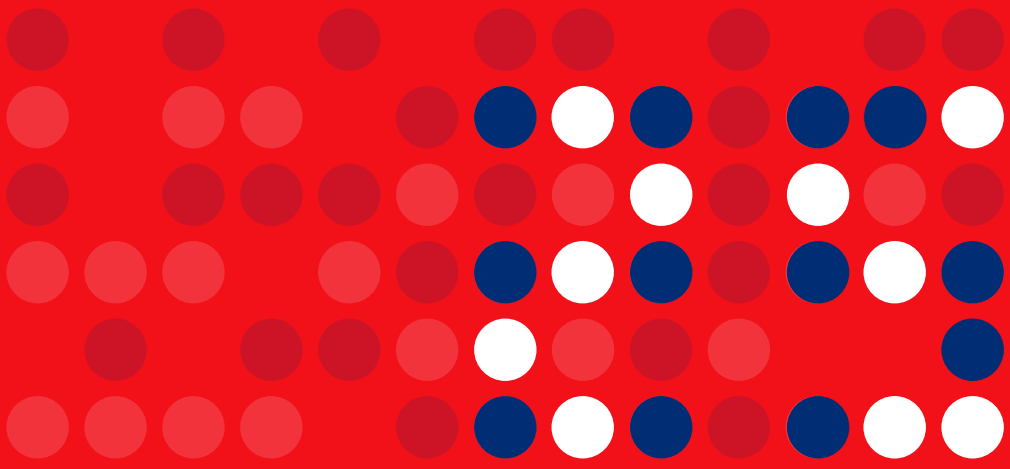
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2025



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

HIV Monitoring

HIV Monitoring Report 2025

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

Interactive PDF user guide

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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 Frisius MC	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:

A	Emma Kinderziekenhuis (EKZ), Amsterdam UMC	Amsterdam
B	Beatrix Kinderziekenhuis (BKZ), UMCG	Groningen
C	Erasmus MC Sophia Kinderziekenhuis	Rotterdam
D	Wilhelmina Kinderziekenhuis (WKZ), UMC	Utrecht

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1. HIV in the Netherlands

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

Introduction

By May 2025, stichting hiv monitoring (SHM) had registered 36,209 individuals with HIV. The vast majority of these (35,181, or 97.2%) agreed to the collection of further clinical data once registered, whereas 1,028 (2.8%) declined to take part. Among those whose clinical data had been collected, most (33,760) were registered with one of the HIV treatment centres in the Netherlands (*Figure 1.1*).

Of the 33,760 individuals registered in the Netherlands, the vast majority were diagnosed with HIV-1 (32,544, or 96%). Only 102 people were diagnosed with HIV-2, while 62 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 in 1998, which accounts for the absence of serological information for most of the remaining 1,052.

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 2024. 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.*

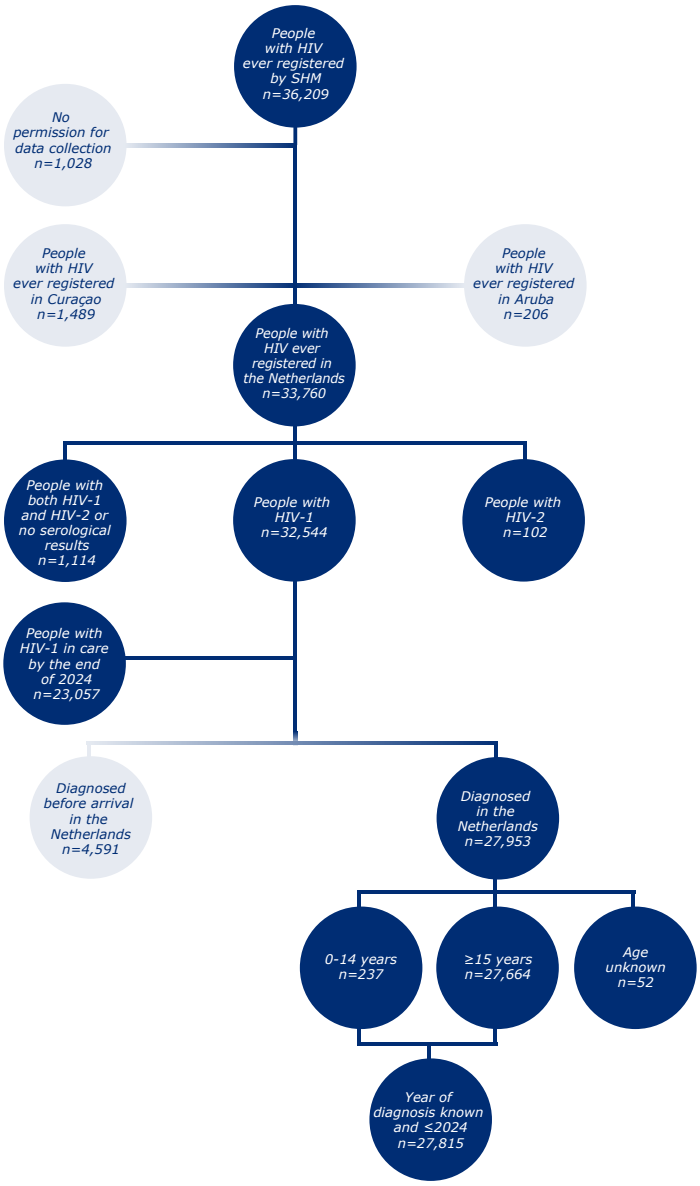
HIV infection	The moment an individual acquires HIV. The time of infection is often unknown.
HIV diagnosis	The moment an HIV infection in an individual is confirmed by blood tests. The time of diagnosis can be weeks, months, or years after infection.
Entry into care	The moment an individual with HIV 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 32,544 individuals in the Netherlands who were ever diagnosed with HIV-1, 4,591 (14%) were born abroad and had a documented HIV diagnosis prior to arrival in the Netherlands (*Figure 1.1*). These 4,591 individuals have been excluded from the analyses on newly diagnosed individuals later in this section. The remaining 27,953 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 4,591 individuals who were born abroad and had a documented HIV-1 diagnosis before arriving in the Netherlands, 1,337 (29%) arrived in the Netherlands in 2022-2024, including 302 in 2024 (*Figure 1.2A*). So far, SHM has registered 641 people who arrived in 2022, which is an increase of 99% compared with the average annual number of 322 migrants in the other years in the period 2018-2024. 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 1,337 people who arrived in 2022-2024 with a documented pre-arrival HIV diagnosis, 659 (49%) were men who have sex with men (MSM), 287 (21%) were other men, 343 (26%) were women, and 48 (4%) were trans people. The median age at the time of arrival was 37 years (interquartile range [IQR] 30-44); 122 (9%) were below 25 years of age, including 12 children under the age of 15, while 134 (10%) were 50 years of age or older. In terms of geographic origins, migrants arrived from:

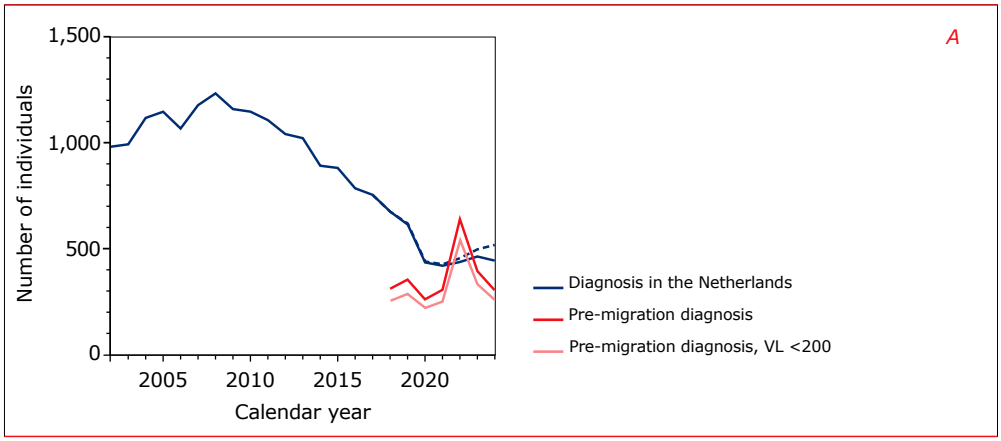
- eastern Europe (429, 32%);
- South America (247, 18%);
- sub-Saharan Africa (169, 13%);
- central Europe (111, 8%);
- western Europe (111, 8%);
- Middle East and north Africa (74, 6%);
- Caribbean (73, 5%);
- south and southeast Asia (62, 5%); and
- other regions (61, 5%).

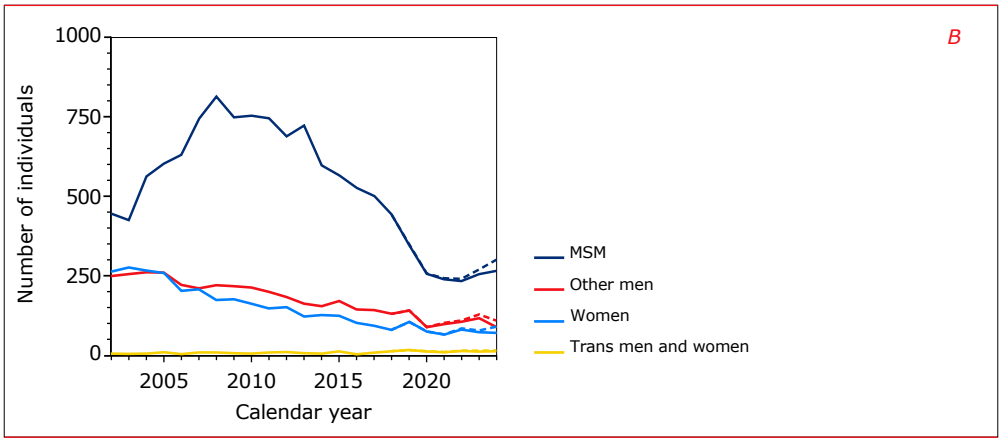
The most commonly reported countries of origin (from where at least 30 individuals with a known HIV diagnosis arrived in the Netherlands) were Ukraine (337, 25%), Brazil (80, 6%), Colombia (63, 5%), Russian Federation (57, 4%), Poland (50, 4%), Turkey (39, 3%), and Curaçao (35, 3%). Individuals from Ukraine and the Russian Federation accounted for 260 (41%) and 38 (6%), respectively, of the 641 people arriving in 2022; these numbers decreased to 24 (8%) and 7 (2%), respectively, in 2024.

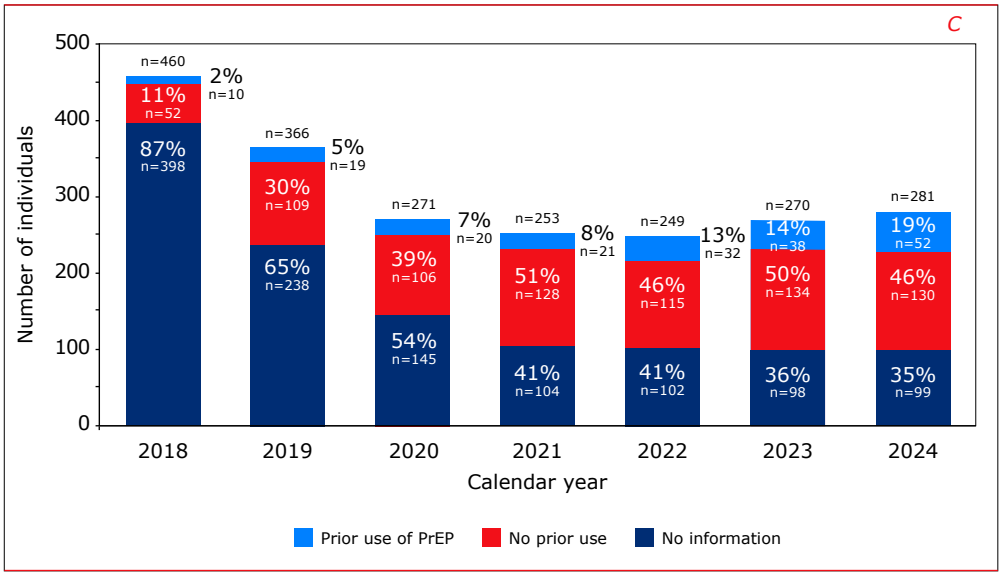
The majority (1,209, or 90%) of the 1,337 people had already started antiretroviral therapy (ART) before arriving in the Netherlands, while 40 (3%) started ART in the Netherlands; for 88 (7%) migrants there was no unequivocal evidence whether they started ART before or after arrival due to uncertainty in date of arrival and/or date of start ART. By the time the 1,337 individuals entered HIV care in

the Netherlands, their median CD4 counts were 660 (IQR 457-900) cells/mm^3, while 1,163 individuals had HIV RNA levels below 1,000 copies/ml (88% of the 1,326 who had an available viral load measurement), including 1,132 individuals with RNA levels below 200 copies/ml (85% of the 1,326 with a viral load measurement).

Figure 1.2: *(A) Annual number of individuals newly diagnosed with HIV-1 in the Netherlands or while living 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 2024, MSM accounted for 60% of the annual number of new diagnoses, other men for 20%, 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. NB: individuals diagnosed in the Netherlands may include people born abroad for whom the date of arrival has not yet been recorded.*







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

Individuals newly diagnosed in the Netherlands

Of the 27,953 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, 237 (1%) were diagnosed as children under 15 years of age: they are described in more detail in *Chapter 8*. Among the 27,815 individuals for whom the date or period of diagnosis was known, 27,580 (99%) were diagnosed at 15 years of age or older. Of these 27,580 individuals, 16,442 (60%) were men who have sex with men, 5,889 (21%) were other men, 4,954 (18%) were women, and 295 (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	2,095		719		561		15		53		3,443	
1996	367		159		100		3		10		639	
1997	421		188		138		5		11		763	
1998	317		155		126		1		11		610	
1999	332		159		150		5		13		659	
2000	355		205		201		5		15		781	
2001	425		230		239		7		17		918	
2002	447		250		265		6		15		983	
2003	427		257		278		10		21		993	
2004	563		263		269		9		13		1,117	
2005	604		262		259		10		11		1,146	
2006	631		223		204		6		4		1,068	
2007	744		213		208		9		4		1,178	
2008	814		223		175		12		9		1,233	
2009	749		219		177		9		6		1,160	
2010	753		214		164		8		8		1,147	
2011	746		201		149		10		1		1,107	
2012	688		186		153		12		3		1,042	
2013	722		164		124		10		1		1,021	
2014	599		156		128		7		2		892	
2015	567		172		126		15		1		881	
2016	528		146		104		5		2		785	
2017	502	502	144	144	95	95	12	12	1	1	754	754
2018	444	444	132	132	82	82	16	16	1	1	675	675
2019	348	350	143	144	107	107	18	18	1	1	617	620
2020	257	260	90	91	76	77	14	14	0	0	437	442
2021	240	245	99	102	67	69	13	13	1	1	420	430
2022	234	242	107	112	82	86	15	16	0	0	438	456
2023	256	271	119	130	75	82	14	15	0	0	464	498
2024	267	301	91	111	72	88	14	17	0	0	444	517
Total	**16,442**	**16,508**	**5,889**	**5,930**	**4,954**	**4,985**	**295**	**301**	**235**	**235**	**27,815**	**27,960**

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 437 in 2020 (*Table 1.1*; *Figure 1.2A*). Thereafter, the number of diagnoses remained around the same level and, so far, 444 new HIV diagnoses have been registered for 2024. However, taking into account the backlog[a] in registration of HIV cases, the projected number of new HIV diagnoses in 2024 after adjustment may be as high as 517.

In MSM, the annual number of diagnoses rose to 814 in 2008, gradually fell to 234 in 2022, and was 267 (adjusted for backlog in registration, 300) in 2024 (*Figure 1.2B*). Among other men and among women, the annual number of new diagnoses has decreased to 91 (adjusted for backlog in registration, 111) and 72 (adjusted for backlog in registration, 88), respectively, in 2024. Finally, the number of new diagnoses among trans men and women was approximately 15 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 *Chapter 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 2024, 52 (19%) of the 281 observed new diagnoses in MSM and trans individuals were in people who reported prior use of PrEP, while 130 (46%) people reported never to have used PrEP. For 99 (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[1]. The estimated number of infections in people living in the Netherlands at the time they acquired HIV decreased from 910 (95% confidence interval [CI] 875-945) in 2010 to 300 (275-320) in 2020. Thereafter, the number of infections appeared to rise, albeit with considerable uncertainty, to 440 (365-500) in 2024 (*Figure 1.3A*). During the same period, the number of newly acquired HIV infections among MSM fell from 710 (680-745) in 2010 to 175 (160-190), and was 310 (250-365) in 2024 (*Figure 1.3B*).

In other men and in women, the estimated numbers of newly acquired infections in 2010 were 115 (95% CI 105-125) and 80 (75-90), respectively. By 2024 this had dropped in both groups, reaching 80 (55-110) in other men and 45 (25-65) 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 2017-2024 were estimated using the European Centre for Disease Prevention and Control (ECDC) HIV Platform Tool.

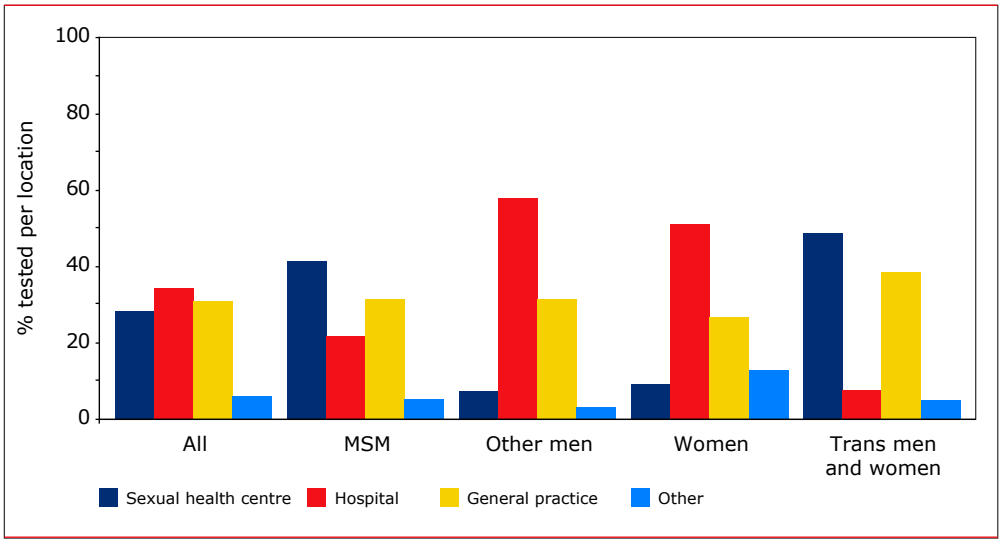
Figure 1.3: *Observed annual number of HIV diagnoses (red) and estimated annual number of newly acquired HIV infections (blue) in: the total population (A), in men who have sex with men (B), in other men (C), in women (D), according to the European Centre for Disease Prevention and Control (ECDC) HIV Platform Tool[1]. The red dashed lines represent the number of diagnoses after adjusting for the delay in notification to SHM, while the blue bands are the uncertainty bounds. The blue dashed lines indicate that estimates in 2021 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 1,273 (95%) of the 1,346 people diagnosed in 2022-2024, while 58 (4%) individuals were known to have been diagnosed abroad. Overall, 362 (28%) of these 1,273 individuals received their first HIV-positive test result at a sexual health centre, 439 (34%) at a hospital, 395 (31%) at a general practice, and 77 (6%) at another location (*Figure 1.4*). Among the 362 individuals diagnosed at sexual health centres, 302 (83%) were MSM, 21 (6%) were other men, 20 (5%) were women, and 19 (5%) were trans men and women, which was similar to the proportions directly reported by sexual health centres for 2024[2]. Among the 459 individuals diagnosed in a hospital, 159 (36%) were MSM, 167 (38%) were other men, 110 (25%) were women, and 3 (1%) were trans men and women, while among the 395 people diagnosed at a general practice 231 (58%) were MSM, 91 (23%) were other men, 58 (15%) were women, and 15 (8%) were trans men and women.

Figure 1.4: *Proportion of individuals diagnosed in 2022–2024, stratified by location of testing and key population. Location of testing in the Netherlands is known for 1,273 (95%) of 1,346 individuals diagnosed, of whom 730 (57%) MSM, 288 (23%) other men, 216 (17%) women, and 39 (3%) trans men and women, while 58 (4%) individuals were diagnosed abroad.*



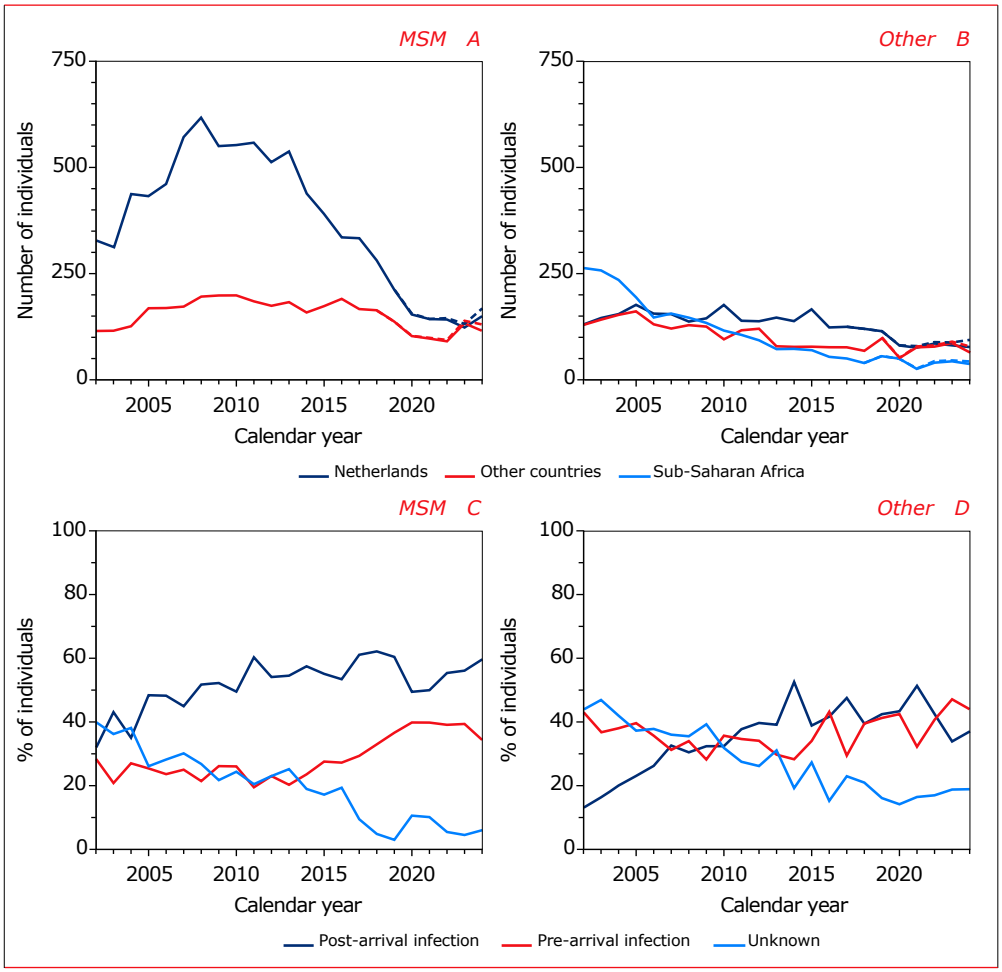
Legend: *MSM = men who have sex with men.*

Geographical region of origin

Of the 19,897 people diagnosed with HIV-1 in 2002-2024 at 15 years of age or older, 11,579 (58%) were born in the Netherlands and 8,318 (42%) outside the Netherlands. Of the 12,130 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 2022-2024), the proportion of MSM of Dutch origin was 55%, down from 72% before 2022, while the proportion of MSM from central Europe was 11%, up from 3% before 2022.

Among the 7,767 individuals other than MSM diagnosed in 2002-2024, 38% originated from the Netherlands, while 31% 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 2022 and 2024, 41% were of Dutch origin (38% before 2022), and 20% originated from sub-Saharan Africa (32% before 2022), while 8% were from central Europe (3% before 2022), and 8% from Eastern Europe (2% before 2022).

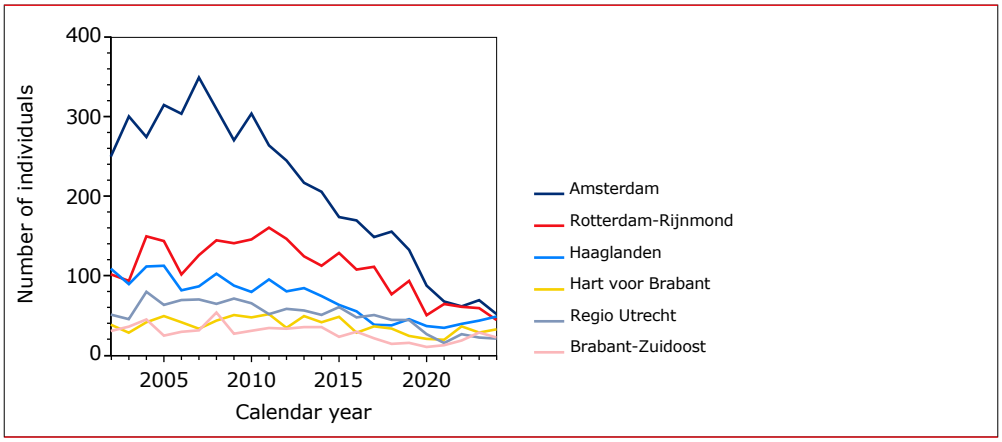
Figure 1.5: *Annual number of diagnoses by region of origin and, for individuals born outside the Netherlands, proportion of pre- and post-arrival infections among: (A, C) men who have sex with men (MSM), and (B, D) other people aged 15 years or older at the time of diagnosis. Of the 757 MSM diagnosed in 2022–2024, 417 (55%) originated from the Netherlands, 140 (18%) from other European countries, 59 (8%) from South America, 38 (5%) from the Caribbean, and 31 (4%) from south and southeast Asia. Of the other 589 people diagnosed in 2022–2024, 244 (41%) originated from the Netherlands, 107 (18%) from other European countries, 119 (20%) from sub-Saharan Africa, 52 (9%) from South America, 18 (3%) from the Caribbean, and 20 (3%) from south and southeast Asia.*



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

Overall, 14% of individuals newly diagnosed in 2022-2024 were living in the Amsterdam public health service (PHS) region at the time of diagnosis, and 13% were living in the Rotterdam- Rijnmond PHS region (*Figure 1.6*). Of the people of Dutch origin diagnosed in these years, 9% and 13%, respectively, were living in each of the above PHS regions, while these proportions were 19% and 12%, respectively, for the people born outside the Netherlands. Among MSM, 16% were living in Amsterdam at the time of diagnosis and 13% were living in Rotterdam-Rijnmond, while among other individuals, 12% were living in Amsterdam and 13% in Rotterdam-Rijnmond. Other PHS regions with at least 5% of the new diagnoses in 2022-2024 were Haaglanden (10%, including Den Haag), Hart voor Brabant (8%, including Den Bosch and Tilburg), Utrecht (5%), and Brabant-Zuidoost (5%, including Eindhoven).

Figure 1.6: *Annual number of diagnoses by public health service (PHS) region. Only PHS regions with at least 5% of the new diagnoses in 2022–2024 are shown.*



HIV infections acquired before arrival in the Netherlands

Among the 1,346 individuals with an HIV diagnosis in the Netherlands in 2022-2024, 685 (51%) were born outside the Netherlands, of whom 340 MSM and 345 other men, women, or trans individuals. Overall, 280 (41%) most likely acquired their HIV infection before arrival in the Netherlands and 324 (47%) 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 81 (12%) 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 340 MSM born outside the Netherlands and diagnosed in 2022-2024, 128 (38%) most likely acquired their HIV infection before moving to the Netherlands, 194 (57%) most likely acquired their infection after arrival, while for 18 (5%) the likelihood of pre- or post-migration could not be determined. Among individuals other than MSM, there were no changes over time since 2010 and in 2022-2024, 152 (44%) most likely acquired HIV before arrival in the Netherlands, 130 (38%) after arrival, and for 63 (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 2024, it was 38 years (IQR 29-51). In 2002-2024, 20% of individuals who received an HIV diagnosis were aged 50 years or older; in 2024, 27% were 50 years or older (*Figure 1.7*).

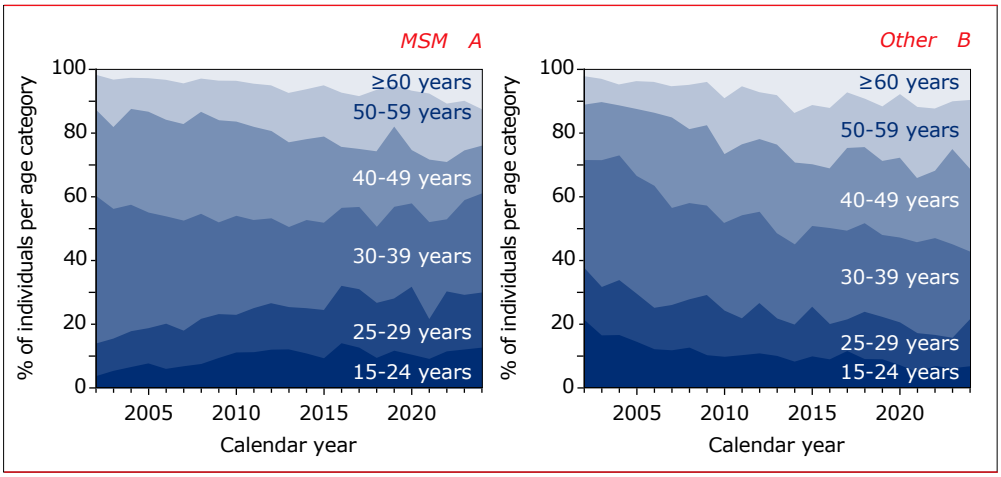
It is worth noting that although the median age at diagnosis in MSM (39 years) did not change between 2002 and 2024, both the proportion diagnosed below 30 years of age and the proportion diagnosed above 50 years of age increased during this period. In 2002, 14% of MSM were younger than 30 years at the time of their diagnosis while 13% were 50 years of age or older; these proportions were 30% and 24%, respectively, in 2024. 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 2024, the annual number of diagnoses among MSM 30 to 50 years of age decreased by 73%, from 457 to 123. During the same period, the number of diagnoses decreased from 173 to 80, or 54%, in MSM younger than 30 years, and from 123 to 64, or 48%, in MSM 50 years of age or older.

There were some age differences between MSM, other men, and women diagnosed in 2022-2024. MSM born in the Netherlands were diagnosed at a median age of 44 years (IQR 31-56), while MSM of foreign origin were diagnosed at a younger median age of 33 years (27-40). Men other than MSM were 44 years (35-54) of age at the time diagnosis, which was somewhat older than the median age of 41 years (31-51) for women. In 2024, 24% of MSM, 32% of other men, and 35% of women were 50 years or older at the time of diagnosis.

HIV diagnoses in people under 25 years of age

Between 2002 and 2024, 2,087 (10%) individuals who received an HIV diagnosis at 15 years of age or older were under 25 years of age (*Figure 1.7*). In 2024, 46 people under 25 years of age were diagnosed with HIV, which amounted to 10% of all people diagnosed with HIV that year. The number of individuals under 25 years of age diagnosed in 2024 was 34 (13%) among MSM, 2 (2%) among other men, and 9 (13%) among women. Of the 46 young people, 24 (52%) were born in the Netherlands, while five originated from South America, five from central Europe, four from sub-Saharan Africa, and eight from elsewhere.

Figure 1.7: *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 2002-2024, the proportion of individuals between 15 and 29 years of age changed from 14% to 30% for MSM, and from 38% to 21% for other individuals. During the same period, the proportion of MSM aged 50 years or older at the time of diagnosis changed from 13% to 24%, while these proportions were 11% and 31% for other individuals.*

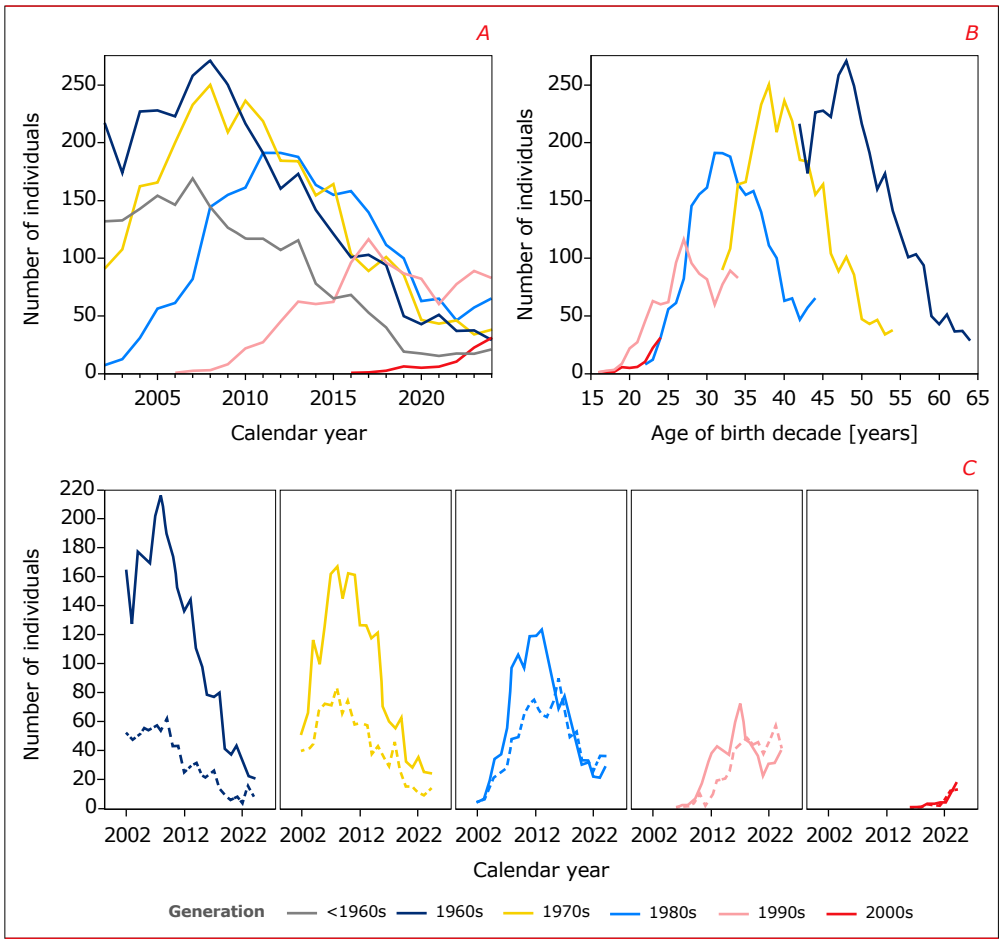


Legend: *MSM = men who have sex with men.*

HIV diagnoses in MSM by birth decades

Over time, MSM from younger generations became involved in HIV transmission although successive generations had lower maximum annual numbers that were reached at younger ages (*Figure 1.8A* and *1.8B*). Both figures also show that in the 1990s and 1980s birth cohorts, after years of decreases, the number of diagnoses is increasing. Separating the curves by region of origin shows that the number of diagnoses among MSM born in the Netherlands and abroad currently show a similar pattern (*Figure 1.8C*).

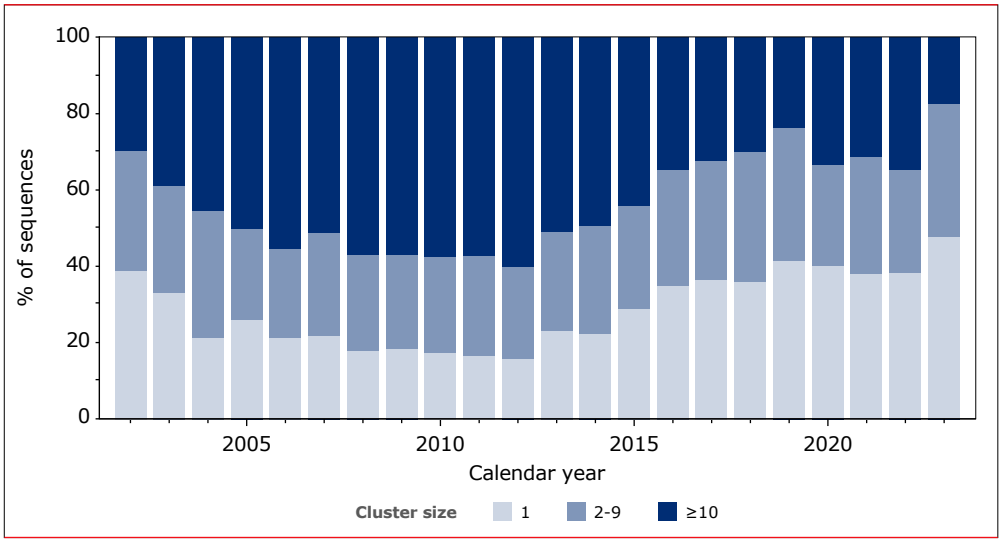
Figure 1.8: *(A) Annual number of new HIV diagnoses among men who have sex with men by birth decade, (B) annual number of diagnoses by age of each birth decade, (C) annual number of HIV diagnoses by birth decade stratified by being born in the Netherlands (solid lines) or abroad (dashed lines). Age of a birth decade is defined as the age of individuals born in the first year of the decade.*



Transmission clusters of MSM

We performed a cluster analysis on the polymerase sequences used for resistance screening that were available for 51% of MSM (see also *Chapter 5*). Clusters were defined as large if they included 10 or more sequences and as small if they included 2 to 9 sequences, and size 1 when sequences were not part of a cluster. The size of clusters indicates the level of onward national transmission and the number clusters of size 1 indicates the level of new or external introductions from abroad. Since 2010, there has been a significant decrease in sequences that were part of large clusters (*Figure 1.9*). Together with the decrease in the annual number of diagnoses up to 2020 (*Figure 1.2B*) this confirms less onwards transmission in the Netherlands. In line with this finding the total number of observed large clusters decreased by 50% from 109 in 2010 to 54 in 2020. Two new large clusters were observed since 2019. In addition, there were still many sequences in small clusters and clusters of size 1 indicating ongoing new introductions from abroad.

Figure 1.9: *Proportion of newly diagnosed men who have sex with men who are part of a large cluster (10 or more sequences), a small cluster (2 to 9 sequences), or a cluster of size 1.*



Entry into care

Of the 1,273 individuals diagnosed with HIV in 2022-2024 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 2024, 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%).

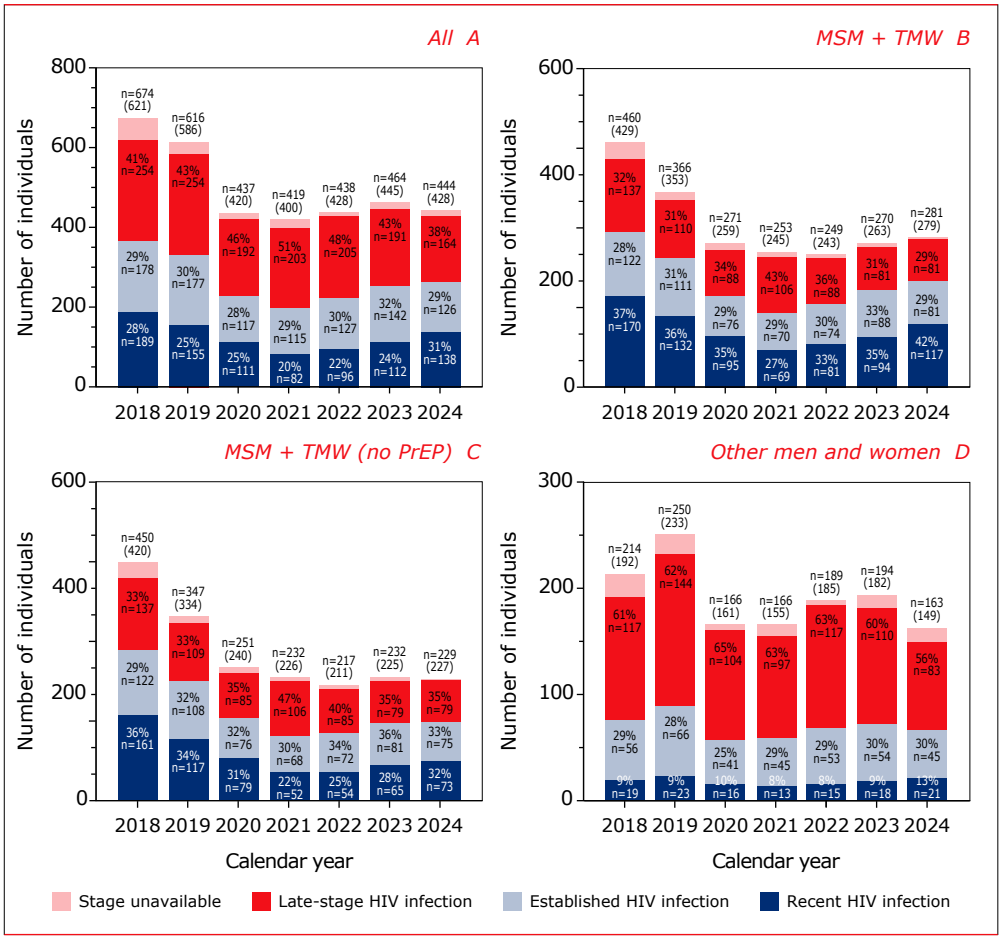
Stage at time of HIV diagnosis

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[5].
- 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 20% in 2021 and then increased to 31%, while the proportion with late-stage HIV was 41% in 2018, increased to 51% in 2021 and was 38% in 2024 (*Figure 1.10A*). 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 63% in 2024. 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 1.10B* and *1.10C*). In other men and women, changes in the proportion diagnosed in each of these three stages were less pronounced (*Figure 1.10D*).

Figure 1.10: *Annual number and proportion of individuals diagnosed with recent, established, or late-stage HIV infection in 2018-2024 (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 month 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.*

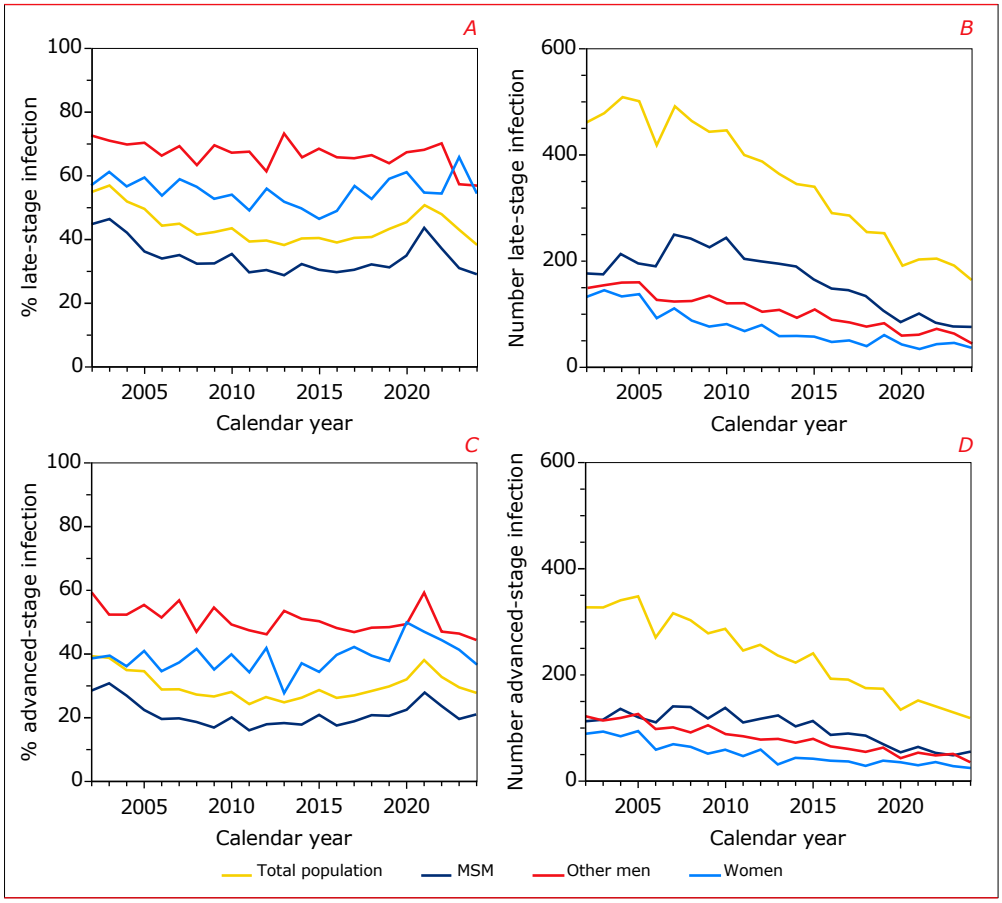


Legend: *MSM = men who have sex with men; TMW = trans men and women; PrEP = pre-exposure prophylaxis.*

Late diagnosis

Overall, 43% of the individuals diagnosed in 2022-2024 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 43% in 2023, and 38% in 2024 (*Figure 1.11A*). This increase between 2013 and 2021 was mainly due to changes in the proportion of MSM diagnosed with late-stage HIV (see also *Figure 1.10B*). 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 2024 (*Figure 1.11C*). 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 1.11B* and *1.11D*). It is worth noting that although newly diagnosed MSM had the lowest proportion of late-stage HIV infections, they accounted for 238 (43%) of all 560 individuals diagnosed with late-stage HIV in 2022-2024.

Figure 1.11: *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 2024, 164 (38%) individuals were diagnosed with late-stage HIV infection: 77 (29%) men who have sex with men (MSM), 46 (57%) other men, 37 (54%) women, and 4 (29%) trans men and women. During the same year, 119 (28%) individuals were diagnosed with advanced-stage HIV infection: 56 (21%) MSM, 36 (44%) other men, 25 (37%) women, and 2 (14%) trans individuals. 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 2022–2024, the stage of infection was unknown for 45 (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 2022-2024, 238 (32%) MSM, 183 (62%) other men, 127 (58%) women and 12 (28%) 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 (61%, or 80 individuals), Eastern Europe and Central Asia (54%, 39 individuals), or from south and southeast Asia (52%, 26 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 2022-2024, late-stage HIV was seen in 54% of MSM, 69% of other men, and 40% of women aged 60 years or older, compared with 21% of MSM, 25% of other men, and 33% of women diagnosed below the age of 30 years (*Table 1.2*; *Figure 1.12*).

Table 1.2: *Characteristics of the 560 individuals with a late-stage HIV infection among the 1,346 individuals diagnosed with HIV in 2022–2024. In total, as a result of missing CD4 cell counts at diagnosis, it was not possible to classify whether 45 (3%) individuals (15 MSM, 20 other men, 10 women, and no trans individuals) 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.*

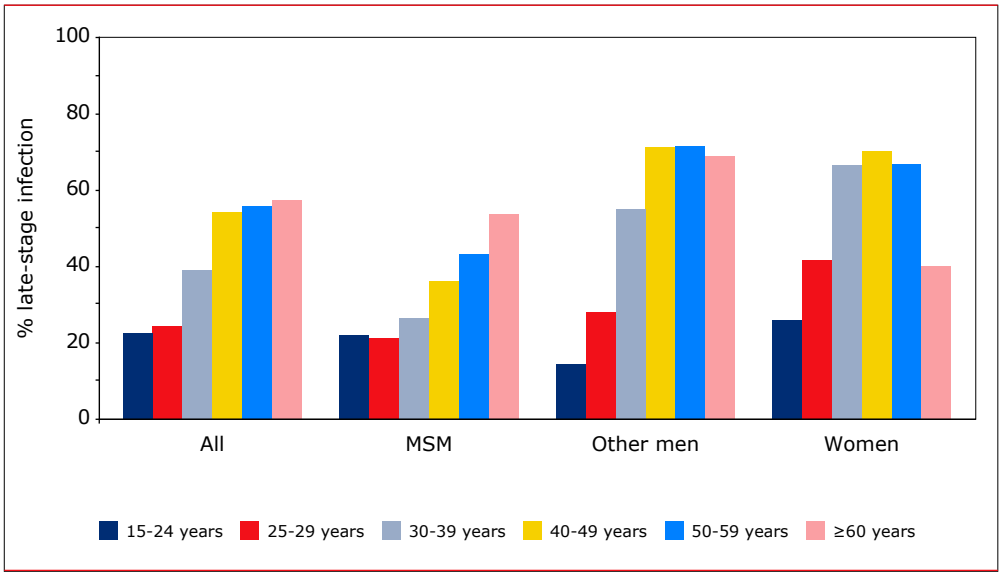
	MSM (n=742)		Other men (n=297)		Women (n=219)		Trans men and women (n=43)		Total (n=1,301)	
	n	%	n	%	n	%	n	%	n	%
Overall	238	32	183	62	127	58	12	28	560	43
Age at diagnosis (years)										
15–24	19	22	1	14	7	26	1	33	28	23
25–29	28	21	7	28	10	42	2	17	47	24
30–39	56	27	44	55	32	67	8	35	140	39
40–49	44	36	60	71	40	70	0	0	144	54
50–59	48	43	40	71	32	67	1	50	121	56
60–69	29	46	19	63	5	42	0	0	53	50
≥70	14	82	12	80	1	33	0	0	27	77
Region of origin										
Western	*138*	*31*	*95*	*57*	*28*	*39*	*2*	*40*	*263*	*38*
The Netherlands	127	31	93	57	26	38	2	40	248	39
Other western*	11	29	2	50	2	40	0	0	15	32
Non-Western	*100*	*34*	*88*	*68*	*99*	*67*	*10*	*26*	*297*	*49*
Sub-Saharan Africa	7	32	29	81	44	60	0	0	80	61
Central Europe	24	31	19	70	9	64	1	50	53	44
Eastern Europe and Central Asia	4	17	10	59	25	86	0	0	39	54
South America	19	32	10	67	8	57	6	26	43	39
Caribbean	12	32	4	50	3	60	2	40	21	38
South and southeast Asia	14	45	5	56	6	86	1	3	26	52
Middle East and north Africa	12	40	8	62	4	79	0	0	24	48
Other/unknown	8	50	3	60	0	0	0	0	11	52
Location of HIV diagnosis										
Sexual health centre	51	17	10	50	4	21	5	26	70	19
Hospital	104	67	128	79	86	78	1	33	319	74
General practice	65	28	33	39	24	43	3	20	125	33
Other/unknown	18	32	12	39	13	38	3	50	46	36
Last negative test†										
(1,2] years	20	29	3	25	2	18	3	60	28	29
(2–4] years	20	34	9	64	13	72	3	33	45	45
>4 years	70	63	23	77	30	70	1	100	124	67
Never tested / not available	128	56	148	72	82	64	5	38	363	63

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 1.12: Proportion of individuals diagnosed with late-stage HIV infection stratified by age category at the time of diagnosis for those diagnosed in 2022-2024 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 (74%) than among those who were tested at a general practice (33%), a sexual health centre (19%), or another testing location (36%). 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 78% in 2024. Late diagnosis was less common (36%) 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 (67%) or who did not report ever having tested for HIV before (63%).

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 560 people diagnosed with late-stage HIV infection in 2022-2024, 233 (42%) were hospitalised within a year of diagnosis, including 192 (34%) as a direct result of their HIV infection. In contrast, only 68 (9%) of the 741 individuals diagnosed with recent or established HIV infection were hospitalised within a year of diagnosis, including

24 (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 560 individuals diagnosed with late-stage HIV infection in 2022-2024, 17 (3%) died within a year of diagnosis, including 9 (2%) who died of AIDS (*Table 1.3*). Among the 741 people diagnosed with recent or established HIV infection, 4 (1%) died within a year of diagnosis, including no one who died of AIDS.

Table 1.3: *Number and proportion of individuals diagnosed in 2022–2024 who were hospitalised or who died within a year of diagnosis, stratified by stage of infection; [a]one accident/violent death, one suicide, one heart/vascular, and one unknown/unclassifiable cause; [b]nine AIDS-related deaths, one lung cancer, one non-AIDS infection, one liver cirrhosis, one heart/vascular, one sudden death, and three unknown/unclassifiable causes.*

		Hospitalisation				Death			
		Total		HIV-related		Total		AIDS-related	
Stage	**n**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Recent or established HIV infection	741	68	9	24	3	[a]4	1	0	0
Late-stage HIV infection	560	233	42	192	34	[b]17	3	9	2
CD4 200-349, no AIDS	169	26	15	12	7	1	1	0	0
CD4 <200, no AIDS	183	48	26	28	15	3	2	1	1
AIDS	208	159	76	152	73	13	6	8	4

Note: *AIDS = AIDS-defining event.*

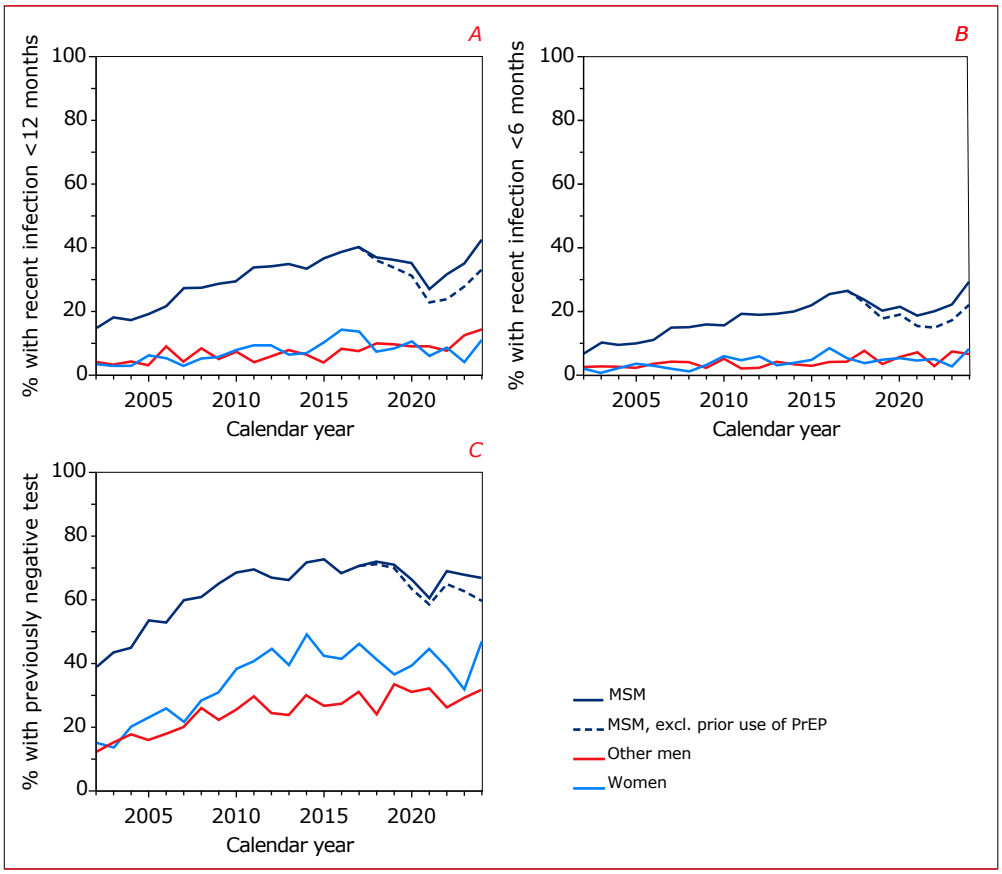
Late diagnosis and prior use of PrEP

Among MSM and trans men and women diagnosed in 2022-2024, 250 (32%) were diagnosed with a late-stage HIV infection (*Figure 1.10B*). When people who reported prior use of PrEP were excluded, the number diagnosed with late-stage HIV reduced to 243, but this represented a slightly higher proportion, 37%, of those diagnosed (*Figure 1.10C*).

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 2022-2024, 26% had evidence of having acquired their HIV infection in the 12 months prior to diagnosis, while 16% had evidence of having acquired HIV in the six months prior to diagnosis (*Figure 1.13A* and *1.13B*). For MSM, these proportions were 37% and 24%, respectively, while they were similar for trans men and women, 35% and 16%, respectively. Among other men and among women these proportions were considerably lower (10% and 5%, respectively).

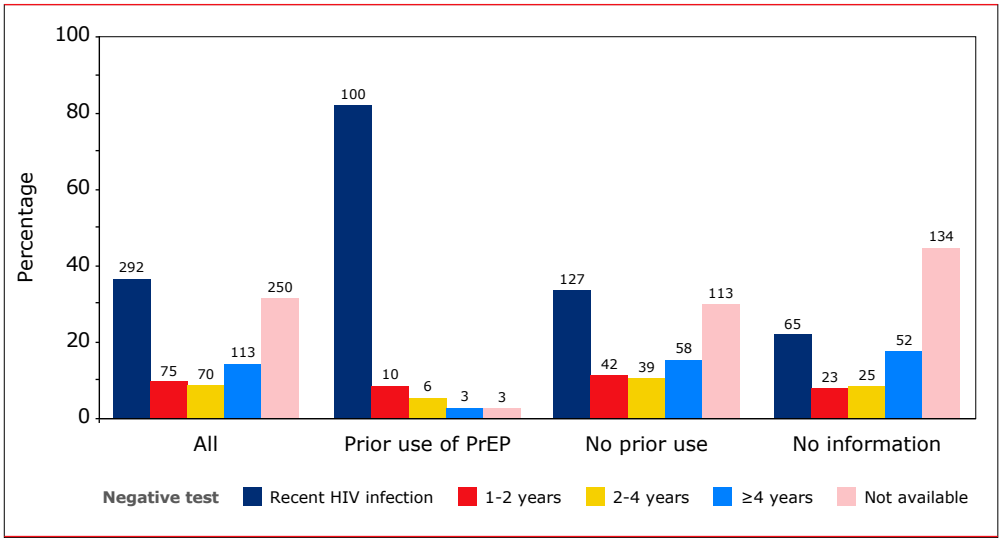
Figure 1.13: *Proportion of people diagnosed (A) with evidence of having acquired their HIV infection at most 12 months prior to their diagnosis, (B) at most 6 months prior to their diagnosis, (C) with a previously negative test at any time prior to their diagnosis. Evidence of a recent infection was (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, 113 (42%) men who have sex with men (MSM), or 73 (33%) MSM when excluding those who reported prior use of pre-exposure prophylaxis (PrEP), 13 (14%) other men, 8 (11%) women, 4 (29%) trans men and women, and 138 (31%) of all 444 individuals diagnosed in 2024 had evidence of having acquired HIV at most 12 months before diagnosis. In the same year, 79 (30%) MSM, or 49 (22%) MSM when excluding those who reported prior use of PrEP, 6 (7%) other men, 6 (8%) women, 3 (21%) trans men and women, and 94 (21%) of all 444 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 36% in 2018-2020, appeared to be lower, 27%, in 2021, and then increased to 42% in 2024 (*Figure 1.13A*). The lower proportion in 2021 may have been, in part, a consequence of disrupted testing services due to the (partial) lockdowns in response to the COVID-19 pandemic and/or changes in sexual behaviour during the pandemic. The 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, 23% in 2021 and 33% in 2024. 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 1.10B* and *1.10C*). 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, 82%, than in people who never used PrEP or for whom no information on PrEP use was available (*Figure 1.14*).

Figure 1.14: *Proportion of men who have sex with men (MSM) and trans men and women diagnosed in 2022–2024 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 26% in 2002 to 57% in 2024. MSM were more likely to have a previously negative HIV test than other men and women. In 2024, 67% of MSM newly diagnosed with HIV had a previously negative test, while this proportion was 39% both in other men and in women (*Figure 1.13C*). Overall, of MSM diagnosed in 2022-2024, 68% reported a previously negative test, meaning that a third (32%) never had an HIV test before their HIV diagnosis (see also *Figure 1.14*). In all three groups (MSM, other men, and women), the proportion of people without a reported previously negative HIV test has remained around the same level since 2010. The proportion with a known previously negative test was highest among those diagnosed at a sexual health centre (80%), compared with 33% of those diagnosed in a hospital, and 57% of those diagnosed at a general practice.

Time between HIV infection and viral suppression

Individuals with a suppressed viral load below 200 copies/ml cannot sexually transmit HIV to other people (undetectable equals untransmittable, or U=U)[6-9]. Hence it is crucial to minimise the time between the moment a person acquires HIV and the point at which they achieve this threshold, 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 2024, the median time from diagnosis to reaching a viral load level below 200 copies/ml decreased from 10.0 months (IQR 4.4-31.1) to 2.0 months (IQR 1.3-3.6). 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 estimated time between infection to diagnosis was the greatest contributing factor to the delay between acquiring HIV and achieving viral suppression. In 2024, this was estimated to be a median of 2.5 years (IQR 1.2-4.7).

Population in care

In total, 23,057 (71%) of the 32,544 individuals with HIV-1 ever registered in the Netherlands were known to be in clinical care by the end of 2024 (*Figure 1.1*; *Table 1.4*). People were considered to be in clinical care if they had visited their treating physician in 2024, or had a CD4 count or HIV RNA measurement in that year, and were still living in the Netherlands. Of the 9,487 people who were not in care by the end of 2024, 4,463 (47%) had died, of whom 2,457 (55%) died before the end of 2014. Another 2,715 (29%) had moved abroad, including 1,209 (45%) who did so before the end of 2014. The remaining 2,309 (24%) individuals:

- were lost to care (2,156, 93%);
- were only diagnosed with HIV in 2025 (82, 4%);
- had only moved to the Netherlands in 2025 (26, 1%); or
- had newly entered care in 2025 (45, 2%).

Of the people who moved abroad, 2,196 (81%) had RNA levels below 200 copies/ml at their last viral load measurement; in those lost to care, that figure was 1,401 (65%).

Table 1.4: Characteristics of the 23,057 people with HIV-1 in clinical care by the end of 2024.

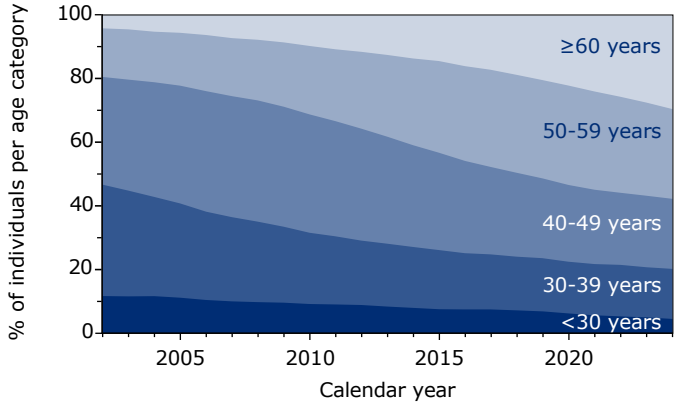
	MSM (n=14,155, 61%)		Other men (n=4,165, 18%)		Women (n=4,371, 19%)		Trans men and women (n=366, 2%)		Total (n=23,057)	
	n	%	n	%	n	%	n	%	n	%
Transmission										
Sex with men	13,077	92	0	0	3,795	87	283	77	17,155	74
Sex with women	11	0	2,669	64	3	0	10	3	2,693	12
Sex, unspecified	970	7	120	3	0	0	39	11	1,129	5
IDU	12	0	200	5	84	2	1	0	297	1
Blood/blood products	21	0	200	5	123	3	4	1	348	2
Other/unknown	64	0	976	23	366	8	29	8	1,435	6
Current age (years)										
0–14	0	0	49	1	47	1	0	0	96	0
15–24	107	1	83	2	101	2	10	3	301	1
25–29	419	3	85	2	123	3	37	10	664	3
30–39	2,295	16	500	12	622	14	142	39	3,559	15
40–49	2,859	20	860	21	1,283	29	79	22	5,081	22
50–59	3,958	28	1,209	29	1,283	29	73	20	6,523	28
60–69	3,230	23	978	23	675	15	23	6	4,906	21
≥70	1,287	9	401	10	237	5	2	1	1,927	8
Region of origin										
The Netherlands	9,212	65	1,872	45	1,219	28	69	19	12,372	54
Sub-Saharan Africa	251	2	956	23	1,697	39	12	3	2,916	13
Western Europe	888	6	143	3	114	3	8	2	1,153	5
Central Europe	589	4	167	4	111	3	6	2	873	4
Eastern Europe and Central Asia	260	2	190	5	271	6	5	1	726	3
South America	1,122	8	301	7	378	9	145	40	1,946	8
Caribbean	642	5	188	5	205	5	69	19	1,104	5
South and southeast Asia	501	4	108	3	264	6	37	10	910	4
Middle East and north Africa	281	2	177	4	75	2	14	4	547	2
Other	328	2	35	1	26	1	0	0	389	2
Unknown	81	1	28	1	11	0	1	0	121	1
Years aware of HIV infection										
<1	267	2	89	2	77	2	13	4	446	2
1–2	527	4	234	6	164	4	30	8	955	4
3–4	569	4	213	5	170	4	38	10	990	4
5–9	2,645	19	726	17	624	14	81	22	4,076	18
10–19	6,329	45	1,553	37	1,693	39	127	35	9,702	42
20–29	2,848	20	1,103	26	1,344	31	65	18	5,360	23
≥30	959	7	231	6	283	6	10	3	1,483	6
Unknown	11	0	16	0	16	0	2	1	45	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 2024 was 53 years (IQR 43-62). This figure has been increasing since 2002 (*Figure 1.15*), 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, more than half of those currently in care (58%) are 50 years or older (60% of MSM, 62% of other men, 50% of women, and 27% of trans men and women), and 30% 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 the management of people with HIV (see *Chapter 6*).

Figure 1.15: *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 2024, these proportions were 5% and 58%, respectively, while 30% 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.*



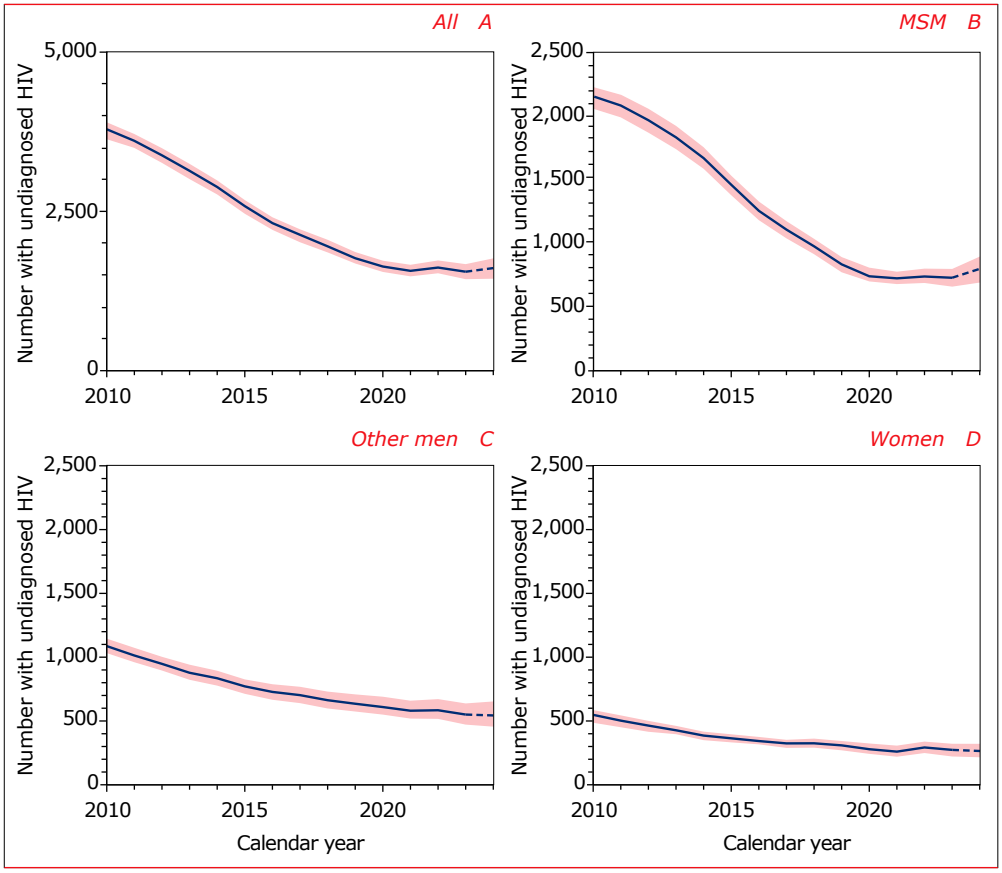
Duration of infection

People in clinical care by the end of 2024 were known with HIV for a median of 15.1 years (IQR 9.3-21.5). Therefore, a large group (72%) of those in care have been living with HIV for more than 10 years, including 30% who have done so for more than 20 years. The median time since diagnosis was 14.5 years for men who have sex with men (MSM), 15.3 years for other men, 17.1 years for women, and 11.5 years for trans men and women.

Undiagnosed population

The estimated number of people with an undiagnosed HIV infection decreased from 3,780 (95% CI 3,670-3,890) in 2010 to 1,610 (1,450-1,760) in 2024 (*Figure 1.16A*). The 1,610 individuals with an undiagnosed HIV infection comprised 1,395 (1,235-1,545) who most likely acquired their HIV infection in the Netherlands and an estimated 215 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 2,145 (2,050-2,225) in 2010 to 805 (690-900) by the end of 2024 (*Figure 1.16B*). Among other men, the estimated number with undiagnosed HIV was 1,085 (1,030-1,145) in 2010 and 545 (455-650) in 2024, while in women these numbers were 550 (500-585) and 265 (210-325), respectively (*Figures 1.16C* and *1.16D*).

Figure 1.16: *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[i]. 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 in the Netherlands by the end of 2024 was 25,890 (95% CI 25,730-26,040), including the estimated 1,610 (1,450-1,760) who remained undiagnosed[1]. Adjusted for backlog in registration, of this total:

- 24,282 individuals (94% of the total number of people with HIV) had been diagnosed, linked to care, and registered by SHM;
- 23,194 (90%, or 96% 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 2024) (*Figure 1.17A*);
- 23,104 (89%, or 95% of those diagnosed and linked to care) had started ART;
- 22,401 (87%, or 97% of those treated) had a most recent HIV RNA measurement below 1,000 copies/ml;
- 22,240 (86%, or 96% of those treated) had a most recent HIV RNA measurement below 200 copies/ml; and
- 21,709 (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 2024 the Netherlands had almost reached the Joint United Nations Programme on HIV/AIDS (UNAIDS) 95-95-95 target for 2025[10]; 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[11]. Of the 21,310 (92%) people still in care by the end of 2024 who had at least one CD4 count measurement in 2022-2024, 17,019 (80%) had a most recent CD4 count of 500 cells/mm^3 or higher.

Viral suppression

In total, 842 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 2024. On closer inspection, 398 (47%) of these individuals did not have an HIV RNA measurement available in 2024; 334 (84%) of these 398 individuals had an HIV RNA level below 200 copies/ml at their last measurement in 2023, 20 (5%) had an HIV RNA level of 200 copies/ml or above, and 44 (11%) also had no HIV RNA measurement in 2023. At the time of analysis, 148 (37%) of the 398 individuals had an RNA measurement in 2025, of which 135 (91%) below 200 copies/ml.

The median HIV RNA level among the 444 (53%) people with a viral load measurement and a viral load level above 200 copies/ml was 5,687 copies/ml (IQR 498-71,877). Of these 444 people, 66 (15%) started therapy after their last available viral load measurement in 2024. 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

Of the people diagnosed and linked to care, 2,156 individuals were lost to care by the end of 2024, and of these:

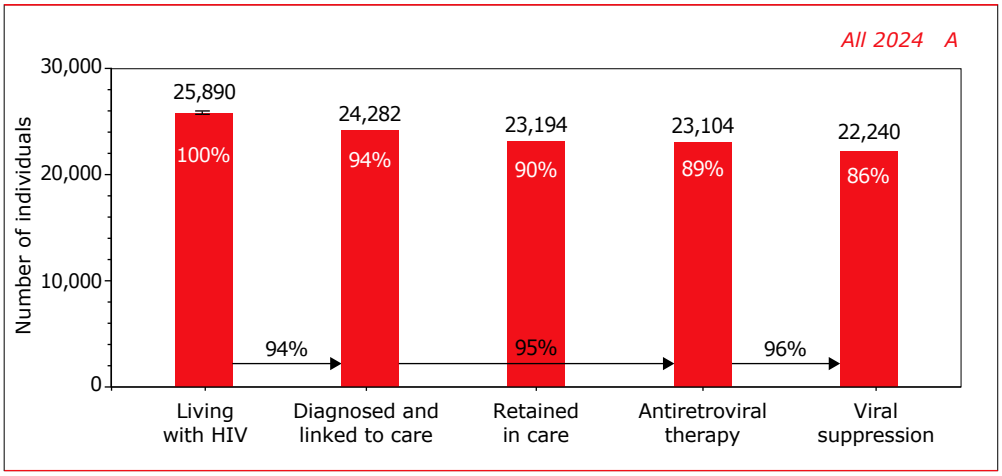
- 1,116 (52%) were last seen for care before the end of 2014;
- 493 (23%) in 2015-2020;
- 101 (5%) in 2021;
- 147 (7%) in 2022; and
- 299 (14%) in 2023[b].

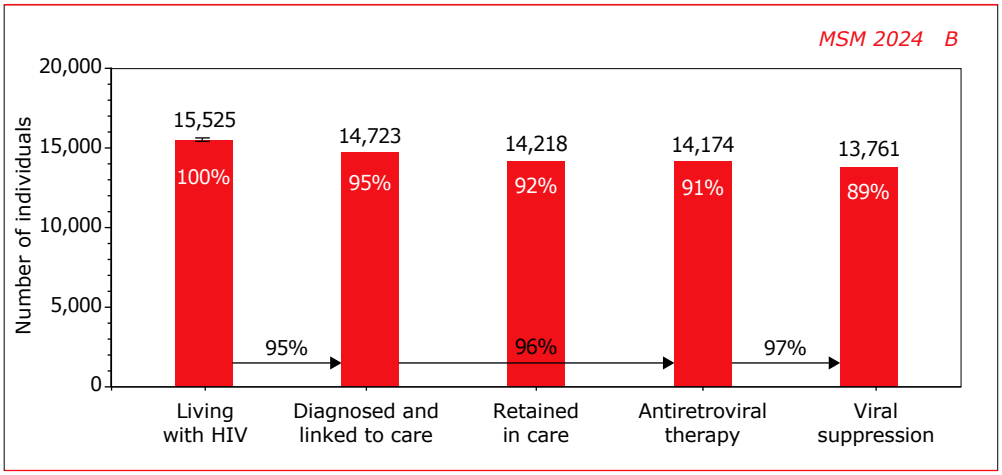
The 1,116 individuals who were lost to care in or before 2014, were excluded from the estimated number of people with HIV and the number of people diagnosed and linked to care. It was assumed to be unlikely that these 1,116 individuals were still living in the Netherlands by the end of 2024 without requiring care or ART during that ten-year period.

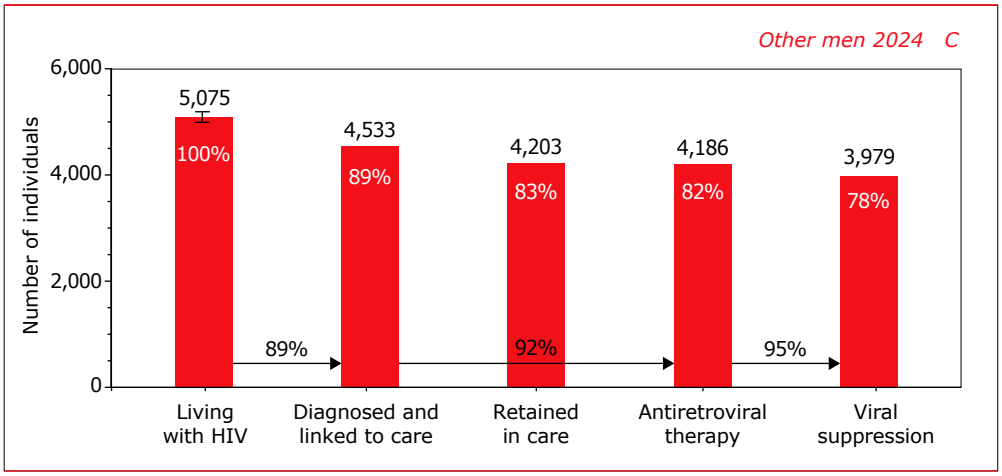
Of the 1,040 individuals lost to care after 2014, 69% were born outside the Netherlands; this proportion was only 46% for those who were still in care by the end of 2024. This suggests that some of those lost to care may have moved abroad; in particular, back to their country of birth. It should be pointed out that 75 (7%) of the 1,040 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 446 individuals last seen for care in 2022 or 2023, 333 (75%) had a suppressed viral load below 200 copies/ml, 65 (15%) had a viral load level above 200 copies/ml, and 48 (11%) had no measurement available. At the time of analysis, 107 (25%) of the 446 individuals had a documented HIV RNA or CD4 count measurement, or a clinic visit in 2025.

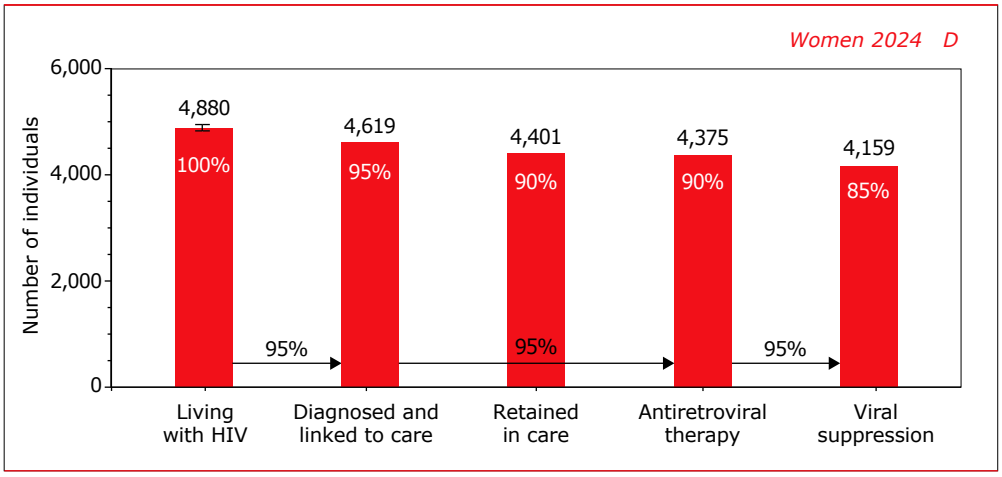
b In addition to the 2,156 individuals lost to care there were 45 individuals who had already been diagnosed by the end of 2024 and were living in the Netherlands but entered care in 2025. These 45 individuals (47 with adjustment for registration delay), as well as the 1,040 lost to care after 2014 (1,042 with adjustment), are counted in the first and second stage of the continuum but not in the other stages.

Figure 1.17: *Continuum of HIV care for people with HIV in the Netherlands by the end of 2024: (A) the total population with HIV-1, (B) men who have sex with men (MSM), (C) other men, and (D) women. Viral suppression was defined as an HIV RNA measurement below 200 copies/ml. 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 for a backlog in registration.*









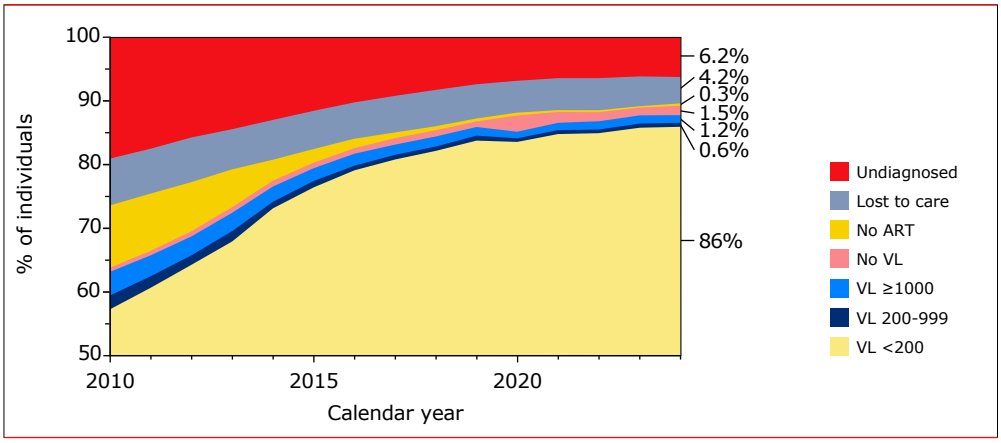
Legend: *MSM = men who have sex with men.*

Transmittable levels of HIV

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 2024 (*Figure 1.18*). In 2010, 57% of the estimated 19,870 (95% CI 19,760-19,985) people with HIV had a suppressed viral load below 200 copies/ml, while this proportion was 86% in 2024. 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 2024. 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 2024, and, to a lesser extent, of a smaller proportion not yet on ART (10% in 2010, 0.3% in 2024).

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 2024 was estimated to be 3,490, 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 3,490 individuals includes the 1,610 (46%) people who were not yet diagnosed by the end of 2024. The remaining 1,880 (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.

Figure 1.18: *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 2024.*



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 2024 was estimated at 15,525 (95% CI 15,415-15,625), of whom 805 (690-900) had yet to be diagnosed. Of these:

- 14,723 (95%) had been diagnosed and linked to care;
- 14,218 (92%) were still in care;
- 14,174 (91%) had started ART; and
- 13,761 (89%) had a most recent HIV RNA below 200 copies/ml, while 13,830 (89%) had a viral load below 1,000 copies/ml.

In terms of the 2025 UNAIDS 95-95-95 target, this translates to 95-96-97, meaning that in MSM, the UNAIDS targets have already been met (*Figure 1.17B*). In total, 10,865 (76%, or 83% of those with a CD4 measurement) of MSM still in care by the end of 2024 had a CD4 count of 500 cells/mm^3 or higher at their last measurement in 2022-2024.

Among other men, the estimated number with HIV in 2024 was 5,075 (95% CI 4,990-5,185), including 545 (455-650) who were not yet diagnosed (*Figure 1.17C*). Of these:

- 4,533 (89%) men had been diagnosed and linked to care;
- 4,203 (83%) were still in care;
- 4,186 (82%) had started ART; and
- 3,979 (78%) had a suppressed viral load below 200 copies/ml, while 4,030 (79%) had a viral load below 1,000 copies/ml,

which translates to 89-92-85 in term of the 2025 UNAIDS 95-95-95 target.

The number of women with HIV was estimated to be 4,880 (95% CI 4,830-4,940), of whom 265 (210-325) were not yet diagnosed (*Figure 1.17D*). Of these women:

- 4,619 (95%) had been diagnosed and linked to care;
- 4,401 (90%) were still in care;
- 4,375 (90%) had started ART; and
- 4,159 (85%) had a suppressed viral load below 200 copies/ml, while 4,199 (86%) had a viral load below 1,000 copies/ml,

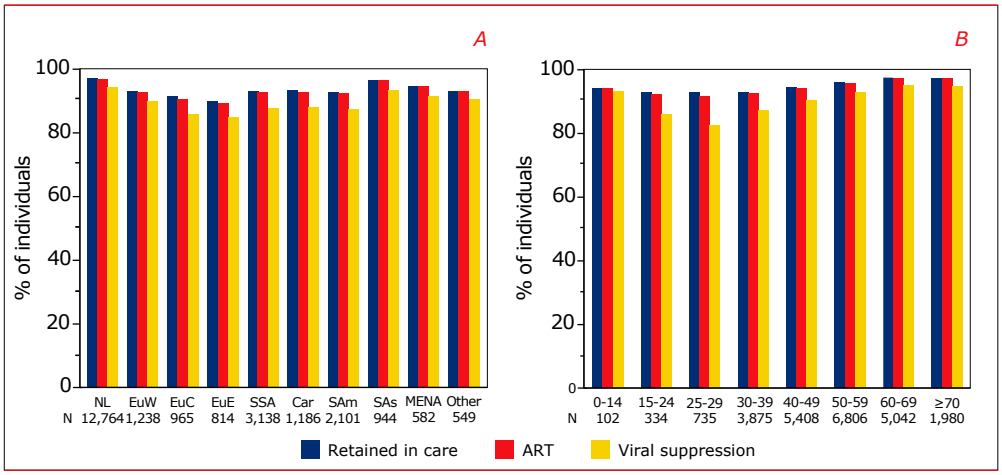
which translates to 95-95-95 in term of the 2025 UNAIDS 95-95-95 target.

Among women and other men still in care by the end of 2024, 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 1.19A*). 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 2024, increased with age, and exceeded 95% in people aged 50 years or older (*Figure 1.19B*). 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 1.19: *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; MENA = Middle East and north Africa; 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 five largest cities in the country (*Table 1.5*). By the end of 2024, more than half (52%) 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 (32%) people with undiagnosed HIV were living in these two regions. The highest number of people with undiagnosed HIV, 320 (250-390), was living in Zeeland/Brabant. 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 2024 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 five most populous 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 46 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	175	1,660	1,486	89
	115–240	1,600–1,725		*89*
Oost	250	3,065	2,813	92
	195–325	3,010–3,135		*92*
Noord-Holland/Flevoland	295	9,450	9,153	97
	245–350	9,395–9,500		*97*
Utrecht	70	1,465	1,391	95
	50–110	1,440–1,500		*95*
Zuid-Holland Noord	235	2,060	1,826	89
	165–300	1,990–2,125		*89*
Zuid-Holland Zuid	230	4,030	3,803	94
	180–310	3,980–4,110		*94*
Zeeland/Brabant	320	3,000	2,679	89
	250–390	2,930–3,070		*89*
Limburg	75	1,160	1,087	94
	45–110	1,130–1,195		*94*
Total	1,655	25,890	24,236	94
	1,535–1,835	25,770–26,070		*94*
City				
Amsterdam	180	6,585	6,404	97
	140–230	6,545–6,635		*97*
Rotterdam	110	2,210	2,101	95
	65–150	2,165–2,255		*95*
Den Haag	110	1,395	1,284	92
	75–160	1,360–1,440		*92*
Utrecht	25	600	575	*95*
	15–55	590–630		*95*
Eindhoven	60	475	420	88
	30–90	450–510		*88*
Total	490	11,270	10,784	96
	405–580	11,190–11,365		*96*

	Retained in care		Antiretroviral therapy		Viral suppression	
	n	%	n	%	n	%
	1,425	86	1,418	85	1,385	83
				95		*98*
	2,723	89	2,715	89	2,596	85
				97		*96*
	8,695	92	8,675	92	8,324	88
				95		*96*
	1,342	92	1,340	92	1,303	89
				96		*97*
	1,772	86	1,757	85	1,693	82
				96		*96*
	3,643	90	3,622	90	3,491	87
				95		*96*
	2,568	86	2,553	85	2,478	83
				95		*97*
	1,026	88	1,024	88	970	84
				94		*95*
	23,194	90	23,104	89	22,240	86
				95		*96*
	6,097	93	6,081	92	5,860	89
				95		*96*
	2,013	91	1,999	90	1,924	87
				95		*96*
	1,250	90	1,237	89	1,194	86
				96		*97*
	559	93	558	*93*	541	*90*
				97		*97*
	388	81	387	81	373	78
				92		*97*
	10,306	91	10,262	91	9,891	88
				95		*96*

In total, 11,270 (95% CI 11,190-11,365) people with HIV were estimated to be living in the five largest cities in the Netherlands, which amounts to 44% of the total number of people in the country with HIV. Of these 10,795 people, 490 (405-580) were estimated to be undiagnosed (30% of the national estimate of 1,610 individuals with an undiagnosed HIV infection). Of the five cities, Amsterdam had the largest population of people with HIV; an estimated 6,585 (6,545-6,635) individuals, of whom 180 (140-230) were still undiagnosed (*Table 1.5*). Of the 11,270 people with HIV in the five largest cities:

- 10,784 (96%) had been diagnosed and linked to care;
- 10,262 (91%, or 95% of those diagnosed) had started ART; and
- 9,891 (88%, or 96% of those on therapy) had a suppressed viral load below 200 copies/ml.

Most 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 96-95-96.

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 1,655 (95% CI 1,535-1,835) individuals living with undiagnosed HIV across the eight STI surveillance regions, is reasonably close to the number of 1,610 (1,450-1,760) 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 2024. 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	703	671	95	669	95	654	93
Fryslân	435	418	96	415	95	406	93
Drenthe	347	335	97	333	96	325	94
Oost							
IJsselland	410	397	97	397	97	383	93
Twente	505	490	97	489	97	468	93
Noord- en Oost-Gelderland	563	545	97	543	96	513	91
Gelderland Midden	833	805	97	804	97	766	92
Gelderland-Zuid	501	485	97	483	96	467	93
Utrecht							
Regio Utrecht	1,391	1,342	96	1,340	96	1,303	94
Noord-Holland/Flevoland							
Flevoland	626	591	94	589	94	561	89
Gooi & Vechtstreek	282	267	95	266	94	258	92
Hollands Noorden	490	463	94	463	94	449	92
Zaanstreek-Waterland	424	397	94	397	94	377	89
Amsterdam	6,701	6,381	95	6,364	95	6,135	92
Kennemerland	630	597	95	597	95	545	87
Zuid-Holland Noord							
Haaglanden	1,826	1,772	97	1,757	96	1,693	93
Zuid-Holland Zuid							
Hollands Midden	623	599	96	596	96	578	93
Rotterdam-Rijnmond	2,823	2,709	96	2,694	95	2,595	92
Dienst Gezondheid & Jeugd ZHZ	356	335	94	332	93	318	89
Zeeland/Brabant							
Zeeland	269	255	95	255	95	241	90
West-Brabant	635	624	98	618	97	603	95
Hart voor Brabant	971	937	96	932	96	911	94
Brabant-Zuidoost	805	752	94	748	93	724	90
Limburg							
Limburg-Noord	457	430	94	429	94	409	90
Zuid Limburg	630	596	95	595	94	560	89
Unknown	46	0	0	0	0	0	0
Total	**24,282**	**23,194**	**95**	**23,104**	**95**	**22,240**	**92**

Trans people

Geographical region of origin

Of the 32,544 individuals with an HIV-1 infection, 452 were trans people; 431 (95%) trans women and 21 (5%) trans men. In this group of 452 individuals, the most commonly-reported regions of origin were South America (177, 39%), the Caribbean (88, 19%), the Netherlands (81, 18%), and south and southeast Asia (43, 10%). Interestingly, many of the trans people originated from only a few specific countries. Among the 177 individuals from South America, there were 44 people from Colombia, 33 from Ecuador, 32 from Brazil, 22 from Venezuela, and 19 from Suriname. Most frequently reported countries of origin in the Caribbean were the former Netherlands Antilles (38) and Cuba (19), while 20 people from south and southeast Asia originated from Thailand.

In total, 150 trans people, or 40% of those born abroad, had a documented HIV-1 diagnosis before moving to the Netherlands. The majority (105, or 85%) of these 123 people had already started ART before arrival. By the time these 105 people entered HIV care in the Netherlands, 76 (72%) had HIV RNA levels below 200 copies/ml, which was somewhat lower than in cis people of whom 84%, or 2,922 out of 3,475, had RNA levels below 200 copies/ml.

Diagnosis

In 2022-2024, 43 trans people were newly diagnosed with HIV in the Netherlands. These 43 individuals were relatively young, with a median age of 33 years (IQR 28-35) at the time of their HIV diagnosis, and most of them (38, 88%) were born abroad. Similar to MSM, the majority of the trans men and women, 49%, received their HIV diagnosis at a sexual health centre (*Figure 1.4*). Among the 43 people, 15 had a recent HIV infection at the time of diagnosis, 16 had an established infection (CD4 counts above 350 cells/mm^3), and 12 had a late-stage HIV infection (CD4 counts below 350 cells/mm^3 or AIDS), which was comparable to the distribution across these stages among MSM.

Population in care

In total, 366 (81%) of the 452 trans people with HIV-1 were known to be in clinical care by the end of 2024. Of the 86 people who were not in care anymore, 21 had died, including seven who died of AIDS, while another 23 had moved abroad. The remainder were either lost to care (35), were only diagnosed in 2025 (two), or only entered HIV care in 2025 (five). In total, 18 of the people who moved abroad and 23 of those lost to care had HIV RNA levels below 200 copies/ml at their last viral load measurement.

Clinical condition

The majority of trans people in clinical care (364, or 99%), had started ART by the end of 2024. Of the 356 people in care with a viral load measurement in 2024, 338 (95%) had a last measurement in that year below 200 copies/ml. The most recent CD4 count in 2022-2024 of those in care stood at a median of 730 (IQR 533-1080) cells/mm^3, which was comparable to the CD4 counts in the total population in care.

HIV-2

In total, 102 of the 33,760 registered individuals with HIV acquired an HIV-2 infection (12 MSM, 34 other men, and 56 women); 7 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 2024, a total of 55 people were still in clinical care, i.e., they visited their treating physician in 2024, or had a CD4 count or HIV RNA measurement in that year, and were still living in the Netherlands. Of the other 47 individuals, 24 had died, seven had moved abroad, and 16 had no contact with HIV care during that year. The median age of those still in care was 65 years (IQR 60-69); 51 (93%) individuals were 50 years or older. The majority (93%) of those in care had been living with HIV-2 for more than 10 years, while 60% had been living with it for more than 20 years.

Clinical condition

Of the 55 people still in care, 49 had a most recent viral load measurement below 200 copies/ml, and 5 people had no available HIV-2 RNA result in 2024; there was one individual with a viral load above 200 copies/ml. Most people in care (40, 73%) had started ART. Of the 15 individuals who were still in care but had not started therapy, 13 had a viral load measurement below 200 copies/ml, while the other 2 people had no HIV-2 RNA measurement in 2024. CD4 counts in the group of 59 people in care were a median of 700 (IQR 500-897) cells/mm^3.

Conclusions

Since 2020 the annual number of new HIV diagnoses has remained around the same level, with 444 new diagnoses recorded in 2024. Notably, among MSM, the annual number of diagnoses appears to be increasing. This increase in HIV diagnoses can, in part, be attributed to a rise in the estimated annual number of newly acquired HIV infections. Two in five newly diagnosed MSM have evidence of having acquired their infection at most one year before. Late-stage HIV infection continues to be a concern among other men, women, and people with certain migratory backgrounds.

In 2024, 19% 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 rise in the proportion of individuals diagnosed with a recent HIV infection compared with 2021. These trends underscore the need to enhance PrEP adherence support and regular HIV testing, thus maximising the effectiveness of PrEP programmes.

Apart from the 444 new HIV diagnoses in 2024, there were 302 people born abroad who arrived in the Netherlands in 2024 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. This highlights the importance of cross-border continuity of care, to ensure seamless integration into the Dutch healthcare system for migrants with HIV, and to reach national and international HIV elimination goals.

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2. Prior use of pre-exposure prophylaxis

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Summary

The proportion of men who have sex with men (MSM) and transgender persons newly diagnosed with HIV in the Netherlands for whom information is recorded in their electronic medical records about use of PrEP prior to being diagnosed with HIV continues to increase and has reached 65.1% in 2024. The number and proportion of MSM and transgender people who reported prior use of PrEP continued to increase from 5.2% (19 of 366 individuals) in 2019 to 18.5% (52 of 281 individuals) in 2024.

For 464 MSM and transgender people there was information available why they did not use PrEP: 42.5% of these 464 individuals had indicated they would have wanted to do so, but either had no access to PrEP (22.5%), were on a PrEP waiting list when they tested HIV positive (2.2%), or tested HIV positive during screening for HIV before initiating PrEP (17.8%). A further 18.9% of MSM and transgender people indicated they did not know that PrEP existed. These proportions were fairly stable over time.

Of the 179 individuals who had used PrEP prior to their HIV diagnosis in the Netherlands, 25 (13.9%) had obtained PrEP through informal means, and 22 (12.3%, most of whom obtained PrEP through informal means) did not receive medical check-ups during PrEP-use.

Of the 144 individuals who reported prior use of PrEP and who received a genotypic resistance test prior to initiation of antiretroviral therapy (ART), 11.8% harboured resistance-associated mutations (RAMs) in the reverse transcriptase (RT) gene that are associated with the use of PrEP. All individuals in whom PrEP-associated RAMs had been detected, were still using PrEP at the moment they tested positive for HIV, or 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, 14 (22.6%) out of 62 tested individuals harboured PrEP-associated 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.

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 PrEP care at the Sexual Health Centers (SHC) of the municipal Public Health Services (GGD), via a national programme from 2019 to 2024, followed by a structural care provision. General practitioners can also prescribe PrEP. The primary target groups are men who have sex with men (MSM) and transgender persons. Prior to this national 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 aged 15 years and older who were newly diagnosed with HIV-1 since 2018 and who reported prior use of PrEP at the time of entry 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.
Among MSM and transgender persons who did not report prior use of PrEP, we investigated their reasons and barriers for not having used PrEP.

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

Data collection

SHM collects data on prior use of PrEP in all people diagnosed with HIV who have entered care in one of the 24 Dutch HIV treatment centers since 1 January 2018. 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 done 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 among individuals who first entered 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 cisgender men had another or unknown mode of HIV acquisition recorded but were known to have male sex partners, they were also included in the MSM group.

A substantial proportion of individuals entering HIV care in the Netherlands, were not 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.

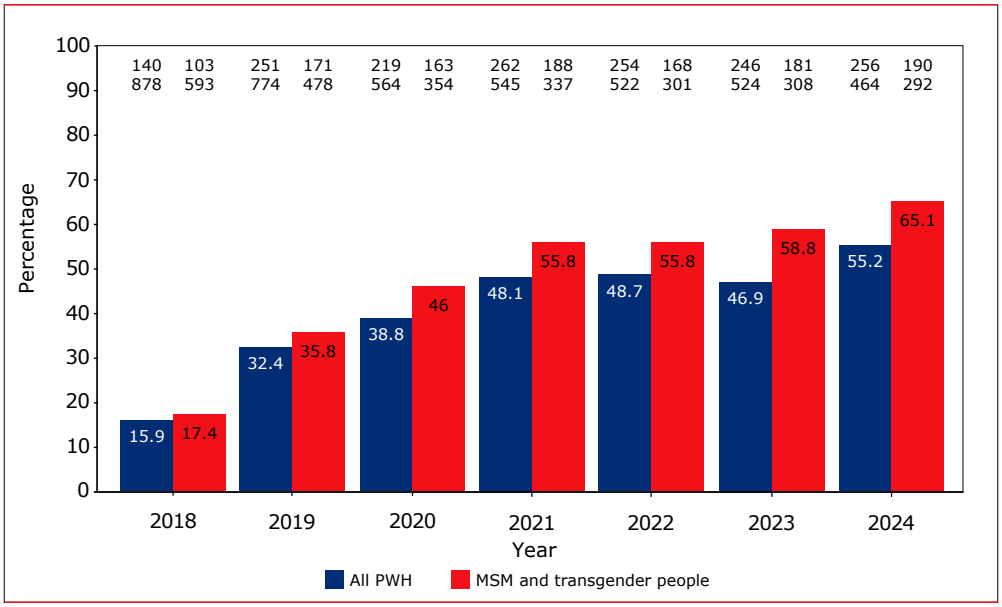
Of note, SHM does not record data about a person's race / ethnicity, nor can we identify second or third generation migrants. In our analyses, we make a distinction between those who are born in the Netherlands and those born in another country, irrespective of race / ethnicity and migrant status of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

Population of interest

Between 1 January 2018 and 31 December 2024 4,271 persons aged 15 years and older were diagnosed with HIV and entered into HIV care. In the EMR of 1,628 (38.1%) individuals, information was recorded on prior use of PrEP. The proportion of individuals for whom this information was available in the EMR increased from 15.9% in 2018, to 55.2% in 2024 (Figure 2.1, blue bars).

Of the 4,271 individuals diagnosed with HIV between 2018 and 2024 and entering HIV care, 2,663 were from the primary target groups of the Dutch PrEP guideline: 2,515 cisgender MSM and 148 transgender persons. In the PrEP target groups, 1,164 (43.7%) out of 2,663 individuals had information about prior PrEP use available in the EMR: increasing from 17.4% in 2018 to 65.1% in 2024 (Figure 2.1, red bars).

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.*

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 4,271 individuals, 1,840 (43.1%) were born in the Netherlands, and the remaining 2,431 (56.9%) individuals were migrants. Of these 2,431 individuals, 779 (32.0%) were already diagnosed with HIV before migrating to the Netherlands.
In the PrEP target groups of 2,663 MSM and transgender persons, 1,224 (46.0%) were born in the Netherlands, 1,439 (54.0%) were migrants of whom 924 individuals had been diagnosed with HIV in the Netherlands, and 513 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 without this information (see *Table 2.1*). The likelihood of information on prior PrEP use being available varied considerably between HIV treatment centers, but was not dependent on the size of the population in care in the HIV treatment centers.

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	1164 (43.7%)	1499 (56.3%)	
Age	33.7 (27.1-45.5)	34.7 (27.5-47.8)	0.091
HIV acquisition group			0.671
MSM	1102 (94.7%)	1413 (94.3%)	
Other men	0 (0.0%)	0 (0.0%)	
Women	0 (0.0%)	0 (0.0%)	
Transgender people	62 (5.3%)	86 (5.7%)	
Region of birth			0.439
Born in the Netherlands	531 (45.6%)	693 (46.2%)	
Migrant, western background	283 (24.3%)	334 (22.3%)	
Migrant, non-western background	350 (30.1%)	472 (31.5%)	
Documented seroconversion in NL or before migration*			0.009
In the Netherlands	433 (68.5%)	491 (60.9%)	
Before migration to the Netherlands	198 (31.3%)	315 (39.1%)	
Unknown / uncertain	1 (0.2%)	0 (0.0%)	
Recent HIV acquisition			
Tested pos. <365 days after last neg. test	415 (35.7%)	321 (21.4%)	<.001
Tested pos. <180 days after last neg. test	242 (20.8%)	159 (10.6%)	<.001
CD4 at HIV diagnosis	473 (291-678)	428 (236-630)	<.001

***Legend:** * Calculated for migrants only.*

PrEP awareness and uptake

For 464 (48.2%) of the 962 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 their reasons for not using PrEP. 'Presumed to be at low risk for HIV' (22.3%), 'Wanted to use PrEP but had no access' (22.5%), and 'Not knowing PrEP existed' (18.9%), were the most commonly reported reasons. In total, 83 (17.8%) individuals had wanted to start using PrEP but tested positive for HIV at screening before entry into PrEP care. Ten individuals (2.2%) reported that they tested HIV positive while on a PrEP programme waiting list.

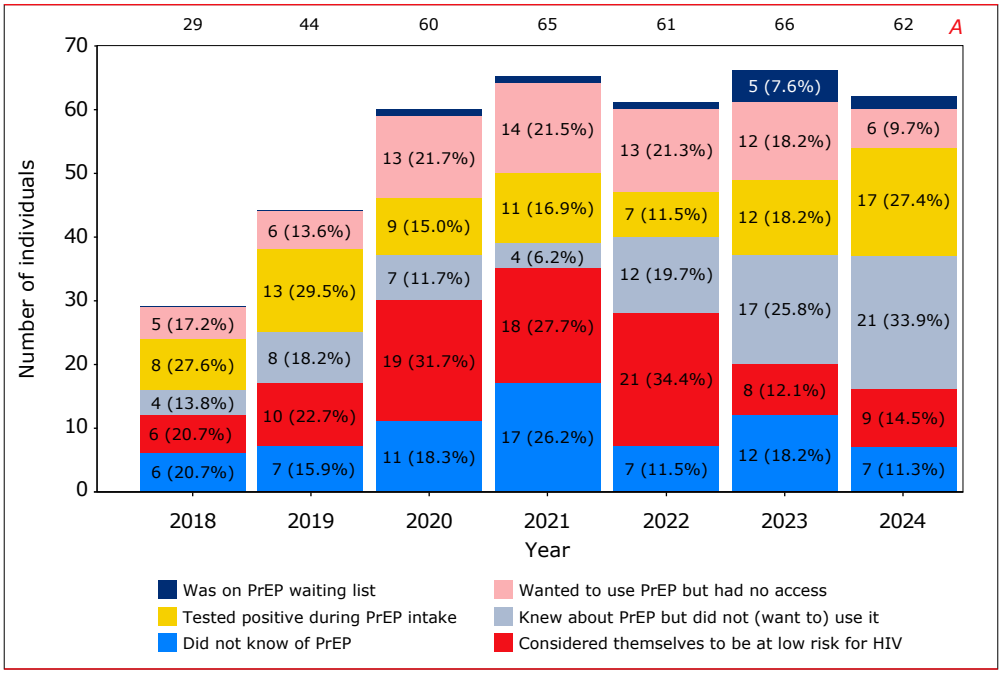
Of the individuals who reported they tested positive for HIV at screening before entry into PrEP care, 51.2% had evidence of a recent infection. Of the individuals who reported they tested positive for HIV while on a waiting list for PrEP care, 50.0% had evidence of a recent infection.

Figure 2.2A shows time trends in the reported reasons for not having used PrEP in MSM and transgender persons. The proportion of individuals reporting they knew about PrEP but did not (want to) use it increased over the years and was 33.9% in 2024.

Individuals indicating that they 'Considered themselves to be at low risk for HIV' (median 39.6 years), 'Did not know of PrEP' (38.6 years), or 'Knew about PrEP but did not (want to) use it' (37.4 years), were older than those who indicated that they 'Tested positive during PrEP intake' (33.5 years), 'Wanted to use PrEP but had no access' (31.6 years), or 'Were on the PrEP waiting list' (33.2 years).

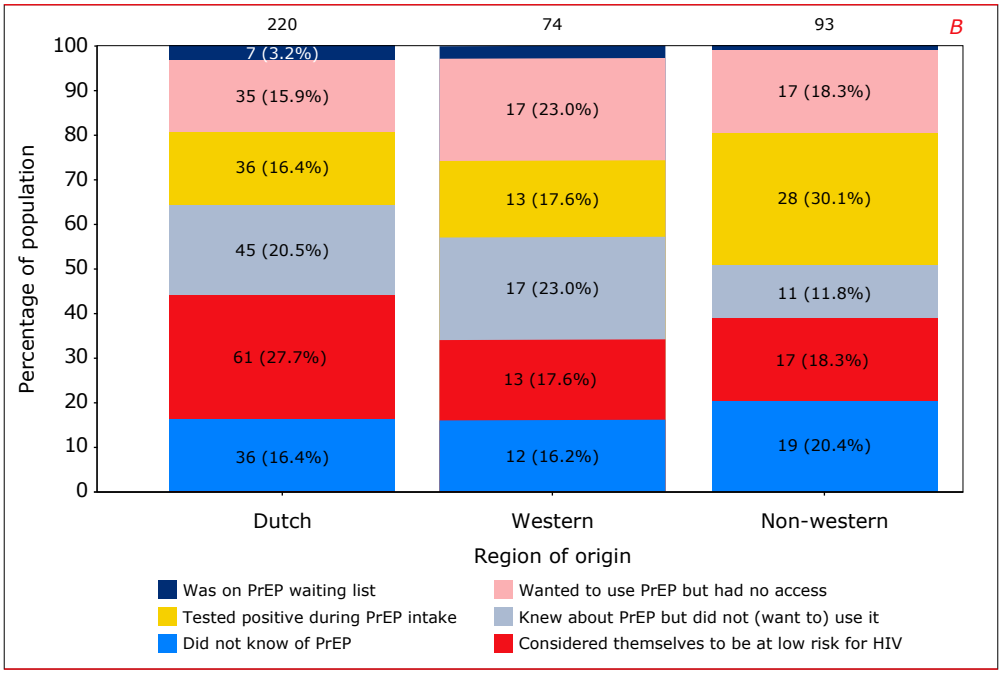
We also compared the reasons for not having used PrEP between people born in the Netherlands, and those originating from western or non-western countries (Figure 2.2B). People born in the Netherlands most frequently reported 'Presumed to be at low risk for HIV'. People born in non-western countries most often reported either 'Tested positive for HIV at screening before entry into a PrEP programme' or 'Not knowing PrEP existed'.

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.*

Prior use of PrEP

Of the 1,628 individuals for whom information on prior use of PrEP was available in the EMR, the majority (1,420, 87.2%) reported no prior use, whereas 208 (12.8%) reported having used PrEP previously (*Table* 2.2).

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	208 (17.8%)	774 (66.2%)	188 (16.1%)	
Age	32.4 (26.9-42.7)	36.7 (28.9-49.7)	27.8 (24.1-33.4)	<.001
HIV acquisition group				<.001
MSM	192 (92.3%)	738 (95.3%)	172 (91.5%)	
Other men	6 (2.9%)	0 (0.0%)	0 (0.0%)	
Women	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Transgender people	10 (4.8%)	36 (4.7%)	16 (8.5%)	
Region of birth				<.001
Born in the Netherlands	94 (45.2%)	438 (56.6%)	0 (0.0%)	
Migrant, western background	53 (25.5%)	149 (19.3%)	82 (43.6%)	
Migrant, non-western background	61 (29.3%)	187 (24.2%)	106 (56.4%)	
Documented seroconversion in NL or before migration*				<.001
In the Netherlands	100 (87.7%)	335 (100%)	0 (0.0%)	
Before migration to the Netherlands	13 (11.4%)	0 (0.0%)	188 (100%)	
Unknown / uncertain	1 (0.9%)	0 (0.0%)	0 (0.0%)	
Recent HIV acquisition				
Tested pos. <365 days after last neg. test	156 (75.0%)	227 (29.3%)	36 (19.1%)	<.001
Tested pos. <180 days after last neg. test	103 (49.5%)	131 (16.9%)	11 (5.9%)	<.001
CD4 at HIV diagnosis	570 (382-730)	434 (250-610)	600 (380-849)	<.001
Late presenter (CD4<350)	41 (19.8%)	292 (37.7%)	44 (23.8%)	<.001
Very late presenter (CD4<200 or AIDS)	13 (6.3%)	155 (20.0%)	15 (8.0%)	<.001
Reason known for not having used PrEP	208 (100%)	387 (50.0%)	79 (42.0%)	<.001
Reasons for not having used PrEP				
Did not know of PrEP		67 (17.3%)	21 (26.6%)	
Presumed to be at low risk for HIV		91 (23.5%)	13 (16.5%)	
Knew PrEP but did not want to use it		73 (18.9%)	3 (3.8%)	
Tested positive at PrEP intake		77 (19.9%)	6 (7.6%)	
Wanted PrEP but had no access		69 (17.8%)	36 (45.6%)	
Was on PrEP waiting list		10 (2.6%)	0 (0.0%)	

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

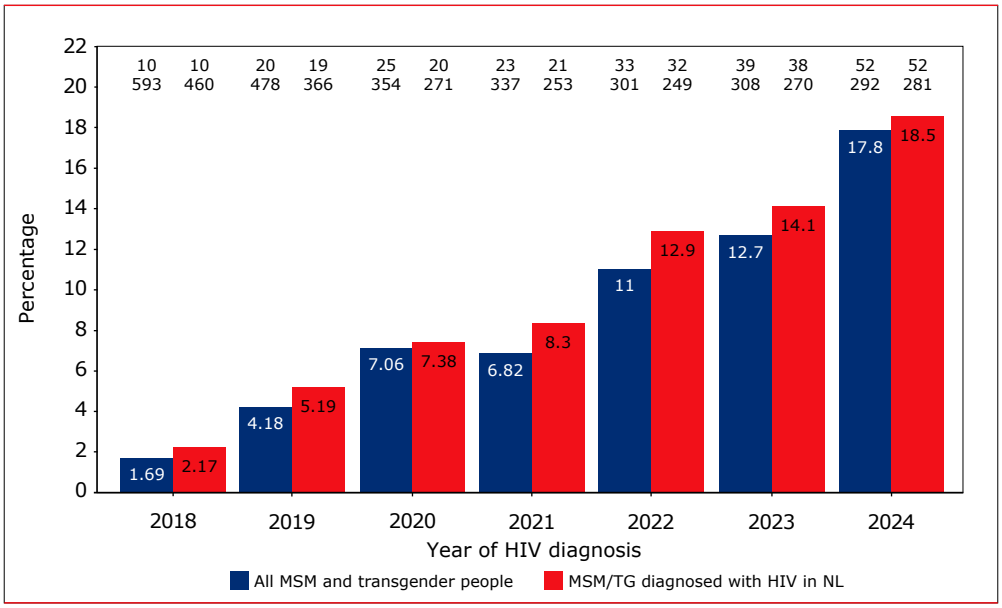
Of the 208 people who reported prior use of PrEP, 202 were from the primary target groups for PrEP in the Netherlands: 192 MSM and 10 transgender persons. The remaining 6 individuals were all cisgender heterosexual men, 4 of whom had

used PrEP prior to migrating to the Netherlands. Of the 208 individuals who reported prior PrEP use, 114 (54.8%) were born abroad. Among these, 85 had used PrEP in the Netherlands, and 29 had used PrEP prior to migrating to the Netherlands, of whom 13 had already been diagnosed with HIV before migration (*Table 2.3*).

Individuals who reported prior use of PrEP were younger and had higher CD4 counts at diagnosis compared to those diagnosed in the Netherlands who did not use PrEP.

We calculated percentages of prior PrEP use of all 2,150 MSM and transgender people who were newly diagnosed with HIV in the Netherlands between 2018 and 2024. 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 whom prior PrEP use was recorded in the EMR has increased since 2019 (Ptrend<0.0001, see Figure 2.3, red bars), with 2.2% in 2018, 5.2% in 2019, 7.4% in 2020, 8.3% in 2021, 12.9% in 2022, 14.1% in 2023, and 18.5% in 2024. When also including MSM and transgender people who were diagnosed with HIV prior to migrating to the Netherlands (n=2,663), the proportions remained similar (see Figure 2.3, blue bars).

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.*



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.*

***Box 2.1:** Socio-demographic and -economic determinants of using PrEP*

We combined data of 879 men who have sex with men (MSM) and transgender persons newly diagnosed with HIV between 2019 and 2024 from whom information on prior PrEP use was available, with registry data from Statistics Netherlands. Of these 879 individuals, 147 had used PrEP prior to HIV diagnosis. Reasons for not using PrEP were: perceived themselves to be at low risk or did not want to use it (n=136), did not know about PrEP (n=72), wanted to use PrEP, but had no access or tested positive for HIV while on the waiting list for PrEP (n=150), or unknown reason (n=374). We assessed missed opportunities and inequities in PrEP uptake using multinomial regression. This model allowed us to simultaneously compare socio-demographic and -economic characteristics over multiple groups: 1) Used PrEP (reference category), 2) perceived themselves at low risk or did not want to use it, 3) did not know about PrEP, 4) had no access, and 5) unknown.

In the multivariable multinomial model, older individuals were somewhat more likely to report not knowing about PrEP before HIV diagnosis, albeit not statistically significant (adjusted relative risk ratio (aRRR)=1.32, 95%CI=0.98-1.78). Individuals with a first generation migration background were less likely to report low perceived risk as the reason for not using PrEP (aRRR=0.46, 95%CI=0.22-0.94). No other factors were identified.

	Low perceived risk / did not want to use PrEP aRRR (95%CI)	**Did not know about PrEP** aRRR (95%CI)	**Wanted to use PrEP but could not** aRRR (95%CI)	**Unknown reason** aRRR (95%CI)
Age, per 10 year increase	1.15 (0.90–1.48)	1.32 (0.98–1.78)	0.99 (0.76–1.28)	1.05 (0.85–1.30)
Migration background				
None	REF	REF	REF	REF
1st generation	0.46 (0.22–0.94)	1.76 (0.75 – 4.11)	1.07 (0.53–2.15)	0.79 (0.44–1.41)
2nd generation	0.93 (0.37–2.33)	1.62 (0.48–5.52)	1.64 (0.68–3.99)	1.08 (0.50–2.35)
Living alone				
No	REF	REF	REF	REF
Yes	0.89 (0.43–1.87)	0.64 (0.27–1.54)	0.71 (0.33–1.52)	0.52 (0.28–0.98)
Highest education level				
High	REF	REF	REF	REF
Low	0.86 (0.35–2.13)	1.88 (0.53–6.60)	0.50 (0.18–1.37)	1.20 (0.58–2.47)
Middle	1.43 (0.69–2.98)	2.81 (0.95–8.37)	1.67 (0.81–3.45)	1.37 (0.74–2.56)
Unknown	1.95 (0.87–4.37)	3.26 (1.08–9.80)	1.24 (0.54–2.88)	1.56 (0.78–3.11)
Level of urbanization of place of residence				
Highest level of urbanization	REF	REF	REF	REF
High level of urbanization	1.93 (0.97–3.81)	1.44 (0.59–3.54)	0.88 (0.41–1.87)	1.58 (0.87–2.88)
Medium – low level of urbanization	0.88 (0.43–1.80)	1.45 (0.61–3.41)	0.99 (0.49–2.00)	1.25 (0.69–2.23)

Access to PrEP and usage patterns

The characteristics of all 208 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. Migrants who initiated PrEP before they migrated to the Netherlands but continued PrEP after they migrated to the Netherlands are included in the former group.

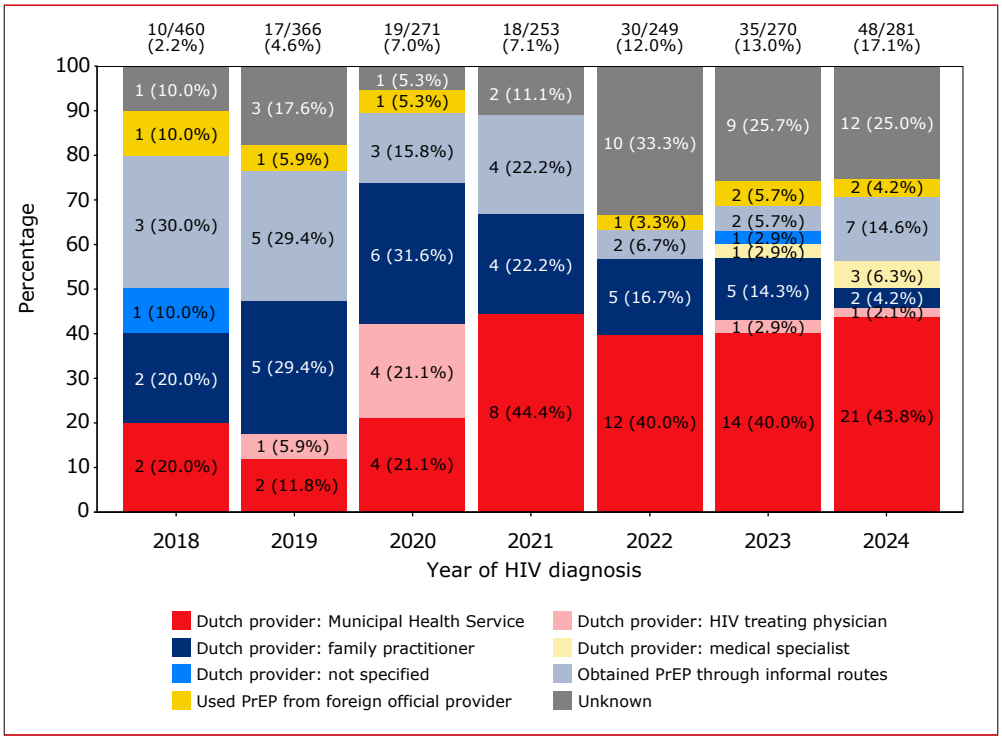
Of the 208 individuals who reported prior PrEP use, 29 (13.9%) were migrants who had used PrEP before moving to the Netherlands. The remaining 179 individuals had used PrEP in the Netherlands, among them 6 had started PrEP prior to migration but continued using it after they arrived in the Netherlands. In the remainder of this chapter we will report on these 179 individuals who used PrEP while living in the Netherlands.

Of the 179 individuals who had used PrEP in the Netherlands, 106 (59.2%) obtained it from a healthcare provider in the Netherlands (see Table 2.3), comprising the Municipal Public Health Service (n=63), family practitioner (29), HIV treatment center (7), and other medical specialist (4). 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 like buyers' club/ internet/store outside the Netherlands (20); from a healthcare provider outside the Netherlands (8); or from a friend living with HIV who had donated some of their own medication (5). There was no information available about the PrEP provider for the remaining 40 individuals.

Dosage schedule information was available for 114 individuals. Of these, 74 (41.3%) reported on-demand use, 36 (20.1%) reported daily use, and 4 (2.2%) reported having used PrEP less than a week. For the remaining 65 individuals (36.3%), no dosage schedule information was available.

Of the 179 individuals who had used PrEP in the Netherlands, 65 (36.3%) had regular medical check-ups at the Municipal Public Health Service, 9 (5.0%) attended an HIV treatment center, 18 (10.1%) were seen by a family practitioner, and 5 (2.8%) were monitored by a medical specialist other than HIV treatment center staff. Twenty two individuals (12.2%) reported that they did not have any medical check-ups, and there was no information available for the remaining 60 individuals (33.5%). Most of the 22 individuals who reported they had received no medical check-ups had obtained PrEP via informal means, only 4 of them had received PrEP from a healthcare provider in the Netherlands (and 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.

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.



The median (IQR) number of days between the last dose of PrEP and testing HIV-positive was calculated only for those individuals for whom the relevant dates were known with sufficient precision (to within a month), and was 31 (0-136) days. A total of 48 (26.8%) individuals tested HIV-positive while still using PrEP. Of the 131 individuals who did not test HIV-positive while taking PrEP, 51 reported having tested HIV-seronegative after their last use of PrEP, while 53 did not have an HIV-test shortly after discontinuing PrEP. There was no information available for the remaining 27 individuals.

Table 2.3: characteristics of individuals who reported use of PrEP.

	PrEP used in the Netherlands	PrEP used abroad	p-value
Number of subjects	179 (86.1%)	29 (13.9%)	
Age	32.5 (26.9-44.5)	31 (26.1-35.1)	0.265
HIV acquisition group			0.001
MSM	170 (95.0%)	22 (75.9%)	
Other men	2 (1.1%)	4 (13.8%)	
Women	0 (0.0%)	0 (0.0%)	
Transgender people	7 (3.9%)	3 (10.3%)	
Region of birth			<.001
Born in the Netherlands	94 (52.5%)	0 (0.0%)	
Migrant, western background	41 (22.9%)	12 (41.4%)	
Migrant, non-western background	44 (24.6%)	17 (58.6%)	
STD diagnosed at entry into care			
HBV (HBV surface antigen positive)	1 (0.6%)	1 (3.4%)	0.139
HBV (HBV core antibody positive)	23 (12.8%)	4 (13.8%)	0.888
HCV (antibody positive)	6 (3.4%)	2 (6.9%)	0.357
Syphilis (RPR/VDRL positive)	53 (29.6%)	10 (34.5%)	0.596
PrEP started before migrating to the Netherlands	6 (3.4%)	29 (100%)	
PrEP provider			<.001
Provider in the Netherlands	106 (59.2%)	0 (0.0%)	
- Public Health Service	63 (35.2%)	0 (0.0%)	
- HIV treatment center	7 (3.9%)	0 (0.0%)	
- Family practitioner	29 (16.2%)	0 (0.0%)	
- Medical specialist	4 (2.2%)	0 (0.0%)	
- No info	3 (1.7%)	0 (0.0%)	
Provider outside of the Netherlands	8 (4.5%)	10 (34.5%)	
Obtained PrEP through informal routes	20 (11.2%)	6 (20.7%)	
From friend living with HIV	5 (2.8%)	1 (3.4%)	
No info	40 (22.3%)	12 (41.4%)	
Seroconversion during PrEP use			
Tested HIV-positive while on PrEP	48 (26.8%)	3 (10.3%)	
HIV-negative test performed after last dose of PrEP	51 (38.9%)	8 (30.8%)	
No HIV-negative test performed after last dose of PrEP	53 (40.5%)	16 (61.5%)	
Unknown if HIV test was performed after last dose of PrEP	27 (20.6%)	2 (7.7%)	
Diagnosed in the Netherlands or before migration			<.001
In the Netherlands	179 (100%)	16 (55.2%)	
Before migration to the Netherlands	0 (0.0%)	13 (44.8%)	
Days between last PrEP use and testing HIV-positive**	31 (0-136)	92 (32-290)	0.101

	PrEP used in the Netherlands	PrEP used abroad	p-value
Recent HIV acquisition			
Tested pos. <365 days after last neg. test	143 (79.9%)	13 (44.8%)	<.001
Tested pos. <180 days after last neg. test	97 (54.2%)	6 (20.7%)	<.001
CD4 at HIV diagnosis	557 (380-730)	570 (460-720)	0.622
PrEP schedule			0.120
On demand	74 (41.3%)	6 (20.7%)	
Daily	36 (20.1%)	9 (31.0%)	
No data	65 (36.3%)	14 (48.3%)	
Used PrEP <1 week	4 (2.2%)	0 (0.0%)	
Duration of PrEP use (days), median (IQR)	122 (30-320)	60 (30-180)	0.644
Routine medical check-ups while on PrEP			<.001
Public Health Service	65 (36.3%)	0 (0.0%)	
Family practitioner	18 (10.1%)	0 (0.0%)	
HIV treatment center	9 (5.0%)	0 (0.0%)	
Other healthcare provider	5 (2.8%)	3 (10.3%)	
No medical check-ups	22 (12.3%)	3 (10.3%)	
No data	60 (33.5%)	23 (79.3%)	
Resistance test performed after testing HIV-positive	144 (80.4%)	11 (37.9%)	<.001
Resistance associated mutations in RT			
M184VI	17 (11.8%)	2 (18.2%)	
K65R	2 (1.4%)	0 (0.0%)	
K70EG	0 (0.0%)	0 (0.0%)	

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

Prior use of PrEP and HIV drug resistance

Genotypic resistance tests were performed in 144 (80.4%) of the 179 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 17 individuals (11.8%). All 17 individuals harboured an M184VI RT RAM, which reduces susceptibility to lamivudine and emtricitabine, and 2 of these individuals also harboured a K65R RT RAM, which is selected for by tenofovir and reduces susceptibility to tenofovir, abacavir, lamivudine and emtricitabine. Selection of K65R has been described to occur more readily in individuals harbouring HIV-1 subtype C, however, these 2 individuals harboured HIV-1 subtype B. It is very unlikely these mutations were already present in the source (i.e. the person they acquired HIV from) and hence would represent transmitted HIV resistance.

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.

Among the 73 individuals who had tested HIV-positive while still using PrEP or within 3 months of discontinuing PrEP, 62 had received a genotypic resistance test, and 14 (22.6%) harboured PrEP-associated RAMs.

In the 29 individuals who had used PrEP prior to migrating to the Netherlands, 11 had genotypic resistance test results available. Of these, 2 showed M184VI RT resistance-associated mutations.

For ease of comparing individuals with and without detected RAMs and those not tested, we provide Appendix Table 2.1, which contains the same data as Table 2.3 but stratified by presence of RAMs.

Prior use of PrEP and response to antiretroviral therapy (ART)

We investigated the virological treatment response to first-line antiretroviral therapy in 193 individuals who reported prior use of PrEP, were diagnosed with HIV in the Netherlands, and subsequently initiated ART. Data on virological treatment response were available for 185 of these 193 individuals. This group included 18 of the 19 individuals (17 who had used PrEP in the Netherlands and an additional 2 who had used PrEP prior to migrating to the Netherlands) with M184VI (with or without K65R) RT RAM, all of whom started a regimen containing an integrase inhibitor. Ten of these 18 individuals received a combination of an integrase inhibitor and a protease inhibitor, with or without additional nucleoside-analogue RT inhibitors (NRTIs).

Of the individuals with either no baseline resistance test results, or whose test showed no evidence of the M184VI or K65R RT RAM, 174 initiated a first-line regimen consisting of:

- an integrase inhibitor plus two NRTIs (n=123)
- a protease inhibitor plus two NRTIs (n=3)
- an integrase inhibitor plus a protease inhibitor, with or without additional NRTIs (n=34)
- an integrase inhibitor plus a non-nucleoside RT inhibitor (n=1)
- a non-nucleoside RT inhibitor plus two NRTIs (n=6)
- lamivudine / dolutegravir (n=7)

The 18 individuals with an RT RAM had a median follow-up time of 147.7 weeks (IQR 56.3-262.7) after initiating ART. In one of these 18 individuals who had an M184VI (but not 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 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 two NRTI, an INSTI, and 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). The remaining 17 individuals with M184VI (two of them also had a K65R) all achieved an optimal treatment response with sustained viral suppression below 200 copies/ml after initiating cART.

For the 174 individuals with no evidence of M184VI (with or without K65R RT RAM) in the baseline resistance test, or for whom no test data were available, all 167 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 100.4 weeks (IQR 48.4-186.9). In 16 individuals a viral rebound (defined as having a viral load measurement above 200 copies/ml following an initial treatment response) was recorded. In two of these individuals, the viral load decreased slowly but steadily over time and eventually reached undetectable. In five of these 16 individuals, the viral rebound was attributed to temporary interruption of ART, which re-suppressed after restarting the same or another ART regimen. In two individuals virological failure occurred: both were switched to a second line regimen after which the viral load durably re-suppressed. In the remaining cases, there was a single or two consecutive viral load measurements above 200 copies/ml without apparent lapse in medication intake, after which viral load suppression was achieved again without changing the regimen.

Summary and Conclusions

The number and proportion of newly diagnosed MSM and transgender individuals entering HIV care who reported prior use of PrEP has continued to rise over time. In 2024, 18.5% (n=52) of newly diagnosed MSM and transgender people reported prior use of PrEP (see also Chapter 1). However, this is probably a conservative estimate, as 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 is likely only partly explained by greater awareness or improved documentation by health care providers, suggesting a true rise in PrEP use among this population. The total number of people who use PrEP in the Netherlands is increasing, both through SHC's and via general practitioners, thereby contributing to more reports of prior PrEP use among people diagnosed with HIV.

The group of individuals who reported prior PrEP use is highly heterogeneous. Of the 208 individuals who reported prior PrEP use, 29 (13.9%) were migrants who had used PrEP before moving to the Netherlands. Among the 179 individuals who used PrEP in the Netherlands, 106 (59.2%) obtained it from a healthcare provider in the Netherlands, while others accesses PrEP through informal channels or from providers abroad. Notably, six individuals who used PrEP did not belong to one of the target groups for PrEP in the Netherlands: these were either migrants who used PrEP prior to migration, or individuals who obtained PrEP through informal means.

Of those who had used PrEP in the Netherlands, 48 (26.8%) were diagnosed with HIV while still using PrEP. Of the 144 individuals who reported prior use of PrEP and who received a genotypic resistance test prior to initiation of ART, 17 (11.8%) were found to harbour resistance mutations that were probably associated with continued PrEP use after seroconversion. Reassuringly, the virological response to ART initiation appeared to be unaffected by prior PrEP use, even in those with detected resistance associated mutations; almost all achieved and maintained viral suppression after starting ART.

A substantial proportion (42.5%) of MSM and transgender people who reported not using PrEP, and for whom information on reasons was available, indicated they would have wanted to use PrEP, but either had no access to PrEP (22.5%), were on a PrEP waiting list at the time when they tested HIV positive (2.2%), or tested HIV positive during screening process before initiating PrEP (17.8%). HIV screening during the intake for PrEP care contributes to earlier detection of HIV.

These findings highlight the importance of improving access to PrEP and ensuring timely initiation for those at risk, as well as the continued need for education, monitoring, and support for individuals using PrEP—both to prevent HIV acquisition and to manage potential drug resistance if HIV infection occurs during PrEP use.

Appendix Table 2.1: *characteristics of individuals who reported use of PrEP, stratified by presence of resistance associated mutations.*

	RAMs detected	No RAMs detected	Not tested, no data	p-value
Number of subjects	19 (9.1%)	136 (65.4%)	53 (25.5%)	
Age	30.9 (27.1-47)	31.8 (26.7-41.3)	33.6 (28.9-43.5)	0.512
HIV acquisition group				0.603
MSM	19 (100%)	126 (92.6%)	47 (88.7%)	
Other men	0 (0.0%)	3 (2.2%)	3 (5.7%)	
Women	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Transgender people	0 (0.0%)	7 (5.1%)	3 (5.7%)	
Region of birth				0.006
Born in the Netherlands	12 (63.2%)	69 (50.7%)	13 (24.5%)	
Migrant, western background	4 (21.1%)	29 (21.3%)	20 (37.7%)	
Migrant, non-western background	3 (15.8%)	38 (27.9%)	20 (37.7%)	
STD diagnosed at entry into care				
HBV (HBV surface antigen positive)	0 (0.0%)	2 (1.5%)	0 (0.0%)	0.586
HBV (HBV core antibody positive)	2 (10.5%)	20 (14.7%)	5 (9.4%)	0.592
HCV (antibody positive)	1 (5.3%)	4 (2.9%)	3 (5.7%)	0.645
Syphilis (RPR/VDRL positive)	5 (26.3%)	40 (29.4%)	18 (34.0%)	0.767
PrEP started before migrating to the Netherlands	3 (15.8%)	12 (8.8%)	20 (37.7%)	
PrEP provider				0.032
Provider in the Netherlands	15 (78.9%)	75 (55.1%)	16 (30.2%)	
- Public Health Service	9 (47.4%)	47 (34.6%)	7 (13.2%)	
- HIV treatment center	2 (10.5%)	2 (1.5%)	3 (5.7%)	
- Family practitioner	4 (21.1%)	23 (16.9%)	2 (3.8%)	
- Medical specialist	0 (0.0%)	2 (1.5%)	2 (3.8%)	
- No info	0 (0.0%)	1 (0.7%)	2 (3.8%)	
Provider outside the Netherlands	0 (0.0%)	9 (6.6%)	9 (17.0%)	
Obtained PrEP through informal routes	1 (5.3%)	17 (12.5%)	8 (15.1%)	
From friend living with HIV	0 (0.0%)	4 (2.9%)	2 (3.8%)	
No info	3 (15.8%)	31 (22.8%)	18 (34.0%)	
Seroconversion during PrEP use				
Tested HIV-positive while on PrEP	13 (68.4%)	29 (21.3%)	9 (17.0%)	<.001
HIV-testing following end of PrEP				<.001
HIV-negative test performed after last dose of PrEP	5 (83.3%)	41 (38.3%)	13 (29.5%)	
No HIV-negative test performed after last dose of PrEP	0 (0.0%)	48 (44.9%)	21 (47.7%)	
Unknown if HIV test was performed after last dose of PrEP	1 (16.7%)	18 (16.8%)	10 (22.7%)	

	RAMs detected	No RAMs detected	Not tested, no data	p-value
Diagnosed in the Netherlands or before migration				<.001
In the Netherlands	17 (89.5%)	134 (98.5%)	43 (81.1%)	
Before migration to the Netherlands	1 (5.3%)	2 (1.5%)	10 (18.9%)	
Unknown / uncertain	1 (5.3%)	0 (0.0%)	0 (0.0%)	
Days between last PrEP use and testing HIV-positive**	0 (0-6.8)	55 (3-184)	38 (3-273)	0.001
Recent HIV acquisition				
Tested pos. <365 days after last neg. test	15 (78.9%)	104 (76.5%)	37 (69.8%)	0.584
Tested pos. <180 days after last neg. test	13 (68.4%)	65 (47.8%)	25 (47.2%)	0.224
CD4 at HIV diagnosis	557 (472-708)	540 (365-718)	605 (380-777)	0.371
ARVs used for PrEP				0.034
TDF/FTC	13 (68.4%)	67 (49.3%)	17 (32.1%)	
Genvoya	0 (0.0%)	0 (0.0%)	1 (1.9%)	
Dolutegravir	0 (0.0%)	0 (0.0%)	1 (1.9%)	
Unspecified	6 (31.6%)	69 (50.7%)	34 (64.2%)	
PrEP schedule				<.001
On demand	10 (52.6%)	58 (42.6%)	12 (22.6%)	
Daily	9 (47.4%)	26 (19.1%)	10 (18.9%)	
No data	0 (0.0%)	48 (35.3%)	31 (58.5%)	
Used PrEP <1 week	0 (0.0%)	4 (2.9%)	0 (0.0%)	
Duration of PrEP use (days)	58 (30-142)	182 (29-344)	61 (15-231)	0.624
Routine medical check-ups while on PrEP				0.011
Public Health Service	10 (52.6%)	47 (34.6%)	8 (15.1%)	
Family practitioner	2 (10.5%)	14 (10.3%)	2 (3.8%)	
HIV treatment center	2 (10.5%)	3 (2.2%)	4 (7.5%)	
Other healthcare provider	0 (0.0%)	4 (2.9%)	4 (7.5%)	
No medical check-ups	0 (0.0%)	20 (14.7%)	5 (9.4%)	
No data	5 (26.3%)	48 (35.3%)	30 (56.6%)	
Resistance test performed after testing HIV-positive	19 (100%)	136 (100%)	0 (0.0%)	<.001
Resistance associated mutations in RT				
M184VI	19 (100%)	0 (0.0%)	0 (0.0%)	
K65R	2 (10.5%)	0 (0.0%)	0 (0.0%)	
K70EG	0 (0.0%)	0 (0.0%)	0 (0.0%)	

3. Social inequalities in people with a new HIV diagnosis compared to the general population

Vita Jongen, Anders Boyd, Ard van Sighem, Marc van der Valk

Summary

To further reduce new HIV diagnoses in the Netherlands, individual and structural barriers hindering prevention must be addressed. We aimed to estimate the disproportional burden of new HIV diagnoses and explore how intersecting socio-demographic, socio-economic, and health-related factors jointly influence the risk of a new HIV diagnosis.

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 selected individuals with a new HIV diagnosis in the Netherlands between 1 January 2012 and 31 December 2023 and matched them to individuals from the general population. 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. Since no data on sexual preference is available in CBS we report results by gender at birth and not by presumed HIV transmission route.

6,055 men and 1,020 women were newly diagnosed with HIV. Having a first or second generation migration background and a low-middle income or income below the poverty line was associated with a higher risk of a new HIV diagnosis for both men and women. Use of mental health care or antidepressants prior to the diagnosis also increased the risk among men; while receiving social welfare and use of antipsychotic medication increased the risk among women. Men with a first-generation migration background, income below the poverty line, and who used antidepressants had the highest predicted probability of an HIV diagnosis (0.036%). Women with a first-generation background, income below the poverty line, who received social welfare, and who used antipsychotic medication had the highest predicted risk (0.019%).

Aim

In the Netherlands, the HIV care continuum has almost reached the 95-95-95 UNAIDS targets in recent years; however, these targets have not yet been met for women and cisgender heterosexual men (see Chapter 1). Dutch health care services are universally accessible, STI and HIV testing is free for specific populations [including men who have sex with men (MSM) and transgender persons], and HIV prevention services, namely PrEP, are available, although PrEP prescriptions have to be paid individually (€ 15-65 per month for daily PrEP depending on pricing by pharmacy) . Both HIV care and STI and HIV prevention services are accessible for both documented and undocumented migrants. Despite these services, there is no longer a decline in the number of new HIV diagnoses (see Chapter 1). This stagnation likely reflects individual, interpersonal, and structural barriers that hinder prevention.

We estimated the disproportional burden of new HIV diagnoses and explored how intersecting socio-demographic, socio-economic, and health-related factors jointly influence the risk of a new HIV diagnosis using data from the ATHENA national HIV cohort and registry data from Statistics Netherlands.

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 2023 (i.e. the most recent data available at CBS).
The following variables from the CBS database were included:

Box 3.1: 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, other (i.e., 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 selected all individuals in the ATHENA cohort who were 18 years or older and newly diagnosed with HIV in the Netherlands between 1 January 2012 and 31 December 2023. Individuals who migrated to the Netherlands with a known pre-migration HIV diagnosis were excluded. We also excluded individuals identifying as transgender as few were included in the ATHENA cohort and the risk of identification was deemed non-negligible. We selected all individuals from the non-public microdata made available by Statistics Netherlands who were aged 18 years and older. We matched each individual newly diagnosed with HIV to all individuals from the general population with the same year of birth, gender, and calendar year of HIV diagnosis. Since no data on sexual preference is available in CBS matching by HIV transmission mode was not possible.

To minimise the risk of personal data inadvertently leading to the identification of an individual, data involving fewer than ten people were not reported.

Description of the population sample

Between 1 January 2012 and 31 December 2023, 6,055 men and 1,020 women were newly diagnosed with HIV, and combined with data from Statistics Netherlands. 2,437 (40%) men and 551 (54%) women were diagnosed with late or advanced stage HIV. These individuals were matched to 75,774,149 men and 66,819,245 women from the general population. 2,466 men and 659 women with HIV had a first or second migration background and 1,388 men and 455 women with HIV had an income below the poverty line.

Social inequalities in new HIV diagnoses in the Netherlands

Compared to the male general population, men with a new HIV diagnosis (Table 2):

- More often had a first or second generation migration background;
- More often had a low-middle income or an income below the poverty line;
- More often used mental health care prior to HIV diagnosis;
- More often used antidepressants before HIV diagnosis;
- Less often used antipsychotic medication before HIV diagnosis.

Women with a new HIV diagnosis:

- More often had a first or second generation migration background;
- More often had a low-middle income or an income below the poverty line;
- More often received social welfare;
- More often used antipsychotic medication.

Table 3.1: Determinants of an HIV diagnosis. Results from multivariable logistic regression.

	Men		Women	
	Adjusted odds ratio	95% Confidence interval	Adjusted odds ratio	95% Confidence interval
Migration background				
None	Reference		Reference	
First generation	2.21	2.08–2.35	4.48	3.87–5.19
Second generation	1.33	1.22–1.44	1.65	1.31–2.07
Income				
High	Reference		Reference	
Middle–low	1.24	1.17–1.31	2.49	2.05–3.01
Below the poverty line[1]	1.75	1.62–1.89	4.71	3.80–5.83
Received social welfare				
No			Reference	
Yes			1.39	1.15–1.67
Used mental health care[2]				
No	Reference			
Yes	1.14	1.01–1.27		
Used antidepressants[3]				
No	Reference		Reference	
Yes	1.66	1.50–1.84	1.23	0.99–1.52
Used anti-psychotic medication[3]				
No	Reference		Reference	
Yes	0.79	0.66–0.94	1.66	1.21–2.28

[1] Income below the poverty line is defined as a household income <120% of 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).

[2] Defined as declared cost (>0 euro) for mental health care.

[3] Use of medication for depression (ATC code N06A) or psychosis (ATC code N05A).

The influence of intersecting factors on the risk of HIV

We generated intersectional strata for men and women combining the socio-demographic and socio-economic variables mentioned above, whereby a stratum corresponded to a unique combination of these variables. For men, we combined categories of migration background (none, first generation, second generation), income (high, middle-low, below poverty line), mental health care use (yes/no), antidepressant use (yes/no), and antipsychotic medication use (yes/no). For women, strata were combined based on migration background, income, receiving social welfare (yes/no), use of antidepressants, and use of antipsychotic medication. This approach yielded 72 strata for both men and women. As age is known to influence HIV risk, we additionally included age in these strata, resulting in a total of 216 potential combinations.

The predicted risk of HIV was small overall, but differed between strata. Men aged between 25-49 years old, with a first generation migration background, an income below the poverty line, and who used antidepressants had the highest risk of newly diagnosed HIV (0.036% predicted risk, 95%CI=0.025-0.052), while men aged ≥50 years with no migration background and a high income had the lowest risk (0.003% predicted risk, 95%CI=0.003-0.004, Figure 1, Table 1). Women aged 25-49 years, with a first generation migration background, an income below the poverty line, who received social welfare, and who used antipsychotic medication had the highest predicted risk of newly diagnosed HIV (0.019%, 95%CI=0.011-0.035, Figure 2.2, Table 2).

Figure 3.1: *Predicted risk of a new HIV diagnosis for each stratum among men. (A) Predicted probabilities, B) Characteristics associated with each stratum. In (B) Color coding indicates categories for each variable. Age: dark blue = ≥50 years, medium blue = 25–49 years, light blue <25 years. Migration background: light red = no migration background, medium red = first generation migration background, dark red = second generation migration background. Income: dark green = below poverty line, medium green = low-middle income, light green = high income. For the other variables (mental health care, antidepressant use, antipsychotic use): darker shades = used, lighter shades = not used.*

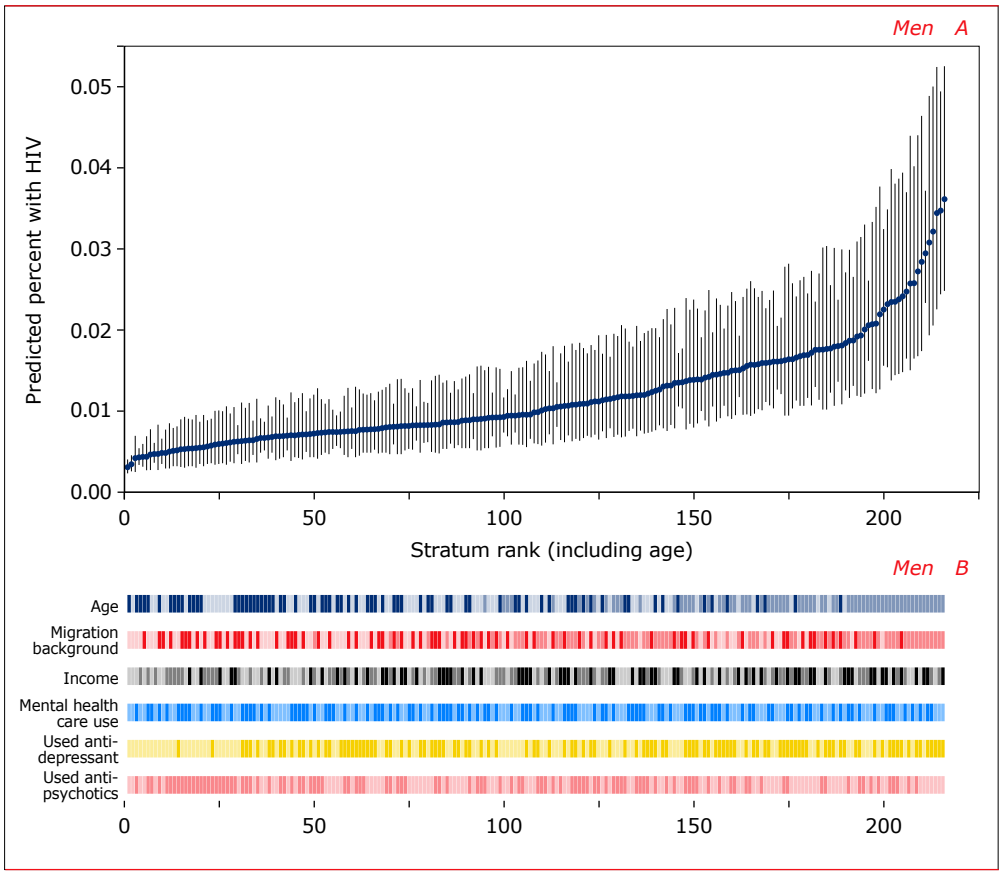


Figure 3.2: *Predicted risk of a new HIV diagnosis for each stratum among women. (A) Predicted probabilities, (B) Characteristics associated with each stratum. In (B) Color coding indicates categories for each variable. Age: dark blue = ≥50 years, medium blue = 25–49 years, light blue <25 years. Migration background: light red = no migration background, medium red = first generation migration background, dark red = second generation migration background. Income: dark green = below poverty line, medium green = low-middle income, light green = high income. For the other variables (received social welfare, antidepressant use, antipsychotic use): darker shades = received/used, lighter shades = not received/used.*

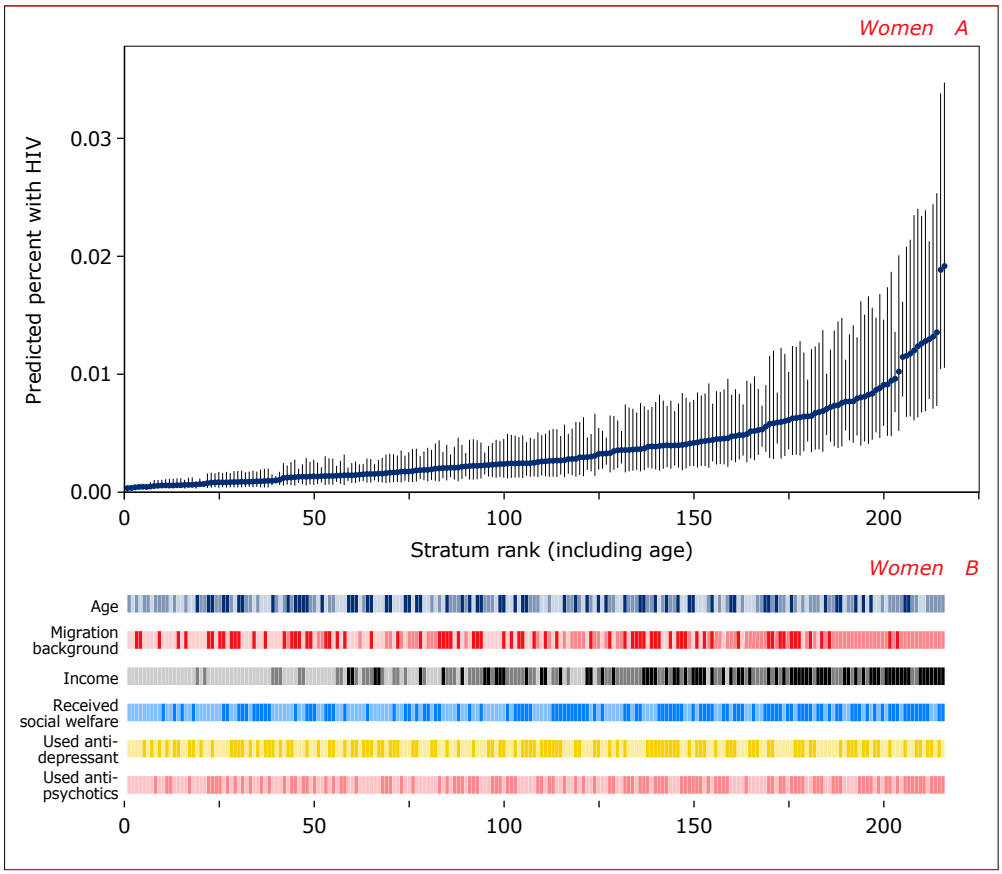


Table 3.2: Strata with the highest and lowest risk of a new HIV diagnoses for men.

Age	Migration background	Income[1]	Mental health care use
Highest risk			
25–49 years	1st generation	Below the poverty line	No
25–49 years	1st generation	Low-middle	No
25–49 years	1st generation	High	No
25–49 years	1st generation	Low-middle	Yes
25–49 years	1st generation	Below the poverty line	Yes
Lowest risk			
≥50 years	2nd generation	High	No
≥50 years	No migration background	Low-middle	No
≥50 years	No migration background	High	Yes
<25 years	No migration background	High	No
≥50 years	No migration backgroynd	High	No

Table 3.3: Strata with the highest and lowest risk of a new HIV diagnoses for women.

Age	Migration background	Income[1]	Received social welfare
Highest risk			
25–49 years	1st generation	Below the poverty line	Yes
25–49 years	1st generation	Below the poverty line	Yes
25–49 years	1st generation	Below the poverty line	No
25–49 years	1st generation	Below the poverty line	No
25–49 years	1st generation	Below the poverty line	Yes
Lowest risk			
≥50 years	No migration background	High	No
<25 years	2nd generation	High	No
≥50 years	2nd generation	High	No
<25 years	No migration background	High	No
≥50 years	No migration background	High	No

Use of anti-depressants	Use of anti-psychotic medication	Sample size	Predicted risk	95%CI
Yes	No	48,704	0.036	0.025–0.052
Yes	No	64,767	0.035	0.024–0.049
Yes	No	29,357	0.034	0.023–0.052
Yes	No	24,122	0.032	0.021–0.050
Yes	No	21,442	0.031	0.019–0.049
No	No	776,745	0.004	0.003–0.006
No	No	11,717,392	0.004	0.003–0.005
No	Yes	18,464	0.004	0.002–0.007
No	No	3,542,066	0.003	0.003–0.004
No	No	12,134,635	0.003	0.002–0.004

Use of anti-depressants	Use of anti-psychotic medication	Sample size	Predicted risk	95%CI
No	Yes	14,577	0.019	0.011–0.035
Yes	Yes	19,408	0.019	0.011–0.034
No	Yes	11,525	0.014	0.007–0.025
Yes	Yes	13,451	0.013	0.007–0.024
Yes	No	74,389	0.013	0.008–0.021
Yes	No	850,512	0.0004	0.0002–0.0006
No	No	381,206	0.0005	0.0002–0.0005
No	No	576,867	0.0003	0.0002–0.0006
No	No	2,846,477	0.0003	0.0002–0.0004
No	No	8,778,458	0.0002	0.0002–0.0004

Conclusions

HIV burden was higher among men and women with a migration background, those with an low-middle income or an income below the poverty line, and those who used mental health related care of medication. We also found that these factors jointly influence the risk of newly diagnosed HIV. These findings allow for more concrete understanding of which subgroups could benefit from improved HIV prevention and testing.

***Box 3.2:** Identifying socio-demographic and socio-economic gaps in HIV care in the Netherlands.*

To assess whether inequalities remain after HIV diagnosis, more detailed information is needed about which individuals might not successfully transition through the steps of the HIV care continuum. To this end, we used data from 21,788 individuals with HIV diagnosed before 31 December 2023 and combined these with registry data from Statistics Netherlands. We modelled socio-demographic, - economic, and health-related determinants of not achieving two milestones in the HIV care continuum, i.e., suppressed viral load and engagement in care. In men who have sex with men (MSM), cisgender heterosexual men and women, having a household income below the poverty line or a low to middle household income was associated with having a detectable viral load. Having a second-generation migration background (i.e., an individual born in the Netherlands who has at least one parent born abroad) or living in a single parent, institutionalized or other type of household was associated with a higher probability of a detectable viral load in only MSM. Younger age was associated with a higher probability of having a detectable viral load in cisgender heterosexual men and women only. Having an household income below the poverty line was also associated with disengagement from care in MSM and cisgender heterosexual men. Efforts to optimize HIV care through specialized interventions should consider individual economic vulnerability.

4. Response to antiretroviral therapy

Ferdinand Wit, Kees Brinkman, Kees van Nieuwkoop, Casper Rokx, Wouter Bierman, Marc van der Valk

Introduction

The primary goals of antiretroviral therapy (ART) are to prevent HIV disease progression, improve clinical outcomes, and prevent 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) has been completed. The decision to initiate ART should always include consideration of a person's comorbid conditions, possible drug resistance, as well as 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[5,8].

Besides preventing clinical events, including but not limited to opportunistic infections and malignancies, the rapid start of ART is also more effective at preventing 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 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 reliable access and good adherence to treatment.

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[17].

Starting antiretroviral therapy

In total, 7,069 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 2015 and December 2024. In *Table 4.1*, we have grouped people by calendar year of ART initiation: 4,605 started in 2015-2019, 517 in 2020, 467 in 2021, 490 in 2022, 518 in 2023, and 472 in 2024. 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. 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 7,069 people known to have initiated ART since January 2015, 4,337 (61.4%) were men who have sex with men (MSM), 1,456 (20.6%) other men, 1,102 (15.6%) women, and 174 (2.5%) were transgender people. Overall, 3,790 (53.6%) originated from the Netherlands. The proportion of people born in the Netherlands has been steadily declining: from 57.2% in 2015-2019, to 45.3% in 2024. There was a steady increase in the proportion of people born in eastern and central Europe (in recent years predominantly from Ukraine); from 6.9% in 2015-2019, to 15.9% in 2024. 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 35 days (interquartile range [IQR] 18-71) for those who entered care in 2015, to 24 days (IQR 13-41) in 2019, to 16 days (IQR 7-29) in 2024. Likewise, 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 (93.8% in 2024), or even within one day (18.9% in 2024).

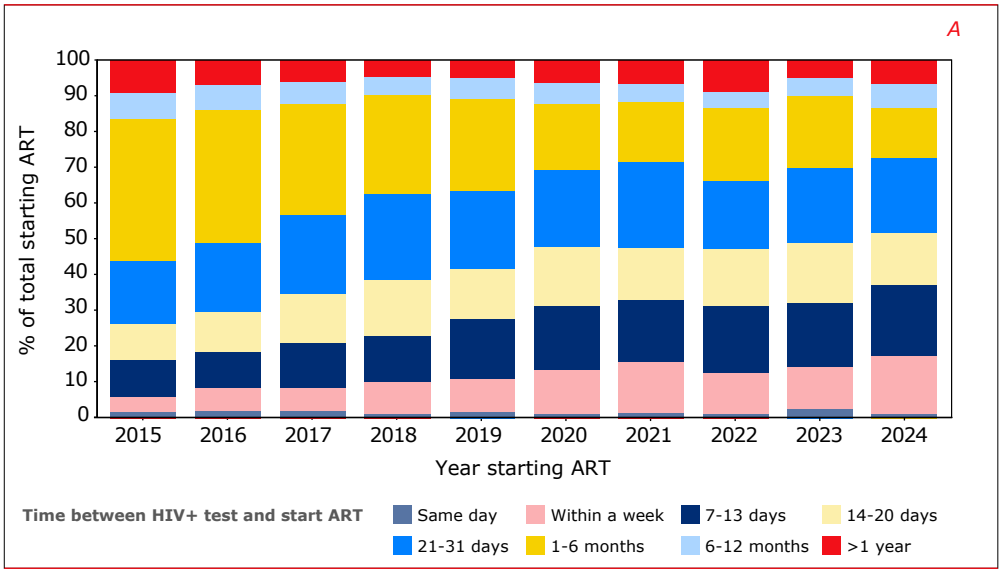
Table 4.1 Characteristics of people starting antiretroviral therapy in 2015–2024.

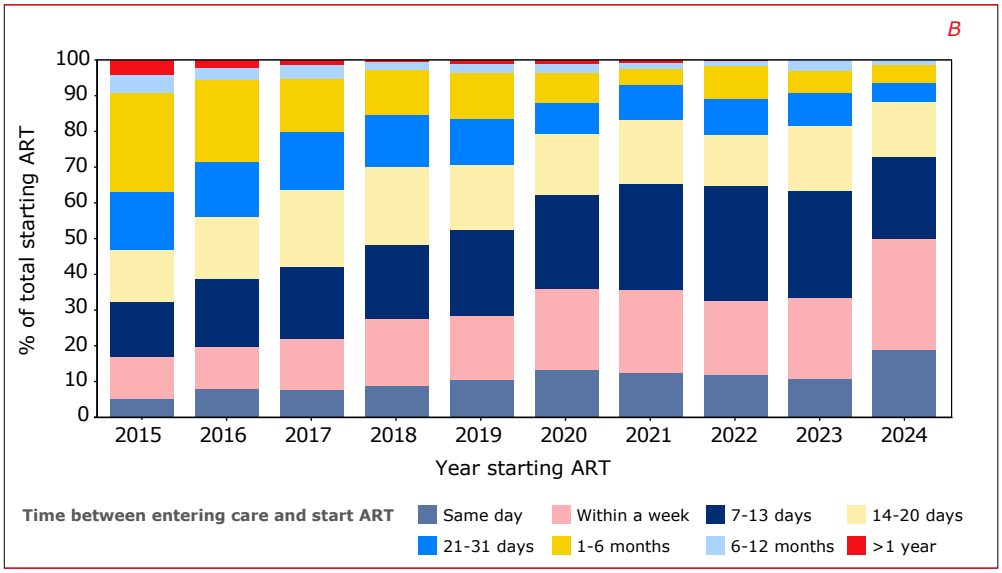
Year of ART initiation		2015–2019	2020	2021	2022	2023	2024	2015–2024
Number of individuals		4,605	517	467	490	518	472	7,069
DEMOGRAPHICS								
Age at ART initiation (years)	Median	39.2	39	39.7	39.6	39.1	37.7	39,1
	Q1	30	30.1	31.2	30.9	30.6	29	30,2
	Q3	49.8	50.2	52.2	50.9	50.2	49.9	50,1
Male sex (at birth)	n	3,938	423	392	390	422	394	5,959
	%	85.5	81.8	83.9	79.6	81.5	83.5	84,3
HIV acquisition group								
MSM	n	2,983	290	271	245	279	269	4,337
	%	64.8	56.1	58	50	53.9	57	61,4
Other men	n	877	111	105	129	131	103	1,456
	%	19	21.5	22.5	26.3	25.3	21.8	20,6
Women	n	664	94	73	100	95	76	1,102
	%	14.4	18.2	15.6	20.4	18.3	16.1	15,6
Transgender people	n	81	22	18	16	13	24	174
	%	1.8	4.3	3.9	3.3	2.5	5.1	2,5
Region of origin								
The Netherlands	n	2,636	259	225	229	227	214	3,790
	%	57.2	50.1	48.2	46.7	43.8	45.3	53,6
Western Europe/North America/	n	234	21	24	13	18	19	329
Australia	%	5.1	4.1	5.1	2.7	3.5	4	4,7
Eastern/central Europe	n	318	62	59	85	77	75	676
	%	6.9	12	12.6	17.3	14.9	15.9	9,6
Latin America and the Caribbean	n	619	75	76	50	81	61	962
	%	13.4	14.5	16.3	10.2	15.6	12.9	13,6
Sub-Saharan Africa	n	418	61	36	62	60	59	696
	%	9.1	11.8	7.7	12.7	11.6	12.5	9,8
Other	n	380	39	47	51	55	44	616
	%	8.3	7.5	10.1	10.4	10.6	9.3	8,7
CLINICAL								

Year of ART initiation		2015–2019	2020	2021	2022	2023	2024	2015–2024
Recent infection (within 12 months of diagnosis)	n	1,199	113	79	89	107	130	1,717
	%	26	21.9	16.9	18.2	20.7	27.5	24.3
Ever having tested HIV-negative	n	2,625	271	234	233	266	262	3,891
	%	57	52.4	50.1	47.6	51.4	55.5	55
CD4 count at start of ART	Median	395	320	303	351	351	410	380
	Q1	200	130	130	150	160	192	180
	Q3	580	555	543	544	563	610	580
HIV RNA (log_{10} cp/ml) at start of ART	Median	4.8	4.9	5.2	4.8	5.1	5	4.8
	Q1	4.1	4.2	4.5	3.9	4.1	4.1	4.2
	Q3	5.4	5.6	5.8	5.6	5.8	5.7	5.5
(Prior) AIDS at start of ART	n	639	108	90	79	92	62	1,070
	%	13.9	20.9	19.3	16.1	17.8	13.1	15.1
Hepatitis B status at start of ART								
HBV-negative (HBsAg-negative)	n	4,346	487	443	454	491	444	6,665
	%	94.4	94.2	94.9	92.7	94.8	94.1	94.3
HBV-positive (HBsAg-positive)	n	122	18	9	28	15	14	206
	%	2.6	3.5	1.9	5.7	2.9	3	2.9
Unknown	n	137	12	15	8	12	14	198
	%	3	2.3	3.2	1.6	2.3	3	2.8
Hepatitis C status at start of ART								
HCV-negative	n	4,410	487	438	462	490	450	6,737
	%	95.8	94.2	93.8	94.3	94.6	95.3	95.3
HCV RNA-positive	n	81	8	6	16	14	6	131
	%	1.8	1.5	1.3	3.3	2.7	1.3	1,9
HCV Ab seropositive	n	56	11	10	4	11	10	102
	%	1.2	2.1	2.1	0.8	2.1	2.1	1.4
Unknown	n	58	11	13	8	3	6	99
	%	1.3	2.1	2.8	1.6	0.6	1.3	1.4
ART started during pregnancy	n	98	10	9	8	13	3	141
	%	2.1	1.9	1.9	1.6	2.5	0.6	2

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 2015-2024 (A) and time between entry into HIV care and initiation of ART in 2015-2024 (B).





Legend: ART = antiretroviral therapy.

There was a slight decrease in the median CD4 count at the start of ART from 395 cells/mm^3 (IQR 200-580) in 2015-2019, to a low of 303 (130-543) in 2021 during COVID-19 lockdowns, followed by an increase to 410 (192-610) cells/mm^3 in 2024. The slightly higher CD4 counts in the period 2015-2019 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.

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, several 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 2013–2024.

Medicine	Authorisation date
TDF/FTC/elvitegravir/cobicistat (Stribild®)	24 May 2013
Dolutegravir (Tivicay®)	16 January 2014
ABC/3TC/dolutegravir (Triumeq®)	01 September 2014
DRV/cobicistat (Rezolsta®)	19 November 2014
TAF/FTC/elvitegravir/cobicistat (Genvoya®)	19 November 2015
TAF/FTC (Descovy®)	21 April 2016
TAF/FTC/rilpivirine (Odefsey®)	21 June 2016
TAF (Vemlidy®)	09 January 2017
TAF/FTC/darunavir/cobicistat (Symtuza®)	21 September 2017
Dolutegravir/rilpivirine (Juluca®)	21 May 2018
TAF/FTC/bictegravir (Biktarvy®)	25 June 2018
Doravirine (Pifeltro®)	22 November 2018
TDF/3TC/doravirine (Delstrigo®)	22 November 2018
3TC/dolutegravir (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; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.*

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

Initial ART regimen

In the period 2015-2024, 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, except for the regimen 3TC/DTG. In the period 2015-2024, 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 more common in recent years, but only in treatment-experienced individuals.

In the studied period, in certain groups of newly diagnosed individuals, a 2-step 'induction-maintenance' approach has sometimes been used, where at the time of ART initiation it is the explicit intention to replace the first ART regimen as soon as possible with another regimen. For the purpose of our analyses here, when the

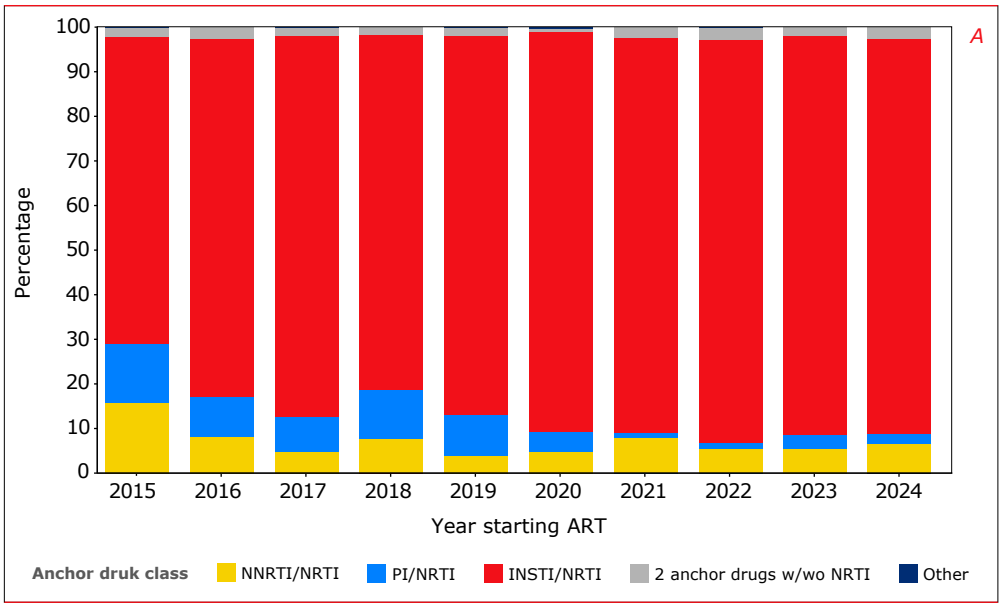
switch happened within 6 months and there was explicit mention of the 'induction-maintenance' approach in the electronic medical records, the starting regimens of the individuals who initiated therapy using this strategy have been set to their second simplified guideline-recommended regimen.
Common examples of this 'induction-maintenance' approach are ART initiation with a regimen containing 2 anchor-drugs plus 2 NRTI in individuals initiating ART during acute HIV infection (often as part of a study protocol) 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. This occurred 294 times. Another common similar strategy is that individuals are started on a dolutegravir-based regimen combined with 2 NRTI (n=258), which is than quickly 'simplified' to either 3TC/DTG or TDF/3TC/DOR, as soon as the first undetectable viral load measurement and/or the results of genotypic resistance testing have become available. Also in these cases, we considered their second simplified guideline-recommended regimen as their starting regimen, unless the reason for the switch was documented to be 'virological failure' or 'toxicity'.

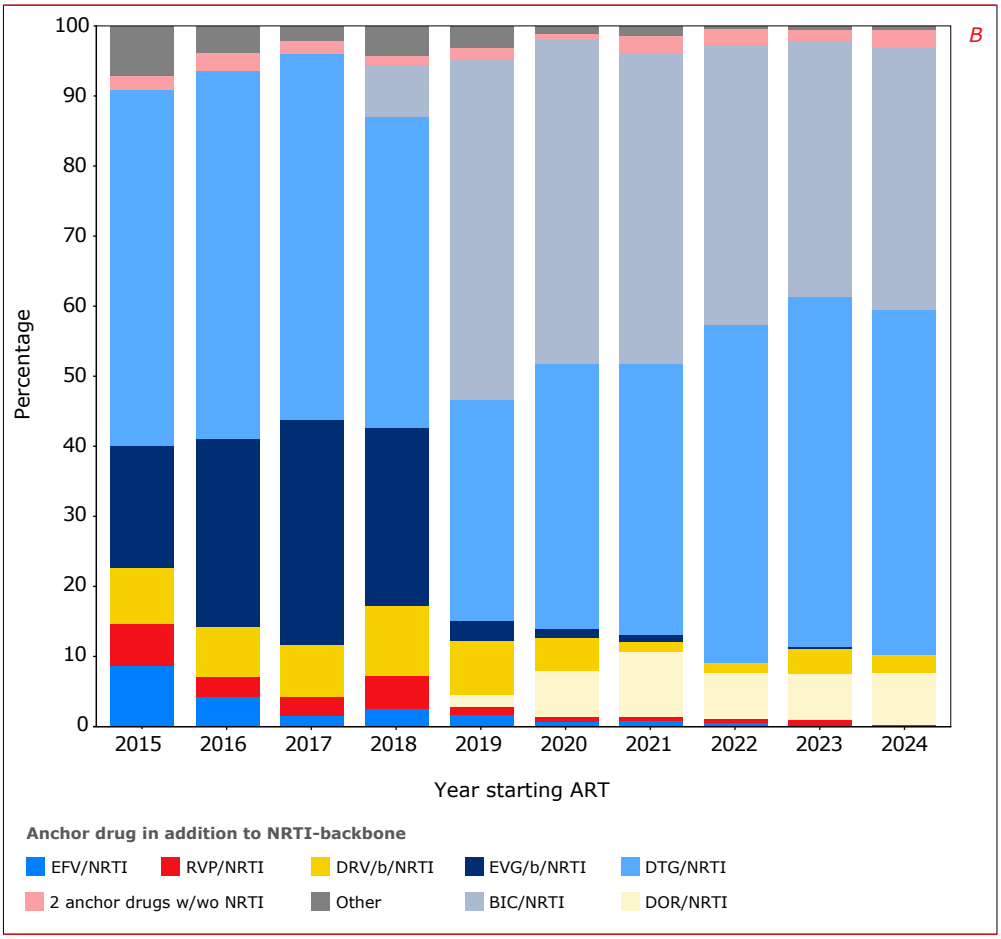
For the 7,069 ART-naïve people who initiated first-line ART between 2015 and 2024, *Figures 4.2A&B* show the trends over time in anchor-drug additions to the NRTI backbone used as part of the initial ART regimen. The use of INSTI in combination with a (mono- or dual-) NRTI backbone as initial therapy, increased from 68.9% in 2015 to 88.8% in 2024 (89.9% including other INSTI-containing dual anchor-drug regimens). The use of NNRTIs in combination with a NRTI backbone as the initial regimen decreased from 15.8% in 2015 to 6.4% in 2024. The use of PIs in combination with a NRTI backbone as the initial regimen also decreased from 13.2% in 2015 to 2.3% in 2024.

In the period 2015-2024, between 0.6% and 2.5% of individuals (2.5% in 2024) initiated ART with 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 when this was deemed to be safe.

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 2015-2024. 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 2015-2024.

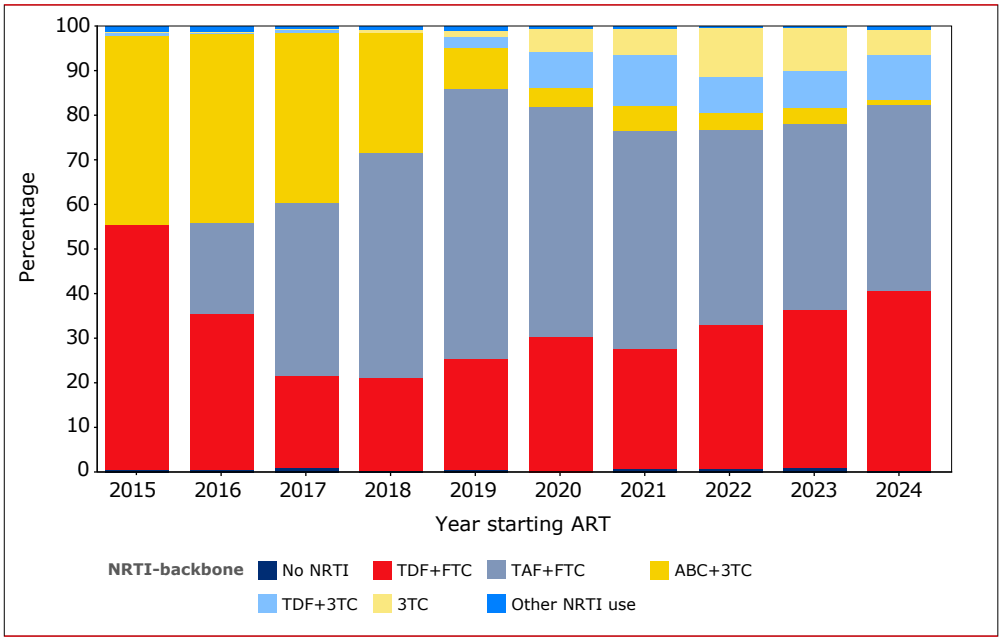




Legend: *ART = antiretroviral therapy; b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; INSTI = integrase inhibitor; NRTI = nucleoside analogue reverse transcriptase inhibitor; 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 2015-2024. The combination of tenofovir disoproxil fumarate (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 60.3% in 2019, but has since slowly declined to 41.5% in 2024. At the same time, TDF use decreased from 54.9% in 2015 to a low of 20.7% in 2017, after which its use increased again to 40.5% in 2024. The use of abacavir steadily decreased from a high of 42.7% of all initial regimens in 2016 to 1.3% in 2024.

Figure 4.3: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2015–2024.*



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

The most common ART regimens initiated in 2015-2024 are presented in *Figure 4.4* and *Table 4.2*. In 2024, the most frequently used initial regimen was TDF/FTC/dolutegravir (38.3%). TAF/FTC/bictegravir was used in 37.5% of initial regimens. Additionally, 7.4% initiated a doravirine-containing, once-daily, fixed-dose combination with lamivudine (3TC) and tenofovir disoproxil fumarate (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*.

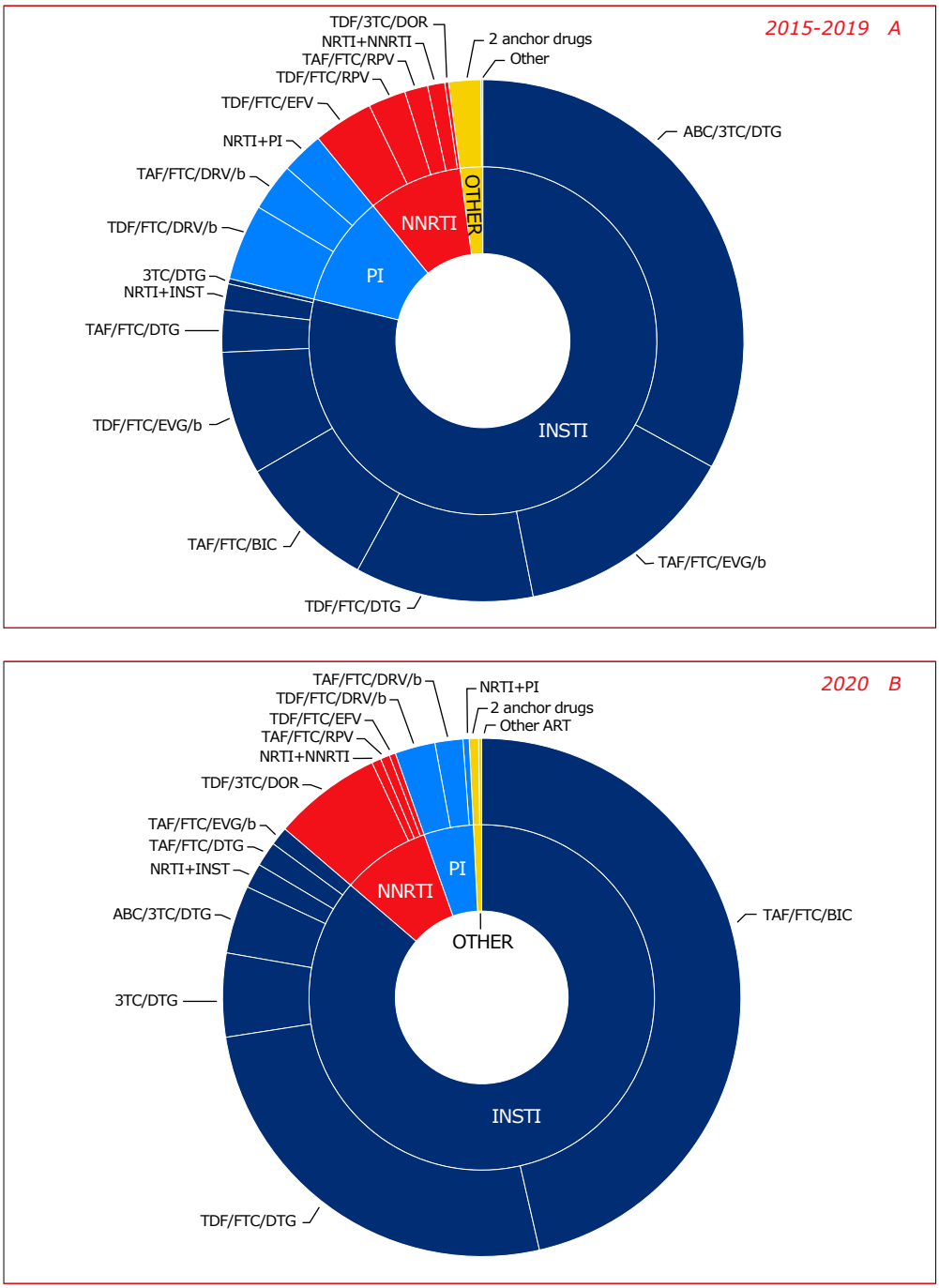
Table 4.2: Initial regimens in 2015–2024.

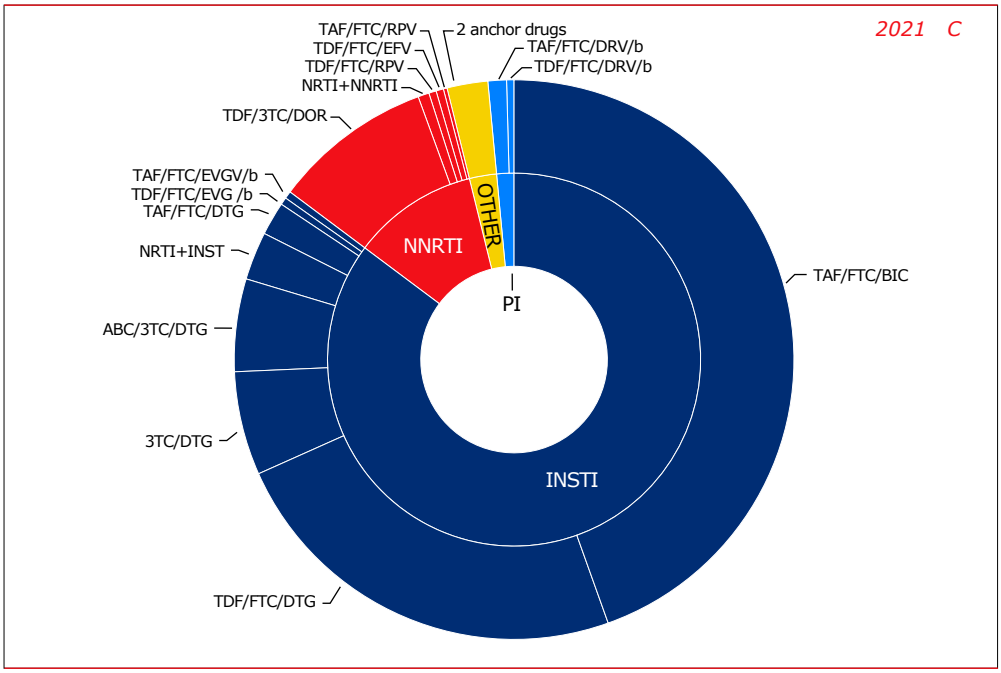
		2015–2019	2020	2021	2022	2023	2024	2015–2024
	n	4,605	517	467	490	518	472	7,069
INSTI + NRTI								
TAF/FTC/BIC	n	399	240	208	194	189	177	1,407
	%	8.7	46.4	44.5	39.6	36.5	37.5	19.9
TAF/FTC/DTG	n	120	8	9	10	9	6	162
	%	2.6	1.5	1.9	2	1.7	1.3	2.3
TDF/FTC/DTG	n	509	135	111	148	176	181	1,260
	%	11.1	26.1	23.8	30.2	34	38.3	17.8
ABC/3TC/DTG	n	1,520	22	25	19	19	6	1,611
	%	33	4.3	5.4	3.9	3.7	1.3	22.8
3TC/DTG	n	15	27	28	53	50	26	199
	%	0.3	5.2	6	10.8	9.7	5.5	2.8
TAF/FTC/EVG/c	n	640	6	2	.	1	.	649
	%	13.9	1.2	0.4	.	0.2	.	9.2
TDF/FTC/EVG/c	n	353	.	2	.	.	.	355
	%	7.7	.	0.4	.	.	.	5
TDF/FTC/RAL	n	34	3	4	1	1	.	43
	%	0.7	0.6	0.9	0.2	0.2	.	0.6
Other NRTI + INSTI	n	40	5	9	8	7	15	84
	%	0.9	1	1.9	1.6	1.4	3.2	1.2
NNRTI + NRTI								
TDF/3TC/DOR	n	11	35	43	31	36	35	191
	%	0.2	6.8	9.2	6.3	6.9	7.4	2.7
TDF/FTC/EFV	n	171	2	2	3	1	1	180
	%	3.7	0.4	0.4	0.6	0.2	0.2	2.5
TDF/FTC/NVP	n	19	.	1	.	.	.	20
	%	0.4	.	0.2	.	.	.	0.3
ABC/3TC/NVP	n	1	.	.	.	.	.	1
	%	0	.	.	.	.	.	0
TAF/FTC/RPV	n	66	3	1	3	2	1	76
	%	1.4	0.6	0.2	0.6	0.4	0.2	1.1
TDF/FTC/RPV	n	107	.	2	.	1	.	110
	%	2.3	.	0.4	.	0.2	.	1.6
Other NRTI + NNRTI	n	29	3	2	.	1	.	35
	%	0.6	0.6	0.4	.	0.2	.	0.5

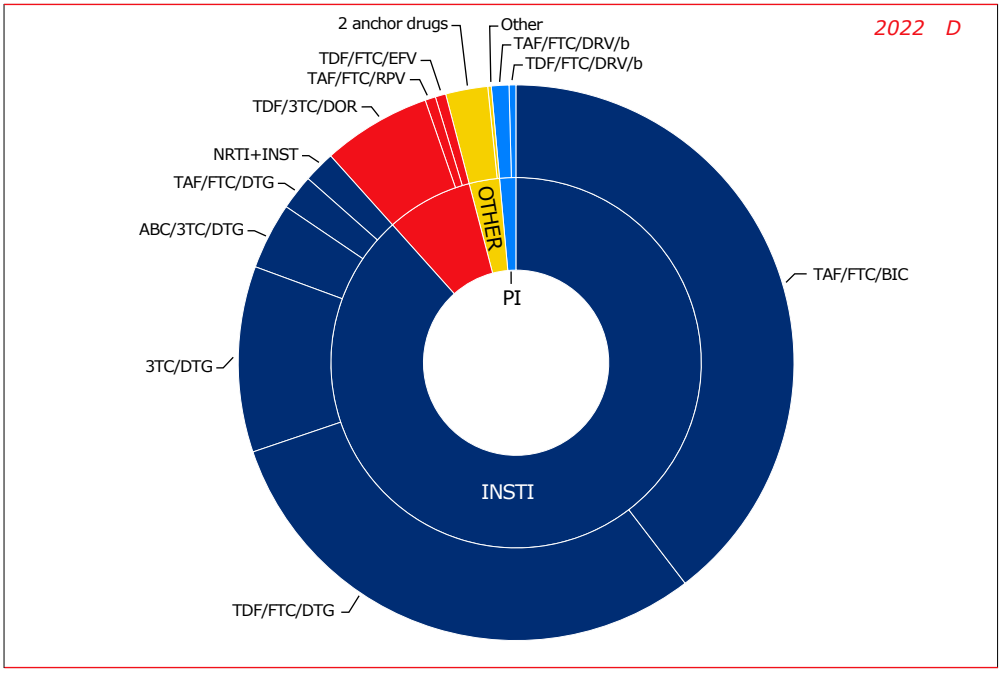
PI + NRTI								
TDF/FTC/ATV/b	n	73	.	.	.	.	.	73
	%	1.6	.	.	.	.	.	1
TAF/FTC/DRV/c	n	136	9	5	5	13	9	177
	%	3	1.7	1.1	1	2.5	1.9	2.5
TDF/FTC/DRV/b	n	217	13	2	2	2	2	238
	%	4.7	2.5	0.4	0.4	0.4	0.4	3.4
TDF/FTC/LPV/r	n	6	.	.	.	.	.	6
	%	0.1	.	.	.	.	.	0.1
Other NRTI + PI	n	42	2	.	.	1	.	45
	%	0.9	0.4	.	.	0.2	.	0.6
2 anchor-drugs								
DTG/DRV/b	n	28	1	4	5	3	1	42
	%	0.6	0.2	0.9	1	0.6	0.2	0.6
DTG/RPV	n	1	.	.	.	.	1	2
	%	0	.	.	.	.	0.2	0
CAB/RPV	n	.	.	.	.	1	.	1
	%	.	.	.	.	0.2	.	0
2 anchor-drugs w/wo NRTI	n	62	2	7	7	4	9	91
	%	1.3	0.4	1.5	1.4	0.8	1.9	1.3
Other ART	n	6	1	.	1	1	2	11
	%	0.1	0.2	.	0.2	0.2	0.4	0.2

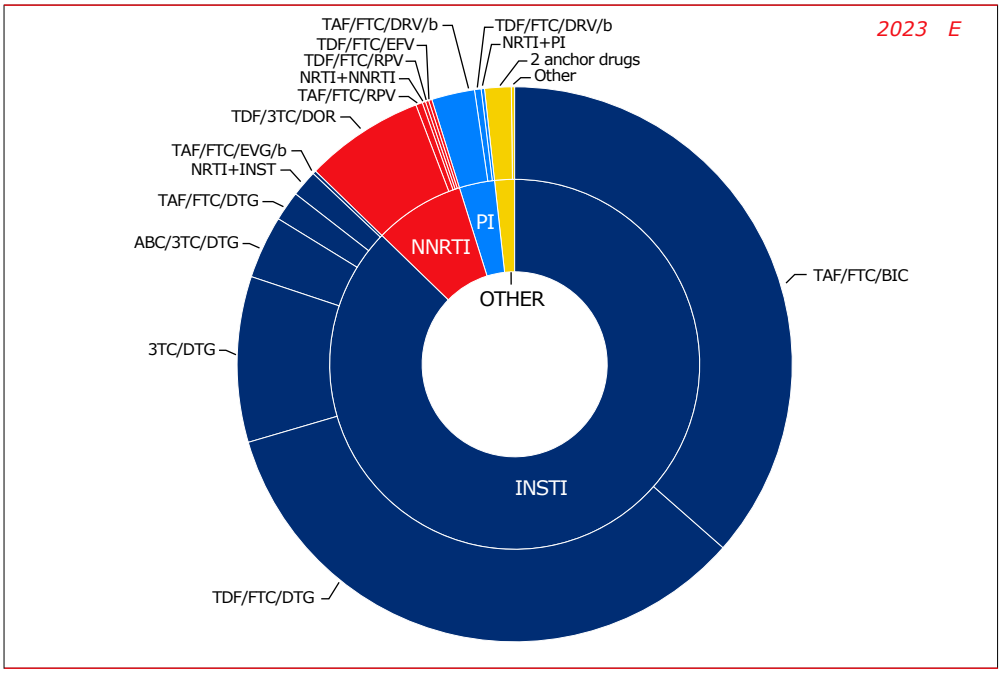
Legend: *b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV = atazanavir; BIC = bictegravir; CAB = cabotegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir;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

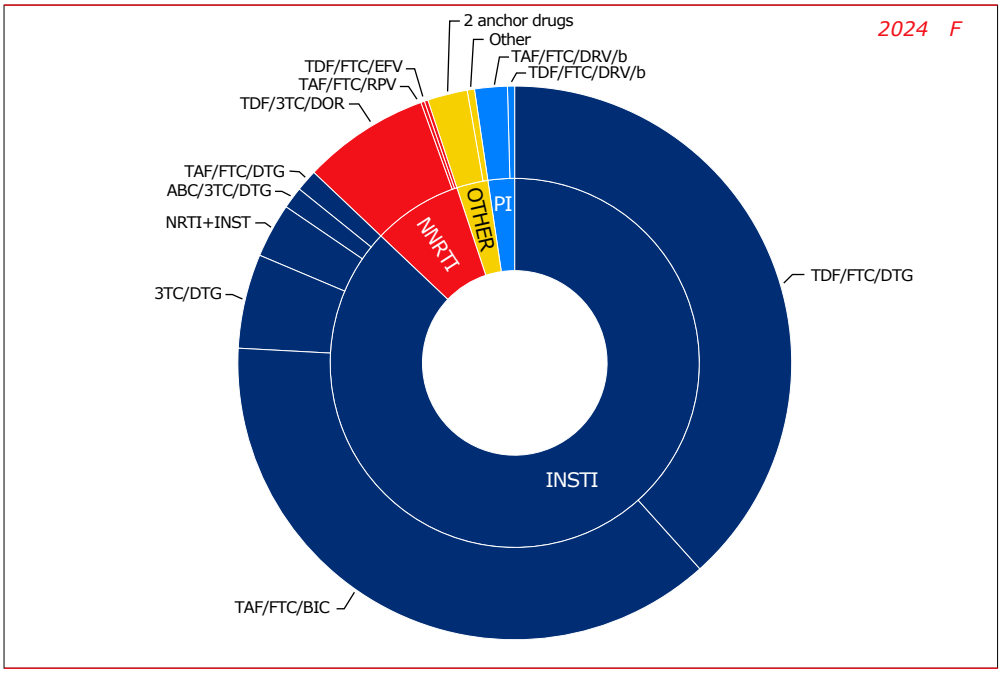
Figure 4.4: The initial antiretroviral therapy regimens given in 2015–2024.




2021 C
TAF/FTC/RPV
2 anchor drugs
TDF/FTC/EFV
TAF/FTC/DRV/b
TDF/FTC/RPV
TDF/FTC/DRV/b
NRTI+NNRTI
TDF/3TC/DOR
TAF/FTC/EVGV/b
TDF/FTC/EVG /b
TAF/FTC/DTG
NRTI+INST
ABC/3TC/DTG
3TC/DTG
TDF/FTC/DTG
NNRTI
OTHER
PI
INSTI
TAF/FTC/BIC


2022 D
2 anchor drugs
Other
TAF/FTC/DRV/b
TDF/FTC/EFV
TDF/FTC/DRV/b
TAF/FTC/RPV
TDF/3TC/DOR
NRTI+INST
TAF/FTC/DTG
ABC/3TC/DTG
3TC/DTG
TDF/FTC/DTG
OTHER
PI
INSTI
TAF/FTC/BIC





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 2024

A total of 26,519 people with HIV were in care and on ART between (part of the period) January 2015 and December 2024. The number of people who had initiated ART and were in active follow-up in the ATHENA cohort grew from 18,157 individuals in 2015 to 22,698 individuals in 2024. 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 had been sufficiently resolved.

Table 4.3 shows the evolution over calendar time of the size, demographical, clinical and ART 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 2024, 22,698 people on ART were in care (for part of or the entire) calendar year. In 2024, 18,522 (81.6%) were men, and 14,191 (62.5%) were MSM. Their median age in 2024 was 53.2 (IQR 42.9-61.5) years. The majority (54.6%) originated from the Netherlands, followed by Latin America / the Caribbean (13.3%) and sub-Saharan Africa (12.0%). They had been diagnosed with HIV a median of 14.7 (IQR 8.9-21.0) years ago and started their first-line ART regimen a median of 12.6 (IQR 8.0-18.5) years ago. Their last measured viral load was <50 copies/ml in 95.6% (98.0% <200 copies/ml), and 80.3% 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 2015–2024.

Calendar year		2015	2020	2021	2022	2023	2024
Total population size	n	18,157	21,363	21,663	22,130	22,528	22,698
Age	Median	48.2	51.0	51.7	52.2	52.7	53.2
	Q1	39.9	41.4	41.9	42.2	42.5	42.9
	Q3	55.5	58.8	59.6	60.2	60.9	61.5
Male sex (at birth)	n	14,805	17,525	17,779	18,079	18,397	18,522
	%	81.5	82.0	82.1	81.7	81.7	81.6
HIV acquisition group							
MSM	n	11,304	13,497	13,670	13,865	14,075	14,191
	%	62.3	63.2	63.1	62.7	62.5	62.5
Other men	n	3,328	3,755	3,820	3,910	3,995	3,992
	%	18.3	17.6	17.6	17.7	17.7	17.6
Women	n	3,350	3,833	3,877	4,042	4,120	4,163
	%	18.5	17.9	17.9	18.3	18.3	18.3
Transgender people	n	175	278	296	313	338	352
	%	1.0	1.3	1.4	1.4	1.5	1.6
Region of origin							
The Netherlands	n	10,985	12,423	12,455	12,443	12,443	12,402
	%	60.5	58.2	57.5	56.2	55.2	54.6
Western Europe/North	n	1,196	1,343	1,354	1,347	1,367	1,355
America/Australia	%	6.6	6.3	6.3	6.1	6.1	6.0
Eastern/central Europe	n	550	919	1,002	1,301	1,425	1,500
	%	3.0	4.3	4.6	5.9	6.3	6.6
Latin America/Caribbean	n	2,014	2,664	2,769	2,837	2,957	3,018
	%	11.1	12.5	12.8	12.8	13.1	13.3
Sub-Saharan Africa	n	2,330	2,560	2,575	2,617	2,670	2,727
	%	12.8	12.0	11.9	11.8	11.9	12.0
Other	n	1,082	1,454	1,508	1,585	1,666	1,696
	%	6.0	6.8	7.0	7.2	7.4	7.5
CD4 at start ART							
No data	n	1,347	2,147	2,307	2,644	2,840	3,004
	%	7.4	10.1	10.6	11.9	12.6	13.2
<50	n	1,876	2,067	2,101	2,122	2,140	2,128
	%	10.3	9.7	9.7	9.6	9.5	9.4
50–199	n	3,883	4,111	4,134	4,136	4,139	4,105
	%	21.4	19.2	19.1	18.7	18.4	18.1
200–349	n	5,527	5,845	5,842	5,833	5,857	5,800
	%	30.4	27.4	27.0	26.4	26.0	25.6
350–499	n	3,045	3,624	3,634	3,666	3,712	3,719
	%	16.8	17.0	16.8	16.6	16.5	16.4
500+	n	2,479	3,569	3,645	3,729	3,840	3,942
	%	13.7	16.7	16.8	16.9	17.0	17.4

Calendar year		2015	2020	2021	2022	2023	2024
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	9.3	12.1	12.8	13.4	14.1	14.7
	Q1	4.9	6.8	7.4	7.9	8.4	8.9
	Q3	15.0	18.2	18.9	19.6	20.3	21.0
Years since start ART	Median	7.0	10.0	10.7	11.3	12.0	12.6
	Q1	3.1	5.7	6.4	7.0	7.5	8.0
	Q3	12.9	15.8	16.5	17.2	17.9	18.5
Current CD4 count							
Missing	n	16	20	27	25	26	20
	%	0.1	0.1	0.1	0.1	0.1	0.1
<50	n	74	62	60	68	61	48
	%	0.4	0.3	0.3	0.3	0.3	0.2
50–199	n	466	442	414	424	416	380
	%	2.6	2.1	1.9	1.9	1.8	1.7
200–349	n	1,492	1,426	1,433	1,464	1,382	1,290
	%	8.2	6.7	6.6	6.6	6.1	5.7
350–499	n	3,080	3,050	3,108	2,984	2,850	2,748
	%	17.0	14.3	14.3	13.5	12.7	12.1
500–749	n	6,804	7,157	7,324	7,378	7,236	7,187
	%	37.5	33.5	33.8	33.3	32.1	31.7
750+	n	6,225	9,206	9,297	9,787	1,0557	1,1025
	%	34.3	43.1	42.9	44.2	46.9	48.6
Viral load <50 c/ml							
Missing	n	10	14	14	18	14	9
	%	0.1	0.1	0.1	0.1	0.1	0.0
≥50 c/ml	n	1,800	996	985	1,083	988	997
	%	9.9	4.7	4.5	4.9	4.4	4.4
<50 c/ml	n	16,347	20,353	20,664	21,029	21,526	21,692
	%	90.0	95.3	95.4	95.0	95.6	95.6
Viral load <200 c/ml							
Missing	n	10	14	14	18	14	9
	%	0.1	0.1	0.1	0.1	0.1	0.0
≥200 c/ml	n	740	475	490	535	498	456
	%	4.1	2.2	2.3	2.4	2.2	2.0
<200 c/ml	n	17,407	20,874	21,159	21,577	22,016	22,233
	%	95.9	97.7	97.7	97.5	97.7	98.0

Calendar year		2015	2020	2021	2022	2023	2024
ART regimen							
ART temporarily interrupted	n	459	390	377	341	293	181
	%	2.5	1.8	1.7	1.5	1.3	0.8
INSTI + NRTI							
TAF/FTC/BIC	n	2	2,688	3,159	3,563	3,927	4,235
	%	0.0	12.6	14.6	16.1	17.4	18.7
TAF/FTC/DTG	n	6	550	526	497	473	449
	%	0.0	2.6	2.4	2.2	2.1	2.0
TDF/FTC/DTG	n	665	764	768	914	981	1,089
	%	3.7	3.6	3.5	4.1	4.4	4.8
ABC/3TC/DTG	n	2,149	2,578	2,179	1,888	1,619	1,377
	%	11.8	12.1	10.1	8.5	7.2	6.1
3TC/DTG	n	20	1,067	1,728	2,365	3,041	3,481
	%	0.1	5.0	8.0	10.7	13.5	15.3
TAF/FTC/EVG/b	n	13	2,511	2,267	2,012	1,806	1,698
	%	0.1	11.8	10.5	9.1	8.0	7.5
TDF/FTC/EVG/b	n	1,337	580	532	459	401	362
	%	7.4	2.7	2.5	2.1	1.8	1.6
TDF/FTC/RAL	n	366	177	159	132	98	97
	%	2.0	0.8	0.7	0.6	0.4	0.4
Other INSTI + NRTI	n	158	257	244	249	243	225
	%	0.9	1.2	1.1	1.1	1.1	1.0
NNRTI + NRTI							
TDF/3TC/DOR	n	2	886	1,403	1,642	1,855	1,997
	%	0.0	4.1	6.5	7.4	8.2	8.8
TDF/FTC/EFV	n	3,001	1,378	1,223	1,054	945	876
	%	16.5	6.5	5.6	4.8	4.2	3.9
TAF/FTC/NVP	n	4	712	721	713	700	683
	%	0.0	3.3	3.3	3.2	3.1	3.0
TDF/FTC/NVP	n	2,220	1,031	915	791	703	641
	%	12.2	4.8	4.2	3.6	3.1	2.8
ABC/3TC/NVP	n	547	355	295	254	213	190
	%	3.0	1.7	1.4	1.1	0.9	0.8
TAF/FTC/RPV	n	7	956	990	951	918	876
	%	0.0	4.5	4.6	4.3	4.1	3.9
TDF/FTC/RPV	n	1,666	602	435	366	320	284
	%	9.2	2.8	2.0	1.7	1.4	1.3
Other NNRTI + NRTI	n	644	317	317	277	252	239
	%	3.5	1.5	1.5	1.3	1.1	1.1

Calendar year		2015	2020	2021	2022	2023	2024
PI + NRTI							
TDF/FTC/ATV/b	n	928	200	156	121	81	67
	%	5.1	0.9	0.7	0.5	0.4	0.3
TAF/FTC/DRV/b	n	2	1,250	1,269	1,271	1,283	1,288
	%	0.0	5.9	5.9	5.7	5.7	5.7
TDF/FTC/DRV/b	n	1,606	463	409	342	269	239
	%	8.8	2.2	1.9	1.5	1.2	1.1
TDF/FTC/LPV/b	n	130	21	17	11	6	5
	%	0.7	0.1	0.1	0.0	0.0	0.0
Other PI + NRTI	n	773	315	239	189	163	140
	%	4.3	1.5	1.1	0.9	0.7	0.6
2 anchor-drugs							
DTG/DRV/b	n	115	348	357	372	382	388
	%	0.6	1.6	1.6	1.7	1.7	1.7
DTG/RPV	n	6	114	130	139	147	152
	%	0.0	0.5	0.6	0.6	0.7	0.7
CAB/RPV injectables *	n	.	36	71	496	721	781
	%	.	0.2	0.3	2.2	3.2	3.4
2 anchor-drugs w/wo NRTI	n	593	430	427	389	375	361
	%	3.3	2.0	2.0	1.8	1.7	1.6
Other ART	n	738	387	350	332	313	297
	%	4.1	1.8	1.6	1.5	1.4	1.3

Legend: *3TC = lamivudine; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; ABC = abacavir; ART = antiretroviral therapy; ATV = atazanavir; BIC = bictegravir; CAB = cabotegravir; 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 22,698 individuals in HIV care and on ART in 2024, the vast majority (87.8%) received a regimen based on one or two NRTIs, combined with either (*Figure 4.5A*) an integrase inhibitor (INSTI) (57.5%), a non-nucleoside reverse transcriptase inhibitor (NNRTI) (25.5%), or a protease inhibitor (PI) (7.9%).

The proportion of individuals who had (temporarily) interrupted ART at the end of the calendar year, decreased from 2.5% in 2015 to 0.7% in 2024. In a later section in this chapter more details are shown about the number, reasons, duration and outcome of these treatment interruptions.

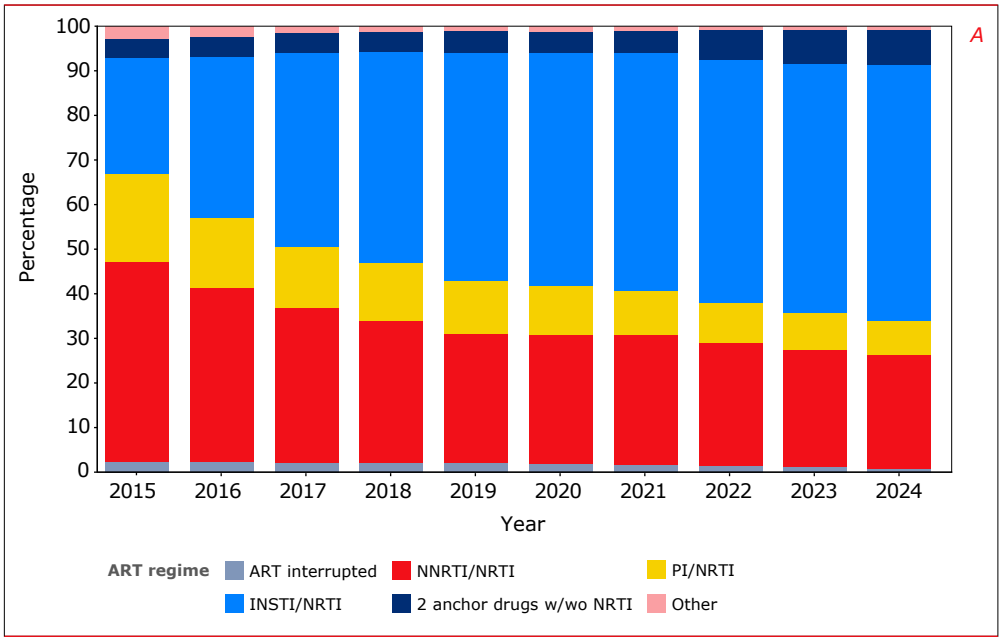
The changes over time in the distribution of specific ART regimens among the population in care in 2015-2024 is presented in *Figure 4.5B* and *4.7* and in *Table 4.3*. The most frequently used regimens in 2024 (used by at least 5% of the population) were:

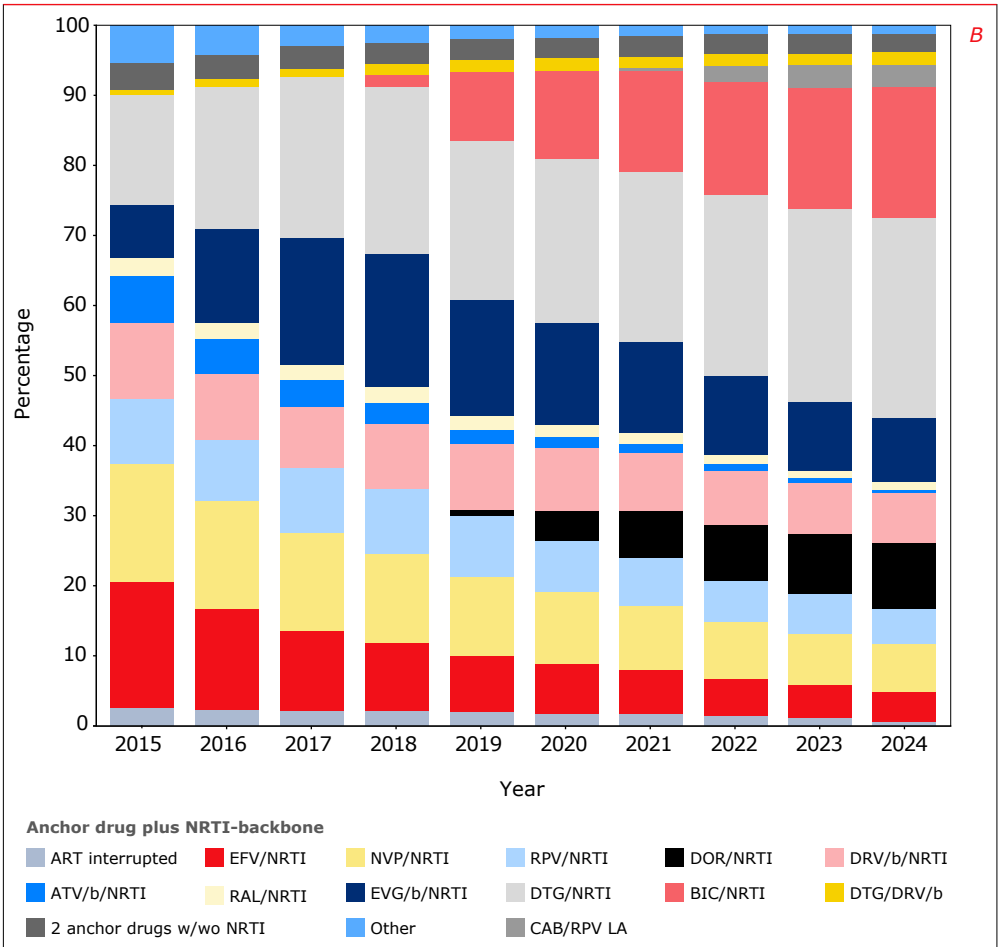
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/bictegravir (BIC) (18.7%);
- dolutegravir (DTG)/lamivudine (3TC) (15.3%);
- tenofovir disoproxil fumarate (TDF)/lamivudine (3TC)/doravirine (DOR) (8.8%);
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/elvitegravir (EVG)/cobicistat (7.5%);
- abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (6.1%); and
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/darunavir (DRV)/cobicistat (5.7%)

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 ABC. 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 2024, 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 7.8%. The most common of these regimens were a combination of cabotegravir/rilpivirine injectables (3.4%), dolutegravir/darunavir/cobicistat (1.7%), and dolutegravir/rilpivirine (0.7%).

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 2015-2024.

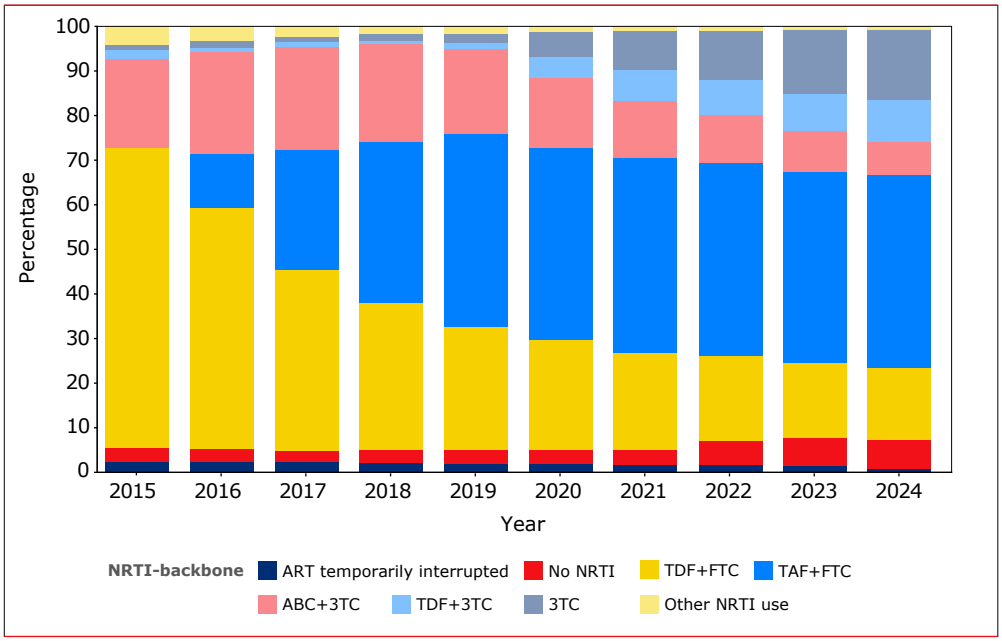




Legend: *ART = antiretroviral therapy; b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; BIC = bictegravir; CAB = cabotegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; INSTI = integrase inhibitor; NRTI = nucleoside analogue reverse transcriptase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

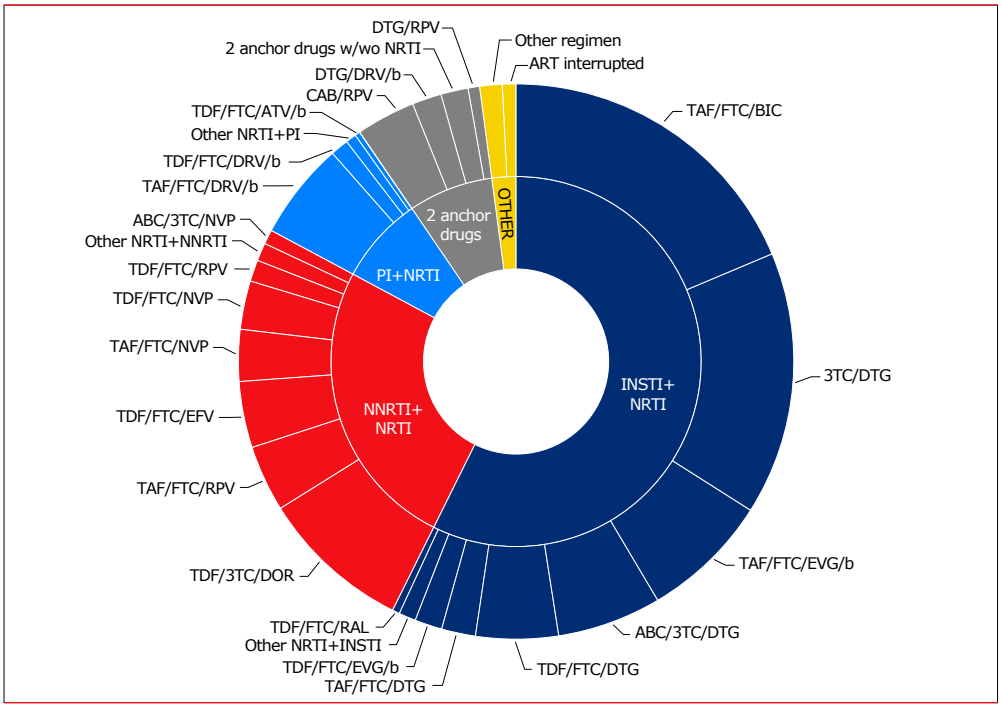
Figure 4.6 provides an overview of the NRTI backbone components of the current ART regimens used in 2015-2024. The combination of tenofovir disoproxil fumarate (TDF) or alafenamide (TAF) with emtricitabine (FTC) was the predominant backbone used, being part of 67.4% of the regimen used in 2015, and slowly declining to 59.2% in 2024. Following its introduction at the end of 2015, use of TAF in ART regimens rapidly increased to about 43% of all regimens used since 2019 and has since remained stable at that level. At the same time, TDF use decreased from 70.7% of all regimens used in 2015 to 29.8% in 2019, after which TDF use slowly continued to decrease to 25.9% in 2024. ABC was used in 21.0% of all regimens in 2015. Following the introduction of the fixed dose combination ABC/3TC/DTG its use increased to 23.6% in 2017, after which its use slowly decreased to 7.8% of all regimens used in 2024.

Figure 4.6: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the current regimen in 2015–2024.*



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

Figure 4.7: Antiretroviral therapy use in 2024.



Legend: *3TC = lamivudine; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; ABC = abacavir; ART = antiretroviral therapy; ATV = atazanavir; BIC = bictegravir; 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 26,519 individuals who were on ART between January 2015 and December 2024, 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.

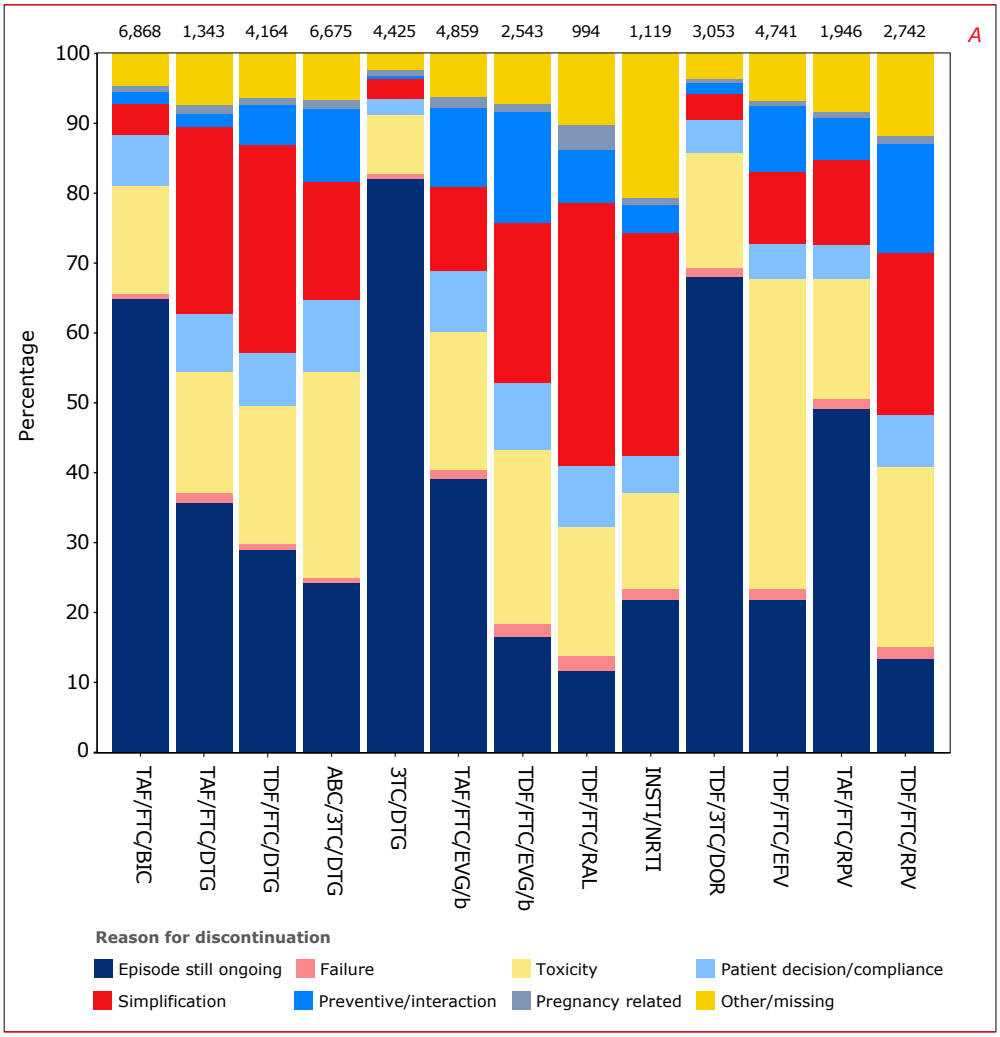
Modification of ART was defined as a change in, or discontinuation of, one or more of the drugs included in the regimen. Simplification to a fixed-drug combination formulation containing the same antiretroviral agents (in the same dose) was not considered a modification of the regimen. Likewise, the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

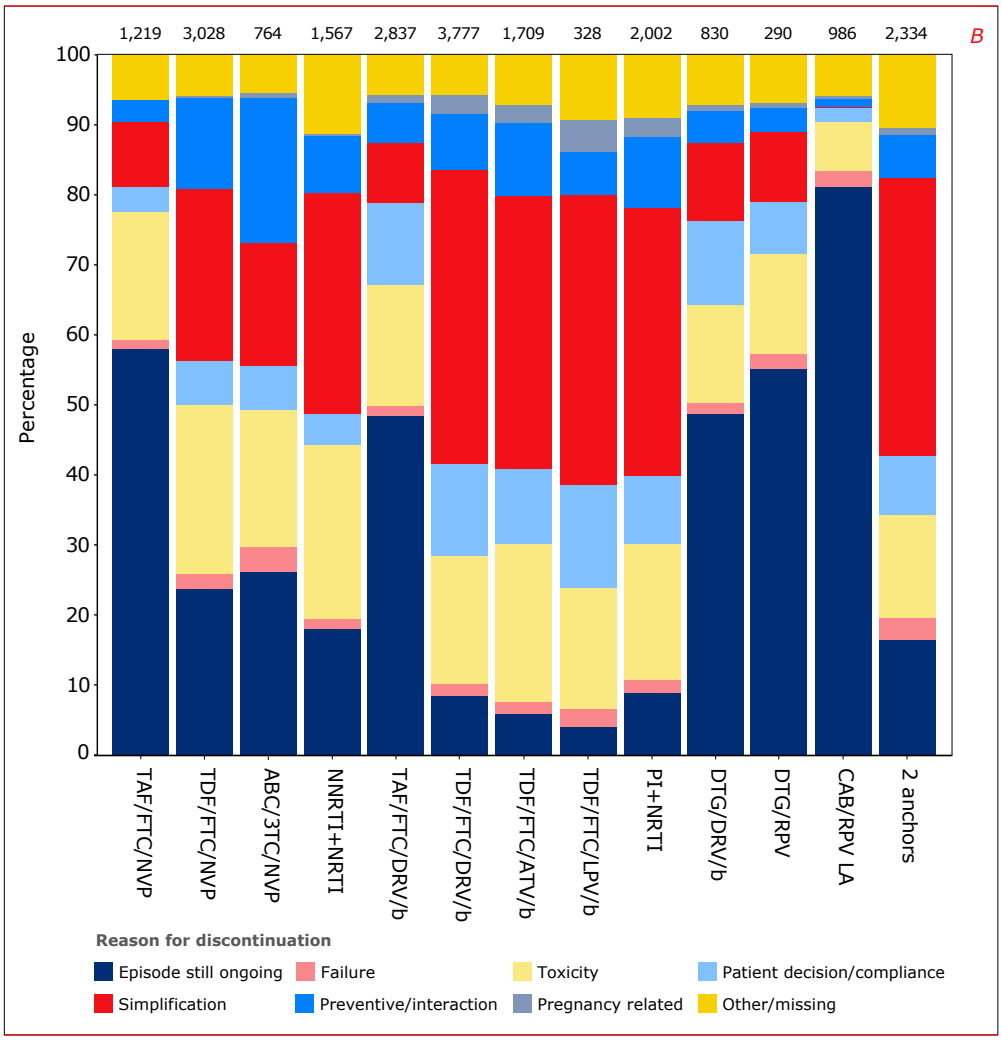
expensive) single tablet regimen (STR) into separately formulated (cheaper) generic components of the original STR, was also not considered a modification. A switch from one pharmacological booster to another was also ignored. We also ignored treatment interruptions that lasted less than 14 days. Whenever 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 regimen, the cumulative persons years of exposure to that 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 2015 to 2024, the cohort of 26,519 individuals on ART accrued a total of 193,960 person years of follow-up, during which a total of 76,730 ART regimen episodes were registered. At the end of the follow-up period in 2024 (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), 32.1% of these regimen episodes were still in use, and 67.9% of the regimen episodes had ended in a regimen modification. The most common reasons for regimen modification were: toxicity (18.8%), treatment simplification (17.2%), patient decision/compliance (7.1%), and preventive modifications (6.7%). In only 1,128 (1.5%) 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, (further) 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 2015-2024, the overall rate of regimen changes was 236.3 modifications per 1,000 person years of follow-up. This rate peaked in 2016 at 340.3 modifications per 1,000 person years, after which the rate continuously decreased to 206.7 in 2022, 174.2 in 2023, and 125.0 in 2024 (*Figure 4.9*).

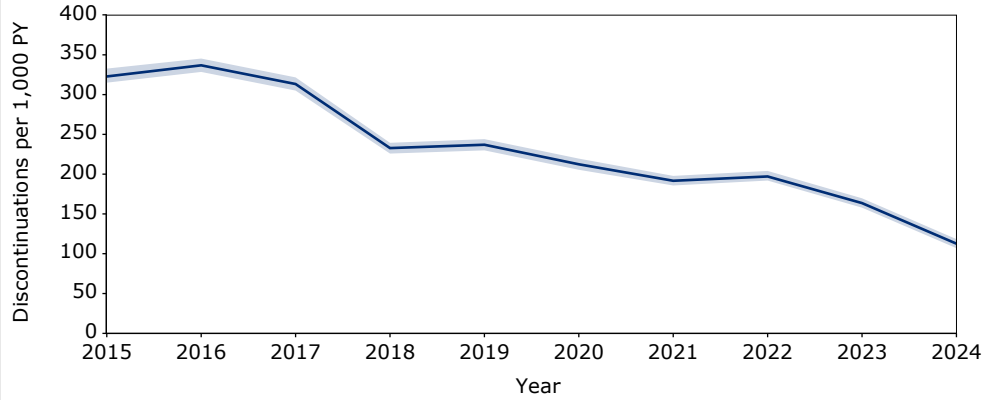
Figure 4.8A&B: Reasons for discontinuation / modification of antiretroviral therapy (ART) used in 2015-2024. The number at the top of each bar represent the total number of treatment episodes with that particular ART regimen.





Legend: *3TC = lamivudine; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; ABC = abacavir; ATV = atazanavir; ART = antiretroviral therapy; BIC = bictegravir; 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 2015–2024.



Legend: Blue band represents the 95% confidence interval.

Table 4.4: *Exposure to various ART regimen and reasons for discontinuation / modification in the period 2015–2024.*

	Person years exposure	Total ART episodes	Reasons for discontinuation / modification			
			Episode still ongoing		Failure	
	PY	n	n	%	n	%
Total dataset	193960	76730	24647	32.1	1128	1.5
INSTI + NRTI						
TAF/FTC/BIC	16776	6868	4441	64.7	56	0.8
TAF/FTC/DTG	3760	1343	477	35.5	21	1.6
TDF/FTC/DTG	7059	4164	1198	28.8	44	1.1
ABC/3TC/DTG	22786	6675	1602	24	66	1
DTG/3TC	9783	4425	3624	81.9	41	0.9
TAF/FTC/EVG/b	18727	4859	1889	38.9	71	1.5
TDF/FTC/EVG/b	7001	2543	422	16.6	43	1.7
TDF/FTC/RAL	1959	994	115	11.6	22	2.2
Other INSTI+NRTI	2070	1119	243	21.7	18	1.6
NNRTI + NRTI						
TDF/3TC/DOR	6619	3053	2074	67.9	39	1.3
TDF/FTC/EFV	16912	4741	1028	21.7	76	1.6
TAF/FTC/NVP	5027	1219	706	57.9	17	1.4
TDF/FTC/NVP	12403	3028	718	23.7	66	2.2
ABC/3TC/NVP	3618	764	199	26	28	3.7
TAF/FTC/RPV	7043	1946	955	49.1	27	1.4
TDF/FTC/RPV	8114	2742	365	13.3	51	1.9
Other NNRTI+NRTI	3676	1567	282	18	24	1.5
PI + NRTI						
TDF/FTC/ATV/b	3742	1709	101	5.9	33	1.9
TAF/FTC/DRV/b	7832	2837	1374	48.4	40	1.4
TDF/FTC/DRV/b	7388	3777	319	8.4	71	1.9
TDF/FTC/LPV/b	448	328	13	4	9	2.7
Other PI+NRTI	4131	2002	180	9	35	1.7
2 anchor-drugs						
DTG/DRV/b	2600	830	404	48.7	13	1.6
DTG/RPV	700	290	160	55.2	6	2.1
CAB/RPV injectables	1636	986	800	81.1	22	2.2
2 anchor-drugs w/wo NRTI	4293	2334	382	16.4	81	3.5
Other ART	4324	2346	317	13.5	107	4.6

Legend: *3TC = lamivudine; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; ABC = abacavir; ART = antiretroviral therapy; ATV = atazanavir; BIC = bictegravir; CAB = cabotegravir; 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.*

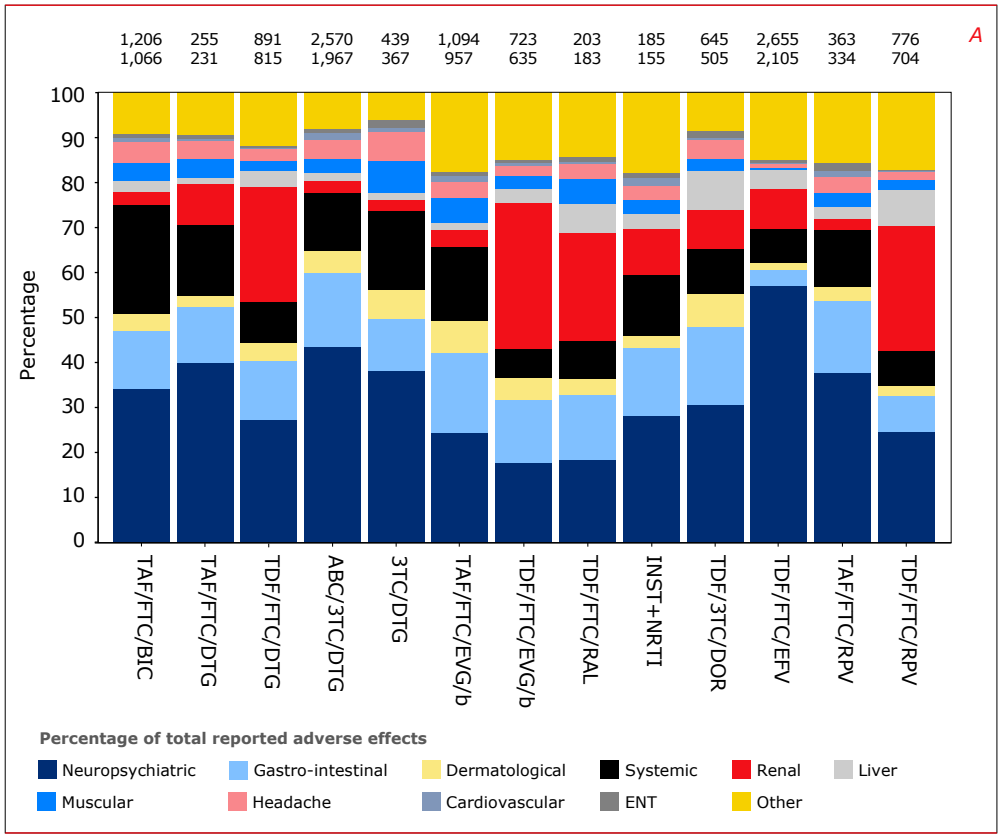
Reasons for discontinuation / modification

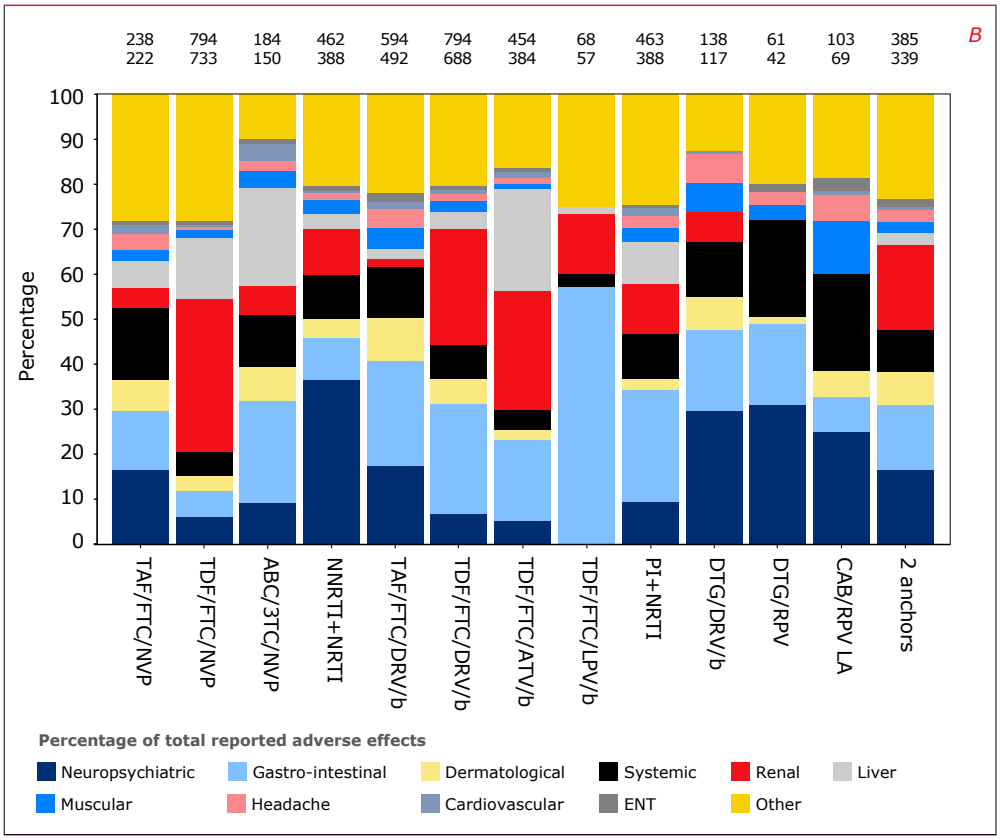
	Toxicity		Patient decision/ compliance		Simplification		Preventive/ interaction		Pregnancy related		Missing / Other reasons	
n	%	n	%	n	%	n	%	n	%	n	%
14428	18.8	5421	7.1	13218	17.2	5111	6.7	796	1	11981	15.6
1066	15.5	509	7.4	300	4.4	120	1.7	57	0.8	319	4.6
231	17.2	113	8.4	359	26.7	27	2	17	1.3	98	7.3
815	19.6	320	7.7	1238	29.7	246	5.9	38	0.9	265	6.4
1967	29.5	685	10.3	1133	17	685	10.3	90	1.3	447	6.7
367	8.3	106	2.4	127	2.9	21	0.5	27	0.6	112	2.5
957	19.7	433	8.9	579	11.9	552	11.4	70	1.4	308	6.3
635	25	242	9.5	583	22.9	405	15.9	25	1	188	7.4
183	18.4	88	8.9	373	37.5	77	7.7	34	3.4	102	10.3
155	13.9	59	5.3	356	31.8	46	4.1	11	1	231	20.6
505	16.5	149	4.9	112	3.7	44	1.4	16	0.5	114	3.7
2105	44.4	239	5	485	10.2	451	9.5	26	0.5	331	7
222	18.2	46	3.8	111	9.1	38	3.1	1	0.1	78	6.4
733	24.2	191	6.3	741	24.5	393	13	11	0.4	175	5.8
150	19.6	49	6.4	134	17.5	156	20.4	5	0.7	43	5.6
334	17.2	98	5	236	12.1	118	6.1	14	0.7	164	8.4
704	25.7	202	7.4	638	23.3	422	15.4	34	1.2	326	11.9
388	24.8	72	4.6	493	31.5	124	7.9	10	0.6	174	11.1
384	22.5	182	10.6	667	39	173	10.1	47	2.8	122	7.1
492	17.3	334	11.8	241	8.5	153	5.4	45	1.6	158	5.6
688	18.2	492	13	1590	42.1	303	8	96	2.5	218	5.8
57	17.4	48	14.6	135	41.2	21	6.4	15	4.6	30	9.1
388	19.4	194	9.7	769	38.4	200	10	59	2.9	177	8.8
117	14.1	100	12	92	11.1	38	4.6	5	0.6	61	7.3
42	14.5	21	7.2	29	10	10	3.4	2	0.7	20	6.9
69	7	20	2	2	0.2	12	1.2	2	0.2	59	6
339	14.5	195	8.4	926	39.7	144	6.2	25	1.1	242	10.4
334	14.2	225	9.6	759	32.4	131	5.6	13	0.6	460	19.6

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 regularly, 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 regimens.

For the 14,428 toxicity-driven regimen modifications, 16,743 adverse effects were recorded. The predominant adverse effects were: neuropsychiatric (mainly insomnia, mood changes, dizziness, and depression) 31.2%; gastrointestinal (mainly diarrhoea and nausea) 13.7%; renal (renal insufficiency and increased serum creatinine) 12.3%; systemic (tiredness, apathy, loss of appetite, weight gain) 11.2%; liver (increased transaminases) 4.8%; 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 2015–2024. 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; ART = antiretroviral therapy; BIC = bictegravir; 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 period 2015-2024, 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 2.1% in 2015 to 0.7% in 2024 (see *Figure 4.11* from the next section on *Virological response*).

During the period 2015-2024, the cohort of 26,519 individuals accrued a total of 193,960 person years of follow-up, in which a total of 76,730 ART regimens were used. In 2,536 individuals a total of 4,176 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 interrupted their ART (74.1%), with their treating physicians becoming aware of the interruption only during the next clinic visit. 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 actively decided to interrupt ART, or thirdly if the interruption was decided on by their treating physician. A further 12.5% of interruptions had ART-associated toxicity as the recorded reason, and 0.8% of interruptions were pregnancy-related.
The median duration of the recorded treatment interruptions was 12.7 (IQR 4.7-31.7) weeks. During many of the longer treatment interruptions the majority of these individuals were effectively temporarily disengaged from care (i.e. they had no visits to the HIV outpatient clinic for more than 6 months). In 65.6% 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=2,088). In 1,018 of these 2,088 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 280 to 720, cells/mm^3). And in 1,253 episodes there was a CD4 count measured during (and at least 60 days after the start of) the treatment interruption (median 320, IQR 133 to 521 cells/mm^3). For 646 treatment interruptions of more than 90 days, a pre-interruption CD4 count was available and also a CD4 count that had been measured during the interruption. During these 646 interruptions the median change in the CD4 count was -120 (IQR -20 to -440) 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 9.4, IQR 3.1-9.7 weeks, in 4 of these 5 episodes one or more viral loads were measured during or shortly after the treatment interruption, in all 4 episodes viremia was detectable with a range from 42 to 1079 copies/ml), and women who interrupted ART after the pregnancy had ended (n=28, median duration of interruption 92, IQR 59-191 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 2015–2024.*

	Duration of interruption (weeks)			Patients	Total episodes
	Median	Q1	Q3	n	n
Total dataset	12.7	4.7	31.7	2536	4176
INSTI + NRTI					
TAF/FTC/BIC	11.3	4.4	30.4	339	450
TAF/FTC/DTG	16.3	5.0	44.1	65	83
TDF/FTC/DTG	12.8	4.4	32.6	177	234
ABC/3TC/DTG	15.1	5.1	36.7	417	580
DTG/3TC	9.7	4.3	21.6	59	67
TAF/FTC/EVG/b	12.3	4.9	30.1	257	337
TDF/FTC/EVG/b	15.6	6.9	33.7	127	188
TDF/FTC/RAL	10.0	4.3	31.7	53	62
Other INSTI+NRTI	7.9	4.3	17.6	40	46
NNRTI + NRTI					
TDF/3TC/DOR	10.0	4.4	26.0	99	119
TDF/FTC/EFV	13.1	4.7	32.7	165	198
TAF/FTC/NVP	12.9	6.0	25.3	28	31
TDF/FTC/NVP	13.9	5.3	45.0	105	126
ABC/3TC/NVP	8.0	4.9	20.7	28	37
TAF/FTC/RPV	7.9	4.3	19.0	63	85
TDF/FTC/RPV	11.6	4.7	36.9	126	145
Other NNRTI+NRTI	9.0	5.4	25.9	51	59
PI + NRTI					
TDF/FTC/ATV/b	15.2	5.2	40.7	106	136
TAF/FTC/DRV/b	12.6	4.7	30.7	189	283
TDF/FTC/DRV/b	13.1	5.0	37.2	270	348
TDF/FTC/LPV/b	21.6	8.6	34.7	22	29
Other PI+NRTI	13.3	4.4	35.7	110	154
2 anchor-drugs					
DTG/DRV/b	10.8	5.0	25.3	55	66
DTG/RPV	16.0	3.9	24.1	12	17
CAB/RPV injectables	7.1	4.3	10.7	13	13
2 anchor-drugs w/wo NRTI	16.9	5.7	31.7	84	121
Other ART	8.2	4.4	24.6	116	148

Legend: *3TC = lamivudine; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; ABC = abacavir; ATV = atazanavir; ART = antiretroviral therapy; BIC = bictegravir; CAB = cabotegravir; 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	%	%
	56	1.3	520	12.5	3093	74.1	34	0.8	473	11.3	65.6
	2	0.4	48	10.7	344	76.4	.	.	56	12.4	79.6
	1	1.2	9	10.8	66	79.5	.	.	7	8.4	68.7
	1	0.4	29	12.4	178	76.1	4	1.7	22	9.4	76.1
	2	0.3	87	15.0	421	72.6	.	.	70	12.1	67.8
	.	.	14	20.9	42	62.7	1	1.5	10	14.9	62.7
	6	1.8	53	15.7	242	71.8	.	.	36	10.7	64.7
	4	2.1	19	10.1	146	77.7	1	0.5	18	9.6	61.2
	4	6.5	11	17.7	36	58.1	3	4.8	8	12.9	46.8
	.	.	6	13.0	27	58.7	.	.	13	28.3	47.8
	4	3.4	17	14.3	83	69.7	.	.	15	12.6	67.2
	5	2.5	21	10.6	138	69.7	1	0.5	33	16.7	51.0
	.	.	3	9.7	23	74.2	.	.	5	16.1	54.8
	2	1.6	9	7.1	103	81.7	2	1.6	10	7.9	51.6
	3	8.1	5	13.5	25	67.6	.	.	4	10.8	67.6
	2	2.4	17	20.0	52	61.2	.	.	14	16.5	70.6
	4	2.8	18	12.4	107	73.8	.	.	16	11.0	54.5
	3	5.1	9	15.3	33	55.9	2	3.4	12	20.3	55.9
	.	.	15	11.0	108	79.4	3	2.2	10	7.4	53.7
	2	0.7	34	12.0	218	77.0	.	.	29	10.2	77.4
	2	0.6	35	10.1	283	81.3	5	1.4	23	6.6	57.8
	1	3.4	2	6.9	24	82.8	1	3.4	1	3.4	58.6
	.	.	21	13.6	109	70.8	9	5.8	15	9.7	66.9
	.	.	3	4.5	57	86.4	.	.	6	9.1	84.8
	1	5.9	2	11.8	13	76.5	.	.	1	5.9	70.6
	.	.	4	30.8	4	30.8	.	.	5	38.5	46.2
	3	2.5	7	5.8	98	81.0	.	.	13	10.7	78.5
	4	2.7	22	14.9	105	70.9	1	0.7	16	10.8	56.1

Virological response

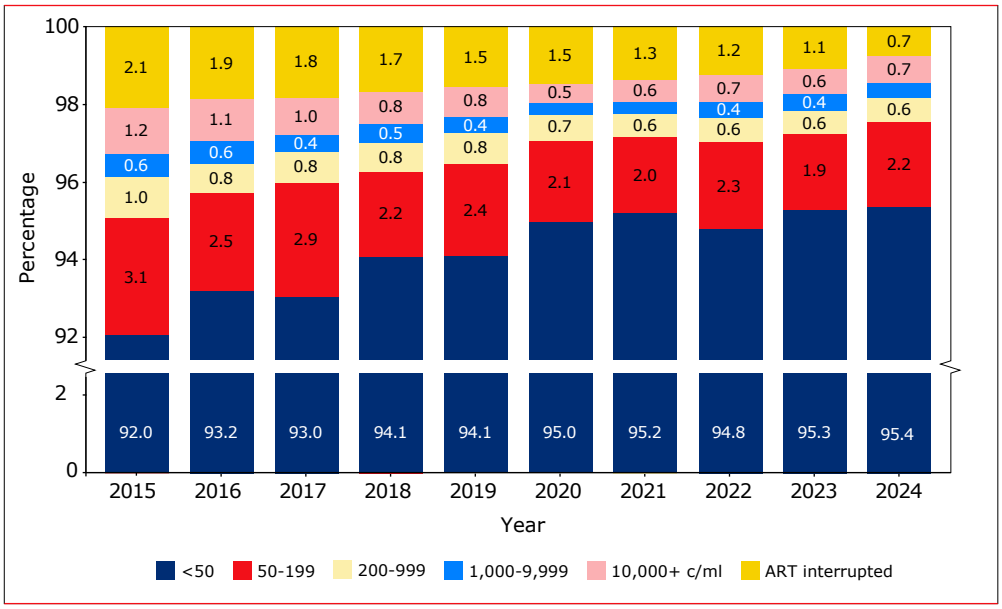
The study population for the analyses in this section consisted of all individuals on ART for more than 6 months who were in care during (part of) the period 2015-2024. For each calendar year between 2015 and 2024 we selected the last measured plasma HIV-RNA load measured in the 24 months prior to 31 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" below 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 (see Box 4.3). 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 last 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 92.0% in 2015 (95.1% <200 copies/ml) to 95.4% (97.5% <200 copies/ml) in 2024. Likewise, all viral load categories higher than 50 copies/ml, decreased slowly over time (the number of analysed viral load measurements and more precise percentages are shown in *Appendix Table 4.2*).

Quantifiable viral loads between 50-199 copies/ml are frequently observed. 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 23,211 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 2015-2024. Of all individuals on ART, 75.4% did not have 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 4.9% this proportion was between >10% and 20% of all viral load measurements. And in 2.8% of all individuals there was evidence of sustained low-level viremia with more than 20% of all their 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 2015-2024.



Box 4.3: Definitions of virological response.

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.

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 2015-2024.
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 have very limited data on adherence. Nevertheless, the maximum viral load measured during

episodes of loss of viral control is much higher (4.5 log10 copies/ml) in those individuals who were known to have discontinued ART compared to individuals who indicated to still use ART (3.0 log10 copies/ml).

A total of 26,449 individuals contributed 199,650 person years of follow-up during the period 2015-2024 (*Table 4.6*). In 4,262 individuals there were 6,827 episodes of loss of viral suppression: in 1,652 individuals there were 2,119 episodes of the loss of viral suppression during a treatment interruption, and in 3,206 individuals there were 4,708 episodes while the subject was continuing the use of ART.

The duration of loss of viral suppression during treatment interruption was less than 0.5 years in 80.4% (n=1,704) of episodes, 6.7% (n=142) lasted between 0.5 and <1.0 years, and 12.9% (n=273) lasted more than 1 year. At the end of the follow-up period investigated, 89.6% (n=1,898) of these episodes had resolved after restarting ART (with the same or a different ART regimen), while 7.8% (n=165) of these episodes were still ongoing, and 2.6% (n=56) of these episodes ended in death, with advanced HIV / AIDS-defining conditions as the predominant cause of death in 39.3% (n=22) 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 6 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.

The large majority (72.3%) of 4,708 episodes of loss of viral suppression that occurred while ART was assessed to have 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, 4.8% lasted between 0.5 and <1.0 years, and 5.4% lasted more than 1 year. In total, 92.4% of episodes had been resolved at the end of the end of follow-up, in 72.1% of episodes without a modification of the used ART regimen, and 20.3% resolved after a regimen modification. 6.5% of episodes were still ongoing at the end of follow-up, and 1.2% (n=56) of these episodes ended in death, again with death because of an advanced-HIV / AIDS-defining condition as the predominant (33.9%, n=19) 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.

Table 4.6: Occurrence of loss of viral suppression during 2015–2024 in individuals on ART for more than 6 months.

	All		MSM + TG		Other men		Women	
Total cohort on ART								
N of subjects	26,449		16,724		4,973		4,752	
PY of follow-up	199,650		128,175		35,102		36,372	
Subjects with failure	4,262		2,080		1,031		1,153	
N of episodes of failure	6,827		2,990		1,721		2,116	
Loss of viral suppression because of ART interruption								
N of subjects	1,652		758		392		502	
N of episodes	2,119		953		509		657	
Duration of failure, n/%								
Single VL measurement	1265	59.7	564	59.2	319	62.7	382	58.1
<0.5 year	439	20.7	202	21.2	119	23.4	118	18.0
0.5 – <1 year	142	6.7	68	7.1	22	4.3	52	7.9
1 – <2 years	129	6.1	57	6.0	29	5.7	43	6.5
2+ years	144	6.8	62	6.5	20	3.9	62	9.4
Highest viral load, log10 median	4.5		4.5		4.7		4.4	
Q1–Q3	3.8–5.2		3.9–5.2		4.0–5.3		3.6–5.0	
Outcome, n/%								
Ongoing	165	7.8	76	8.0	41	8.1	48	7.3
Restarted, resolved	1898	89.6	852	89.4	449	88.2	597	90.9
Died while still off ART	56	2.6	25	2.6	19	3.7	12	1.8
Cause of death, n / %								
Advanced HIV / AIDS	22	39.3	9	36.0	8	42.1	5	41.7
Non-AIDS malignancies	7	12.5	2	8.0	3	15.8	2	16.7
Cardiovascular disease	3	5.4	2	8.0	1	5.3	.	.
Non-AIDS infection	1	1.8	.	.	1	5.3	.	.
Liver disease	3	5.4	1	4.0	2	10.5	.	.
Lung disease	6	10.7	2	8.0	2	10.5	2	16.7
Non-natural death	1	1.8	1	4.0	.	.	.	.
Alcohol and substance use	3	5.4	2	8.0	.	.	1	8.3
Other causes	2	3.6	1	4.0	1	5.3	.	.
Unknown	6	10.7	4	16.0	.	.	2	16.7
Sudden death	2	3.6	1	4.0	1	5.3	.	.

	All		MSM + TG		Other men		Women	
Loss of viral suppression while on ART								
N of subjects	3,206		1,542		798		866	
N of episodes	4,708		2,037		1,212		1,459	
Duration, n/%								
Single VL measurement	3406	72.3	1514	74.3	871	71.9	1021	70.0
<0.5 year	822	17.5	345	16.9	215	17.7	262	18.0
0.5 – 1 year	225	4.8	88	4.3	52	4.3	85	5.8
1 – 2 years	138	2.9	51	2.5	42	3.5	45	3.1
2+ years	117	2.5	39	1.9	32	2.6	46	3.2
Highest viral load during episode,	3.0		2.8		3.0		3.2	
median, Q1-Q3	2.5-3.9		2.5-3.6		2.6-4.1		2.6-4.1	
Outcome, n/%								
Resolved, no switch	3395	72.1	1502	73.7	870	71.8	1023	70.1
Ongoing, no switch	257	5.5	124	6.1	77	6.4	56	3.8
Resolved, switched	955	20.3	377	18.5	237	19.6	341	23.4
Ongoing, switched	45	1.0	16	0.8	9	0.7	20	1.4
Died, no switch	31	0.7	9	0.4	9	0.7	13	0.9
Died, switched	25	0.5	9	0.4	10	0.8	6	0.4
Cause of death, n/%								
Advanced HIV / AIDS	19	33.9	6	33.3	7	36.8	6	31.6
Non-AIDS malignancies	11	19.6	2	11.1	4	21.1	5	26.3
Cardiovascular disease	2	3.6	.	.	.	.	2	10.5
Non-AIDS infection	3	5.4	2	11.1	.	.	1	5.3
Liver disease	.	.	.	.	.	.	.	.
Lung disease	.	.	.	.	.	.	.	.
Non-natural death	1	1.8	.	.	1	5.3	.	.
Alcohol and substance use	2	3.6	1	5.6	.	.	1	5.3
Other causes	2	3.6	1	5.6	1	5.3	.	.
Unknown	7	12.5	3	16.7	3	15.8	1	5.3

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

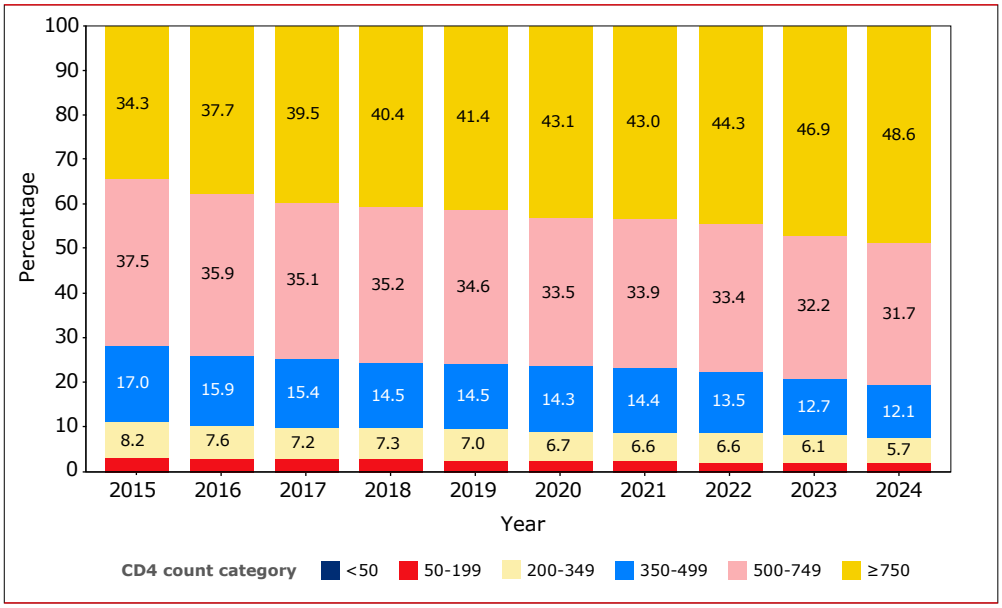
Immunological response

After initiation of ART, most people get durably suppressed 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[18,19]. 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[20]. Median CD4 counts in men without HIV are on average approximately 830 cells/mm^3 and around 1,000 cells/mm^3 in women, but this varies according to factors such as age, ethnicity, and smoking behaviour[21,22]. The level of recovery of the immune system is strongly correlated to the risk for adverse health outcomes, i.e. morbidity and mortality because of AIDS-defining and other clinical events (also see *Chapter 5*)[23-27].

Immunological response by calendar year

Of all individuals who were on ART in the period 2015-2024, CD4 count data are shown in *figures 4.12*. The percentage of individuals on ART with a normalised CD4 count (i.e. with a CD4 count over 500 cells/mm^3) increased from 72.8% in 2015 to 80.3% in 2024. The percentage of individuals on ART with CD4 counts below 350 cells/mm^3 slowly continued to decrease from 11.2% in 2015 to 7.5% in 2024. 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 4.12: 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 (2015–2020)

The distribution of pre-ART CD4 counts in ART-naïve individuals initiating first-line ART has remained fairly constant in the period between 2015 and 2024 (*Figure 4.13*). In 2024, 24.6% of individuals initiating ART had a CD4 count below 200 cells/mm^3, and another 18.6% had a CD4 count between 200 and <350 cells/mm^3. This distribution closely resembles the CD4 counts at HIV diagnosis (see Chapter 1).

We also assessed the immunological response in individuals who started first-line ART between in 2015-2019 to allow for a potential duration of follow-up of 5 years. The level of viral suppression after initiating ART were not taken into account in this analysis, but are generally very high. Nor were temporary treatment interruptions taken into account. The changes in the CD4 count distribution following ART initiation are visualized in *Figure 4.14A*. Whereas at the initiation of ART 24.7% of individuals had a CD4 count below 200 cells/mm^3 and 18.0% had a CD4 count between 200 and <350 cells/mm^3, these proportions had decreased after 5 years of ART to 1.6% with a CD4 count below 200 cells/mm^3 and 6.1% 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 4.14B* 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 10.5% of individuals who initiate ART with a CD4 below 50 remain below 200 after 5 years of ART, and only 3.0% 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 4.13: *The pre-ART CD4 count in ART-naïve individuals initiating first-line ART by calendar year (missing measurements/data were not taken into account).*

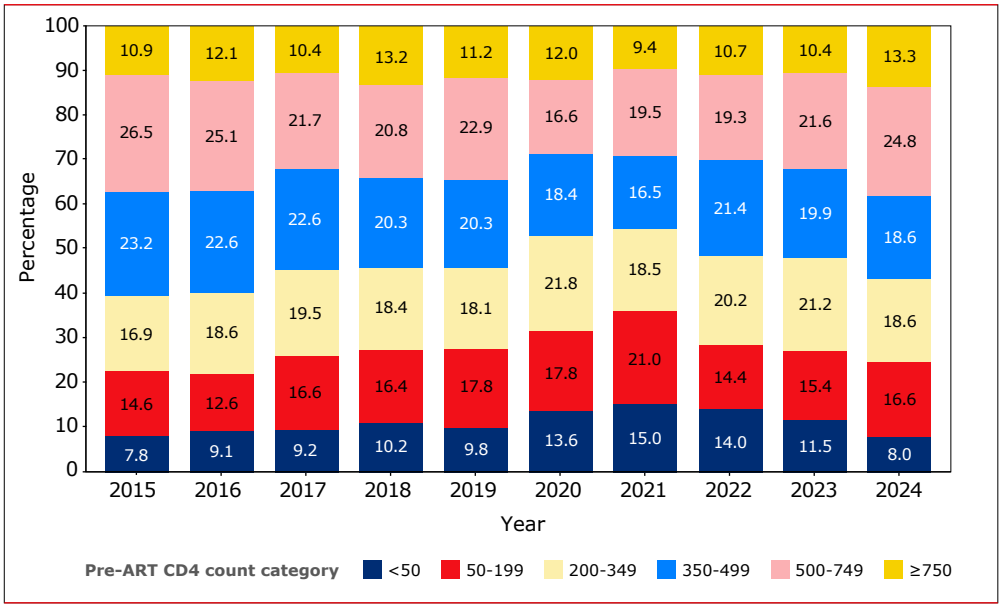
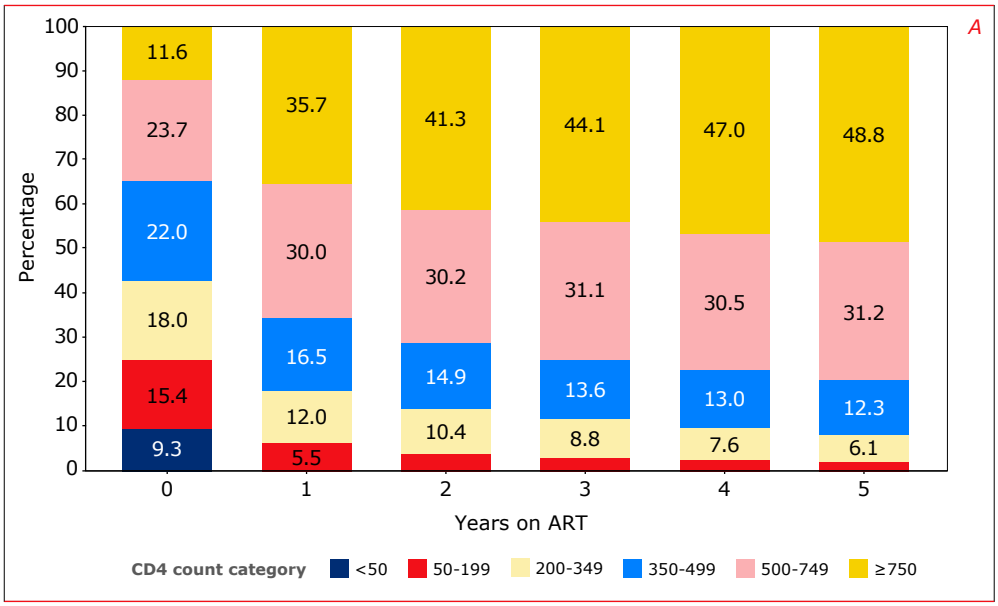


Figure 4.14A&B: *Changes in CD4 count distribution over 5 years following the start of antiretroviral therapy (ART) in 2015–2019 (A) and stratified for the last measured CD4 count prior to start of ART (B).*



B

CD4 count category

	<50					
750+		0.5	2.1	3.0	5.2	9.1
500-749		4.7	11.1	18.3	19.4	22.1
350-499		16.6	26.6	26.9	30.3	27.3
200-349		40.3	38.5	36.0	32.8	30.9
50-199		35.3	20.6	15.1	11.5	9.9
<50	100	2.6	1.1	0.8	0.8	0.6

	50-199					
750+		2.3	5.3	7.2	9.8	12.2
500-749		16.3	23.4	28.9	32.6	34.4
350-499		30.2	31.7	31.9	31.1	33.6
200-349		36.8	33.1	26.6	22.8	16.8
50-199	100	13.9	6.2	4.9	3.3	2.7
<50		0.5	0.3	0.5	0.3	0.3

	200-349					
750+		13.6	20.9	23.5	29.0	33.9
500-749		41.7	45.5	48.7	47.2	46.3
350-499		31.3	23.6	20.4	18.4	16.0
200-349	100	13.2	9.4	7.0	4.8	3.4
50-199		0.3	0.5	0.3	0.5	0.4
<50		0.0	0.0	0.1	0.0	0.0

	350-499					
750+		36.7	44.8	47.7	52.9	54.5
500-749		43.7	41.3	41.9	38.0	38.0
350-499	100	18.3	12.6	8.9	7.8	6.3
200-349		1.1	0.8	1.0	1.1	0.9
50-199		0.2	0.1	0.4	0.2	0.3
<50		0.0	0.4	0.1	0.0	0.0

	500-749					
750+		59.4	66.1	71.5	71.5	71.2
500-749	100	37.9	31.1	25.3	25.4	26.1
350-499		2.4	2.4	2.6	2.3	2.1
200-349		0.1	0.2	0.3	0.4	0.3
50-199		0.2	0.2	0.1	0.3	0.3
<50		0.0	0.0	0.1	0.1	0.0

	750+					
750+	100	91.9	92.6	91.0	92.6	90.8
500-749		7.1	6.6	8.2	6.6	8.1
350-499		0.2	0.4	0.6	0.6	0.8
200-349		0.2	0.2	0.2	0.2	0.2
50-199		0.4	0.2	0.0	0.0	0.0
<50		0.2	0.0	0.0	0.0	0.0

0 1 2 3 4 5 | 0 1 2 3 4 5

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 2015 and 2024, 7,069 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 16 (IQR 7-29) days in 2024.
- Between 2015 and 2021 there was a slowly decreasing trend in the CD4 count at ART initiation. However, since 2022 the CD4 count at the start of ART has risen slightly again. In 2024, 24.6% of individuals initiating ART had a CD4 count below 200 cells/mm^3, and another 18.6% 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 2024, 89.9% of initial regimens contained an integrase inhibitor. In 2024, the most frequently used initial regimens were TDF/FTC/dolutegravir (38.3%), TAF/FTC/bictegravir (37.5%), and TDF/3TC/doravirine (7.4%).

In care and receiving ART in 2024

- The number of people on ART and in active follow-up in the ATHENA cohort grew from 17,202 individuals in 2015 to 22,215 individuals in 2024.
- In 2024, the vast majority (87.8%) of individuals received a regimen based on one or two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with an integrase inhibitor (57.5%), a non-nucleoside reverse transcriptase inhibitor (25.5%) or a protease inhibitor (7.9%).
- Long-acting injectables (cabotegravir/rilpivirine) were used by 3.4%.
- The population had been diagnosed with HIV a median of 14.7 (IQR 8.9-21.0) years ago, and started their first-line ART regimen a median of 12.6 (IQR 8.0-18.5) years ago.
- Their last measured viral load was <50 copies/ml in 95.6% (<200 copies/ml in 98.0%), and 80.3% 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 (18.8%), treatment simplification (17.2%), patient decision/compliance (7.1%), and preventive modifications (6.7%). In only 1,128 (1.5%) regimen the reported reason for modification was virological treatment failure. The rate of ART regimen modifications continues to decrease over time from a peak of 340.3 modifications per 1,000 person years of follow-up in 2016 to 206.7 in 2022, 174.2 in 2023, and 125.0 in 2024.

- The proportion of the treated population that at any moment has temporarily interrupted ART continues to decrease, from 2.1% in 2015 to 0.7% in 2024, indicating the improved ease of use and tolerability of modern ART regimen.
- In 2,536 individuals a total of 4,176 treatment interruptions (of 14 days or longer) were recorded. The median duration of the recorded treatment interruptions was 12.7 (IQR 4.7-31.7) weeks. Many long interruptions constitute temporary disengagement from care. During longer treatment interruptions the CD4 counts often drops significantly, and is strongly associated with death due to advanced HIV/AIDS.

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Appendix

Appendix Table 4.1: *Frequency of and reasons for discontinuation / modification of various ART regimen in the period 2015–2024.*

				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	16776	6868	4441	56	3.3	1066	63.5
TAF/FTC/DTG	3760	1343	477	21	5.6	231	61.4
TDF/FTC/DTG	7059	4164	1198	44	6.2	815	115.4
ABC/3TC/DTG	22786	6675	1602	66	2.9	1967	86.3
DTG/3TC	9783	4425	3624	41	4.2	367	37.5
TAF/FTC/EVG/b	18727	4859	1889	71	3.8	957	51.1
TDF/FTC/EVG/b	7001	2543	422	43	6.1	635	90.7
TDF/FTC/RAL	1959	994	115	22	11.2	183	93.4
Other INSTI+NRTI	2070	1119	243	18	8.7	155	74.9
NNRTI + NRTI							
TDF/3TC/DOR	6619	3053	2074	39	5.9	505	76.3
TDF/FTC/EFV	16912	4741	1028	76	4.5	2105	124.5
TAF/FTC/NVP	5027	1219	706	17	3.4	222	44.2
TDF/FTC/NVP	12403	3028	718	66	5.3	733	59.1
ABC/3TC/NVP	3618	764	199	28	7.7	150	41.5
TAF/FTC/RPV	7043	1946	955	27	3.8	334	47.4
TDF/FTC/RPV	8114	2742	365	51	6.3	704	86.8
Other NNRTI+NRTI	3676	1567	282	24	6.5	388	105.5
PI + NRTI							
TDF/FTC/ATV/b	3742	1709	101	33	8.8	384	102.6
TAF/FTC/DRV/b	7832	2837	1374	40	5.1	492	62.8
TDF/FTC/DRV/b	7388	3777	319	71	9.6	688	93.1
TDF/FTC/LPV/b	448	328	13	9	20.1	57	127.1
Other PI+NRTI	4131	2002	180	35	8.5	388	93.9
2 anchor-drugs							
DTG/DRV/b	2600	830	404	13	5.0	117	45.0
DTG/RPV	700	290	160	6	8.6	42	60.0
CAB/RPV LA	1636	986	800	22	13.4	69	42.2
2 anchors w/wo NRTI	4293	2334	382	81	18.9	339	79.0

Legend: *PY = person years of exposure; 3TC = lamivudine; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; ABC = abacavir; ART = antiretroviral therapy; ATV = atazanavir; BIC = bictegravir; CAB = cabotegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; LA = long acting; 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)
509	30.3	300	17.9	120	7.2	57	3.4	319	19.0
113	30.1	359	95.5	27	7.2	17	4.5	98	26.1
320	45.3	1238	175.4	246	34.8	38	5.4	265	37.5
685	30.1	1133	49.7	685	30.1	90	3.9	447	19.6
106	10.8	127	13.0	21	2.1	27	2.8	112	11.4
433	23.1	579	30.9	552	29.5	70	3.7	308	16.4
242	34.6	583	83.3	405	57.8	25	3.6	188	26.9
88	44.9	373	190.4	77	39.3	34	17.4	102	52.1
59	28.5	356	171.9	46	22.2	11	5.3	231	111.6
149	22.5	112	16.9	44	6.6	16	2.4	114	17.2
239	14.1	485	28.7	451	26.7	26	1.5	331	19.6
46	9.2	111	22.1	38	7.6	1	0.2	78	15.5
191	15.4	741	59.7	393	31.7	11	0.9	175	14.1
49	13.5	134	37.0	156	43.1	5	1.4	43	11.9
98	13.9	236	33.5	118	16.8	14	2.0	164	23.3
202	24.9	638	78.6	422	52.0	34	4.2	326	40.2
72	19.6	493	134.1	124	33.7	10	2.7	174	47.3
182	48.6	667	178.3	173	46.2	47	12.6	122	32.6
334	42.6	241	30.8	153	19.5	45	5.7	158	20.2
492	66.6	1590	215.2	303	41.0	96	13.0	218	29.5
48	107.1	135	301.1	21	46.8	15	33.5	30	66.9
194	47.0	769	186.1	200	48.4	59	14.3	177	42.8
100	38.5	92	35.4	38	14.6	5	1.9	61	23.5
21	30.0	29	41.4	10	14.3	2	2.9	20	28.6
20	12.2	2	1.2	12	7.3	2	1.2	59	36.1
195	45.4	926	215.7	144	33.5	25	5.8	242	56.4

Appendix Table 4.2: *Virological treatment response in 2015–2024 in people who started ART at least months earlier.*

	Total population	Viral load categories (c/ml)											
			<50	50–199		200–999		1,000–9,999		10,000+		ART interrupted	
Calendar year	N	N	%	N	%	N	%	N	%	N	%	N	%
2015	17,935	16,504	92.02	550	3.07	188	1.05	107	0.60	212	1.18	374	2.09
2016	18,733	17,457	93.19	471	2.51	147	0.78	112	0.60	199	1.06	347	1.85
2017	19,425	18,074	93.05	571	2.94	155	0.80	81	0.42	187	0.96	357	1.84
2018	20,114	18,919	94.06	439	2.18	156	0.78	100	0.50	163	0.81	337	1.68
2019	20,728	19,499	94.07	499	2.41	162	0.78	89	0.43	160	0.77	319	1.54
2020	21,134	20,072	94.97	441	2.09	144	0.68	65	0.31	102	0.48	310	1.47
2021	21,358	20,329	95.18	418	1.96	135	0.63	59	0.28	130	0.61	287	1.34
2022	21,900	20,755	94.77	493	2.25	139	0.63	92	0.42	156	0.71	265	1.21
2023	22,353	21,301	95.29	435	1.95	136	0.61	91	0.41	145	0.65	245	1.10
2024	22,604	21,555	95.36	492	2.18	145	0.64	88	0.39	160	0.71	164	0.73

5. HIV drug resistance

Noga Shalev, Ard van Sighem, Ferdinand Wit, Annemarie Wensing, Jeroen van Kampen, Thijs van de Laar, Suzanne Jurriaans, Marc van der Valk

Key findings

Baseline drug resistance

- Between 2015 and 2024, 39% of individuals newly diagnosed with HIV in the Netherlands underwent baseline screening for HIV drug resistance. Clinically significant drug resistance was identified in 11.4%.
- The rate of baseline drug resistance increased from 5% in 2015 to 20% in 2024. This increase was largely driven by HIV-1 subtype A6 IN L74I resistance-associated polymorphism, impacting cabotegravir susceptibility only.
- To date, baseline drug resistance has had no observed impact on antiretroviral treatment response. We found no differences in rates of virological suppression between participants with and without baseline drug resistance.

Acquired drug resistance

- Of 24,028 participants in HIV care through 2024, 3,022 (12.6%) were tested for acquired HIV drug resistance. Clinically significant resistance was identified in 1,633 (6.8%) participants.
- Between 2000 and 2024, the proportion of sequences with clinically significant resistance associated mutations decreased from 78.1% to 31.1%.
- Resistance to newer treatment strategies, including second-generation integrase inhibitors and long-acting cabotegravir/rilpivirine, has been documented and requires future monitoring.
- Participants with a history of acquired drug resistance were less likely to be virologically suppressed at last observation than participants without a history of acquired drug resistance (92% vs 83%, respectively), attesting to the ongoing importance of adherence support.

Introduction

Monitoring for HIV drug resistance is integral to HIV surveillance and care. In this chapter, we describe trends in the prevalence of baseline and acquired HIV drug resistance in the Netherlands. In this year's report, we include participants who were alive and in care at year end 2024. For an analyses of HIV drug resistance in the ATHENA cohort since its inception, please refer to prior SHM monitoring reports.

We identified resistance-associated mutations [RAMs] using Stanford University's HIV Drug Resistance Database mutation analysis algorithm (version 9.5) [HIVdb] and the International Antiviral Society-USA HIV drug resistance mutation chart[1,2]. We used the HIVdb to calculate cumulative drug penalty scores for each antiretroviral agent, based on all RAMs identified in each sequence. We converted this score into a five-point drug resistance scale: susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance. We designated all intermediate- and high-level resistance as clinically significant. Due to the increasing importance of long-acting cabotegravir/rilpivirine [CAB/RPV] in HIV treatment, we also considered the cabotegravir resistance-associated polymorphism IN L74I in HIV-1 subtype A6 and low-level resistance to RPV clinically significant[3,4]. We use the term "RAM" to refer to both naturally occurring polymorphisms and to mutations acquired due to selective antiretroviral pressure; when relevant, the polymorphic nature of the RAM is discussed.

The distribution HIV-1 subtypes among newly diagnosed individuals has become increasingly important, due to subtype-specific polymorphisms conferring clinically significant drug resistance. The most common of these polymorphisms are RT E138A in non-B subtypes (reducing susceptibility to rilpivirine) and the IN L74I in subtype A6 (reducing susceptibility to cabotegravir)[1,5]. We discuss the impact of HIV-1 subtype on antiretroviral resistance in detail throughout the chapter.

Baseline resistance

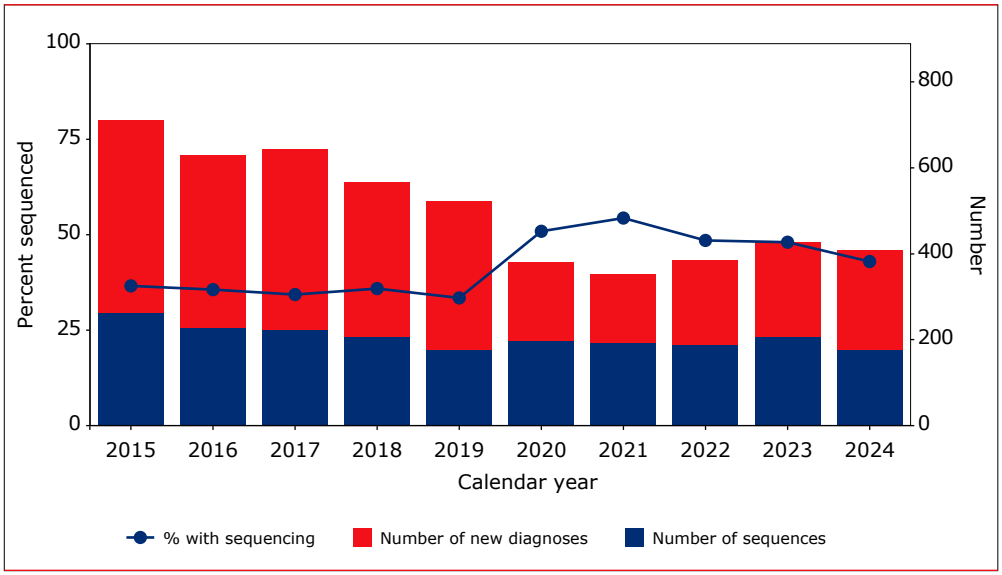
Baseline resistance refers to the detection of RAMs prior to the initiation of antiretroviral treatment. Baseline resistance may occur due to transmission of a drug-resistant HIV strain or due to naturally occurring polymorphisms associated with specific HIV-1 subtypes. Since 2003, Dutch guidelines recommend baseline resistance screening in all newly diagnosed individuals entering HIV care[6]. Implementation of these guidelines has been partial, varying significantly by treatment centre.

In our analysis of baseline resistance trends, we include ATHENA participants who met the following criteria: diagnosed with HIV between 2015 and 2024 while living in the Netherlands; screened within 60 days of HIV diagnosis and before initiating antiretroviral therapy; remained in care at year-end 2024; and reported no history of PreP use. Pre-treatment drug resistance associated with PrEP use is discussed elsewhere in this report (see Prior use of pre-exposure prophylaxis).

Screening frequency and baseline characteristics

Between 2015 and 2024, 5,197 individuals were diagnosed with HIV-1 in the Netherlands, of whom 2,039 (39.2%) were screened for baseline drug resistance. Baseline screening increased over time (Figure 5.1).

Figure 5.1: Proportion of newly diagnosed participants screened for baseline resistance, 2015–2024 (n=5,197).



In 2,039 individuals with baseline resistance screening, 2,028 reverse transcriptase, 1,671 protease, and 640 integrase sequences were available for review. Eighty-two percent of individuals undergoing baseline screening were male, 59.7% were MSM, and 53.1% were born in the Netherlands.

We observed notable shifts in the distribution of HIV-1 subtypes among newly diagnosed participants. Over the past decade, a decrease in the proportion of HIV-1 subtype B was complemented by an increase in HIV-1 subtypes A, C and recombinant forms. HIV-1 subtype varied significantly by mode of transmission (Figure 5.2)[7].

Figure 5.2: HIV-1 subtypes identified at baseline resistance screening, by transmission group, 2015–2024 (n=2,039).

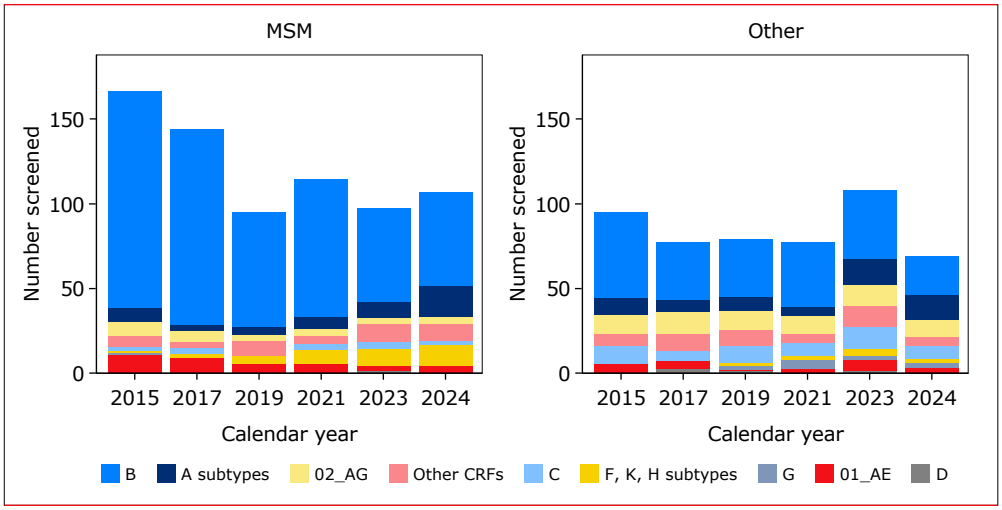


Figure 5.3 shows the region of birth of individuals with HIV-1 B and A subtypes. Since 2019, a greater proportion of individuals with HIV-1 subtype A were born in Central and Eastern Europe[8,9]. The proportion of subtype A6 as a fraction of all subtype A strains identified at baseline screening (n=170) has increased over the past decade (Figure 5.4). Sixty-three percent of participants with subtype A6 were born in Central and Eastern Europe and 28.6% were born in the Netherlands. Conversely, of 5,197 participants diagnosed with HIV between 2015 and 2024, 448 (8.6%) were born in Central and Eastern Europe; of these, 183 underwent baseline drug resistance testing and 49 (27.8%) had subtype A6 detected.

Figure 5.3: HIV-1 subtype by region of birth in participants screened for baseline resistance, 2015–2024 (n=2,039).

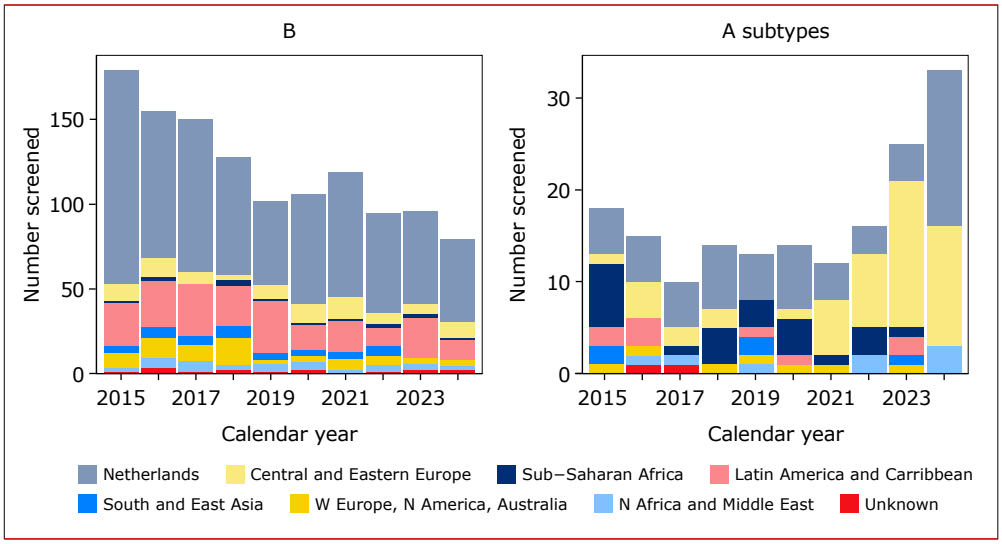
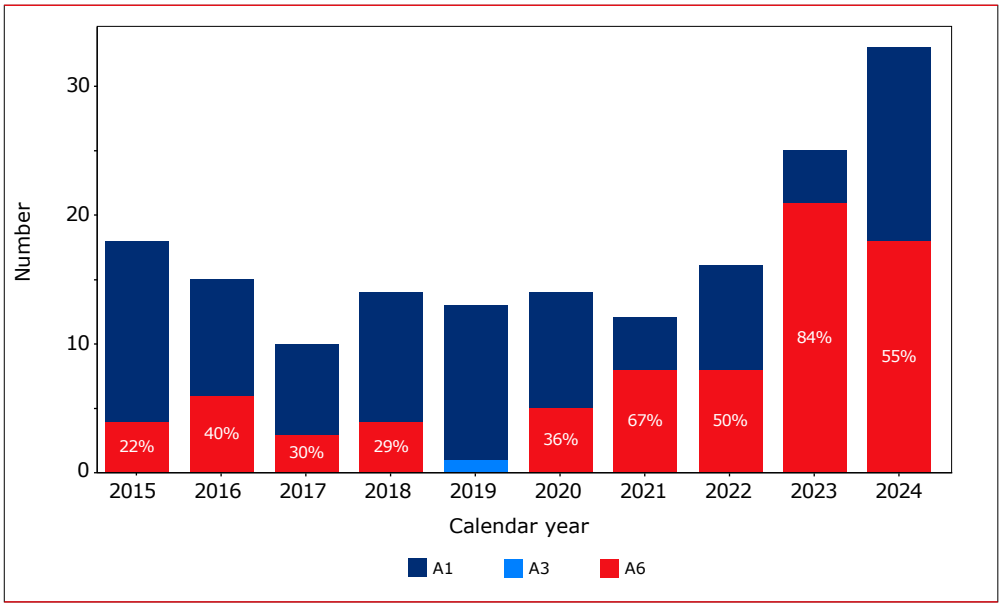


Figure 5.4: Distribution of HIV-1 A sub-subtypes in participants with subtype A identified at baseline resistance screening, 2015–2024 (n=170).



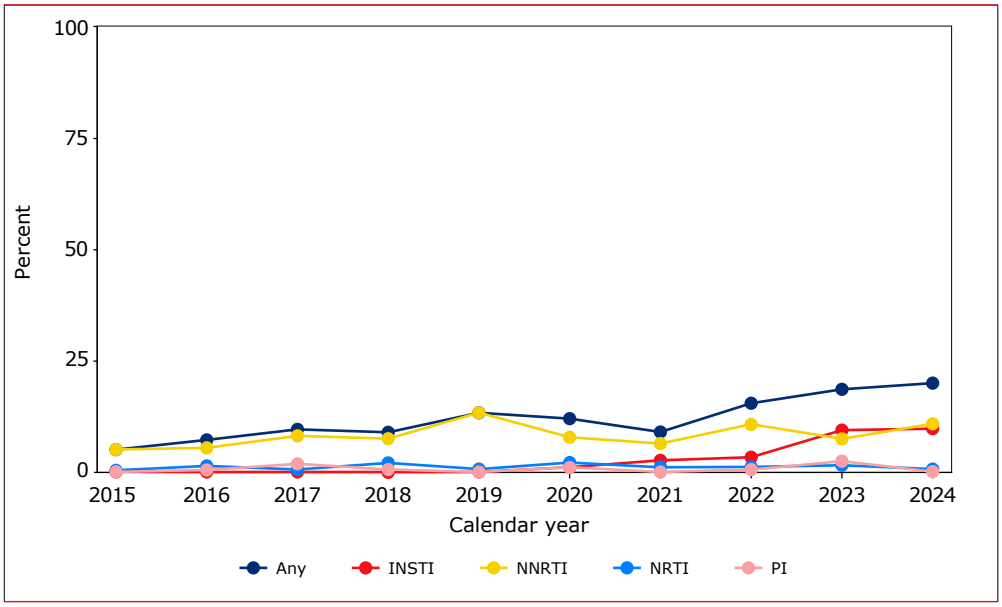
Patterns of baseline resistance

Of 2,039 individuals undergoing baseline screening, 233 (11.4%) had evidence of clinically significant resistance. The proportion of participants with clinically significant baseline resistance fluctuated between 5% and 20% over the past decade, with a pronounced increase after 2020 (Table 5.1 and Figure 5.5). This temporal increase coincides with the increasing prevalence of HIV-1 subtype A6 in the Netherlands and is discussed in further detail below. Baseline RAMs conferring resistance to NNRTIs, NRTIs, PIs, and INSTIs were observed in 162 (7.9%), 22 (1.1%), 14 (0.7%) and 49 (2.4%) of screened participants, respectively. Of 233 participants with baseline RAMs, 220 (94.4%) had one RAM, 12 (5.1%) had two RAMs, and 1 (<1%) had three RAMs.

Table 5.1: *Proportion of participants with clinically significant RAMs detected at baseline screening, by affected drug class, 2015–2024 (n=2,039).*

Year	Any	NRTI	NNRTI	PI	INSTI
2015	5	0.4	5	0	0
2016	7.1	1.3	5.3	0.4	0
2017	9.5	0.5	8.1	1.8	0
2018	8.8	2	7.4	0.5	0
2019	13.2	0.6	13.2	0	0
2020	11.9	2.1	7.7	1	1
2021	8.9	1	6.3	0	2.6
2022	15.4	1.1	10.6	0.5	3.2
2023	18.5	1.5	7.3	2.4	9.3
2024	19.9	0.6	10.8	0	9.7

Figure 5.5: Baseline HIV-1 drug resistance by antiretroviral class, 2015–2024 (n=2,039).



Of 640 participants with baseline integrase sequencing, 49 (7.6%) had integrase RAMs detected; 48 had HIV-1 subtype A6. All 48 participants with integrase sequencing and subtype A6 harboured the cabotegravir-associated IN L74I RAM; four of these participants also had RAMs conferring NNRTI resistance (two with RT K103N; one with RT G190S, K101E, and E138A; and one with RT E138A). An additional participant had HIV-1 subtype B with IN G140S, conferring resistance to the first-generation integrase inhibitors raltegravir and elvitegravir. No baseline resistance to dolutegravir or bictegravir was detected. Overall, 44 of 49 (90%) participants with baseline INSTI resistance harboured the subtype A6 IN L74I polymorphism only.

Baseline NNRTI resistance was detected in 162 participants. Of these, 56 (34.3%) had RT E138A only and 33 (20.2%) had RT K103N only; other NNRTI RAMs and RAM combinations occurred at a frequency of less than 5%. Of the 56 participants with RT E138A alone, 32 (57.1%) had HIV-1 subtype B; the remaining 24 (42.9%) had non-B subtypes and recombinant forms in which the RT E138A may be considered polymorphic.

Substitutions RT M184V/I, conferring resistance to the cytidine analogues lamivudine and emtricitabine [3TC/FTC], were identified in 6 participants. In three, 3TC/FTC resistance was accompanied by additional NRTI mutations, including one individual with the tenofovir-associated RAM RT K65R. In 3 participants with RT M184V/I, PrEP use history was not documented; the remaining 3 participants (including the individual with RT K65R) were documented to have not used PrEP.

Forty-four percent of people with clinically significant baseline resistance were born in the Netherlands, 11.2% in Latin America and the Caribbean, 11.2% in Sub-Saharan Africa and 22.7% in Central and Eastern Europe. Seventy-three percent of participants with the subtype A6 L74I RAM were born in Central and Eastern Europe and 23% were born in the Netherlands. Compared to people born in the Netherlands, people born in Central and Eastern Europe had 3.9 [CI 2.7 - 5.7] times the odds of any clinically significant RAMs and 15.6 [CI 7.9 - 32.9] times the odds of INSTI RAMs, driven by the high prevalence of HIV-1 subtype A6 in these regions (see Baseline characteristics). People born in Sub-Saharan Africa had higher odds of NNRTI-associated RAMs compared to people born in the Netherlands (unadjusted OR 1.8 [95%CI 1.1- 2.9).

Table 5.2 shows the number and proportion of RAMs occurring in at least 1% of participants with baseline resistance.

Table 5.2: Most frequent RAMs identified at baseline screening, 2015–2024 (n=233).

RAM	Class	Number	Percent^
E138A	NNRTI	63	27
L74I	INSTI	48	20.6
K103N	NNRTI	44	18.9
K101E	NNRTI	12	5.2
E138G	NNRTI	9	3.9
K103S	NNRTI	9	3.9
K238T	NNRTI	8	3.4
G190A	NNRTI	8	3.4
Y181C	NNRTI	7	3
E138K	NNRTI	6	2.6
M184V	NRTI	4	1.7
P225H	NNRTI	4	1.7
E138Q	NNRTI	4	1.7
Y318F	NNRTI	2	0.9
V106M	NNRTI	2	0.9
H221Y	NNRTI	2	0.9
G190E	NNRTI	2	0.9
G190S	NNRTI	2	0.9
M184I	NRTI	2	0.9

^Because participants could have more than one RAM, total adds up to greater than 100%.

Impact on antiretroviral therapy

Among participants with baseline resistance, NNRTI RAMs were observed in 162 (69.5%), INSTI RAMs in 49 (21%), NRTI RAMs in 22 (9.4%) and PI RAMs in 14 (6%). Table 5.3 shows commonly used ART drug classes affected by baseline resistance, by order of impact.

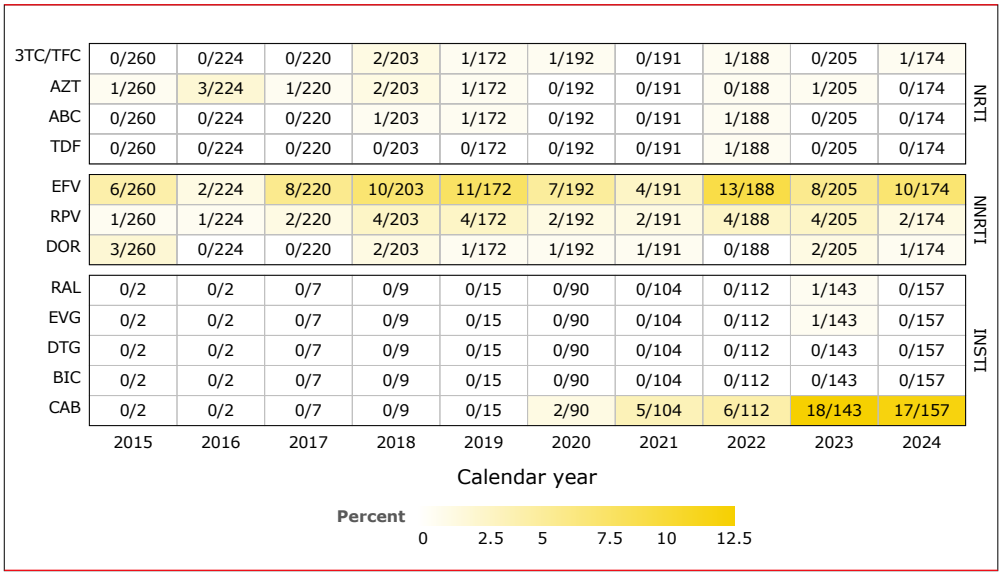
Table 5.3: Number and proportion of individuals with baseline resistance by drug class, 2015–2024 (n=233).

Class	Agents	Number	Percent^
2nd gen NNRTI	ETR, RPV	106	45.5
1st gen NNRTI	EFV, NVP	88	37.8
2nd gen INI	CAB	48	20.6
3rd gen NNRTI	DOR	11	4.7
Cytidine analogues	3TC, FTC	6	2.6
2nd gen PIs	ATV, FPV, LPV, TPV	5	2.1
1st gen INI	EVG, RAL	1	0.4
Tenofovir prodrugs	TDF	1	0.4

^Because participants could be resistant to more than one class, totals add up to greater than 100%.

Figure 5.6 shows the proportion of sequences with baseline resistance by drug and drug class, restricted to commonly used therapy. Within each cell, the numerator represents the number of sequences with RAMs and the denominator represents the number of available sequences.

Figure 5.6: Baseline HIV-1 drug resistance for commonly used antiretroviral agents, 2015-2024 (n=2,039).



To date, we observe no impact of baseline resistance on rates of virological suppression. Restricting the analysis to those who started antiretroviral therapy in 2023, the proportion of participants with virological suppression at year end 2024 in individuals with and without transmitted RAMs was 93.4% and 93%, respectively.

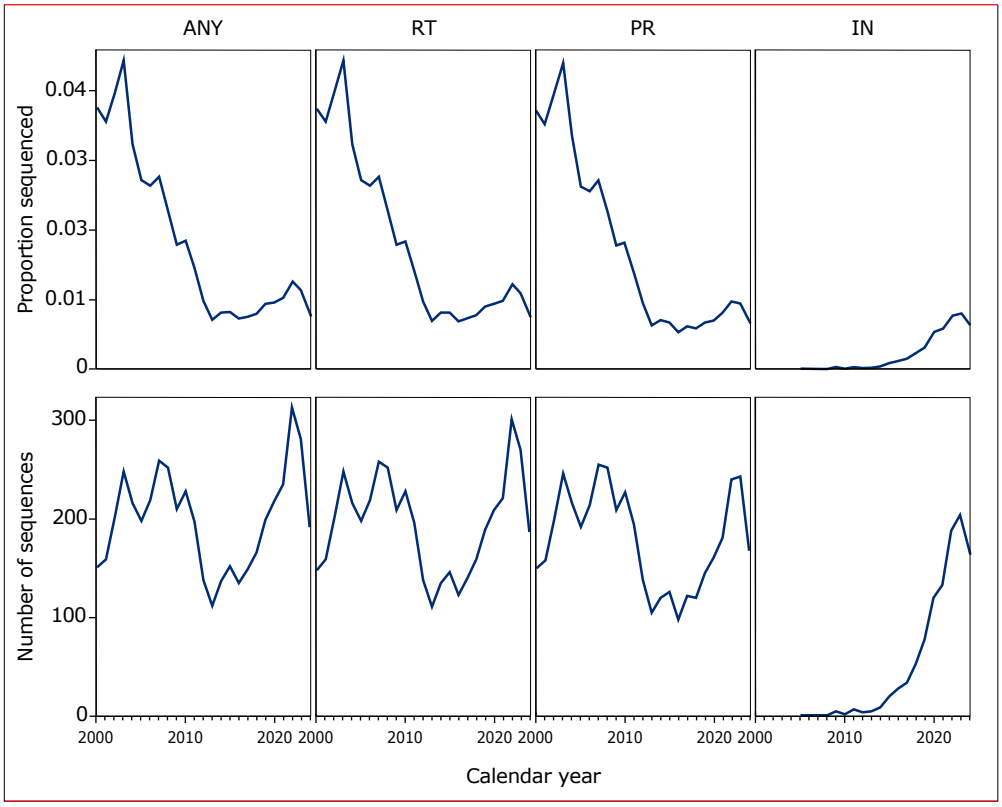
Acquired resistance

Acquired HIV drug resistance emerges in the setting of incomplete virological suppression during antiretroviral treatment. In the Netherlands, rates of virological suppression have improved significantly over time (see chapter 4 Response to combination antiretroviral therapy), leading to lower rates of RAMs detected at treatment failure. In the following sections, we describe patterns of acquired drug resistance in ATHENA participants who had at least one genotype performed more than 14 days after starting antiretroviral therapy and who were in care at year end 2024 . Antiretroviral therapy was defined as receipt of any antiretroviral agent or agent combination.

Testing frequency and baseline characteristics

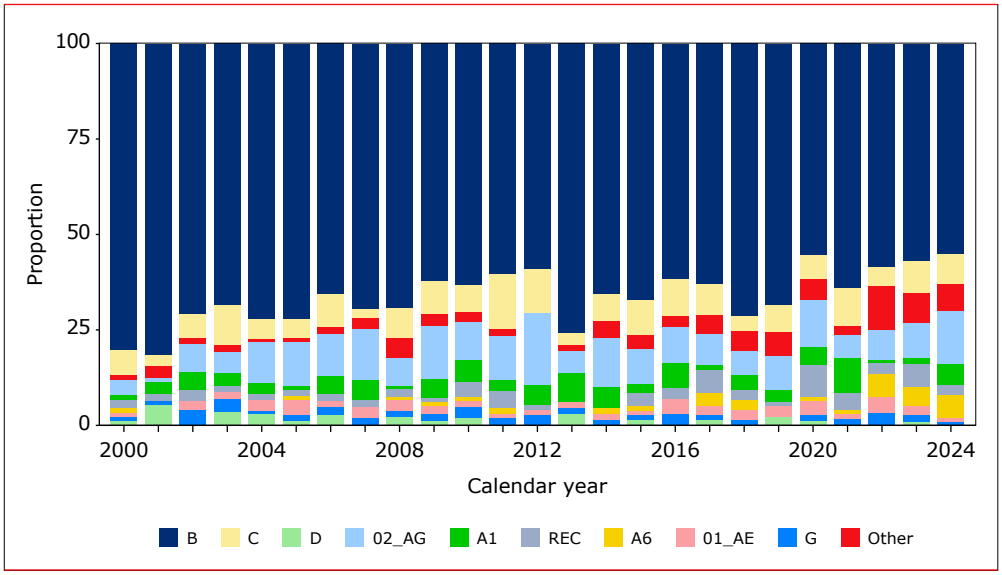
Between 1990 and 2024, 5,258 HIV-1 sequences were obtained from 3,022 people at least 14 days after first ART initiation. The mean number of sequences per participant was 3 (range 1-16) and the mean time from ART initiation to first sequence was 7.7 years (range 14 days – 33 years). Reverse transcriptase, protease, and integrase sequencing was obtained in 5,143, 4,764 and 1,059 samples, and 2,991, 2,777, and 788 participants, respectively. The number of sequences and the proportion of participants sequenced per year is shown in Figure 5.7. The proportion of sequences performed per year as a fraction of the number of participants in care has steadily decreased, from 4.4% in 2000 to 0.8% in 2024.

Figure 5.7: Proportion of participants in care undergoing drug resistance testing and number of sequences performed (n=24,028).



Of 3,022 participants tested for acquired RAMs, 2,193 (72.6%) were men, 1,475 (48.8%) were MSM and 1,182 (39%) heterosexual. One thousand three hundred and twenty-five participants (43.8%) were born in the Netherlands, followed by 658 (21.8.%) born in Sub-Saharan Africa, and 547 (18.1%) in Latin America and the Caribbean. HIV-1 subtype B was detected in 2,056 (68%) participants; an increase in the proportion of non-B subtypes was observed over time (Figure 5.8).

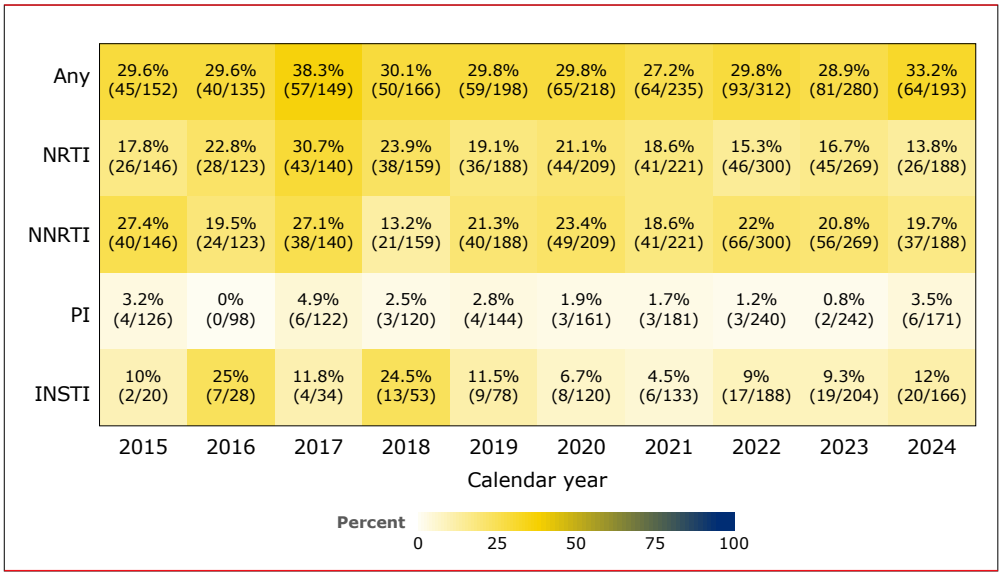
Figure 5.8: HIV-1 subtype in participants tested for acquired resistance (n=3,022).



Patterns of acquired resistance

Of the 5,258 samples obtained, 2,649 (50.4%) sequences from 1,633 individuals had at least one clinically significant RAM detected. NRTI, NNRTI, PI, and INSTI RAMs were detected in 2062 (39.2%), 1,622 (30.8%), 712 (13.5%), and 114 (2.2%) sequences, respectively. Single, dual, and triple class resistance was detected in 1,158 (22%), 1,121 (21.3%), 370 (7%) sequences, respectively; no single sequence contained RAMs to all four main treatment classes. Between 2000 and 2024, the proportion of sequences with any clinically significant RAMs decreased from 78.1% to 33.1%. Figure 5.9 shows the proportion of sequences with RAMs detected over the past decade, by drug class.

Figure 5.9: Proportion of sequences with HIV-1 RAMs, by drug class, 2015–2024 (n=5,258).



Numbers in parentheses represent the number of sequences with RAMs/number of available sequences.

Impact on antiretroviral therapy

Because RAMs may be retained as integrated ("archived") proviral sequences in host cells, data from sequential genotypes is needed to determine the impact of cumulative RAMs in individual participants[10]. In the remainder of this chapter, we present data on cumulative resistance patterns in 1,633 participants with any acquired RAMs. We begin with an overview of resistance by drug class. We then proceed to discuss drug-specific scenarios of particular relevance to current antiretroviral management.

Overview

At year end 2024, 24,028 participants were in care; of these, 1,633 (6.8%) had a history of acquired RAMs. Of 1,633 individuals with acquired RAMs, 1,310 (80%) had any NRTI resistance, 1,067 (65.3%) had NNRTI resistance, 375 (23%) had PI resistance, and 96 (5.9%) had integrase resistance. Resistance to an entire drug class was less frequent and varied by class: complete class resistance to NRTIs, NNRTIs, PIs and INSTIs occurred in 253 (15.5%), 212 (13%), 24 (1.5%) and 20 (1.2%) participants, respectively.

Six hundred and sixty-three participants (40.6%) had evidence of single class resistance, 728 (44.6%) had dual class resistance, 240 (14.7%) had triple class resistance, and two individuals had quadruple class resistance. The two participants with quadruple class resistance had a history of mono- or dual-NRTI exposure. The most frequent pattern of class resistance observed was dual-class NRTI + NNRTI resistance (n=558, 34.1%), followed by single class NRTI resistance (n=355, 21.7%) and single-class NNRTI resistance (n=253, 15.5%) (Table 5.4).

Table 5.4: Patterns of acquired resistance, by drug class (n = 1,633)

ART Drug Class	Number	Percent
NNRTI, NRTI	558	34.2
NRTI	355	21.7
NNRTI	253	15.5
NNRTI, NRTI, PI	212	13
NRTI, PI	135	8.3
INSTI	35	2.1
INSTI, NNRTI, NRTI	26	1.6
INSTI, NRTI	20	1.2
PI	20	1.2
INSTI, NNRTI	11	0.7

Resistance to antiretroviral "anchor" drugs used in current HIV management varied widely. Clinically significant resistance to doravirine was observed in 364 (22.2%) participants with a history of acquired RAMs; resistance to darunavir was observed in 34 participants (2.1%); resistance to the second-generation oral integrase inhibitors dolutegravir and bictegravir was detected in 32 (2%). These data represent resistance patterns observed irrespective of antiretroviral treatment history.

Participants with a history of acquired drug resistance were less likely to be virologically suppressed at last observation than participants without a history of acquired drug resistance (92% vs 83%, respectively).

Cytidine analogues

The cytidine analogues lamivudine and emtricitabine [3TC/FTC] form part of most first-line antiretroviral regimens and of oral PrEP. Resistance to 3TC/FTC emerges early in antiretroviral treatment failure and is almost universally caused by RT M184V/I RAMs[11]. Among 1,633 participants with acquired resistance, 1,108 (67.8%) had RT M184V/I identified on any sequence. One hundred and eighty-seven (11.5%) harboured the RT M184V/I as the sole RAM.

Among 1,108 participants with a history of RT M184V/I, we found no differences in rates of virological suppression by presence or absence of cytidine analogues in the current regimen (83.5% and 84.5%, respectively). Twenty patients with a history of RT M184V/I were treated with the dual-agent single tablet regimen dolutegravir/lamivudine; all twenty (100%) were virologically suppressed at last viral load measurement.

Integrase inhibitors

Understanding the emergence of INSTI resistance is important, given their central role in current HIV management[12]. Integrase inhibitors form the base ("anchor") of current antiretroviral regimens in 1,206 (73.9%) people with any acquired resistance.

Of 788 participants with integrase sequencing, 96 (12.2%) had INSTI RAMs detected. The most frequent INSTI RAMs identified were IN N155H (n=25, 26%), followed by the subtype A6 IN L74I (n=24, 25%) and IN R263K (n=16, 16.7%) (Table 5.5). In fifteen of twenty-four participants with the HIV-1 subtype A6 IN L74I polymorphism, no additional RAMs were identified. Excluding these 15 individuals from the analysis, only 81 participants had acquired INSTI resistance (10.3% of participants with INSTI sequencing, 0.3% of participants in care at year end 2024).

Table 5.5: INSTI RAMs detected in participants with post-treatment integrase resistance (n=96).

RAM	N	Percent^
N155H	25	26
L74I*	24	25
R263K	16	16.7
Q148R	9	9.4
E92Q	8	8.3
E138K	7	7.3
S147G	6	6.2
T66I	5	5.2
N155S	3	3.1
G140S	3	3.1
G118R	3	3.1
Y143C	3	3.1
Y143R	3	3.1
T66A	3	3.1
E138A	3	3.1
T66K	2	2.1
G140A	2	2.1
Q148H	1	1
E92G	1	1
F121C	1	1

**Considered a RAM in HIV-1 subtype A6 only. ^Percent represents proportion of participants with INSTI resistance harbouring each RAM; because participants could have more than one RAM, proportions exceed 100%.*

At time of first INSTI failure, 41 (42.7%) participants had been previously exposed to NNRTI and PI based therapy, 15 (15.6%) had been exposed to PI-based therapy only and 13 (13.5%) had been exposed to NNRTI-based therapy only; 23 (24%) had been treated with INSTI-based therapy only prior to the detection of INSTI RAMs (Table 5.6). Fifty-one (57.2%) participants with INSTI RAMs had no previously documented acquired resistance to either NNRTIs or PIs.

Forty-nine participants (50.5%) with INSTI RAMs had been treated with second generation INSTIs but not with a first generation INSTI. Nine participants had been treated with CAB prior to first integrase failure (CAB/RPV resistance is discussed in detail in the following section). Three participants with no documented history of INSTI treatment had INSTI-associated RAMs; none had been screened for transmitted drug resistance. Two of these participants had HIV-1 subtype A6 with IN L74I; the other participant had HIV-1 subtype B, a history of PI-based treatment only, and harboured IN L74IM and IN Y143C.

Five participants with INSTI RAMs had been screened for baseline drug resistance; four had no resistance and one had HIV-1 subtype A6 IN L74I detected.

Table 5.6: *Treatment characteristics of participants with acquired INSTI RAMs (n=96).*

	Number (precent)
Drug class exposure prior to INSTI resistance	
NNRTI, PI	41 (42.7%)
INSTI only	23 (24.0%)
PI	15 (15.6%)
NNRTI	13 (13.5%)
Unknown	4 (4.2%)
Type of integrase exposure	
Second generation only	47 (49.0%)
First generation only	34 (35.4%)
Both first and second generation	12 (12.5%)
No history of integrase exposure	3 (3.1%)
History of cabotegravir use	
No	87 (90.6%)
Yes	9 (9.4%)
History of dolutegravir monotherapy	
No	88 (91.7%)
Yes	8 (8.3%)
History of mono- or dual-NRTI therapy	
No	80 (83.3%)
Yes	16 (16.7%)

	Number (precent)
Birth region	
Netherlands	30 (31.2%)
Central and Eastern Europe	25 (26.0%)
Latin America and Caribbean	17 (17.7%)
Sub-Saharan Africa	17 (17.7%)
N Africa and Middle East	4 (4.2%)
W Europe, N America, Australia	3 (3.1%)
Gender	
Male	65 (67.7%)
Female	31 (32.3%)
Transmission group	
Heterosexual	38 (39.6%)
MSM/W	36 (37.5%)
Unknown	10 (10.4%)
IVDU	5 (5.2%)
Sexual transmission NOS	4 (4.2%)
Other	3 (3.1%)
HIV-1 subtype	
B	44 (45.8%)
A6	24 (25.0%)
02_AG	13 (13.5%)
REC	5 (5.2%)
C	4 (4.2%)
A1	3 (3.1%)
01_AE	2 (2.1%)
06_cpx	1 (1.0%)

Long-acting agents

The long-acting injectable combination CAB/RPV was introduced as a treatment option in the Netherlands in 2021. Nine-hundred and seventy ATHENA participants have received treatment with CAB/RPV. Of these, 17 (1.8%) participants underwent sequencing at least 14 days after starting CAB/RPV and within a year of discontinuing CAB/RPV.

CAB/RPV RAMs were detected in 14 participants treated with long-acting therapy. Pre-treatment reverse transcriptase sequencing was available in 9 and integrase sequencing in 3; 2/9 participants had NNRTI RAMs prior to CAB/RPV treatment and 0/3 had INSTI RAMs detected prior to treatment. The pre-treatment clinical characteristics of participants with CAB/RPV resistance at treatment failure are shown in Table 5.7.

Table 5.7: Select pre-treatment characteristics in participants with CAB/RPV resistance (n=14).

	Number (%)
Prior class resistance	
NNRTI	1 (7.1%)
NNRTI, NRTI	1 (7.1%)
None	12 (85.7%)
RT RAMs	
K103R, M184V, D67N, A98G	1/9 (11.1%)
Y188L	1/9 (11.1%)
None	7/9 (77.8%)
INSTI RAMs	
None	3/3 (100.0%)
History of INSTI treatment	
No	1 (7.1%)
Yes	13 (92.9%)
History of first generation INSTI treatment	
No	7 (50.0%)
Yes	7 (50.0%)
History of NNRTI treatment	
No	7 (50.0%)
Yes	7 (50.0%)
History of first generation NNRTI treatment	
No	8 (57.1%)
Yes	6 (42.9%)

In post-treatment sequencing, all 14 participants had NNRTI RAMs and 10 participants had INSTI RAMs (Table 5.8). One participant with HIV-1 subtype A6 IN L74I polymorphism did not have pretreatment sequencing available; this participant had an acquired IN N155S detected in post-CAB/RPV sequencing.

Table 5.8: Pre- and post-treatment RAMs in participants with acquired resistance to CAB/RPV (n=14).

HIV-1 Subtype	RT RAMS pre	INSTI RAMs pre	RT RAMs post	INSTI RAMs post
A6	Not performed	Not performed	E138K	N155S, L74I
B	None	Not performed	K101EQ, E138K, M230L, K238N	N155H
B	Not performed	Not performed	K101N, E138K, M184IV	None
B	None	Not performed	E138K	None
B	None	Not performed	K101E, K103R, V179D, Y181C	None
B	Not performed	Not performed	K101E, E138K	E138K, Q148R
B	None	Not performed	E138K, V90I	E138D
B	None	None	K101E	None
C	Y188L	None	V179I, Y188L	E138A, G140A, Q148R
C	Not performed	Not performed	K103N, Y181C, T215YSC, H221Y, A98S	E138A, S147G, N155H, R263K, T97A
02_AG	K103R, M184V, D67N, A98G	None	K103R, E138K, A98G	S147G, N155H
02_AG	None	Not performed	V106A, E138A, V179I	E138K, Q148R
02_AG	None	Not performed	K101P, V90I	E138K, Q148R
REC	Not performed	Not performed	Y181C, H221Y	F121C

Conclusions

Over the past decade, the rate of baseline drug resistance has increased from 5% in 2015 to 20% in 2024. This increase was driven largely by the HIV-1 subtype A6 IN L74I polymorphism, impacting cabotegravir susceptibility. Given the increasing prevalence of non-B subtypes in the Netherlands, baseline sequencing is required to identify both transmitted RAMs and subtype-specific polymorphisms that may impact HIV treatment efficacy. To date, baseline drug resistance has had no appreciable impact on treatment response.

Rates of acquired drug resistance have decreased substantially over the past twenty-five years. Improved antiretroviral efficacy and a higher barrier to the emergence of resistance have led to fewer RAMs detected at treatment failure. Nonetheless, resistance to second-generation INSTIs and long-acting CAB/RPV have been observed and require close monitoring. Participants with a history of acquired drug resistance had lower rates of virological suppression, attesting to the ongoing importance of adherence support.

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6. Morbidity and mortality

Ferdinand Wit, Berend van Welzen, Marc van der Valk

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 8.9 in 1996, to 6.5 in 2000, to 5.8 in 2005, to 3.0 in 2010, to 2.3 in 2015 and has remained constant at around 2.0 since 2017. In 2024 the ratio was 1.9 times the observed age- and sex-standardized mortality in the general population of the Netherlands. In all investigated subgroups, the ratio of the observed over expected mortality declined over time but at the end of follow-up in 2024 remained substantially elevated. 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 8.41 deaths per 1,000 person years in 2019, to 9.07 in 2020 and 10.76 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 9.54 deaths per 1,000 person years had not completely returned to pre-COVID-19 levels. And in 2023 and 2024 the observed mortality rate had again increased, to 11.12 and 11.34 deaths per 1,000 person years, respectively. However, in 2022-2024 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 increasing average age 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 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.

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[5-9]), 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).

When looking at secondary CVD events, we observed a decreased risk over time in men, whereas the risk remained stable for women. This difference is thus far unexplained and needs more study.

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[4,10,11]. 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 not 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.

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 are more likely to be older. This is in line with data from other cohorts, including the Swiss HIV cohort and RESPOND cohort[15-19]. 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[20].

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, 3.3% of adults used five or more non-antiretroviral comedications alongside their ART regimen, and this steadily increased to 16.9% of adults in active follow up in 2024. 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.

Introduction

Since the introduction of combined antiretroviral therapy (ART) in 1996, the life expectancy of people with HIV (PWH) has markedly improved[21]; in a subgroup of recently-diagnosed, effectively-treated individuals, it was shown to be similar to that of the general population in the Netherlands[22]. Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased[23], morbidity and/or mortality associated with non-AIDS-related diseases has increased among PWH during the ART era[24-29]. 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[30-32]. For example pulmonary hypertension[33], bone disease, and non-traumatic bone fractures[34-36] have each been reported to be more common in PWH. Just as with individuals without HIV, traditional risk factors (such as tobacco use[12], alcohol abuse, and viral hepatitis co-infection[37]) 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[38,39].

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 32,093 adult individuals ever registered by SHM – which includes 706 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[40]. 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 2020-2024. We standardised these estimates according to the age distribution of the population during the period 2020-2024 (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[41]. Indirect standardisation compares the incidence rates in the study and reference period (2020-2024) 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 32,093 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 2020, but the observed mortality rate was noticeably higher in 2021 during the COVID-19 pandemic with 10.8 (9.4-12.2). In 2024 the observed crude mortality rate had increased to 11.3 (10.0-12.9) per 1,000 PYFU (*Figure 6.1A*). 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 5.9 per 1,000 PYFU in 2024. The ratio of the observed mortality among PWH compared to the age/sex-adjusted mortality observed in the general population, decreased from 8.9 in 1996, to 6.5 in 2000, to 5.8 in 2005, to 3.0 in 2010, to 2.3 in 2015 and has remained constant at around 2.0 since 2017. In 2024 the ratio was 1.9.

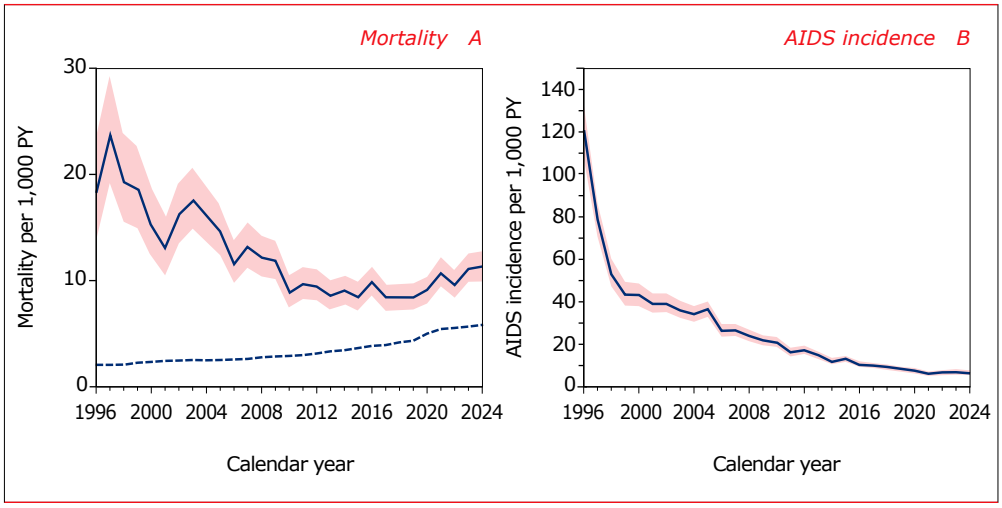
We repeated the analysis of mortality for various subgroups of interest (*Figure 6.1C*). The analyses were stratified based on region of origin (native Dutch, migrants with Western background, and migrants with non-Western background), HIV transmission category (men who have sex with men, other men who 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 2024" 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 2024. In all investigated subgroups, the ratio of the observed over expected mortality declined over time but at the end of follow-up in 2024 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 subgroup diagnosed with HIV since 2010 and 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 (21.4% of the 98 observed deaths in this subgroup were classified as of non-natural causes: accidents, violence, suicide, euthanasia, substance abuse, psychiatric disease).

Underlying causes of death

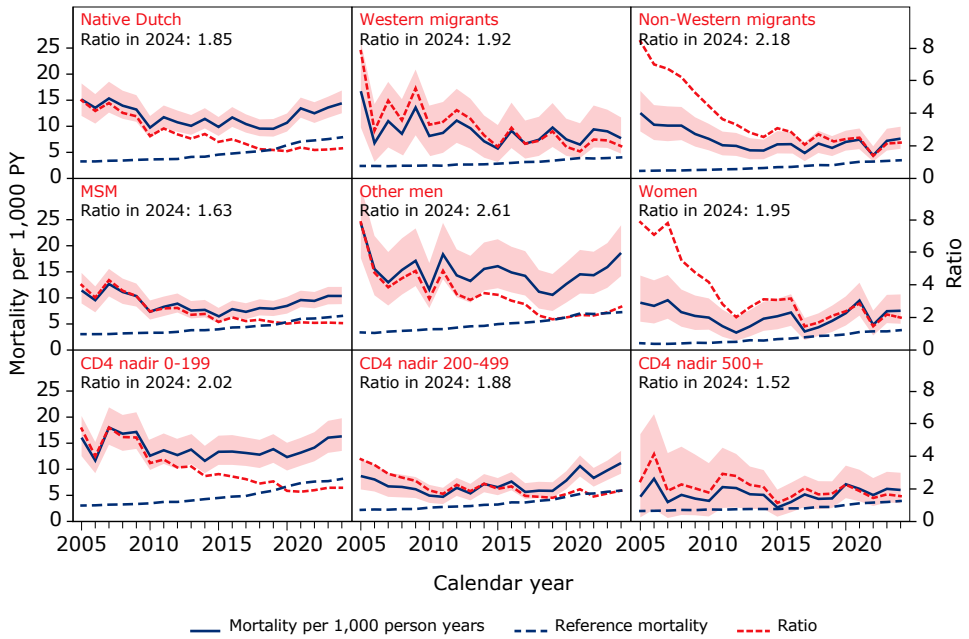
Observed underlying causes of death are presented in *Figure 6.1D* (with exact numbers and percentages presented in *Appendix Table 6.1*). Although the AIDS-related death rate has decreased significantly since the advent of ART, the continued occurrence of deaths due to AIDS is driven largely by the 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[42]. *Table 6.1* 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 2015-2024. Individuals who died of AIDS were more frequently female, non-MSM males 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 (60.3% had advanced HIV at diagnosis with a CD4 cell count below 200 cells/mm^3). In 50.2% of cases, they did not have controlled viremia, and 26.5% of this group was not receiving any ART at the time of death, either because ART had not yet been started or had been discontinued (*Table 6.1*).

Among individuals who died of advanced HIV / AIDS but who 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 6.1D*), primarily as a consequence of the ever increasing size and increasing average age of the population of people with HIV in the Netherlands. In recent years, the category 'Sudden death' has been introduced for individuals who died suddenly and unexpectedly within a precise cause being known. 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 6.2*.

Figure 6.1A-D: *(A) Annual mortality and (B) incidence of AIDS in 32,093 PWH in the Netherlands after entry into HIV care from 1996 onwards. (C) Annual mortality in various subgroups 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 2024. (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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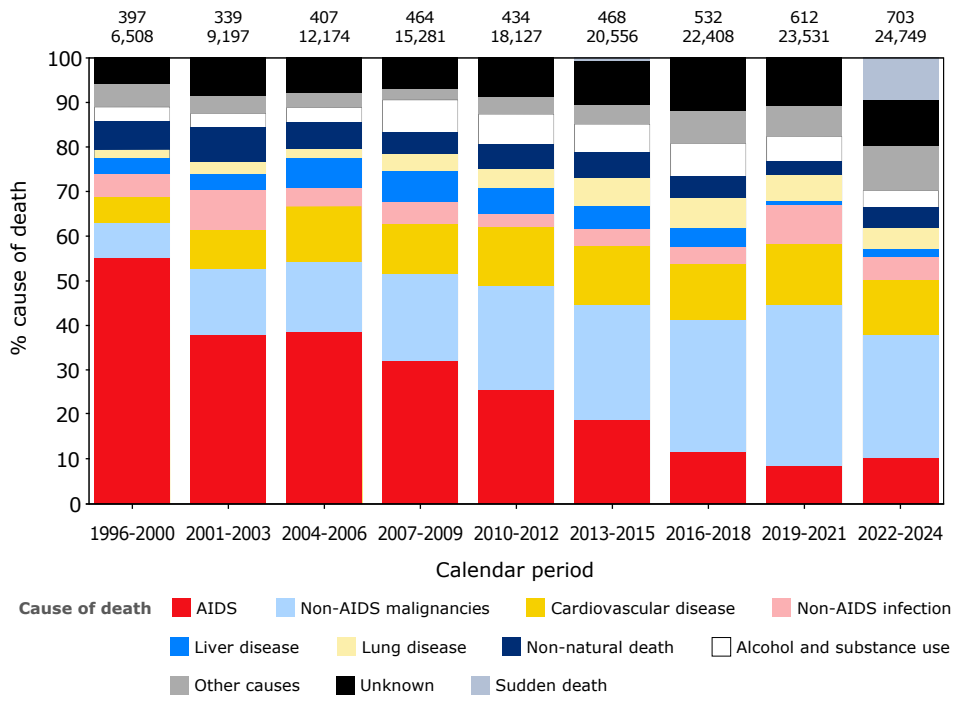


Table 6.1: *Characteristics of adults with HIV who died of AIDS compared to adults with HIV who died of non-AIDS causes in the period 2015-2024.*

	Died of AIDS	Died of non-AIDS causes	p-value
Number of subjects	219 (10.9%)	1,782 (89.1%)	
Age	56.6 (46-66.6)	61.6 (53.9-70.5)	<.001
Transmission category			<.001
MSM	95 (43.4%)	1,026 (57.6%)	
Other men	75 (34.2%)	395 (22.2%)	
Women	33 (15.1%)	193 (10.8%)	
Transgender	3 (1.4%)	12 (0.7%)	
IDU	6 (2.7%)	122 (6.8%)	
Blood contact	2 (0.9%)	32 (1.8%)	
Pediatric	5 (2.3%)	2 (0.1%)	
Region of origin			<.001
Native Dutch	130 (59.4%)	1,259 (70.7%)	
Western migrants	18 (8.2%)	166 (9.3%)	
Non-Western migrants	67 (30.6%)	352 (19.8%)	
Unknown origin	4 (1.8%)	5 (0.3%)	
Years since HIV diagnosis	8.73 (0.8-18.3)	16.7 (9.83-23.5)	<.001
Years since start cART	6 (0.46-14.3)	14.4 (8.09-20)	<.001
CD4 at HIV diagnosis	134 (41-338)	300 (130-520)	<.001
Late HIV diagnosis (CD4<350 at entry in care)	165 (76.4%)	988 (55.5%)	<.001
Advanced HIV diagnosis (CD4<200 at entry in care)	132 (60.3%)	636 (35.7%)	<.001
CD4 nadir	60 (20-132)	160 (60-270)	<.001
Last CD4 measured before death	150 (55-350)	520 (327-734)	<.001
Not undetectable at date of death	105 (50.2%)	1,569 (88.3%)	<.001
Not on cART at date of death	58 (26.5%)	164 (9.2%)	<.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.*

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 6.2*, 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.

In individuals who had initiated early ART (i.e. within 12 months of their last negative HIV test, or within 12 months of a diagnosed acute HIV infection [Fiebig stages I-V]), the risk of death was significantly lower compared to individuals who did not initiate ART early (relative risk 0.74, 95% CI 0.57-0.97, p=0.027).
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 6.3*). 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 6.1*). The number of recorded suicides among people with HIV in the Netherlands in the period 2011 to 2024 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[43,44].

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 2024, a total of 190 instances of euthanasia were recorded; 27% of cases occurred in patients who died of AIDS, 41% in patients who died of non-AIDS-defining malignancies, and the remaining 32% 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 32,093 adult PWH ever registered in the SHM database, the incidence of first AIDS-defining events decreased sharply from 120.6 (95% CI 108.1-134.2) in 1996 to 6.2 (5.2-7.4) cases per 1,000 PYFU in 2024 (*Figure 6.1B*). *Appendix Table 6.4* gives an overview of the first AIDS-defining events occurring between 1996 and 2024. The most common first AIDS-defining events between 2020 and 2024 (n=765) were:

- *Pneumocystis jirovecii* pneumonia (21% of all events);
- oesophageal candidiasis (19%);
- recurrent bacterial pneumonia (12%);
- Kaposi's sarcoma (8%);
- AIDS-defining lymphoma (8%);
- tuberculosis (8%, of which pulmonary 4% and extrapulmonary 4%);
- AIDS-related wasting (5%);
- cytomegalovirus-associated end organ disease (4%);
- herpes simplex virus chronic ulcer (4%);
- AIDS dementia complex / HIV encephalopathy (3%); and
- toxoplasmosis of the brain (2%).

Risk factors for AIDS-defining events are shown in *Appendix Table 6.2*.

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;
- were born in a non-Western country;
- 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 virological 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 2024, 27,527 individuals contributed a total of 292.8 thousand PYFU, during which 3,856 CDC-B and/or CDC-C (AIDS-defining events) were diagnosed. This resulted in an incidence rate of 13.2 events per 1,000 PYFU (2,133 CDC-B events, 7.3 events/1,000 PYFU; 1,723 CDC-C/AIDS events, 5.9 events/1,000 PYFU) (*Table 6.2*). 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 of AIDS-defining illnesses in the 200-349 and 350-499 cells/mm^3 strata remained substantial, with 9.8 and 5.4 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 compared to 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 6.6 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 (RR 1.55, 95%CI 1.15-2.11), 60-69 years old (RR 1.79, 95%CI 1.28-2.50), over 70 years old (RR 2.65, 95%CI 1.76-4.00). Of note, the nadir pre-ART CD4 count was not statistically significantly associated with incident AIDS-defining conditions in this analysis.
In the period 2020-2024, Kaposi's sarcoma occurred not much less frequently in people with suppressed viremia (n=35, 40.7%) compared to people not on ART or with poorly controlled viremia (n=51, 59.3%).

Table 6.2: *CDC-B and CDC-C/AIDS events occurring between 2000 and 2024 in individuals on ART, while having an undetectable viral load.*

CD4 category (cells/mm³)	CDC events (n)	CDC B events (n)	CDC C events (n)	PYFU follow-up (x1,000)	Incidence rate CDC events (/1,000 PY) (95%CI)	Incidence rate CDC-B events (/1,000 PY) (95%CI)	Incidence rate CDC-C events (/1,000 PY) (95%CI)
0-50	432	179	253	1.1	411 (373-451)	170 (146-197)	241 (212-272)
50-199	815	419	396	11.4	71.4 (66.6-76.5)	36.7 (33.3-40.4)	34.7 (31.4-38.3)
200-349	749	420	329	33.8	22.2 (20.6-23.8)	12.4 (11.3-13.7)	9.74 (8.72-10.9)
350-499	696	382	314	58.3	11.9 (11.1-12.9)	6.55 (5.91-7.24)	5.39 (4.81-6.02)
500-749	732	453	279	102.2	7.16 (6.65-7.70)	4.43 (4.03-4.86)	2.73 (2.42-3.07)
750+	432	280	152	86.1	5.02 (4.56-5.52)	3.25 (2.88-3.66)	1.77 (1.50-2.07)
Total	3,856	2,133	1,723	292.8	13.2 (12.8-13.6)	7.28 (6.98-7.60)	5.88 (5.61-6.17)

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 2024 a cumulative total of 1,214 cases of tuberculosis were diagnosed in 1,007 individuals, of which 712 (58.7%) were pulmonary cases and 502 (41.3%) were extrapulmonary/disseminated tuberculosis cases. During that same period, 590 cases of atypical mycobacterial infections were diagnosed in 519 individuals: 103 pulmonary and 487 extrapulmonary cases of atypical mycobacterial infections. *Figures 6.2.A* & *B* and *Appendix Table 6.4* describe the incidence over calendar time of tuberculosis and atypical mycobacterial infections.

Geographical region of origin

Migrants who originated from non-Western regions (72.6% of cases, 33.9% of the population) were strongly overrepresented among the tuberculosis cases, while those who were born in the Netherlands (14.9% of cases, 50.6% of the population) were strongly underrepresented. Migrants originating from Western regions (which includes countries from eastern Europe) represented 11.7% of cases and 14.9% of the population. Region of origin was not strongly associated with the incidence of atypical mycobacterial infections. *Table 6.3* 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

4.9% of the individuals diagnosed with pulmonary tuberculosis and 4.6% 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 4.9% for pulmonary and 17.0% 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.

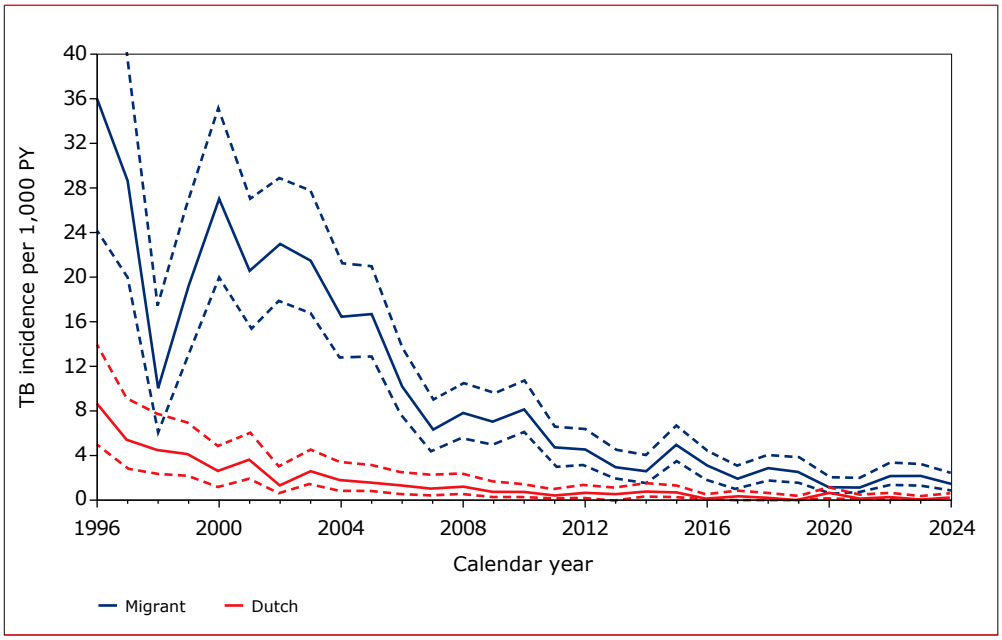
SHM has been collecting data on LTBI screening and treatment since 2018. IGRA testing during an episode in which active TB was diagnosed, was excluded from this dataset. A limitation of our analysis of LTBI screening is that we do not have data on whether, at the time of IGRA testing, the individual had complaints that may have been caused by tuberculosis, which then prompted the treating physician to perform IGRA testing. In 22.5% 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 2,857 individuals. In 280 (9.8%) of these individuals LTBI testing was positive, and 105 (37.5%) of those received a course of LTBI treatment. LTBI treatment consisted of:

- isoniazid plus rifampicin (typically for a duration of three months) in 35 individuals;
- isoniazid monotherapy (typically for a duration of six to nine months) in 53 individuals; and
- rifampicin monotherapy (typically for a duration of four months) in four individuals.

A further 13 individuals received another non-standard treatment. In the 280 individuals who tested positive on LTBI screening, four 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 three cases of pulmonary tuberculosis were diagnosed, 2 of these 3 had received a course of LTBI preventive treatment. Of the 175 individuals with positive LTBI screening who did not receive LTBI treatment, 23 (13.1%) were known to have been diagnosed with and treated for active tuberculosis prior to the LTBI screening.

Figure 6.2A-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).



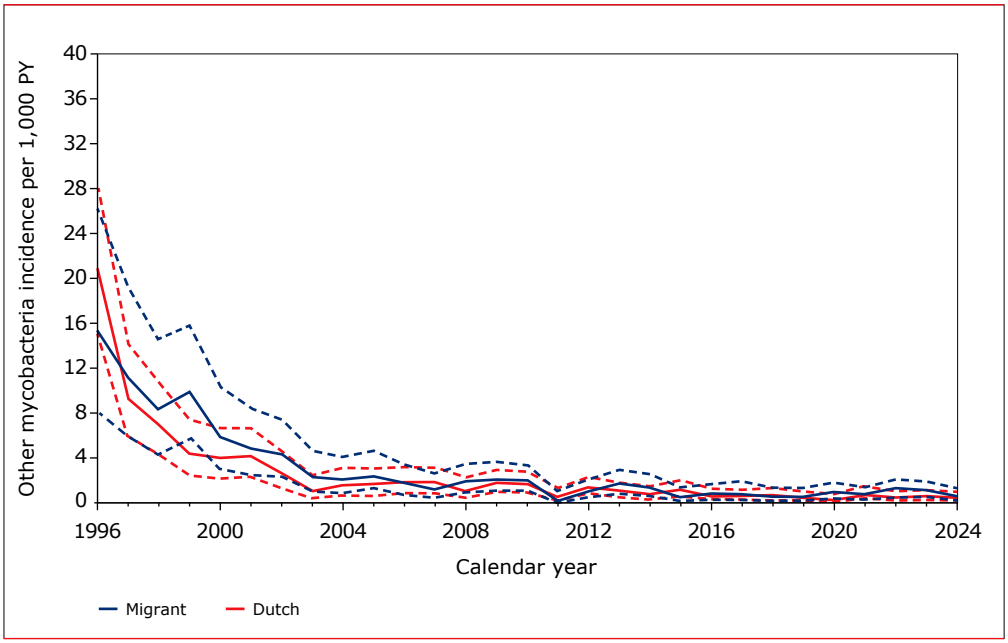


Table 6.3: Characteristics at the time individuals were diagnosed with tuberculosis or atypical mycobacterial infections for the first time.

	Tuberculosis	Atypical mycobacterial infections	p-value
Number of subjects	1,007 (66.0%)	519 (34.0%)	
Age	37 (30.7-44.6)	40.1 (34.5-48.2)	<.001
Transmission category			<.001
MSM	213 (21.2%)	228 (43.9%)	
Other men	374 (37.1%)	156 (30.1%)	
Women	310 (30.8%)	96 (18.5%)	
Transgender	19 (1.9%)	5 (1.0%)	
IDU	61 (6.1%)	25 (4.8%)	
Blood contact	28 (2.8%)	6 (1.2%)	
Pediatric	2 (0.2%)	3 (0.6%)	
Region of origin			<.001
Native Dutch	180 (17.9%)	286 (55.1%)	
Western migrants	95 (9.4%)	60 (11.6%)	
Non-Western migrants	727 (72.2%)	173 (33.3%)	
Unknown origin	5 (0.5%)	0 (0.0%)	
Diagnosed before HIV diagnosis	230 (22.8%)	33 (6.4%)	<.001
Years since HIV diagnosis	0.92 (0.5-4.87)	1.13 (0.58-6.64)	0.006
Years since start cART	0.44 (0-1.25)	0.63 (0.26-1.28)	<.001
CD4 at HIV diagnosis	196 (65-401)	40 (10-200)	<.001
Late HIV diagnosis (CD4<350 at entry in care)	456 (68.3%)	381 (84.1%)	<.001
Advanced HIV diagnosis (CD4<200 at entry in care)	674 (66.9%)	405 (78.0%)	<.001
CD4 nadir	120 (40-250)	20 (10- 50)	<.001
Last CD4 measured before event	200 (86-358)	70 (20-160)	<.001
Not undetectable at date of event	179 (17.8%)	129 (24.9%)	0.001
Not on cART at date of event	717 (71.2%)	251 (48.4%)	<.001

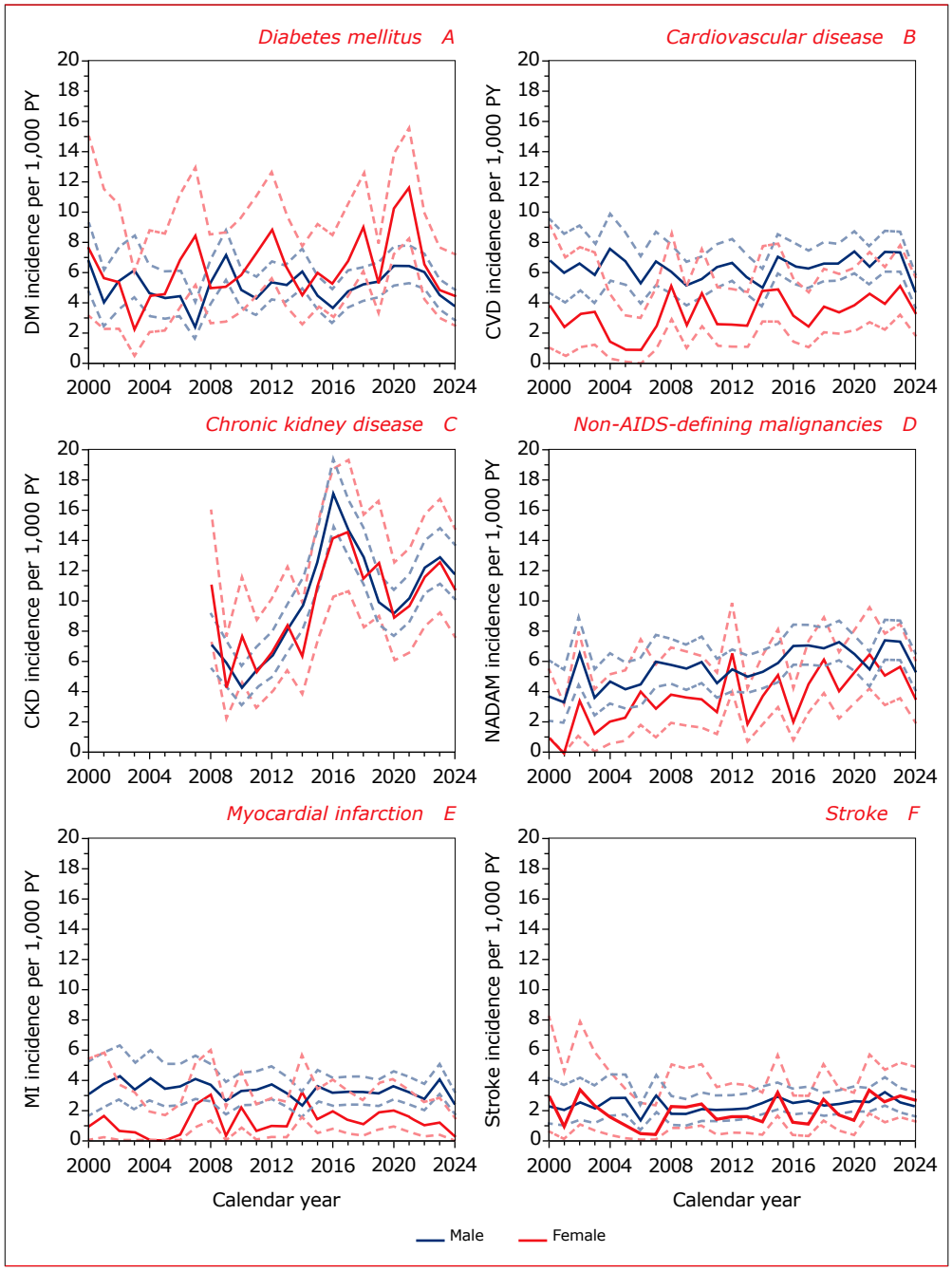
Non-AIDS-defining events

Of the 32,093 adult PWH ever registered with SHM, 31,746 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; 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 6.3A-F*).

Figure 6.3A–F: *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, stratified by gender.*



Diabetes mellitus

Of the 31,746 individuals aged 18 years and over, who were in follow up in, or after January 2000, a total of 2,033 (1,563 men and 470 women) were diagnosed with type 2 diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 6.3A*), and in 2024 was 3.7 (95% CI 2.9-4.8) per 1,000 PYFU in men and 4.4 (2.5-7.2) per 1,000 PYFU in women. In men, the age-standardised incidence ratio declined over time and was significantly lower in 2010-2019 and 2020-2024 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 6.4*).

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;
- hypertension;
- a latest CD4 cell count below 200 cells/mm^3;
- treatment with NRTI mono or dual treatment prior to the modern combination ART era (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 6.5*).

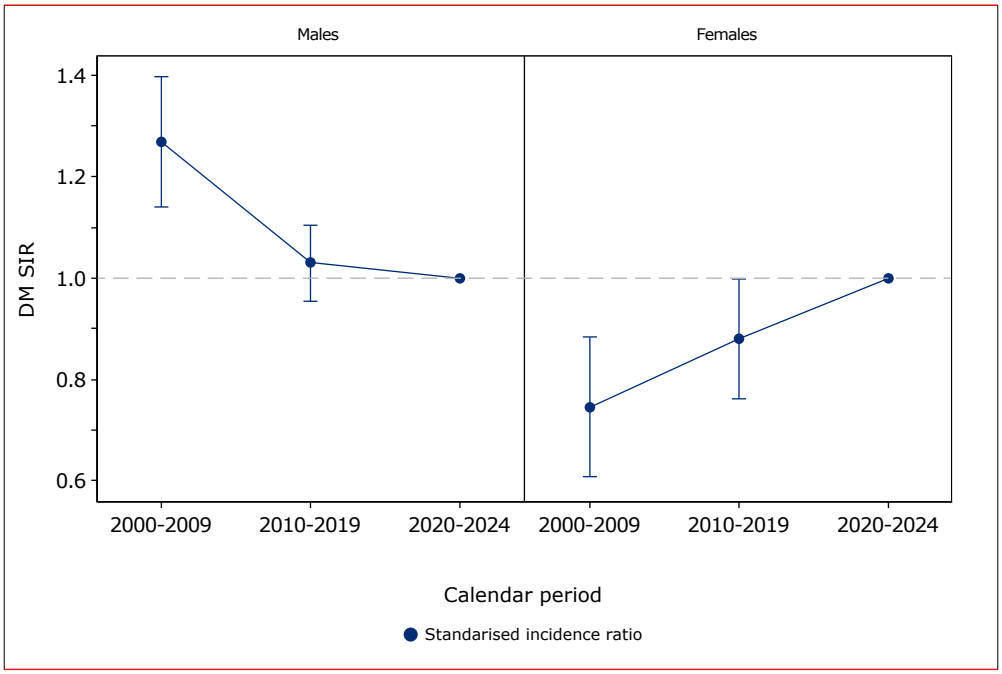
Moreover, the risk of new-onset diabetes in the periods 2000-2009 and 2010-2019 was significantly higher than in the period 2020-2024. Starting ART within 12 months of the last negative HIV test was also associated with a lower risk of new-onset diabetes. Note that multivariate analysis showed that the 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 6.5* & *Figure 6.5*). 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 6.4: *Crude incidence of diabetes mellitus per 1,000 person years of follow up in 2000-2009, 2010-2019 and 2020-2024 and age-standardised incidence ratio (indirect method) with 95% confidence intervals.*

Calendar year	Male		Female	
	Incidence/1,000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1,000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000-2009	5.2 (4.6-5.7)	1.27 (1.14-1.40)	5.7 (4.7-6.8)	0.75 (0.61-0.88)
2010-2019	5.0 (4.7-5.4)	1.03 (0.96-1.11)	6.6 (5.7-7.5)	0.88 (0.76-1.00)
2020-2024	5.5 (5.0-6.0)	1 (reference)	7.6 (6.4-9.0)	1 (reference)

Figure 6.4: *Age-standardised incidence ratio (indirect method) with 95% confidence intervals of diabetes mellitus per 1,000 person years of follow up in 2000-2009, 2010-2019 and 2020-2024.*



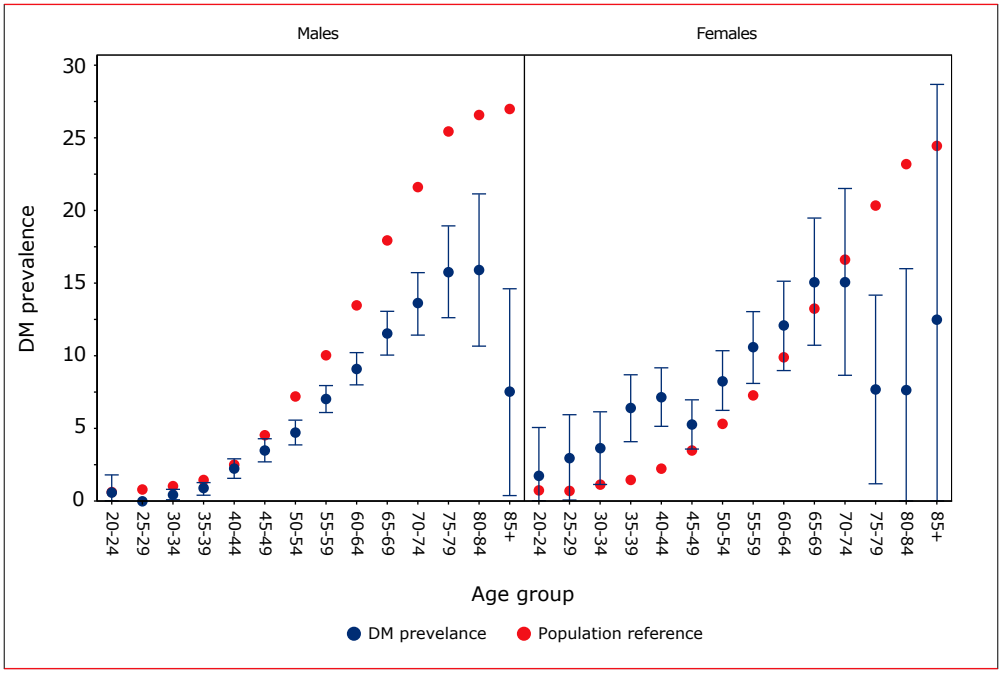
**Standardised according to the observed age distribution between 2020-2024.*

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

Table 6.5: Prevalence of diabetes mellitus in people with HIV stratified by age and sex in 2024, 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 12-9-2025).

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	163	0.6 (0.0-1.8)	0.71	1	58	1.7 (0.0-5.1)	0.7
25-29	0	556	0.0 (0.0-0.0)	0.78	4	132	3.0 (0.1-6.0)	0.75
30-34	6	1,304	0.5 (0.1-0.8)	1.07	8	217	3.7 (1.2-6.2)	1.13
35-39	15	1,705	0.9 (0.4-1.3)	1.51	28	436	6.4 (4.1-8.7)	1.45
40-44	41	1,836	2.2 (1.6-2.9)	2.62	45	626	7.2 (5.2-9.2)	2.22
45-49	72	2,042	3.5 (2.7-4.3)	4.64	36	678	5.3 (3.6-7.0)	3.46
50-54	116	2,425	4.8 (3.9-5.6)	7.16	59	710	8.3 (6.3-10.3)	5.29
55-59	206	2,925	7.0 (6.1-8.0)	10.12	63	596	10.6 (8.1-13.0)	7.3
60-64	238	2,612	9.1 (8.0-10.2)	13.54	52	431	12.1 (9.0-15.1)	9.95
65-69	195	1,684	11.6 (10.1-13.1)	17.96	39	258	15.1 (10.7-19.5)	13.24
70-74	134	986	13.6 (11.5-15.7)	21.71	18	119	15.1 (8.7-21.6)	16.62
75-79	82	519	15.8 (12.7-18.9)	25.52	5	65	7.7 (1.2-14.2)	20.35
80-84	30	188	16.0 (10.7-21.2)	26.65	3	39	7.7 (0.0-16.1)	23.22
85+	4	53	7.5 (0.4-14.7)	27.02	2	16	12.5 (0.0-28.7)	24.4

Figure 6.5: Prevalence of diabetes mellitus in people with HIV stratified by age and sex in 2024, 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 12-9-2025).



Cardiovascular disease

From January 2000 onwards, 2,167 individuals (1,915 men and 252 women) experienced one or more fatal or non-fatal cardiovascular event. Of these individuals:

- 1,040 had a myocardial infarction;
- 819 had a stroke;
- 159 had a coronary artery bypass graft;
- 796 had a coronary angioplasty or stenting; and
- 25 had a carotid endarterectomy.

The crude incidence over time remained stable and was lower in women than in men (*Figure 6.3B*). The age-standardised incidence ratio in men and women declined over time (*Table 6.6* & *Figure 6.6*).

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;
- treatment with NRTI mono or dual treatment prior to the modern combination ART era;
- 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 2020-2024, independent of other variables included in the analysis (*Appendix Table 6.5*). 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 1.49 to 1.42, 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 0.99 (95% CI 0.88-1.11);
- at 30-60 ml/min the IRR was 1.50 (1.27-1.77);
- at 15-30 ml/min, the IRR was 4.22 (3.12-5.72); and
- at 0-15 ml/min the IRR was 3.21 (1.97-5.24).

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 2024 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 6.7* & *Figure 6.7*).

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 6.8* & *Figure 6.8*). 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 6.6 & Figure 6.6: Crude incidence of primary cardiovascular disease per 1,000 person years of follow up in 2000–2009, 2010–2019, and 2020–2024 and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Incidence/1,000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1,000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000–2009	6.3 (5.7–6.9)	1.69 (1.54–1.85)	2.6 (1.9–3.4)	1.37 (0.99–1.74)
2010–2019	6.3 (5.9–6.7)	1.20 (1.12–1.28)	3.5 (2.9–4.2)	1.11 (0.91–1.31)
2020–2024	6.7 (6.1–7.3)	1 (reference)	4.2 (3.4–5.3)	1 (reference)

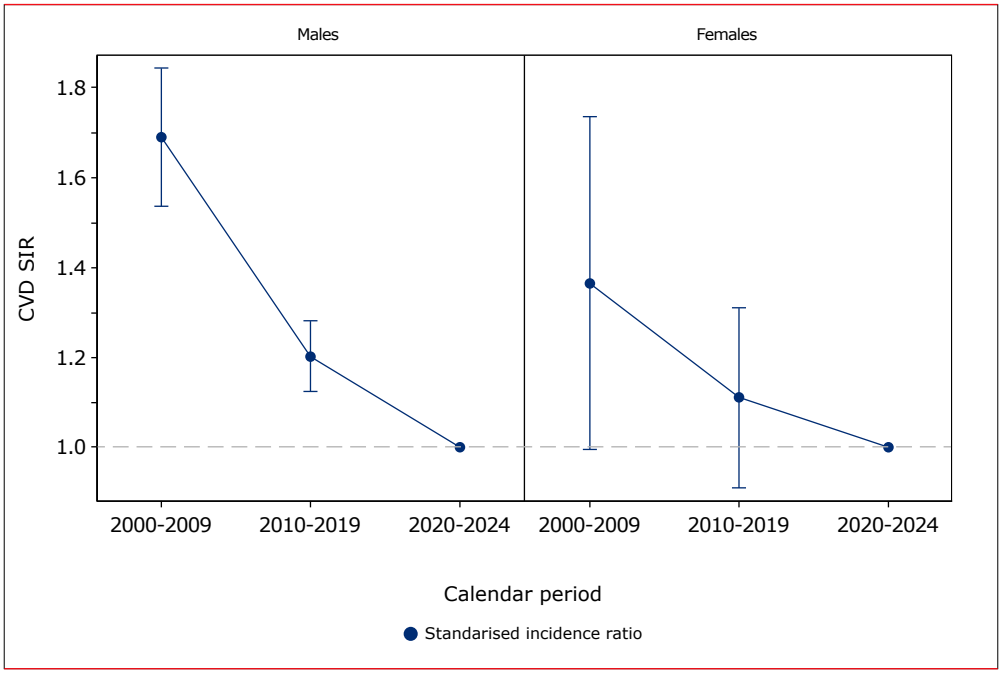
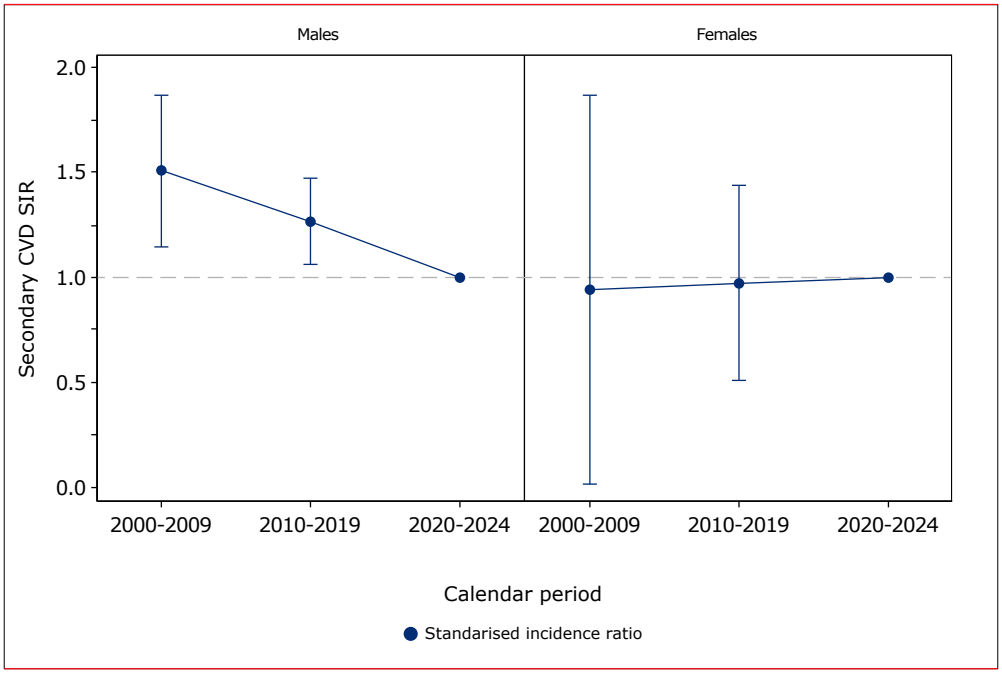


Table 6.7 & Figure 6.7: Crude incidence of secondary cardiovascular disease per 1,000 person years of follow up in 2000-2009, 2010-2019, and 2020-2024 and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Incidence/1,000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1,000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000-2009	29.9 (23.3-37.9)	1.51 (1.16-1.87)	13.8 (3.8-35.4)	0.94 (0.02-1.87)
2010-2019	26.2 (22.1-30.8)	1.27 (1.06-1.47)	20.9 (12.2-33.5)	0.98 (0.51-1.44)
2020-2024	21.0 (16.8-25.8)	1 (reference)	21.5 (11.5-36.8)	1 (reference)



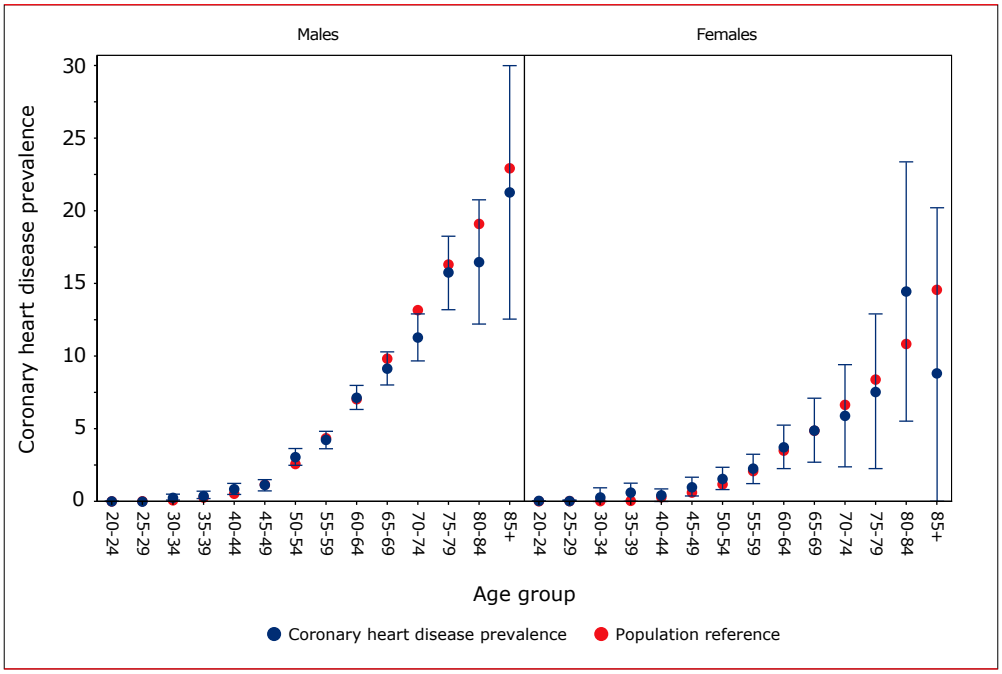
**Standardised according to the observed age distribution in 2020-2024.*

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

Table 6.8 & Figure 6.8 : Prevalence of coronary artery disease in people with HIV stratified by age and sex in 2024, compared to the prevalence observed in the general Dutch population in 2024 (https://www.staatvenz.nl/kerncijfers/coronaire-hartziekten-aantal-patiënten-bekend-bij-de-huisarts, accessed 12-9-2025).

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	163	0.0 (0.0-0.0)	0.03	0	58	0.0 (0.0-0.0)	0.02
25-29	0	556	0.0 (0.0-0.0)	0.05	0	132	0.0 (0.0-0.0)	0.03
30-34	5	1,304	0.4 (0.0-0.7)	0.11	1	217	0.5 (0.0-1.4)	0.05
35-39	11	1,705	0.6 (0.3-1.0)	0.29	4	436	0.9 (0.0-1.8)	0.13
40-44	23	1,836	1.3 (0.7-1.8)	0.71	4	626	0.6 (0.0-1.3)	0.36
45-49	33	2,042	1.6 (1.1-2.2)	1.69	10	678	1.5 (0.6-2.4)	0.84
50-54	106	2,425	4.4 (3.6-5.2)	3.62	16	710	2.3 (1.2-3.3)	1.67
55-59	176	2,925	6.0 (5.2-6.9)	6.32	19	596	3.2 (1.8-4.6)	2.94
60-64	266	2,612	10.2 (9.0-11.3)	9.92	23	431	5.3 (3.2-7.5)	4.93
65-69	219	1,684	13.0 (11.4-14.6)	13.97	18	258	7.0 (3.9-10.1)	6.96
70-74	158	986	16.0 (13.7-18.3)	18.72	10	119	8.4 (3.4-13.4)	9.46
75-79	116	519	22.4 (18.8-25.9)	23.2	7	65	10.8 (3.2-18.3)	11.91
80-84	44	188	23.4 (17.4-29.5)	27.11	8	39	20.5 (7.8-33.2)	15.43
85+	16	53	30.2 (17.8-42.5)	32.57	2	16	12.5 (0.0-28.7)	20.65

Legend: *CI = confidence intervals.*



Trends in cardiovascular risk factors

Figures 6.9A and *6.9B* 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 2024, 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 37.2%, 10.2% and 2.7%, respectively. In women, these proportions were 31.5%, 19.7% and 12.9%, respectively.

Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the population 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 6.9A–B: *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. 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.*

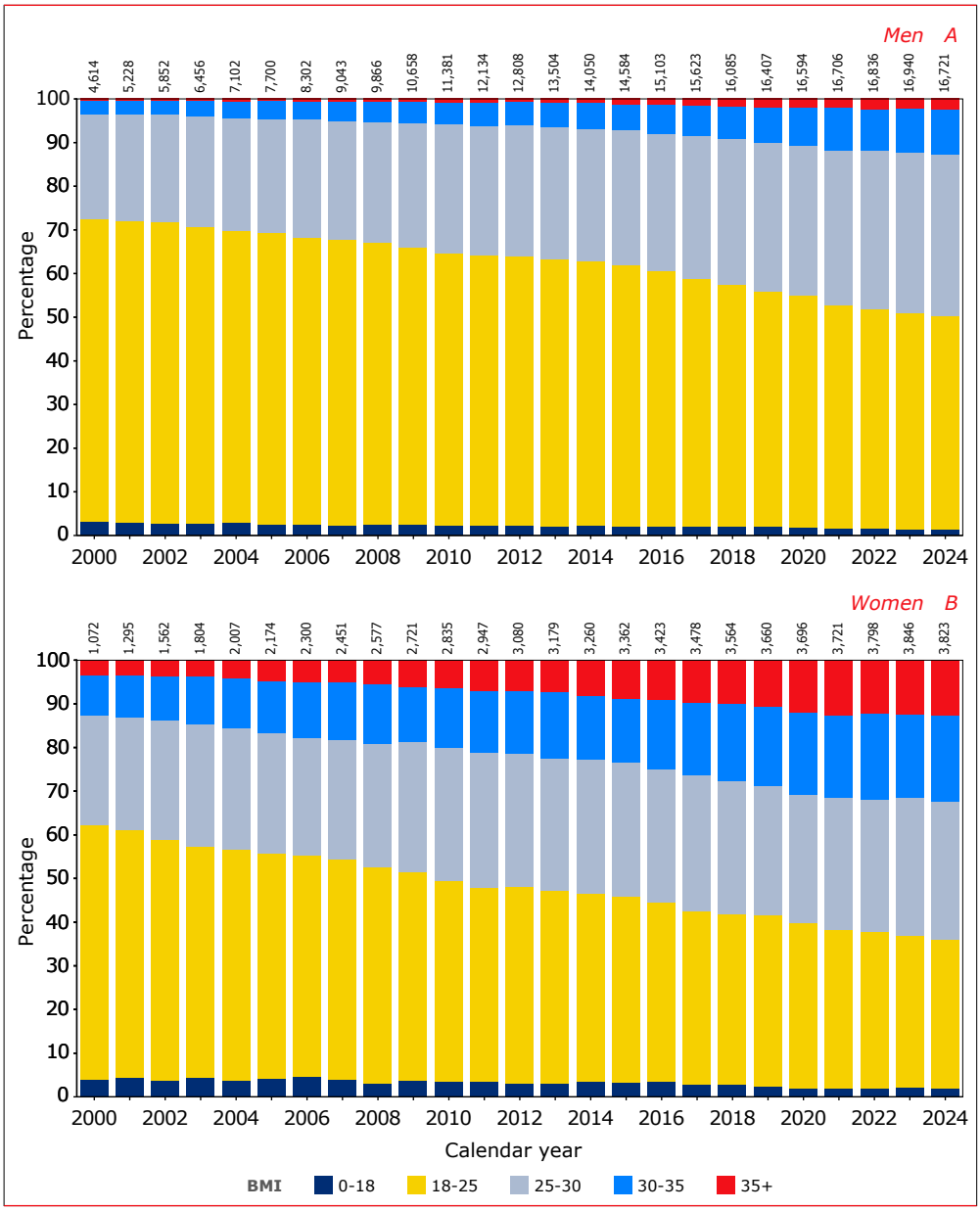


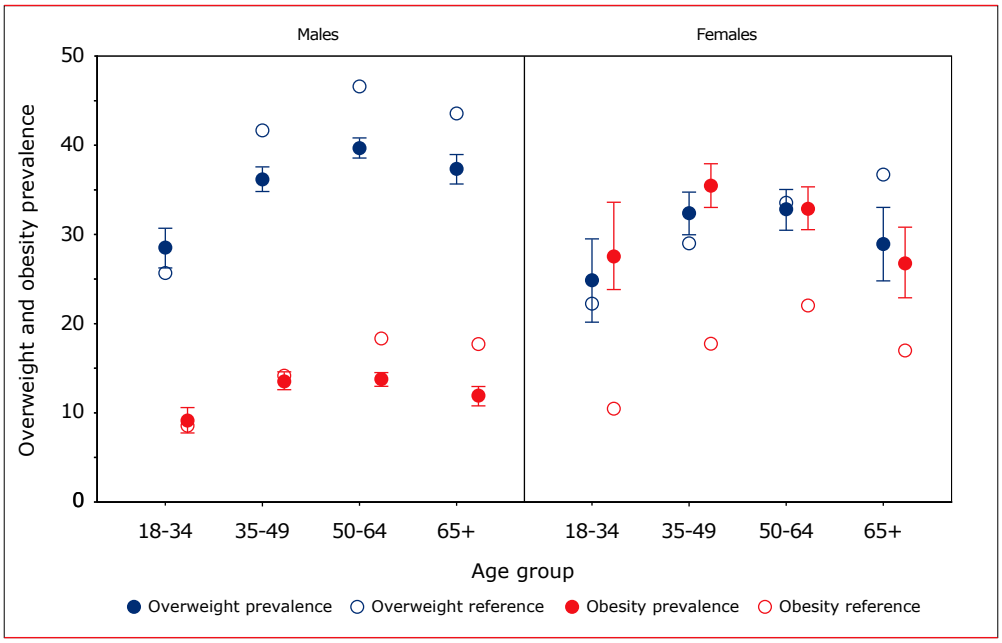
Table 6.9 and *Figure 6.10* shows a comparison with the general Dutch population of the age- and sex-stratified prevalence of overweight and obesity in 2024. Males aged 35 and older were significantly less often overweight or obese than the general Dutch male population, while women in all age strata were more likely to be obese. Whereas in adult men of all age groups, the proportion classified as obese (13.0%) was somewhat lower than the proportion found in the general Dutch male population (14.6%), in women of all age groups there was more obesity (32.7%) than in the general Dutch female population (16.8%)[45].

There were substantial differences between those of Dutch origin, Western migrants and non-Western migrants: among males, 11.7% of Dutch men, 13.2% of Western migrants and 15.9% of non-Western migrants were obese. In females, however, those figures were 23.7%, 23.6%, and 38.7%, 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 2.09, 95%CI 1.86-2.36, p<0.001; obese IRR 5.10, 95%CI 4.47-5.82, p<0.001), as well as with CKD (overweight IRR 1.18, 95%CI 1.08-1.28, p<0.001; obese IRR 1.15, 95%CI 1.02-1.30, p=0.023) (*Appendix Table 6.5*). Overweight and obesity were not associated with an increased risk of CVD and non-AIDS malignancies.

Table 6.9: *Age- and sex-stratified prevalence of overweight and obesity in 2024, compared to the general Dutch population in 2024 (source: https://www.vzinfo.nl/overgewicht/volwassenen, accessed 12-9-2025).*

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	1,560	446	28.6 (26.3-30.8)	25.7	143	9.2 (7.7-10.6)	8.5
35-49	4,752	1,722	36.2 (34.9-37.6)	41.7	646	13.6 (12.6-14.6)	14.3
50-64	7,235	2,875	39.7 (38.6-40.9)	46.6	999	13.8 (13.0-14.6)	18.4
65+	3,174	1,185	37.3 (35.7-39.0)	43.6	379	11.9 (10.8-13.1)	17.7
Females							
18-34	330	82	24.8 (20.2-29.5)	22.3	95	28.8 (23.9-33.7)	10.5
35-49	1,458	472	32.4 (30.0-34.8)	29.1	517	35.5 (33.0-37.9)	17.8
50-64	1,571	515	32.8 (30.5-35.1)	33.6	512	32.6 (30.3-34.9)	22
65+	469	136	29.0 (24.9-33.1)	36.7	126	26.9 (22.9-30.9)	17

Figure 6.10: Distribution of the body mass index (BMI) over the age groups for men, and women, in 2024, compared to the general Dutch population in 2024.



Legend: BMI = body mass index.

Chapter 10 on Quality of Care contains more information on the 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[26]. 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[46,47]. 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 6.11A* and *6.11B* for men and women. The percentage of men with normal kidney function decreased over time from 74.5% in 2007, to 40.1% in 2024, and this pattern was similar in women. Typically, eGFR decreases with increased age, as shown in *Figure 6.12*, 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

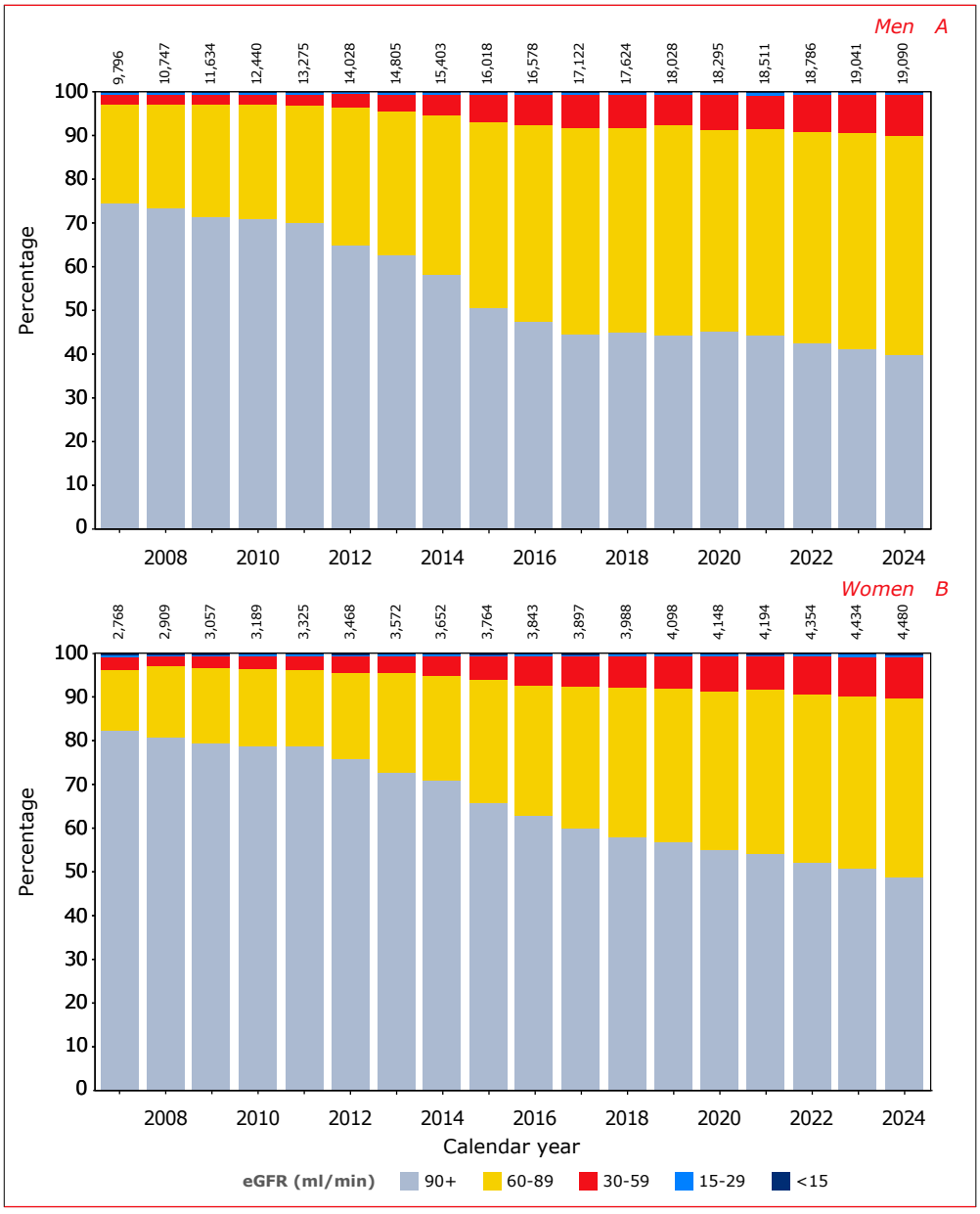
In individuals with an eGFR above 60ml/min/1.73m^2 at the time of inclusion in the analyses, who did not have a previously confirmed CKD, the crude incidence of CKD (defined as eGFR below 60ml/min/1.73m^2 confirmed by a second test at least 26 weeks later) varied over time (*Figure 6.3C*). Routine collection 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 10.2 in 2020-2024. In women, the incidence rose from 10.4 to 10.8 cases per 1,000 PYFU during the same periods (*Table 6.10*). However, the age-standardised incidence ratio in men and women was significantly lower in the 2020-2024 period (*Table 6.10*).

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;
- treatment with NRTI mono or dual treatment prior to the modern combination ART era; and
- chronic HBV and HCV co-infection (*Appendix Table 6.5*).

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 6.11A-B: *Distribution of categories of estimated glomerular filtration rate (eGFR) at the end of each calendar year in (A) men, and (B) women. For each individual, the last available measurement in each year was selected. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.*



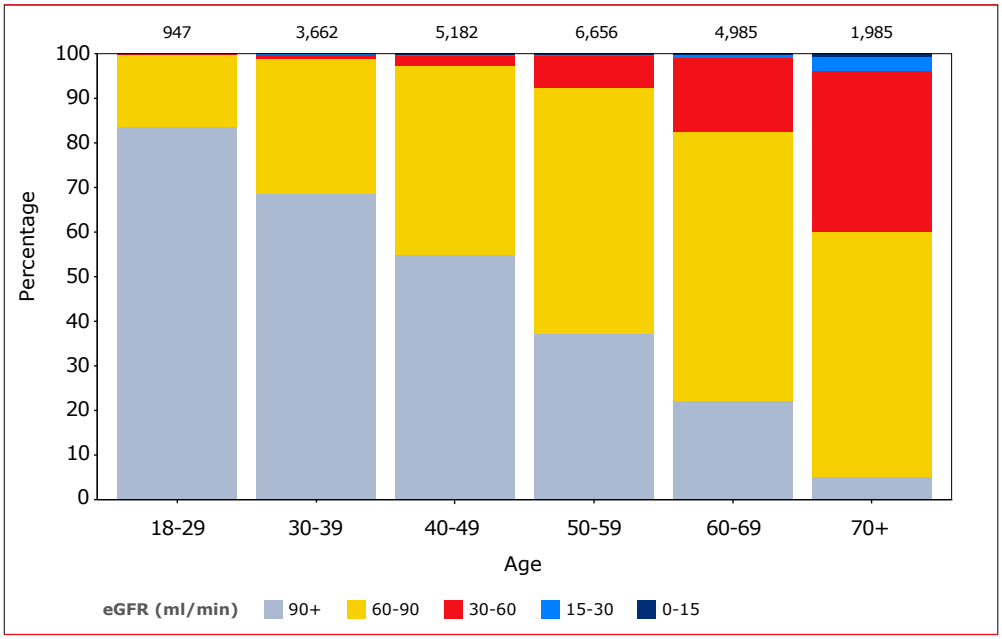
Legend: *eGFR = estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60-89 ml/min/1.73m²: mildly reduced; 30-59 ml/min/1.73m²: moderately reduced; 15-29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

Table 6.10: Crude chronic kidney disease incidence per 1,000 person years of follow up in 2008–2019, and 2020–2024, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Incidence/1,000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1,000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2008–2019	9.9 (9.3–10.5)	1.30 (1.21–1.38)	10.4 (9.0–11.8)	1.37 (1.19–1.55)
2020–2024	10.2 (9.4–11.0)	1 (reference)	10.8 (9.1–12.8)	1 (reference)

**Standardised according to the observed age distribution in 2020–2024.*
***Legend:** CI = confidence interval; PYFU = person years.*

Figure 6.12: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2024 for different age categories. For each individual, the last available measurement in 2024 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 2024, 2,669 diagnoses of non-AIDS-defining malignancies (NADM) in 2,445 unique individuals were recorded in SHM's database. An additional 1,108 patients were diagnosed with one or more non-melanoma skin cancers, but these were not included in the present analysis. *Table 6.11* 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) (13.5%);
- prostate cancer (11.5%);
- invasive anal cancer (excluding pre-malignant AIN, 11.3%);
- haematological malignancies (excluding AIDS-defining non-Hodgkin's lymphoma, 11.1%); and
- head and neck cancers (8.2%).

Figure 6.13A 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 6.13B*, 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 over time of NADM in men and women is shown in *Figure 6.3D*. The age-standardised incidence in men statistically significantly decreased over time (*Table 6.12* & *Figure 6.14*). 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.

Demographic and clinical factors independently associated with an increased risk of a first non-AIDS-defining malignancy were (*Appendix Table 6.5*):

- 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 received NRTI mono or dual treatment prior to the initiation of modern combination ART had an independently increased risk for NADM, compared with those who were therapy-naïve prior to starting ART (relative risk [RR] 1.18, 95% CI 1.03-1.34). 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 0.79, 95% CI 0.60-1.06) 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 2024, the overall five-year survival rate following the most common non-AIDS-defining malignancies are shown in *Table 6.11* and *Figure 6.15*. Table 5.7 also shows the distribution and crude 5-year survival rates of the subgroup of NADM diagnosed in the last 10 years of follow-up. For nearly all 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).

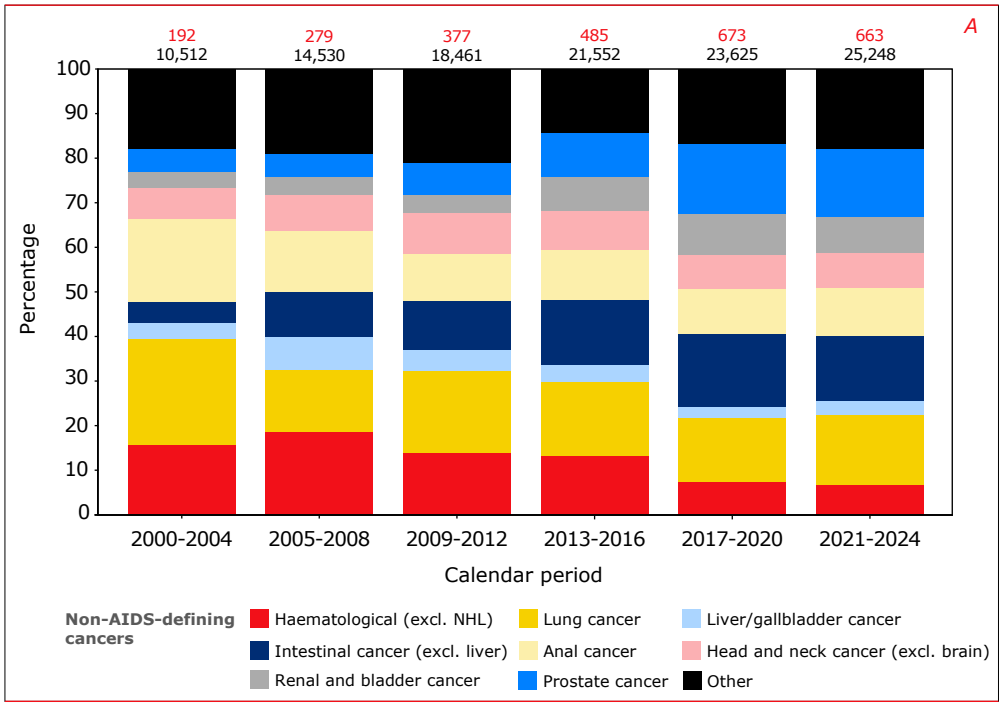
We calculated the age- and sex-stratified incidence of non-AIDS-defining malignancy (including non-melanoma skin cancer) per 1,000 person years of follow up in the period 2015-2024, and compared with the incidence in the general Dutch population in 2024 (*Table 6.13* & *Figure 6.16*). The incidence of 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.

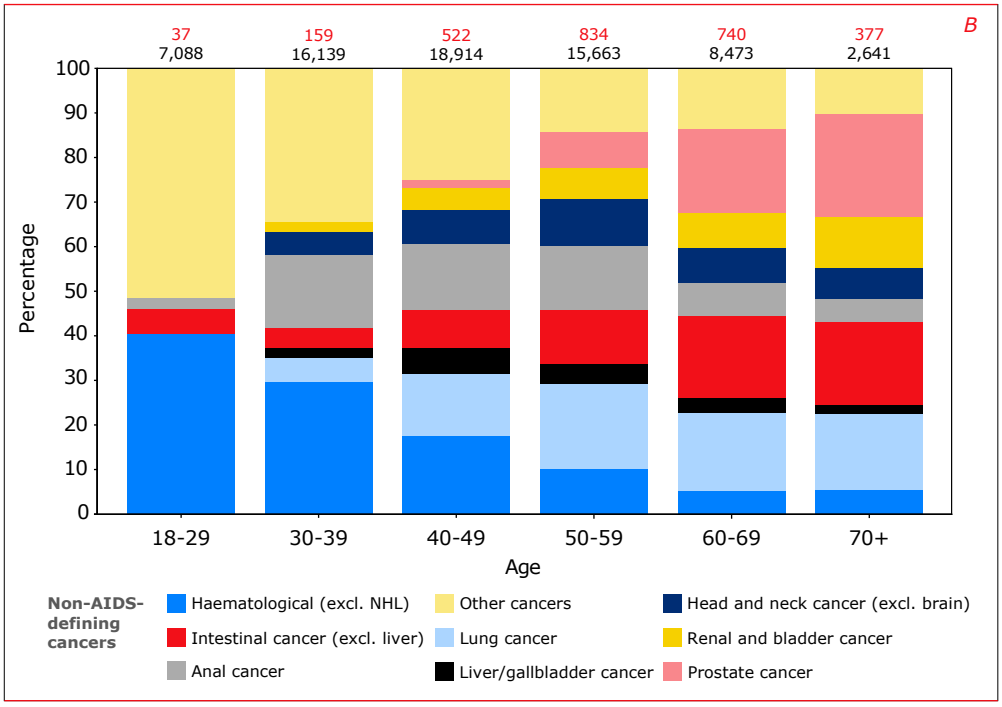
Table 6.11: Most common non-AIDS-defining malignancies diagnosed in 2000-2024, and a subgroup diagnosed in the last 10 year between 2014-2024, excluding non-melanoma skin cancer and pre-malignant lesions found by cervical and anal screening.

	2000-2024			2014-2024		
Non-AIDS malignancy	**# of malignancies**	**%**	**Five-year survival (%)**	**# of malignancies**	**%**	**Five-year survival (%)**
Lung cancer	437	16.4	17.5	263	15.3	23.2
Intestinal cancer (excl. liver)	361	13.5	33.5	269	15.6	33.0
Prostate cancer	307	11.5	78.9	249	14.5	78.9
Anal cancer	302	11.3	67.5	177	10.3	69.8
Hematological (excl. NHL)	295	11.1	65.1	148	8.6	66.7
Head and neck cancer (excl. brain)	218	8.2	55.9	137	8.0	57.3
Renal and bladder cancer	187	7.0	63.7	146	8.5	62.1
Other cancers	128	4.8	41.8	75	4.4	40.5
Malignant melanoma	125	4.7	78.2	78	4.5	84.6
Liver/gallbladder cancer	100	3.7	14.3	49	2.8	17.5
Breast cancer	79	3.0	78.8	50	2.9	74.1
Testicular cancer	49	1.8	90.9	24	1.4	90.6
Gynecological cancer (excl. cervical)	41	1.5	70.0	24	1.4	68.0
CNS cancer	40	1.5	51.8	34	2.0	42.3

***Legend:** CNS = central nervous system; excl. = excluding; NHL = non-Hodgkin's lymphoma.*

Figure 6.13A-B: *Relative changes in non-AIDS-defining malignancies (A) between 2000 and 2024 and (B) with increasing age, 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).*

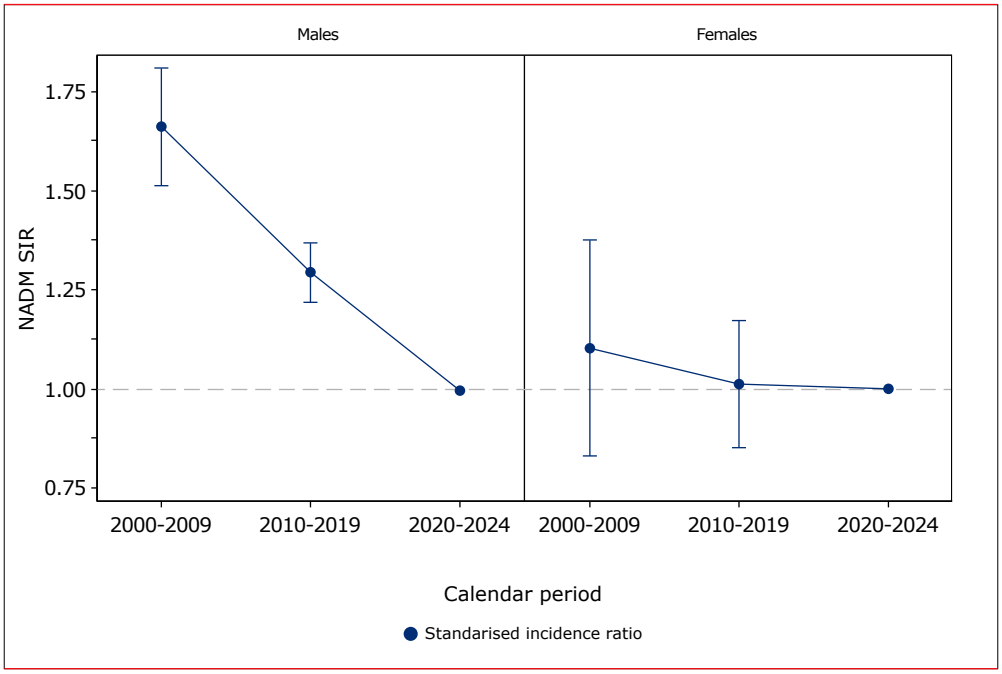




Legend: excl. NHL = excluding non-Hodgkin's lymphoma.

Table 6.12 & Figure 6.14: *Crude non-AIDS-defining malignancy incidence per 1,000 person years of follow up in 2000-2009, 2010-2019, and 2020-2024, and age-standardised incidence ratio with 95% confidence intervals.*

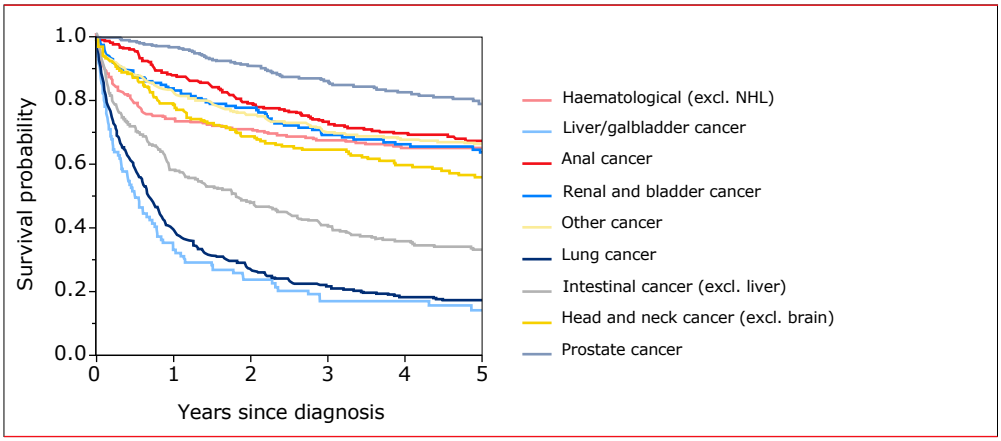
Calendar year	Male		Female	
	Incidence/1,000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1,000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000-2009	6.4 (5.9-7.0)	1.66 (1.51-1.81)	3.1 (2.4-4.0)	1.10 (0.83-1.38)
2010-2019	7.5 (7.1-7.9)	1.30 (1.22-1.37)	4.4 (3.8-5.2)	1.01 (0.85-1.17)
2020-2024	7.9 (7.3-8.5)	1 (reference)	5.9 (4.9-7.0)	1 (reference)



**Standardised according to the observed age distribution in 2020-2024.*

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

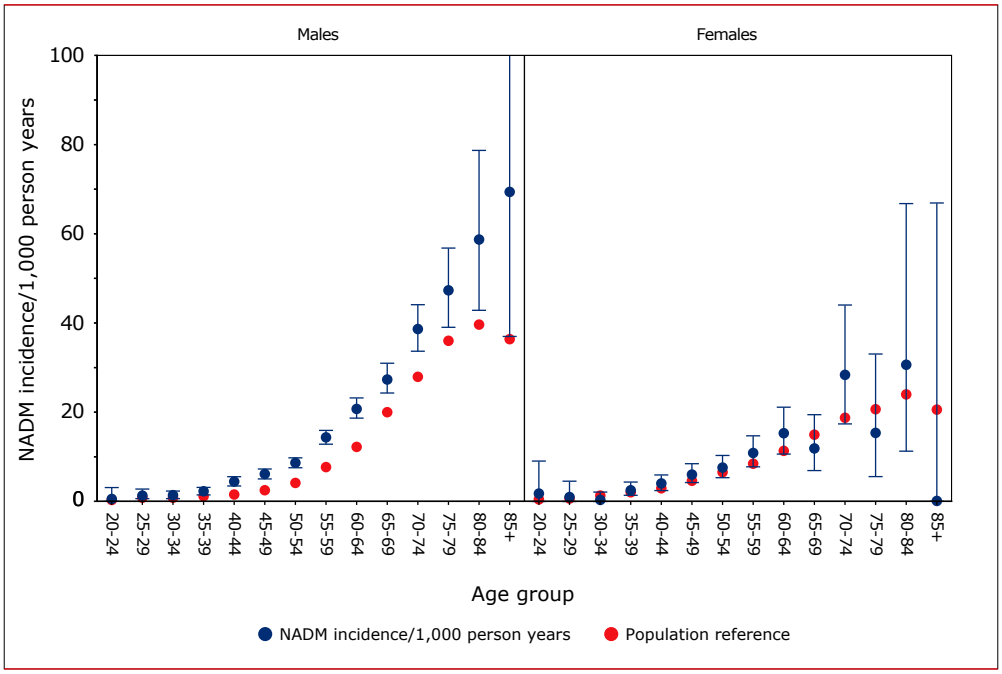
Figure 6.15: *Estimated five-year survival following the diagnosis of the most common non-AIDS-defining malignancies diagnosed between 1 January 2000 and 31 December 2024.*



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

Table 6.13 & Figure 6.16: *Age- and sex-stratified incidence of non-AIDS-defining malignancy (including non-melanoma skin cancer) per 1,000 person years of follow up in 2015-2024, compared to the incidence in the general Dutch population in 2024 (https://www.vzinfo.nl/kanker/leeftijd-en-geslacht, accessed 12-9-2025).*

Age categories	Males				Females			
	Person-years of follow-up	Number of NADM	Incidence/ 1,000PY (95%CI)	Incidence general population	Person-years of follow-up	Number of NADM	Incidence/ 1,000PY (95%CI)	Incidence general population
20-24	1825	1	0.5 (0.0-3.1)	0.32	618	1	1.6 (0.0-9.0)	0.32
25-29	6374	9	1.4 (0.6-2.7)	0.58	1268	1	0.8 (0.0-4.4)	0.63
30-34	11129	14	1.3 (0.7-2.1)	0.75	2819	1	0.4 (0.0-2.0)	1.24
35-39	13761	31	2.3 (1.5-3.2)	1.08	4447	11	2.5 (1.2-4.4)	2.07
40-44	16629	76	4.6 (3.6-5.7)	1.54	5444	21	3.9 (2.4-5.9)	3.28
45-49	20853	128	6.1 (5.1-7.3)	2.41	5858	36	6.1 (4.3-8.5)	4.7
50-54	25278	219	8.7 (7.6-9.9)	4.22	5188	39	7.5 (5.3-10.3)	6.32
55-59	23243	334	14.4 (12.9-16.0)	7.63	3861	42	10.9 (7.8-14.7)	8.27
60-64	15973	334	20.9 (18.7-23.3)	12.28	2421	37	15.3 (10.8-21.1)	10.94
65-69	9888	272	27.5 (24.3-31.0)	20.07	1336	16	12.0 (6.8-19.5)	15.07
70-74	5648	218	38.6 (33.6-44.1)	27.9	702	20	28.5 (17.4-44.0)	18.66
75-79	2413	114	47.2 (39.0-56.8)	35.96	395	6	15.2 (5.6-33.1)	20.65
80-84	766	45	58.7 (42.8-78.6)	39.74	196	6	30.6 (11.2-66.7)	24.02
85+	187	13	69.5 (37.0-119)	36.42	55	0	0.0 (0.0-66.9)	20.69



Multimorbidity

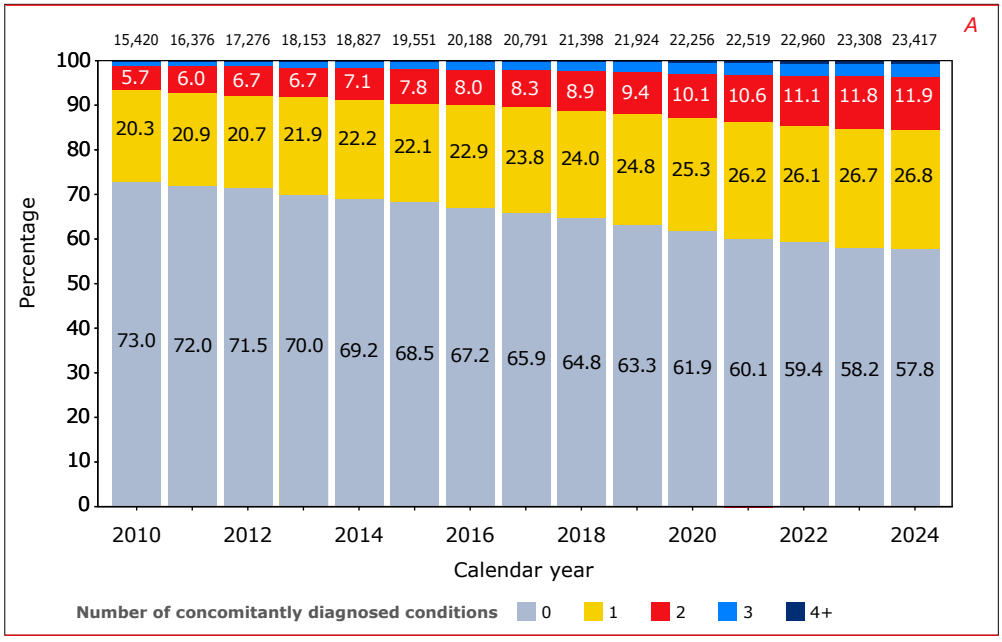
We investigated changes over time in the prevalence of non-AIDS multimorbidity. HIV infections and AIDS diagnoses did not contribute to the multimorbidity count. The following comorbidities and conditions were taken into account:

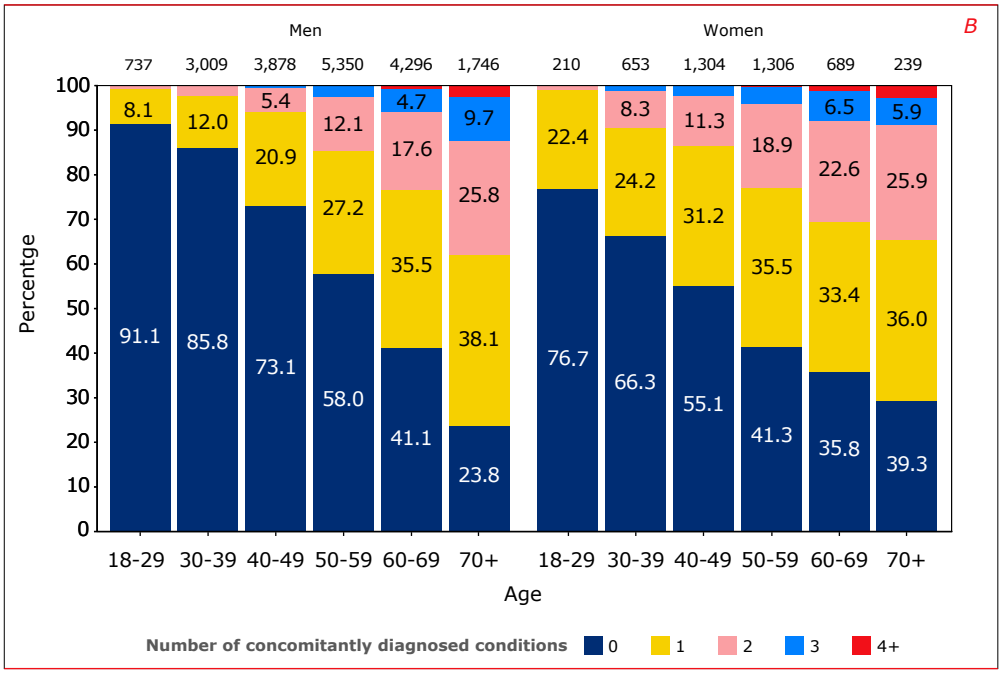
1. **Cardiovascular disease** (either myocardial infarction, coronary artery bypass grafting, coronary angioplasty or stenting, and carotid endarterectomy)
2. **Stroke**
3. **Non-AIDS-defining malignancies**, excluding non-melanoma skin cancers and pre-malignant lesions found at cervical/anal screening
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 160 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.

Figure 6.17A shows the prevalence of each individual comorbidity over calendar time. *Figure 6.17B* shows the distribution of the number of concomitantly-diagnosed conditions in various age categories of the adult male and female population in 2024. The number of concomitant conditions was slightly higher in women than in men for all age categories. After adjusting for the variables listed in *Appendix Table 6.2*, multimorbidity was independently associated with increased risk of mortality (RR 2.04 (1.97-2.11), p<0.001, per additional comorbidity diagnosed).

Figure 6.17A-B: *(A) Prevalence of non-AIDS multimorbidity in the adult population over calendar time. (B) Prevalence of non-AIDS multimorbidity by gender in the adult population in 2024. 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[a]) of the comedications. Note that coformulated combinations, such as cotrimoxazole, have a single ATC code and therefore increase the comedication count by one.

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

In 2024, 26.3% of adults in active follow up had no recorded comedication use, 26.4% used one comedication, 14.3% used two comedications, 9.5% used three comedications, and 6.5% used four comedications. A further 16.9% 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 6.18*): 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 6.19*) 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 2007-2024, polypharmacy was also associated with an increased risk of death (RR 2.31 (2.11-2.53), $p<0.001$) 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 2024 are listed in *Table 6.14*. A notable difference with what we reported last year is that in 2024 lipid lowering agents were used by 6,209 individuals compared to 5,155 individuals in 2023, an increase of 20.4% caused by the guideline change for primary CVD prophylaxis based on the findings of the REPRIEVE study[7].

Table 6.14: Use of comedications in 2024.

Comedication use in 2024	N	%
ATC group		
Vitamins	6732	10.8
Lipid modifying agents	6209	10.0
Drugs for acid related disorders	4330	6.9
Agents acting on the renin-angiotensin system	3947	6.3
Psycholeptics drugs (antipsychotics, anxiolytics, hypnotics, sedatives)	3703	5.9
Antithrombotic agents	3307	5.3
Drugs for obstructive airway diseases	3175	5.1
Drugs used in diabetes	2882	4.6
Psychoanaleptics (antidepressants, psychostimulants)	2614	4.2
Urological drugs	2039	3.3
Calcium channel blockers	1933	3.1
Mineral supplements	1912	3.1
Beta blocking agents	1867	3.0
Antianemic drugs	1360	2.2
Antibacterial drugs	1348	2.2
Diuretic drugs	1337	2.1
Analgesic drugs	1327	2.1
Sex hormones and modulators of the genital system	1260	2.0
Topical dermatological corticosteroids	1199	1.9
Corticosteroids systemic	1137	1.8
Cardiac therapy	862	1.4
Nasal preparations	825	1.3
Antiviral drugs	776	1.2
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	558	0.9
Antiepileptic drugs	540	0.9
Antimycotic drugs	510	0.8
Drugs affecting bone structure and mineralization	483	0.8
Immunosuppressants drugs	434	0.7
Thyroid therapy	396	0.6
Ophthalmological drugs	380	0.6
Other nervous system drugs	263	0.4
Anti-inflammatory and antirheumatic drugs	251	0.4

Figure 6.18: 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.

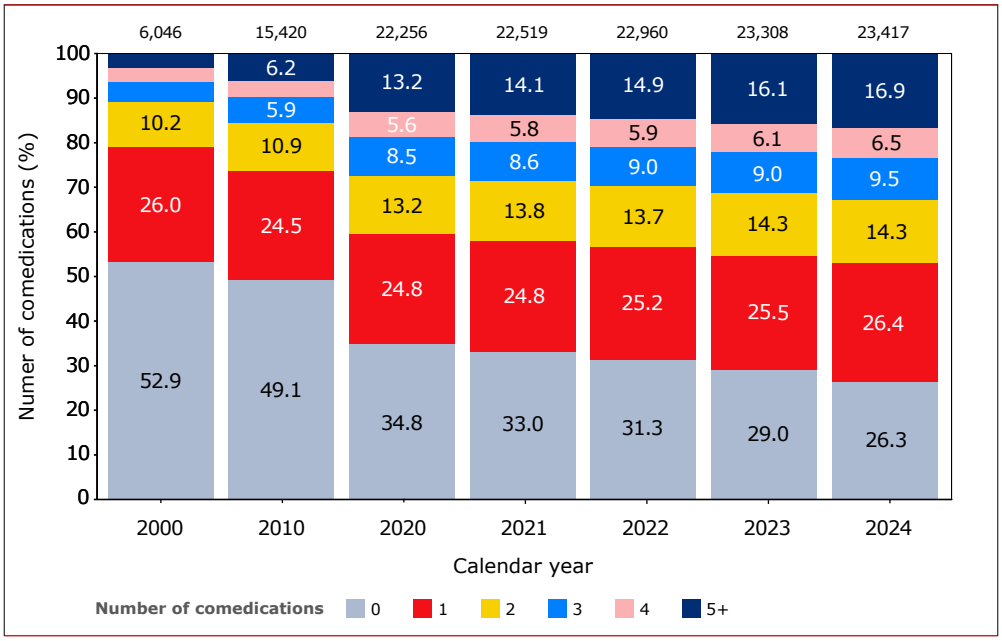
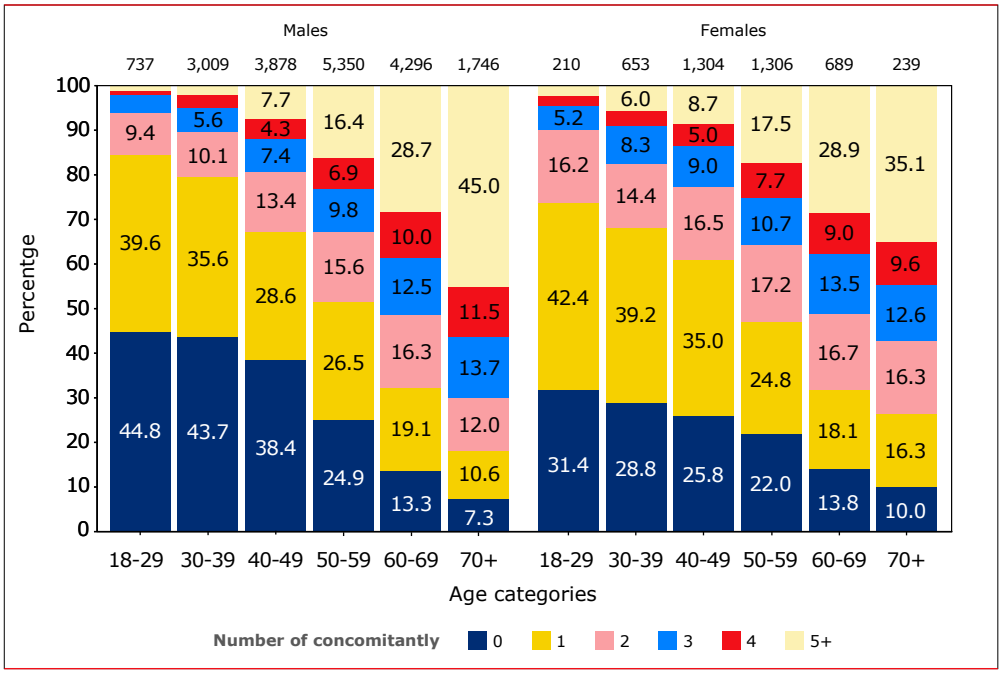


Figure 6.19: Number of comedications used by age group and gender in 2024. The numbers at the top of each bar represent the number of individuals contributing data to that age/gender category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



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Appendix: supplementary tables

Appendix Table 6.1: *Absolute number of causes of death among PWH during the periods 1996–2024.*

Cause of death	1996–2000		2001–2003		2004–2006	
	n	%	n	%	n	%
AIDS (subtotal)	221	55.7	130	38.3	159	39.1
Infection	71	17.9	57	16.8	94	23.1
Malignancy	61	15.4	32	9.4	47	11.5
Unclassifiable	89	22.4	41	12.1	18	4.4
Non-AIDS malignancies	30	7.6	50	14.7	63	15.5
CVD (subtotal)	23	5.8	29	8.6	51	12.5
MI	12	3.0	8	2.4	18	4.4
Stroke	3	0.8	5	1.5	7	1.7
Other CVD	8	2.0	16	4.7	26	6.4
Non-AIDS infection	21	5.3	31	9.1	16	3.9
Liver disease	15	3.8	12	3.5	28	6.9
Lung disease	7	1.8	9	2.7	8	2.0
Non-natural death (subtotal)	25	6.3	27	8.0	28	6.9
Accident / violence	6	1.5	9	2.7	8	2.0
Suicide	12	3.0	16	4.7	17	4.2
Euthanasia	7	1.8	2	0.6	3	0.7
Alcohol, substance abuse, psychiatric disease	12	3.0	10	2.9	10	2.5
Other causes	21	5.3	13	3.8	14	3.4
Unknown	22	5.5	28	8.3	30	7.4
Sudden death	.	.	.	.	.	.
Total	**397**	**100**	**339**	**100**	**407**	**100**

Legend: *CVD = cardiovascular disease.*

2007–2000		2010–2012		2013–2015		2016–2018		2019–2021		2022–2024	
n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
150	32.3	111	25.6	90	19.2	63	11.8	55	9.0	73	10.4
100	21.6	76	17.5	51	10.9	14	2.6	16	2.6	27	3.8
38	8.2	29	6.7	29	6.2	32	6.0	26	4.2	38	5.4
12	2.6	6	1.4	10	2.1	17	3.2	13	2.1	8	1.1
90	19.4	103	23.7	119	25.4	158	29.7	218	35.6	192	27.3
52	11.2	56	12.9	63	13.5	68	12.8	86	14.1	91	12.9
18	3.9	18	4.1	19	4.1	12	2.3	37	6.0	22	3.1
6	1.3	12	2.8	6	1.3	13	2.4	12	2.0	17	2.4
28	6.0	26	6.0	38	8.1	43	8.1	37	6.0	52	7.4
23	5.0	12	2.8	17	3.6	20	3.8	54	8.8	37	5.3
33	7.1	28	6.5	26	5.6	22	4.1	6	1.0	9	1.3
17	3.7	17	3.9	29	6.2	36	6.8	34	5.6	35	5.0
35	7.5	34	7.8	43	9.2	47	8.8	34	5.6	43	6.1
15	3.2	9	2.1	9	1.9	13	2.4	8	1.3	20	2.8
20	4.3	24	5.5	33	7.1	33	6.2	26	4.2	22	3.1
.	.	1	0.2	1	0.2	1	0.2	.	.	1	0.1
21	4.5	20	4.6	14	3.0	19	3.6	20	3.3	16	2.3
13	2.8	17	3.9	20	4.3	38	7.1	42	6.9	71	10.1
30	6.5	36	8.3	46	9.8	61	11.5	63	10.3	71	10.1
.	.	.	.	1	0.2	.	.	.	.	65	9.2
464	**100**	**434**	**100**	**468**	**100**	**532**	**100**	**612**	**100**	**703**	**100**

Appendix Table 6.2: *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)		0.004	1 (reference)		0.050
Western migrants	0.96 (0.85-1.08)	0.477		1.26 (1.08-1.47)	0.004	
non-Western migrants	0.87 (0.79-0.96)	0.005		1.04 (0.92-1.17)	0.507	
Unknown origin	1.96 (1.14-3.39)	0.016		1.08 (0.55-2.10)	0.826	
HIV-1 transmission route						
MSM	1 (reference)		<.001	1 (reference)		0.222
Other men	1.20 (1.10-1.32)	<.001		0.98 (0.86-1.12)	0.820	
Women	0.88 (0.77-0.99)	0.040		0.93 (0.81-1.08)	0.344	
Transgender	0.79 (0.44-1.44)	0.447		1.13 (0.69-1.87)	0.620	
IDU	1.49 (1.26-1.76)	<.001		0.74 (0.58-0.94)	0.014	
Blood contact	0.84 (0.64-1.10)	0.212		0.83 (0.59-1.16)	0.275	
Pediatric transmission	1.28 (0.61-2.68)	0.514		1.25 (0.65-2.40)	0.496	
Age*						
18-29	0.89 (0.65-1.22)	0.474	<.001	1.04 (0.85-1.28)	0.712	<.001
30-39	1 (reference)			1 (reference)		
40-49	1.59 (1.37-1.83)	<.001		1.05 (0.92-1.18)	0.474	
50-59	2.75 (2.39-3.17)	<.001		1.25 (1.09-1.43)	0.001	
60-69	4.87 (4.20-5.64)	<.001		1.36 (1.15-1.61)	<.001	
70+	11.63 (9.93-13.61)	<.001		1.91 (1.49-2.44)	<.001	
CD4 cell count**						
0-50	7.44 (6.28-8.81)	<.001	<.001	6.44 (5.28-7.85)	<.001	<.001
050-199	3.68 (3.27-4.15)	<.001		2.70 (2.32-3.14)	<.001	
200-349	1.77 (1.58-1.98)	<.001		1.64 (1.42-1.90)	<.001	
350-499	1.32 (1.18-1.48)	<.001		1.20 (1.03-1.39)	0.018	
500-749	1 (reference)			1 (reference)		
750+	0.87 (0.78-0.97)	0.016		1.12 (0.95-1.32)	0.160	
Per year longer on cART with HIV RNA>1,000 cp/mL	1.06 (1.04-1.07)	<.001	<.001	1.05 (1.03-1.08)	<.001	<.001
Treatment status						
Treatment-experienced at start cART	0.96 (0.87-1.05)	0.335		0.66 (0.58-0.75)	<.001	
Treatment-naive at start	1 (reference)			1 (reference)		

			Death			AIDS
Risk factors	**RR (95%CI)**	**p-value**	**Overall p-value**	**RR (95%CI)**	**p-value**	**Overall p-value**
Prior AIDS event	1.62 (1.50-1.75)	<.001				
Hepatitis B virus positive	1.26 (1.12-1.42)	<.001		0.97 (0.82-1.15)	0.726	
Hepatitis C virus positive	1.50 (1.33-1.70)	<.001		1.23 (1.04-1.46)	0.014	
Body mass index *						
0-18	3.34 (2.98-3.74)	<.001	<.001			
18-25	1 (reference)					
25-30	0.67 (0.61-0.73)	<.001				
30+	0.82 (0.71-0.94)	0.004				
Smoking status						
Current smoker	1.24 (1.11-1.37)	<.001	<.001	0.75 (0.67-0.84)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	1.91 (1.73-2.11)	<.001		0.92 (0.81-1.05)	0.235	
Early cART***	0.74 (0.57-0.97)	0.027		1.20 (0.94-1.54)	0.148	

**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 6.3: *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/ 1,000PY (95%CI)**	**N**	**PY**	**Incidence/ 1,000PY (95%CI)**	**N**	**PY**	**Incidence/ 1,000PY (95%CI)**	**N**	**PY**	**Incidence/ 1,000PY (95%CI)**
0-50	74	3,487	21.2 (16.7-26.6)	4	1,846	2.2 (0.6-5.5)	16	369	43.4 (24.8-70.4)	54	1,272	42.5 (31.9-55.4)
050-199	269	12,460	21.6 (19.1-24.3)	31	6,826	4.5 (3.1-6.4)	61	1,414	43.1 (33.0-55.4)	177	4,220	41.9 (36.0-48.6)
200-349	484	28,740	16.8 (15.4-18.4)	76	16,420	4.6 (3.6-5.8)	112	2,727	41.1 (33.8-49.4)	296	9,593	30.9 (27.4-34.6)
350-499	665	54,121	12.3 (11.4-13.3)	119	31,872	3.7 (3.1-4.5)	162	5,376	30.1 (25.7-35.1)	384	16,873	22.8 (20.5-25.2)
500-749	999	129,383	7.7 (7.2-8.2)	233	76,352	3.1 (2.7-3.5)	277	13,364	20.7 (18.4-23.3)	489	39,667	12.3 (11.3-13.5)
750+	738	184,750	4.0 (3.7-4.3)	193	108,470	1.8 (1.5-2.0)	258	21,762	11.9 (10.5-13.4)	287	54,518	5.3 (4.7-5.9)

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

Appendix Table 6.4: *Absolute number of first AIDS events among PWH during the periods 1996–1999, 2000–2004, 2005–2009, 2010–2014, 2015–2019, and 2020–2024.*

CDC event	1996–1999	2000–2004	2005–2009	2010–2014	2015–2019	2020–2024	Total	
	N	N	N	N	N	N	N	%
AIDS dementia complex – HIV encephalopathy	34	40	56	41	26	20	217	2.88
Bacterial pneumonia, recurring	41	53	77	65	111	90	437	5.79
CMV colitis/proctitis	1	.	1	1	4	5	12	0.16
CMV disease	21	33	29	35	8	.	126	1.67
CMV oesophagitis	.	.	.	.	.	2	2	0.03
CMV meningo-encefalitis	.	.	.	.	1	.	1	0.01
CMV pneumonitis	.	.	.	.	12	22	34	0.45
CMV retinitis	26	19	16	13	13	4	91	1.21
Candidiasis oesophagitis	221	216	274	228	169	148	1,256	16.65
Candidiasis lungs/bronchial/trachea	4	13	9	7	5	4	42	0.56
Cervical cancer, invasive	2	6	5	6	6	1	26	0.34
Coccidioimycosis, extrapulmonary / disseminated	.	.	1	.	.	.	1	0.01
Cryptococcosis, extrapulmonary / disseminated	18	29	39	12	15	2	115	1.52
Cryptosporidiosis	18	15	9	14	5	5	66	0.87
Cystoisosporiasis	1	11	5	1	.	.	18	0.24
HIV wasting	43	45	76	77	69	41	351	4.65
HSV chronic ulcer	1	.	4	4	24	28	61	0.81
HSV oesophagitis	.	.	.	.	.	1	1	0.01
HSV pneumonitis	.	.	1	.	.	1	2	0.03
Herpes simplex virus	27	33	58	44	15	.	177	2.35
Histoplasmosis, extrapulmonary / disseminated	5	13	12	8	2	1	41	0.54
Kaposi sarcoma	133	129	192	155	99	64	772	10.23
Leishmaniasis visceral	.	1	3	2	1	.	7	0.09
Microsporidiosis	11	1	2	2	.	1	17	0.23
Mycobacterium avium/kansasii, extrapulmonary / disseminated	21	23	24	14	9	3	94	1.25
Mycobacterium avium/kansasii, pulmonary	2	2	1	1	9	5	20	0.27
Mycobacterium other / unspecified, extrapulmonary / disseminated	18	13	8	11	7	5	62	0.82
Mycobacterium other / unspecified, pulmonary	2	2	5	10	4	5	28	0.37
Non-Hodgkin`s lymphoma (NHL)	48	73	97	96	93	58	465	6.16

CDC event	1996–1999	2000–2004	2005–2009	2010–2014	2015–2019	2020–2024	Total	
	N	N	N	N	N	N	N	%
Penicilliosis	.	.	1	.	.	.	1	0.01
Pneumocystis jirovecii extrapulmonary	.	1	3	1	1	1	7	0.09
Pneumocystis jirovecii pneumonia	268	303	315	298	213	158	1,555	20.61
Primary CNS lymphoma	5	6	8	7	5	1	32	0.42
Progressive multifocal leukoencephalopathy	14	20	37	27	10	9	117	1.55
Salmonella sepsis, recurring	2	.	.	1	.	.	3	0.04
Toxoplasmosis of the brain	56	94	62	54	33	16	315	4.17
Tuberculosis, extrapulmonary / disseminated	56	113	91	60	41	30	391	5.18
Tuberculosis, pulmonary	80	168	133	96	71	34	582	7.71
Total	**1,179**	**1,475**	**1,654**	**1,391**	**1,081**	**765**	**7,545**	**100.00**

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

Appendix Table 6.5: *Adjusted risk factors for non-AIDS-defining morbidity.*

	Cardiovascular disease		
	IRR (95%CI)	**p-value**	**Overall p-value**
Region of birth			
Native Dutch	1 (reference)	.	0.178
Western migrants	0.97 (0.83-1.13)	0.699	.
Unknown origin	1.19 (0.53-2.65)	0.674	.
HIV-1 transmission route			
MSM	1 (reference)	.	<.001
Other men	1.19 (1.06-1.34)	0.003	.
Women	0.76 (0.65-0.89)	<.001	.
Transgender	1.40 (0.84-2.33)	0.202	.
IDU	1.02 (0.77-1.34)	0.893	.
Blood contact	1.00 (0.71-1.40)	0.987	.
Pediatric transmission	0.00 (0.00-99.99)	0.998	.
Age *			
18-29	0.52 (0.28-0.95)	0.033	<.001
30-39	1 (reference)	.	.
40-49	2.87 (2.28-3.62)	<.001	.
50-59	5.89 (4.70-7.39)	<.001	.
60-69	9.46 (7.46-11.98)	<.001	.
70+	15.85 (12.23-20.54)	<.001	.
CD4 cell count **			
0-50	2.66 (1.81-3.90)	<.001	<.001
050-199	1.77 (1.43-2.19)	<.001	.
200-349	1.19 (1.01-1.39)	0.037	.
350-499	1.12 (0.98-1.28)	0.097	.
500-749	1 (reference)	.	.
750+	1.24 (1.11-1.39)	<.001	.
Per year longer with CD4<200 cells/mm^3	1.02 (1.00-1.05)	0.063	.
Prior AIDS event	1.10 (1.00-1.22)	0.059	.
Per year longer on cART while HIV RNA>1,000 cp/mL	1.01 (0.98-1.04)	0.592	.
Treatment status			
Not (yet) started cART	1.15 (0.93-1.42)	0.186	0.075
NRTI-experienced at start cART	1.14 (1.00-1.30)	0.053	.
Treatment-naive at start	1 (reference)	.	.
Per year longer on cART	1.00 (0.99-1.01)	0.649	.
Early cART within 12 months after last HIV-negat	1.08 (0.85-1.38)	0.531	.

	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 (reference)	.	<.001	1 (reference)	.	<.001	1 (reference)	.	<.001
	0.96 (0.82–1.13)	0.624	.	0.98 (0.82–1.17)	0.853	.	0.95 (0.83–1.09)	0.468	.
	0.20 (0.03–1.41)	0.105	.	0.68 (0.22–2.12)	0.510	.	1.52 (0.86–2.69)	0.148	.
	1 (reference)	.	0.077	1 (reference)	.	<.001	1 (reference)	.	<.001
	1.05 (0.93–1.19)	0.456	.	1.36 (1.20–1.53)	<.001	.	1.11 (1.00–1.24)	0.041	.
	0.99 (0.85–1.15)	0.896	.	0.98 (0.85–1.13)	0.764	.	1.58 (1.41–1.77)	<.001	.
	0.39 (0.14–1.04)	0.059	.	1.06 (0.64–1.74)	0.827	.	1.05 (0.61–1.81)	0.865	.
	1.28 (0.98–1.66)	0.070	.	1.47 (1.09–1.99)	0.012	.	1.76 (1.38–2.25)	<.001	.
	1.33 (0.97–1.82)	0.078	.	1.37 (1.01–1.85)	0.040	.	1.35 (1.02–1.77)	0.033	.
	1.24 (0.29–5.22)	0.773	.	0.52 (0.13–2.15)	0.371	.	3.18 (0.93–10.82)	0.064	.
	0.67 (0.40–1.13)	0.130	<.001	0.61 (0.42–0.89)	0.009	<.001	0.27 (0.12–0.62)	0.002	<.001
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	2.46 (1.95–3.10)	<.001	.	1.54 (1.30–1.81)	<.001	.	2.69 (2.08–3.47)	<.001	.
	4.61 (3.68–5.79)	<.001	.	2.45 (2.07–2.90)	<.001	.	7.83 (6.13–9.99)	<.001	.
	10.00 (7.92–12.62)	<.001	.	3.55 (2.94–4.28)	<.001	.	20.17 (15.78–25.79)	<.001	.
	17.83 (13.85–22.96)	<.001	.	3.75 (2.92–4.82)	<.001	.	37.14 (28.68–48.09)	<.001	.
	2.31 (1.51–3.54)	<.001	<.001	4.29 (3.12–5.89)	<.001	<.001	2.68 (1.81–3.97)	<.001	<.001
	1.93 (1.55–2.41)	<.001	.	1.76 (1.41–2.20)	<.001	.	1.79 (1.47–2.19)	<.001	.
	1.36 (1.16–1.59)	<.001	.	1.10 (0.93–1.31)	0.251	.	1.16 (1.01–1.33)	0.030	.
	1.07 (0.93–1.22)	0.340	.	1.04 (0.90–1.20)	0.608	.	1.07 (0.96–1.19)	0.240	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	0.98 (0.87–1.11)	0.767	.	1.27 (1.13–1.43)	<.001	.	0.92 (0.84–1.01)	0.067	.
	0.99 (0.96–1.02)	0.432	.	1.01 (0.98–1.03)	0.695	.	0.98 (0.96–1.01)	0.183	.
	1.15 (1.04–1.27)	0.006	.	1.30 (1.17–1.44)	<.001	.	1.11 (1.02–1.21)	0.012	.
	1.00 (0.97–1.02)	0.798	.	0.99 (0.96–1.02)	0.583	.	0.97 (0.94–0.99)	0.010	.
	1.35 (1.10–1.65)	0.004	0.001	1.56 (1.29–1.89)	<.001	<.001	0.33 (0.23–0.47)	<.001	<.001
	1.18 (1.03–1.34)	0.015	.	1.25 (1.08–1.45)	0.003	.	1.10 (0.98–1.24)	0.123	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	1.01 (1.00–1.02)	0.040	.	1.00 (0.99–1.01)	0.880	.	0.99 (0.98–1.00)	0.043	.
	0.79 (0.60–1.06)	0.115	.	0.62 (0.43–0.87)	0.007	.	1.04 (0.87–1.26)	0.655	.

	Cardiovascular disease		
	IRR (95%CI)	p-value	Overall p-value
Body mass index *			
0–18	1.31 (1.00–1.72)	0.049	0.012
18–25	1 (reference)	.	.
25–30	1.01 (0.91–1.12)	0.902	.
30+	1.11 (0.95–1.29)	0.204	.
Hepatitis B virus positive	1.01 (0.84–1.21)	0.936	.
Hepatitis C virus positive	1.02 (0.87–1.20)	0.795	.
Hypertension	1.17 (1.07–1.29)	<.001	.
Smoking status			
Current smoker	1.78 (1.59–2.00)	<.001	<.001
Never smoker	1 (reference)	.	.
Past smoker	1.46 (1.30–1.65)	<.001	.
Calendar year period			
2000–2009	1.57 (1.32–1.88)	<.001	<.001
2010–2019	1.23 (1.09–1.39)	<.001	.
2020–2024	1 (reference)	.	.
Recent use of ABC ***	1.49 (1.34–1.66)	<.001	.
Per year longer on LOP/r	1.00 (0.99–1.01)	0.750	.
Per year longer on IDV	1.00 (0.99–1.01)	0.776	.
Prior diabetes	1.96 (1.70–2.27)	<.001	.
Current use of bictegravir	1.46 (1.19–1.79)	<.001	.
Current use of dolutegravir	1.26 (1.10–1.44)	<.001	.
Current use of elvitegravir	1.04 (0.86–1.26)	0.670	.
Current use of raltegravir	1.64 (1.38–1.96)	<.001	.
Current use of cabotegravir	1.05 (0.50–2.23)	0.890	.
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		.	.
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
2.04 (1.64-2.55)	<.001	<.001	1.25 (0.87-1.79)	0.222	<.001	1.27 (0.98-1.64)	0.074	0.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
0.86 (0.77-0.96)	0.005	.	2.09 (1.86-2.36)	<.001	.	1.18 (1.08-1.28)	<.001	.
0.87 (0.73-1.03)	0.107	.	5.10 (4.47-5.82)	<.001	.	1.15 (1.02-1.30)	0.023	.
1.52 (1.29-1.78)	<.001	.	1.15 (0.96-1.37)	0.132	.	1.35 (1.17-1.56)	<.001	.
1.04 (0.88-1.23)	0.629	.	0.98 (0.82-1.18)	0.865	.	1.12 (0.98-1.28)	0.094	.
0.92 (0.83-1.01)	0.086	.	1.19 (1.09-1.31)	<.001	.	1.05 (0.98-1.14)	0.183	.
1.54 (1.36-1.73)	<.001	<.001	1.08 (0.96-1.22)	0.190	<.001	0.79 (0.72-0.87)	<.001	<.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
1.64 (1.45-1.85)	<.001	.	1.22 (1.08-1.37)	0.001	.	0.98 (0.90-1.07)	0.714	.
1.07 (0.90-1.27)	0.445	0.001	1.51 (1.25-1.83)	<.001	<.001	2.12 (1.76-2.55)	<.001	<.001
1.22 (1.08-1.36)	<.001	.	1.24 (1.09-1.41)	0.001	.	1.77 (1.62-1.94)	<.001	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	.	.		.	.		.	.
	.	.		.	.		.	.
	.	.		.	.		.	.
	.	.		.	.	1.26 (1.10-1.43)	<.001	.
	.	.	1.77 (1.45-2.15)	<.001	.	2.45 (2.13-2.83)	<.001	.
	.	.	1.49 (1.30-1.70)	<.001	.	2.85 (2.62-3.10)	<.001	.
	.	.	1.08 (0.89-1.31)	0.439	.		.	.
	.	.	2.29 (1.92-2.74)	<.001	.		.	.
	.	.	0.59 (0.22-1.59)	0.299	.	0.45 (0.19-1.10)	0.079	.
	.	.	1.02 (1.00-1.03)	0.007	.		.	.
	.	.	1.02 (1.00-1.05)	0.085	.		.	.
	.	.	1.05 (1.02-1.07)	<.001	.		.	.
	.	.		.	.	1.00 (0.99-1.01)	0.593	.
	.	.		.	.	1.00 (1.00-1.01)	0.122	.
	.	.		.	.	1.66 (1.48-1.87)	<.001	.
	.	.		.	.	1.39 (1.25-1.54)	<.001	.
	.	.		.	.	1.31 (1.13-1.52)	<.001	.

Appendix Table 6.6: *Specific CDC-B and CDC-C (AIDS) events occurring in individuals on ART with undetectable viral load between 2000 and 2024.*

		All events		0-50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Aspergillosis, invasive pulmonary	16	0.4%	3	0.7%
	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis oropharyngeal	1,051	27.1%	128	29.4%
	Candidiasis vulvovaginal, frequent/persistent	56	1.4%	2	0.5%
	Cardiomyopathy, HIV-related	5	0.1%	0	0.0%
	Cardiomyopathy, with HIV-related component	31	0.8%	1	0.2%
	Diarrhea, HIV-related >=30 days	66	1.7%	2	0.5%
	Fever e.c.i. / HIV-related	6	0.2%	0	0.0%
	HIV-associated nephropathy (HIVAN)	28	0.7%	5	1.1%
	Herpes zoster, multidermatomal	42	1.1%	4	0.9%
	Herpes zoster, recurring / multidermatomal unspecified	211	5.4%	10	2.3%
	Herpes zoster, unidermatomal recurrent	59	1.5%	3	0.7%
	Listeriosis	1	0.0%	0	0.0%
	Myelopathy, HIV-related	10	0.3%	0	0.0%
	Neuropathy, HIV-related	130	3.4%	2	0.5%
	Neuropathy, with HIV-related component	125	3.2%	1	0.2%
	Nocardiosis	2	0.1%	1	0.2%
	Oral Hairy Leucoplakia (OHL)	59	1.5%	2	0.5%
	Pelvic inflammatory disease	11	0.3%	0	0.0%
	Thrombocytopenia, HIV-related	157	4.1%	7	1.6%
	Thrombocytopenia, with HIV-related component	43	1.1%	6	1.4%
	Weight loss >10%, HIV-related / unknown cause	39	1.0%	5	1.1%
Subtotal		**2,149**	**55.5%**	**182**	**41.8%**

CD4 category										
	050–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
5	0.6%	2	0.3%	0	0.0%	2	0.3%	4	0.9%
1	0.1%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
266	32.4%	211	28.1%	164	23.6%	164	22.3%	118	27.1%
5	0.6%	12	1.6%	13	1.9%	20	2.7%	4	0.9%
2	0.2%	0	0.0%	0	0.0%	1	0.1%	2	0.5%
5	0.6%	4	0.5%	4	0.6%	9	1.2%	8	1.8%
7	0.9%	17	2.3%	13	1.9%	19	2.6%	8	1.8%
1	0.1%	2	0.3%	0	0.0%	1	0.1%	2	0.5%
4	0.5%	4	0.5%	7	1.0%	4	0.5%	4	0.9%
2	0.2%	8	1.1%	9	1.3%	10	1.4%	9	2.1%
40	4.9%	47	6.3%	38	5.5%	48	6.5%	28	6.4%
9	1.1%	4	0.5%	9	1.3%	21	2.9%	13	3.0%
0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
4	0.5%	2	0.3%	0	0.0%	3	0.4%	1	0.2%
9	1.1%	19	2.5%	33	4.7%	40	5.4%	27	6.2%
11	1.3%	17	2.3%	34	4.9%	38	5.2%	24	5.5%
0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
15	1.8%	13	1.7%	9	1.3%	12	1.6%	8	1.8%
0	0.0%	4	0.5%	0	0.0%	5	0.7%	2	0.5%
30	3.7%	32	4.3%	37	5.3%	39	5.3%	12	2.8%
3	0.4%	14	1.9%	4	0.6%	13	1.8%	3	0.7%
5	0.6%	8	1.1%	8	1.1%	6	0.8%	7	1.6%
424	**51.7%**	**422**	**56.2%**	**382**	**54.9%**	**455**	**62.0%**	**284**	**65.1%**

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
CDC-C events	AIDS dementia complex – HIV encephalopathy	50	1.3%	6	1.4%
	Bacterial pneumonia, recurring	362	9.3%	13	3.0%
	CMV colitis/proctitis	1	0.0%	1	0.2%
	CMV disease	19	0.5%	4	0.9%
	CMV oesophagitis	2	0.1%	1	0.2%
	CMV meningo-encefalitis	2	0.1%	2	0.5%
	CMV pneumonitis	1	0.0%	0	0.0%
	CMV retinitis	26	0.7%	11	2.5%
	Candidiasis oesophagitis	319	8.2%	50	11.5%
	Candidiasis lungs/bronchial/trachea	12	0.3%	2	0.5%
	Cervical cancer, invasive	13	0.3%	0	0.0%
	Coccidioimycosis, extrapulmonary / disseminated	1	0.0%	0	0.0%
	Cryptococcosis, extrapulmonary / disseminated	18	0.5%	10	2.3%
	Cryptosporidiosis	12	0.3%	2	0.5%
	Cystoisosporiasis	2	0.1%	0	0.0%
	HIV wasting	31	0.8%	16	3.7%
	HSV chronic ulcer	46	1.2%	2	0.5%
	HSV oesophagitis	3	0.1%	0	0.0%
	HSV pneumonitis	2	0.1%	0	0.0%
	Herpes simplex virus	66	1.7%	10	2.3%
	Histoplasmosis, extrapulmonary / disseminated	3	0.1%	2	0.5%
	Kaposi sarcoma	145	3.7%	12	2.8%
	Leishmaniasis visceral	5	0.1%	1	0.2%
	Microsporidiosis	6	0.2%	2	0.5%
	Mycobacterium avium/kansasii, extrapulmonary / disseminated	34	0.9%	12	2.8%
	Mycobacterium avium/kansasii, pulmonary	8	0.2%	1	0.2%
	Mycobacterium other / unspecified, extrapulmonary / disseminated	14	0.4%	5	1.1%
	Mycobacterium other / unspecified, pulmonary	7	0.2%	1	0.2%
	Non-Hodgkin`s lymphoma (NHL)	206	5.3%	8	1.8%
	Pneumocystis jirovecii extrapulmonary	1	0.0%	0	0.0%
	Pneumocystis jirovecii pneumonia	101	2.6%	38	8.7%
	Primary CNS lymphoma	9	0.2%	1	0.2%
	Progressive multifocal leukoencephalopathy	24	0.6%	9	2.1%
	Toxoplasmosis of the brain	31	0.8%	14	3.2%
	Tuberculosis, extrapulmonary / disseminated	62	1.6%	11	2.5%
	Tuberculosis, pulmonary	79	2.0%	6	1.4%
Subtotal		**1,723**	**44.5%**	**253**	**58.2%**
Total		**3,872**	**100.0%**	**435**	**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	%
9	1.1%	6	0.8%	11	1.6%	12	1.6%	6	1.4%
71	8.7%	80	10.7%	98	14.1%	67	9.1%	33	7.6%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
4	0.5%	4	0.5%	4	0.6%	1	0.1%	2	0.5%
0	0.0%	0	0.0%	1	0.1%	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%	0	0.0%	0	0.0%	1	0.2%
8	1.0%	2	0.3%	4	0.6%	1	0.1%	0	0.0%
78	9.5%	58	7.7%	52	7.5%	50	6.8%	31	7.1%
1	0.1%	5	0.7%	0	0.0%	3	0.4%	1	0.2%
3	0.4%	3	0.4%	2	0.3%	5	0.7%	0	0.0%
0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
5	0.6%	2	0.3%	0	0.0%	1	0.1%	0	0.0%
2	0.2%	1	0.1%	4	0.6%	2	0.3%	1	0.2%
1	0.1%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
11	1.3%	1	0.1%	2	0.3%	1	0.1%	0	0.0%
7	0.9%	2	0.3%	7	1.0%	18	2.5%	10	2.3%
1	0.1%	0	0.0%	1	0.1%	0	0.0%	1	0.2%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	0.5%
9	1.1%	14	1.9%	17	2.4%	11	1.5%	5	1.1%
0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
18	2.2%	32	4.3%	30	4.3%	35	4.8%	18	4.1%
3	0.4%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
3	0.4%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
13	1.6%	4	0.5%	3	0.4%	1	0.1%	1	0.2%
3	0.4%	1	0.1%	0	0.0%	1	0.1%	2	0.5%
5	0.6%	3	0.4%	1	0.1%	0	0.0%	0	0.0%
2	0.2%	0	0.0%	2	0.3%	1	0.1%	1	0.2%
55	6.7%	48	6.4%	45	6.5%	33	4.5%	17	3.9%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
33	4.0%	16	2.1%	9	1.3%	4	0.5%	1	0.2%
3	0.4%	4	0.5%	0	0.0%	1	0.1%	0	0.0%
9	1.1%	3	0.4%	2	0.3%	1	0.1%	0	0.0%
11	1.3%	5	0.7%	0	0.0%	1	0.1%	0	0.0%
12	1.5%	13	1.7%	5	0.7%	9	1.2%	12	2.8%
16	2.0%	20	2.7%	14	2.0%	18	2.5%	5	1.1%
396	**48.3%**	**329**	**43.8%**	**314**	**45.1%**	**279**	**38.0%**	**152**	**34.9%**
820	**100.0%**	**751**	**100.0%**	**696**	**100.0%**	**734**	**100.0%**	**436**	**100.0%**

7. Viral hepatitis

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Key findings

Hepatitis C (2015–2024)

- Of individuals with HIV in care between 2015 and 2024, 99% were screened at least once for hepatitis C (HCV).
- Of the 26,743 individuals who were ever screened for HCV, 960 were diagnosed with primary HCV infection and 182 individuals with reinfection between 2015-2024.
- The majority of recent HCV infections occurred in MSM (n=280/302 [93%])
- In 2024, 42 individuals were diagnosed with HCV, including 8 re-infections. Twenty- three individuals with an HCV diagnosis in 2024 (55%) originated from European countries other than the Netherlands.
- 96% of individuals in care had received treatment for HCV and 99% were successfully treated and achieved treatment-induced clearance of HCV.

Hepatitis B

- Screening for hepatitis B (HBV) has improved over time. In 2024, 94.2% of participants in care had at least one HBV serological assay performed and 73% had complete serological profiles available.
- A total of 1,325 participants have a history of chronic HBV, of whom 879 remain surface antigen positive at last evaluation. Close to 90% of participants with a history of chronic HBV are treated with a tenofovir prodrug and cytidine analogue.
- Probable or definite severe liver disease was documented in 18% of participants with a history of chronic HBV. In this group, hepatocellular carcinoma and death due to liver disease occurred in less than 1%.
- Between 2015 and 2024, 3,989 vaccine-eligible MSM entered care. By 2024, 41% had serological evidence of HBV vaccination and an additional 26.5% were documented as vaccinated; 28% had no evidence of vaccination or vaccine-derived immunity.

Hepatitis A

- Screening for hepatitis A (HAV) has improved over time. The proportion of participants with serological testing for HAV increased from 49% in 2015 to 83% in 2024.
- The last outbreak of acute HAV occurred in 2017, with an annual total of 54 cases. Since 2020, less than 5 cases of acute HAV have been reported annually.
- By 2024, 39% of MSM entering care had serological evidence of immunity to HAV and an additional 25% had received at least one dose of HAV vaccine. Thirty-six percent had no evidence of HAV vaccination or immunity.

Introduction

People with HIV are vulnerable to infection with viral hepatitis, due to shared routes of transmission including but not limited to sexual practices and substance use[1,2]. In this chapter, we describe the epidemiology of chronic and acute viral hepatitis in people with HIV in the Netherlands. We focus primarily on hepatitis C [HCV] and hepatitis B [HBV] (including hepatitis delta virus), the most common causes of chronic viral hepatitis in the Netherlands. We provide brief overviews of acute hepatitis due to Hepatitis A and E viruses. In our analysis, we included individuals registered in the SHM database who had at least one HIV care visit between 2015 and 2024 at time of database closure in May 2025.

Hepatitis C virus (HCV)

Box 7.1: 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.

Recent HCV infection[3,4]

1. Case definition of recent HCV according to preferred criteria[3]:
   Positive anti-HCV IgG with a documented negative anti-HCV IgG within the past 12 months,
   or:
   detectable HCV RNA in the presence with either a documented negative HCV RNA test, or a negative anti-HCV IgG within the past 12 months.
2. Case definition of acute HCV according to alternative criteria[3]:
   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.

Hepatitis C reinfection
Detectable HCV RNA after an earlier achieved SVR, 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[5].

Of the 27,082[a] individuals who were in care between 2015 and 2024:
- 99% were screened at least once for HCV with anti-HCV or HCV RNA.

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.

Follow-up screening

Individuals with a negative first HCV test

Among individuals who had a negative first HCV test and who remained in care for at least one year:

- 82% had a second HCV test at some point during follow up;
- Repeat screening was highest among MSM (90%);
- And lowest for individuals who acquired HIV through heterosexual contact (67%).

As most HCV infections are observed among MSM[6], the following analysis on testing frequency is reported for MSM only.

The median cumulative number of repeated HCV tests among HCV negative MSM was 6 tests (IQR: 3-10).

Overall, the percentage of HCV seronegative MSM with HCV testing in a calendar year:

- Varied between 34% in 2015 and 47% in 2019;
- 38% of the MSM in care were tested for HCV in 2024.

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 7.1*). From the diagnosis data we known that the median age at diagnosis of recent HCV was 44 years (IQR 36-50) (*Table 7.2A*), while in the age range 40-50 years, 42% had at least one test in 2024.

Individuals with a history of HCV infection

Screening with HCV RNA among those at risk of HCV reinfection is an important factor in identifying HCV reinfection. As most HCV reinfections are observed among MSM[6], the following analysis on testing frequency is reported for MSM only.

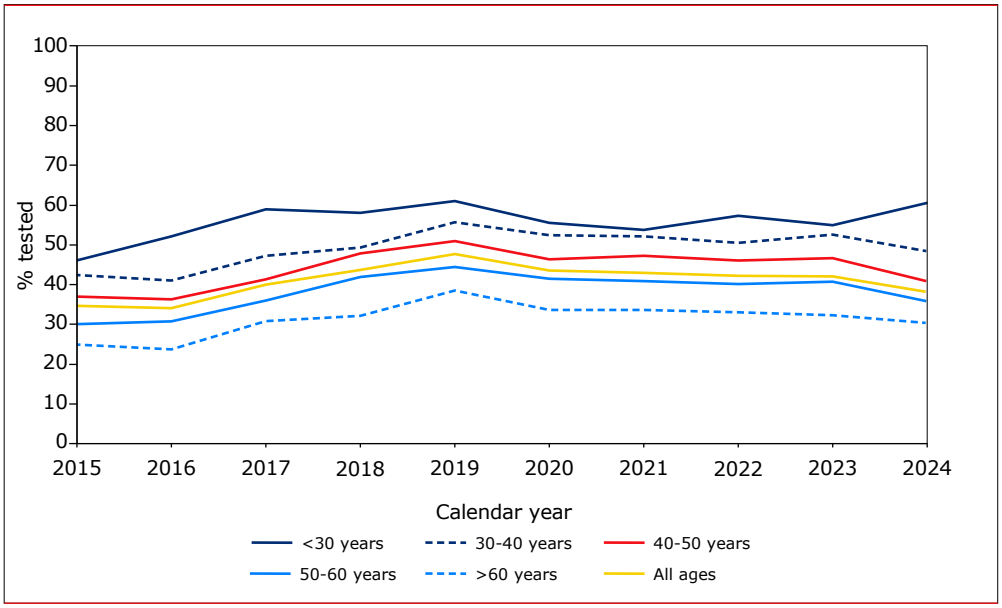
Among MSM with HIV at risk of reinfection after treatment-induced or spontaneous clearance of HCV, the percentage of MSM with repeated HCV RNA testing declined from 53% in 2015 to 37% in 2024. The median cumulative number of repeated HCV RNA tests among MSM with a history of HCV was 10 (IQR: 5-16).

Targeted screening, based on the presence of incident transaminase elevations

National guidelines advice additional annual HCV screening for MSM who report behaviour associated with increased risk of acquiring HCV[5]. The above-described HCV RNA follow up testing data may include MSM who are not considered at risk of HCV reinfection anymore by their treating physician. However, we cannot exclude these individuals 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 inflammation. This might be reflected by the observed higher proportion of repeat HCV screening among MSM with elevated transaminase levels (defined as 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 elevated transaminase level varied between 60% and 77% in 2015-2024.

Figure 7.1: The percentage of men who have sex with men (MSM) without HCV and susceptible to primary HCV infection with an HCV test in a calendar year, stratified by age.



Number of diagnoses of primary HCV infection and reinfection between 2015–2024

As of 31 December 2024, 27,082 people with HIV (aged 15 years or older at the time of their HIV-1 diagnosis) had been in care between 2015 and 2024 and were registered by Stichting hiv monitoring (*Figure 7.2*). Of those individuals, 26,743 (99%) were screened for HCV co-infection: 2,560 (10%) ever had a positive result with an HCV antibody test and/or HCV RNA test. Of whom 960 (38%) had a first diagnosis of HCV between 2015 and 2024. When focusing on the diagnoses between 2015 and 2024, HCV RNA data were not documented in 33 of the 960 individuals (3%), of whom:

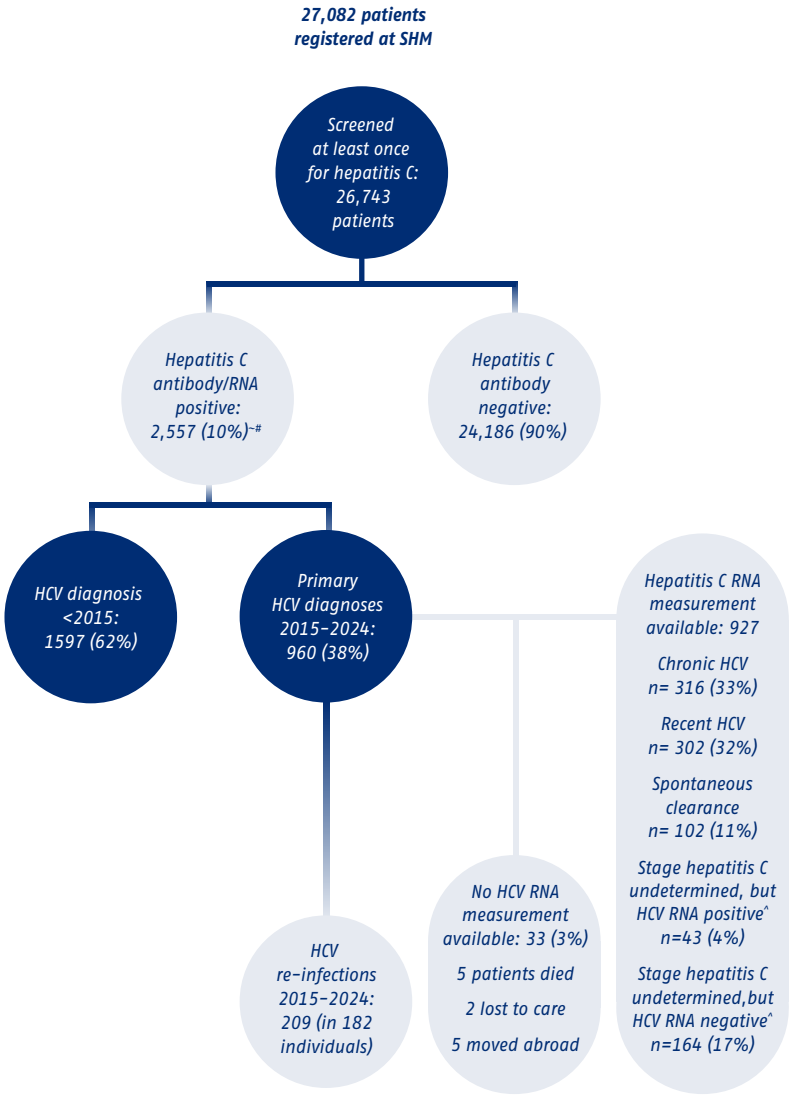
- 5 had died;
- 2 had been lost to care;
- 5 had moved abroad; and
- 21 do not have a known reason for an undocumented HCV RNA outcome.

In total, 927 individuals were diagnosed with HCV infection from 2015 to 2024, and had documented HCV RNA data:

- 316 (33%) were classified as having a chronic HCV infection at the time of their diagnosis.
- 302 (32%) were diagnosed with a recent HCV infection;
- 102 (11%) had evidence of spontaneous clearance of HCV;
- 43 individuals had one positive HCV RNA test result, and no follow-up results, rendering it impossible to determine the stage of their HCV infection at the time of diagnosis (35 individuals are no longer in care and another 4 newly entered care in 2024).
- 164(18%) had a positive HCV antibody test result accompanied with an negative HCV RNA test.
  - 144/164 (89%) individuals originated from outside the Netherlands, mainly from eastern and central Europe (n=105).
  - 23/164 (14%) newly entered care in 2024 and all but one individual originated from outside the Netherlands.

Between 2015 and 2024, 209 HCV reinfections occurred in 182 individuals (*Figure 7.2*).

Figure 7.2: *Flowchart of individuals with HIV in care and diagnosed with hepatitis C virus (HCV) between 2015-2024.*



~ 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

Between 2015 and 2024, 102 individuals spontaneously cleared their HCV infection.

- 65 (64%) cases were defined as definitive clearance.
- 37 (36%) as possible spontaneous clearance.

Table 7.1 shows the demographic characteristics of those with spontaneous clearance compared to all individuals with HCV.

***Table 7.1:** Demographic characteristics of individuals with HCV RNA positive first hepatitis C virus infection (HCV) and those who spontaneously cleared HCV registered in the SHM database, 2015–2024.*

	No spontaneous clearance	Spontaneous clearance	Total	p
Total N (%)	825 (89.0)	102 (11.0)	927	
Age at HCV diagnosis (Median (IQR))	43.3 (36.8 to 50.3)	44.6 (35.1 to 53.1)	43.4 (36.5 to 50.4)	0.512
Gender at birth				0.942
Men	705 (85.5)	88 (86.3)	793 (85.5)	
Women	120 (14.5)	14 (13.7)	134 (14.5)	
Region				0.033
Netherlands	334 (40.5)	45 (44.1)	379 (40.9)	
Other	308 (37.3)	23 (22.5)	331 (35.7)	
Europe	72 (8.7)	11 (10.8)	83 (9.0)	
Caribbean/South America	64 (7.8)	15 (14.7)	79 (8.5)	
Southeast Asia	30 (3.6)	5 (4.9)	35 (3.8)	
Sub-Saharan Africa	17 (2.1)	3 (2.9)	20 (2.2)	
HIV transmission mode				0.083
Men who have sex with men	496 (60.1)	69 (67.6)	565 (60.9)	
Heterosexual	128 (15.5)	19 (18.6)	147 (15.9)	
People who use/used injecting drugs	104 (12.6)	5 (4.9)	109 (11.8)	
Other	97 (11.8)	9 (8.8)	106 (11.4)	
ART				1.000
ART	813 (98.5)	100 (98.0)	913 (98.5)	
No ART	12 (1.5)	2 (2.0)	14 (1.5)	
Deaths	37 (4.5)	4 (3.9)	41 (4.4)	0.995

Demographic characteristics of individuals with a primary HCV diagnosis between 2015 and 2024

In total, 618/927 individuals could be definitively classified as having either chronic (n=316), or recent (n=302) HCV infection at the time of their primary HCV diagnosis. Most of these were male (83% and 99%, respectively).

The majority of individuals with chronic HCV was not born in the Netherlands (*Table 7.2A*), 29% of the individuals diagnosed with chronic HCV between 2015 and 2024 originated from Eastern Europe and 12% from central Europe. Sixteen percent (51/316) of the individuals with chronic HCV reported (former) injecting drug use. Another 18% reported heterosexual contact as the most likely mode of HIV transmission. However, the mode of transmission for HCV is mostly unknown and may differ from the reported HIV transmission mode. For example, 10 individuals with heterosexual contact as the most likely mode of HIV transmission, had documented (former) injecting drug use.

Among the individuals with a recent HCV infection, 69% was born in the Netherlands and 93% were MSM.

Table 7.2A: Demographic characteristics of individuals with HIV and diagnosed with a chronic or recent HCV infection between 2015–2024.

HCV status	Chronic HCV	Recent HCV
Total N (%)	316	302
Age at HCV diagnosis (Median (IQR))	41.5 (35.2 to 48.7)	45.2 (37.6 to 52.2)
Gender at birth		
Men	261 (82.6)	299 (99.0)
Women	55 (17.4)	3 (1.0)
Region		
Netherlands	104 (32.9)	209 (69.2)
Caribbean/South America	25 (7.9)	30 (9.9)
Sub-Saharan Africa	12 (3.8)	1 (0.3)
Western Europe	28 (8.9)	25 (8.3)
Central Europe	39 (12.3)	8 (2.6)
Eastern Europe	89 (28.2)	6 (2.0)
Southeast Asia	14 (4.4)	11 (3.6)
Other	5 (1.6)	12 (4.0)
HIV transmission route		
Men who have sex with men	167 (52.8)	280 (92.7)
Heterosexual	57 (18.0)	12 (4.0)
Other	41 (13.0)	8 (2.6)
People who use/used injecting drugs	51 (16.1)	2 (0.7)
ART		
ART	310 (98.1)	302 (100.0)
No ART	6 (1.9)	
Deaths	14 (4.4)	15 (5.0)

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

The HCV genotype was determined and documented in the clinical records of 542 of the 618 (88%) individuals with chronic or recent HCV. *Table 7.2B* shows the genotype distribution.

Table 7.2B: *Frequency of HCV genotypes among individuals with a primary HCV diagnosis between 2015–2024.*

HCV status	Chronic HCV	Recent HCV	Total
Total N (%)	316	302	618
Total determined	276 (87%)	266 (88%)	542 (88%)
Genotype			
1	166 (60%)	173 (65%)	339 (62%)
1a	129	167	296
1b	33	4	37
1a/b, 1c, 1e	4	2	6
2	11 (3%)	8 (3%)	19 (4%)
3	53 (19%)	18 (7%)	71 (13%)
4	45 (14%)	67 (25%)	112 (21%)
5/6	1 (<1%)		1 (<1%)

Changes over time

Number of diagnoses of primary HCV and reinfection

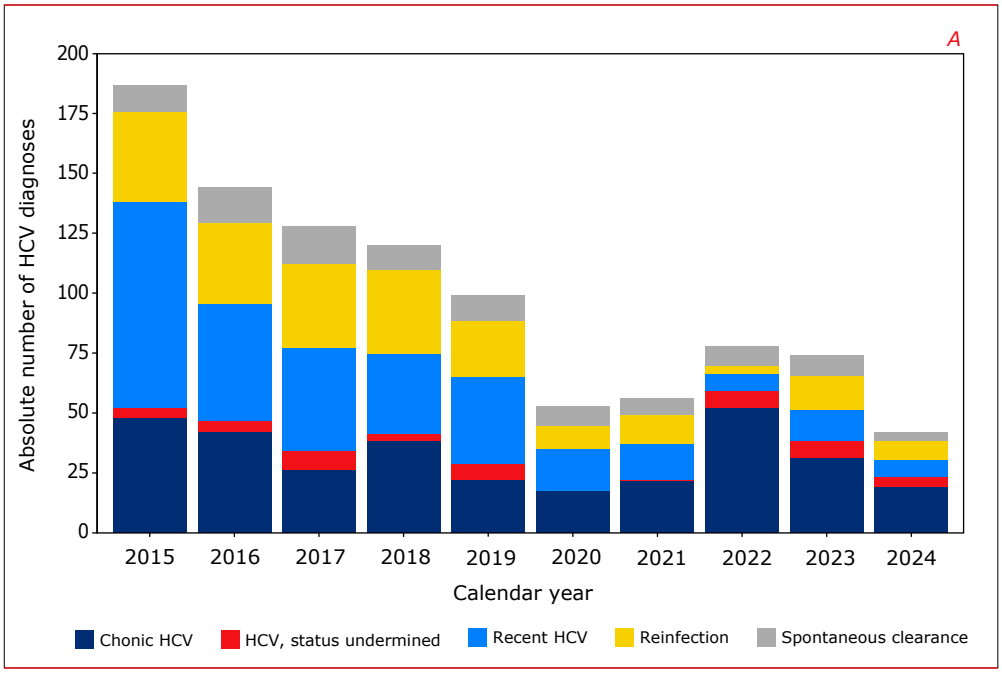
Between 2015 and 2024, 972 HCV diagnoses with detectable HCV RNA occurred (763 primary infections and 209 reinfections). The annual number of primary HCV diagnoses (ie with detectable HCV RNA) and HCV reinfection decreased from 187 cases in 2015 to 78 and 74 in 2022 and 2023, respectively. The decreasing trend continued through 2024, reaching 42 cases (*Figure 7.3A*). The distribution of different stages at HCV diagnosis has shifted over time, with recent HCV diagnoses occurring more frequently in 2015 and 2016, and the number of chronic HCV diagnoses became most frequent from 2022 onwards. The number of reinfections decreased from 37 in 2015 to 8 in 2024.

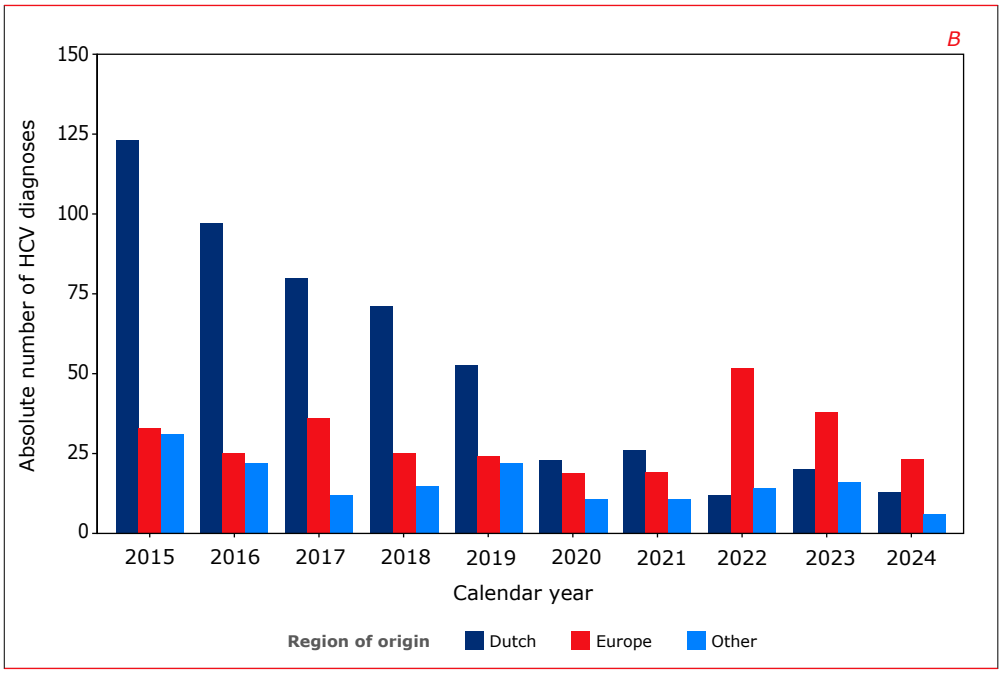
Of the HCV diagnoses with detectable HCV RNA between 2015 and 2024, 518 (53%) originated from the Netherlands, 14% from Eastern Europe, 9% from Western Europe and 8% from Central Europe. Between 2015 and 2021, the majority of individuals with an HCV diagnosis originated from the Netherlands. But the number of individuals born in the Netherlands decreased and since 2022, 55% of the individuals originated from other European countries than the Netherlands (*Figure 7.3B*). Most commonly reported countries in this region were Ukraine(61, 6%) and Poland (56, 6%).
Of the individuals originating from the Netherlands, 475 (92%) were MSM. While in Central and Eastern Europe, HCV diagnoses were more often among PWIDs (23% and 32%)(*Figure 7.3C*).

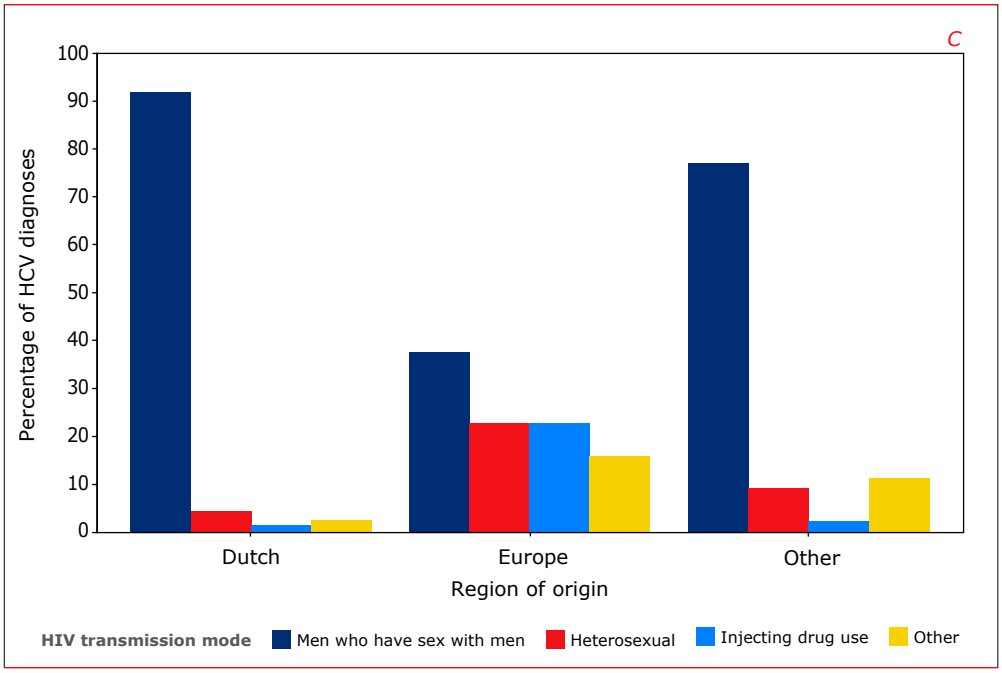
Prevalence of detectable HCV RNA

Figure 7.3D shows the percentage of individuals with detectable HCV RNA over time. Individuals contributed follow-up time to the analysis if they were screened for HCV and in care between 2015 and 2024. HCV RNA positivity was based on the last available HCV RNA test result before the end of that calendar year. The overall percentage of individuals with detectable HCV RNA decreased from 4.0% in 2015 to 0.3% in 2024. In MSM, the highest percentage of HCV RNA positivity was 3.8% in 2015; by 2022, the percentage of positive HCV RNA in this group had decreased to 0.2% and stabilizes around the 0.2% in the most recent years.

Figure 7.3: (A) Absolute number of diagnoses of hepatitis C virus (HCV) co-infection with detectable HCV RNA, (B) number of HCV diagnoses of HCV with detectable HCV RNA, stratified by region of origin, (C) Percentage of HCV diagnoses with detectable HCV RNA per HIV transmission group, and (D) detectable HCV RNA, per calendar year.






C
100
90
80
70
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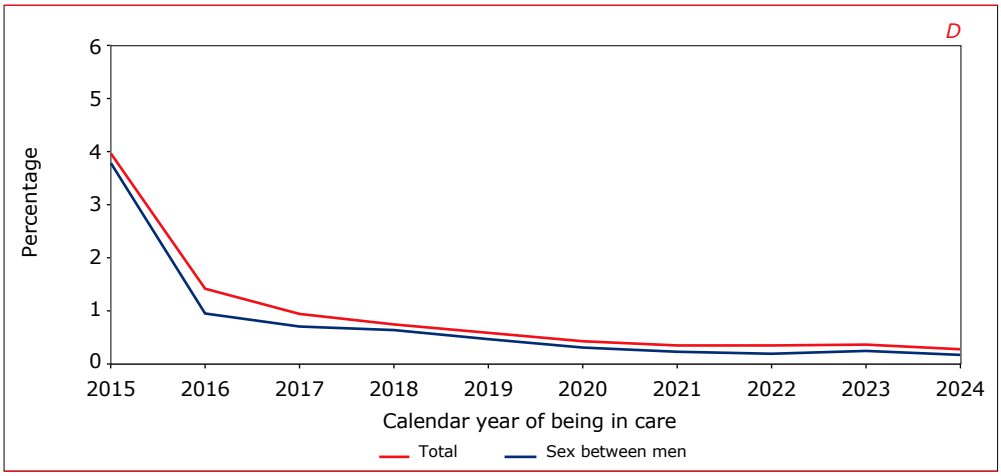
0
Percentage of HCV diagnoses
Dutch
Europe
Other
Region of origin
HIV transmission mode
Men who have sex with men
Heterosexual
Injecting drug use
Other


D
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3
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1
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2019
2020
2021
2022
2023
2024
Calendar year of being in care
Total
Sex between men

Incidence of new HCV infections

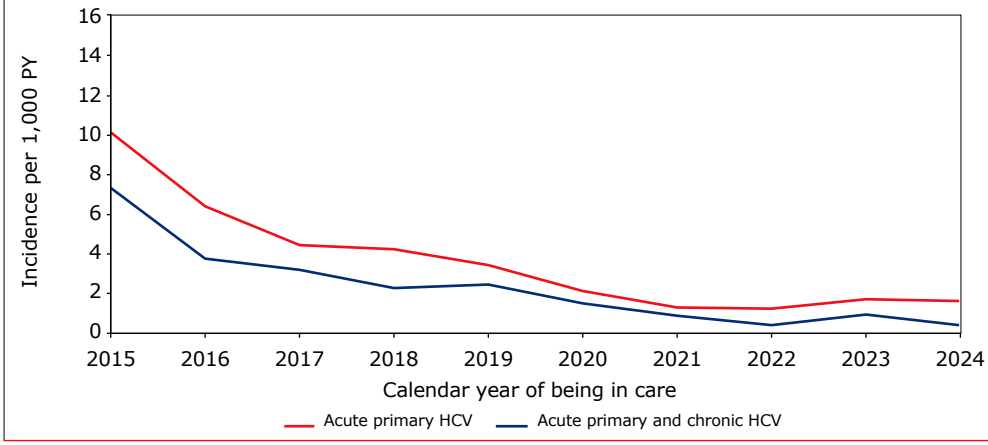
The incidence of primary infection is calculated for individuals with a first documented HCV infection, based on the date of their first positive HCV antibody or HCV RNA test result. The definition of recent HCV infection is consistent with the one given in the European AIDS Treatment Network's (NEAT) preferred criteria[7]. We have expanded this definition to include alternative criteria[3,4]. 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.

There were important differences in the incidence of primary recent HCV infection in terms of HIV transmission category. Between 2015 and 2024, the majority of recent HCV infections occurred in MSM (n=280/302 [93%]). 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 two out of the 490 PWID or former PWID. 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. Twelve cases occurred among individuals who had acquired HIV heterosexually (*Table 7.2*).

Figure 7.4 shows both the incidence of recent primary HCV infection and all primary HCV diagnoses among MSM over time. Between 2015 and 2024, the overall rate of primary HCV infection was 3.0 per 1,000 person years (PY) (95% confidence interval [CI]2.79-3.28).
The incidence of primary infection decreased from 10.1 per 1,000 PY (95% CI 8.31-12.12) in 2015 to 1.62 per 1,000 PY (95% CI 0.98-2.54) in 2024.

When looking at those with recent HCV, the overall rate of recent HCV infection, including cases with a rise in ALT levels, among MSM was 2.2 per 1,000 PY (95% CI 1.98-2.52). The incidence of recent HCV infection decreased sharply from 7.32 cases per 1,000 PY (95%CI 5.82-9.08) in 2015 to 0.95 cases per 1,000 PY (95%CI 0.49-1.65) in 2023 and 0.43 cases per 1,000 PY (95% CI 0.14-1.00) in 2024.

Figure 7.4: Incidence of recent primary hepatitis C infection (blue line) and all primary recent and chronic HCV diagnoses (red line) among men who have sex with men per calendar year.



Legend: HCV = hepatitis C virus.

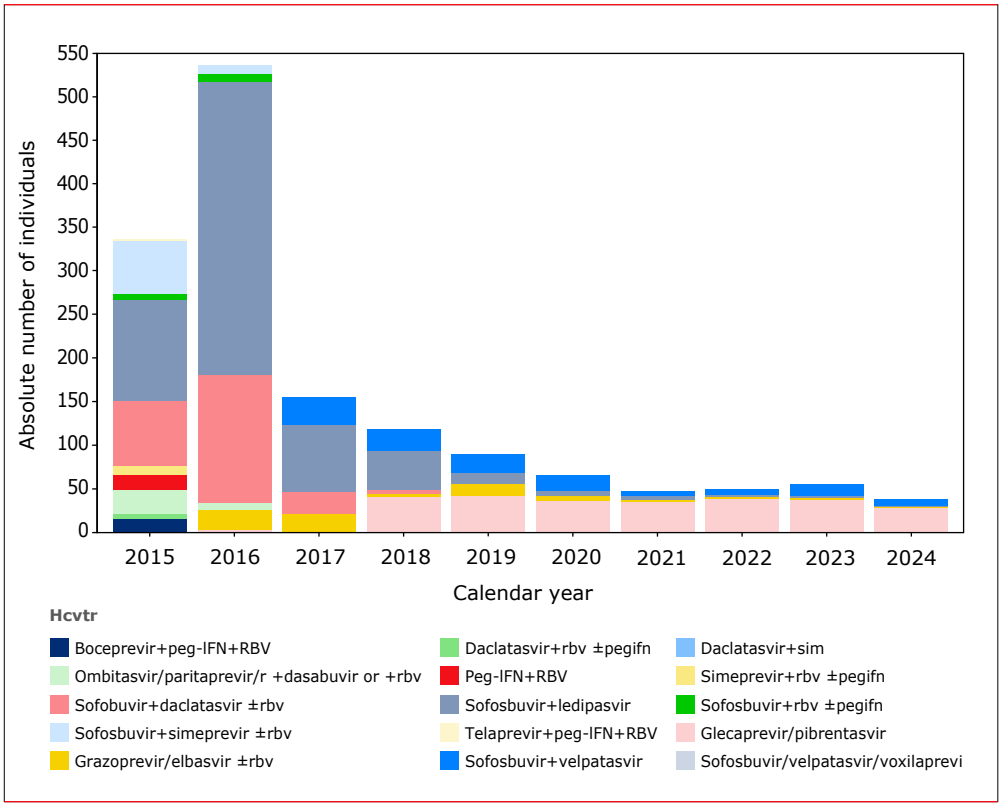
HCV treatment

The primary aim of HCV treatment is to achieve a sustained virological response (SVR)[8]. Since 2012, the introduction of the first generation of direct acting agents (DAA) improved the HCV treatment efficacy[9,10] and efficacy was further improved with the introduction of all-oral DAAs from 2014 onwards. Initially, with government restrictions, only for a defined group of individuals with severe liver fibrosis and cirrhosis. And by the end 2015, it was made available for all individuals with chronic HCV, regardless of fibrosis state. An overview of DAA-containing HCV treatment combinations currently available in the Netherlands can be found at https://hcvrichtsnoer.nl/.

Of the individuals ever diagnosed with primary chronic, recent HCV, or a reinfection, 1,328 received HCV treatment between 2015 and 2024; with in total 1,499 treatment episodes, including those who received HCV treatment more than once (people who were unsuccessfully treated and those who reacquired HCV after prior successful treatment). In total, documented regimens comprised:

- 16 regimens with (peg-) interferon+ RBV (only used in 2015);
- 18 regimens with first generation PI; and
- 1,459 regimens with all-oral direct-acting antiviral treatment (DAAs).

Figure 7.5: 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 DAAs

Figure 7.5 shows the number of individuals who started HCV treatment per calendar year. Between 2015 and 2024, 1,308 individuals were known to have started a DAA regimen; 130 of those had been treated more than once with a DAA regimen for a total of 1,459 treatment episodes. The most common reasons for receiving DAA treatment more than once were: reinfection after earlier DAA treatment-induced clearance (n=80), and no SVR or discontinuation of first DAA treatment episode due to a lack of early virological response (n=44), or toxicity (n=9).

Of the total 1,459 DAA treatment episodes, 302 occurred in 2015, and 536 in 2016. The number of treatment episodes subsequently decreased to 38 in 2024 (*Figure 7.5*).

The most frequently used DAA regimens were:

1. sofosbuvir plus ledipasvir +/- RBV (n=591);
2. pibrentasvir/glecaprevir (n=261), most commonly used since 2020;
3. sofosbuvir plus daclatasvir +/- RBV (n=248);
4. sofosbuvir plus velpatasvir (n=128).

Treatment outcomes

1,444 out of 1,459 DAA treatment episodes had been completed at least 12 weeks prior to the database lock. In 1,426 treatment episodes follow up HCV RNA data was available, and in 18 there was no data after treatment completion:

- In 1,383 of the 1,427 treatment episodes (97%), SVR12 was achieved.
- No SVR was achieved in 44 treatment episodes among 43 individuals.
- For the remaining 18 treatment episodes, no follow-up data on SVR were available: four people died shortly after being treated and 12 cases had a last clinical visit shortly after treatment discontinuation. For the remaining two cases there were no reported HCV RNA tests available.

SVR rates were comparable for individuals who received HCV treatment for the first time and those who were retreated. SVR was lower in individuals with severe liver disease (96% vs 98%). In terms of HIV transmission risk groups, SVR rates were 98% among MSM, 95% among PWID or former PWID, and 95% among individuals who acquired HIV through heterosexual contact.

Among the 43 individuals who did not achieve SVR:

- 31 were successfully retreated with another DAA regimen;
- 1 individual was unsuccessfully retreated
- 12 were not retreated:
  - three individuals died;
  - three moved abroad;
  - one individual is lost to care;
  - one individual is pending SVR determination;
  - and for the remaining individuals, the reason for not being retreated is unknown.
- In total, the results of 18 mutation tests were documented among the 32 individuals who did not achieve SVR.
  - 10 mutations among 6 individuals were identified:
    - 6 mutations in the NS5A region(30R, 93.S, T58P, Y93H, A75V, T99S)
    - 3 mutations in the NS3 region (S122T, I/V170I, Q80K)
    - 1 mutation in the NS5B (A/T/V150V)

HCV reinfection

Reinfection with HCV following successful treatment or spontaneous clearance has been reported mainly in MSM with HIV[20,21], with high rates of reinfection found among MSM in the Netherlands, Germany[22] and the United Kingdom[23,24].

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.

Between 2015 and 2025, 2,423 individuals met the above criteria (1,886 after SVR, 537 after spontaneous clearance). Of those 2,423 individuals, 209 reinfections among 182 individuals were documented. The median time between SVR or spontaneous clearance and HCV reinfection was 1.3 years (IQR 0.6-2.8). There was an increase in the time to reinfection from less than one year in 2015 to 6 years in 2024.

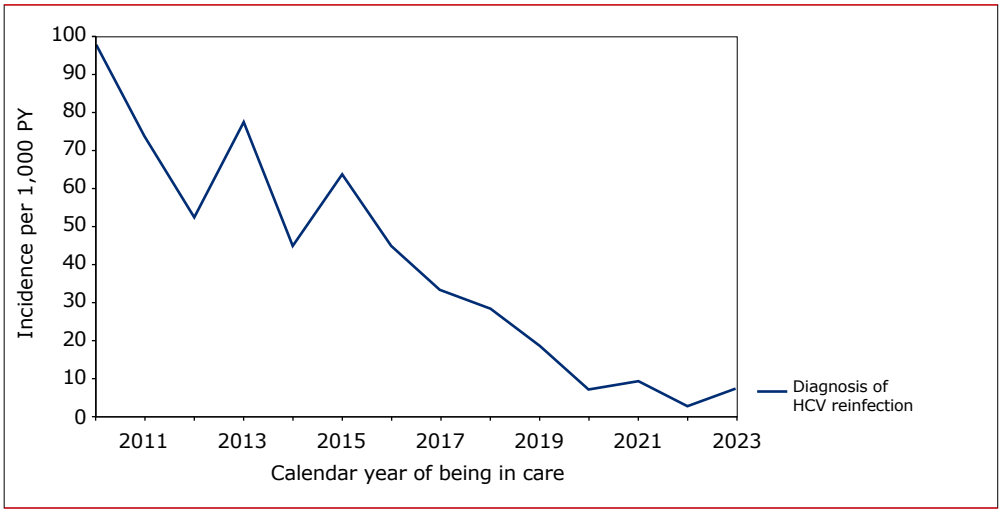
Most individuals who became reinfected were MSM (163 out of 182, 90%). Another 4 were PWID or former PWID (2%). For the remaining 15 individuals, documented HIV transmission routes were heterosexual contact (n=6) and another or unknown (n=9).

Of the 209 reinfections, 7 (3%) were spontaneously cleared and 192 (83%) were retreated (189 with DAA, 3 with interferon+/- boceprevir/telaprevir). The median time to retreatment after reinfection was 3 months (IQR 2-6)

We calculated the incidence of reinfection between 2015 and 2024. Follow-up time was from the date of SVR, date of spontaneous clearance, or from 1 January 2015 onwards, until the earliest date of HCV reinfection, death, or last known contact. The incidence of HCV reinfection for the total population was 13 reinfections per 1,000 PY (95% CI 12-15), and for MSM it was 17 reinfections per 1,000 PY (95% CI 15-20).

Because most reinfections occurred among MSM, the incidence of HCV reinfection over time is shown only for MSM (*Figure 7.6*). This incidence decreased from 62 reinfections per 1,000 PY in 2015 to 17 per 1,000 PY in 2019, and then declined to 7 reinfections per 1,000 PY in 2023, and 5 per 1,000 PY in 2024. However, the incidence of HCV reinfections showed some fluctuation in the recent calendar years.

Figure 7.6: Incidence of hepatitis C reinfection after earlier treatment-induced and spontaneous 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 7.7 shows the HCV continuum of care, based on the number of people known to be in HIV care as of 31 December 2024 and with a HCV diagnosis between 2015 and 2025 or a not yet cleared HCV infection diagnosed before 2015. Individuals were categorised according to their last documented HCV infection episode. In total 1,604 individuals were linked to HIV care with an active HCV infection between 2015 and 2024, 1,422 individuals had primary HCV infection, and 182 individuals had an HCV reinfection.

Of the 1,604 individuals linked to HIV care:

- 1,226 (76%) were retained in care;
- 378 individuals were no longer in care (165 had died; 114 had moved abroad; and 99 were lost to care). Among the 213 individuals who were lost to care or who moved abroad
  - 133 had a negative HCV RNA test result before they left care and
  - for 80 individuals the last HCV RNA measurement was detectable;
- 1,186 (96%) of those still alive and in care had received treatment for HCV;
- 1,166 (98%) of those still alive, in care and who had received treatment, had completed HCV treatment and had data available to calculate HCV treatment response (SVR12).

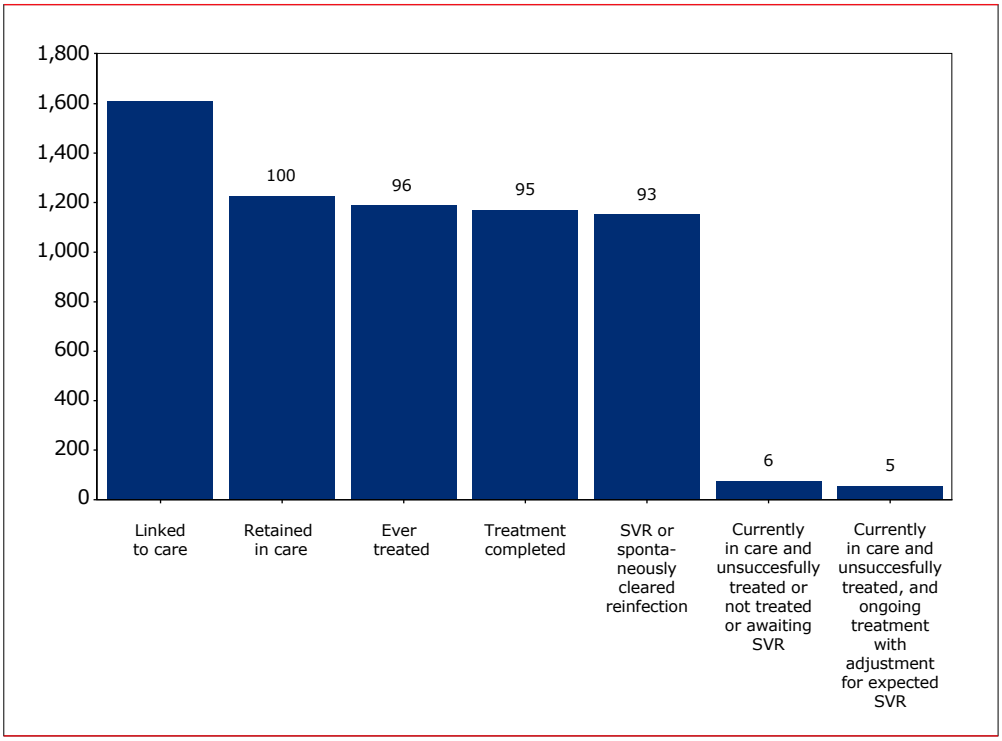
Overall, 1,146 of the 1,166 people in care in 2024 who completed treatment (98%) achieved SVR, including those who were retreated after earlier treatment failure. Another 5 individuals with HCV reinfection had a negative last HCV RNA test result, without documentation of HCV treatment. It is likely these individuals spontaneously cleared their HCV infection, bringing the total of individuals with a treatment-induced or spontaneous clearance of their most recent HCV episode to 1,151.

The remaining 75 (6%) of 1,226 individuals known to be alive and in care on 31 December 2024, were still in need of HCV treatment (n=55) or awaiting the SVR after treatment (n=20):

Of these, 35 (3%) individuals had never been treated for HCV, 9 were born in the Netherlands, and 21 were born in Western, central or eastern Europe. All individuals received ART. The percentage of untreated individuals was higher among PWID (8%), people who acquired HIV through heterosexual contact (6%), and people with an unknown HIV transmission mode (4%), than among MSM (1%).

For 20/75 individuals SVR could not yet be determined, 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 19 of the 20 (96%) will achieve SVR. This results in an estimate of individuals 56 (75-19=56) who have yet to be treated or were unsuccessfully treated.

Figure 7.7: Hepatitis C continuum of care including individuals in care with an active HCV infection between 2015 and 2024. (Percentages of those who retained in care are reported at the top of each bar).



Legend: SVR=sustained virological response.

Liver-related morbidity and mortality in individuals with HCV

Additional data from liver biopsy pathology reports, transient elastography, radiology reports, or a combination of those sources, were available for:

- 1,586 of the 1,885 individuals in care between 2014 and 2025 and ever diagnosed chronic or recent HCV and without other viral hepatitis (i.e. HBV, HCV/chronic HBV: n=103);
- 418/1,885 (22%) individuals had evidence of severe chronic liver disease (presumptive and definitive categories combined);
- definitive severe chronic liver disease was documented for 92 (5%) individuals with HCV co-infection.

Data on hepatocellular carcinoma (HCC) showed that between 2015 and 2024:

- 8 (0.4%) cases of hepatocellular carcinoma (HCC) were reported among 1,885 individuals with HCV and without other viral hepatitis (i.e. HBV or HDV).
- 3 of the 8 individuals with HCC were born in the Netherlands.
- No cases of HCC were reported among DAA treated individuals without cirrhosis or fibrosis.

Between 2015 and 2024, among the 1,855 individuals with HCV and without other viral hepatitis (i.e. HBV or HDV):

- 199 (11%) deaths from any cause occurred;
- 17 (0.9%) deaths were liver-related.
  - 15 individuals who died of a liver-related cause were treated for HCV (10 with DAAs and 5 with older regimens).
  - 16/17 individuals were known to have liver cirrhosis.

Hepatitis B virus

Hepatitis B is a vaccine-preventable disease caused by the hepatitis B virus [HBV]. HBV is sexually- and parenterally-transmitted and causes both acute and chronic hepatitis. The following sections describe HBV epidemiology among 27,082 ATHENA cohort participants who had at least one HIV care visit between 2015 and 2024.

We used three serological markers of HBV infection to determine an individual's HBV clinical state: hepatitis B surface antigen (HBsAg), anti-hepatitis B surface antibodies (anti-HBs), and anti-hepatitis B core antibodies (anti-HBc) (see Box 7B). For each participant, we determined the HBV serological profile by combining assay results across time. When all three assays were available at any point during the observation, the profile was considered "complete". When all three assays were available or when HBsAg was positive, we designated the serological profile as "interpretable". Otherwise, the profile was considered "incomplete".

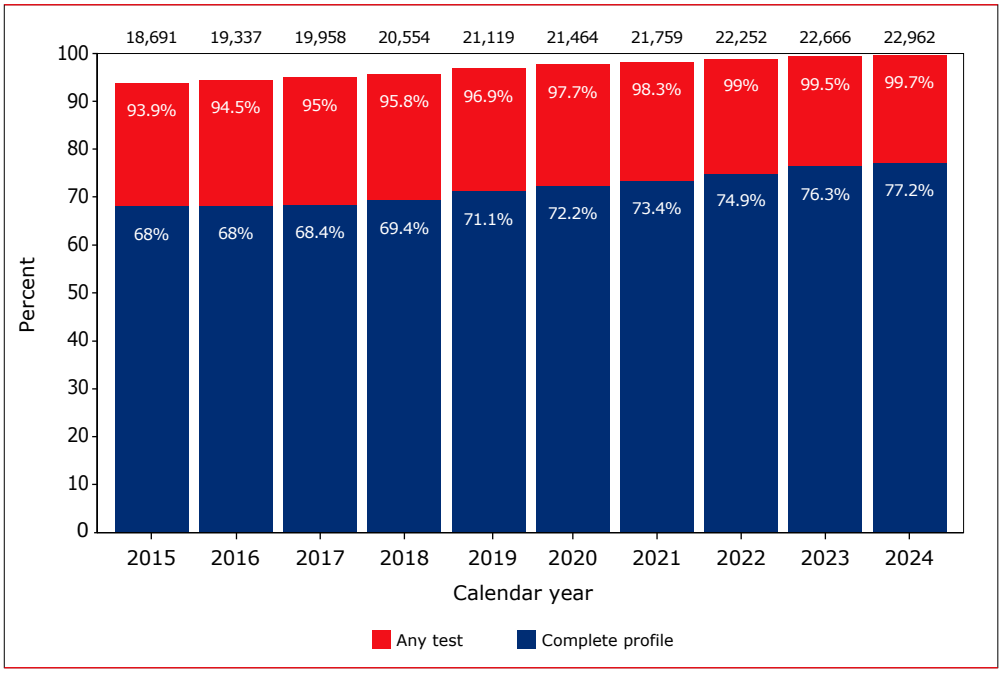
Box 7B: Interpretation of HBV serological profiles.

HBV Clinical state	HBsAg	Anti-HBs	Anti-HBc
Chronic infection	Positive	Negative	Positive
Resolved infection	Negative	Positive	Positive
Vaccine-derived immunity	Negative	Positive	Negative
Susceptible, never infected	Negative	Negative	Negative
Isolated core antibody positive	Negative	Negative	Positive

HBV testing

Of 27,082 participants, 26,806 (99%) had any of the three key HBV serological markers performed at any time since entry to care. The proportion of participants in care with any HBV serology increased over time, from 40.7% in 2000 to 94.2% in 2024. Complete serological profiles were available for 25.2% of participants in care in 2000 and 73% in 2024 (Figure 7.8).

Figure 7.8: Proportion of participants with any HBV testing and with complete HBV serological profiles, 2015–2024.

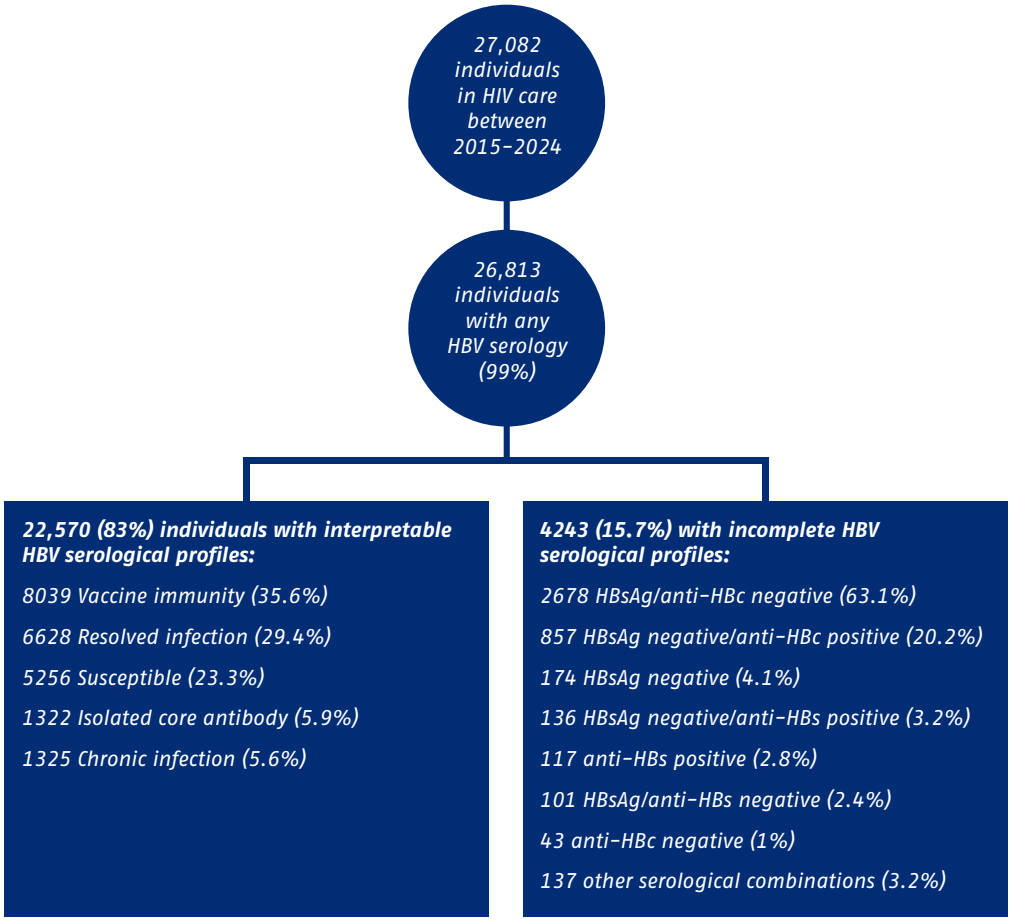


Numbers above bars represent the number of participants in care.

HBV serological profiles

An interpretable HBV profile was available in 22,570 (83%) participants (Figure 7.9). Of these 8,039 (35.6%) had a serological profile consistent with vaccine acquired immunity, 6,628 (29.4%) with resolved infection, and 5,256 (23.3%) remained HBV susceptible.

Figure 7.9: HBV serological profiles in participants with at least one HIV care visit between 2015–2024.



One thousand three hundred and fifty-four participants (5.1%) were ever HBsAg positive. To distinguish between participants with acute versus chronic HBV, we reviewed the duration of HBsAg positivity. We considered HBV infection to be acute if the following two conditions were present: 1) documented negative HBsAg followed by surface antigenemia; 2) documented clearance of HBsAg within 180 days of first detection. Individuals with surface antigenemia lasting 180 days or more, or in whom the duration could not be ascertained, were categorized as having chronic HBV.

Twenty-nine participants had a documented negative HBsAg followed by surface antigenemia lasting less than 180 days, with confirmed loss of HBsAg. We considered these participants to have resolved acute HBV. The remaining 1,325 had evidence of HBsAg antigenemia lasting ≥180 days or of unknown duration and are discussed in greater detail in the section on chronic HBV.

The demographic characteristics of people with interpretable HBV profiles are shown in Table 7.3.

Table 7.3: *Demographic characteristics of participants with interpretable HBV profiles (n=22,570).*

	Immunized (N=8,039)	Resolved (N=6,628)	Susceptible (N=5,256)	Isolated core (N=1,322)	Chronic (N=1,325)
Gender					
Male	7,017 (87.3%)	5,716 (86.2%)	3,781 (71.9%)	984 (74.4%)	1,141 (86.1%)
Female	1,022 (12.7%)	912 (13.8%)	1,475 (28.1%)	338 (25.6%)	184 (13.9%)
Transmission group					
MSM/W	5,866 (73.0%)	4,579 (69.1%)	2,312 (44.0%)	550 (41.6%)	790 (59.6%)
Heterosexual	1,558 (19.4%)	1,408 (21.2%)	2,344 (44.6%)	503 (38.0%)	378 (28.5%)
Unknown	292 (3.6%)	271 (4.1%)	345 (6.6%)	109 (8.2%)	75 (5.7%)
Sexual transmission NOS	177 (2.2%)	123 (1.9%)	110 (2.1%)	20 (1.5%)	29 (2.2%)
IVDU	53 (0.7%)	157 (2.4%)	52 (1.0%)	114 (8.6%)	36 (2.7%)
Other	93 (1.2%)	90 (1.4%)	93 (1.8%)	26 (2.0%)	17 (1.3%)
Birth region					
Netherlands	4,388 (54.6%)	3,476 (52.4%)	2,842 (54.1%)	460 (34.8%)	590 (44.5%)
Latin America and Carribbean	1,217 (15.1%)	895 (13.5%)	776 (14.8%)	136 (10.3%)	175 (13.2%)
Sub-Saharan Africa	471 (5.9%)	965 (14.6%)	586 (11.1%)	419 (31.7%)	292 (22.0%)
W Europe, N America, Australia	759 (9.4%)	490 (7.4%)	266 (5.1%)	94 (7.1%)	72 (5.4%)
Central and Eastern Europe	592 (7.4%)	332 (5.0%)	424 (8.1%)	116 (8.8%)	91 (6.9%)
South and East Asia	350 (4.4%)	349 (5.3%)	168 (3.2%)	62 (4.7%)	80 (6.0%)
N Africa and Middle East	212 (2.6%)	98 (1.5%)	163 (3.1%)	30 (2.3%)	19 (1.4%)
Unknown	50 (0.6%)	23 (0.3%)	31 (0.6%)	5 (0.4%)	6 (0.5%)

Chronic HBV

One thousand three hundred twenty-five individuals (5.9%) with interpretable HBV profiles had evidence of HBsAg antigenemia lasting greater than 180 days, meeting our definition of chronic HBV infection. Of these, 879 (3.2%) were HBsAg positive at last observation while 446 (33.7%) had documented loss HBsAg. Two hundred and forty-five participants (18.5%) achieved a functional cure, defined as loss of HBsAg with gain of anti-HBsAb.

Probable or definite severe liver disease was documented in 236 (17.8%) participants with a history of chronic HBV, of whom 102 (7.7%) had documented cirrhosis and 14 had hepatocellular carcinoma (for the definition of severe liver disease see Box 7.1). One hundred and forty-one deaths occurred among participants with a history of chronic HBV, of which 11 (7.8%) were attributable to liver-related causes. As a proportion of the 1,325 participants with a history of chronic HBV, less than 1% died of liver-related causes.

Table 7.4: Laboratory and clinical characteristics of participants with a history of chronic HBV (n=1,325).

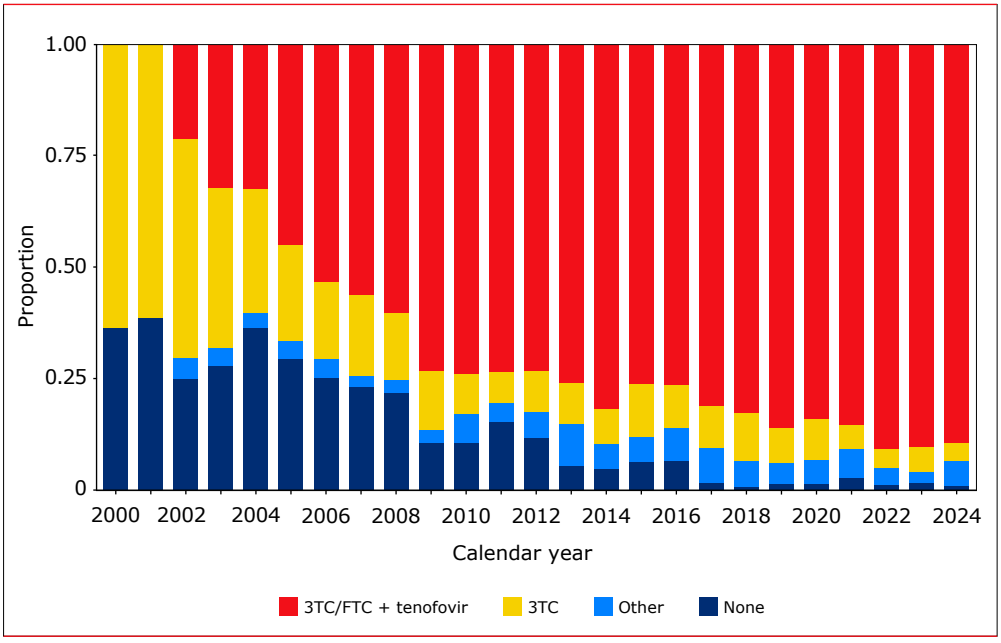
	HBsAg+ (N=879)	HBsAg−/anti-HBs+ (N=245)	HBsAg−/anti-HBs− (N=201)	Total (N=1,325)
HBV DNA <500 copies/ml				
No	90 (11.2%)	25 (16.8%)	19 (13.7%)	134 (12.3%)
Yes	714 (88.8%)	124 (83.2%)	120 (86.3%)	958 (87.7%)
NA	75	96	62	233
Cirrhosis				
No	803 (91.4%)	234 (95.5%)	186 (92.5%)	1,223 (92.3%)
Yes	76 (8.6%)	11 (4.5%)	15 (7.5%)	102 (7.7%)
Severe liver disease				
None/NA	699 (79.5%)	223 (91.0%)	167 (83.1%)	1,089 (82.2%)
Probable	132 (15.0%)	13 (5.3%)	22 (10.9%)	167 (12.6%)
Confirmed	48 (5.5%)	9 (3.7%)	12 (6.0%)	69 (5.2%)
Hepatocellular carcinoma				
No	867 (98.6%)	244 (99.6%)	200 (99.5%)	1,311 (98.9%)
Yes	12 (1.4%)	1 (0.4%)	1 (0.5%)	14 (1.1%)
Death from any cause				
No	785 (89.3%)	215 (87.8%)	184 (91.5%)	1,184 (89.4%)
Yes	94 (10.7%)	30 (12.2%)	17 (8.5%)	141 (10.6%)

Treatment of chronic hepatitis B

The goal of HBV treatment is to reduce viral replication and thus prevent hepatic inflammation and liver disease progression[11]. Suppression of HBV DNA has been shown to reduce the risk of HCC and overall mortality in individuals with HIV/HBV coinfection[12,13]. Antiretroviral agents with activity against HBV include the cytidine analogues lamivudine and emtricitabine, and tenofovir prodrugs.

HBV treatment data was available in 1,320 of 1,325 (99.6%) individuals ever diagnosed with chronic HBV (reasons for missingness were death (2) and loss to follow up (3)). Figure 7.10 shows changes in prescribed HBV treatment regimens over the past 25 years. In 2000, 63.6% of participants with chronic HBV received a lamivudine-containing regimen while the rest received no anti-HBV treatment; in 2015, 74.6% received a regimen containing tenofovir and a cytidine analogue, while 8.2% were untreated; by 2024, 88.6% were treated with a tenofovir and a cytidine analogue while only 1.6% were untreated. When individuals who achieved functional cure are excluded from the analysis, 99.1% of individuals with a history chronic HBV are currently treated with at least one anti-HBV agent and 89% receive a tenofovir-containing regimen.

Figure 7.10: Evolution of HBV treatment strategies, 2000–2024 (n=1,320).



Coinfection with other hepatitis viruses

People with chronic hepatitis B may be coinfected with other hepatitis viruses, including hepatitis C, D, and E.

HCV, HDV and HEV testing was performed in 1,320 (99.6%), 465 (35%), and 159 (12%) of participants with chronic HBV[14].One hundred and fifteen participants (8.7%) had a history of chronic HBV-HCV coinfection. Twenty-seven participants (2%) had evidence of HDV coinfection by either positive antibody or RNA; of these, 8 had evidence of HDV viremia. Three participants had a history of chronic HBV and evidence of past HEV infection; no participant had both chronic HBV/HEV coinfection. No participant was coinfected with more than one chronic viral hepatitis virus.

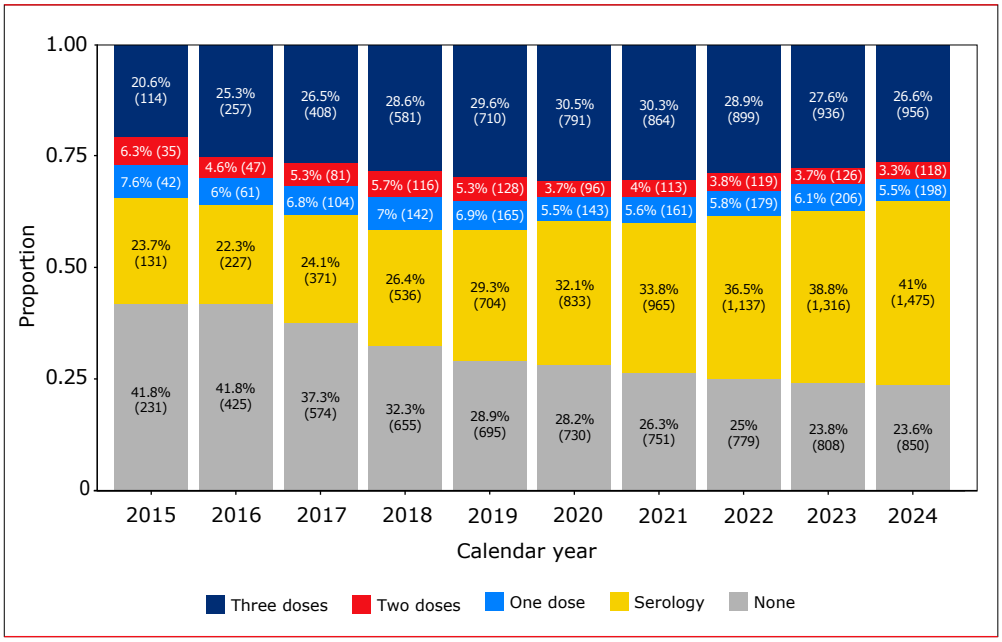
HBV vaccination

Dutch guidelines recommend HBV vaccination in all MSM[15]. We estimated the proportion of vaccine-eligible MSM entering care between 2015 and 2024 who had evidence of HBV vaccination. Vaccine-eligible MSM were defined as having no evidence of past or current HBV infection by serology (ie neither HBSAg nor anti-HBc positive).

Data on vaccine administration within the ATHENA cohort is incomplete. We reviewed vaccine administration records, baseline data, and HBV serology to determine cumulative vaccination status. Participants who were documented to be vaccinated in the baseline questionnaire were considered to have received a full (3 dose) series of any HBV-containing vaccine. Serological evidence of vaccination was defined as the presence of anti-HBs and absence of anti-HBc. All data were carried forward for each observation year, assuming that the most recent status persists until a new event is recorded. Once vaccine-derived immunity was documented by serology, the serological status was considered permanent. As participants entered and left the cohort, we calculated the cumulative proportion of participants with serological evidence of vaccine-derived immunity or evidence of HBV vaccination.

Between 2015 and 2024, a total of 5,177 MSM entered care. Of these, 1,118 were either anti-HBc positive or HBsAg positive at entry, leaving 3,989 vaccine-eligible MSM in the analysis. By 2024, 1,475 (41%) participants had serological evidence of HBV immunization, 956 (26.6%) were documented to be vaccinated or to have received 3 doses of HBV vaccine, 118 (3.3%) had received two doses of HBV vaccine, and 198 (5.5%) had received one dose (Figure 7.11). Eight hundred and fifty vaccine eligible participants (23.6%) had no evidence of either HBV vaccination or vaccine-derived immunity.

Figure 7.11: Cumulative Hepatitis B immunity and vaccination status in vaccine-eligible MSM entering care, 2015–2024 (n=3,989).



Hepatitis A virus

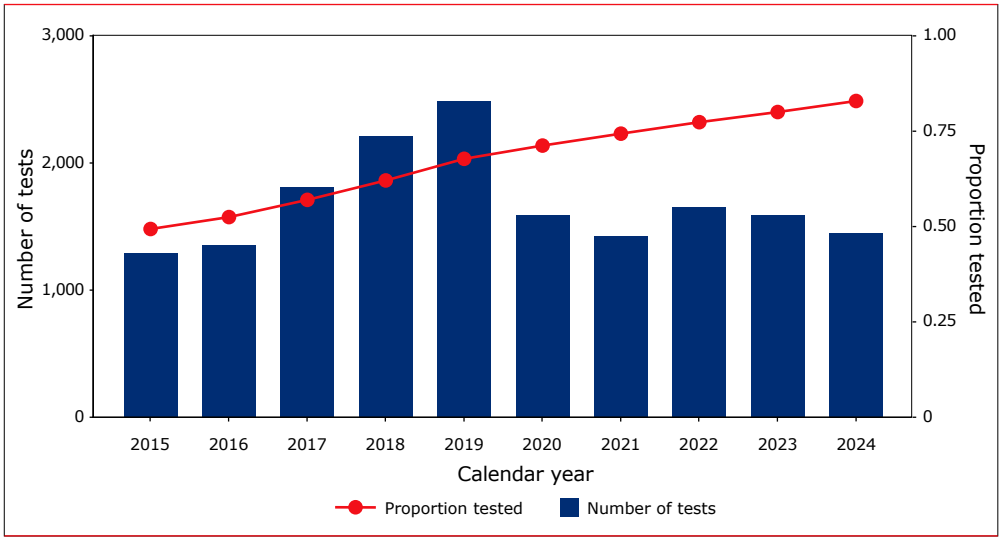
Hepatitis A is a vaccine-preventable infection caused by the hepatitis A virus (HAV). HAV is transmitted via the fecal-oral route, including through anal-oral sexual contact. HAV causes acute hepatitis without establishing chronicity.

A diagnosis of acute HAV is made on the basis of serology and clinical features compatible with acute viral hepatitis. Serological assays include anti-HAV IgM and liver enzyme measurement. Immunity to HAV is determined using anti-HAV IgG serology. Anti-HAV IgG seropositivity confirms lifelong immunity to HAV but does not distinguish between vaccine-induced and infection-acquired immunity.

HAV testing

Of 27,082 individuals with at least one HIV care visit over the past decade, 19,334 (71.4%) were ever tested for hepatitis A. By 2024, 83% of participants in care had at least one serological assay for hepatitis A performed. The number of annual tests and the cumulative proportion of participants tested for hepatitis A is shown in Figure 7.12.

Figure 7.12: Number of tests and cumulative proportion of participants tested for hepatitis A, 2015–2024 (n=27,082).



Of the 19,334 individuals seen in care over the past decade in whom HAV serology was performed, 12,693 (65.6%) had evidence of immunity to HAV. Between 2015 and 2024, the proportion of patients with positive anti-HAV serology was largely unchanged (58.3% and 55.7%, respectively). Mean HAV seropositivity was highest in people born in sub-Saharan Africa (91.1%), followed by those born in North Africa and the Middle East (79.1%); 54.1% of people born in the Netherlands were seropositive. The HAV seropositivity rate was 66.2% in women, compared to 58.6% in men. MSM had lower mean seropositivity than other HIV transmission groups, 57.8% versus 63.1%, respectively.

Acute HAV

A diagnosis of acute HAV was determined on the basis of available clinical and serological data. Acute HAV was defined as either 1) a diagnosis of laboratory-confirmed and/or symptomatic acute HAV documented in the medical record; or 2) positive anti-HAV IgM serology with ALT ≥ 3 times the upper limit of normal (ULN) within 3 months of IgM detection. We restricted our analysis to episodes occurring over the past decade.

Between 2015 and 2024, 79 participants had a diagnosis of lab-confirmed and/or symptomatic acute HAV documented in the medical record and an additional 28 individuals had acute HAV by laboratory criteria, giving a total of 107 cases of acute HAV. The median number of acute HAV cases annually was 6. In 2016-2017, an outbreak of hepatitis A among sexually active MSM was identified across Europe[16]. In 2017, 54 cases of acute HAV were documented in the ATHENA cohort. Since 2020, the annual number of acute HAV cases has remained under 5. One hundred and six (94.2%) acute HAV cases occurred in men, of whom 93 (87.6%) were MSM (Figure 7.13). The majority of cases occurred in people born in the Netherlands (n=50, 46.7%) (Figure 7.14).

Figure 7.13: Number of acute HAV cases by year and transmission group, 2015–2024 (n=106).

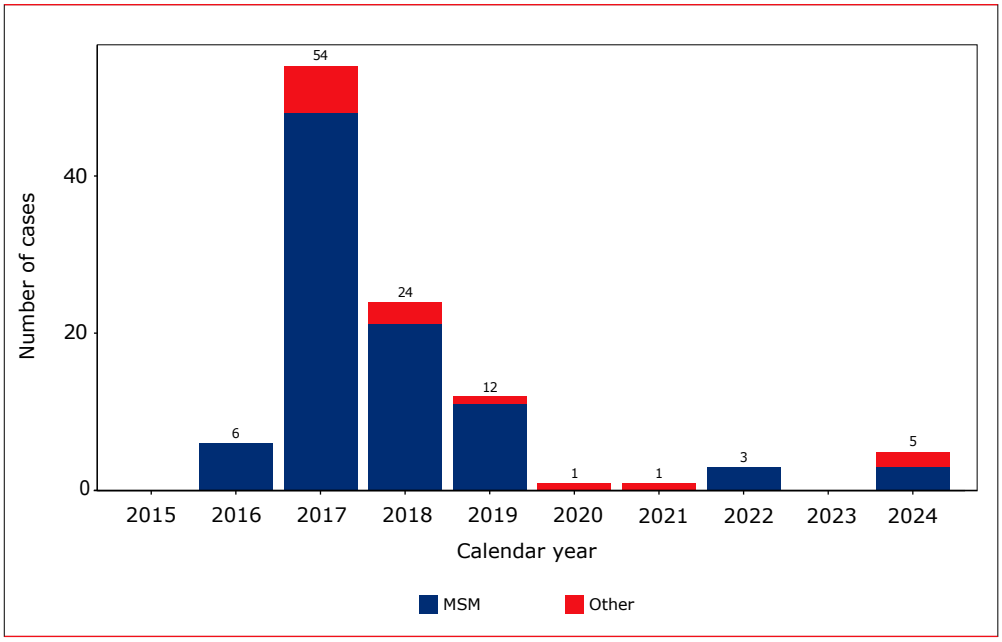
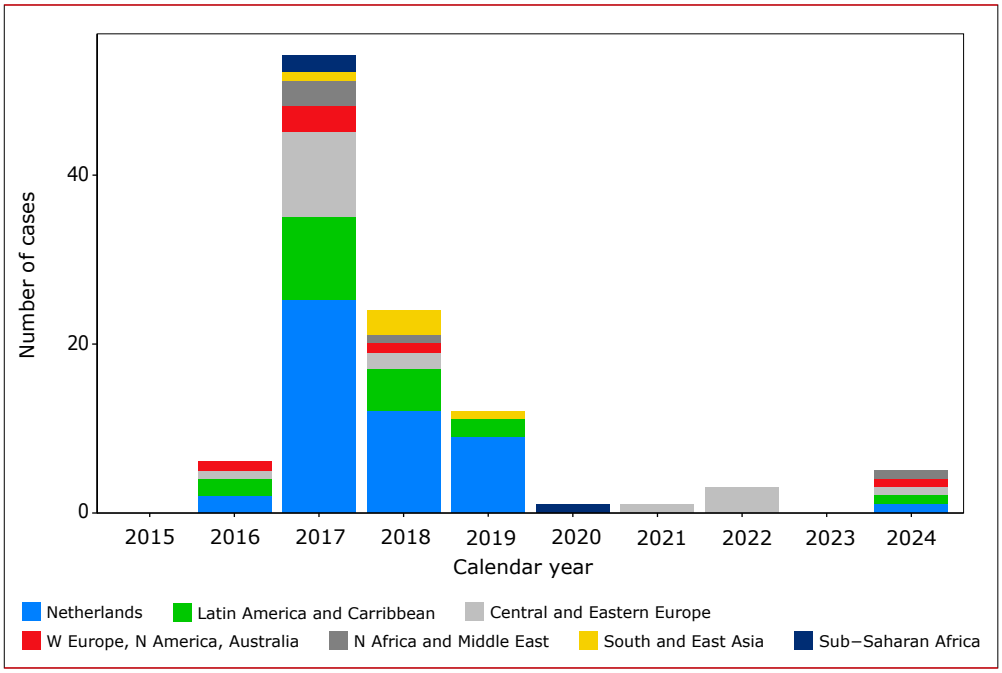


Figure 7.14: Number of acute HAV cases by year and birth region, 2015–2024 (n=106).



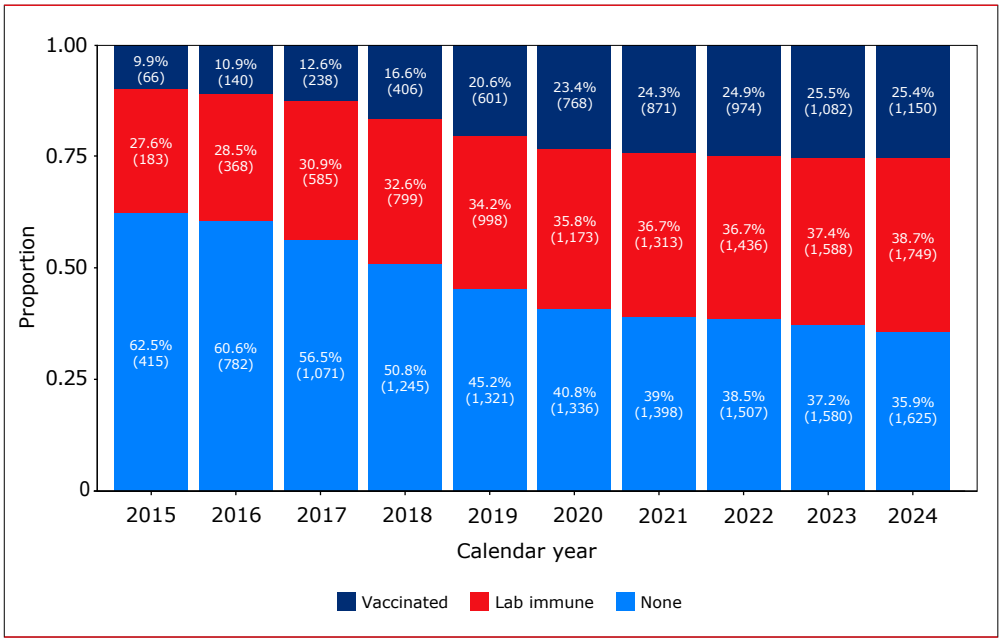
HAV vaccination

Dutch guidelines recommend HAV vaccination in MSM[5,17]. We estimated HAV vaccine coverage among 5,177 MSM who entered care between 2015 and 2024. For each participant, we reviewed data available from the baseline visit, vaccine administration record, and laboratory analyses. Participants were considered to be immune to hepatitis A if they had evidence of anti-HAV IgG. Participants were considered vaccinated if they had received at least one dose of HAV vaccine.

All data were carried forward for each observation year, assuming that the most recent status persists until a new event is recorded. Once vaccination was documented, vaccination status was considered permanent. As participants entered and left the cohort, we calculated the cumulative proportion of participants with evidence of either HAV vaccination or HAV immunity by serology.

By 2024, 1,749 (38.7%) MSM entering care over the past decade had evidence of immunity to HAV by serology and an additional 1,150 (25.4%) had received at least one dose of HAV vaccine or were documented to be vaccinated in the clinical chart. A total of 1,625 (35.9%) participants had no evidence of either HAV vaccination or HAV immunity by serology (Figure 7.15).

Figure 7.15: Cumulative Hepatitis A immunity and vaccination status in MSM entering care, 2015–2024 (n=5,177).



Hepatitis E virus

Hepatitis E virus [HEV] is increasingly recognized as a cause of acute viral hepatitis[18]. Like HAV, HEV is transmitted via the oral-fecal route. Unlike HAV, acute HEV may lead to chronic infection. There is currently no anti-HEV vaccine available in the Netherlands.

Testing for acute and chronic HEV relies on a combination of HEV IgM, HEV RNA and HEV IgG measurements in a clinically compatible setting. Testing for resolved infection is determined by detection of anti-HEV IgG antibodies.

Of the 27,082 people in HIV care between 2015 and 2024, 2,275 (8.3%) were ever tested for HEV, 276 (12.1%) of whom had evidence of HEV infection. Of participants with any evidence of HEV infection, 1,912 (84%) were male and 1,365 (60%) were MSM. Fifty-seven participants (2.5%) had evidence of acute HEV, 50 of whom had positive IgM only and 7 of whom had detectable HEV RNA (> 10 IU/ml). A single individual had evidence of chronic HEV, with RNA detected for greater than 6 months.

Conclusions

Over the past decade, we note significant improvements in screening, treatment, and prevention of viral hepatitis in the SHM cohort.

Between 2015 and 2024, 927 individuals were diagnosed with primary HCV infection (including 302 recent infections) and 182 individuals were diagnosed with in total 209 reinfections. Recent HCV infection and reinfections occurred more often among MSM, 93% of the recent infections and 90% of the reinfections were among MSM. By the end of 2024, 99% of individuals had been screened for HCV. Between 2015 and 2024, the number of individuals with an HCV diagnosis, including reinfections, has decreased from 187 to 42. The proportion of individuals with a HCV diagnosis and born in the Netherlands also decreased and since 2022, more than half of those with an HCV diagnosis originated from other European countries than the Netherlands. Of the individuals in care between 2015 and 2025, 96% had received treatment for HCV and 99% were successfully treated (including retreatment after earlier treatment failure) and achieved treatment-induced clearance of HCV. Effective treatment with DAAs has reduced the proportion of individuals with positive HCV RNA to 0.3%. HCV reinfection continues to occur but rates have declined.

Screening for HBV has improved over time, with nearly 100% of participants having at least one HBV serological assay available by 2024. One thousand three hundred and twenty-five individuals (5.9%) with interpretable HBV profiles had evidence of chronic HBV infection; 879 (3.2%) remain HBsAg positive at last observation. About 90% percent of individuals with a history of chronic HBV receive an antiretroviral regimen containing a tenofovir prodrug, the optimal agent for treating HIV/HBV coinfection[19].

Evidence of severe liver disease was documented in 22% of individuals with a history of HCV and 18% of participants with a history of chronic HBV. Rates of hepatocellular carcinoma and liver-related deaths in participants with severe liver disease are low.

Vaccination against HBV and HAV in MSM remains incomplete. Among MSM entering care between 2015 and 2024, 24% of vaccine-eligible individuals had no evidence of HBV vaccination or vaccine-induced immunity by the end of observation; 36% had no evidence of HAV vaccination or immunity.

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8. Children with HIV

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Box 8.1: 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 2024	Individuals with HIV who had a documented clinic visit or lab measurement in 2024.
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 8.2: Outline of the paediatric ATHENA cohort in the Netherlands: all children with HIV registered in the ATHENA cohort before 31 December 2024. (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=411).
2. Population of those diagnosed as a child and in care in 2024 (n=331):
   - under the age of 15 in 2024 (n=96); includes 78 adopted children.
   - aged 15-18 years in 2024 (n=50); includes 41 adopted children.
   - aged 18 years and over in 2024 (n=185); includes 28 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 8.2*)[a]:

- demographics
- clinical characteristics
- treatment regimens between 2015-2024.
- long-term virological and immunological responses to treatment between 2015-2024.

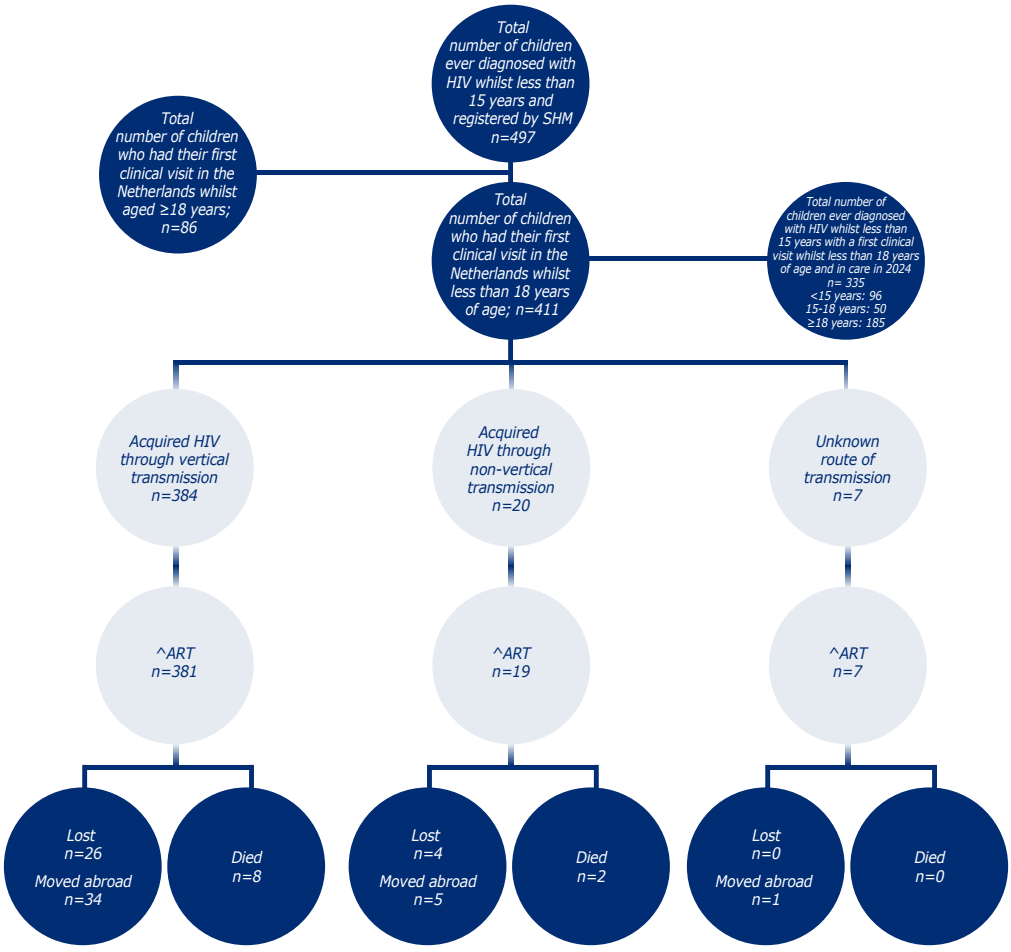
The limit of 15 years is aligned with the definition of children used by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO)[1,2].

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

Between 1998 and 2024, the SHM database includes 497 registered individuals diagnosed with HIV while under 15 years of age (*Figure 8.1*). Of these, 411 children entered care in the Netherlands before the age of 18. The remaining 86 individuals who were diagnosed as a child, entered care in the Netherlands *after* the age of 18; 83% (n=71) of those were born outside the Netherlands. And the other 15 were born in the Netherlands, all, except one, of the individuals born in the Netherlands were diagnosed with HIV before 1990 and they were already 18 years or older before the start of the registration.

Figure 8.1: *Overview of total population children with HIV registered in SHM database as of 31 December 2024.*



Legend: *^ of the total number of children who acquired HIV through a vertical, non-vertical or an unknown route of transmission. ART = antiretroviral therapy.*

The remainder of this chapter will focus on the 411 children diagnosed under the age of 15 and who entered care in the Netherlands before the age of 18. The majority (97%) 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 16.2-17.6) (*Table 8.1*).

The most commonly reported region of birth was Sub Saharan Africa (n=237, 49%) and the Netherlands (n=113, 28%); 61 (15%) children were born in other regions, including the Caribbean, Latin America, Europe and Asia.

Table 8.1: *Demographic and HIV-related characteristics of 411 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 (%)	411	384 (93.4)	20 (4.9)	7 (1.7)
HIV treatment centre				
Paediatric care	400 (97.3)	377 (98.2)	16 (80.0)	7 (100.0)
Adult care	11 (2.7)	7 (1.8)	4 (20.0)	
Gender				
Female	210 (51.1)	196 (51.0)	12 (60.0)	2 (28.6)
Male	201 (48.9)	188 (49.0)	8 (40.0)	5 (71.4)
Child region of origin				
Sub-Saharan Africa	237 (57.7)	214 (55.7)	16 (80.0)	7 (100.0)
Netherlands	113 (27.5)	111 (28.9)	2 (10.0)	
Other/unknown	61 (14.8)	59 (15.4)	2 (10.0)	
Mother region of origin				
Sub-Saharan Africa	201 (48.9)	188 (49.0)	8 (40.0)	5 (71.4)
Other/unknown	175 (42.6)	163 (42.4)	10 (50.0)	2 (28.6)
Netherlands	35 (8.5)	33 (8.6)	2 (10.0)	
Adopted	155 (37.7)	153 (39.8)		2 (28.6)
Age at HIV diagnosis				
Median (IQR)	1.2 (0.3 to 4.3)	1.0 (0.2 to 3.5)	11.5 (7.4 to 14.3)	10.9 (10.2 to 11.7)
ART-treated	407 (99.0)	381 (99.2)	19 (95.0)	7 (100.0)
Therapy-naïve at ART initiation	357 (86.9)	334 (87.0)	16 (80.0)	7 (100.0)
CD4 at ART initiation				
Median (IQR)	535.0 (273.5 to 1,127.5)	550.0 (278.0 to 1,210.0)	323.5 (176.5 to 472.0)	475.0 (320.0 to 570.0)
CD4 Z-score at ART initiation				
Median (IQR)	-0.9 (-1.3 to -0.5)	-0.9 (-1.4 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.*

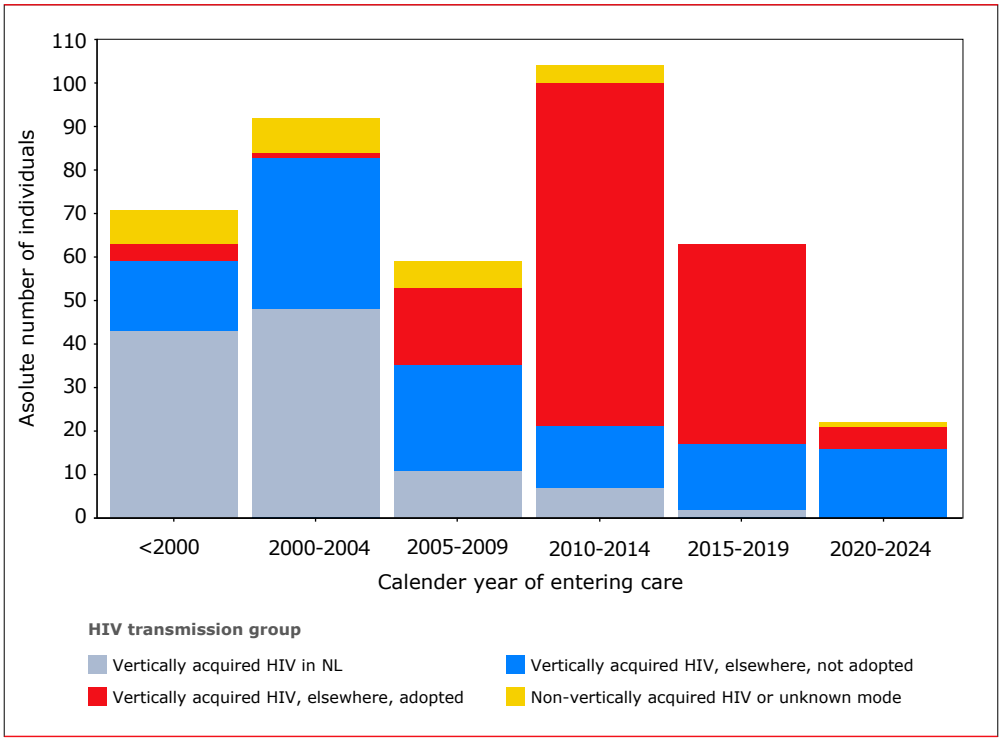
Mode of transmission

The majority (93%) of the children registered acquired HIV through vertical transmission. (*Figure 8.1*).

Vertical transmission

- Between 1998 and 2024, 384 children entered care after acquiring HIV through vertical transmission. (*Table 8.1*)
- 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] 0.2-3.5 years).
- 98% received care in a paediatric HIV treatment centre in the Netherlands.
- ART initiation was documented for 99% of the children.
- 56% (n=214) of the children were born in sub-Saharan Africa.
- 29% (n=111) of the children were born in the Netherlands.
- 8% of the children born in the Netherlands (9 out of 111), had two Dutch parents.

Figure 8.2: *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 8.2 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 63 in 2015-2019 and 22 in 2020-2024. 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 2024, 20 children were registered as having acquired HIV through non-vertical transmission (*Table 8.1*); 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.

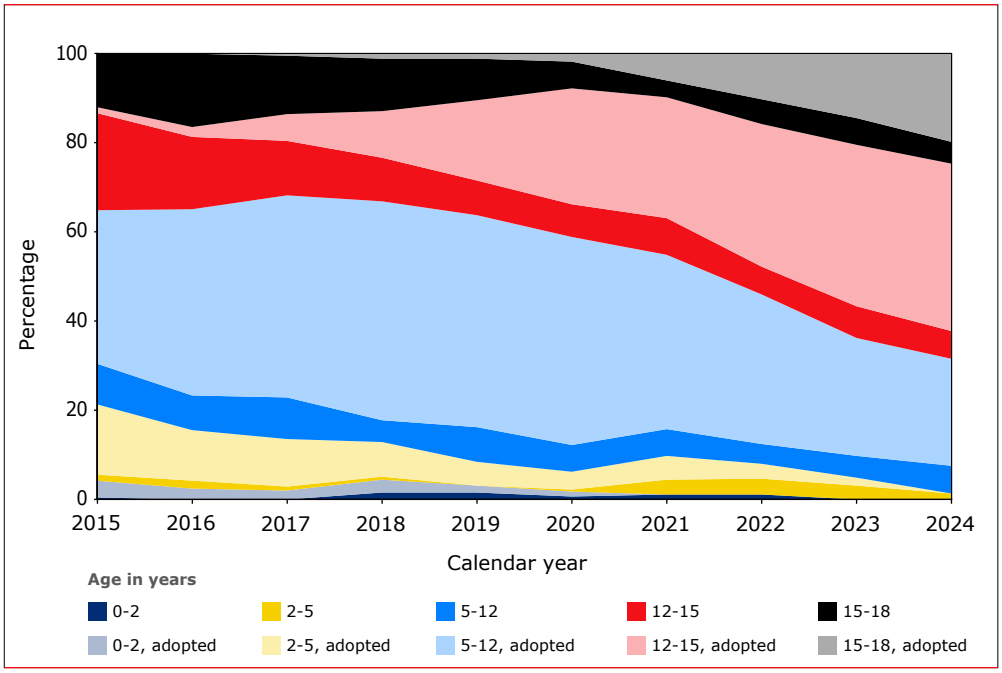
Unknown route of HIV transmission

- For 7 children with HIV, the route of transmission remains unknown (*Table 8.1*).
- Their median age at diagnosis was 10.9 years (IQR 10.2-11.7).
- All children had started ART.

Age distribution

Figure 8.3 shows the age distribution of children receiving HIV care in the last 10 years (2015-2024). Between 2015 and 2019, around 50% of the children was aged between aged 5-12. Whilst the proportion of children aged between 12 and 18 years increased from 41% in 2020 to 68% in 2024. In 2024, 82% of children aged< 18 years was adopted.

Figure 8.3: 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 2015 and 2024. 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 2015 and 2024 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 411 children who entered care in the Netherlands before 18 years of age, 407 (99%) started ART; 357 (87%) of them were treatment-naive at the start of ART and 50 (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 2015 onwards have been included. Children were grouped by calendar year of ART initiation: 25 children started an ART regimen in 2015-2016, 30 in 2018-2019 and 6 in 2020-24. For 14 children, the year of ART initiation is not known. All these children were born outside the Netherlands.

Initial antiretroviral regimen

Of the 61 registered children known to have initiated ART between 2015 and 2024:

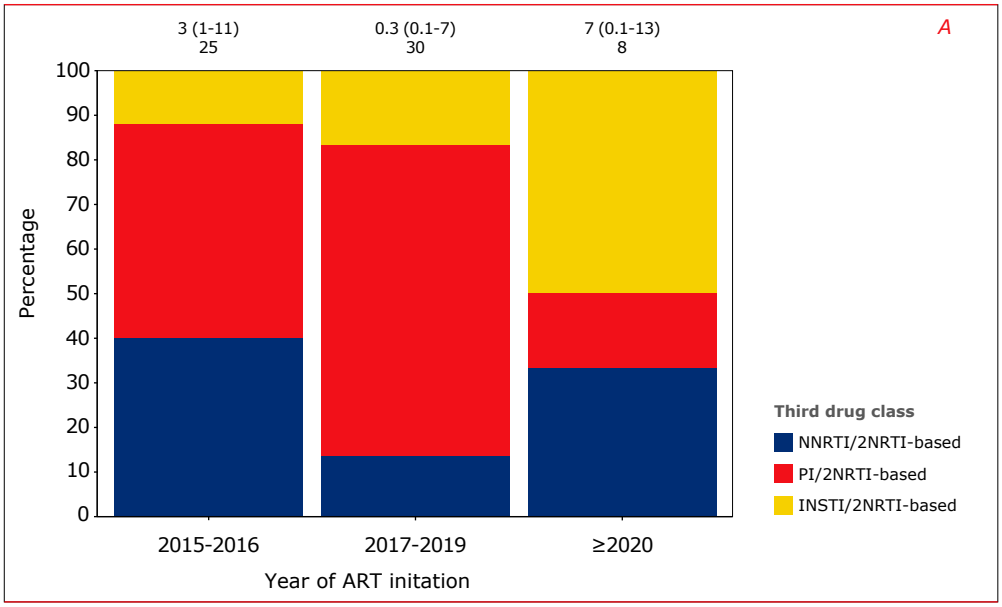
- 56% were treated with a first-line regimen that included a protease inhibitor (PI) and two or more nucleoside reverse transcriptase inhibitors (NRTIs);
- 26% were treated with a non-nucleoside reverse transcriptase inhibitor (NNRTI) with two or more NRTIs; and
- 18% were treated with an integrase inhibitor-based first-line with two or more NRTs regimen.

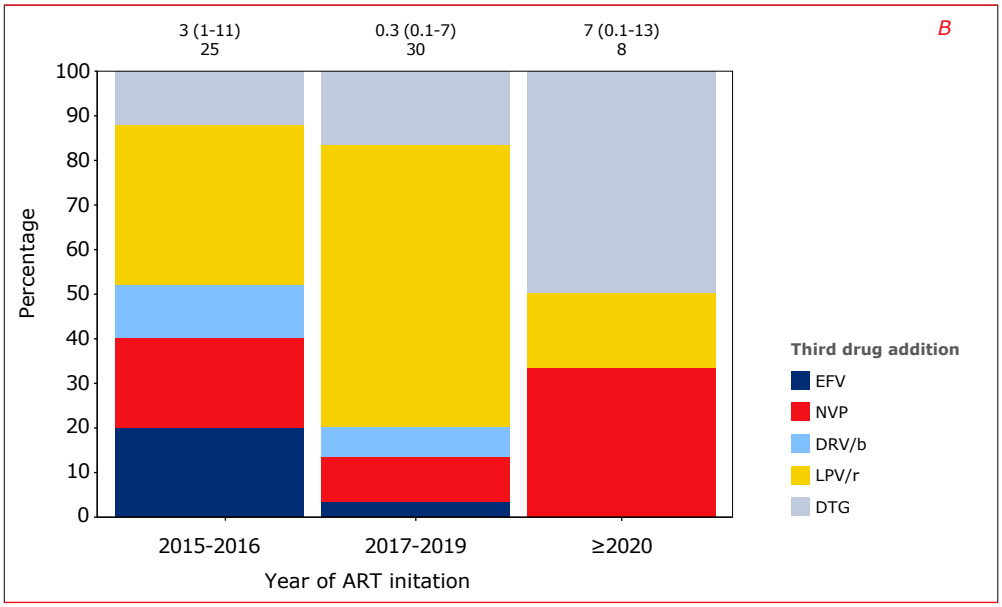
Notably, a substantial proportion of the first line regimens were already initiated before the first clinical visit in one of the Dutch treatment centres. Thirty-two (52%) of the 61 children were already using treatment before entry care in the Netherlands. When taking into account initial regimens started in the Netherlands only (n=29), these first-line regimens included:

- a PI (45%)
- NNRTI (21%) and
- an INSTI (34%).

Figure 8.4 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 (47%). Following its introduction in 2014, the integrase inhibitor dolutegravir was included in the initial ART regimen given to 12% of the children who initiated a first-line regimen in 2015 and 2016 and increased 50% of the children who initiated treatment between 2020-2024.

Figure 8.4: *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

Forty-five of the 61(74%) children who discontinued their first-line treatment regimen, the median time spent on first-line regimen among children who had started ART between 2015 and 2024 was 16 months (IQR 1-39). Discounting weight-related dose changes, the most important reasons for changing included simplification (33%), toxicity (11%) and virological failure (7%).

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 8.1*]). Initial virological response is reported for the first two years after starting ART between 2015-2024. Long-term virological response is reported by time-updated age for those who used ART for at least 24 months.

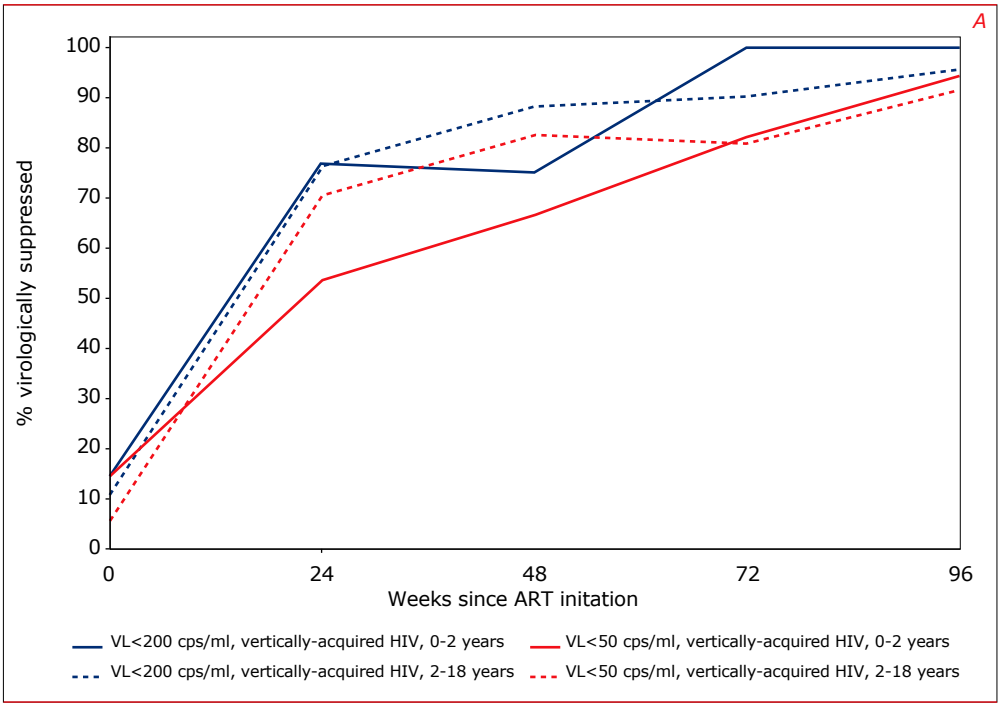
Initial response to ART

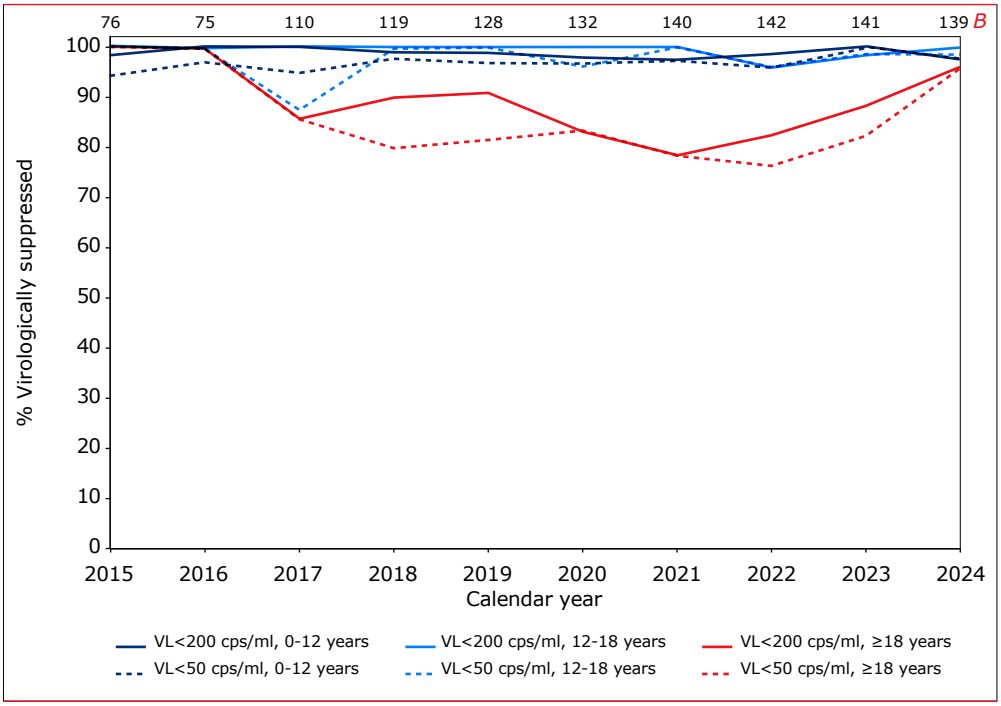
This analysis used data from the 51 children who were registered with SHM and had started ART between 2015-2024 and who had viral load data available in the first 24 months after ART initiation. Children were stratified by age at ART initiation, resulting in the following categories:
(1) 0-2 years, n=25
(2) 2-18 years, n=26

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 2015-2024 of ART initiation. *Figures 8.5A* shows viral suppression rates among children who initiated ART between 2015 and 2024:

- Among children who were aged 0-2 years at the time of ART initiation, viral suppression <200 copies/ml rates increased from 76% after 24 weeks, to 100% after two years. Viral suppression <50 copies/ml rates were 56% and 94% after 24 weeks, and two years.
- Among children who were aged 2-18 years at ART initiation, viral suppression <200 copies/ml rates increased from 76% after 24 weeks, to 88% after one year of ART, and 96% after two years, viral suppression <50 copies/ml rates were : 71%, 82% and 91% after 24 weeks, one and two years.

Figure 8.5: *Viral suppression following antiretroviral therapy (ART) initiation: (A) during the first two years of ART 2015–2024, (B) time-dependent and age-dependent viral suppression rates for children in care between 2015 and 2024 with at least two years with ART. 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 presented for children from 2015 onwards.

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 8.5B*). 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.

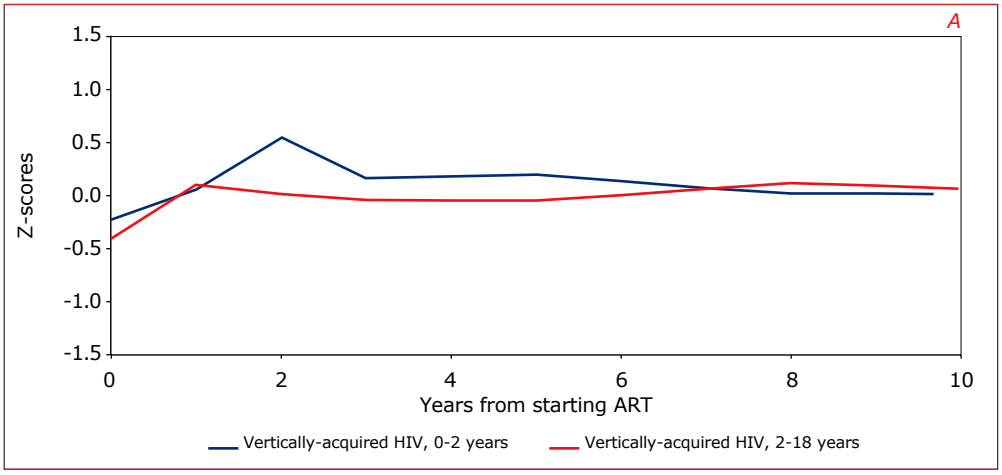
CD4 Z-scores represent the standard deviation from the reference values for HIV-negative children. They were calculated for CD4 cell counts to correct for age-related differences. All absolute CD4 T-cell counts were transformed into Z-scores by subtracting the age-related reference value for the age 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 8.6 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 2015 and 2024 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 (*Figure 8.6*).

Figure 8.6: *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 2015 and 2024).*



Legend: *ART = antiretroviral therapy. Blue: age at ART initiation 0–2 years. Red: age at ART initiation 2–18 years.*

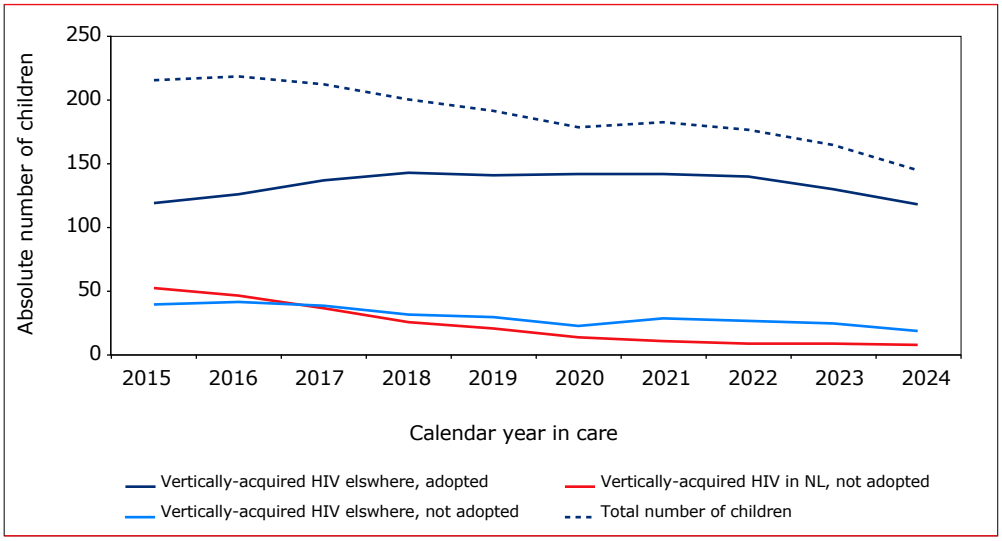
Currently in clinical care

Of the 411 children with HIV ever registered by SHM, and who entered care in the Netherlands before the age of 18, 331 (81%) were still in care in 2024 and 80 were no longer in care. Of these 80 individuals:

- Ten had died;
- 40 had moved abroad;
- 30 were lost to care.

Of the 331 individuals still in care, 146 of them were under the age of 18 (*Figure 8.1*). Figure 8.7 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 2024, this figure had declined to 146, 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 8.7: *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

- 146 were younger than 18 years at the end of 2024
- 96 were younger than 15 years
- The median age was 13 years (IQR 11-16) as of 31 December 2024.

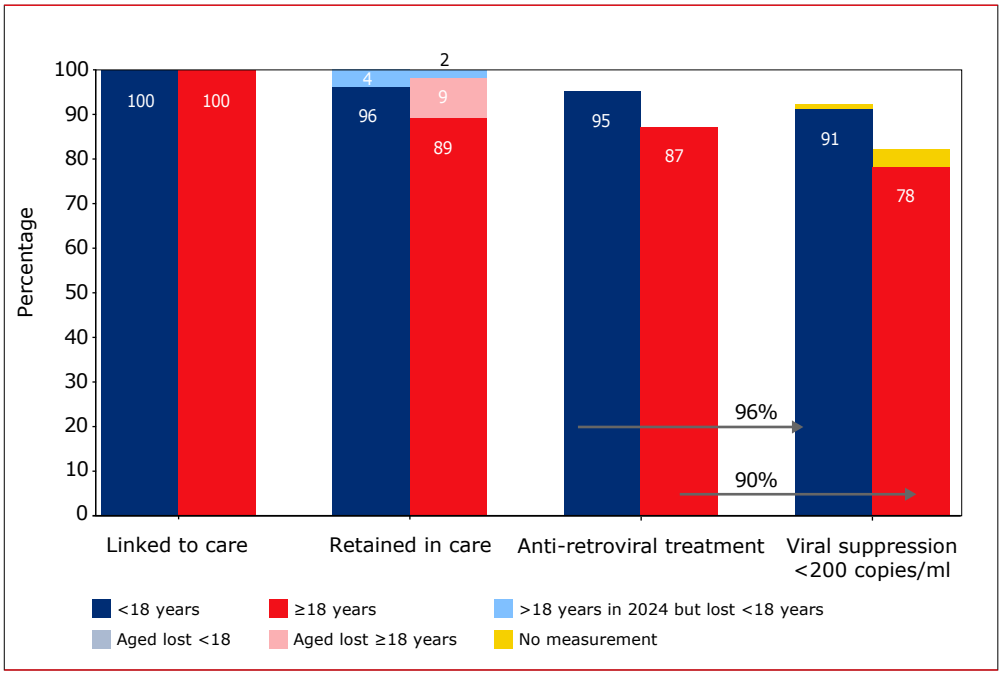
Currently in clinical care and 18 years or older

- 185 were older than 18 years at the end of 2024
- The median age was 26 years (IQR 23-31) as of 31 December 2024

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 2024 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 8.8*).

Figure 8.8: *Continuum of care by age, as of 31 December 2024. The numbers in and above the bars indicate the proportion of individuals.*



Individuals were stratified by age on 31 December 2024 and categorised as:
(1) current age, under 18 years
(2) current age, 18 years or older

Continuum of care: current age under 18 years

- 152 children were linked to care, registered by SHM, still alive and not reported to have moved abroad
- 146 (96%) were retained in care: six children were lost to care, however three of them were deregistered and may have been lost to care or may be waiting to be re-registered at another paediatric HIV treatment centre.
- 95% (1145) had ART during their last clinical visit in 2024.
- 91% (139) of all individuals linked to care had a most recent HIV RNA measurement below 200 copies/ml (96% of those on ART).

Continuum of care: current age 18 years or older

- 209 individuals were linked to care, registered by SHM, still alive and not reported to have moved abroad.
- 89% (185) were retained in care. The remaining 24 (17 of whom were born outside the Netherlands) were lost to care: 6 before they turned 18; 18 when they were older than 18 years of age.
- 87% (1181) had ART during their last clinical visit in 2024.
- 78% (163) of all individuals linked to care had a most recent HIV RNA measurement below 200 copies/ml (90% of those on ART).

It is worth noting that 7 of the 24 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.

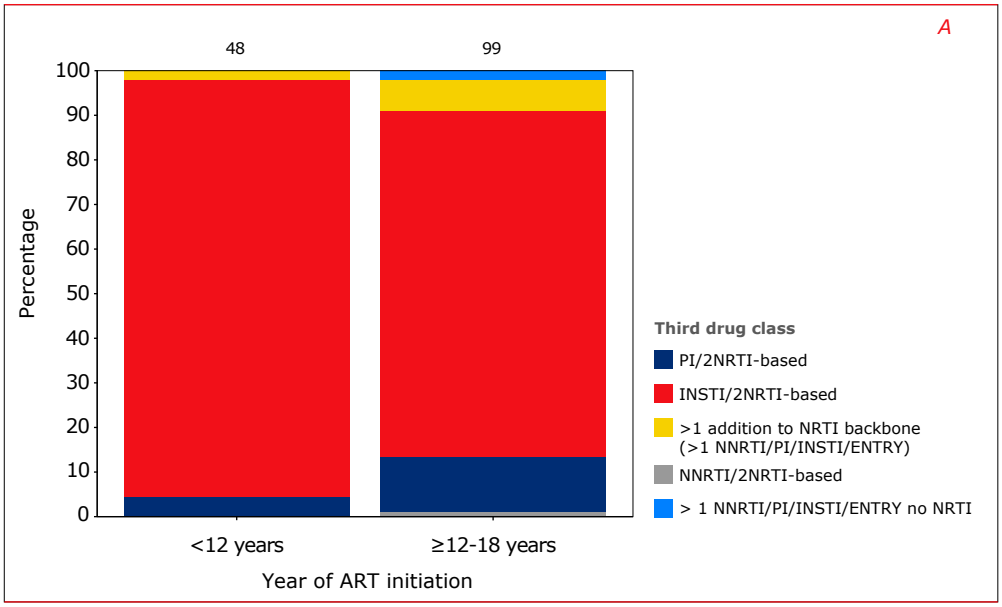
In care and on ART in 2024

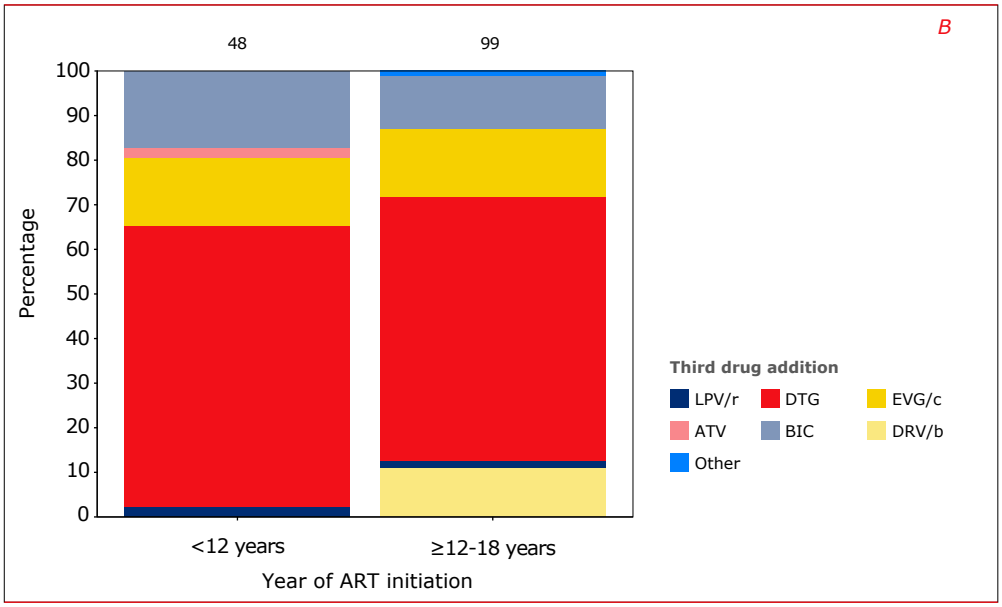
Of the 146 children known to be in care in 2024 and under 18 years of age, 145 had ART during their last reported clinical visit. The distribution of current ART use is shown in *Figure 8.9*, according to age on 31 December 2024

Among those under 12 years of age, INSTI-based regimens were the most commonly-used (93%), with dolutegravir (63%) and bictegravir (17%) the most common individual third agents.

In children aged between 12 and 18 years, 78% were using an INSTI-based regimen, 12% a PI-containing regimen and 9% a combination with PI or NNRTI with INSTI. Among those using an INSTI-based regimen, dolutegravir was most common (60%), followed by elvitegravir (15%) and bictegravir (12%).

Figure 8.9: *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 411 children ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 155 (38%) had been adopted by Dutch parents. The percentage of adopted children newly entering care increased from 6% before the year 2000 to 76% between 2010-2014, 73% between 2015-2019 and was 23% between 2020-2024 (*Figure 8.2*), with a median age at the time of entering care of 2.7 years (IQR 1.5-4.7). Overall:

- 111 (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;

Figure 8.7 shows the number of adopted children still in care and under 18 years of age. As of 31 December 2024, 147 children were alive and in care and 119 of them were aged below 18 years. Their median age was 15 years (IQR 12-18).
Eight 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 2024;

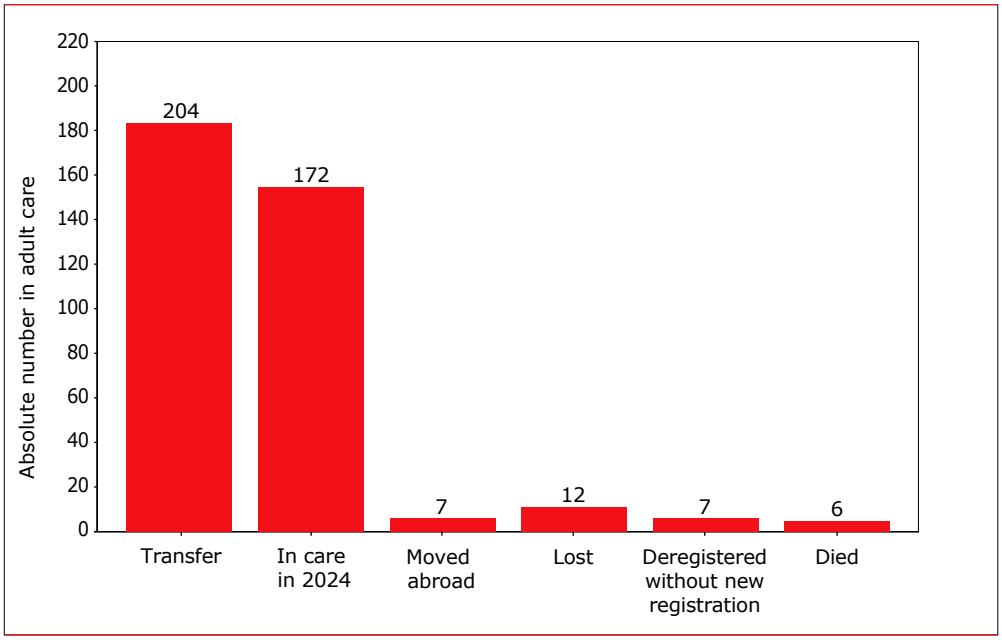
- All in care in 2024 had an undetectable viral load (equal to or below 200 copies/ml) in their most recent HIV RNA measurement and 96% had an undetectable viral load <50 copies/ml.

Transfer to adult care

Of the 411 children ever registered by SHM who were under the age of 18 when they entered care in the Netherlands, 204 children had reached the age of 18 and above, and had transferred from paediatric care to adult care by 31 December 2024. Figure 8.10 shows the follow up status of the 204 adolescents who transferred to adult care:

- 172(84%) were still in care in 2024;
- 7 (3%) had moved abroad;
- 7 (3%) were deregistered at the paediatric centre but have not yet been registered at an adult treatment centre (which could be due to an administrative delay or they may have been lost during transition to adult care);
- 12 (6%) were lost to care – and
- 6 (3%) had died.

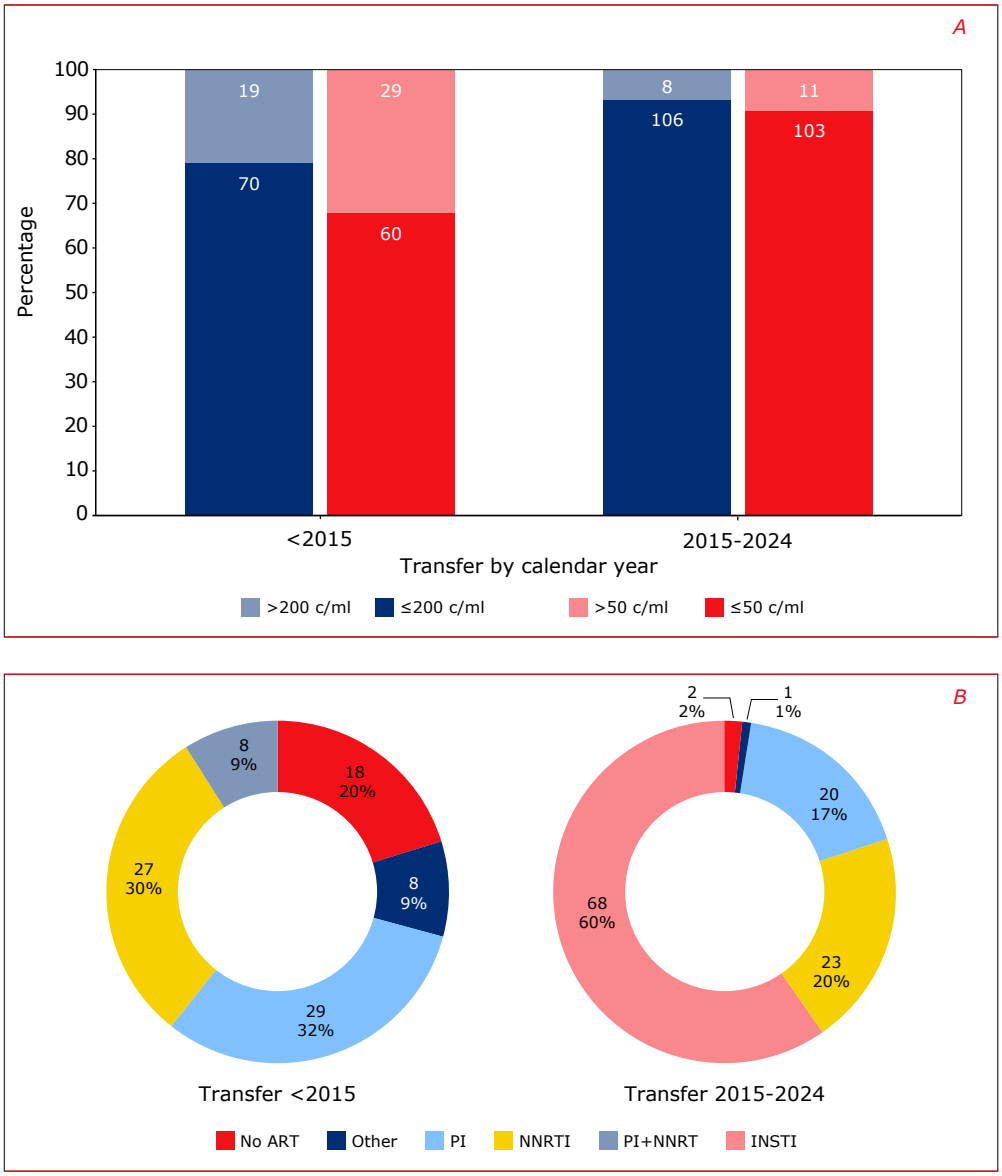
Figure 8.10: Follow up status, as of 31 December 2024, of children who transferred to adult care.



The median age for their last visit to paediatric care was 18.1 years (IQR 17.7-18.8). 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 8.4 years (IQR 4.9-12.3).

Overall, at the time of their last clinical visit to paediatric care, 27 adolescents (13%) 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 (20%). 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 7% and from 33% to 10% for >200 copies/ml and 50 copies/ml respectively(Figure 8.11A).

Figure 8.11: 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.



During their last visit to paediatric care, 90% of the 204 adolescents received ART, 3% adolescents had not yet started ART and 7% 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 8.11B).

Among adolescents who transferred to adult care before 2015, 30% were on an NNRTI-based regimen and 32% on a PI-based regimen. These percentages differed for adolescents who transferred in or after 2015: 60% were on an integrase-based regimen, 20% on an NNRTI-based regimen and 20% on a PI-based regimen.

Of the 172 adolescents who transferred to adult care, and who were still in care in 2024, 168 (98%) were receiving ART in 2024. Seventy-two percent of these were on an integrase inhibitor-based regimen. In total, 91% of the 172 had HIV RNA levels below 200 copies/ml and 88% below 50 copies/ml in 2024.

Summary

Of the 411 children with HIV ever registered by SHM who were under the age of 18 when they entered care in the Netherlands, 81% 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. The proportion of children who initiated ART with an INSTI containing regimen increased from 12% in 2015-2016 to 50% in 2020-2024. Ninety-nine percent of children in care in 2024 were receiving ART. Current regimens in use include an integrase inhibitor for 90% of the children.

Very high long-term viral suppression rates were observed in children with HIV who initiated ART in or after 2015. However, those response rates fell when children reached the age of 18. We have seen overall viral suppression rates of 87% 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 93%. Within the group of young adolescents who made their transfer to adult care, we also observed a shift in the ART regimens that were used during their transfer over time, with INSTI containing regimens being used more often.

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 2024, when compared to children under the age of 18 (90% versus 96% 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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9. 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]. 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. Since 2015, ART is 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 the Netherlands, pregnant women receive opting-out HIV antibody testing during the first trimester of pregnancy[7]. In addition to the ART that a pregnant woman receives, newborns who are perinatally exposed to HIV are receiving PEP as soon as possible after birth.[39]

This year's report focuses on women who were pregnant during the years 2016 to 2024, 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 9.1A shows the characteristics of the 668 women with HIV with at least one registered pregnancy when receiving care in the Netherlands between 2016 and 2024.
These women were born in:

- the Netherlands: 178 (27%)
- sub-Saharan Africa: 298 (45%)
- the Caribbean/Latin America region: 88 (13%)
- and other regions: 104 (16%), including 53 women from Central or Eastern Europe, and 24 women from South and Southeast-East Asia.

Diagnosis

The majority of the 668 women (n=572, 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, 96 women were diagnosed during their pregnancy. The majority of the women with a diagnosis in the pregnancy were diagnosed in the national pregnancy screening program. The proportion of women newly diagnosed varied between 8% and 27% for the years 2016-2024. These 96 women were born in:

- the Netherlands: 23/178 (13%)
- sub-Saharan Africa: 44/298 (15%)
- the Caribbean/Latin America region: 13/88 (15%)
- and other regions: 16/104 (15%)

The median time between conception and diagnosis among newly diagnosed women was 13 weeks (IQR: 10-18):

- 55% received their diagnosis during the first trimester of pregnancy,
- 35% in their second trimester,
- and 9% in their third trimester.

Fifty-five of the 96 newly diagnosed women reported an earlier negative HIV antibody test, the remaining 41 women did not report ever having tested for HIV before. Within the SHM database, it is not recorded whether the 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 blood sampling for the HIV test and first contact with one of the HIV treatment centres was 9 days (interquartile range [IQR] 6-17). The median time between the first visit to a treatment centre and receiving antiretroviral therapy was also 8 days (IQR 1-15). 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 562 cells/mm^3 (IQR 380-767) for all women, 7% of the women had a first CD4 cell count after conception that was lower than 200 cells/ mm^3 and 22% of the women their first CD4 cell count after conception was <350 cells/ mm^3. A lower median CD4 cell count was seen among women who were newly diagnosed with HIV (and started ART) during pregnancy (320 cells/mms, IQR 210-455). However, as CD4 cell counts during pregnancy are lower because of haemodilution,[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 9.1A*).

Mode of HIV acquisition

The self-reported mode of HIV acquisition among the 688 women was (*Table 9.1A*):

- Heterosexual contact: 587 (88%)
- Vertical transmission: 39 (6%)
- Other: 42 (6%), including exposure to contaminated blood or medical procedures (n=17), injecting drug use (n=3) and unknown mode (n=22).

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:

- 24 (4%) were known to have moved abroad, two of the women moved in their pregnancy,
- 23 were lost to follow-up (3%) and
- 7 (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 30 months (IQR: 2-55) 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 two women had a documented ART regimen reported during their last clinical visit; and
- three women had detectable HIV RNA (min. RNA = 591 copies/mL, max. = 56 234 copies/ml) during the last clinical visit.

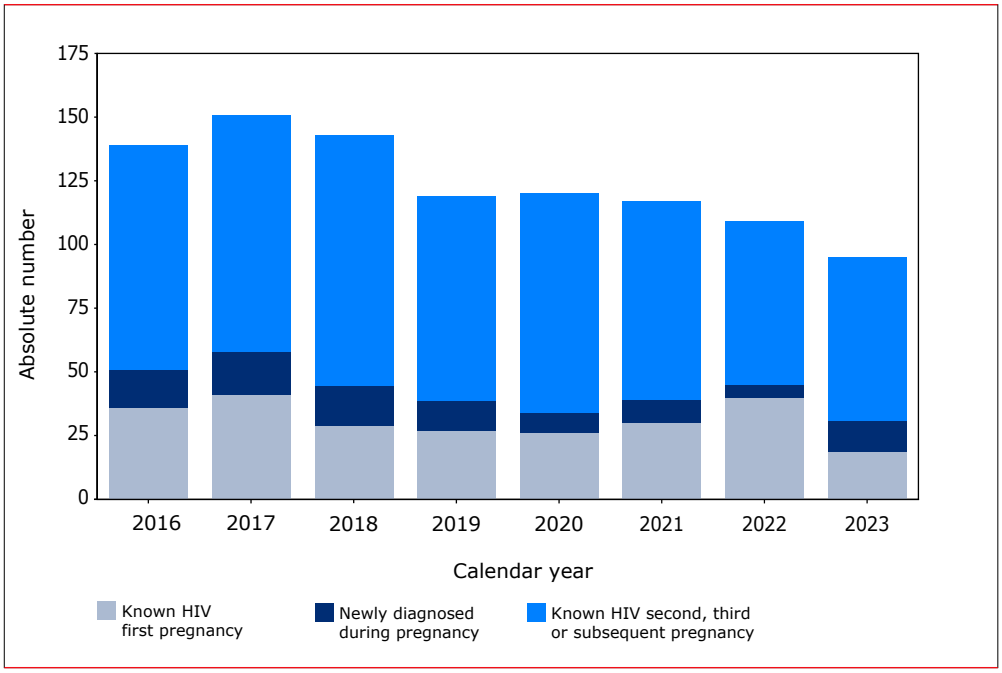
In total, 19 of the 23 pregnancies among women who became eventually lost to follow-up resulted in a live-birth, four pregnancies ended before 24 weeks. Vertical transmission or breastfeeding at the time of last clinical visit was not reported in any of these pregnancies.

Seven of the 668 women with a pregnancy between 2016 and 2024 were documented to have died during follow up, after their pregnancy. Their median age was 39 years (IQR: 32-46). Three of them delivered a child and in the other women the pregnancy was terminated by induced abortion. Two out of seven women died of aids-related causes and for four women the cause of death was a non-aids-related and one cause of death was unknown.

Number of pregnancies in women with HIV over time

In total, 1,035 pregnancies among the 668 women were reported between 2016 and 2024. 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 95 in 2023 (*Figure 9.1*). In the SHM database, the median age of all women with HIV in care is increasing from 45 years (IQR: 38-53) in 2016 to 51 years (IQR: 42-59) in 2024. The median age of women with a pregnancy was 33 (IQR:29-37) and did not change over time. 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 eight in 2020, but varied as a proportion of the total number of pregnancies per year, between 7 and 13%. Each year, approximately 80 women with HIV and a previous pregnancy, became pregnant again (*Figure 9.1*).

Figure 9.1: *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 (2024). Therefore, the most recent calendar year is not shown in the figure.*

Pregnancy-related characteristics

Overall, 668 women accounted for 1,035 registered pregnancies:

- 21% of the women had one registered pregnancy,
- 27% had two registered pregnancies,
- 52% of the women had three or more registered pregnancies (*Table 9.1B*).

Table 9.1A: Maternal characteristics: of pregnant women with HIV registered and monitored by stichting hiv monitoring between 2016-2024

	Total	Nether-lands	Sub-Saharan Africa	Caribbean/ South America	Other	p
Total number of women N (%)	668	178 (26.6)	298 (44.6)	88 (13.2)	104 (15.6)	
HIV diagnosis before pregnancy	572 (85.6)	155 (87.1)	254 (85.2)	75 (85.2)	88 (84.6)	0.93
Newly diagnosed during pregnancy	96 (14.4)	23 (12.9)	44 (14.8)	13 (14.8)	16 (15.4)	
Age at start of first pregnancy following HIV diagnosis Median (IQR)	33.2 (28.9. to 36.9)	31.9 (28.0 to 35.8)	33.3 (29.0 to 36.9)	34.4 (29.7 to 37.8)	34.1 (29.4 to 38.5)	0.008
HIV transmission route						
Heterosexual contact	587 (87.9)	156 (87.6)	271 (90.9)	85 (96.6)	75 (72.1)	<0.001
Vertical transmission	42 (6.3)	9 (5.1)	8 (2.7)	1 (1.1)	24 (23.1)	
Other~	39 (5.8)	13 (7.3)	19 (6.4)	2 (2.3)	5 (4.8)	
First CD4 count in pregnancy Median (IQR)	561.5 (380.0 to 766.8)	642.0 (485.0 to 837.0)	514.5 (352.5 to 727.0)	570.0 (350.0 to 758.5)	530.5 (395.0 to 811.8)	0.001
CD4 percentage Median (IQR)	32.4 (23.5 to 40.0)	37.6 (27.6 to 42.8)	29.2 (20.7 to 37.7)	28.9 (23.9 to 36.6)	32.0 (25.7 to 40.7)	0.002
First CD4 count when newly diagnosed during pregnancy Median (IQR)	320.0 (210.0 to 455.0)	355.0 (296.5 to 540.0)	260.0 (179.0 to 443.2)	306.0 (190.0 to 470.0)	360.0 (265.0 to 420.0)	0.346
CD4 percentage when newly diagnoses during pregnancy Median (IQR)	22.4 (15.8 to 26.0)	26.1 (23.0 to 32.0)	20.9 (12.6 to 23.0)	16.5 (13.0 to 21.3)	23.5 (18.6 to 24.6)	0.075

~ Mode of HIV transmission was exposure to contaminated blood or medical procedures (n=17), injecting drug use (n=3), or unknown (n=19).

Table 9.1B: Pregnancy-related characteristics of pregnant women with HIV registered and monitored by stichting hiv monitoring between 2016-2024.

	Total	Nether-lands	Sub-Saharan Africa	Caribbean/ South America	Other	p
Total number of pregnancies N (%)	1,035	276 (26.7)	474 (45.8)	129 (12.5)	156 (15.1)	
Total number of pregnancies ever after 2016						
3	540 (52.2)	127 (46.0)	277 (58.4)	65 (50.4)	71 (45.5)	0.006
2	276 (26.7)	88 (31.9)	101 (21.3)	40 (31.0)	47 (30.1)	
1	219 (21.2)	61 (22.1)	96 (20.3)	24 (18.6)	38 (24.4)	
Pregnancy outcome						
Delivery after at least 24 weeks	683 (66.0)	186 (67.4)	308 (65.0)	82 (63.6)	107 (68.6)	0.507
Miscarriage or stillbirth, <24 weeks	218 (21.1)	51 (18.5)	109 (23.0)	24 (18.6)	34 (21.8)	
Induced abortion, <24 weeks	131 (12.7)	38 (13.8)	55 (11.6)	23 (17.8)	15 (9.6)	
Unknown	3 (0.3)	1 (0.4)	2 (0.4)			
Mode of delivery						
Vaginal	466 (45.0)	142 (51.4)	196 (41.4)	52 (40.3)	76 (48.7)	0.162
Caesarean, secondary	109 (10.5)	18 (6.5)	57 (12.0)	18 (14.0)	16 (10.3)	
Caesarean, elective	101 (9.8)	25 (9.1)	49 (10.3)	12 (9.3)	15 (9.6)	
Pregnancy duration was <24 weeks	353 (34.1)	90 (32.6)	167 (35.2)	47 (36.4)	49 (31.4)	
Unknown	6 (0.6)	1 (0.4)	5 (1.1)			
Pregnancy duration						
≥37 weeks	599 (57.9)	154 (55.8)	278 (58.6)	71 (55.0)	96 (61.5)	0.183
32-37 weeks	68 (6.6)	27 (9.8)	21 (4.4)	11 (8.5)	9 (5.8)	
24-32 weeks	15 (1.4)	5 (1.8)	8 (1.7)		2 (1.3)	
<24 weeks	353 (34.1)	90 (32.6)	167 (35.2)	47 (36.4)	49 (31.4)	
Birth weight (grams) Median (IQR)	3,102.5 (2,766.2 to 3,483.8)	3,117.5 (2,646.2 to 3,417.0)	3,125.0 (2,809.5 to 3,520.0)	3,061.5 (2,776.2 to 3,485.0)	3,075.0 (2,790.0 to 3,485.0)	0.462
Perinatal death	5 (0.5)	2 (0.7)	3 (0.6)			

Table 9.1C: ART initiation among pregnant women with HIV registered and monitored by stichting hiv monitoring between 2016-2024.

	Total	Nether-lands	Sub-Saharan Africa	Caribbean/ South America	Other	p
Total number of births N (%)	683	186 (27.2)	308 (45.1)	82 (12.0)	107 (15.7)	
Antiretroviral therapy started						
Before pregnancy	576 (84.3)	162 (87.1)	254 (82.5)	69 (84.1)	91 (85.0)	0.587
During pregnancy	107 (15.7)	24 (12.9)	54 (17.5)	13 (15.9)	16 (15.0)	
Latest available plasma HIV RNA level prior to delivery						
<50 copies/ml	660 (96.6)	182 (97.9)	294 (95.5)	80 (97.6)	104 (97.2)	0.460
50-500 copies/ml	15 (2.2)	3 (1.6)	9 (2.9)	2 (2.4)	1 (0.9)	
>500 copies/ml	4 (0.6)		4 (1.3)			
Unknown	4 (0.6)	1 (0.5)	1 (0.3)		2 (1.9)	
Time between delivery and latest HIV RNA measurement (weeks)						
Median (IQR)	2.4 (1.0 to 4.3)	2.5 (1.0 to 4.5)	2.4 (0.9 to 4.0)	2.6 (1.3 to 4.4)	2.6 (0.9 to 4.3)	0.777

Pregnancy outcome

The 1,035 pregnancies resulted in 683 (66%) births ≥24 weeks (including both live and stillbirths), including 13 twin pregnancies. A total of 349 (34%) pregnancies ended in miscarriage or still birth <24 weeks or abortion; 218 (21%) were miscarriages or still births<24 weeks and 131 (13%) were abortions. For the remaining three (<1%) pregnancies, the outcome is unknown due to missing data(*Table 9.1B*).

Pregnancy duration, preterm birth and perinatal death

A total of 683 pregnancies lasted at least 24 weeks and are therefore counted as a birth (*Table 9.1B*):

- 599 (88%) of the pregnancies lasted at least 37 weeks,
- 83 (12%) pregnancies resulted in preterm birth (defined as a pregnancy duration of 24-37 weeks). It is worth noting that 35/83 preterm births had a pregnancy duration of 36 weeks.
- 1 live birth had an unknown pregnancy duration.

The prevalence of preterm birth is higher compared to that in the general population (7%)[29].

Perinatal death, including antepartum death, occurred in five (<1%) births. Congenital disorders were registered for 18 infants.

Mode of delivery

If viral suppression during pregnancy is 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 63% of women of Latin America or Caribbean origin. Sixteen percent of newborns were delivered by an elective Caesarean section and another 15% by a secondary Caesarean section (*Table 9.1B*).

In terms of mode of delivery, 96% of the women who delivered vaginally had an HIV RNA below 50 copies/ml. This figure was 93% 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 secondary Caesarean section were obstetric indications such as foetal distress and failure to progress in the second stage of labour.

A therapy (ART) uptake and therapy response in pregnant women

Therapy uptake

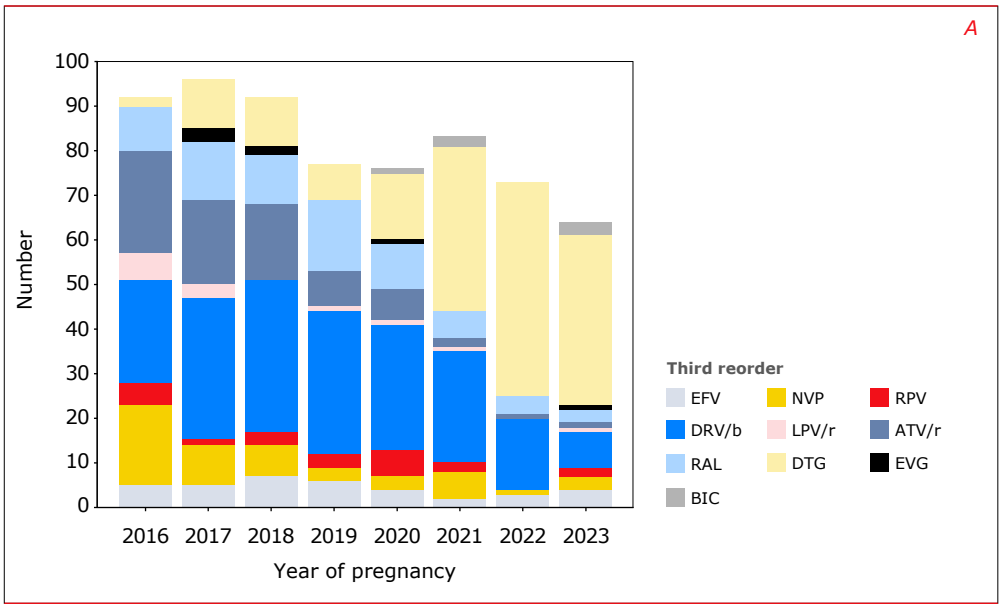
From 2016 onwards, during the 683 pregnancies lasting at least 24 weeks, all women received ART during the pregnancy:

- in 576 (84%) pregnancies, ART was initiated before pregnancy
- in 107 (16%) pregnancies, ART was started during pregnancy (Table 9.1C). Including 20 women who were diagnosed before their pregnancy. In total, two women discontinued treatment before delivery.

For 681 out of the 683 pregnancies, information on ART regimens during delivery was available. *Figure 9.2A* 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 2023.

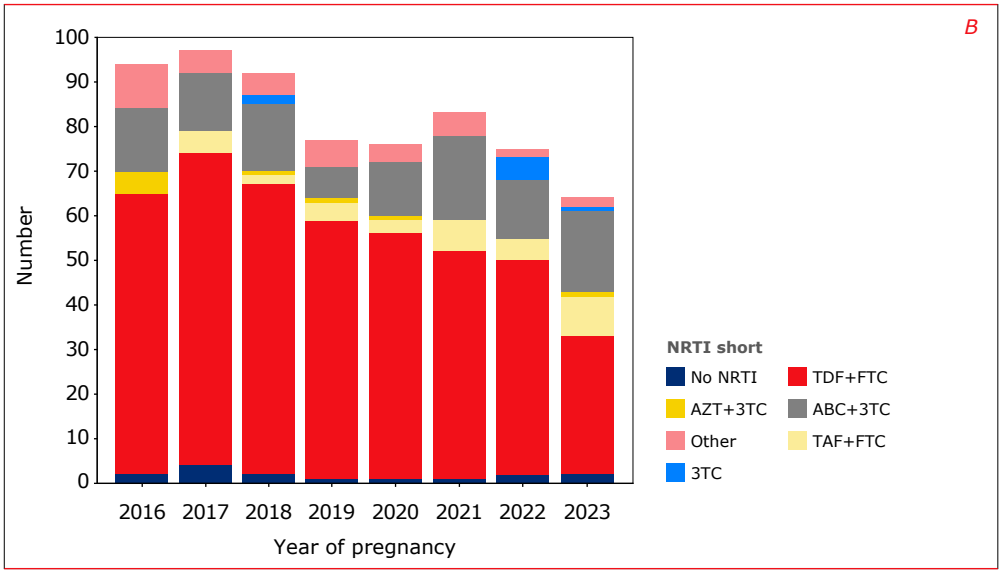
- Integrase inhibitors (INSTI) use increased from 4% in 2016 to 64% in 2023.
- Use of NNRTIs decreased from 30% in 2016 to 14% in 2023
- Use of PIs decreased from 56% to 16%(*Figure 6.2C*).
- In 18 pregnancies a two-drug regimen was used, which were combination of NRTI+INSTI or PI+INSTI.

Figure 9.2A: *The most commonly used third-drug additions to the nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone used as part of ART regimens during 500 pregnancies in 2016–23 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 9.2B: *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 (2024). 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 9.2C: Antiretroviral class use stratified by calendar year period regimens during pregnancies in 2016–2023, 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 (2024). Therefore, the most recent calendar year is not shown in the figure.

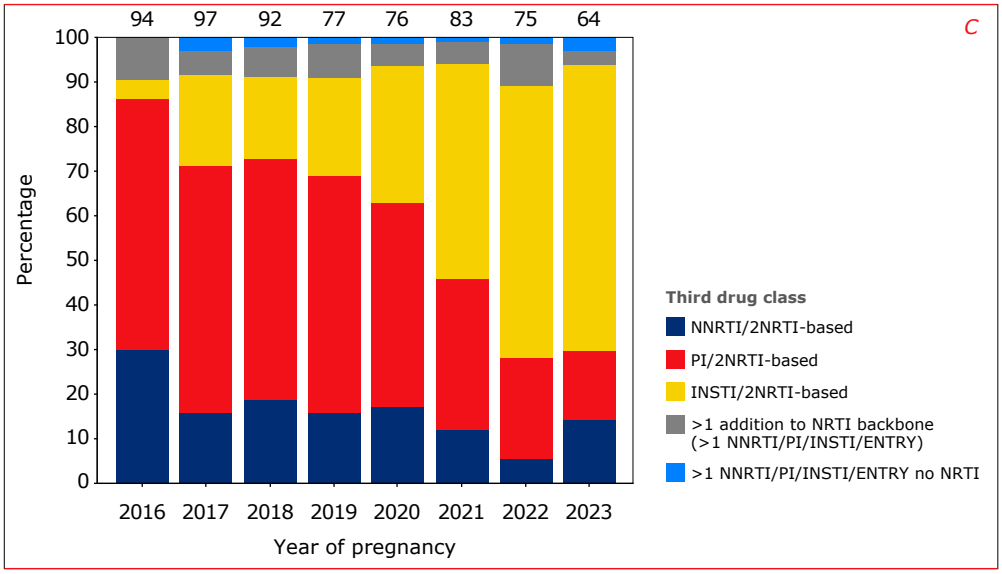


Figure 9.2B provides an overview of the components of the NRTI backbone used during pregnancy between 2016 and 2023. The most commonly prescribed backbones were the combination of:

- Tenofovir disoproxil fumarate and emtricitabine (TDF+FTC) (66%).
- Abacavir and lamivudine (ABC+3TC) (17%).
- Tenofovir alafenamide and emtricitabine (TAF+FTC) (6%)

A switch in ART regimen was reported during 234 pregnancies. While no reason was documented in 22 cases, the most common documented reason for switching in the remaining pregnancies was pregnancy-related (n=142). In 30% of all pregnancy-related switches a cobicistat-boosted regimen was replaced. Other common pregnancy-related switches included a switch from an integrase-containing regimen to a protease inhibitor (darunavir or atazanavir) or 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 2024. All women had an HIV RNA level below 50 copies/ml at the time of delivery.

Therapy response

Figure 9.3 shows the percentage of women on ART and their latest available plasma HIV RNA level prior to delivery. In 80% of the deliveries this HIV RNA measurement was within 4 weeks prior to delivery. HIV RNA levels were categorised as below 50 copies/ml, 50-500 copies/ml, and above 500 copies/ml.[a]

- Overall 97% of the mothers had an HIV RNA below 50 copies/ml, 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.

In total, 19 women had HIV RNA levels above 50 copies/ml (50-500 copies/ml: n=15, >500 copies/ml: n=4, median RNA=153 copies/ml; minimum=53, maximum=15,500) prior to delivery(*Table 9.2*).

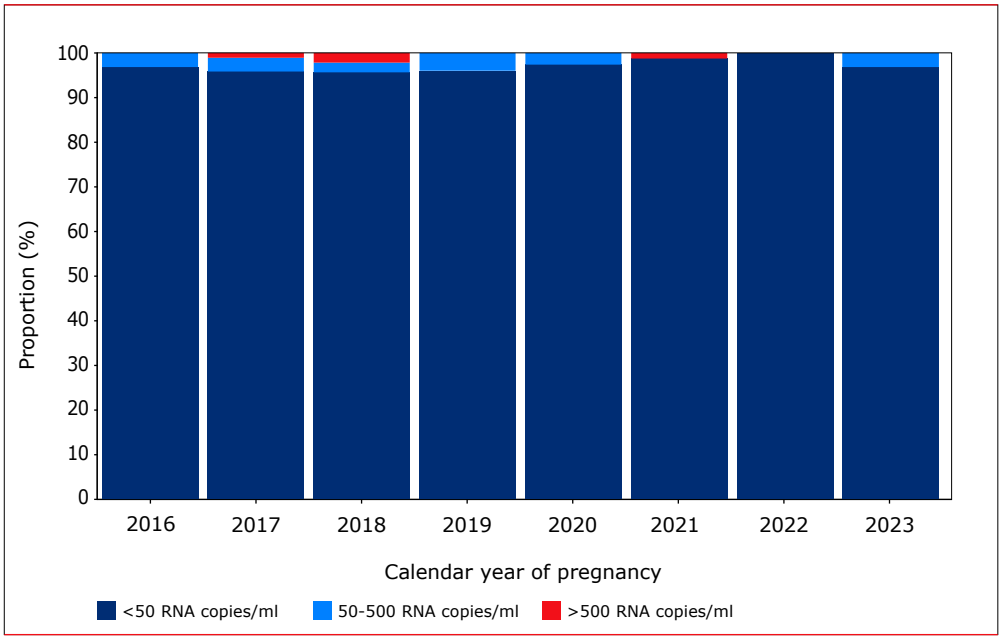
a Dutch guidelines allow a vaginal delivery with HIV RNA below 500 copies/ml and declining viral loads[13] or with a undetectable HIV RNA <50 or <20 copies/ml, depending on the used assay.

Table 9.2: Overview of characteristics of 19 women with a detectable HIV RNA level prior to delivery.

Women with detectable HIV RNA	19	
Age (median, IQR)	32 (27–36)	
Newly diagnosed during pregnancy	7 (37)	6 women were diagnosed after the first trimester.
ART initiated during pregnancy	7 (37)	
ARV at time of detectable HIV RNA*		
INSTI-containing	11 (57)	
NNRTI-containing	2 (11)	
PI-containing	6 (32)	
Mode of delivery		RNA (minimum; maximum)
Caesarean section	13 (69)	53, 15,500 copies/ml
Vaginal	4 (21)	70, 1,003 copies/ml
Unknown	2 (10)	
Zidovudine during delivery		
Yes	14 (74)	
No	4 (21)	
Unknown	2 (10)	
Evaluation of drug resistance	14 /19	• Pre-treatment drug resistance data was available to 9 women: 2/9 NRTI-associated resistance mutations were found • Drug resistance data after ART initiation was available for 8 women: 5 sequences harboured resistance to at least one NNRTI; and for 3 also resistance to at least one NRTI. • In 3 women the resistance mutation was measured during the pregnancy.

**None of the women used a two-drug regimen at time of detectable HIV RNA.*

Figure 9.3: 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 (2024). Therefore, the most recent calendar year is not shown in the figure.

Vertical transmission rate in the Netherlands

Between 2016 and 2024, 683 births were registered in the Netherlands among mothers known to live with HIV prior to conception or first diagnosed during pregnancy. All mothers received ART during their pregnancy and in 97% of the pregnancies the HIV RNA was below 50 copies/ml. 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 683 pregnancies lasting 24 weeks or longer, 71 were excluded from this analysis: 48 because of insufficient follow up between delivery and the time of database closure; and 23 because the women were no longer in care (3 had moved abroad and nine were reported as lost to care during the postpartum period).

For the remaining 612 pregnancies in 486 women, ART was initiated before conception or during pregnancy in 81% and 19% of cases, respectively. The majority of women used an integrase inhibitor-containing regimen during the postpartum period (51%). The use of integrase inhibitor increased from 24% in 2016, to 57% in 2020 and 88% in 2024.

In 39 (6%) of these 612 pregnancies, ART was discontinued postpartum:

- The most common documented reason was a patient decision (n=26).
- In two cases the documented reason was elite controller or long-term non-progressor[b].
- In 3 cases the documented reason was experienced ART toxicity.
- In 8 cases the documented reason was end of pregnancy and in one case the reason was not reported.

In 16 out of the 39 cases, therapy was restarted after a median of 4.6 weeks (IQR 2-10). In the remaining 23 cases, ART was not restarted postpartum, however 15 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 82(13%) of the 612 pregnancies analysed. When taking into account >200 copies/ml as a detection margin, 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 573/612 (94%) women with documented continued use of ART postpartum:
- 63 (12%) had at least one episode of an HIV RNA level above 50 copies/ml (median HIV RNA=257 copies/ml, minimum=52 and maximum=85,900 copies/ml)
- 35 (6%) had a HIV RNA level above 200 copies/ml,
- 25 had more than one episode of an HIV RNA level above 50 copies/ml during the postpartum period.
- 14 of the 63 women with an HIV RNA above 50 copies/ml were newly diagnosed with HIV during the pregnancy.
- 49/63 women were diagnosed and treated before conception, of whom 67% (n=33) had earlier episodes of detectable HIV RNA levels more than 6 months after the start of initial ART.

In the 39/612 (6%) women who discontinued the use of ART postpartum:
- One woman did not had HIV RNA measurements;
- 19 (49%) had at least one episode of an HIV RNA level above 50 copies/ml (median HIV RNA=19,800 copies/ml, minimum 617 and maximum 450,000 copies/ml).
- 19 women remained virally suppressed during the postpartum period:
  - 11 women eventually restarted ART;
  - 1 woman who became virally unsuppressed after the postpartum period;
  - 5 women with 7 pregnancies continued to report high CD4 cell counts and HIV RNA levels <50 copies/ml in the absence of ART;

Breastfeeding

In the Netherlands, pregnant women with sustained virological suppression are informed about the possibility of breastfeeding. The final decision about the baby feeding is a result of a shared decision by the patient and health care professional. Breastfeeding in such cases is recommended for a maximum of six months.

Data about the baby feeding were available for 540 of the 612 pregnancies, and breastfeeding was reported in 49 pregnancies (the duration of breastfeeding was not documented). It is noteworthy that all women had documented use of ART and that all women had HIV RNA levels below 50 copies/ml during or below the detection limit of the used assay during the first 6 months of the postpartum period. The median number of HIV RNA measurements during the first 6 months after delivery among the 49 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 of HIV in the Netherlands has become very rare in pregnant women using ART during the period 2016 to 2024, resulting in a very low perinatal HIV infection rate. 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 was more often the case in 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 all pregnant women, and close monitoring is especially needed in women who were newly diagnosed with HIV after conception and those with a history of virological failure.

Although most women were aware of living with HIV prior to their pregnancy, 14% were newly diagnosed during pregnancy. Based on SHM data, 24% of them originated from the Netherlands and 76% 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 of 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 its continuation postpartum. We observed an increasing proportion of women who received integrase inhibitors during pregnancy as well as during the postpartum period. However, therapy compliance after delivery requires close attention. 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]. The aetiology of preterm delivery is complex and multifactorial, it is unclear whether ART use or other demographic or 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, it has become standard of care that ART is used at conception and not interrupted after 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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10. 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 individuals in outpatient care at the 23 dedicated treatment centres, SHM can provide a nationwide overview of the outcome of care for individuals. 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), and hepatitis B and C virus and syphilis screening for all individuals in care and for men who have sex with men (MSM) separately. 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]. As in last year's report, we focus our indicators on primary and secondary prevention of cardiovascular disease. We evaluate center-specific completeness of information for the following indicators: smoking, lipid profile, and blood pressure measurement.

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 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 (based on former Dutch recommendations), we report the percentage who received a prescription for statins and those with an LDL cholesterol at or below the recommended limits in (i.e., target LDL cholesterol)[5]. The results of the REPRIEVE study[6] have led to an updated recommendation in the EACS and Dutch guidelines of the prescription for statins when a 10-year risk of cardiovascular disease event was ≥2.5% for those

aged <50 years, ≥5% when aged between 50 and 69 years and ≥7.5% when aged above 70 years[7,8]. Reporting in accordance with the revised recommendations has not been assessed for the calendar years 2020–2023, as the revised recommendations were not yet implemented in clinical practice during these years. For the year 2024, we report an additional analysis on the percentage of individuals who received prescription for statins in which outcomes under the former and revised guidelines are compared.

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 10.1.

This analysis relates to all individuals who were diagnosed with HIV and who are currently in care at one of the 23 HIV treatment centres in the Netherlands. 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 23 HIV treatment centres individually. Each HIV treatment centre is referenced by a number, which is used consistently across all figures in this chapter. These centre numbers do not correspond with those used in the map with centre overview at page 5 of this report.

***Box 10.1:** 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		
Total, HDL or LDL cholesterol	The percentage of individuals who had a total, HDL or LDL cholesterol measurement during the calendar year[1].	40 years old or older
Blood pressure	The percentage of individuals who had at least one blood pressure measurement during the calendar year.	
All cardiovascular parameters	The percentage of individuals who had total, HDL and LDL cholesterol and blood pressure measurement during the calendar year.	
Information on cardiovascular event risk		
SCORE2(-OP)	The percentage of individuals 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 individuals 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[2] and differentiated by age: ≥2.5% when aged <50; ≥5% aged 50-69 years; ≥7.5% when aged ≥70 years
Target LDL cholesterol		
	The percentage of individuals 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[2]
Antihypertensive medication use		
	The percentage of individuals who received a prescription for antihypertensive mediation during the calendar year.	• All individuals with high blood pressure[3] • And stratified by hypertension grades[4]
Target blood pressure		
	The percentage of individuals 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 individuals on antihypertensive medication

Abbreviations: *HDL = high-dense lipoprotein; LDL = low-density lipoprotein.*

1 *Calendar year is defined as running from 1 January to 31 December.*

2 *Details on these scores can be found in the following website: https://u-prevent.com and also references[3,4,7,8].*

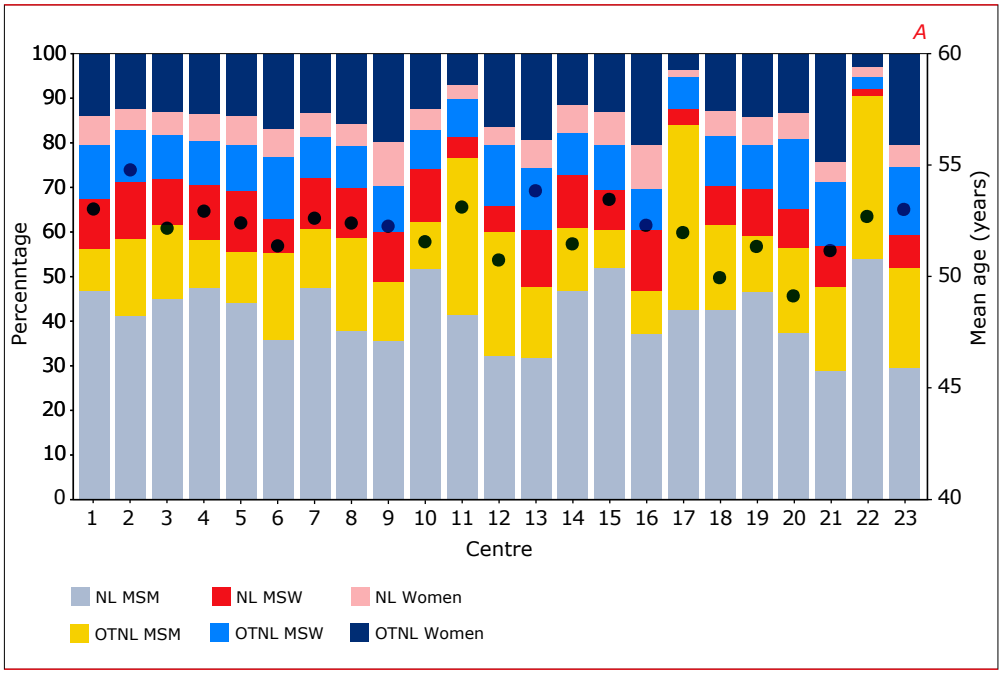
3 *Defined as a diastolic blood pressure ≥90 mmHg.*

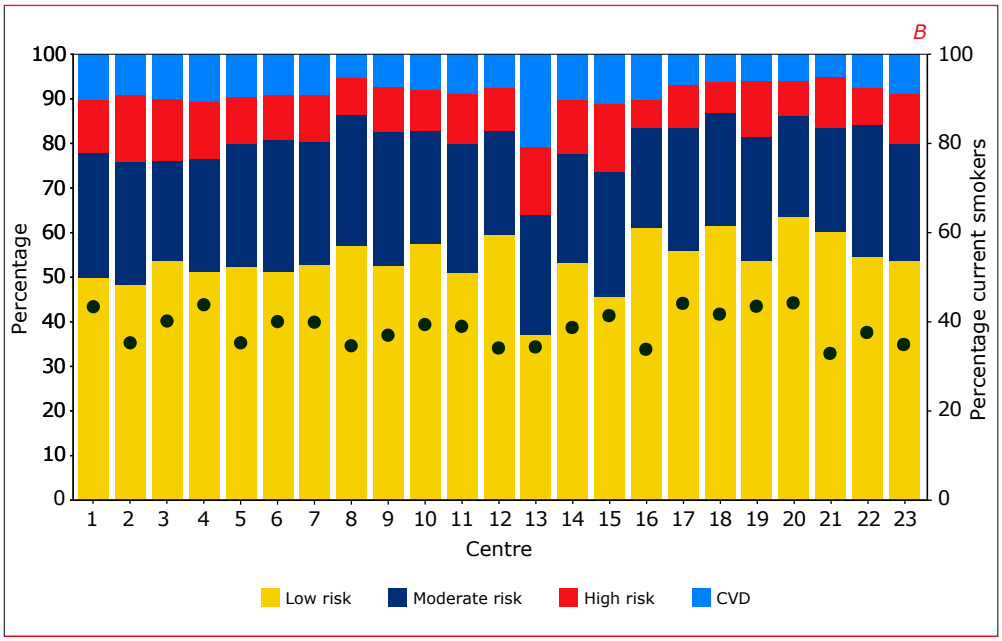
4 *Defined as hypertension Grade 1 BP 140-159/90-99 mmHg; Grade 2 Hypertension BP 160-179/100-109 mmHg; Grade 3 Hypertension BP > 180/110 mmHg[8].*

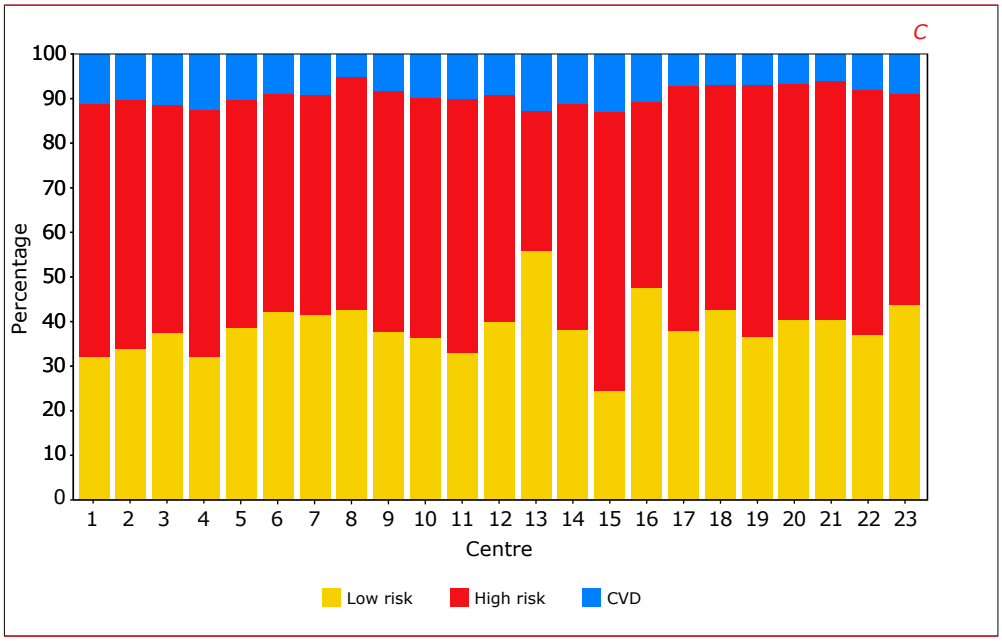
Centre overview

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 10.1A). The distribution of individuals with low (<5%), moderate (5-10%), and high (>10%) predicted 10-year risk of cardiovascular disease according to the former recommendations, for those who have not had a cardiovascular disease event, and the percent with cardiovascular disease are also provided for each treatment centre (Figure 10.1B). Figure 10.1C shows the distribution of individuals with low and high predicted 10-year risk of cardiovascular disease according to the new recommendations. 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 individuals who are currently smoking.

Figure 10.1: *Description of the patient 'mix' for individuals in care (A), distribution of cardiovascular disease risk according to the former recommendations and smoking status (B), and the distribution of cardiovascular risk according to the new recommendations in 2024 in the Netherlands (C).*







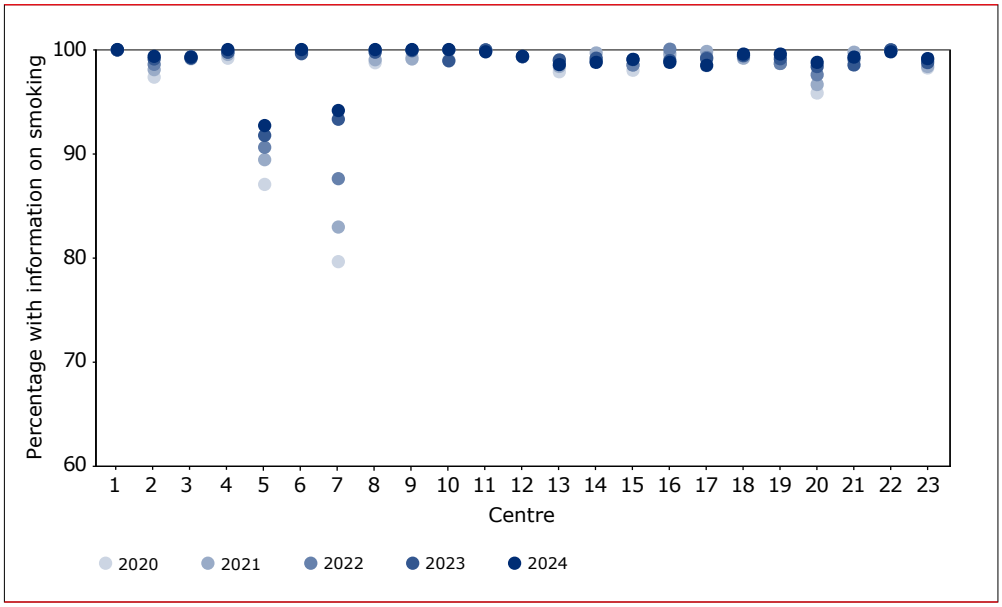
Note: *In A, the bars in this chart show the percentage of individuals per centre according to geographical origin/mode of transmission/gender group. In A, black dots represent the mean age of individuals in care at each centre. In B, black dots represent the percent of current smokers of individuals 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 were assessed 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

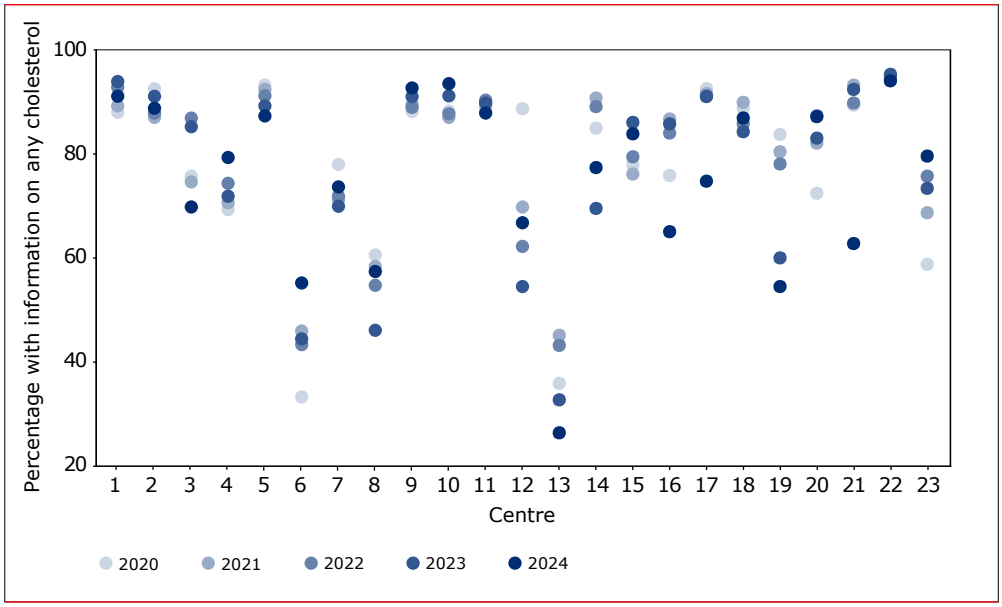
To provide an understanding of how indicators have evolved, each indicator in *Box 10.1* has been reported for its corresponding focus population on an annual basis between 2020 and 2024. For example, the indicator 'information on smoking' has been provided for individuals who were 40 years old or older and were in care in 2020, 2021, 2022, 2023, and 2024.

Figure 10.2: *Information on smoking; in other words, individuals who ever had information on their smoking status during each year between 2020 and 2024.*



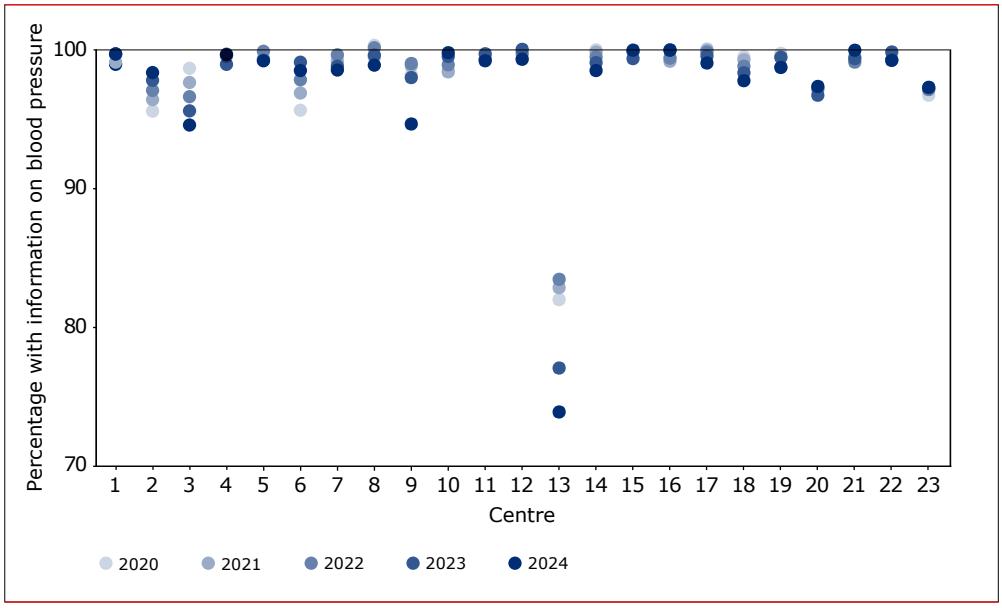
Legend: *Data are provided for individuals 40 years old or older. Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 10.1.*

Figure 10.3: Information on total cholesterol; in other words, individuals who had a total, LDL or HDL cholesterol measurement during each year between 2020 and 2024.



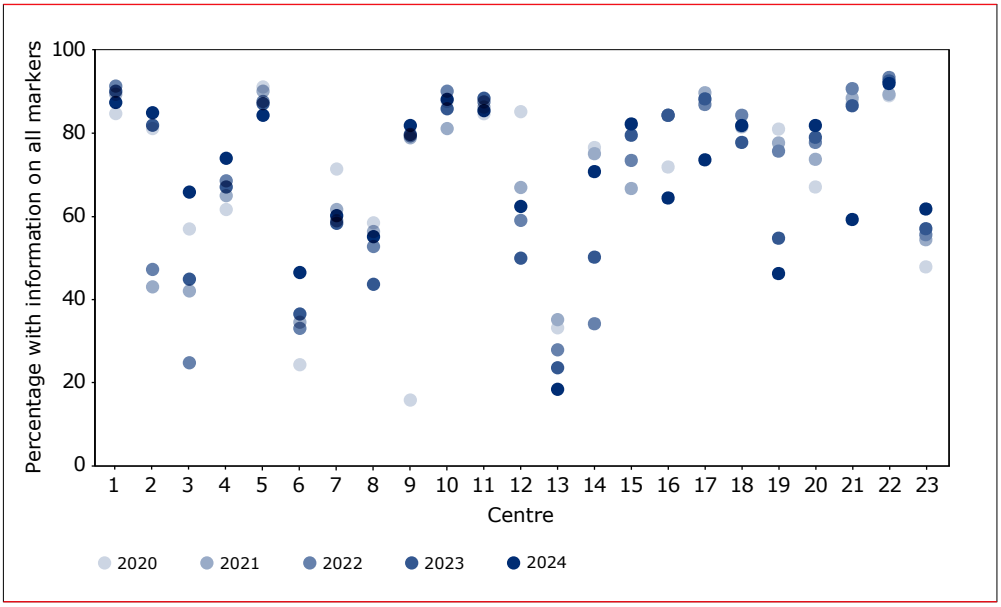
Legend: Data are provided for individuals 40 years old or older. Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 10.1.

Figure 10.4: Information on blood pressure; in other words, individuals who had a blood pressure measurement during each year between 2020 and 2024.



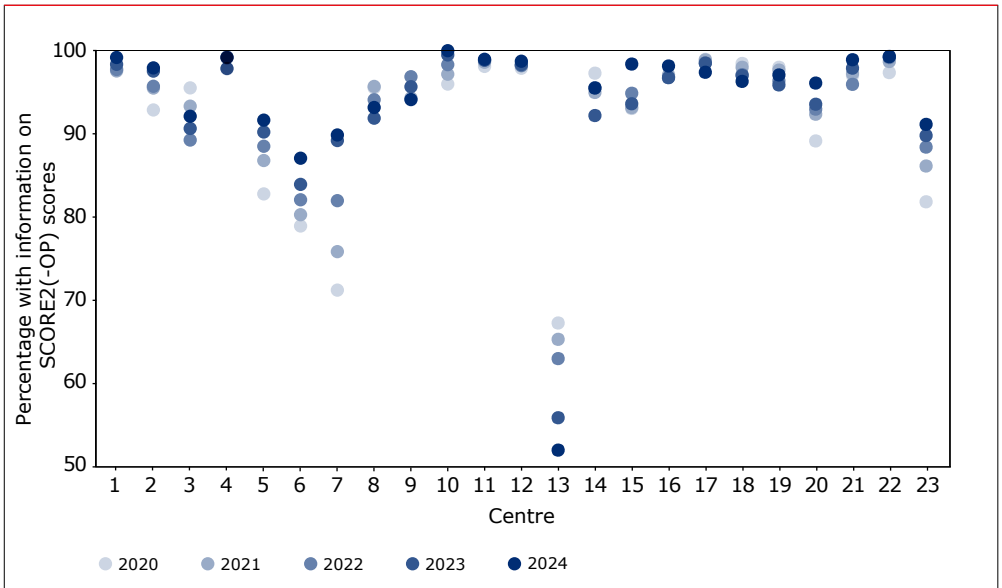
Legend: Data are provided for individuals 40 years old or older. Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 10.1.

Figure 10.5: *Information on all cardiovascular parameters; in other words, individuals who had total, HDL, LDL cholesterol and blood pressure measurement during each year between 2020 and 2024.*



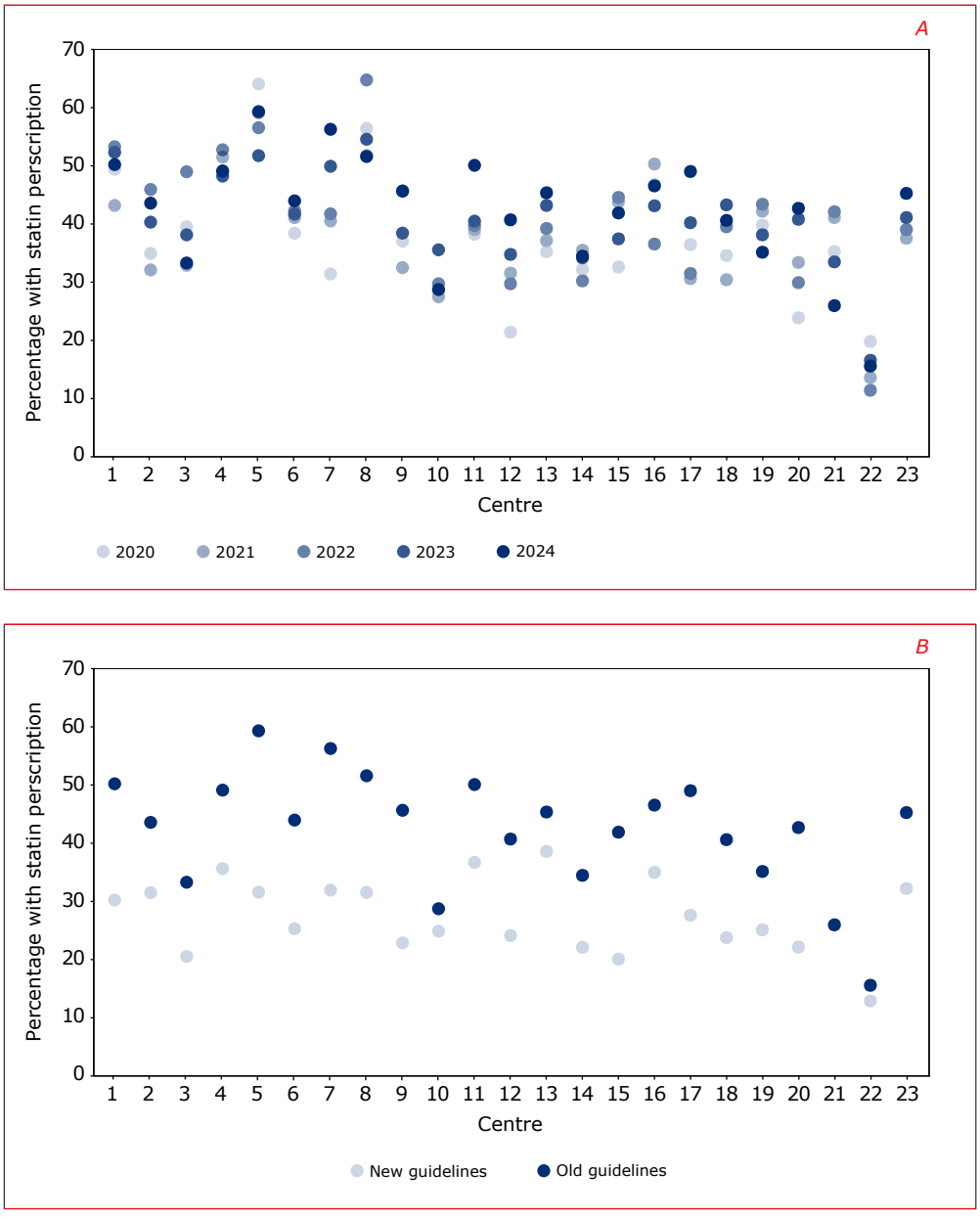
Legend: *Data are provided for individuals 40 years old or older. Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 10.1.*

Figure 10.6: *Information on cardiovascular event risk during each year between 2020 and 2024.*



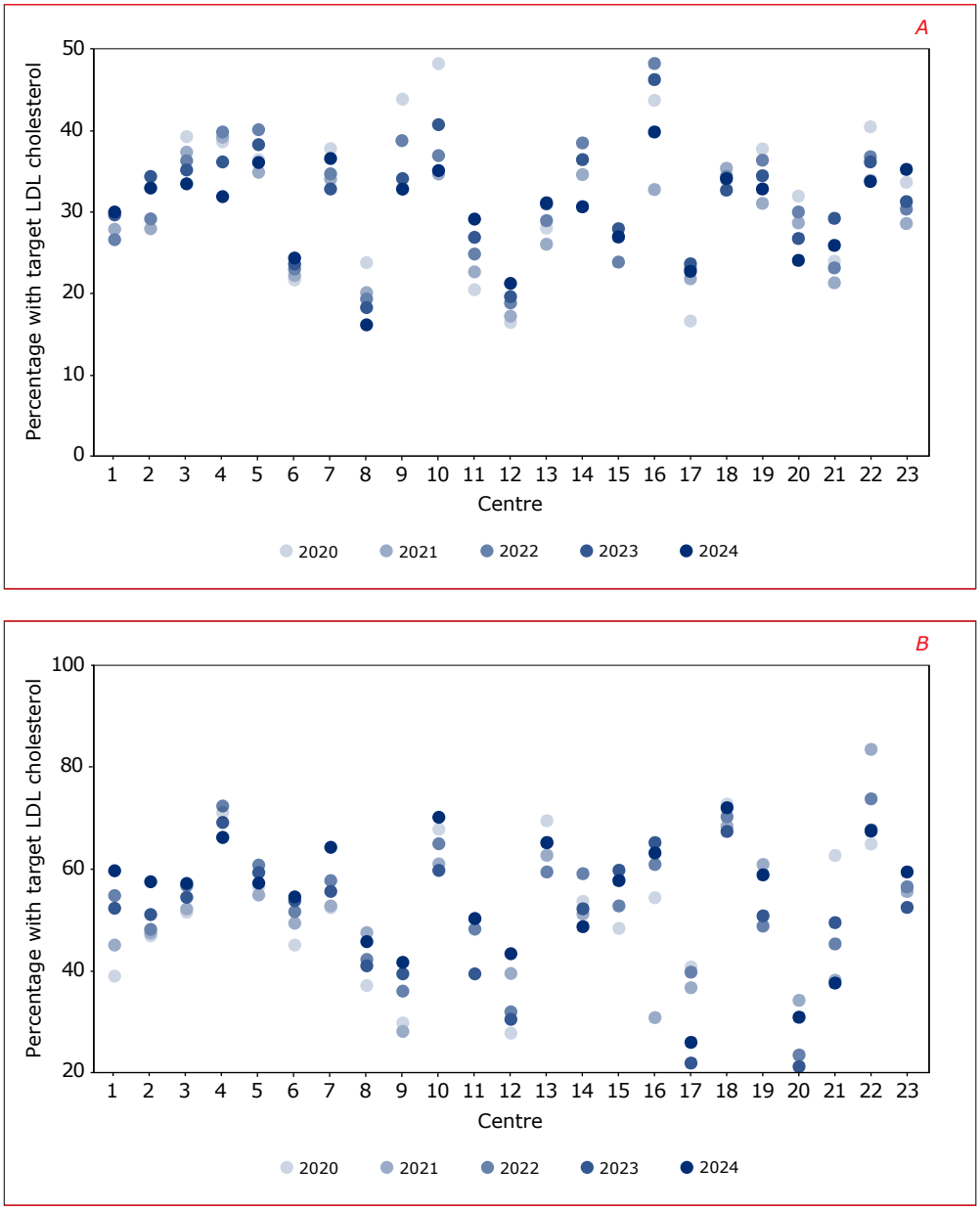
Legend: *The indicator represents individuals who had enough information to have their cardiovascular disease assessed by the SCORE2 (40–69 year olds) or SCORE2-OP (70 year olds or older). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 10.1.*

Figure 10.7: *Statin use; in other words, individuals who had a predicted 10-year cardiovascular event risk-score (A) greater than 10%, using the SCORE2(-OP) and received a prescription for statins during each year between 2020 and 2024 and (B) high cardiovascular event risk-score defined according to the old and new recommendations for the year 2024.*



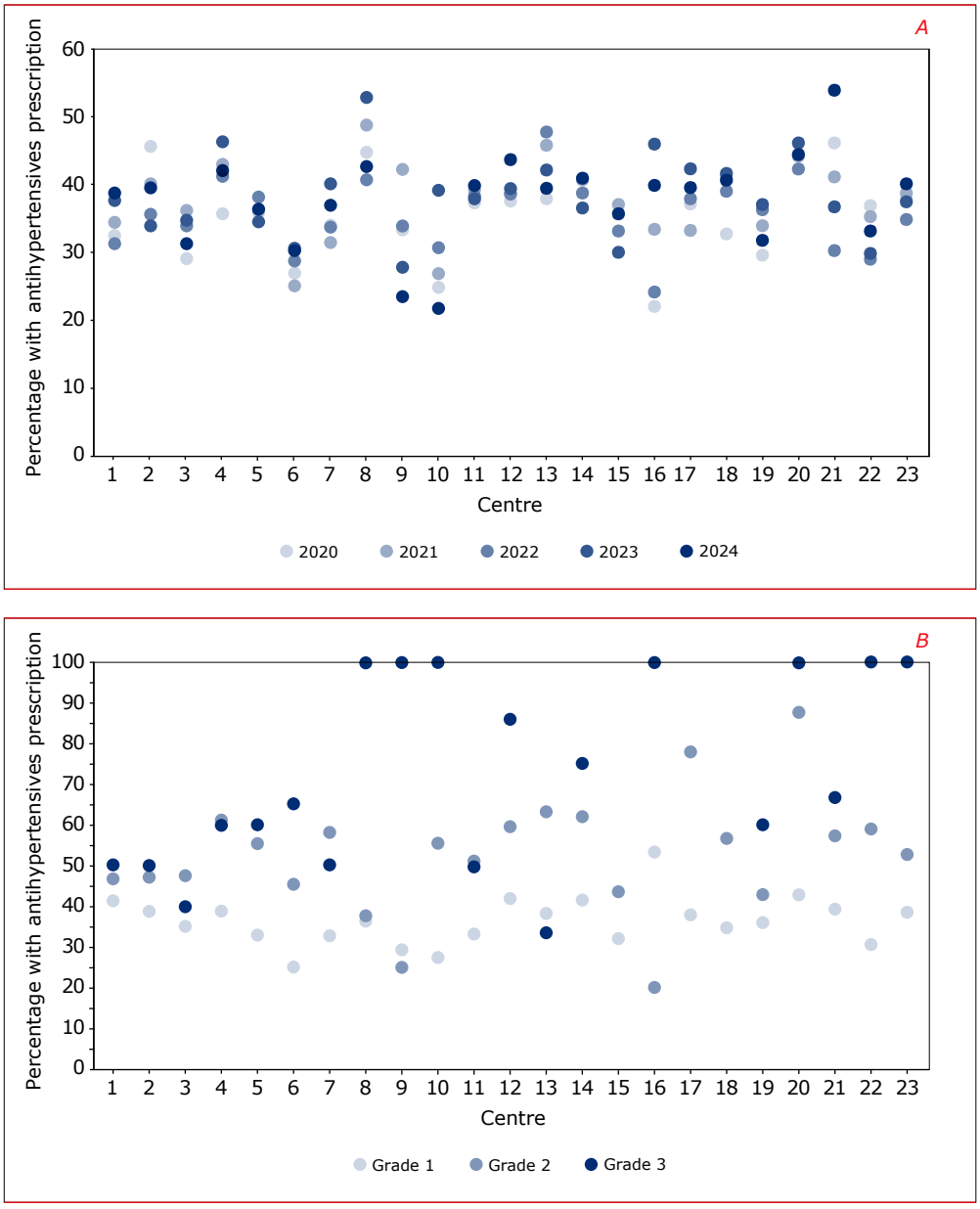
Legend: *Data are provided for those whose predicted 10-year cardiovascular risk were assessed with SCORE2 (i.e., 40-69 year olds) or SCORE2-OP (i.e., 70 year olds or older). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 10.1.*

Figure 10.8: *Target LDL cholesterol; in other words, individuals 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 2020 and 2024.*



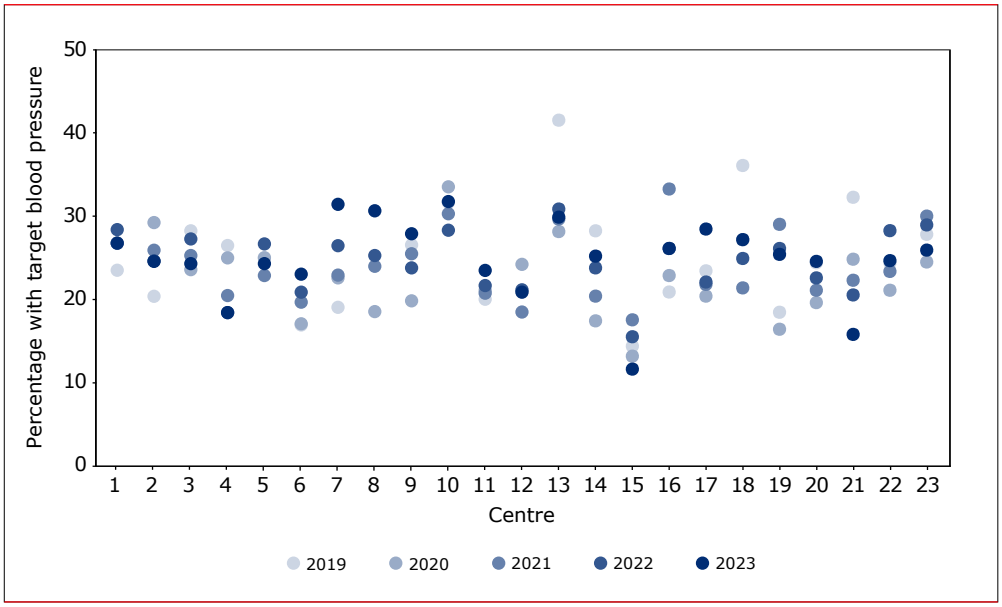
Legend: *Data are provided for those whose 10-year cardiovascular risk were assessed with SCORE2 (i.e., 40-69 year olds) or SCORE2-OP (i.e., 70 year olds or older). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 10.1.*

Figure 10.9: *Antihypertensive medication use; in other words, individuals who had high blood pressure and received a prescription for antihypertensive medication during each year between 2020 and 2024. (A) high blood pressure defined as a diastolic blood pressure ≥90 mmHg and (B) by different grades of hypertension for the year 2024.*



Legend: *(A) Data are provided for those who had high blood pressure, defined as ever having a diastolic blood pressure ≥90 mmHg. (B) Data provided for those with hypertension, defined as grade 1 blood pressure 140–159/90–99 mmHg; grade 2 Hypertension blood pressure 160–179/100–109 mmHg; grade 3 Hypertension blood pressure > 180/110 mmHg Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 10.1.*

Figure 10.10: *Target blood pressure; in other words, individuals who were receiving antihypertensive medication and had a blood pressure below age-specific thresholds during each year between 2020 and 2024.*



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 10.1.*

Centre performance

As reported in earlier studies, both the number of individuals 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[9-11].

Regarding centre volume, a smaller number of individuals 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 above or below the national average. This assessment depends on the number of individuals included when calculating the indicator (an overview of this method is provided in *Box 10.2*). Statistical interpretation is unreliable when centre sizes are small, hence we do not draw conclusions on whether these centres fall below the national average.

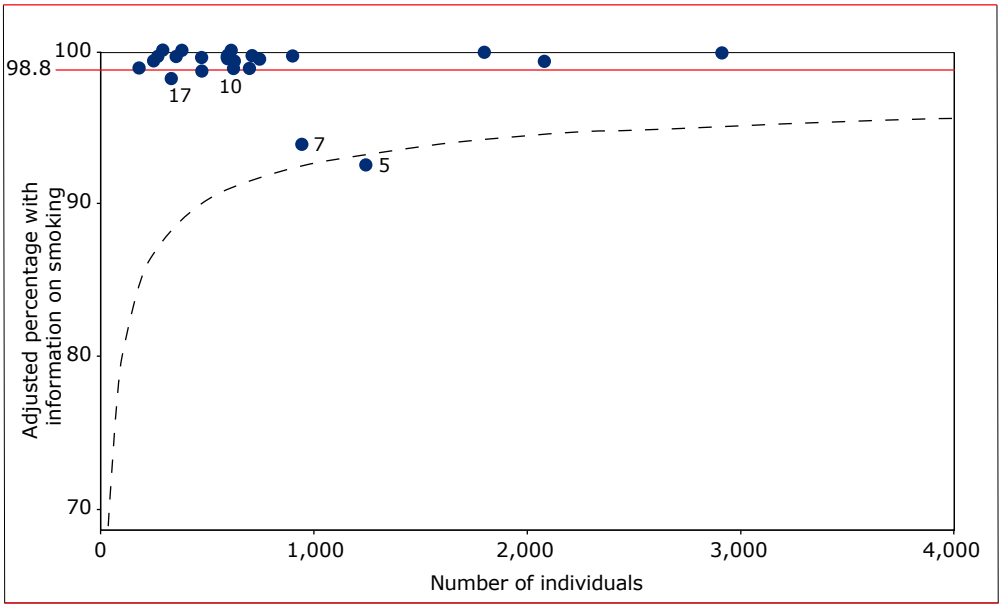
Regarding patient mix, individual-level factors, such as age and mode of transmission, are known to be associated with several indicators. If performance indicators are different across centres, it could be that the variation in the characteristics of individuals attending those centres is driving these differences. We have therefore adjusted all indicators by year of birth and geographical origin/mode of transmission/gender (*Box 10.2*). For this section, we have used all the indicators and populations defined in *Box 10.1*, while accounting for the issues described above. Only indicators from 2024 were considered in this analysis.

Box 10.2: Funnel plots to compare centres to the national average.

What types of problems occur when evaluating indicators?	
Centres treating fewer individuals	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).

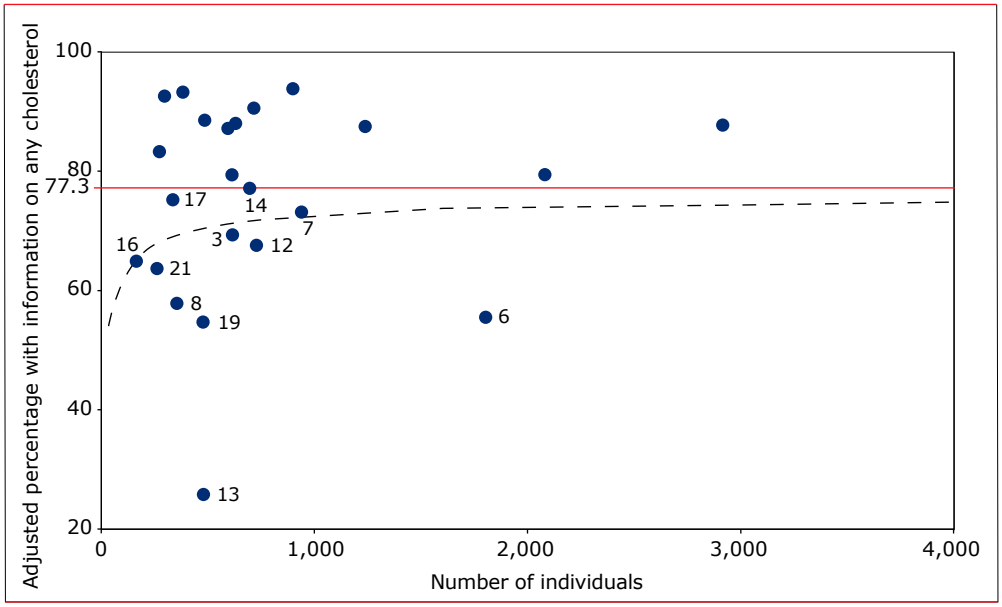
What is a funnel plot[12]?	
A funnel plot is a graphical depiction that allows us to compare a centre's indicator to the national average. It can help account for the problems listed above. The following are key components of this plot:	
Patient size	The *x*-axis depicts the number of individuals considered in a given indicator. For example, this number could be the total number of individuals in care in 2024, etc.
Adjusted %	The *y*-axis depicts the percentage of individuals 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 individuals 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 10.11: *Information on smoking; in other words, individuals who ever had information on their smoking status in 2024. The percentage with information on smoking has been adjusted for patient mix and is plotted as a function of the number of individuals who entered care.*



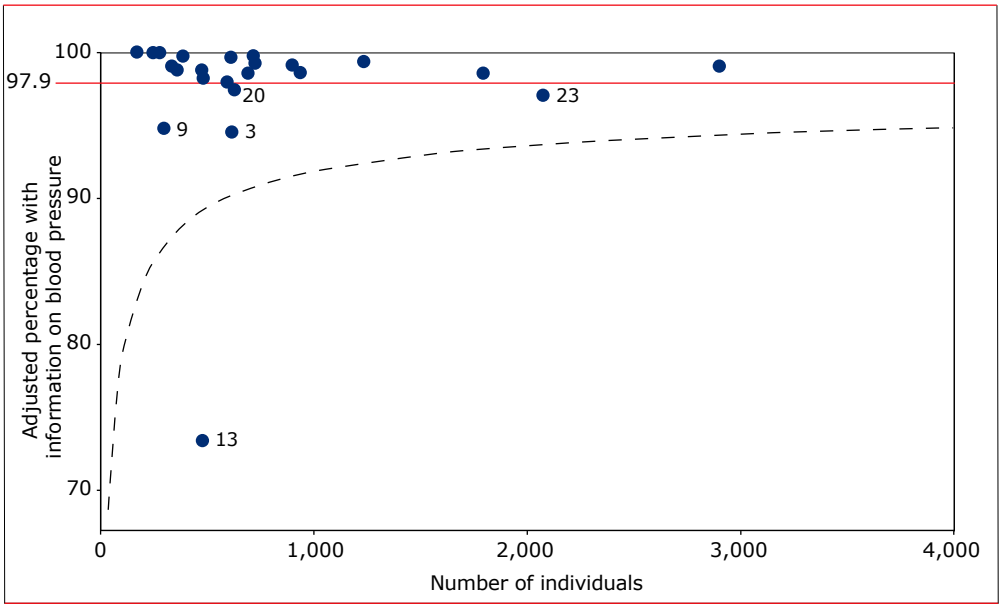
Legend: *Data are provided for individuals 40 years old or older. Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 10.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 10.2).*

Figure 10.12: *Information on any cholesterol; in other words, individuals who had a total, HDL or LDL cholesterol measurement in 2024. The percentage with information on total cholesterol has been adjusted for patient mix and is plotted as a function of the number of individuals who entered care.*



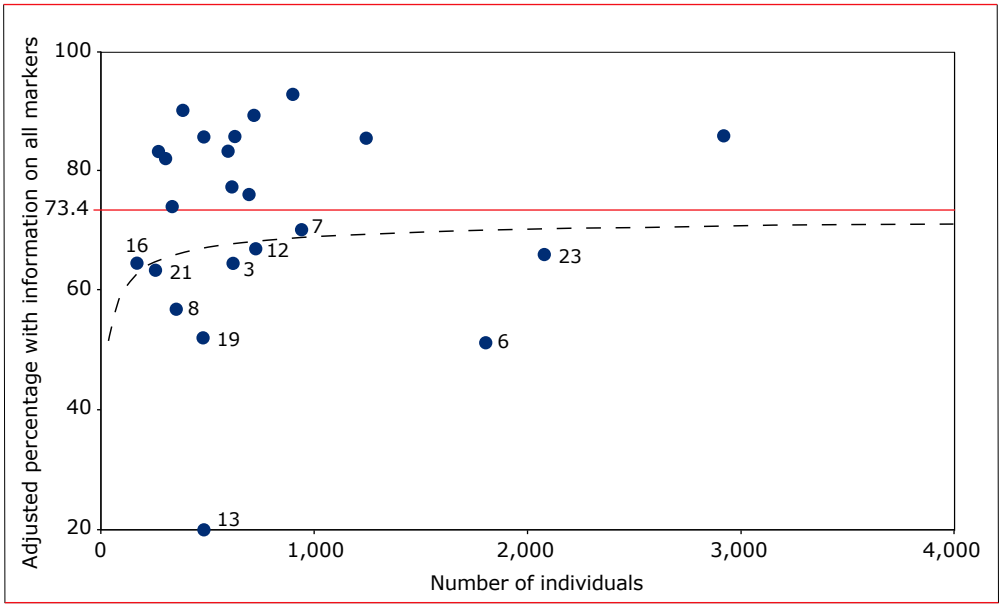
Legend: *Data are provided for individuals 40 years old or older. Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 10.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 10.2).*

Figure 10.13: *Information on blood pressure; in other words, individuals who had a blood pressure measurement in 2024. The percentage with information on blood pressure has been adjusted for patient mix and is plotted as a function of the number of individuals who entered care.*



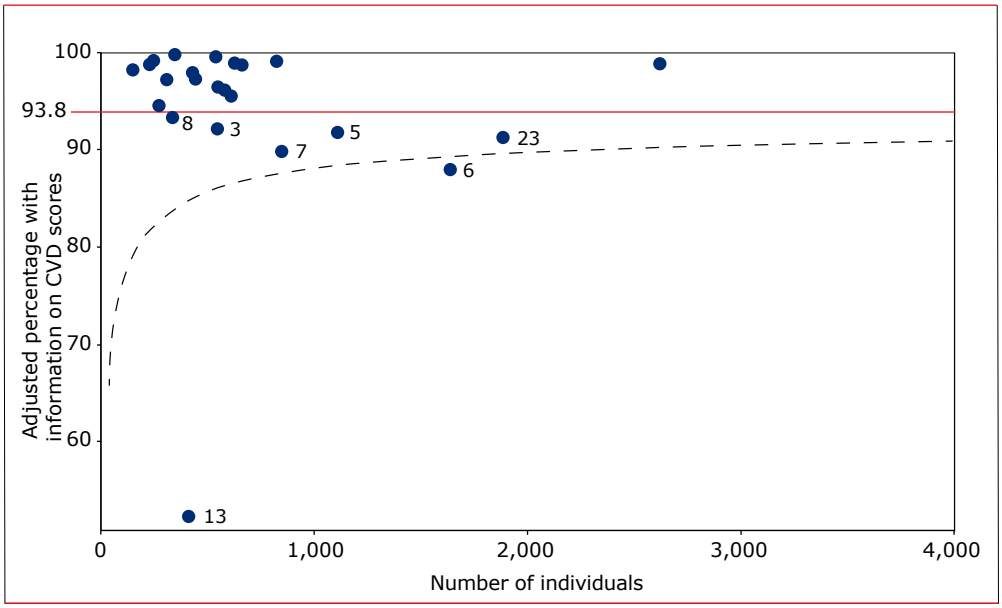
Legend: *Data are provided for individuals 40 years old or older. Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 10.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 10.2).*

Figure 10.14: *Information on all cardiovascular parameters; in other words, individuals who had total, HDL, LDL cholesterol and blood pressure measurement in 2024. The percentage with information on all cardiovascular parameters has been adjusted for patient mix and is plotted as a function of the number of individuals who entered care.*



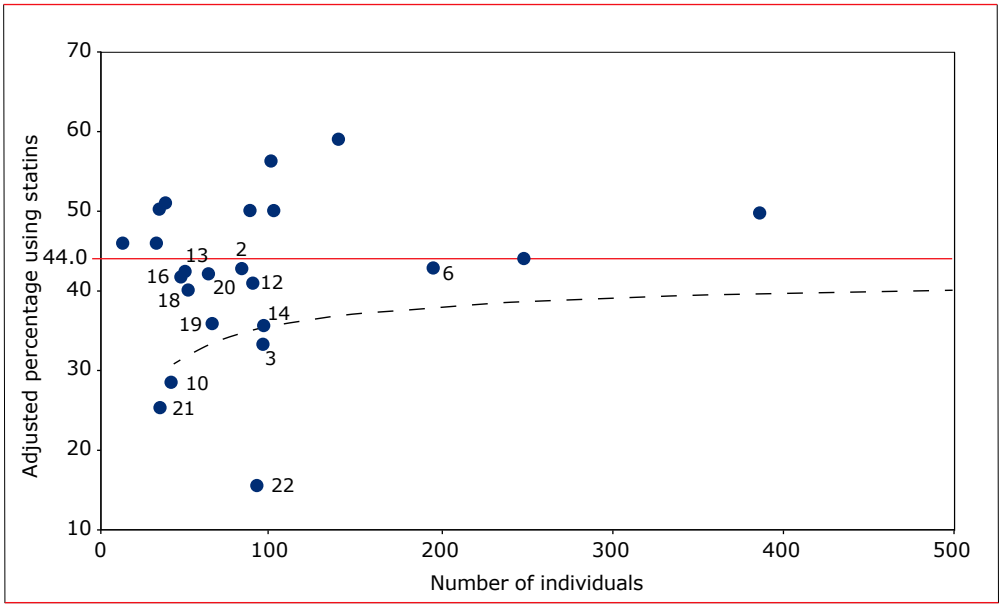
Legend: *Data are provided for individuals 40 years old or older. Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 10.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 10.2).*

Figure 10.15: *Information on cardiovascular event risk in 2024. 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 individuals who entered care.*



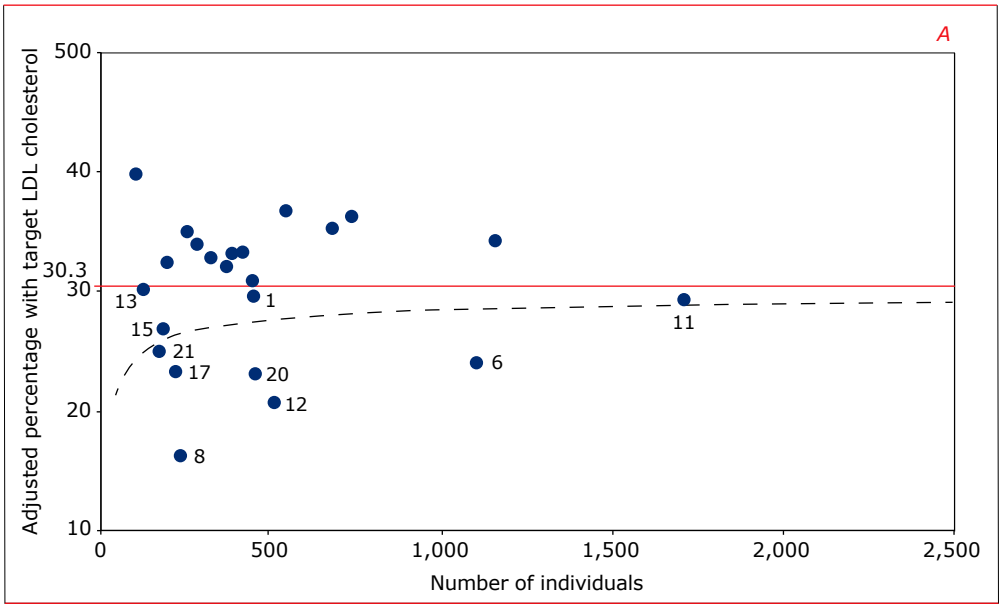
Legend: *The indicator represents individuals who had enough information to have their cardiovascular disease assessed by the SCORE2 (40–69 year olds) or SCORE2-OP (70 year olds or older). Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 10.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 10.2).*

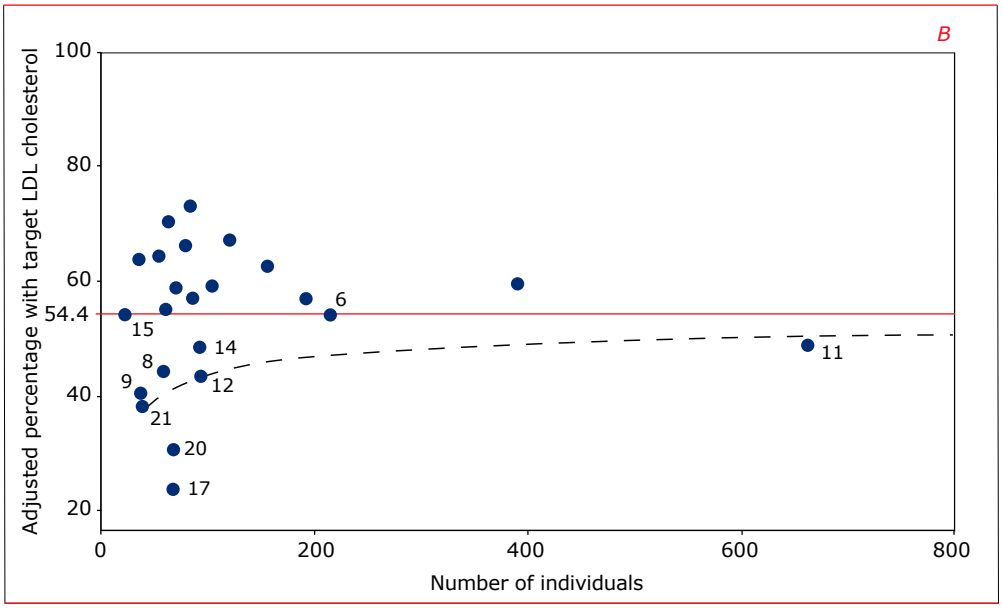
Figure 10.16: *Statin use; in other words individuals who had a predicted 10-year cardiovascular event risk-score greater than 10%, using the SCORE2(-OP) and received a prescription for statins in 2024. The percentage with statin use has been adjusted for patient mix and is plotted as a function of the number of individuals 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). Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 10.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 10.2).*

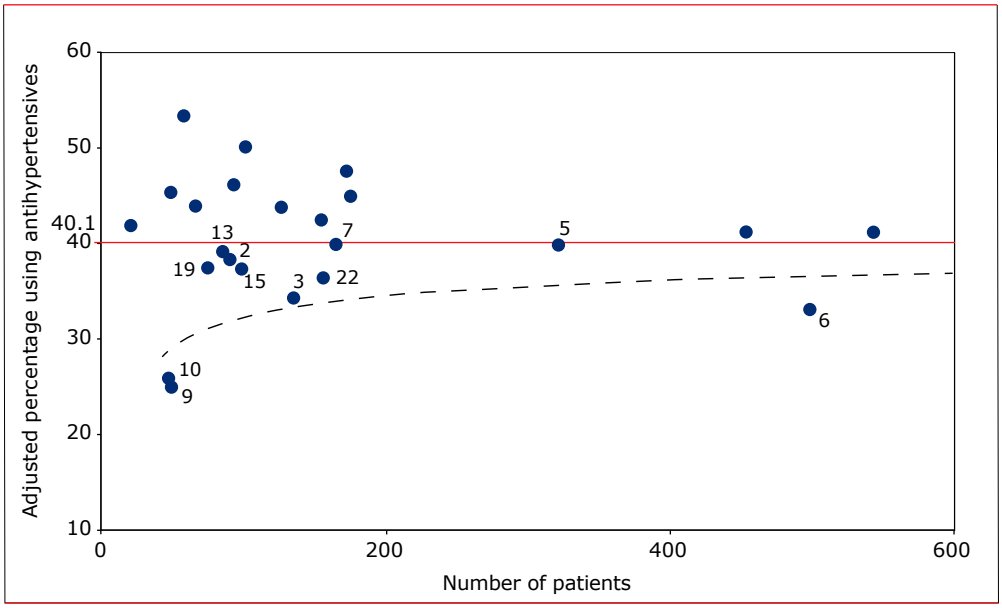
Figure 10.17: *Target LDL cholesterol; in other words, individuals who had a predicted 10-year cardiovascular event risk-score greater than 10%, using the SCORE2(-OP), without (A) or with a prescription for statins (B), and had an LDL cholesterol level ≤2.6 mmol/mL in 2024. The percentage with target LDL cholesterol has been adjusted for patient mix and is plotted as a function of the number of individuals who entered care.*





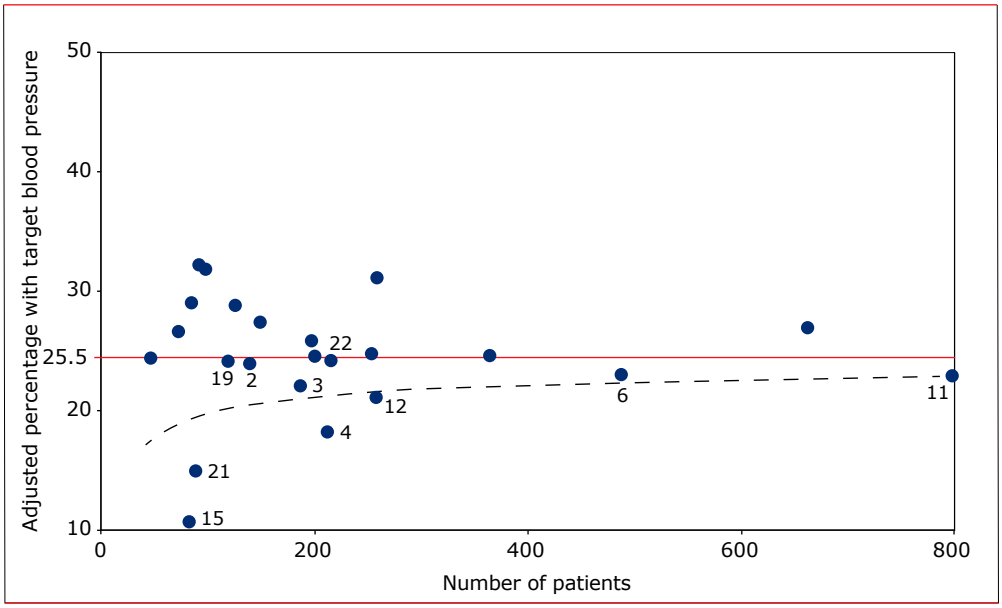
Legend: *Data are provided for those whose 10-year cardiovascular risk were assessed with SCORE2 (i.e., 40-69 year olds) or SCORE2-OP (i.e., 70 year olds or older). The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 10.2).*

Figure 10.18: *Antihypertensive medication use; in other words, individuals who had high blood pressure and received a prescription for antihypertensive medication in 2024. The percentage with antihypertensive medication use has been adjusted for patient mix and is plotted as a function of the number of individuals 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 10.2).*

Figure 10.19: *Target blood pressure; in other words, individuals who were receiving antihypertensive medication and had a blood pressure below age-specific thresholds in 2024. The percentage with target blood pressure has been adjusted for patient mix and is plotted as a function of the number of individuals 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 10.2).*

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:

- In 2024, the national average for having data available were: 99% for smoking, 98% for blood pressure, 77% for total-, HDL- or LDL- cholesterol. However, there was substantial variation in the percentage of individuals with information on total, HDL- or LDL- cholesterol across centres. 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.
- In 2024, the national average for having all the information to predict 10-year risk of a cardiovascular event was 94%. However, two centres had percentages that were lower-than-expected compared to the national average.
- More than 80% of individuals 40 years or older had information on their predicted 10-year risk of a cardiovascular disease event for all but one centre. For one centre, 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. Based on the former recommendations, 44% of the individuals with high risk had a statins prescription in 2024. When high cardiovascular disease risk was based on the updated recommendations, to only 28% of the individuals with a high predicted 10-year CVD risk statins were prescribed.
- 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 individuals had a prescription for statins. The national average in 2024 was 54%. Three centres, 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 individuals did not receive a prescription for statins, but this percentage was high across all centres.
- Overall, 40% of the individuals with high blood pressure in 2024 received an antihypertensive prescription. There was also slight between-centre variation in the percentage of individuals with high blood pressure who received an antihypertensive prescription and some centres have shown decreases in the percentage of individuals with high blood pressure who received an antihypertensive prescription. However, when individuals with high blood

pressure were stratified according to their grade of hypertension, antihypertensive prescription increased with grade of hypertension Likewise, there was slight between-centre variation in the percentage of individuals 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 HIV treatment centres had levels of these indicators that were much lower-than-expected when compared to the national average of 24%.

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. There remains a possibility that in some cases information may be missed in the data collection. Certain data related to cardiovascular disease could be missing simply because these data are not measured at the HIV treatment centre. We were not able to include people without the information to predict 10-year risk of a cardiovascular event when analysing the indicators on statin and antihypertensive medication. Finally, we do not have the specific reasons why people 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 variation across centres. Nevertheless, certain centres should strive to increase the percentage of individuals with information on cholesterol measurements and risk assessment of cardiovascular disease events. Less than half of the of individuals with a predicted high 10-year risk of a cardiovascular event used statins and this national average was lower under the updated recommendations to assess high 10-year risk. This analysis provides insight into the provision of cardiovascular diseases care at the different treatment centres.

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11. The Amsterdam Cohort Studies (ACS) on HIV infection: annual report 2024

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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/inject drugs (PWUD/PWID) was initiated in 1985 and discontinued in 2016.

In 2024, the cohort celebrated the milestone of 40 years of follow-up. 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 [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.

Collaborating institutes and funding

Within the ACS, the following institutes collaborated in 2024 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): Department of Medical Microbiology and Infection prevention, Laboratory of Experimental Virology (LEV), Experimental Immunology, Laboratory for Viral Immune Pathogenesis, and Internal Medicine (Department of Infectious Disease)
- **Stichting hiv monitoring** (SHM)

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 (*Rijksinstituut voor Volksgezondheid en Milieu - Centrum voor Infectieziektenbestrijding, 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 study protocol for the MSM cohort was approved by the Amsterdam UMC medical ethics committee in 2022.

The Amsterdam Cohort Studies (ACS)

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

In 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. During the 40-year follow-up period, minor changes in the inclusion criteria for ACS were introduced, mainly concerning HIV status and age. 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 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). Currently, eligible for enrolment are individuals of at least 16 years old, who were assigned male sex at birth and who have not undergone gender reassignment surgery, live in the Amsterdam area or are involved in MSM-related activities in Amsterdam, and who have had sex with at least one man in the preceding six months.

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.

All (sexual) behavioural data are collected by questionnaires, coordinated by the GGD Amsterdam, and clinical data (for PWH) are provided by SHM. Every 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.

As of 31 December 2024, 3,024 MSM have been included in the ACS since its initiation in 1984. These MSM contributed a total of 70,270 cohort visits at the GGD Amsterdam. Of these 3,024 MSM, 608 were living with HIV at entry into the study and 267 seroconverted for HIV during follow-up.

At 31 December 2024, 664 HIV-negative participants and 42 participants with HIV were in follow-up (meaning that they had at least one study visit in 2023 or 2024). Of these, 645 HIV-negative participants and 38 participants with HIV had at least one visit in 2024. 33 newly enrolled in the cohort in 2024, all MSM without HIV with a median age of 35 years at enrolment. After 2 years without any HIV seroconversions, two MSM seroconverted in 2024.

In this chapter, we report on the MSM actively participating in the ACS in 2024:
- The median age was 47 years at their last cohort visit in 2024;
- The majority was born in the Netherlands (84%) and a resident of Amsterdam (79%);
- 80% of the MSM had a college/university degree.

The cohort of people who use or inject drugs (PWUD/PWID) – discontinued

Between 1984 and 2016, a total of 1,661 PWUD had been included in the ACS of whom 1,303 had at least two cohort visits (the maximum number of visits was 78).[1] 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[2], and publications.[1,3-5]

ACS biobank

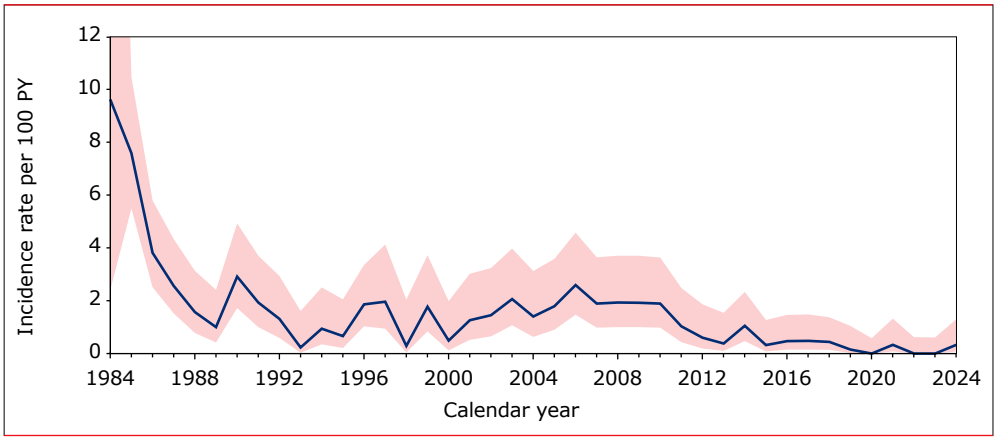
The ACS biobank, at the Amsterdam UMC, location AMC, stores all samples (plasma/serum, peripheral blood mononuclear cells) taken in the context of the ACS study. In addition to samples taken at routine ACS study visits, the biobank also contains samples collected for sub-studies and affiliated studies embedded in the ACS. Over the past 40 years, more than 350,000 samples have been stored for ongoing and future research.

ACS in 2024: 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 11.1). Between 1985 and 1993 HIV incidence declined significantly, then stabilized between 1993 and 1996, before rising again in the period 1996 to 2009. Since 2009, the HIV incidence decreased again. After two years of zero seroconversions, two participants seroconverted in 2024.

Figure 11.1: HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984–2024.



PrEP use

354/664 (53%) participants without HIV reported PrEP use in 2024. Of these, 185 (53.1%) obtained PrEP through the national PrEP program at the Centre of Sexual Health, 143 (40.4%) through their GP, 9 (2.5%) through an Internal Medicine specialist or another physician and 14 (4.0%) obtained their pills through informal routes (e.g. cross-border clinics, sexual or social networks, self-prescribed or online offered pills).

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 is in accordance with the standard care offered by the Centre of Sexual Health Amsterdam. Chlamydia and gonorrhoea were tested with nuleic acid amplification techniques using urine samples and pharyngeal and rectal swabs. Syphilis was screened for by *Treponema pallidum* haemagglutination assay.

In 2024, STI data were available from the Centre of Sexual Health Amsterdam for 671 MSM (with 1,649 visits including extra STI visits) participating in the ACS. Of these, 154 (23.0%) had at least one positive bacterial STI test (94 (14.0%) gonorrhoea, 75 (11.2%) chlamydia and 21 (3.1%) syphilis). For MSM with and without HIV, 11 out of 38 (28.9%), and 143 out of 633 (22.6%), MSM had at least one positive bacterial STI test, respectively.

Until August 2024, participants using PrEP were screened for STIs 3-monthly, whereas other participants were screened 6-monthly, according to national PrEP guidelines. Following the revised national PrEP guidelines, STI screening is now offered 6-monthly to both PrEP-users and those not using PrEP. Trends of any bacterial STI incidence among MSM without HIV, and stratified for PrEP use and no PrEP use, between 2009 and 2024 are shown in figure 11.2 and 11.3. The annual incidence rate of any bacterial STI for MSM without HIV increased over time (Figure 11.2). MSM who used PrEP in the preceding 6 months were diagnosed with STIs more often than MSM who did not (Figure 11.3).

Figure 11.2: Any bacterial STI incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM) without HIV with at least two study visits, 2009-2024.

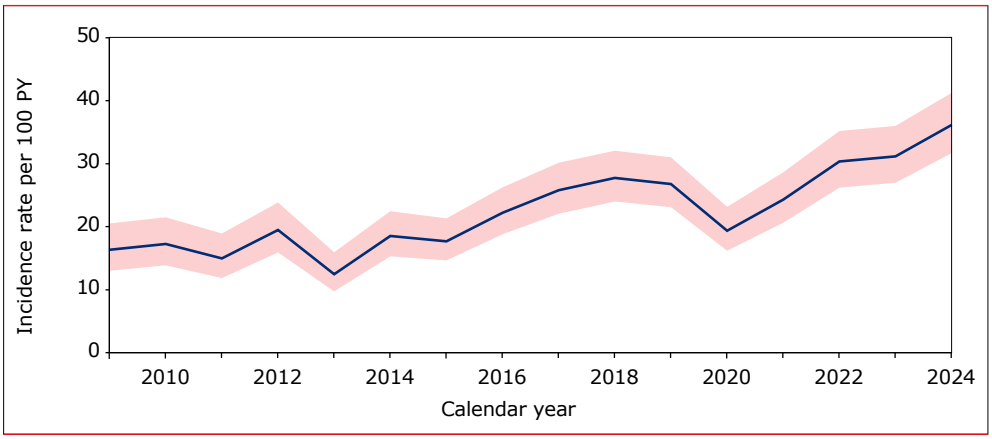
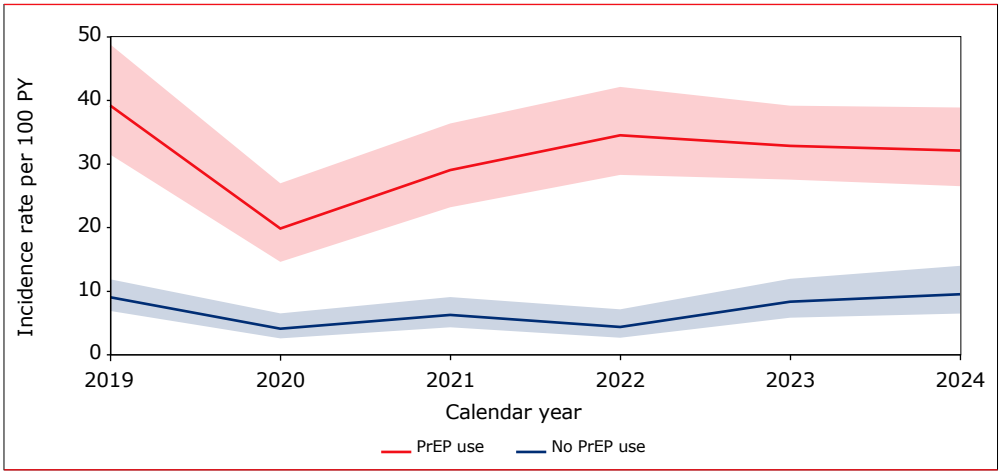


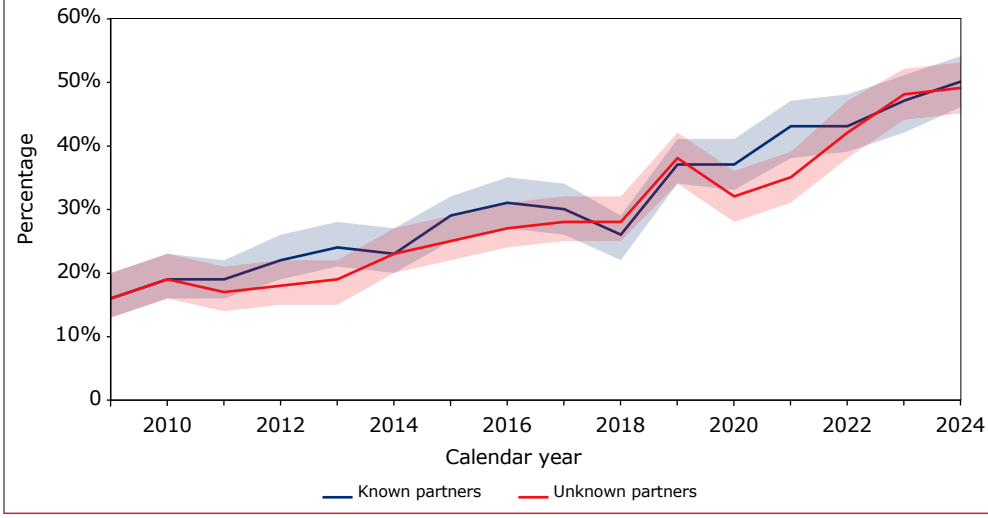
Figure 11.3: Any bacterial STI incidence per calendar year in the Amsterdam Cohort Studies (ACS) stratified by PrEP use in the preceding 6 months, among men who have sex with men (MSM) without HIV with at least two study visits, 2009-2024.



Sexual behaviour

Condomless anal sex with a casual partner was reported by 320 of 664 (48%) MSM without HIV in 2024. Trends in recent (i.e., in preceding 6 months) condomless anal sex among MSM without HIV continued to show an increase from 2009 onwards (Figure 11.4). Among 354 MSM using PrEP in 2024, 267 (75.4%) reported recent condomless anal sex in 2024. Among 291 MSM not using PrEP in 2024, 53 (18.2%) reported recent condomless anal sex.

Figure 11.4: Proportion of men reporting condomless anal sex (CAS) with casual partners per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM) without HIV with at least two study visits, 2009-2024.



ACS 2024 research highlights

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 other factors, e.g. beliefs, attitude, subjective norms, and perception of risk, in relation to self-reported vaccination uptake[6]. 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.

Influenza-like illness symptoms due to endemic human coronavirus reinfections are not influenced by the length of the interval separating reinfections

Little is known about the disease following human coronavirus reinfections occurring several years after the previous infection, once humoral immunity has waned. To investigate this, disease symptoms were monitored during human coronavirus reinfection intervals in the Amsterdam Cohort Studies.[7] Importantly, we found no influence of reinfection interval length on the disease manifestation. We found that after a long period with no infection by a human coronavirus, the absence of immune-boosting does not make people more ill when they eventually do catch the virus. We conclude that, once a human coronavirus has been fully adapted to its host and the vast majority of people having been infected at least once, there may not be an urgent need to repeatedly vaccinate the general immunocompetent population against that human coronavirus.

Polyfunctionality and breadth of HIV-1 antibodies are associated with delayed disease progression

Despite the availability of effective treatment, HIV-1 still causes significant mortality and morbidity across the globe. Alternative ways for protection or treatment against HIV-1 are needed. Antibody-mediated effector functions could potentially contribute to the effectiveness of novel approaches. However, we need more information on which antibody properties are associated with these potential beneficial functions of antibodies. Studying antibody responses during natural HIV-1 infection can provide guidance on this topic. We identified several antibody properties that were associated with reduced HIV-1 disease progression in the Amsterdam Cohort Studies of individuals with untreated HIV-1.[8] High levels of IgG1 and low levels of IgG2 and IgG4, broad and polyfunctional antibodies and interaction with immune proteins FcγRs and C1q, were all associated with delayed disease progression. Subsequently, effective strategies against HIV-1 will likely require multiple different components. The antibody properties described in this study can contribute to a more detailed bio-molecular roadmap for antibody-based strategies for HIV-1 prevention, therapy and cure.

HIV-1 vaccine field

One of the main goals of the HIV-1 vaccine field is the generation of recombinant envelope glycoprotein (Env) immunogens that can elicit protective broadly neutralizing antibody (bNAb) responses. The first-generation recombinant HIV-1 Env immunogens consisted of unstable complexes that expose non-neutralizing antibody (non-NAb) epitopes, which are normally not exposed on infectious viral Env. It took several years of iterative design to generate soluble SOSIP trimers of native-like Env immunogens. The basis of these immunogens are HIV-1 Env

sequences from the Amsterdam Cohort Studies. The essential SOSIP modifications include the truncation of gp41 at position 664, a disulfide bond (501C-605C) to covalently link the gp120 and gp41 subunits, an Ile-to-Pro mutation (I559P) to prevent conformational transitions to the post-fusion state and an RRRRRR (R6) multibasic motif to enhance furin cleavage. The determination of these Env SOSIP trimer structures led to a plethora of further structure-based stabilizing mutations and novel Env trimer designs. Significantly, several of these native-like Env SOSIP trimers that are based on an Env sequence from the Amsterdam Cohort Studies, are currently being tested in phase I clinical vaccine trials.[9-11]

Energy demanding RNA and protein metabolism drive dysfunctionality of HIV-specific T cell changes during chronic HIV infection

A small group of people with HIV (PWH) is able to control their infection without the need of antiviral therapy. In these so-called long-term non-progressors (LTNP), an effective CD8 T cell response is thought to maintain the immunological control of HIV. Here we studied the virus specific CD8 T cells from PWH from the Amsterdam Cohort Studies to gain molecular insights in CD8 T cell functionality in HIV infection.[12] We observed that HIV-specific CD8 T cells from PWH who are unable to control their infection, show a functional impairment already during the asymptomatic phase of infection and differed from LTNP with regards to cytokine signaling and mitochondrial function. Targeting the mitochondria to improve the immune function, indeed showed an increase in IFNγ release upon antigen stimulation. This indicates that treatment strategies to enhance the cellular metabolism and improve mitochondrial function may improve virus specific CD8 T cell responses and aid a controlling immune response in chronic infection.

Current and upcoming ACS research projects

Data collected within the ACS are currently used for multiple research projects. As 2024 marked the 40th anniversary of the study, we are studying trends in HIV and STI incidence and sexual behaviour over 40 years of follow-up. Sexual behaviour, including anal sex with casual and steady partners, in relation to both condom and PrEP use, is currently being studied in greater detail. Trends and current norms and negotiation experiences regarding condom use are also being analysed.

Quantitative and qualitative studies on individual and contextual motives underlying choices of HIV prevention strategies (including condoms, PrEP, and viral load sorting) are ongoing, and conducted in collaboration with Maastricht University. Data on PrEP surfing, defined as using the PrEP status of sexual partners as HIV prevention strategy, are currently being analyzed. Data of ACS are also used in research into the mapping of the PrEP need, use and care in Amsterdam;

i.e. the PrEP cascade. More research is in preparation on doxyPEP, as well as on motivations for MSM to use long-acting PrEP modalities and preferences regarding implementation.

In the context of the COVID-19 pandemic, we are investigating 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 nonproblematic substance use.

Data Preparedness of the Amsterdam Cohort Studies

The ACS team supports the Open Science movement, and aims to improve the findability, accessibility, interoperability, and reusability (FAIR) of the ACS (meta) data. In 2024, to enhance the Open Science principles within the ACS, the "Data Preparedness of the Amsterdam Cohort Studies" project was undertaken. This project was funded by ZonMw under the "Stimuleringsimpuls FAIR-data voor Pandemische Paraatheid" program (grant number 10710032320005; € 50,000; 2024).

The evaluation of the FAIRness of the ACS (meta)data revealed that improvements could be made in all four aspects of FAIR: findability, accessibility, reusability and interoperability. Key improvement points include: (1) making metadata findable and accessible by making the metadata available in the National Health Catalogue, (2) publishing data request forms and the ACS data request process online, and (3) making the data dictionary accessible online again. This includes the launch of a new website for researchers: www.acsresearch.nl. Initial steps have been taken to implement these improvements. The evaluation of obstacles in requesting ACS data showed that a clearer understanding of participant consent over the years is needed. This would help to efficiently determine whether data requests can be processed, and for which participants and periods. Additionally, the evaluation revealed that the data request procedure was unclear for both internal and external researchers. The solution to this issue involved revising the data application form and developing a flowchart of the data request procedure, so researchers know wat to expect in advance.

As a continuation of the project, we aim to further implement the identified improvements regarding the findability, accessibility, interoperability, and reusability of the ACS (meta)data. A follow-up grant application has been submitted to NWO (Open Science Infrastructure | Open Science NL) for this purpose.

Steering committee

In 2024 the steering committee met four times. Ten proposals for use of ACS data or samples (serum/PBMC) were submitted to the committee: four from Experimental Immunology (EXIM, Amsterdam UMC, location AMC) and six from Medical Microbiology and Infection Prevention (MMI, Amsterdam UMC, location AMC). Two proposals were collaborations between EXIM Amsterdam UMC and Radboud MC. The ACS reviewed the proposals and suggested major revisions in some cases, after which all requests were approved.

Research Meetings

An internal ACS research meeting with Amsterdam UMC and GGD researchers was held on April 11th, 2024, during which six ACS researchers presented research findings.

Publications in 2024 that included ACS data

- Brinkkemper M, Kerster G, Brouwer PJM, Tran AS, Torres JL, Ettema RA, Nijhuis H, Allen JD, Zhu W, Gao H, Lee WH, Bijl TPL, Snitselaar JL, Burger JA, Bontjer I, Olijhoek W, Ravichandran R, van Breemen MJ, Del Moral-Sánchez I, Derking R, Sliepen K, Ozorowski G, Crispin M, Montefiori DC, Claireaux M, Ward AB, van Gils MJ, King NP, Sanders RW. Mosaic and mixed HIV-1 glycoprotein nanoparticles elicit antibody responses to broadly neutralizing epitopes. PLoS Pathog. 2024 Oct 3;20(10):e1012558. doi: 10.1371/journal.ppat.1012558.
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PhD theses in 2024 that included ACS data

- Lisa van Pul. Host-control of HIV: balance between immunity and immunopathology. 2 February 2024
- Tom Caniels. Guided by glycoproteins: insights from antibody responses enable viral vaccine design. 11 March 2024
- Marloes Grobben. Polyfunctional antibodies in viral disease; Detecting, controlling and preventing infections with antiviral antibodies. 15 March 2024
- M. Ferdyansyah Sechan. New Insights into Protective Immunity against Endemic Human Coronaviruses. 9 September 2024
- Mitch Brinkkemper. Multivalent nanoparticle vaccine candidates against sarbecoviruses and HIV-1. 8 November 2024

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12. HIV in Curaçao

Diederik van de Wetering, Esther Rooijakkers, Ashley Duits, Ard van Sighem

Introduction

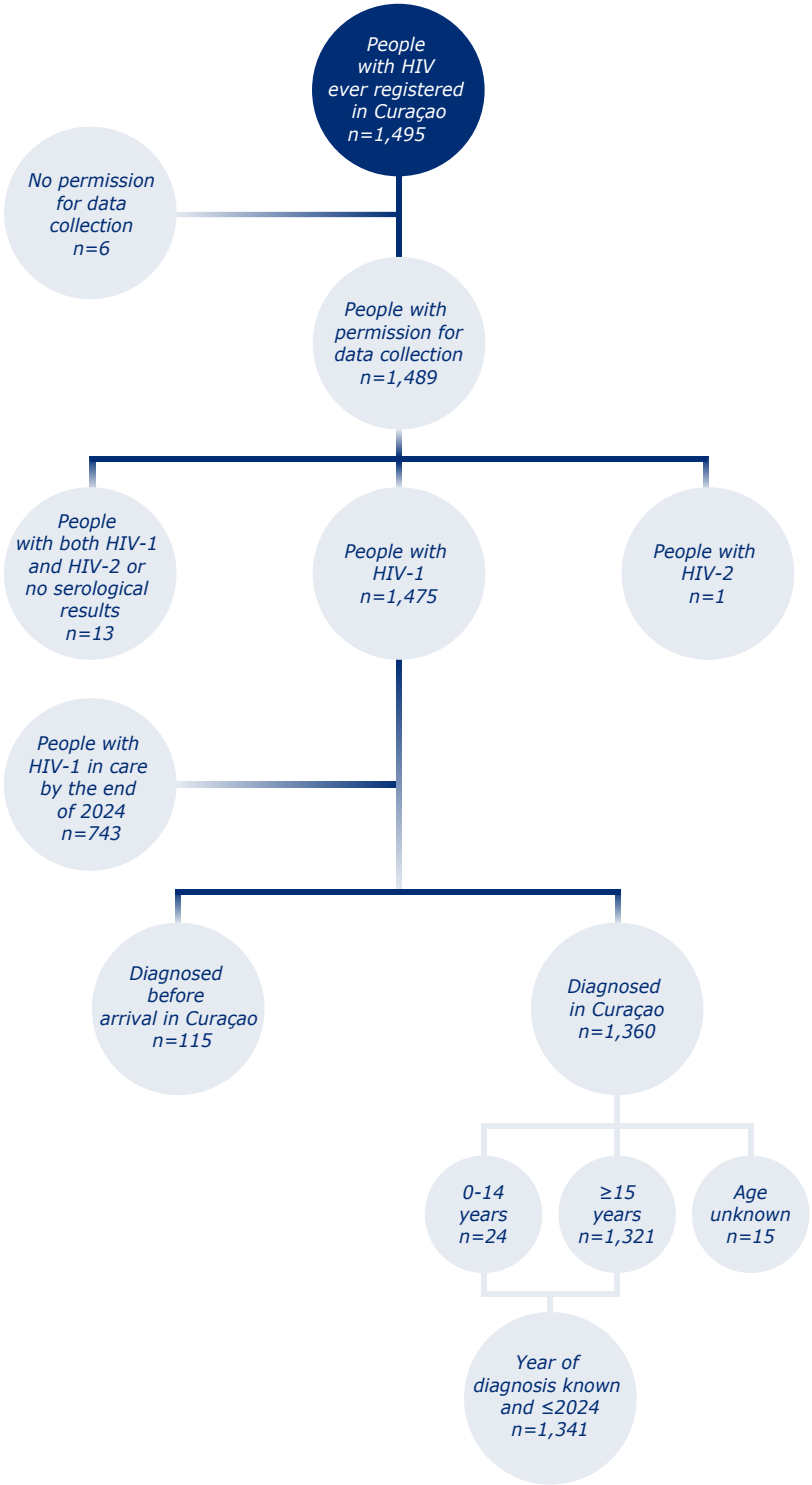
Since 2005, stichting hiv monitoring (SHM) has assisted in collecting demographic and clinical data on individuals with HIV receiving care at the sole general hospital St. Elisabeth Hospital and its successor Curaçao Medical Center in Willemstad, Curaçao. An extensive database has been established as 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, 1,489 individuals with HIV recorded by SHM have been registered in Curaçao who gave permission for further data collection. Of these people, the majority were diagnosed with HIV-1 (n=1,475, or 99%), while one individual was diagnosed with HIV-2, and three had antibodies against both HIV-1 and HIV-2 (*Figure 12.1*). For 10 individuals, serological results on HIV type were not available in the SHM database.

The population with HIV-1 in Curaçao

Of the 1,475 individuals in Curaçao with HIV-1, 115 (8%) had a documented HIV diagnosis prior to arrival in Curaçao (*Figure 12.1*). The remaining 1,360 individuals were newly diagnosed while living in Curaçao, or their date of arrival in Curaçao has not yet been recorded in the SHM database.

Figure 12.1: *Overview of the population with HIV registered in Curaçao.*



Individuals diagnosed before arriving in Curaçao

The 115 individuals with a documented HIV-1 diagnosis prior to arrival in Curaçao included 99 (85%) people who were registered with an HIV treatment centre in the Netherlands prior to moving to Curaçao (*Figure 12.1*). The majority of these 99 individuals (n=74, or 75%) originated from the former Netherlands Antilles, while 20 (20%) were born in the Netherlands and five (5%) were born elsewhere. The other 16 individuals with pre-migration diagnosis were also born abroad, including 6 in Venezuela. Eight of the 11 people arriving in Curaçao in 2022-2024 with a documented HIV-1 diagnosis prior to arrival had a suppressed viral load below 200 copies/ml (*Figure 12.2*).

Individuals newly diagnosed in Curaçao

Altogether, 1,360 individuals were newly diagnosed while living in Curaçao, or information on where they lived at the time of diagnosis was not yet available (*Figure 12.1*). For 19 (1%) of these 1,360 individuals, the date or interval of diagnosis was not recorded in the SHM database, or they were diagnosed in 2025. Of the remaining 1,341 individuals, 1,001 (75%) were born in the former Netherlands Antilles, 116 (9%) originated from Haiti, 94 (7%) from the Dominican Republic, 28 (2%) from Jamaica, 27 (2%) from Colombia, 21 (2%) from Venezuela, and 54 (4%) from other countries.

The 1,341 individuals comprised (*Table 12.1*):

- 267 (20%) men who have sex with men (MSM);
- 570 (43%) other men,
  - 334 (59%) of whom reported sex with women as the most likely mode of transmission
  - 236 (41%) reported other or unknown modes of transmission;
- 474 (35%) women,
  - 461 (97%) of whom reported sex with men as the most likely mode of transmission
  - 13 (3%) reported other or unknown modes of transmission;
- 6 transgender men and women;
- 24 (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 30 in most recent calendar years (*Table 12.1*; *Figure 12.2*).

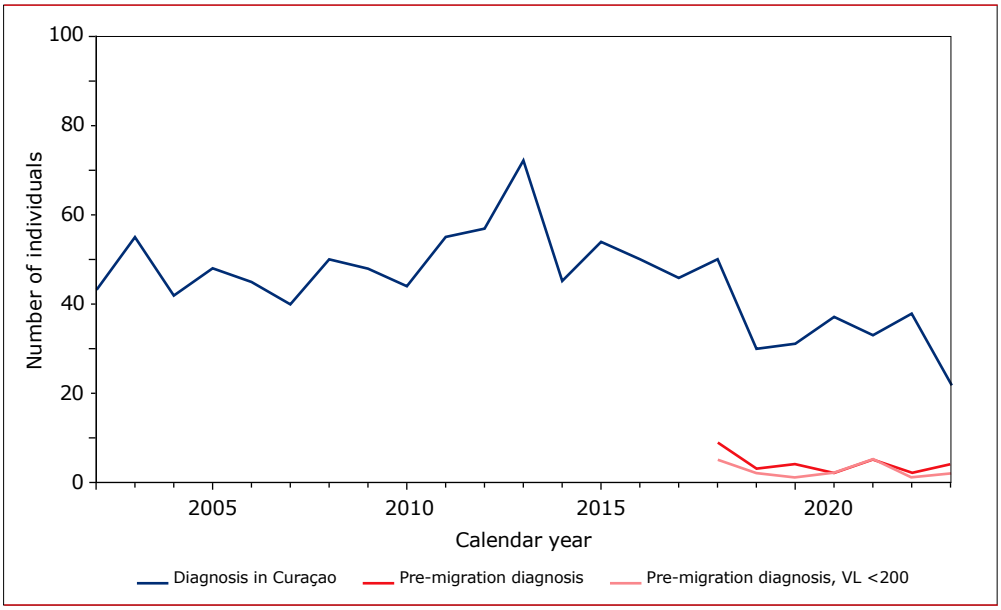
Table 12.1: Annual number of HIV-1 diagnoses in Curaçao among men who have sex with men, other men, women, and trans men and women diagnosed at 15 years of age and over, and children under 15 years.

Year of diagnosis	MSM	Other men	Women	Trans men and women	<15 years of age	Total
≤2001	41	136	109	1	19	306
2002	7	19	17	0	0	43
2003	8	28	19	0	0	55
2004	3	23	16	0	0	42
2005	12	19	17	0	0	48
2006	6	22	17	0	0	45
2007	12	18	10	0	0	40
2008	11	17	20	1	1	50
2009	9	17	21	0	1	48
2010	4	19	21	0	0	44
2011	12	19	24	0	0	55
2012	13	18	26	0	0	57
2013	18	30	22	1	1	72
2014	17	14	14	0	0	45
2015	16	23	13	1	1	54
2016	11	23	15	1	0	50
2017	15	18	13	0	0	46
2018	17	13	19	1	0	50
2019	7	15	8	0	0	30
2020	7	12	12	0	0	31
2021	4	22	10	0	1	37
2022	3	16	14	0	0	33
2023	8	19	11	0	0	38
2024	6	10	6	0	0	22
Total	**267**	**570**	**474**	**6**	**24**	**1,341**

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

Note: *data collection for 2024 may not have been finalised at the time of writing.*

Figure 12.2: 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 93 individuals diagnosed in 2022-2024, the median age at diagnosis was 36 years (interquartile range [IQR] 28-49), with no differences between men and women. Of these 93 individuals:

- 26 (28%) were younger than 30 years of age at the time of diagnosis;
- 26 (28%) were aged between 30 and 39 years;
- 18 (19%) were aged between 40 and 49 years; and
- 23 (25%) were aged 50 years and over.

People in clinical care

In total, 743 (50%) of the 1,475 registered individuals with HIV-1 were known to be in clinical care in Curaçao by the end of 2024. People were considered to be in clinical care if they had visited their treating physician in 2024, or had a CD4 cell count or HIV RNA measurement during that year, and had not moved abroad. Of the 732 individuals who, according to this definition, were not in care by the end of 2024:

- 240 (33%) were known to have died;
- 202 (28%) had moved abroad; and
- 281 (38%) were lost to care

The remaining 9 individuals only entered HIV care in 2024. Of the 281 people lost to care, 58 (21%) had their last visit within a year of entering care, while another 31 (11%) had no follow-up visit after entering care. Of those lost to care:

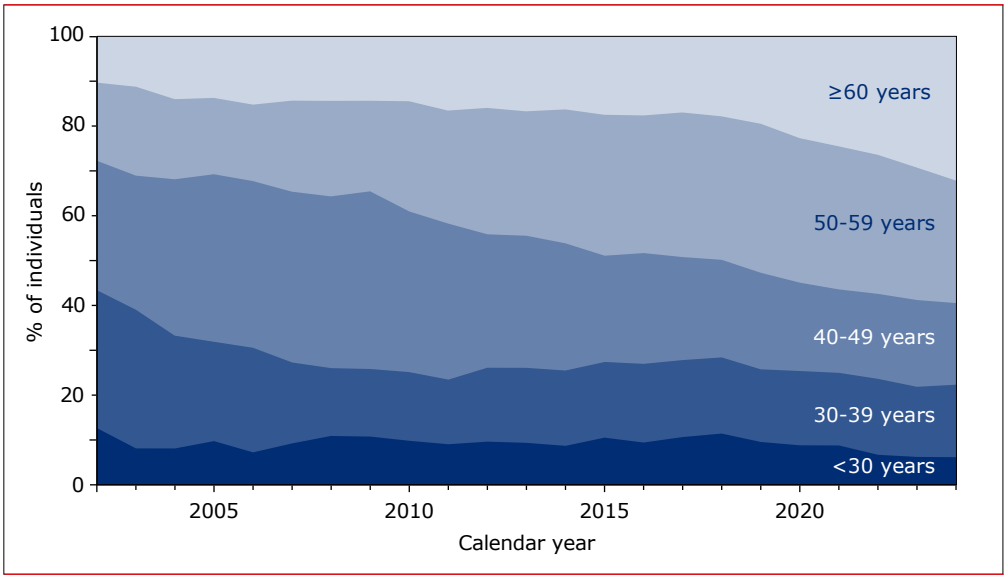
- 165 (59%) originated from the former Netherlands Antilles;
- 47 (17%) were from Haiti;
- 29 (10%) were from the Dominican Republic; and
- 40 (14%) were from other countries.

The 743 people in clinical care in 2024 included 10 individuals who did not have a clinical visit, CD4 cell count or HIV RNA measurement in 2023, but had previously received care for their HIV infection. One of these individuals had not been in care for more than three years.

Ageing population

The median age of the population in care by the end of 2024 was 54 years (IQR 42-62), a figure which has been increasing since 2002 (*Figure 12.3*). 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, 59% all people currently in care are aged 50 years and over, including 58% of men and 62% of women. Almost a third of those in care (32%) are 60 years and over.

Figure 12.3: 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 2024, these proportions were 6% and 59%, respectively, while 32% 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 2024 had been diagnosed with HIV a median of 12.5 years (IQR 6.7-19.0) previously. Therefore, a large group (62%) has lived with HIV for more than 10 years; 22% for more than 20 years (*Table 12.2*). The median time since diagnosis was 12.1 years for MSM, 11.5 years for other men, and 13.3 years for women.

Table 12.2: *Characteristics of the 743 individuals with an HIV-1 infection in clinical care in Curaçao by the end of 2024.*

	MSM (n=156, 21%)		Other men (n=305, 41%)		Women (n=281, 38%)		Total* (n=743)	
	n	%	n	%	n	%	n	%
Transmission								
Sex with men	115	74	–	–	272	97	388	52
Sex with women	1	1	170	56	0	0	171	23
Sex, partner unspecified	39	25	7	2	0	0	46	6
Other/unknown	1	1	128	42	9	3	138	19
Current age (years)								
0–14	0	0	1	0	2	1	3	0
15–24	5	3	7	2	7	2	19	3
25–29	4	3	12	4	8	3	24	3
30–39	32	21	48	16	40	14	120	16
40–49	37	24	48	16	49	17	135	18
50–59	41	26	82	27	80	28	203	27
60–69	28	18	76	25	72	26	176	24
≥70	9	6	31	10	23	8	63	8
Country of origin								
Former Netherlands Antilles	128	82	239	78	188	67	556	75
The Dominican Republic	2	1	10	3	41	15	53	7
Haiti	0	0	28	9	25	9	53	7
Colombia	10	6	8	3	4	1	22	3
Venezuela	7	4	8	3	2	1	17	2
Jamaica	0	0	3	1	11	4	14	2
The Netherlands	6	4	3	1	0	0	9	1
Other	3	2	6	2	10	4	19	3
Years aware of HIV infection								
<1	5	3	9	3	5	2	19	3
1–2	12	8	30	10	23	8	65	9
3–4	6	4	31	10	17	6	54	7
5–9	35	22	59	19	49	17	144	19
10–19	66	42	116	38	112	40	294	40
20–29	22	14	50	16	64	23	136	18
≥30	10	6	10	3	9	3	29	4
Unknown	0	0	0	0	2	1	2	0

**includes one trans individual*

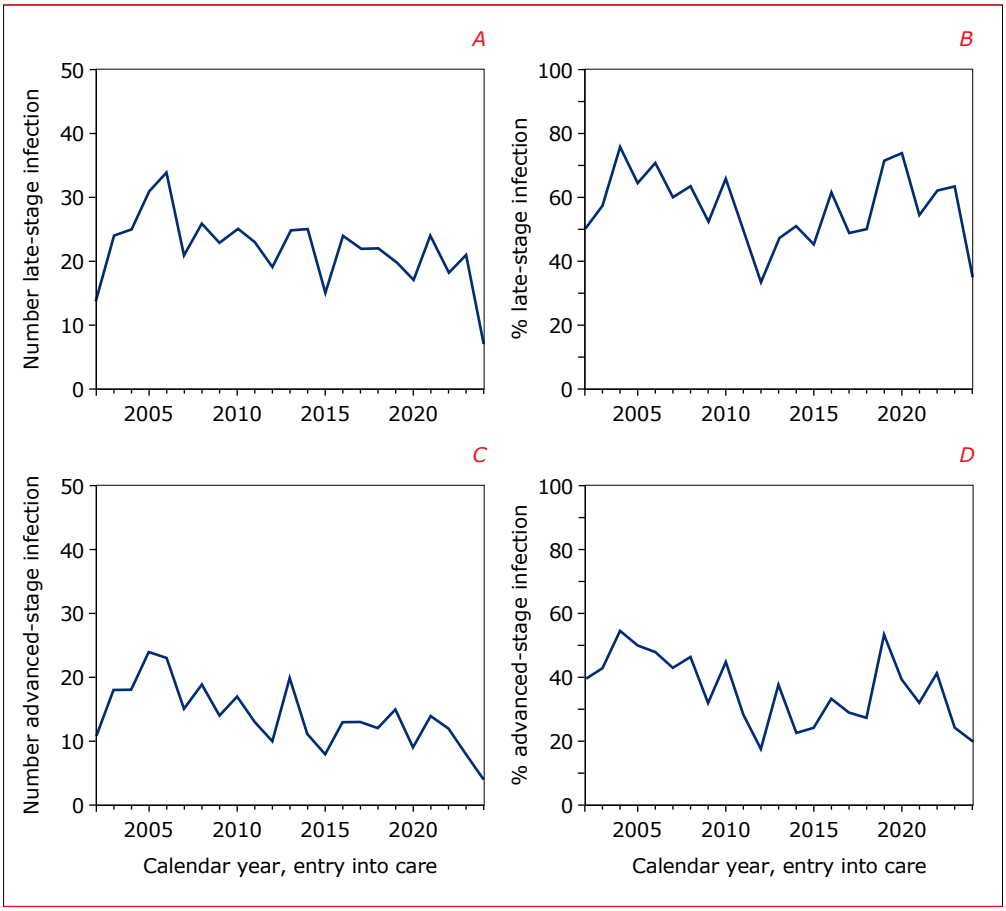
Legend: *MSM = men who have sex men.*

Late presentation

Among the 1,340 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 2002-2021, and remained at a high level of 56% among those entering care in 2022-2024 (*Figures 12.4A* and *12.4B*). There were no significant differences in the proportion of individuals with late presentation in 2022-2024 between MSM (77%), other men (54%), and women (50%).

Advanced HIV infection (i.e. with a CD4 cell count below 200 cells/mm^3 or AIDS) was found in 36% of individuals entering care in 2002-2021 and in 29% of those entering care in 2022-2024 (*Figures 12.4C* and *12.4D*). In total, 4 (4%) of the individuals who entered care in 2022-2024 presented with an AIDS-defining disease.

Figure 12.4: *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 2022–2024, 46 (56%) individuals presented with late HIV disease while 24 (29%) 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 2022–2024, the stage of infection was unknown for 14 (15%) individuals.*



Antiretroviral therapy (ART)

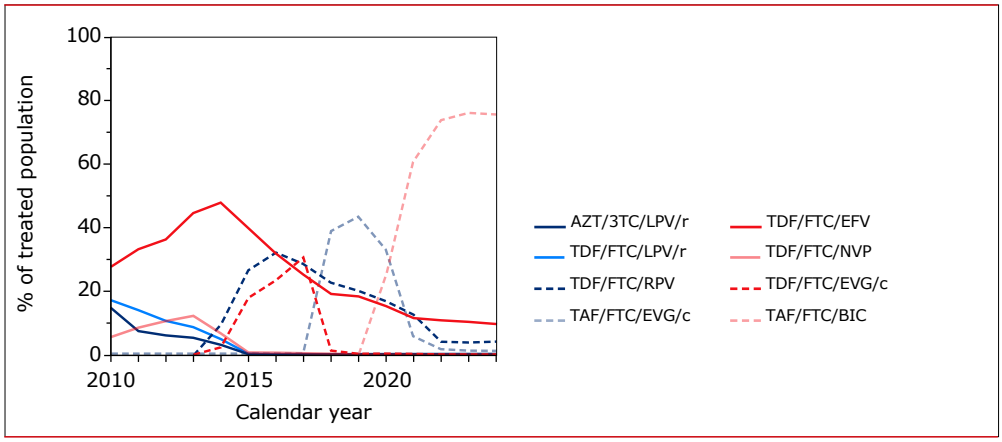
In total, 1,367 (93%) of the 1,475 registered individuals with HIV-1 had started antiretroviral therapy by the end of 2024. Of the 108 people who had not started therapy by that time, two managed to achieve HIV RNA levels below the lower limit of quantification without therapy, while 93 people were no longer in care, including 35 who had died. The other 13 individuals started therapy in 2025, or their ART may not have been recorded yet.

Over time there have been clear shifts in the ART regimens prescribed in Curaçao (*Figure 12.5*). Of the 736 people who were still in care and had started ART by the end of 2024:

- 559 (76%) were being treated with a combination of tenofovir alafenamide, emtricitabine, and bictegravir;
- 72 (10%) with tenofovir disoproxil, emtricitabine, and efavirenz; and
- 32 (4%) with tenofovir disoproxil, emtricitabine, and rilpivirine.

Among the 736 people, 19 (3%) had (temporarily) interrupted ART by the end of 2024. Of the remaining 717 individuals on ART, the majority (713, 99%) used a once-daily regimen, with 675 (94%) being treated with a fixed-dose, single tablet regimen.

Figure 12.5: *Percentage of individuals treated with antiretroviral therapy (ART) by specific regimens over calendar time. At the end of 2024, 76% were receiving TAF/FTC/BIC, 10% TDF/FTC/EFV, and 4% TDF/FTC/RPV.*

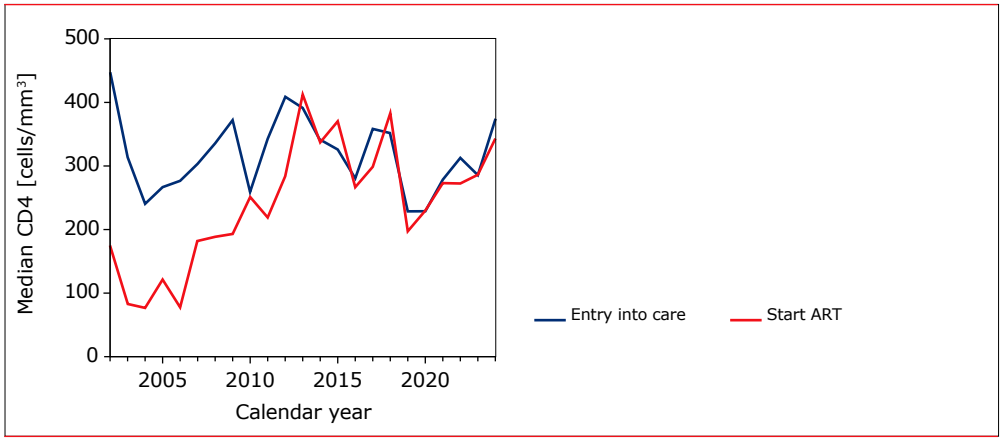


Legend: *AZT = zidovudine; 3TC = lamivudine; LPV/r = ritonavir-boosted lopinavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; RPV = rilpivirine; EFV = efavirenz; NVP = nevirapine; EVG/c = cobicistat-boosted elvitegravir; BIC = bictegravir.*

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 12.6*). 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 2022-2024, 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:

- 30% had a measurement below 200 CD4 cells/mm^3;
- 29% had a measurement between 200 and 349 cells/mm^3;
- 16% had a measurement between 350 and 499 cells/mm^3; and
- 25% had CD4 cell counts of 500 cells/mm^3 or higher.

Figure 12.6: *Changes over calendar time in median CD4 cell counts at entry into care and at the start of antiretroviral therapy (ART). In 2022-2024, CD4 cell counts at entry into care were 315 cells/mm^3 (interquartile range [IQR] 163-517) and were similar, 308 cells/mm^3 (IQR 155-517), at the start of therapy.*

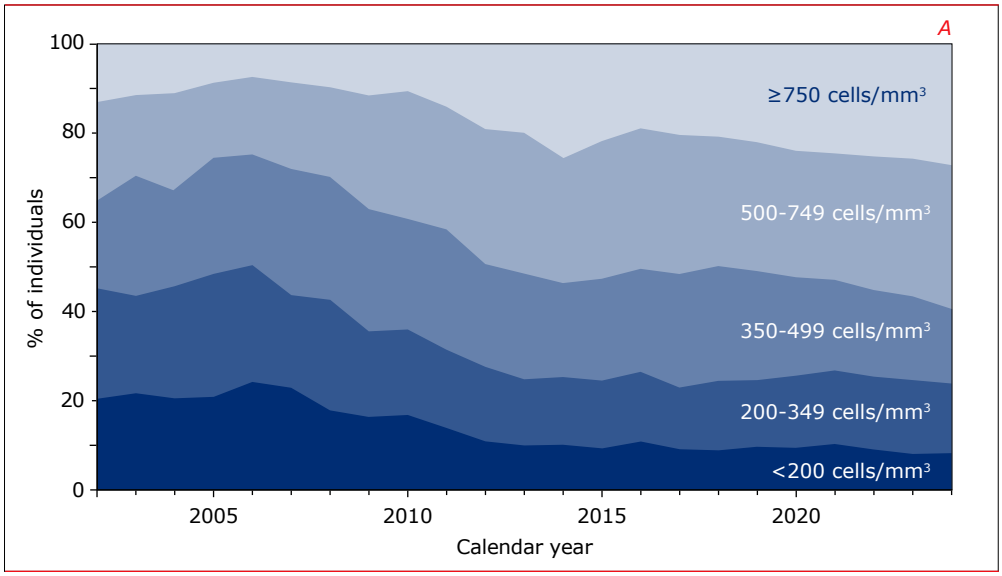


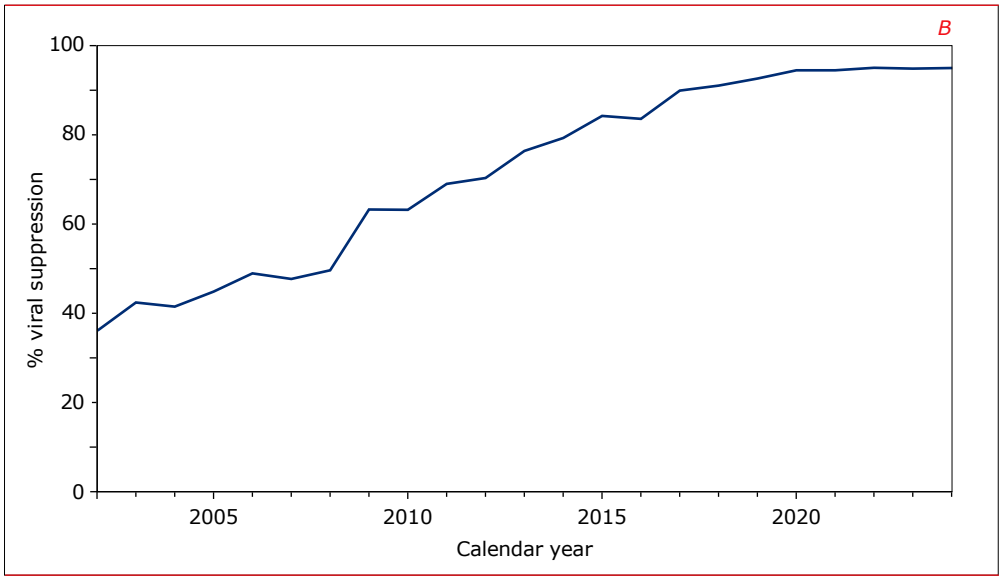
Legend: *ART = antiretroviral therapy.*

Therapy outcome

In the total population still in care by the end of 2024, the median current CD4 cell count was 487 cells/mm^3 (IQR 295-687). CD4 cell counts were highest in MSM (549 cells/mm^3; IQR 320-745) followed by women (527 cells/mm^3; IQR 292-710) and other men (434 cells/mm^3; IQR 285-615). The proportion of individuals with a most recent CD4 cell count below 350 cells/mm^3 decreased from 45% in 2002 to 24% in 2024 (*Figure 12.7A*). 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 12.7B*).

Figure 12.7: 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.





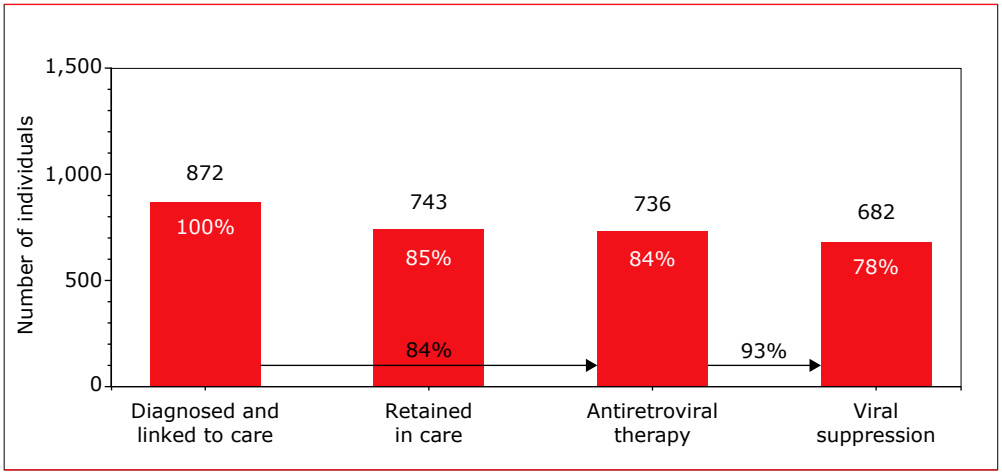
Continuum of HIV care

In total, 872 individuals had been diagnosed and linked to care, registered by SHM, had received HIV care in 2014 or later, and were not recorded in the SHM database as having died or moved abroad (*Figure 12.8*). Altogether:

- 743 people (or 85% 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 2024;
- 736 (or 84% of those diagnosed and linked to care) of whom had started ART;
- 717 (97% of those who started therapy) of whom had an HIV RNA measurement available in 2024; and
- 682 (95%, or 93% of those treated) of those had a most recent HIV RNA level below 200 copies/ml.

Overall, 78% of the 872 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 84-93: 84% of all people diagnosed receive antiretroviral therapy, and 93% of people receiving ART have a suppressed viral load[2].

Figure 12.8: *Continuum of HIV care for the population with HIV-1 in Curaçao diagnosed and linked to care by the end of 2024. 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 736 individuals who had started ART, 54 (7%) did not have a suppressed viral load. On closer inspection, 19 (35%) of these individuals were found to have no documented HIV RNA measurement in 2024. The remaining 35 (65%) had a viral load measurement in 2024, but with HIV RNA levels exceeding 200 copies/ml. Of these 35 individuals, four 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 2024, of whom:

- 152 (44%) were last seen for care before the end of 2014;
- 88 (31%) between 2014 and 2020;
- 21 (7%) in 2021;
- 8 (3%) in 2022; and
- 12 (4%) in 2023.

The 152 individuals who were lost to care before the end of 2014 were excluded from the number of people diagnosed and linked to care. It is unlikely that these 152 individuals are still living in Curaçao without requiring care or ART. In total, 43 (33%) of the 129 individuals lost to care after 2014 were born outside the former Netherlands Antilles, including 12 in Haiti and 9 in the Dominican Republic. For those still in care by the end of 2024, the percentage of people born outside the former Netherlands Antilles falls to 25%. 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.

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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13. HIV in Aruba

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Introduction

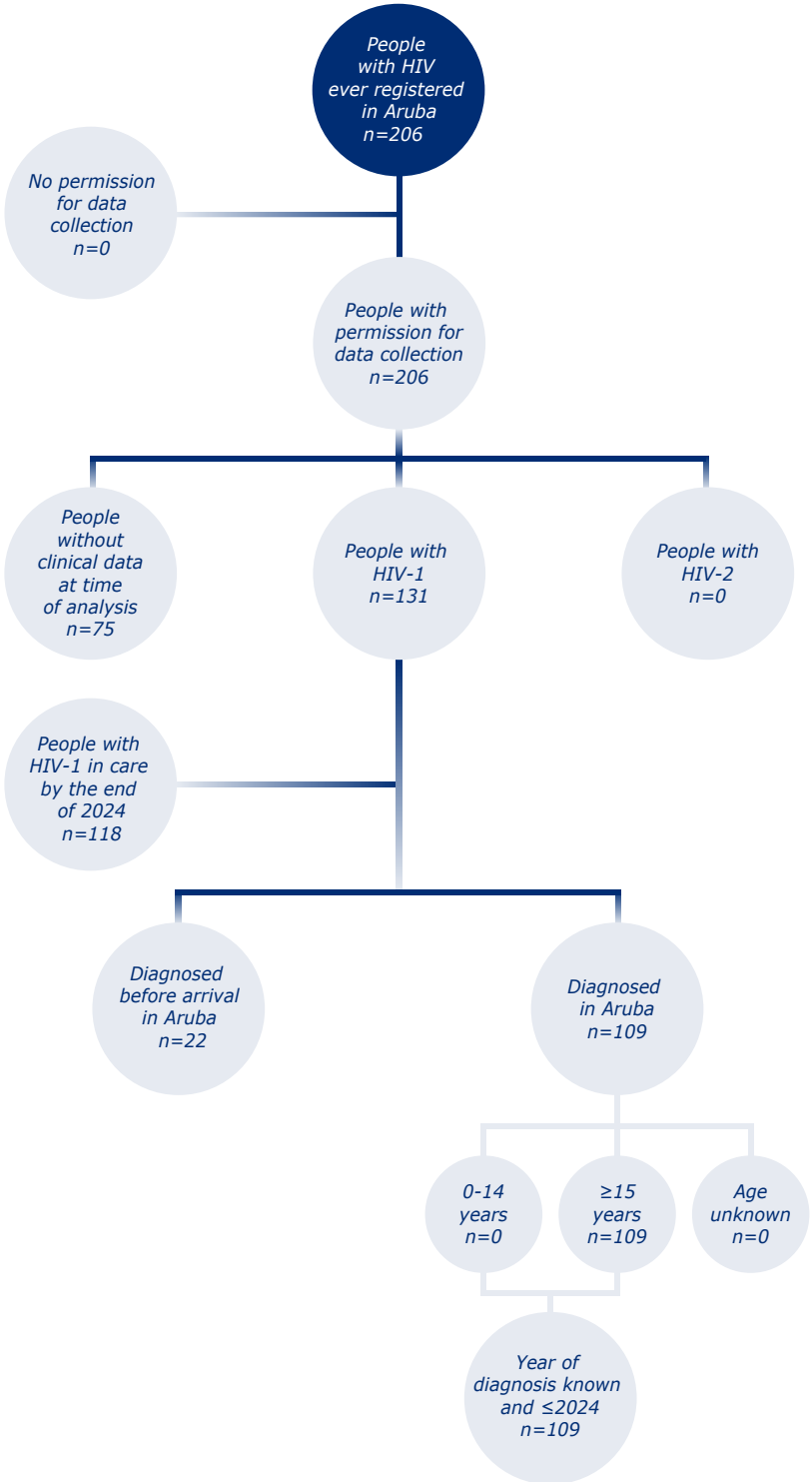
Since 2024, stichting hiv monitoring (SHM) has assisted in collecting demographic and clinical data on individuals with HIV receiving care at the Horacio Oduber Hospital in Oranjestad, Aruba. This hospital is the only institution in Aruba that can provide care and treatment to people with HIV. As inclusion of people with HIV in SHM is still ongoing, the first analyses of people in care in Aruba presented in this chapter may not yet be representative of the entire population of people with HIV.

In total, 206 individuals with HIV recorded by SHM have been registered in Aruba; all of them gave permission for further data collection. Of these individuals, 75 were only recently included in the database and, at the time of analysis, no clinical data had been collected (*Figure 13.1*). The other 131 individuals with HIV were all diagnosed with an HIV-1 infection.

Population with HIV in Aruba

Of the 131 individuals in Aruba with HIV-1, 22 (17%) had a documented HIV diagnosis prior to arrival in Aruba (*Figure 13.1*). The remaining 109 individuals were newly diagnosed while living in Aruba, or their date of arrival in Aruba has not yet been recorded in the SHM database.

Figure 13.1: *Overview of the population with HIV registered in Aruba.*



Individuals diagnosed before arriving in Aruba

The 22 individuals with a documented HIV-1 diagnosis prior to arrival in Aruba included 10 people who were registered with an HIV treatment centre in the Netherlands or Curaçao prior to moving to Aruba (*Figure 13.1*). All 10 individuals originated from the former Netherlands Antilles, including 8 from Aruba. The other 12 individuals with pre-migration diagnosis were born in other countries, including 9 in Colombia. Seven of the 12 people arriving in Aruba in 2022-2024 with a documented HIV-1 diagnosis prior to arrival already had a suppressed viral load below 200 copies/ml.

Individuals newly diagnosed in Aruba

Altogether, 109 individuals were newly diagnosed while living in Aruba (*Figure 13.1*). Of these 109 individuals, 50 (46%) were born in Aruba, 19 (17%) originated from Venezuela, 18 (17%) from Colombia, and 22 (20%) from other countries.

The 109 individuals comprised:

- 77 (71%) men who have sex with men (MSM);
- 17 (16%) other men,
  - 12 of whom reported sex with women as the most likely mode of transmission
  - 5 reported other or unknown modes of transmission;
- 13 (12%) women, who all reported sex with men as the most likely mode of transmission;
- 2 (2%) transgender women.

All 109 individuals were 15 years of age or older at the time of diagnosis. Among the 41 (38%) individuals diagnosed in 2022-2024, the median age at diagnosis was 36 years (interquartile range [IQR] 30-51). Of these 41 individuals:

- 10 (24%) were younger than 30 years of age at the time of diagnosis;
- 14 (34%) were aged between 30 and 39 years;
- 6 (15%) were aged between 40 and 49 years; and
- 11 (27%) were aged 50 years and over.

People in clinical care

In total, 118 (90%) of the 131 registered individuals with HIV-1 were known to be in clinical care in Aruba by the end of 2024. People were considered to be in clinical care if they had visited their treating physician in 2024, or had a CD4 cell count or HIV RNA measurement during that year, and were still living in Aruba. Of the 13 individuals who, according to this definition, were not in care by the end of 2024, 3 were known to have died, 3 had moved abroad, and 7 were lost to care. Of note, five of the individuals lost care had first been in care in the Netherlands or Curaçao but no data had been collected yet after arrival in Aruba.

Age and duration of infection

The median age of the population in care by the end of 2024 was 44 years (IQR 35-57) (*Figure 13.2*). In total, 42% all people were 50 years or older. People in care by the end of 2024 had been diagnosed with HIV a median of 5.1 years (IQR 1.8-8.5) previously; 18% had lived with HIV for more than 10 years (*Table 13.1*). Most likely, these figures for age and duration of infection underestimate the true distribution in the population in care because 59 (50%) of the 118 people for whom data were collected, were diagnosed in 2020 or later.

Figure 13.2: *Age distribution of the population with HIV-1 in clinical care in Aruba over calendar time. In 2024, 13% of the people in care were younger than 30 years of age, whereas 42% were 50 years 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.*

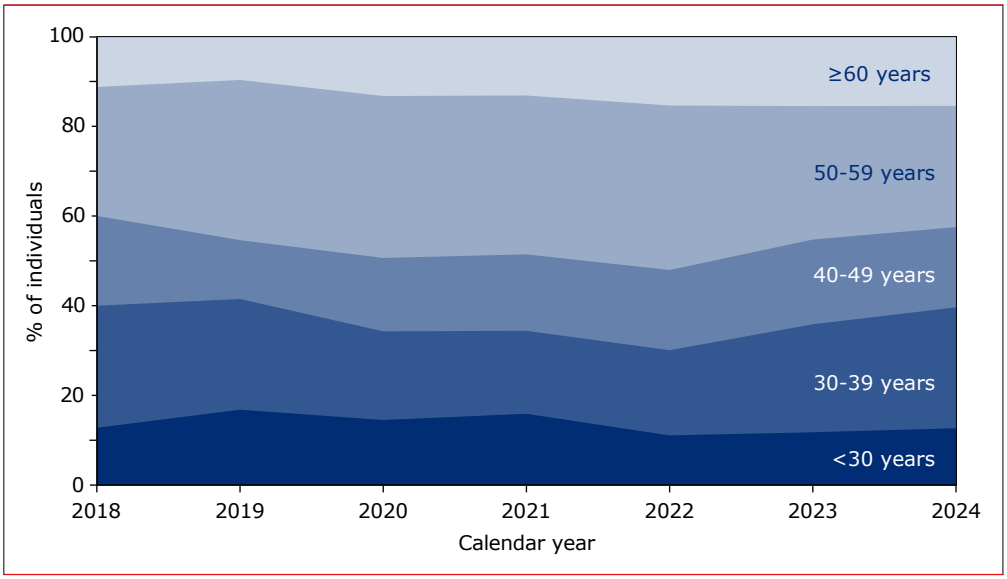


Table 13.1: *Characteristics of the 118 individuals with an HIV-1 infection in clinical care in Aruba by the end of 2024.*

	MSM (n= 85, 72%)		Other men (n=20, 17%)		Women (n=11, 9%)		Total * (n=118)	
	n	%	n	%	n	%	n	%
Transmission								
Sex with men	81	95	–	–	11	100	92	78
Sex with women	1	1	13	65	0	0	14	12
Sex, partner unspecified	3	4	3	15	0	0	7	6
Other/unknown	0	0	4	20	0	0	5	4
Current age (years)								
0–14	0	0	0	0	0	0	0	0
15–24	3	4	0	0	0	0	3	3
25–29	9	11	2	10	1	9	12	10
30–39	25	29	3	15	2	18	32	27
40–49	15	18	3	15	3	27	21	18
50–59	24	28	5	25	3	27	32	27
60–69	9	11	5	25	0	0	14	12
≥70	0	0	2	10	2	18	4	3
Country of origin								
Aruba	41	48	6	30	2	18	50	42
Colombia	17	20	5	25	2	18	24	20
Venezuela	15	18	4	20	1	9	21	18
Other	12	14	5	25	6	54	23	19
Years aware of HIV infection								
<1	3	4	1	5	1	9	5	4
1–2	23	27	9	45	5	45	38	32
3–4	13	15	3	15	0	0	16	14
5–9	33	39	2	10	3	27	38	32
10–19	11	13	4	20	0	0	16	14
≥20	2	2	1	5	2	18	5	4

**includes two trans individuals*

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

Late diagnosis

Among the 41 individuals diagnosed in 2022-2024, 15 (47%) had a late-stage HIV infection at the time of diagnosis. This refers to individuals who were diagnosed 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]. For 9 individuals, the stage of infection could not be determined. Advanced HIV infection (i.e. with a CD4 cell count below 200 cells/mm^3 or AIDS) was found in 13 (41%) of individuals diagnosed in 2022-2024. In total, 6 (15%) of the individuals who were diagnosed in 2022-2024 presented with an AIDS-defining disease.

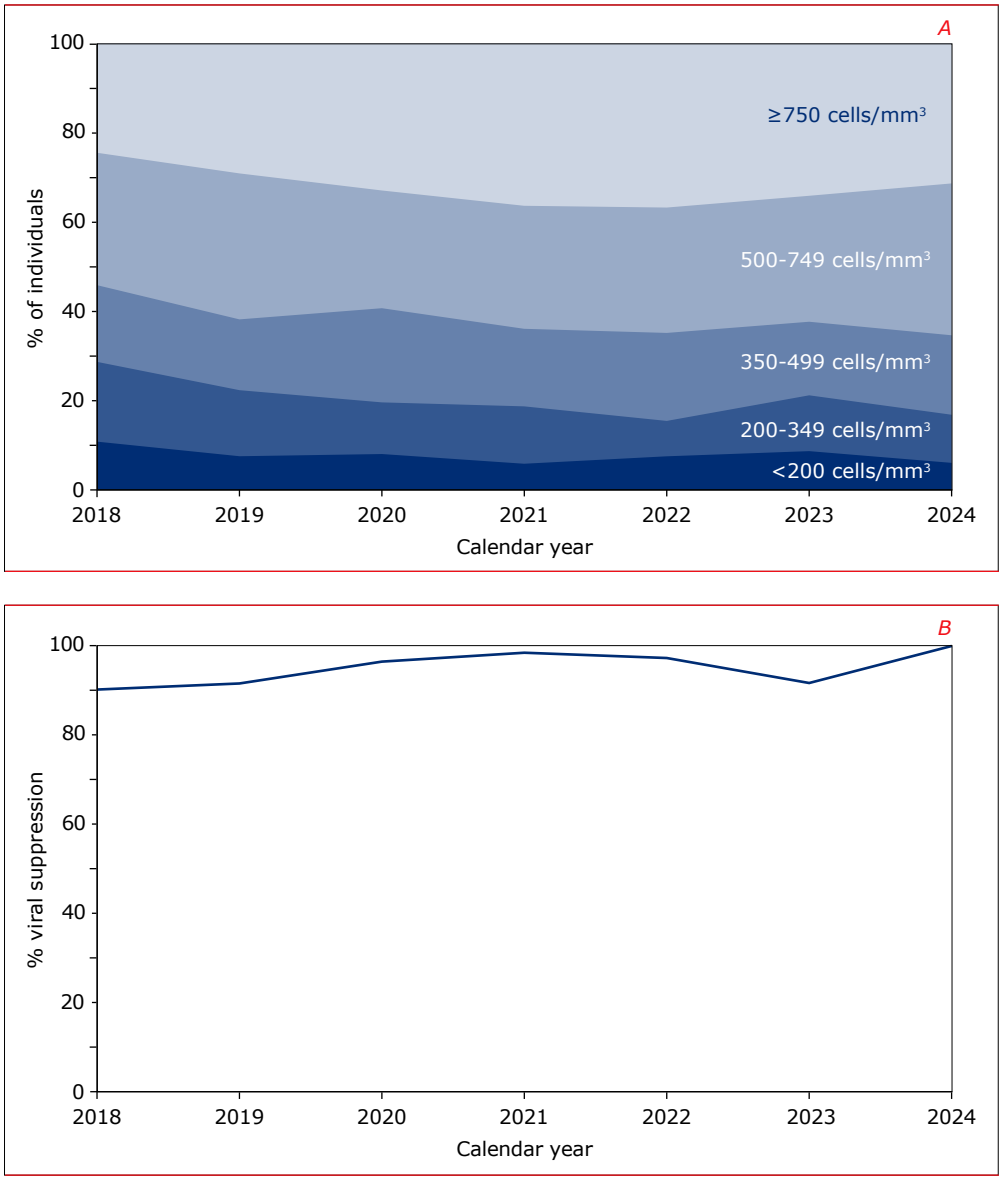
Antiretroviral therapy (ART)

At least 126 (96%) of the 131 registered individuals with HIV-1 had started antiretroviral therapy by the end of 2024. For the other 5 individuals no ART had been recorded yet at the time of analysis. Of the 114 people who were still in care and had started ART by the end of 2024, 99 (87%) were being treated with a combination of tenofovir alafenamide, emtricitabine, and bictegravir, 9 (8%) with tenofovir disoproxil, emtricitabine, and efavirenz, and 6 with other combinations. All 114 individuals used a once-daily regimen.

Therapy outcome

In the total population still in care by the end of 2024, the median current CD4 cell count was 616 cells/mm^3 (IQR 441-844). The proportion of individuals with a most recent CD4 cell count below 350 cells/mm^3 decreased from 29% in 2018 to 17% in 2024 (*Figure 13.3A*). During the same time, among individuals with a viral load measurement, the proportion with HIV RNA levels lower than 200 copies/ml was above 90% (*Figure 13.3B*).

Figure 13.3: 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.



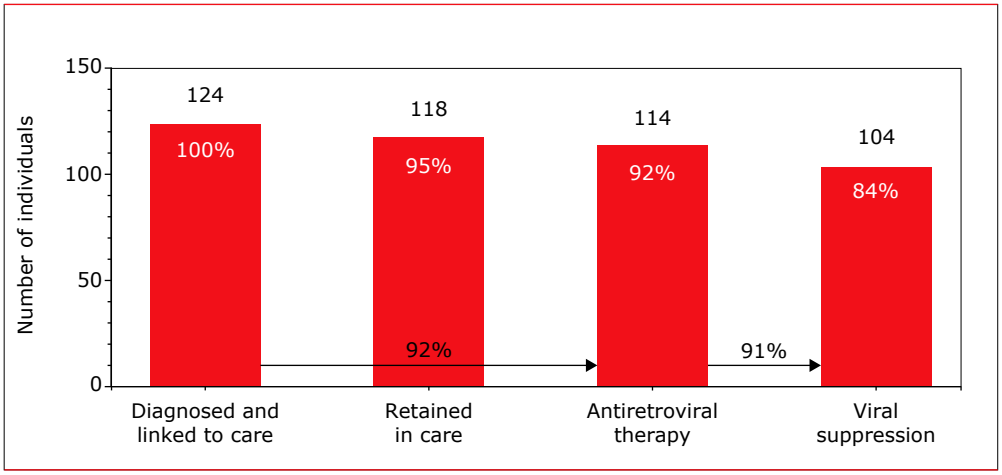
Continuum of HIV care

In total, 124 individuals had been diagnosed and linked to care, registered by SHM, had received HIV care in 2014 or later, and were not recorded in the SHM database as having died or moved abroad (*Figure 13.4*). Altogether:

- 118 people (or 95% 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 2024;
- 114 (or 92% of those diagnosed and linked to care) of whom had started ART;
- 104 (91% of those who started therapy) of whom had an HIV RNA measurement available in 2024; and
- 104 (100%, or 91% of those treated) of those had a most recent HIV RNA level below 200 copies/ml.

Overall, 84% of the 124 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 Aruba stands at 92-91: 92% of all people diagnosed receive antiretroviral therapy, and 91% of people receiving ART have a suppressed viral load[2].

Figure 13.4: *Continuum of HIV care for the population with HIV-1 in Aruba diagnosed and linked to care by the end of 2024. 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 could 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.

Conclusion

This first analysis of people in care in Aruba, using data collected in SHM, shows that Aruba appears to be on the way to reach two of the three UNAIDS 95-95-95 targets. However, data presented here may not be fully representative of the entire population with HIV in care. Inclusion of people with HIV in SHM is still ongoing and more in depth analyses will only be possible in the coming years.

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