. These include 14 of the 15 individuals with M184VI (with or without K65R) RT RAM, all of whom started a regimen containing an integrase inhibitor. Nine of these combined the integrase inhibitor together with a protease inhibitor with or without additional nucleoside-analogue RT inhibitors (NRTIs). The remaining 5 individuals combined an integrase inhibitor with two NRTIs.

a All RT RAMs mentioned in this chapter start and end with capital letters; i.e. M184VI ends in the capital letter 'i' and should not be confused with the number 1.

Of the individuals with either no baseline resistance test results, or whose test showed no evidence of the M184VI or K65R RT RAM, 120 initiated a first-line regimen consisting of:

- an integrase inhibitor plus two NRTIs (n=83)
- a protease inhibitor plus two NRTIs (n=3)
- an integrase inhibitor plus a protease inhibitor, with or without additional NRTIs (n=27)
- a non-nucleoside RT inhibitor plus two NRTIs (n=4)
- lamivudine / dolutegravir (n=3)

The 14 individuals with an RT RAM had a median follow-up time of 132.0 (IQR 78.9-238.3) weeks after initiating ART. In one of these 14 individuals with a M184VI (but without K65R) RT RAM the first-line regimen was discontinued due to a persistent suboptimal virological efficacy. This individual's plasma viral load had initially become undetectable three months after starting on tenofovir alafenamide / emtricitabine / bictegravir. However, in the following two-year period all eight recorded viral load measurements showed detectable viremia. The highest recorded value was 253 copies/ml. Eventually, ART was switched to a triple-class regimen consisting of 2 NRTI plus an INSTI plus a boosted protease inhibitor, after which the viral load durably became undetectable. Later, the regimen was simplified to a two-class single-tablet regimen (bictegravir / TAF / emtricitabine).
In another individual with M184VI (but without K65R) RT RAM the plasma viral load quickly dropped to below 100 copies/mL, but remained detectable on all measurements up to 1.5 years after initiating cART with dolutegravir / TDF / emtricitabine (range 61-97 copies/mL).
The remaining 12 individuals with M184VI (two of them also had a K65R) all had an optimal treatment response with successfully sustained viral suppression after initiating cART.

For the 120 individuals with no evidence of M184VI (with or without K65R RT RAM) in the baseline resistance test or for whom no test data was available, all 118 individuals with viral load measurements available at least four months after the initiation of ART showed an adequate initial virological treatment response (defined as a decrease to below 200 copies/ml). The median follow-up time was 82.1 (IQR 41.4-168.8) weeks. In seven individuals a viral rebound (defined as having a viral load measurement above 200 copies/ml following an initial treatment response) was recorded. In six of these seven individuals the viral rebound occurred because they temporarily interrupted the use of ART. Five of these six individuals re-suppressed after restarting the same or another ART regimen, except for

one individual who developed virological failure after restarting the same NNRTI-based triple regimen, and was subsequently switched to a second line regimen containing a protease inhibitor plus integrase inhibitor after which the viral load durably re-suppressed. The three individuals who initiated ART with dolutegravir / lamivudine all quickly became undetectable and experienced no viral breakthrough.

Conclusions

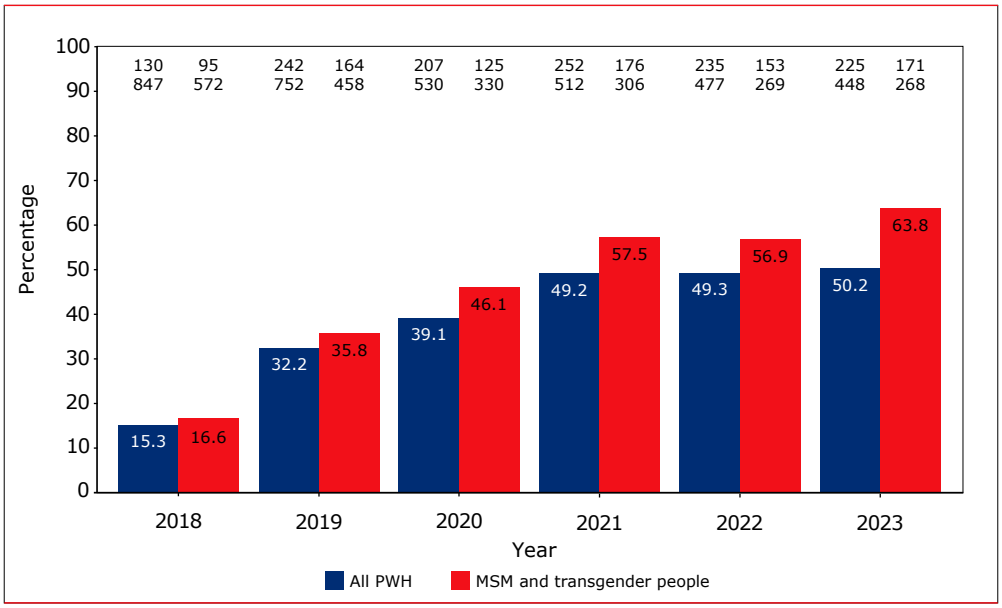
The number and proportion of newly diagnosed MSM and transgender individuals entering HIV care who reported prior use of PrEP continued to increase. In 2023, 14.2% (n=38) of newly diagnosed MSM and transgender people reported prior use of PrEP. However, this is probably a conservative estimate because in this analysis individuals for whom no explicit information about prior PrEP use was recorded in their EMR were considered not to have used PrEP. The observed increase over time cannot be completely explained by health care providers being more aware of and hence better documenting prior PrEP use.

The individuals who indicated they had used PrEP are a very heterogeneous group. Of the 149 individuals who reported prior PrEP use, 24 (16.1%) were migrants who had used PrEP before moving to the Netherlands. There were 125 individuals who had used PrEP in the Netherlands, 76 (60.8%) obtained it from a healthcare provider in the Netherlands. Seven individuals who had used PrEP did not belong to one of the target groups for PrEP in the Netherlands, these were either migrants who used PrEP before migrating to the Netherlands, or they were individuals who had obtained PrEP through informal means.

Of those individuals who had used PrEP in the Netherlands, 37 (29.6%) were diagnosed with HIV while still using PrEP. Of the 111 individuals who reported prior use of PrEP and who received a genotypic resistance test prior to initiation of ART, 15 (13.5%) were found to harbour resistance mutations that were probably associated with the continued use of PrEP after seroconversion. Reassuringly, the virological treatment response after initiation of ART appeared to be unaffected by the prior use of PrEP, also in those individuals where resistance mutations had been detected.

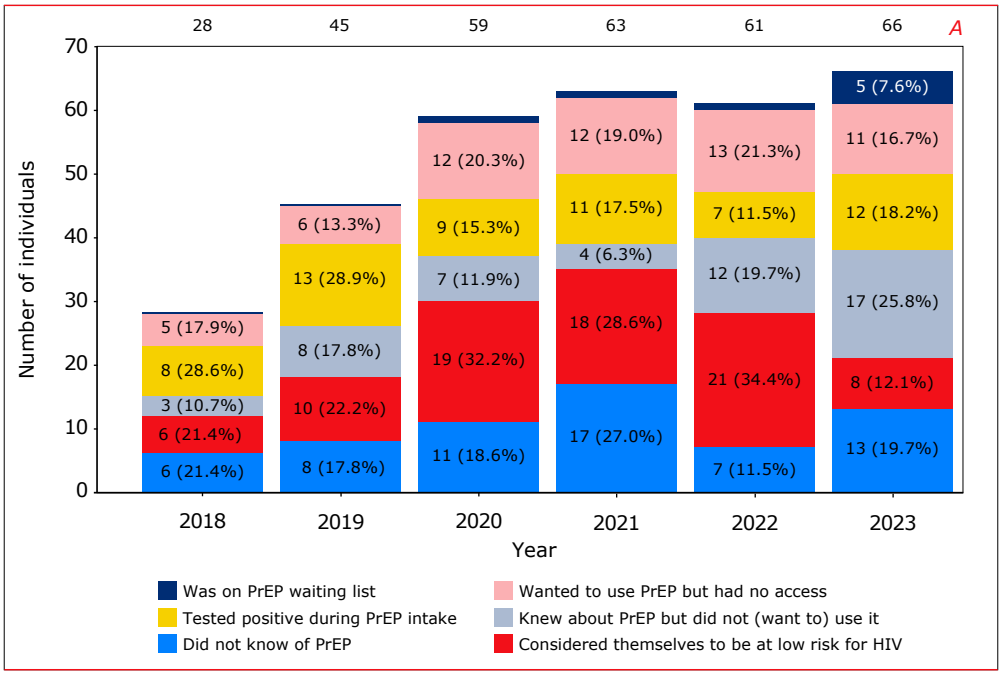
A substantial proportion (40.1%) of MSM and transgender people who reported they did not use PrEP and for whom information were available on the reasons for not doing so, had indicated they would have wanted to do so, but either had no access to PrEP (22.3%), were on a PrEP waiting list when they seroconverted (2.1%), or tested HIV positive while being screened for HIV before initiating PrEP (16.8%).

Figure 2.1: *Number and proportion of individuals diagnosed with HIV per calendar year for whom information on prior use of PrEP is available.*



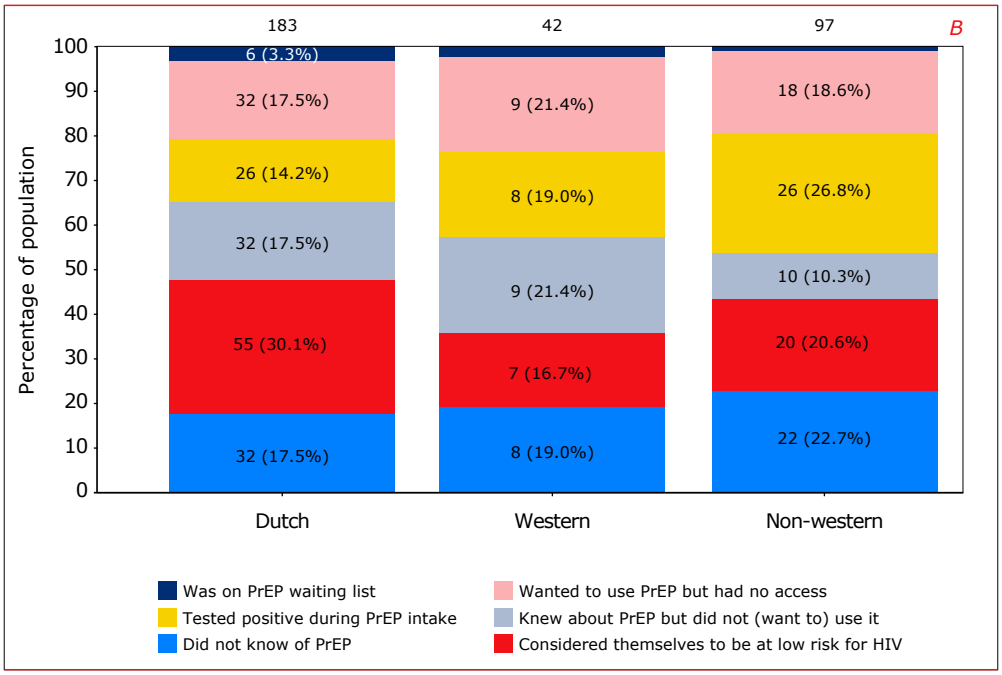
Legend: *The numbers in the top line are the number of individuals for whom information on prior use of PrEP is available in their electronic medical records. The second line is the total cohort size of each calendar year.*

Figure 2.2A: *Time trends in the reported reasons for not having used PrEP in MSM and transgender persons newly diagnosed with HIV in the Netherlands.*



Legend: *The numbers in the top line are the total number of MSM and transgender persons per calendar year for whom the reason was known why they had not used PrEP.*

Figure 2.2B: *Reported reasons for not having used PrEP in MSM and transgender persons newly diagnosed with HIV in the Netherlands, stratified by region of birth*



Legend: *The numbers in the top line are the total number of people born on the Netherlands, in western countries, and in non-western countries for whom the reason was known why they had not used PrEP.*

Figure 2.3: Time trends in the number and proportion of MSM and transgender people newly diagnosed with HIV who reported prior use of PrEP.

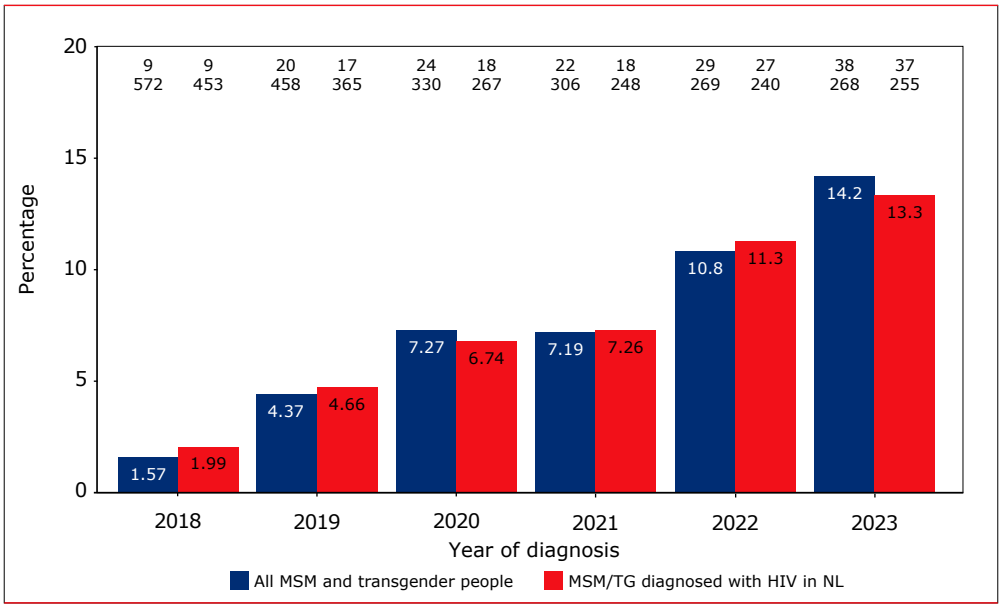


Figure legend: *The numbers in the top line are the number of people who reported prior use of PrEP. The numbers in the second line are the cohort size of that calendar year.*

Figure 2.4: Time trends in the number and proportion of MSM and transgender people newly diagnosed with HIV reporting prior use of PrEP while living in the Netherlands, stratified by PrEP provider.

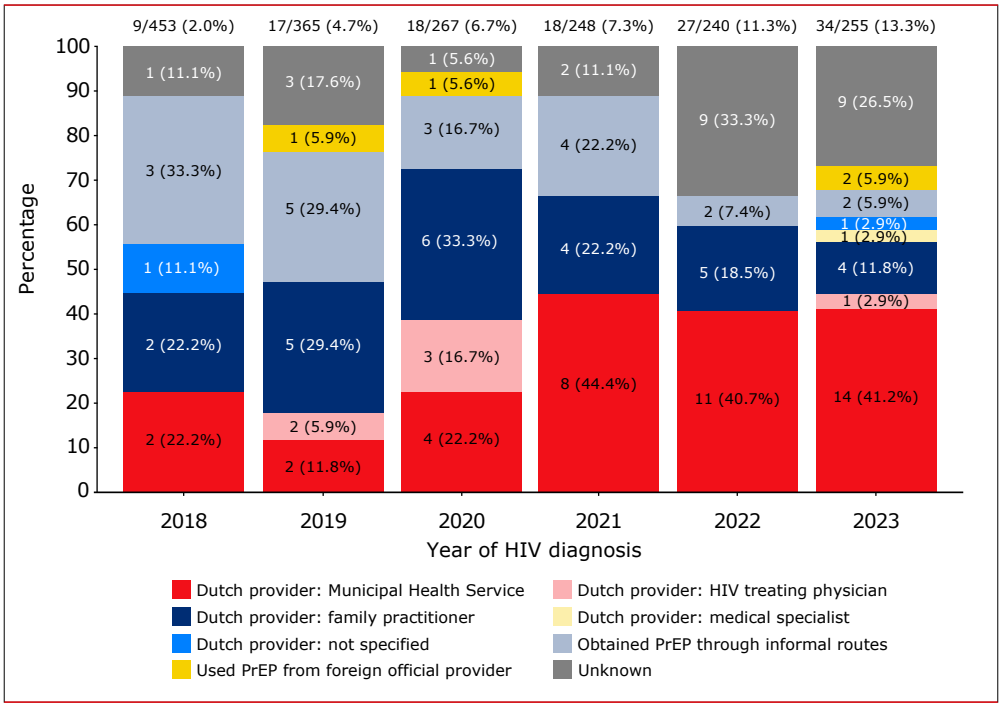


Table 2.1: *Comparison of characteristics of MSM and transgender persons (ie PrEP target groups) who did or did not have information available on prior PrEP use*

	Info on PrEP available	No info available	p-value
Number of subjects	911 (41.4%)	1292 (58.6%)	
Age	34 (27.8-46.4)	35.3 (27.9-48.1)	0.215
HIV acquisition group			1.000
MSM	864 (94.8%)	1226 (94.9%)	
Other men	0 (0.0%)	0 (0.0%)	
Women	0 (0.0%)	0 (0.0%)	
Transgender people	47 (5.2%)	66 (5.1%)	
Region of birth			0.255
Born in the Netherlands	428 (47.0%)	626 (48.5%)	
Migrant, western background	151 (16.6%)	181 (14.0%)	
Migrant, non-western background	332 (36.4%)	485 (37.5%)	
Documented seroconversion in NL or before migration*			0.656
In the Netherlands	129 (26.7%)	138 (20.7%)	
Before migration to the Netherlands	149 (30.8%)	226 (33.9%)	
Unknown / uncertain	205 (42.4%)	302 (45.3%)	
Recent HIV acquisition			
Tested pos. <365 days after last neg. test	314 (34.5%)	291 (22.5%)	<.001
Tested pos. <180 days after last neg. test	185 (20.3%)	140 (10.8%)	<.001
CD4 at HIV diagnosis	460 (283-660)	420 (230-616)	<.001

Legend: ** Calculated for migrants only.*

Table 2.2: Comparison of individuals with and without prior use of PrEP

	Prior use of PrEP	No prior use, target groups, diagnosed in NL	No prior use, other groups, diagnosed abroad	p-value
Number of subjects	149 (16.2%)	629 (68.5%)	140 (15.3%)	
Age	32.4 (27.1-43.5)	37.2 (29.2-49.8)	28.7 (24.6-33.4)	<.001
HIV acquisition group				<.001
MSM	140 (94.0%)	596 (94.8%)	128 (91.4%)	
Other men	6 (4.0%)	0 (0.0%)	0 (0.0%)	
Women	1 (0.7%)	0 (0.0%)	0 (0.0%)	
Transgender people	2 (1.3%)	33 (5.2%)	12 (8.6%)	
Region of birth				<.001
Born in the Netherlands	68 (45.6%)	361 (57.4%)	0 (0.0%)	
Migrant, western background	26 (17.4%)	89 (14.1%)	37 (26.4%)	
Migrant, non-western background	55 (36.9%)	179 (28.5%)	103 (73.6%)	
Documented seroconversion in NL or before migration*				<.001
In the Netherlands	42 (51.9%)	89 (33.2%)	0 (0.0%)	
Before migration to the Netherlands	12 (14.8%)	0 (0.0%)	140 (100%)	
Unknown / uncertain	27 (33.3%)	179 (66.8%)	0 (0.0%)	
Recent HIV acquisition				
Tested pos. <365 days after last neg. test	108 (72.5%)	181 (28.8%)	30 (21.4%)	<.001
Tested pos. <180 days after last neg. test	70 (47.0%)	107 (17.0%)	11 (7.9%)	<.001
CD4 at HIV diagnosis	570 (379-720)	420 (241-600)	593 (365-832)	<.001
Late presenter (CD4<350)	30 (20.3%)	244 (38.8%)	34 (24.5%)	<.001
Very late presenter (CD4<200 or AIDS)	10 (6.7%)	127 (20.2%)	9 (6.4%)	<.001
Reason known for not having used PrEP	n.a.	322 (51.2%)	59 (42.1%)	<.001
Reasons for not having used PrEP				
Did not know of PrEP	n.a.	62 (19.3%)	15 (25.4%)	
Presumed to be at low risk for HIV	n.a.	82 (25.5%)	12 (20.3%)	
Knew PrEP but did not want to use it	n.a.	51 (15.8%)	2 (3.4%)	
Tested positive at PrEP intake	n.a.	60 (18.6%)	4 (6.8%)	
Wanted PrEP but had no access	n.a.	59 (18.3%)	26 (44.1%)	
Was on PrEP waiting list	n.a.	8 (2.5%)	0 (0.0%)	

*Legend: target group = MSM and transgender people; n.a. = not applicable; * Calculated for migrants only.*

Table 2.3: characteristics of individuals who reported use of PrEP

	PrEP used in the Netherlands	PrEP used abroad	p-value
Number of subjects	125 (83.9%)	24 (16.1%)	
Age	32.7 (27.1-46)	30.6 (25.9-34.3)	0.093
HIV acquisition group			<.001
MSM	123 (98.4%)	17 (70.8%)	
Other men	2 (1.6%)	4 (16.7%)	
Women	0 (0.0%)	1 (4.2%)	
Transgender people	0 (0.0%)	2 (8.3%)	
Region of birth			<.001
Born in the Netherlands	68 (54.4%)	0 (0.0%)	
Migrant, western background	17 (13.6%)	9 (37.5%)	
Migrant, non-western background	40 (32.0%)	15 (62.5%)	
STD diagnosed at entry into care			
HBV (HBV surface antigen positive)	1 (0.8%)	1 (4.2%)	0.189
HBV (HBV core antibody positive)	18 (14.4%)	4 (16.7%)	0.774
HCV (antibody positive)	2 (1.6%)	0 (0.0%)	0.533
Syphilis (RPR/VDRL positive)	34 (27.2%)	9 (37.5%)	0.308
PrEP started before migrating to the Netherlands	3 (2.4%)	24 (100%)	
PrEP provider			<.001
Provider in the Netherlands	76 (60.8%)	0 (0.0%)	
- Public Health Service	41 (32.8%)	0 (0.0%)	
- HIV treatment center	5 (4.0%)	0 (0.0%)	
- Family practitioner	26 (20.8%)	0 (0.0%)	
- Medical specialist	1 (0.8%)	0 (0.0%)	
- No info	3 (2.4%)	0 (0.0%)	
Provider outside of the Netherlands	4 (3.2%)	7 (29.2%)	
Obtained PrEP through informal routes	15 (12.0%)	5 (20.8%)	
From friend living with HIV	3 (2.4%)	1 (4.2%)	
No info	27 (21.6%)	11 (45.8%)	
Seroconversion during PrEP use			
Tested HIV-positive while on PrEP	37 (29.6%)	2 (8.3%)	
HIV-negative test performed after last dose of PrEP	32 (36.4%)	7 (31.8%)	
No HIV-negative test performed after last dose of PrEP	35 (39.8%)	14 (63.6%)	
Unknown if HIV test was performed after last dose of PrEP	21 (23.9%)	1 (4.5%)	
Seroconverted in the Netherlands or before migration			<.001
In the Netherlands	108 (86.4%)	2 (8.3%)	
Before migration to the Netherlands	0 (0.0%)	12 (50.0%)	
Unknown / uncertain	17 (13.6%)	10 (41.7%)	

	PrEP used in the Netherlands	PrEP used abroad	p-value
Days between last PrEP use and testing HIV-positive **	26 (0-132)	86 (61-121)	0.250
Recent HIV acquisition			
Tested pos. <365 days after last neg. test	98 (78.4%)	10 (41.7%)	<.001
Tested pos. <180 days after last neg. test	65 (52.0%)	5 (20.8%)	0.005
CD4 at HIV diagnosis	540 (374-727)	581 (471-680)	0.478
ARVs used for PrEP			0.066
TDF/FTC	66 (52.8%)	8 (33.3%)	
Genvoya	0 (0.0%)	1 (4.2%)	
Unspecified	58 (46.4%)	15 (62.5%)	
PrEP schedule			0.761
On demand	45 (36.0%)	6 (25.0%)	
Daily	30 (24.0%)	6 (25.0%)	
No data	46 (36.8%)	12 (50.0%)	
Used PrEP <1 week	3 (2.4%)	0 (0.0%)	
Duration of PrEP use (days)	112 (30-291)	49 (22-211)	0.617
Routine medical check-ups while on PrEP			<.001
Public Health Service	41 (32.8%)	0 (0.0%)	
Family practitioner	17 (13.6%)	0 (0.0%)	
HIV treatment center	7 (5.6%)	0 (0.0%)	
Other healthcare provider	2 (1.6%)	2 (8.3%)	
No medical check-ups	17 (13.6%)	3 (12.5%)	
No data	41 (32.8%)	19 (79.2%)	
Resistance test performed after testing HIV-positive	101 (80.8%)	10 (41.7%)	<.001
Resistance associated mutations in RT			
M184VI	13 (12.9%)	2 (20.0%)	
K65R	2 (2.0%)	0 (0.0%)	

Table legend: ** Calculated for migrants only; ** Zero days means person was diagnosed with HIV during PrEP use STI sexually transmitted infection*

3. Identifying gaps in HIV care in the Netherlands using data from Statistics Netherlands

Vita Jongen, Anders Boyd, Nina Schat, Rosan van Zoest, Ard van Sighem, Marc van der Valk

Summary

To continue the path towards zero new HIV infections we need more focused insight into why certain people do not successfully progress through the steps of the HIV care continuum and as a result, could still have a detectable HIV-1-RNA. The results from this chapter are based on calculations by SHM using non-public microdata from Statistics Netherlands (CBS). CBS is an independent organisation that collects, processes and publishes reliable statistical data on residents of the Netherlands.

We combined all data from individuals with HIV registered by SHM and data from CBS within a secure SHM-CBS environment. The data were combined using date of birth, gender and the four numbers of an individual's postcode. We used all data between 2011 and 2022.

We were able to successfully combine the SHM/CBS data of 28,294 individuals. (92% of all individuals ever linked to care in the SHM database in 2022). 5,736 individuals had migrated or died by 2022, according to CBS or SHM and were subsequently excluded from the dataset. Additionally, we excluded individuals <18 years of age (n=648), with HIV-2 (n=164), who had not been in care for over 10 years (n=23), and who had no data in 2022 (n=5,568). Thus, 21,880 individuals were included in the analyses.

Compared to the general population in the Netherlands, individuals ever linked to HIV care:

- were more often male;
- were less often <25 years of age;
- had more often a first generation migration background;
- lived more often in a single-person household;
- had more often an income <120% of the social minimum;
- more often received social welfare; and
- more often received specialist mental health care.

Having an adequately suppressed HIV-1 RNA was largely correlated with income and age among MSM, women and other men. Viral suppression among individuals with an income <120% of the social minimum was always less than 95%. Lower income and younger age were also related to increased disengagement from care and being diagnosed with late stage HIV among MSM, women and other men.

Box 3.1: Definitions used in this chapter

Term	Definition
Disengagement from care	Individuals ever linked to care who did not attend an HIV clinical visit in the 2022 calendar year (but did attend visits prior to 2022).
Late-stage HIV diagnosis	Defined as a CD4 count <350 cells/mm3 or an AIDS-defining event regardless of CD4 count at the moment of diagnosis, and no evidence of having acquired HIV in the 12 months before diagnosis.
Linked to care	All individuals with at least one HIV clinical visit between 2011 and 2022 and who did not pass away or move abroad.
On ART	All individuals who started ART before or in 2022.
Recent HIV infection	Defined as evidence of having acquired HIV in the 12 months before diagnosis, based on a negative or indeterminate western blot at the time of diagnosis, or a reported last negative HIV test at most 12 months before diagnosis.
Retention in care	All individuals with a clinical visit or a CD4/viral load measurement in 2022.
Viral suppression	Defined as an HIV-1 RNA <200 copies/mL.

Aim

The Netherlands is on track to achieve the UNAIDS 95-95-95 targets before 2025 (see Chapter 1). In 2023, an estimated 25,240 individuals (95% CI 25,075-25,390) were living with HIV. Of these, 21,753 individuals (86%) had a most recent HIV-1 RNA measurement <200 copies/mL. While this proportion is high, it nonetheless means that approximately 3,487 (14%) individuals with HIV in the Netherlands (including individuals unaware of their HIV status) are likely to have a detectable HIV-1 viral load. To continue on the path towards zero new HIV infections, we need more focused insight into why certain people have suboptimal progression through the HIV care continuum and/or disengage from care. Moreover, data on how the HIV epidemic is shaped by socio-demographic and -economic differences are lacking in the Netherlands and could aid in more targeted prevention strategies in populations disproportionally burdened by HIV.

Data from SHM provide information relating to socio-demographic (e.g., date of birth, gender at birth) and health-related factors of the population with HIV. However, SHM lacks information on other societal factors that could indicate social disparity and delayed progression through the HIV care continuum, such as an individual's socio-economic status or level of education. Moreover, SHM cannot provide information on the socio-demographic characteristics of people who disengage from HIV care in the Netherlands. If these data were combined with external data from Statistics Netherlands, the resulting information could more precisely identify specific gaps in care.

Methods

The results from this chapter are based on calculations done by SHM using non-public microdata from Statistics Netherlands (CBS) and Vektis C.V.. CBS is an independent organization that collects, processes and publishes reliable statistical data on residents in the Netherlands. We combined all data from individuals with HIV registered by SHM and data from CBS within a secure SHM-CBS environment. The data were combined using date of birth, gender and the four numbers of an individual's postcode. Combining of the data is done by CBS and researchers have no access to postal codes. As data registration at CBS takes longer to complete than at SHM, we used data for all individuals who were diagnosed with HIV up until 31 December 2022 (i.e. the most recent data available at CBS).

The following variables from the CBS database were included:

Box 3.2: Description of variables included from Statistics Netherlands

Variable	Description
Education level	Classified as: 1. Primary: defined as completed pre-vocational secondary education ('VMBO) and/or first three years of senior general secondary education ('HAVO') or pre-university level ('VWO') 2. Secondary: Completed secondary vocational education (MBO), senior general secondary education ('HAVO') or pre-university level ('VWO') 3. College/University: completed higher vocational education (HBO) or university
Migration background	Based on the country of birth of the parents and the individual. Migration background was categorized as follows: • Dutch: the individual and both parents were born in the Netherlands or both parents were born in the Netherlands, but the individual was not. • First generation migration background: The individual and at least one parent was born abroad. • Second generation migration background: An individual born in the Netherlands who has at least one parent born abroad.
Employment status	Defined as the primary source of income within households: wages, business income, social welfare, retirement or benefits (including disability and unemployment)
Gender	Defined as the gender registered in the administration of the local municipality.
Household composition	Categorized as: single person household, living together with or without children, single parent households or other (e.g., institutionalized, other multi-person households)

Household income	Defined as income according to the social minimum (the minimal amount of financial resources required to achieve a minimally acceptable lifestyle). The social minimum is determined and adjusted bi-annually by the Ministry of Social Affairs and Employment (https://www.uwv.nl/nl/toeslag/sociaal-minimum).
Long term care act (WLZ)	Defined as declared costs (>0 euro) as part of the long term care act. This entails care with stay and care at home, elderly care, psychiatric care, care during chronic illness, and care for individuals with a disability.
Mental health care (basic)	Defined as declared costs (>0 euro) for basic mental health care
Mental health care (specialized)	Defined as declared cost (>0 euro) for specialized mental health care
Social welfare	Defined as receiving social welfare within a year
Use of antipsychotics	Use of medication for psychosis (ATC code N05A)
Use of anti-depressants	Use of medication for depression (ATC code N06A)

We used annual data concerning socio-demographic and socio-economic information for our analyses. Information from a given year (e.g. 2022) was based on data registered at the end of the previous calendar year (e.g. registered by 31 December 2021). Individuals who had migrated or passed away were excluded from the study population in the calendar year following migration or death.

To minimise the risk of personal data inadvertently leading to the identification of an individual, data involving fewer than ten people were not reported. When the number of individuals between steps in the HIV care continuum (i.e. between retention in care and having ART been prescribed) amounted to fewer than five people, a range of values that included the minimum and maximum number of possible people was reported instead.

Description of the population sample

In 2022, there were 30,730 individuals ever registered in the SHM database. We were able to successfully combine the data of 28,294 (92%) individuals with data from CBS. 5,736 individuals had migrated or died by 2022, according to CBS or SHM and were subsequently excluded from the dataset. Additionally, we excluded individuals <18 years of age (n=648), with HIV-2 (n=164), who had not been in care for over 10 years (n=23), and who had no data in 2022 (n=5,568). Thus, 21,880 individuals were included in the following analyses.

Social inequalities in living with HIV in the Netherlands

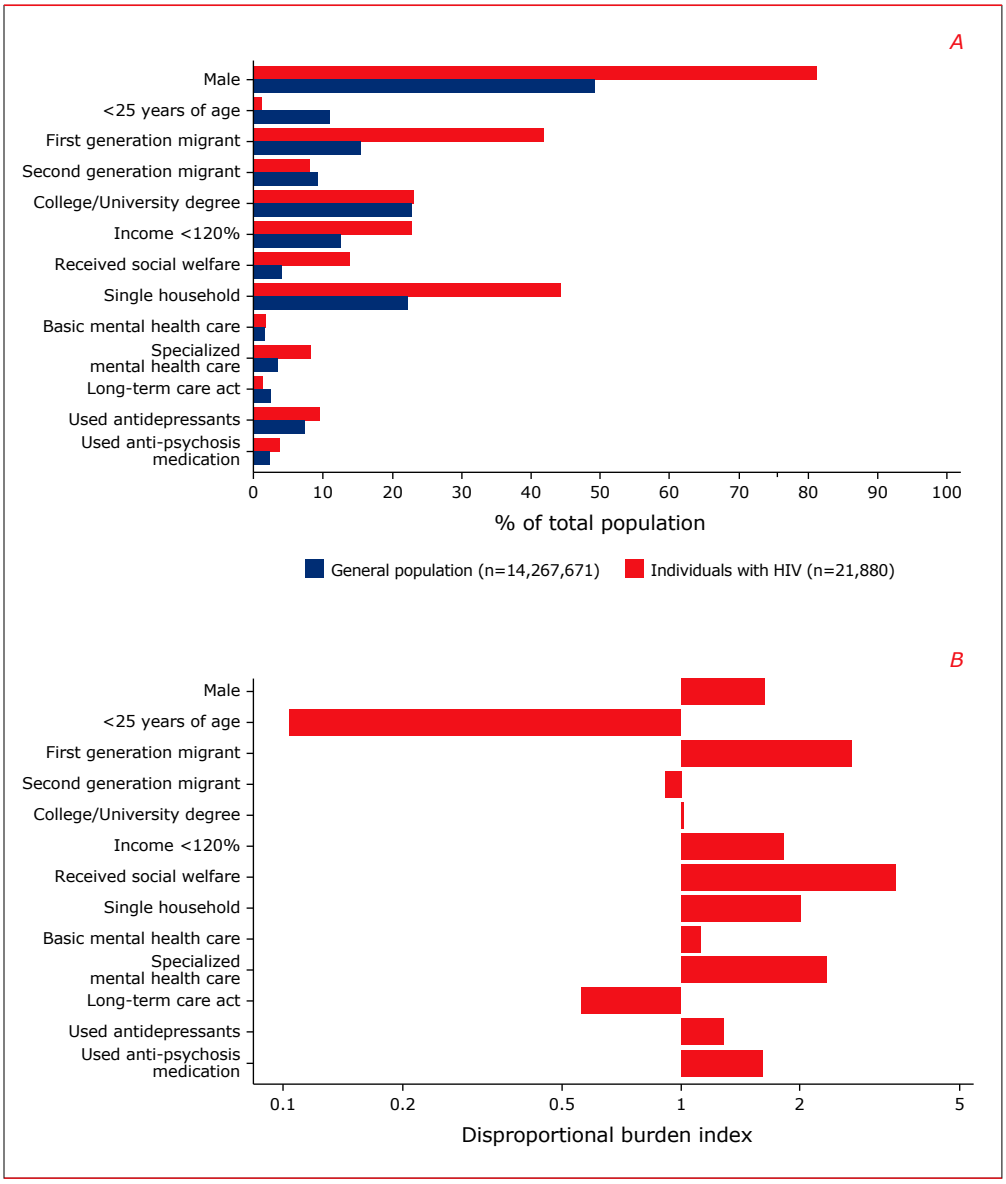
All individuals for whom demographic information was available were compared to the general population in the Netherlands aged 18 years or older (Figure 3.1).

Compared to the general population in the Netherlands, individuals ever linked to HIV care:

- were more often male;
- were less often <25 years of age;
- had more often a first generation migration background;
- lived more often in a single-person household;
- had more often an income <120% of the social minimum;
- more often received social welfare; and
- more often received specialist mental health care.

To quantify the disproportional burden of socio-demographic, -economic and health-related determinants between people with HIV and the general population, we divided the percent with a given determinant among those with HIV by the percent with the same determinant in the general population (defined herein as the “disproportional burden index”). An index of 1 indicates no disproportional burden; <1 a lower observed proportion compared to general population, and >1 a higher observed proportion.

Figure 3.1: Socio-demographic and socio-economical description of the general population aged 18 years or older and individuals with HIV in care in the Netherlands

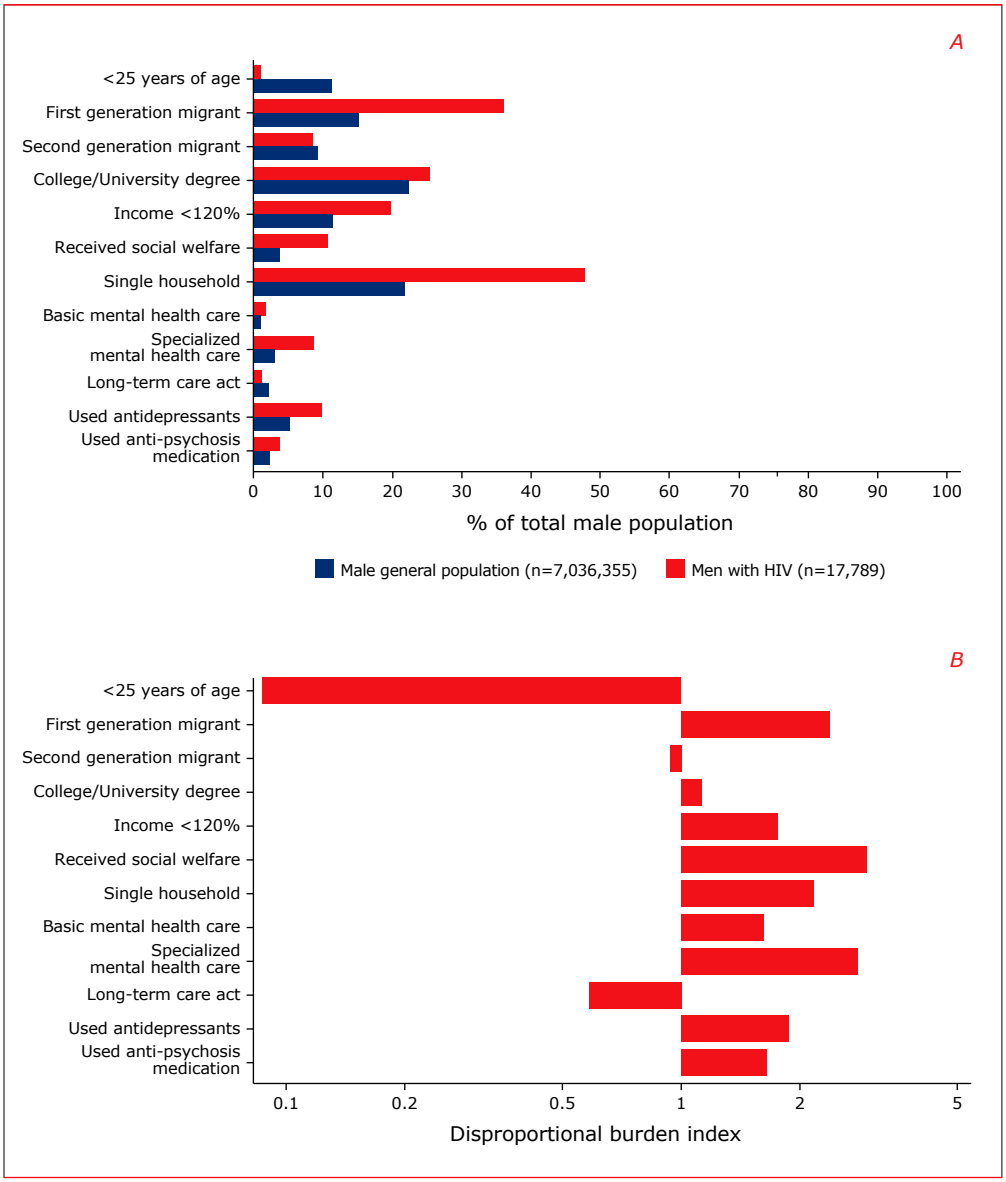


To assess the effect of gender on social disparities, we stratified the analyses by gender. As sexual preference is not available for the general population within the CBS environment, MSM and other men were combined in this analysis.

For men, differences between determinants were similar to the total population (Figure 3.2A). The disproportional burden for men with HIV was most evident for the following socio-demographic, -economic and health related determinants (Figure 3.2B): being <25 years of age (index=0.09), having a first generation migration background (index=2.4), receiving social welfare (index=3.0), living in a single-person household (index=2.2), and having used specialized mental health care (index=2.8).

Figure 3.2A: *Socio-demographic and socio-economical description among men of the general population and men with HIV in care in the Netherlands*

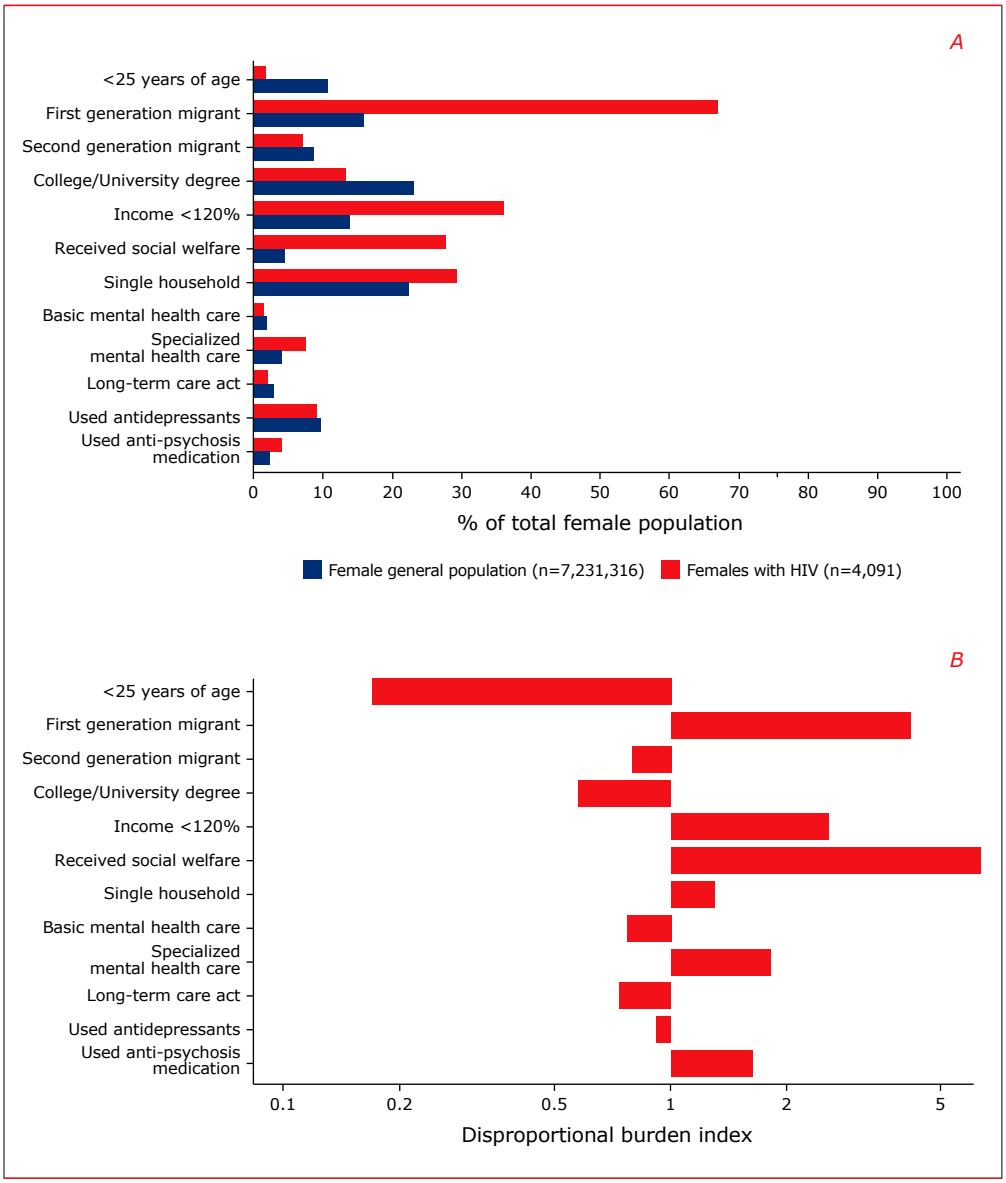
Figure 3.2B: *Disproportional burden index among men*



For women, the differences between the general population and women with HIV were even more distinct: having a first generation migration background (index=4.2), an income <120% of the social minimum (index=2.6), and receiving social welfare (index=6.3) (Figure 3.3Aa and 3.3B).

Figure 3.3A: *Socio-demographic and socio-economical description among women of the general population and women with HIV in care in the Netherlands*

Figure 3.3B: *Disproportional burden index among women*



New HIV diagnoses and late presentation from 2015 onwards

Between 2015 and 2022, 4,652 individuals with a new HIV diagnosis were registered with SHM and combined with data from CBS. Of these, 2,000 individuals had a late stage HIV diagnosis (i.e., CD4 <350/mm3 and/or an AIDS defining event at time of HIV diagnosis): 971 MSM, 380 women, 619 other men, and 30 transgender persons. Using multivariable Bayesian logistic regression we assessed the impact of socio-demographic, -economic and health related determinants on late presentation. As gender and sexual preference largely impacted the outcome, analyses were stratified for MSM, women, and other men. Transgender persons were excluded due to small numbers. To assess whether the contribution of determinants that were associated with a late diagnosis changed over time, we visualized them from 2015 onwards. For visualization purposes, women and other men were combined to reduce the risk of identifying individuals.

Older MSM, those in a two-person household with or without kids, and those with an income <120% of the social minimum had higher odds of being diagnosed with late stage HIV. The distribution of these determinants remained similar over time among MSM diagnosed with late stage HIV (Figure 3.4A). Similarly, older women and other men, and women and other men with an income <300% of the social minimum had higher odds of being diagnosed with late stage HIV. Type of household had no effect. Over time, the proportion of women and other men diagnosed with late stage HIV with an income <120% seemed to increase slightly (Figure 3.4B).

Figure 3.4: *Impact of socio-demographic and socio-economic determinants on being diagnosed with late stage HIV*

Figure 3.4A: *Men who have sex with men*

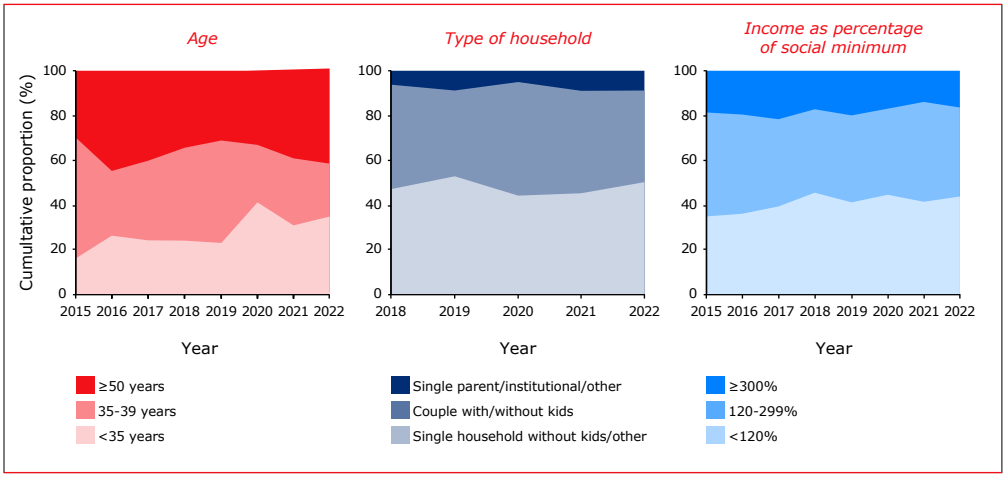
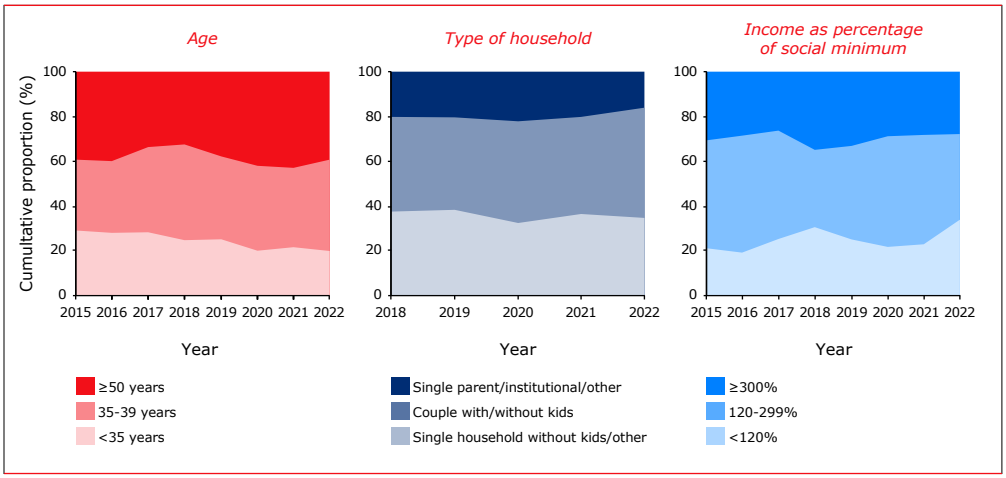


Figure 3.4B: *Women and other men*



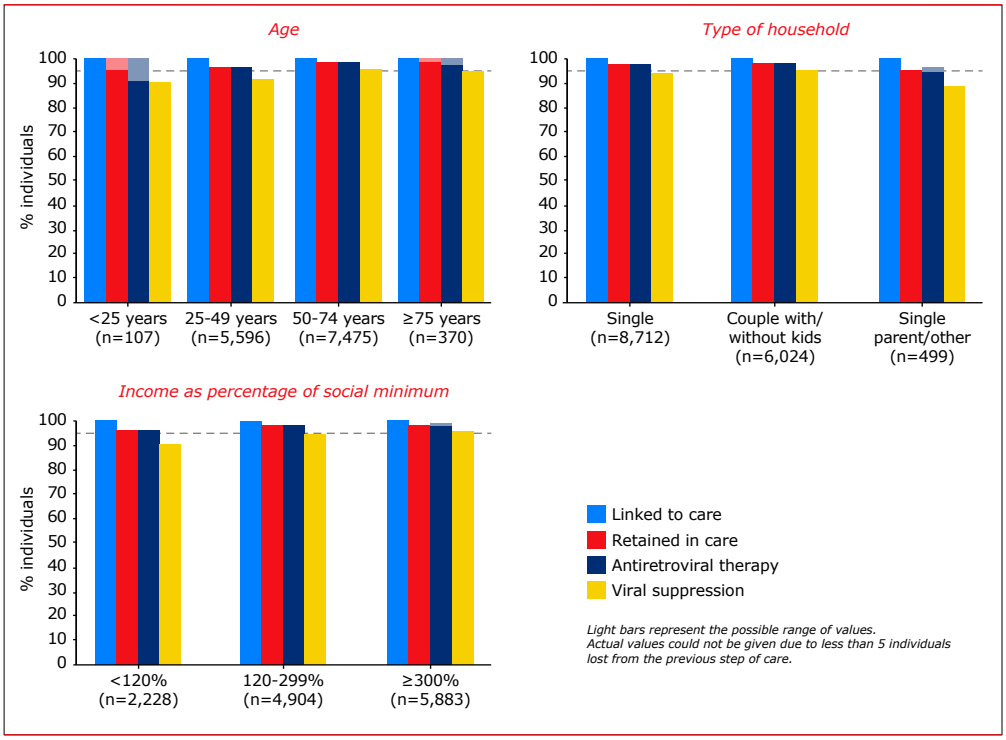
HIV Care Continuum

Using multivariable Bayesian logistic regression we assessed socio-demographic, -economic, and health related determinants for having a detectable viral load (i.e., a HIV RNA >200 cells/mL). As gender and sexual preference largely impacted the outcome, analyses were stratified for MSM, women and other men. We generated HIV care continuums for those determinants that were significantly associated with having a detectable viral load.

Men who have sex with men

Viral suppression was less than 95% among MSM <50 years of age, living in a single or single parent/other (e.g., institutionalized) household and those with an income <120% of the social minimum. Figure 3.5 shows the HIV care continua among MSM, stratified by age, type of household, and income as a percentage of the social minimum.

Figure 3.5: HIV care continuum in 2022 among MSM

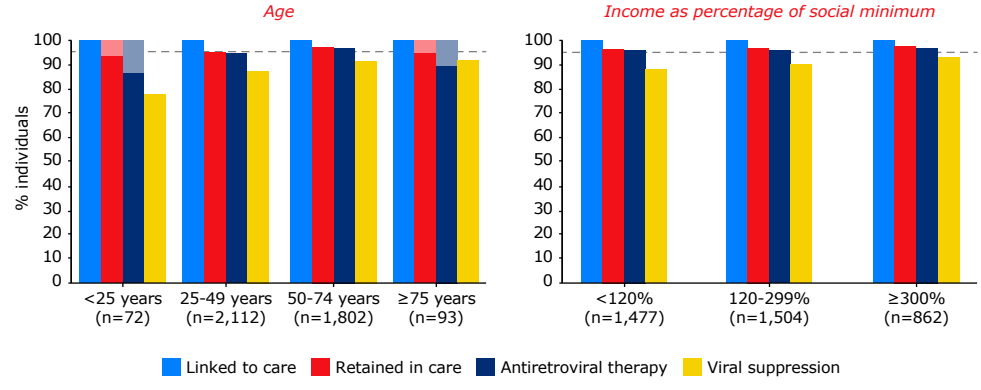


The red dashed line represents 95%.

Women

The effect of lower age and lower income on viral suppression was even stronger among women compared to MSM. While older women and women with an income ≥300% of the social minimum were more often virally suppressed, viral suppression was below 95% across all categories of income. In contrast to MSM, household type did not affect viral suppression among women. Figure 3.6 shows the HIV care continua among women, stratified by age and income.

Figure 3.6: HIV care continuum in 2022 among women

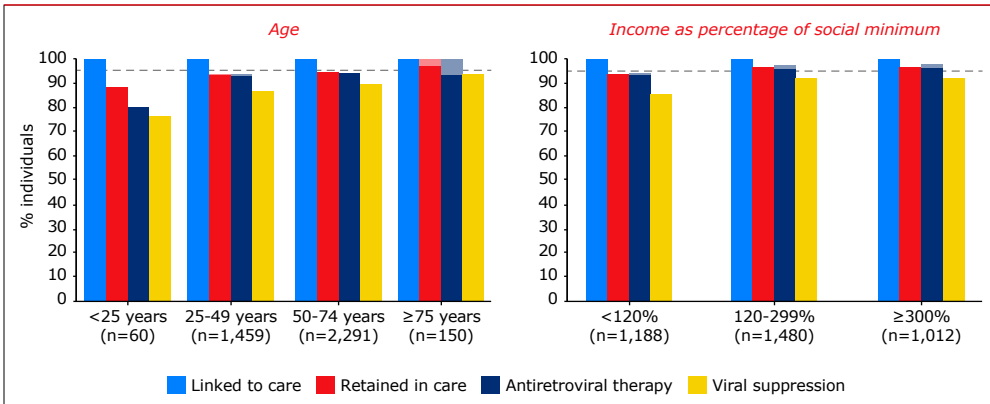


The red dashed line represents 95%.

Other men

The effect of lower age and lower income on viral suppression was also strong among other men. Similar to what was observed among women, viral suppression was below 95% across all categories of age and income. Household type also did not affect viral suppression among other men. Figure 3.7 shows the HIV care continua among other men, stratified by age and income.

Figure 3.7: HIV care continuum in 2022 among other men



The red dashed line represents 95%.

Disengagement from care

In total, 299 MSM and 394 women and other men disengaged from care until 2022. We again assessed the effect of socio-demographic, -economic, and health related determinants on disengagement from care using multivariable Bayesian logistic regression, stratified for MSM, women and other men. Women and other men were taken together due to small numbers. Determinants that were significantly associated with disengagement from care were visualized using bar graphs.

Younger MSM, those living in a single parent or other (e.g., institutionalized) household and those with an income <120% of the social minimum were more likely to disengage from care before 2022 (Figure 3.8).
Similarly, younger women and other men and those with an income <120% of the social minimum were more likely to disengage from care. Additionally, women and other men who had a detectable viral load at their last viral load measurement were more likely to disengage from care (Figure 3.9).

Figure 3.8: Determinants of disengagement from care among MSM

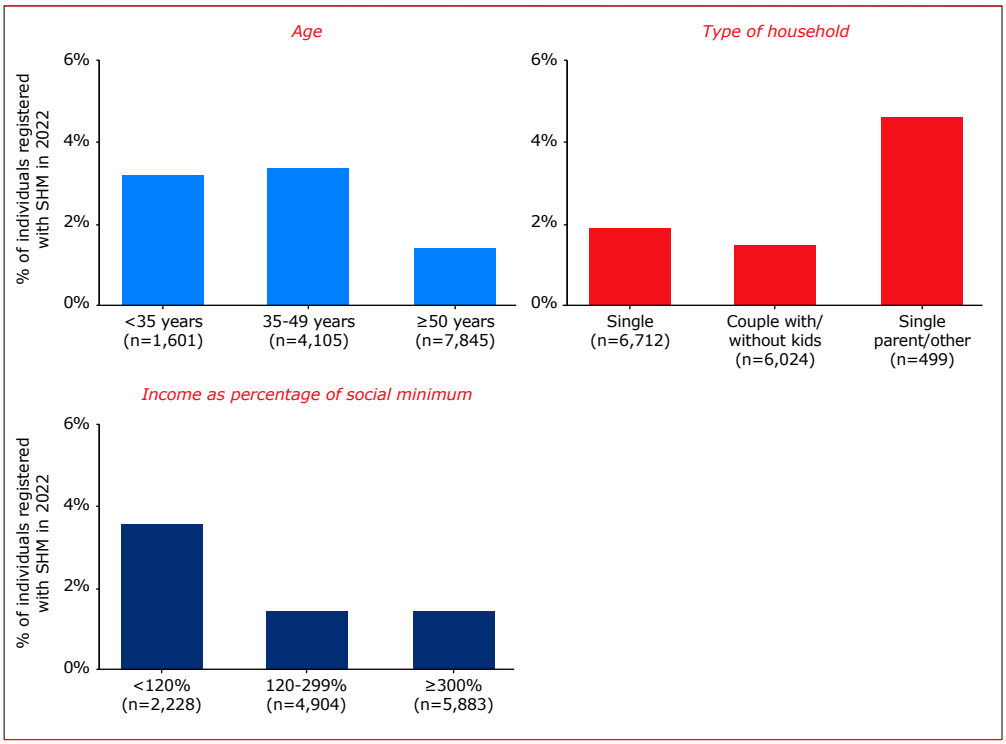
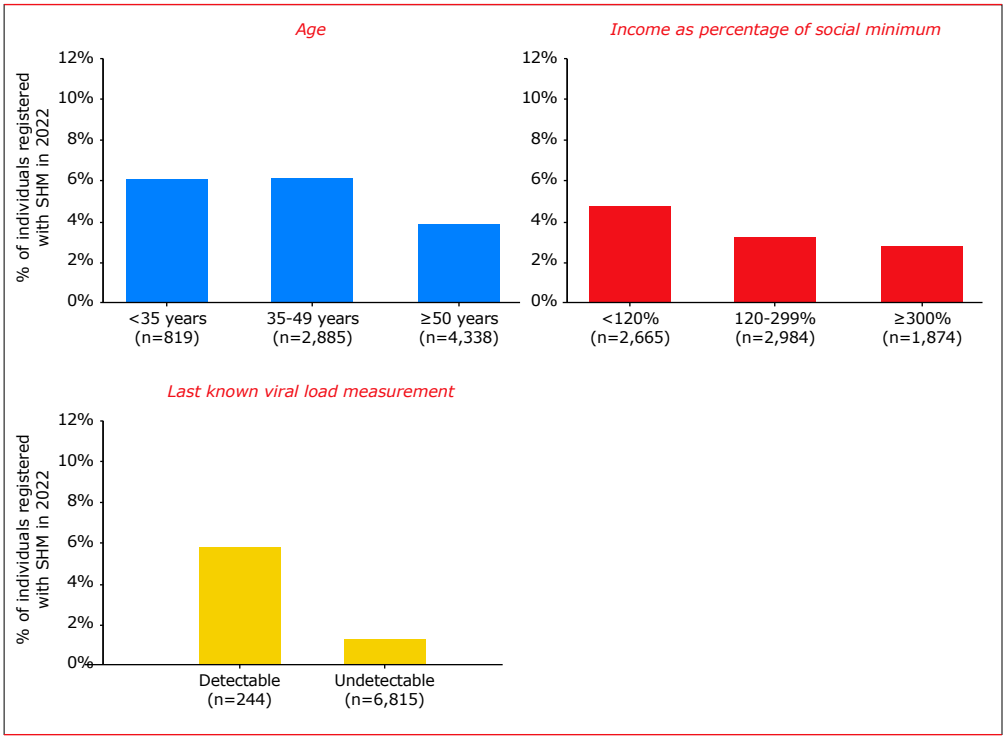


Figure 3.9: Determinants of disengagement from care among women and other men



Conclusions

In 2022, there was strong evidence for a disproportional burden of HIV infection among men and women when comparing socio-demographic, ecnonomic, and health-related data from individuals diagnosed with HIV and the general population in the Netherlands. Additionally, while the HIV care continuum mentioned in Chapter 1 almost reaches the 95-95-95 UNAIDS targets, the HIV care continuum is suboptimal among those with lower incomes. Income, age and household size seem to largely impact progression through the HIV care continuum, as well as engagement in care and stage of HIV diagnosis.

Box 3.3: an interactive tool to guide HIV prevention and care in the Netherlands

The Netherlands aims to end HIV transmission within the country by 2027. Although significant progress has been made, new innovative approaches are needed to reach this goal. We are working on an online, interactive tool that is developed using an existing research platform and allows a low threshold, workable interface for use in HIV prevention and care. The dashboard could hopefully support regions in the Netherlands in evaluating existing and developing new strategies aimed at optimizing HIV prevention and care.

The online dashboard is built using data from SHM and Statistics Netherlands (CBS). The dashboard is updated yearly with statistics on the number of new HIV diagnoses, disease stage and the number of people at each step of the HIV care continuum using UNAIDS definitions, as well as information about PrEP use. All statistics can be stratified by region and key population (i.e., women, men who have sex with men, other men, and transgender people), and viewed over time from 2010 to 2023.

For professionals who work with the community we have developed a more in-depth version of the dashboard which, among other things, includes information on health care consumption prior to HIV diagnosis. A password is needed to access this part of the dashboard which can be requested individually.

The dashboard was developed in collaboration with the Amsterdam Health & Technology Institute using R shiny. Version 3 of the dashboard is currently available online at: https://dashboard.hiv-monitoring.nl/nl

4. Response to antiretroviral therapy

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

Introduction

The primary goals of antiretroviral therapy (ART) are to prevent HIV disease progression, improve clinical outcomes, and prevent onward HIV transmission[1,2]. Treatment guidelines across the globe recommend the initiation of ART as soon as possible in all people diagnosed with HIV, irrespective of CD4 count, HIV viral load or clinical disease stage. In people with very low CD4 counts or with active opportunistic infections, ART is often started as soon as possible, while in others ART is started after the initial evaluation (complete medical history, physical examination, and laboratory testing including genotypic resistance testing) has been completed. The decision to initiate ART should always include consideration of a person's comorbid conditions and readiness to start and maintain ART[3-7]. In general, the guidelines of the Dutch Association of HIV Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) follow the US Department of Health and Human Services guidelines[8].

Besides preventing clinical events, including but not limited to opportunistic infections and malignancies, the rapid start of ART is also more effective at preventing onward transmission of HIV than deferral of treatment[9,10]. People with HIV on ART with an undetectable viral load in their blood have no risk of onward sexual transmission of HIV, (i.e. undetectable equals untransmittable, or U = U[11-16]). Sustained suppression of HIV replication requires selection of appropriate treatment and good adherence to treatment.

The use of guideline-recommended ART regimen generally results in sustained suppression of HIV viral to undetectable levels. However, in the setting or repeated and/or prolonged episodes of loss of viral suppression while on ART, the used antiretroviral agents continue to exert selective pressures that may result in the selection of viral strains harbouring drug resistance-associated mutations. Over time, further accumulation of resistance-associated mutations in the HIV genome can occur, thereby increasing the risk of poor clinical outcomes[16-22].

In this chapter, we describe trends over time in the use of ART, and trends in the virological and immunological responses to ART during the last 10 calendar years, in adults registered by "stichting hiv monitoring" (SHM) and enrolled in the ATHENA cohort[23]. We also analyse the presence of transmitted and acquired HIV drug resistance.

Starting antiretroviral therapy

In total, 7,860 ART-naïve people with HIV were aged 15 years or above at the time of diagnosis and initiated first-line ART in the Netherlands between January 2014 and December 2023. SHM systematically collects the date of entry into the Netherlands for people born in other countries. For an increasing proportion of these people it is known if they have been diagnosed with HIV and started ART before or after entering the Netherlands. In *Table 4.1*, we have grouped people by calendar year of ART initiation: 5,299 started in 2014-2018, 682 in 2019, 509 in 2020, 452 in 2021, 470 in 2022, and 448 in 2023. People diagnosed with HIV in other countries who had already initiated ART prior to arriving in the Netherlands are not included in this analysis.

Of the 7,860 people known to have initiated ART since January 2014, 4,993 (63.5%) were men who have sex with men (MSM), 1,532 (19.5%) other men, 1,180 (15.0%) women, and 155 (2.0%) were transgender people. Overall, 4,479 (57.0%) originated from the Netherlands. The proportion of people born in the Netherlands has been steadily declining: from 60.8% in 2014-2018, to 51.2% in 2019, 51.5% in 2020, 49.3% in 2021, 47.4% in 2022, to 45.1% in 2023. There was a steady increase in the proportion of people born in eastern and central Europe (in recent years predominantly from Ukraine); from 5.8% in 2014-2018, to 14.7% in 2023. The proportion of people from other world regions only fluctuated slightly.

Prompt initiation of ART following HIV diagnosis has increased over time, reflecting implementation and uptake of evolving HIV treatment guidelines (*Figure 4.1A*). Among people with an accurate date of HIV diagnosis in our database who started ART in the Netherlands, the median time between HIV diagnosis and ART initiation shifted from 42 days (interquartile range [IQR] 22-99) for those who entered care in 2014, to 25 (IQR 14-40) in 2018, to 19 (IQR 11-31) days in 2023. The time between entering care in an HIV treatment center and starting ART decreased over time (*Figure 4.1B*). The vast majority of newly diagnosed, ART-naïve people entering care in the Netherlands initiated ART within one month (93.4% in 2023). People originating from sub-Saharan Africa, the Caribbean, north Africa and the middle East, and eastern Europe were overrepresented among those starting more than 1 month after HIV diagnosis. The delay between a positive HIV test result and initiating ART was mostly driven by a longer period between HIV diagnosis and being linked to care in an HIV treatment center.

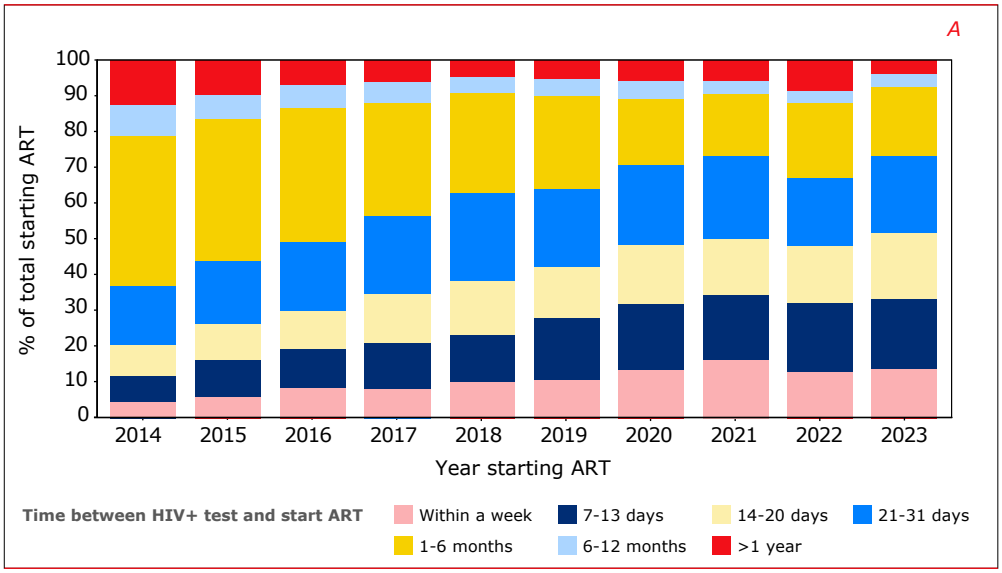
Table 4.1 Characteristics of people starting antiretroviral therapy in 2014–2023.

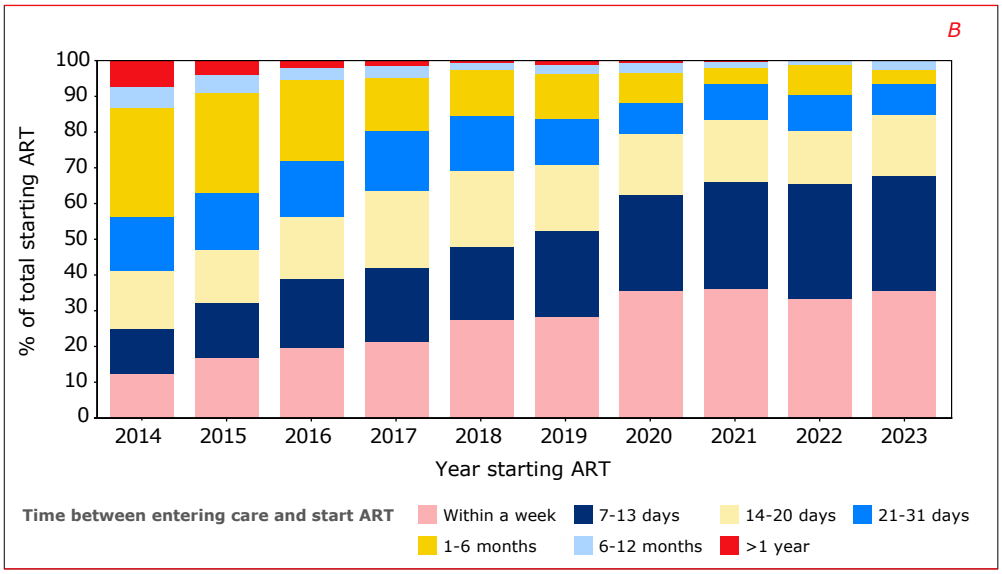
Year of ART initiation		**2014–2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2014–2023**
Number of individuals		5,299	682	509	452	470	448	7,860
DEMOGRAPHICS								
Age at ART initiation (years)	Median	39.4	39.3	39.2	40	39.6	38.8	39.4
	Q1–Q3	30.3–49.5	30–49.7	30.2–50.3	31.3–52.3	31.4–51.3	30.6–50.5	30.4–50
Male sex (at birth)	n	4582	557	417	377	375	367	6,675
	%	86.5	81.7	81.9	83.4	79.8	81.9	84.9
HIV acquisition group								
MSM	n	3,576	383	287	263	237	247	4,993
	%	67.5	56.2	56.4	58.2	50.4	55.1	63.5
Other men	n	930	159	110	100	123	110	1,532
	%	17.6	23.3	21.6	22.1	26.2	24.6	19.5
Women	n	717	123	92	73	95	80	1,180
	%	13.5	18	18.1	16.2	20.2	17.9	15
Transgender people	n	76	17	20	16	15	11	155
	%	1.4	2.5	3.9	3.5	3.2	2.5	2
Region of origin								
The Netherlands	N	3,220	349	262	223	223	202	4,479
	%	60.8	51.2	51.5	49.3	47.4	45.1	57
Western Europe/North America/	n	276	26	21	21	13	14	371
Australia	%	5.2	3.8	4.1	4.6	2.8	3.1	4.7
Eastern/central Europe	n	307	58	62	59	79	66	631
	%	5.8	8.5	12.2	13.1	16.8	14.7	8
Latin America and the Caribbean	n	654	118	70	72	50	73	1,037
	%	12.3	17.3	13.8	15.9	10.6	16.3	13.2
Sub-Saharan Africa	n	462	71	58	36	56	51	734
	%	8.7	10.4	11.4	8	11.9	11.4	9.3
Other	n	380	60	36	41	49	42	608
	%	7.2	8.8	7.1	9.1	10.4	9.4	7.7

Year of ART initiation		2014–2018	2019	2020	2021	2022	2023	2014–2023
CLINICAL								
Recent infection (within 12 months of diagnosis)	n	1,395	158	110	75	89	94	1,921
	%	26.3	23.2	21.6	16.6	18.9	21	24.4
Ever having tested HIV-negative	n	3,092	372	272	227	229	238	4,430
	%	58.4	54.5	53.4	50.2	48.7	53.1	56.4
CD4 count at start of ART	Median	403	368	325	301	360	360	385
	Q1–Q3	220–580	169–570	140–557	130–540	150–557	183–570	200–570
HIV RNA (log_{10} cp/ml) at start of ART	Median	4.7	4.8	4.9	5.2	4.8	5.1	4.8
	Q1–Q3	4.1–5.3	4.1–5.5	4.2–5.6	4.5–5.8	3.9–5.6	4.2–5.7	4.1–5.4
(Prior) AIDS at start of ART	n	686	102	105	88	78	76	1,135
	%	12.9	15	20.6	19.5	16.6	17	14.4
Hepatitis B status at start of ART								
HBV-negative (HBsAg-negative)	n	4,952	640	471	420	434	425	7,342
	%	93.5	93.8	92.5	92.9	92.3	94.9	93.4
HBV-positive (HBsAg-positive)	n	142	16	18	10	24	10	220
	%	2.7	2.3	3.5	2.2	5.1	2.2	2.8
Unknown	n	205	26	20	22	12	13	298
	%	3.9	3.8	3.9	4.9	2.6	2.9	3.8
Hepatitis C status at start of ART								
HCV-negative	n	5,055	644	479	420	442	415	7,455
	%	95.4	94.4	94.1	92.9	94.0	92.6	94.8
HCV RNA-positive	n	97	10	8	5	16	12	148
	%	1.8	1.5	1.6	1.1	3.4	2.7	1.9
HCV Ab seropositive	n	73	9	10	10	4	9	115
	%	1.4	1.3	2.0	2.2	0.9	2.0	1.5
Unknown	n	74	19	12	17	8	12	142
	%	1.4	2.8	2.4	3.8	1.7	2.7	1.8
ART started during pregnancy	n	99	18	10	9	8	6	150
	%	1.9	2.6	2	2	1.7	1.3	1.9

Legend: *ART = antiretroviral therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; NRTI = nucleoside analogue reverse transcriptase inhibitor.*

Figure 4.1A&B: Time between HIV diagnosis and initiation of antiretroviral therapy (ART) in 2014-2023 (A) and time between entry into HIV care and initiation of ART in 2014-2023 (B).





Legend: ART = antiretroviral therapy.

There was a slight decrease in the median CD4 count at the start of ART from 403 cells/mm^3 (IQR 220-580) in 2014-2018, to a low of 301 (130-540) in 2021 during COVID-19 lockdowns, followed by an increase to 360 (183-570) cells/mm^3 in 2023. The slightly higher CD4 counts in the period 2014-2018 are mainly caused by the substantial group people already in care but not on ART (because of their high CD4 counts), most of whom subsequently initiated ART in 2015 and 2016 following the 2015 guideline change recommending ART for all, irrespective of CD4 count. In the period 2014-2018, at the start of ART, 12.9% of individuals had already been diagnosed with an AIDS-defining condition; this increased to 17.0% in 2023.

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

Changes in the use of initial ART regimen

Data from clinical trials on contemporary antiretroviral drugs have shown good outcomes in terms of viral suppression, convenience, tolerability, and toxicity. Over the past years, these new antiretroviral drugs and new, once-daily, fixed-dose combination regimens have been approved in the Netherlands (*Box 4.1*). In this section, we evaluate the post-approval implementation of these new drugs/regimens in HIV treatment.

Box 4.1: Approval dates of new antiretroviral drugs/regimens for HIV treatment in the Netherlands in 2013–2023.

Medicine	Authorisation date
TDF/FTC/EVG/cobicistat (Stribild®)	24 May 2013
DTG (Tivicay®)	16 January 2014
ABC/3TC/DTG (Triumeq®)	01 September 2014
DRV/cobicistat (Rezolsta®)	19 November 2014
TAF/FTC/EVG/cobicistat (Genvoya®)	19 November 2015
TAF/FTC (Descovy®)	21 April 2016
TAF/FTC/RPV (Odefsey®)	21 June 2016
TAF (Vemlidy®)	09 January 2017
TAF/FTC/DRV/cobicistat (Symtuza®)	21 September 2017
DTG/RPV (Juluca®)	21 May 2018
TAF/FTC/BIC (Biktarvy®)	25 June 2018
Doravirine (Pifeltro®)	22 November 2018
TDF/3TC/Doravirine (Delstrigo®)	22 November 2018
3TC/DTG (Dovato®)	03 July 2019
Cabotegravir (Vocabria®)	17 December 2020
Rilpivirine (Rekambys®)	17 December 2020
Fostemsavir (Rukobia®)	04 February 2021
Lenacapavir (Sunlenca®)	17 August 2022

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 ART regimen

In the period 2014-2023, all guideline-recommended first-line ART regimen consist of a nucleoside-analogue reverse transcriptase inhibitor (NRTI) backbone, plus one anchor-drug. The NRTI-backbone usually consists of two NRTI, with the exception of the regimen 3TC/DTG. In the period 2014-2023, the recommended anchor-drugs are from the integrase inhibitor (INSTI), non-nucleoside RT inhibitor (NNRTI), or protease inhibitor (PI) class. The use of other ART regimen, i.e. dual-anchor class regimen with or without the addition of NRTI, have become much more common in recent years, but only in treatment-experienced individuals.

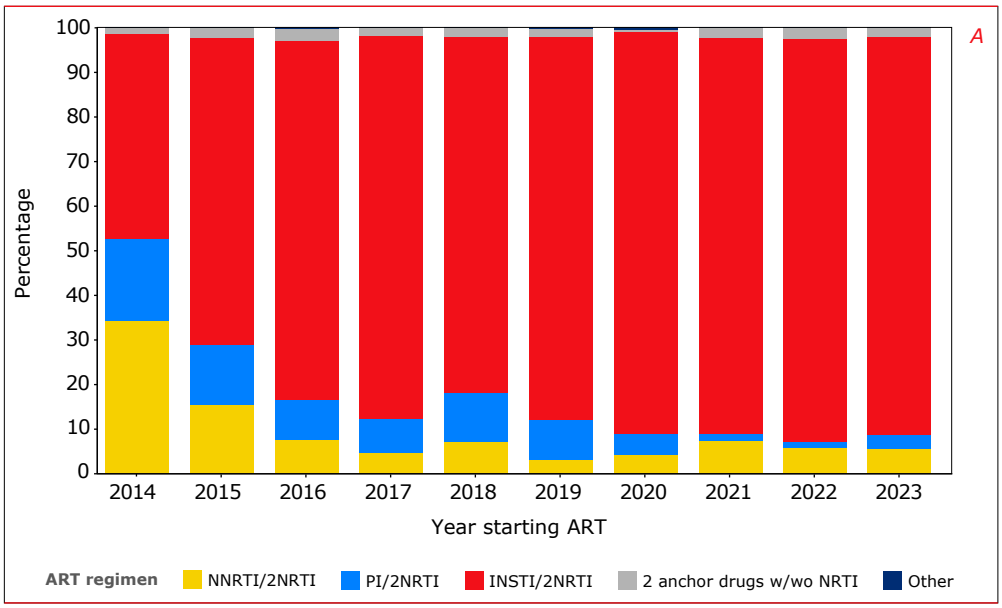
In recent years, in certain groups of newly diagnosed individuals, ART is initiated with a regimen containing 2 anchor-drugs plus 2 NRTI, with the intention to simplify this regimen as soon as possible. This includes individuals initiating ART during an acute HIV infection or individuals with low CD4 counts and opportunistic infections who quickly initiate ART before the results of HIV genotypic resistance testing (and HBV testing) have become available. In these individuals, ART is subsequently simplified to a guideline-recommended regimen as soon as the first undetectable viral load measurement and/or the results of the genotypic resistance testing have become available. The starting regimens of the individuals who initiated therapy using this strategy have been set to their second simplified guideline-recommended regimen.

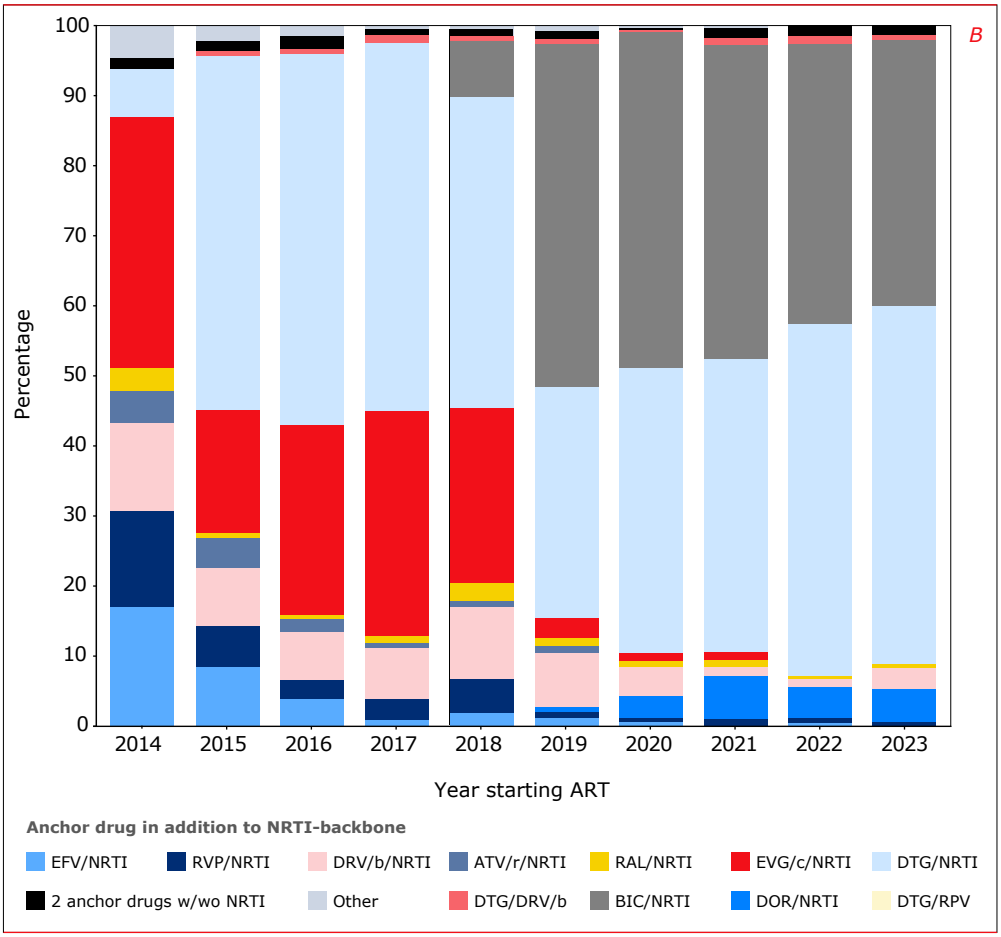
For the 7,860 ART-naïve people who initiated first-line ART between 2014 and 2023, *Figures 4.2A&B* show the trends over time in anchor-drug additions to the NRTI backbone used as part of the initial ART regimen. The use of INSTI in combination with a (mono- or dual-) NRTI backbone as initial therapy, increased from 46.0% in 2014 to 89.3% in 2023 (91.3% including other INSTI-containing dual anchor-drug regimen). The use of NNRTIs in combination with a NRTI backbone as the initial regimen decreased from 33.9% in 2014 to 5.4% in 2023. The use of PIs in combination with a NRTI backbone as the initial regimen also decreased from 18.6% in 2016 to 3.3% in 2022.

In the period 2014-2023, between 1% and 2.5% of individuals (2.0% in 2023) used a dual anchor-drug regimen. As explained above, this excludes individuals in whom the abovementioned strategy was implemented of starting with a dual anchor-drug regimen quickly followed by a simplification to a standard guideline-recommended regimen.

Figure 4.2B shows all anchor drug additions to the NRTI backbone that were used as part of the initial regimen in at least 5% of individuals during one or more calendar years between 2014-2023. The regimens that were used less frequently have therefore been included in the category 'other' in *Figure 4.2B*. Full details on the initial regimens are shown in Table 4.2.

Figure 4.2A&B: Anchor-class (A) and individual anchor-drug (B) plus nucleoside reverse transcriptase backbone used as part of the initial regimen in 2014-2023.



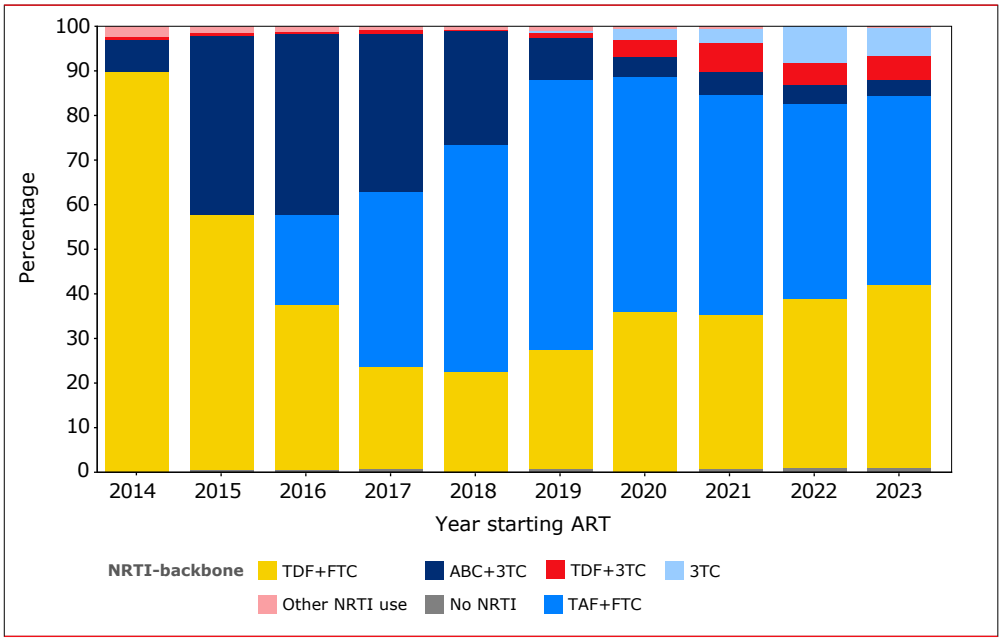


Legend: *ART = antiretroviral therapy; b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; ENTRY = entry inhibitor; INSTI = integrase inhibitor; NRTI = nucleoside analogue reverse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

Figure 4.3 provides an overview of the NRTI backbone components of the initial regimens used in 2014-2023. The combination of tenofovir disoproxil (TDF) or alafenamide (TAF) with emtricitabine (FTC) was the predominant backbone prescribed. Following its introduction at the end of 2015, use of TAF in in initial

ART regimens rapidly increased with a maximum of 61.0% in 2019, but has since slowly declined to 42.6% in 2023. At the same time, TDF use decreased from 90.9% in 2014 to a low of 22.1% in 2018, after which its use increased again to 46.7% in 2023. The use of abacavir steadily decreased from a high of 41.0% of all initial regimens in 2016 to 3.4% in 2023.

Figure 4.3: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2014–2023.*



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

The most common ART regimens initiated in 2014-2023 are presented in *Figure 4.4* and *Table 4.2*. In 2023, the most frequently used initial regimen was TDF/FTC/dolutegravir (39.5%). TAF/FTC/bictegravir was used in 37.7% of initial regimens. Additionally, 4.7% initiated a doravirine-containing, once-daily, fixed-dose combination with lamivudine (3TC) and tenofovir disoproxil (TDF). *Table 4.2* provides more detail on the 'other' initial regimens and other calendar years that are not further specified in *Figures 4.2A&B*, *4.3* and *4.4*.

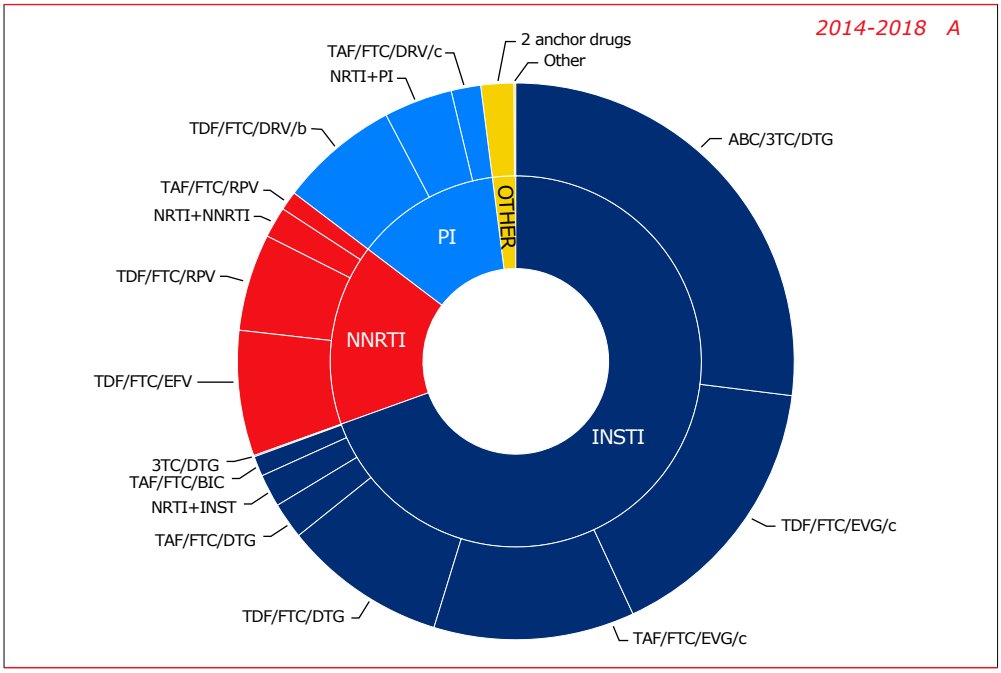
Table 4.2: Initial regimens in 2014–2023.

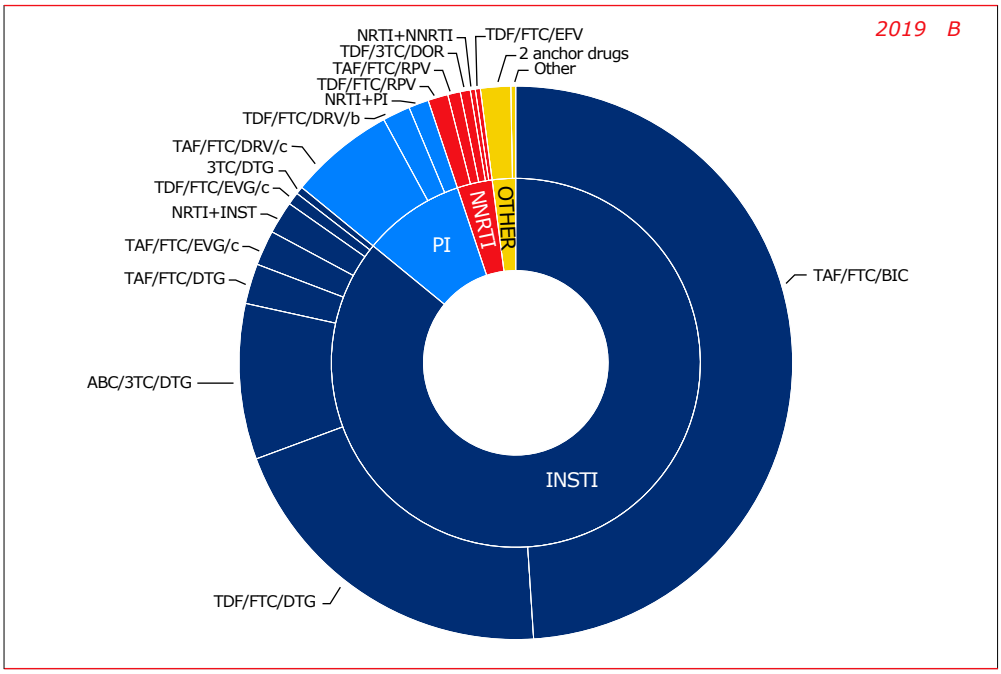
		2014–2018	2019	2020	2021	2022	2023	2014–2023
	n	5,299	682	509	452	470	448	7,860
INSTI + NRTI								
TAF/FTC/BIC	n	62	334	243	202	187	169	1,197
	%	1.2	49	47.7	44.7	39.8	37.7	15.2
DTG/3TC	n	4	3	12	14	37	28	98
	%	0.1	0.4	2.4	3.1	7.9	6.3	1.2
ABC/3TC/DTG	n	1429	62	23	23	20	15	1572
	%	27	9,1	4,5	5,1	4,3	3,3	20
TDF/FTC/DTG	n	503	139	162	141	169	177	1,291
	%	9,5	20,4	31.8	31.2	36	39.5	16.4
TAF/FTC/DTG	n	112	16	8	10	8	6	160
	%	2.1	2.3	1.6	2.2	1.7	1.3	2
TAF/FTC/EVG/c	n	618	14	6	2	.	.	640
	%	11.7	2.1	1.2	0.4	.	.	8.1
TDF/FTC/EVG/c	n	854	5	.	2	.	.	861
	%	16,1	0,7	.	0.4	.	.	11
TDF/FTC/RAL	n	64	6	3	4	1	.	78
	%	1,2	0,9	0.6	0.9	0.2	.	1
Other NRTI + INST	n	37	7	4	3	3	5	59
	%	0.7	1	0.8	0.7	0.6	1.1	0.8
NNRTI + NRTI								
TDF/FTC/EFV	n	386	8	2	2	3	.	401
	%	7,3	1,2	0.4	0.4	0.6	.	5.1
TDF/FTC/NVP	n	50	1	.	1	.	.	52
	%	0,9	0,1	.	0.2	.	.	0.7
TDF/FTC/RPV	n	299	2	.	2	.	1	304
	%	5,6	0,3	.	0.4	.	0.2	3.9
TDF/3TC/DOR	n	.	4	16	27	20	21	88
	%	.	0,6	3.1	6	4.3	4.7	1.1
ABC/3TC/NVP	n	7	.	.	.	.	.	7
	%	0.1	.	.	.	.	.	0.1
TAF/FTC/RPV	n	59	5	3	1	3	2	73
	%	1.1	0.7	0.6	0.2	0.6	0.4	0.9
Other NRTI + NNRTI	n	38	1	1	.	.	.	40
	%	0.7	0.1	0.2	.	.	.	0.5

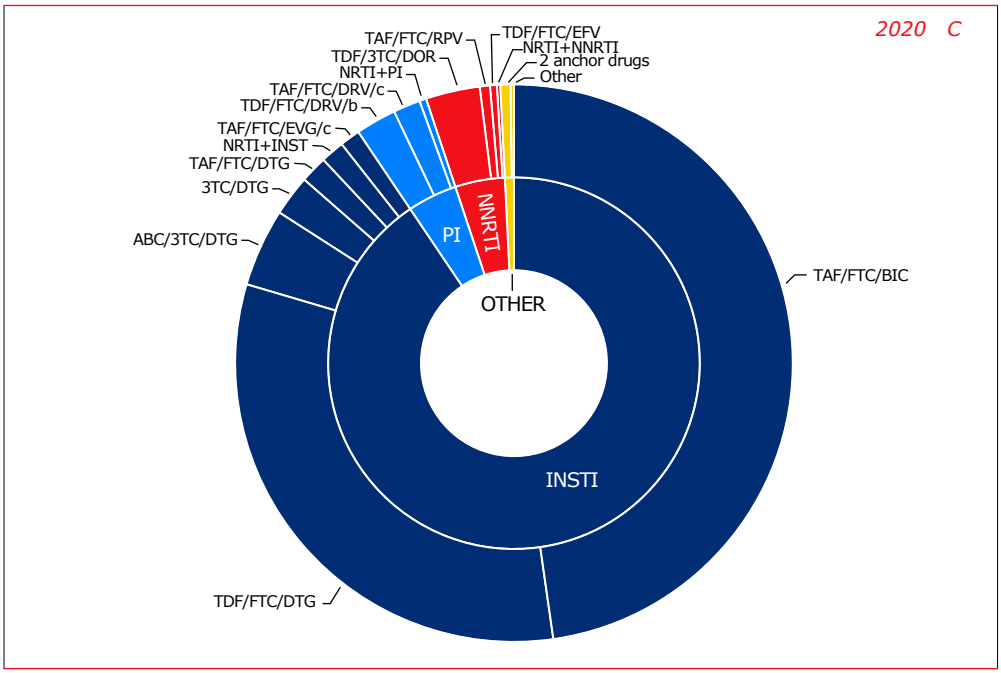
		2014–2018	2019	2020	2021	2022	2023	2014–2023
	n	5,299	682	509	452	470	448	7,860
PI + NRTI								
TDF/FTC/ATV/b	n	123	6	.	.	.	.	129
	%	2,3	0,9	.	.	.	.	1.6
TAF/FTC/DRV/c	n	91	42	8	5	5	12	163
	%	1.7	6.2	1.6	1.1	1.1	2.7	2.1
TDF/FTC/DRV/b	n	368	11	12	2	2	2	397
	%	6,9	1,6	2.4	0.4	0.4	0.4	5.1
TDF/FTC/LPV/r	n	10	.	.	.	.	.	10
	%	0,2	.	.	.	.	.	0.1
Other NRTI + PI	n	78	2	2	.	.	1	83
	%	1.5	0.3	0.4	.	.	0.2	1.1
2 anchor drugs								
DTG/DRV/b	n	25	3	1	4	5	3	41
	%	0.5	0.4	0.2	0.9	1.1	0.7	0.5
DTG/RPV	n	.	1	.	.	.	.	1
	%	.	0.1	.	.	.	.	0
2 anchor drugs w/wo NRTI	n	76	8	2	7	7	5	105
	%	1.4	1.2	0.4	1.5	1.5	1.1	1.3
Other ART	n	6	2	1	3	4	2	26
	%	0.1	0.3	0.1	0.3	0.5	0.3	0.5

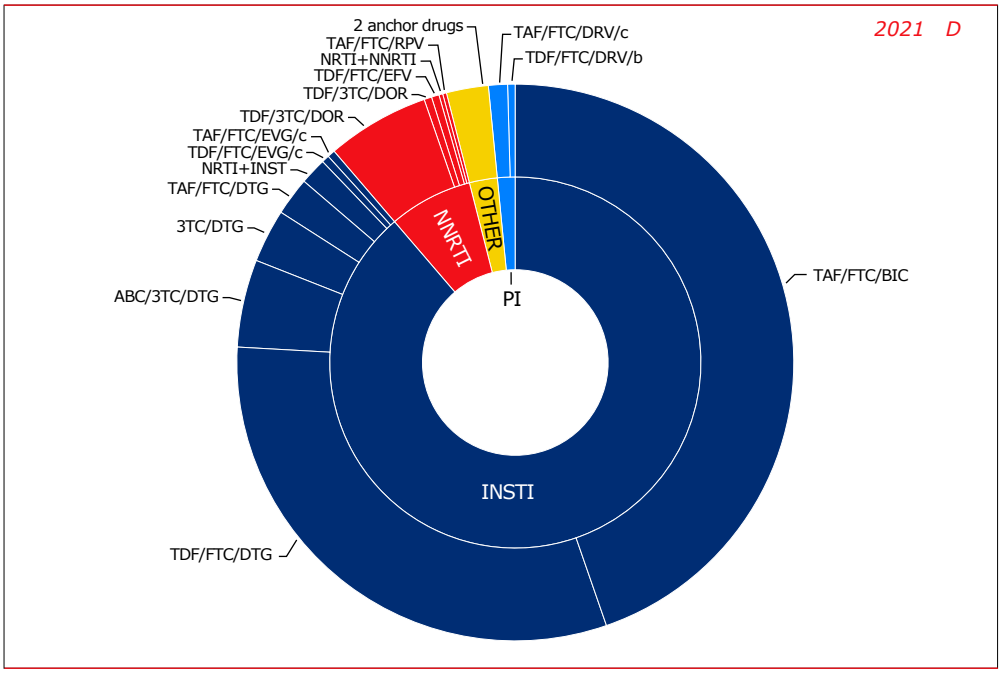
Legend: *ARVs = antiretroviral drugs; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; BIC = bictegravir; CI = confidence interval; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG =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

Figure 4.4: The initial antiretroviral therapy regimens given in 2014–2023.






2020 C
TAF/FTC/RPV
TDF/3TC/DOR
NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/DRV/b
TAF/FTC/EVG/c
NRTI+INST
TAF/FTC/DTG
3TC/DTG
ABC/3TC/DTG
TDF/FTC/DTG
TDF/FTC/EFV
NRTI+NNRTI
2 anchor drugs
Other
TAF/FTC/BIC
PI
NNRTI
OTHER
INSTI


2021 D
2 anchor drugs
TAF/FTC/RPV
NRTI+NNRTI
TDF/FTC/EFV
TDF/3TC/DOR
TDF/3TC/DOR
TAF/FTC/EVG/c
TDF/FTC/EVG/c
NRTI+INST
TAF/FTC/DTG
3TC/DTG
ABC/3TC/DTG
TDF/FTC/DTG
TAF/FTC/DRV/c
TDF/FTC/DRV/b
TAF/FTC/BIC
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NNRTI
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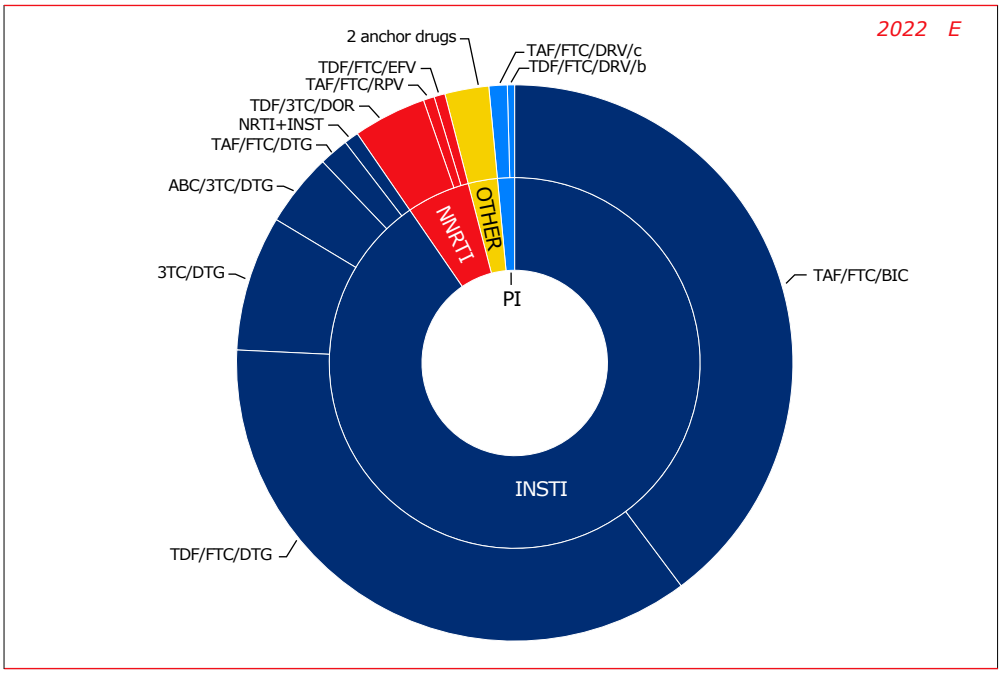
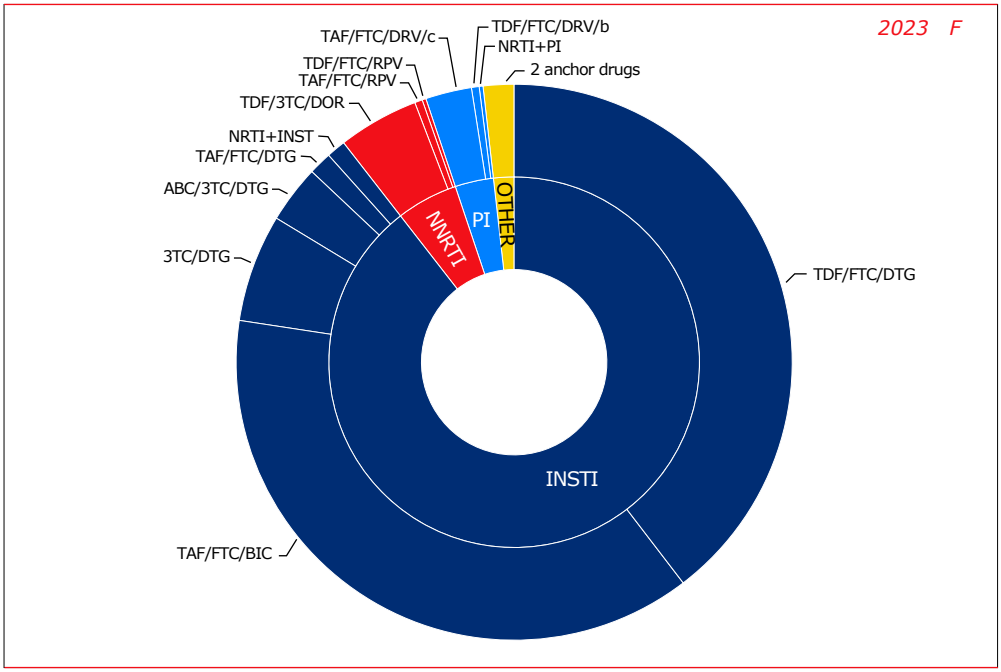




Legend: *3TC = lamivudine; ABC = abacavir; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; BIC = bictegravir; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase inhibitor; NNRTI = non-nucleoside reverse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

In care and on ART in the Netherlands in 2023

A total of 25,939 people with HIV were in care and on ART between (part of the period) January 2014 and December 2023. The number of people who had initiated ART and were in active follow-up in the ATHENA cohort grew from 17,202 individuals in 2014 to 22,215 individuals in 2023. As ATHENA is an open cohort, over time new individuals enrol into the cohort as they enter HIV care in one of the Dutch HIV treatment centers, or they leave the cohort when they die, move abroad, withdraw consent, or otherwise become lost to follow-up. Contrary to our analyses in previous Monitoring Reports, in this section we have not excluded people who (temporarily) interrupted ART from the analyses. Most of these individuals had medical, psychiatric, and/or psycho-social issues that temporarily prevented them from continuing ART, and most of them re-started ART when those issues are sufficiently resolved.

Table 4.3 shows the evolution over calendar time of the size, demographical, clinical and antiretroviral treatment characteristics of the treated individuals who constitute the ATHENA cohort. For selected calendar years a cross section of the cohort is shown of all people in active follow-up in the cohort during that particular calendar year. For each included individual the status at the last clinic visit of that calendar year was used. In 2023, 22,215 people on ART were in care (for part of or the entire) calendar year. Overall, 18,155 (81.7%) were men, and 13,931 (62.7%) were MSM. Their median age in 2023 was 52.8 (IQR 42.7-60.9) years. The majority (55.5%) originated from the Netherlands, followed by Latin America / the Caribbean (13.0%) and sub-Saharan Africa (11.8%). They had been diagnosed with HIV a median of 14.1 (IQR 8.4-20.4) years ago, and started their first-line ART regimen a median of 12 (IQR 7.5-17.9) years ago. Their last measured viral load was <50 copies/ml in 95.8% (97.9% <200 copies/ml), and 79.2% had a last measured CD4 count of 500 cells/mm^3 or higher.

Table 4.3: Characteristics of people in care receiving antiretroviral therapy between 2014–2023.

Calendar year		2014	2019	2020	2021	2022	2023
Total	n	17,202	20,899	21,292	21,570	21,970	22,215
	%	13.7	16.7	17	17.2	17.6	17.8
Age	Median	47.7	50.4	51	51.7	52.2	52.8
	Q1	39.8	41	41.4	41.9	42.2	42.7
	Q3	54.8	58.1	58.8	59.6	60.3	60.9
Male sex (at birth)	n	13969	17138	17473	17708	17959	18155
	%	81.2	82	82.1	82.1	81.7	81.7
HIV acquisition group							
MSM	n	10623	13200	13467	13627	13798	13931
	%	61.8	63.2	63.2	63.2	62.8	62.7
Other men	n	3206	3702	3746	3807	3877	3923
	%	18.6	17.7	17.6	17.6	17.6	17.7
Women	n	3230	3756	3814	3855	4002	4049
	%	18.8	18	17.9	17.9	18.2	18.2
Transgender people	n	143	241	265	281	293	312
	%	0.8	1.2	1.2	1.3	1.3	1.4
Region of origin							
The Netherlands	n	10423	12268	12398	12426	12398	12340
	%	60.6	58.7	58.2	57.6	56.4	55.5
Western Europe/North	n	1129	1319	1338	1343	1329	1343
America/Australia	%	6.6	6.3	6.3	6.2	6	6
Eastern/central Europe	n	480	829	912	995	1276	1381
	%	2.8	4	4.3	4.6	5.8	6.2
Latin America/Caribbean	n	1899	2566	2648	2747	2804	2884
	%	11	12.3	12.4	12.7	12.8	13
Sub-Saharan Africa	n	2271	2517	2549	2565	2597	2631
	%	13.2	12	12	11.9	11.8	11.8
Other	n	1000	1400	1447	1494	1566	1636
	%	5.8	6.7	6.8	6.9	7.1	7.4
CD4 at start ART							
No data	n	1246	1980	2144	2301	2620	2787
	%	7.2	9.5	10.1	10.7	11.9	12.5
<50	n	1821	2038	2065	2097	2106	2103
	%	10.6	9.8	9.7	9.7	9.6	9.5
50–199	n	3807	4082	4095	4111	4103	4083
	%	22.1	19.5	19.2	19.1	18.7	18.4
200–349	n	5424	5783	5822	5817	5798	5796
	%	31.5	27.7	27.3	27	26.4	26.1
350–499	n	2824	3569	3610	3616	3639	3666
	%	16.4	17.1	17	16.8	16.6	16.5
500+	n	2080	3447	3556	3628	3704	3780
	%	12.1	16.5	16.7	16.8	16.9	17

Calendar year		2014	2019	2020	2021	2022	2023
Viral load at start ART	Median	4.9	4.9	4.9	4.9	4.9	4.9
	Q1	4.3	4.3	4.3	4.3	4.3	4.3
	Q3	5.3	5.3	5.3	5.3	5.4	5.4
Years known HIV+	Median	8.9	11.4	12.1	12.8	13.4	14.1
	Q1	4.6	6.3	6.8	7.4	7.9	8.4
	Q3	14.5	17.4	18.2	18.9	19.6	20.4
Years since start ART	Median	6.5	9.3	10	10.7	11.3	12
	Q1	2.9	5.1	5.7	6.4	7	7.5
	Q3	12.5	15.1	15.8	16.5	17.2	17.9
Current CD4 count							
missing	n	13	24	23	28	24	23
	%	0.1	0.1	0.1	0.1	0.1	0.1
<50	n	61	67	64	60	79	58
	%	0.4	0.3	0.3	0.3	0.4	0.3
50–199	n	495	462	438	407	412	403
	%	2.9	2.2	2.1	1.9	1.9	1.8
200–349	n	1549	1466	1414	1421	1441	1345
	%	9	7	6.6	6.6	6.6	6.1
350–499	n	3225	3009	3035	3092	2962	2796
	%	18.7	14.4	14.3	14.3	13.5	12.6
500–749	n	6566	7231	7132	7293	7327	7146
	%	38.2	34.6	33.5	33.8	33.4	32.2
750+	n	5293	8640	9186	9269	9725	10444
	%	30.8	41.3	43.1	43	44.3	47
Viral load <50 c/ml							
Missing	n	5	12	16	17	20	12
	%	0	0.1	0.1	0.1	0.1	0.1
≥50 c/ml	n	1918	1153	985	954	1014	913
	%	11.1	5.5	4.6	4.4	4.6	4.1
<50 c/ml	n	15279	19734	20291	20599	20936	21290
	%	88.8	94.4	95.3	95.5	95.3	95.8
Viral load <200 c/ml							
Missing	n	5	12	16	17	20	12
	%	0	0.1	0.1	0.1	0.1	0.1
≥200 c/ml	n	859	581	466	465	491	454
	%	5	2.8	2.2	2.2	2.2	2
<200 c/ml	n	16338	20306	20810	21088	21459	21749
	%	95	97.2	97.7	97.8	97.7	97.9

Calendar year		2014	2019	2020	2021	2022	2023
ART regimen							
ART temporarily interrupted	n	484	375	361	341	297	191
	%	2.8	1.8	1.7	1.6	1.4	0.9
INSTI + NRTI							
TAF/FTC/BIC	n	2	2060	2689	3152	3538	3821
	%	0	9.9	12.6	14.6	16.1	17.2
DTG/3TC	n	5	306	1064	1722	2341	2823
	%	0	1.5	5	8	10.7	12.7
ABC/3TC/DTG	n	325	3099	2573	2176	1880	1669
	%	1.9	14.8	12.1	10.1	8.6	7.5
TAF/FTC/DTG	n	4	601	544	522	489	473
	%	0	2.9	2.6	2.4	2.2	2.1
TDF/FTC/DTG	n	227	738	757	762	896	994
	%	1.3	3.5	3.6	3.5	4.1	4.5
TAF/FTC/EVG/b	n	12	2812	2507	2262	2012	1847
	%	0.1	13.5	11.8	10.5	9.2	8.3
TDF/FTC/EVG/b	n	770	657	583	532	456	406
	%	4.5	3.1	2.7	2.5	2.1	1.8
TDF/FTC/RAL	n	472	185	178	160	132	109
	%	2.7	0.9	0.8	0.7	0.6	0.5
Other INSTI + NRTI	n	161	265	253	238	245	244
	%	0.9	1.3	1.2	1.1	1.1	1.1
NNRTI + NRTI							
TDF/3TC/DOR	n	2	168	885	1398	1634	1794
	%	0	0.8	4.2	6.5	7.4	8.1
TDF/FTC/EFV	n	3623	1546	1378	1222	1051	965
	%	21.1	7.4	6.5	5.7	4.8	4.3
ABC/3TC/NVP	n	575	419	355	294	254	225
	%	3.3	2	1.7	1.4	1.2	1
TAF/FTC/NVP	n	3	734	712	719	709	694
	%	0	3.5	3.3	3.3	3.2	3.1
TDF/FTC/NVP	n	2405	1119	1031	917	790	726
	%	14	5.4	4.8	4.3	3.6	3.3
TAF/FTC/RPV	n	4	1088	955	988	950	932
	%	0	5.2	4.5	4.6	4.3	4.2
TDF/FTC/RPV	n	1787	686	601	436	369	336
	%	10.4	3.3	2.8	2	1.7	1.5
Other NNRTI + NRTI	n	789	323	314	315	274	245
	%	4.6	1.5	1.5	1.5	1.2	1.1

Calendar year		2014	2019	2020	2021	2022	2023
PI + NRTI							
TDF/FTC/ATV/b	n	1185	256	201	157	122	87
	%	6.9	1.2	0.9	0.7	0.6	0.4
TAF/FTC/DRV/b	n	1	1197	1244	1262	1261	1281
	%	0	5.7	5.8	5.9	5.7	5.8
TDF/FTC/DRV/b	n	1777	547	464	410	345	291
	%	10.3	2.6	2.2	1.9	1.6	1.3
TDF/FTC/LPV/b	n	216	28	20	16	12	9
	%	1.3	0.1	0.1	0.1	0.1	0
Other PI + NRTI	n	1006	404	316	241	192	177
	%	5.8	1.9	1.5	1.1	0.9	0.8
2 anchor drugs							
CAB/RPV injectables *	n	.	5	36	71	497	686
	%	.	0	0.2	0.3	2.3	3.1
DTG/DRV/b	n	25	340	346	355	367	372
	%	0.1	1.6	1.6	1.6	1.7	1.7
DTG/RPV	n	3	88	115	130	138	138
	%	0	0.4	0.5	0.6	0.6	0.6
2 anchor drugs w/wo NRTI	n	589	456	429	425	386	370
	%	3.4	2.2	2	2	1.8	1.7
Other ART	n	750	397	381	347	333	310
	%	4.4	1.9	1.8	1.6	1.5	1.4

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

** Some individuals using this regimen were participating in a clinical trial.*

Among the 22,215 individuals in HIV care and on ART in 2023, the vast majority (91.0%) received a regimen based on one or two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with either (*Figure 4.5A*) an integrase inhibitor (INSTI) (55.8%), a non-nucleoside reverse transcriptase inhibitor (NNRTI) (26.6%), or a protease inhibitor (PI) (8.6%).

The proportion of individuals who had (temporarily) interrupted ART at the end of the calendar year, decreased from 2.8% in 2014 to 0.7% in 2023. In a later section in this chapter more details are shown about then number, reasons, duration and outcome of these treatment interruptions.

The changes of time in the distribution of specific ART regimen among the population in care in 2023 is presented in *Figure 4.5B* and *4.7* and in *Table 4.3*. The most frequently used regimens (used by at least 5% of the population) were:

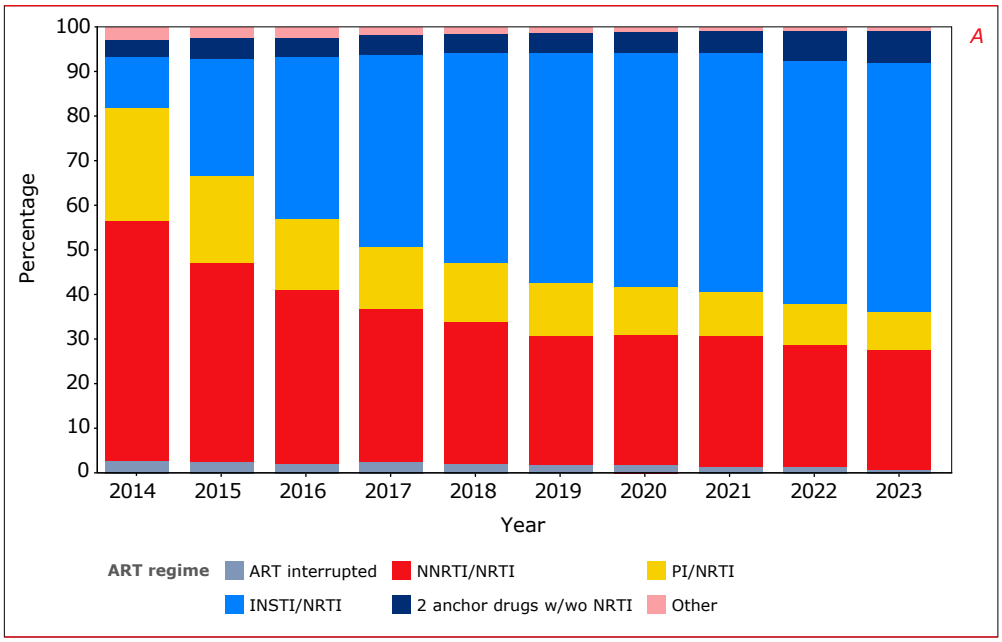
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/bictegravir (BIC) (17.2%);
- dolutegravir (DTG)/lamivudine (3TC) (12.7%);
- tenofovir alafenamide (TAF)/ emtricitabine (FTC)/elvitegravir (EVG)/cobicistat (8.3%);
- tenofovir disoproxil fumarate (TDF)/ lamivudine (3TC)/doravirine (DOR) (8.1%);
- abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (7.5%); and
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/darunavir (DRV)/cobicistat (5.8%)

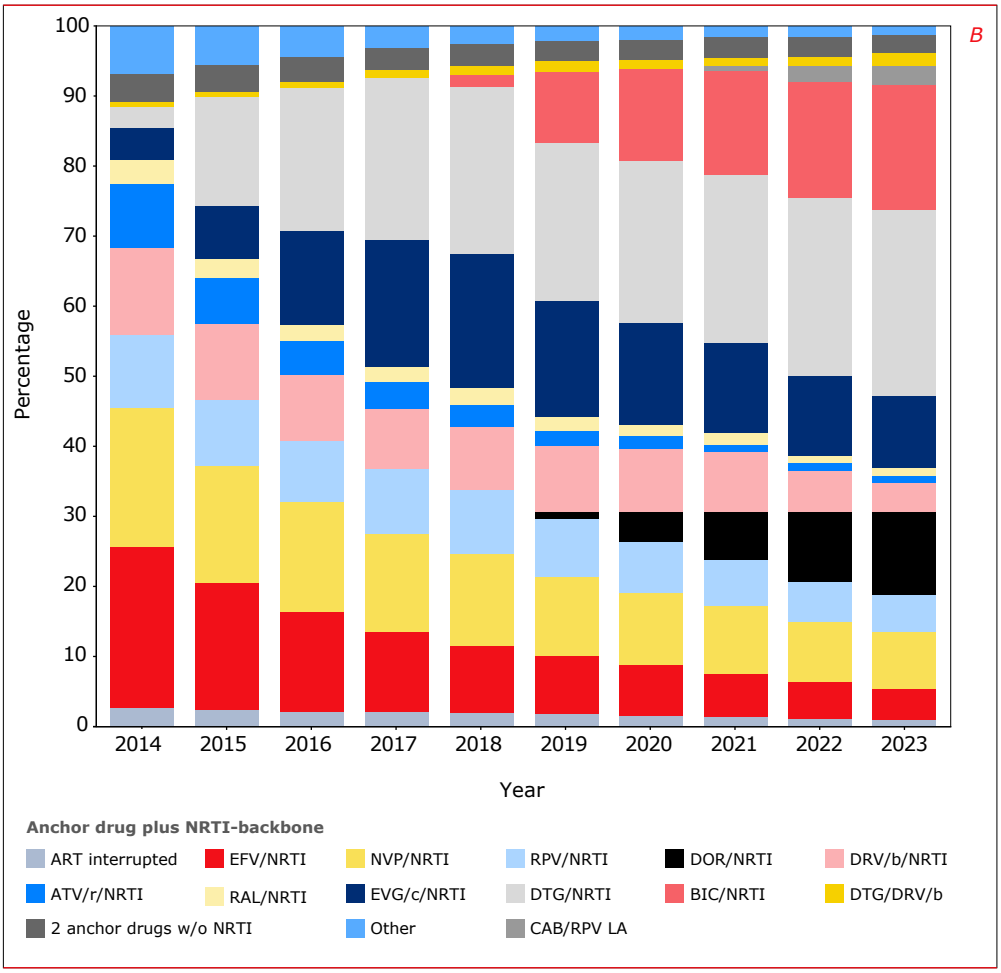
The use of ABC/3TC/DTG has decreased substantially following the DHHS guideline change from one of the "Recommended Initial Regimens for Most People With HIV" to a regimen recommended as part of "Other Initial Antiretroviral Regimens for Certain Clinical Scenarios" because of concerns over a potential increase in the risk of cardiovascular events by the use of abacavir. The use of this regimen decreased from 14.8% in 2014 to 7.5% in 2023, mainly driven by simplifications to 3TC/DTG. In our cohort the use of ABC has also been shown to be independently associated with a higher risk of cardiovascular events (see Chapter 5, Morbidity and Mortality).

In 2023, the use of regimens consisting of 2 anchor drugs (an NNRTI, PI, or INSTI) with or without one or two additional NRTI, continued to increase to 7.4%. The most common of these regimens were a combination of cabotegravir/rilpivirine injectables (3.1%), dolutegravir/darunavir/cobicistat (1.7%), and dolutegravir/rilpivirine (0.6%).

Of those on ART with a plasma HIV RNA measurement in 2023, 95.8% had a viral load below 50 copies/ml, and 97.9% had a viral load below 200 copies/ml. In 2023, 79.2% had a CD4 count of 500 cells/mm^3 or higher.

Figure 4.5A&B: Anchor-drug class (A) and individual anchor-drugs (B) plus nucleoside reverse transcriptase backbone used as part of the current regimen in 2014-2023.

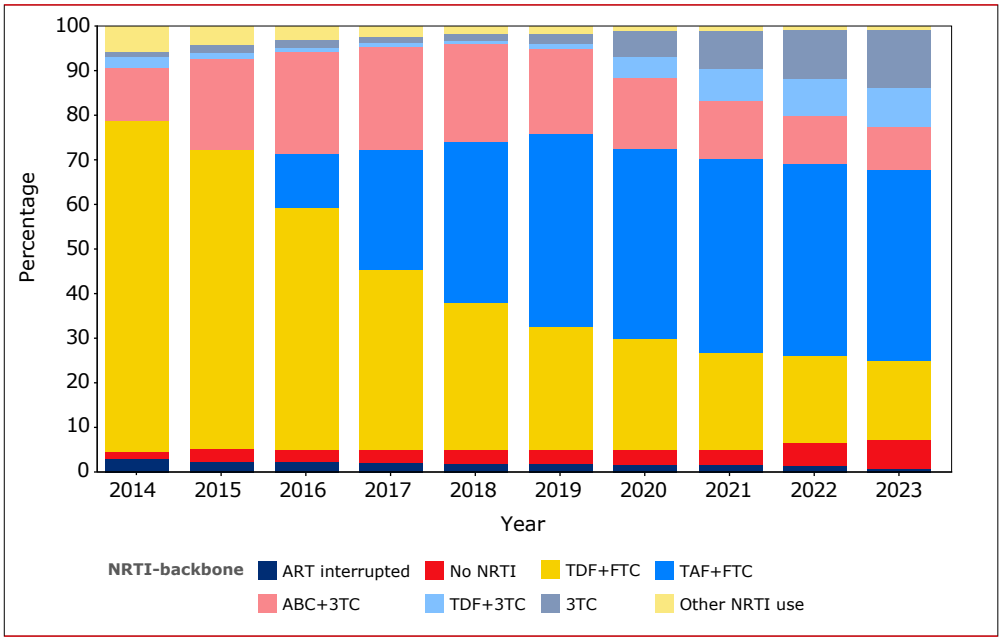




Legend: *ART = antiretroviral therapy; b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; ENTRY = entry inhibitor; INSTI = integrase inhibitor; NRTI = nucleoside analogue reverse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

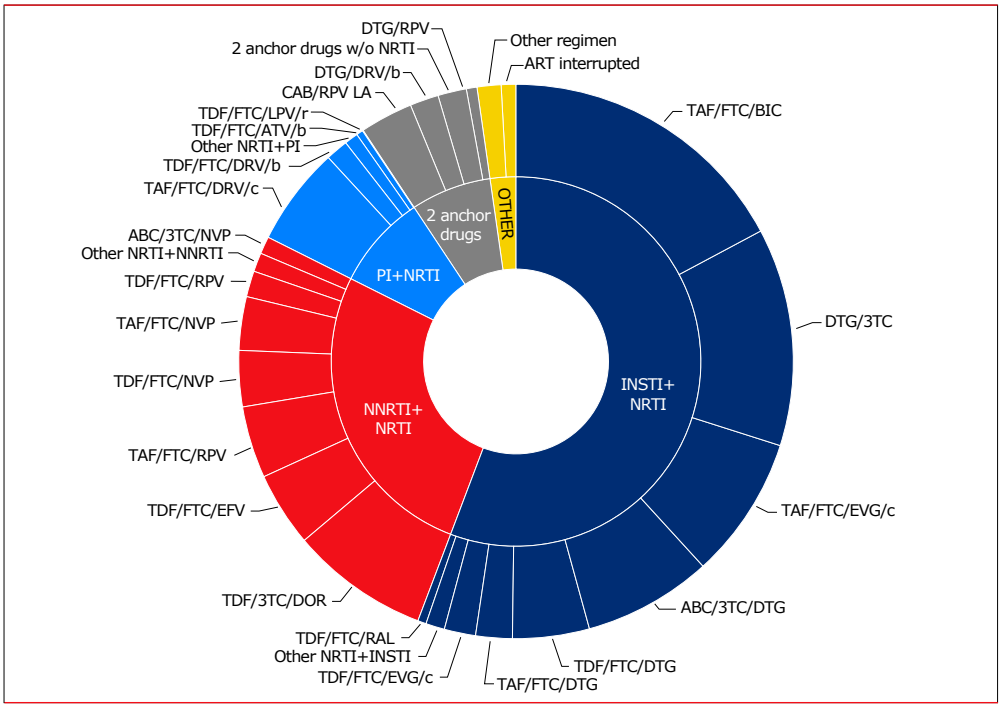
Figure 4.6 provides an overview of the NRTI backbone components of the current ART regimens used in 2014-2023. The combination of tenofovir disoproxil (TDF) or alafenamide (TAF) with emtricitabine (FTC) was the predominant backbone used, being part of 78.7% of the regimen used in 2014, and slowly declining to 69.9% in 2023. Following its introduction at the end of 2015, use of TAF in ART regimens rapidly increased with a maximum of 43.2% of all regimens used in 2019, and has since remained stable at that level. At the same time, TDF use decreased from 78.6% of all regimens used in 2014 to 29.9% in 2019, after which TDF use remained stable at that level until 2023. Abacavir was used in 13.6% of all regimen in 2014. Following the introduction of the fixed dose combination ABC/3TC/DTG its use increased to 23.7% in 2017, after which its use slowly decreased to 9.7% of all regimen used in 2023.

Figure 4.6: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the current regimen in 2014–2023.*



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

Figure 4.7: antiretroviral therapy use in 2023.



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

Modifications and interruptions of ART use

For the 25,939 individuals who were on ART between (part of the period between) January 2014 and December 2023, we assessed the frequency and reported reasons for modifications and (temporary) interruptions of ART. The unit of analysis for this section is therefore the treatment episodes, and a single individual can contribute multiple treatment episodes with multiple regimens to this analysis.

Modification of ART was defined as a change in, or discontinuation of, one or more of the drugs included in the regimen. Simplification to a fixed-drug combination formulation containing the same antiretroviral agents (in the same dose) was not considered a modification of the regimen. Likewise, the breakup of a (more

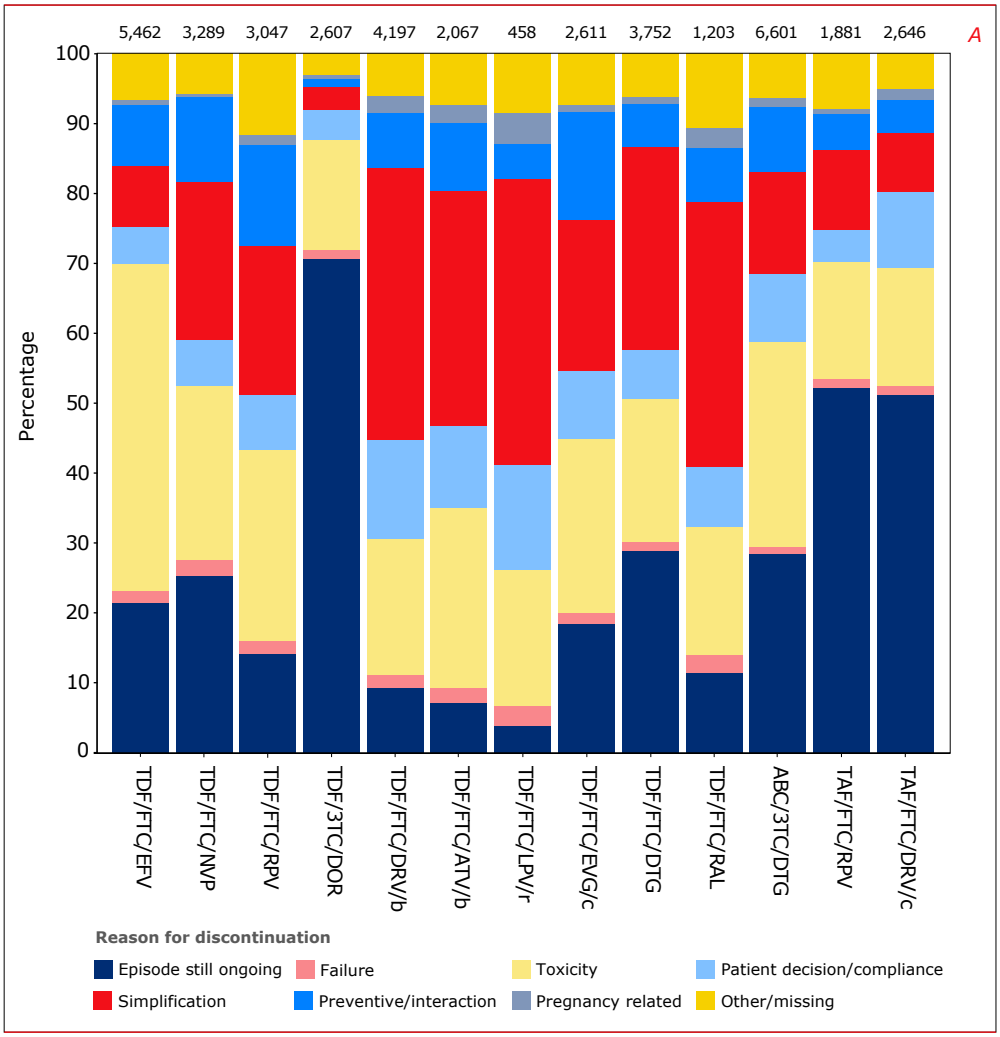
expensive) single tablet regimen (STR) into separately formulated (cheaper) generic components of the original STR, was also not considered a modification. A switch from one pharmacological booster to another was also ignored. We also ignored treatment interruptions that lasted less than 14 days. Whenever an individual became lost to follow-up (e.g. because they moved abroad) this was not considered to be a regimen discontinuation, instead regimens used at the end of available follow-up were categorized as "treatment episode still ongoing".
For each commonly used regimen we report the total number of treatment episodes with that particular regimen, the cumulative persons years of exposure to that particular regimen, the frequency of treatment modifications, and the distribution of the reasons for modification of that regimen. The denominator for these analyses is the total number of treatment episodes with any particular regimen (*Table 4.4*).

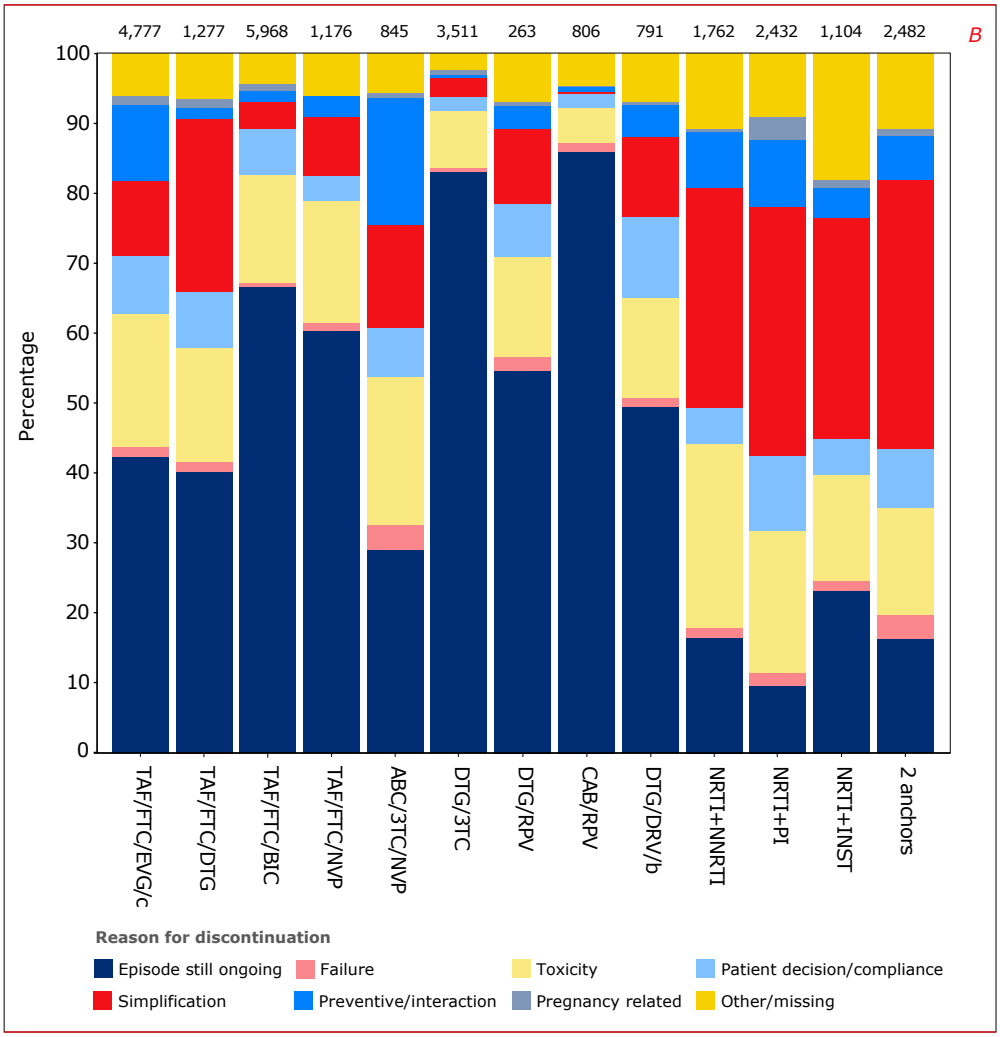
During the period 2014 to 2023, the cohort of 25,939 individuals on ART accrued a total of 187,467 person years of follow-up, during which a total of 69,621 ART regimen episodes were registered. At the end of the follow-up period in 2023 (but for some individuals follow-up ended earlier, i.e. because they died, moved out of the country, or otherwise became disengaged from HIV care), 34.3% of these regimen episodes were still in use, and 65.7% of the regimen episodes had ended in a regimen modification. The most common reasons for regimen modification were: toxicity (21.7%), treatment simplification (18.6%), patient decision/compliance (7.9%), and preventive modifications (7.2%). In only 1,218 (1.7%) regimens the reported reason for modification was virological treatment failure. Specific reasons for 'preventive modifications' consist of (CVD) risk optimization, prevention of long term renal, bone and metabolic toxicities, drug-drug interactions, weight gain, etc.

Table 4.4 provides these statistics for all commonly used regimen and *Figure 4.8A&B* provides a visual presentation of the same data. However, it should be noted that the average duration of exposure varies greatly for different regimen, which biases cross-regimen comparisons and making them difficult to interpret. Treatment options that have been available for a shorter amount of time, are by virtue of that fact alone more likely to be still in use. *Appendix Table 4.1* provides the rates of the various reasons for treatment modifications for each particular regimen per 1,000 person years of cumulative exposure.

During the period 2014 to 2023, the overall rate of regimen changes was 320.7 modifications per 1,000 person years of follow-up. This rate peaked in 2015 and 2016 at 331 and 340 modifications per 1,000 person years, after which the rate continuously decreased to 204 in 2022 and 141 in 2023 (*Figure 4.9*).

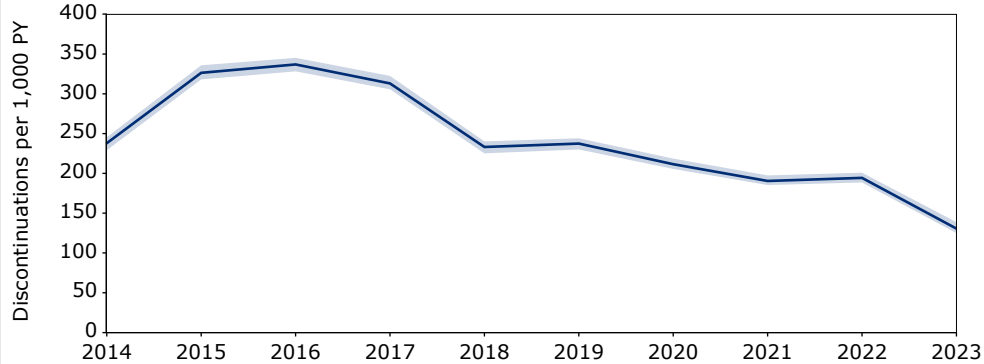
Figure 4.8A&B: Reasons for discontinuation / modification of antiretroviral therapy (ART) used in 2014-2023. The number at the top of each bar represent the total number of treatment episodes with that particular ART regimen.





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

Figure 4.9: Rate of regimen modifications in 2014–2023.



Legend: Blue band represents the 95% confidence interval.

Table 4.4: *Exposure to various ARV regimen and reasons for discontinuation / modification in the period 2014–2023.*

	Person years exposure	Total ARV episodes	Reasons for discontinuation / modification			
			Episode still ongoing		Failure	
	PY	n	n	%	n	%
Total dataset	187467	69621	23877	34.3	1218	1.7
INSTI + NRTI						
TAF/FTC/BIC	13206	5968	3970	66.5	48	0.8
DTG/3TC	6855	3511	2910	82.9	32	0.9
ABC/3TC/DTG	21934	6601	1890	28.6	62	0.9
TAF/FTC/DTG	3409	1277	511	40	21	1.6
TDF/FTC/DTG	6288	3752	1091	29.1	41	1.1
TAF/FTC/EVG/c	17249	4777	2031	42.5	64	1.3
TDF/FTC/EVG/c	7128	2611	479	18.3	46	1.8
TDF/FTC/RAL	2384	1203	137	11.4	32	2.7
Other INSTI+NRTI	2023	1104	256	23.2	18	1.6
NNRTI + NRTI						
TDF/3TC/DOR	4906	2607	1841	70.6	36	1.4
TDF/FTC/EFV	19895	5462	1158	21.2	108	2
ABC/3TC/NVP	4073	845	245	29	32	3.8
TAF/FTC/NVP	4416	1176	710	60.4	15	1.3
TDF/FTC/NVP	14236	3289	833	25.3	80	2.4
TAF/FTC/RPV	6268	1881	983	52.3	25	1.3
TDF/FTC/RPV	9440	3047	426	14	62	2
Other NNRTI+NRTI	4227	1762	289	16.4	29	1.6
PI + NRTI						
TDF/FTC/ATV/b	4920	2067	145	7	50	2.4
TAF/FTC/DRV/c	6736	2646	1356	51.2	37	1.4
TDF/FTC/DRV/b	8903	4197	393	9.4	78	1.9
TDF/FTC/LPV/r	686	458	18	3.9	13	2.8
Other PI+NRTI	5064	2432	235	9.7	50	2.1
2 anchor drugs						
CAB/RPV injectables	977	806	692	85.9	12	1.5
DTG/DRV/b	2326	791	391	49.4	11	1.4
DTG/RPV	586	263	144	54.8	5	1.9
2 anchor drugs w/wo NRTI	4552	2482	408	16.4	89	3.6
Other ART	4778	2606	335	12.9	122	4.7

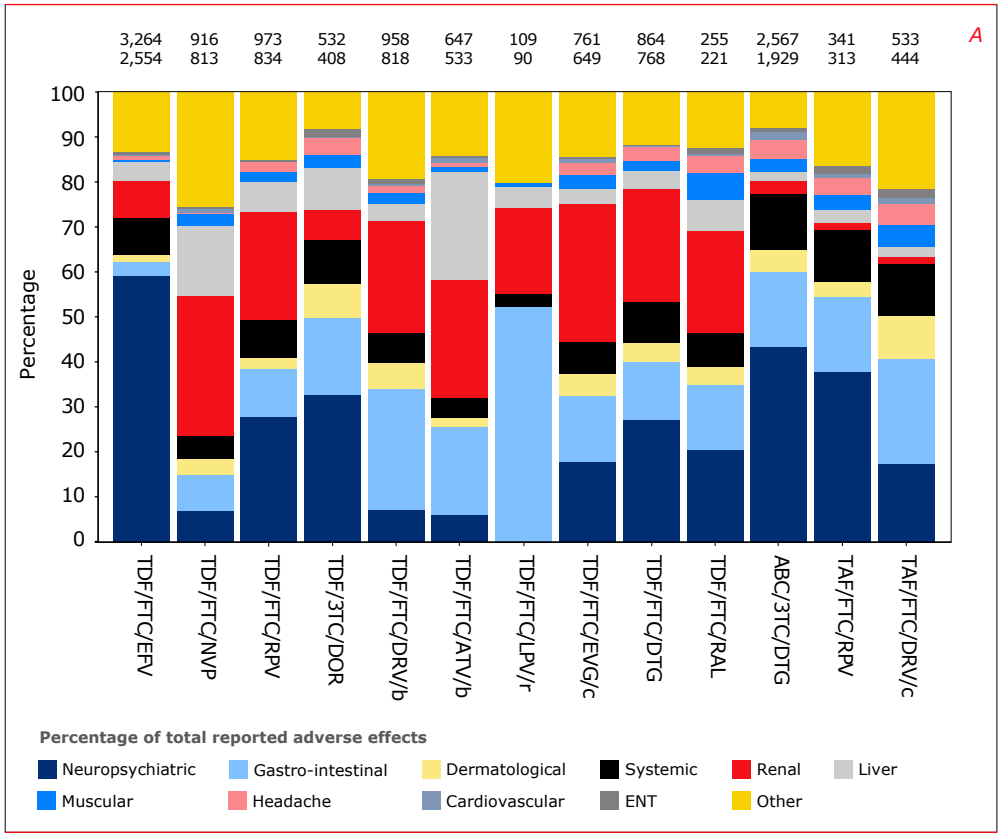
Legend: *3TC = lamivudine; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; ABC = abacavir; ATV = atazanavir; ARVs = antiretroviral drugs; BIC = bictegravir; ART = antiretroviral therapy; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG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

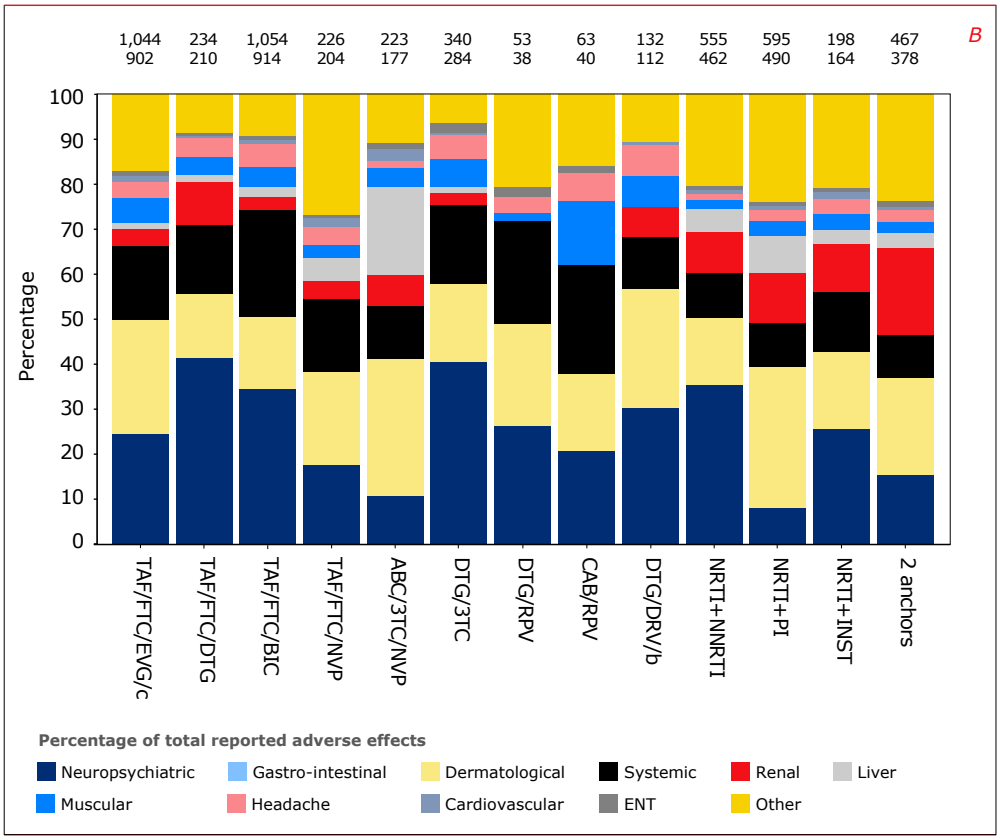
Reasons for discontinuation / modification

	Toxicity		Patient decision/ compliance		Simplification		Preventive/ interaction		Pregnancy related		Missing / Other reasons	
n	%	n	%	n	%	n	%	n	%	n	%
15140	21.7	5477	7.9	12963	18.6	5030	7.2	847	1.2	5069	7.3
914	15.3	394	6.6	231	3.9	88	1.5	53	0.9	270	4.5
284	8.1	71	2	93	2.6	17	0.5	21	0.6	83	2.4
1929	29.2	648	9.8	955	14.5	613	9.3	86	1.3	418	6.3
210	16.4	100	7.8	316	24.7	21	1.6	16	1.3	82	6.4
768	20.5	263	7	1091	29.1	229	6.1	37	1	232	6.2
902	18.9	399	8.4	514	10.8	511	10.7	69	1.4	287	6
649	24.9	254	9.7	568	21.8	398	15.2	25	1	192	7.4
221	18.4	102	8.5	456	37.9	92	7.6	36	3	127	10.6
164	14.9	60	5.4	345	31.3	50	4.5	11	1	200	18.1
408	15.7	116	4.4	84	3.2	29	1.1	14	0.5	79	3
2554	46.8	293	5.4	475	8.7	474	8.7	35	0.6	365	6.7
177	20.9	61	7.2	125	14.8	149	17.6	7	0.8	49	5.8
204	17.3	42	3.6	100	8.5	33	2.8	1	0.1	71	6
813	24.7	222	6.7	736	22.4	404	12.3	12	0.4	189	5.7
313	16.6	87	4.6	214	11.4	97	5.2	14	0.7	148	7.9
834	27.4	240	7.9	648	21.3	440	14.4	43	1.4	354	11.6
462	26.2	90	5.1	555	31.5	136	7.7	11	0.6	190	10.8
533	25.8	240	11.6	696	33.7	198	9.6	54	2.6	151	7.3
444	16.8	289	10.9	223	8.4	123	4.6	40	1.5	134	5.1
818	19.5	592	14.1	1633	38.9	329	7.8	99	2.4	255	6.1
90	19.7	67	14.6	188	41	23	5	20	4.4	39	8.5
490	20.1	262	10.8	865	35.6	225	9.3	85	3.5	220	9
40	5	15	1.9	2	0.2	8	1	.	.	37	4.6
112	14.2	93	11.8	89	11.3	36	4.6	4	0.5	55	7
38	14.4	20	7.6	28	10.6	8	3	2	0.8	18	6.8
378	15.2	211	8.5	946	38.1	156	6.3	27	1.1	267	10.8
391	15	246	9.4	787	30.2	143	5.5	25	1	557	21.4

The nature and severity of (presumed) ART-related toxicities leading to modification of the regimen have changed considerably over time. Because of the availability of a large number of potent and well-tolerated recommended and alternative regimens, with new treatment options becoming available nearly every year, as well as the very low risk of viral breakthrough following a switch, the threshold for modifying a regimen has become much lower over the years. *Figure 4.10A&B* provides a visual breakdown of the reported ART-related adverse events leading to the modification of the various regimen. As more than one adverse event can be reported for each toxicity-driven regimen modification, the total number of adverse events reported in *Figure 4.10A&B* is greater than the number of regimen. For the 15,140 toxicity-driven regimen modifications, 17,874 adverse effects were recorded. The predominant adverse effects were: neuropsychiatric (mainly insomnia, mood changes, dizziness, and depression) 31.6%; gastrointestinal (mainly diarrhoea and nausea) 14.7%; renal (renal insufficiency and increased serum creatinine) 12.3%; systemic (tiredness, apathy, and loss of appetite) 10.6%; liver (increased transaminases) 5.3%; and dermatological (rash due to medication, itching) 4.3%.

Figure 4.10A&B: *Adverse effects resulting in toxicity-related modifications of ART regimen used in the period 2014-2023. The bars represent the distribution of all reported adverse effects, by regimen. The numbers above the bars represent 1) the total number of adverse effects reported as reasons for regimen modification (top row), and 2) the total number of times that particular regimen was modified because of adverse effects (bottom row).*





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

Treatment interruptions

We have analysed treatment interruptions separately from regimen modifications. During the last 10 years, the proportion of individuals at any particular time that have interrupted their use of ART has continued to decrease. The proportion of individuals who had started ART at least 6 months ago, who at yearly cross-sectional evaluation of the virological response were observed to have (temporarily) interrupted ART, decreased from 2.4% in 2014 to 0.8% in 2023 (see *Figure 4.11* from the next section on *Virological response*).

During the period 2014 to 2023, the cohort of 25,939 individuals accrued a total of 187,467 person years of follow-up, in which a total of 69,621 ART regimen were used. In 2,905 individuals a total of 4,815 treatment interruptions (of 14 days or longer) were recorded (*Table 4.5*). However, it must be assumed that many more treatment interruptions have not been disclosed and hence have gone unrecorded in the medical dossier (see also the next paragraph on loss of viral suppression where we show evidence of frequent episodes of loss of viral suppression that resuppress to undetectable levels without a change in the used regimen).
In the majority of the treatment interruptions it was the patients themselves who decided to interrupt their ART (71.5%), with their treating physicians becoming aware of the interruption only during the next clinic visit. A further 12.9% of interruptions had ART-associated toxicity as the recorded reason, and 3.2% of interruptions was pregnancy-related. Unfortunately, we cannot with certainty determine from the available data if these treatment interruptions were caused by the circumstances of the patient (e.g. unintentionally running out of medicine while on vacation), or secondly if the patients themselves decided to interrupt ART, or thirdly if the interruption was decided on by their treating physician.
The median duration of the recorded treatment interruptions was 13.7 (IQR 5.0-37.1) weeks. During many of the longer treatment interruption the majority of these individuals were effectively temporarily disengaged from care. In 59.1% of the interruptions the same regimen as that was used at the start of the treatment interruption was restarted.

We evaluated the median change in CD4 count during treatment interruptions of more than 90 days duration (n=2,109). In 1,101 of these 2,109 treatment interruptions of at least 90 days duration a pre-interruption CD4 count had been measured within 180 days of the start of the interruption (median 478, IQR 281 to 702, cells/mm^3). And in 1,282 episodes there was a CD4 count measured during (but at least 60 days after the start of) the treatment interruption (median 330, IQR 134 to 520 cells/mm^3). For 715 treatment interruptions of more than 90 days, a pre-interruption CD4 count was available and also a CD4 count had been measured during the interruption. During these 715 interruptions the median change in the CD4 count was -130 (IQR -30 to -260) cells/mm^3.

The treatment interruptions because of pregnancy-related reasons break down into: women who interrupted ART because of a "wish for pregnancy" (n=1), women who interrupted ART during pregnancy (n=5, median duration of interruption 9.6, IQR 3.1-9.7 weeks), and women who interrupted ART after the pregnancy had ended (n=37, median duration of interruption 87, IQR 60-163 weeks). We do not know if these pregnancy-related treatment interruptions were initiated by the treating physicians or if the women themselves decided to interrupt ART.

Table 4.5: Frequency, duration and reasons for treatment interruptions in the period 2014–2023.

	Duration of interruption (weeks)			Patients	Total episodes
	Median	Q1	Q3	n	n
Total dataset	12.6	4.7	31.6	2565	4224
INSTI + NRTI					
TAF/FTC/BIC	10.9	4.4	28.1	273	350
DTG/3TC	8.9	4.3	17.6	38	45
ABC/3TC/DTG	14.9	5.0	36.7	398	542
TAF/FTC/DTG	16.3	5.0	41.9	58	73
TDF/FTC/DTG	13.1	4.4	32.7	145	182
TAF/FTC/EVG/c	12.4	4.9	28.4	237	304
TDF/FTC/EVG/c	15.0	6.1	30.4	141	202
TDF/FTC/RAL	9.7	4.1	21.9	61	73
Other INSTI+NRTI	7.6	4.3	16.3	42	47
NNRTI + NRTI					
TDF/3TC/DOR	9.4	4.3	23.4	75	86
TDF/FTC/EFV	13.7	4.8	35.1	213	256
ABC/3TC/NVP	8.3	4.3	23.7	33	46
TAF/FTC/NVP	13.0	6.0	27.1	29	31
TDF/FTC/NVP	14.5	5.4	34.9	132	152
TAF/FTC/RPV	7.9	4.3	20.3	55	74
TDF/FTC/RPV	11.6	4.7	36.9	157	183
Other NNRTI+NRTI	13.4	5.4	26.1	64	74
PI + NRTI					
TDF/FTC/DRV/b	12.5	4.7	34.9	322	428
TDF/FTC/ATV/b	14.2	4.6	40.4	145	194
TDF/FTC/LPV/r	15.6	7.6	34.7	33	45
TAF/FTC/DRV/c	12.4	4.8	29.4	160	232
Other PI+NRTI	14.0	4.4	36.7	151	214
2 anchor drugs					
CAB/RPV injectables	7.7	2.9	20.6	9	9
DTG/DRV/b	11.4	5.6	29.3	55	63
DTG/RPV	17.9	4.1	24.1	9	14
2 anchor drugs w/wo NRTI	16.1	5.7	31.7	94	138
Other ART	8.7	4.4	26.9	134	167

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

							Reasons for interruption				Restarted same regimen
	Failure		Toxicity		Patient decision/ compliance		Pregnancy related		Other		
	n	%	n	%	n	%	n	%	n	%	%
	63	1.5	569	13.5	3101	73.4	43	1.0	448	10.6	63.6
	1	0.3	42	12.0	262	74.9	.	.	45	12.9	75.4
	.	.	11	24.4	28	62.2	1	2.2	5	11.1	66.7
	1	0.2	89	16.4	389	71.8	.	.	63	11.6	67.2
	1	1.4	8	11.0	57	78.1	.	.	7	9.6	68.5
	1	0.5	26	14.3	136	74.7	3	1.6	16	8.8	70.9
	6	2.0	49	16.1	221	72.7	.	.	28	9.2	66.4
	4	2.0	27	13.4	151	74.8	1	0.5	19	9.4	60.9
	4	5.5	11	15.1	46	63.0	3	4.1	9	12.3	46.6
	.	.	6	12.8	28	59.6	.	.	13	27.7	46.8
	3	3.5	14	16.3	62	72.1	.	.	7	8.1	62.8
	7	2.7	39	15.2	169	66.0	1	0.4	40	15.6	49.2
	3	6.5	8	17.4	30	65.2	.	.	5	10.9	67.4
	.	.	3	9.7	23	74.2	.	.	5	16.1	54.8
	3	2.0	16	10.5	123	80.9	2	1.3	8	5.3	52.6
	2	2.7	16	21.6	45	60.8	.	.	11	14.9	71.6
	5	2.7	25	13.7	131	71.6	.	.	22	12.0	54.6
	4	5.4	12	16.2	41	55.4	2	2.7	15	20.3	54.1
	4	0.9	41	9.6	347	81.1	5	1.2	31	7.2	60.5
	.	.	26	13.4	149	76.8	6	3.1	13	6.7	56.7
	1	2.2	5	11.1	36	80.0	2	4.4	1	2.2	53.3
	2	0.9	29	12.5	180	77.6	.	.	21	9.1	77.2
	.	.	26	12.1	154	72.0	16	7.5	18	8.4	64.5
	.	.	3	33.3	3	33.3	.	.	3	33.3	44.4
	.	.	3	4.8	53	84.1	.	.	7	11.1	76.2
	1	7.1	1	7.1	12	85.7	.	.	.	.	71.4
	5	3.6	10	7.2	108	78.3	.	.	15	10.9	76.1
	5	3.0	23	13.8	117	70.1	1	0.6	21	12.6	53.9

Virological response

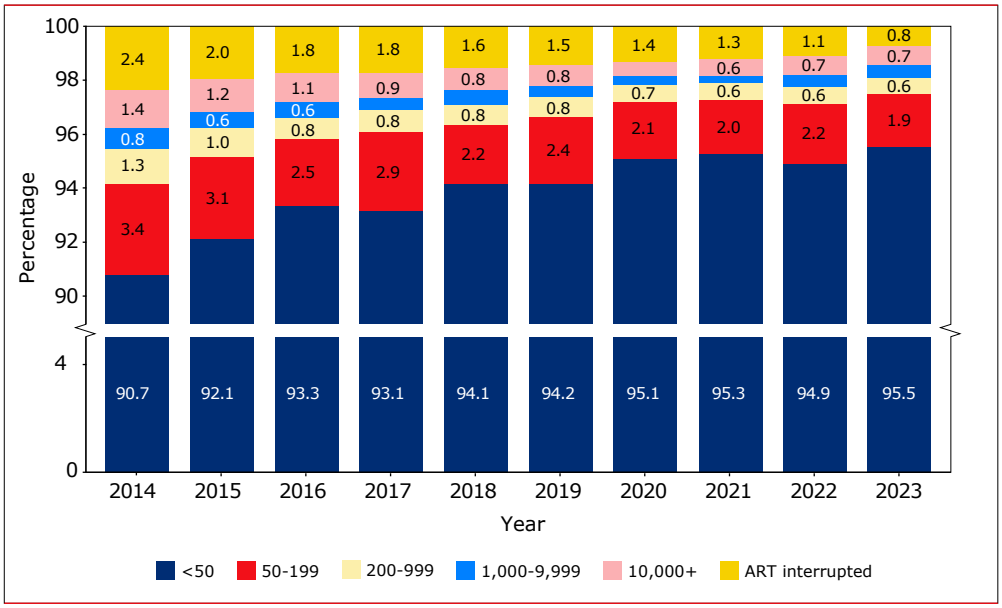
The study population for the analyses in this section consisted of all individuals on ART for more than 6 months who were in care during (part of) the period 2014-2023. For each calendar year between 2014 and 2023 we selected the last measured plasma HIV-RNA load measured in the 24 months prior to 31 December of that year. In the rare cases that no viral load had been measured in the investigated calendar nor in the year prior, that individual was excluded from the analysis of that calendar year.

Viral load measurements were classified into 6 categories: <50 copies/ml ("undetectable", this includes "residual viremia" between 20-50 copies/ml), 50-199 copies/ml ("low-level viremia", and isolated "blips"), 200-999 copies/ml, 1,000-9,999 copies/ml, and 10,000+ copies/ml. If at the moment of the last viral load measurement ART was (temporarily) interrupted this was categorized as a separate category.

Figure 4.11 shows the distribution of the yearly cross-sectional viral load evaluations. During the 10 years of follow-up, the proportion of individuals on ART for more than 6 months who had a viral load <50 copies/ml increased from 90.7% in 2014 (94.1% <200 copies/ml) to 95.5% (97.4% <200 copies/ml) in 2023. Likewise, all viral load categories higher than 50 copies/ml, decreased slowly over time (the number of analysed measurements and more precise percentages are shown in *Appendix Table 4.2*).

Quantifiable viral loads between 50-199 copies/ml are frequently observed in this population. When a single isolated viral load measurement between 50-199 copies/ml occurs preceded by and followed by viral load measurements <50 copies/ml this is often referred to as a "blip". We investigated which proportion of the population on ART shows signs of sustained low-level viremia, i.e. individuals who had multiple consecutive viral load measurements between 50-199 copies/ml while on ART. We calculated what proportion of all viral load measurements within individuals classifies as low-level viremia, in all 22,217 individuals who had started ART more than 6 months earlier, who had not interrupted ART, and who had at least 5 viral load measurements available for analysis in the period 2014-2023. Of all individuals on ART, 74.8% had not a single viral load measurement between 50-199 copies/ml. In 16.9% of individuals the proportion of viral load measurements between 50-199 copies/ml was between >0% and 10%. In a further 5.3% this proportion was between >10% and 20% of all viral load measurements. And in just 2.9% of all individuals there was evidence of sustained low-level viremia with more than 20% of all viral load measurements being between 50-199 copies/ml.

Figure 4.11: Yearly cross-sectional analysis of virological treatment response in people on ART for at least 6 months in 2014–2023.



Box 4.3: Definitions of virological response and HIV drug resistance.

Virological response

Viral suppression
HIV viral load below 50 copies/ml in individuals on antiretroviral therapy (ART) for more than six months. This includes residual viremia between 20-50 copies/ml.

The last measured viral load measurement prior to 31 December of each calendar year was included in the analysis, irrespective of (temporary) treatment interruptions.

Viral 'blips'
A single quantifiable viral load measurement between 50-199 copies/ml, preceded by and followed by viral load measurements <50 copies/ml.

Low-level viremia
Two or more consecutive viral load measurements between 50-199 copies/ml.

Loss of viral suppression
Any viral load measurements of at least 200 copies/ml in individuals on ART for more than six months.

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 ART.

The 2022 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations [24].

Acquired HIV drug resistance
High-level resistance to at least one antiretroviral drug, detected at the time of an HIV viral load above 500 copies/ml, among people receiving ART for at least four months.

The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.6) was used to infer antiretroviral drug susceptibility and resistance scores [25,26].

Loss of viral suppression

Loss of viral suppression was defined as a viral load measurement of at least 200 copies/ml in individuals on ART for more than six months. We assessed the frequency, magnitude, duration and outcome of all episodes of loss of viral suppression in all individuals on ART for more than 6 months and in care in the period 2014-2023.
Each individual could contribute more than one episode of loss of viral suppression to this analysis. We analysed episodes of loss of viral suppression that occurred during an ART interruption separately from those that occurred while ART had been used continuously. All analyses were stratified for MSM plus transgender people, other men, and women.
In those episodes that occurred while ART use was continued, we investigated whether or not the episode of loss of viral control resolved with or without a change in the ART regimen used. A major limitation is that we do not have data on adherence, and only a very limited number of ARV plasma concentrations are available. Nevertheless, the maximum viral load measured during episodes of loss of viral control is much higher (4.5 log10 copies/ml) in those individuals for whom we know ART had been discontinued compared to individuals who indicated to still use ART (3.0 log10 copies/ml) indicating that the distinction is meaningful.

A total of 25,911 individuals contributed 191,116 person years of follow-up during the period 2014-2023 (*Table 4.6*). In 4,307 individuals there were 6,896 episodes of loss of viral control: in 1,669 individuals there were 2,109 episodes of the loss of viral control during a treatment interruption, and in 3,220 individuals there were 4,787 episodes while the subject was continuing the use of ART.

The duration of loss of viral suppression during a treatment interruption is primarily determined by the duration of the treatment interruption: 78.2% of these episodes had a duration of less than 0.5 years, 7.6% lasted between 0.5 and <1.0 years, and 14.1% lasted more than 1 year. At the end of the follow-up period investigated, 90.4% of these episodes had resolved after restarting ART (with the same or a different ART regimen), while 7.2% of these episodes were still ongoing, and 2.4% of these episodes ended in death, with advanced HIV / AIDS-defining conditions as the predominant cause of death in 41.2% of cases, which is a much higher proportion compared to the distribution of the causes of death in the overall population in HIV care in the Netherlands (see Chapter 5 on *Morbidity and mortality* of this Monitoring Report). Compared to the group of MSM and transgender people, the other men, and even more so the women, are overrepresented among those with loss of viral suppression because of treatment interruption. In chapter 3 we explored which factors are associated with loss of virologic control using data from SHM and Statistics Netherlands.

The large majority (71.7%) of episodes of loss of viral suppression that occurred while ART had been used continuously, consisted of a single viral load measurement above 200 copies/ml, 17.5% of these episodes consisted of 2 or more consecutive viral loads above 200 copies/ml but lasted <0.5 years, 5.2% lasted between 0.5 and <1.0 years, and 5.7% lasted more than 1 year. 92.9% of episodes had been resolved at the end of the study period, in 71.6% of episodes without a modification of the used ART regimen, and 21.3% resolved after a regimen modification. 5.7% of episodes were still ongoing at the end of the follow-up period, and 1.2% of these episodes ended in death, again with death because of an advanced-HIV / AIDS-defining condition as the predominant (40.0%) cause of death.
Compared to the group of MSM and transgender people, the other men, and even more so the women, are strongly overrepresented among those with loss of viral suppression. Women also more often modified their ART regimen before the episode of loss of viral control resolved.

In *Box 4.4* we show a summary of the findings of 3 recent studies that used the SHM dataset to investigate the virological response to three relatively new guideline-recommended treatment options (DTG/3TC; long-acting CAB/RPV and TDF/FTC/DOR) that are frequently used in treatment-experienced people with HIV in the Netherlands.

In the next section we report on the development of HIV drug resistance.

Table 4.6: Occurrence of loss of viral suppression during 2013–2024 in individuals on ART for more than 6 months.

	All		MSM + TG		Other men		Women	
Total cohort on ART								
N of subjects	25,911		16,346		4,902		4,663	
PY of follow-up	191,116		122,420		33,844		34,851	
N of episodes of failure	6,896		3,039		1,711		2,146	
Subjects with failure	4,307		2,107		1,028		1,172	
Loss of viral suppression because of ART interruption								
N of subjects	1,669		762		388		519	
N of episodes	2,109		946		493		670	
Duration of failure								
Single VL measurement	1181	56.0	522	55.2	293	59.4	366	54.6
<0.5 year	469	22.2	221	23.4	119	24.1	129	19.3
0.5 – <1 year	160	7.6	77	8.1	27	5.5	56	8.4
1 – <2 years	144	6.8	57	6.0	32	6.5	55	8.2
2+ years	155	7.3	69	7.3	22	4.5	64	9.6
Highest viral load	4.5		4.6		4.7		4.4	
$\log^{10}$ median, Q1–Q3	3.9–5.1		3.9–5.1		4.1–5.3		3.6–5.0	
Outcome								
Ongoing	151	7.2	73	7.7	37	7.5	41	6.1
Restarted, resolved	1907	90.4	851	90.0	440	89.2	616	91.9
Died while still off ART	51	2.4	22	2.3	16	3.2	13	1.9
Cause of death								
advanced HIV / AIDS	21	41.2	8	36.4	6	37.5	7	53.8
Non-AIDS malignancies	7	13.7	2	9.1	3	18.8	2	15.4
Cardiovascular disease	2	3.9	1	4.5	1	6.3	.	.
Non-AIDS infection	1	2.0	.	.	1	6.3	.	.
Liver disease	3	5.9	1	4.5	2	12.5	.	.
Lung disease	6	11.8	2	9.1	2	12.5	2	15.4
Non-natural death	1	2.0	.	.	.	.	1	7.7
Alcohol and substance use	1	2.0	1	4.5	.	.	.	.
Other causes	3	5.9	2	9.1	1	6.3	.	.
Unknown	6	11.8	5	22.7	.	.	1	7.7

	All		MSM + TG		Other men		Women	
Loss of viral suppression while on ART								
N of subjects	3,220		1,555		795		870	
N of episodes	4,787		2,093		1,218		1,476	
Duration								
Single VL measurement	3428	71.6	1565	74.8	857	70.4	1006	68.2
<0.5 year	839	17.5	348	16.6	209	17.2	282	19.1
0.5 - 1 year	248	5.2	86	4.1	72	5.9	90	6.1
1 - 2 years	158	3.3	57	2.7	48	3.9	53	3.6
2+ years	114	2.4	37	1.8	32	2.6	45	3.0
Highest viral load during episode	3.0		2.8		3.1		3.2	
median, Q1-Q3	2.5-4.0		2.5-3.6		2.6-4.2		2.6-4.2	
Outcome								
Resolved, no switch	3429	71.6	1548	74.0	874	71.8	1007	68.2
Ongoing, no switch	227	4.7	100	4.8	58	4.8	69	4.7
Resolved, switched	1021	21.3	408	19.5	258	21.2	355	24.1
Ongoing, switched	50	1.0	17	0.8	10	0.8	23	1.6
Died, no switch	34	0.7	12	0.6	8	0.7	14	0.9
Died, switched	26	0.5	8	0.4	10	0.8	8	0.5
Cause of death								
advanced HIV / AIDS	24	40.0	7	35.0	9	50.0	8	36.4
Non-AIDS malignancies	11	18.3	3	15.0	3	16.7	5	22.7
Cardiovascular disease	3	5.0	.	.	.	.	3	13.6
Non-AIDS infection	3	5.0	2	10.0	.	.	1	4.5
Liver disease	.	.	.	.	.	.	.	.
Lung disease	.	.	.	.	.	.	.	.
Non-natural death	2	3.3	2	10.0	.	.	.	.
Alcohol and substance use	1	1.7	.	.	1	5.6	.	.
Other causes	4	6.7	1	5.0	2	11.1	1	4.5
Unknown	12	20.0	5	25.0	3	16.7	4	18.2

Legend: *MSM = men who have sex with men; TG = transgender people; PY = person years; ART = antiretroviral therapy; VL = viral load.*

Box 4.4: Summary of recent studies using SHM data.

Title: Dolutegravir/Lamivudine Is Noninferior to Continuing Dolutegravir- and Non-Dolutegravir-Based Triple-Drug Antiretroviral Therapy in Virologically Suppressed People With Human Immunodeficiency Virus: DUALING Prospective Nationwide Matched Cohort Study[27].

Background: Confirming the efficacy of dolutegravir/lamivudine in clinical practice solidifies recommendations on its use.

Methods: Prospective cohort study (DUALING) in 24 human immunodeficiency virus (HIV) treatment centers in the Netherlands. HIV RNA-suppressed cases were on triple-drug antiretroviral regimens without prior virological failure or resistance and started dolutegravir/lamivudine. Cases were 1:2 matched to controls on triple-drug antiretroviral regimens by the use of dolutegravir-based regimens, age, sex, transmission route, CD4+ T-cell nadir, and HIV RNA zenith. The primary endpoint was the treatment failure rate in cases versus controls at 1 year by intention-to-treat and on-treatment analyses with 5% noninferiority margin.

Results: The 2040 participants were 680 cases and 1380 controls. Treatment failure in the 390 dolutegravir-based cases versus controls occurred in 8.72% and 12.50% (difference: -3.78% [95% confidence interval (CI), -7.49% to .08%]) by intention-to-treat and 1.39% and 0.80% (difference: 0.59% [95% CI, -.80% to 1.98%]) by on-treatment analyses. The treatment failure risk in 290 non-dolutegravir-based cases was also noninferior to controls. Antiretroviral regimen modifications unrelated to virological failure explained the higher treatment failure rate by intention-to-treat. A shorter time on triple-drug antiretroviral therapy and being of non-Western origin was associated with treatment failure. Treatment failure, defined as 2 consecutive HIV RNA >50 copies/mL, occurred in 4 cases and 5 controls but without genotypic resistance detected. Viral blips occurred comparable in cases and controls but cases gained more weight, especially when tenofovir-based regimens were discontinued.

Conclusions: In routine care, dolutegravir/lamivudine was noninferior to continuing triple-drug antiretroviral regimens after 1 year, supporting the use of dolutegravir/lamivudine in clinical practice.

Title: Real-world effectiveness and tolerability of switching to doravirine-based antiretroviral therapy in people with HIV: a nationwide, matched, prospective cohort study[28].

Background: Currently, real-world data on doravirine are scarce. In a national prospective cohort, we assessed the effectiveness and tolerability of switching to doravirine-based antiretroviral therapy (ART) in people with HIV.

Methods: We did a nationwide, matched, prospective cohort study of people with HIV without previous virological failure and stable for at least 12 months on non-doravirine-containing triple or dual ART switching to doravirine before Sept 1, 2020 (exposed group). Participants in the exposed group were matched 1:2 to individuals continuing stable non-doravirine-containing ART, on age, sex, HIV acquisition category, time since ART initiation, calendar time, pre-ART CD4-count, pre-ART plasma viral load (PVL) and anchor drug class before switching. The primary outcome was protocol-defined virological failure (PDVF; PVL of ≥200 copies per mL) in the intention-to-treat (ITT) population at week 104, with participants modifying their regimen or becoming lost to follow-up considered as PDVF (non-inferiority margin +5%). In contrast, in the on-treatment population, those who modified their regimen or became lost to follow-up were censored from that moment onwards. Tolerability was a secondary outcome.

Findings: In total, 590 participants in the exposed group and 1180 participants in the unexposed group (of whom 55·3% used integrase strand transfer inhibitor-based regimens) were included. In the ITT analysis, PDVF occurred in 135 (22·9%) exposed participants and in 295 (25·0%) unexposed participants (risk difference -2·12%, upper limit of the one-sided 95% CI +1·40%). In the on-treatment analysis, 10 (2·2%) of 455 non-censored exposed participants and 26 (2·9%) of 885 non-censored unexposed participants had PDVF (risk difference -0·70%, upper limit of the one-sided 95% CI +0·73%). All exposed participants with a PVL of 200 copies or more per mL resuppressed without regimen modification: no confirmed virological failure (two consecutive PVLs of ≥200 copies per mL) was observed. 104 (17·6%) exposed participants and 211 (17·9%) unexposed participants modified their regimen. 73 (12.4%) exposed participants discontinued doravirine due to adverse events: abnormal dreams (1·7%) and insomnia (1·5%) were most common.

Interpretation: Switching to doravirine in well suppressed people with HIV without previous virological failure was non-inferior compared with continuing non-doravirine-containing regimens after 2 years in a real-world setting.

Title: Effectiveness of bi-monthly long-acting injectable cabotegravir and rilpivirine as maintenance treatment of HIV-1: results from the Dutch ATHENA national observational cohort.
Vita Jongen, Ferdinand Wit, Anders Boyd, Arne van Eeden, Annemarie Brouwer, Robert Soetekouw, Rachida El Moussaoui, Janneke Stalenhoef, Kim Sigaloff, Tatiana Mudrikova, Jet Gisolf, David Burger, Annemarie Wensing, Marc van der Valk.
Lancet HIV, 2024 *in press*.

Background: Real-world data demonstrating long-term effectiveness of long-acting injectable cabotegravir and rilpivirine (CAB/RPV) are scarce. We assessed the effectiveness of CAB/RPV in all individuals who switched to CAB/RPV in the Netherlands.

Methods: We used data from the ATHENA cohort, an ongoing observational nationwide HIV cohort. In primary analysis, we matched individuals who commenced CAB/RPV and had no history of virological failure (VF) (i.e., ≥1 plasma HIV RNA ≥1000 copies/mL, hereafter "exposed") 1:2 to individuals using oral antiretroviral therapy (ART) (hereafter "unexposed"). We assessed the effectiveness of CAB/RPV using restricted mean survival time (RMST) until loss of virologic control (≥1 plasma HIV RNA ≥200 copies per mL). In secondary analysis, we assessed loss of virologic control in individuals who commenced CAB/RPV with previous VF and/or an unsuppressed HIV-1 RNA at CAB/RPV initiation.

Findings: In primary analysis, 585 exposed and 1,170 unexposed individuals were included between February 2018-August 2023. Median follow-up was 1.3 year [IQR=0.9-1.7]. Fourteen exposed (2.4%) and 29 unexposed (2.5%) individuals experienced loss of virologic control, with no difference in RMST (difference= 0.026, 95%CI=-0.029-0.080). Seven exposed individuals re-suppressed without regimen change. Seven switched ART, of whom six had documented integrase inhibitor (INSTI) and/or non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistance. No unexposed individuals switched ART after loss of virologic control. In secondary Powered by Editorial Manager® and ProduXion Manager® from Aries Systems Corporation analysis, 105 individuals were included. During a median follow up of 1.4 years [IQR=0.8-1.8], nine (8.6%) experienced loss of virologic control; five had INSTI- and/or NNRTI-resistance.

Interpretation: Switching to CAB/RPV was not associated with a higher risk of loss of virologic control among individuals without previous VF compared to oral ART. However, INSTI and/or NNRTI mutations were selected in 43% of individuals with CAB/RPV failure, compared to none with oral ART. The high risk of loss of virologic control among individuals with previous VF and/or an unsuppressed HIV-1 RNA at CAB/RPV initiation warrants more careful monitoring.

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 be selected: mutations in the genetic structure of HIV can detrimentally affect the ability of a particular drug, or combination of drugs, to block replication of the virus. All current antiretroviral drugs, including newer classes, are at risk of becoming partially or fully inactive due to the emergence of drug-resistant HIV[29].

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

We evaluated the presence of mutations in the HIV genome that are associated with drug resistance. The 2022 International Antiviral Society-USA (IAS-USA) HIV drug resistance mutation list was used to score major resistance-associated mutations[24]. Furthermore, we assessed the association between these mutations and the susceptibility to antiretroviral drugs. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.6) was used to infer antiretroviral drug susceptibility scores for each sequence according to a five-level scheme: susceptible; potential low-level resistance; low-level resistance; intermediate resistance; and high-level resistance[25,26]. The definitions of transmitted and acquired-HIV drug resistance used in our analyses are summarised in *Box 4.3*.

As of December 2023, 9,523 HIV-1 sequences had been obtained from 9,195 ART-naïve people prior to initiation of ART in between 2003 and 2023. 9,508 reverse transcriptase sequences were available from 9,183 individuals, 8,945 protease sequences were available from 8,632 individuals, and 588 integrase sequences were available from 587 individuals.

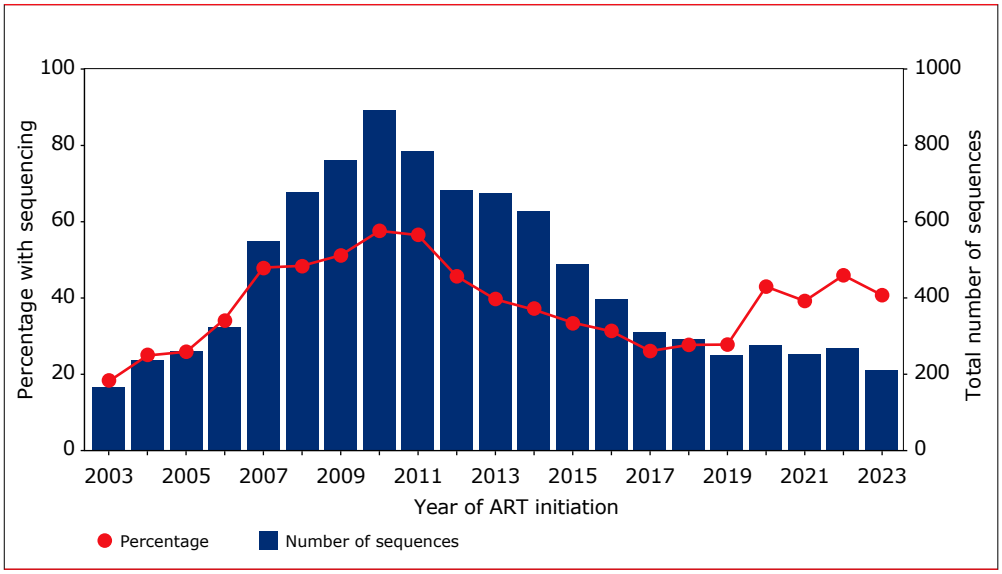
Screening for drug-resistant HIV before treatment initiation

Since 2003 Dutch treatment guidelines have included a recommendation to screen for HIV drug resistance in all people newly diagnosed with HIV at the time of entry into care. Transmitted HIV drug resistance occurs when people acquire an HIV strain that harbours drug-resistant mutations. Drug-resistant variants of HIV may remain dormant, awaiting more favourable replication conditions after treatment has started[30-32]. These dormant mutant variants may not be detected, which can make it difficult to distinguish between drug-susceptible and drug-resistant

strains[33]. Ideally, the presence of transmitted resistance should be identified as close as possible to the moment of infection in people who are antiretroviral (ARV)-naïve before initiating ART. Furthermore, individuals with insufficient coverage of pre-exposure prophylaxis (PrEP) for HIV could acquire HIV and if continuing to take PrEP, could develop resistance mutations associated with these antiretrovirals. Resistance mutations associated with specifically PrEP use are described in more detail in Chapter 2.

In total, 9,523 HIV-1 sequences were obtained between 2003 and 2023 from 9,195 ARV-naïve people before they initiated ART. The number of sequences and the percentage of ARV-naïve people with sequencing before ART initiation peaked in 2010 and have steadily declined since then (*Figure 4.12*). If someone had more than one sequence available before ART 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 (65.7%), while 15.3% were women. Most people with an available pre-treatment sequence originated from the Netherlands (58.7%) or sub-Saharan Africa (11.2%). The main HIV-1 subtype was B (73.2%), followed by non-B subtypes (26.8%), including recombinant form CRF_02AG (6.7%), subtype C (5.1%), and CRF_01AE (3.7%).

Figure 4.12: *The annual number of sequences and the percentage of ARV-naïve people with sequencing before ART.*

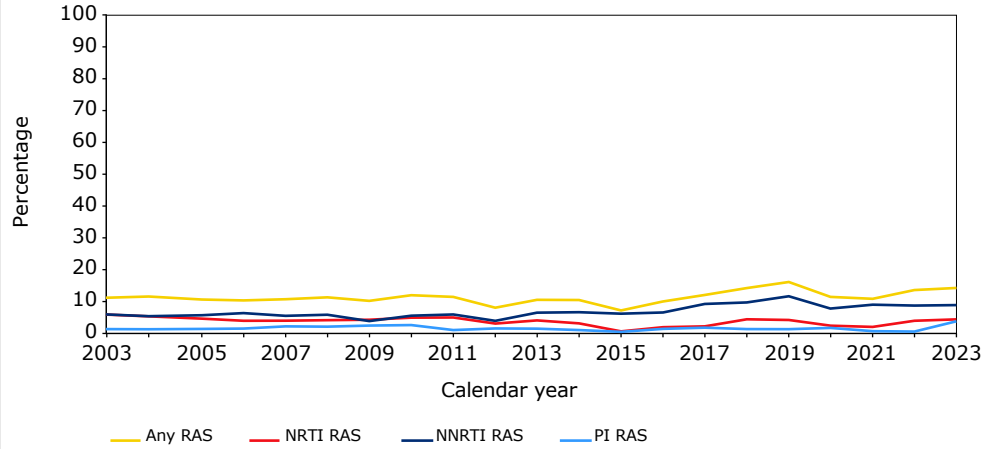


Legend: *ART = antiretroviral therapy.*

HIV drug resistance before treatment initiation

In total, at least one or more major resistance-associated mutation[24] was found in 1,030 (11.2%) of the ART-naïve people tested for resistance, including 370 (4.0%) with NRTI-associated resistance mutations, 590 (6.4%) with NNRTI-associated resistance mutations, and 162 (1.8%) with PI-associated resistance mutations. The prevalence of transmitted drug resistance was low and remained stable between 2003 and 2023 (*Figure 4.13*).

Figure 4.13: *The annual percentage of people with evidence of transmitted HIV drug resistance over time. Transmitted drug resistance was defined as the presence of at least one resistance-associated mutation detected before initiation of ART. The 2022 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[24].*



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

In total, 301 (3.3%) individuals screened for drug resistance before ART initiation harboured high-level resistance[25,26] to at least one antiretroviral drug: 53 (0.6%) to at least one NRTI; 226 (2.5%) to at least one NNRTI; and 37 (0.4%) to at least one PI. On the basis of the available resistance data, 96.8% were fully susceptible to all antiretroviral drugs: 2.8% (260) harboured high-level resistance to one drug class; 0.3% (29) to two drug classes; and less than 0.1% (five) to three drug classes (i.e., NRTIs, NNRTIs and PIs).

It should be emphasised that this does not mean that entire drug classes are rendered unsuitable for use in antiretroviral combinations. Even for people with resistance to all three classes, it often remains possible to construct fully efficacious ART combinations.

Integrase inhibitor resistance before HIV treatment initiation

In total, 587 people had an integrase sequence available prior to ART initiation, of whom all but 13 were ARV-naïve. Only one major integrase resistance-associated mutation was detected in these individuals (Y143Y/C).

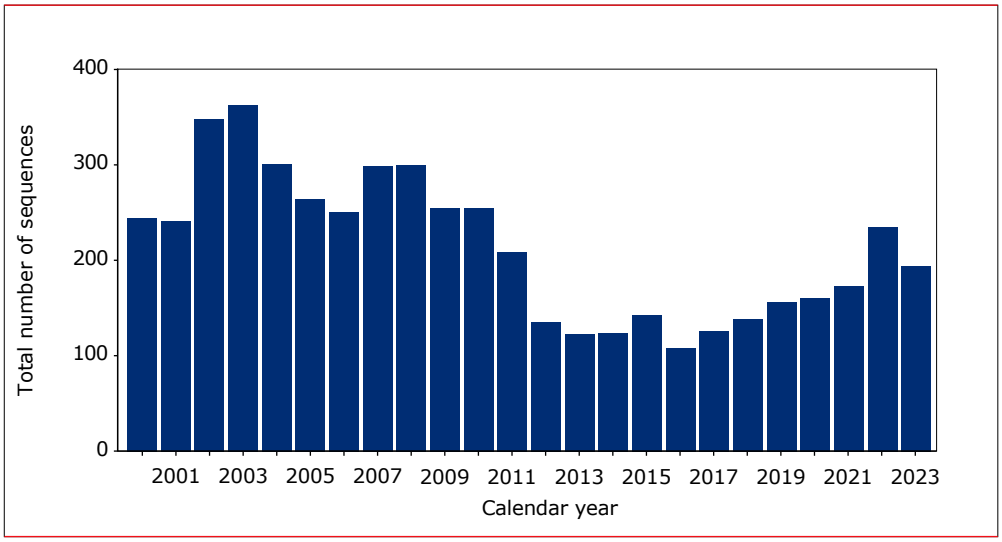
Acquired HIV drug resistance

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

In this section, we describe the level of acquired drug resistance detected among the treated population with a viral load above 500 copies/ml, and resistance test results available after at least four months of ART in between 2000 and 2023. If ART had been interrupted more than two weeks before the test, the sequence was excluded from the analysis. As of December 2023, 5,147 HIV-1 sequences had been obtained from 3,071 people who received ART for at least four months in between 2000 and 2023. 3,732 sequences were from 2,312 people who had been ART-naïve before initiating ART. 5,050 reverse transcriptase sequences were available from 3,039 individuals, 4,790 protease sequences were available from 2,880 individuals, and 716 integrase sequences were available from 547 individuals.

The number of sequences in this group was consistently above 200 between 2000 and 2010, substantially declined in 2011, then slightly increased until 2023 (*Figure 4.14*). The median time between initial start of ART and resistance testing was 5.9 years (IQR 3.2-10.0). The main HIV-1 subtype was B (66.6%), followed by recombinant form CRF_02AG (11.3%), and subtype C (6.0%).

Figure 4.14: The annual number of HIV-1 sequences in people who received ART for at least four months.



Overall, sequences from people pre-treated with monotherapy or dual therapy were disproportionally represented: 1,415 (27.5%) sequences were obtained from 759 (24.7%) pre-treated people, and 3,732 (72.5%) sequences were obtained from 2,312 (75.5%) people who had started ART while not being pre-treated with NRTI mono- or dual-therapy. However, over time this difference became less distinct: in 2000, 72.8% of sequences were obtained from pre-treated people, compared with 36.1% in 2005, and less than 14% from 2010 onwards.

Of the 5,147 sequences obtained when the HIV RNA was above 500 copies/ml, 3,012 (58.5%) harboured high-level resistance to at least one antiretroviral drug. High-level NRTI resistance was detected in 3,040 (59.1%) sequences; of those, 2,584 (85.0%) harboured high-level resistance to emtricitabine or lamivudine. Notably, of the 1,872 individuals ever identified as harbouring the M184V or M184I mutation who were still in care in 2023, 1,196 (63.7%) were still on ART containing lamivudine or emtricitabine, of whom 944 (78.9%) had undetectable HIV-RNA at their last visit. In addition, 1,808 (35.8%) harboured high-level resistance to at least one NNRTI, and 1,041 (21.7%) to at least one PI.

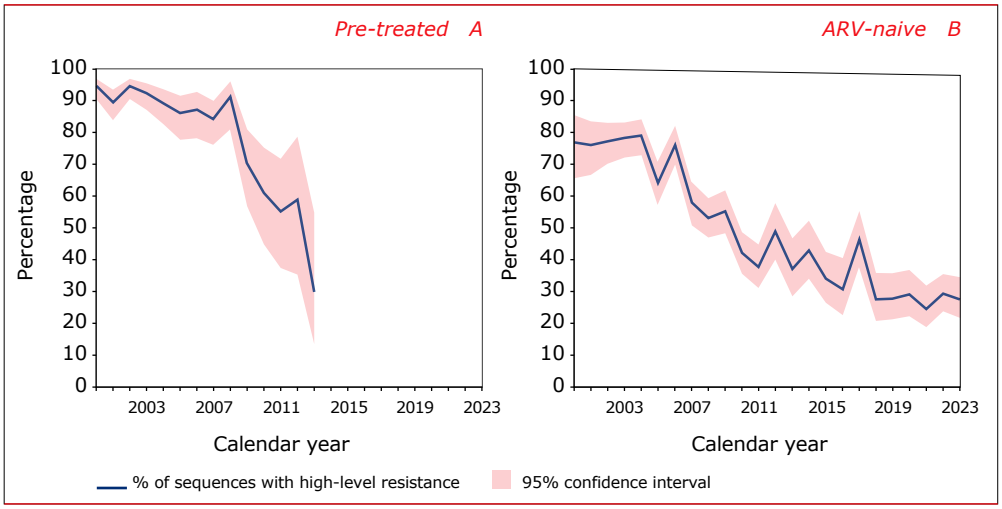
Previous antiretroviral drug exposure

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

Among pre-treated people, the annual percentage of sequences harbouring high-level resistance to at least one drug was 94.9% (95% CI 90.5-97.3) in 2000, 61.1% (44.6-75.4) in 2010, and 29.4% (12.8-54.2) in 2013 (*Figure 4.15A*). The availability of new drugs both in existing and new drug classes largely explains the decline since 2008[34]. In recent years (2014-2023), both the number of pre-treated people, and the number of sequences from pre-treated people, were too low to provide meaningful percentages.

Among previously ARV-naïve people, high-level resistance to at least one drug was detected among 77.3% (95% CI 65.7-85.8) of sequences in 2000, 49.2% (40.3-58.1) in 2012, and 27.6% (21.6-34.6) in 2023 (*Figure 4.15B*). Over time, the difference in acquired drug resistance detected among pre-treated and ARV-naïve people has disappeared.

Figure 4.15: The annual percentage of sequences with evidence of high-level resistance to any antiretroviral drug, obtained at the time of virological failure when receiving antiretroviral therapy (ART), by prior antiretroviral (ARV) drug exposure, among A) people who were pre-treated with mono or dual nucleoside-analogue reverse transcriptase inhibitors, and B) previously antiretroviral drug-naïve people. The shaded area represents the 95% confidence interval.



Acquired HIV drug resistance among previously ARV-naïve people

In the remainder of our analysis, we focus solely on the 2,312 people who had not been pre-treated with NRTI mono- or dual-therapy before combination ART initiation. Overall, 2,046 (54.8%) of the 3,732 sequences from previously ARV-naïve people receiving ART harboured at least one major resistance mutation, which were associated with resistance to NRTI (1,585, or 42.5%), NNRTI (1,271, or 34.1%), or PI (380, or 10.2%).

In *Figure 4.16A.* the annual percentage of sequences harbouring high-level resistance is presented for each antiretroviral drug class. In 2000:

- 77.3% (95%CI 65.7-85.8) of sequences harboured high-level resistance to at least one NRTI;
- 27.7% (18.2-39.7) harboured high-level resistance to at least one NNRTI; and
- 49.2% (37.4-61.2) harboured high-level resistance to at least one PI.

The percentage of sequences with high-level resistance declined over time for these three drug classes, and in 2012:

- 49.2% (95%CI 40.3-58.1) of sequences harboured high-level resistance to at least one NRTI;
- 33.9% (25.9-42.9) harboured high-level resistance to at least one NNRTI; and
- 5.1% (2.3-10.9) harboured high-level resistance to at least one PI.

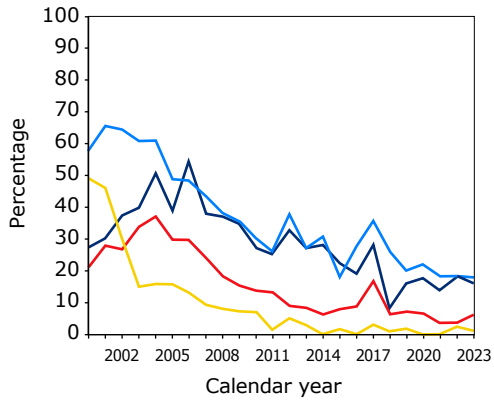
By 2023, these percentages were down to:

- 27.6% (95%CI 21.6-34.6) of sequences harbouring high-level resistance to at least one NRTI;
- 16.3% (11.5-22.6) harbouring high-level resistance to at least one NNRTI; and
- 1.3% (0.3-5.1) harbouring high-level resistance to at least one PI.

The percentage of sequences with at least one resistance mutation to all three drug classes (i.e., NRTI, NNRTI, and PI) also declined over time: from 9.1% (95% CI 4.1-18.8) in 2000 to 0% in 2014.

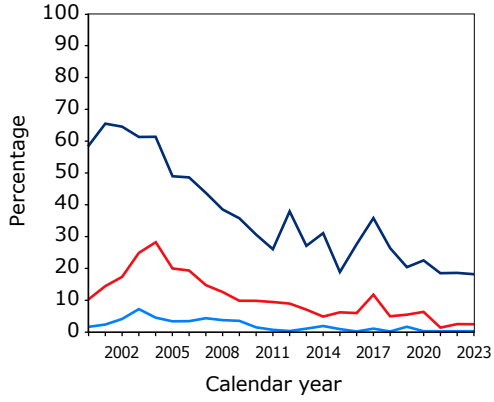
The annual percentage of sequences harbouring high-level resistance to individual antiretroviral drugs are presented in *Figure 4.16B-D*. The annual percentage of sequences harbouring major resistance mutations to specific drugs are outlined in *Appendix Table 4.3A-C*. *Figure 4.16E*, meanwhile, shows the annual percentage of sequences harbouring at least one high-level resistance mutation to all three drug classes. It should be pointed out that drug resistance does not disappear when viral replication is successfully suppressed or re-suppressed, but instead remains viably archived in the viral reservoir.

Figure 4.16: *The annual percentage of sequences with evidence of high-level resistance by drug class and antiretroviral drug, obtained at the time of virological failure when receiving antiretroviral therapy (ART), among previously antiretroviral drug-naïve people. Results are shown by A) antiretroviral drug class: high-level resistance to at least one drug within class, B) antiretroviral drug: high-level resistance to nucleoside reverse transcriptase inhibitors, C) antiretroviral drug: high-level resistance to non-nucleoside reverse transcriptase inhibitors, D) antiretroviral drug: high-level resistance to protease inhibitors, and E) high-level resistance to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors.*



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

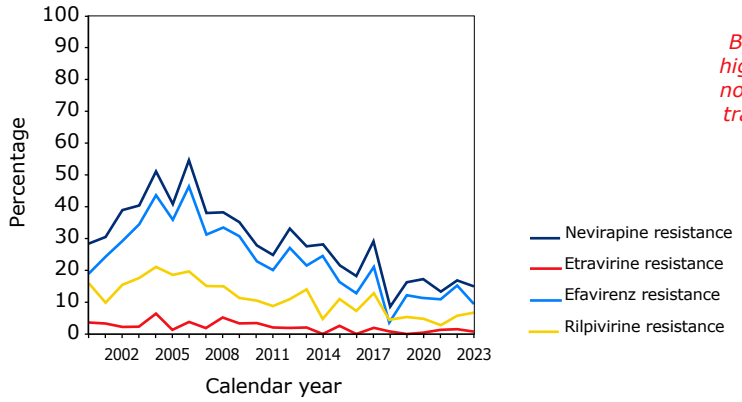
- Nucleoside reverse transcriptase inhibitor resistance (except emtricitabine/lamivudine)
- Emtricitabine/lamivudine resistance
- Non-nucleoside reverse transcriptase inhibitor resistance
- Protease inhibitor resistance



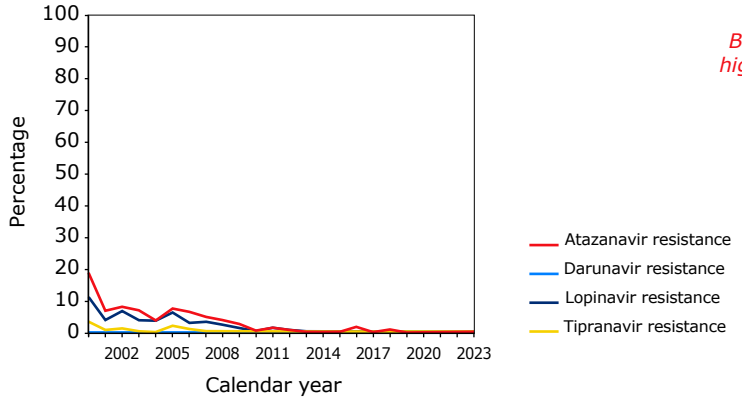
B
By antiretroviral drug: high-level resistance to nucleoside reverse transcriptase inhibitors

- Lamivudine/emtricitabine resistance
- Abacavir resistance
- Tenofovir resistance

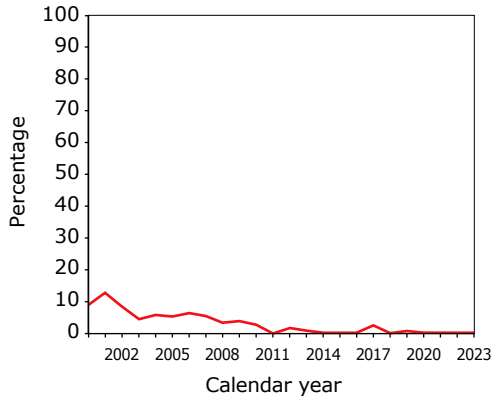
C
By antiretroviral drug: high-level resistance to non-nucleoside reverse transcriptase inhibitors



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



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



Legend: *NRTIs = nucleoside analogue reverse transcriptase inhibitors.*

Note: *The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.6) was used to infer antiretroviral drug susceptibility scores for each sequence, according to a five-level scheme: susceptible; potential low-level resistance; low-level resistance; intermediate resistance; and high-level resistance[25,26].*

Acquired integrase inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on ART was relatively rare. The available 716 integrase sequences originated from 547 people who received ART for at least four months; 51 were pre-treated with monotherapy or dual NRTI therapy before initiating ART, and 496 were ARV-naïve before initiating ART. The median time between initial ART initiation and testing for integrase inhibitor resistance was 10.5 years (IQR 4.8-16.2). For each person, we used the most recent sequence in our analysis.

At least one acquired major mutation associated with integrase inhibitor resistance was detected in 58 of 547 individuals (observed in 77 of 716 sequences), which resulted in high-level resistance to at least one integrase inhibitor[24,25]. When assessing the last available integrase sequence of these 58 individuals, the following major INSTI resistance mutations were detected (numbers are given in parenthesis):

- N155H (19) and N155H/N (six);
- R263K (eight) and R263R/K (three);
- E92Q (six) and E92E/Q (three);
- Y143R (one) and Y143Y/C (one);
- T66I (three) and T66I/T (one);
- Q148H (one), Q148Q/H (one), Q148R (two); and
- S147G (one), S147S/G (one).

Minor mutations detected were at positions:

- T97 (any, nine; T97A, seven; T97T/A, two);
- T66 (any, five; T66T/A, three; T66T/K, one; T66K, one);
- L74 (any mutation, one; L74I/M, one);
- G140 (any, four; G140S, two; G140G/S, two); and
- E138 (any, two; E138K, two).

Seven of the 58 individuals who harboured major INSTI resistance mutations had ever received INSTI-monotherapy.

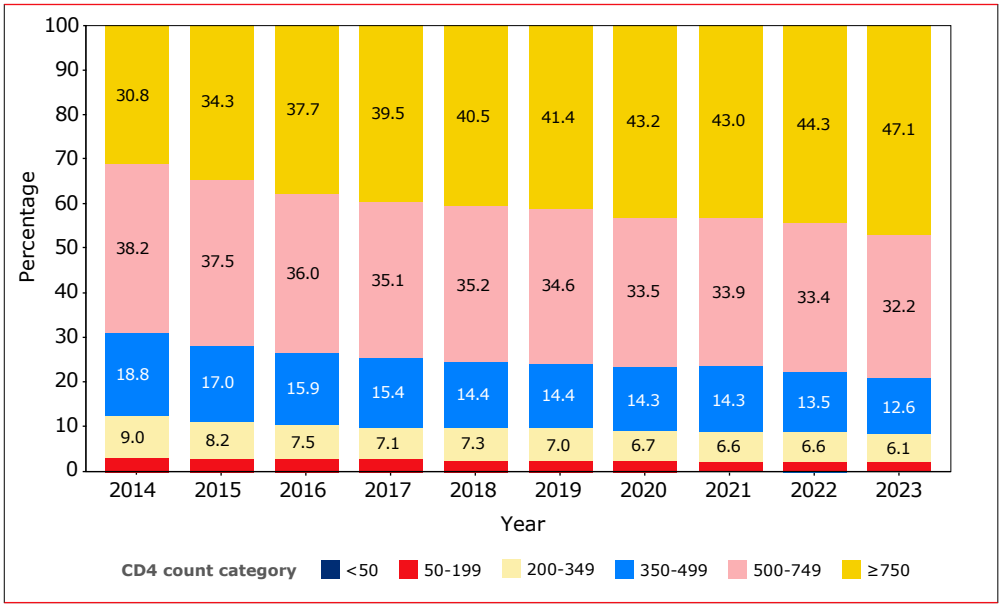
Immunological response

After initiation of ART, most people durably suppress plasma HIV RNA to levels below <50 copies/ml, and this is accompanied by recovery of the CD4 count. Failure to durably suppress HIV replication is associated with poorer recovery of the CD4 count[18,35]. In case of frequent and/or prolonged loss of viral suppression, HIV disease progression can develop with a significant decrease of the CD4 count and the occurrence of opportunistic diseases. However, even in the setting of prolonged viral suppression, a protracted and/or incomplete recovery of the CD4 count (i.e. a CD4 count persistently below 350 cells/mm^3) may still occur. This is a situation reported to be associated with an increased risk of progression to AIDS and development of non-AIDS-defining diseases[19]. Normal CD4 counts in men without HIV are on average approximately 830 cells/mm^3 and around 1000 cells/mm^3 in women, but this varies according to factors such as age, ethnicity, and smoking behaviour[36,37]. The clinical benefit of ART is strongly related to the level of recovery of the immune status (also see *Chapter 3*)[38-42].

Immunological response by calendar year

Of all individuals who were on ART in the period 2014 to 2023, CD4 count data are shown in *figures 4.17*. The percentage of individuals on ART with a normalised CD4 count (i.e. with a CD4 count over 500 cells/mm^3) increased from 69.0% in 2014 to 79.3% in 2013. The percentage of individuals on ART with CD4 counts below 350 cells/mm^3 slowly continued to decrease from 12.2% in 2014 to 8.1% in 2023. These favourable changes in the distribution of the CD4 count in the treated population is a consequence of 1) the current guidelines recommending ART initiation as soon as possible after HIV diagnosis and irrespective of the CD4 count, 2) a more pronounced immune recovery with longer ART use, 3) increasing virological suppression rates, and 4) attrition by the higher mortality rates in individuals with low CD4 counts.

Figure 4.17: Last available CD4 count of the population on ART by calendar year (missing measurements/data were not taken into account).



Immunological response after ART initiation (2014–2019)

The distribution of pre-ART CD4 counts in ART-naïve individuals initiating first-line ART has remained fairly constant in the period between 2014 and 2023 (*Figure 4.18*). In 2023, 25.2% of individuals initiating ART had a CD4 count below 200 cells/mm^3, and another 22.4% had a CD4 count between 200 and <350 cells/mm^3. This trend closely resembles the CD4 counts at HIV diagnosis (see Chapter 1).

We also assessed the immunological response in individuals who started ART between in 2014-2019 to allow for a potential follow-up of 5 years. The level of viral suppression and treatment interruptions after initiating ART were not taken into account in this analysis, but are generally very high. The changes in the CD4 count distribution following ART initiation are visualized in *Figure 4.19A*. Whereas at the initiation of ART 22.4% of individuals had a CD4 count below 200 cells/mm^3 and another 18.2% had a CD4 count between 200 and <350 cells/mm^3, these proportions had decreased after 5 years of ART to 7.2% with a CD4 count below 200 cells/mm^3 and 11.9% between 200 and <350 cells/mm^3.

The speed and magnitude of the changes of the CD4 count after ART initiation strongly depend on the pre-ART CD4 count. The heatmap in *Figure 4.19B* shows the 5-year evolution of the CD4 count distribution stratified by the baseline CD4 count. The CD4 count distributions in all pre-ART CD4 count strata show favourable changes over time, but fail to converge even after 5 years of ART. Virtually all individuals who initiate ART while in the higher CD4 count strata remain in these higher strata, or increase their CD4 counts even further. The vast majority of individuals who initiate ART in the lower CD4 count strata have reached the higher CD4 count strata after 5 years of ART: only 10.3% of individuals who initiate ART with a CD4 below 50 remain below 200 after 5 years of ART, and only 3.6% of individuals who initiate ART with a CD4 between 50 and <200 remain below 200 after 5 years of ART. A limitation of this analysis is that attrition because of increased mortality in those who fail to increase their CD4 count is not taken into account.

Figure 4.18: *The pre-ART CD4 count in ART-naïve individuals initiating first-line ART by calendar year (missing measurements/data were not taken into account).*

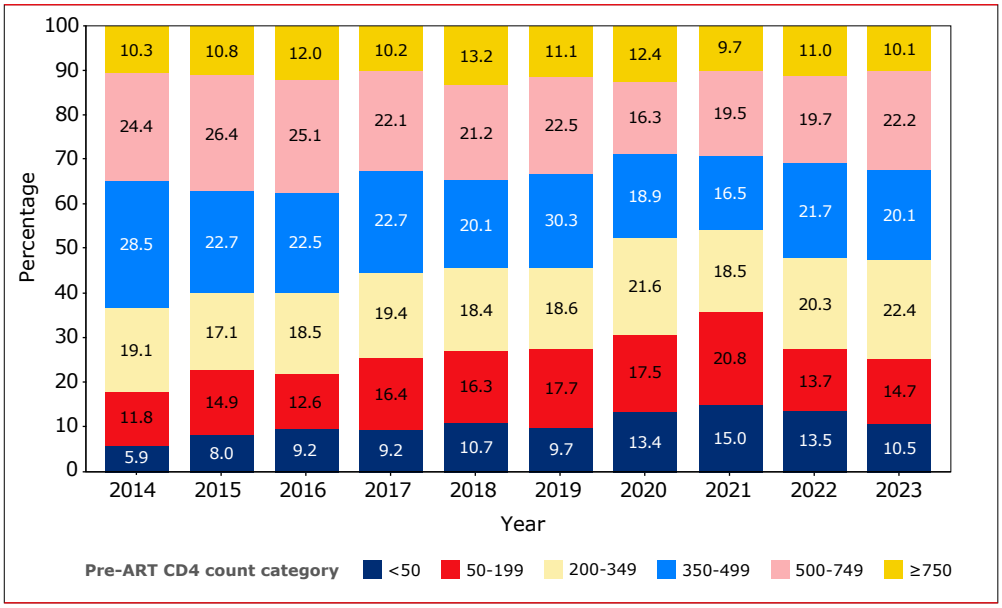
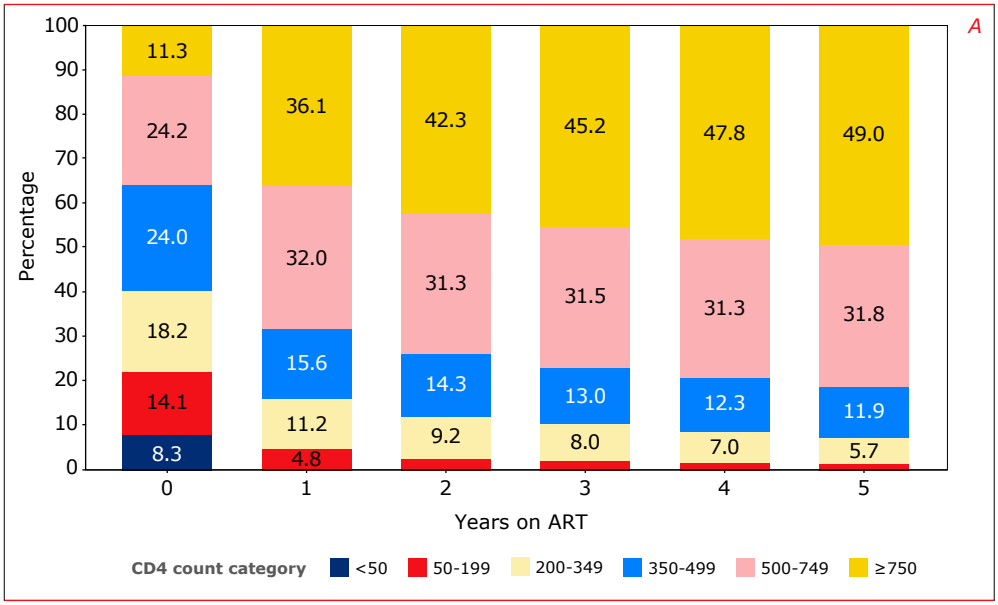
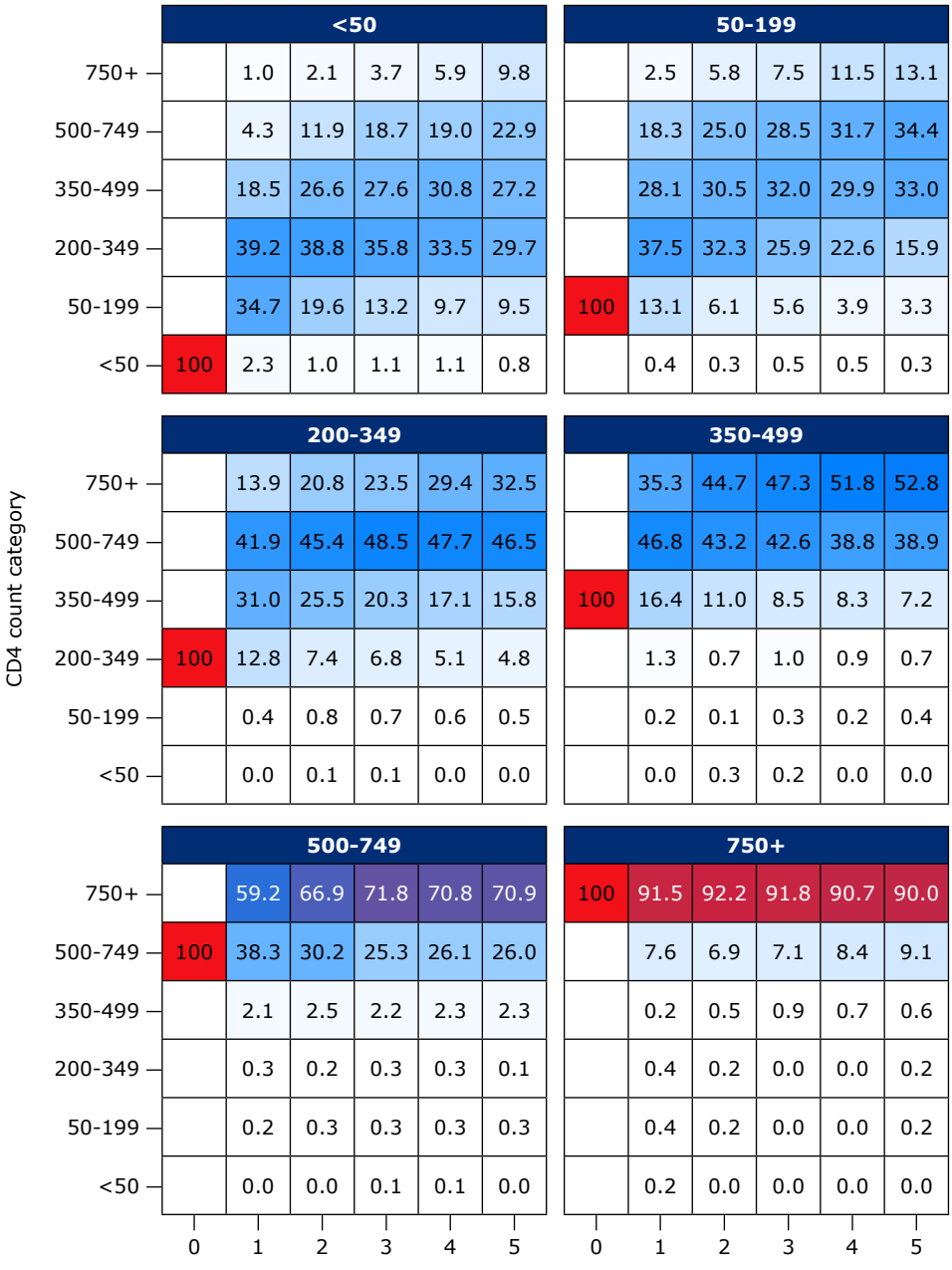


Figure 4.19A&B: Changes in CD4 count distribution over 5 years following the start of antiretroviral therapy (ART) in 2014-2019 (A) and stratified for the last measured CD4 count prior to start of ART (B).



B



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

Summary and conclusions

Starting ART and the initial regimen

- Between 2014 and 2023, 7,860 newly diagnosed individuals aged 15 years and older entered into HIV care in the Netherlands and initiated first-line ART.
- Rapid initiation of ART following a diagnosis of HIV infection, irrespective of CD4 count, has generally resulted in a shorter median time to initiation of ART following diagnosis, which was 19 (IQR 11-31) days in 2023.
- Between 2014 and 2021 there was a slowly decreasing trend in the CD4 count at ART initiation. However, in 2022 and 2023 the CD4 count at the start of ART has risen slightly again. In 2023, 25.2% of individuals initiating ART had a CD4 count below 200 cells/mm^3, and another 22.4% had a CD4 count between 200 and <350 cells/mm^3. Immunological recovery was much better when ART was started at a higher CD4 count.
- In 2023, 91.3% of initial regimens contained an integrase inhibitor. In 2023, the most frequently used initial regimen was TDF/FTC/dolutegravir (39.5%). TAF/FTC/bictegravir was used in 37.7% of initial regimens.

In care and receiving ART in 2023

- The number of people on ART and in active follow-up in the ATHENA cohort grew from 17,202 individuals in 2014 to 22,215 individuals in 2023.
- In 2023, the vast majority (91.0%) of individuals received a regimen based on one or two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with an integrase inhibitor (55.8%), a non-nucleoside reverse transcriptase inhibitor (26.6%) or a protease inhibitor (8.6%).
- Long-acting injectables (cabotegravir/rilpivirine) were used by 3.1%.
- The population had been diagnosed with HIV a median of 14.1 (IQR 8.4-20.4) years ago, and started their first-line ART regimen a median of 12 (IQR 7.5-17.9) years ago.
- Their last measured viral load was <50 copies/ml in 95.8% (<200 copies/ml in 97.9%), and 79.2% had a last measured CD4 count of 500 cells/mm^3 or higher.
- ART regimens were modified often, with the most common reasons for regimen modification being (mostly mild) toxicity (21.7%), treatment simplification (18.6%), patient decision/compliance (7.9%), and preventive modifications (7.2%). In only 1,218 (1.7%) regimen the reported reason for modification was virological treatment failure. The rate with which ART regimens were modified slowly decreased over time.
- The proportion of the treated population that at any moment has temporarily interrupted ART continues to decrease, from 2.8% in 2014 to 0.7% in 2023, indicating the improved tolerability of modern ART regimen.

- In 2,905 individuals a total of 4,815 treatment interruptions (of 14 days or longer) were recorded. The median duration of the recorded treatment interruptions was 13.7 (IQR 5.0-37.1) weeks. Many long interruptions constitue temporary disengagement of care. During longer treatment interruptions the CD4 counts often drops significantly.

Virological and immunological response and drug resistance

The overall viral suppression rates of the population with HIV receiving ART is high and has continued to improve. Among the limited number of individuals who experienced virological failure, the annual percentage with acquired drug resistance remained low; this is in line with findings in other high-income settings[43,44].

Transmitted drug resistance was rare, and the overall prevalence was low and stable over time, in line with rates reported by other European countries[45].

Integrase inhibitor resistance data remain limited. Only one case of transmitted integrase inhibitor resistance was detected among the 587 people tested by the end of 2023. Detected rates of acquired integrase inhibitor resistance among available sequences remained low, with only a handful of cases with significant resistance to dolutegravir or bictegravir.

Virtually all individuals who initiated first-line ART who had high (500+ cells/mm^3) CD4 counts at the start of treatment, remained in the higher CD4 strata. Contrary, 10.3% of individuals who initiate ART with a CD4 below 50 cells/mm^3 remain below 200 cells/mm^3 after 5 years of ART, and 3.6% of individuals who initiate ART with a CD4 between 50 cells/mm^3 and <200 cells/mm^3 remain below 200 cells/mm^3 after 5 years of ART.

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Appendix

Appendix Table 4.1: *Frequency of and reasons for discontinuation / modification of various ARV regimen in the period 2014–2023.*

				Stop reasons (n & rate per 1,000PY)			
					Failure		Toxicity
Calendar year	Exposure (PY)	Total episodes (N)	Ongoing episodes (n)	(n)	(rate)	(n)	(rate)
INSTI + NRTI							
TAF/FTC/BIC	13206	5968	3970	48	3.6	914	69.2
DTG/3TC	6855	3511	2910	32	4.7	284	41.4
ABC/3TC/DTG	21934	6601	1890	62	2.8	1929	87.9
TAF/FTC/DTG	3409	1277	511	21	6.2	210	61.6
TDF/FTC/DTG	6288	3752	1091	41	6.5	768	122.1
TAF/FTC/EVG/c	17249	4777	2031	64	3.7	902	52.3
TDF/FTC/EVG/c	7128	2611	479	46	6.5	649	91.0
TDF/FTC/RAL	2384	1203	137	32	13.4	221	92.7
Other INSTI+NRTI	2023	1104	256	18	8.9	164	81.1
NNRTI + NRTI							
TDF/3TC/DOR	4906	2607	1841	36	7.3	408	83.2
TDF/FTC/EFV	19895	5462	1158	108	5.4	2554	128.4
ABC/3TC/NVP	4073	845	245	32	7.9	177	43.5
TAF/FTC/NVP	4416	1176	710	15	3.4	204	46.2
TDF/FTC/NVP	14236	3289	833	80	5.6	813	57.1
TAF/FTC/RPV	6268	1881	983	25	4.0	313	49.9
TDF/FTC/RPV	9440	3047	426	62	6.6	834	88.3
Other NNRTI+NRTI	4227	1762	289	29	6.9	462	109.3
PI + NRTI							
TDF/FTC/ATV/b	4920	2067	145	50	10.2	533	108.3
TAF/FTC/DRV/c	6736	2646	1356	37	5.5	444	65.9
TDF/FTC/DRV/b	8903	4197	393	78	8.8	818	91.9
TDF/FTC/LPV/r	686	458	18	13	18.9	90	131.1
Other PI+NRTI	5064	2432	235	50	9.9	490	96.8
2 anchor drugs							
CAB/RPV	977	806	692	12	12.3	40	40.9
DTG/DRV/b	2326	791	391	11	4.7	112	48.2
DTG/RPV	586	263	144	5	8.5	38	64.8
2 anchors w/wo NRTI	4552	2482	408	89	19.6	378	83.0

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

Stop reasons (n & rate per 1,000PY)									
Patient choice		Simplification		Prevention		Pregnancy		Other reasons	
(n)	(rate)	(n)	(rate)	(n)	(rate)	(n)	(rate)	(n)	(rate)
394	29.8	231	17.5	88	6.7	53	4.0	270	20.4
71	10.4	93	13.6	17	2.5	21	3.1	83	12.1
648	29.5	955	43.5	613	27.9	86	3.9	418	19.1
100	29.3	316	92.7	21	6.2	16	4.7	82	24.1
263	41.8	1091	173.5	229	36.4	37	5.9	232	36.9
399	23.1	514	29.8	511	29.6	69	4.0	287	16.6
254	35.6	568	79.7	398	55.8	25	3.5	192	26.9
102	42.8	456	191.3	92	38.6	36	15.1	127	53.3
60	29.7	345	170.6	50	24.7	11	5.4	200	98.9
116	23.6	84	17.1	29	5.9	14	2.9	79	16.1
293	14.7	475	23.9	474	23.8	35	1.8	365	18.3
61	15.0	125	30.7	149	36.6	7	1.7	49	12.0
42	9.5	100	22.6	33	7.5	1	0.2	71	16.1
222	15.6	736	51.7	404	28.4	12	0.8	189	13.3
87	13.9	214	34.1	97	15.5	14	2.2	148	23.6
240	25.4	648	68.6	440	46.6	43	4.6	354	37.5
90	21.3	555	131.3	136	32.2	11	2.6	190	44.9
240	48.8	696	141.5	198	40.2	54	11.0	151	30.7
289	42.9	223	33.1	123	18.3	40	5.9	134	19.9
592	66.5	1633	183.4	329	37.0	99	11.1	255	28.6
67	97.6	188	273.9	23	33.5	20	29.1	39	56.8
262	51.7	865	170.8	225	44.4	85	16.8	220	43.4
15	15.4	2	2.0	8	8.2	0	0.0	37	37.9
93	40.0	89	38.3	36	15.5	4	1.7	55	23.6
20	34.1	28	47.8	8	13.6	2	3.4	18	30.7
211	46.4	946	207.8	156	34.3	27	5.9	267	58.7

Appendix Table 4.2: Virological treatment response in 2014–2023 in people who started ART at least months earlier.

Calendar year	Total population N	Viral load categories (c/ml)											
			<50		50–199		200–999		1,000–9,999		10,000+		ART interrupted	
		N	%	N	%	N	%	N	%	N	%	N	%
2014	17,016	15,442	90.75	580	3.41	216	1.27	134	0.79	230	1.35	414	2.43
2015	17,916	16,497	92.08	552	3.08	187	1.04	106	0.59	214	1.19	360	2.01
2016	18,715	17,458	93.28	469	2.51	145	0.77	112	0.60	199	1.06	332	1.77
2017	19,405	18,075	93.15	568	2.93	156	0.80	82	0.42	183	0.94	341	1.76
2018	20,082	18,904	94.13	437	2.18	156	0.78	103	0.51	163	0.81	319	1.59
2019	20,686	19,476	94.15	501	2.42	161	0.78	89	0.43	157	0.76	302	1.46
2020	21,089	20,047	95.06	440	2.09	144	0.68	66	0.31	101	0.48	291	1.38
2021	21,306	20,297	95.26	418	1.96	137	0.64	59	0.28	128	0.60	267	1.25
2022	21,794	20,675	94.87	490	2.25	136	0.62	93	0.43	156	0.72	244	1.12
2023	22,119	21,132	95.54	421	1.90	141	0.64	96	0.43	160	0.72	169	0.76

Appendix Table 4.3A–C: Acquired drug resistance: annual percentage of available sequences with major resistance mutations after virological failure by antiretroviral drug, associated with people who received combination antiretroviral therapy and were previously antiretroviral drug-naïve. Results are shown by A) major resistance mutations to nucleoside reverse transcriptase inhibitors, B) major resistance mutations to non-nucleoside reverse transcriptase inhibitors, and C) major resistance mutations to protease inhibitors.

A

Treatment/mutation	Calendar year									
	2019		2020		2021		2022		2023	
	n	%	n	%	n	%	n	%	n	%
Emtricitabine/lamivudine		(N=133)		(N=115)		(N=125)		(N=180)		(N=150)
K65R. E or N	6	4.5	5	4.3	2	1.6	4	2.2	3	2
M184V or I	27	20.3	25	21.7	23	18.4	35	19.4	25	16.7
Abacavir		(N=130)		(N=112)		(N=121)		(N=174)		(N=145)
K65R. E or N	4	3.1	4	3.6	2	1.7	3	1.7	2	1.4
L74V	2	1.5	3	2.7	0	0	0	0	0	0
Y115F	2	1.5	3	2.7	0	0	0	0	0	0
M184V	20	15.4	18	16.1	13	10.7	23	13.2	18	12.4
Tenofovir		(N=129)		(N=110)		(N=123)		(N=176)		(N=147)
K65R. E or N	4	3.3	5	3.9	4	3.4	2	1.6	5	2.6
K70R	1	0.8	1	0.8	0	0	1	0.8	1	0.5

B

	Calendar year									
	2019		2020		2021		2022		2023	
Treatment/mutation	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Nevirapine		(N=134)		(N=110)		(N=124)		(N=175)		(N=146)
L100I	0	0	0	0	0	0	0	0	0	0
K101P	0	0	0	0	0	0	0	0	0	0
K103N or S	13	9.7	10	9.1	12	9.7	17	9.7	6	4.1
V106A or M	1	0.7	4	3.6	0	0	1	0.6	4	2.7
V108I	6	4.5	4	3.6	2	1.6	3	1.7	3	2.1
Y181C or I	7	5.2	8	7.3	5	4	6	3.4	8	5.5
Y188L. C or H	2	1.5	1	0.9	0	0	4	2.3	0	0
G190A	0	0	1	0.9	2	1.6	1	0.6	4	2.7
M230L	1	0.7	0	0	1	0.8	1	0.6	0	0
Etravirine		(N=125)		(N=107)		(N=122)		(N=175)		(N=142)
L100I	0	0	0	0	0	0	0	0	0	0
L101P	0	0	0	0	0	0	0	0	0	0
Y181C. I or V	0	0	0	0	2	1.6	3	1.7	1	0.7
Efavirenz		(N=128)		(N=106)		(N=122)		(N=175)		(N=141)
L100I	0	0	0	0	0	0	0	0	0	0
K101P	0	0	0	0	0	0	0	0	0	0
K103N or S	13	10.2	10	9.4	12	9.8	17	9.7	6	4.3
V106M	1	0.8	1	0.9	0	0	1	0.6	0	0
V108I	3	2.3	1	0.9	2	1.6	2	1.1	2	1.4
Y181C or I	1	0.8	2	1.9	2	1.6	4	2.3	2	1.4
Y188L	1	0.8	0	0	0	0	4	2.3	0	0
G190S or A	0	0	1	0.9	2	1.6	6	3.4	3	2.1
P225H	1	0.8	0	0	1	0.8	1	0.6	0	0
M230L	0	0	0	0	2	1.6	3	1.7	2	1.4
Rilpivirine		(N=129)		(N=107)		(N=122)		(N=177)		(N=143)
L100I	0	0	0	0	0	0	0	0	0	0
K101E or P	1	0.8	2	1.9	2	1.6	5	2.8	4	2.8
E138A. G. K. Q or R	7	5.4	11	10.3	6	4.9	13	7.3	12	8.4
V179L	0	0	0	0	0	0	0	0	0	0
Y181C. I or V	4	3.1	3	2.8	3	2.5	4	2.3	4	2.8
Y188L	1	0.8	0	0	0	0	4	2.3	0	0
H221Y	3	2.3	2	1.9	2	1.6	6	3.4	1	0.7
F227C	0	0	0	0	0	0	0	0	0	0
M230I or L	1	0.8	0	0	1	0.8	1	0.6	0	0

C

	Calendar year									
	2019		2020		2021		2022		2023	
Treatment/mutation	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Atazanavir		(N=105)		(N=82)		(N=98)		(N=119)		(N=128)
I50L	0	0	0	0	0	0	0	0	0	0
I84V	1	1	0	0	0	0	0	0	0	0
N88S	0	0	0	0	0	0	0	0	0	0
Darunavir		(N=104)		(N=82)		(N=98)		(N=119)		(N=128)
I47V	0	0	0	0	0	0	0	0	1	0.8
I50V	0	0	0	0	0	0	0	0	0	0
I54M or L	0	0	0	0	0	0	0	0	0	0
L76V	0	0	0	0	0	0	0	0	0	0
I84V	0	0	0	0	0	0	0	0	0	0
Lopinavir		(N=105)		(N=82)		(N=98)		(N=119)		(N=128)
V32I	0	0	0	0	0	0	0	0	0	0
I47V or A	0	0	0	0	0	0	0	0	1	0.8
I50V	0	0	0	0	0	0	0	0	0	0
I54V. L or M	1	1	0	0	0	0	0	0	0	0
L76V	1	1	0	0	0	0	0	0	0	0
V82A. F. T or S	0	0	0	0	0	0	0	0	0	0
I84V	1	1	0	0	0	0	0	0	0	0
Tipranavir		(N=104)		(N=82)		(N=98)		(N=119)		(N=127)
I47V	0	0	0	0	0	0	0	0	0	0
Q58E	0	0	1	1.2	1	1	0	0	1	0.8
T74P	0	0	0	0	0	0	0	0	0	0
V82L or T	0	0	0	0	0	0	0	0	0	0
N83D	0	0	0	0	0	0	0	0	0	0
I84V	0	0	0	0	0	0	0	0	0	0

5. Morbidity and mortality

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Summary

AIDS, mortality and causes of death

AIDS-related deaths have decreased dramatically since ART became available in the Netherlands in 1996. The limited number of deaths from AIDS each year mainly occur among those who present late for care with already advanced immunodeficiency. Death is increasingly more likely to be the result of a non-AIDS cause, with non-AIDS malignancies and CVD being the most common. This not only reflects the increased risk of non-AIDS morbidity in individuals with more advanced HIV infection, but also the continuously increasing age of the population of individuals in care. As a result, on average, the mortality rate among people with HIV in the Netherlands remains substantially higher than in the general Dutch population. In the late 1990s and 2000s, the excess mortality was high but was quickly decreasing over time. Several studies have even found that mortality rates in individuals on ART who achieve CD4 cell counts above 500 cells/mm^3, may even drop below general population rates[1,2]. However, in the total population of people with HIV in the Netherlands the rate of decline of the observed excess mortality is slowing down over the years. The ratio of the observed mortality among PWH compared to the age/sex-adjusted mortality observed in the general population, decreased from 9.94 in 1996, to 6.54 in 2000, to 5.83 in 2005, to 3.03 in 2010, to 2.33 in 2015 and has remained constant at around 2.0 since 2017. In 2023 the ratio was 2.01 times the observed age- and sex-standardized mortality in the general population of the Netherlands. In all investigated sub groups, the ratio of the observed over expected mortality declined over time but at the end of follow-up in 2023 remained substantially higher than one. The native Dutch, men who have sex with men, and those with higher pre-ART nadir CD4 counts had the lowest excess mortality.

In 2021, for the first time there was a substantial increase in the absolute mortality rate in people with HIV in the Netherlands during the period 2019 to 2021; from 8.46 deaths per 1000 person years in 2019, to 9.14 in 2020 and 10.77 in 2021. The slightly increased mortality rates in 2020 and 2021 appear mostly driven by an increase in the number of non-AIDS infectious causes of death, which include COVID-19-related deaths. Even though the observed mortality rate increased in 2020 and 2021, the ratio of the observed over expected mortality remained stable because this increase in mortality in people with HIV coincides with – and is

proportional to – the excess mortality of ca. 10% that was observed in the general Dutch population in 2020 and 2021 (as well as in other Western countries) because of COVID-19-related deaths and other indirect adverse health effects of the COVID-19 epidemic in the Netherlands[3]. In 2022 the observed mortality rate of 9.79 deaths per 1,000 person years had not completely returned to pre-COVID-19 levels. And in 2023 the observed mortality rate had again increased, to 11.46 deaths per 1,000 person years. However, in 2022 and 2023 the ratio of the observed over the expected age/sex-adjusted mortality remained stable, suggesting the slight increase in the mortality rate is driven by the continued ageing of the population of people with HIV and perhaps also other general factors in the Netherlands.

Cardiovascular disease and diabetes

Whereas the crude incidence of CVD and diabetes mellitus in men and women was found to have remained relatively stable, the age-standardised incidence for CVD declined over time in men and women, while the age-adjusted incidence for diabetes mellitus only declined in men and in fact increased slightly over time for women. When comparing the age- and sex-stratified prevalence of diabetes mellitus in the population of people with HIV with that observed in the general Dutch population, we observed that in men the prevalence of diabetes was lower in all age strata, while in women aged 20 up to 69 year old the observed prevalence of diabetes was higher compared to the prevalence in the general population. The age- and sex-stratified prevalence of coronary artery disease (myocardial infarction, angina pectoris) in both men and women with HIV was fairly equal compared to the reference prevalence in the general population. However, we cannot exclude the possibility that people with HIV who develop coronary artery disease have poorer survival compared those in the general population, possibly leading to survivorship bias. This requires further study.

The observed decline over time in the age-adjusted CVD incidence may suggest improved awareness, prevention (including switching from drugs associated with an increased risk of diabetes mellitus[4] and myocardial infarction[5,6]), 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 ART at higher CD4 cell counts, but also due to an increase in the proportion of individuals who have used ART long enough to reach high CD4 cell counts). A recent paper from the RESPOND cohort study confirmed our own findings that also in the current era, a significant association between CVD incidence and recent abacavir use continues to be visible and is not explained by preferential use of abacavir in individuals at increased CVD or CKD risk[7]. Apart from the association of incident CVD with abacavir-use, another recent paper from the RESPOND cohort study confirmed our finding that the use of

integrase inhibitors was associated with an increased risk of incident CVD, although statistical power was low and potential for unmeasured confounding and channelling bias cannot fully be excluded[8].
When looking at secondary CVD events, we observed a decreased risk over time in men, whereas it increased for women. This increase is thus far unexplained and needs more study.
Importantly, individuals who had initiated ART earlier after HIV acquisition (i.e. within 12 months of a last negative HIV test), had a significantly lower risk of type 2 diabetes mellitus (RR 0.60, 95% CI 0.41-0.87, p=0.007), independent of other traditional and HIV-related risk factors. The observation that the age-standardised incidence ratios for diabetes mellitus increased in women requires further study – but the observed increasing average BMI and high (and continuously increasing) prevalence of obesity in women might partially explain this observation. Finally, the general risk factors observed for diabetes mellitus and CVD (including age, hypertension, smoking, and obesity) were similar to those previously reported in other studies[9–11]. Several of these risk factors are more prevalent among people with HIV[12].

Overweight and obesity

The clinical significance of the continued increase in the prevalence of obesity over time in women, especially in migrant women from non-Western countries, requires further study. Males in all age strata were less often overweight or obese than the general Dutch male population, while women in all age strata were much more likely to be obese. Recent results suggest that weight gain after starting ART is associated with lower mortality for normal-weight individuals, but they show no clear benefit for overweight or obese individuals[13]. However, another study found that weight gain after starting ART 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[14]. 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 population of PWH, and to study the impact of interventions, such as the use of statins and antihypertensive therapy, in modifying disease risk.

In our cohort, we found that obesity and being overweight were significant risk factors for developing new-onset diabetes, cardiovascular disease and CKD, but 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 ART and the use of specific antiretroviral drugs (the integrase strand transfer inhibitors and tenofovir alafenamide, in particular) while controlling for demographic characteristics, traditional risk factors, and confounders.

Renal insufficiency

Since 2008, there has been a steady increase in the incidence of new-onset chronic kidney disease (CKD). As expected, older individuals and those with traditional risk factors such as hypertension were found to be at increased risk of CKD, as were individuals with advanced immunodeficiency. The age-standardised incidence ratio in men and women was significantly lower in the 2020-2023 period. In addition, other studies have also reported hepatitis B and C virus co-infection[15,16], and the use of tenofovir disoproxil fumarate, atazanavir/ritonavir and lopinavir/ritonavir, to be additional independent predictors of chronic renal impairment[17]. Moreover, renal impairment in the population with HIV is associated with an increased risk of cardiovascular disease[18]. The increase in CKD in our population appears to be largely caused by the more frequent 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 age-stratified incidence of non-AIDS-defining malignancy (including non-melanoma skin cancer) was significantly higher in men than the observed cancer incidence in the general Dutch male population. The relatively low cumulative follow-up time and number of events per age-group in women limits the statistical power of the analysis. However, the observed incidence in each age group appears to be rather similar to the observed cancer incidence in the general Dutch female population. The most common non-AIDS-defining malignancies (NADM) in the Netherlands are lung, intestinal, anal, prostate, and head and neck cancers, as well as Hodgkin's lymphoma. Despite the increasing average age of the cohort, the crude incidence of NADM has remained stable over time, and we even observed a decline in age-standardised incidence of NADM in men, and to a lesser extent in women. In addition, our analyses showed that individuals diagnosed with NADM a more likely to be older. This is in line with data from other cohorts, including the Swiss HIV cohort and RESPOND cohort [19–23]. Additional risk factors for NADM identified in our analyses were: current or past smoking; a CD4 cell count below 350 cells/mm^3; not being on ART, or having been pre-treated with NRTI before the start of ART; and a prior AIDS diagnosis. Other studies have reported that the effect of immunodeficiency may be stronger for infection-related non-AIDS-defining

malignancies[24]. Importantly, individuals who had initiated ART earlier after HIV acquisition (i.e. within 12 months of a last negative HIV test), had a somewhat lower risk of NADM (RR 0.77, 95% CI 0.57-1.05, p = 0.097), independent of other traditional and HIV-related risk factors.

Multimorbidity and polypharmacy

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

Polypharmacy, defined as the concomitant use of five or more medications in addition to ART, is also slowly 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, 3.2% of adults used five or more non-antiretroviral comedications alongside their ART regimen, and this steadily increased to 16.0% of adults in active follow up in 2023. 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. Polypharmacy was also strongly and independently associated with an increased risk of death, independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities.

SARS-CoV-2 and COVID-19

In 2023 the number of registered SARS-CoV-2 infections (n=463) and COVID-19-related hospitalizations (n=29) dropped sharply. In 2023, just 2 people with HIV were reported to have died as a direct consequence of COVID-19 in the Netherlands.

Introduction

Since the introduction of combined antiretroviral therapy (ART) in 1996, the life expectancy of people with HIV (PWH) has markedly improved[25]; in a subgroup of recently-diagnosed, effectively-treated individuals, it was shown to be similar to that of the general population in the Netherlands[26]. Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased[27], morbidity and/or mortality associated with non-AIDS-related diseases has increased among PWH during the ART era[28–33]. Examples of these include renal and liver disease, diabetes mellitus, myocardial infarction, stroke, osteoporosis, and non-AIDS-defining malignancies.

Various reports suggest that the risk of non-AIDS-related morbidity may be higher in individuals with HIV treated with ART, than in individuals without HIV of comparable age[9-11]. For example pulmonary hypertension[37], bone disease, and non-traumatic bone fractures13-15 have each been reported to be more common in PWH. Just as with individuals without HIV, traditional risk factors (such as tobacco use[41], alcohol abuse, and viral hepatitis co-infection[42]) also contribute to the increased risk of certain non-AIDS-related comorbidities in people 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 PWH include metabolic abnormalities such as dyslipidaemia; insulin resistance; hypertension; diabetes; and changes in body composition, which may be driven partly by the use of ART, as well as by sustained, residual HIV-associated immune activation and inflammation, despite effective ART[43,44].

In this chapter, we report on mortality and its causes for adult (18 years and over) PWH using updated stichting hiv monitoring (SHM) data. We look at a total of 31,096 adult individuals ever registered by SHM – which includes 661 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 PWH.

Definitions

AIDS is defined as having experienced any of the United States' Centers for Disease Control (CDC) category C conditions[45]. In contrast to the US approach, a CD4 cell count below 200 cells/mm^3 in the absence of an AIDS-defining condition, does not qualify as AIDS in our analyses.

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. We use this period of time because of the large number of episodes of renal dysfunction that revert shortly after three months, and therefore 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 2000-2009, 2010-2019, and 2000-2023. We standardised these estimates according to the age distribution of the population during the period 2020-2023 (divided into the following age classes: 18-29, 30-39, 40-49, 50-59, 60-69, and 70 years and over), using the indirect method[46]. Indirect standardisation compares the incidence rates in the study and reference (period: 2020-2023) 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 PWH 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 ART within 12 months of the last negative HIV test;
- known time spent with CD4 cell count below 200 cells/mm^3;
- known time spent with plasma HIV RNA above 1,000 copies/ml while on ART;
- time on ART;
- specific antiretroviral drugs used;
- prior diagnosis of AIDS;
- presence of chronic active hepatitis B and/or C virus infection;
- hypertension, diabetes mellitus, and other chronic comorbidities;
- smoking; and
- calendar period.

Mortality

Mortality was investigated in all 31,096 adult PWH ever registered in the SHM database. The mortality rate was 18.2 (95% confidence interval [CI] 13.5-23.9) per 1,000 person years of follow up (PYFU) in 1996 and declined to 8.9 (95% CI 7.4-10.6) per 1,000 PYFU in 2010. It has since remained stable at that 2010 level up to 2022, but the observed mortality rate was noticeably higher in 2021 during the COVID-19 pandemic with 10.8 (9.4-12.2). In 2023 the observed crude mortality rate had increased to 11.5 (10.0-13.0) per 1,000 PYFU (*Figure 5.1A*). Despite the overall improvement over time, the mortality rate in adult PWH remained well above the age-matched and gender-matched mortality observed in the general population in the Netherlands, which was 5.7 per 1,000 PYFU in 2023. The ratio of the observed mortality among PWH compared to the age/sex-adjusted mortality observed in the general population, decreased from 9.94 in 1996, to 6.54 in 2000, to 5.83 in 2005, to 3.03 in 2010, to 2.33 in 2015 and has remained constant at around 2.0 since 2017. In 2023 the ratio was 2.01.

This excess mortality can be only partly ascribed to individuals who already had AIDS at the time of their HIV diagnosis, even less so in recent years. When these individuals were excluded from the analysis, the mortality rate decreased from 14.1 (9.8-19.6) per 1,000 PYFU in 1996 to 10.4 (8.9-12.0) per 1,000 PYFU in 2023.

We repeated the analysis of mortality for various sub groups of interest (*Figure 5.1C*). The analyses were stratified based on region of origin (native Dutch, migrants with Western background, and migrants with non-Western background), HIV transmission category (men who have sex with men, other men who acquired HIV heterosexually, and women) and pre-ART nadir CD4 count (0-199, 200-499, and 500 and more cells/mm^3). The "Ratio in 2023" mentioned in the top right corner of each panel is the ratio of the observed crude mortality rate over the age/sex-adjusted expected mortality in 2023. In all investigated sub groups, the ratio of the observed over expected mortality declined over time but at the end of follow-up in 2023 remained substantially higher than one. The native Dutch, MSM, and those with higher pre-ART nadir CD4 counts had the lowest excess mortality. The observed excess mortality in the sub group who had a pre-ART nadir CD4 count of 500 and more cells/mm^3 was partly driven by a high rate of non-natural causes of death (27.4% of the 84 observed deaths in this sub group were classified to be from non-natural causes: accidents, violence, suicide, euthanasia, substance abuse, psychiatric disease).

Underlying causes of death

Observed underlying causes of death are presented in *Appendix Table 5.1.* Although the AIDS-related death rate has decreased significantly since the advent of ART, the continued occurrence of deaths due to AIDS is driven largely by the persistent high proportion of newly diagnosed people with HIV who present late for care with advanced immune deficiency. As such, the rate falls short of the aim of zero AIDS-related deaths by 2027, as stated in the Netherlands' Updated National Action Plan on STIs, HIV and Sexual Health, 2023-2027[47]. *Table 5.1* shows the characteristics of adults with HIV who died of AIDS, compared to those who died of non-AIDS causes during the last 10 years, the period 2014-2023. Individuals who died of AIDS were more frequently female, non-MSM and/or migrants, more recently diagnosed with HIV, had been on ART for a shorter period of time, and had much lower CD4 cell counts at diagnosis (58.6% had advanced HIV at diagnosis with a CD4 cell count below 200 cells/mm^3). In addition, these individuals had much lower nadir CD4 cell counts. In 49.8% of cases, they did not have controlled viremia, and 23.2% of this group was not receiving any ART at the time of death, either because ART had not been started or had been discontinued (*Table 5.1*).

Among individuals who died of AIDS but did not classify as late or advanced presenters (i.e. they had a CD4 cell count above 350 cells/mm^3 at diagnosis), the cause of death was relatively more likely to be an AIDS-related haematological malignancy, which are also known to occur in people on suppressive ART with high CD4 cell counts. The proportion and absolute number of deaths due to non-

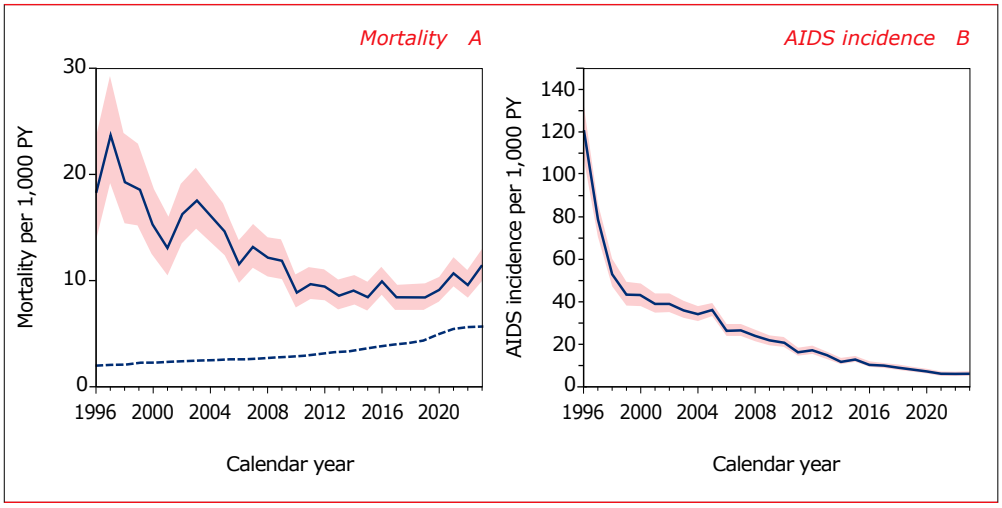
AIDS-defining conditions have increased significantly over time (*Figure 5.1.D*), primarily as a consequence of the ever increasing size and increasing average age of the population of people with HIV in the Netherlands. People with HIV who were born in the Netherlands, MSM and men in general are overrepresented among those who died of non-AIDS causes, because people in these three (overlapping) categories have a higher average age compared to migrants, HIV transmission categories other than MSM, and women. Independent risk factors for death and for being diagnosed with an AIDS-defining condition are listed in *Appendix Table 5.2*.

***Table 5.1:** Characteristics of adults with HIV who died of AIDS compared to adults with HIV who died of non-AIDS causes in the period 2014-23.*

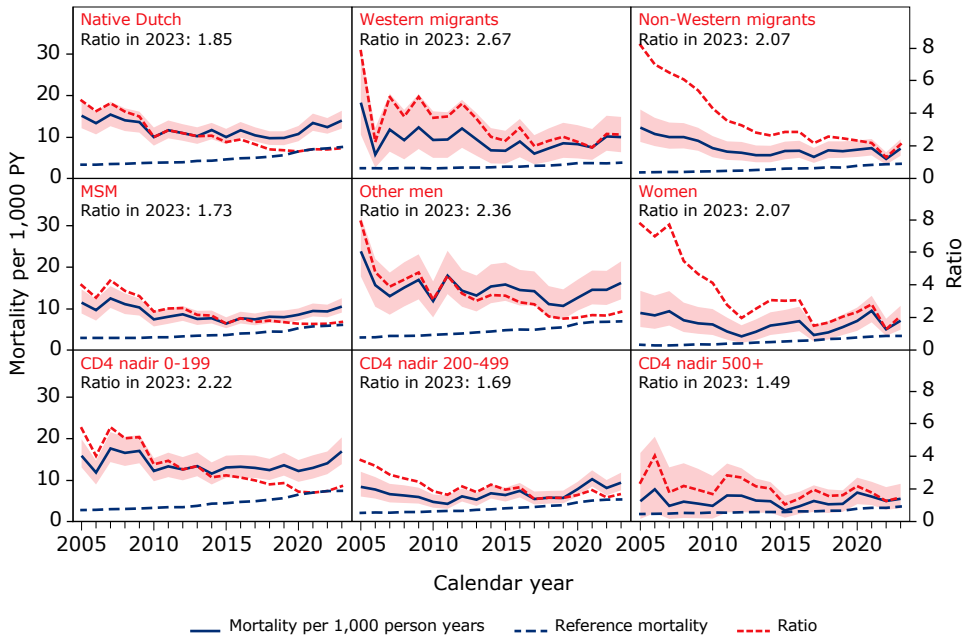
	Died of AIDS	Died of non-AIDS causes	p-value
Number of subjects	220 (11.6%)	1676 (88.4%)	
Age	56.2 (46.9-65.2)	61.1 (53.3-69.7)	<.001
Transmission category			<.001
MSM	98 (44.5%)	957 (57.1%)	
Other men	72 (32.7%)	375 (22.4%)	
Women	35 (15.9%)	179 (10.7%)	
Transgender	3 (1.4%)	11 (0.7%)	
IDU	7 (3.2%)	118 (7.0%)	
Blood contact	0 (0.0%)	33 (2.0%)	
Pediatric	5 (2.3%)	3 (0.2%)	
Region of origin			0.003
Native Dutch	139 (63.2%)	1187 (70.8%)	
Western migrants	16 (7.3%)	140 (8.4%)	
Non-Western migrants	62 (28.2%)	345 (20.6%)	
Unknown origin	3 (1.4%)	4 (0.2%)	
Years since HIV diagnosis	8.61 (0.72- 18)	16 (9.34-22.9)	<.001
Years since start cART	6.03 (0.43-13.8)	13.7 (7.28-19.2)	<.001
CD4 at HIV diagnosis	140 (50-336)	300 (120-517)	<.001
Late HIV diagnosis (CD4<350 at entry in care)	166 (76.5%)	936 (55.9%)	<.001
Advanced HIV diagnosis (CD4<200 at entry in care)	129 (58.6%)	611 (36.5%)	<.001
CD4 nadir	60 (20-134)	150 (57-262)	<.001
Last CD4 measured before death	170 (50-350)	507 (320-720)	<.001
Not undetectable at date of death	105 (49.8%)	1448 (86.8%)	<.001
Not on cART at date of death	51 (23.2%)	149 (8.9%)	<.001

***Legend:** ART = combination antiretroviral therapy. Data shown are n (%) for categorical variables and median (interquartile ranges) for continuous variables. CD4 cell counts are expressed as cells/mm^3, IDU = intravenous drug use.*

Figure 5.1.A-D: *(A) Annual mortality and (B) incidence of AIDS in 31,096 PWH in the Netherlands after entry into HIV care from 1996 onwards. (C) Annual mortality in various sub groups of interest after entry into HIV care from 2000 onwards. Solid lines represent the incidence, while the shaded areas are the 95% confidence intervals. The dashed line is the mortality rate for age-matched and sex-matched individuals from the general population in the Netherlands. The "ratio" is the ratio of observed over age/sex-standardized mortality in the Netherlands in 2023. (D) Relative changes in causes of death in different calendar periods since the introduction of combination antiretroviral therapy (ART) in the Netherlands. The numbers at the top of each bar represent the total number of deaths and the total number of individuals that were at risk during that calendar period. Mortality attributed to 'alcohol use' refers to deaths due to complications of alcohol-related liver cirrhosis.*



Mortality over time by group *C*



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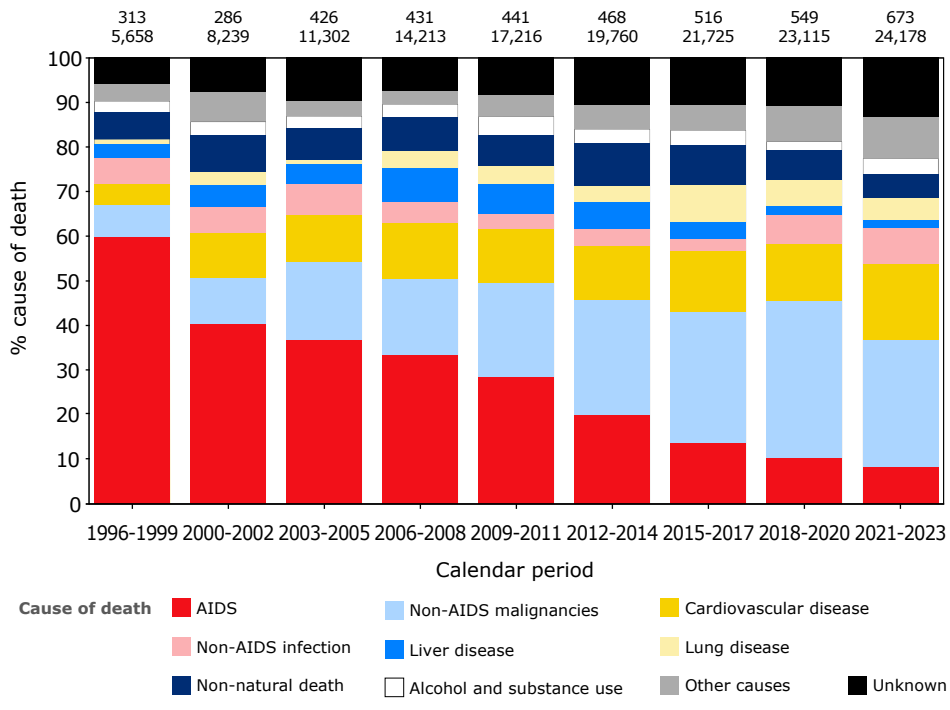


Risk factors associated with mortality

We used Poisson regression analysis to examine factors associated with mortality in individuals from the moment they started ART. After correction for all variables listed in *Appendix Table 5.2*, including time-updated age and time-updated lagged CD4 cell counts, we found that, in general, risk of death was higher in (heterosexual) 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 (PWID);
- had a prior AIDS diagnosis;
- were co-infected with the hepatitis B virus (HBV) or hepatitis C virus (HCV);
- were underweight;
- were current or past smokers;
- had spent more time with an HIV RNA level above 1,000 copies/ml while on ART; or
- had a current CD4 cell count less than 750 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 migrants becoming lost to care (*Appendix Table 5.3*). In native Dutch individuals the risk of becoming lost to care was not linked to their CD4 cell count. In contrast, people from all other non-Dutch groups were far more likely to become lost to care if they had very low CD4 cell counts. One explanation could be that those born overseas often return to their families in their country of origin when they experience a severe deterioration in health. As a result, it is likely that mortality rates in these groups have been considerably underestimated.

Suicide and euthanasia

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 5.1*). The number of recorded suicides among people with HIV in the Netherlands in the period 2011 to 2023 was stable at around ten recorded cases per calendar year, which is a much higher rate than the known rates of suicide in the general Dutch population. The latter has been stable in the last 10 years; at between 10.4-11.2 instances per 100,000 individuals per year, compared to more than 40 instances per 100,000 person years in the population with HIV[48].

For patients with a serious somatic condition, who opted for euthanasia in the terminal disease stage, the underlying somatic condition was recorded as the cause of death. In the entire follow-up period from 1996 to 2023, a total of 183 instances of euthanasia were recorded; 28% of cases occurred in patients who died of AIDS, 39% in patients who died of non-AIDS-defining malignancies, and the remaining 33% in patients who died of other diseases. Our definition of euthanasia does not include the use of standard practice palliative care, like palliative sedation in the terminal phase of the underlying disease.

AIDS-defining events

In the group of 31,096 adult PWH ever registered in the SHM database, the incidence of first AIDS-defining events decreased sharply from 121.0 (95% CI 108.5-134.6) in 1996 to 6.3 (5.3-7.5) cases per 1,000 PYFU in 2023 (*Figure 5.1B*). *Appendix Table 5.4* gives an overview of the first AIDS-defining events occurring between 1996 and 2023. The most common first AIDS-defining events between 2000 and 2023 (n=575) were:

- Pneumocystis jirovecii pneumonia (23% of all events);
- esophageal candidiasis (19%);
- recurrent bacterial pneumonia (10%);
- Kaposi's sarcoma (9%);
- AIDS-defining lymphoma (8%);
- tuberculosis (7%, pulmonary 3%, extrapulmonary 4%);
- AIDS-related wasting (6%);
- cytomegalovirus-associated end organ disease (4%);
- AIDS dementia complex / HIV encephalopathy (3%); and
- toxoplasmosis of the brain (2%).

Risk factors for AIDS-defining events are shown in *Appendix Table 5.2*.

In the present analyses, we concentrate on the first occurrence of any AIDS-defining event after the start of ART. 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 ART; or
- were co-infected with HCV.

Because the main findings of the analysis of AIDS events after the start of ART were heavily influenced by events occurring shortly after the start of ART and/or while HIV-1 RNA was still detectable, we also analysed the incidence of CDC-B (moderately symptomatic HIV disease) and AIDS-defining events in individuals who had started ART 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 ART. Events were classified into CD4 strata based on the current or previously measured CD4 cell 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. Cervical dysplasia was excluded from this analysis.

Between 1 January 2000 and 31 December 2023, 27,402 individuals contributed a total of 285.2 thousand PYFU, during which 3,396 CDC-B and/or CDC-C (AIDS-defining events) were diagnosed. This resulted in an incidence rate of 11.9 events per 1,000 PYFU (1,870 CDC-B events, 6.6 events/1,000 PYFU; 1,526 CDC-C/AIDS events, 5.4 events/1,000 PYFU) (*Table 5.2*). As expected, the incidence rates were highest in the CD4 strata below 200 cells/mm^3. Although the incidence rates declined sharply in the higher CD4 strata, the incidence rates in the 200-349 and 350-499 cells/mm^3 strata remained substantial, with 10.6 and 5.3 AIDS-defining illnesses/1,000 PYFU, respectively. The incidence rates of AIDS-defining illnesses in the CD4 strata of 500-749 and over 750 cells/mm^3 were 2.7 (95% CI 2.4-3.1) and 1.8 (1.5-2.1) 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); and
- chronic genital Herpes simplex virus (HSV) ulcers

Appendix Table 5.6 shows the type and number of HIV-related diagnoses by CD4 strata. We repeated the Poisson regression for risk factors for AIDS, limited to individuals on ART with undetectable viral load and a current CD4 count of at least 500 cells/mm^3. We found that the main risk factor for incident AIDS-defining conditions in this subgroup was higher age: compared to those aged 30-39 years old, the IRR was significantly increased in those aged 50-59 (IRR 2.31, 95%CI 1.57-3.41), 60-69 years old (2.49, 95%CI 1.63-3.82), over 70 years old (3.12, 95%CI 1.83-5.34). Of note, the nadir pre-ART CD4 count was not statistically significantly associated with incident AIDS-defining conditions in this analysis (IRR 1.04 per 100 cells/mm^3 higher, 95%CI 0.98-1.10, p=0.19).

Table 5.2: *CDC-B and CDC-C/AIDS events occurring between 2000 and 2023 in individuals on ART, while having an undetectable viral load.*

CD4 category (cells/mm^3)	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	276	115	161	0.6	435 (385-490)	181 (150-218)	254 (216-296)
50-199	650	331	319	9.3	70.3 (65.0-75.9)	35.8 (32.0-39.8)	34.5 (30.8-38.5)
200-349	687	365	322	30.4	22.6 (20.9-24.3)	12.0 (10.8-13.3)	10.6 (9.46-11.8)
350-499	635	345	290	54.4	11.7 (10.8-12.6)	6.34 (5.69-7.05)	5.33 (4.73-5.98)
500-749	708	436	272	100.2	7.07 (6.56-7.61)	4.35 (3.95-4.78)	2.71 (2.40-3.06)
750+	440	278	162	90.3	4.87 (4.43-5.35)	3.08 (2.73-3.46)	1.79 (1.53-2.09)
Total	3396	1870	1526	285.2	11.9 (11.5-12.3)	6.56 (6.26-6.86)	5.35 (5.09-5.63)

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

Tuberculosis and atypical mycobacterial infections

Between 1 January 1996 and 31 December 2023 a cumulative total of 1,180 cases of tuberculosis were diagnosed in 980 individuals, of which 691 (58.6%) were pulmonary cases and 489 (41.4%) were extrapulmonary/disseminated tuberculosis cases. During that same period, 571 cases of atypical mycobacterial infections were diagnosed in 500 individuals: 99 pulmonary and 472 extrapulmonary cases of atypical mycobacterial infections. *Figures 5.2.A & B* and *Appendix Table 5.4* describe the incidence over calendar time of tuberculosis and atypical mycobacterial infections.

Geographical region of origin

Migrants who originated from non-Western regions (73.2% of cases, 34.9% of the population) were strongly overrepresented among the tuberculosis cases, while those who were born in the Netherlands (15.1% of cases, 51.4% of the population) were strongly underrepresented. Migrants originating from Western regions (which includes countries from eastern Europe) represented 10.9% of cases and 13.1% of the population. Region of origin was not strongly associated with the incidence of atypical mycobacterial infections. *Table 5.3* describes some key characteristics of the individuals diagnosed with either tuberculosis or atypical mycobacterial infection. In case individuals had multiple diagnoses, the date of the first event was used.

Disease-related mortality rates

5.1% of the individuals diagnosed with pulmonary tuberculosis and 4.5% of the individuals diagnosed with extrapulmonary tuberculosis died within 365 days of the diagnosis, with the reported cause of death being 'AIDS' or 'infection'. The disease-related mortality rates within 365 days of diagnosis were 6.1% for pulmonary and 17.6% for extrapulmonary atypical mycobacterial infections.

Latent tuberculosis infection screening

The current national guidelines recommend performing screening for latent tuberculosis infection (LTBI) in all individuals newly diagnosed with HIV who are at increased risk for tuberculosis (migrants from high-endemic regions or individuals who have been in close contact with cases of tuberculosis). The recommended method for LTBI screening is the interferon gamma release assay (IGRA) in combination with a tuberculin skin test (Mantoux test). Treatment of individuals in whom LTBI has been diagnosed considerably lowers their risk of developing tuberculosis.

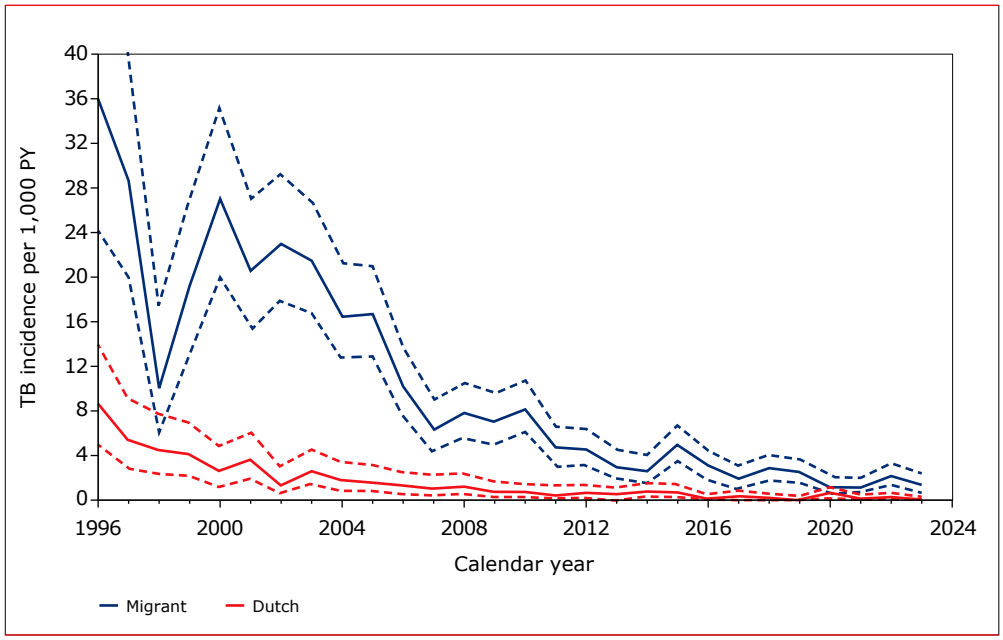
SHM has been collecting data on LTBI screening and treatment since 2018. IGRA testing during an episode in which active TB was diagnosed, was excluded from this dataset. A limitation of our analysis of LTBI screening is that we do not have data on whether, at the time of IGRA testing, the individual had complaints that may have been caused by tuberculosis, which then prompted the treating physician to perform IGRA testing. In 22.8% of cases a chest X-ray or CT-scan was taken, indicating that in some of these instances the individual might also have had pulmonary symptoms at the moment of IGRA testing.

Since 1 January 2018, SHM has recorded LTBI screening using IGRA with or without an additional tuberculin skin test in 2,394 individuals. In 232 (9.7%) of these individuals LTBI testing was positive, and 82 (35.3%) of those received a course of LTBI treatment. LTBI treatment consisted of:

- isoniazid plus rifampicin (typically for a duration of three months) in 29 individuals;
- isoniazid monotherapy (typically for a duration of six to nine months) in 42 individuals; and
- rifampicin monotherapy (typically for a duration of four months) in three individuals.

A further eight individuals received another non-standard treatment. In the 232 individuals who tested positive on LTBI screening, two cases of tuberculosis were diagnosed later during follow-up: one case of active extrapulmonary tuberculosis developed (four months after diagnosis) while that individual was receiving treatment consisting of rifampicin plus isoniazid, and one case of pulmonary tuberculosis was diagnosed 3 years after diagnosis of untreated LTBI. Of the 150 individuals with positive LTBI screening who did not receive LTBI treatment, 21 (14.0%) were known to have been diagnosed with and treated for active tuberculosis prior to the LTBI screening.

Figure 5.2.A & B: Crude incidence rates of tuberculosis and nontuberculous mycobacterial infections in Dutch and migrants per 1,000 person years of follow up (solid lines) and 95% confidence intervals (dashed lines).



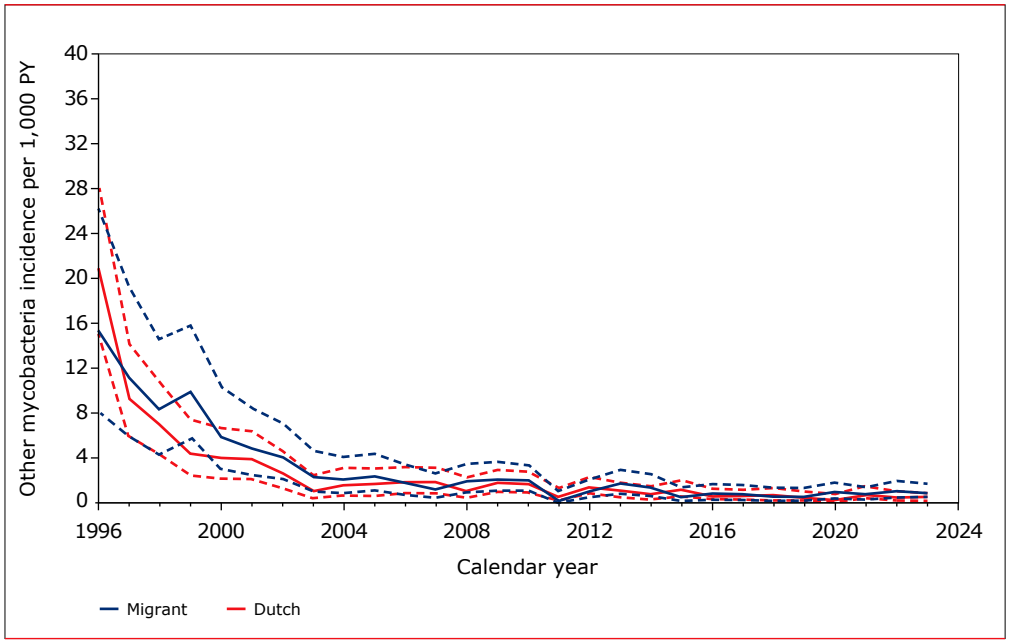


Table 5.3: Characteristics at the time individuals were diagnosed with tuberculosis or atypical mycobacterial infections for the first time.

	Tuberculosis	Atypical mycobacterial infections	p-value
Number of subjects	980 (66.2%)	500 (33.8%)	
Age	36.9 (30.6-44.5)	40 (34.5- 48)	<.001
Transmission category			<.001
MSM	206 (21.0%)	220 (44.0%)	
Other men	365 (37.2%)	149 (29.8%)	
Women	304 (31.0%)	92 (18.4%)	
Transgender	16 (1.6%)	5 (1.0%)	
IDU	60 (6.1%)	25 (5.0%)	
Blood contact	27 (2.8%)	6 (1.2%)	
Pediatric	2 (0.2%)	3 (0.6%)	
Region of origin			<.001
Native Dutch	176 (18.0%)	279 (55.8%)	
Western migrants	90 (9.2%)	50 (10.0%)	
Non-Western migrants	709 (72.3%)	171 (34.2%)	
Unknown origin	5 (0.5%)	0 (0.0%)	
Diagnosed before HIV diagnosis	225 (23.0%)	32 (6.4%)	<.001
Years since HIV diagnosis	0.92 (0.5- 4.7)	1.12 (0.57- 6.5)	0.007
Years since start cART	0.42 (0-1.16)	0.62 (0.25-1.22)	<.001
CD4 at HIV diagnosis	199 (61-400)	40 (10-200)	<.001
Late HIV diagnosis (CD4<350 at entry in care)	444 (68.5%)	368 (84.6%)	<.001
Advanced HIV diagnosis (CD4<200 at entry in care)	656 (66.9%)	391 (78.2%)	<.001
CD4 nadir	120 (40-250)	20 (10- 50)	<.001
Last CD4 measured before event	210 (102-370)	90 (30-190)	<.001
Not undetectable at date of event	172 (17.6%)	121 (24.2%)	0.003
Not on cART at date of event	702 (71.6%)	247 (49.4%)	<.001

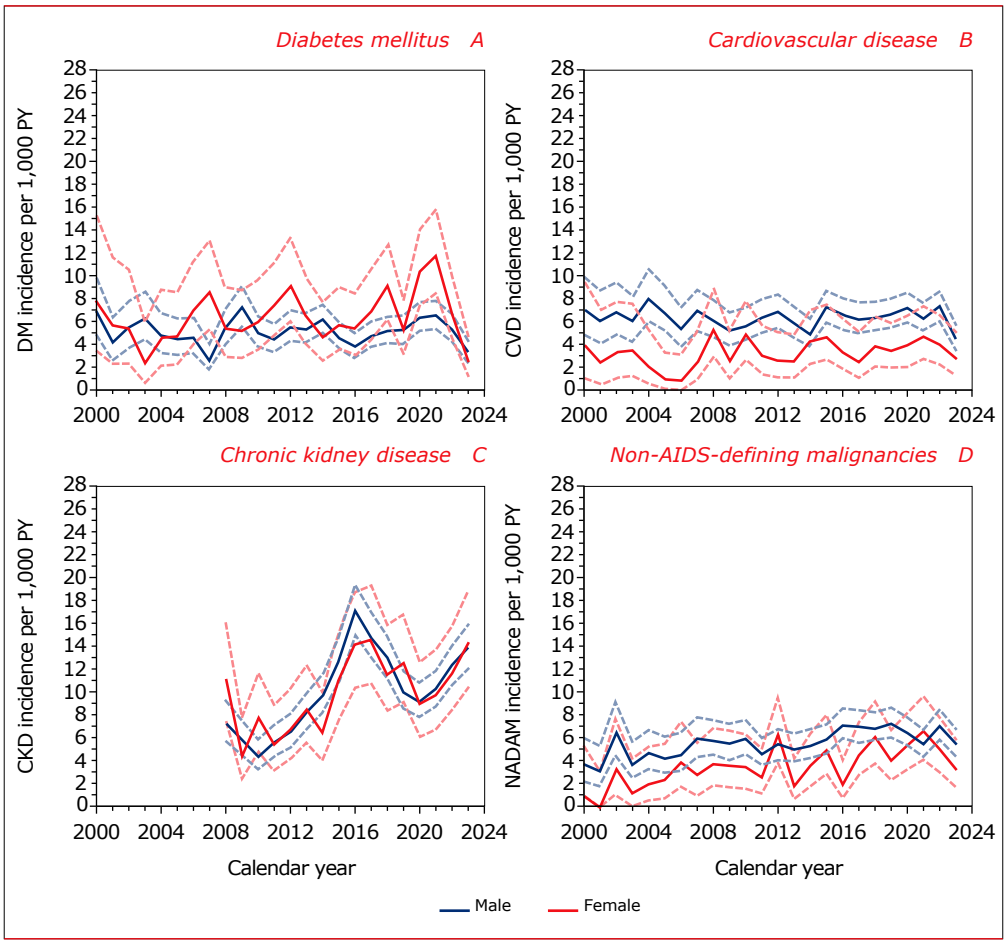
Non-AIDS-defining events

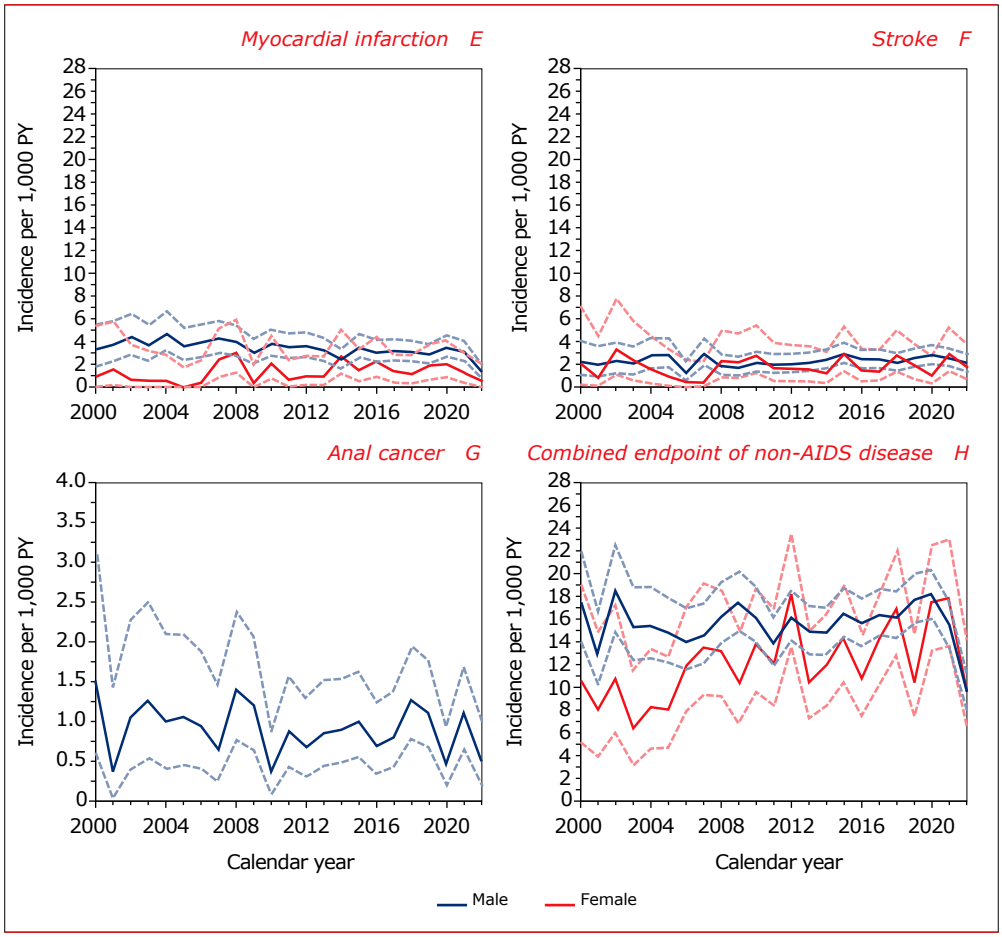
Of the 31,096 adult PWH ever registered with SHM, 30,747 were aged 18 years and over while in follow up in, or after January 2000. For these treated and untreated adults, we report incidence figures and risk factors for:

- diabetes mellitus;
- a composite cardiovascular disease endpoint (and also separately for myocardial infarction and stroke);
- non-AIDS-defining malignancies (both overall and separately for anal cancer); and
- chronic kidney disease (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 5.3.A-H*).

Figure 5.3.A-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.*





Diabetes mellitus

Of the 30,747 individuals aged 18 years and over, who were in follow up in, or after January 2000, a total of 1,898 (1,457 men and 441 women) were diagnosed with type 2 diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 5.3A*), and in 2023 was 3.2 (95% CI 2.4-4.3) per 1,000 PYFU in men and 2.4 (1.0-4.7) per 1,000 PYFU in women. In men, the age-standardised incidence ratio declined over time and was significantly lower in 2010-2019 and 2020-2023 than in 2000-2009. In women, however, an opposite effect was seen, as the age standardised incidence in significantly increased over the observation period (*Table 5.4A*).

Demographic and clinical factors independently associated with an increased risk of new-onset diabetes mellitus were:

- non-Dutch/Western origin;
- older age group;
- a BMI greater than 25 kg/m^2 or below 18 kg/m^2;
- hypertension;
- a latest CD4 cell count below 200 cells/mm^3;
- pre-treatment with nucleoside analogue reverse transcriptase inhibitors (NRTIs) prior to starting ART (in particular zidovudine and didanosine);
- treatment with the integrase inhibitors bictegravir, dolutegravir or raltegravir (but not elvitegravir and cabotegravir) and
- a prior AIDS diagnosis (*Appendix Table 5.5*).

Moreover, the risk of new-onset diabetes in the periods 2000-2009 and 2010-2019 was significantly higher than in the period 2020-2023. Starting ART within 12 months of the last negative HIV test was also associated with a lower risk of new-onset diabetes. Note that multivariate analysis showed that the higher age-adjusted incidence rates of diabetes in women are largely explained by their higher BMI.

We compared the age- and sex-stratified prevalence of diabetes mellitus in the population of people with HIV with that observed in the general Dutch population (*Table & Figure 5.4B*). In men the prevalence of diabetes was significantly lower in nearly all age strata, while in women aged up to 65 year old the observed prevalence of diabetes was higher compared to the reference values in the general population.

Table 5.4A: *Crude incidence of diabetes mellitus per 1,000 person years of follow up in 2000–2009, 2010–2019 and 2020–2023 and age-standardised incidence ratio (indirect method) with 95% confidence intervals.*

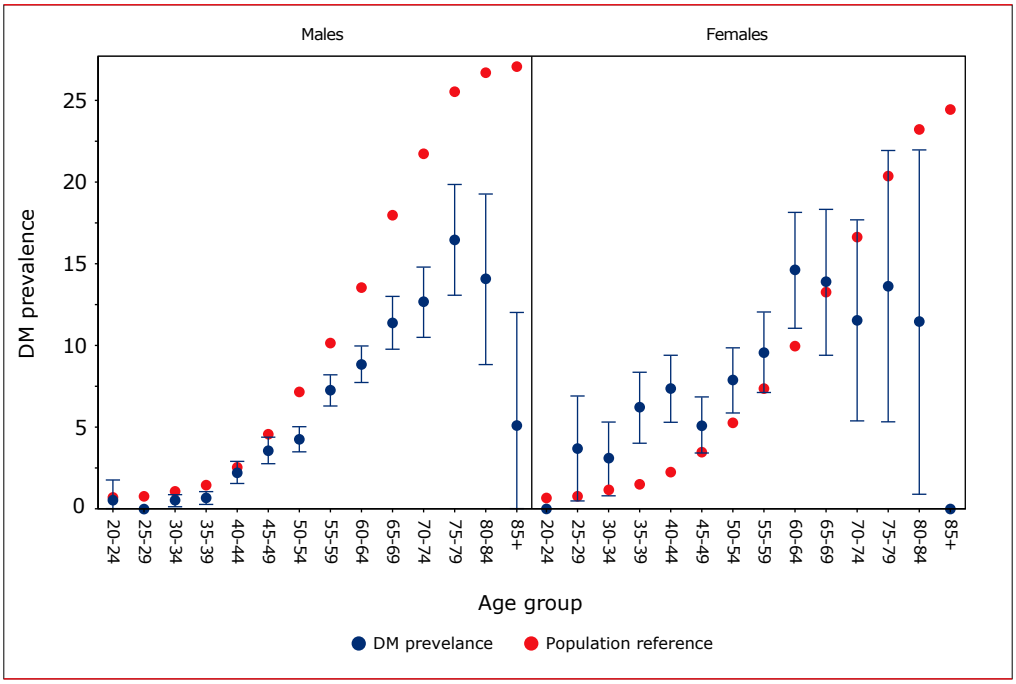
Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000–2009	5.2 (4.7–5.7)	1.28 (1.15–1.40)	5.7 (4.7–6.9)	0.75 (0.61–0.89)
2010–2019	5.0 (4.7–5.4)	1.03 (0.96–1.11)	6.6 (5.7–7.5)	0.86 (0.75–0.98)
2020–2023	5.5 (4.9–6.1)	1 (reference)	7.8 (6.5–9.4)	1 (reference)

**Standardised according to the observed age distribution between 2020–2023.*

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

Table & Figure 5.4B: *Prevalence of diabetes mellitus in people with HIV stratified by age and sex in 2023, compared to the prevalence of diabetes mellitus type 2 in the general Dutch population in 2021 (https://www.vzinfo.nl/diabetes-mellitus/leeftijd-en-geslacht, accessed 10-9-2024).*

Age group (years)	Males				Females			
	Events (n)	Group size (n)	Prevalence % (95%CI)	General population prevalence (%)	Events (n)	Group size (n)	Prevalence % (95%CI)	General population prevalence (%)
20-24	1	167	0.6 (0.0-1.8)	0.71	0	64	0.0 (0.0-0.0)	0.7
25-29	0	563	0.0 (0.0-0.0)	0.78	5	135	3.7 (0.5-6.9)	0.75
30-34	7	1,345	0.5 (0.1-0.9)	1.07	7	227	3.1 (0.8-5.3)	1.13
35-39	11	1,601	0.7 (0.3-1.1)	1.51	29	467	6.2 (4.0-8.4)	1.45
40-44	42	1,867	2.2 (1.6-2.9)	2.62	46	625	7.4 (5.3-9.4)	2.22
45-49	73	2,031	3.6 (2.8-4.4)	4.64	33	644	5.1 (3.4-6.8)	3.46
50-54	110	2,571	4.3 (3.5-5.1)	7.16	55	700	7.9 (5.9-9.9)	5.29
55-59	213	2,932	7.3 (6.3-8.2)	10.12	53	553	9.6 (7.1-12.0)	7.3
60-64	217	2,449	8.9 (7.7-10.0)	13.54	56	384	14.6 (11.1-18.1)	9.95
65-69	170	1,494	11.4 (9.8-13.0)	17.96	32	231	13.9 (9.4-18.3)	13.24
70-74	117	925	12.6 (10.5-14.8)	21.71	12	104	11.5 (5.4-17.7)	16.62
75-79	76	462	16.5 (13.1-19.8)	25.52	9	66	13.6 (5.4-21.9)	20.35
80-84	24	171	14.0 (8.8-19.2)	26.65	4	35	11.4 (0.9-22.0)	23.22
85+	2	39	5.1 (0.0-12.1)	27.02	0	11	0.0 (0.0-0.0)	24.4



Cardiovascular disease

From January 2000 onwards, 2,008 individuals (1,779 men and 229 women) experienced one or more fatal or non-fatal cardiovascular event. Of these individuals:

- 972 had a myocardial infarction;
- 751 had a stroke;
- 145 had a coronary artery bypass graft;
- 738 had a coronary angioplasty or stenting; and
- 20 had a carotid endarterectomy.

The crude incidence over time remained stable and was lower in women than in men (*Figure 5.3B*). The age-standardised incidence ratio in men and women declined over time (*Table 5.5A*).

In the analysis of risk factors, those associated with cardiovascular disease were:

- older age group;
- male gender, MSM had lower risk than other men;
- a latest CD4 cell count below 350 cells/mm^3
- a prior AIDS diagnosis; as well as having a longer duration of severe immunodeficiency defined as cumulative number of years with a CD4 count <200 cells/mm^3;
- pre-treatment with NRTIs before starting ART;
- use of abacavir (either currently or in the last six months);
- current use of dolutegravir, raltegravir or bictegravir (borderline significant) (but not elvitegravir or cabotegravir);
- current and past smoking;
- the presence of diabetes mellitus; and
- the presence of hypertension.

Estimated cardiovascular risk using the D:A:D algorithm was also higher during 2000-2009 and 2010-2019 than during 2020-2023, independent of other variables included in the analysis (*Appendix Table 5.5*). 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 1.47 to 1.38, $p<0.001$. Compared to having an eGFR above 90 ml/min, having an eGFR below 60 ml/min was independently associated with a higher risk of CVD:

- at 60-90 ml/min, the IRR was 1.01 (95% CI 0.89-1.30);
- at 30-60 ml/min the IRR was 1.51 (1.27-1.80);
- at 15-30 ml/min, the IRR was 4.04 (2.91-5.61); and
- at 0-15 ml/min the IRR was 3.41 (2.06-5.65).

From January 2000 onwards, 282 men and 34 women experienced a fatal or non-fatal secondary cardiovascular event: 169 had a myocardial infarction, 158 had a stroke (note that 11 persons experienced both a secondary MI and a secondary stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2023 in men and women with a prior cardiovascular event was 26.1 (23.1-29.3) and 22.3 (15.5-31.2), respectively. The crude rate and age-standardised incidence ratio (SIR; indirect method) of secondary myocardial infarction and stroke per 1,000 PYFU decreased significantly over time in men while it increased in women (*Table 5.5B*).

We compared the age- and sex-stratified prevalence of coronary artery disease (which includes myocardial infarction, angina pectoris) in the population of people with HIV with that observed in the general Dutch population (*Table & Figure 5.5C*). In men and women the prevalence of coronary artery disease was fairly equal in all age strata compared to the reference values in the general population.

***Table 5.5A-B:** Crude incidence of primary (A) and secondary (B) cardiovascular disease per 1,000 person years of follow up in 2000-2009, 2010-2019, and 2020-2023 and age-standardised incidence ratio with 95% confidence intervals.*

Primary CVD		**Male**		**Female**
Calendar year	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000-2009	6.4 (5.8-7.0)	1.75 (1.59-1.91)	2.7 (2.0-3.5)	1.45 (1.06-1.84)
2010-2019	6.3 (5.9-6.7)	1.23 (1.15-1.31)	3.5 (2.9-4.2)	1.17 (0.96-1.39)
2020-2023	6.4 (5.8-7.0)	1 (reference)	3.9 (3.0-5.0)	1 (reference)

Secondary CVD		**Male**		**Female**
Calendar year	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000-2009	31.2 (24.2-39.5)	1.54 (1.18-1.91)	15.2 (4.1-39.0)	0.46 (0.01-0.92)
2010-2019	26.4 (22.2-31.0)	1.22 (1.02-1.41)	21.0 (12.3-33.7)	0.67 (0.35-0.98)
2020-2023	22.2 (17.3-28.0)	1 (reference)	28.7 (15.3-49.1)	1 (reference)

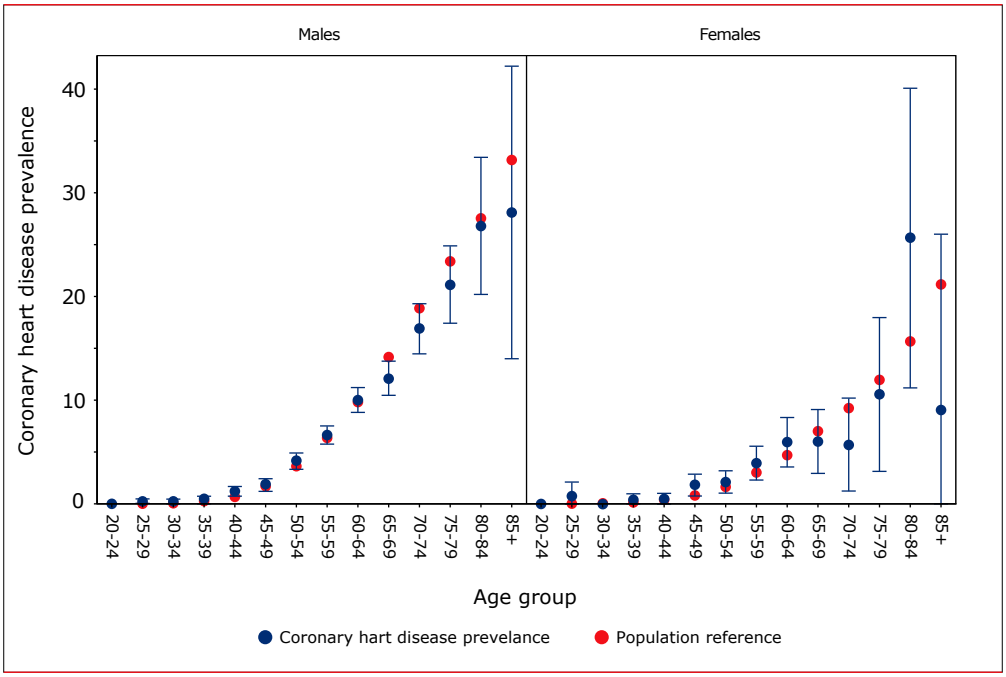
**Standardised according to the observed age distribution in 2020-2023.*

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

Table & Figure 5.5C: *Prevalence of coronary artery disease in people with HIV stratified by age and sex in 2023, compared to the prevalence observed in the general Dutch population in 2023 (https://www.staatvenz.nl/kerncijfers/coronaire-hartziekten-aantal-patiënten-bekend-bij-de-huisarts, accessed 10-9-2024).*

Age group (years)	Males				Females			
	Events (n)	Group size (n)	Prevalence % (95%CI)	General population prevalence (%)	Events (n)	Group size (n)	Prevalence % (95%CI)	General population prevalence (%)
20-24	0	167	0.0 (0.0-0.0)	0.03	0	64	0.0 (0.0-0.0)	0.02
25-29	1	563	0.2 (0.0-0.5)	0.05	1	135	0.7 (0.0-2.2)	0.03
30-34	3	1,345	0.2 (0.0-0.5)	0.1	0	227	0.0 (0.0-0.0)	0.06
35-39	7	1,601	0.4 (0.1-0.8)	0.28	2	467	0.4 (0.0-1.0)	0.12
40-44	23	1,867	1.2 (0.7-1.7)	0.64	3	625	0.5 (0.0-1.0)	0.35
45-49	38	2,031	1.9 (1.3-2.5)	1.77	12	644	1.9 (0.8-2.9)	0.82
50-54	108	2,571	4.2 (3.4-5.0)	3.59	15	700	2.1 (1.1-3.2)	1.62
55-59	196	2,932	6.7 (5.8-7.6)	6.42	22	553	4.0 (2.3-5.6)	3.05
60-64	246	2,449	10.0 (8.9-11.2)	9.85	23	384	6.0 (3.6-8.4)	4.77
65-69	182	1,494	12.2 (10.5-13.8)	14.19	14	231	6.1 (3.0-9.1)	7.03
70-74	157	925	17.0 (14.6-19.4)	18.93	6	104	5.8 (1.3-10.3)	9.26
75-79	98	462	21.2 (17.5-24.9)	23.44	7	66	10.6 (3.2-18.0)	12
80-84	46	171	26.9 (20.3-33.5)	27.61	9	35	25.7 (11.2-40.2)	15.71
85+	11	39	28.2 (14.1-42.3)	33.27	1	11	9.1 (0.0-26.1)	21.25

Legend: *CI = confidence intervals.*



Trends in cardiovascular risk factors

Figures 5.4A and *5.4B* 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 2023, the proportion of men with available BMI data who were overweight (25-30 kg/m^2) or obese (WHO class I: 30-35 kg/m^2 and WHO class II/III: 35 kg/m^2 or over), was 36.5%, 10.0% and 2.6%, respectively. In women, these proportions were 30.9%, 20.0% and 12.2%, respectively.

Table 5.5D and *Figure 5.4C* shows a comparison with the general Dutch population of the age- and sex-stratified prevalence of overweight and obesity in 2023. Males aged 35 and older were significantly less often overweight or obese than the general Dutch male population, while women in all age strata were more likely to be obese.

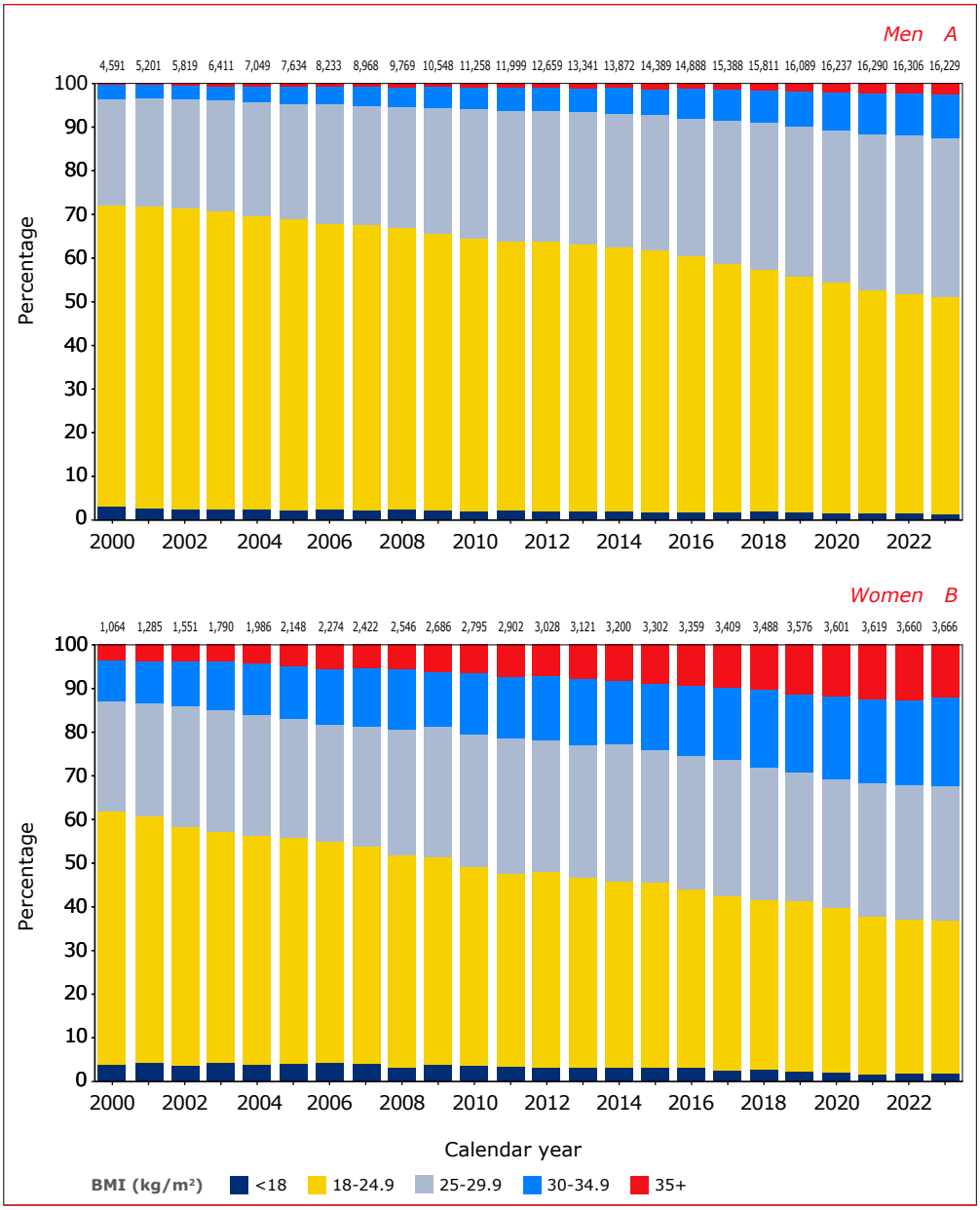
Table 5.5D: *Age- and sex-stratified prevalence of overweight and obesity in 2023, compared to the general Dutch population (source: https://www.vzinfo.nl/overgewicht/volwassenen, accessed 10-9-2024).*

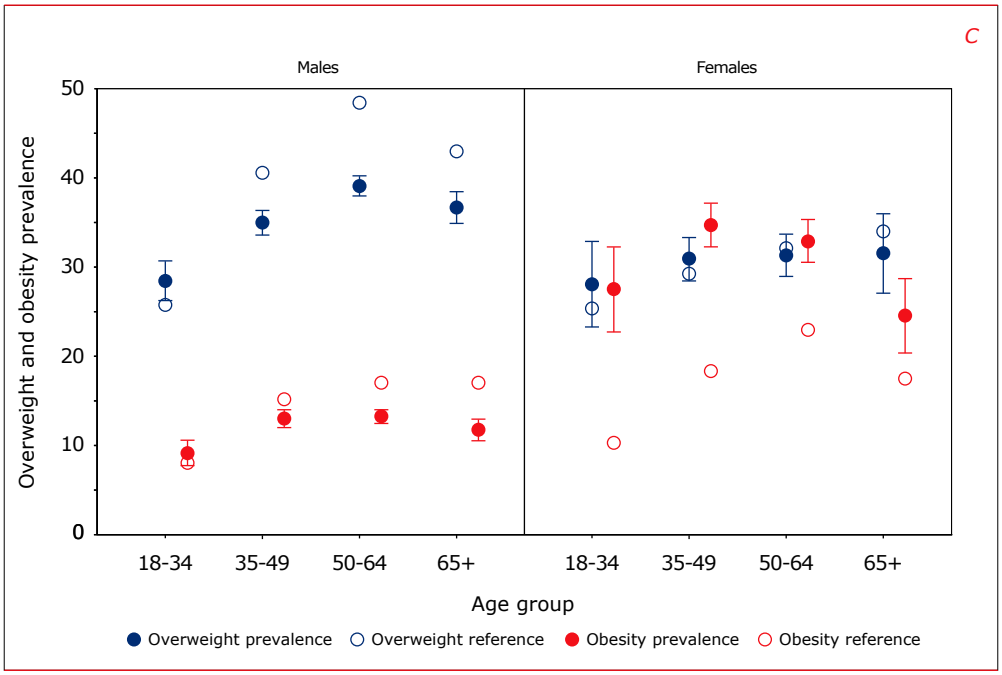
Age group (years)	Group size (n)	Over-weight (n)	Overweight prevalence % (95%CI)	General population overweight prevalence (%)	Obesity (n)	Obesity prevalence % (95%CI)	General population obesity prevalence (%)
Males							
18-34	1,582	451	28.5 (26.3-30.7)	25.8	145	9.2 (7.7-10.6)	8.1
35-49	4,634	1,623	35.0 (33.7-36.4)	40.6	605	13.1 (12.1-14.0)	15.2
50-64	7,165	2,804	39.1 (38.0-40.3)	48.4	956	13.3 (12.6-14.1)	17.1
65+	2,848	1,046	36.7 (35.0-38.5)	43	336	11.8 (10.6-13.0)	17.1
Females							
18-34	341	96	28.2 (23.4-32.9)	25.4	94	27.6 (22.8-32.3)	10.3
35-49	1,450	449	31.0 (28.6-33.3)	29.1	504	34.8 (32.3-37.2)	18.4
50-64	1,460	458	31.4 (29.0-33.7)	32.2	481	32.9 (30.5-35.4)	23
65+	415	131	31.6 (27.1-36.0)	34	102	24.6 (20.4-28.7)	17.5

Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the population with HIV. This analysis revealed that the increase was at least partially driven by changes over time in population demographic characteristics (age, non-Western region of origin, HIV transmission category) and time since first initiating ART, and that this effect was more marked in men than in women. With regard to specific antiretroviral drugs, the use of bictegravir, dolutegravir, rilpivirine and tenofovir alafenamide were all independently associated with higher body weight.

Figure 5.4C shows the distribution of BMI according to age groups in 2023 for men and women, compared to the reference proportions from the general Dutch population. Whereas in adult men of all age groups, the proportion classified as obese (12.6%) was somewhat lower than the proportion found in the general Dutch male population (13.5%), in women of all age groups there was more obesity (32.2%) than in the general Dutch female population (17.2%)[49]. There were substantial differences between those of Dutch origin, Western migrants and non-Western migrants: among males, 11.3% of Dutch men, 13.8% of Western migrants and 15.2% of non-Western migrants were obese. In females, however, those figures were 23.5%, 21.8%, and 38.5%, respectively. Being overweight (a BMI between 25-30) or being obese (a BMI over 30) were both independently associated with an increased risk of diabetes (overweight IRR 2.23, 95%CI 1.97-2.53, p<0.001; obese IRR 5.41, 95%CI 4.71-6.21, p<0.001), as well as with CKD (overweight IRR 1.15, 95%CI 1.05-.25, p=0.002; obese IRR 1.14, 95%CI 1.00-1.30, p=0.043). Being obese was independently associated with CVD (overweight IRR 1.03, 95%CI 0.92-1.15, p=0.61; obese IRR 1.22, 95%CI 1.04-1.43, p=0.015) (*Appendix Table 5.5*). Overweight and obesity were not associated with an increased risk of non-AIDS malignancies.

Figure 5.4: *Distribution of the body mass index (BMI) at the end of each calendar year in (A) men, and (B) women, as a percentage of the total number of men and women with a known BMI in each year, and (C) distribution of the BMI categories over the age groups for men, and women, in 2023, compared to the general Dutch population. 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).*





Legend: *BMI = body mass index.*

Several topics that in previous editions of the SHM Monitoring Report were part of this Chapter are in this edition of the Monitoring Report included in Chapter 9 on Quality of Care: prevalence and treatment of hypertension; the proportion of treated hypertensive individuals attaining treatment goals; the proportion of individuals with a SCORE2 or SCORE2-OP predicted 10-year risk greater than 10%, without a history of CVD, that received a prescription for statins; the proportion of high-risk individuals receiving statins who attained treatment goals.

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 the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations[50]. 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 ART. Of these equations, both the Cockcroft-Gault and the CKD-EPI equations have been validated in individuals with HIV[50,51]. However, because the CKD-EPI equation is the one most often used in clinical practice, we have chosen to report eGFR values as estimated by this equation. The distribution of eGFR categories in ml/min/1.73m^2 (90 or above, normal kidney function; 60-89, mildly reduced; 30-59, moderately reduced; 15-29, severely reduced; and below 15, very severely reduced kidney function) is shown in *Figures 5.5A* and *5.5B* for men and women. The percentage of men with normal kidney function decreased over time from 74.5% in 2007, to 41.5% in 2023, and this pattern was similar in women. Typically, eGFR decreases with increased age, as shown in *Figure 5.6*, and therefore the decrease in the proportion of individuals with normal function over time is likely due, in part, to the increasing age of individuals in care.

CKD incidence and risk factors

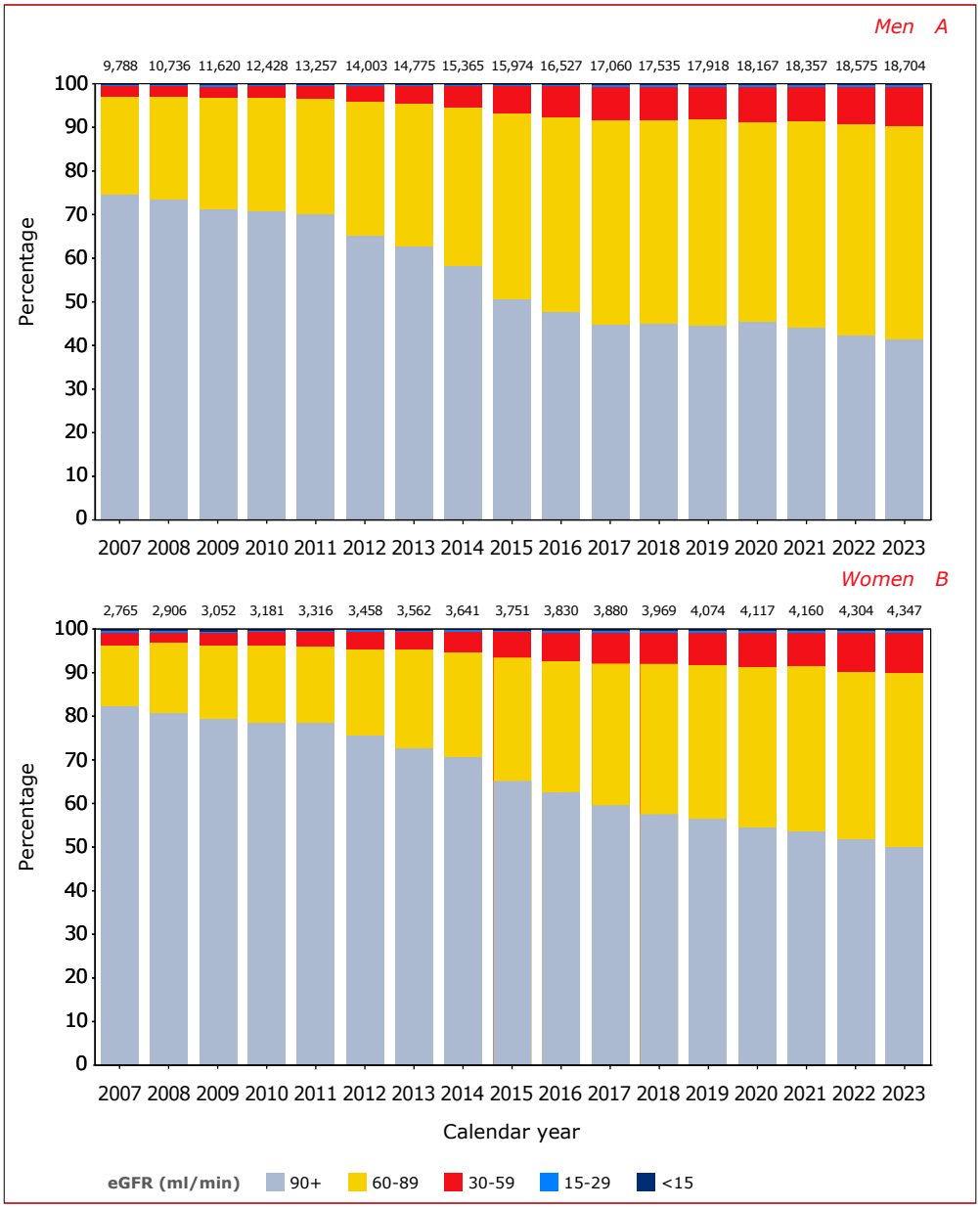
In individuals with an eGFR above 60ml/min/1.73m^2 at the time of inclusion in the analyses, who did not have a previously confirmed CKD, the crude incidence of CKD (defined as eGFR below 60ml/min/1.73m^2 confirmed by a second test at least 26 weeks later) varied over time (*Figure 5.3C*). Routine collection 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 9.9 cases per 1,000 PYFU in the period 2008-19 to 10.5 in 2020-23. In women, the incidence rose from 10.3 to 11.0 cases per 1,000 PYFU during the same periods (*Table 5.6*). However, the age-standardised incidence ratio in men and women was significantly lower in the 2020-2023 period (*Table 5.6*).

Risk factors for CKD included:

- female gender;
- Dutch origin;
- low current CD4 cell count (below 350 cells/mm^3);
- a prior AIDS diagnosis;
- belonging to the HIV transmission risk group of people who inject drugs;
- older age group;
- being underweight or overweight / obese;
- hypertension;
- diabetes mellitus;
- cardiovascular disease;
- pre-treatment with monotherapy and dual therapy with nucleoside analogues before the start of ART; and
- chronic HBV and HCV co-infection (*Appendix Table 5.5*).

When current use of cobicistat, rilpivirine, dolutegravir, and bictegravir were added to the model, the increased risk of CKD over calendar time completely disappeared (even reversed). This strongly suggests that the increase in CKD seen in recent years is largely due to increases in serum creatinine caused by ARV-induced reversible inhibition of two transporters that mediate tubular secretion of creatinine, without affecting the true glomerular filtration rate (namely, organic cation transporter 2 [OCT2], and multidrug and toxin extrusion transporter [MATE1]) and is therefore not a true increase in CKD.

Figure 5.5: *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.*



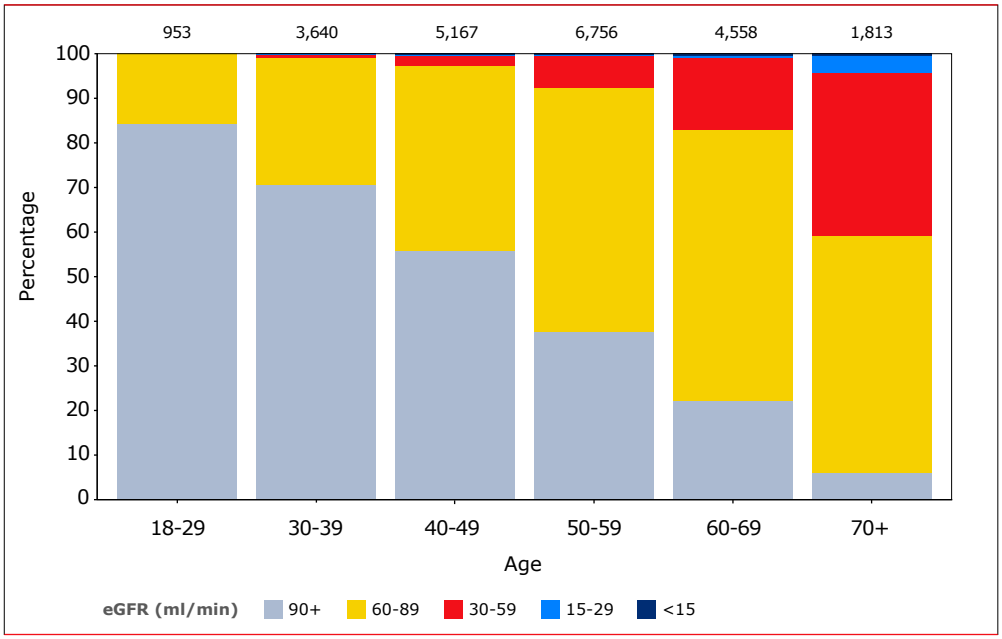
Legend: *eGFR = estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60–89 ml/min/1.73m²: mildly reduced; 30–59 ml/min/1.73m²: moderately reduced; 15–29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

Table 5.6: Crude chronic kidney disease incidence per 1,000 person years of follow up in 2008–2019, and 2020–2023, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2008–2019	9.9 (9.2–10.5)	1.25 (1.17–1.33)	10.3 (9.0–11.7)	1.33 (1.15–1.51)
2020–2023	10.5 (9.6–11.5)	1 (reference)	11.0 (9.0–13.3)	1 (reference)

**Standardised according to the observed age distribution in 2020–2023.*
***Legend:** CI = confidence interval; PYFU = person years.*

Figure 5.6: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2023 for different age categories. For each individual, the last available measurement in 2023 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 2023, 2,462 diagnoses of non-AIDS-defining malignancies in 2,259 unique individuals were recorded in SHM's database. An additional 1,022 patients were diagnosed with one or more non-melanoma skin cancers, but these were not included in the present analysis. *Table 5.7* shows the most common types of non-AIDS-defining cancer:

- lung cancer (16.4%);
- intestinal cancer (mainly oesophageal, gastric, intestinal, and rectal cancers, but excluding hepato-cellular carcinoma and cancer of gallbladder and biliary tract, 13.0%);
- invasive anal cancer (excluding pre-malignant AIN, 11.7%);
- haematological malignancies (excluding AIDS-defining non-Hodgkin's lymphoma, 11.2%);
- prostate cancer (11.2%); and
- head and neck cancers (8.3%).

Figure 5.7 shows the 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 5.8*, 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 5.3D*. The age-standardised incidence in men statistically significantly decreased over time (*Table 5.8A*). 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 temporal trend for women was similar – the age-standardised incidence decreased (although not significantly) over time (*Table 5.8A*).

Demographic and clinical factors independently associated with an increased risk of a first non-AIDS-defining malignancy were (*Appendix Table 5.5*):

- older age group;
- people born in the Netherlands, and migrants from Western countries;
- low body mass index;
- lower current CD4 cell count (CD4 below 350 cells/mm^3);
- prior AIDS;
- chronic HBV co-infection; and
- current or past smoking.

Furthermore, people who had been pre-treated with mono or dual-NRTI-based regimes prior to starting ART had an independently increased risk for NADM, compared with those who were therapy-naïve prior to starting ART (relative risk [RR] 1.19, 95% CI 1.04-1.35). Of note, independent of all other risk factors investigated, people who initiated ART within 12 months of their last negative HIV test had a borderline significant lower risk for NADM (RR 0.77, 95% CI 0.57-1.05) than other therapy-naïve people who started ART (i.e. those who either had an unknown duration of HIV infection, or a duration of more than 12 months).

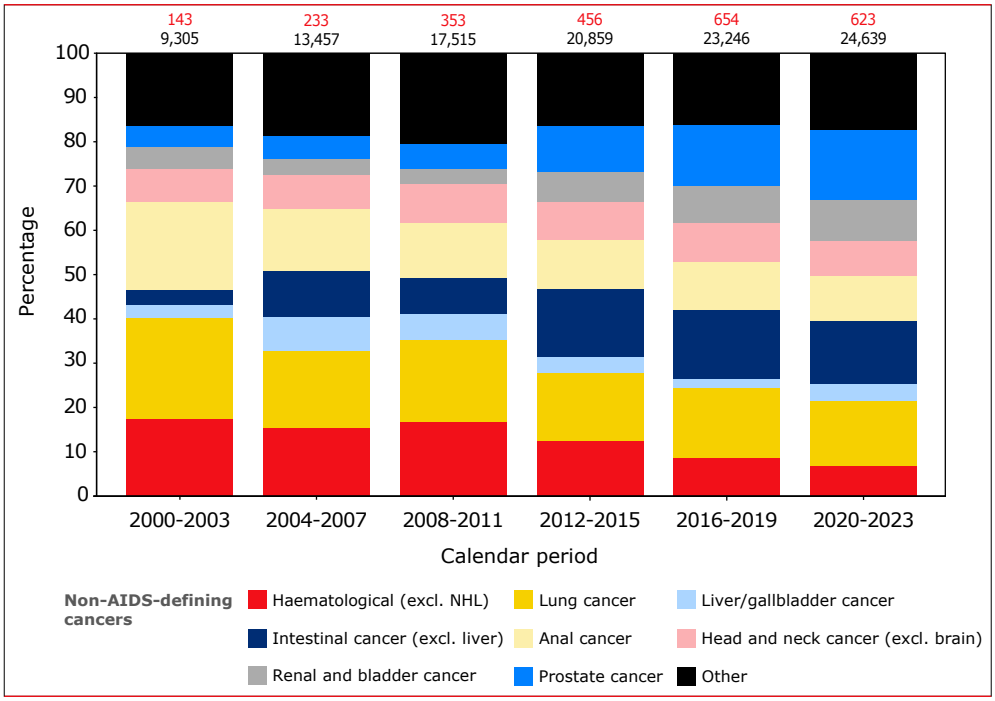
In the period from 1 January 2000 to 31 December 2023, the overall five-year survival rate following the most common non-AIDS-defining malignancies are shown in *Table 5.7* and *Appendix Figure 5.1.* Table 5.7 also shows the distribution and crude 5-year survival rates of the sub-group of NADM diagnosed in the last 10 years of follow-up. The crude 5-year survival rates of liver cancer improved substantially from 19.1% in the period 2000-2023, to 38.8% in the 10-year period 2014-2023, however because of low numbers the uncertainty of this latter estimate is high. For nearly all other NADM we observed no clinically significant change in the crude 5-year survival rates (but with slightly improved survival for lung cancer and malignant melanoma).

We calculated the age- and sex-stratified incidence of non-AIDS-defining malignancy (including non-melanoma skin cancer) per 1,000 person years of follow up in the period 2015-2023, and compared with the incidence in the general Dutch population in 2023 (*Table* & *Figure 5.8B*). The incidence of NADM in all age groups (with at least 15 events) in men was significantly higher than the observed cancer incidence in the general Dutch male population. The relatively low cumulative follow-up time and number of events per age-group in women limits the statistical power of the analysis. However, the observed incidence in each age group appears to be rather similar to the observed cancer incidence in the general Dutch female population.

Anal cancer

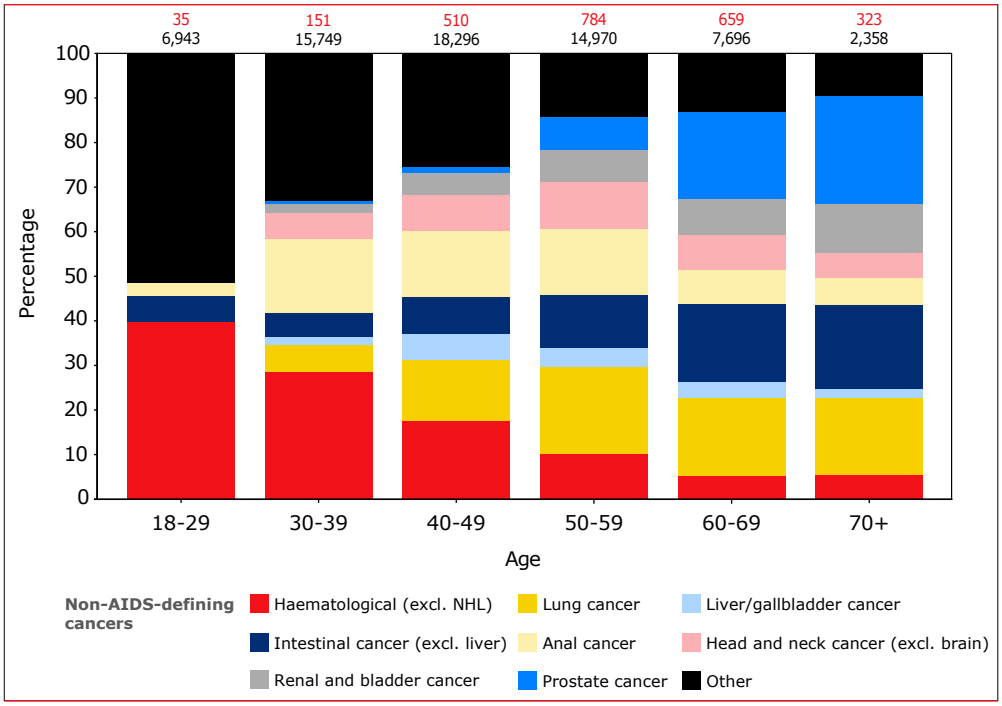
In total, 276 men with HIV and 11 women with HIV were diagnosed with anal cancer. Among men with HIV, the incidence of anal cancer fluctuated between 0.3 and 1.5 cases per 1,000 PYFU between 2000 and 2023 (*Figure 5.3G*). A 2023 study examined trends in incidence of and mortality after anal cancer diagnosis in people living with HIV, including the effect of AIN/anal cancer screening from 2007 onwards, in the Netherlands [52]. It found that anal cancer incidence slowly declined in MSM but not in non-MSM and women, and also that men diagnosed with anal cancer during screening had improved survival compared to those that were diagnosed while not participating in a screening program, probably because they were diagnosed at an earlier disease stage.

Figure 5.7: *Relative changes in non-AIDS-defining malignancies between 2000 and 2023 in PWH in the Netherlands. The numbers at the top of each bar represent the number of non-AIDS-defining cancer diagnoses (top number) and the total number of individuals in care during that calendar period (bottom number).*



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

Figure 5.8: Relative changes in non-AIDS-defining malignancies with increasing age in PWH with HIV in the Netherlands. The numbers at the top of each bar represent the number of individuals at risk and the number of cancer diagnoses in that age category between 2000 and 2023.



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

Table 5.7: Most common non-AIDS-defining malignancies diagnosed in 2000-2023, and a sub-group diagnosed in the last 10 year between 2014-2023, excluding non-melanoma skin cancer and pre-malignant lesions found by cervical and anal screening.

	2000-2023			2014-2023		
Non-AIDS malignancy	**# of malignancies**	**%**	**Five-year survival (%)**	**# of malignancies**	**%**	**Five-year survival (%)**
Lung cancer	403	16.4	16.1	229	15.0	21.6
Intestinal cancer (excl. liver/gallbladder)	321	13.0	32.1	231	15.2	31.6
Anal cancer	287	11.7	66.7	161	10.6	68.4
Hematological (excl. NHL)	276	11.2	64.1	132	8.7	65.6
Prostate cancer	275	11.2	79.7	218	14.3	80.3
Head and neck cancer (excl. brain)	205	8.3	56.7	124	8.1	58.9
Renal and bladder cancer	172	7.0	62.8	131	8.6	60.8
Other cancers	125	5.1	42.5	72	4.7	41.3
Malignant melanoma	114	4.6	77.9	67	4.4	85.3
Liver/gallbladder cancer	98	4.0	15.6	47	3.1	23.0
Breast cancer	70	2.8	75.7	41	2.7	67.8
Testicular cancer	47	1.9	90.1	23	1.5	89.7
Gynecological cancer (excl. cervical)	36	1.5	71.1	19	1.2	69.6
CNS cancer	33	1.3	60.3	27	1.8	50.2

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

Table 5.8A: Crude non-AIDS-defining malignancy incidence per 1,000 person years of follow up in 2000-2009, 2010-2019, and 2020-2023, and age-standardised incidence ratio with 95% confidence intervals.

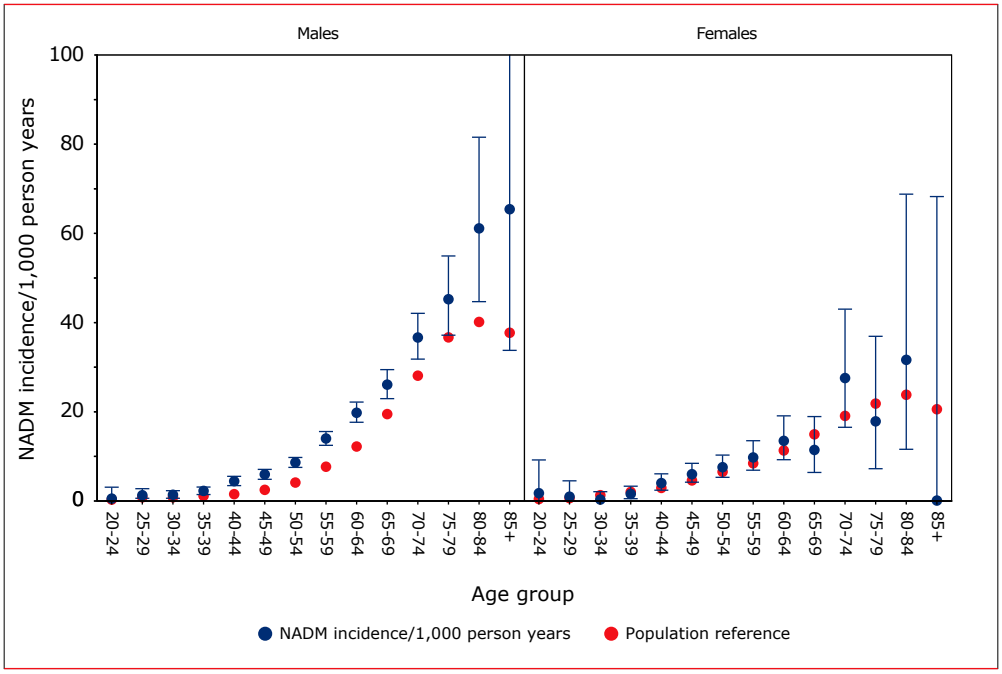
Calendar year	**Male**		**Female**	
	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000-2009	6.4 (5.9-7.0)	1.64 (1.49-1.78)	3.1 (2.4-4.0)	1.29 (0.97-1.61)
2010-2019	7.5 (7.1-8.0)	1.29 (1.22-1.37)	4.5 (3.8-5.2)	1.10 (0.93-1.27)
2020-2023	7.7 (7.0-8.4)	1 (reference)	5.5 (4.4-6.8)	1 (reference)

**Standardised according to the observed age distribution in 2020-2023.*

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

Table & Figure 5.8B: Age- and sex-stratified incidence of non-AIDS-defining malignancy (including non-melanoma skin cancer) per 1,000 person years of follow up in 2015-2023, compared to the incidence in the general Dutch population in 2023.

Age categories	Males				Females			
	Person-years of follow-up	Number of NADM	Incidence/ 1000PY (95%CI)	Incidence general population	Person-years of follow-up	Number of NADM	Incidence/ 1000PY (95%CI)	Incidence general population
20-24	1782	1	0.6 (0.0-3.1)	0.33	603	1	1.7 (0.0-9.2)	0.31
25-29	6241	9	1.4 (0.7-2.7)	0.62	1237	1	0.8 (0.0-4.5)	0.61
30-34	10776	15	1.4 (0.8-2.3)	0.79	2766	1	0.4 (0.0-2.0)	1.34
35-39	13401	30	2.2 (1.5-3.2)	1.07	4359	7	1.6 (0.6-3.3)	2.09
40-44	16309	72	4.4 (3.5-5.6)	1.52	5306	21	4.0 (2.4-6.0)	3.01
45-49	20514	122	5.9 (4.9-7.1)	2.48	5745	35	6.1 (4.2-8.5)	4.58
50-54	24895	214	8.6 (7.5-9.8)	4.23	5076	38	7.5 (5.3-10.3)	6.48
55-59	22854	319	14.0 (12.5-15.6)	7.71	3780	37	9.8 (6.9-13.5)	8.33
60-64	15693	311	19.8 (17.7-22.1)	12.27	2368	32	13.5 (9.2-19.1)	11.33
65-69	9738	254	26.1 (23.0-29.5)	19.58	1307	15	11.5 (6.4-18.9)	14.94
70-74	5567	204	36.6 (31.8-42.0)	28.12	689	19	27.6 (16.6-43.0)	19.04
75-79	2357	107	45.4 (37.2-54.9)	36.59	391	7	17.9 (7.2-36.9)	21.83
80-84	753	46	61.1 (44.7-81.5)	40.14	190	6	31.6 (11.6-68.8)	23.83
85+	184	12	65.4 (33.8-114)	37.65	54	0	0.0 (0.0-68.3)	20.69



Multimorbidity

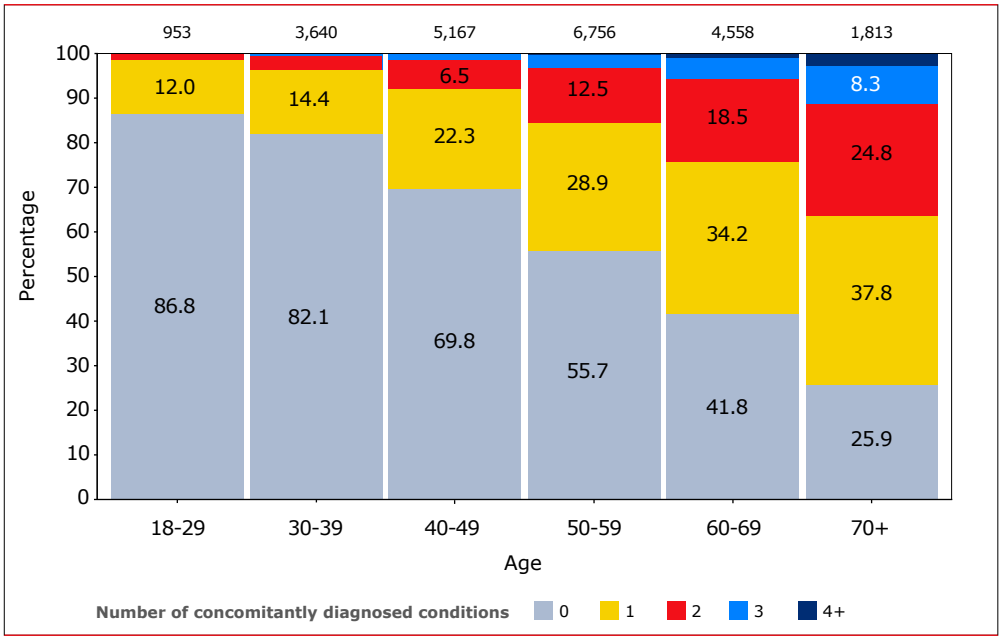
We investigated changes over time in the prevalence of non-AIDS multimorbidity. HIV infections and AIDS diagnoses did not contribute to the multimorbidity count. The following comorbidities and conditions were taken into account:

1. **Cardiovascular disease** (either myocardial infarction, coronary artery bypass grafting, coronary angioplasty or stenting, and carotid endarterectomy)
2. **Stroke**
3. **Non-AIDS-defining malignancies**, excluding non-melanoma skin cancers and pre-malignant lesions found at cervical/anal screening
4. **Chronic kidney disease** (eGFR below 30 ml/min/1.73 m^2)
5. **Diabetes mellitus** (according to D:A:D diagnostic criteria)
6. **Hypertension**, defined as the use of antihypertensive drugs and/or measured grade 2 (or higher) hypertension with systolic pressure at or above 60 mmHg and/or diastolic pressure at or above 100 mmHg
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 5.2 shows the prevalence of each individual comorbidity over calendar time. *Figure 5.9* shows the distribution of the number of concomitantly-diagnosed conditions in various age categories of the adult population in 2023. The number of concomitant conditions was slightly higher in women than in men for all age categories (*Appendix Figure 5.3*). After adjusting for the variables listed in *Appendix Table 5.2*, multimorbidity was independently associated with increased risk of mortality (RR 2.05, 95% CI 1.97-2.12, p<0.001, per additional comorbidity diagnosed).

Figure 5.9: *Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2023. 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 drugs are excluded from this count. We further excluded the ATC categories "Vitamins (A11)" and "Mineral supplements (A12)" for the count. We counted individual ATC codes (Anatomical Therapeutic Chemical classification systema) of the comedications. Note that coformulated combinations, such as cotrimoxazole, have a single ATC code and therefore increase the comedication count by one.

In 2023, 27.7% of adults in active follow up had no recorded comedication use, 26.8% used one comedication, 14.3% used two comedications, 8.9% used three comedications, and 6.2% used four comedications. A further 16.0% used five or more non-antiretroviral comedications in addition to their ART regimen, which qualifies as polypharmacy.

The prevalence of polypharmacy among adults has increased over time (*Figure 5.10*): in 2000, just 3.3% of adults used five or more non-antiretroviral comedications in addition to their ART 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 5.11*) used more comedications, primarily because they have been diagnosed with a higher number of comorbidities. 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. Finally, in adults receiving ART in the period 2007-2023, polypharmacy was also associated with an increased risk of death (RR 2.30, 95% CI 2.09-2.53, $p<0.001$) independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities (i.e. multimorbidity). All comedications used by at least 250 adults with HIV in care in 2023 are listed in *Table 5.9*.

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

Table 5.9: Use of comedications in 2023.

Comedication use in 2023	N	%
ATC group		
Vitamins	6805	11.5
Lipid modifying agents	5155	8.7
Drugs for acid related disorders	4145	7.0
Agents acting on the renin-angiotensin system	3699	6.3
Psycholeptics drugs (antipsychotics, anxiolytics, hypnotics, sedatives)	3583	6.1
Antithrombotic agents	3106	5.3
Drugs for obstructive airway diseases	3050	5.2
Drugs used in diabetes	2568	4.3
Psychoanaleptics (antidepressants, psychostimulants)	2495	4.2
Mineral supplements	2042	3.5
Urological drugs	1906	3.2
Beta blocking agents	1765	3.0
Calcium channel blockers	1759	3.0
Antianemic drugs	1338	2.3
Antibacterial drugs	1291	2.2
Diuretic drugs	1265	2.1
Sex hormones and modulators of the genital system	1195	2.0
Corticosteroids systemic	1106	1.9
Topical dermatological corticosteroids	1083	1.8
Analgesic drugs	894	1.5
Antiepileptic drugs	885	1.5
Cardiac therapy	840	1.4
Nasal preparations	789	1.3
Antiviral drugs	745	1.3
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	551	0.9
Antimycotic drugs	531	0.9
Drugs affecting bone structure and mineralization	486	0.8
Immunosuppressants drugs	387	0.7
Thyroid therapy	383	0.6
Ophthalmological drugs	348	0.6
Other nervous system drugs	258	0.4
Anti-inflammatory and antirheumatic drugs	253	0.4

Figure 5.10: 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.

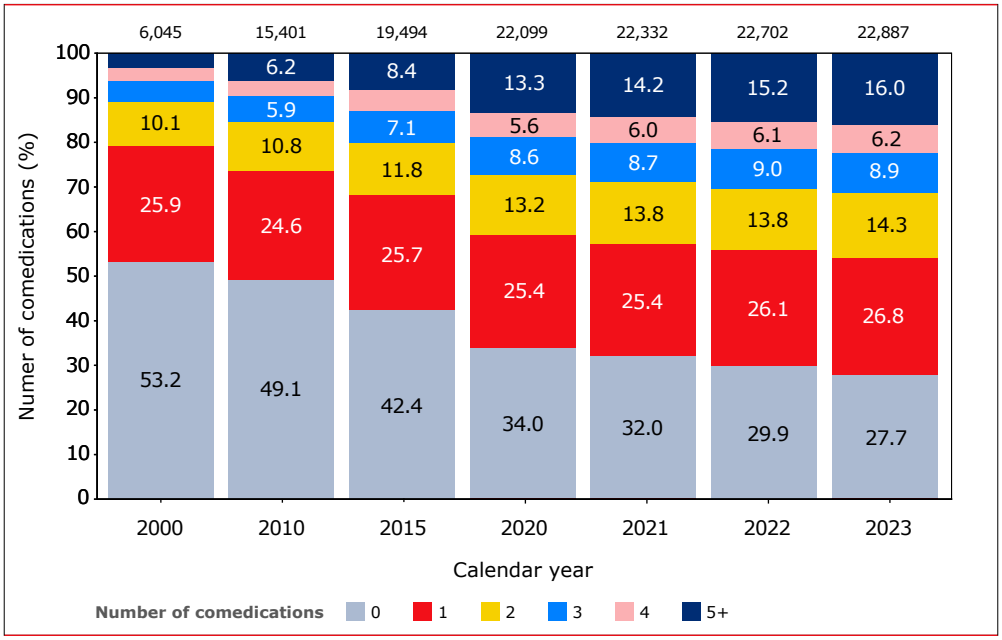
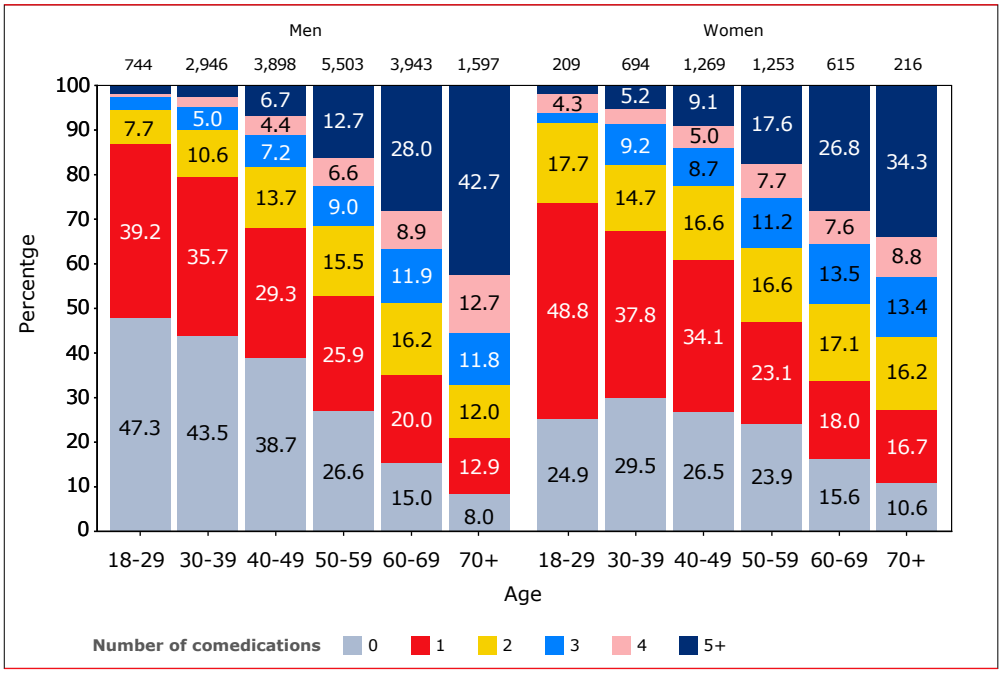


Figure 5.11: Number of comedications used by age group and gender in 2023. The numbers at the top of each bar represent the number of individuals contributing data to that age/gender category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



SARS-CoV-2 and COVID-19

In a recent study, we described the incidence, risk factors, and outcomes of COVID-19 in PWH in the Netherlands using data collected up to 31 December 2021. We found that risk of severe COVID-19 outcomes was increased in individuals with uncontrolled HIV replication, low CD4 count and prior AIDS diagnosis, independent of general risk factors like higher age, comorbidity burden and migrants originating from non-Western countries[53]. Here we present an updated analysis of the incidence, and outcomes of COVID-19 in people living with HIV in the Netherlands using data collected up to 31 December 2023.

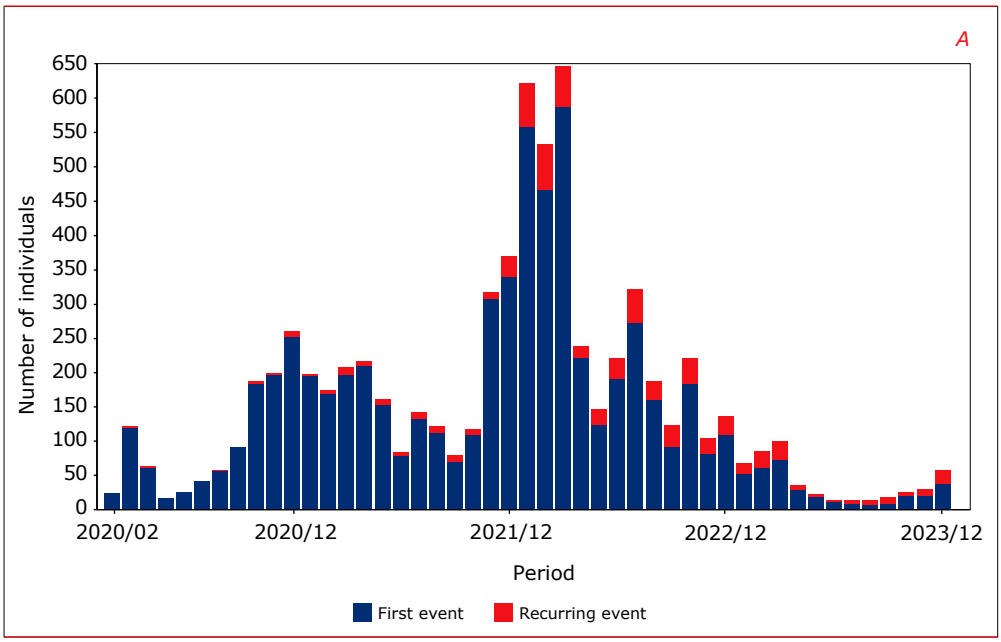
Stichting HIV Monitoring (SHM) records diagnosis of, and hospitalisations for COVID-19, using information available in the electronic medical records (EMRs) of the HIV treatment centers. SHM has not established links to other COVID-19 care providers and cohorts / datasets, nor to SARS-CoV-2 vaccination data repositories. Objective measures of COVID-19 disease severity could often not be recorded by

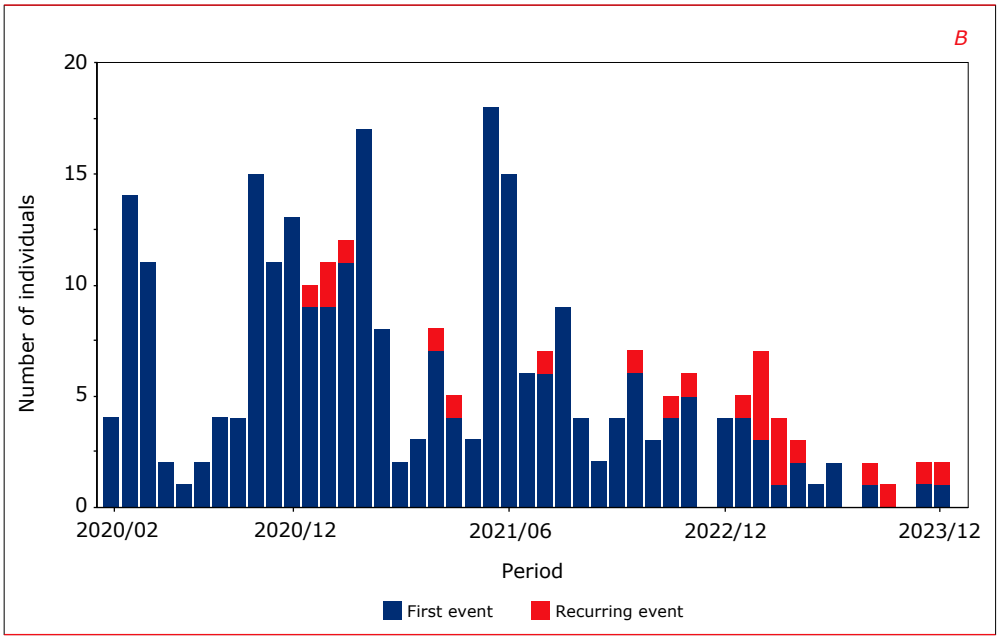
SHM, as these data were not systematically recorded in EMRs, especially for people who weren't hospitalised. In addition, detailed information on COVID-19 disease severity was often not available for patients who had been hospitalised for COVID-19, if the hospital differed from the one in which they received their HIV care. Therefore, we used data on hospitalisation for COVID-19 as a proxy for COVID-19 disease severity.

SHM has collected data on 7,183 COVID-19 events diagnosed between 1 February 2020 and 31 December 2023 in 6,462 individuals (Figure 5.12.A). There were 1,047 COVID-19 events recorded in 2020, 2,055 in 2021, 3,468 in 2022, and only 463 in 2023 (for 150 COVID-19 events no exact date was recorded). A total of 721 COVID-19 events occurred in individuals who had previously been diagnosed with COVID-19. Of the 7,183 recorded COVID-19 events, 279 (3.9%) resulted in hospitalisation (Figure 5.12.B); 46 (0.6%) of which required ICU admission. There were 81 hospitalizations in 2020, 111 in 2021, 58 in 2022, and just 29 in 2023. Table 5.10 describes the characteristics of the individuals that were diagnosed with (or hospitalized for) COVID-19, with individuals that had multiple COVID-19 events contributing only one (the most severe) event. The characteristics of the overall population living with HIV in care in the Netherlands in 2022 (the year in which the largest number of COVID-19 diagnoses were recorded) is also described in *Table 5.10*. Compared to the total population living with HIV, those who were hospitalised for COVID-19 were older, were more likely to have acquired HIV through heterosexual contact (both men and women), and were more likely to be born in sub-Saharan Africa or Latin America (including the Caribbean). Overall, men were not more likely than women to be diagnosed with or hospitalised for COVID-19; however, MSM were much less likely while the other (mostly heterosexual) men were more likely.
Regarding HIV-related characteristics, there were only minor differences between people living with HIV who were diagnosed with COVID-19, and the total population living with HIV, with the overwhelming majority being on ART, with a plasma HIV-1 viral load below 200 cps/mL, and a high median CD4 cell count well above 500 cells/mm^3. There were, however, noticeable differences between people diagnosed with COVID-19 who were hospitalised and those who weren't hospitalised; for example, the former had generally been HIV-positive for longer, but this is most likely driven by the fact that those who were hospitalised were on average eight years older. Furthermore, those who were hospitalised had lower current and nadir CD4 cell counts, and had more frequently had a prior AIDS diagnosis, compared to those not hospitalised (*Table 5.10*).
The bottom half of *Table 5.10* shows the distribution of selected comorbidities among individuals diagnosed with COVID-19. All investigated comorbidities were much more prevalent among the group that was hospitalised, resulting in a higher total multimorbidity count in the hospitalised group.

In total, 45 (0.63%) of the 6,462 individuals diagnosed with one (or more) COVID-19 event(s) were reported to have died as a direct result of COVID-19 (Figure 5.12.C). There were 13 COVID-19-related deaths recorded in 2020, 21 in 2021, 9 in 2022, and just 2 in 2023.

Figure 5.12.A-C: *Incidence of COVID-19 diagnoses (A), hospitalizations (B) and deaths (C) over calendar time.*

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5
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Number of individuals
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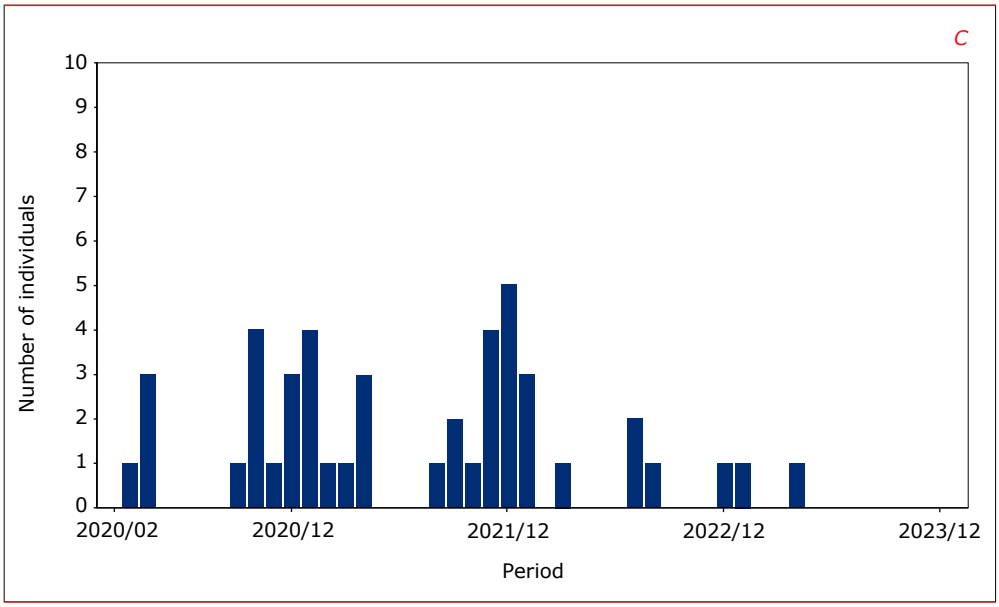
2020/12
2021/06
2022/12
2023/12
Period
First event
Recurring event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2023/12
Period

Table 5.10: Characteristics of individuals diagnosed with COVID-19.

	All PWH in 2022	Hospitalised	Not hospitalised
N	**21,901**	**268**	**6,194**
Age, years	51.1 (41.3-59.0)	59.8 (51.3-66.6)	49.9 (39.5-58.4)
Male sex	81.8%	79.1%	81.9%
HIV transmission category			
MSM	63.5%	42.9%	66.5%
Other men	18.3%	36.25	15.5%
Women	18.2%	20.9%	18.1%
Region of origin			
Netherlands / Europe / North America	69.8%	55.6%	64.8%
Sub-Saharan Africa	12.1%	16.0%	8.8%
Latin America / Caribbean	12.9%	17.2%	12.8%
Other regions	5.3%	11.2%	13.6%
Years known to be HIV positive	12.5 (7.2-18.6)	15.5 (8.4-21.9)	12.3 (6.7-18.5
On ART	97.3%	96.1%	98.9%
HIV viral load >200 cps/mL	3.3%	8.5%	2.2%
Current CD4 count, mm^3	690 (507-905)	550 (350-790)	710 (530-920)
Nadir CD4 count, mm^3	250 (120-385)	159 (50-270)	262 (136-410)
Prior AIDS diagnosis	22.3%	38.8%	18.9%
Comorbidities			
Obesity (BMI>30 kg/m^2)	12.4%	25.2%	14.1%
Diabetes mellitus type 2	5.2%	23.3%	5.4%
Cardiovascular disease	3.6%	12.4%	3.9%
Stroke	1.8%	7.4%	2.1%
Hypertension (grade 2+ or on medication)	13.4%	32.2%	16.0%
Non-AIDS-defining malignancy	3.5%	10.5%	4.1%
Chronic kidney disease (eGFR<60 ml/min)	0.8%	7.8%	0.8%
Multimorbidity count			
0	62.2%	38.0%	65.9%
1	24.5%	25.2%	24.5%
2	9.9%	20.5%	7.3%
3 or more	3.4%	16.3%	2.2%

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

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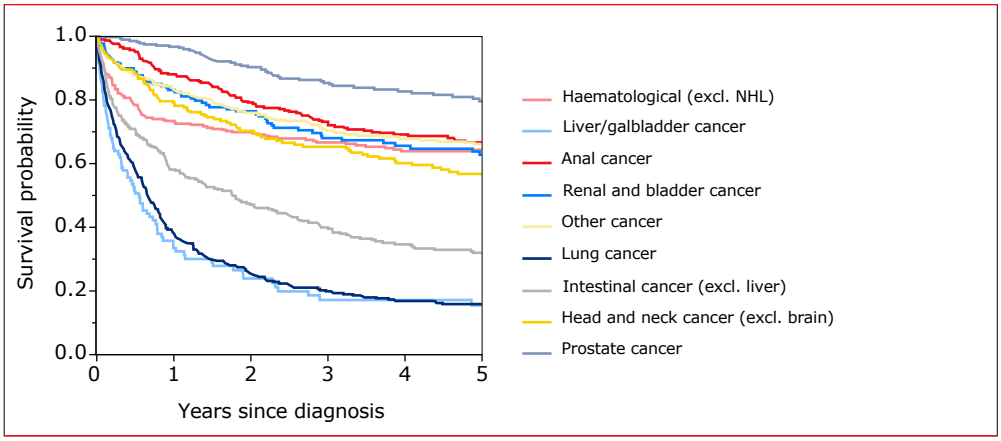
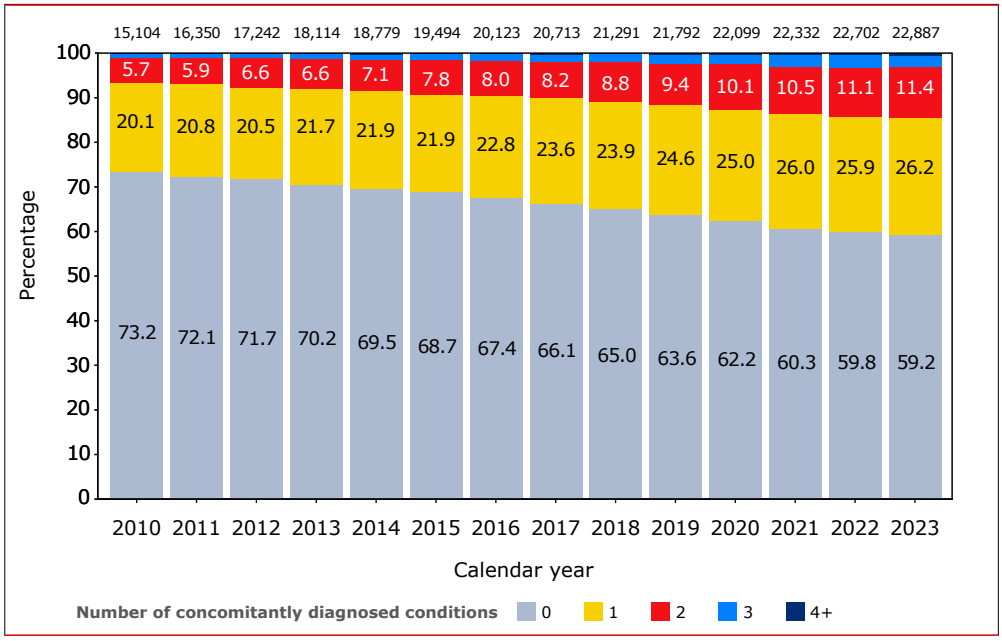
Appendix: supplementary figures and tables

Appendix Figure 5.1: *Estimated five-year survival following the diagnosis of the most common non-AIDS-defining malignancies diagnosed between 1 January 2000 and 31 December 2023.*

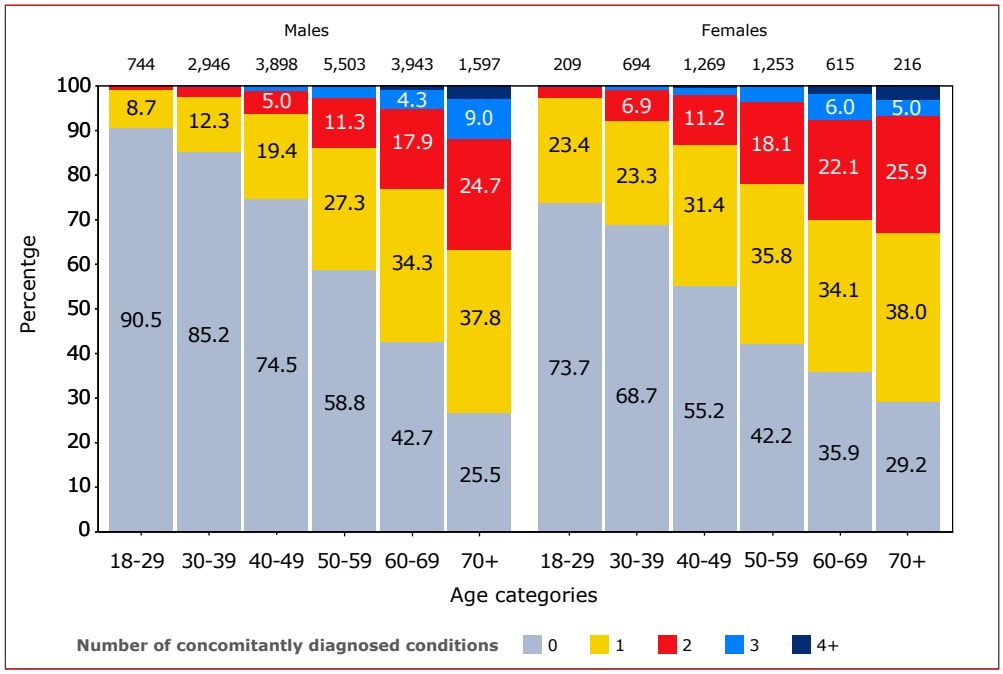


Legend: *KM = Kaplan-Meier; excl. = excluding; NHL = non-Hodgkin's lymphoma.*

Appendix Figure 5.2: *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 Figure 5.3: *Prevalence of non-AIDS multimorbidity by gender in the adult population in 2023. 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 Table 5.1: *Absolute number of causes of death among PWH during the periods 1996–2023.*

	Calendar period									
Causes of death	**96–99**	**00–04**	**05–09**	**10–14**	**15–19**	**20–23**	**2020**	**2021**	**2022**	**2023**
1. AIDS										
1.1 AIDS – infection	58	90	169	118	31	25	5	3	5	12
1.2 AIDS – malignancy	52	53	71	45	56	38	6	9	14	9
1.3 AIDS – unclassifiable	79	72	14	10	28	14	4	4	2	4
Subtotal	*189*	*215*	*254*	*173*	*115*	*77*	*15*	*16*	*21*	*25*
2. Non-AIDS malignancies	21	79	132	182	275	259	70	70	56	63
3. Cardiovascular disease										
3.1 Myocardial infarction	9	31	28	31	28	44	14	13	8	9
3.2 Stroke	2	10	9	14	18	23	3	7	10	3
3.3 Other CVD	4	20	42	50	68	75	11	16	20	28
Subtotal	*15*	*61*	*79*	*95*	*114*	*142*	*28*	*36*	*38*	*40*
4. Non-AIDS infection	19	45	29	24	33	70	16	30	12	12
5. Liver disease	10	22	54	48	27	14	2	4	4	4
6. Lung disease	4	13	24	30	67	40	7	11	10	12
7. Non-natural death										
7.1 Accident or violence	5	11	22	17	16	17	2	4	5	6
7.2 Suicide	9	23	35	45	53	36	14	8	7	7
7.3 Euthanasia	4	8	.	2	1	.	.	.	.	.
Subtotal	*18*	*42*	*57*	*64*	*70*	*53*	*16*	*12*	*12*	*13*
8. Alcohol and substance use	8	15	25	23	22	25	4	7	8	6
9. Other causes	11	29	26	38	57	78	15	22	19	22
10. Unknown	18	50	53	71	88	112	24	26	30	32
Total	**313**	**571**	**733**	**748**	**868**	**870**	**197**	**234**	**210**	**229**

Legend: *CVD = cardiovascular disease.*

Appendix Table 5.2: Adjusted risk factors for death and AIDS among PWH.

	Death			AIDS		
Risk factors	**RR (95%CI)**	**p-value**	**Overall p-value**	**RR (95%CI)**	**p-value**	**Overall p-value**
Region of birth						
Native Dutch	1 (reference)		0.010	1 (reference)		0.128
Western migrants	0.97 (0.85-1.11)	0.669		1.24 (1.04-1.48)	0.015	
Non-Western migrants	0.89 (0.80-0.98)	0.018		1.04 (0.92-1.18)	0.497	
Unknown origin	2.12 (1.20-3.74)	0.010		1.03 (0.53-2.01)	0.935	
HIV-1 transmission route						
MSM	1 (reference)		<.001	1 (reference)		0.264
Other men	1.16 (1.05-1.28)	0.004		0.95 (0.83-1.08)	0.422	
Women	0.89 (0.78-1.01)	0.080		0.93 (0.80-1.07)	0.295	
Transgender	0.85 (0.46-1.59)	0.609		1.24 (0.72-2.16)	0.439	
IDU	1.46 (1.23-1.74)	<.001		0.75 (0.58-0.96)	0.022	
Blood contact	0.83 (0.62-1.11)	0.210		0.82 (0.58-1.17)	0.278	
Pediatric transmission	1.33 (0.63-2.81)	0.449		1.20 (0.63-2.31)	0.576	
Age *						
18-29	0.86 (0.63-1.19)	0.365	<.001	1.07 (0.87-1.32)	0.520	<.001
30-39	1 (reference)			1 (reference)		
40-49	1.58 (1.36-1.83)	<.001		1.07 (0.94-1.21)	0.306	
50-59	2.79 (2.42-3.22)	<.001		1.26 (1.10-1.45)	0.001	
60-69	4.99 (4.29-5.79)	<.001		1.29 (1.08-1.54)	0.005	
70+	12.24 (10.41-14.39)	<.001		1.83 (1.42-2.36)	<.001	
CD4 cell count **						
0-50	11.04 (9.30-13.09)	<.001	<.001	7.27 (5.92-8.94)	<.001	<.001
50-199	4.50 (3.98-5.09)	<.001		2.87 (2.46-3.35)	<.001	
200-349	2.03 (1.80-2.28)	<.001		1.56 (1.34-1.82)	<.001	
350-499	1.38 (1.23-1.55)	<.001		1.23 (1.05-1.43)	0.008	
500-749	1 (reference)			1 (reference)		
750+	0.87 (0.77-0.99)	0.030		1.08 (0.91-1.28)	0.359	
Per year longer on cART with HIV RNA>1000 cp/mL	1.05 (1.04-1.07)	<.001	<.001	1.04 (1.02-1.07)	<.001	<.001
Treatment status						
Treatment-experienced at start cART	0.94 (0.86-1.03)	0.188		0.63 (0.56-0.72)	<.001	
Treatment-naive at start	1 (reference)			1 (reference)		
Prior AIDS event	1.65 (1.52-1.78)	<.001				
Hepatitis B virus positive	1.25 (1.10-1.41)	<.001		1.04 (0.86-1.24)	0.706	

			Death			AIDS
Risk factors	**RR (95%CI)**	**p-value**	**Overall p-value**	**RR (95%CI)**	**p-value**	**Overall p-value**
Hepatitis C virus positive	1.55 (1.36-1.77)	<.001		1.22 (1.01-1.46)	0.037	
Body mass index *						
<18	3.11 (2.77-3.50)	<.001	<.001			
18-25	1 (reference)					
25-30	0.68 (0.62-0.75)	<.001				
30+	0.84 (0.73-0.97)	0.018				
Smoking status						
Current smoker	1.22 (1.09-1.37)	<.001	<.001	0.75 (0.66-0.84)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	1.97 (1.78-2.18)	<.001		0.94 (0.82-1.07)	0.334	
Early cART ***	0.82 (0.62-1.08)	0.159		1.21 (0.93-1.58)	0.150	

**Time-updated.*

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

****ART started within 12 months of the last HIV-negative test.*

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

***Appendix Table 5.3:** Lost to care (no follow up after 31 December 2021) by region of origin and time-updated CD4 cell count.*

		Total population			Native Dutch			Western migrants			non-Western migrants		
Last CD4 count	**N**	**PY**	**Incidence/ 1000PY (95%CI)**	**N**	**PY**	**Incidence/ 1000PY (95%CI)**	**N**	**PY**	**Incidence/ 1000PY (95%CI)**	**N**	**PY**	**Incidence/ 1000PY (95%CI)**
0-50	73	3,479	21.0 (16.4-26.4)	7	1,975	3.5 (1.4-7.3)	16	310	51.7 (29.5-83.9)	50	1,195	41.8 (31.1-55.2)
050-199	258	12,673	20.4 (17.9-23.0)	33	6,915	4.8 (3.3-6.7)	48	1,444	33.3 (24.5-44.1)	177	4,315	41.0 (35.2-47.5)
200-349	516	27,939	18.5 (16.9-20.1)	84	16,257	5.2 (4.1-6.4)	97	2,139	45.3 (36.8-55.3)	335	9,543	35.1 (31.4-39.1)
350-499	692	53,658	12.9 (12.0-13.9)	122	31,987	3.8 (3.2-4.6)	139	4,433	31.4 (26.4-37.0)	431	17,239	25.0 (22.7-27.5)
500-749	1,042	12,5751	8.3 (7.8-8.8)	246	73,800	3.3 (2.9-3.8)	249	11,003	22.6 (19.9-25.6)	547	40,948	13.4 (12.3-14.5)
750+	790	163,555	4.8 (4.5-5.2)	205	97,445	2.1 (1.8-2.4)	231	17,301	13.4 (11.7-15.2)	354	48,809	7.3 (6.5-8.0)

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

Appendix Table 5.4: *Absolute number of first AIDS events among PWH during the periods 1996–1999, 2000–2004, 2005–2009, 2010–2014, 2015–2019, and 2020–2023.*

CDC event	1996–1999	2000–2004	2005–2009	2010–2014	2015–2019	2020–2023	Total	
	N	N	N	N	N	N	N	%
AIDS dementia complex – HIV encephalopathy	34	40	54	42	25	15	210	2.87
Bacterial pneumonia, recurring	41	53	77	65	109	56	401	5.48
CMV colitis/proctitis	1	.	1	1	4	2	9	0.12
CMV disease	21	33	29	35	8	.	126	1.72
CMV esophagitis	.	.	.	.	.	1	1	0.01
CMV meningo-encefalitis	.	.	.	.	1	.	1	0.01
CMV pneumonitis	.	.	.	.	11	18	29	0.40
CMV retinitis	26	19	16	13	13	1	88	1.20
Candidiasis esophagitis	221	215	274	222	164	109	1205	16.47
Candidiasis lungs/bronchial/trachea	4	13	9	7	5	4	42	0.57
Cervical cancer, invasive	2	6	5	6	5	1	25	0.34
Coccidioimycosis, extrapulmonary / disseminated	.	.	1	.	.	.	1	0.01
Cryptococcosis, extrapulmonary / disseminated	18	29	39	12	15	2	115	1.57
Cryptosporidiosis	18	15	9	14	4	4	64	0.87
Cystoisosporiasis	1	11	5	1	.	.	18	0.25
HIV wasting	43	45	77	77	70	33	345	4.72
HSV chronic ulcer	1	.	4	3	22	27	57	0.78
HSV esophagitis	.	.	.	.	.	1	1	0.01
HSV pneumonitis	.	.	1	.	.	1	2	0.03
Herpes simplex virus	27	33	58	44	15	.	177	2.42
Histoplasmosis, extrapulmonary / disseminated	5	13	12	8	2	1	41	0.56
Kaposi sarcoma	134	131	192	155	97	50	759	10.37
Leishmaniasis visceral	.	1	2	2	1	.	6	0.08
Microsporidiosis	11	1	2	2	.	1	17	0.23
Mycobacterium avium/kansasii, extrapulmonary / disseminated	21	23	23	14	9	1	91	1.24
Mycobacterium avium/kansasii, pulmonary	1	1	1	1	9	5	18	0.25
Mycobacterium other / unspecified, extrapulmonary / disseminated	18	13	8	10	5	1	55	0.75
Mycobacterium other / unspecified, pulmonary	2	2	5	10	4	3	26	0.36
Non-Hodgkin`s lymphoma (NHL)	48	73	96	98	93	43	451	6.16

CDC event	1996–1999	2000–2004	2005–2009	2010–2014	2015–2019	2020–2023	Total	
	N	N	N	N	N	N	N	%
Penicilliosis	.	.	1	.	.	.	1	0.01
Pneumocystis jirovecii extrapulmonary	.	1	3	1	1	1	7	0.10
Pneumocystis jirovecii pneumonia	269	302	315	297	214	130	1527	20.87
Primary CNS lymphoma	5	6	8	7	5	1	32	0.44
Progressive multifocal leukoencephalopathy	14	20	37	27	10	7	115	1.57
Salmonella sepsis, recurring	2	.	.	1	.	.	3	0.04
Toxoplasmosis of the brain	56	93	62	54	32	14	311	4.25
Tuberculosis, extrapulmonary / disseminated	56	112	91	59	38	24	380	5.19
Tuberculosis, pulmonary	80	167	133	93	68	18	559	7.64
Total	**1,180**	**1,471**	**1,650**	**1,381**	**1,059**	**575**	**7,316**	**100.00**

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

Appendix Table 5.5: *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	1.20 (1.08-1.32)	<.001	.	1.60 (1.34-1.90)	<.001	.
Region of birth						
Netherlands	1 (reference)	.	0.026	1 (reference)	.	0.466
Other	1.08 (1.01-1.16)	0.026	.	0.96 (0.86-1.07)	0.467	.
HIV-1 transmission route						
MSM	1 (reference)	.	<.001	1 (reference)	.	0.021
Heterosexual	1.17 (1.07-1.27)	<.001	.	1.18 (1.03-1.35)	0.014	.
IDU	1.30 (1.08-1.56)	0.005	.	1.21 (0.91-1.61)	0.188	.
Blood contact	1.16 (0.91-1.47)	0.227	.	1.15 (0.79-1.68)	0.458	.
Age *						
18-29	0.64 (0.49-0.83)	<.001	<.001	0.44 (0.23-0.82)	0.010	<.001
30-39	1 (reference)	.	.	1 (reference)	.	.
40-49	2.05 (1.81-2.31)	<.001	.	2.74 (2.17-3.46)	<.001	.
50-59	3.82 (3.38-4.31)	<.001	.	5.94 (4.73-7.46)	<.001	.
60-69	6.50 (5.70-7.41)	<.001	.	9.66 (7.60-12.28)	<.001	.
70+	10.27 (8.76-12.04)	<.001	.	16.21 (12.37-21.24)	<.001	.
CD4 cell count **						
0-50	3.95 (3.14-4.96)	<.001	<.001	2.79 (1.84-4.24)	<.001	<.001
050-199	1.71 (1.48-1.98)	<.001	.	1.42 (1.13-1.80)	0.003	.
200-349	1.23 (1.11-1.37)	<.001	.	1.25 (1.06-1.46)	0.008	.
350-499	1.04 (0.95-1.14)	0.396	.	1.02 (0.88-1.18)	0.789	.
500-749	1 (reference)	.	.	1 (reference)	.	.
750+	1.12 (1.04-1.22)	0.005	.	1.24 (1.10-1.40)	<.001	.
Per year longer with CD4<200 cells/mm^3	1.01 (0.99-1.03)	0.458	.	1.03 (1.00-1.06)	0.044	.
Prior AIDS event	1.21 (1.13-1.29)	<.001	.	1.16 (1.04-1.29)	0.007	.
Per year longer on cART while HIV RNA>1000 cp/mL	1.02 (1.00-1.03)	0.108	.	1.00 (0.97-1.03)	0.919	.
Treatment status						
Not (yet) started cART	1.19 (1.04-1.35)	0.009	<.001	1.06 (0.85-1.33)	0.605	0.031
Treatment-experienced at start cART	1.28 (1.17-1.40)	<.001	.	1.20 (1.05-1.37)	0.008	.
Treatment-naive at start	1 (reference)	.	.	1 (reference)	.	.
Per year longer on cART	1.00 (1.00-1.01)	0.196	.	1.00 (0.99-1.01)	0.995	.
Early cART within 12 months after last HIV-negat	0.80 (0.66-0.98)	0.030	.	1.06 (0.81-1.40)	0.669	.

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
0.99 (0.84-1.18)	0.929	.	1.21 (1.04-1.40)	0.013	.	0.63 (0.55-0.72)	<.001	.
1 (reference)	.	0.004	1 (reference)	.	<.001	1 (reference)	.	<.001
0.84 (0.75-0.95)	0.004	.	1.53 (1.37-1.71)	<.001	.	0.77 (0.70-0.85)	<.001	.
1 (reference)	.	0.020	1 (reference)	.	<.001	1 (reference)	.	0.028
0.98 (0.85-1.13)	0.782	.	1.39 (1.22-1.60)	<.001	.	0.99 (0.88-1.12)	0.913	.
1.35 (1.02-1.78)	0.035	.	1.50 (1.08-2.07)	0.014	.	1.53 (1.18-1.98)	0.001	.
1.34 (0.95-1.90)	0.099	.	1.43 (1.00-2.04)	0.051	.	1.18 (0.87-1.62)	0.293	.
0.85 (0.53-1.35)	0.482	<.001	0.64 (0.45-0.93)	0.019	<.001	0.34 (0.15-0.74)	0.007	<.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
2.38 (1.89-3.00)	<.001	.	1.55 (1.30-1.84)	<.001	.	3.05 (2.32-4.02)	<.001	.
4.60 (3.66-5.78)	<.001	.	2.44 (2.04-2.92)	<.001	.	8.53 (6.55-11.12)	<.001	.
9.60 (7.58-12.16)	<.001	.	3.75 (3.07-4.58)	<.001	.	23.18 (17.77-30.24)	<.001	.
16.93 (13.02-22.01)	<.001	.	4.17 (3.18-5.48)	<.001	.	41.00 (30.95-54.30)	<.001	.
3.42 (2.27-5.16)	<.001	<.001	5.79 (4.15-8.06)	<.001	<.001	1.67 (0.94-2.98)	0.083	<.001
1.96 (1.56-2.47)	<.001	.	1.79 (1.42-2.27)	<.001	.	1.58 (1.27-1.97)	<.001	.
1.36 (1.16-1.60)	<.001	.	1.11 (0.93-1.32)	0.255	.	1.19 (1.03-1.38)	0.015	.
1.08 (0.94-1.24)	0.290	.	1.02 (0.88-1.19)	0.779	.	1.04 (0.93-1.17)	0.470	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
0.92 (0.81-1.05)	0.201	.	1.23 (1.08-1.40)	0.002	.	0.94 (0.85-1.04)	0.234	.
1.00 (0.97-1.02)	0.788	.	1.00 (0.97-1.03)	0.930	.	0.99 (0.97-1.02)	0.515	.
1.14 (1.03-1.28)	0.014	.	1.29 (1.15-1.44)	<.001	.	1.13 (1.04-1.24)	0.006	.
1.00 (0.97-1.03)	0.833	.	0.99 (0.96-1.02)	0.340	.	0.98 (0.95-1.01)	0.127	.
1.23 (0.99-1.53)	0.063	0.023	1.49 (1.21-1.83)	<.001	<.001	0.38 (0.27-0.55)	<.001	<.001
1.17 (1.01-1.34)	0.031	.	1.31 (1.13-1.52)	<.001	.	1.18 (1.04-1.34)	0.012	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
1.00 (0.99-1.01)	0.659	.	1.01 (1.00-1.02)	0.055	.	0.98 (0.97-0.99)	<.001	.
0.62 (0.43-0.88)	0.008	.	0.63 (0.42-0.94)	0.023	.	0.98 (0.80-1.21)	0.863	.

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
Body mass index *						
0-18	1.51 (1.26-1.81)	<.001	<.001	1.18 (0.88-1.59)	0.266	0.011
18-25	1 (reference)	.	.	1 (reference)	.	.
25-30	1.23 (1.14-1.32)	<.001	.	1.02 (0.91-1.14)	0.739	.
30+	2.07 (1.89-2.28)	<.001	.	1.25 (1.05-1.47)	0.010	.
Hepatitis B virus positive	1.22 (1.09-1.36)	<.001	.	0.98 (0.81-1.19)	0.844	.
Hepatitis C virus positive	1.05 (0.94-1.18)	0.399	.	1.05 (0.88-1.25)	0.595	.
Hypertension	1.14 (1.07-1.21)	<.001	.	1.23 (1.11-1.35)	<.001	.
Smoking status						
Current smoker	1.37 (1.27-1.48)	<.001	<.001	1.82 (1.61-2.06)	<.001	<.001
Never smoker	1 (reference)	.	.	1 (reference)	.	.
Past smoker	1.38 (1.28-1.50)	<.001	.	1.49 (1.31-1.70)	<.001	.
Calendar year period						
2000-2010	1.28 (1.17-1.40)	<.001	<.001	1.68 (1.43-1.98)	<.001	<.001
2011-2015	1.17 (1.08-1.26)	<.001	.	1.34 (1.16-1.55)	<.001	.
2016-2022	1 (reference)	.	.	1 (reference)	.	.
Recent use of ABC ***		.	.	1.49 (1.33-1.68)	<.001	.
Per year longer on LOP/r		.	.	1.00 (0.99-1.01)	0.425	.
Per year longer on IDV		.	.	1.00 (0.99-1.01)	0.828	.
Current use of bictegravir		.	.	1.24 (0.91-1.67)	0.171	.
Current use of dolutegravir		.	.	1.40 (1.19-1.64)	<.001	.
Current use of elvitegravir		.	.	1.03 (0.81-1.30)	0.828	.
Current use of raltegravir		.	.	1.82 (1.51-2.19)	<.001	.
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 rilpivirine		.	.		.	.

**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; ART = combination antiretroviral therapy; LOP/r = lopinavir/ritonavir; IDV = indinavir; ABC = abacavir; ZDV = zidovudine; d4T = stavudine; ddI = didanosine; BMI: <18 kg/m² = underweight; 18-25 kg/m² = normal; 25-30 kg/m² = overweight;>30 kg/m² = severely overweight.*

Non-AIDS-defining malignancy			Diabetes mellitus			CKD		
IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
1.96 (1.54-2.49)	<.001	<.001	1.45 (1.01-2.07)	0.045	<.001	1.26 (0.96-1.67)	0.099	0.020
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
0.90 (0.80-1.02)	0.096	.	2.26 (1.98-2.57)	<.001	.	1.16 (1.06-1.27)	0.002	.
1.00 (0.83-1.21)	0.974	.	5.46 (4.73-6.30)	<.001	.	1.12 (0.98-1.28)	0.101	.
1.63 (1.39-1.92)	<.001	.	1.11 (0.91-1.34)	0.316	.	1.38 (1.18-1.62)	<.001	.
1.08 (0.90-1.29)	0.392	.	0.97 (0.80-1.18)	0.771	.	1.23 (1.07-1.42)	0.004	.
0.94 (0.85-1.04)	0.248	.	1.20 (1.08-1.33)	<.001	.	1.10 (1.01-1.19)	0.030	.
1.51 (1.33-1.72)	<.001	<.001	1.04 (0.91-1.18)	0.564	0.001	0.81 (0.73-0.90)	<.001	<.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
1.68 (1.48-1.91)	<.001	.	1.23 (1.09-1.40)	0.001	.	0.99 (0.90-1.09)	0.865	.
0.97 (0.84-1.13)	0.716	0.936	1.83 (1.53-2.18)	<.001	<.001	1.39 (1.18-1.64)	<.001	<.001
0.99 (0.87-1.12)	0.862	.	1.52 (1.31-1.77)	<.001	.	1.44 (1.29-1.61)	<.001	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	.	.		.	.		.	.
	.	.		.	.		.	.
	.	.		.	.		.	.
	.	.	1.89 (1.45-2.46)	<.001	.	2.43 (2.03-2.91)	<.001	.
	.	.	1.74 (1.48-2.05)	<.001	.	3.21 (2.89-3.55)	<.001	.
	.	.	1.22 (0.97-1.55)	0.094	.		.	.
	.	.	2.40 (2.00-2.89)	<.001	.		.	.
	.	.	1.01 (1.00-1.02)	0.066	.		.	.
	.	.	1.02 (0.99-1.04)	0.178	.		.	.
	.	.	1.02 (0.99-1.04)	0.171	.		.	.
	.	.		.	.	0.99 (0.98-1.00)	0.260	.
	.	.		.	.	1.01 (1.00-1.02)	0.012	.
	.	.		.	.	1.63 (1.43-1.86)	<.001	.
	.	.		.	.	1.32 (1.14-1.52)	<.001	.
	.	.		.	.	1.51 (1.33-1.71)	<.001	.
	.	.		.	.	1.35 (1.15-1.59)	<.001	.

Appendix Table 5.6: *Specific CDC-B and CDC-C (AIDS) events occurring in individuals on ART with undetectable viral load between 2000 and 2023.*

		All events		0-50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Aspergillosis, invasive pulmonary	13	0.4%	2	0.7%
	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis oropharyngeal	894	26.2%	82	29.5%
	Candidiasis vulvovaginal, frequent/persistent	56	1.6%	1	0.4%
	Cardiomyopathy, HIV-related	6	0.2%	0	0.0%
	Cardiomyopathy, with HIV-related component	27	0.8%	1	0.4%
	Diarrhea, HIV-related >=30 days	62	1.8%	1	0.4%
	Fever e.c.i. / HIV-related	6	0.2%	0	0.0%
	HIV-associated nephropathy (HIVAN)	22	0.6%	2	0.7%
	Herpes zoster, multidermatomal	35	1.0%	3	1.1%
	Herpes zoster, recurring / multidermatomal unspecified	197	5.8%	6	2.2%
	Herpes zoster, unidermatomal recurrent	49	1.4%	3	1.1%
	Listeriosis	1	0.0%	0	0.0%
	Myelopathy, HIV-related	10	0.3%	0	0.0%
	Neuropathy, HIV-related	120	3.5%	2	0.7%
	Neuropathy, with HIV-related component	114	3.3%	1	0.4%
	Nocardiosis	2	0.1%	1	0.4%
	Oral Hairy Leucoplakia (OHL)	55	1.6%	1	0.4%
	Pelvic inflammatory disease	9	0.3%	0	0.0%
	Thrombocytopenia, HIV-related	130	3.8%	4	1.4%
	Thrombocytopenia, with HIV-related component	39	1.1%	5	1.8%
	Weight loss >10%, HIV-related / unknown cause	35	1.0%	2	0.7%
Subtotal		**1883**	**55.2%**	**117**	**42.1%**

CD4 category										
	050–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
3	0.5%	1	0.1%	1	0.2%	2	0.3%	4	0.9%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
211	32.3%	175	25.4%	146	23.0%	160	22.5%	120	27.0%
5	0.8%	9	1.3%	17	2.7%	19	2.7%	5	1.1%
2	0.3%	0	0.0%	2	0.3%	1	0.1%	1	0.2%
4	0.6%	3	0.4%	4	0.6%	8	1.1%	7	1.6%
6	0.9%	16	2.3%	9	1.4%	22	3.1%	8	1.8%
1	0.2%	2	0.3%	0	0.0%	1	0.1%	2	0.5%
4	0.6%	3	0.4%	5	0.8%	5	0.7%	3	0.7%
1	0.2%	7	1.0%	6	0.9%	12	1.7%	6	1.4%
23	3.5%	52	7.6%	39	6.1%	47	6.6%	30	6.8%
6	0.9%	4	0.6%	4	0.6%	16	2.3%	16	3.6%
0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
4	0.6%	1	0.1%	1	0.2%	1	0.1%	3	0.7%
8	1.2%	15	2.2%	30	4.7%	40	5.6%	25	5.6%
9	1.4%	14	2.0%	32	5.0%	37	5.2%	21	4.7%
0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
13	2.0%	11	1.6%	10	1.6%	11	1.5%	9	2.0%
0	0.0%	4	0.6%	0	0.0%	3	0.4%	2	0.5%
25	3.8%	27	3.9%	31	4.9%	31	4.4%	12	2.7%
3	0.5%	12	1.7%	3	0.5%	14	2.0%	2	0.5%
5	0.8%	8	1.2%	6	0.9%	8	1.1%	6	1.4%
334	**51.1%**	**366**	**53.2%**	**346**	**54.4%**	**438**	**61.7%**	**282**	**63.5%**

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
CDC-C events	AIDS dementia complex – HIV encephalopathy	45	1.3%	5	1.8%
	Bacterial pneumonia, recurring	345	10.1%	14	5.0%
	CMV disease	19	0.6%	4	1.4%
	CMV esophagitis	2	0.1%	1	0.4%
	CMV meningo-encefalitis	1	0.0%	1	0.4%
	CMV pneumonitis	1	0.0%	0	0.0%
	CMV retinitis	19	0.6%	4	1.4%
	Candidiasis esophagitis	275	8.1%	29	10.4%
	Candidiasis lungs/bronchial/trachea	12	0.4%	2	0.7%
	Cervical cancer, invasive	14	0.4%	1	0.4%
	Coccidioimycosis, extrapulmonary / disseminated	1	0.0%	0	0.0%
	Cryptococcosis, extrapulmonary / disseminated	16	0.5%	5	1.8%
	Cryptosporidiosis	11	0.3%	4	1.4%
	Cystoisosporiasis	2	0.1%	0	0.0%
	HIV wasting	17	0.5%	7	2.5%
	HSV chronic ulcer	43	1.3%	2	0.7%
	HSV esophagitis	3	0.1%	0	0.0%
	HSV pneumonitis	2	0.1%	0	0.0%
	Herpes simplex virus	61	1.8%	7	2.5%
	Histoplasmosis, extrapulmonary / disseminated	4	0.1%	3	1.1%
	Kaposi sarcoma	125	3.7%	8	2.9%
	Leishmaniasis visceral	5	0.1%	1	0.4%
	Microsporidiosis	5	0.1%	2	0.7%
	Mycobacterium avium/kansasii, extrapulmonary / disseminated	27	0.8%	5	1.8%
	Mycobacterium avium/kansasii, pulmonary	5	0.1%	0	0.0%
	Mycobacterium other / unspecified, extrapulmonary / disseminated	10	0.3%	3	1.1%
	Mycobacterium other / unspecified, pulmonary	5	0.1%	0	0.0%
	Non-Hodgkin`s lymphoma (NHL)	192	5.6%	7	2.5%
	Pneumocystis jirovecii extrapulmonary	1	0.0%	0	0.0%
	Pneumocystis jirovecii pneumonia	73	2.1%	23	8.3%
	Primary CNS lymphoma	9	0.3%	1	0.4%
	Progressive multifocal leukoencephalopathy	22	0.6%	7	2.5%
	Toxoplasmosis of the brain	21	0.6%	8	2.9%
	Tuberculosis, extrapulmonary / disseminated	53	1.6%	4	1.4%
	Tuberculosis, pulmonary	80	2.3%	3	1.1%
Subtotal		**1526**	**44.8%**	**161**	**57.9%**
Total		**3409**	**100.0%**	**278**	**100.0%**

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

CD4 category										
	050–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
6	0.9%	8	1.2%	10	1.6%	7	1.0%	9	2.0%
54	8.3%	82	11.9%	86	13.5%	71	10.0%	38	8.6%
2	0.3%	3	0.4%	5	0.8%	2	0.3%	3	0.7%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
5	0.8%	2	0.3%	7	1.1%	1	0.1%	0	0.0%
65	10.0%	62	9.0%	44	6.9%	44	6.2%	31	7.0%
2	0.3%	4	0.6%	1	0.2%	2	0.3%	1	0.2%
4	0.6%	1	0.1%	2	0.3%	5	0.7%	1	0.2%
0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
7	1.1%	3	0.4%	0	0.0%	1	0.1%	0	0.0%
0	0.0%	1	0.1%	3	0.5%	2	0.3%	1	0.2%
1	0.2%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
6	0.9%	1	0.1%	2	0.3%	1	0.1%	0	0.0%
7	1.1%	4	0.6%	5	0.8%	16	2.3%	9	2.0%
1	0.2%	0	0.0%	1	0.2%	0	0.0%	1	0.2%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	0.5%
6	0.9%	13	1.9%	16	2.5%	14	2.0%	5	1.1%
0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
12	1.8%	27	3.9%	30	4.7%	32	4.5%	16	3.6%
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	0.2%
12	1.8%	5	0.7%	3	0.5%	2	0.3%	0	0.0%
1	0.2%	1	0.1%	0	0.0%	1	0.1%	2	0.5%
3	0.5%	3	0.4%	0	0.0%	1	0.1%	0	0.0%
1	0.2%	0	0.0%	2	0.3%	1	0.1%	1	0.2%
48	7.4%	45	6.5%	42	6.6%	31	4.4%	19	4.3%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
24	3.7%	12	1.7%	6	0.9%	7	1.0%	1	0.2%
3	0.5%	3	0.4%	1	0.2%	1	0.1%	0	0.0%
8	1.2%	4	0.6%	2	0.3%	1	0.1%	0	0.0%
6	0.9%	5	0.7%	1	0.2%	1	0.1%	0	0.0%
13	2.0%	7	1.0%	6	0.9%	12	1.7%	11	2.5%
17	2.6%	24	3.5%	15	2.4%	14	2.0%	7	1.6%
319	**48.9%**	**322**	**46.8%**	**290**	**45.6%**	**272**	**38.3%**	**162**	**36.5%**
653	**100.0%**	**688**	**100.0%**	**636**	**100.0%**	**710**	**100.0%**	**444**	**100.0%**

6. Viral hepatitis

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

Background

Infection with hepatitis C virus (HCV) and hepatitis B virus (HBV) is generally uncommon in the Netherlands. It is estimated that 0.1% to 0.4% of the general Dutch population has evidence of exposure to HCV or HBV[1,2]. Infection with hepatitis D virus (HDV), which requires HBV infection, is suspected to be even less common in the Netherlands and is more often found in individuals from specific, high-endemic regions (e.g., west/central Africa and eastern Europe)[3]. In contrast, HCV, HBV and HBV/HDV co-infections are far more prevalent in individuals living with HIV due to shared routes of transmission[4].

Individuals with chronic HCV and HBV are at risk of developing liver fibrosis, which, in time, may lead to cirrhosis and/or result in end-stage liver disease or hepatocellular carcinoma (HCC)[5,6]. Progression to severe liver disease takes on average 20 to 30 years in individuals with HCV or HBV, and is accelerated in the presence of other factors such as smoking, alcohol abuse, older age and the occurrence of other liver diseases [e.g., metabolic dysfunction-associated steatotic liver disease (MASLD)][7,8,9]. While progression of liver disease was faster in people living with HIV and viral hepatitis prior to the availability of combination antiretroviral therapy (ART), the rate of such progression in those with optimally-managed HIV has since become increasingly similar to that in individuals with HCV or HBV alone[10,11]. Meanwhile, co-infection with HBV-HDV is known to be highly associated with severe liver-related outcomes compared to HBV alone[12]; causing accelerated progression to end-stage liver disease in individuals living with HIV despite effective ART[13].

Infection with hepatitis A virus (HAV) and hepatitis E virus (HEV) is more frequent in the general Dutch population compared to HBV and HCV. Both HAV and HEV are transmitted by way of the intestine and can cause acute inflammatory liver disease that usually resolves without treatment[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]. Markers of previous HEV infection can be detected in roughly 10% of the general population[17]. HAV and HEV infections rarely cause death in adults, yet a small minority of individuals with HEV will develop chronic infection and/or damage to tissues/organs outside the liver

(such as neuralgic amyotrophy, Guillain-Barre syndrome, meningoencephalitis, glomerulonephritis, and thrombocytopenia)[18]. HEV infection is thought to persist and develop 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.

Hepatitis C virus (HCV)

Box 6.1: Definitions of hepatitis C infection.

Primary HCV infection
First documented HCV infection.

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

Acute HCV infection[19,20]

1. Case definition of recent HCV 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 seroconversion within the past 12 months.
2. Case definition of acute HCV according to alternative criteria[19]:
   Detectable HCV RNA in association with a rise in alanine aminotransferase (ALT) (above 200 IU/l) with a documented normal ALT within the past 12 months.

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

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

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

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

Severe (chronic) liver disease
Presumptive, based on clinically documented evidence of:
- bleeding from gastric or oesophageal varices, hepatic encephalopathy or hepatorenal syndrome, and/or
- chronic liver disease based on radiographically-documented or endoscopically-documented evidence of the presence of portal hypertension in terms of oesophageal varices, ascites, splenomegaly, and reversal of portal blood flow and/or cirrhosis.

Definitive if there is:
- a liver transplantation, or
- presumptive evidence, combined with a pathology, histology, or transient elastography report documenting severe liver fibrosis or cirrhosis (Metavir score F3-F4 or transient elastography stiffness ≥8kPa).

HCV screening over time

In the Netherlands the national guidelines for the treatment and monitoring of HIV recommend HCV screening during the first clinical visit after HIV diagnosis, and additional annual HCV screening for MSM who report behaviour associated with increased risk of acquiring HCV[21]. Of the 30,967[a] individuals ever registered in the SHM database, 96% have been screened at least once for HCV; anti-HCV or HCV RNA. Screening for HCV among the individuals with HIV ever registered with stichting hiv monitoring (SHM) has increased over calendar time. In 2000, 27% of the individuals with HIV in care had never been screened for the presence of HCV infection in that specific calendar year (*Figure 6.1A*). However, over time, a strong

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

and steady increase in the percentage of individuals with a known HCV status has been observed and in 2023, 0.9% of the individuals in care had never been screened for HCV co-infection. In 2023, unknown HCV status was relatively more common among individuals with heterosexually-acquired HIV (1.6%), or with another or unknown mode of HIV acquisition (2.0%), and relatively less common among MSM (0.4%) and people who inject drugs (PWID) or former PWID (0.7%).

Follow-up screening

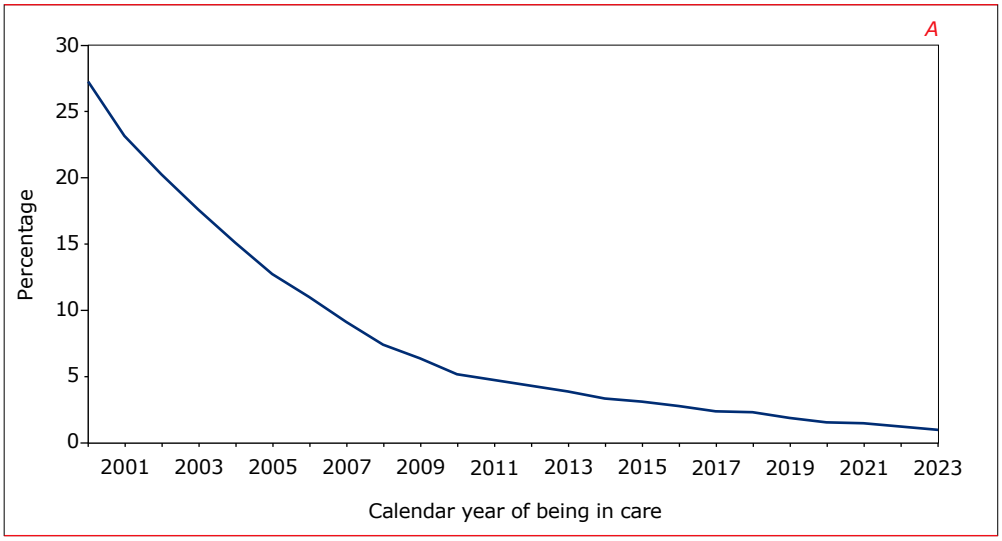
Among individuals who had a negative first HCV test and who remained in care for at least one year, 79% had a second HCV test at some point during follow up. This proportion was highest for MSM, of whom 88% had a second HCV test, and lowest for individuals who acquired HIV through heterosexual contact (64%).

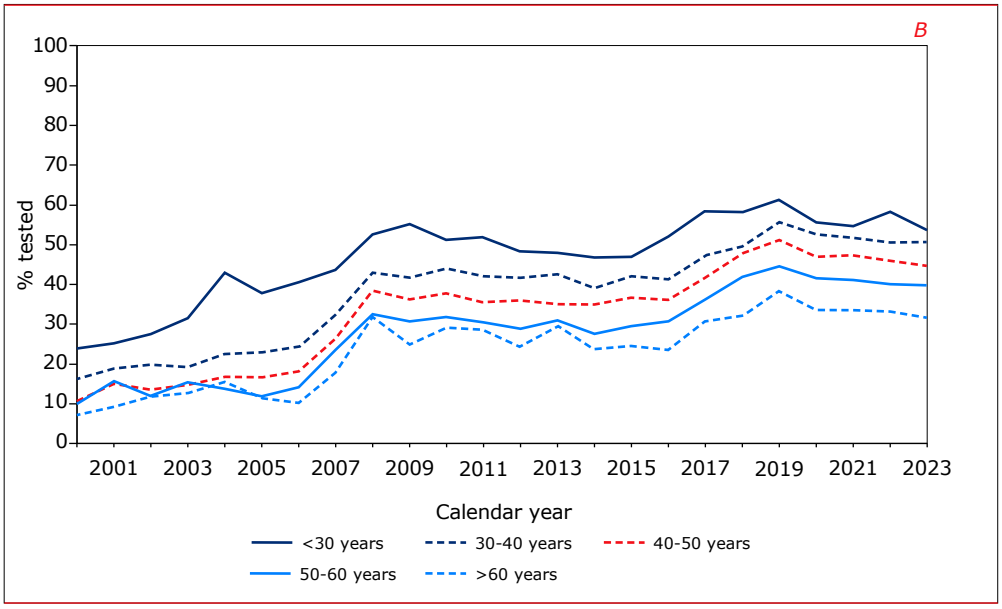
As most HCV infections are observed among MSM[22], the following analysis on testing frequency is reported for MSM only. Overall, the percentage of HCV seronegative MSM with at least one HCV test in a calendar year increased over time, from 13% in 2000 to 48% in 2019. However, testing frequency among HCV seronegative MSM decreased to 42% in 2022 and 41% in 2023. When testing was stratified by age, the highest percentage of testing was seen among MSM under 30 years of age, and testing decreased with increasing age (*Figure 6.1B*). Nevertheless, the median age for diagnosis of recent HCV was 43 years (IQR 36-50) (*Table 6.2A*), while in the age range 40-50 years, 44% had at least one test in 2023.

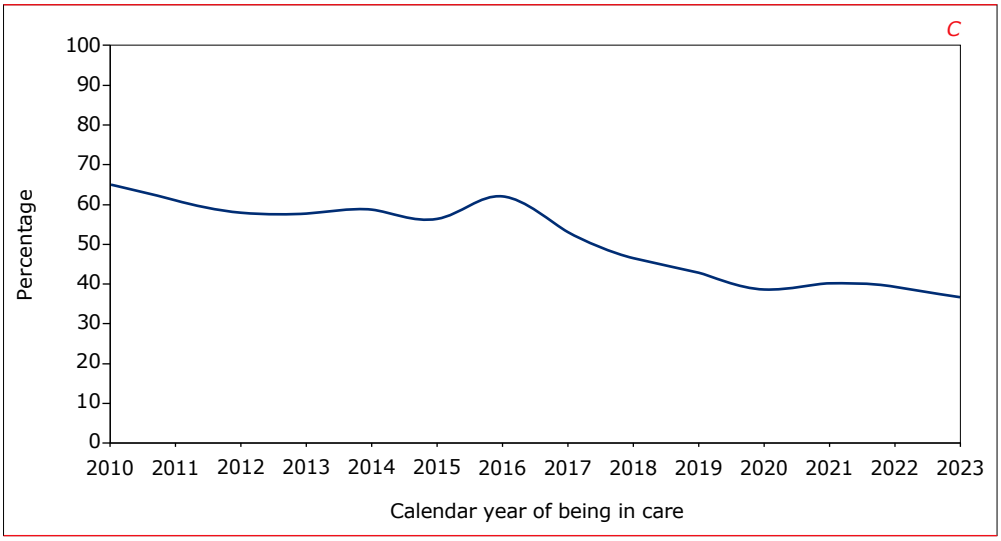
Screening for HCV RNA among those at risk of HCV reinfection is an important factor in identifying HCV reinfection. Among MSM living with HIV at risk of reinfection after treatment-induced, or spontaneous clearance of HCV, the percentage of MSM with an HCV RNA test during a calendar year varied between 54% and 65% in 2010-16, but declined to 37% in 2020, and 36% in 2023 (*Figure 6.1C*). It is worth noting that these data may include MSM who are no longer considered at risk of HCV reinfection by their treating physician, as data on HCV-related risk-taking behaviour are not available to SHM. Also of note is that repeated HCV screening among MSM at risk of HCV reinfection might be guided by a policy of targeted screening, based on the presence of incident transaminase elevations as an indicator of liver damage. This might be reflected by the observed higher proportion of repeated HCV screening among MSM with elevated transaminase levels (an increase of at least 50% compared to the last measured ALT value). In those at risk of HCV reinfection and incident transaminase elevations, the overall percentage of men with an HCV test following this elevated transaminase level was 70% in 2012-2022[b], but declined to 60% in 2023 (*Figure 6.1D*).

b Transaminase data became routinely available from 2012 onwards.

Figure 6.1: (A) Percentage of individuals in care with an unknown hepatitis C status per calendar year of care, (B) the percentage of men who have sex with men (MSM) who were susceptible to primary HCV infection with an HCV test, stratified by age, (C) the percentage of MSM at risk of HCV reinfection with an HCV RNA test, (D) and the percentage of MSM at risk of HCV reinfection with an HCV RNA test following an incident elevated transaminase level.



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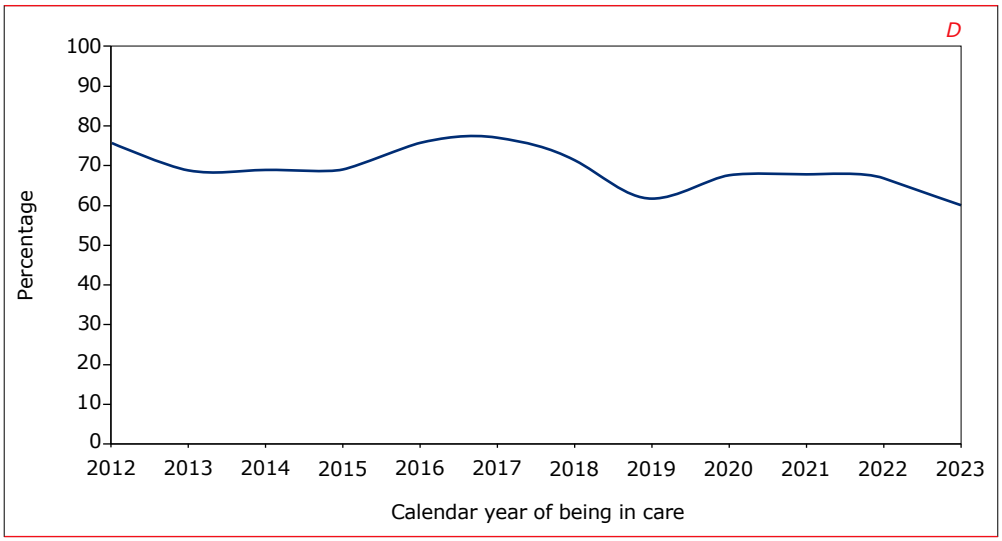
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Individuals with HCV

As of May 2024, 30,967 adults (aged 15 years or older at the time of their HIV-1 diagnosis) had been registered by stichting hiv monitoring. Of those individuals, 29,847 (96%) were ever screened for HCV co-infection and had been in care at one of the HIV treatment centres: 3,236 (11%) had a positive result with an HCV antibody test and/or HCV RNA test. This confirms that HCV is far more prevalent among the population with HIV than is estimated to be the case among the general Dutch population (*Figure 6.2*).

HCV RNA data were not documented in 156 of the 3,236 cases (5%), of whom:

- 113 have died;
- 22 have been lost to care;
- 12 have moved abroad; and
- 9 do not have a known reason for an undocumented HCV RNA outcome.

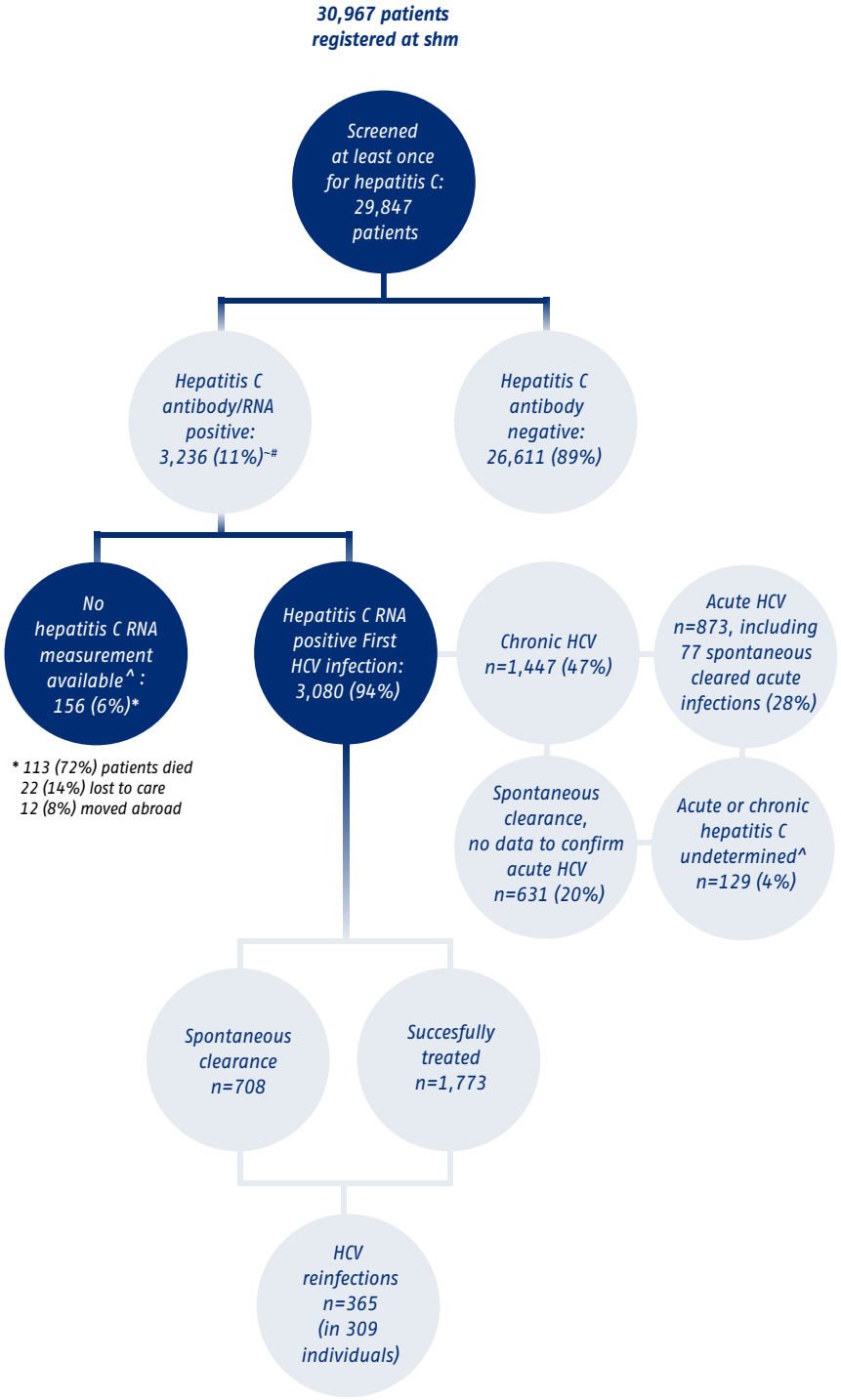
In total, 3,080 individuals were diagnosed with an HCV infection, with documented HCV RNA data for:

- 1,447 (47%) who were classified as having a chronic HCV infection at the time of their diagnosis.
- 873 (28%) who were initially diagnosed with an acute HCV infection, of whom;
  - 77 spontaneously cleared their infection
  - 796 became chronic HCV infections or were treated within 6 months of diagnosis.
- 631 (20%) who had evidence of spontaneous clearance of HCV but could not be classified as having a recent HCV infection at the time of their HCV diagnosis.

The remaining 129 individuals with available HCV RNA data had one positive HCV RNA test result, but no registered follow-up results, rendering it impossible to determine whether their HCV infection was acute or chronic at the time of diagnosis. This group of individuals has therefore been excluded from the analysis. The majority (n=102) of individuals with no HCV follow-up data were no longer in care in 2023. Of those still in care, 41% newly entered care in 2023 and originated from Ukraine.

In total, 1,773 of the individuals with a primary HCV infection had a treatment-induced clearance of their primary HCV infection (including old and new treatment regimens). Another 708 individuals spontaneously cleared their primary HCV infection. In total, 365 HCV reinfections occurred in 309 individuals. The majority (78%) of those with a primary infection who are not at risk of an HCV reinfection (i.e. those without SVR or spontaneous clearance of HCV) are no longer in care. The paragraph describing the continuum of HCV care gives more detail on those who remain in care, without clearance of their HCV infection.

Figure 6.2: Flowchart of individuals living with HIV tested at least once for hepatitis C virus (HCV).



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

Spontaneous clearance of HCV

In total, 708 individuals spontaneously cleared their HCV infection. Among the 873 individuals with primary recent hepatitis, 77 (9%) cases of spontaneous clearance were observed. Another 631 cases of spontaneous clearance were observed among individuals who could not be classified as having a primary acute infection. Compared to all individuals with HCV, those with spontaneous clearance of HCV were more likely to be female, less likely to be Dutch, and more likely to be from the sub-Saharan Africa or the Caribbean and South America regions (p<0.001) (*Table 6.1*).

Table 6.1: *Demographic characteristics of individuals with HIV/hepatitis C virus (HCV) and those who spontaneously cleared HCV registered in the SHM database, 1998–2023.*

	No spontaneous clearance	Spontaneous clearance	Total	p
Total N (%)	2,372 (77.0)	708 (23.0)	3,080	
Age at HCV diagnosis (Median (IQR))	40.2 (34.2 to 47.0)	41.0 (35.3 to 48.3)	40.4 (34.4 to 47.3)	0.009
Sex at birth				<0.001
Men	2064 (87.0)	547 (77.3)	2611 (84.8)	
Women	308 (13.0)	161 (22.7)	469 (15.2)	
Region				<0.001
Netherlands	1,402 (59.1)	312 (44.1)	1714 (55.6)	
Other	359 (15.1)	170 (24.0)	529 (17.2)	
Europe	302 (12.7)	86 (12.1)	388 (12.6)	
Caribbean/South America	160 (6.7)	69 (9.7)	229 (7.4)	
Sub-Saharan Africa	68 (2.9)	49 (6.9)	117 (3.8)	
Southeast Asia	81 (3.4)	22 (3.1)	103 (3.3)	
HIV transmission route				<0.001
Men who have sex with men	1,369 (57.7)	324 (45.8)	1,693 (55.0)	
People who use/used injecting drugs	528 (22.3)	147 (20.8)	675 (21.9)	
Heterosexual	241 (10.2)	141 (19.9)	382 (12.4)	
Other	234 (9.9)	96 (13.6)	330 (10.7)	
ART				0.76
ART	2,296 (96.8)	683 (96.5)	2,979 (96.7)	
No ART	76 (3.2)	25 (3.5)	101 (3.3)	
Deaths	475 (20.0)	113 (16.0)	588 (19.1)	0.018

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

In total, 2,320 individuals could be definitively classified as having either chronic (n=1,447), or recent (n=873) HCV infection at the time of their primary HCV diagnosis. Most of these were male (81% and 99%, respectively), and the majority originated from the Netherlands (chronic: 771/1,447 [53%]; recent: 662/873 [76%]) (Table 6.2A). Fifty-seven percent of the registered individuals who acquired HIV through injecting drug use (IDU) had chronic HCV (473 of the total 833 people who use/used injecting drugs [PWID]). Among MSM (17,841), 3% (597) had chronic HCV and 5% (819) had documented recent HCV.

The HCV genotype was determined and documented in the clinical records of 1,299 of the 1,447 (90%) individuals with chronic HCV. Of the individuals with a genotype (Table 6.2B):

- 62% (n=802) harboured HCV genotype 1, varying across 61% (n=492) with type 1a and 15% (n=119) with type 1b. For 24% (n=191) of those with genotype 1, the subtype was 1a/b, 1c , 1e or not further specified
- 5% (n=63) harboured HCV genotype 2
- 17% (n=227) harboured HCV genotype 3
- 16% (n=205) harboured HCV genotype 4

HCV genotype was also documented for 796 of the 873 (91%) individuals with recent HCV. They were most likely to harbour either genotype 1 (71%, n=562) or genotype 4 (21%, n=169). Of the 562 with genotype 1, 85% (n=478) harboured genotype 1a and 4% (n=22) with genotype 1b. For 11% of the people with genotype 1, the subtype was 1a/b, 1c , 1e or not further specified.

New HCV diagnoses in 2023

In 2023, 42 individuals were newly diagnosed with primary HCV, of whom 40 (95%) had detectable HCV RNA. Twenty-two newly entered care in 2023. Two individuals had a first HCV antibody positive test result, with a negative HCV RNA test result, which might indicate a spontaneously cleared HCV infection. Of these 42 individuals with a primary HCV diagnosis in 2023, 12% were born in the Netherlands and 62% were born in eastern or central Europe. For diagnoses among individuals who were born outside the Netherland and who were newly entering care, it cannot be determined with certainty that these concern new diagnoses or already known infections with a first documented positive test result in the Netherlands.

In terms of HIV risk group for all 42 diagnoses of primary HCV in 2023, 45% were MSM, 21% acquired HIV through heterosexual contact, 21% were PWID and 12% of the individuals had an unknown or other reported mode of HIV transmission. The modes of HCV acquisition were mostly unknown for those who acquired HIV through heterosexual contact. All 9 PWID with a new HCV diagnosis in 2023 migrated from mainly Eastern or Central Europe.

The HCV genotype was determined and documented for 23 of the 42 (55%) individuals with a primary HCV diagnosis in 2023. Of the individuals with a genotype:

- 48% (n=11) had genotype 1a,
- 30% (n=7) had HCV genotype 3a, and
- other reported genotypes were 1b, 2a/c and 4d.

At time of database closure, 20 individuals were known to have started HCV treatment, predominantly with glecaprevir/pibrentasvir.

Table 6.2A: Demographic characteristics of individuals with HIV/hepatitis C virus (HCV) registered in the SHM database, 1998–2023.

HCV status	Chronic HCV	Recent HCV	Total population screened for HCV
Total N (%)	1,447 (4.8)	873 (2.9)	29,847
Age at HCV diagnosis (Median (IQR))	38.8 (33.0 to 45.1)	43.4 (36.0 to 49.9)	40.4 (34.4 to 47.1)
Sex at birth			
Men	1,172 (81.0)	864 (99.0)	2,4407 (81.8)
Women	275 (19.0)	9 (1.0)	5,440 (18.2)
Region			
Netherlands	771 (53.3)	662 (75.8)	15,573 (52.2)
Caribbean/South America	98 (6.8)	57 (6.5)	3,980 (13.3)
Sub-Saharan Africa	53 (3.7)	11 (1.3)	3,935 (13.2)
Other	258 (17.8)	49 (5.6)	3,296 (11.0)
Europe	216 (14.9)	69 (7.9)	1,971 (6.6)
Southeast Asia	51 (3.5)	25 (2.9)	1,092 (3.7)
HIV transmission route			
Men who have sex with men	597 (41.3)	819 (93.8)	1,7841 (59.8)
Heterosexual	186 (12.9)	33 (3.8)	8,691 (29.1)
Other	191 (13.2)	14 (1.6)	2,482 (8.3)
People who use/used injecting drugs	473 (32.7)	7 (0.8)	833 (2.8)
ART			
ART	1,392 (96.2)	869 (99.5)	29,013 (97.2)
No ART	55 (3.8)	4 (0.5)	834 (2.8)
Died	382 (26.4)	65 (7.4)	3,777 (12.7)

**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; ART = combination antiretroviral therapy.*

Table 6.2B: Frequency of HCV genotypes among individuals with a primary HCV diagnosis, 1998–2023.

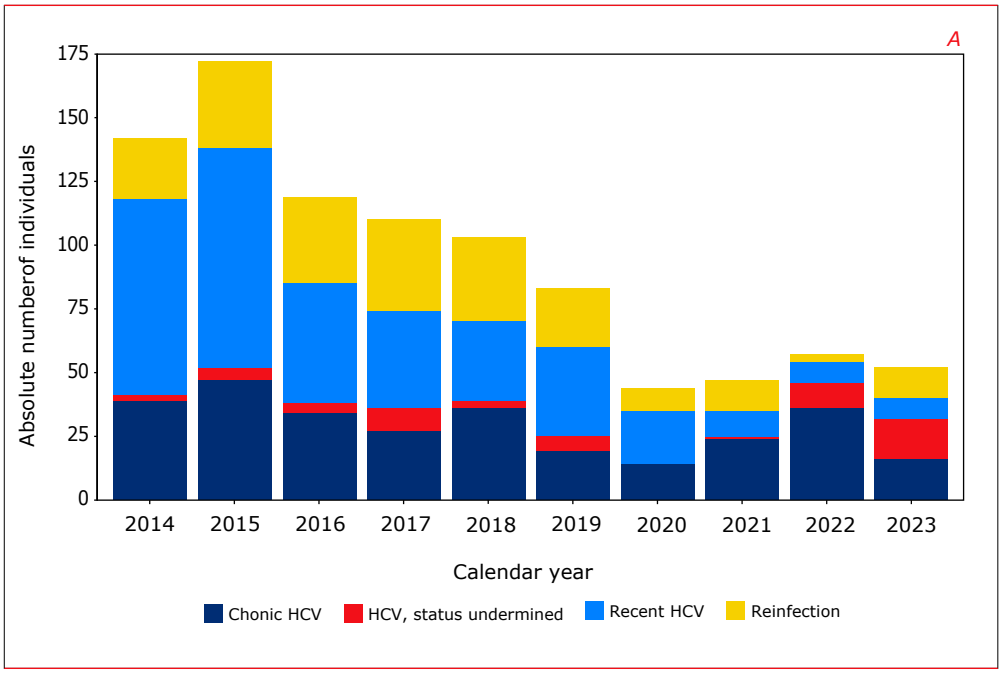
HCV status	Total	Chronic HCV	Recent HCV
Total N (%)	2,320	1,447 (62.4)	873 (37.6)
Total determined	2,095	1,299	796
Genotype			
1	1364 (65)	802 (61.7)	562 (70.6)
1a	970	492	478
1b	141	119	22
1a/b, 1c, 1e or not specified	253	191	62
2	102 (4.9)	63 (4.9)	39 (4.9)
3	252 (12.0)	227 (15.7)	25 (3.1)
4	374 (17.8)	205 (17.5)	169 (21.2)
5/6	3 (0.1)	2 (0.2)	1 (0.1)

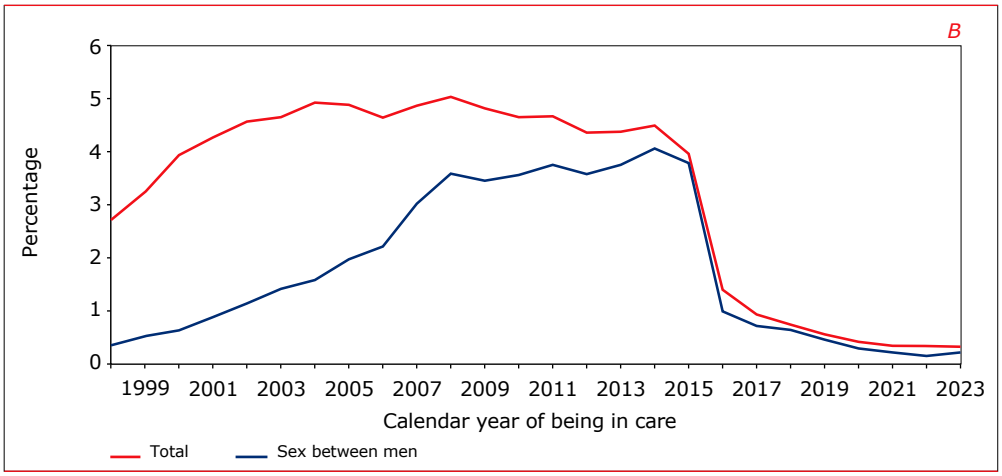
Changes in HCV epidemiology over time

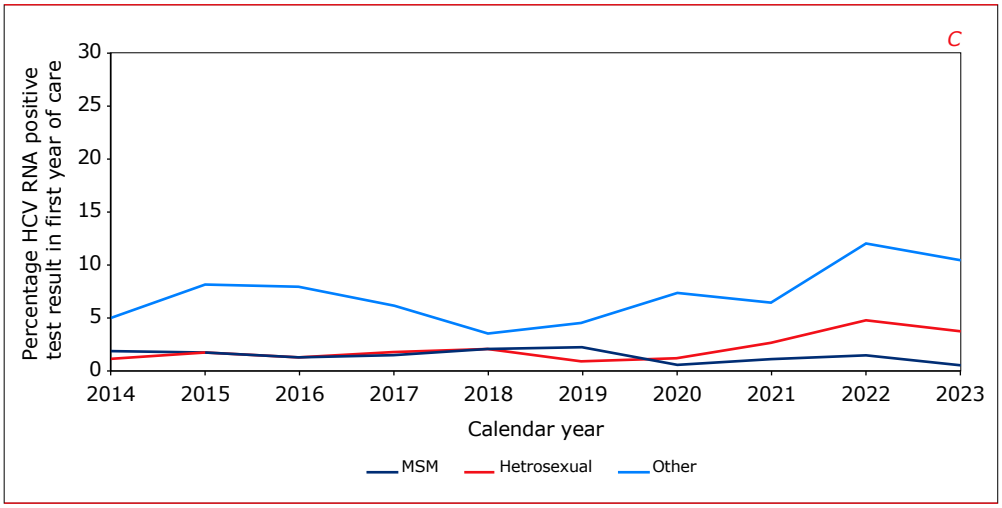
Number of diagnoses of primary HCV and HCV reinfections in the last 10 years

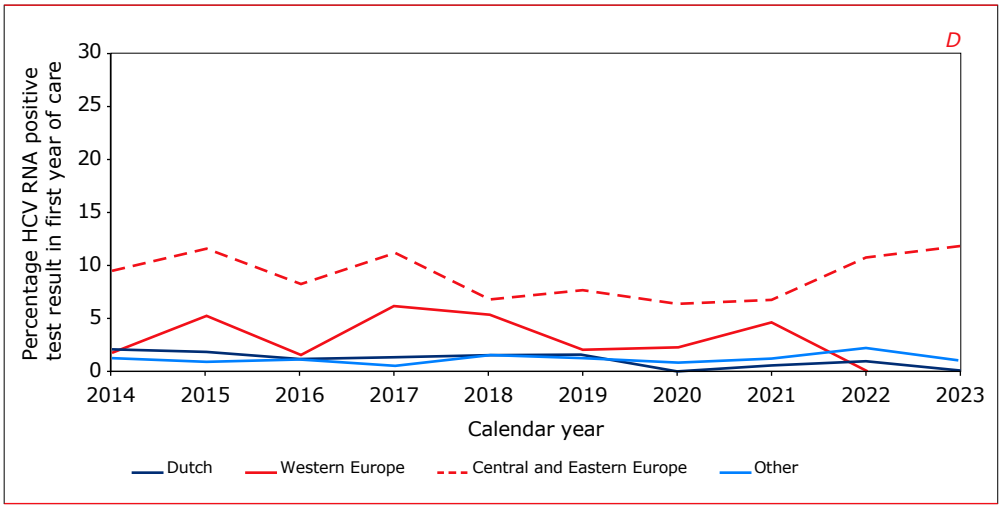
The annual number of primary HCV diagnoses (i.e., with detectable HCV RNA) and HCV reinfections has decreased from 142 and 172 cases in 2014 and 2015 to 44 and 47 in 2020 and 2021. The decreasing trend is levelling off with 57 and 52 cases in 2022 and 2023, respectively (*Figure 6.3A*). During these years, primary HCV was more often diagnosed among individuals from Eastern Europe compared to earlier years. Notably, the proportion of recent primary HCV infections and HCV reinfections is decreasing.

Figure 6.3: (A) Absolute number of diagnoses of primary hepatitis C virus (HCV) co-infection with detectable HCV RNA, and prevalence of: (B) detectable HCV RNA, per calendar year, (C) primary HCV among individuals newly entering care in the Netherlands stratified by transmission risk group (the category PWID is combined with the category other modes of HIV transmission, due to the small number of PWID newly entering into care, (D) primary HCV among individuals newly entering care in the Netherlands stratified by region of origin.









Prevalence of individuals with detectable HCV RNA

Figure 6.3B shows the percentage of individuals with a positive HCV RNA over calendar time. Individuals contributed follow-up time to the analysis if they were in care in a specific calendar year. The HCV RNA positivity was based on a last available HCV RNA test result before the end of that calendar year. The overall percentage of individuals with detectable HCV RNA varied between 2.7% in 1998 and 5.0% in 2008, before dropping to 0.3% in 2023. In MSM, the highest percentage of HCV RNA positivity was 4% in 2014; by 2022, the percentage of positive HCV RNA tests in this group had decreased sharply to 0.22% in 2021 and stabilized around 0.20% in more recent years.

Prevalence of individuals newly entering into care in the Netherlands

The prevalence of individuals with detectable HCV RNA at time of newly entering into care was between 0.5% and 2.2% among MSM (*Figure 6.3C*). However, in more recent years, an increase in the prevalence of detectable HCV RNA was seen among individuals who acquired HIV through heterosexual contact and other modes of transmission including PWID. Stratified prevalence of detectable HCV RNA by region of origin indicated that this increase was within individuals originating from European countries other than the Netherlands, mainly eastern and central Europe (*Figure 6.3D*).

Incidence of new HCV infections over time

The incidence of primary infection is calculated for individuals with a first documented HCV infection, based on the date of their first positive HCV antibody or HCV RNA test result. This paragraph describes the incidence of recent HCV infection, including only cases of primary recent HCV infection (first diagnosis of HCV). The definition of recent HCV infection is consistent with the one given in the European AIDS Treatment Network's (NEAT) preferred criteria[19]. We have expanded this definition to include alternative criteria[19,20]. This alternative definition is based on (i) detectable HCV RNA associated with an acute rise in alanine aminotransferase (ALT) greater than five times the upper limit of normal (above 200 U/l), and (ii) a documented normal ALT within the past 12 months, together with (iii) no change in antiretroviral regimen in the last six months. As SHM has only routinely collected ALT levels since 2012, incidence rates including the alternative criteria are reported from 2012 onwards.

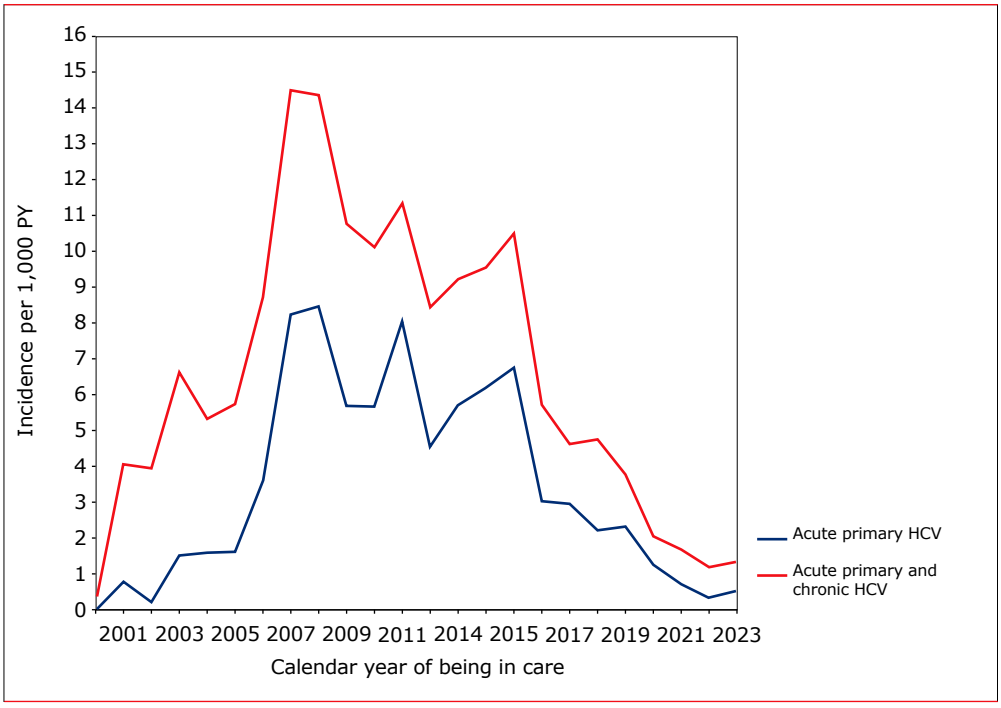
There were important differences in the incidence of the first diagnosis of recent HCV infection in terms of HIV transmission category. The vast majority of recent HCV infections occurred in MSM (n=819/873 [94%]). In contrast to the high prevalence of HCV in PWID or former PWID, the overall incidence of recent HCV in this group was low, occurring in only seven cases. This is probably due to the high background prevalence of HCV infection in former PWID, the fact that injecting drug use has become very uncommon in the Netherlands, and the effective harm-reduction programmes implemented in addictive care centres in the Netherlands. Thirty-three cases occurred among individuals who had acquired HIV heterosexually.

Figure 6.4 shows both the incidence of recent primary HCV infection and all primary HCV diagnoses among MSM over time. The overall rate of primary HCV infection was 6.8 per 1,000 person years (PY) (95% confidence interval [CI]6.4-7.12). The incidence of primary infection increased from 0.46 per 1,000 PY (95% CI 0.05-1.67) in 2002 to a peak of 8.6 per 1,000 PY (95% CI 6.6-11.2) in 2007

and decreased to 0.4 per 1,000 PY (95% CI 0.6-1.9) in 2022. When looking at those with recent HCV, the overall rate of recent HCV infection among MSM was 3.7 per 1,000 PY (95% CI 3.5-4.0).

When the preferred NEAT recent HCV definition was used, the incidence increased from 0 diagnoses per 1,000 PY in 2000, to a peak of 8.7 and 8.6 per 1,000 PY in 2007 and 2008, respectively. By 2015, the incidence was 7.6 diagnoses per 1,000 PY. It then declined to 3.8 per 1,000 PY in 2016, before further decreasing to 1.7 diagnoses per 1,000 PY in 2020, 0.48 per 1,000 PY in 2022 and 0.80 per 1,000 PY in 2023.

Figure 6.4: *Incidence of recent primary hepatitis C infection (blue line) and all recent primary and chronic HCV diagnoses (red line) among men who have sex with men per calendar year.*



Legend: *HCV = hepatitis C virus.*

Treatment for HCV infection

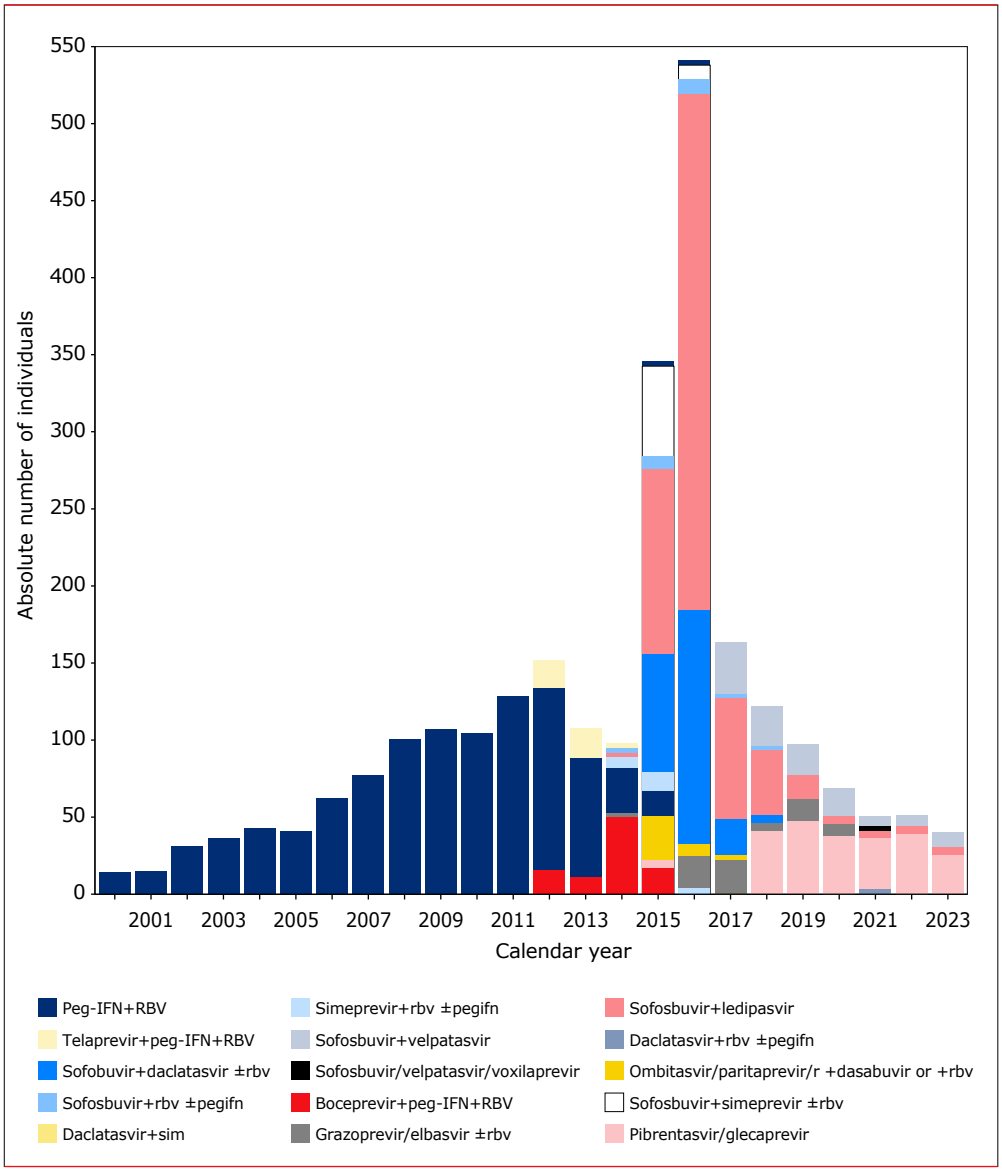
The primary aim of HCV treatment is to achieve a sustained virological response (SVR)[23] and the treatments used have changed markedly in recent years. In the past, treatment consisted of interferon alpha (IFN alpha), and subsequently pegylated interferon alpha (PEG-IFN alpha), in combination with ribavirin (RBV) for a period of 24 or 48 weeks, depending on HCV genotype.

In April 2012, the first generation HCV NS3/4a protease inhibitors (PI) boceprevir and telaprevir (DAAs active against HCV genotype 1) became available in the Netherlands[24,25]. 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 with chronic HCV, regardless of fibrosis state. Shortly thereafter, additional novel DAAs became available. An overview of DAA-containing HCV treatment combinations currently available in the Netherlands can be found at https://hcvrichtsnoer.nl/.

Figure 6.5 shows the absolute number of individuals who have started HCV treatment per calendar year. Of the individuals ever diagnosed with primary chronic or recent HCV, or a reinfection, 1,934 have ever received HCV treatment; of those, 675 have received HCV treatment more than once (this includes people who were unsuccessfully treated and those who reacquired HCV after prior successful treatment). In total, documented regimens comprised:

- 1001 regimens with (peg-) interferon+ RBV;
- 137 regimens with first generation PI; and
- 1,471 regimens with all-oral direct-acting antiviral treatment (DAAs).

Figure 6.5: *Number of individuals with HIV/HCV starting hepatitis C treatment per calendar year.*



Legend: *HCV=hepatitis C virus; RBV=ribavirin; PEG-IFN=pegylated interferon*

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[26]. 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 DAAs

In total, at the time of the database lock on 1 May 2024, 1,319 individuals were known to have started a DAA regimen between 2014 and 2024; 152 of those had been treated more than once with a DAA regimen with, in total, 1,471 treatment episodes. The most common reasons for receiving DAA treatment more than once were: reinfection after earlier DAA treatment-induced clearance (n=75), and no SVR or discontinuation of first DAA treatment episode due to a lack of early virological response (n=36), or toxicity (n=8).

Of the total 1,471 DAA treatment episodes, 15 occurred in 2014, 310 in 2015, and 547 in 2016. The number of treatment episodes subsequently decreased to 39 in 2023 (*Figure 6.5*).

The most frequently used DAA regimens were:

1. sofosbuvir plus ledipasvir +/- RBV (n=605);
2. sofosbuvir plus daclatasvir +/- RBV (n=263);
3. pibrentasvir/glecaprevir (n=232) (most commonly used regimen in 2022 and 2023);
4. sofosbuvir plus velpatasvir (n=123).

Treatment outcomes

HCV RNA data were collected up to 1 May 2024. At that point, 1,437 out of 1,471 treatment episodes had been completed with one of the DAA regimens, and sufficient time had elapsed since discontinuation of treatment to enable calculation of the SVR12 rate. In 1,422 treatment episodes, follow up HCV RNA data was available and for 15 there was no data after treatment discontinuation:

- In 1,386 of the 1,422 treatment episodes (96%), SVR12 was achieved.
- No SVR was achieved in 36 treatment episodes among 33 individuals.
- For the remaining 15 treatment episodes, no follow-up data on SVR were available: four people died shortly after being treated, and six cases had there last clinical visit shortly after treatment discontinuation. For the remaining five cases there were no reported HCV RNA tests available to assess treatment outcome at time of database closure.

SVR rates were comparable for individuals who received HCV treatment for the first time and those with prior HCV treatment. SVR was lower for individuals with severe liver disease (96% vs 98%, p=0.006). In terms of HIV transmission risk groups, SVR rates were 98% among MSM (98%), 94% among PWID or former PWID, and 96% among individuals who acquired HIV through heterosexual contact (p=0.02).

Among the 33 individuals who did not achieve SVR:

- 22 were successfully retreated with another DAA regimen;
- seven were not retreated, three individuals have died and one has moved abroad;
- three were unsuccessfully retreated; and
- the remaining individual had an awaiting SVR status at time of database closure.

- In total 15 mutation tests were documented among the 33 individuals who did not achieve SVR.
  - 7 mutations among 4 individuals were identified:
    - 4 mutations in the NS5A region
    - 3 mutations in the NS3 region
  - All mutations were identified after the first treatment failure.
  - There was no information on mutations for the three unsuccessfully retreated individuals.

HCV reinfection

Reinfection with HCV following successful treatment or spontaneous clearance has been reported mainly in MSM living with HIV[27,28], with high rates of reinfection found among MSM in the Netherlands, Germany[29] and the United Kingdom[30,51].

To identify possible HCV reinfection among individuals who previously had HCV, we selected people who initially achieved an SVR after receiving any type of HCV treatment, and individuals with spontaneous clearance of HCV. In total, 2,263 individuals were susceptible for HCV reinfection (1,665 after SVR, 598 after spontaneous clearance). Of those 2,263 individuals, 365 reinfections among 309 individuals (14%) were documented. The median time between SVR or spontaneous clearance and HCV reinfection was 1.4 years (IQR 0.7-3.1).

Most individuals who became reinfected were MSM (259 out of 309, or 84%). Another 29 were PWID or former PWID (9%). For the remaining 22 individuals, documented HIV transmission routes were heterosexual contact (n=10) and another or unknown (n=11).

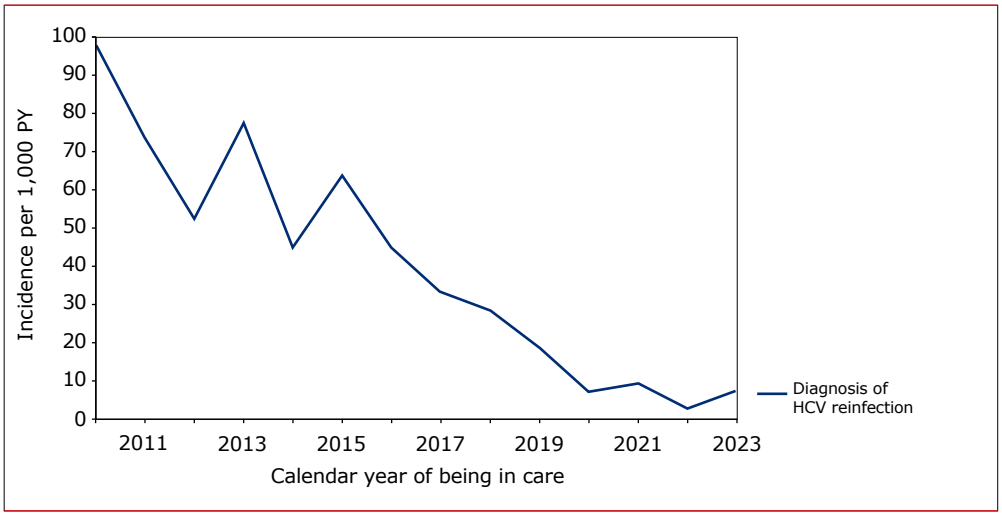
Of the 365 reinfections, 333 (91%) were retreated (256 with DAA, 77 with interferon+/- boceprevir/telaprevir). The median time to retreatment after reinfection diagnosis, stratified by calendar year of reinfection, was:

- Prior to 2015: 33 months (IQR 5-73)
- Between 2015 and 2017: 4 months (IQR 2-11)
- From 2018 onwards: 3 months (IQR 2-6)

We calculated the incidence of reinfection between 2010 and 2024. Follow-up time was from the date of SVR, date of spontaneous clearance, or from 1 January 2010 onwards, until the earliest date of HCV reinfection, death, or last known contact. The incidence of HCV reinfection for the total population was 20 reinfections per 1,000 PY (95% CI 18-22), and for MSM it was 26 reinfections per 1,000 PY (95% CI 23-29).

Because most reinfections occurred among MSM, the incidence of HCV reinfection over time is shown only for MSM (*Figure 6.6*). This incidence decreased from 98 reinfections per 1,000 PY in 2010 to 44 per 1,000 PY in 2015, and then declined to 11 reinfections per 1,000 PY in 2019, and 3.2 per 1,000 PY in 2023. A decline in the incidence of reinfection in MSM has been observed since 2015. However, the incidence of HCV reinfections showed some fluctuation in the more recent calendar years.

Figure 6.6: *Incidence of hepatitis C reinfection after earlier treatment-induced clearance among men who have sex with men, per calendar year.*



Legend: *HCV = hepatitis C virus; PY = person year.*

Continuum of care for those with diagnosed HCV

Figure 6.7 shows the HCV continuum of care, based on the number of people known to be in HIV care as of 31 December 2023. Individuals were categorised according to their last documented HCV infection episode. In total 2,303 individuals were linked to HIV care, 1,994 individuals had a primary HCV infection, and 309 individuals had a reinfection.

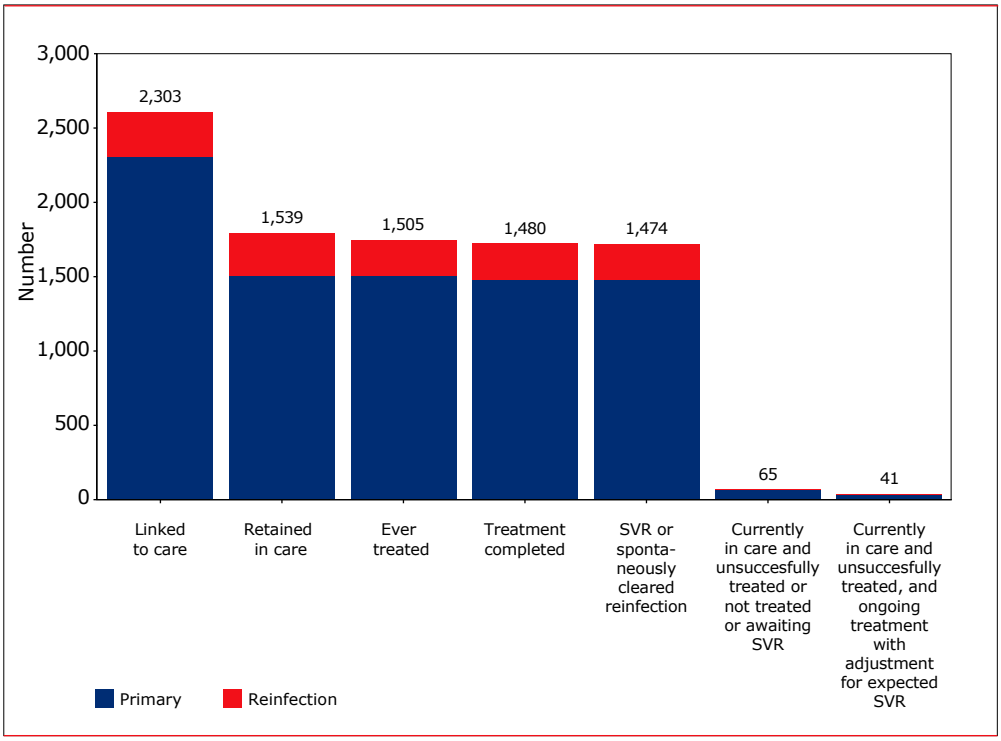
Of the 2,303 individuals linked to HIV care:

- 1,539 (69%) were retained in care;
- 764 individuals were no longer in care (441 had died; 184 had moved abroad; and 139 were lost to care);
- 1,505 (98%) of those still alive and in care had received treatment for HCV (with DAAs or a pegylated interferon-containing regimen);
- 1,480 (96%) of those still alive, in care and who had received treatment, had completed HCV treatment with enough data available to calculate the HCV treatment response (SVR12 for DAAs and SVR24 for the older regimens).

Overall, 1,459 of the 1,480 people in care in 2023 who completed treatment (99%) had achieved an SVR, including those who had achieved an SVR on a pegylated interferon-containing regimen and those who were retreated after earlier treatment failure. Another 15 individuals with HCV reinfection had a negative last HCV RNA test result, without documentation of HCV treatment. It is likely they spontaneously cleared their HCV infection, bringing the total of individuals with a treatment-induced or spontaneous clearance of their most recent HCV episode to 1,474.

As a result, 65 (4%) of the 1,539 individuals known to be alive and in care in one of the Dutch HIV treatment centres on 31 December 2023, were still in need of HCV treatment: 34 (2%) individuals had never been treated for HCV. Forty-four percent of the individuals without treatment were born in the Netherlands, and 44% were born in Western, central or eastern Europe. All had started ART, but 2 the individuals who started ART, had detectable HIV RNA levels. The percentage untreated was higher among PWID (4%), people who acquired HIV through heterosexual contact (6%), and people with an unknown HIV transmission mode (5%), than among MSM (1%). Of the 25 individuals for whom SVR could not yet be calculated, all had been treated with novel DAA combinations. For that reason, we have extrapolated the observed DAA SVR rate for these individuals and assumed that 25 of the 24 (96%) will achieve SVR. This results in a more realistic estimate of individuals (65-24=41) who have yet to be treated or were unsuccessfully treated.

Figure 6.7: Hepatitis C continuum of care.



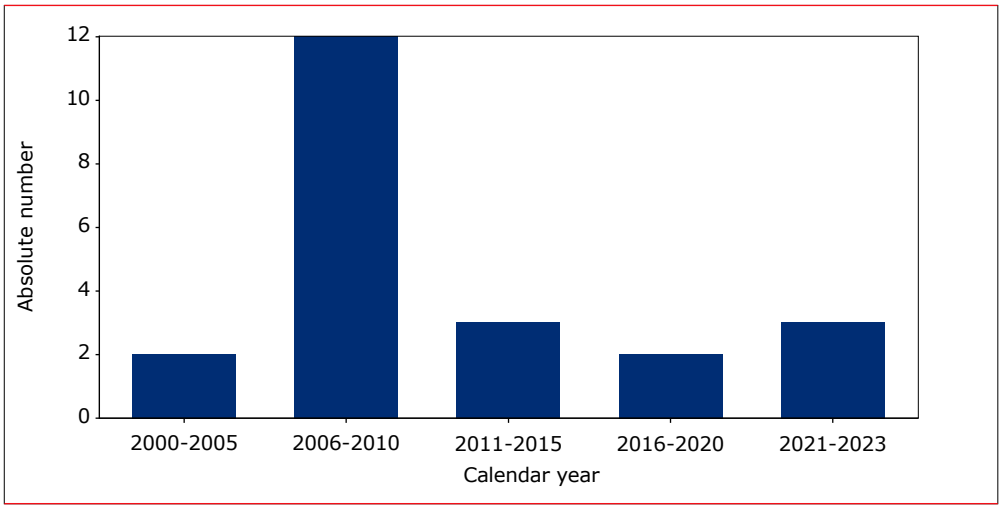
***Legend:** SVR=sustained virological response.*

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 1,750 of the 2,098 individuals with HCV and without other viral hepatitis (i.e. HBV or HDV). A review of these additional data shows that severe chronic liver disease was considered to be present (presumptive and definitive categories combined) in 503 (23%) of the 2,098 individuals with HCV co-infection, and 29% of those with additional liver-related data. Definitive severe chronic liver disease was documented for 124 (6%) individuals with HCV co-infection.

Between 1998 and 2023, 23 (1.1%) cases of hepatocellular carcinoma (HCC) were reported among 2,098 individuals with HCV and without other viral hepatitis (i.e. HBV or HDV). *Figure 6.8* shows that the annual number of new HCC diagnoses declined from 2010 onwards. 15 of the 23 individuals with HCC were born in the Netherlands. In recent years, there were no cases of HCC reported among DAA treated individuals without a known diagnosis of cirrhosis or fibrosis.

Figure 6.8: *Absolute number of annually-reported HCC cases among individuals with HCV and without other chronic viral hepatitis coinfections (i.e., HBV and HDV) over time.*

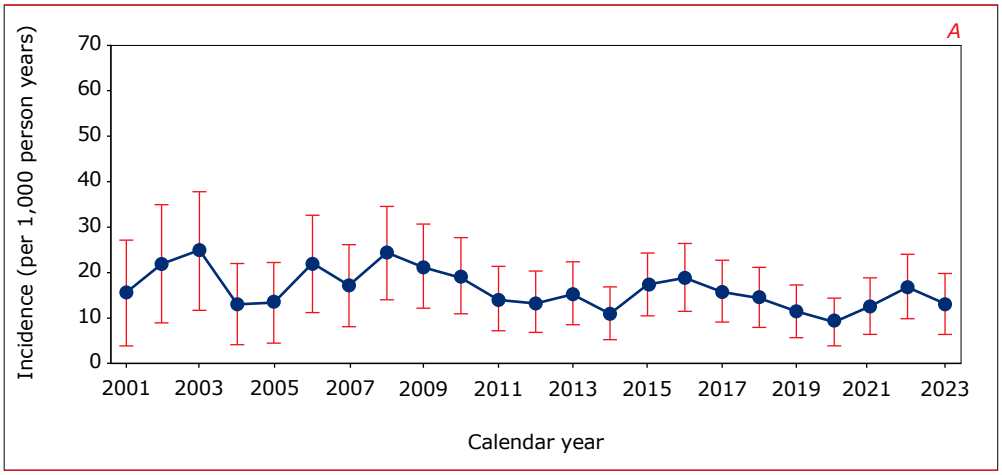


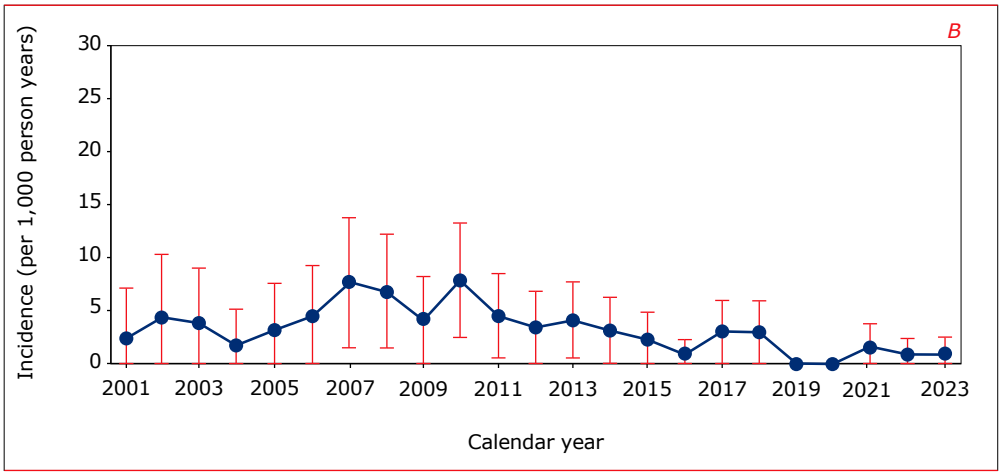
Mortality

All-cause mortality

Among the 2,098 individuals with HCV and without other viral hepatitis (i.e. HBV or HDV), 19% died from any cause. For individuals with HCV the incidence rate of death from any cause, adjusted for age and gender of the SHM population, was 18.9 per 1,000 PY in 2002-11, and 14.3 per 1,000 PY from 2012 onwards (*Figure 6.9A*). In MSM with HCV, these incidence rates were 7.5 per 1,000 PY in 2002-11, and 6.3 per 1,000 PY from 2012 onwards. In PWID with HCV, these incidence rates were 37.2 per 1,000 PY in the period 2002-11, and 37.6 per 1,000 PY from 2012 onwards.

Figure 6.9: Annual: (A) all-cause mortality rate, and (B) mortality related to liver disease (adjusted for age and gender of the SHM population), in 2,098 individuals with HIV who were ever diagnosed with recent or chronic HCV and without other viral hepatitis (i.e. HBV or HDV).





Liver-related mortality

In total, 72 (3%) individuals with HCV and without other viral hepatitis (i.e. HBV or HDV) died of a liver-related cause between 2002 and 2023. For individuals with HCV, the incidence rate of death from a liver-related cause, adjusted for age and gender of the SHM population, was 5.1 per 1,000 PY in 2002-11. This decreased to 1.9 per 1,000 PY from 2012 onwards (*Figure 6.9B*). In MSM with HCV, these incidence

rates were 2.6 per 1,000 PY in 2002-11 and 0.8 per 1,000 PY from 2012 onwards. In PWID with HCV, these incidence rates were 8.2 per 1,000 PY in 2002-11 and 4.2 per 1,000 PY from 2012 onwards.

Hepatitis B virus (HBV)

***Box 6.2:** Definitions of hepatitis B serological profiles.*

	HBV serological results		
	HBsAg	**Anti-HBs antibody**	**Anti-HBc antibody**
Active HBV infection*	Pos	–	–
HBsAg-negative phase with anti-HBs	Neg/ND	Pos	Pos
HBsAg-negative phase without anti-HBs	Neg	Neg	Pos
Vaccinated†	Neg	Pos	Neg/ND
Non-immune‡	Neg/ND	Neg	Neg

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

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

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

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

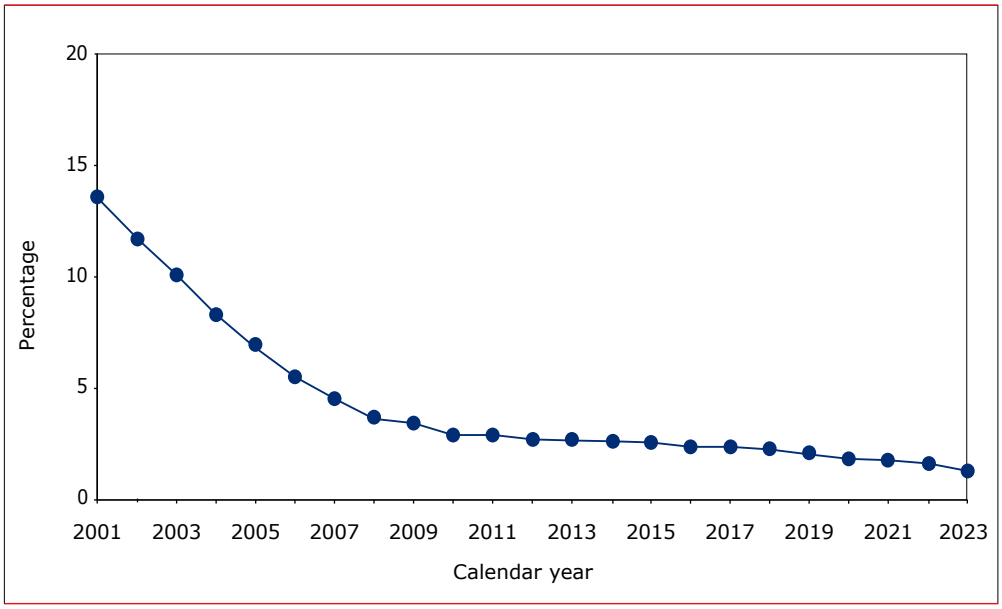
HBV screening

Ninety-seven percent of the 30,967 individuals living with HIV ever registered in the SHM database have been screened for at least one serological marker of HBV, comprising:

- Hepatitis B surface antigen (HBsAg)
- Anti-hepatitis B surface (anti-HBs) antibodies, and/or
- Anti-hepatitis B core (anti-HBc) antibodies

Screening for HBV infection in individuals living with HIV in care has improved over calendar time. In 2001, 13.6% of individuals had not been screened for HBV infection (*Figure 6.10*). Since then, the percentage of individuals living with HIV without HBV screening has decreased markedly, with 1.3% of all individuals living with HIV in care having no measured HBV serological markers in 2023 (*Figure 6.10*).

Figure 6.10: Percentage of individuals in care without any hepatitis B virus serological test per calendar year of care.



HBV serological profiles

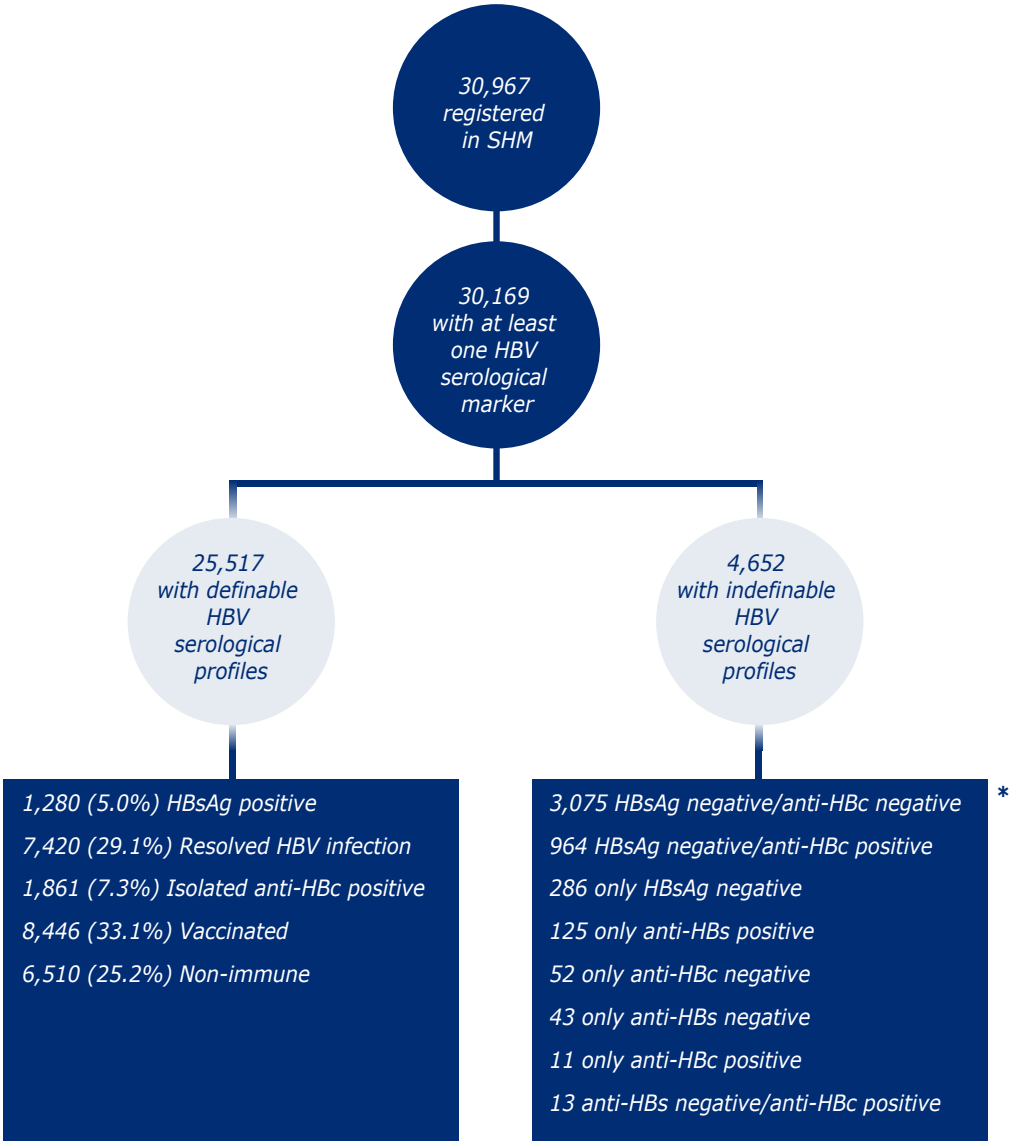
HBV serological profiles could be defined for 25,517 (85%) of the 30,169 screened individuals (*Figure 6.10*). A full HBV serological battery is not routinely performed in individuals living with HIV; therefore, any results from an HBV serological test were assumed to remain the same over time until a new serological test was carried out. The distribution of HBV serological profiles at the last visit are given in *Figure 6.11*.

The remaining 4,652 (15%) individuals either:

- had insufficient information to establish an HBV serological profile (n=4,569); or
- were previously HBsAg-positive, no longer had anti-HBc antibodies and did not have anti-HBs antibodies (n=83)

The demographic characteristics of people with definable HBV serological profiles are compared in *Table 6.3*.

Figure 6.11: *Flowchart of individuals living with HIV registered in the SHM database with testing for hepatitis B virus (HBV). Information was obtained from the most recent serological result.*



**The 83 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 6.3: Demographic characteristics of individuals living with HIV in care, according to their hepatitis B virus (HBV) serological profile as registered in the SHM database.

	HBV serological profile*, n (%)				
	HBV infection	HBsAg-negative phase with anti-HBs	HBsAg-negative phase without anti-HBs	Vaccinated	Non-immune
Total number	1,280	7,420	1,861	8,446	6,510
Sex at birth					
Male	1,089 (85%)	6,367 (86%)	1,406 (76%)	7,360 (87%)	4,771 (73%)
Female	191 (15%)	1,053 (14%)	455 (24%)	1,086 (13%)	1,739 (27%)
Region of origin					
The Netherlands	522 (41%)	3,882 (52%)	695 (37%)	4,639 (55%)	3,504 (54%)
Europe	77 (6%)	508 (7%)	125 (7%)	675 (8%)	349 (5%)
Sub-Saharan Africa	327 (26%)	1,150 (16%)	578 (32%)	576 (7%)	768 (12%)
Caribbean/South America	149 (12%)	976 (13%)	173 (9%)	1,213 (15%)	969 (15%)
Southeast Asia	73 (6%)	317 (4%)	74 (4%)	280 (3%)	183 (3%)
Other	132 (10%)	647 (9%)	207 (11%)	1,063 (13%)	737 (11%)
HIV transmission group					
Men who have sex with men	696 (54%)	4,990 (67%)	774 (42%)	6,140 (73%)	2,901 (45%)
Heterosexual	394 (31%)	1,622 (22%)	669 (36%)	1,653 (20%)	2,835 (44%)
Injecting drug use	57 (4%)	245 (3%)	204 (11%)	81 (1%)	121 (2%)
Other	133 (10%)	563 (8%)	2!4 (12%)	572 (7%)	653 (10%)
ART	1,234 (96%)	7,230 (97%)	1,790 (96%)	8,337 (99%)	6,349 (98%)
Deaths	288 (23%)	1,264 (17%)	362 (19%)	507 (6%)	833 (13%)

**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; ART = combination antiretroviral therapy.*

Individuals with an HBV infection

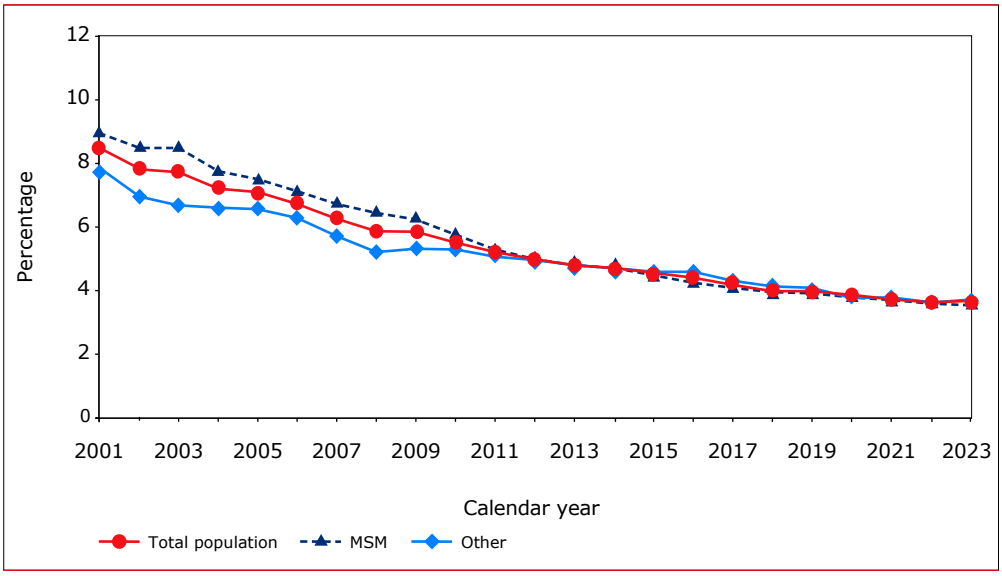
Prevalence of active HBV infection

Of the 30,169 individuals ever screened for at least one HBV serological marker, 29,820 had an HBsAg test. Of these, a total of 1,729 (6%) received a positive HBsAg test result. Over time, 232 (13%) of these individuals became HBsAg-negative and acquired anti-HBs antibodies (i.e. HBsAg-negative phase with anti-HBs) and an additional 217 (13%) became HBsAg-negative without acquiring anti-HBs antibodies (i.e. HBsAg-negative phase without anti-HBs). The remaining 1,280 (74%) individuals continued clinical care up until their last visit in care with HBsAg-positive serology.

The prevalence of HBsAg-positive serology was 7.7% in 2001, which slowly decreased to 3.5% in 2023 (*Figure 6.12*). This decline could be the result of several factors, including lower numbers of individuals with incident HBV (as a result of increased vaccination coverage among MSM[31], and the preventive effect of HIV treatment with an ART regimen that includes tenofovir disoproxil fumarate [TDF] / tenofovir alafenamide fumarate [TAF]), and a minority of individuals becoming HBsAg-negative during treatment[32].

As is the case for HCV co-infection, the percentage of individuals living with HIV in care who have chronic HBV is considerably higher than the rate found in the general Dutch population. Individuals with HBV were predominantly male (1,089 out of a total 1,280, or 85%), in line with those with HCV (*Table 6.3*). However, compared with people with HCV, those with HBV were more likely to have been born in sub-Saharan Africa and to have acquired HIV through heterosexual contact.

Figure 6.12: *Prevalence of HBsAg-positive serology per calendar year.*



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

Treatment for chronic HBV infection

The treatment for chronic HBV infection aims to reduce viral replication of HBV. As HBV DNA is the parameter most directly influenced by therapy with either nucleoside or nucleotide analogues, HBV DNA undetectability is an appropriate surrogate marker for treatment response. Persistent lowering of HBV DNA levels has also been shown to reduce the risk of HCC and overall mortality in individuals with HIV-HBV[33,34]. A few antiviral agents used for treatment of HIV, such as lamivudine, and particularly TDF/TAF, are also active against HBV.

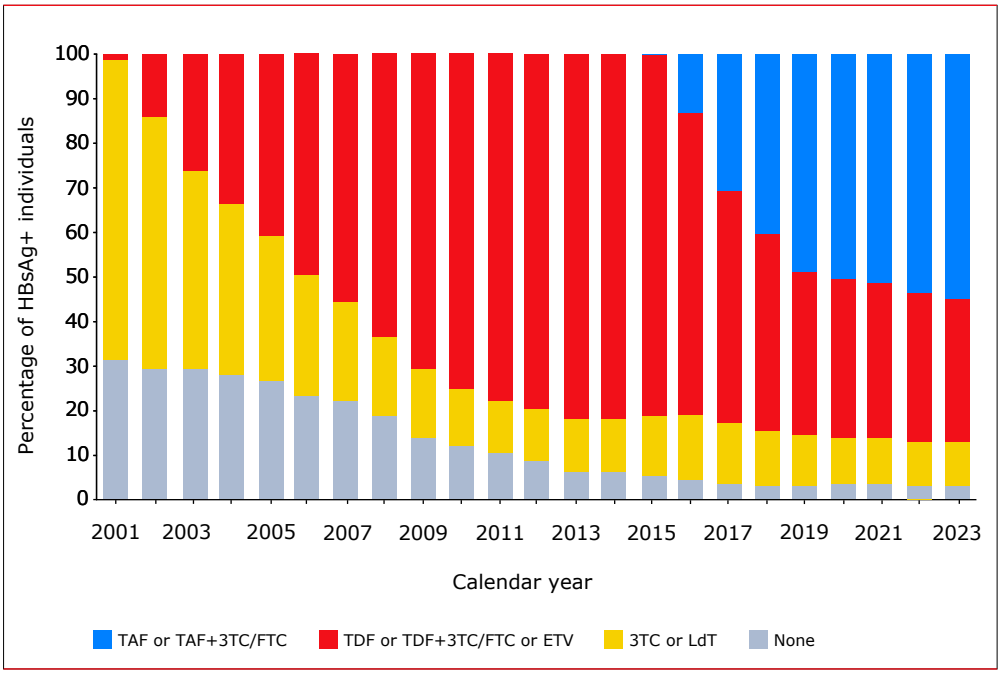
Of the 1,729 individuals with HIV in the SHM database who have ever had an HBsAg-positive serological test result, 1,668 (96%) ever received an ART regimen that included one or more agents with activity against both HIV and HBV. The reasons the remaining 61 individuals never received anti-HBV treatment included:

- death prior to start of treatment (n=16);
- loss to follow up (n=43); or
- lack of sufficient information (n=2).

Most people with active HBV received treatment containing lamivudine in 2001 (*Figure 6.13*). TDF-based ART (with or without lamivudine or emtricitabine) for combined HIV and HBV treatment was first used in 2002 (n=84/615, 14%) and became more commonly used than lamivudine in 2005. TAF-based ART (with or without lamivudine or emtricitabine) was first used in 2016 (n=135/1,063, 13%).

In 2023, most individuals with HBV were receiving TAF-based ART (n=611/1,110, 55%), closely followed by TDF-based ART (n=352/1,110, 32%), and lamivudine-based ART (n=113/1,110, 10%), or no anti-HBV-containing ART (n=34/1,110, 3%). Of the 34 individuals who were not on an anti-HBV containing ART, 24 (73%) no longer had HBsAg-positive serology.

Figure 6.13: 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; HBsAg+ = hepatitis B surface antigen positive.*

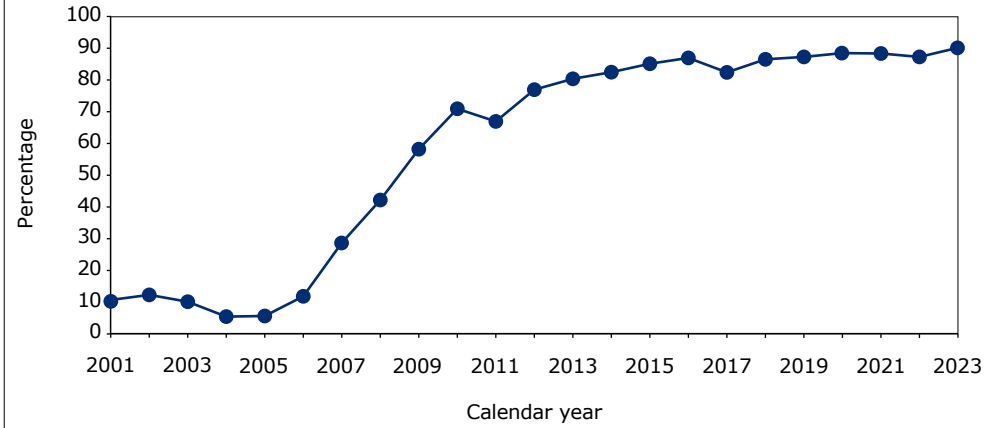
Note: *The categories of anti-HBV agents were: none, 3TC or LdT, TDF or TDF+3TC/FTC or ETV, and TAF or TAF+3TC/FTC. 3TC and LdT should not be combined and TDF and ETV can be combined under special circumstances[35].*

We examined the HBV DNA levels per calendar year in the population of individuals with HIV and HBV. In many treatment centres, HBV DNA is not routinely collected after the first negative HBV DNA result during treatment with TDF/TAF, so long as HIV RNA is undetectable. Therefore HBV DNA measurements were available, on average, in 23% of individuals with HBV for each year.

Figure 6.14 shows the percentage of those over time with an undetectable HBV DNA level below 20 IU/ml, as a percentage of the total number of individuals with an HBV DNA measurement. For HBV DNA measurements with a detection limit other than 20 IU/ml, we used the detection limit of the specific assay (below 20, below 100, below 200, below 400, below 1,000, or below 2,000 IU/ml).

In 2001-2005, 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 ART, reaching 80% in 2013. In 2023, 90% of individuals with HIV and HBV had an undetectable HBV DNA level (*Figure 6.14*).

Figure 6.14: *Percentage of individuals with undetectable hepatitis B virus (HBV) DNA levels by assay, with a detection limit of <20, <100, <200, <400, <1,000, or <2,000 IU/ml HBV DNA per calendar year, regardless of HBeAg status.*



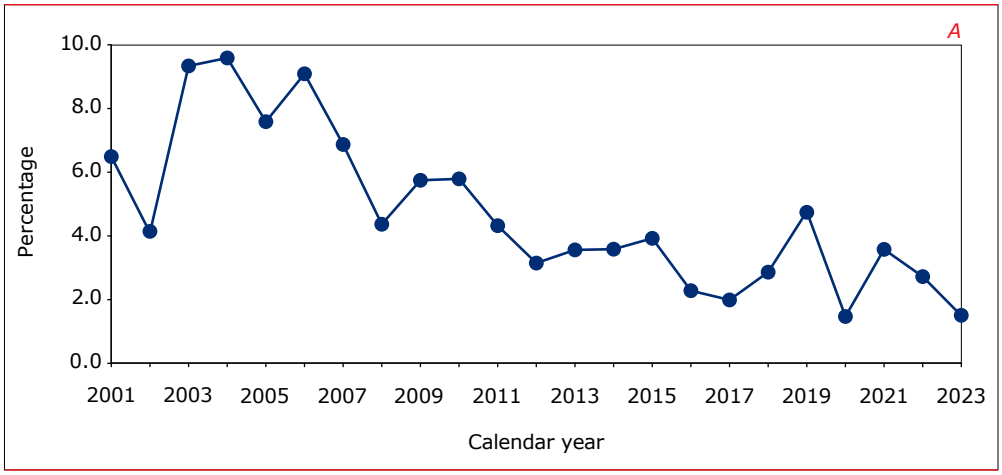
There are other serological outcomes associated with a more favourable prognosis in individuals with HBV[36]. Persistently negative hepatitis B "e" antigen (HBeAg) is associated with lower levels of HBV DNA replication. It also confers a favourable long-term outcome with low risk of cirrhosis and HCC, so long as transaminase and HBV DNA levels are low[37].

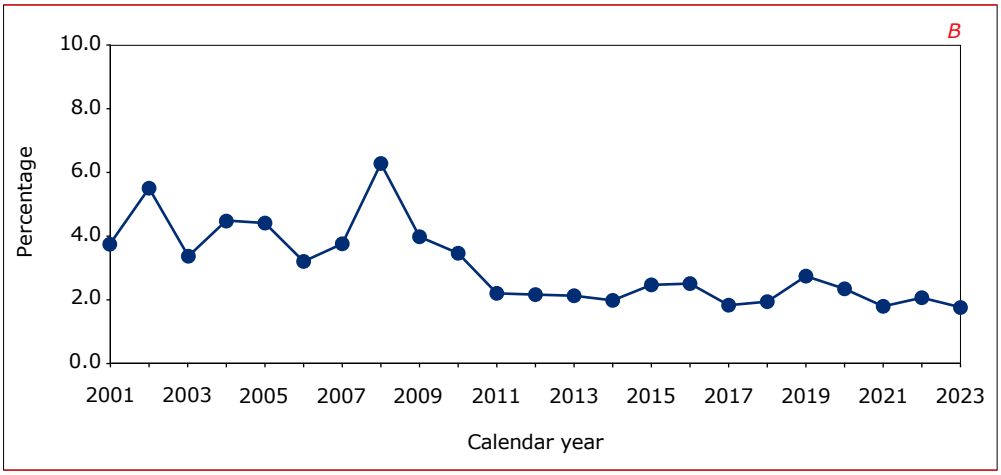
In those individuals with HBeAg-positive status, the loss of HBeAg, known as HBeAg seroclearance, is therefore a desired endpoint. Persistently negative hepatitis B surface antigen (HBsAg) is associated with reduced viral activity, very low risk of developing HCC, and improved survival. For all individuals with HBV, the loss of HBsAg, known as HBsAg seroclearance or "functional" cure, is the penultimate goal of HBV therapy.

We examined the rates of HBeAg and functional cure per calendar year in the population of individuals with HIV and HBV. For these analyses, any results from an HBV serological test were assumed to remain the same over time until a new serological test was carried out. The percentage of individuals with HBeAg seroclearance ranged from 4.1% to 9.6% between 2001 and 2010, and slowly declined to 1.5% in 2023 (*Figure 6.15A*). Similarly, the percentage of individuals with HBsAg seroclearance was higher between 2001 and 2010, ranging from 3.2% to 5.7%, and slowly declined to 1.7% in 2023 (*Figure 6.15B*).

Individuals with HIV-HBV who initiate ART at very low CD4+ cell counts, are more likely to have seroclearance due to an immuno-inflammatory reaction with accelerated CD4+ cell increases[38]. The higher percentages with seroclearance before 2010 could be due, in part, to the higher percentage of individuals with HIV and HBV initiating ART with severe immunosuppression during this period. It could also be due to the decrease in the number of individuals with recent HBV infection, who were more likely to clear their HBsAg, as TDF-containing ART became more widespread[32]. Furthermore, the number of HBeAg tests peaked in 2004 at 116, before slowly declining to 23 tests in 2023. The number of HBsAg tests peaked in 2008 at 231, before decreasing less dramatically to reach 117 tests in 2023. The lower percentage with seroclearance after 2010 might also be due to the lower testing rates in individuals with HIV and HBV.

Figure 6.15: *(A) Percentage of hepatitis B "e" positive (HBeAg) individuals with HIV and HBV having HBeAg-seroclearance, and (B) percentage of all individuals with HIV and HBV having hepatitis B surface antigen-seroclearance. Both are shown by calendar year.*

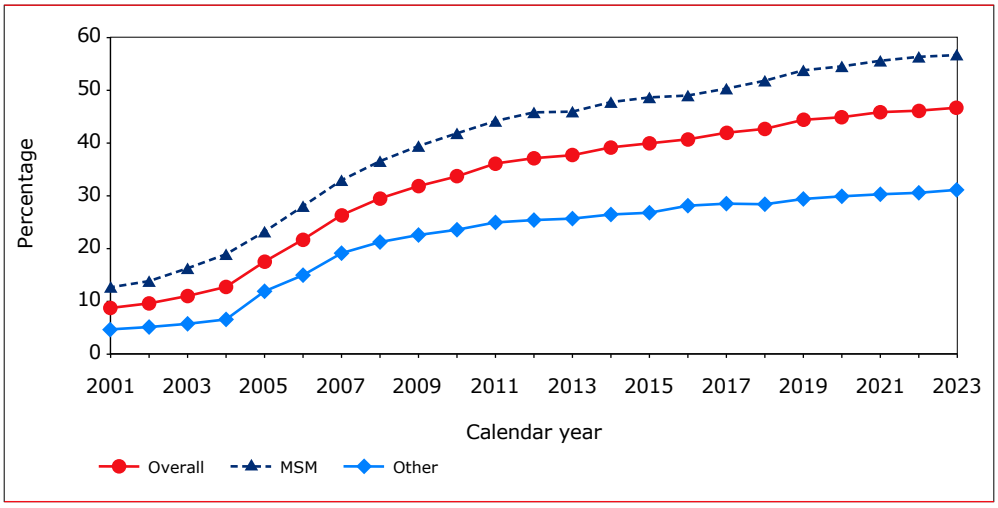




HBV vaccination in individuals living with HIV

Of the 24,548 individuals with definable HBV serological profiles, 8,446 (33%) 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 (without previous evidence of HBsAg-positive serology) were considered, the prevalence of HBV vaccination status increased from 9% in 2001 to 47% in 2023 *(Figure 6.16)*. The largest increase in HBV vaccination was observed in MSM, likely due to the national vaccination campaign targeting these individuals from 2002 onwards[31].

Figure 6.16: *Prevalence of hepatitis B vaccination per calendar year.*



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

HBV non-immune status in individuals living with HIV

Of the 25,517 individuals with definable HBV serological profiles, 6,510 (26%) had serological evidence of being non-immune and non-exposed to HBV at their last visit. When the 4,652 individuals with undefinable HBV serological profiles were considered, 91 of the 260 with an anti-HBs antibody test did not have detectable anti-HBs antibodies, and 3,792 of the 4,329 without an anti-HBs antibody test were not reported to have been vaccinated by their treating physician. Therefore, at most, 10,393 (34%) of the 30,169 individuals screened for HBV remained susceptible to infection at the time of their last visit (6,510 non-immune; 91 with an undefinable HBV profile and anti-HBs antibody negative; and 3,792 with an undefinable HBV profile and missing data on anti-HBs antibody status, and no physician-reported vaccination).

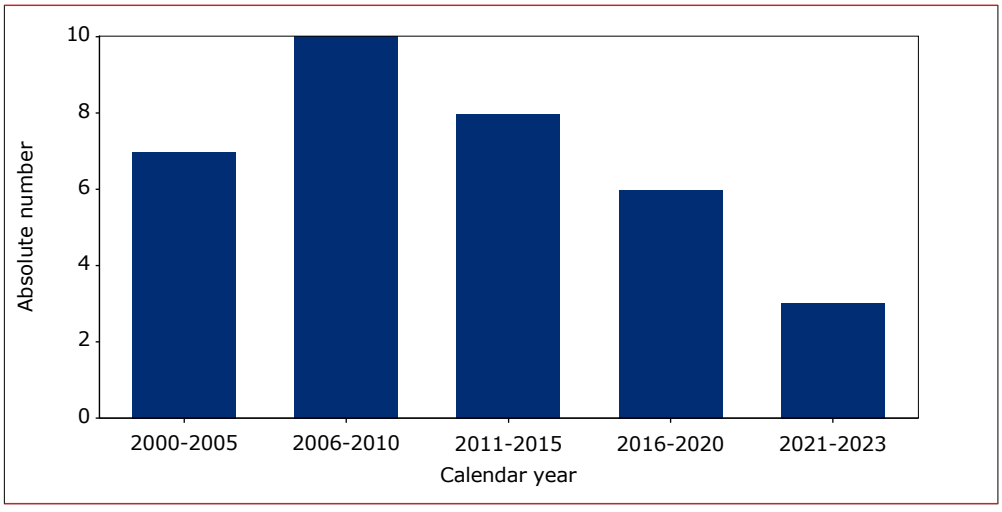
Individuals at risk, and MSM in particular, should be actively counselled about HBV vaccination. However, they may be protected from HBV infection by the use of tenofovir (TDF), or tenofovir alafenamide (TAF), as part of their ART regimen, according to findings reported by an international study, and one of the Dutch HIV treatment centres[39,40]. Data from SHM show that, of those people who remained at risk of acquiring HBV, 84% were being treated with an ART regimen that included TDF or TAF; for MSM, this percentage was 85%.

Liver-related morbidity

Additional data from liver biopsy pathology reports, transient elastography, radiology reports, or a combination of those sources, were available for 1,273 of the 1,584 individuals with HBV and without other viral hepatitis (i.e. HCV or HDV). A review of these additional data shows that severe chronic liver disease, according to our definition, was considered to be present (presumptive and definitive categories combined) in 263 (17%) of the 1584 individuals with HBV. Definitive severe chronic liver disease was documented for 76 (5%) with HBV.

Figure 6.17 shows that the annual number of new HCC diagnoses declined from 2010 onwards. HCC was found in 34 (2.2%) individuals with HBV co-infection, 18 of whom were born in the Netherlands, nine in sub-Saharan Africa, and three in South America. Roughly half (18, 52.9%) of HCC diagnosis were found in individuals with documented liver cirrhosis.

Figure 6.17: *Absolute number of annually-reported HCC cases among individuals with HBV and without other viral hepatitis (i.e, HCV or HDV) over time.*

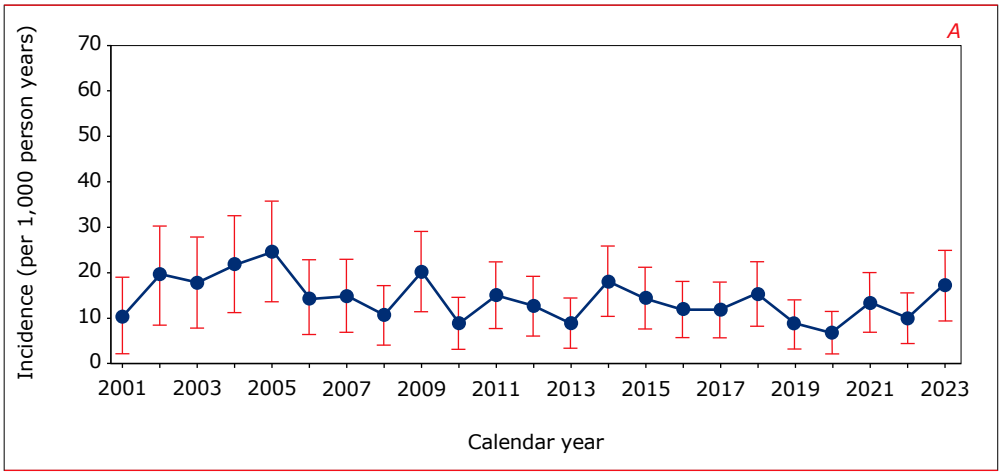


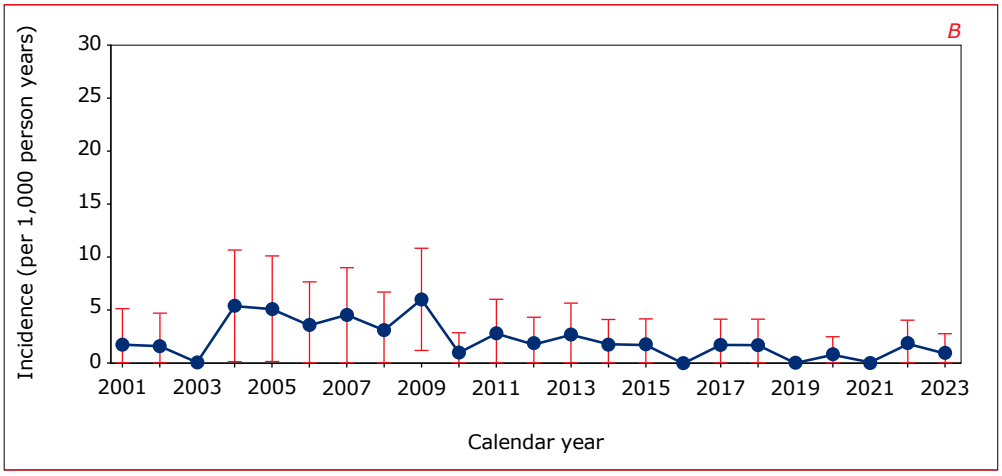
Mortality

All-cause mortality

Nineteen percent (n=308) of the 1,584 individuals with HBV and without other viral hepatitis (i.e. HCV or HDV) died of any cause. For individuals with an HBV infection the incidence rate of death from any cause, adjusted for age and gender of the SHM population, was 16.4 per 1,000 PY in 2002-11, and 12.5 per 1,000 PY from 2012 onwards (*Figure 6.18A*). In MSM with HBV, these incidence rates were 13.1 per 1,000 PY in 2002-11 and 10.6 per 1,000 PY from 2012 onwards. In PWID with HBV, these incidence rates were 68.5 per 1,000 PY in 2002-11 and 86.2 per 1,000 PY from 2012 onwards.

Figure 6.18: *Annual: (A) all-cause mortality rate, and (B) mortality related to liver disease (adjusted for age and gender of the SHM population), in 1,573 HIV-1-positive individuals who were ever diagnosed with active HBV and without other viral hepatitis (i.e., HCV or HDV).*





Liver-related mortality

In total, 35 individuals with HBV and without other viral hepatitis (i.e. HCV or HDV) died of a liver-related cause. For individuals with an HBV infection, the incidence rate of liver-related death, adjusted for age and gender of the SHM population, was 3.4 per 1,000 PY in 2002-11 and decreased to 1.2 per 1,000 PY from 2012 onwards (*Figure 6.18B*). In MSM with HBV, these incidence rates were 3.2 per 1,000 PY in 2002-11 and 1.2 per 1,000 PY from 2012 onwards. In PWID with HBV only, these incidence rates were 10.9 per 1,000 PY in 2002-11 and 8.1 per 1,000 PY from 2012 onwards.

Multiple infections with HBV, HCV and hepatitis D virus (HDV)

Prevalence of individuals with HBV-HCV, HBV-HDV and HBV-HCV-HDV

Of the 30,967 individuals living with HIV ever registered by SHM, 30,399 (98%) had been screened for HBV (i.e. HBsAg), HCV (i.e. anti-HCV antibodies) or HDV (i.e. IgG or IgM anti-HDV antibodies or presence of HDV RNA). Of those with HIV ever registered by 2023, there were:

- 225 (0.7%) individuals who ever had HBV-HCV;
- 23 (0.1%) individuals who ever had HBV-HDV; and
- 10 (<0.1%) individuals with HBV-HCV-HDV.

It should be noted that by 2023:

- 416 of the 1,729 (24%) individuals who ever had HBV had been tested for HDV;
- 33 (8%) of the 416 testing positive for HDV antibodies had an indication of past or current HDV infection;
- 20 of the 33 were tested for HDV RNA; and
- 13 of these were found to have detectable HDV RNA, indicating active HDV.

Morbidity and mortality in individuals with HBV-HCV, HBV-HDV and HBV-HCV-HDV

Of the 258 individuals with multiple viral hepatitis, 74 (29%) had presumptive or definitive severe chronic liver disease: 60 with HBV-HCV, seven with HBV-HDV and seven with HBV-HCV-HDV.

HCC was found in 6 (2%) individuals with multiple viral hepatitis: 5 with HBV-HCV, one with HBV-HDV and none with HBV-HCV-HDV. In the individuals with multiple viral hepatitis, 80 deaths were observed, of which 14 (18%) were liver-related. The number of overall and liver-related deaths, respectively, were distributed across co-infection groups as follows: 75 and 13 with HBV-HCV, one and one with HBV-HDV and four and none with HBV-HCV-HDV.

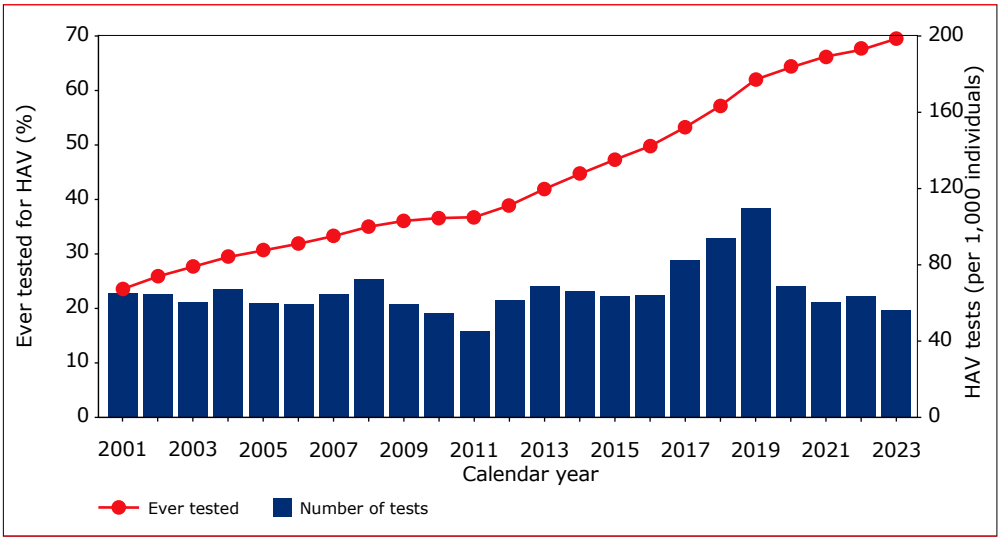
Hepatitis A virus (HAV)

HAV screening

Screening for HAV involves testing for IgG anti-HAV antibodies (to establish past or current HAV infection, or HAV vaccination response) and/or IgM anti-HAV antibodies (to establish acute HAV infection). Sixty-three percent (n=19,606) of the 30,967 individuals living with HIV ever registered in the SHM database have been screened for HAV. The frequency of screening for HAV in individuals living with HIV has been consistent over the past two decades (*Figure 6.19*).

Between 2001 and 2016, roughly 46 to 72 HAV tests per 1,000 individuals were conducted each year. In 2017, 2018 and 2019, screening frequency increased to 82, 94 and 110 HAV tests per 1,000 individuals per year, respectively. In 2020, screening frequency returned to 69 HAV tests per 1,000 individuals and was 57 HAV tests per 1,000 individuals in 2023. The percentage of individuals who have ever been tested for HAV was 24% in 2001, and steadily increased to 69% in 2023 (*Figure 6.19*).

Figure 6.19: *Percentage ever tested for anti-HAV antibodies and anti-HAV antibody testing frequency, per calendar year.*



Legend: *HAV = hepatitis A virus.*

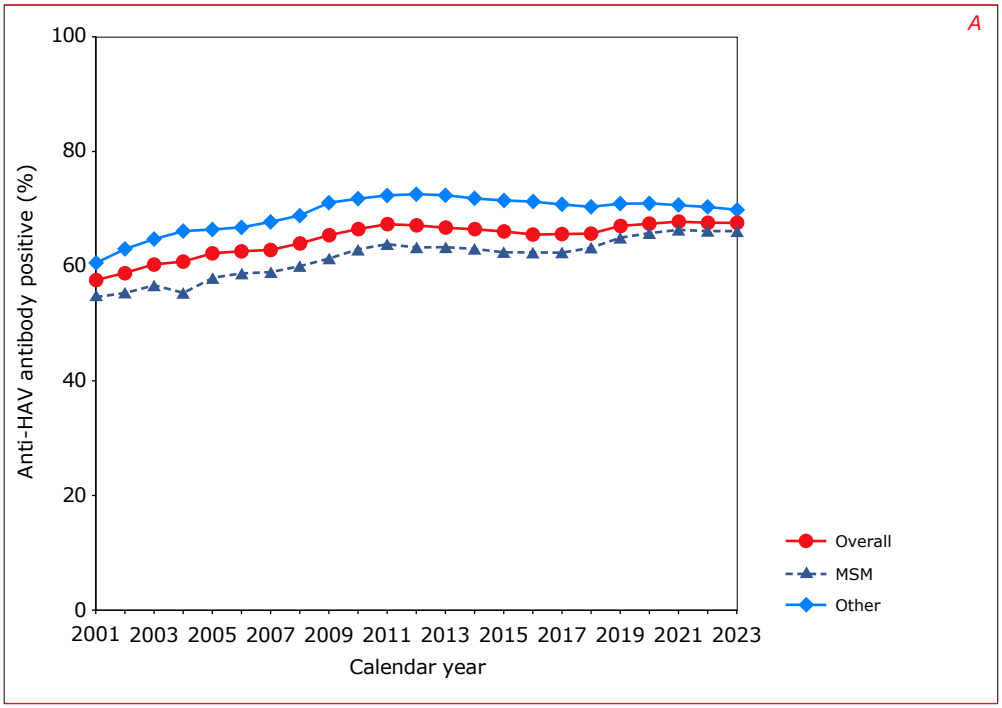
HAV seropositivity

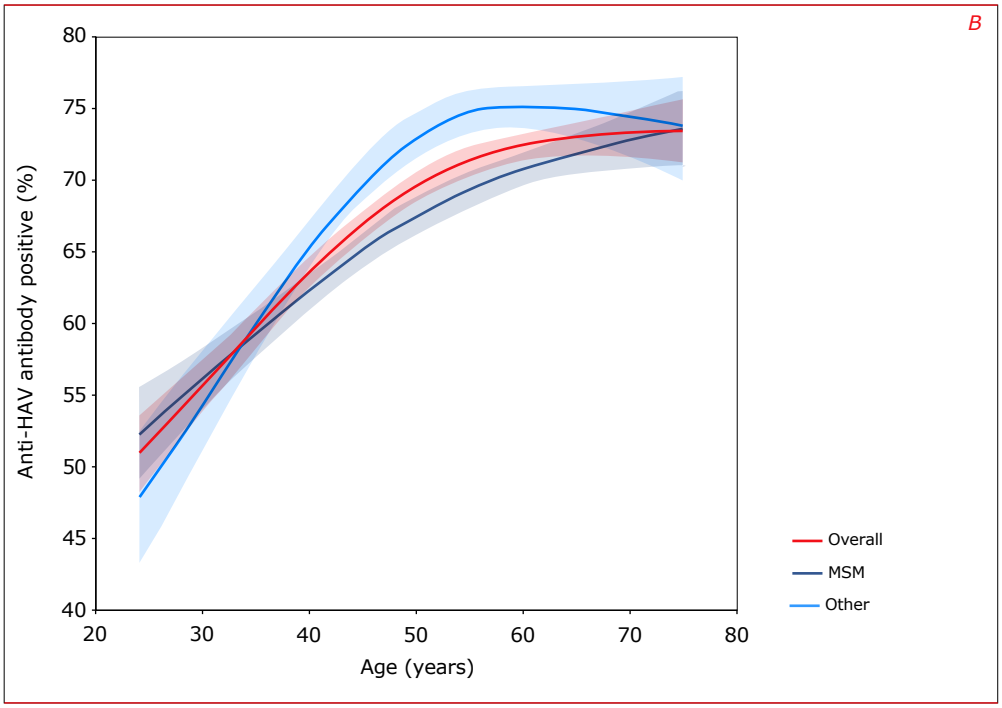
Of the 19,602 individuals ever screened for HAV, a total of 13,250 (68%) had a positive anti-HAV antibody test result:

- 66% were observed in MSM;
- 65% in PWID;
- 72% in heterosexuals; and
- 66% in people from other transmission groups.

The prevalence of anti-HAV antibody positivity was 57% in 2001 and then slowly increased to 68% in 2023 (*Figure 6.20A*). For MSM, the prevalence of anti-HAV antibody positivity was 55% in 2001, and it also slowly increased, reaching 66% in 2023. For all other transmission groups, the prevalence of anti-HAV antibody positivity was 60% in 2001 and 70% in 2023.

Figure 6.20: *Percentage with anti-HAV antibodies per: (A) calendar year, and (B) age in years.*





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

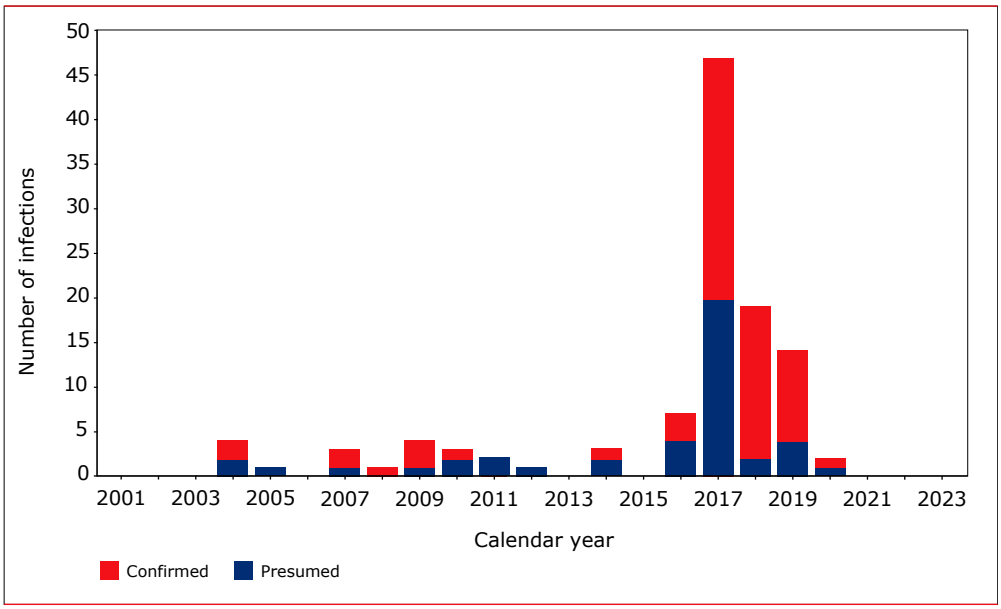
Epidemiological studies have highlighted the strong relationship between increasing anti-HAV antibody positivity and increasing age[41]. This age-dependent relationship was also observed in the 19,602 individuals ever screened for HAV (*Figure 6.20B*). Overall, anti-HAV antibody positivity was 58% for individuals below the age of 40, and 70% for those aged 40 and above. For MSM, anti-HAV antibody positivity was 58% for individuals below the age of 40, and 68% for those aged 40 and above. For all other transmission categories, anti-HAV antibody seropositivity was 58% for individuals below the age of 40, and 73% for those aged 40 and above.

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 2001 and 2021, there were 108 reported cases of acute HAV infection (n=69, presumed; n=39, confirmed), of which 86 (80%) were observed in MSM, 14 (13%) in heterosexuals, and 8 (7%) in those with other transmission categories.

Cases of acute HAV were first documented in 2001, and the number of acute HAV cases were lower than seven per year until 2017, when 47 cases of acute HAV infection were documented (n=27, presumed; n=20, confirmed) (*Figure 6.21*). This figure decreased to 19 in 2018 and 14 in 2019. Of the 82 documented cases occurring between 2017 and 2019, 71 (87%) were observed in MSM. This increase in HAV infections was part of a European-wide outbreak of HAV among sexually-active MSM in 201742. In 2023, there were no cases of acute HAV infection.

Figure 6.21: *Number of reported cases of confirmed and presumed acute HAV infection per calendar year.*

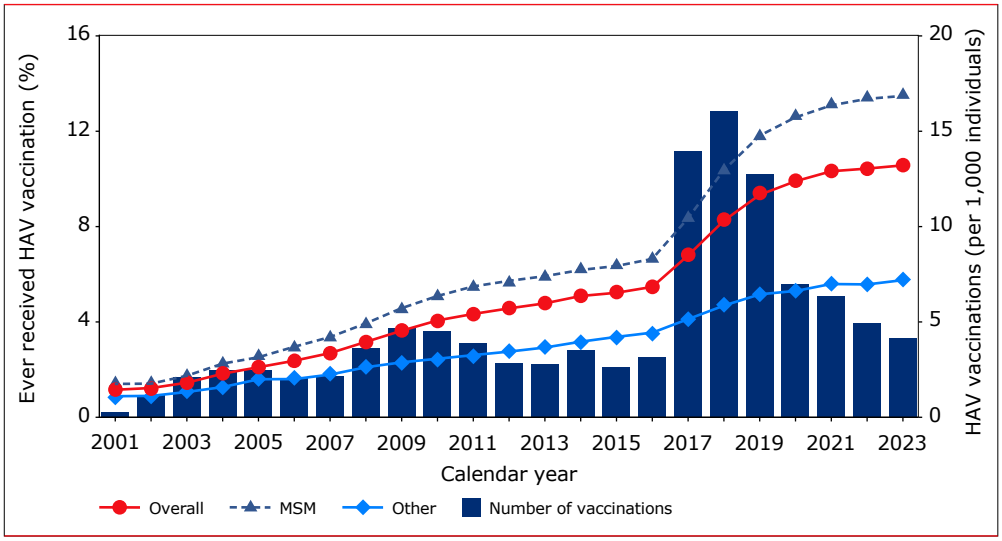


Of the 118 reported cases of acute HAV infection, 64 (54%) were recorded to have severe clinical symptoms. Severe chronic liver disease, according to our definition, was considered to be present (presumptive and definitive categories combined) in 21 (18%) of those with a reported acute HAV infection. 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 individuals living with HIV

Information on HAV vaccination status was obtained from clinical files and was unknown for the majority of individuals ever registered by SHM. Of the 30,967 individuals living with HIV ever registered in the SHM database, 2,519 (8%) 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)[43]. HAV vaccination frequency was consistently lower than, or equal to five vaccinations per 1,000 individuals living with HIV from 2001 to 2016. It increased substantially to 14 and 16 vaccinations per 1,000 individuals in 2017 and 2018, respectively (*Figure 6.22*). Accordingly, the percentage reported to have ever received an HAV vaccination was 1.8% in 2001, 4.0% in 2016, and 8.1% in 2023. In MSM, this percentage was 2.3% in 2001, 5.1% in 2016, and 10.9% in 2023.

Figure 6.22: *Percentage that ever received an HAV vaccination and HAV vaccination frequency per calendar year.*



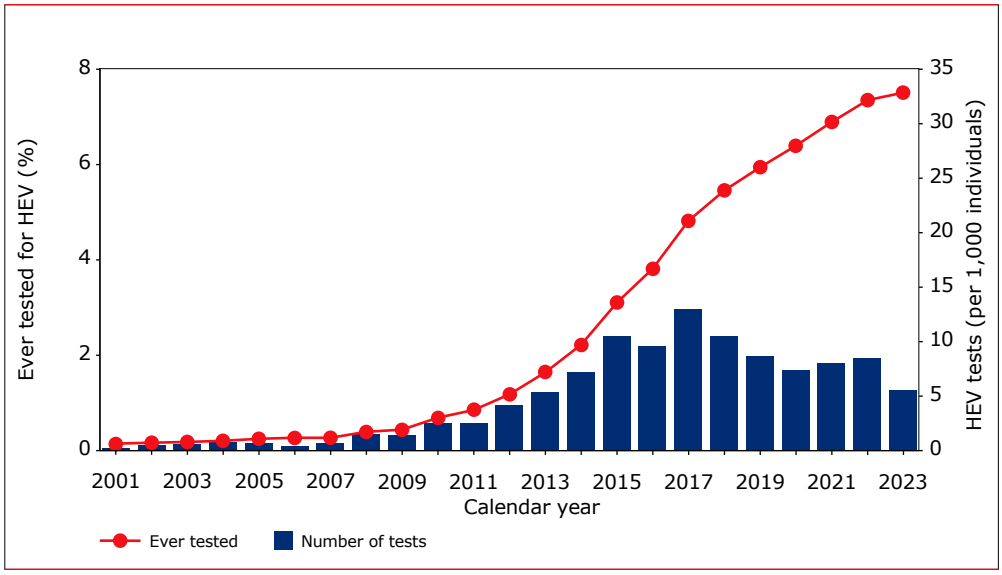
Legend: *HAV = hepatitis A virus; MSM = men who have sex with men.*

Hepatitis E virus (HEV)

HEV screening and seropositivity

Screening for HEV involves testing for IgG anti-HEV antibodies or HEV antigen (to establish past or current infection), or a combination of HEV RNA and/or IgM anti-HEV antibodies (to establish acute HEV infection). Six percent of the 30,967 individuals living with HIV ever registered in the SHM database have been screened for HEV. The screening frequency for HEV infection in individuals living with HIV in care was low between 2001 and 2010, reaching a maximum of two tests per 1,000 individuals (*Figure 6.23*). HEV testing frequency rapidly increased from three tests per 1,000 individuals in 2011, to 13 tests per 1,000 individuals in 2017. In 2023, this frequency was six tests per 1,000 individuals.

Figure 6.23: *Percentage ever tested for anti-HEV antibodies and anti-HEV antibody testing frequency per calendar year.*



Legend: *HEV = hepatitis E virus.*

Individuals with acute HEV diagnoses

Of the 2,000 individuals who were in care between 2001 and 2023, and who were ever screened for HEV, 267 (13%) were newly diagnosed as having past or current HEV infection (*Figure 6.24*). Of these individuals, 166 (62%) were MSM, 64 (24%) heterosexuals, six (2%) PWID, and 31 (12%) were from other transmission groups. The largest number of new diagnoses were observed between 2013 and 2020 (*Figure 6.23*), mainly due to the higher frequency of HEV testing among individuals living with HIV. The percentage of individuals newly diagnosed with past or current HEV infection ranged from 9% in 2004 to 14% in 2023 (*Figure 6.25*).

Of all individuals tested for HEV and in care between 2001 and 2023, there were 56 individuals diagnosed with acute HEV infection, of whom 40 were MSM, 9 were heterosexuals and 7 from other transmission groups. Only two of these cases were confirmed to have progressed to chronic infection (i.e., positive HEV RNA lasting more than three months). One of these individuals was treated with ribavirin and both were able to resolve their infection (i.e. achieve undetectable HEV RNA after chronic infection had been established).

Figure 6.24: *Number of individuals newly identified with past or current HEV infection and with acute HEV infection per calendar year. Blue bars represent the percentage of newly-identified HEV infections that were confirmed as acute HEV infections.*

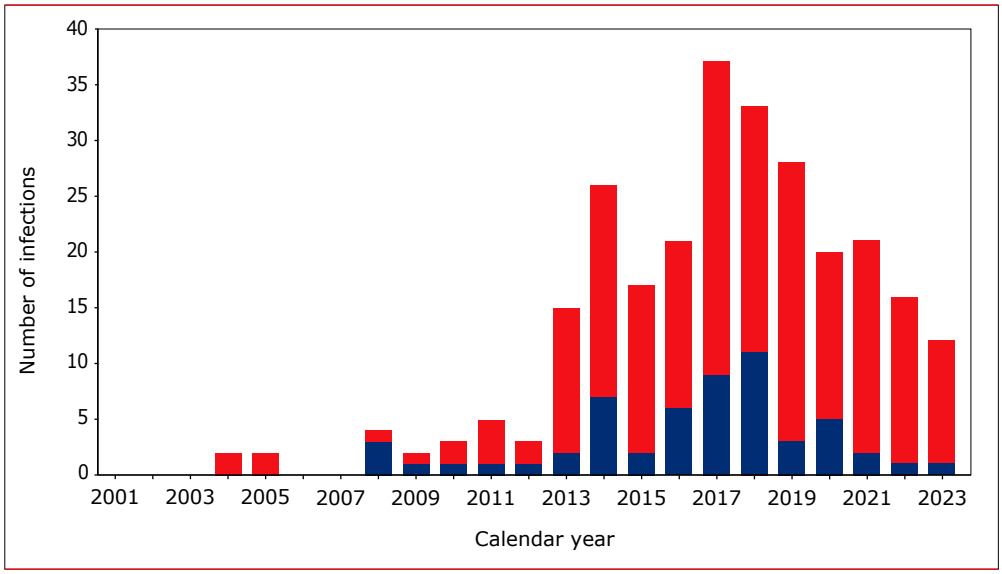
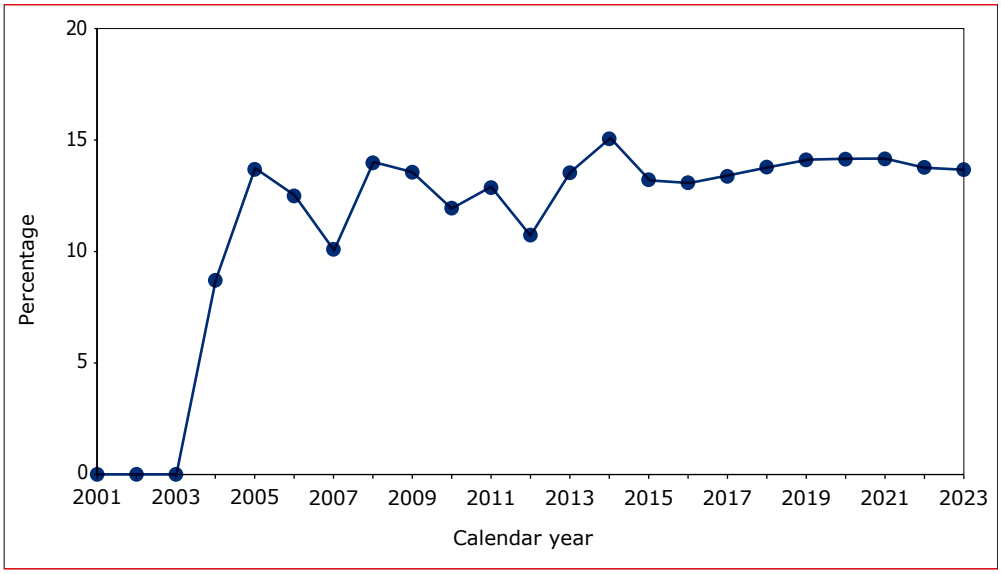


Figure 6.25: Percentage ever infected with HEV per calendar year.



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

Conclusions

Five percent of individuals living with HIV ever registered between 1998 and 2023 in the SHM database, have been documented as having chronic HCV at some stage, and 3% have been documented as having had a recent HCV infection. Acute HCV infection occurred more often among MSM (5%), while reinfection of HCV was documented in 18% of the MSM ever diagnosed with primary HCV.

Our data clearly show that novel DAAs, which arrived in 2014, have entirely replaced PEG-IFN-containing regimens. In addition, the number of individuals living with HIV receiving treatment for HCV has rapidly increased. More than 1,300 individuals have now received, or are currently receiving, treatment with novel DAAs. Overall, 96% of all individuals with sufficient follow-up data to calculate an SVR were found to have been cured. When retreatment was taken into account, the SVR for the last course of treatment was 99%. This high cure rate has reduced the number of individuals with HIV and HCV remaining in need of HCV treatment to 41 in 2023. A Dutch study describing barriers to DAA treatment among people with HIV, found that the appearing barriers were mostly patient-related,

and included a low frequency of clinical visits and refusal by patients[49]. Overall, a rapid reduction in the prevalence of active HCV infections was achieved, with prevalence in MSM having declined to 0.20% in recent years. Successful treatment of HCV has also prevented onward transmission of HCV, which is reflected in the decreasing incidence of recent HCV infections in recent years since 2015[22,50]. However, our data shows that this decrease in levelling off in 2022 and 2023. In line with earlier reports[27,30,44,51], HCV reinfection after successful treatment has been observed, the rate of reinfections has strongly declined over the previous years, but this declining trend did not continued in the recent years. Our data showed a decrease in annual HCV testing, while screening for HCV RNA among those at risk of HCV reinfection is an important factor in identifying HCV reinfection. This might have led to an underestimation of the incidence of HCV reinfections.

Six percent of the individuals living with HIV ever in care had HBsAg-positive serology. The prevalence of HBsAg-positive serostatus has decreased over time from 7.7% in 2001 to 3.5% in 2023 overall, and across all transmission groups, mostly as a result of increased HBV vaccination rates[31], together with the treatment-as-prevention effect of TDF/TAF in ART-treated individuals. Nonetheless, an estimated 34% of all individuals living with HIV have either not been exposed to HBV, or have not been successfully vaccinated, and may remain at risk of acquiring HBV. Since 84% of all individuals still at risk of acquiring HBV infection use an ART regimen that includes TDF/TAF, their risk is probably very low, due to sustained chemoprophylaxis. The remaining 16% of the individuals living with HIV ever registered remain unprotected against HBV, which represents an estimated six percent of the total population of individuals living with HIV screened for hepatitis B. Few individuals were tested for HDV infection and, of those who were tested, a small percentage had evidence of active HDV.

Among the individuals living with HIV ever registered by SHM, 23% of those with chronic HCV and 17% of those with chronic 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 remained at increased risk of having a liver-related cause of death, although this risk has declined since 2012. The overall mortality rate has decreased in individuals with HIV/HCV and HIV/HBV co-infections since 2012, yet the rate remained much higher for PWIDs with HCV or HBV, compared to other transmission groups.

Over half of the individuals ever registered by SHM have been tested for anti-HAV antibodies, with testing frequency consistent across calendar years. The percentage of tested individuals found to have anti-HAV antibodies was no different between MSM and other transmission groups, but it was more than double the percentage found in the general Dutch population[45]. The percentage of people living with HIV with anti-HAV antibodies was higher in older age groups, as would be expected from the general epidemiology of HAV infection[41]. Among the individuals diagnosed with HAV, almost half reported having severe symptoms during their infection, while three individuals 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 8%; this could be due to incomplete data on HAV vaccination. Despite the high prevalence of anti-HAV antibodies, the fact that only half of the individuals ever registered by SHM were tested for anti-HAV immunity, and vaccine uptake was low, could signal that a substantial percentage of individuals remain at risk of HAV infection. Indeed, the majority of HAV diagnoses that were registered in the SHM database were observed in HAV-susceptible MSM between 2017 and 2019.

Almost one in 18 individuals ever registered by SHM have been screened for HEV. Testing frequency of HEV has increased substantially since 2014, probably due to awareness of HEV infection in Europe and its recognised role in hepatitis and liver-related disease[18]. With increased testing, the number of individuals newly diagnosed with past or current HEV infection, or with acute HEV infection, also increased from 2014 onwards. Nevertheless, the percentage of individuals ever identified as having an HEV infection has remained stable at between 9% and 15% over the past decade. This percentage is similar to figures found in the Dutch general population[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 acute HCV (re)infection. In particular, efforts should continue to increase HBV vaccination rates among individuals living with HIV who remain at increased risk of acquiring HBV, particularly those who are not receiving an antiretroviral regimen containing TDF or TAF, and those who previously failed to respond to vaccination[46]. Already, the provision of highly-effective DAA regimens for all known individuals living with HIV and HCV has coincided with reductions in the burden of severe chronic liver disease, hepatocellular carcinoma, and mortality related to liver disease. In addition, these novel regimens have a beneficial impact on the risk of ongoing HCV transmission. Importantly, regular HCV RNA screening among individuals who have been successfully treated for HCV infection and who remain at risk of reinfection, is recommended to ensure early detection of new HCV infections. This should be combined with behavioural interventions aimed at MSM to prevent HCV reinfection after successful treatment of HCV.

HDV clinical practice guidelines from the European Association for the Study of the Liver suggest that individuals with chronic hepatitis B infection should be tested at least once for HDV[36]. In the Netherlands, 24% of individuals who ever had HBV had been tested for HDV infection; the reasons for this low percentage need to be clarified. This information could help to establish whether HDV infection in the Netherlands is a substantial contributor to liver-related morbidity and mortality in individuals living with HIV with HBV infection, as found in other settings[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 HAV infection reports have been uncommon over the last two decades, the recent HAV outbreak in MSM[41] 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 annually for HEV[47]. However, data from SHM and a meta-analysis found no noteworthy increase in HEV prevalence among individuals living with HIV[48], and only two patients in the SHM database were diagnosed with chronic HEV infection. We recommend following current European guidance, which advises 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 individuals living with HIV.

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7. Children with HIV

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Box 7.1: Chapter definitions.

Child with HIV	A child diagnosed with HIV before the age of 15[1,2], whose first visit to a Dutch HIV treatment centre was before the age of 18 years.
Infection	The moment a child acquires HIV.
Diagnosis	The moment HIV is diagnosed in a child.
Registration	The moment an HIV physician or nurse notifies SHM of a child (in care) and the child's details are recorded in the SHM database. Registration usually takes place within a few months of entering care, but can take longer. Demographic and clinical data from the time of HIV diagnosis can only be collected after registration.
In care in 2023	Individuals with HIV who had a documented clinic visit or lab measurement in 2023.
Vertically-acquired HIV	Transmission of HIV from a woman with HIV to a child during pregnancy, delivery, or breastfeeding.
Non-vertically-acquired HIV	Transmission of HIV through sexual contact or contact with contaminated blood or blood products.
ART	Antiretroviral therapy: a combination of at least three antiretroviral drugs from two different antiretroviral drug classes, or at least three nucleoside reverse transcriptase inhibitors.
Viral suppression_200	Any viral load measurement below 200 copies/ml, except for time points in the past where tests had quantification limits higher than 200 copies/ml.
Viral suppression_50	Any viral load measurement below 50 copies/ml, except for time points in the past where tests had quantification limits higher than 50 copies/ml.

Box 7.2: Outline of the paediatric ATHENA cohort in the Netherlands: all children with HIV registered in the ATHENA cohort before 31 December 2023. (Children = individuals under 15 years of age at the time of diagnosis who made a first visit to a Dutch HIV treatment centre before the age of 18 years.)

1. Children who were diagnosed under the age of 15 and who entered care in the Netherlands before the age of 18 (n=406).
2. Population of those diagnosed as a child and in care in 2023 (n=335):
   - under the age of 15 in 2023 (n=111); includes 91 adopted children.
   - aged 15-18 years in 2023 (n=52); includes 38 adopted children.
   - aged 18 years and over in 2023 (n=172); includes 20 adopted children.

Background

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

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

Here we report on the following for children diagnosed with HIV before the age of 15, who have ever received care at one of the paediatric and/or adult HIV treatment centres in the Netherlands while under the age of 18 (*Box 7.2*)[a]:

- demographics
- clinical characteristics
- treatment regimens between 2014-2023.
- long-term virological and immunological responses to treatment between 2014-2023.

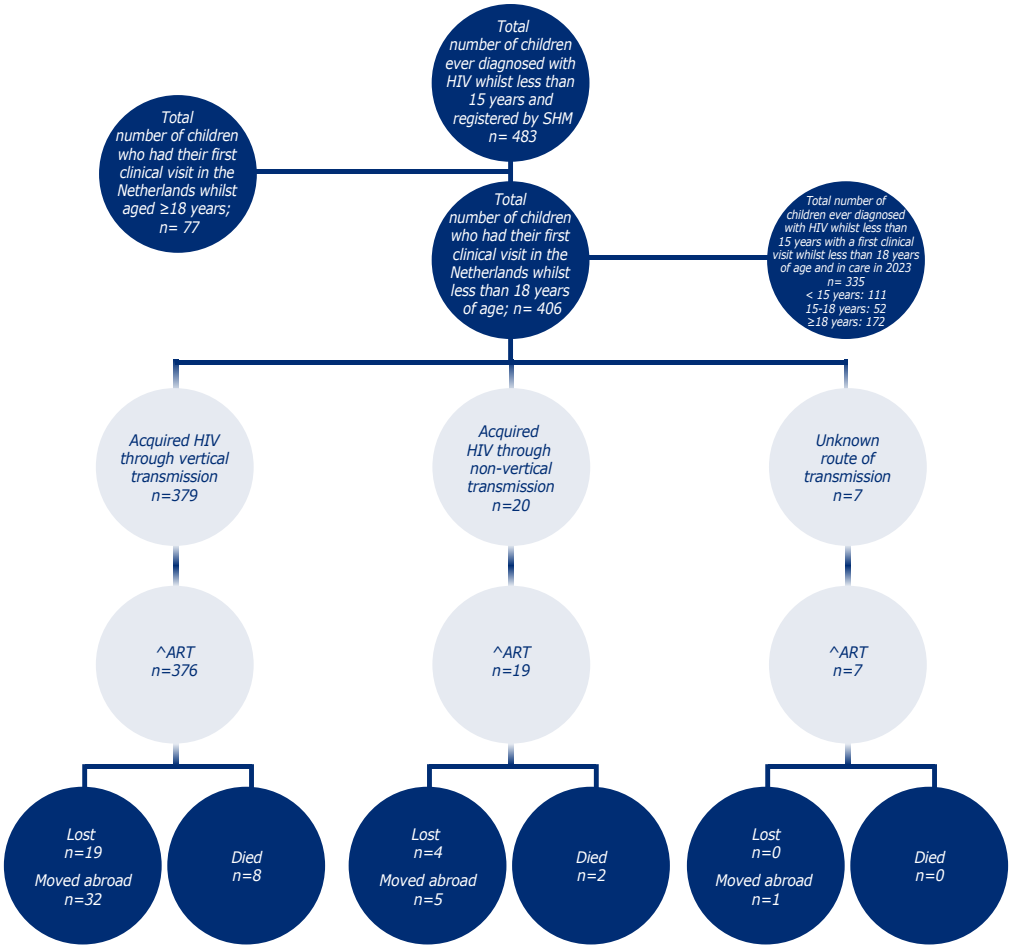
The limit of 15 years is aligned with the definition of children used by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO)[1,2].

a The adapted inclusion of children from including children with an diagnosis before 18 years of age to those diagnosed before the age of 15 years resulted in a lower number of children described compared to the SHM Monitoring report of 2019 and earlier.

Ever registered

As of 31 December 2023 the SHM database includes 483 registered individuals diagnosed with HIV while under 15 years of age (Figure 7.1). Of these, 406 children entered care in the Netherlands before the age of 18. The remaining 77 individuals who were diagnosed as a child, entered care in the Netherlands after the age of 18; 80% (n=62) of those were born outside the Netherlands. And the other 15 were born in the Netherlands.

Figure 7.1: Overview of total population children with HIV registered in SHM database as of 31 December 2023.



***Legend:** ^ of the total number of children who acquired HIV through a vertical, non-vertical or an unknown route of transmission. Legend: ART = antiretroviral therapy.*

The remainder of this chapter will focus on the 406 children diagnosed under the age of 15 and entered care in the Netherlands before the age of 18.

The majority (98%) of this group entered HIV care at a paediatric HIV treatment centre in the Netherlands; nine children entered care at an adult HIV treatment centre at a median age of 17 years (IQR 16.5-17.5) (*Table 7.1*).

The most commonly reported region of birth was Sub Saharan Africa (n=237, 58%) and the Netherlands (n=112, 28%); 57 (14%) children were born in other regions, including the Caribbean, Latin America, Europe and Asia.

***Table 7.1:** Demographic and HIV-related characteristics of 406 children with HIV ever registered by SHM who were diagnosed before 15 years of age and entered care in the Netherlands below the age of 18.*

Characteristics	Total	Vertical transmission	Non-vertical transmission	Route of transmission unknown
Total N (%)	406	379 (93.3)	20 (4.9)	7 (1.7)
HIV treatment centre				
Paediatric care	397 (97.8)	374 (98.7)	16 (80.0)	7 (100.0)
Adult care	9 (2.2)	5 (1.3)	4 (20.0)	
Gender				
Female	208 (51.2)	194 (51.2)	12 (60.0)	2 (28.6)
Male	198 (48.8)	185 (48.8)	8 (40.0)	5 (71.4)
Child region of origin				
Sub-Saharan Africa	237 (58.4)	214 (56.5)	16 (80.0)	7 (100.0)
Netherlands	112 (27.6)	110 (29.0)	2 (10.0)	
Other/unknown	57 (14.0)	55 (14.5)	2 (10.0)	
Mother region of origin				
Sub-Saharan Africa	200 (49.3)	187 (49.3)	8 (40.0)	5 (71.4)
Other/unknown	171 (42.1)	159 (42.0)	10 (50.0)	2 (28.6)
Netherlands	35 (8.6)	33 (8.7)	2 (10.0)	
Adopted	153 (37.7)	151 (39.8)		2 (28.6)
Age at HIV diagnosis				
Median (IQR)	1.3 (0.3 to 4.3)	1.1 (0.2 to 3.6)	11.5 (7.4 to 14.3)	10.9 (10.2 to 11.7)
ART-treated				
ART-treated	402 (99.0)	376 (99.2)	19 (95.0)	7 (100.0)
Therapy-naïve at ART initiation				
Naive	354 (87.2)	331 (87.3)	16 (80.0)	7 (100.0)
CD4 at ART initiation				
Median (IQR)	527 (272 to 1146)	546 (275 to 1215)	324 (177 to 472)	475 (320 to 570)
CD4 Z-score at ART initiation				
Median (IQR)	-0.9 (-1.3 to -0.5)	-0.9 (-1.3 to -0.5)	-0.8 (-1.2 to -0.5)	-0.4 (-0.6 to -0.3)
VL (log copies/ml) at ART initiation				
Median (IQR)	5.1 (4.5 to 5.8)	5.2 (4.5 to 5.8)	4.3 (4.0 to 5.5)	4.9 (4.7 to 5.0)

***Legend:** *Data are number (%) of children or median (interquartile range). ART = antiretroviral therapy; VL = viral load.*

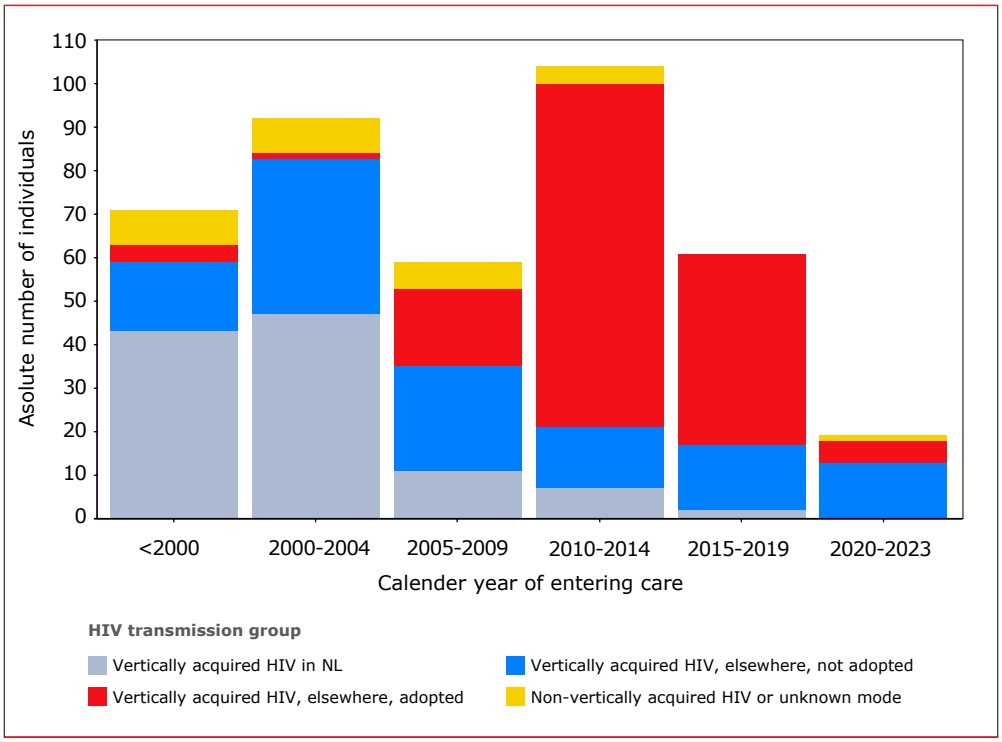
Mode of transmission

The majority (93%) of the children registered acquired HIV through vertical transmission. (*Figure 7.1*).

Vertical transmission

- Between 1998 and 2023, 379 children entered care after acquiring HIV through vertical transmission. (*Table 7.1*).
- 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] 0.2-3.6 years).
- 99% received care in a paediatric HIV treatment centre in the Netherlands.
- ART initiation was documented for 99% of the children.
- 57% (n=214) of the children were born in sub-Saharan Africa.
- 29% (n=110) of the children were born in the Netherlands.
- 8% of the children born in the Netherlands (9 out of 110), had two Dutch parents.

Figure 7.2: *Number of children with HIV by year of entering care in the Netherlands, stratified by mode of HIV transmission and adoption status.*



Note: *The numbers of children with non-vertically-acquired HIV or unknown mode of HIV transmission entering care were too small for stratification by mode of acquisition.*

Decline in vertical transmission of HIV in the Netherlands since 2005

Figure 7.2 shows the number of registered children by year of entering care, mode of transmission, and region of origin. The number newly entering care in the Netherlands has fallen over time from 104 in 2010-14 to 61 in 2015-2019 and 19 in 2020-2023. This drop is likely linked to the declining number of adopted children newly entering care over time. Standard HIV screening for pregnant women, introduced nationally in 2004[13,14], is responsible for the strong decline in vertical transmission in the Netherlands from 2005 onwards.

Non-vertical transmission

- Between 1998 and 2023, 20 children were registered as having acquired HIV through non-vertical transmission (*Table 7.1*); the most likely modes (reported in the medical chart) were heterosexual transmission (n=8, 40%) and contact with contaminated blood and blood products or medical procedures (n=12, 60%). Reporting on the latter category stopped in 1997 for children born in the Netherlands, and in 2009 for all children, regardless of country of birth. Further details regarding this latter category are not available. Six out of these 12 individuals are still in care and currently all of them are older than 18 years.
- The median age for children with a registered mode of non-vertical HIV transmission to receive their diagnoses was 11.5 years (IQR 7.14-14.3); the median age of diagnosis for those who acquired HIV by heterosexual transmission was higher at 14.7 years (IQR 13.8-14.9); those who acquired HIV through contact with contaminated blood and blood products or medical procedures were younger at time of HIV diagnosis (median age 8.59 (IQR: 5.89-11.5).
- In total, 95% of these children had started ART.
- 80% were born in sub-Saharan Africa.
- 20% received care in an adult HIV treatment centre.

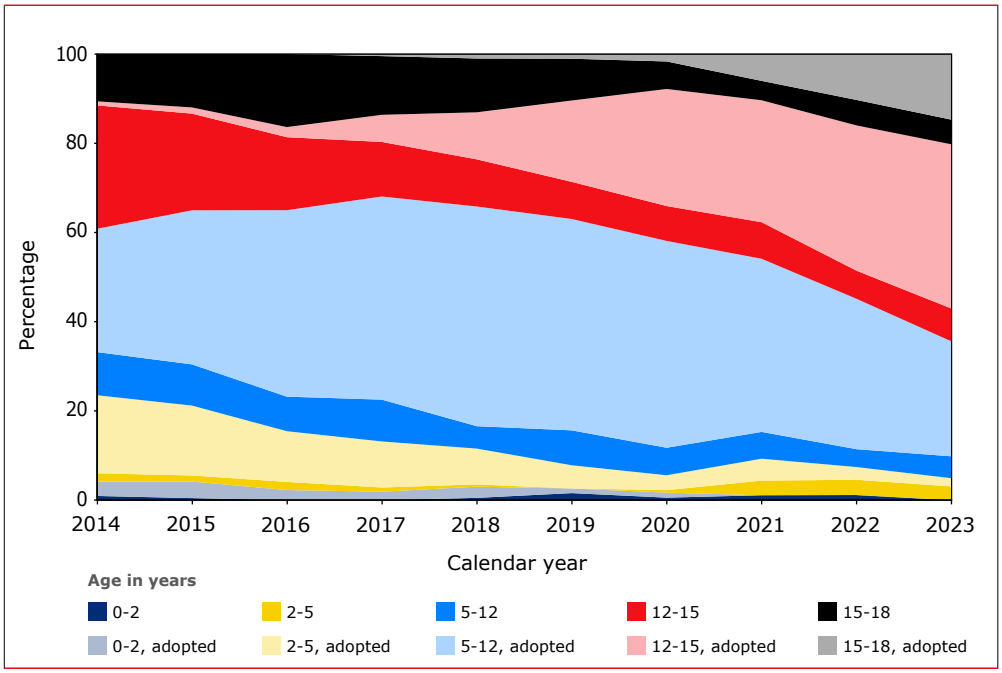
Unknown route of HIV transmission

- For 7 children with HIV, the route of transmission remains unknown (*Table 7.1*).
- Their median age at diagnosis was 10.9 years (IQR 10.2-11.7).
- All children had started ART.

Age distribution

Figure 7.3 shows the age distribution of children receiving HIV care in the last 10 years (2014-2023). Between 2014 and 2019, the proportion of children aged 5-12 increased. This was mainly due to a relative increase in the rates of children adopted in those age groups. Whilst the proportion of children aged between 12 and 18 years increased from 37% in 2019 to 64% in 2023. In 2023, 79% of children with HIV aged between 5 and 18 years was adopted.

Figure 7.3: Time-dependent age distribution of children with HIV in care over time. The shaded areas represent the proportion of adopted children.



Low mortality rates

No children registered with SHM were reported to have died before the age of 18 between 2014 and 2023. The mortality rate therefore remains very low, with a total of two deaths when aged <18 years recorded since the start of registration. Both children died from AIDS before 2010. However, between 2014 and 2023 eight young adults who had been diagnosed with HIV as children, died in adulthood; their median age at death was 26.6 years (IQR 24-29). Five of these young adults died from AIDS, three of a non-AIDS related cause.

Antiretroviral treatment

Of the 406 children who entered care in the Netherlands before 18 years of age, 402 (99%) started ART; 354 (88%) of them were treatment-naive at the start of ART and 48 (12%) had previously been exposed to monotherapy or dual therapy (i.e. were pre-treated). In total, four children never received ART; all are no longer in care, and the last date of contact for them was between 1998 and 2010.

For the purposes of this analysis, both pre-treated and treatment-naive children who initiated ART from 2014 onwards have been included. Children were grouped by calendar year of ART initiation: 52 children started an ART regimen in 2014-2017 and 21 in 2018-23. For 14 children, the year of ART initiation is not known. All these children were born outside the Netherlands.

Initial antiretroviral regimen

Of the 73 registered children known to have initiated ART between 2014 and 2023:

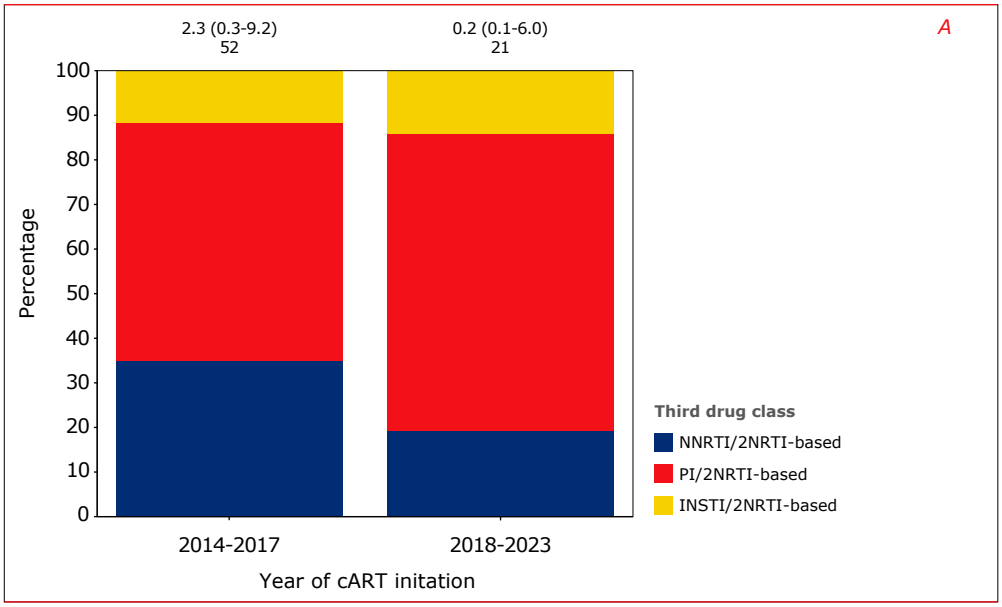
- 58% were treated with a first-line regimen that included a protease inhibitor (PI) and two or more nucleoside reverse transcriptase inhibitors (NRTIs);
- 30% were treated with a non-nucleoside reverse transcriptase inhibitor (NNRTI) with two or more NRTIs; and
- 12% were treated with an integrase inhibitor-based first-line with two or more NRTs regimen.

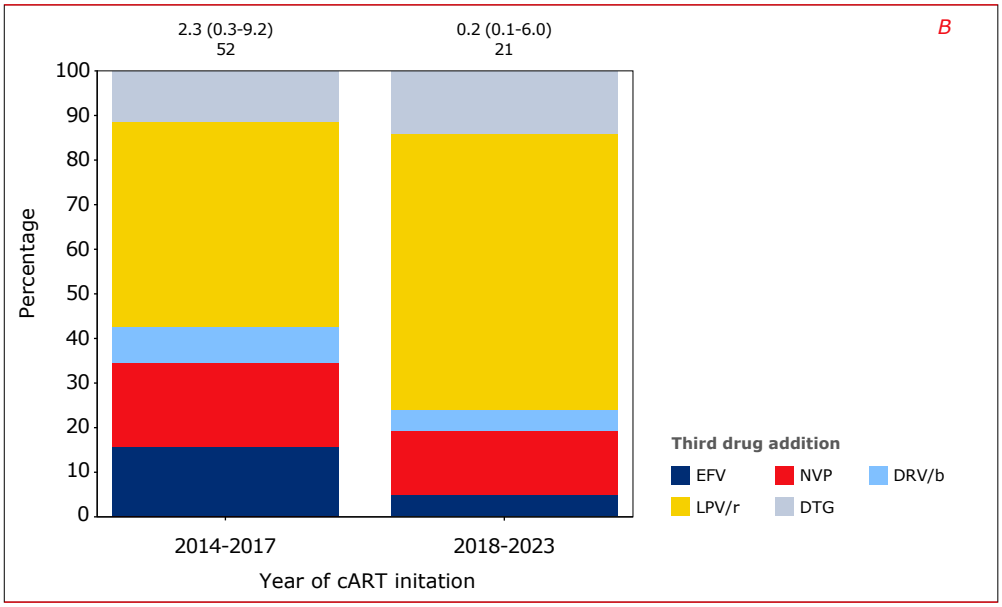
Notably, a substantial proportion of the first line regimens were already initiated before the first clinical visit in one of the Dutch treatment centres. Forty (55%) of the 73 children were already using treatment before entry care in the Netherlands. When taking into account initial regimens started in the Netherlands only (n=40), these first-line regimens included:

- a PI (48%)
- a NNRTI (24%) and
- an INSTI (27%).

Figure 7.4 shows the trends over time for the third-drug additions to the NRTI backbone as part of the initial ART regimens, stratified by calendar period of starting ART. Among children, ritonavir boosted lopinavir was the most commonly-used PI (51%). Following its introduction in 2014, the integrase inhibitor dolutegravir was included in the initial ART regimen given to 33% of the children who initiated a first-line regimen between 2018-2023.

Figure 7.4: *Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial ART regimen, stratified by calendar year period, according to (A) antiretroviral class, and (B) specific third drugs. Numbers above the bars represent the total number of individuals initiating ART in that calendar year period. Median ages and interquartile ranges above the bars represent the ages of individuals at the time of ART initiation[b].*





Legend: *ART = 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.*

b These figures include initial regimens that were started before entry in care in the Netherlands.

Discontinuation of the initial ART regimen

Among those who discontinued their first-line treatment regimen, the median time spent on first-line regimen among children who had started ART between 2014 and 2023 was 15.0 months (IQR 1-38). Discounting weight-related dose changes, 56 children (77%) discontinued their first-line treatment regimen. The most important reasons for changing included simplification (38%) and toxicity (11%). Virological failure was the reason given in 5% of cases and in 13% the reason was unknown.

Virological response

Virological response to ART was assessed based on viral suppression (i.e. viral load below 200 copies/ml and 50 copies/ml, [*Box 7.1*]). Initial virological response is reported for the first two years after starting ART between 2014-2023. Long-term virological response is reported by time-updated age for those who used ART for at least 24 months.

Initial response to ART

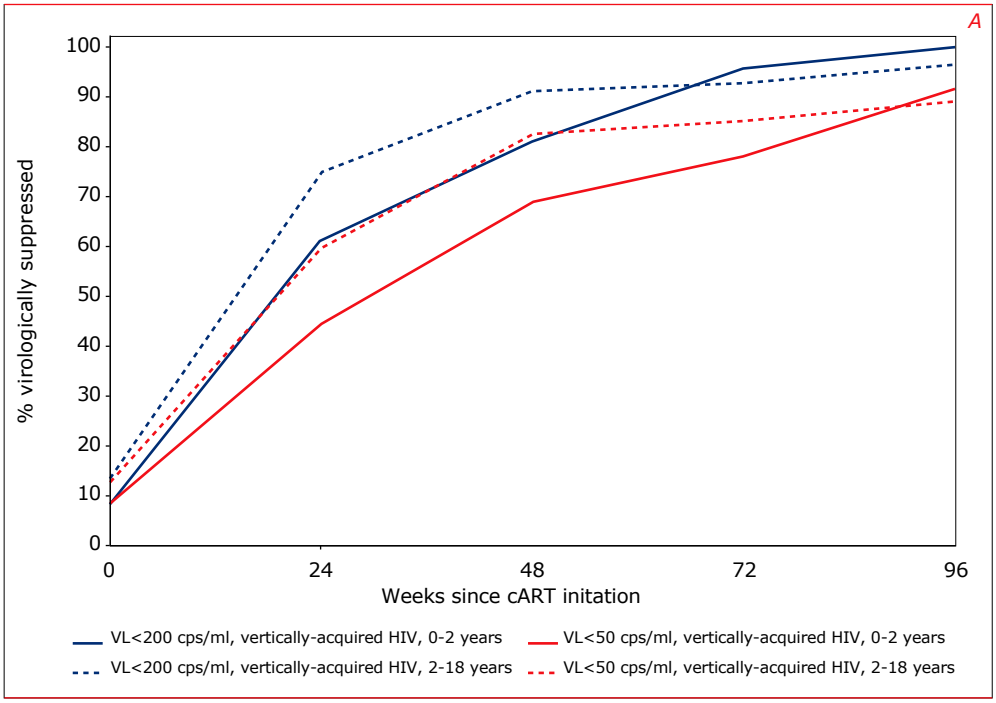
This analysis used data from the 69 children who were registered with SHM and had started ART between 2014-2023 and who had viral load data available in the first 24 months after ART initiation. Children were stratified by age at ART initiation, resulting in the following categories:

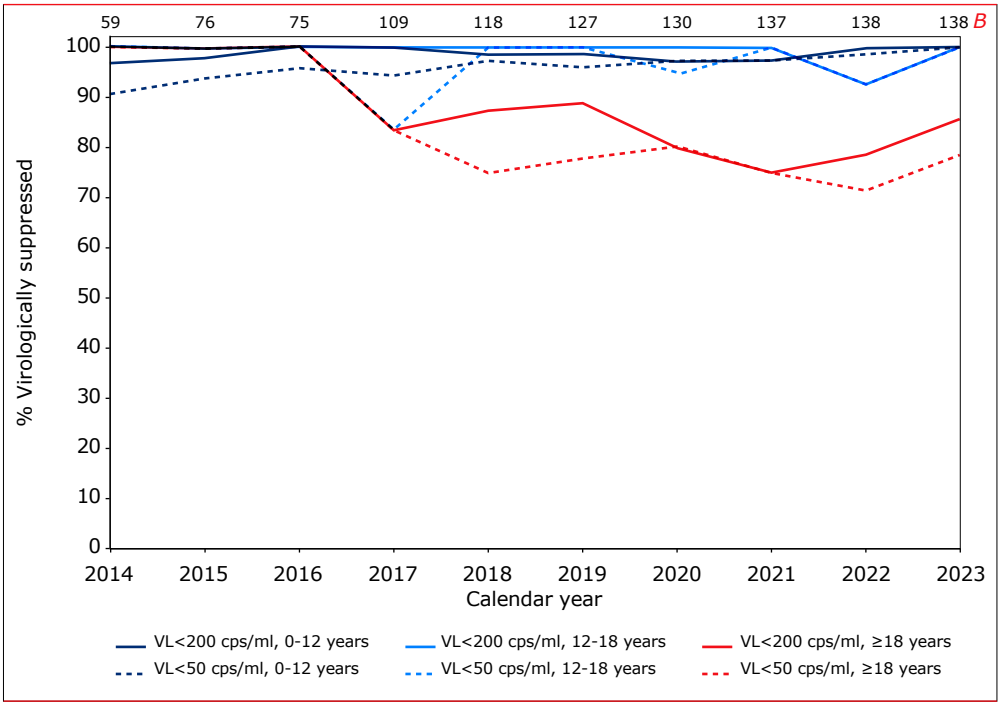
(1) 0-2 years, n=34
(2) 2-18 years, n=35

Among the children who started ART, we assessed their viral suppression rates at 24-week intervals while they were on ART. Viral load measurements closest to each 24-week time point (plus or minus 8 weeks) were included in the analysis. Viral suppression rates are shown for the calendar period 2014-2023 of ART initiation. *Figures 7.5A* shows viral suppression rates among children who initiated ART between 2014 and 2023:

- Among children who were aged 0-2 years at the time of ART initiation, viral suppression <200 copies/ml rates increased from 61% after 24 weeks, to 81% after one year of ART, to 100% after two years. Viral suppression <50 copies/ml rates were 44%, 69% and 92% after 24 weeks, one and two years.
- Among children who were aged 2-18 years at ART initiation, viral suppression <200 copies/ml rates increased from 75% after 24 weeks, to 91% after one year of ART, and 96% after two years, viral suppression <50 copies/ml rates were : 60%, 83% and 89% after 24 weeks, one and two years.

Figure 7.5: *Viral suppression following antiretroviral therapy (ART) initiation: (A) during the first two years of ART 2014–2023, (B) time-dependent and age-dependent viral suppression rates for children in care between 2014 and 2023 after two years of ART with ART initiation from 2011 onwards. Viral suppression is defined as any viral load measurements below 200 copies/ml and below 50 copies/ml, except for time points in the past where tests were used with quantification limits above 200 copies/ml or 50 copies/ml. The numbers above the bars represent the total number of individuals with an viral load measurement.*





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

Long-term virological response

Among the children who were using ART for more than 24 months, we assessed viral suppression rates by calendar year of follow up. The latest viral load measurement in each calendar year was included in the analysis. Viral suppression rates (<200 copies/ml and <50 copies/ml) were stratified by calendar period of ART initiation, to account for changes in the use of ART regimens.

Time-updated age of HIV RNA measurements was calculated, and children were stratified by the following time-updated age ranges:

(1) 0-12 years
(2) 12-18 years
(3) 18 years or older

Age and time-updated HIV RNA viral suppression rates were consistently high among children aged below 18 years. However, viral suppression rates decreased once the age of 18 years was reached (*Figure 7.5B*). Of note: the small patient size per calendar year made the oldest age group more susceptible to having larger differences in viral suppression rates.

Immunological response

Earlier reports have shown that the clinical benefit of ART is strongly related to the degree to which the CD4 cell count recovers[15]. Given that normal CD4 cell counts in younger children are highly age-dependent[16], it is more appropriate to analyse time-dependent CD4 count trajectories, expressing CD4 counts as Z-scores in which counts are standardised in relation to age.

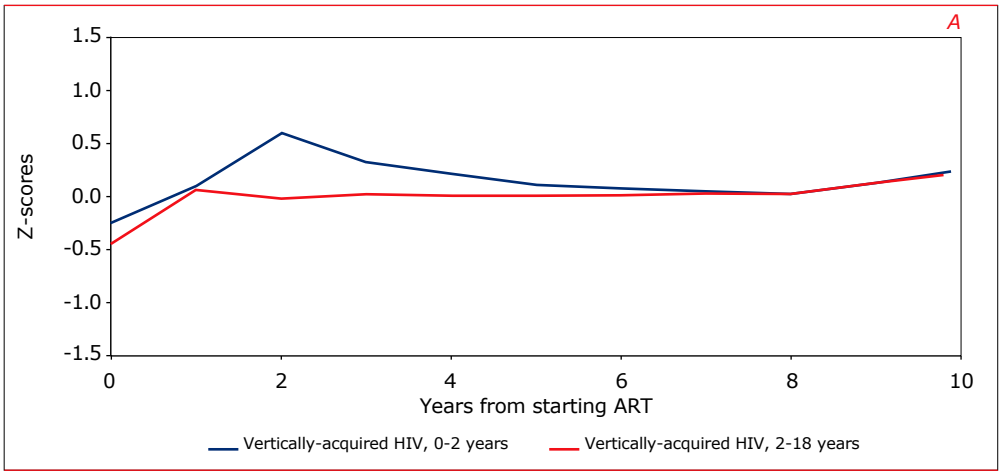
CD4 Z-scores represent the standard deviation from the reference values for HIV-negative children. They were calculated for CD4 cell counts to correct for age-related differences. All absolute CD4 T-cell counts were transformed into Z-scores by subtracting the age-related reference value for the age at the time of the CD4 measurement[17], and dividing the outcome by the age-related standard deviation.

A Z-score of zero represents the age-appropriate median. A CD4 Z-score of minus 1 indicates that a child's CD4 cell count is 1 standard deviation below the age-specific median of the HIV-negative population.

Figure 7.6 shows the changes in CD4 T-cell Z-scores among children with HIV, stratifying those with vertically-acquired HIV by age at initiation of ART.

For those who initiated ART between 2014 and 2023, CD4 Z-scores increased significantly for both age groups in the year following ART initiation. However, in the second year the increase in CD4 Z-scores was less pronounced for children aged between 2-18 years at time of ART initiation, resulting in higher CD4 Z-scores among the youngest children (*Figure 7.6*).

Figure 7.6: Changes in Z-scores for CD4 T-cell counts among children with HIV, stratified by age at initiation of antiretroviral therapy (ART), who initiated ART between 2014 and 2023).



Legend: ART = antiretroviral therapy.

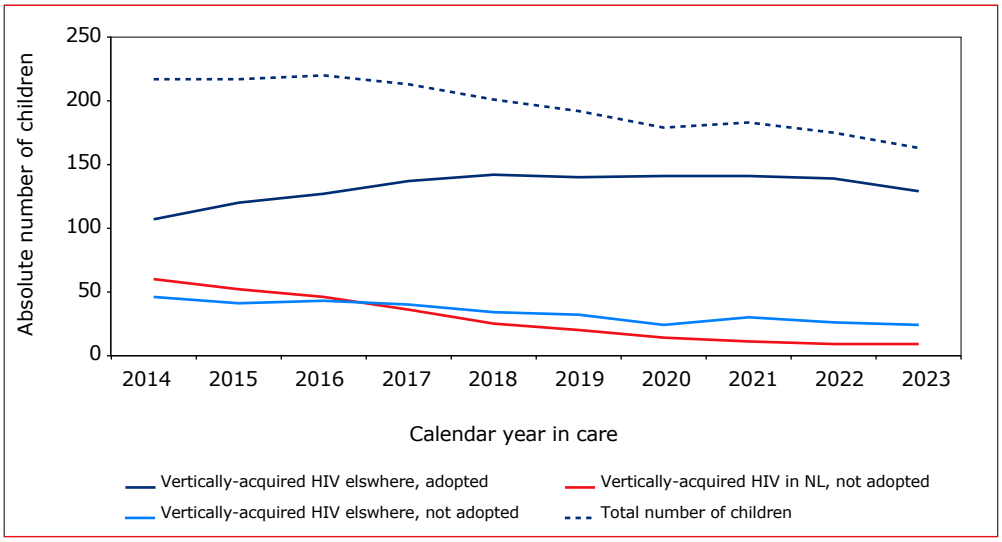
Currently in clinical care

Of the 406 children with HIV ever registered by SHM, and who entered care in the Netherlands before the age of 18, 335 (82%) were still in care in 2023 and 71 were no longer in care. Of these 71 individuals:

- Ten had died;
- 38 had moved abroad;
- 23 were lost to care.

Of the 335 individuals still in care, 163 of them were under the age of 18 (*Figure 7.1*). *Figure 7.7* shows the number of children under 18 years of age in care, for each calendar year. This figure reached its peak in 2016, with 220 children. However by 2023, this figure had declined to 163, mainly due to the fact that more children are reaching the age of 18 years and, at the same time, fewer children are newly entering care.

Figure 7.7: Number of children aged <18 years known to be in care at the end of each calendar year shown by mode of HIV transmission and adoption status. Note: Children with non-vertically-acquired HIV are not reported as a separate category due to their small numbers, but they are included in the total number of children in care.



Currently in care and under 18 years of age

- 163 were younger than 18 years at the end of 2023
- 111 were younger than 15 years
- The median age was 13 years (IQR 10-16) as of 31 December 2023

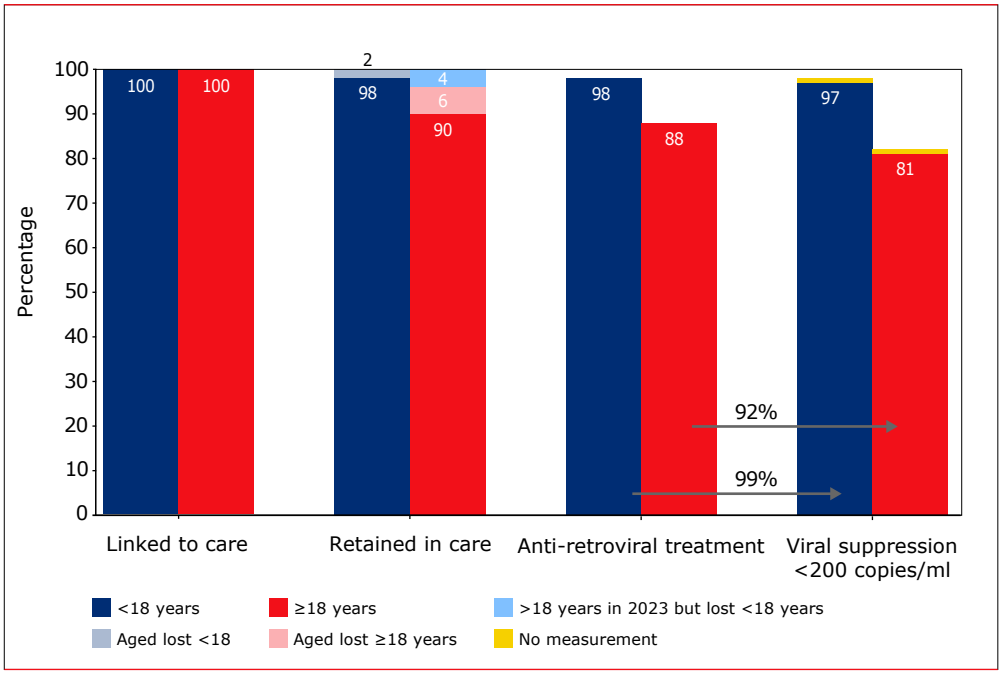
Currently in clinical care and 18 years or older

- 172 were older than 18 years at the end of 2023
- The median age was 26 years (IQR 23-30) as of 31 December 2023

Continuum of care

A 'continuum of care' was constructed based on the total number of children with HIV ever registered by SHM, who were still alive on 31 December 2023 and were not reported to have moved abroad. This continuum of care depicts engagement in HIV care across a number of key indicators. The final one of these is the number of children whose most recent HIV RNA measurement was below 200 copies/ml (*Figure 7.8*).

Figure 7.8: Continuum of care by age, as of 31 December 2023. The numbers in and above the bars indicate the proportion of individuals.



Individuals were stratified by age on 31 December 2023 and categorised as:
(1) current age, under 18 years
(2) current age, 18 years or older

Continuum of care: current age under 18 years

- 166 children were linked to care, registered by SHM, still alive and not reported to have moved abroad.
- 98% (163) were retained in care: three children, all were born outside the Netherlands, were lost to care.
- 98% (162) had ART during their last clinical visit in 2023.
- 97% (161) of all individuals linked to care had a most recent HIV RNA measurement below 200 copies/ml (99% of those on ART).

Continuum of care: current age 18 years or older

- 192 individuals were linked to care, registered by SHM, still alive and not reported to have moved abroad.
- 90% (172) were retained in care. The remaining 20 (16 of whom were born outside the Netherlands) were lost to care: 8 before they turned 18; 12 when they were older than 18 years of age.
- 88% (169) had ART during their last clinical visit in 2023.
- 81% (155) of all individuals linked to care had a most recent HIV RNA measurement below 200 copies/ml (92% of those on ART).

It is worth noting that 12 of the 20 young adults who were lost to care had their last clinical contact at a paediatric HIV treatment centre. They were deregistered and may have been lost during transition to adult care, or may be waiting to be re-registered at an adult treatment centre.

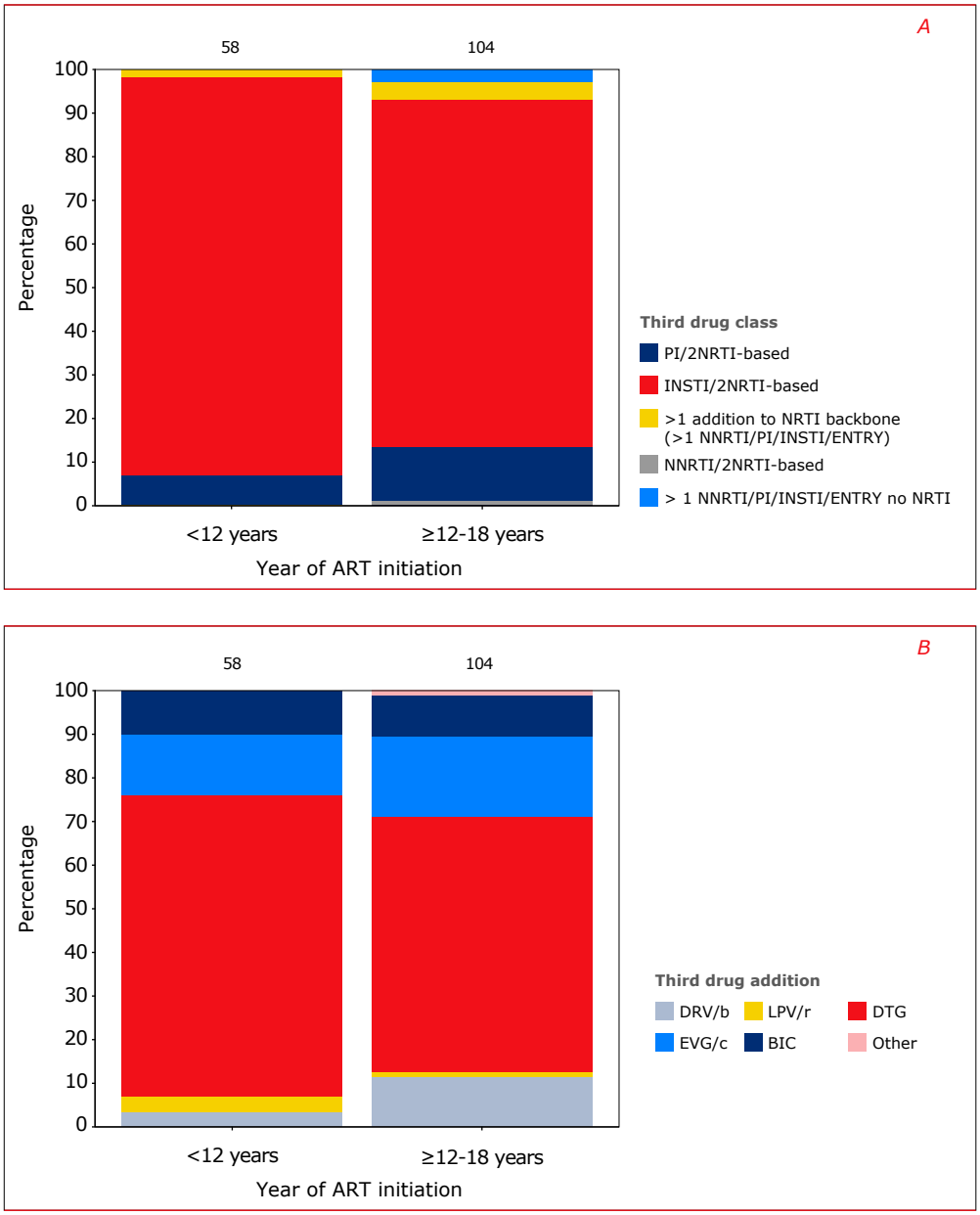
In care and on ART in 2023

Of the 163 children known to be in care in 2023 and under 18 years of age, 162 had ART during their last reported clinical visit. The distribution of current ART use is shown in *Figure 7.9*, according to age on 31 December 2023.

Among those under 12 years of age, INSTI-based regimens were the most commonly-used (91%), with dolutegravir (89%) and elvitegravir (14%) the most common individual third agents.

In children aged between 12 and 18 years, 80% were using an INSTI-based regimen, 13% a PI-containing regimen and 7% a combination with PI or NNRTI with INSTI. Among those using an INSTI-based regimen, dolutegravir was most common (59%), followed by elvitegravir (18%). Overall, 16 children used bictegravir.

Figure 7.9: 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 ART in that particular calendar year period.



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

Special Populations

Adopted children

Of the 406 children ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 153 (38%) had been adopted by Dutch parents. The percentage of adopted children newly entering care increased from 6% <2000 to 76% between 2010-2014, 72% between 2015-2019 and was 26% between 2020-2023 (*Figure 7.2*), with a median age at the time of entering care of 2.7 years (IQR 1.6-5.0). Overall:

- 110 (72%) children were already receiving ART before they entered care in the Netherlands;
- 17 (11%) children were treated with monotherapy or dual therapy before the start of ART;
- All children had ART during follow up in clinical care at one of the Dutch HIV treatment centres;
- Four adopted children are no longer in care because of lost to follow up, moved abroad or died);
- All children known to be in care were still receiving treatment in 2023;
- All in care in 2023 had an undetectable viral load (equal to or below 200 copies/ml) in their most recent HIV RNA measurement and 98% had an undetectable viral load <50 copies/ml.

Initially, at the time of entering care in the Netherlands, only 66 (43%) of the 153 children had a viral load below 200 copies/ml and 26% below 50 copies/ml.

Figure 7.7 shows the number of adopted children still in care and under 18 years of age. As of 31 December 2023, 149 children were alive and in care and 129 of them were aged below 18 years. Their median age was 14 years (IQR 12-17).

Transfer to adult care

Of the 406 children ever registered by SHM who were under the age of 18 when they entered care in the Netherlands, 187 children had reached the age of 18 and above, and had transferred from paediatric care to adult care by 31 December 2023.

Figure 7.10: Follow up status, as of 31 December 2023, of children who transferred to adult care.

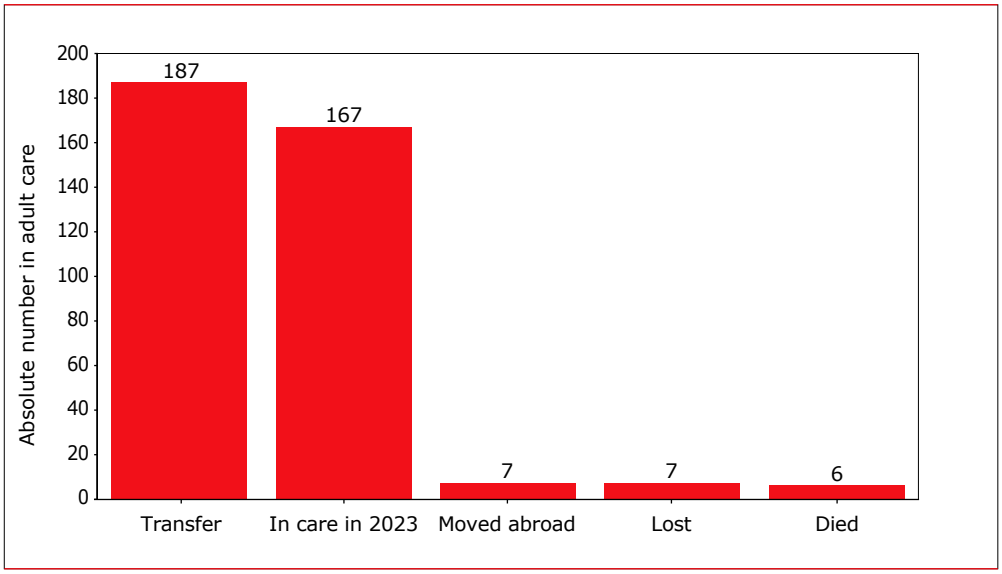
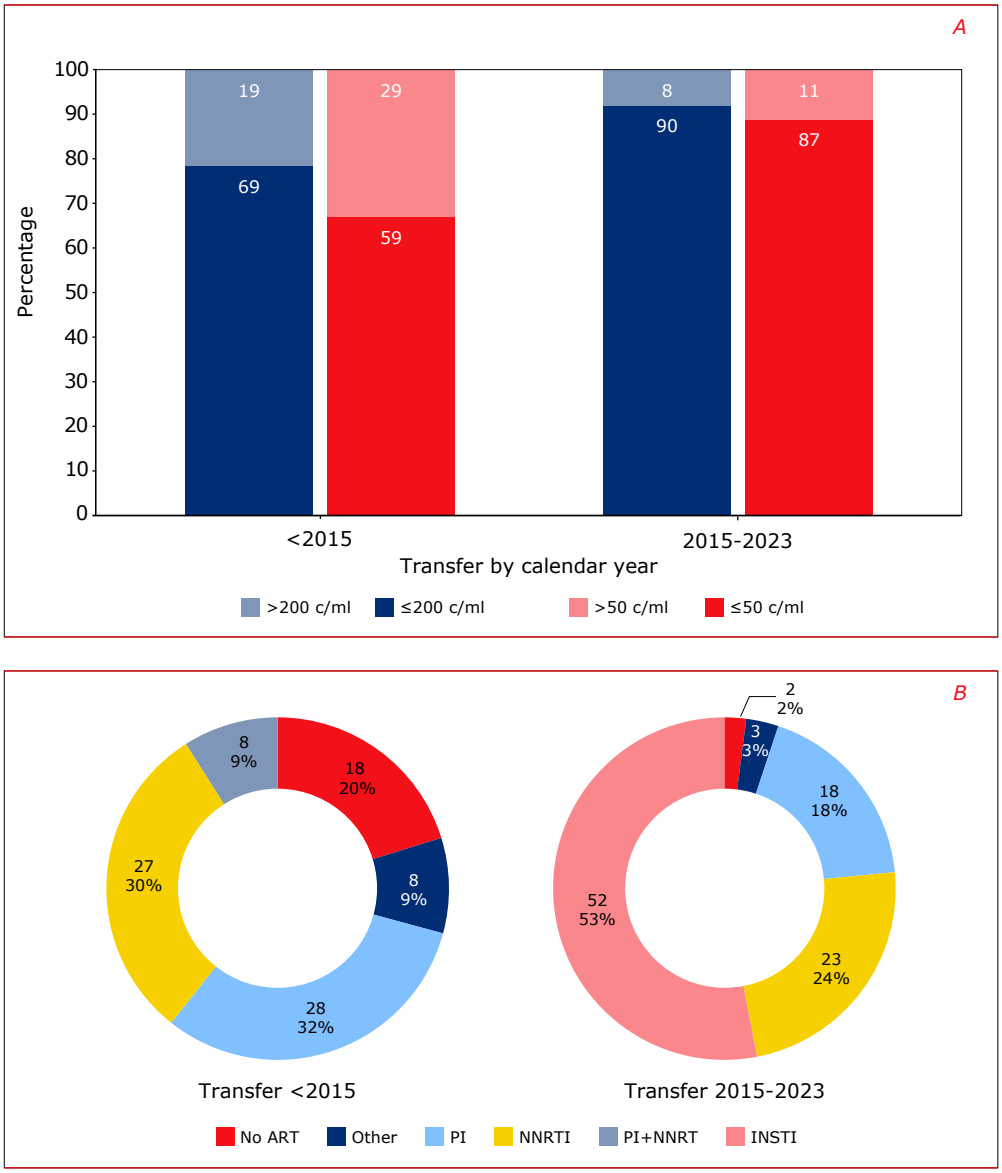


Figure 7.11: HIV RNA (A) and ART regimens (B) at last visit in paediatric care of children who transferred to adult care, stratified by calendar year of transfer .



The median age for their last visit to paediatric care was 18.1 years (IQR 17.7-18.7). The median time between their last visit to paediatric care and their first visit to adult care was 4 months (IQR 3-6). Time in care after transfer until their last documented clinical visit was 8.0 years (IQR 4.6-11.9).

Figure 7.10 shows the follow up status of the 187 adolescents who transferred to adult care:

- 167 (89%) were still in care in 2023;
- 7 (3%) were lost to care;
- Seven (4%) had moved abroad; and
- Six (3%) had died.

Overall, at the time of their last clinical visit to paediatric care, 27 adolescents (15%) had an HIV RNA level above 200 copies/ml (median 5230; IQR 11115-47072). When taking into account 50 copies/ml, 40 adolescents had an HIV RNA > 50 copies/ml (22%). This figure is more or less comparable to results from the UK and Ireland, where three quarters of adolescents were virologically suppressed at the time of transition[18]. However, we observed a lower proportion of detectable HIV RNA levels among young adolescents who made their transfer to adult care in or after 2015 compared to those who transferred before 2015, from 21% to 8% and from 33% to 11% for >200 copies/ml and 50 copies/ml respectively(*Figure 7.11A)*.

During their last visit to paediatric care, 89% of the 187 adolescents received ART, 3% adolescents had not yet started ART and 8% had discontinued ART. Reported reasons for discontinuation were: decision by adolescent or low adherence. Before 2015 there were more frequent occurrences of individuals not on ART at time of transfer, compared to 2015 or later (20% and 2%, respectively, *Figure 7.11B*).

Among adolescents who transferred to adult care before 2015, 30% were on an NNRTI-based regimen and 28% on a PI-based regimen. These percentages differed for adolescents who transferred in or after 2015: 53% were on an integrase-based regimen, 24% on an NNRTI-based regimen and 18% on a PI-based regimen.
Of the 167 adolescents who transferred to adult care, and who were still in care in 2023, 164 (98%) were receiving ART in 2023. Seventy percent of these were on an integrase inhibitor-based regimen. In total, 90% of the 167 had HIV RNA levels below 200 copies/ml and 87% below 50 copies/ml in 2023.

Summary

Of the 406 children with HIV ever registered by SHM who were under the age of 18 when they entered care in the Netherlands, 83% remained in care in the Netherlands.

A substantial proportion of the children newly registered since 2010 are children who were adopted by Dutch parents. It is worth noting that the annual number of newly registered children who were adopted by Dutch parents has been decreasing since 2015, which has contributed to the decline in the overall number of newly registered children with HIV in the Netherlands since 2015.
Vertical transmission is the main mode of HIV transmission for children with HIV in the Netherlands. The majority of children with vertically-acquired HIV were born outside the Netherlands. Vertical transmission of HIV within the Netherlands has become rare, reflecting the success of standardised HIV screening during the first trimester of pregnancy[13].

Non-vertical transmission of HIV is less frequently reported in the Netherlands. Five percent of children included in the SHM database had acquired HIV through non-vertical modes of transmission. Contact with contaminated blood or blood products and medical procedures were most commonly reported modes of transmission for this group. These modes have not been reported since 2009.

None of the children who entered care over the last 10 years died before the age of 18. However eight young adults over the age of 18, who had been diagnosed with HIV as a child, did die in the past 10 years. These deaths included AIDS-related causes of death.

In total 99% of children with HIV, who had ever received care in the Netherlands, have received ART. Those who did not receive ART are no longer in care, but had been in care at an earlier point in time before guidelines were revised to recommend that ART be initiated for everyone with HIV, regardless of CD4 counts. Ninety-eight percent of children in care in 2023 were receiving ART. Current regimens in use include an integrase inhibitor for 91% of the children.

Very high long-term viral suppression rates were observed in children with HIV who initiated ART in or after 2014. However, those response rates fell when children reached the age of 18. We have seen overall viral suppression rates of 85% at the time of transition to adult care, which is around the age of 18. Nonetheless, transition to adult care with an undetectable viral load increased over time, from 79% to 92%.

The continuum of care showed a high retention-in-care rate among children under 18 years of age. Moreover, a substantially lower proportion of those aged 18 years and over had suppressed HIV RNA levels by the end of 2023, when compared to children under the age of 18 (92% versus 99% among those in care and receiving ART).

Recommendations

The provision of care for children with HIV in the Netherlands has resulted in generally favourable outcomes, with no reported mortalities in recent years and good long-term virological and immunological responses to treatment for those under the age of 18. Additionally, the number of children with HIV in paediatric care is decreasing as a result of targeted efforts to prevent mother-to-child transmission, as well as a fall in the number of adopted HIV-positive children in recent years. However, an increasing proportion of the children registered with SHM has now reached the age of 18 and transitioned to adult care. This period of transition is associated with lower levels of viral suppression and lower care retention rates, hence this group requires special attention.

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8. Pregnancies in women with HIV

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Introduction

The most common mode of HIV acquisition for children aged 0 to 15 years worldwide is vertical transmission[1]. Vertical transmission of HIV mainly occurs perinatally during labour and delivery, or postnatally during breastfeeding. Less common is transplacental transmission in utero. Without intervention, the risk of vertical transmission varies between 15% and 45%[2,3]. Since the introduction of combination antiretroviral therapy (ART) in pregnant women, the risk of vertical transmission has been dramatically reduced to less than 1%[4,5].

Recommendations for the treatment of HIV during pregnancy have changed over time. Previously, the timing of the initiation of ART was based on the maternal CD4 cell count. As a result, a substantial proportion of women who did not need to start ART according to their CD4 cell count, started it for the first time during pregnancy, with the sole purpose of reducing maternal HIV RNA to limit the risk of vertical transmission. In many of these cases, ART was discontinued after delivery. In 2015 general treatment guidelines were revised, and ART was recommended for all individuals regardless of their CD4 cell count[6]. As a result, most women with HIV are already receiving ART at the time of conception and are advised to continue therapy during pregnancy and postpartum.

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

This year's report focuses on women who were pregnant during the years 2016 to 2023, as this population reflects current treatment guidelines. The follow-up and therapy outcomes of all pregnant women in care during the period 1996 to 2018 were described in detail in the *2019 SHM Monitoring report*[8].

Demographics

Maternal characteristics

Geographical region of origin

Table 8.1A shows the characteristics of the 620 women with HIV with a registered one or more pregnancies when receiving care in the Netherlands between 2016 and 2023. Of these women, 450 (73%) were of non-Dutch origin and 170 (27%) were born in the Netherlands. The majority of women of non-Dutch origin were born in sub-Saharan Africa (n=276, 45%) or in the Caribbean/South America region (n=82, 13%). Ninety-two (15%) women originated from other regions, including 44 women from Central or Eastern Europe, and 23 women from South and Southeast-East Asia. The above information on country or region of origin is based on country of birth, data on migration background is not registered within SHM. However, these information is available within the environment of Statistics Netherlands (CBS). Box 8.1 gives an overview of socio-demographic and socio-economical characteristics of pregnant women in HIV care, using data from CBS if available.

Diagnosis

The majority of the 620 women (n=534, 86%) were aware of their HIV diagnosis before becoming pregnant; this proportion did not differ between women of Dutch and non-Dutch origin. In total, 86 women were newly diagnosed during their pregnancy. The proportion of women newly diagnosed varied between 3% and 11% for the years 2016-2023. These 86 women were born in:

- the Netherlands: 22/86 (13%)
- sub-Sahara Africa: 37/86 (13%)
- the Caribbean/Latin America region: 12/86 (15%)
- and other regions: 15/86 (16%)

The median time between conception and diagnosis among newly diagnosed women was 13 weeks (IQR: 10-18). Of this total, 58% received their diagnosis during the first trimester of pregnancy, 34% in their second trimester, and 8% in their third trimester. Fifty of the 86 newly diagnosed women reported an earlier negative HIV antibody test. It is not known whether these earlier tests were part of the national pregnancy screening.

For women who were newly diagnosed during the pregnancy, the median time between the date of the HIV test and first contact with one of the HIV treatment centres was 8 days (interquartile range [IQR] 6-15). The median time between the first visit to a treatment centre and receiving antiretroviral therapy was also 8 days (IQR 1-16). The moment a woman receives her HIV diagnosis from here obstetric caregiver and is referred to an HIV treatment centre is not recorded.

Clinical characteristics

Based on the first CD4 cell measurement after conception, median CD4 cell count was 548 cells/mm^3 (IQR 380-750) for all women. A lower median CD4 cell count was seen among women who were newly diagnosed with HIV (and started ART) during pregnancy (340 cells/mms, IQR 210-453). However, as CD4 cell counts during pregnancy are affected by haemodilution, which results in lower CD4 cell counts[9], CD4 cell percentages may be a more reliable parameter. These were also found to be lower than average among the group of women newly diagnosed during pregnancy (*Table 8.1A*).

Mode of HIV acquisition

Among the 620 women, heterosexual contact was the most common self-reported mode of HIV acquisition (88%). Nine women reported mode of exposure to contaminated blood, while, for three women of non-Dutch origin, the reported most likely mode of transmission was injecting drug use. Thirty-nine pregnant women acquired HIV through vertical transmission themselves. For the remaining 21 women, the mode of acquisition was unknown (*Table 8.1A*).

Population no longer in care

Based on SHM data, a total of 43 (7%) women were no longer in care in the Netherlands; of these:

- 17 (3%) were known to have moved abroad,
- 21 were lost to follow-up (3%) and
- 5 (1%) women were documented to have died during follow up.

No significant differences were observed between women of Dutch and non-Dutch origin in terms of those lost to follow-up. Of the women lost to follow-up, all except one women were lost to follow-up after their pregnancy ended; with a median time between delivery and last clinical visit of 19 months (IQR: 2-61) and 19 women had at least one clinical visit after the pregnancy Of the women who were lost to follow-up:

- seven women started ART during their pregnancy, all were newly diagnosed with HIV;
- all but one woman had a documented ART regimen reported during their last clinical visit; and
- three women had detectable HIV RNA results (min RNA= 591 and max= 34,144 copies/ml) during the last clinical visit.

In total, 16 of the 21 pregnancies among women who became eventually lost to follow-up resulted in a live-birth, two in an abortion and three in a miscarriage before 24 weeks. Vertical transmission or breastfeeding at the time of last clinical visit was not reported in any of the pregnancies.

Five of the 620 women with a pregnancy between 2016 and 2023 were documented to have died during follow up, after their pregnancy. Their median age was 39 years (IQR: 32-44). Three of the five women delivered a child and in two cases the pregnancy was ended by induced abortion. Two out of five women died of aids related causes and for two women the cause of death was a non-aids related malignancy.

***Box 8.1:** Identifying socio-demographic and socio-economic characteristics of pregnant women with HIV, using data from Statistic Netherlands*

Background

Perinatal transmission of HIV has reduced since ART became available for pregnant women. However, timely initiation of ART is important. Therefore, pregnant women in the Netherlands are screened for HIV through the Dutch national pregnancy screening program. The HIV prevalence observed in this program has been stable over the last few years at 0.05%[1]. We identified socio-demographic and economic characteristics of pregnant women with HIV and compared these with characteristics of pregnant women without HIV.

Methods

Data from SHM provide some information on socio-demographic characteristics of pregnant women with HIV (e.g. age and gender at birth). However SHM is unable to provide other societal characteristics of pregnant women such as socio-economic status or education level. To fill in these gaps in knowledge, SHM analyzed non-public data from Statistics Netherlands (CBS). CBS is an independent organization that collects, processes and publish statistical data on Dutch residents (*Chapter 3*). Data of women registered by SHM and who were pregnant

during the years 2016-2023 were combined with data from CBS. These data were analyzed within a secure CBS environment. Socio-demographic and economic characteristics of women diagnosed in the pregnancy were compared to a random selection of 1% of women without HIV who declared pregnancy-related health costs in 2020. To minimize the risk of data leading to the identification of an individual, results including less than 10 observations were not reported. Results are based on calculations by SHM using non-public microdata from Statistics Netherlands and Vektis C.V.

Results

529 (85%) out of the of 620 pregnant women with HIV registered and monitored by SHM between 2016-2023 could be combined with available CBS data in the same year as the onset of the pregnancy.

Pregnant women with HIV and time of HIV diagnosis.

Of the women with HIV who were pregnant between 2016 and 2023, 458 were diagnosed with HIV before their pregnancy in the observation period, whilst 71 women were diagnosed HIV during the pregnancy.

Compared to already diagnosed women, newly diagnosed women were more often (*Figure Box 8.1*):

- aged below 25 years (24% vs 10%),
- had a second generation migration background (18% vs 13%),
- lived in a household without children (32% vs 16%) and
- lived in a middle or low urbanized region (27% vs 22%)

Newly diagnosed women during the pregnancy

To identify socio-demographic and economic characteristics of women who were newly diagnosed with HIV during the pregnancy, socio-economical characteristics of the 71 newly diagnosed pregnant women were compared with 2,987 pregnant women without HIV.

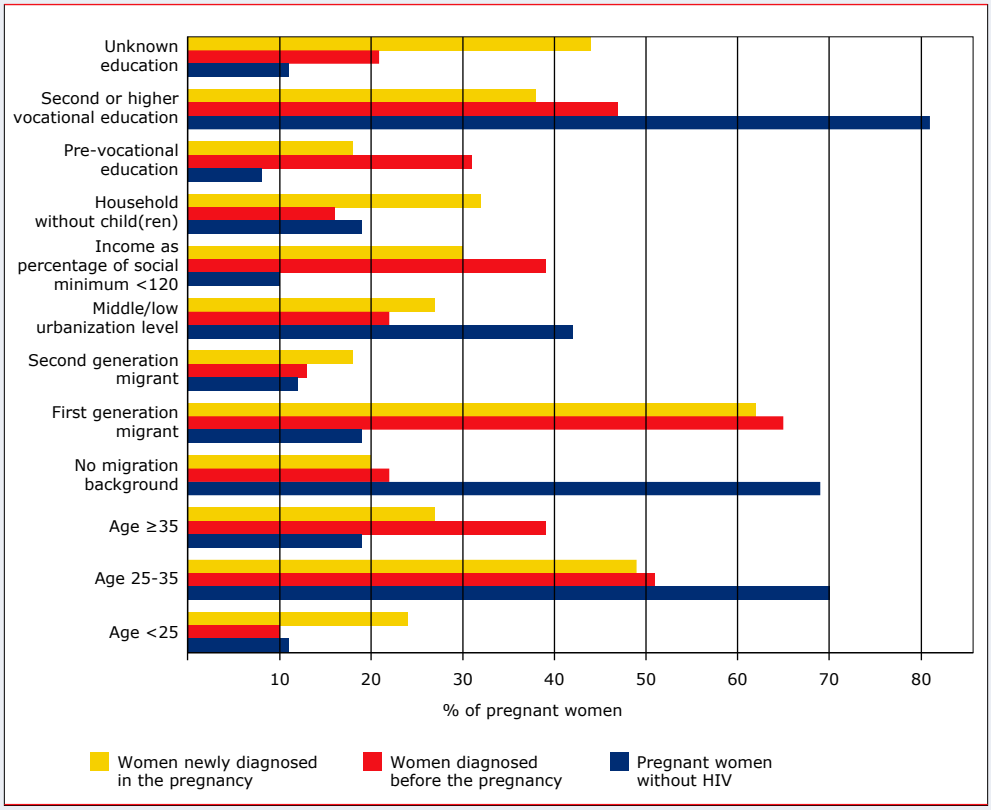
Compared to the general population of pregnant women without HIV, newly diagnosed women(*Figure Box 8.1*):

- more often had a first or second generation migration background (62% and 18% vs 19% and 12%)
- more often had an income below 120% of the social minimum (30% vs 10%)
- more often lived in a household without children (32% vs 19%) and
- less often lived in a middle or low urbanized region (27% vs 42%).

Conclusions

Compared to pregnant women with a known HIV status, women who were newly diagnosed during a pregnancy in or after 2016 were younger and more often had a second generation migration background. When compared to the general population of pregnant women, women who were newly diagnosed with HIV in the pregnancy, more often lived in a household without children, and had a lower income. These data provide more insight into sub-populations of women with potentially higher HIV prevalence, which may help in developing prevention and screening strategies. Women newly diagnosed with HIV in the pregnancy more often had a migration background, including women with a second generation migration background. These are women who are born in the Netherlands and who had at least one parent who was born abroad. However, one fifth of newly diagnosed women did not have a migration background. This finding confirms the need of the universal pregnancy screening for HIV.

Figure Box 8.1: Socio-demographic and socio-economical description of women with HIV and a documented pregnancy between 2016 and 2023.



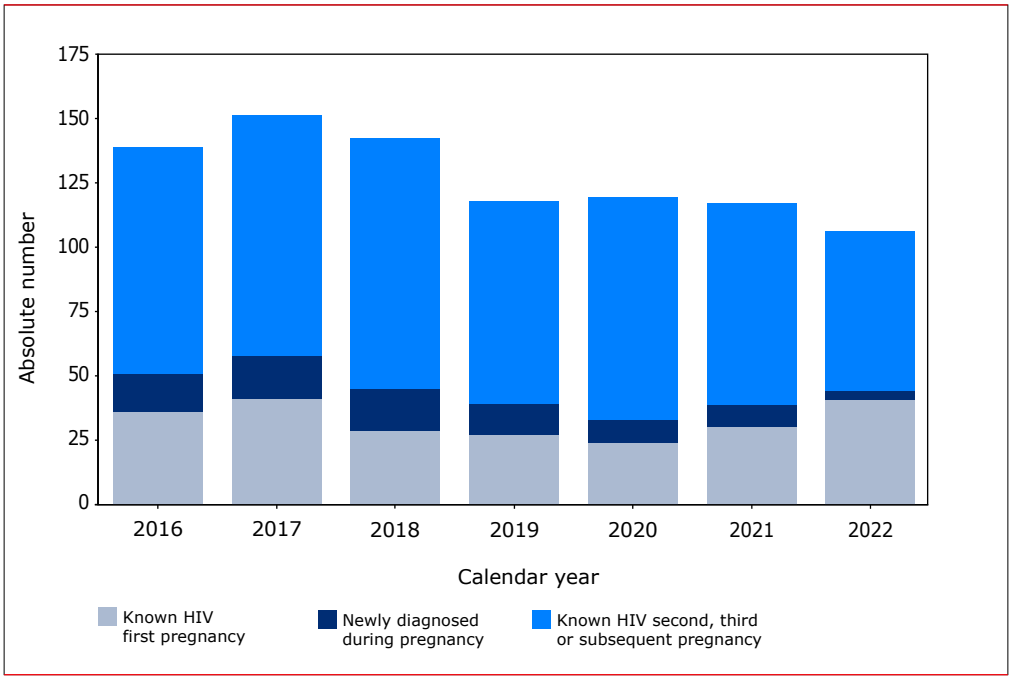
Reference

1. Procesmonitor PSIE 2022. RIVM/TNO 2024 C.P.B. van der Ploeg (TNO), J.A.M. Odijk (RIVM), M. van Lent (RIVM)

Number of pregnancies in women with HIV over time

In total, 940 pregnancies among the 620 women were reported between 2016 and 2023. The absolute annual number of pregnancies in women with HIV in care in the Netherlands is following a downward trend from 151 in 2017 to 106 in 2022 (*Figure 8.1.*)The median age of women in care was 45 years (IQR: 38-25) in 2016 and 49 years (IQR: 41-58) in 2022. The downward trend in the absolute number of pregnancies is possibly reflecting the increasing age of women in care. The number of women newly diagnosed with HIV during pregnancy varied between 17 in 2017 and three in 2022, but varied as a proportion of the total number of pregnancies per year, between 3-11%. The number of second, third or subsequent pregnancies in women who had already received an HIV diagnosis was approximately 80 per year (*Figure 8.1*).

Figure 8.1: *Absolute number of first and subsequent pregnancies per year, stratified by whether HIV status was already known before pregnancy, or newly diagnosed during pregnancy. Note: there is backlog in data collection of pregnancy related data for pregnancies starting in the most recent year in the SHM database (2023). Therefore, the most recent calendar year is not shown in the figure.*



Pregnancy-related characteristics

Overall, 620 women accounted for 940 registered pregnancies: 22% of the women had one registered pregnancy, 27% had two registered pregnancies, and 52% of the women had three or more registered pregnancies (*Table 8.1B*).

***Table 8.1A:** Maternal characteristics: of pregnant women with HIV registered and monitored by stichting hiv monitoring between 2016-2023*

	Total	Nether-lands	Sub-Saharan Africa	Caribbean/ South America	Other	p
Total number of women N (%)	620	170 (27.4)	276 (44.5)	82 (13.2)	92 (14.8)	
HIV diagnosis before pregnancy	534 (86.1)	148 (87.1)	239 (86.6)	70 (85.4)	77 (83.7)	0.880
Newly diagnosed during pregnancy	86 (13.9)	22 (12.9)	37 (13.4)	12 (14.6)	15 (16.3)	
Age at start of first pregnancy following HIV diagnosis Median (IQR)	33.3 (29.2 to 37.0)	31.9 (28.1 to 35.9)	33.6 (29.4 to 37.0)	34.4 (29.9 to 38.1)	34.1 (29.7 to 38.6)	0.011
HIV transmission route						
Heterosexual contact	548 (88.4)	151 (88.8)	252 (91.3)	79 (96.3)	66 (71.7)	<0.001
Vertical transmission	39 (6.3)	9 (5.3)	6 (2.2)	1 (1.2)	23 (25.0)	
Other~	33 (5.3)	10 (5.9)	18 (6.5)	2 (2.4)	3 (3.3)	
First CD4 count in pregnancy Median (IQR)	547.0 (380.0 to 750.0)	611.0 (447.0 to 830.0)	498.5 (360.8 to 712.5)	590.0 (362.5 to 764.2)	500.0 (371.2 to 750.0)	0.021
CD4 percentage Median (IQR)	32.2 (23.4 to 39.1)	36.9 (28.2 to 40.6)	28.8 (21.8 to 36.8)	35.0 (21.8 to 39.8)	32.3 (26.1 to 38.0)	0.018
First CD4 count when newly diagnosed during pregnancy Median (IQR)	340.0 (210.0 to 453.0)	355.0 (293.0 to 520.0)	270.0 (165.8 to 432.8)	408.0 (219.0 to 470.0)	320.0 (265.0 to 390.0)	0.375
CD4 percentage when newly diagnoses during pregnancy Median (IQR)	22.4 (15.8 to 26.0)	27.8 (24.5 to 33.3)	20.9 (13.2 to 23.0)	16.5 (13.8 to 21.9)	21.1 (19.3 to 22.8)	0.081

~ *Mode of HIV transmission was exposure to contaminated blood (n=9), injecting drug use (n=3), unknown (n=21).*

Table 8.1B: Pregnancy-related characteristics of pregnant women with HIV registered and monitored by stichting hiv monitoring between 2016-2023

	Total	Nether-lands	Sub-Saharan Africa	Caribbean/ South America	Other	p
Total number of pregnancies N (%)	940	252 (26.8)	430 (45.7)	119 (12.7)	139 (14.8)	
Total number of pregnancies ever after 2016						
3	487 (51.8)	114 (45.2)	248 (57.7)	61 (51.3)	64 (46.0)	0.039
2	249 (26.5)	75 (29.8)	96 (22.3)	34 (28.6)	44 (31.7)	
1	204 (21.7)	63 (25.0)	86 (20.0)	24 (20.2)	31 (22.3)	
Pregnancy outcome						
Delivery after at least 24 weeks	617 (65.6)	168 (66.7)	278 (64.7)	73 (61.3)	98 (70.5)	0.276
Miscarriage or stillbirth, <24 weeks	201 (21.4)	48 (19.0)	100 (23.3)	23 (19.3)	30 (21.6)	
Induced abortion, <24 weeks	119 (12.7)	35 (13.9)	50 (11.6)	23 (19.3)	11 (7.9)	
Unknown	3 (0.3)	1 (0.4)	2 (0.5)			
Mode of delivery						
Vaginal	421 (44.8)	128 (50.8)	179 (41.6)	45 (37.8)	69 (49.6)	0.134
Caesarean, secondary	95 (10.1)	24 (9.5)	46 (10.7)	12 (10.1)	13 (9.4)	
Caesarean, elective	94 (10.0)	15 (6.0)	47 (10.9)	16 (13.4)	16 (11.5)	
Pregnancy duration was <24 weeks	324 (34.5)	84 (33.3)	153 (35.6)	46 (38.7)	41 (29.5)	
Unknown	7 (1)	1 (<1)	6 (1)	0	0	
Pregnancy duration						
>=37 weeks	542 (57.7)	141 (56.0)	249 (57.9)	64 (53.8)	88 (63.3)	0.235
32-37 weeks	61 (6.5)	24 (9.5)	20 (4.7)	9 (7.6)	8 (5.8)	
24-32 weeks	13 (1.4)	3 (1.2)	8 (1.9)	0	2 (1.4)	
<24 weeks	324 (34.5)	84 (33.3)	153 (35.6)	46 (38.7)	41 (29.5)	
Unknown	1|(<1)	0	1|(<1)	0	0	
Birth weight (grams) Median (IQR)	3100.0 (2770.0 to 3470.0)	3117.5 (2693.8 to 3411.0)	3100.0 (2790.0 to 3515.0)	3038.0 (2780.0 to 3470.0)	3115.0 (2822.5 to 3523.0)	0.639
Perinatal death	5 (0.5)	2 (0.8)	3 (0.7)	0	0	0.587

Table 8.1C: ART initiation among pregnant women with HIV registered and monitored by stichting hiv monitoring between 2016–2023

	Total	Nether-lands	Sub-Saharan Africa	Caribbean/ South America	Other	p
Total N (%)	617	168 (27.2)	278 (45.1)	73 (11.8)	98 (15.9)	
Antiretroviral therapy started						
Before pregnancy	521 (84.4)	145 (86.3)	232 (83.5)	61 (83.6)	83 (84.7)	0.724
During pregnancy	96 (15.6)	23 (13.6)	46 (16.5)	12 (16.4)	15 (15.3)	
No antiretroviral therapy during pregnancy	0	0	0	0	0	0.011
Latest available plasma HIV RNA level prior to delivery						
<50 copies/ml	586 (95.0)	163 (97.0)	257 (92.4)	71 (97.3)	95 (96.9)	0.286
50–500 copies/ml	17 (2.8)	4 (2.4)	10 (3.6)	2 (2.7)	1 (1.0)	
>500 copies/ml	4 (0.6)	0	4 (1.4)	0	0	
Unknown	10 (1.6)	1 (0.6)	7 (2.5)	0	2 (2.0)	
Time between delivery and latest HIV RNA measurement (weeks)						
Median (IQR)	2.6 (1.0 to 4.3)	2.6 (1.1 to 4.4)	2.6 (0.9 to 4.1)	2.9 (1.4 to 4.4)	2.6 (0.8 to 4.2)	0.857

Pregnancy outcome

The 940 pregnancies resulted in 617 (65%) births ≥24 weeks (including both live and stillbirths), including 10 twin pregnancies. A total of 320 (34%) pregnancies ended in miscarriage or still birth <24 weeks or abortion; 201 (21%) were miscarriages or still births<24 weeks and 119 (13%) were abortions. For the remaining three (<1%) pregnancies, the outcome is unknown due to missing data.

Pregnancy duration, preterm birth and perinatal death

A total of 617 pregnancies lasted at least 24 weeks and are therefore counted as a birth. The duration of these pregnancies is known in 616 cases. Overall, 542 of 617(88%) pregnancies lasted at least 37 weeks, whereas 74 (12%) pregnancies resulted in preterm birth (defined as a pregnancy duration of 24-37 weeks). The prevalence of preterm birth is higher compared to that in the general population (7%)[29]. It is worth noting that 44% of the preterm births had a pregnancy duration of 36 weeks.

Perinatal death, including antepartum death, occurred in five (1%) births. Congenital disorders were registered for 15 infants.

Mode of delivery

If viral suppression during pregnancy can be achieved with ART, vaginal delivery is recommended for women with HIV[10,11]. However, in the presence of detectable HIV RNA levels at, or near the time of delivery, elective Caesarean section is recommended to minimise the risk of vertical transmission. The European AIDS Clinical Society (EACS) guidelines state that elective Caesarean section should be carried out if HIV RNA concentration is above 50 copies/ml in weeks 34-36 of pregnancy[12], whereas Dutch guidelines allow a vaginal delivery with HIV RNA below 500 copies/ml and declining viral loads[13]. In such cases intravenous zidovudine is given during labour.

Overall, 68% of newborns were delivered vaginally; 76% of the women of Dutch origin delivered vaginally, compared to 64% of women of SSA origin or 61% of women of Latin America or Caribbean origin. Fifteen percent of newborns were delivered by an elective Caesarean section and another 16% by a secondary Caesarean section.

In terms of mode of delivery, 98% of the women who delivered vaginally had an HIV RNA below 50 copies/ml. This figure was 94% for women who delivered by elective Caesarean section, and 91% for those with a secondary (unplanned) Caesarean section ($p<0.0001$). Among women who delivered by secondary Caesarean section, the HIV RNA was between 53 and 550 copies/ml. The most common reported reasons for Caesarean section were foetal distress and failure to progress in the second stage of labour.

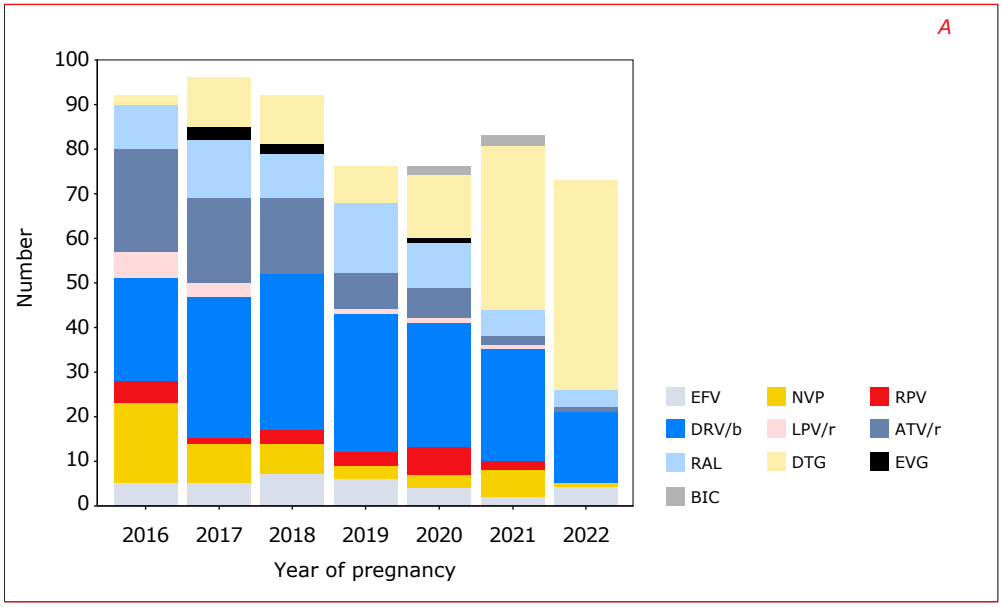
A therapy (ART) uptake and therapy response in pregnant women

Therapy uptake

From 2016 onwards, during the 617 pregnancies lasting at least 24 weeks, all women received ART: in 521 (84%) pregnancies, women were already on ART at the time of conception, while in 96 (16%) pregnancies, ART was started during pregnancy (*Table 8.1C*).

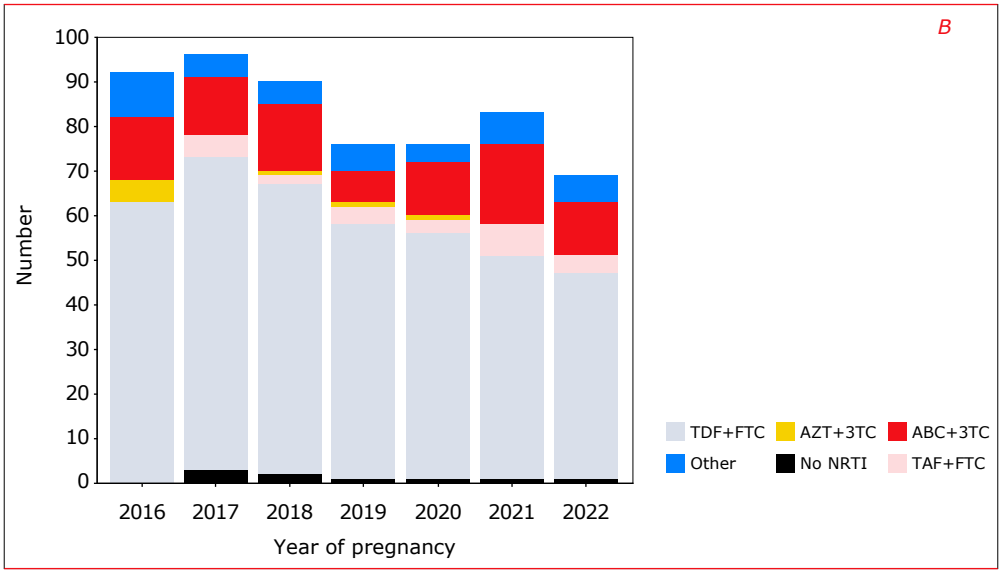
For 613 out of the 617 pregnancies, information on ART regimens was available. *Figure 8.2A* shows the most commonly used third-drug additions to the nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone as part of ART in pregnant women and during delivery between 2016 and 2022. The use of integrase inhibitors (INSTI) in pregnancy increased from 4% in 2016 to 55% in 2022. This increase coincides with a decrease in the use of NNRTI-containing regimens from 30% in 2016 to 7% in 2022 and a decrease in the use of PI from 55% to 23%(*Figure 8.2C*). In 13 pregnancies a two-drug regimen was used, which were combinations of NRTI+INSTI or PI+INSTI.

Figure 8.2A: *The most commonly used third-drug additions to the nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone used as part of ART regimens during pregnancies in 2016-2022 with an minimum duration 24 weeks.*



Note: *there is backlog in data collection of pregnancy related data for pregnancies starting in the most recent year. Therefore, the most recent calendar year is not shown in the figure.*

Figure 8.2B: *The nucleoside reverse transcriptase (NRTI) backbone used as part of ART regimens during pregnancies in 2016-2022 with an minimum duration 24 weeks.*



Note: *there is backlog in data collection of pregnancy related data for pregnancies starting in the most recent year in the SHM database (2023). Therefore, the most recent calendar year is not shown in the figure.*

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

Figure 8.2C: Antiretroviral class use stratified by calendar year period regimens during pregnancies in 2016–2022, with an minimum duration 24 weeks. Note: there is backlog in data collection of pregnancy related data for pregnancies starting in the most recent year in the SHM database (2023). Therefore, the most recent calendar year is not shown in the figure.

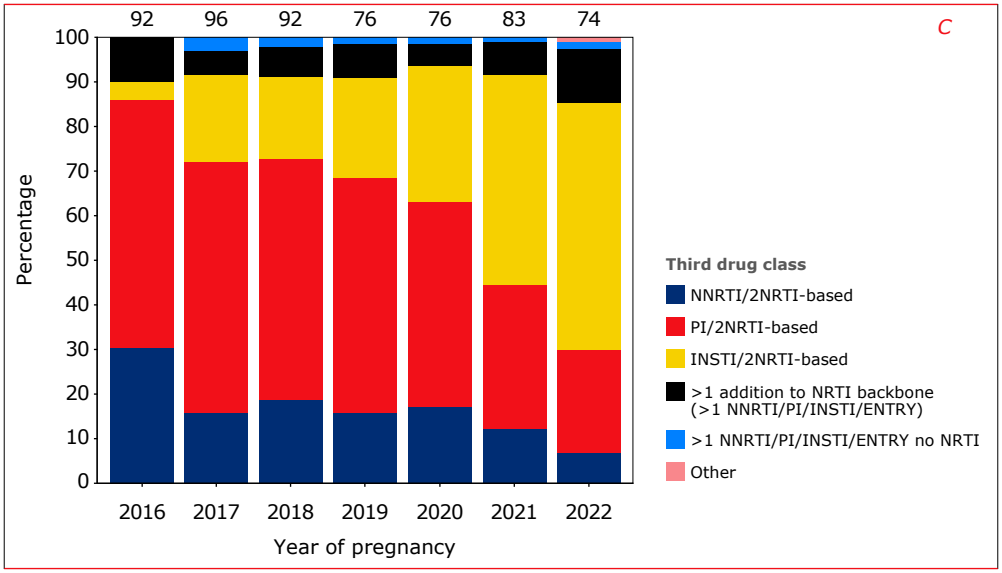


Figure 8.2B provides an overview of the components of the NRTI backbone used during pregnancy between 2016 and 2022. The most commonly prescribed backbone was the combination of tenofovir disoproxil fumarate and emtricitabine (TDF+FTC) (69%), followed by a combination of abacavir and lamivudine (ABC+3TC) (16%).

A switch in ART regimen was reported during 191 pregnancies. While no reason was documented in 5 cases, the most common documented reason for switching in the remaining pregnancies was pregnancy-related (n=128). In 40% of the pregnancy-related switches a cobicistat-boosted regimen was discontinued. Other common pregnancy-related switches included ART that was switched from an integrase-containing regimen to a protease inhibitor (darunavir or atazanavir). Other common switches were within the class of integrase inhibitors, particularly from dolutegravir or elvitegravir to raltegravir. After switching, 2% of the women used a regimen which included a non-preferred antiretroviral (ARV) agent, except in the special circumstances outlined in the most recent guidelines[14].

Due to reduced serum levels of cobicistat during the second and third trimesters of pregnancy, and hence also reduced levels of darunavir and elvitegravir when boosted with cobicistat, regimens containing cobicistat were no longer recommended during pregnancy from 2018 onwards[15]. In the Netherlands, cobicistat at the time of delivery was used in four pregnancies between 2018 and 2022. All women had an HIV RNA level below 50 copies/ml at the time of delivery.

Therapy response

Figure 8.3 shows the percentage of women on ART and their latest available plasma HIV RNA level prior to delivery. HIV RNA levels were categorised as below 50 copies/ml, 50-500 copies/ml, and above 500 copies/ml.[a]

In 97% of the overall births, the mothers had an HIV RNA level below 50 copies/ml at the time of delivery, and 3% had an HIV RNA level above 50 copies/ml. The proportion of women with an HIV RNA below 50 copies/ml at the time of delivery was above 95% in all years, with exception of 2017.

In total, 20 women had HIV RNA levels above 50 copies/ml (50-500 copies/ml: n=16, >500 copies/ml: n=4, median RNA=128 copies/ml; minimum=53, maximum= 15500) prior to delivery.

a Dutch guidelines allow a vaginal delivery with HIV RNA below 500 copies/ml and declining viral loads[13] or with a undetectable HIV RNA <50 or <20 copies/ml, depending on the used assay. Elite controller or long-term non-progressor refers to an individual with HIV who is able to control HIV without ART and maintain a CD4 cell count in normal range.

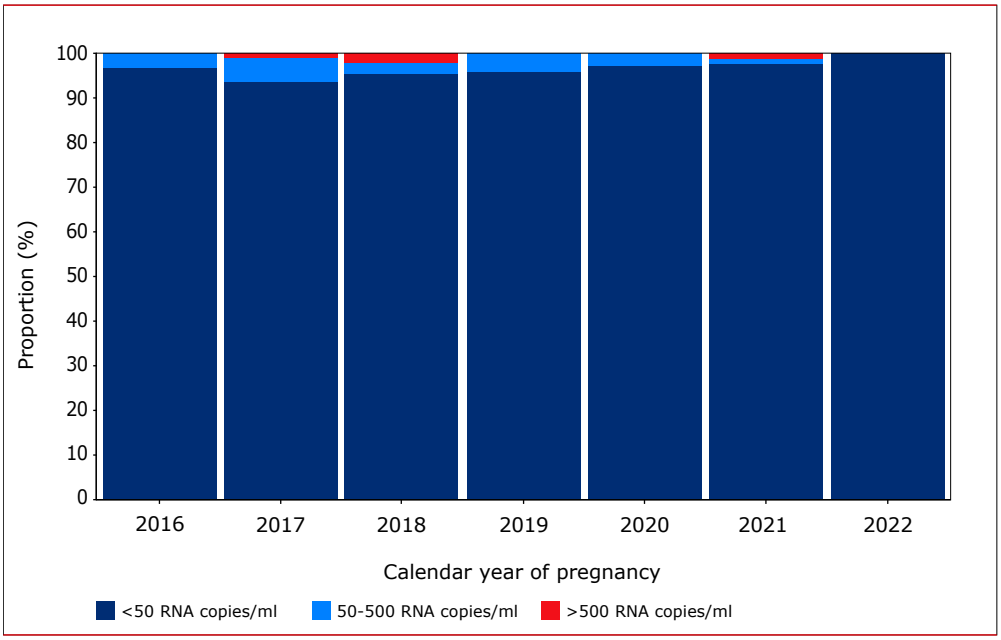
Table 8.2: Overview of characteristics of women with a detectable HIV RNA level prior to delivery.

Women with detectable HIV RNA	20 (n,%)	
Newly diagnosed during pregnancy	8 (40)	6 women were diagnosed after the first trimester.
ART initiated during pregnancy	8 (40)	
ARV at time of detectable HIV RNA*		
INSTI-containing	9 (45)	
NNRTI-containing	2 (10)	
PI-containing	8 (40)	
Unknown regimen	1 (5)	
Mode of delivery		RNA (minimum; maximum)
Caesarean section	13 (65)	53, 15500 copies/ml
Vaginal	6 (30)	70, 1003 copies/ml
Unknown	1 (5)	
Zidovudine during delivery		
Yes	13 (65)	
No	6 (30)	
Unknown	1 (5)	
Evaluation of drugs resistance	14	4/14 women with a sequence were found to have high-level drug-resistance to at least one NNTRI; 3/4 had a sequence within 4 months after the start of ART and for 1 woman resistance was evaluated for the first time more than 4 months after ART was initiated and was evaluated in the pregnancy.

**None of the women used a two-drug regimen at time of detectable HIV RNA*

At time of database closure, no vertical transmission was reported among the infants born to mothers who had HIV RNA levels above 50 copies/ml at the time of delivery.

Figure 8.3: Distribution of women using ART with their latest HIV RNA levels prior to delivery: <50 copies/ml, 50-500 copies/ml, or >500 copies/ml for pregnancies with a minimum duration of 24 weeks.



Note: there is backlog in data collection of pregnancy related data for pregnancies starting in the most recent year in the SHM database (2023). Therefore, the most recent calendar year is not shown in the figure.

Vertical transmission rate in the Netherlands

Between 2016 and 2023, 617 births were registered in the Netherlands among mothers who knew they had HIV prior to conception, or were first diagnosed during pregnancy. All mothers received ART during their pregnancy. Vertical transmission in the Netherlands has become extremely rare and this resulted in a very low vertical transmission rate in pregnant women on ART in the Netherlands, which is in line with low reported vertical transmission rates in other western European countries[16,17,18,19]. To avoid inadvertently identification of individuals in cases of rare events (which we defined as <5), we will not report the rate of vertical transmission.

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 therapy and virological suppression rates during the postpartum period, as well as breastfeeding rates.

Therapy

Of the 617 pregnancies lasting 24 weeks or longer, 81 were excluded from this analysis: 57 because of insufficient follow up between delivery and the time of database closure; and 24 because the women were no longer in care (one had moved abroad and nine were reported as lost to care during the postpartum period).

For the remaining 536 pregnancies in 436 women, ART was initiated before conception or during pregnancy in 80% and 20% of cases, respectively. The majority of women used an integrase inhibitor-containing regimen during the postpartum period (47%). The use of integrase inhibitor increased from 24% in 2016, to 58% in 2020 and 61% in 2023.

In 34 of these 536 pregnancies, ART was discontinued postpartum:

- The most common documented reason was a decision by the patient (n=21).
- In two cases the documented reason was elite controller or long-term non-progressor.[b]
- In 3 cases the documented reason was toxicity.
- And in 8 cases the documented reason was end of pregnancy.

In 15 out of the 34 cases, therapy was restarted after a median of five weeks (IQR 3-11). In the remaining 19 cases, ART was not restarted postpartum, however 12 women did start again after the postpartum period had ended. Six women did not have a documented restart of ART at the time of database closure.

Virological outcome

Detectable viremia postpartum was defined as at least one HIV RNA measurement above 50 copies/ml during the postpartum period. On the basis of this definition:

- Detectable HIV RNA >50 copies/ml was observed in 14% of the 536 pregnancies analysed. When taking into account >200 copies/ml, 9% of the pregnancies had a detectable HIV RNA.

b Elite controller or long-term non-progressor refers to an individual with HIV who is able to control HIV without ART and maintain a CD4 cell count in normal range.

For the subset of women with documented continued use of ART postpartum:

- 55 (11%) had an HIV RNA level above 50 copies/ml (median HIV RNA=257 copies/ml, minimum=52 and maximum=85900 copies/ml)
- and 31 (6%) had a HIV RNA level above 200 copies/ml,
- 23 of whom had more than one episode of an HIV RNA level above 50 copies/ml during the postpartum period.
- Twelve of the 55 women with an HIV RNA above 50 copies/ml were newly diagnosed with HIV during the pregnancy, whilst 43 women were diagnosed before the onset of the pregnancy and had also already started ART. Seventy-four percent (n=32) had earlier episodes of detectable HIV RNA levels more than 6 months after the start of ART.

In the 34 women who discontinued the use of ART postpartum:

- 19 (56%) experienced viral rebound (median HIV RNA=19,800 copies/ml, minimum 617 and maximum 450000 copies/ml).
- 13 women had an undetectable HIV RNA level during the post-partum period, including 8 women who did not restart ART after discontinuing therapy during the postpartum period;
  - Three of these 8 women continued to report high CD4 cell counts and low HIV RNA levels in the absence of ART;
  - Three experienced a viral rebound after the postpartum period;
  - Five cases remained virally suppressed (two of whom eventually restarted ART).

Breastfeeding

The option of breastfeeding for women with sustained virological suppression is discussed based on shared decision-making in the Netherlands. Breastfeeding in such cases is recommended for a maximum of six months.

Breastfeeding data were available for 470 of the 536 pregnancies, and was reported in 39 pregnancies (the duration of breastfeeding was not documented). It is noteworthy that all women had documented use of ART and that all except one women had HIV RNA levels below 50 copies/ml during the first 6 months of the postpartum period. In one case the measured HIV RNA was below 75 copies/ml and the subsequent HIV RNA measurement was also undetectable, it is not registered if the mother was breastfeeding at time of these HIV RNA measurements. The median number of HIV RNA measurements during the first 6 months after delivery among the 39 pregnancies with reported breastfeeding was 2 HIV RNA measurements (IQR 1-4 measurements). No cases of vertical transmission were documented.

Summary and conclusions

All women with a registered pregnancy since 2016 have received ART during their pregnancy. More than 97% had an HIV RNA level below 50 copies/ml around the time of delivery and 99% had an HIV RNA level below 500 copies/ml. Vertical transmission in the Netherlands has become very rare, resulting in a very low vertical transmission rate in pregnant women using ART during the period 2016 to 2023. This finding is comparable to the low figures reported in other western European countries[16,17,18,19].

A small proportion of women had detectable HIV RNA levels near the time of delivery. This included women who were newly diagnosed with HIV and thus started ART during the pregnancy, and women who were already using ART at conception but had earlier episodes of detectable HIV RNA levels. To maintain a low rate of vertical transmission of HIV, it is important to provide multidisciplinary care for – and close monitoring of – women newly diagnosed with HIV after conception, as well as those with a history of virological failure.

Although most women were aware of their HIV status prior to their pregnancy, 14% were newly diagnosed during pregnancy. Based on SHM data, 27% of the women originated from the Netherlands and 73% were of non-Dutch origin. Interestingly, a substantial number of women who were newly diagnosed in their pregnancy had an earlier recorded negative HIV test. Unfortunately data on the reason for these earlier tests is not collected. Hence it is not known whether these tests were part of the national pregnancy screening brought about by an earlier pregnancy, or because of other underlying reasons for testing.
In most of newly diagnosed women, the diagnosis was a result of the national pregnancy screening for HIV, syphilis and hepatitis B (PSIE)[21]. This screening is offered to all women in the first trimester of pregnancy. However, our data showed that some women received their HIV diagnosis during the second or third trimester of pregnancy, which could complicate the timely start of ART. It should be pointed out that in the general population timely screening within PSIE is only achieved in 75% of all women[22]. This may be a result of late booking of the first antenatal clinical visit. However, PSIE reports a decline in timely screening since the introduction of the non-invasive prenatal testing (NIPT)[21]. This test was allowed after 11 weeks of pregnancy and may result in taking a single blood sample to test for HIV, HBV and syphilis as well as the NIPT test, at the same time.
Due to technical improvements, the NIPT is offered from 10 weeks pregnancy onwards as from April 2023 as part of the national pre- and neonatal screening programme[20].

Finally, ART has been recommended for all individuals regardless of CD4 cell count since 2015, including postpartum. We observed an increasing proportion of women who received integrase inhibitors during pregnancy as well as during the postpartum period. From 2016 onwards, 11% of women who continued to use ART postpartum had at least one episode of viraemia. In earlier studies, adherence to therapy has been reported to deteriorate during the postpartum period[23,24,25,26,27,28].

The proportions of preterm births and Caesarean sections among women with HIV were higher than those observed in the general population (12% and 31% compared to 7% and 17%[29]). Other studies have found a high prevalence of caesarean sections in women with undetectable HIV RNA levels[30], compared to the general population[31] or a higher rate of premature delivery[40]. However as invasive perinatal procedures, such as foetal blood sampling or the placement of a foetal scalp electrode, are contraindicated in women with HIV[13] the threshold to perform a Caesarean section is generally lower. It is not clear whether this lower threshold contributed to the higher number of Caesarean sections observed. In addition, premature delivery has been linked to ART use, especially in the first 12 weeks of pregnancy[32,33,34]. As the aetiology of preterm delivery is complex and multifactorial, it is unclear whether this or other, for example socio-economic factors, can explain the high proportion of preterm births[35]. The association between various ARVs and adverse pregnancy outcomes, including low birthweight, has been evaluated in different studies, with conflicting results[36].

Recommendations

As a result of changes in the guidelines concerning treatment of HIV in 2015, ART is more likely to be used at conception and continued post-delivery. This is expected to result in a greater number of women with undetectable HIV RNA levels earlier in their pregnancy and around the time of delivery.

Women with HIV who start ART during pregnancy require a high degree of support; not only during the pregnancy itself to ensure suppressed HIV RNA levels at the time of delivery, but also post-partum to maintain adherence to ART, especially if they wish to breastfeed. As an alternative to formula feeding, some care providers now discuss the option of breastfeeding (for a maximum period of six months) with women who have sustained undetectable viremia and no issues with therapy or visit adherence, based on shared decision-making. This is not (yet) common practice throughout the Netherlands, but is expected to become more common in the next few years. Women who decide to exclusively breastfeed should be closely monitored clinically and virologically, along with their infants[37,38]. In the Netherlands, this monitoring is described in the HIV exposure follow up protocol for newborns[39].

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9. Quality of care

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Introduction

One of the missions of SHM is to contribute to the quality of HIV care in the Netherlands. Via the collection of pseudonymised data from patients in outpatient care at the 24 dedicated treatment centres, SHM can provide a nationwide overview of the outcome of care for patients. This unique overview allows SHM to facilitate assessment of the quality of HIV care in the Netherlands.

The Dutch Association of HIV-Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) has issued a variety of indicators to reflect the quality of health care provided to individuals with HIV. These include, for example, HIV outcome indicators (e.g., the percentage with HIV viral suppression), hepatitis B and C virus and syphilis screening for men who have sex with men (MSM) and percentage vaccinated against hepatitis B virus. Given the broad range of indicators, SHM, along with members of the Quality Commission from the NVHB, has decided to focus on only one set of key indicators that will be described in this year's report.

As individuals with HIV have increased their lifespans with the use of effective antiretroviral therapy, age-related comorbidities have increased in prevalence[1]. One of the more concerning comorbidities is cardiovascular disease[2]. Similar to last year's report, we have decided to bring more focus to primary and secondary prevention of cardiovascular disease. These include whether or not centres have provided information on smoking and other items that are needed for cardiovascular disease screening, such as total cholesterol, HDL- and LDL-cholesterol and blood pressure.

The SCORE-2 for individuals aged 40-69 years old and the SCORE2-OP for individuals 70 years old or older are often used in clinical care to understand the 10-year risk of developing a cardiovascular disease event for those who have not yet had such an event[3,4]. We also provide information on whether the SCORE2 or SCORE2-OP were able to be calculated for these age groups. For individuals with a 10-year risk of a cardiovascular disease event of 10% or higher, we report the percentage who received a prescription for statins and those with an LDL cholesterol at or below the recommended limits in Dutch guidelines (i.e., target LDL cholesterol)[5].

Finally, we report the percentage of individuals who had high blood pressure and received a prescription for antihypertensive medication and, conversely, the percentage of individuals who received an antihypertensive medication and had a blood pressure at or below the recommended limits in Dutch guidelines (i.e., target blood pressure)[5]. The full list of indicators, their definitions and in which populations these indicators were analyzed are provided in Box 9.1.

This analysis relates to all individuals who were diagnosed with HIV and who are currently in care at one of the 24 HIV treatment centres in the Netherlands. Considering that this chapter describes the role of the individual in a medical context, we describe all individuals with HIV who are receiving, or have received, medical care at an HIV treatment centre as patients. To facilitate presentation, we have decided to provide mostly figures describing changes over the last 5 years and comparison of indicators between individual centres and the national average. Indicators are reported for the 24 HIV treatment centres individually. Each HIV treatment centre is referenced by a number, which is used consistently across all figures in this chapter.

Box 9.1: Definitions of specific indicators and focus populations.

Specific indicator	Definition	Focus population
Information on smoking		
	The number of patients who ever gave information on their smoking status.	40 years old or older
Information needed for cardiovascular disease screening		
Any cholesterol	The percentage of patients who had a total, HDL or LDL cholesterol measurement during the calendar year.	40 years old or older
Blood pressure	The percentage of patients who had at least one blood pressure measurement during the calendar year.	
All cardiovascular parameters	The percentage of patients who had total, HDL and LDL cholesterol and blood pressure measurement during the calendar year.	
Information on cardiovascular event risk		
	The percentage of patients who had enough information to have their SCORE2(-OP) cardiovascular risk assessment during the calendar year.	40-69 year olds (SCORE2) or 70 year old or older (SCORE2-OP), without a history of CVD
Statin use		
	The percentage of patients who received a prescription for statins during the calendar year.	40 years old or older with SCORE2 or SCORE2-OP predicted 10-year risk greater than 10%, without a history of CVD[a]

a Details on these scores can be found on the following website: https://u-prevent.com and also references[3,4].

Target LDL cholesterol		
	The percentage of patients who had an LDL cholesterol level ≤2.6 mmol/mL during the calendar year.	40 years old or older with SCORE2 or SCORE2-OP predicted 10-year risk greater than 10%, without a history of CVD[a]
Antihypertensive medication use		
	The percentage of patients who received a prescription for antihypertensive medication during the calendar year.	All patients with high blood pressure[b]
Target blood pressure		
	The percentage of patients who had a systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg (for those 18-64 years old), or a systolic blood pressure <140 mmHg and diastolic blood pressure <80 mmHg (for those 65 years old or older)	All patients on antihypertensive medication

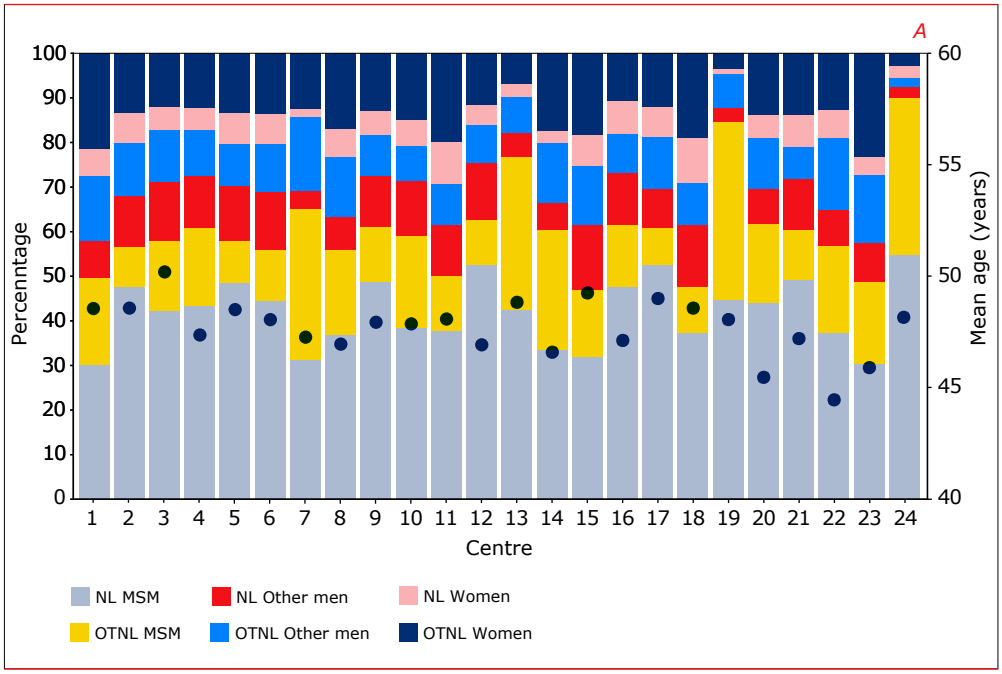
Abbreviations: *CVD = cardiovascular disease; HDL = high-dense lipoprotein; LDL = low-density lipoprotein.*

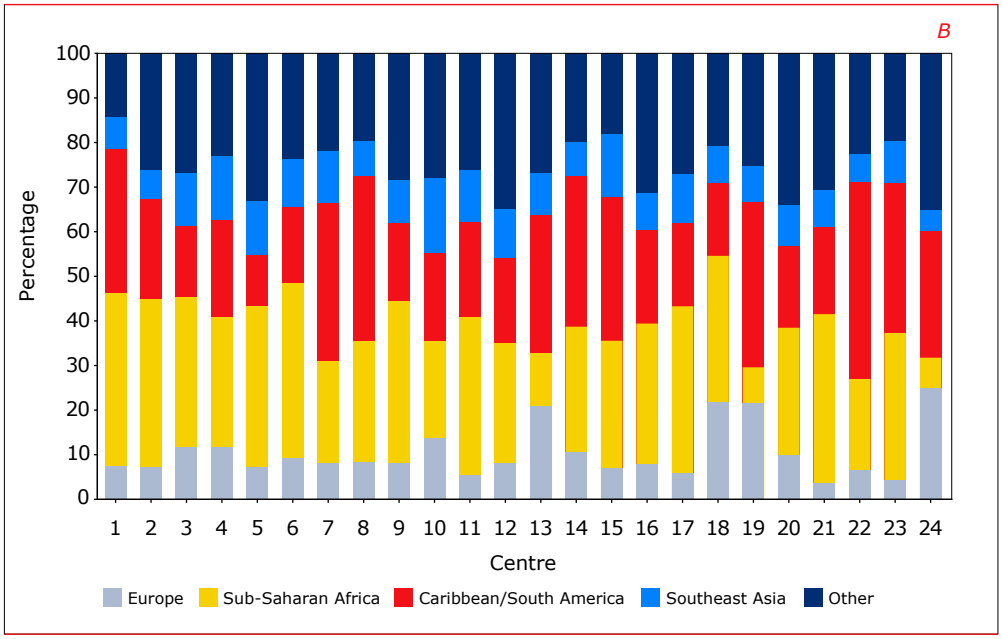
b Defined as a diastolic blood pressure ≥90 mmHg.

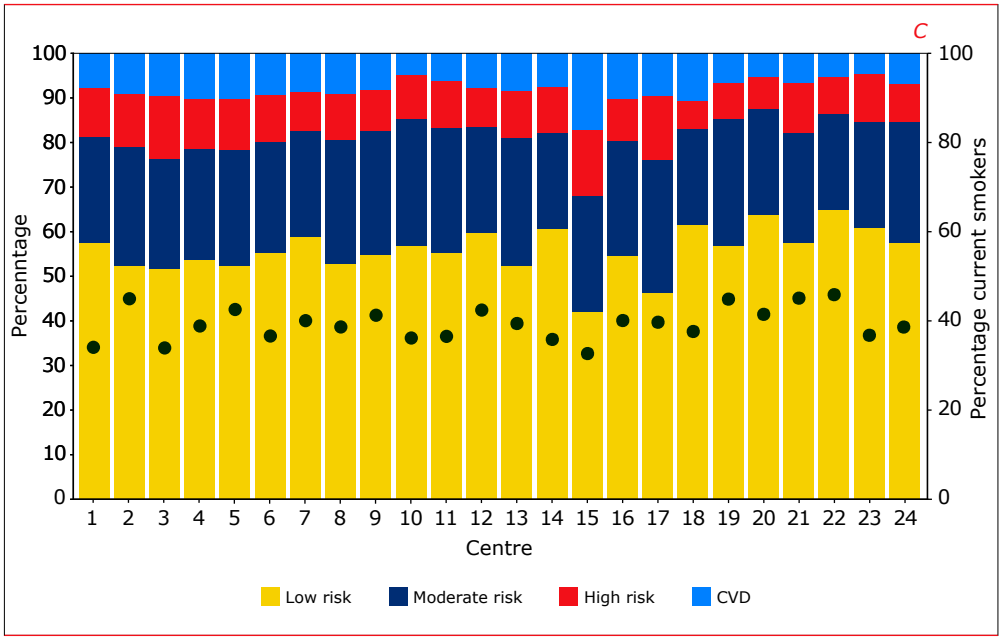
Centre overview

To provide an understanding of the patient 'mix' across centres, the distribution of geographical origin/mode of HIV acquisition/gender groups and age have been provided for each centre (*Figure 9.1A*). For patients who are other than Dutch, the distribution of region of origin is also given for each treatment centre (*Figure 9.1B*). Finally, the distribution of patients with low (<5%), moderate (5-10%), and high (>10%) predicted 10-year risk of cardiovascular disease, for those who have not had a cardiovascular disease event, and the percent with cardiovascular disease are also provided for each treatment centre (*Figure 9.1C*). Predicted 10-year cardiovascular risk was assessed with SCORE2 (i.e., 40-69 year olds) or SCORE2-OP (i.e., 70 year olds or older). These are presented alongside the percentage of patients who are currently smoking.

Figure 9.1: *Description of the patient 'mix' for patients in care (A) and distribution of region of origin for other than Dutch individuals living with HIV in care (B), as well as cardiovascular disease risk and smoking status (C), in 2023 in the Netherlands.*







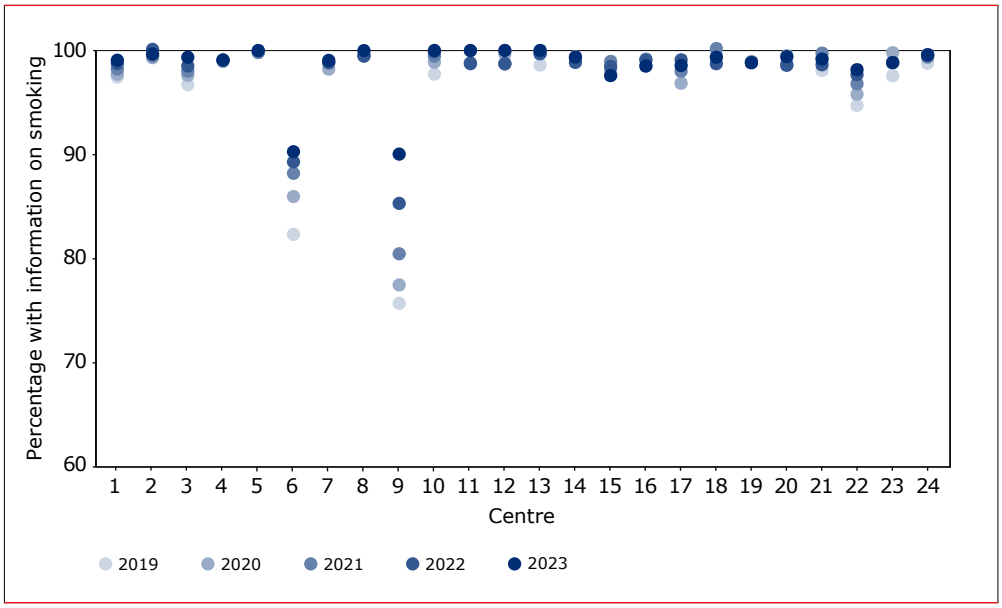
Note: *The bars in this chart show the percentage of individuals per centre according to geographical origin/ mode of transmission/gender group. In A, black dots represent the mean age of patients in care at each centre. In C, black dots represent the percent of current smokers of patients in care at each centre. This panel distinguishes those who already have cardiovascular disease (CVD) and those who are low, moderate or high risk according to the predicted 10-year cardiovascular risk with SCORE2 (i.e., 40-69 year olds) or SCORE2-OP (i.e., 70 year olds or older).*

Legend: *CVD=cardiovascular disease; MSM = men who have sex with men; MSW = men who exclusively have sex with women; OTNL = other than Dutch.*

Evolution of indicators over time

To provide an understanding of how indicators have evolved, each indicator in *Box 9.1* has been reported for its corresponding focus population on an annual basis between 2019 and 2023. For example, the indicator 'information on smoking' has been provided for individuals who were 40 years old or older and were in care in 2019, 2020, 2021, 2022, and 2023.

Figure 9.2: *Information on smoking; in other words, patients who ever had information on their smoking status during each year between 2019 and 2023.*

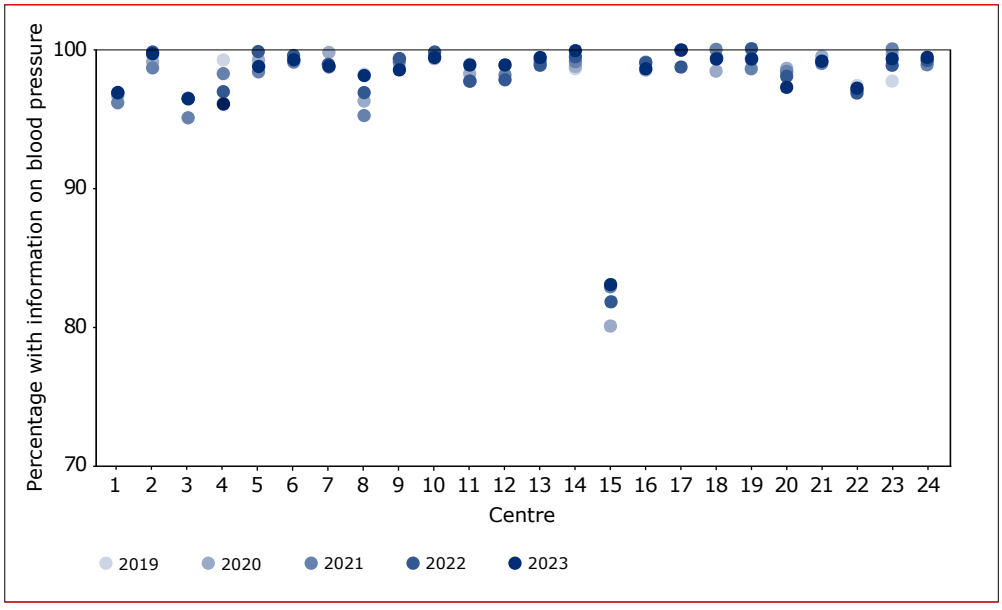


Legend: *Data are provided for patients 40 years old or older. Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 9.1.*

Figure 9.3: Information on any cholesterol; in other words, patients who had a total, LDL or HDL cholesterol measurement during each year between 2019 and 2023.

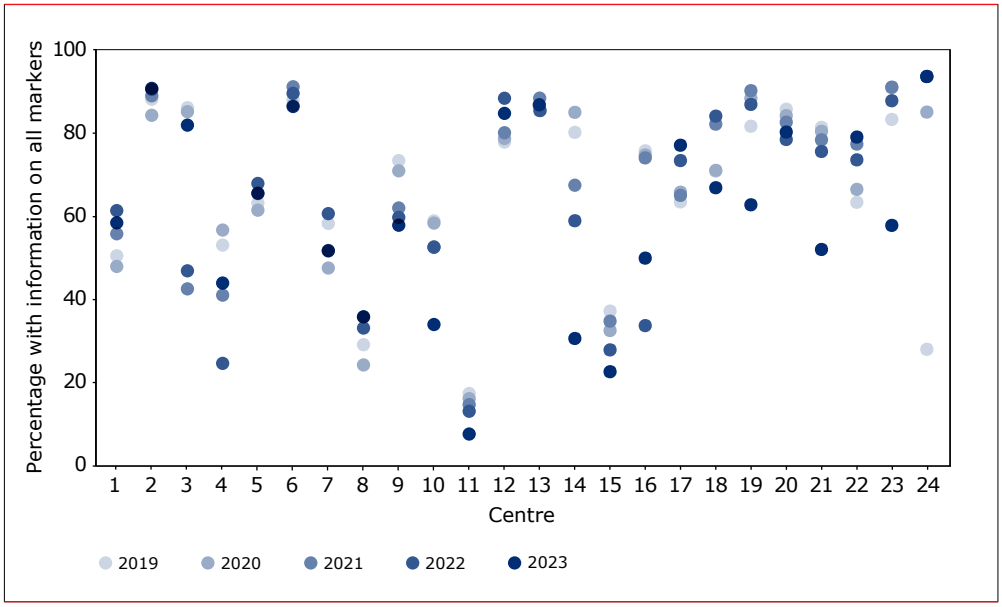
Legend: Data are provided for patients 40years old or older. Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 9.1.

Figure 9.4: Information on blood pressure; in other words, patients who had a blood pressure measurement during each year between 2019 and 2023.



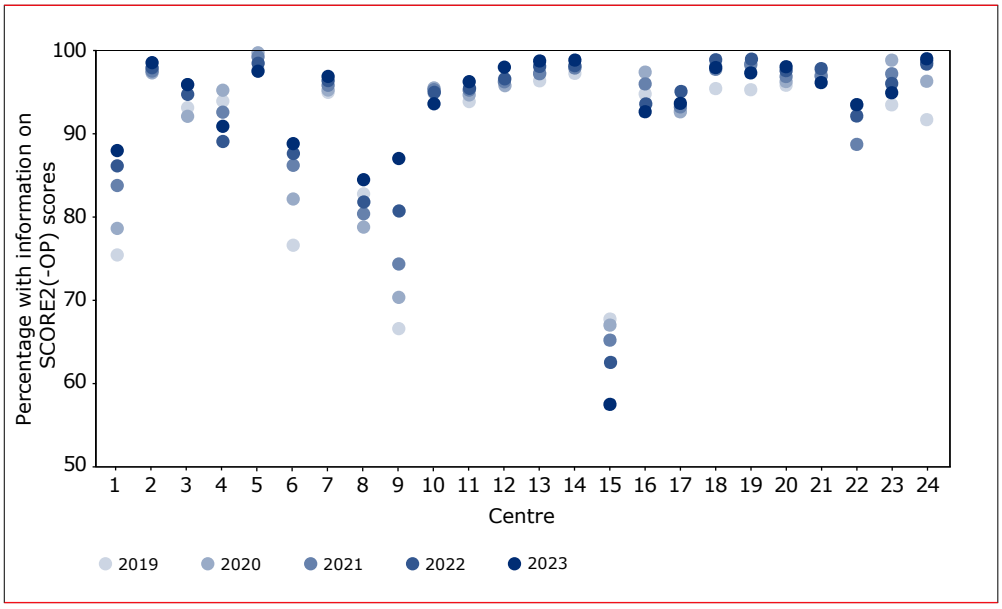
Legend: Data are provided for patients 40 years old or older. Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 9.1.

Figure 9.5: *Information on all cardiovascular parameters; in other words, patients who had total, HDL, LDL cholesterol and blood pressure measurement during each year between 2019 and 2023.*



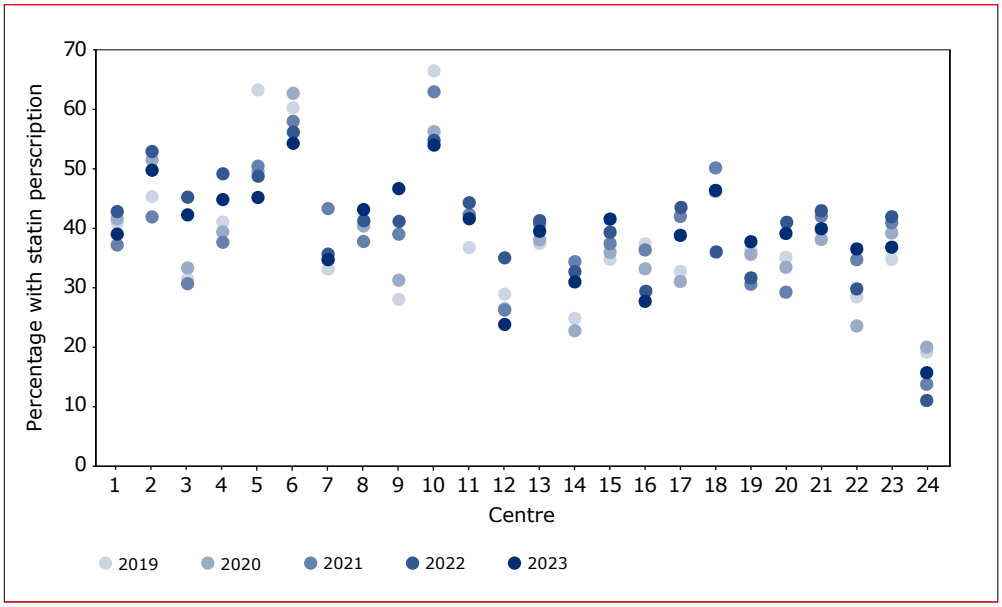
Legend: *Data are provided for patients 40 years old or older. Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 9.1.*

Figure 9.6: *Information on cardiovascular event risk during each year between 2019 and 2023.*



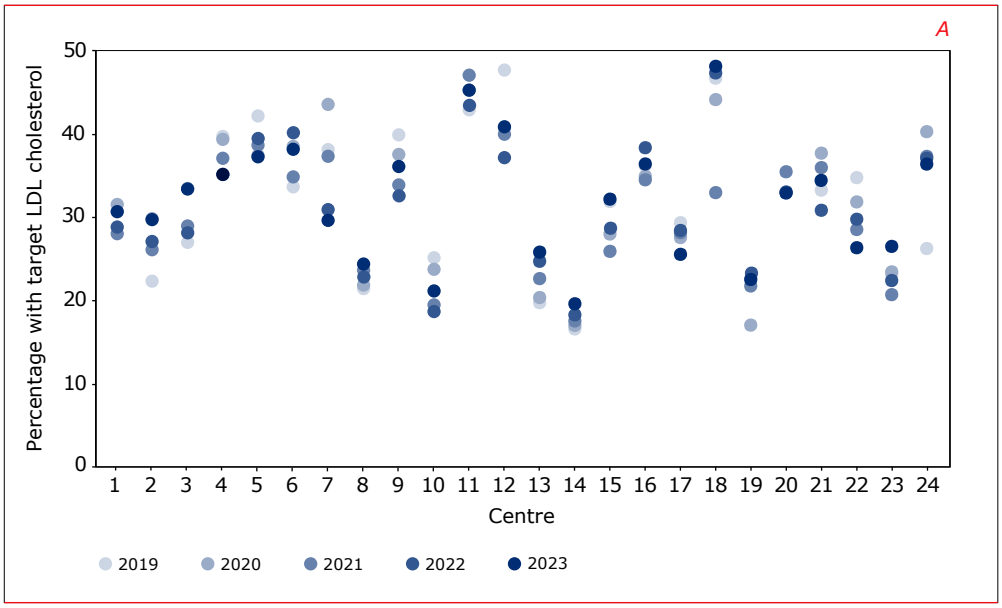
Legend: *The indicator represents patients who had enough information to have their cardiovascular disease assessed by the SCORE2 (40–69 year olds) or SCORE2-OP (70 year olds or older). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 9.1.*

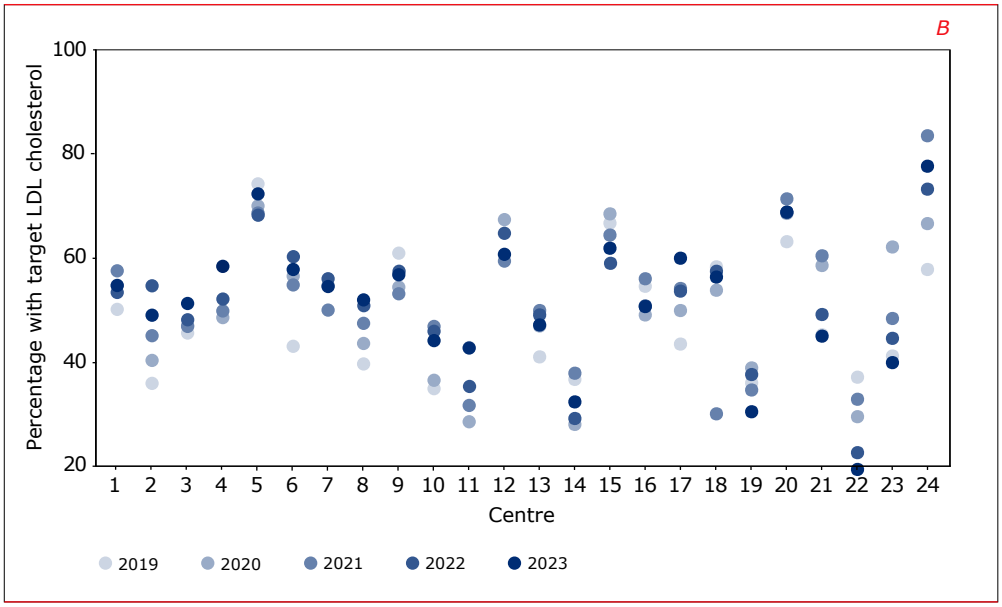
Figure 9.7: *Statin use; in other words, patients who had a predicted 10-year cardiovascular event risk-score greater than 10%, using the SCORE2(-OP) and received a prescription for statins during each year between 2019 and 2023.*



Legend: *Data are provided for those whose predicted 10-year cardiovascular risk were assessed with SCORE2 (i.e., 40-69 year olds) or SCORE2-OP (i.e., 70 year olds or older). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 9.1.*

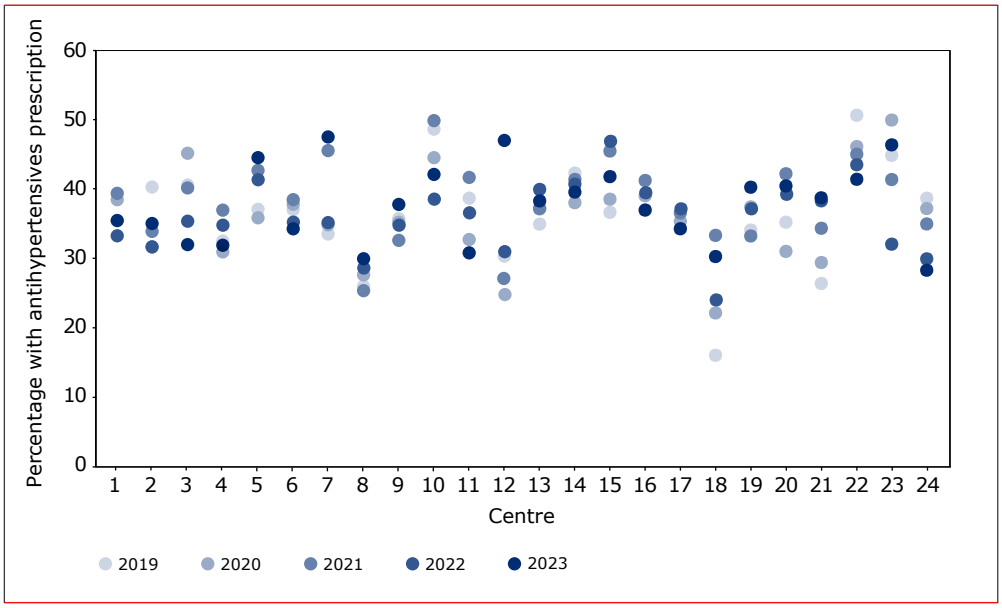
Figure 9.8: *Target LDL cholesterol; in other words, patients who had a predicted 10-year cardiovascular event risk-score greater than 10%, using the SCORE2(-OP), without (A) and with a prescription for statins (B), and had an LDL cholesterol level ≤2.6 mmol/mL during each year between 2019 and 2023.*





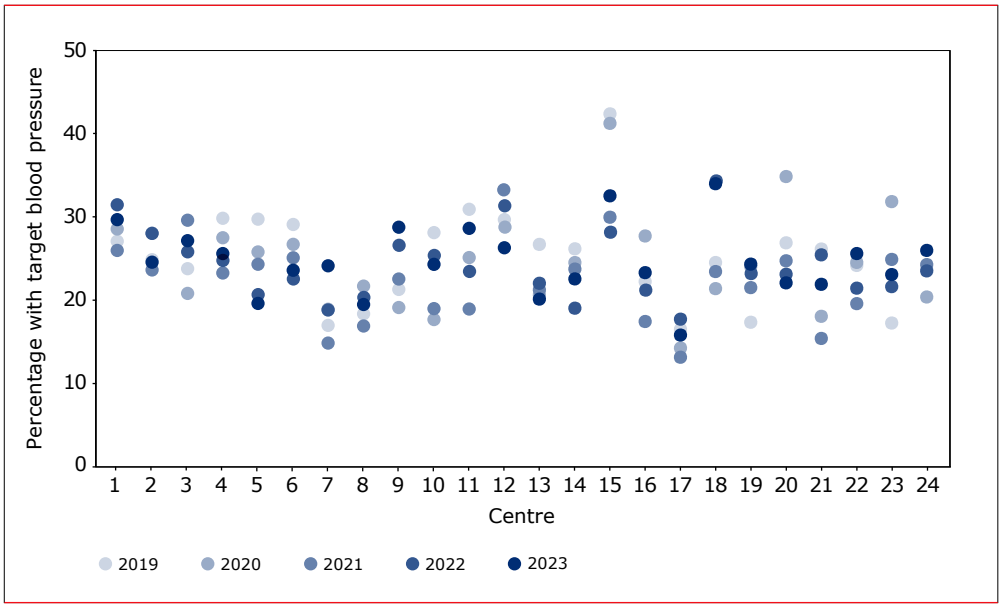
Legend: *Data are provided for those whose 10-year cardiovascular risk were assessed with SCORE2 (i.e., 40-69 year olds) or SCORE2-OP (i.e., 70 year olds or older). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 9.1.*

Figure 9.9: Antihypertensive medication use; in other words, patients who had high blood pressure and received a prescription for antihypertensive medication during each year between 2019 and 2023.



Legend: Data are provided for those who had high blood pressure, defined as ever having a diastolic blood pressure ≥90 mmHg. Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 9.1.

Figure 9.10: *Target blood pressure; in other words, patients who were receiving antihypertensive medication and had a blood pressure below age-specific thresholds during each year between 2019 and 2023*



Legend: *Age-specific thresholds refers to the following: systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg (for those 18-64 years old), or a systolic blood pressure <140 mmHg and diastolic blood pressure <80 mmHg (for those 65 years old or older). Data are provided for those on antihypertensive medication. Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 9.1.*

Centre performance

As reported in earlier studies, both the number of patients in care (i.e., the centre 'volume'), and the patient characteristics of a given centre (i.e., the patient 'mix'), may have an impact on the reported indicators[6-8].

Regarding centre volume, a smaller number of patients at an HIV treatment centre increases the chance that an indicator is more variable. When this occurs, it is difficult to distinguish whether a low-level indicator is the result of performing below expectations or having excessive variation. For this reason, we compare each centre's indicator to the national average and provide statistical guidance as to whether a given centre falls below the national average. This assessment depends on the number of patients included when calculating the indicator (an overview of this method is provided in *Box 9.2*). Statistical interpretation is unreliable when centre sizes are small, hence we do not draw conclusions on whether these centres fall below the national average.

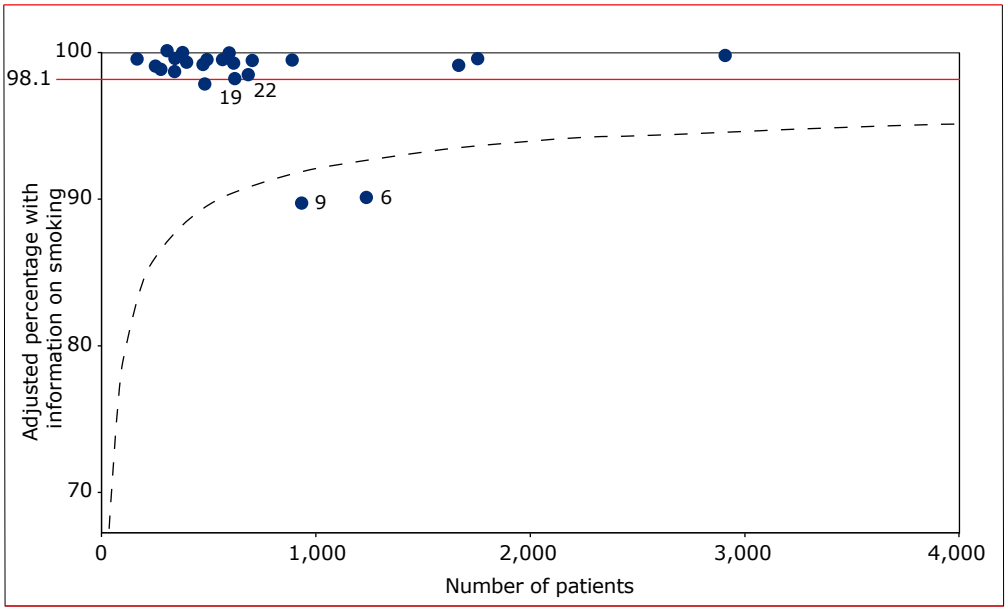
Regarding patient mix, individual-level factors, such as age and mode of transmission, are known to be associated with several indicators. If performance indicators are different across centres, it could be that the variation in the characteristics of patients attending those centres is driving these differences. We have therefore adjusted all indicators by year of birth and geographical origin/mode of transmission/gender (*Box 9.2*). For this section, we have used all the indicators and populations defined in *Box 9.1*, while accounting for the issues described above. Only indicators from 2023 were considered in this analysis.

Box 9.3: Funnel plots to compare centres to the national average.

What types of problems occur when evaluating indicators?	
Centres treating fewer patients	Centres of a smaller size are expected to have a wider variation in 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 differ 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], other than Dutch MSM, Dutch men who exclusively have sex with women [MSW], other than Dutch MSW, Dutch women, and other than Dutch women).

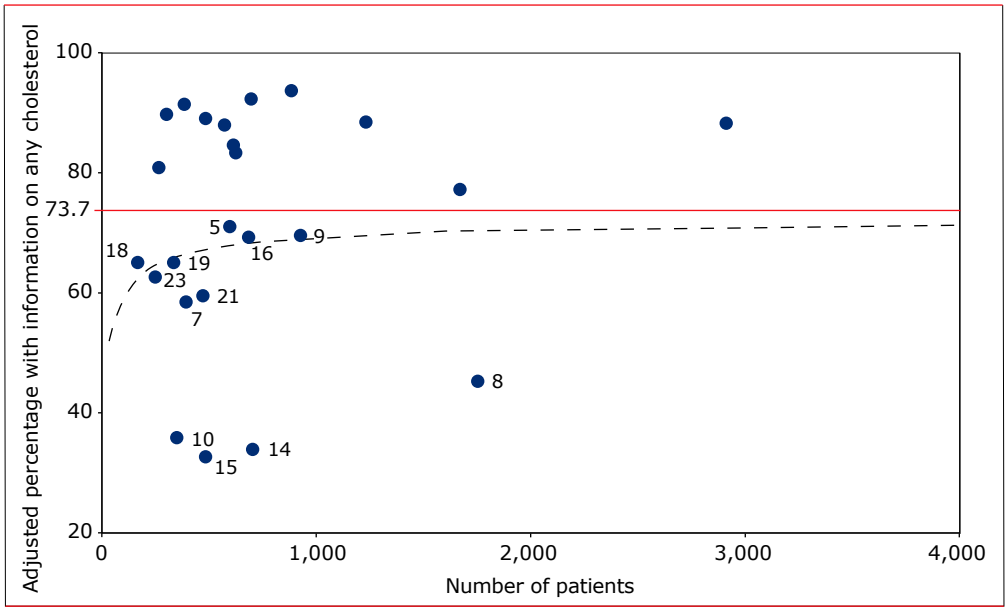
What is a funnel plot[9]? A funnel plot is a graphical depiction that allows us to compare a centre's indicator to the national average. It can help account for the problems listed above. The following are key components of this plot:	
Patient size	The *x*-axis depicts the number of patients considered in a given indicator. For example, this number could be the total number of patients in care in 2023, 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.

Figure 9.11: *Information on smoking; in other words, patients who ever had information on their smoking status in 2023. The percentage with information on smoking has been adjusted for patient mix and is plotted as a function of the number of patients who entered care.*



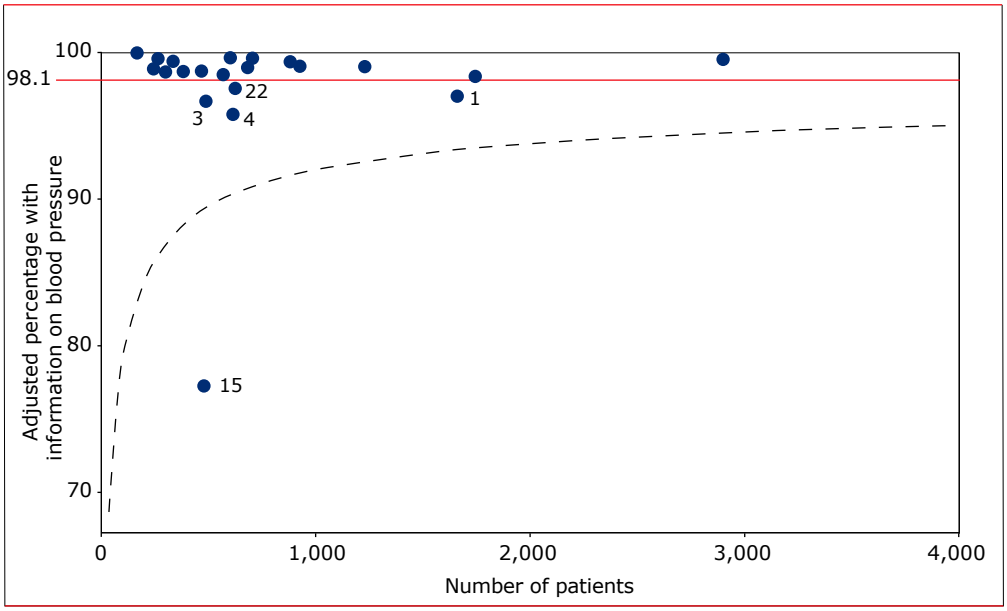
Legend: *Data are provided for patients 40 years old or older. Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 9.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 9.3).*

Figure 9.12: *Information on any cholesterol; in other words, patients who had a total, HDL or LDL cholesterol measurement in 2023. The percentage with information on any cholesterol has been adjusted for patient mix and is plotted as a function of the number of patients who entered care.*



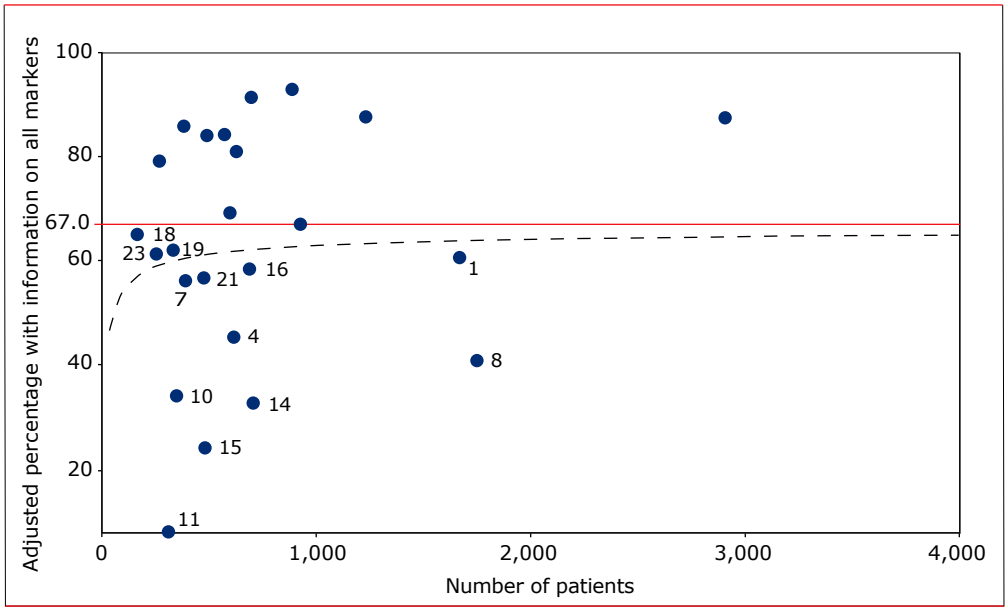
Legend: *Data are provided for patients 40 years old or older. Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 9.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 9.3).*

Figure 9.13: *Information on blood pressure; in other words, patients who had a blood pressure measurement in 2023. The percentage with information on blood pressure has been adjusted for patient mix and is plotted as a function of the number of patients who entered care.*



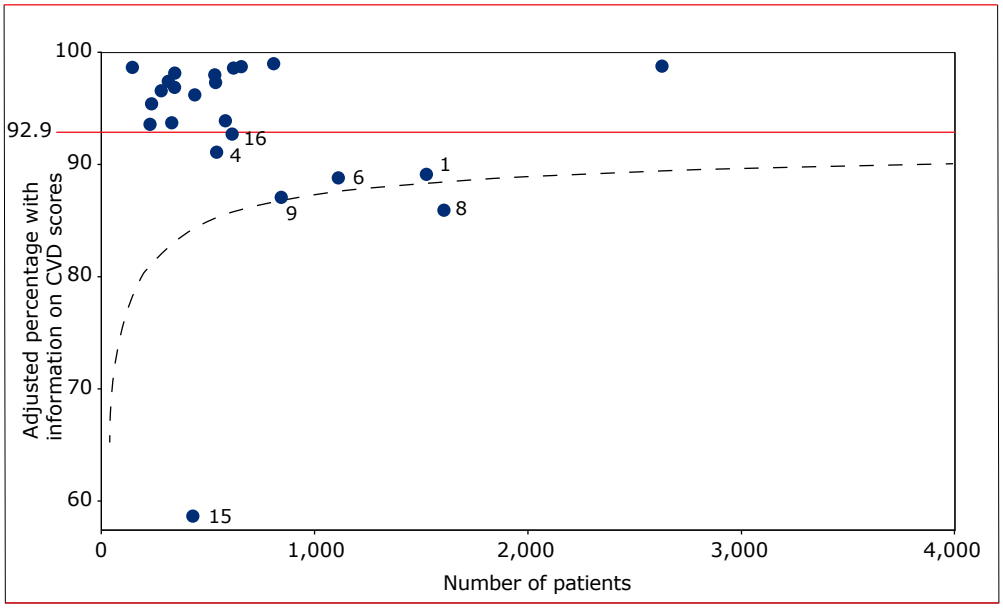
Legend: *Data are provided for patients 40 years old or older. Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 9.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 9.3).*

Figure 9.14: Information on all cardiovascular parameters; in other words, patients who had total, HDL, LDL cholesterol and blood pressure measurement in 2023. The percentage with information on all cardiovascular parameters has been adjusted for patient mix and is plotted as a function of the number of patients who entered care.



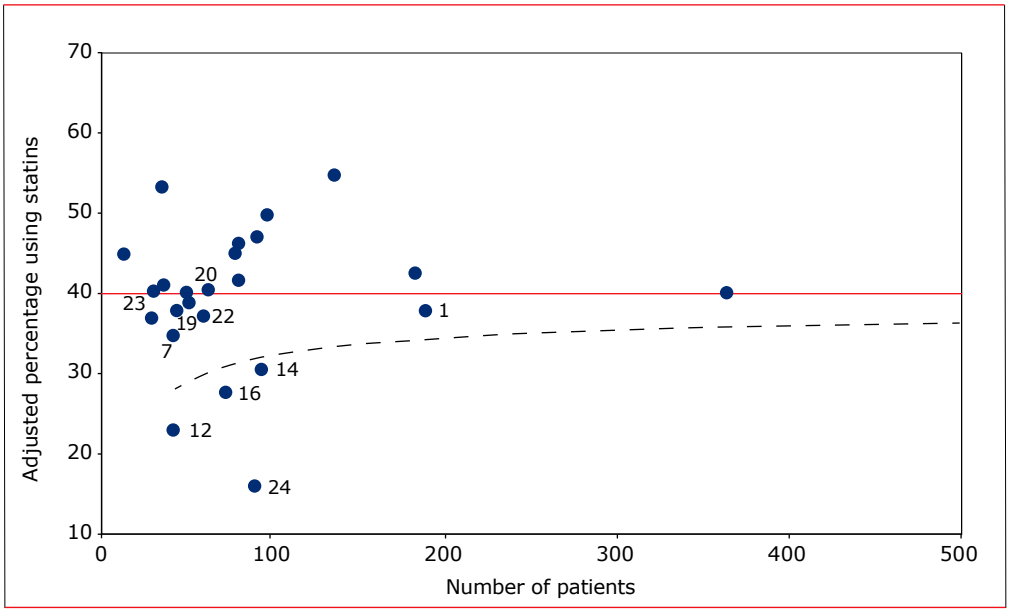
Legend: Data are provided for patients 40 years old or older. Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 9.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 9.3).

Figure 9.15: *Information on cardiovascular event risk in 2023. The percentage with information on cardiovascular event risk assessment has been adjusted for patient mix and is plotted as a function of the number of patients who entered care.*



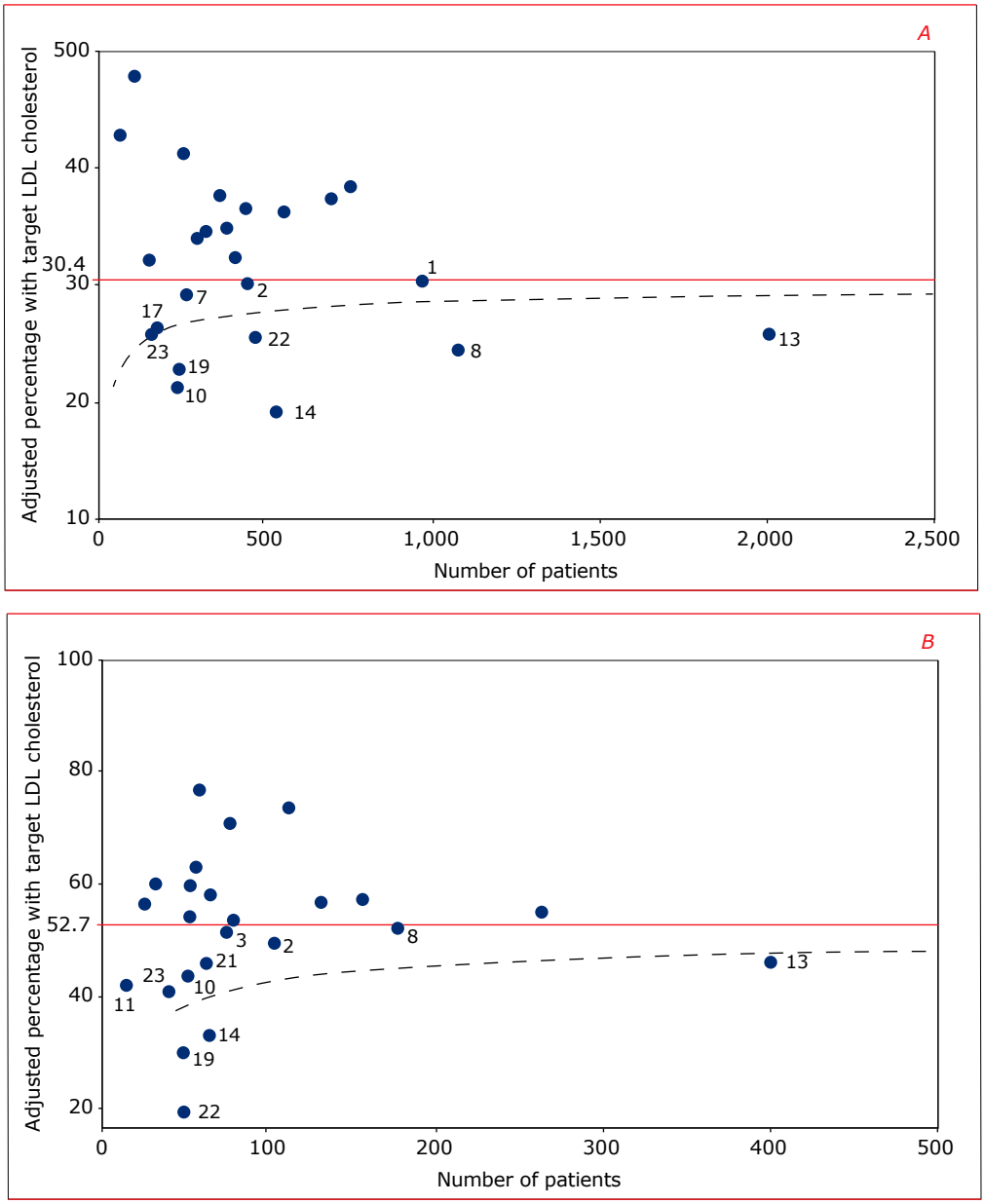
Legend: *The indicator represents patients who had enough information to have their cardiovascular disease assessed by the SCORE2 (40–69 year olds) or SCORE2-OP (70 year olds or older). Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 9.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 9.3).*

Figure 9.16: *Statin use; in other words patients who had a predicted 10-year cardiovascular event risk-score greater than 10%, using the SCORE2(-OP) and received a prescription for statins in 2023. The percentage with statin use has been adjusted for patient mix and is plotted as a function of the number of patients who entered care.*



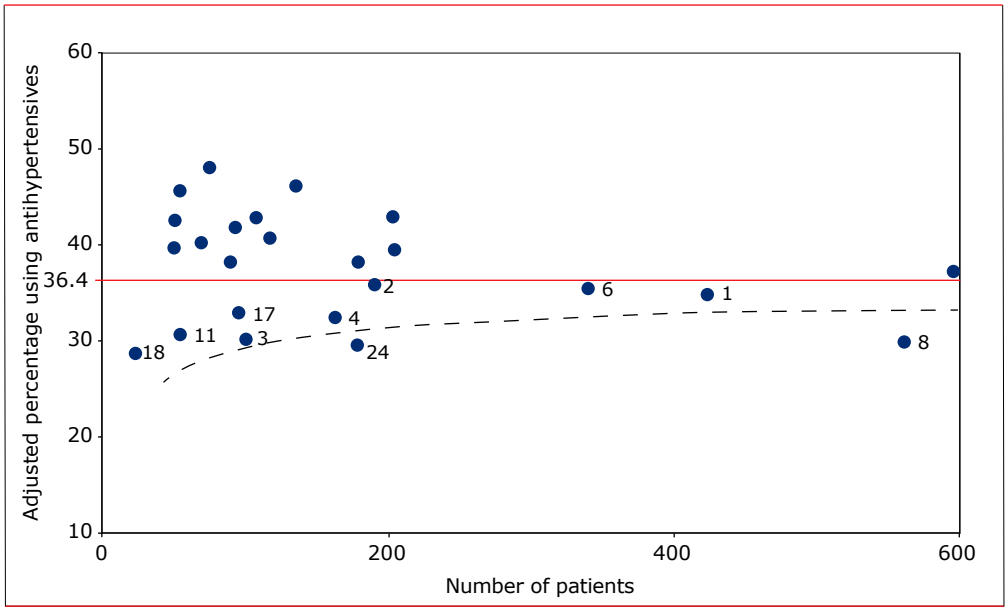
Legend: *Data are provided for those whose predicted 10-year cardiovascular risk were assessed with SCORE2 (i.e., 40-69 year olds) or SCORE2-OP (i.e., 70 year olds or older). The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 9.3).*

Figure 9.17: *Target LDL cholesterol; in other words, patients who had a predicted 10-year cardiovascular event risk-score greater than 10%, using the SCORE2(-OP), with (A) or without a prescription for statins (B), and had an LDL cholesterol level ≤2.6 mmol/mL in 2023. The percentage with target LDL cholesterol has been adjusted for patient mix and is plotted as a function of the number of patients who entered care.*



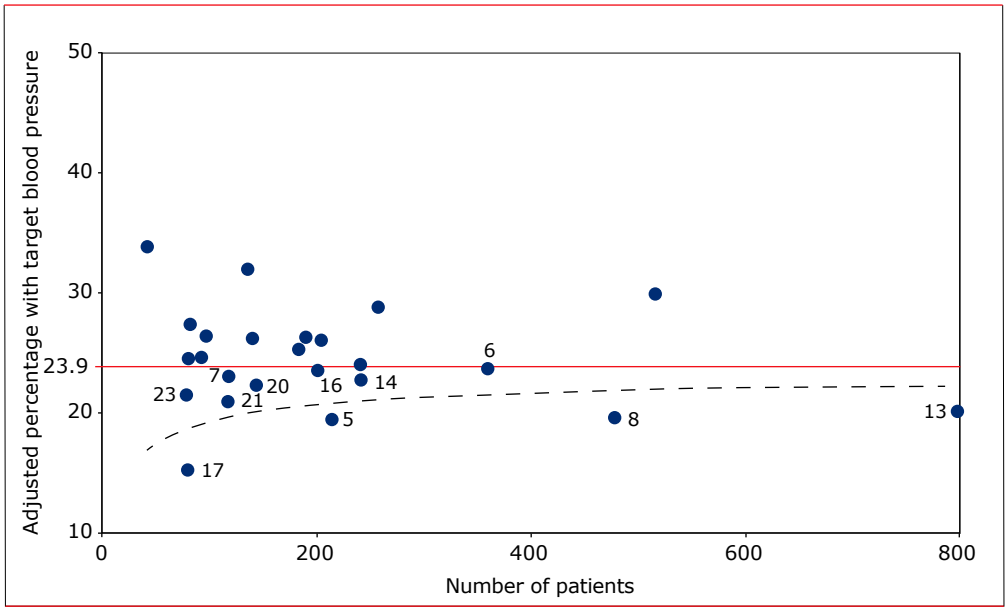
Legend: *Data are provided for those whose 10-year cardiovascular risk were assessed with SCORE2 (i.e., 40-69 year olds) or SCORE2-OP (i.e., 70 year olds or older). The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 9.3).*

Figure 9.18: *Antihypertensive medication use; in other words, patients who had high blood pressure and received a prescription for antihypertensive medication in 2023. The percentage with antihypertensive medication use has been adjusted for patient mix and is plotted as a function of the number of patients who entered care.*



Legend: *Data are provided for those who had high blood pressure, defined as ever having a diastolic blood pressure ≥90 mmHg. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 9.3).*

Figure 9.19: *Target blood pressure; in other words, patients who were receiving antihypertensive medication and had a blood pressure below age-specific thresholds in 2023. The percentage with target blood pressure has been adjusted for patient mix and is plotted as a function of the number of patients who entered care.*



Legend: *Age-specific thresholds refers to the following: systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg (for those 18-64 years old), or a systolic blood pressure <140 mmHg and diastolic blood pressure <80 mmHg (for those 65 years old or older). Data are provided for those on antihypertensive medication. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 9.3).*

Key findings and conclusions

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

- Most centres had information on smoking status and blood pressure. However, there was substantial variation in the percentage of patients with information on total-, HDL- or LDL- cholesterol. This led to a number of centres with percentages of information needed for cardiovascular disease screening that were much lower-than-expected compared to the national average.
- More than 80% of patients 40 years or older had information on their predicted 10-year risk of a cardiovascular disease event for all but one centre. For two centres, this percentage was much lower-than-expected compared to the national average. Nevertheless, many of the centres demonstrated marked improvement in this indicator over the past five years.
- Among those with a high (i.e., 10%) predicted 10-year risk of a cardiovascular disease event, when using the SCORE2(-OP), there was substantial variation in the percentage who received a prescription for statins. Although some centres have shown increases in the percentage with high cardiovascular disease risk who received statins over the past five years, this percentage remains low nationally.
- Among those with a high predicted 10-year risk of a cardiovascular disease event, when using the SCORE2(-OP), there was some variation in the percentage with target LDL cholesterol when patients had a prescription for statins. One centre, however, had a much lower-than-expected percentage with target LDL for this specific group. There was less variation in the percentage with target LDL cholesterol when patients did not receive a prescription for statins, but this percentage was high across all centres.
- There was also slight between-centre variation in the percentage of patients with high blood pressure who received an antihypertensive prescription. Likewise, there was slight between-centre variation in the percentage of patients taking antihypertensive medication who had achieved a target blood pressure. For most centres, these percentages were similar over the last five years. Some of the larger HIV treatment centres had levels of these indicators that were much lower-than-expected when compared to the national average.

Nevertheless, these conclusions must be considered in light of the data collection methods used by SHM. Much of the data is obtained through electronic medical records, which might have incomplete information on items, such as smoking status and antihypertensive medication. Furthermore, primary prevention of cardiovascular disease for many of the smaller centres is commonly done by general practitioners or periphery healthcare centres. Certain data related to cardiovascular disease could be missing simply because these data are not measured at the HIV treatment centre. Finally, we do not have the specific reasons why patients are not taking antihypertensive medications or statins, which could be unrelated to the care given at the HIV treatment centre.

Care related to cardiovascular disease does have some variation across centres. Nevertheless, certain centres should strive to increase the percentage of patients with information on cholesterol measurements and risk assessment of cardiovascular disease events. Some centres may also want to think about increasing the percentage of patients on statins or antihypertensive medication, especially those who are at higher risk of a cardiovascular disease event. This analysis provides insight into the provision of cardiovascular diseases care at the different treatment centres.

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10. The Amsterdam Cohort Studies (ACS) on HIV infection: annual report 2023

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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 (PWUD/PWID) was initiated in 1985 and discontinued in 2016.

From the outset, research in the ACS has taken a multidisciplinary approach, integrating epidemiology, social science, virology, immunology, and clinical medicine in one study team. This unique collaboration has been highly productive, significantly contributing to the knowledge and understanding of many different aspects of HIV-1 infection, as well as other infections such as STI [e.g., viral hepatitis B and C (HBV and HCV) and human papillomavirus (HPV)]. This expertise, in turn, has contributed directly to advances in prevention, diagnosis, and management of these infections.

In 2023, the cohort reached 39 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 39 years, the emphasis changed to accommodating changing knowledge gaps and needs. 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[3]. In the past years, investigating the epidemiology, determinants, course of infections and pathogenesis of HIV, sexually transmitted (STI), blood-borne and other infections, and to evaluate the effect of interventions have become an important component of the ACS research programme.

Collaborating institutes and funding

Within the ACS, the following different institutes collaborated in 2023 to bring together data and biological sample collections, and to conduct research:

- **Public Health Service of Amsterdam** (*Gemeentelijke Gezondheidsdienst Amsterdam*, GGD Amsterdam): Department of Infectious Diseases
- **Amsterdam University Medical Centers, location Academic Medical Center (AMC)** (Amsterdam UMC): Departments of Medical Microbiology, Experimental Immunology, and Internal Medicine (Division of Infectious Disease);
- **Stichting HIV Monitoring** (HIV Monitoring Foundation, SHM);

In previous years, Sanquin Blood Supply Foundation, Medical Center Jan van Goyen, and the HIV Focus Center of the DC-Clinics also contributed to sample and data collection, still being used in current research projects.
In addition, there are numerous collaborations between the ACS and other research groups, both within and outside the Netherlands. The ACS is financially supported by the Centre for Infectious Disease Control Netherlands of the National Institute for Public Health and the Environment (*Centrum voor Infectieziektenbestrijding-Rijksinstituut voor Volksgezondheid en Milieu*, RIVM-CIb).

Ethics statement

The ACS has been conducted in accordance with the ethical principles set out in the Helsinki declaration. Participation in the ACS is voluntary and written informed consent is obtained from each participant. The most recent version for the MSM cohort was approved by the Amsterdam UMC medical ethics committee in 2022; for the (closed) PWID cohort, in 2009.

The Amsterdam Cohort Studies (ACS)

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

Between 1984 and 1985, men who had had sexual contact with at least one other man in the preceding six months were enrolled, independent of their HIV status. In the first 6 months of the recruitment period, 750 MSM, of which one-third with HIV, were enrolled. From 1985 to 1988, men without HIV 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. Between 1988 and 1998, MSM with HIV were also enrolled because of the cohort involvement in HIV treatment trials. From 1995 to 2004, only men aged 30 years or younger, with at least one male sexual partner in the previous six months, could be included the study. Since 2005, men without HIV of all age groups have been eligible to

participate in the ACS if they live in, or are closely connected to the city of Amsterdam and have had at least one male sexual partner in the preceding six months. In line with the advice issued by the International Scientific Advisory Committee in 2013, the cohort continues to strive to recruit young MSM (aged 30 years or younger). From 2022 onwards, we aim to actively follow 825 MSM (750 without HIV and 75 with HIV). Individuals of at least 16 years old, who were assigned male sex at birth and not having undergone gender reassignment surgery, live in the Amsterdam area or are involved in MSM-related activities in Amsterdam, and having had sex with at least one man in the preceding six months are eligible for enrolment. Active recruitment campaigns (e.g., online advertisements, promotional activities in gay venues in Amsterdam) are organized approximately once every two years.

Men who seroconverted for HIV within the ACS remained in the cohort until 1999, when follow-up of a selection of MSM with HIV was transferred to the MC Jan van Goyen. In 2003, the 'HIV Research in Positive Individuals' (*Hiv Onderzoek onder Positieven*, HOP) protocol was initiated. Individuals with a recent HIV infection when entering the study at the GGD Amsterdam, and those who seroconverted for HIV during follow-up within the cohort, continue to return for study visits at the GGD Amsterdam, or at an HIV treatment centre. Blood samples from these participants are stored at the ACS Biobank long-term storage and analyses. All (sexual) behavioural data are collected on a six-monthly basis by questionnaires, coordinated by the GGD Amsterdam, and clinical data are provided by SHM.

As of 31 December 2023, 2,989 MSM have been included in the ACS since its initiation in 1984. Of these 2,989 MSM, 607 were living with HIV at entry into the study and 264 seroconverted for HIV during follow-up. Every three to six months, participants complete a standardised questionnaire designed to obtain data regarding: medical history, (sexual) behaviour and substance use, uptake of prevention measures (including PrEP, doxyPEP, and condom use) underlying psychosocial determinants, health care use, signs of depression and other psychological disorders, and demographics. Moreover, blood is collected for diagnostic tests and storage at the ACS biobank. In total, the GGD Amsterdam has been visited 68,892 times by MSM since 1984.

In 2023, 682 participants were in follow-up (meaning that they had at least one study visit in the year 2022 or 2023), of whom 635 were actively participating through at least one visit in the year 2023.

In this chapter, we report on the MSM actively participating in the ACS in 2023:
- 38 newly enrolled in the cohort in 2023, of whom all 38 were MSM without HIV and no MSM with HIV; with a median age of 35 years at inclusion were enrolled;
- The median age was 45 years at their last cohort visit in 2023;
- The majority was born in the Netherlands (83%), and a resident of Amsterdam (80%), respectively;
- 85% of the MSM had a college degree or higher.

The cohort of people who use or inject drugs (PWUD/PWID) – discontinued

Between 1984-2016, a total of 1,661 PWUD had been included in the ACS of whom 1,303 had at least two cohort visits (maximum 78 visits)[2]. Study enrolment and data collection continued until 2014 and February 2016, respectively. Data and samples from these participants of this cohort are still being used for research. For more details, we refer to previous monitoring reports[1] and a few publications[2, 4-6].

ACS biobank

The ACS biobank stores all samples (plasma/serum, peripheral blood mononuclear cells) taken in the context of the ACS study, at the Amsterdam UMC, location AMC. In addition to samples taken at routine ACS study visits, it also includes samples collected for sub-studies and affiliated studies embedded in the ACS.

Subgroup studies and affiliated studies

AGE_hIV cohort study

The AGE_hIV cohort study is 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. The AGE_hIV study was started in October 2010 and aims to assess the prevalence and incidence of a broad range of comorbidities, along with known risk factors for these comorbidities, in people with HIV aged 45 years and over. It also strives to determine the extent to which comorbidities, their risk factors and their relation to quality of life, differ between groups of people with and without HIV. Participants undergo a comprehensive assessment for comorbidities and completed a questionnaire at intake. Every two years, participants complete follow-up research questionnaires, and attend the GGD for body measurements and to provide a blood sample. So far six such study rounds have been completed.

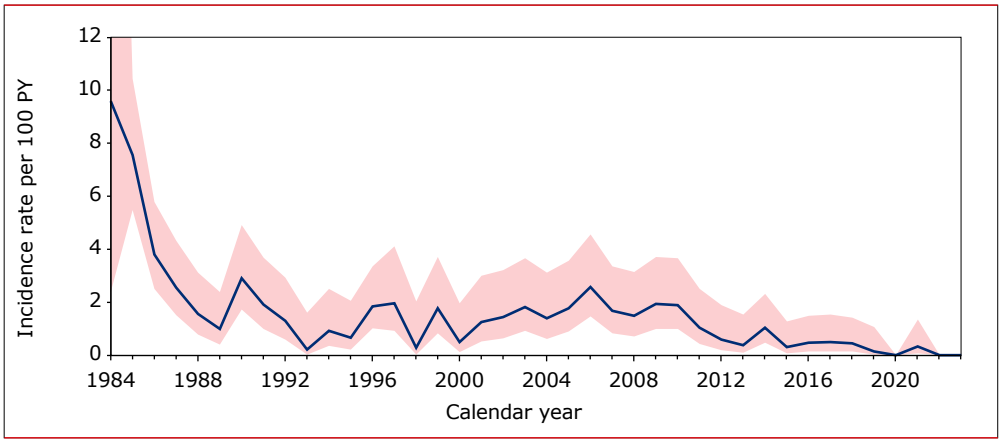
In total, 598 participants with HIV and 550 individuals without HIV were enrolled between October 2010 and September 2012. People with HIV (PWH) were included through the Amsterdam UMC, location AMC, HIV outpatient clinic, and participants without HIV but with similar sexual behaviour / drug use patterns via the Centre of Sexual Health Amsterdam (486) and the ACS (64). All participants were aged 45 years and over, and participants without HIV were as comparable as possible to participants with HIV with respect to age, gender, ethnicity, and risk behaviour. In 2023, the sixth round was completed, and the seventh round was started. In total, 410 participants without HIV had a sixth round visit.

ACS in 2023: HIV/STI and sexual behaviour among MSM

HIV incidence

The observed HIV incidence rate among MSM participating in the ACS has declined over time (*Figure 10.1*). Between 1985 and 1993 it declined significantly, then stabilised between 1993 and 1996, before rising in the period 1996 to 2009. Since 2009, the HIV incidence has decreased significantly. In 2022 and 2023, no MSM participating in the ACS seroconverted for HIV.

Figure 10.1: *HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984–2023.*



PrEP use

Use of PrEP has increased since 2015. Data on recent PrEP use was available for 490 MSM without HIV actively participating in the ACS in 2023, of whom 232 (47.3%) reported PrEP use in the preceding six months. Of these 232 PrEP users, 104 (44.8%) obtained PrEP through the national PrEP program at the Centre of Sexual Health, 99 (42.7%) through their GP; 13 (5.6%) through a PrEP study, 7 (3.0%) through an Internal Medicine specialist or a PrEP prescribing physician, and 6 (2.6%) obtained their pills through informal routes (e.g., *sexual or social networks, or online offered pills*); of the remaining 3 (1.3%) PrEP users, data on PrEP uptake route were not available.

STI screening

Since October 2008, all MSM participating in the ACS are routinely screened for bacterial STIs during their cohort visits (in addition to HIV testing). This conforms with the standard care offered by the Centre of Sexual Health Amsterdam. Chlamydia and gonorrhoea were detected by polymerase chain reaction techniques using urine samples and pharyngeal and rectal swabs. Syphilis was detected by *Treponema pallidum* haemagglutination assay.

In 2023, STI data were available from the Centre of Sexual Health Amsterdam for 639 MSM participating in the ACS. Of these 639 MSM, 129 (20.2 %) MSM had at least one positive bacterial STI test (79 (12.4%) gonorrhoea, 62 (9.7%) chlamydia and 13 (2.0%) syphilis). For MSM with and without HIV, 13 out of 37 (35.1%), and 116 out of 602 (19.3%), MSM had at least one positive bacterial STI test, respectively.

Following national PrEP guidelines, those who use PrEP are screened for STIs more often (i.e., 3-monthly) compared to those not using PrEP (i.e., 6-monthly). As the STI testing frequency differ between PrEP using and non-PrEP using participants, STI incidence rates are complex to compare between these groups and, therefore, are not reported here.

ACS 2023 research highlights

A genetic variation in fucosyltransferase 8 accelerates HIV-1 disease progression indicating a role for N-glycan fucosylation

Core fucosylation by fucosyltransferase 8 (FUT8) is an important posttranslational modification that impacts components of the immune system. Genetic variations in FUT8 can alter its function and could, therefore, play a role in the antiviral immune response and pathogenesis of HIV-1. This study analysed the effect of a single nucleotide polymorphism (SNP) in FUT8 on the clinical course of HIV-1 infection[7]. In the ACS, we observed that the presence of the minor allele of SNP rs4131564 in the FUT8 gene was associated with accelerated disease progression. Although we did not observe an effect of the SNP on T cell activation and functionality, this study underscoring a role for N-glycan fucosylation in HIV pathogenesis.

Noncanonical-NF-κB activation and DDX3 inhibition reduces the HIV-1 reservoir by elimination of latently infected cells ex-vivo

HIV-1 continues to be a major global health challenge. Current HIV-1 treatments are effective but need lifelong adherence. An HIV-1 cure should eliminate the latent viral reservoir that persists in people living with HIV-1. Different methods have been investigated that focus on reactivation and subsequent elimination of the HIV-1 reservoir, and it is becoming clear that a combination of compounds with different mechanisms of actions might be more effective. In this study we targeted two host factors for the elimination of the viral reservoir: inhibitor of apoptosis proteins that control apoptosis and the DEAD-box helicase DDX3, facilitating HIV mRNA transport/translation[8]. We show in ex-vivo experiments using PBMC from ACS participants, that targeting of these host factors with SMAC mimetics and DDX3 inhibitors induce reversal of viral latency and eliminate HIV-1-infected cells.

Comprehensive harm reduction programs substantially reduce new HIV and viral hepatitis infections among PWID

Although the Netherlands, Canada and Australia were early adopters of harm reduction for PWID, their respective HIV and hepatitis C epidemics differ. This study[5] using novel methodologies and data from three cities, Amsterdam, Vancouver and Melbourne, showed that dual engagement with needle and syringe exchange and opioid agonist therapy programs reduced the risk of HIV infection by 41% and the risk of hepatitis B and C infection by 76% and 72%, respectively, when compared to no or suboptimal engagement to these programs research. Study findings are also summarized and published in a policy brief[9].

Mpox vaccination intention and uptake MSM participating in the ACS

In response to the 2022 mpox outbreak, vaccination was offered in the Netherlands to MSM at increased risk for mpox. Among the MSM participants of the ACS, we studied the intention to vaccinate, as well as e.g. beliefs, attitude, subjective norms, and perception of risk, in relation to self-reported vaccination uptake[10]. While this study found that the intention to vaccinate for mpox was high among MSM in the ACS, the high intent did not necessarily result in vaccine uptake. Mpox risk perception might have played a more pivotal role in getting vaccinated, which may be related to the evolution of vaccination eligibility criteria and accessibility to the vaccine.

Current and upcoming ACS research projects

Data collected within the ACS are used for multiple research projects at present. In the context of the COVID-19 pandemic, we are investigating the SARS-CoV-2 seroconversion among MSM participating in the ACS over time. Furthermore, data on alcohol and other substance use among these ACS participants have been analysed to estimate the frequency and its determinants of problematic and non-problematic substance use. We are updating estimates of HCV-infection incidence and spontaneous-clearance rates among the ACS participants, along with associated factors. Sexual behaviour including anal sex with casual and steady partners, in relation to both condom and PrEP use, is currently studied in greater detail. Regarding PrEP use, data on PrEP surfing, defined as using the PrEP status of sexual partners as HIV prevention strategy, are currently being analysed. Qualitative research to identify barriers and missed opportunities of PrEP-uptake, PrEP-care- and PrEP-use among MSM with and without HIV and previous PrEP experience are ongoing. We are also planning to contribute to the mapping of the PrEP need, use, and care in Amsterdam; i.e. the PrEP cascade. More upcoming research is in preparation related to condom use and norms regarding condom use.

Furthermore, in the context of pandemic preparedness, the ACS team is working on a project to identify how *findable*, *accessible*, *interchangeable* and *reusable* (i.e. *FAIR*) the ACS data are, in order to make improvements in this where possible. Moreover, the ethical and legal barriers to starting (sub)studies within the ACS are examined, in order to arrive at a roadmap to quickly start a research project on an emerging disease.

Steering committee

In 2023 the steering committee gathered on five occasions. Seven proposals for use of ACS data or samples (serum/PBMC) were submitted to the committee: three from Experimental Immunology (Amsterdam UMC, location AMC), three from Medical Microbiology and Infection Prevention (Amsterdam UMC, location AMC), and one from the GGD Amsterdam. One proposal was an international collaboration with a group of Ulm University in Germany. Three proposals were collaborations within the ACS between the GGD and MMI Amsterdam UMC. The ACS reviewed the proposal and suggested minor revisions in some cases, after which all requests were approved.

Publications in 2023 that included ACS data

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1. Liza N. Coyer, Sex, drugs, PrEP and STI: Trends among men who have sex with men. 13 January 2023
2. Joanna Kaczorowska. Colonization, transmission and long-term dynamics of anelloviruses in humans. 13 April 2023
3. Cormac M. Kinsella. Computational discovery of viruses and their hosts. 11 September 2023
4. Silvia Achia Nieuwenburg - Early syphilis infection among men who have sex with men. 22 December 2023

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Amsterdam Cohort Studies (ACS) participants

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11. Curaçao

Diederik van de Wetering, Esther Rooijakkers, Ashley Duits, Ard van Sighem

Introduction

Since 2005, stichting hiv monitoring (SHM) has assisted in collecting demographic and clinical data on individuals with HIV receiving care at the sole general hospital St. Elisabeth Hospital and its successor Curaçao Medical Center in Willemstad, Curaçao. An extensive database has been established as a result of this registration and monitoring. This is unique for the region and gives a clear picture of the population with HIV, the effectiveness of HIV care, and the challenges that exist in this relatively small Caribbean setting. This chapter presents a concise overview of the current situation for people with HIV in Curaçao.

In total, 1,458 individuals with HIV recorded by SHM have been registered in Curaçao. Of these people, the majority were diagnosed with HIV-1 (n=1,444, or 99%), while one individual was diagnosed with HIV-2, and three had antibodies against both HIV-1 and HIV-2 (*Figure 11.1*). For 10 individuals, serological results on HIV type were not available in the SHM database.

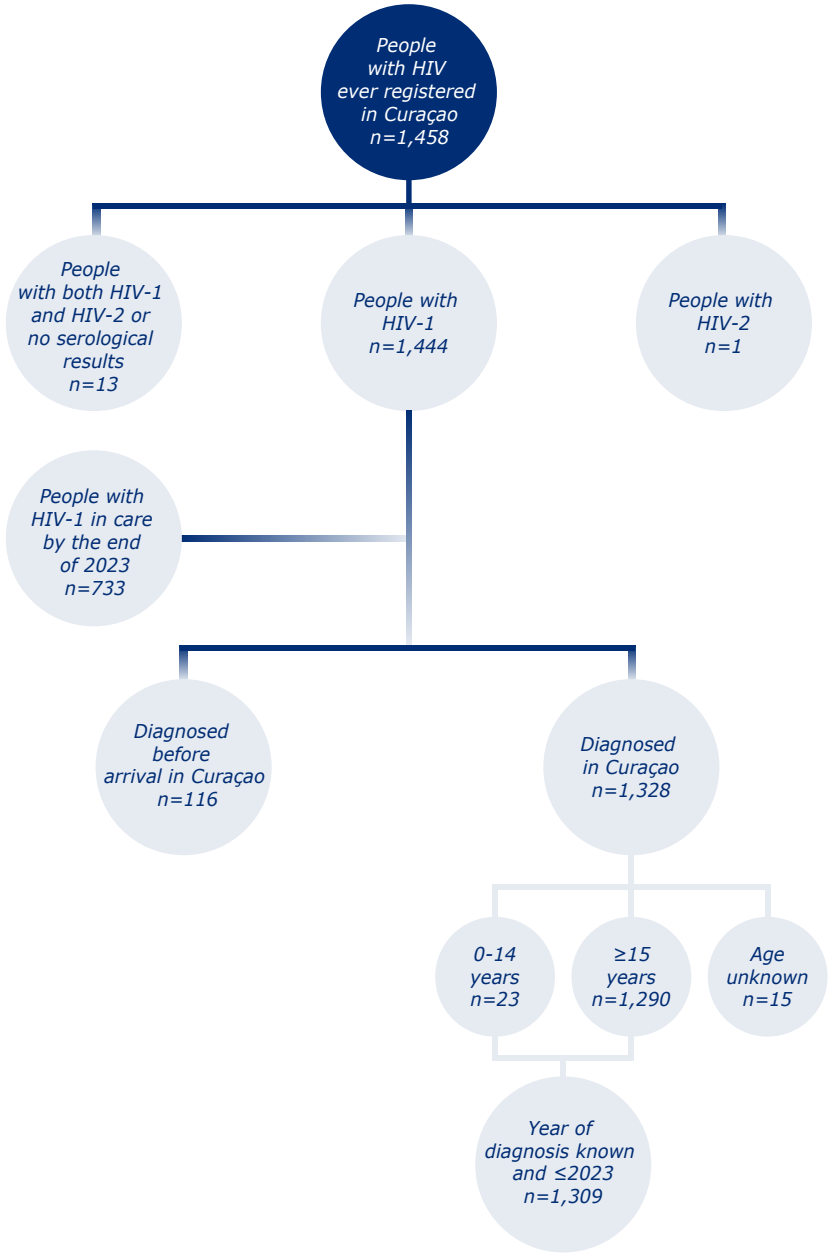
The population with HIV-1 in Curaçao

Of the 1,444 individuals in Curaçao with HIV-1, 116 (8%) had a documented HIV diagnosis prior to arrival in Curaçao (*Figure 11.1*). The remaining 1,328 individuals were newly diagnosed while living in Curaçao, or their date of arrival in Curaçao has not yet been recorded in the SHM database.

Individuals diagnosed before arriving in Curaçao

The 116 individuals with a documented HIV-1 diagnosis prior to arrival in Curaçao included 98 (84%) people who were registered with an HIV treatment centre in the Netherlands prior to moving to Curaçao (*Figure 11.1*). The majority of these 98 individuals (n=73, or 74%) originated from the former Netherlands Antilles, while 20 (20%) were born in the Netherlands and five (5%) were born elsewhere. The other 18 individuals with pre-migration diagnosis were also born abroad, including 5 in Venezuela. All 8 people arriving in Curaçao in 2021-2023 with a documented HIV-1 diagnosis prior to arrival had a suppressed viral load below 200 copies/ml (*Figure 11.2*).

Figure 11.1: *Overview of the population with HIV registered in Curaçao.*



Individuals newly diagnosed in Curaçao

Altogether, 1,328 individuals were newly diagnosed while living in Curaçao, or information on where they lived at the time of diagnosis was not yet available (*Figure 11.1*). Of these 1,328 individuals, 990 (75%) were born in the former Netherlands Antilles, 117 (9%) originated from Haiti, 95 (7%) from the Dominican Republic, 28 (2%) from Jamaica, 22 (2%) from Colombia, 20 (2%) from Venezuela, and 56 (4%) from other countries.

For 19 (1%) of the 1,328 individuals diagnosed while living in Curaçao, the date or interval of diagnosis was not recorded in the SHM database, or they were diagnosed in 2023. The remaining 1,309 individuals comprised (*Table 11.1*):

- 257 (20%) men who have sex with men (MSM);
- 560 (43%) other men,
  - 333 (59%) of whom reported sex with women as the most likely mode of transmission
  - 227 (41%) reported other or unknown modes of transmission;
- 464 (35%) women,
  - 450 (97%) of whom reported sex with men as the most likely mode of transmission
  - 14 (3%) reported other or unknown modes of transmission;
- 5 transgender men and women;
- 23 (2%) children diagnosed before the age of 15 years.

Between 2000 and 2018, the annual number of newly-diagnosed infections hovered around 50, before decreasing to around 35 in most recent calendar years (*Table 11.1*; *Figure 11.2*).

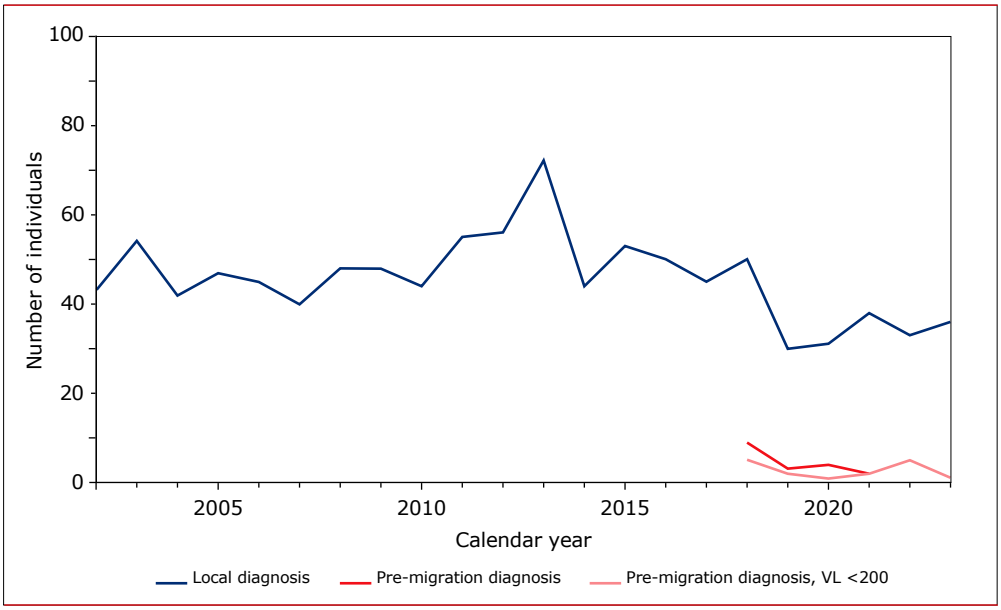
Table 11.1: Annual number of HIV-1 diagnoses in Curaçao among men who have sex with men, other men, women, and trans men and women diagnosed at 15 years of age and over, and children under 15 years.

Year of diagnosis	MSM	Other men	Women	Trans men and women	<15 years of age	Total
≤2001	41	136	109	1	18	305
2002	7	19	17	0	0	43
2003	8	28	18	0	0	54
2004	3	23	16	0	0	42
2005	11	19	17	0	0	47
2006	6	22	17	0	0	45
2007	12	18	10	0	0	40
2008	10	17	19	1	1	48
2009	9	17	21	0	1	48
2010	4	19	21	0	0	44
2011	12	19	24	0	0	55
2012	12	18	26	0	0	56
2013	18	30	22	1	1	72
2014	16	14	14	0	0	44
2015	16	23	12	1	1	53
2016	12	23	15	0	0	50
2017	14	18	13	0	0	45
2018	17	13	19	1	0	50
2019	7	15	8	0	0	30
2020	7	12	12	0	0	31
2021	5	22	10	0	1	38
2022	3	16	14	0	0	33
2023	7	19	10	0	0	36
Total	**257**	**560**	**464**	**5**	**23**	**1,309**

Note: *Data collection for 2023 may not have been finalised at the time of writing.*

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

Figure 11.2: *Annual number of individuals newly diagnosed with HIV-1 in Curaçao (by year of diagnosis) or with documented diagnosis abroad before moving to Curaçao (by year of arrival). VL <200: individuals with documented diagnosis abroad before moving to Curaçao who already had a suppressed viral load below 200 copies/ml by the time they entered HIV care in Curaçao. NB: information on diagnosis abroad and date of arrival in Curaçao has been recorded for all newly registered individuals since early 2018, but is not yet available for everyone.*



Among the 107 individuals diagnosed in 2021-2023, the median age at diagnosis was 36 years (interquartile range [IQR] 28-50), with no differences between men and women. Of these 107 individuals:

- 31 (29%) were younger than 30 years of age at the time of diagnosis;
- 28 (26%) were aged between 30 and 39 years;
- 23 (21%) were aged between 40 and 49 years; and
- 25 (23%) were aged 50 years and over.

People in clinical care

In total, 733 (51%) of the 1,444 registered individuals with HIV-1 were known to be in clinical care in Curaçao by the end of 2023. People were considered to be in clinical care if they had visited their treating physician in 2023, or had a CD4 cell count or HIV RNA measurement during that year, and had not moved abroad. Of the 711 individuals who, according to this definition, were not in care by the end of 2023:

- 228 (32%) were known to have died;
- 196 (28%) had moved abroad; and
- 280 (39%) were lost to care

The remaining 7 individuals only entered HIV care in 2024. Of the 280 people lost to care, 56 (20%) had their last visit within a year of entering care, while another 30 (11%) had no follow-up visit after entering care. Of those lost to care:

- 164 (59%) originated from the former Netherlands Antilles;
- 49 (18%) were from Haiti;
- 29 (10%) were from the Dominican Republic; and
- 38 (14%) were from other countries.

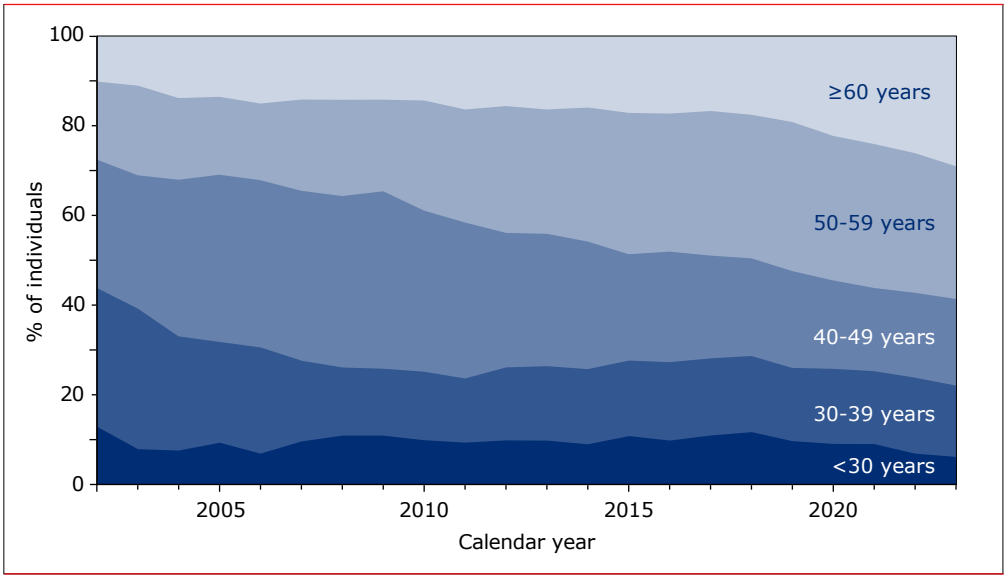
The 733 people in clinical care in 2023 included 8 individuals who did not have a clinical visit, CD4 cell count or HIV RNA measurement in 2022, but had previously received care for their HIV infection. Three of these individuals had not been in care for more than three years.

Of the 696 people who were still in care by the end of 2019, i.e., the last year before the COVID-19 pandemic, 39 (6%) did not have a clinical visit or HIV RNA or CD4 measurement in 2020. Of these 39 people, 3 had died and 10 were back in care in 2023 (including 3 individuals who had moved to the Netherlands), while the remaining 26 individuals were still lost to care.

Ageing population

The median age of the population in care by the end of 2023 was 54 years (IQR 41-61), a figure which has been increasing since 2002 (*Figure 11.3*). This increase is mainly a result of the improved life expectancy of individuals with HIV following the introduction of combination antiretroviral therapy (ART). As a result, more than half of all people currently in care (59%) are aged 50 years and over, including 57% of men and 63% of women. More than a quarter of those in care (29%) are 60 years and over.

Figure 11.3: *Increasing age of the population with HIV-1 in clinical care in Curaçao over calendar time. In 2002, 13% of the people in care were younger than 30 years of age, whereas 28% were 50 years and over. In 2023, these proportions were 6% and 59%, respectively, while 29% of people in care were 60 years of age and over. The proportion of people in clinical care as of 31 December of each calendar year is shown according to those who were <30 years of age, 30-39 years, 40-49 years, 50-59 years, and 60 years and over.*



Duration of infection

People in care by the end of 2023 had been diagnosed with HIV a median of 11.9 years (IQR 6.3-18.3) previously. Therefore, a large group (59%) has lived with HIV for more than 10 years; 20% for more than 20 years (*Table 11.2*). The median time since diagnosis was 12.4 years for MSM, 10.6 years for other men, and 12.8 years for women.

Table 11.2: Characteristics of the 733 individuals with an HIV-1 infection in clinical care in Curaçao by the end of 2023.

	MSM (n= 151, 21%)		Other men (n=303, 41%)		Women (n=278, 38%)		Total * (n=733)	
	n	%	n	%	n	%	n	%
Transmission								
Sex with men	110	73	–	–	268	96	379	52
Sex with women	1	1	172	57	0	0	173	24
Sex, partner unspecified	39	26	8	3	0	0	47	6
Other/unknown	1	1	123	41	10	4	134	18
Current age (years)								
0–14	0	0	1	0	2	1	3	0
15–24	4	3	5	2	6	2	15	2
25–29	4	3	13	4	8	3	25	3
30–39	28	19	51	17	36	13	116	16
40–49	40	26	51	17	51	18	142	19
50–59	49	32	83	27	85	31	217	30
60–69	16	11	72	24	68	24	156	21
≥70	10	7	27	9	22	8	59	8
Country of origin								
Former Netherlands Antilles	127	84	240	79	186	67	554	76
The Dominican Republic	1	1	10	3	40	14	51	7
Haiti	0	0	27	9	25	9	52	7
Colombia	8	5	7	2	4	1	19	3
Venezuela	6	4	8	3	2	1	16	2
Jamaica	0	0	3	1	10	4	13	2
The Netherlands	6	4	3	1	0	0	9	1
Other	3	2	5	2	11	4	19	3
Years aware of HIV infection								
<1	7	5	17	6	9	3	33	5
1–2	6	4	36	12	25	9	67	9
3–4	11	7	22	7	14	5	47	6
5–9	35	23	62	20	51	18	149	20
10–19	61	40	112	37	116	42	289	39
20–29	22	15	48	16	54	19	124	17
≥30	9	6	6	2	8	3	23	3
Unknown	0	0	0	0	1	0	1	0

** Includes one trans individual.*

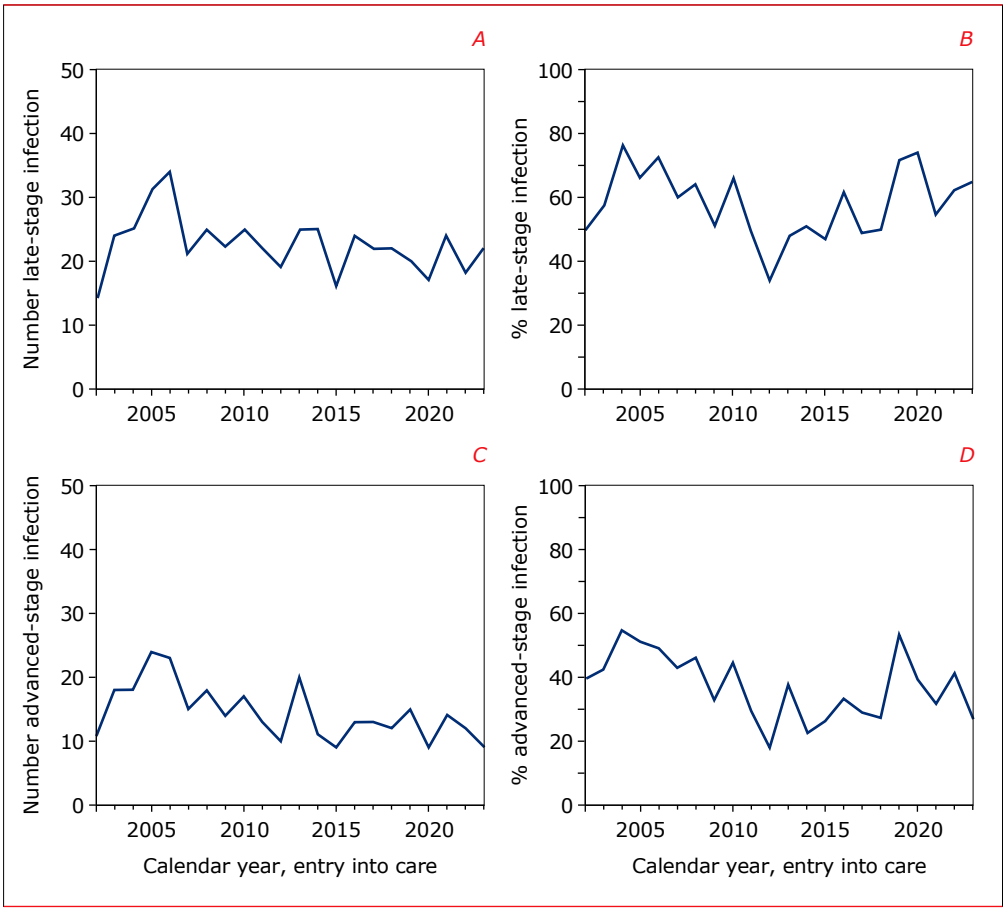
***Legend:** MSM = men who have sex men.*

Late presentation

Among the 1,309 people diagnosed with HIV-1 while living in Curaçao, a large proportion of those who have entered care since 2002 were late presenters. This refers to individuals who entered care with a CD4 cell count below 350 cells/mm^3, or with an AIDS-defining event, regardless of CD4 cell count, and who had no HIV-negative test in the 12 months prior to entry into care[1]. The proportion of late presenters was 56% among individuals entering care in 2002-2020, and remained at a high level of 60% among those entering care in 2021-2023 (*Figures 11.4A* and *11.4B*). There were no significant differences in the proportion of individuals with late presentation in 2021-2023 between MSM (63%), other men (62%), and women (55%).

Advanced HIV infection (i.e. with a CD4 cell count below 200 cells/mm^3 or AIDS) was found in 37% of individuals entering care in 2002-2020 and in 33% of those entering care in 2021-2023 (*Figures 11.4C* and *11.4D*). In total, 7 (6%) of the individuals who entered care in 2021-2023 presented with an AIDS-defining disease.

Figure 11.4: *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. In 2021-2023, 64 (60%) individuals presented with late HIV disease while 35 (33%) were advanced presenters. Late-stage HIV infection: CD4 cell counts below 350 cells/mm³ or having AIDS, regardless of CD4 cell count, and no HIV-negative test in the 12 months prior to entry into care. Advanced-stage HIV infection: CD4 cell counts below 200 cells/mm³ or having AIDS, and no HIV-negative test in the 12 months prior to entry into care. As a pre-therapy CD4 cell 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. In 2021-2023, the stage of infection was unknown for 17 (14%) individuals.*



Antiretroviral therapy (ART)

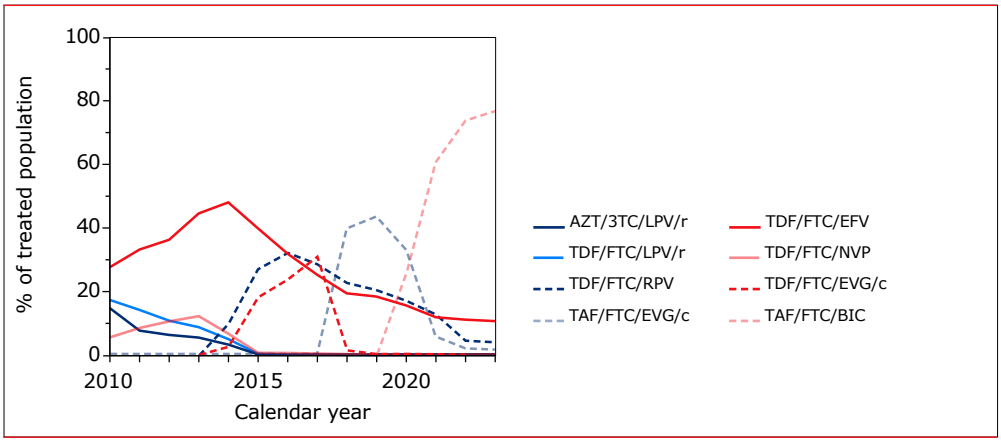
In total, 1,339 (93%) of the 1,444 registered individuals with HIV-1 had started antiretroviral therapy by the end of 2023. Of the 105 people who had not started therapy by that time, two managed to achieve HIV RNA levels below the lower limit of quantification without therapy, while 90 people were no longer in care, including 35 who had died. The other 13 individuals started therapy in 2024, or their ART may not have been recorded yet.

Over time there have been clear shifts in the ART regimens prescribed in Curaçao (*Figure 11.5*). Of the 727 people who were still in care and had started ART by the end of 2023:

- 77% were being treated with a combination of tenofovir alafenamide, emtricitabine, and bictegravir;
- 11% with tenofovir disoproxil, emtricitabine, and efavirenz; and
- 4% with tenofovir disoproxil, emtricitabine, and rilpivirine.

The majority (98%) used a once-daily regimen, with 94% being treated with a fixed-dose, single tablet regimen.

Figure 11.5: *Percentage of individuals treated with antiretroviral therapy (ART) by specific regimens over calendar time. At the end of 2023, 77% were receiving TAF/FTC/BIC, 11% TDF/FTC/EFV, and 4% TDF/FTC/RPV.*

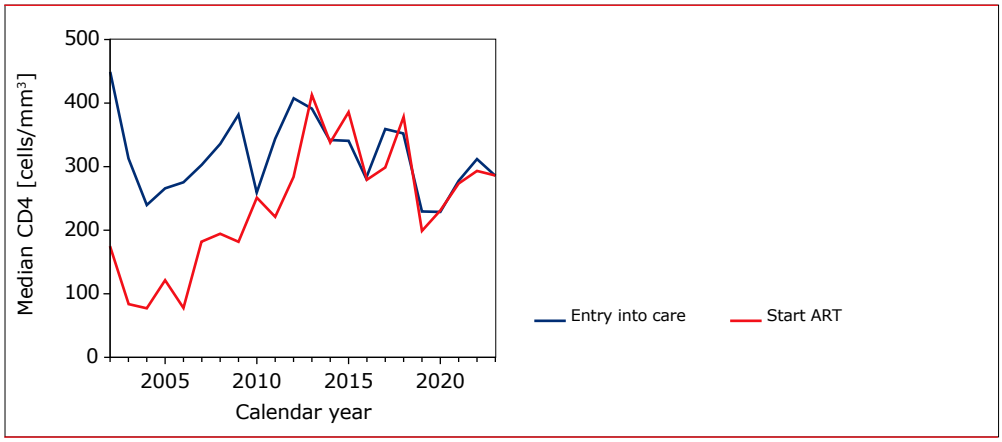


Legend: *AZT = zidovudine; 3TC = lamivudine; LPV/r = ritonavir-boosted lopinavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; RPV = rilpivirine; EFV = efavirenz; NVP = nevirapine; EVG/c = cobicistat-boosted elvitegravir; BIC = bictegravir.*

Since the mid-2000s, there has been an increase in CD4 cell counts at the start of ART, reflecting changes in guidelines on when to initiate therapy (*Figure 11.6*). CD4 cell counts at entry into care and at the start of therapy are now almost identical, which implies that people rapidly start ART after entry into care. In 2021-2023, 93% of people received ART within six months of entering care, irrespective of their CD4 cell count. During the same period, for those with available CD4 cell count data at the start of therapy:

- 33% had a measurement below 200 CD4 cells/mm^3;
- 27% had a measurement between 200 and 349 cells/mm^3;
- 14% had a measurement between 350 and 499 cells/mm^3; and
- 27% had CD4 cell counts of 500 cells/mm^3 or higher.

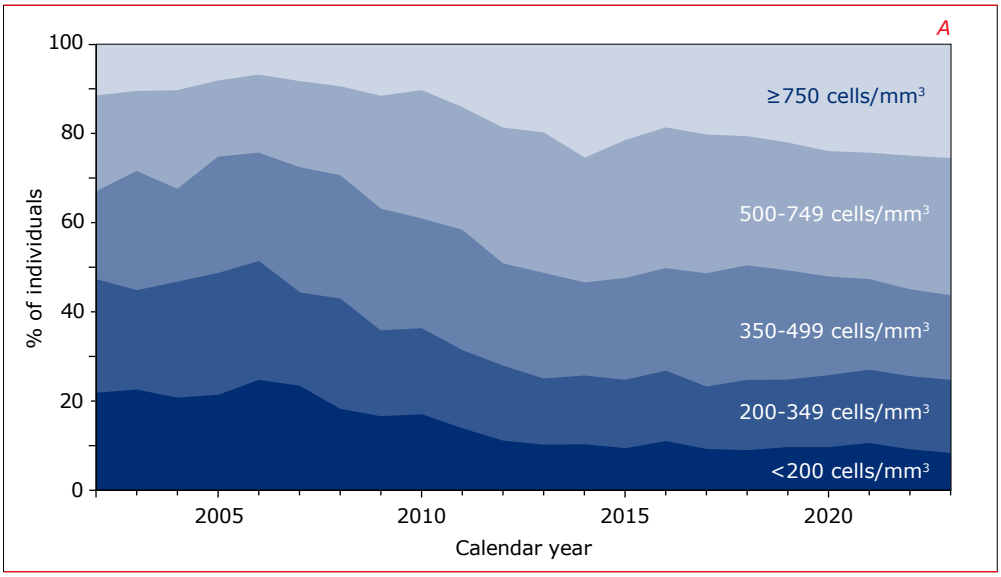
Figure 11.6: *Changes over calendar time in median CD4 cell counts at entry into care and at the start of antiretroviral therapy (ART). In 2021–2023, CD4 cell counts at entry into care were 285 cells/mm^3 (interquartile range [IQR] 163–477) and were similar, 285 cells/mm^3 (IQR 148–517), at the start of therapy.*

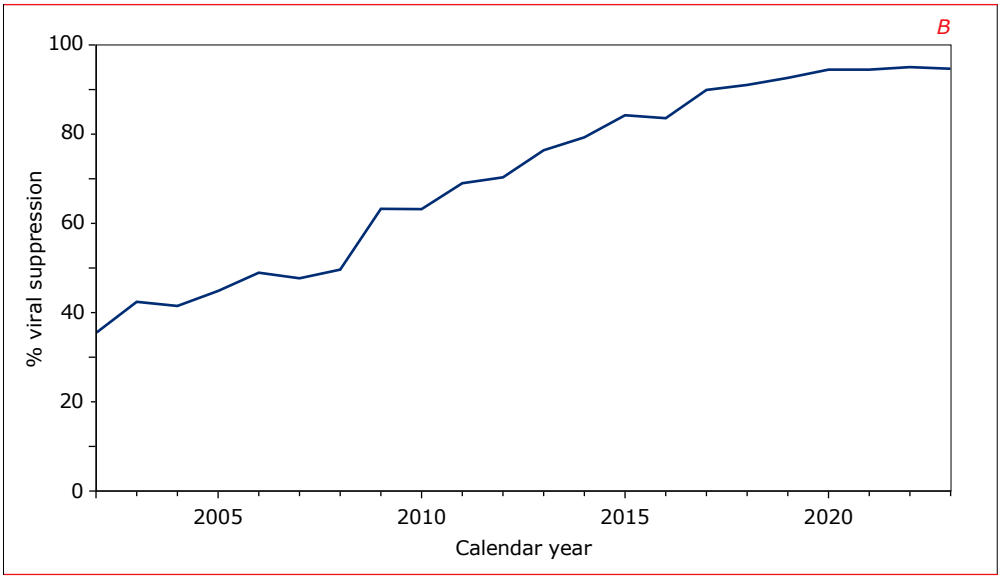


Therapy outcome

In the total population still in care by the end of 2023, the median current CD4 cell count was 473 cells/mm^3 (IQR 292-681). CD4 cell counts were highest in women (545 cells/mm^3; IQR 323-793) followed by MSM (491 cells/mm^3; IQR 291-679) and other men (413 cells/mm^3; IQR 285-607). The proportion of individuals with a most recent CD4 cell count below 350 cells/mm^3 decreased from 52% in 2002 to 24% in 2023 (*Figure 11.7A*). During the same time, among individuals with a viral load measurement, the proportion with HIV RNA levels lower than 200 copies/ml increased from 36% to 95% (*Figure 11.7B*).

Figure 11.7: *Proportion of people in care by the end of each calendar year (A) stratified by most recent CD4 cell count, and (B) with HIV RNA <200 copies/ml at their last viral load measurement in each calendar year.*





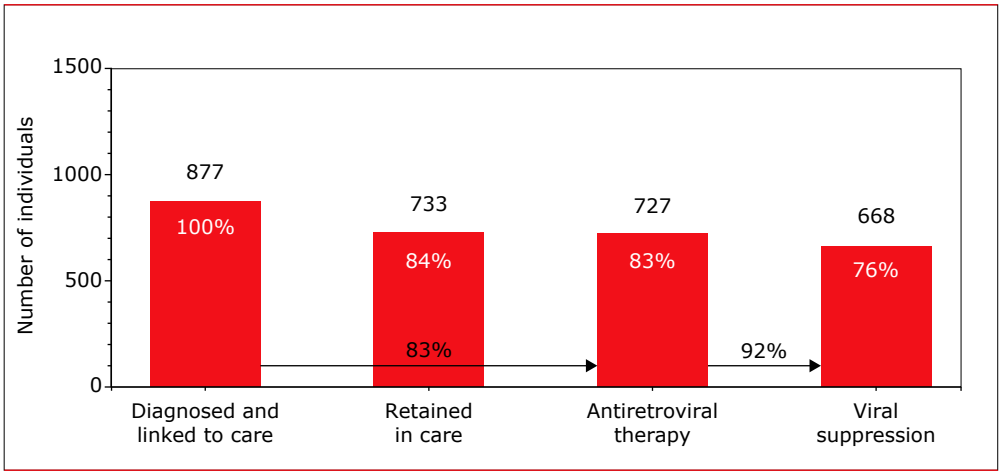
Continuum of HIV care

In total, 877 individuals had been diagnosed and linked to care, registered by SHM, had received HIV care in 2013 or later, and were not recorded in the SHM database as having died or moved abroad (*Figure 11.8*). Altogether:

- 733 people (or 84% of those diagnosed and linked to care) were still in care, having had at least one HIV RNA or CD4 cell count measurement, or a clinical visit in 2023;
- 727 (or 83% of those diagnosed and linked to care) of whom had started ART;
- 705 (97% of those who started therapy) of whom had an HIV RNA measurement available in 2023; and
- 668 (95%, or 92% of those treated) of those had a most recent HIV RNA level below 200 copies/ml.

Overall, 76% of the 877 individuals diagnosed and ever linked to care, had a suppressed viral load. In terms of the Joint United Nations Programme on HIV/AIDS' (UNAIDS) 95-95-95 target for 2025, the current estimate for the second and third "95" for Curaçao stands at 83-92: 83% of all people diagnosed receive antiretroviral therapy, and 92% of people receiving ART have a suppressed viral load[2].

Figure 11.8: *Continuum of HIV care for the population with HIV-1 in Curaçao diagnosed and linked to care by the end of 2023. Percentages at the top of the bars are calculated relative to the number of people diagnosed and linked to care, while percentages at the bottom correspond to the second and third of UNAIDS' 95-95-95 targets.*



It is worth noting that we did not estimate the total number of people with HIV, including those not yet diagnosed. Estimation of the undiagnosed population is based on trends over calendar time in observed diagnoses and CD4 cell counts at the time of diagnosis. A requirement for this estimate is that all diagnoses are reported in the SHM database, and this was not yet the case. In addition, the estimated number with undiagnosed HIV would not include populations that are less likely to reach HIV care in Curaçao, such as undocumented migrants, and would therefore underestimate the true number with undiagnosed HIV.

Viral suppression

Of the 727 individuals who had started ART, 59 (8%) did not have a suppressed viral load. On closer inspection, 22 (37%) of these individuals were found to have no documented HIV RNA measurement in 2023. The remaining 37 (63%) had a viral load measurement in 2023, but with HIV RNA levels exceeding 200 copies/ml. Of these 37 individuals, six only started ART 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 31 individuals with HIV RNA levels above 200 copies/ml had started ART longer than six months previously.

Lost to care

In total, 281 individuals were lost to care by the end of 2023, of whom:

- 137 (49%) were last seen for care before the end of 2013;
- 95 (34%) between 2013 and 2019;
- 10 (4%) in 2020;
- 23 (8%) in 2021; and
- 16 (6%) in 2022.

The 137 individuals who were lost to care before 2013 were excluded from the number of people diagnosed and linked to care. It is unlikely that these 137 individuals are still living in Curaçao without requiring care or ART. In total, 51 (35%) of the 144 individuals lost to care after 2013 were born outside the former Netherlands Antilles, including 16 in Haiti and 12 in the Dominican Republic. For those still in care by the end of 2023, the percentage of people born outside the former Netherlands Antilles 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 care offered to individuals with HIV in Curaçao has improved considerably, as evidenced by the increasing proportion of individuals with a suppressed viral load. In addition, timely registration of HIV RNA measurements in the SHM database has also improved, enabling better monitoring of progress towards achieving UNAIDS' 95-95-95 goals for 2025. However, the proportion of people entering care with late-stage HIV infection remained high in recent years. Furthermore, the relatively high proportion of people lost to care is worrisome and may result in underreporting of death and outmigration. Among those lost to care is a substantial group of 26 individuals who were last seen for care in 2019 (i.e. the last year before the COVID-19 pandemic) and have not yet returned.

Recommendations

Curaçao is in a unique position in the Caribbean, in that data on individuals with HIV in care are regularly collected and monitored. However, it is important that the quality of these data is maintained and that the collected data remain representative of the population with HIV.

Early start of ART in adults appears possible, but long-term, continuous follow up should be guaranteed to optimise its effect. The continuum of care for Curaçao illustrates that while almost everyone who is still in care has started antiretroviral therapy, 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 at the hospital. It is hoped that this will improve retention in care in the near future.

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

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