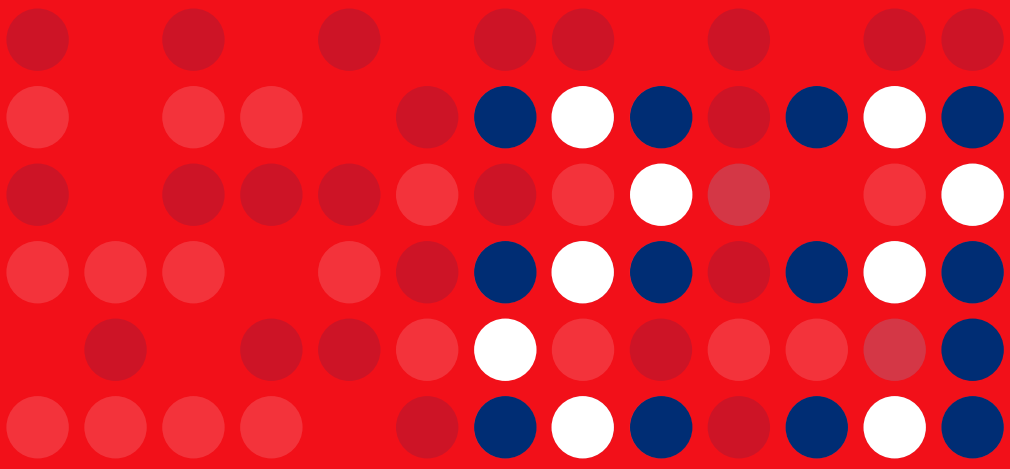
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2023



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

Monitoring Report 2023

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

Interactive PDF user guide

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

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

Reference numbers

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Monitoring the HIV population in the Netherlands is a collaborative effort between stichting hiv monitoring (SHM) and 24 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.

In 2023 the following health institutes were recognized as centres for adult HIV care (in alphabetical order of city):

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

In 2023 the following health institutes were recognized as centres for paediatric HIV care:

A	Emma Kinderziekenhuis (EKZ), Amsterdam UMC, locatie AMC	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, Casper Rokx, Eline Op de Coul

Key findings

2022 at a glance

By the end of 2022, there were 24,400 people with HIV in the Netherlands, including an estimated 1,390 with an undiagnosed HIV infection. Altogether, 86% of this total, and 92% of those diagnosed and ever linked to care, had a suppressed viral load.

Of the 393 people with a new HIV diagnosis, 213 (54%) were MSM, 96 (24%) were other men, 70 (18%) were women, and 14 (4%) were trans men and women.

Adjusted for delay in reporting people with HIV to SHM, there were 461 new HIV diagnoses: 250 MSM, 112 other men, 83 women, and 16 trans men and women.

In total, 31% of all people newly diagnosed with HIV were aged 50 years or older at the time of diagnosis.

Of the 21,987 people with HIV-1 in care by the end of 2022, 56% were 50 years or older and 26% were 60 years or older. In total, 68% of people who are still in care have lived with HIV for more than 10 years.

Trends

2010–2022

The adjusted number of newly diagnosed HIV infections fell by 61% from 1,174 to 461, while among men who have sex with men (MSM) this dropped by 67%, from 768 to 250.

The estimated annual number of newly acquired HIV infections decreased by 85%, from 930 to 140. For MSM this fell by 88%, from 700 to 80.

2002–2022
The proportion of MSM under the age of 30 at the time of diagnosis increased from 15% to 31%. For those aged 50 or older in this group, this figure rose from 12% to 30%.

2020–2022
Of all people newly diagnosed in 2020-2022, 23% were diagnosed within 12 months of HIV infection; in MSM, this proportion was 32%.

In focus: PrEP
In 2022, 13% of MSM and trans men and women with a new HIV diagnosis reported prior use of PrEP, while 47% had not used PrEP. Information on prior use of PrEP was not available for the remaining 41%.

In focus: late-stage HIV 2020–2022
In 2020-2022, 575 (48%) individuals have been diagnosed with late-stage HIV infection. This figure comprises 261 MSM, 186 other men, 120 women, and 8 trans men and women, which is 38%, 69%, 57%, and 22%, respectively, of the total number diagnosed in each group.

In the under-30 years of age category, 30% of MSM, 38% of other men, and 38% of women were diagnosed with late-stage HIV infection. The proportion of individuals with late-stage HIV increased with age: it was found in 55% of MSM, 85% of other men and 67% of women diagnosed at 60 years of age or older.

Introduction

By May 2023, stichting hiv monitoring (SHM) had registered 33,940 individuals with HIV. The vast majority of these (33,022, or 97.3%) agreed to the collection of further clinical data once registered, whereas 918 (2.7%) declined to take part. Among those whose clinical data is collected, most (31,844) are registered with one of the HIV treatment centres in the Netherlands (*Figure 1.1*) while 1,418 are registered with the Curaçao Medical Center in Willemstad, Curaçao (see *Chapter 9*). A comparatively small group of 240 individuals are registered in both countries.

Of those registered in the Netherlands, the vast majority were diagnosed with HIV-1 (30,598, or 96%). Only 101 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, which accounts for the absence of serological information for most of the remaining 1,083.

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 2022. This is followed by a brief overview of trans people with HIV-1. The chapter concludes with an outline of the population with an HIV-2 infection.

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

Infection	The moment an individual acquires HIV. The time of infection is often unknown.
Diagnosis	The moment an HIV infection is identified in an individual. 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.

***Box 1.2:** MSM, other men, women, and trans men and women*

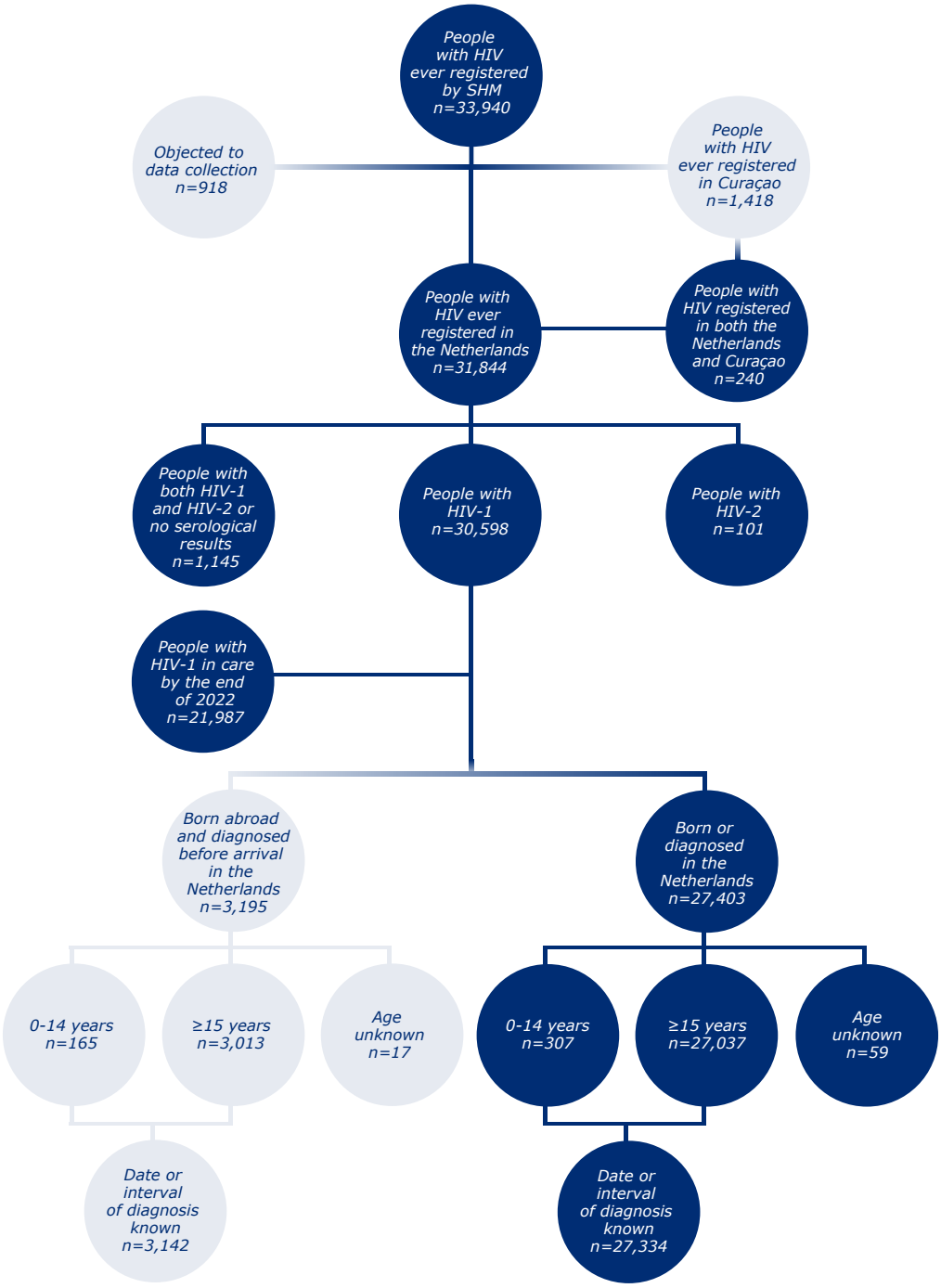
In this year's Monitoring Report, we adopt a classification of MSM, other men, women, and trans men and women that is slightly different from the definitions used in previous reports. Trans men and trans women are now considered as a separate population that includes everyone who identifies with a gender different from the one assigned at birth. Among cis individuals, MSM, or men who have sex with men, include all men who reported sex with men as the most likely route of transmission or who reported having male sex partners around the presumed time of HIV acquisition. All other cis men and all cis women are classified as 'other men' and 'women', respectively.

HIV-1

Individuals with HIV-1

Of the 30,598 individuals in the Netherlands who were ever diagnosed with HIV-1, 3,195 (10%) were born abroad and had a documented HIV diagnosis prior to arrival in the Netherlands (*Figure 1.1*). These 3,195 individuals have been excluded from the analyses on newly diagnosed individuals later in this section. The remaining 27,403 individuals were newly diagnosed while living in the Netherlands, or their date of arrival in the country has not yet been recorded in the SHM database.

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



Individuals diagnosed before arriving in the Netherlands

Of the 3,195 individuals who were born abroad and had a documented HIV-1 diagnosis before arriving in the Netherlands, 1,028 (32%) arrived in the Netherlands in 2020 or later (*Figure 1.2A*). So far, SHM has registered 454 migrants who arrived in 2022, which is an increase of 52% compared with the average annual number of migrants in 2018-2021. 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.

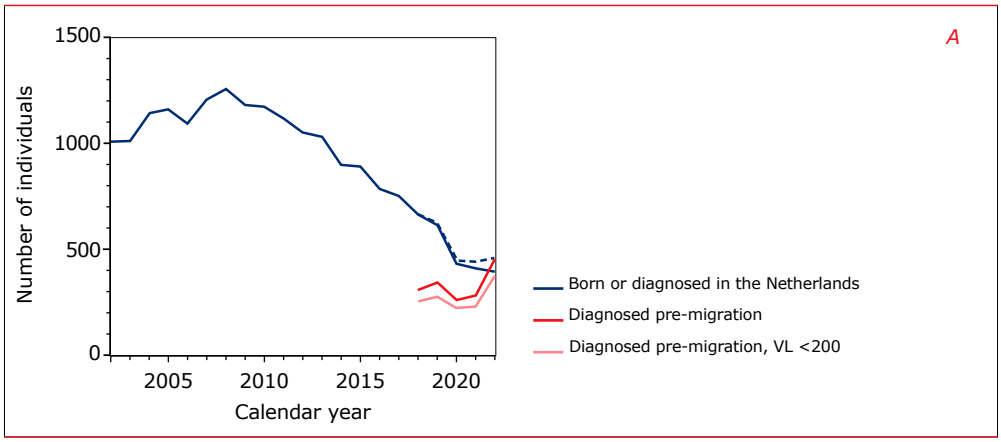
Of the 1,028 migrants who arrived in 2020 or later with a documented pre-arrival HIV diagnosis, 561 (55%) were men who have sex with men (MSM), 207 (20%) were other men, 231 (22%) were women, and 29 (3%) were trans people. The median age at the time of arrival was 36 years (interquartile range [IQR] 30-42); 85 (8%) were below 25 years of age, including nine children under the age of 15, while 98 (10%) were 50 years of age or older. In terms of geographic origins, migrants arrived from:

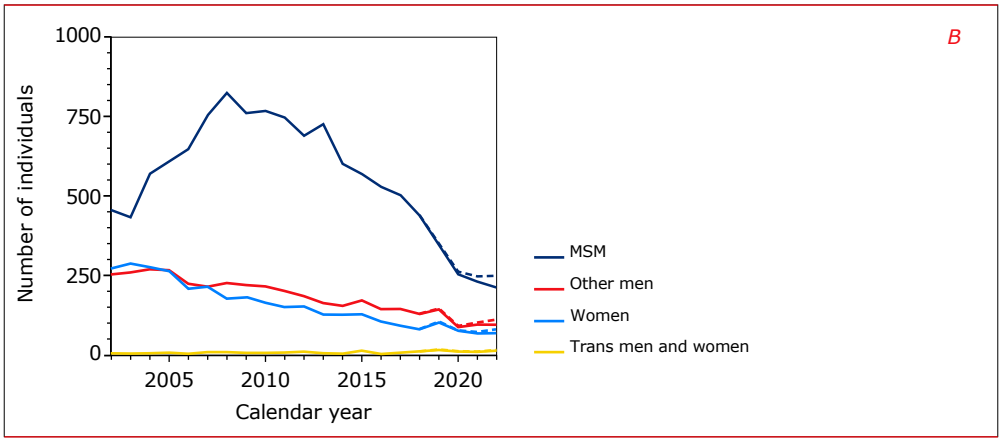
- eastern Europe (309, 30%)
- South America (195, 19%);
- sub-Saharan Africa (127, 12%);
- central Europe (88, 9%);
- western Europe (84, 8%);
- Caribbean (78, 8%);
- North Africa and Middle East (46, 4%);
- South and southeast Asia (43, 4%); and
- other regions (58, 6%).

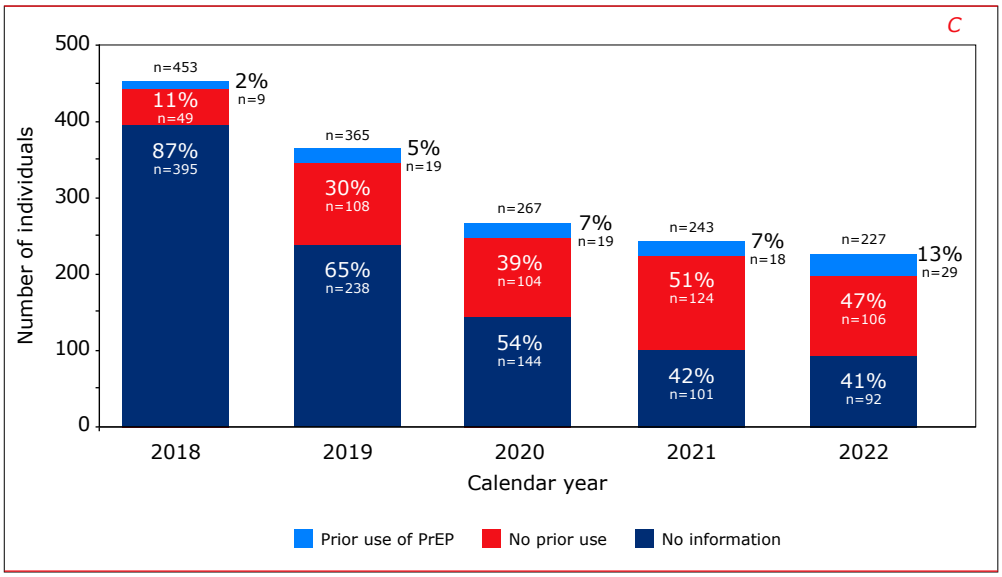
The most commonly reported countries of origin (from where at least 25 individuals with HIV arrived in the Netherlands) were Ukraine (204, 20%), Brazil (64, 6%), Russian Federation (63, 6%), Poland (48, 5%), Curaçao (42, 4%), and Colombia (40, 4%). Individuals from Ukraine and the Russian Federation accounted for 187 (41%) and 33 (7%), respectively, of the 454 migrants arriving in 2022.

The majority (958, or 94%) of the 1,028 migrants had already started antiretroviral therapy (ART) before arriving in the Netherlands. By the time they entered HIV care in the Netherlands, their median CD4 counts were 640 (IQR 440-850) cells/mm^3, while 871 individuals had HIV RNA levels below 1,000 copies/ml (87% of the 1,004 who had an available viral load measurement), including 852 individuals with RNA levels below 200 copies/ml (85% of those with a viral load measurement).

Figure 1.2: *(A) Annual number of individuals newly diagnosed with HIV-1 in the Netherlands (by year of diagnosis) or with documented diagnosis abroad before moving to the Netherlands (by year of arrival), (B) annual number of individuals newly diagnosed with HIV-1 in the Netherlands and aged 15 years or older at the time of diagnosis, according to key population, and (C) annual number of new diagnoses in men who have sex with men (MSM) and trans men and women stratified by whether or not prior use of PrEP was reported. In 2022, MSM accounted for 54% of the annual number of new diagnoses, other men for 24%, women for 18%, and trans men and women for 4%. Dashed lines indicate the number of diagnoses after adjusting for a delay in notification to SHM. VL <200: individuals with documented diagnosis abroad before moving to the Netherlands who already had a suppressed viral load below 200 copies/ml by the time they entered HIV care in the Netherlands.*







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

Individuals newly diagnosed in the Netherlands

Of the 27,403 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, 307 (1%) were diagnosed as children under 15 years of age: they are described in more detail in *Chapter 5*. Among the 27,334 individuals for whom the date or period of diagnosis was known, 27,035 (99%) were diagnosed at 15 years of age or older. Of these 27,035 individuals, 16,113 (60%) were men who have sex with men, 5,766 (21%) were other men, 4,920 (18%) were women, and 236 (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 with an asterisk are adjusted to reflect a delay in notification to SHM and due to rounding may not add up to the total number reported in the last column.*

Year of diagnosis	MSM	Other men	Women	Trans men and women	<15 years of age	Total
≤1995	2,137	748	577	14	55	3,531
1996	373	160	99	2	10	644
1997	430	195	143	3	11	782
1998	321	161	130	1	11	624
1999	338	159	154	6	15	672
2000	364	209	209	4	16	802
2001	432	231	247	7	18	935
2002	457	255	274	6	15	1,007
2003	433	261	288	6	21	1,009
2004	570	270	278	7	14	1,139
2005	609	268	264	9	12	1,162
2006	648	225	210	5	7	1,095
2007	752	215	216	11	10	1,204
2008	825	227	179	10	16	1,257
2009	761	221	182	8	10	1,182
2010	768	217	166	8	15	1,174
2011	747	202	152	9	9	1,119
2012	690	186	154	12	10	1,052
2013	727	164	128	7	6	1,032
2014	602	155	128	6	8	899
2015	569	173	130	15	4	891
2016	529	145	106	4	2	786
2017	503	146	94	9	1	753
2018	440	130	82	13	1	666
*2018**	*440*	*130*	*82*	*13*	*1*	*667*
2019	348	144	104	17	1	614
*2019**	*354*	*147*	*106*	*17*	*1*	*625*
2020	255	88	77	12	0	432
*2020**	*264*	*91*	*80*	*12*	*0*	*447*
2021	232	97	69	11	1	410
*2021**	*248*	*104*	*74*	*12*	*1*	*439*
2022	213	96	70	14	0	393
*2022**	*250*	*112*	*83*	*16*	*0*	*461*
2023	40	18	10	0	0	68
Total	**16,113**	**5,766**	**4,920**	**236**	**299**	**27,334**

**Numbers adjusted for a delay in notification*

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

Decreasing number of diagnoses

The annual registered number of new HIV diagnoses has fallen steadily since 2008 (*Table 1.1; Figure 1.2A*). That downward trend continued in 2022 with 393 registered new HIV diagnoses. However, after taking into account a projected backlog[a] in registration of HIV cases, the decreasing trend appears to be levelling off, with an adjusted number of 461 new HIV diagnoses in 2022.

In MSM, the annual number of diagnoses rose to 825 in 2008 and gradually fell to 213 (adjusted 250) in 2022 (*Figure 1.2B*). Among other men and among women, the annual number of new diagnoses has decreased to 96 (adjusted 112) and 70 (adjusted 83), respectively, in 2022. Finally, the number of new diagnoses among trans men and women varied between approximately ten and fifteen in most recent calendar years.

SHM collects data on prior use of PrEP in all individuals newly diagnosed with HIV since 2018 (see for more details *Special Report 1.2*). Among MSM and trans individuals, who are the primary target groups of the national pre-exposure prophylaxis (PrEP) programme, the proportion of people reporting prior use of PrEP, has steadily increased over calendar time (*Figure 1.2C*). In 2022, 29 (13%) of the 227 observed new diagnoses in MSM and trans individuals were in people who reported prior use of PrEP, while 106 (47%) people reported never to have used PrEP. For 92 (41%) individuals, information on prior use of PrEP was not available.

Decreasing number of newly acquired infections

The observed changes over time in the number of HIV diagnoses are, in part, a consequence of changes in the annual number of newly acquired HIV infections. The estimated number of infections decreased from 930 (95% confidence interval [CI] 890-960) in 2010 to 140 (80-240) in 2022 (*Figure 1.3A*), which is a reduction of 85% (73-91). During the same period, the number of newly acquired HIV infections among MSM fell by 88% (78-95), from 700 (670-720) in 2010 to 80 (40-150) in 2022 (*Figure 1.3B*).

In other men, the estimated number of newly acquired infections in 2010 was 120 (95% CI 110-140), which was similar to the estimated number of 100 (90-110) in women. By 2022 this had dropped sharply in both groups, reaching 30 (10-90) in other men and 30 (10-70) in women; respective reductions of 75% (21-91) and 74% (29-91) (*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 2018-2022 were estimated using the European Centre for Disease Prevention and Control (ECDC) HIV Platform Tool[10].

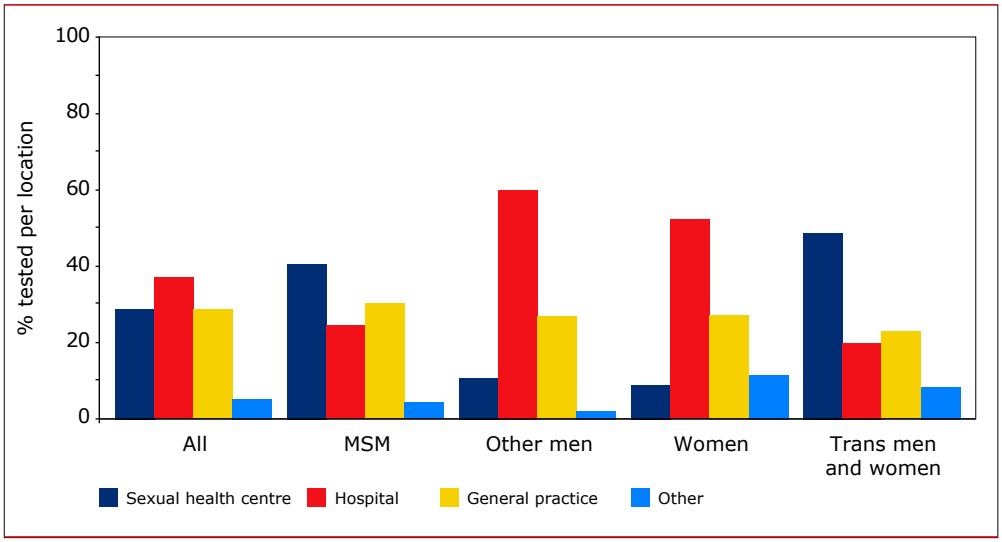
Figure 1.3: *Observed annual number of HIV diagnoses (red) and estimated annual number of newly acquired HIV infections (blue) in: the total population (A), in men who have sex with men (B), in other men (C), in women (D), according to the European Centre for Disease Prevention and Control (ECDC) HIV Platform Tool[10]. The red dashed lines represent the number of diagnoses after adjusting for the delay in notification to SHM, while the pink bands are the uncertainty bounds. The blue dashed lines indicate that estimates in 2020 and later are still uncertain, as these are quite sensitive to the observed number of diagnoses in those years.*

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 1,177 (95%) of the 1,234 people diagnosed in 2020-2022, while 38 (3%) individuals were known to have been diagnosed abroad. Overall, 338 (29%) of these 1,177 individuals received their first HIV-positive test result at a sexual health centre, 436 (37%) at a hospital, 340 (29%) at a general practice, and 63 (5%) at another location (*Figure 1.4*). Among those diagnosed at sexual health centres in 2022, 80% were MSM, 7% were other men, 8% were women, and 5% were trans men and women, which was similar to the proportions directly reported by sexual health centres[1].

Figure 1.4: *Proportion of individuals diagnosed in 2020-2022, stratified by location of testing and key population. Location of testing is known for 1,177 (95%) of 1,234 individuals diagnosed, of whom 677 (57%) MSM, 260 (22%) other men, 205 (17%) women, and 35 (3%) trans men and women.*



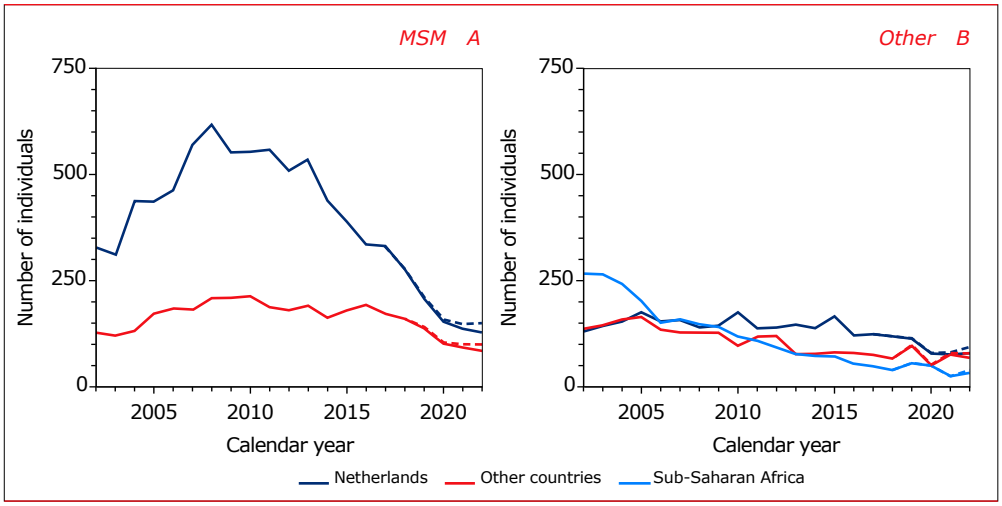
Legend: *MSM = men who have sex with men.*

Geographical region of origin

In total, 11,202 (41%) people diagnosed with HIV-1 at 15 years of age or older were born outside the Netherlands. Of the 16,113 MSM, 72% 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 2020-2022), the proportion of MSM of Dutch origin was 60%, down from 72% before 2020, while the proportion of MSM from central Europe was 10%, up from 3% before 2020.

Among the 10,922 individuals other than MSM, 39% originated from the Netherlands, while 31% originated from sub-Saharan Africa, 9% from South America, 5% from the Caribbean, and 4% from south and southeast Asia (*Figure 1.5B*). Between 2020 and 2022, 44% were of Dutch origin (39% before 2020), and 20% originated from sub-Saharan Africa (32% before 2020), while 8% were from central Europe, up from 3% before 2020.

Figure 1.5: *Annual number of diagnoses by region of origin among: (A) men who have sex with men (MSM), and (B) other people aged 15 years or older at the time of diagnosis. Of the 700 MSM diagnosed in 2020-2022, 420 (60%) originated from the Netherlands, 124 (18%) from other European countries, 60 (9%) from South America, 30 (4%) from south and southeast Asia, and 26 (4%) from the Caribbean. Of the other 534 people diagnosed in 2020-2022, 233 (44%) originated from the Netherlands, 73 (14%) from other European countries, 107 (20%) from sub-Saharan Africa, 45 (8%) from South America, 28 (5%) from the Caribbean, and 19 (4%) from south and southeast Asia.*



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

Overall, 17% of individuals newly diagnosed in 2020-2022 were living in the Amsterdam public health service (PHS) region at the time of diagnosis, and 14% were living in the Rotterdam- Rijnmond PHS region. Of the people of Dutch origin diagnosed in these years, 13% and 12%, respectively, were living in each of the above PHS regions, while these proportions were 23% and 16%, respectively, of the people of foreign origin. Among MSM, 19% were living in Amsterdam at the time of diagnosis and 13% were living in Rotterdam-Rijnmond, while among other individuals, 15% were living in Amsterdam and 15% in Rotterdam-Rijnmond.

Other PHS regions with at least 5% of the new diagnoses since 2020 were Haaglanden (8%, including Den Haag), Hart voor Brabant (6%, including Den Bosch and Tilburg), and Utrecht (5%).

Increasingly older 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 2022, it was 40 years (IQR 30-52). In 2002-2022, 19% of individuals who received an HIV diagnosis were aged 50 years or older; in 2022, 31% were 50 years or older (*Figure 1.6*)[2].

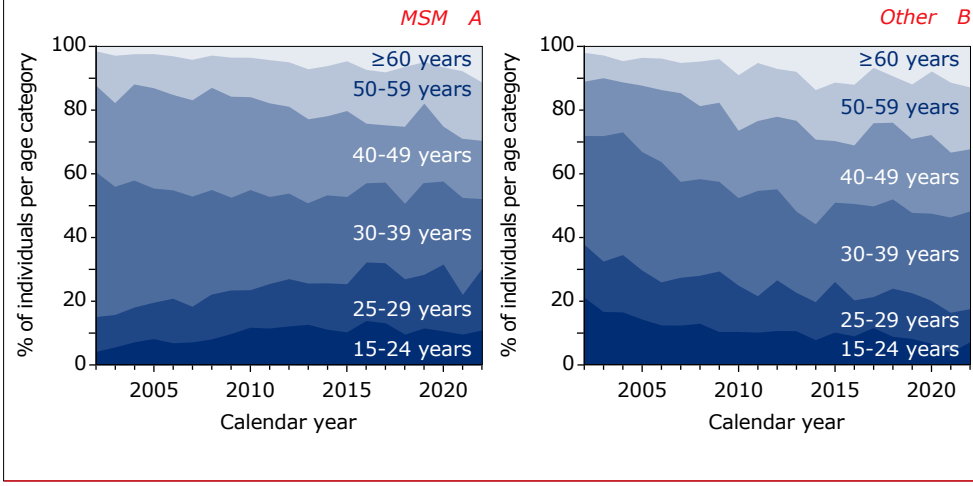
It is worth noting that although the median age at diagnosis in MSM (39 years) did not change between 2002 and 2022, both the proportion diagnosed below 30 years of age and the proportion diagnosed above 50 years of age increased during this period. In 2002, 15% of MSM were younger than 30 years at the time of their diagnosis while 12% were 50 years of age or older; these proportions were 31% and 30%, respectively, in 2022. 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 2022, the annual number of diagnoses among MSM 30 to 50 years of age decreased by 82%, from 464 to 85. During the same period, the number of diagnoses decreased from 181 to 65, or 64%, in MSM younger than 30 years, and from 123 to 63, or 49%, in MSM 50 years of age or older.

There were some age differences between MSM, other men, and women diagnosed in 2020-2022. MSM born in the Netherlands were diagnosed at a median age of 46 years (IQR 32-56), while MSM of foreign origin were diagnosed at a much younger median age of 32 years (27-40). Men other than MSM were 45 years (35-54) of age at the time diagnosis, which was somewhat older than the median age of 39 years (30-51) for women. In 2022, 30% of MSM, 42% of other men, and 26% of women were 50 years or older at the time of diagnosis.

Young people

Between 2002 and 2022, 2,055 (11%) individuals who received an HIV diagnosis at 15 years of age or older were under 25 years of age (*Figure 1.6*). In 2022, 37 young people (all aged 18 or older) were diagnosed with HIV, which amounted to 9% of all people diagnosed with HIV that year. The number of young individuals diagnosed in 2022 was 24 (12%) among MSM, none among other men, and 13 (19%) among women. Of the 37 young people, 16 (43%) were born in the Netherlands, while eight originated from South America, five from central Europe, three from sub-Saharan Africa, two from the Caribbean, and three from elsewhere.

Figure 1.6: Age distribution at the time of diagnosis among: (A) men who have sex with men (MSM), and (B) other men and women with HIV-1. In 2002-2022, the proportion of individuals between 15 and 29 years of age changed from 15% to 31% for MSM, and from 38% to 18% for other individuals. During the same period, the proportion of MSM aged 50 years or older at the time of diagnosis changed from 12% to 30%, while these proportions were 11% and 32% for other individuals.



Legend: MSM = men who have sex with men.

Entry into care

Of the 1,177 individuals diagnosed with HIV in 2020-2022 for whom the diagnosis setting was known, 58% entered HIV care within a week of diagnosis, 83% within two weeks, 96% within four weeks, and 97% within six weeks. For individuals diagnosed in 2022, these proportions were 58%, 84%, 95%, and 97%, respectively. The proportion in care within four weeks was 94% for individuals who received their first HIV-positive test at a sexual health centre, and similar for those who tested HIV-positive in a hospital (96%), at a general practice (95%), or at other locations (98%). 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%).

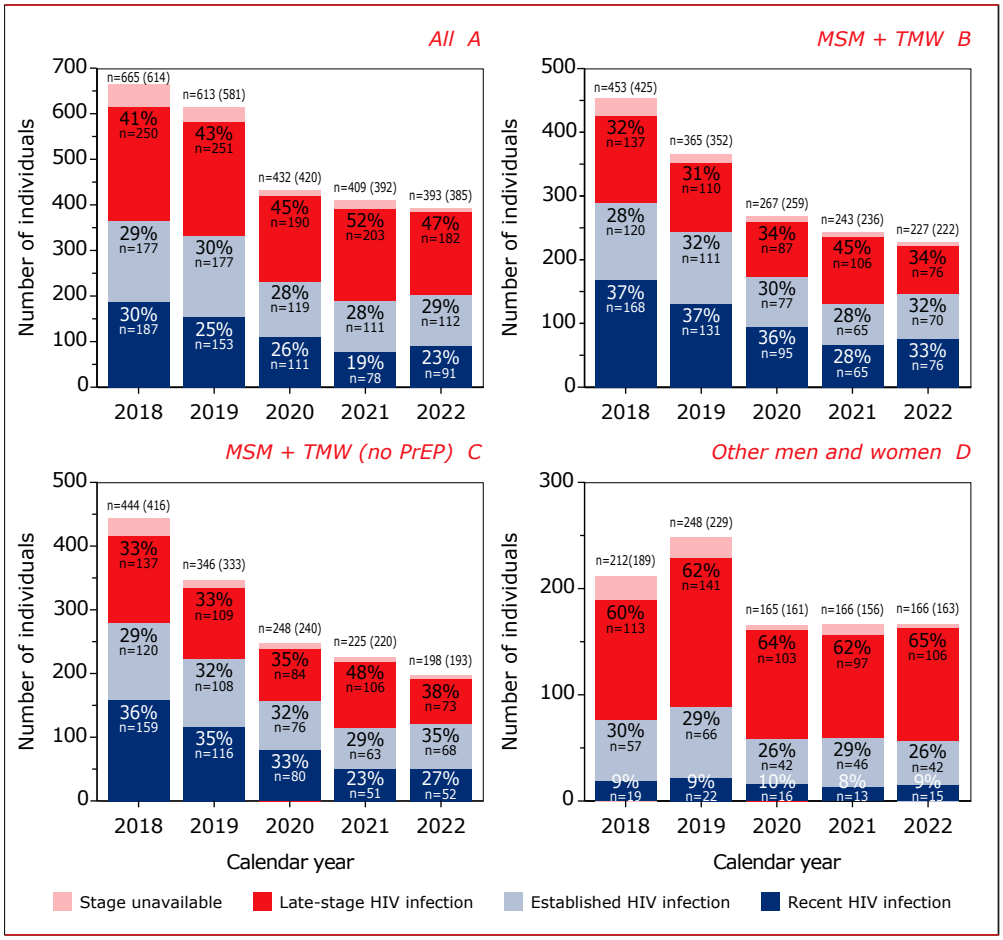
Stage at time of HIV diagnosis

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[3].
- 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.

Between 2018 and 2022, the proportion of individuals diagnosed with recent HIV infection decreased from 30% to 24%, while the proportion with late-stage HIV increased from 41% to 47% (*Figure 1.7A*). Meanwhile, there were only minor changes in the proportion with established HIV infection. On closer inspection, these changes were to some extent the result of a decreasing number of MSM and trans men and women relative to the total annual number of newly diagnosed HIV infections, from 68% in 2018 to 58% in 2022. Besides, changes in the proportion of MSM and trans men and women diagnosed with recent, established, or late-stage HIV were also the result of the increasing share of people reporting prior use of PrEP among the annual number of new HIV diagnoses (*Figure 1.7B* and *1.7C*). In other men and women, changes in the proportion diagnosed in each of these three stages were less pronounced (*Figure 1.7D*).

Figure 1.7: *Annual number and proportion of individuals diagnosed with recent, established, or late-stage HIV infection in 2018-2022 (A) in the total population aged 15 years or older at the time of diagnosis, (B) in men who have sex with men (MSM) and trans men and women, (C) in MSM and trans men and women excluding those who reported prior use of pre-exposure prophylaxis, and (D) in other men and women. Recent HIV infection was (i) a negative or indeterminate blot at the time of diagnosis, or (ii) a last negative test at most 12 months or 6 months prior to diagnosis; established HIV infection: no recent HIV infection, CD4 counts above 350 cells/mm³, and not having AIDS at the time of diagnosis; late-stage HIV infection: no recent HIV infection, CD4 counts below 350 cells/mm³ or having AIDS, regardless of CD4 count. Numbers above the bars are the total number of diagnoses in each year, while numbers in brackets are the number of diagnoses excluding individuals whose stage at diagnosis is unavailable. Percentages inside the bars are relative to the number in brackets for late-stage and established HIV 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, 48% of the individuals diagnosed in 2020-2022 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, and then increased to 45% in 2020, 52% in 2021, and 47% in 2022 (*Figure 1.8A*). This increase was mainly due to changes in the proportion of MSM diagnosed with late-stage HIV (see also *Figure 1.7B*). The proportion of individuals diagnosed with advanced HIV disease (i.e. with a CD4 count below 200 cells/mm^3 or AIDS-defining event, and no evidence of having acquired HIV in the previous 12 months), has followed a similar pattern, and reached 32% in 2022 (*Figure 1.8C*). Although the downward trend in these *proportions* appears to have halted after 2013, the *number* of individuals diagnosed with late-stage or advanced-stage HIV infection continued to decrease, albeit gradually (*Figure 1.8B* and *1.8D*). It is worth noting that although newly diagnosed MSM had the lowest proportion of late-stage HIV infections, they accounted for 261 (45%) of all 575 individuals diagnosed with late-stage HIV in 2020-2022.

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

Among individuals diagnosed with HIV in 2020-2022, 261 (38%) MSM, 186 (69%) other men, and 120 (57%) women had a late-stage HIV infection. Late-stage HIV infections, in relative terms, were most common among people originating from sub-Saharan Africa (65%, or 73 individuals), from south and southeast Asia (61%, 28 individuals), or from central Europe (55%, or 63 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 2020-2022, late-stage HIV was seen in 55% of MSM, 85% of other men, and 67% of women aged 60 years or older, compared with 30% of MSM, 38% of other men, and 38% of women diagnosed below the age of 30 years (*Table 1.2; Figure 1.9*).

Figure 1.8: *Proportion and number of individuals classified as having: (A, B) late-stage, or (C, D) advanced-stage HIV infection at the time of diagnosis. In 2022, 182 (47%) individuals were diagnosed with late-stage HIV infection: 72 (34%) men who have sex with men (MSM), 67 (71%) other men, 39 (57%) women, and 4 (31%) trans men and women. During the same year, 122 (32%) individuals were diagnosed with advanced-stage HIV infection: 44 (21%) MSM, 45 (48%) other men, 31 (45%) women, and 2 (15%) trans men and women. Late-stage HIV infection: CD4 counts below 350 cells/mm³ or having AIDS, regardless of CD4 count. Advanced-stage HIV infection: CD4 counts below 200 cells/mm³ or having AIDS. As a CD4 count measurement close to the time of diagnosis and before start of therapy was sometimes missing, the stage of the HIV infection could not be determined for all individuals. In 2020-2022, the stage of infection was unknown for 37 (3%) individuals.*

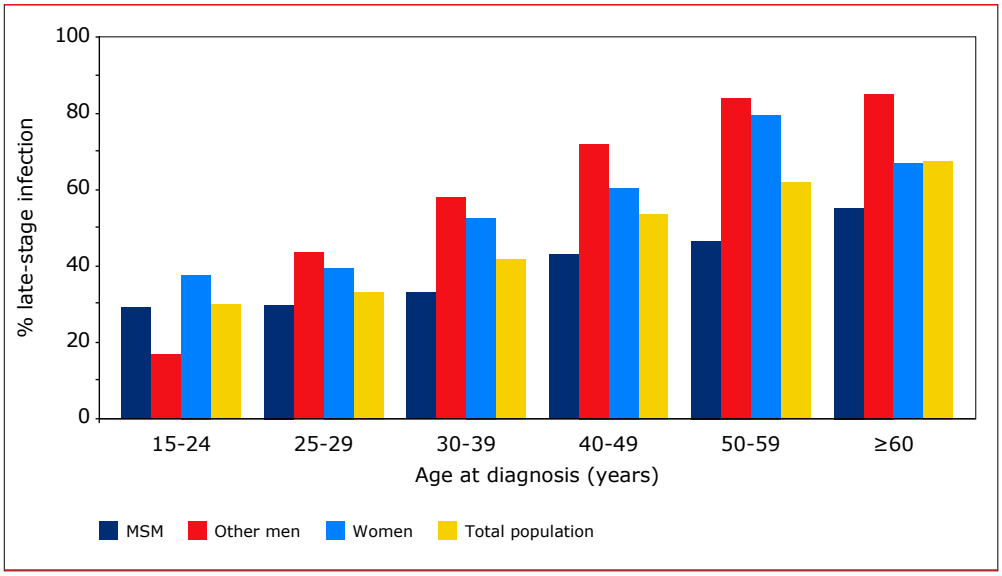
Legend: *MSM = men who have sex with men.*

Table 1.2: *Characteristics of the 575 individuals with a late-stage HIV infection among the 1,234 individuals diagnosed with HIV in 2020-2022. In total, as a result of missing CD4 cell counts at diagnosis, it was not possible to classify whether 37 (3%) individuals (19 MSM, 11 other men, 6 women, and 1 trans individual) had a late-stage HIV infection. For each of the five groups (MSM, other men, women, trans men and women, and total), percentages represent the proportion with late-stage infection of the total number of individuals diagnosed in each category listed in the first column.*

	MSM (n=681)		Other men (n=270)		Women (n=210)		Trans men and women (n=36)		Total (n=1,197)	
	n	%	n	%	n	%	n	%	n	%
Overall	261	38	186	69	120	57	8	22	575	48
Age at diagnosis (years)										
15-24	20	29	1	17	9	38	0	0	30	30
25-29	35	30	10	43	11	39	4	31	60	33
30-39	59	33	44	58	32	52	3	21	138	42
40-49	54	43	49	72	23	61	0	0	126	53
50-59	61	47	48	84	35	80	1	33	145	62
60-69	20	44	23	82	9	64	0	0	52	60
≥70	12	92	11	92	1	100	0	0	24	92
Region of origin										
Western	*170*	*38*	*104*	*72*	*43*	*51*	*2*	*29*	*319*	*47*
The Netherlands	157	38	102	73	39	49	2	29	300	47
Other western*	13	35	2	50	4	80	0	0	19	41
Non-Western	*91*	*39*	*82*	*65*	*77*	*62*	*6*	*21*	*256*	*50*
Sub-Saharan Africa	3	30	28	74	42	65	0	0	73	65
Central Europe	34	49	20	67	9	64	0	0	63	55
South America	17	30	9	82	6	40	3	19	35	36
Caribbean	11	44	4	36	3	33	2	29	20	38
South and southeast Asia	15	54	5	72	7	88	1	33	28	61
North Africa and the Middle-East	5	31	11	61	1	50	0	0	17	47
Other/unknown	6	21	5	45	9	75	0	0	20	36
Location of HIV diagnosis										
Sexual health centre	56	21	13	48	3	17	3	19	75	23
Hospital	117	70	124	83	83	80	3	43	327	77
General practice	67	34	39	57	21	38	0	0	127	38
Other/unknown	21	47	10	42	13	39	2	40	46	43
Last negative test†										
1-2 years	26	35	4	33	2	22	2	33	34	33
2-4 years	23	35	10	59	6	46	2	50	41	41
≥4 years	66	67	26	74	33	70	0	0	125	68
Never tested / not available	146	66	146	80	79	65	4	44	375	70

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

Figure 1.9: Proportion of individuals diagnosed with late-stage HIV infection stratified by age category at the time of diagnosis for those diagnosed in 2020-2022 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 (77%) than among those who were tested at a general practice (38%), a sexual health centre (23%), or another testing location (43%). 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 76% in 2022. Late diagnosis was less common (37%) 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 (68%) or who did not report ever having tested for HIV before (70%).

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 575 people diagnosed with late-stage HIV infection in 2020-2022, 249 (43%) were hospitalised within a year of diagnosis, including 206 (36%) as a direct result of their HIV infection. In contrast, only 66 (11%) of the 622 individuals diagnosed with recent or established HIV infection were hospitalised within a year of diagnosis, including

19 (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 575 individuals diagnosed with late-stage HIV infection in 2020-2022, 23 (4%) died within a year of diagnosis, including 16 (3%) who died of AIDS (*Table 1.3*). Among the 622 people diagnosed with recent or established HIV infection, 6 (1%) died with a year of diagnosis, including no one who died of AIDS.

Table 1.3: *Number and proportion of individuals diagnosed in 2020–2022 who were hospitalised or who died within a year of diagnosis, stratified by stage of infection.*

		Hospitalisation				Death			
		Total		HIV-related		Total		AIDS-related	
Stage	**n**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Recent or established HIV infection	622	66	11	19	3	6	1	0	0
Late-stage HIV infection	575	249	43	206	36	23	4	16	3
CD4 200–349, no AIDS	167	20	12	10	6	1	1	0	0
CD4 <200, no AIDS	187	55	29	32	17	4	2	3	2
AIDS	221	174	79	164	74	18	8	13	6

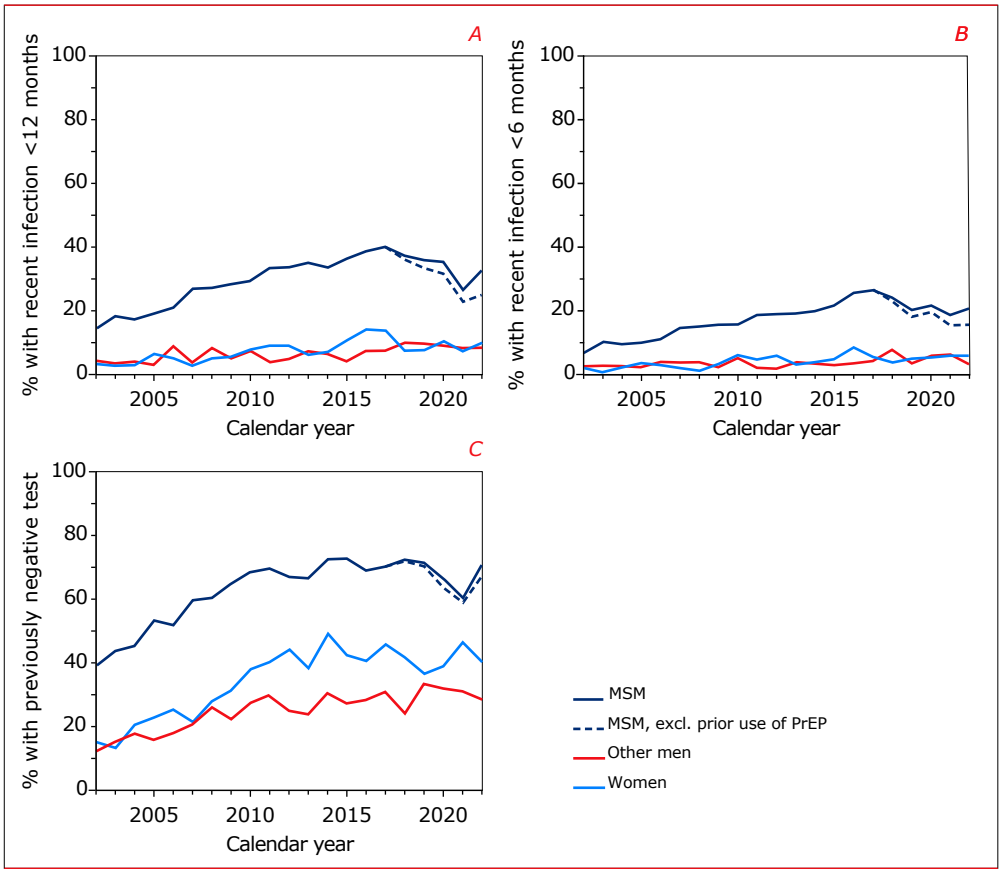
Late diagnosis and prior use of PrEP

Among MSM and trans men and women diagnosed in 2020-2022, 269 (38%) were diagnosed with a late-stage HIV infection (*Figure 1.7B*). When people who reported prior use of PrEP were excluded, the number diagnosed with late-stage HIV reduced to 263, but this represented a slightly higher proportion, 40%, of those diagnosed (*Figure 1.7C*).

Recent infection

Although many individuals are diagnosed with a late-stage HIV infection, a considerable proportion of people receive their HIV diagnosis early in the course of their infection. In total, among the individuals diagnosed in 2020-2022, 23% had evidence of having acquired their HIV infection in the 12 months prior to diagnosis, while 14% had evidence of having acquired HIV in the six months prior to diagnosis (*Figure 1.10A* and *1.10B*). For MSM, these proportions were 32% and 20%, respectively, while they were similar for trans men and women, 38% and 22%, respectively. Among other men and among women these proportions were considerably lower (9% and 5%, respectively).

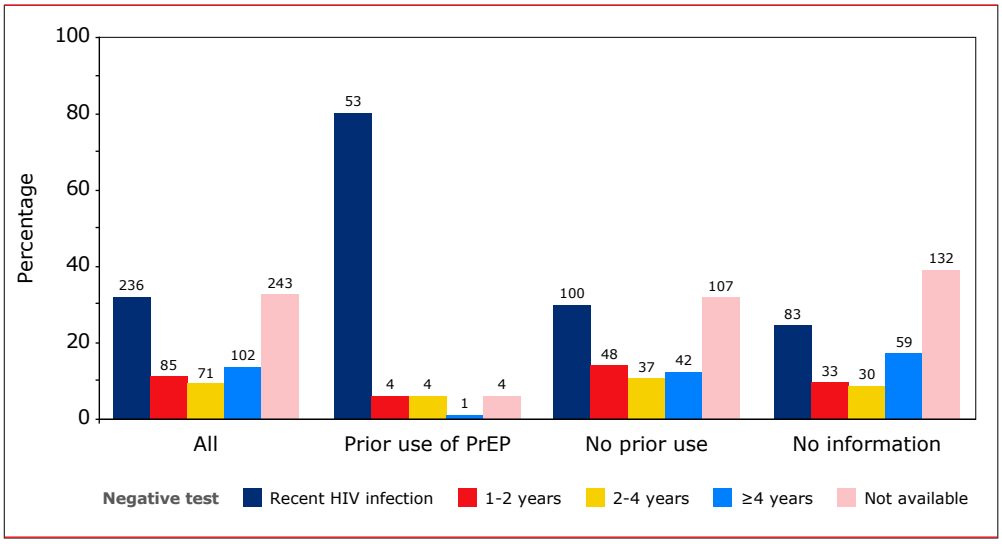
Figure 1.10: *Proportion of people diagnosed (A) with evidence of having acquired their HIV infection at most 12 months prior to their diagnosis, (B) at most 6 months prior to their diagnosis, (C) with a previously negative test at any time prior to their diagnosis. Evidence of a recent infection was (i) a negative or indeterminate blot at the time of diagnosis, or (ii) a last negative test at most 12 months or 6 months prior to diagnosis. In total, 70 (33%) men who have sex with men (MSM), or 46 (25%) MSM when excluding those who reported prior use of pre-exposure prophylaxis (PrEP), 8 (8%) other men, 7 (10%) women, 6 (43%) trans men and women, and 91 (23%) of all 393 individuals diagnosed in 2022 had evidence of having acquired HIV at most 12 months before diagnosis. In the same year, 44 (21%) MSM, or 29 (16%) MSM when excluding those who reported prior use of PrEP, 3 (3%) other men, 4 (6%) women, 2 (14%) trans men and women, and 53 (13%) of all 393 individuals had evidence of having acquired HIV at most six months before diagnosi.*



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 33% in 2022 (*Figure 1.10A*). This increase in 2022 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 25% in 2022. A similar reduction in the proportion with recent HIV infection after excluding individuals reporting prior use of PrEP was seen in the combined population of MSM and trans men and women (*Figure 1.7B* and *1.7C*). The reason that the proportion with recent HIV infection decreased after excluding people reporting prior use of PrEP is that in this group of former PrEP users, the proportion diagnosed with recent HIV infection was much higher, 80%, than in people who never used PrEP or for whom no information on PrEP use was available (*Figure 1.11*).

Figure 1.11: *Proportion of men who have sex with men (MSM) and trans men and women diagnosed in 2020–2022 whose most recent negative HIV test was less than 1 year (i.e. recent HIV infection, including those with negative or indeterminate blot at the time of diagnosis), 1 to 2 years, 2 to 4 years, or more than 4 years prior to their HIV diagnosis, or who reported never having tested for HIV, overall and stratified by whether or not they reported prior use of PrEP. Numbers above the bars are the number of individuals diagnosed in each category and represented by each bar.*

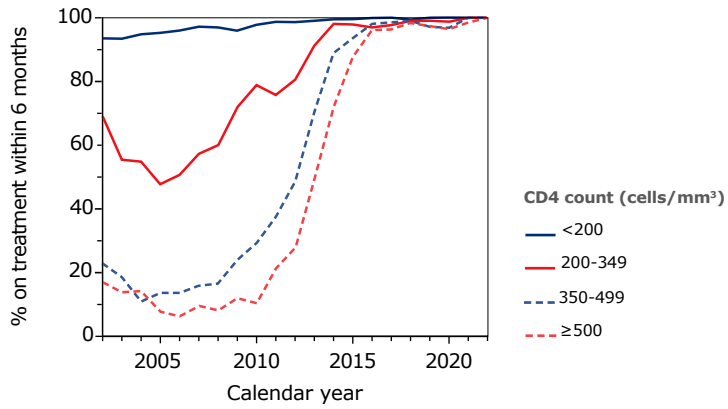


The proportion of people with a recorded previously negative HIV test any time before their HIV diagnosis increased from 25% in 2002 to 55% in 2022. MSM were more likely to have a previously negative HIV test than other men and women. In 2022, 71% of MSM newly diagnosed with HIV had a previously negative test, which was similar to 70% of MSM diagnosed in the period 2018-2020, but higher than 60% of MSM diagnosed in 2021 (*Figure 1.10C*). Overall, of MSM diagnosed in 2020-2022, 66% reported a previously negative test, meaning that a third (33%) never had an HIV test before their HIV diagnosis (see also *Figure 1.11*). The proportion with a negative test among other men and women diagnosed in 2022 was 28% and 40%, respectively, which was similar to the proportions in 2018-2021 (30% and 40%, respectively). The proportion with a known previously negative test was highest among those diagnosed at a sexual health centre (77%), compared with 31% of those diagnosed in a hospital, and 67% of those diagnosed at a general practice.

Antiretroviral therapy

Of the 27,035 individuals diagnosed at 15 years of age or older, 26,166 (97%) had started antiretroviral therapy (ART) by May 2023. Over the past two decades, ART has increasingly been initiated earlier in the course of an HIV infection (*Figure 1.12*). This is a consequence of people being diagnosed sooner, on average, after acquiring their HIV infection, and treatment guidelines recommending immediate initiation of ART, regardless of CD4 count[4]. Prior to 2015, individuals with higher CD4 counts were less likely to start therapy shortly after an HIV diagnosis, but after the treatment guidelines changed that year, there is now almost no delay between diagnosis and start of therapy. In 2022, across all CD4 strata, at least 95% of people who were diagnosed with HIV that year started ART within six months.

Figure 1.12: Proportion of individuals who started antiretroviral therapy (ART) within six months of their HIV diagnosis by CD4 count at the time of diagnosis. Individuals were considered only if they had more than six months of follow up after diagnosis. Of all individuals diagnosed in 2020–2022, 100% of those with CD4 counts below 200 cells/mm³, 99% of those with CD4 counts between 200 and 349 cells/mm³, 99% of those with CD4 counts between 350 and 499 cells/mm³, and 98% of those with CD4 counts of 500 cells/mm³ or above had started ART within six months of diagnosis.



Time between HIV infection and viral suppression

Individuals with a suppressed viral load below 1,000 copies/ml cannot transmit HIV to other people (undetectable equals untransmittable, or U=U)[5–8]. Hence it is crucial to minimise the time between the moment a person acquires HIV and the point at which they achieve this threshold[9], 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 2022, the median time from diagnosis to reaching a viral load level below 200 copies/ml decreased from 0.85 years (IQR 0.38-2.64) to 0.16 years (IQR 0.11-0.27), or from 10.2 months (IQR 4.5-31.7) to 1.9 months (IQR 1.4-3.3). The median time to reaching a viral load level below 1,000 copies/ml was somewhat shorter, being 0.56 years (IQR 0.24-2.12) years, or 6.7 months (IQR 2.9-25.4), in 2010, and 0.14 years (IQR 0.10-0.20), or 1.7 months (IQR 1.2-2.4) in 2022. This decrease in time to viral suppression was achieved mainly as a result of starting therapy sooner after entry into care, and individuals with HIV reaching viral suppression faster once therapy had begun. The time from infection

to diagnosis was the greatest contributing factor to the delay between acquiring HIV and achieving viral suppression. In 2022, this was estimated to be a median of 3.5 years (IQR 1.7-6.4).

Population in care

In total, 21,987 (72%) of the 30,598 individuals with HIV-1 ever registered in the Netherlands were known to be in clinical care by the end of 2022 (*Figure 1.1*; *Table 1.4*). People were considered to be in clinical care if they had visited their treating physician in 2022, or had a CD4 count or HIV RNA measurement in that year, and were still living in the Netherlands. Of the 8,611 people who were not in care by the end of 2022, 3,950 (46%) had died, of whom 2,147 (54%) died before the end of 2012. Another 2,398 (28%) had moved abroad, including 899 (37%) who did so before the end of 2012. The remaining 2,263 (26%) individuals:

- were lost to care (2,112, 93%);
- were only diagnosed with HIV in 2023 (68, 3%);
- had only moved to the Netherlands in 2023 (32, 1%); or
- had newly entered care in 2023 (51, 2%).

Of the people who moved abroad, 1,893 (79%) had RNA levels below 200 copies/ml at their last viral load measurement; in those lost to care, that figure was 1,378 (65%).

Table 1.4: Characteristics of the 21,987 people with HIV-1 in clinical care by the end of 2022.

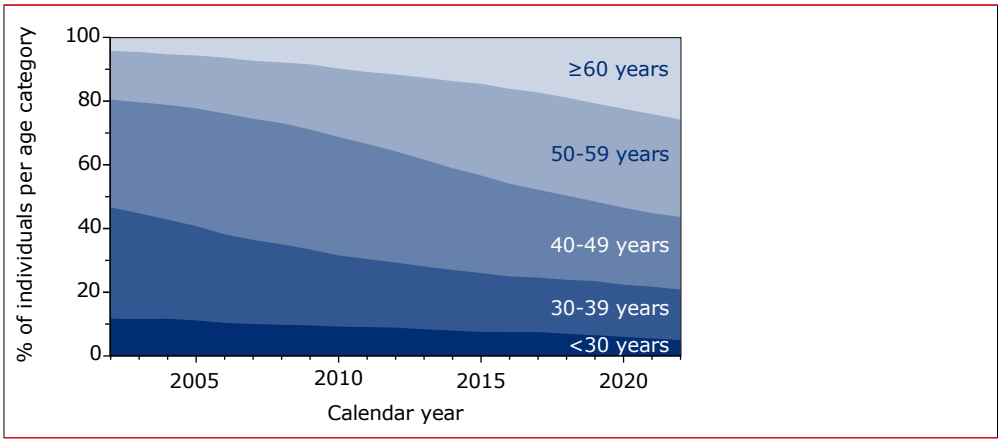
	MSM (n=13,621, 62%)		Other men (n=3,974, 18%)		Women (n=4,120, 19%)		Trans men and women (n=272, 1%)		Total (n=21,987)	
	n	%	n	%	n	%	n	%	n	%
Transmission										
Sex with men	12,591	93	0	0	3,575	87	213	78	16,379	74
Sex with women	8	0	2,577	65	1	0	7	3	2,593	12
Sex, unspecified	944	7	93	2	0	0	22	8	1,059	5
IDU	11	0	199	5	84	2	0	0	294	1
Blood/blood products	15	0	180	5	109	3	4	2	308	1
Other/unknown	52	0	925	23	351	9	26	10	1,354	6
Current age (years)										
0–14	0	0	58	0	6	2	0	0	124	1
15–24	101	1	65	2	98	2	7	3	271	1
25–29	501	4	93	2	129	3	21	8	744	3
30–39	2,161	16	518	13	700	17	109	40	3,488	16
40–49	2,893	21	804	20	1,192	30	68	25	4,957	23
50–59	4,225	31	1,243	31	1,196	29	55	20	6,719	31
60–69	2,680	20	848	21	546	13	11	4	4,085	19
≥70	1,060	8	345	9	193	5	1	0	1,599	7
Region of origin										
The Netherlands	9,172	67	1,850	47	1,206	29	52	19	12,280	56
Sub-Saharan Africa	212	2	917	23	1,598	39	6	2	2,733	12
Western Europe	846	6	141	4	113	3	12	4	1,112	5
Central Europe	491	4	159	4	102	2	2	1	754	3
Eastern Europe and Central Asia	218	2	129	3	183	4	4	1	534	2
South America	1,029	8	280	7	362	9	105	39	1,776	8
Caribbean	577	4	177	4	191	5	54	20	999	5
South and southeast Asia	460	3	100	3	255	6	27	10	842	4
Other	541	4	193	5	95	2	9	3	838	4
Unknown	75	1	28	1	15	0	1	0	119	1
Years aware of HIV infection										
<1	215	2	95	2	72	2	13	5	395	2
1–2	505	4	198	5	163	4	27	10	893	4
3–4	871	6	262	7	217	5	26	10	1,376	6
5–10	3,003	22	731	18	637	14	52	19	4,423	20
10–20	5,850	43	1,605	40	1,770	43	107	39	9,332	42
20–30	2,477	18	912	23	1,068	26	39	14	4,496	20
>30	688	5	156	4	179	4	5	2	1,028	5
Unknown	12	0	15	0	14	0	3	1	44	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 2022 was 52 years (IQR 42-60). This figure has been increasing since 2002 (*Figure 1.13*), which is mainly a result of the improved life expectancy of people with HIV following the introduction of combination antiretroviral therapy (ART). Moreover, individuals are being diagnosed at an increasingly older age, as discussed earlier in this chapter. Consequently, approximately half of those currently in care (56%) are 50 years or older (58% of MSM, 59% of other men, 47% of women, and 25% of trans men and women), and 26% are 60 years or older. As the population with HIV continues to age, the number of individuals with age-related comorbidities also increases. These conditions are known to complicate HIV infection management (see *Chapter 3*).

Figure 1.13: *Increasing age of the population with HIV-1 in clinical care over calendar time. In 2002, 12% of the individuals in care were younger than 30 years of age, whereas 20% were 50 years or older. In 2022, these proportions were 5% and 56%, respectively, while 26% 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 2022 were known with HIV for a median of 13.8 years (IQR 8.4-20.1). Therefore, a large group (68%) of those in care have been living with HIV for more than 10 years, including 25% who have done so for more than 20 years. The median time since diagnosis was 13.3 years for men who have sex with men (MSM), 14.2 years for other men, 15.9 years for women, and 11.0 years for trans men and women.

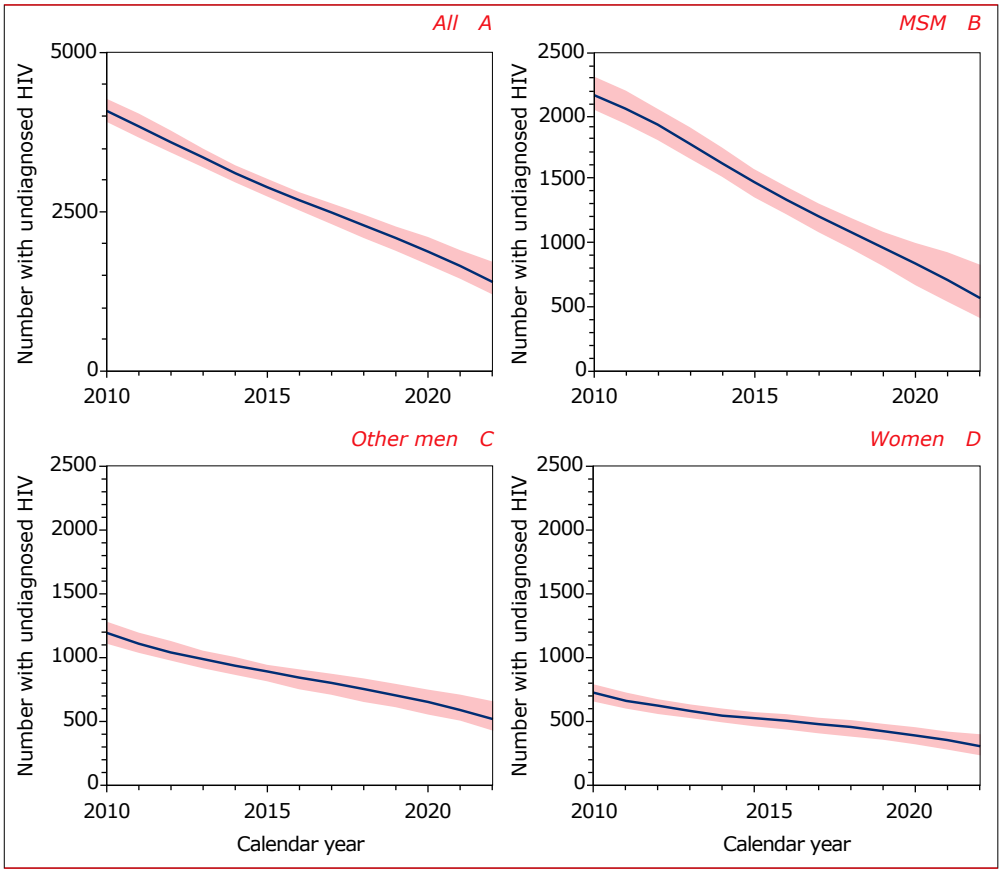
Treated population

By the end of 2022, almost all individuals in care had started ART, and 96% of them were using a once-daily regimen. Of the 115 individuals who had not yet started ART by the end of 2022, 13 (11%) were known to have started therapy in 2023, while another 31 (27%) individuals were diagnosed with HIV in 2022, so it is likely that their therapy has yet to be recorded in the SHM database. ART is discussed in more detail in *Chapter 2*.

Undiagnosed population

The estimated number of people with an undiagnosed HIV infection decreased from 4,080 (95% CI 3,910-4,270) in 2010 to 1,390 (1,210-1,710) in 2022, representing a reduction of 66% (58-70) (*Figure 1.14A*). This decrease was mostly driven by MSM, among whom the number of undiagnosed HIV cases fell by 74% (61-82) from 2,170 (2,050-2,320) in 2010 to 570 (410-840) by the end of 2022 (*Figure 1.14B*). Among other men, the estimated number with undiagnosed HIV was 1,190 (1,110-1,280) in 2010 and 520 (420-660) in 2022, while in women these numbers were 720 (650-780) and 300 (230-400), respectively (*Figures 1.14C* and *1.14D*).

Figure 1.14: *Estimated number of people with undiagnosed HIV in the Netherlands: (A) overall, (B) men who have sex with men (MSM), (C) other men, and (D) women, according to the European Centre for Disease Prevention and Control (ECDC) HIV Platform Tool[110]. Estimates for the overall population do not include trans individuals and children.*



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

Continuum of HIV care – national level

The total number of people with HIV by the end of 2022 was 24,400 (95% CI 24,220-24,720), including the estimated 1,390 (1,210-1,710) who remained undiagnosed[10]. Adjusted for registration delays, of this total:

- 23,011 individuals (94% of the total number of people with HIV) had been diagnosed, linked to care, and registered by SHM;
- 22,102 (91%, 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 2022) (*Figure 1.15A*);
- 21,978 (90%, or 96% of those diagnosed and linked to care) had started ART;
- 21,251 (87%, or 97% of those treated) had a most recent HIV RNA measurement below 1,000 copies/ml;
- 21,094 (86%, or 96% of those treated) had a most recent HIV RNA measurement below 200 copies/ml; and
- 20,537 (84%, or 93% of those treated) had a most recent measurement below 50 copies/ml.

The estimated total number of people with HIV and the number diagnosed and linked to care excluded 307 people who, according to data from Statistics Netherlands, had died or moved abroad by the end of 2022 but whose date of death or migration had not been recorded in the SHM database.

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 2022 the Netherlands had almost reached the Joint United Nations Programme on HIV/AIDS (UNAIDS) 95-95-95 target for 2025; with the estimate standing at 94-96-96, or 94-96-97 if 1,000 copies/ml, and 94-96-93 if 50 copies/ml is used as a threshold of viral suppression[11]. Of the people still in care by the end of 2022, 16,183 (76%, or 78% of those with a CD4 measurement) had a most recent CD4 count of 500 cells/mm^3 or higher, which was measured, at most, three years earlier.

Viral suppression

In total, 865 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 2022. On closer inspection, 380 (44%) of these individuals did not have an HIV RNA measurement available in 2022; 273 (72%) of these 380 individuals had an RNA level below 200 copies/ml at their last measurement in 2021.

Of the 485 (56%) people with a viral load measurement and a viral load level above 200 copies/ml, 63 (13%) started therapy after their last available viral load measurement in 2022. Another 29 (6%) had only started therapy in the six months prior to that last measurement and may not have had sufficient follow up to achieve a documented suppressed viral load.

Lost to care

Based on SHM data only, 2,112 individuals were lost to care by the end of 2022, and of these:

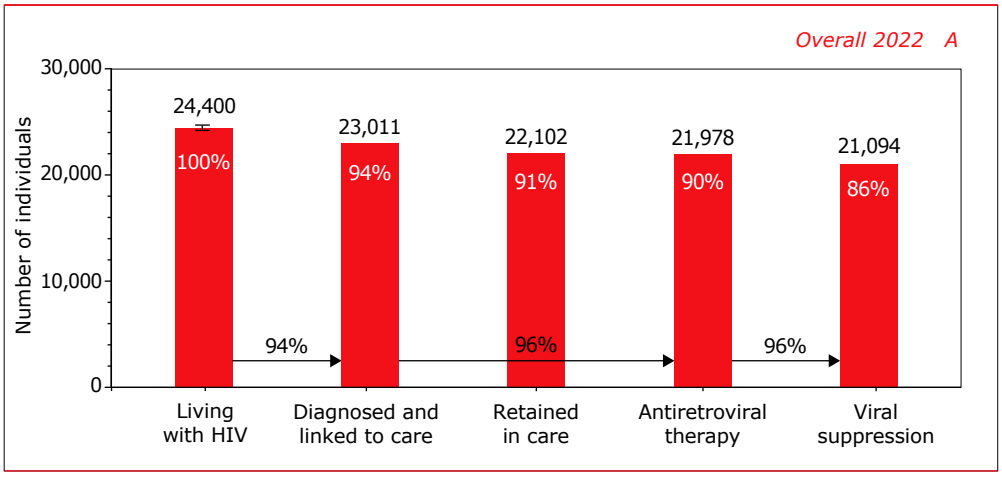
- 952 (45%) were last seen for care before the end of 2012;
- 584 (28%) in 2013-2018;
- 116 (5%) in 2019;
- 148 (7%) in 2020; and
- 312 (15%) in 2021[b].

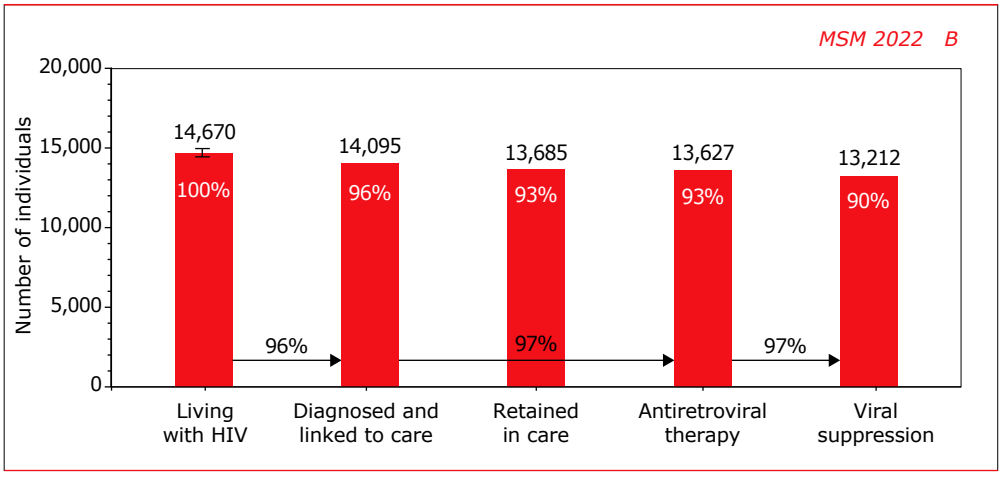
The 952 individuals who were lost to care in or before 2012, were excluded from the estimated number of people with HIV and the number of people diagnosed and linked to care. It was assumed to be unlikely that these 952 individuals were still living in the Netherlands by the end of 2022 without requiring care or ART during that ten-year period.

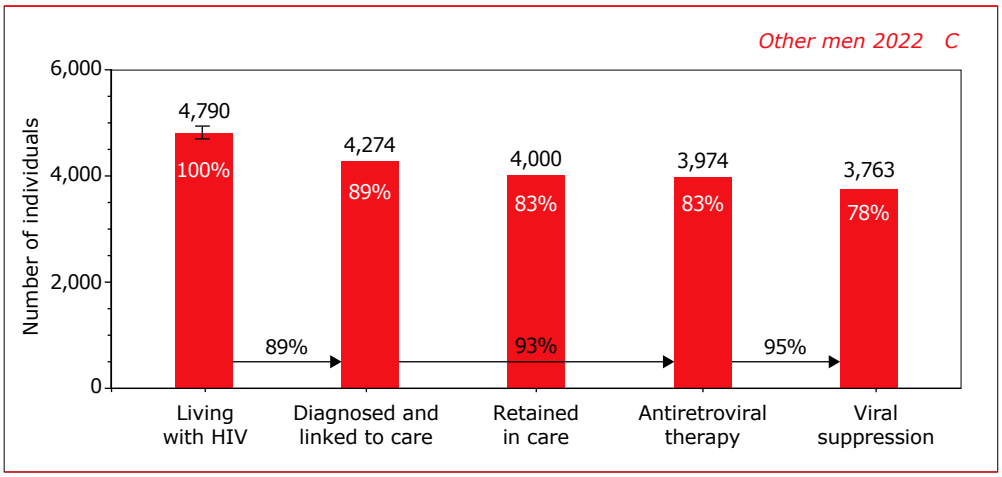
Of the 1,160 individuals lost to care after 2012, 68% were born outside the Netherlands; this proportion was only 44% for those who were still in care by the end of 2022. This suggests that some of those lost to care may have moved abroad; in particular, back to their country of birth. Indeed, according to data from Statistics Netherlands, 259 (22%) of the 1,160 individuals lost to care after 2012 had moved abroad, while another 48 (4%) had died by the end of 2022. It should be pointed out that 163 (14%) 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.

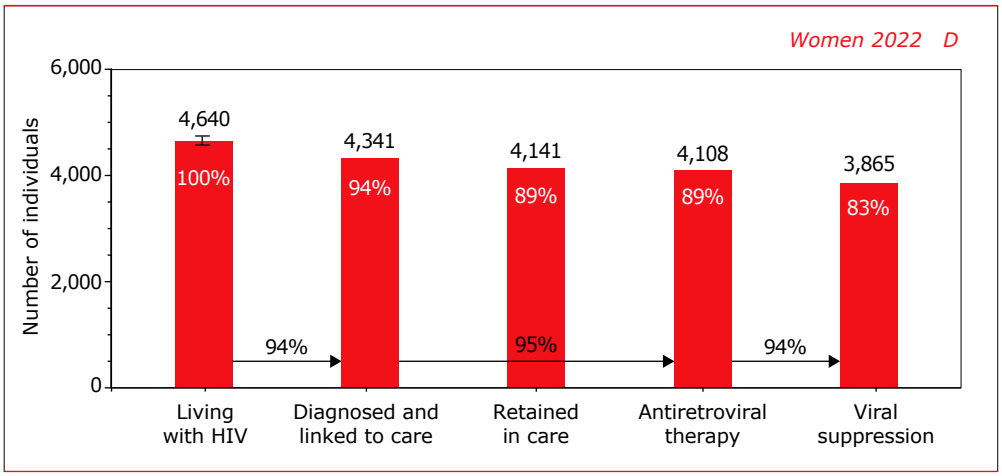
b In addition to the 2,112 individuals lost to care there were 51 individuals who had already been diagnosed by the end of 2022 and were living in the Netherlands but entered care in 2023. These 51 individuals (55 with adjustment for registration delay), as well as the 853 (1,160 minus 307) lost to care after 2012 (854 with adjustment), are counted in the first and second stage of the continuum but not in the other stages.

Figure 1.15: *Continuum of HIV care for people with HIV in the Netherlands by the end of 2022: (A) the total population with HIV-1, (B) men who have sex with men (MSM), (C) other men, and (D) women. Percentages at the top of the bars are calculated relative to the number with HIV, while percentages at the bottom correspond to the UNAIDS' 95-95-95 targets for 2025. Numbers were adjusted to reflect reporting delays, while the numbers in the first two bars in each panel were also adjusted using data on death and migration from Statistics Netherlands.*









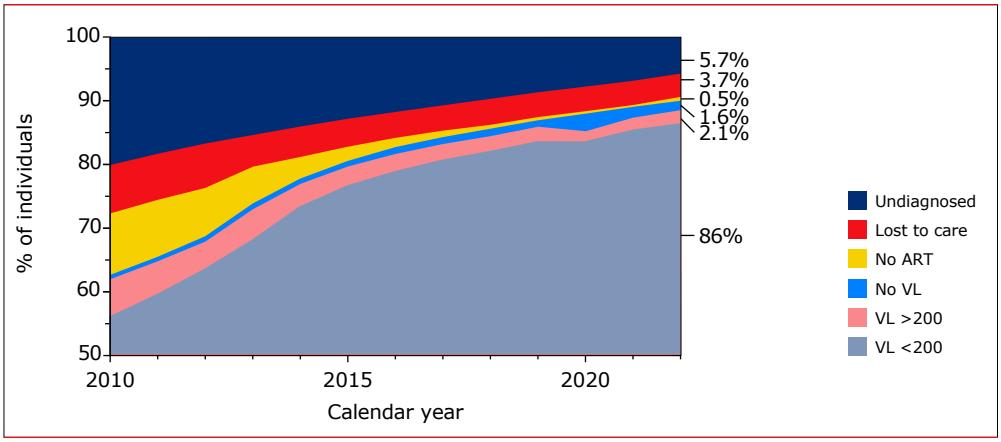
Legend: *MSM = men who have sex with men.*

Transmittable levels of virus

The proportion of people with HIV living in the Netherlands (at the end of each calendar year) who had a confirmed viral load level below 200 copies/ml, grew steadily between 2010 and 2022 (*Figure 1.16*). In 2010, 56% of the estimated 20,300 (95% CI 20,130-20,490) people with HIV had a suppressed viral load below 200 copies/ml, while this proportion was 86% in 2022. During the same period, the proportion with a viral load below 1,000 copies/ml grew from 58% in 2010 to 87% in 2022. This increase was mainly the result of a reduction in the proportion of people unaware of their infection, from 20% in 2010 to 6% in 2022, and, to a lesser extent, of a smaller proportion not yet on ART (10% in 2010, 0.5% in 2022).

The number of individuals with HIV who were likely to have an unsuppressed viral load by the end of 2022 was estimated to be 3,311, or 14% of all people with HIV, which is the difference between the first and the last stage in the HIV care continuum. These individuals may still pass HIV onto uninfected individuals. This number is likely to be an overestimate of the true number with an unsuppressed viral load in the Netherlands because, as discussed above, some of the people who were lost to care may have moved abroad and may be receiving HIV care outside the Netherlands. Additionally, 2% of all people with HIV had no viral load measurement in 2022 but it is likely that many now have viral load levels below 200 copies/ml, as they all started ART.

Figure 1.16: *Estimated proportions of people with HIV across the various stages in the HIV care continuum. Proportions in 2013–2022 were adjusted using data on death and migration from Statistics Netherlands. The numbers to the right of the graph are the proportions in 2022.*



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 2022 was estimated at 14,670 (95% CI 14,510-14,930), of whom 570 (410-840) had yet to be diagnosed. Of these:

- 14,095 (96%) had been diagnosed and linked to care;
- 13,685 (93%) were still in care;
- 13,627 (93%) had started ART; and
- 13,212 (90%) had a most recent HIV RNA below 200 copies/ml, while 13,280 (91%) had a viral load below 1,000 copies/ml.

In terms of the 2025 UNAIDS 95-95-95 target, this translates to 96-97-97, meaning that in MSM, the UNAIDS targets have already been met (*Figure 1.15B*). In total, 10,461 (71%, or 81% of those with a CD4 measurement) of MSM still in care by the end of 2022 had a CD4 count of 500 cells/mm^3 or higher at their last measurement in 2020-2022.

Among other men, the estimated number with HIV in 2022 was 4,790 (95% CI 4,700-4,930), including 520 (420-660) who were not yet diagnosed (*Figure 1.15C*). Of these:

- 4,274 (89%) men had been diagnosed and linked to care;
- 4,000 (83%) were still in care;
- 3,974 (83%) had started ART; and
- 3,763 (78%) had a suppressed viral load below 200 copies/ml, while 3,806 (79%) had a viral load below 1,000 copies/ml.

The number of women with HIV was estimated to be 4,640 (95% CI 4,570-4,740), of whom 300 (230-400) were not yet diagnosed (*Figure 1.15D*). Of these women:

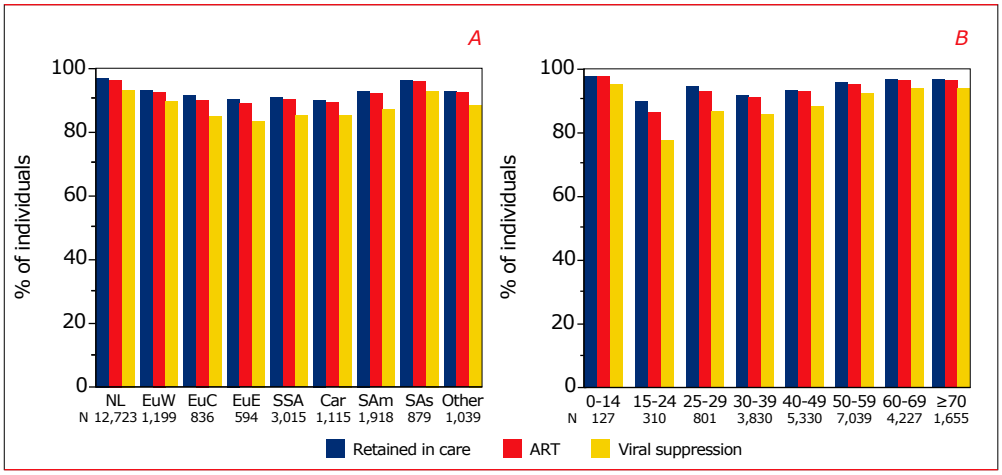
- 4,341 (94%) had been diagnosed and linked to care;
- 4,141 (89%) were still in care;
- 4,108 (89%) had started ART; and
- 3,865 (83%) had a suppressed viral load below 200 copies/ml, while 3,910 (84%) had a viral load below 1,000 copies/ml.

Among women and other men still in care by the end of 2022, the proportion with viral suppression was 94%, which was somewhat lower than among MSM (97%).

Continuum of care by region of origin and age

Individuals of Dutch origin generally engaged more with the various stages of the care continuum than people from other countries (*Figure 1.17A*). Engagement with all stages of the care continuum was highest among the youngest age group. Levels of engagement were generally lower in the other age groups, but both the proportion of people who were still in care and the proportion who had started ART by the end of 2022, increased with age, and exceeded 95% in people aged 50 years or older (*Figure 1.17B*). As a consequence, the proportion of people with viral suppression also increased with age; rising from 78% among those aged 15 to 24 years, to more than 90% for people aged 50 years or older.

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



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

Continuum of care 2021

We re-estimated the continuum of HIV care for 2021 and found that, by the end of that year, there were 24,390 (95% CI 24,190-24,650) people with HIV in the Netherlands, which was somewhat higher than the estimated 24,110 (23,910-24,500) outlined in last year's report[12]. The number diagnosed (22,746 compared to 22,712), the number retained in care (21,511 compared to 21,502), and the number of those who started ART (21,430 compared to 21,397) were very similar to last year's report, while the number with viral suppression (20,600 compared to 20,490) was also somewhat higher in the re-estimation. This is because the modest backlog in the collection of 2021 data on viral load measurements has now been cleared. The number of people with HIV and the number diagnosed in 2021 decreased to 24,080 (95% CI 23,880-24,340) and 22,436, respectively, after excluding 310 people who, according to data from Statistics Netherlands, had died (29) or moved abroad (281) by the end of 2021 but whose date of death or migration had not been recorded in the SHM database.

Continuum of HIV care – regional level

We also determined the continuum of care (including the first stage: estimated number of people with HIV) for the eight STI surveillance regions[c] in the Netherlands, and for the four largest cities in the country (*Table 1.5*). By the end of 2022, more than half (54%) 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 520 (40%) people with undiagnosed HIV were living in these two regions. All eight regions had reached or were close to reaching most of the UNAIDS' 95-95-95 targets for 2025, and the proportion of all people with HIV who had a suppressed viral load below 200 copies/ml varied between 82% and 89%, or between 83% and 90% 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 2022 for the total population with HIV-1 living in the Netherlands in each of the eight sexually-transmitted infection (STI) surveillance regions, or in one of the four major cities. For each region or city, percentages on the first row are relative to the estimated number of people with HIV, while those on the second row correspond to UNAIDS' 95-95-95 targets. For 192 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	150	1,510	1,359	90
	90-230	1,450-1,590		90
Oost	130	2,750	2,623	95
	100-170	2,720-2,790		95
Noord-Holland/Flevoland	260	9,190	8,931	97
	220-310	9,150-9,240		97
Utrecht	60	1,400	1,340	96
	40-80	1,380-1,420		96
Zuid-Holland Noord	170	1,890	1,721	91
	110-230	1,830-1,950		91
Zuid-Holland Zuid	260	3,910	3,645	93
	200-370	3,840-4,010		93
Zeeland/Brabant	200	2,690	2,486	93
	150-260	2,630-2,750		93
Limburg	70	1,090	1,020	93
	50-120	1,070-1,140		93
Total	1,300	24,420	23,126	95
	1,170-1,460	24,300-24,590		95
City				
Amsterdam	140	6,380	6,236	98
	120-210	6,350-6,440		98
Rotterdam	110	2,130	2,022	95
	70-160	2,090-2,180		95
Den Haag	110	1,340	1,229	92
	70-170	1,290-1,400		92
Utrecht	20	570	556	97
	10-30	570-590		95
Total	370	10,420	10,043	96
	310-480	10,350-10,530		96

	Retained in care		Antiretroviral therapy		Viral suppression	
	n	%	n	%	n	%
	1,295	86	1,290	86	1,245	83
				95		97
	2,538	92	2,526	92	2,428	88
				96		96
	8,456	92	8,418	92	8,080	88
				94		96
	1,287	92	1,282	92	1,243	89
				96		97
	1,644	87	1,629	86	1,553	82
				95		95
	3,456	88	3,419	87	3,270	84
				94		96
	2,359	88	2,349	87	2,260	84
				94		96
	950	87	950	87	908	83
				93		96
	21,985	90	21,862	90	20,987	86
				95		96
	5,917	93	5,895	92	5,677	89
				95		96
	1,911	90	1,889	89	1,804	85
				93		96
	1,174	88	1,160	87	1,106	83
				94		95
	536	93	533	93	519	90
				96		97
	9,538	92	9,476	91	9,106	87
				94		96

In total, 10,420 (95% CI 10,350-10,530) people with HIV were estimated to be living in the four largest cities in the Netherlands, which amounts to 42% of the total number of people in the country with HIV. Of these 10,420 people, 370 (310-480) were estimated to be undiagnosed (27% of the national estimate of 1,390 individuals with an undiagnosed HIV infection). Of the four cities, Amsterdam had the largest population of people with HIV; an estimated 6,380 (6,350-6,440) individuals, of whom 140 (120-210) were still undiagnosed (*Table 1.5*). Of the 10,420 people with HIV in the four largest cities:

- 10,043 (96%) had been diagnosed and linked to care;
- 9,476 (92%, or 94% of those diagnosed) had started ART; and
- 9,106 (87%, or 96% of those on therapy) had a suppressed viral load.

All four cities had reached or were close to reaching the UNAIDS' 95-95-95 targets for 2025 with the current combined estimate for the cities standing at 96-94-96.

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 1,300 (95% CI 1,170-1,460) individuals living with undiagnosed HIV across the eight STI surveillance regions, is reasonably close to the number of 1,390 (1,210-1,710) we have estimated for the total nationwide population. Another source of uncertainty that is not quantified in the estimates, is that information on the region or city where people are living, is only recorded when people first enrol in care, or move to another HIV treatment centre. People moving in or out of a region or city without changing their HIV treatment centre, will not have their region of residence updated in the SHM records.

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 2022. 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	642	615	96	613	95	589	92
Fryslân	400	380	95	378	94	365	91
Drenthe	318	301	95	299	94	290	91
Oost							
IJsselland	398	389	98	386	97	373	94
Twente	468	454	97	449	96	436	93
Noord- en Oost-Gelderland	532	513	96	511	96	491	92
Gelderland Midden	789	762	97	760	96	722	92
Gelderland-Zuid	437	421	96	420	96	405	93
Utrecht							
Regio Utrecht	1,340	1,287	96	1,282	96	1,243	93
Noord-Holland/Flevoland							
Flevoland	603	566	94	559	93	530	88
Gooi & Vechtstreek	278	265	95	263	95	254	92
Hollands Noorden	480	447	93	444	92	425	88
Zaanstreek-Waterland	412	386	94	385	94	371	90
Amsterdam	6,547	6,215	95	6,190	95	5,954	91
Kennemerland	612	577	94	577	94	546	89
Zuid-Holland Noord							
Haaglanden	1,721	1,644	96	1,629	95	1,553	90
Zuid-Holland Zuid							
Hollands Midden	591	562	95	559	95	537	91
Rotterdam-Rijnmond	2,718	2,570	95	2,543	94	2,431	89
Dienst Gezondheid & Jeugd ZHZ	336	324	96	317	94	302	90
Zeeland/Brabant							
Zeeland	253	236	93	235	93	212	84
West-Brabant	602	586	97	583	97	566	94
Hart voor Brabant	901	859	95	856	95	835	93
Brabant-Zuidoost	731	679	93	676	92	648	89
Limburg							
Limburg-Noord	426	394	92	394	92	373	88
Zuid Limburg	594	556	94	556	94	535	90
Unknown	192	117	61	116	60	106	55
Total	**23,318**	**22,102**	**95**	**21,978**	**94**	**21,094**	**90**

Trans people

Geographical region of origin

Of the 30,598 individuals with an HIV-1 infection, 334 were trans people; 317 (95%) trans women and 17 (5%) trans men. In this group of 334 individuals, the most commonly-reported regions of origin were South America (125, 37%), the Caribbean (71, 21%), the Netherlands (63, 19%) and south and southeast Asia (33, 10%). Interestingly, many of the trans people originated from only a few specific countries. Among the 125 individuals from South America, there were 31 people from Ecuador, 25 from Brazil, 21 from Colombia, 15 from Suriname, and 14 from Venezuela. Most frequently reported countries of origin in the Caribbean were the former Netherlands Antilles (34) and Cuba (16), while 17 people from south and southeast Asia originated from Thailand.

In total, 92 trans people, or 34% of those born abroad, had a documented HIV-1 diagnosis before moving to the Netherlands. The majority (63) of these 92 people had already started ART before arrival. By the time these 63 people entered HIV care in the Netherlands, 46 (73%) had HIV RNA levels below 200 copies/ml, which was lower than in cis people of whom 83%, or 1,883 out of 2,270, had RNA levels below 200 copies/ml.

Diagnosis

In 2020-2022, 37 trans individuals were newly diagnosed with HIV while living in the Netherlands. These 37 people were relatively young, with a median age of 32 years (IQR 29-35) at the time of their HIV diagnosis, and most of them (30) 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 37 trans individuals, 14 were diagnosed with a recent HIV infection, 14 with established, and 8 with late-stage HIV infection, which was comparable to the distribution across these stages among MSM; for 1 individual the stage of infection could not be determined. Trans individuals took somewhat longer to reach HIV care than other people, with 86% being in care within four weeks of diagnosis compared to 96% of other people diagnosed in 2020-2022.

Population in care

In total, 272 (81%) of the 334 trans individuals with HIV-1 were known to be in clinical care by the end of 2022. Of the 62 people who were not in care anymore, 14 had died, including four who died of AIDS and two individuals whose cause of death was recorded as suicide. Another 17 had moved abroad. The remainder were either lost to care (26), only moved to the Netherlands in 2023 (three), or only entered HIV care in 2023 (two). In total, 12 of the people who moved abroad and 18 of those lost to care had RNA levels below 200 copies/ml at their last viral load measurement.

Clinical condition

The majority of trans people in clinical care (266, or 98%), had started ART by the end of 2022. Of the 266 people in care with a viral load measurement in 2022, 251 (94%) had a last measurement in that year below 200 copies/ml; this proportion was 96% when considering individuals who had started therapy. The most recent CD4 count in 2020-2022 of those in care stood at a median of 730 (IQR 520-932) cells/mm^3, which was comparable to the CD4 counts in the total population in care.

HIV-2

In total, 101 of the 31,844 registered individuals with HIV acquired an HIV-2 infection (12 MSM, 34 other men, and 55 women); 13 of these were diagnosed in 2012 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 2022, a total of 60 people were still in clinical care, 22 had died, seven had moved abroad, and 12 had no contact with HIV care during that year. The median age of those still in care was 63 years (IQR 56-67); 53 (88%) individuals were 50 years or older. The majority (90%) of those in care had been living with HIV-2 for more than 10 years, while 45% had been living with it for more than 20 years.

Clinical condition

Of the 60 people still in care, 48 had a most recent viral load measurement below 200 copies/ml, and 11 people had no available HIV-2 RNA result in 2022; there was one individual with a viral load above 200 copies/ml. Most people in care (42, 70%) had started ART. Of the 18 individuals who were still in care but had not started therapy, 13 had a viral load measurement below 200 copies/ml, while the other 5 people had no RNA measurement in 2022. CD4 counts in the group of 60 people in care were a median of 680 (IQR 527-868) cells/mm^3.

Conclusions

Since 2008 there has been a steady decrease in the annual number of new HIV diagnoses; in recent years, that figure has fallen below 500. However, this downward trend appeared to level off in 2022 with 393 (adjusted 461) new diagnoses, compared to 410 (adjusted 439) in 2021. The decrease in HIV diagnoses can, in part, be attributed to a fall in the estimated annual number of newly acquired HIV infections. However, as a result of disrupted testing services in 2020 and 2021 due to the (partial) lockdowns in response to COVID-19, the number of diagnoses in these years may be slightly lower than expected if we look at the long-term declining trend.

In 2022, 13% of the new HIV diagnoses among MSM and trans men and women were in people who reported prior use of PrEP. These people with prior use of PrEP accounted almost entirely for the rebound in the proportion of individuals diagnosed with a recent HIV infection compared with 2021.

Apart from the approximately 461 new HIV diagnoses in 2022, there were another 454 people born abroad who arrived in the Netherlands in 2022 and had a documented HIV-1 diagnosis prior to arrival. These 454 individuals included 185 (41%) people from Ukraine and represented an increase of 52% compared with the average number in 2018-2021. The majority of the migrants had already started antiretroviral therapy before arriving in the Netherlands and had a suppressed viral load.

A large proportion (48%) of newly diagnosed individuals already had late-stage HIV infection (i.e. CD4 counts below 350 cells/mm^3 or AIDS, and no evidence of a recent HIV infection) at the time of diagnosis. The downward trend in the proportion diagnosed with late-stage HIV has halted, and numbers appear to be increasing in the most recent years. This may, in part, be a consequence of increased efforts by healthcare professionals on HIV indicator condition-guided testing. The increase may also be a result of earlier diagnosis in other groups: the rapid diagnosis of people with early HIV infection, in combination with decreasing numbers of people newly acquiring an HIV infection, mean the undiagnosed population is mainly comprised of people who have been living with HIV for longer periods. That being the case, the observed proportion with late-stage HIV stems from a combination of underlying dynamics in transmission and diagnosis, and may be less suitable as an indicator of late-stage HIV. The absolute number diagnosed with late-stage HIV is more useful; this number is still steadily, albeit gradually, decreasing.

In recent years, almost all newly diagnosed individuals started ART within six months of diagnosis, irrespective of the stage of their HIV infection. This earlier therapy, combined with increased testing, earlier diagnosis, and a decreasing number of newly acquired HIV infections, has resulted in the Netherlands now being close to achieving the UNAIDS' 2025 targets of 95-95-95, with the current figures standing at 94-96-96[13].

Recommendations

The backlog in the collection of data on people with HIV (of whom SHM had been notified) was below the pre-specified maximum (one year) for all treatment centres. This was due, in part, to the implementation of an automated import of laboratory measurements (LabLink) into the SHM database. As a result, a reassessment of the continuum of HIV care for 2021 showed that the difference in the number of individuals in each stage was less than one percent, compared to the figures presented in last year's report. Nevertheless, in all stages of the care continuum the number of people was found to be greater than last year's reported figures, illustrating a delay in notifying SHM of people with HIV. Although the impact of delayed notification is expected to be small in terms of data on a national level, it may be more pronounced for regional or city-level data, where numbers are smaller. For that reason, it remains crucial that SHM is promptly notified of people with HIV in care.

One of the care continuum indicators that is not performing as well as some others, is the proportion of people who are still in care. In total, 1,160 individuals who were (1) diagnosed in or before 2022, (2) had received HIV care in the last ten years, and (3) had been registered with SHM, were recorded as lost to care (i.e. they did not visit their HIV physician or nurse in 2022, but they were not known to have died or moved abroad). The large proportion of people born abroad among those lost to care suggests that some may have left the Netherlands and are now receiving care in a different country. According to data from Statistics Netherlands, this appeared to be indeed the case, with 259 (22%) of the 1,160 having moved out of the country. Worryingly, 14% of people considered lost to care planned a transfer of care to another treatment centre but there was no confirmation that they did indeed register at a new centre. A procedure compliant with current privacy regulations has recently been implemented to follow-up on these individuals once they have arrived at their new centre. As a result, the proportion lost to care due to planned transfer of care should decrease in the coming years.

When compared with older age categories, HIV care continuum indicators were less favourable in young people between 15 and 24 years of age. One in five of those who were diagnosed and entered into HIV care had an unsuppressed viral load. On closer inspection, the largest gap in the cascade in *Figure 1.1B* appears to be the proportion with a suppressed viral load below 200 copies/ml among those who started ART. Improving viral suppression in these young individuals, thereby maintaining their health and preventing transmission of HIV, is one of the many steps on the road to zero new HIV infections.

The decrease in the number of new HIV diagnoses is likely, in part, to be the result of various positive developments mentioned earlier in this chapter. These include: earlier diagnosis; starting therapy sooner; a larger proportion of people with viral suppression; and a smaller number living with undiagnosed HIV. In the third quarter of 2019, pre-exposure prophylaxis (PrEP) became available on a national level for those at highest risk of acquiring HIV, which was an important extension of the available preventive measures. Although most people enrolled in the PrEP programme are adequately protected from acquiring HIV, some people drop out prematurely as illustrated by the considerable proportion of new diagnoses among MSM and trans men and women who reported prior use of PrEP. In order to more fully achieve a sustained and steeper reduction in the number of new HIV infections, access to PrEP care as well as care for individuals using PrEP needs to be further optimised.

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Special reports

1.1 Prior use of pre-exposure prophylaxis

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Summary

The number and proportion of MSM and transgender persons who report prior use of PrEP continued to increase: 6.8% in 2021 and 12.0% in 2022 of MSM and transgender persons newly diagnosed with HIV in the Netherlands reported prior use of PrEP.

Of the individuals who reported prior use of PrEP and who received a genotypic resistance test prior to initiation of ART, 20% were diagnosed with HIV strains that harbour resistance mutations that are associated with the use of PrEP. Reassuringly, the virological treatment response after initiation of ART appears to be unaffected by the prior use of PrEP, also in those individuals where resistance mutations had been detected.

A substantial proportion (40.1%) of MSM and transgender people who reported they did not use PrEP, had indicated they would have wanted to do so, but either had no access to PrEP (21.7%), were on a PrEP waiting list when they seroconverted (1.3%), or tested HIV positive while being screened for HIV before initiating PrEP (17.1%).

Aims

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

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

In the group of MSM and transgender persons who did not report prior use of PrEP, we investigated their reasons and barriers for not having used PrEP.

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

Data collection

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

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

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

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

Population of interest

Data on prior use of PrEP had been collected for all 2,926 adults who entered into HIV care in one of the 24 Dutch HIV treatment centers and had been newly diagnosed with HIV between 1 January 2018 and 31 December 2022. In the EMR of 992 (33.9%) individuals, information was recorded on prior use of PrEP. The proportion of individuals for whom this information was available in the EMR increased from 15.1% in 2018, to 31.8% in 2019, 38.8% in 2020, 49.7% in 2021, and 50.5% in 2022 (Figure 1, blue bars).

Of the 2,926 individuals diagnosed with HIV between 2018 and 2022, 1,819 were from the primary target groups of the Dutch PrEP programme: 1,737 cisgender MSM and 82 transgender persons (73 transgender women, and 9 transgender men). In the PrEP target groups of MSM and transgender persons, 687 (37.8%) out of 1,819 individuals had information about prior PrEP use available in the EMR: 16.3% in 2018, 35.3% in 2019, 45.5% in 2020, 57.6% in 2021, and 58.5% in 2022 (Figure 1, red bars).

The proportion of individuals newly entering in HIV care in the Netherlands, who were not born in the Netherlands, has been increasing over time. Of the 2,926 individuals, 1,370 (46.8%) were born in the Netherlands, and the remaining 1,556 (53.2%) individuals were migrants. Of these 1,556 migrants, 418 (26.9%) individuals were already diagnosed with HIV before migrating to the Netherlands, and 298 (19.2%) individuals had a negative HIV-test after they migrated to the Netherlands and hence are considered to have acquired HIV in the Netherlands. For the remaining 840 (54.0%) migrants, we could not ascertain the country were they acquired HIV, because although these individuals first tested HIV positive in the Netherlands, they had no documented negative HIV test in the Netherlands.

The demographic characteristics of the group for whom EMR information on prior PrEP use was available were largely similar to those for whom it was not (see *Table 1*). Information on prior PrEP use for MSM was slightly more likely to be available than it was for heterosexuals and other HIV acquisition categories. For transgender women however, this information was less likely to be available.

Of the 992 individuals for whom information on prior use of PrEP was available, the majority (886, or 89.3%) reported no such use, whereas 106 (or 10.7%) reported prior PrEP use (*Table 2*). In terms of breakdown by gender:

- 103 of the 823 cisgender men reported prior PrEP use;
- one of the six transgender men reported prior PrEP use;
- one of the 134 cisgender women reported prior PrEP use; and
- one of the 29 transgender women reported prior PrEP use

Of the 103 cisgender males, 97 likely acquired HIV through sexual contact with other men, 2 men through heterosexual contact, 2 men through other routes (both through sexual contact, but without information about the sex of their partners), and for 2 men the HIV acquisition route was unknown. The one cisgender female, the one transgender female, and the one transgender male, all acquired HIV through sexual contact with males. In total, 99 of the 106 individuals who reported prior use of PrEP belonged to the primary target groups for PrEP in the Netherlands.

The 106 individuals who reported prior use of PrEP were younger, and had higher CD4 counts at diagnosis compared to those who did not use PrEP.

PrEP awareness and uptake

For 299 (50.9%) of the 588 MSM and transgender individuals who reported no prior PrEP use, information was available on why they had not done so. 'Presumed to be at low risk for HIV' (27.4%), 'Wanted to use PrEP but had no access' (21.7%), and 'Not knowing PrEP existed' (21.1%) were the most commonly reported reasons. Of the 65 individuals who indicated that they had wanted to use PrEP but had no access, 29 were born in the Netherlands, 36 were migrants of whom 17 were already diagnosed with HIV before they came to the Netherlands. In total, 51 (17.1%) individuals had wanted to start using PrEP but tested HIV-positive at screening before entry into a PrEP programme. Four individuals (1.3%, all born in the Netherlands) reported that they seroconverted while on a PrEP programme waiting list.

Figure 2 shows time trends in the reported reasons for not having used PrEP in MSM and transgender persons.

We used the data from Statistics Netherlands (CBS) to further characterize the MSM and transgender people who had a recorded reason for not using PrEP. Those who indicated they had a knowledge gap about PrEP (either they did not know PrEP, or they did not perceive themselves at high risk for HIV, or they did not want to use PrEP) were compared to those who indicated they could not obtain PrEP in

time (they knew about PrEP and were willing to use it but did not have access to PrEP, or tested positive while on a PrEP waiting list or during PrEP intake). Of those who indicated they had a knowledge gap, 108 individuals could be successfully matched with datasets from Statistics Netherlands. Of those who indicated they could not obtain PrEP in time, 71 individuals could be successfully matched with datasets from Statistics Netherlands. Table 3 shows the main findings expressed as column percentages. Because of the low number of individuals, these analyses are exploratory and should not be overinterpreted.

Older individuals, and those with lower scholarly attainment, were more likely to have a PrEP knowledge gap. Place of residency (4 biggest cities vs. other) showed no associations with PrEP knowledge and access. Those with a low income, those who did not live in the country's 4 largest cities, and individuals with a non-Western migrant background were not more likely to report a PrEP knowledge gap.

Prior use of PrEP

We calculated percentages of prior PrEP use of all 1,819 MSM and transgender people who were diagnosed with HIV between 2018 and 2022 for which SHM collected data on prior PrEP use. 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 for which prior PrEP use was recorded has increased since 2019 (P_{trend}=0.0007, see Figure 3, blue bars), with:

- 1.6%, or 9 out of 553 individuals, in 2018;
- 4.6%, or 20 out of 433 individuals, in 2019;
- 7.0%, or 22 out of 314 individuals, in 2020;
- 6.8%, or 19 out of 278 individuals, in 2021;
- 12.0%, or 29 out of 241 individuals, in 2022.

When limiting the population by excluding those individuals who were diagnosed with HIV prior to migrating to the Netherlands, the proportions were similar: 2.0% in 2018, 4.7% in 2019, 6.8% in 2020, 6.6% in 2021, and 11.9% in 2022 (see Figure 3, red bars).

The characteristics of the 106 individuals who reported prior use of PrEP are shown in *Table 4*, with a stratification by those who used PrEP in the Netherlands and those who used it while living abroad, with migrants who initiated PrEP before they migrated to the Netherlands but who continued using PrEP after they migrated to the Netherlands being included into the former group.

Access to PrEP and usage patterns

Of the 106 individuals who reported prior PrEP use, 17 (16.0%) were migrants who had used PrEP before moving to the Netherlands. There were 89 individuals who had used PrEP in the Netherlands, 3 of these had started PrEP before migrating to the Netherlands but continued using it until after they migrated to the Netherlands. In the remainder of this chapter we will report on these 89 individuals.

Of the 89 individuals who had used PrEP, 53 (59.6%) obtained it from a healthcare provider in the Netherlands (see Table 4), comprising the Municipal Health Service (25), family practitioner (22), and HIV treatment centre (4). There was no further detailed information available for 2 individuals. The remaining individuals for whom this information was recorded, obtained their PrEP:

- from a buyers' club/internet/store outside of the Netherlands (14);
- from a healthcare provider outside of the Netherlands (2); or
- from a friend living with HIV who had donated some of their own medication (2).

There was no information available about the PrEP provider for the remaining 18 individuals.

For 49 of the 89 individuals who reported using PrEP, did so in the form of co-formulated tenofovir disoproxil fumarate / emtricitabine. For the remaining 40 individuals there was no further information available on the specific antiretrovirals used, but most likely they too used co-formulated tenofovir disoproxil fumarate / emtricitabine.

Dosage schedule information was available for 52 individuals:

- 22 individuals (24.7%) reported on-demand use
- 21 individuals (23.6%) reported daily use
- 6 individuals (6.7%) reported intermittent use (i.e. a fixed schedule but not seven days a week)
- 3 individuals (3.4%) reported having used PrEP less than a week

For the remaining 39 individuals (42.9%), no dosage schedule information was available.

Of the 89 individuals who reported prior PrEP use, 27 (30.3%) had regular medical check-ups by the Public Health Service during that period. 5 individuals (5.6%) attended an HIV treatment centre, 11 (12.4%) were seen by a family practitioner,

and 1 individual (1.1%) was checked by a medical specialist other than HIV treatment centre staff. Thirteen individuals (14.6%) reported that they did not have any medical check-ups, and there was no information available for the remaining 32 individuals (36.0%).

Of the 17 individuals who had used PrEP before migrating to the Netherlands, 2 were known to have seroconverted in the Netherlands (in an earlier HIV test performed after migration they had tested negative). Eight of those 17 individuals had already tested HIV positive before migrating to the Netherlands, and for 7 individuals it is uncertain if they seroconverted before or after migrating to the Netherlands.

The median (IQR) number of days between the last dose of PrEP and testing HIV-positive was calculated only for those individuals for which the relevant dates were known with sufficient precision (to within a month) and was 17 (0-113) days. A total of 26 (28.6%) individuals tested HIV-positive while still using PrEP. Of the 65 individuals who did not test HIV-positive while taking PrEP, 25 reported having tested HIV-seronegative after their last use of PrEP, while 25 did not have an HIV-test shortly after discontinuing the use of PrEP. There was no information available for 15 individuals.

PrEP and possible drug resistance

Genotypic resistance test results were available for 65 (73.0%) of the 89 individuals who reported having used PrEP when first entering HIV care. Reverse transcriptase (RT) resistance-associated mutations (RAM)[a], associated with the use of PrEP, were detected in 13 individuals (20.0%). All 13 individuals harboured an M184VI RT RAM (which decreases susceptibility to lamivudine and emtricitabine), and 2 of these also harboured a K65R RT RAM (which is selected for by tenofovir and decreases susceptibility to tenofovir, abacavir, lamivudine and emtricitabine).

All 13 individuals in whom M184VI RT RAM (with or without K65R RT RAM) had been detected, were still using PrEP at the moment they tested HIV positive, or they had last used PrEP only a few weeks before testing positive.

Prior use of PrEP and antiretroviral therapy (ART)

Data on the first-line ART and subsequent virological treatment response was available for 105 of all 106 individuals who reported prior use of PrEP. This includes the 13 individuals with M184V/I (with or without K65R RT RAM), all of whom started a regimen containing an integrase inhibitor. Eight of these combined the

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.

integrase inhibitor together with a protease inhibitor with or without additional nucleoside-analogue RT inhibitors (NRTIs). The remaining five individuals combined an integrase inhibitor with two NRTIs.

Of the remaining 92 individuals with either no baseline resistance test results, or whose test showed no evidence of the M184VI or K65R RT RAM, 64 initiated a first-line regimen consisting of:

- an integrase inhibitor plus two NRTIs (n=59)
- a protease inhibitor plus two NRTIs (n=4)
- an integrase inhibitor plus a protease inhibitor, with or without additional NRTIs (n=24)
- a non-nucleoside RT inhibitor plus two NRTIs (n=2)
- lamivudine / dolutegravir (n=3)

The 13 individuals with an M184V (but without K65R) RT RAM had a median follow-up time of 84.0 (IQR 39.4-184.3) weeks after initiating ART. In one of these 13 individuals the first-line regimen was discontinued due to a persistent suboptimal virological efficacy. This individual's plasma viral load had initially become undetectable three months after starting on tenofovir alafenamide / emtricitabine / bictegravir. However, in the following two-year period all eight recorded viral load measurements showed detectable viremia. The highest recorded value was 253 copies/ml. Eventually, ART was switched to a triple-class regimen consisting of 2 NRTI plus an INSTI plus a boosted protease inhibitor, after which the viral load durably became undetectable. Later, the regimen was simplified to a two-class single-tablet regimen.
In another individual with M184V (but without K65R) RT RAM the plasma viral load quickly dropped to below 100 copies/mL, but remained detectable on all measurements up to 1.5 years after initiating cART (range 61-97 copies/mL).
The remaining 11 individuals with M184V (two of them also had a K65R) all had an optimal treatment response with successfully sustained viral suppression after initiating cART.

For the 92 individuals with no evidence of M184VI (with or without K65R RT RAM) in the baseline resistance test or for whom no test data was available, all 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 77.5 (IQR 27.9-145.6) weeks. In six individuals a viral rebound (defined as having a viral load measurement above 200 copies/ml following an initial treatment response) was

recorded. In five of these six individuals the viral rebound occurred because they temporarily interrupted the use of ART. Four of these five individuals re-suppressed after restarting the same or another ART regimen, except for one individual who developed virological failure after restarting the same NNRTI-based triple regimen, and was subsequently switched to a second line regimen containing a protease inhibitor plus integrase inhibitor after which the viral load durably re-suppressed. The three individuals who initiated ART with dolutegravir / lamivudine all quickly became undetectable and experienced no viral breakthrough.

Conclusions

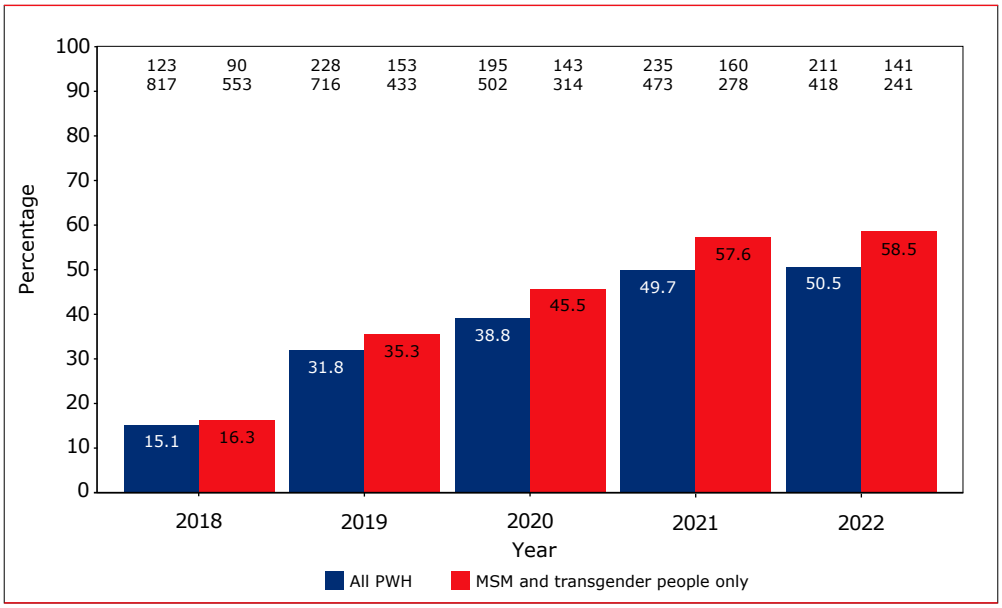
The number and proportion of newly diagnosed MSM and transgender individuals entering HIV care who reported prior use of PrEP continued to increase. In 2022, 12.0% (n=29) of newly diagnosed MSM and transgender people reported prior use of PrEP. However, this is probably a conservative estimate because in this analysis individuals for whom no explicit information about prior PrEP use was recorded in their EMR were considered not to have used PrEP. The observed increase over time cannot be completely explained by health care providers being more aware of and hence better documenting prior PrEP use.

The individuals who indicated they had used PrEP are a very heterogeneous group. 56 (52.8%) of them were migrants, 17 (16.0%) of whom had already stopped using PrEP before they migrated to the Netherlands. Of those individuals who had used PrEP in the Netherlands, 53 (59.6%) had obtained PrEP through a Dutch health care provider. A few individuals who had used PrEP did not belong to one of the target groups for PrEP in the Netherlands, these were either migrants who used PrEP before migrating to the Netherlands, or they were individuals who had obtained PrEP through informal means.

Of those individuals who had used PrEP in the Netherlands, 26 (28.6%) were diagnosed with HIV while still using PrEP. Of the 65 individuals who reported prior use of PrEP and who received a genotypic resistance test prior to initiation of ART, 13 (20%) were found to harbour resistance mutations that were probably associated with the continued use of PrEP after seroconversion. Reassuringly, the virological treatment response after initiation of ART appeared to be unaffected by the prior use of PrEP, also in those individuals where resistance mutations had been detected.

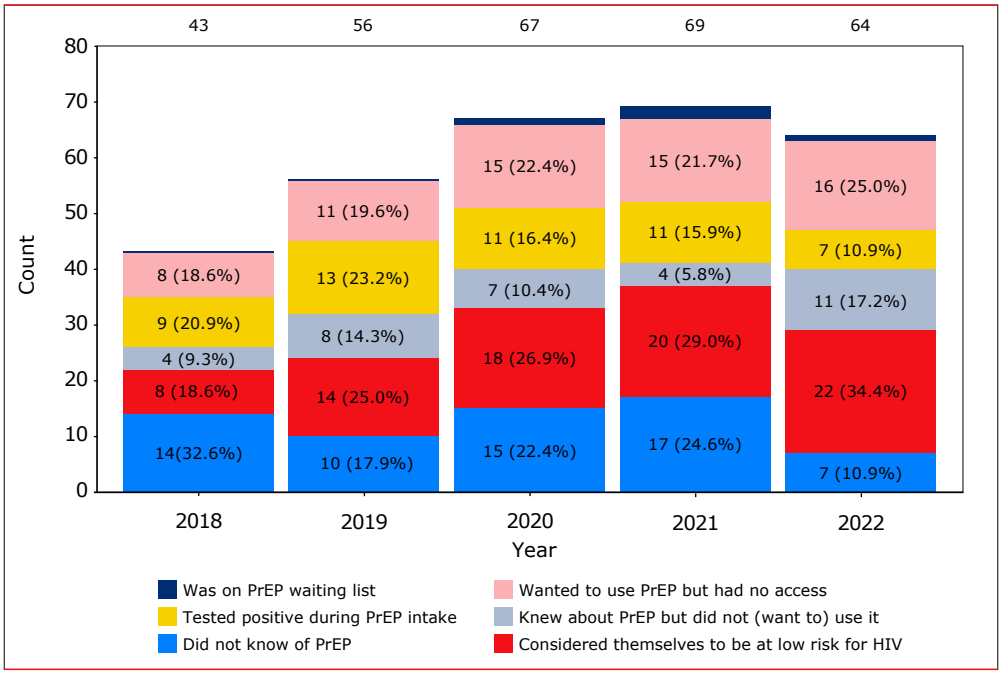
A substantial proportion (40.1%) of MSM and transgender people who reported they did not use PrEP, had indicated they would have wanted to do so, but either had no access to PrEP (21.7%), were on a PrEP waiting list when they seroconverted (1.3%), or tested HIV positive while being screened for HIV before initiating PrEP (17.1%).

Figure 1: *Number and proportion of individuals diagnosed with HIV per calendar year for whom information on prior use of PrEP is available.*



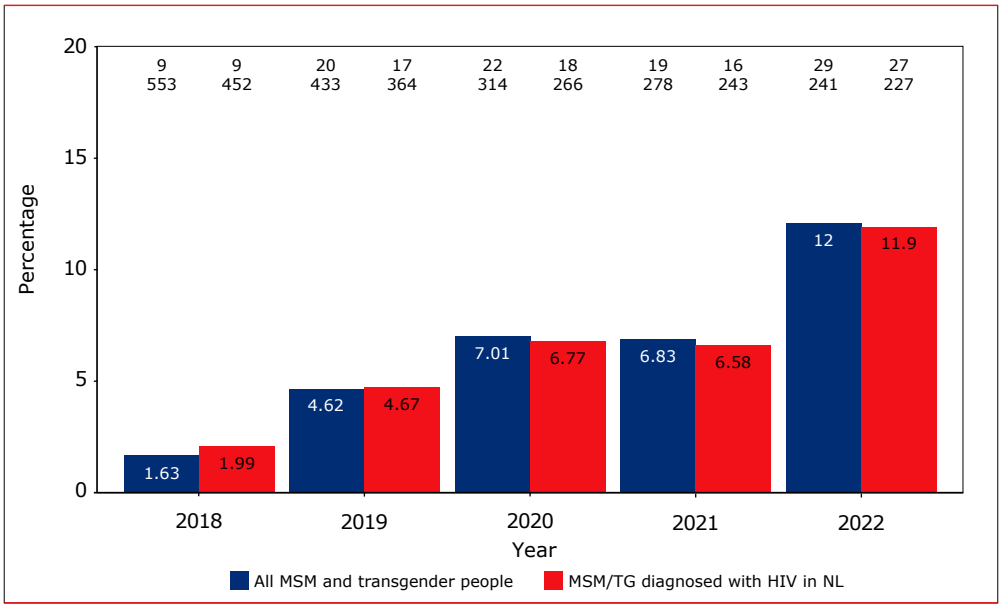
Legend: *The numbers in the top line are the number of individuals for whom information on prior use of PrEP is available in their electronic medical records. The second line is the total cohort size of each calendar year.*

Figure 2: Time trends in the reported reasons for not having used PrEP in MSM and transgender persons.



***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 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.

Figure 4: *Time trends in the number and proportion of individuals newly diagnosed with HIV reporting prior use of PrEP, stratified by PrEP provider.*

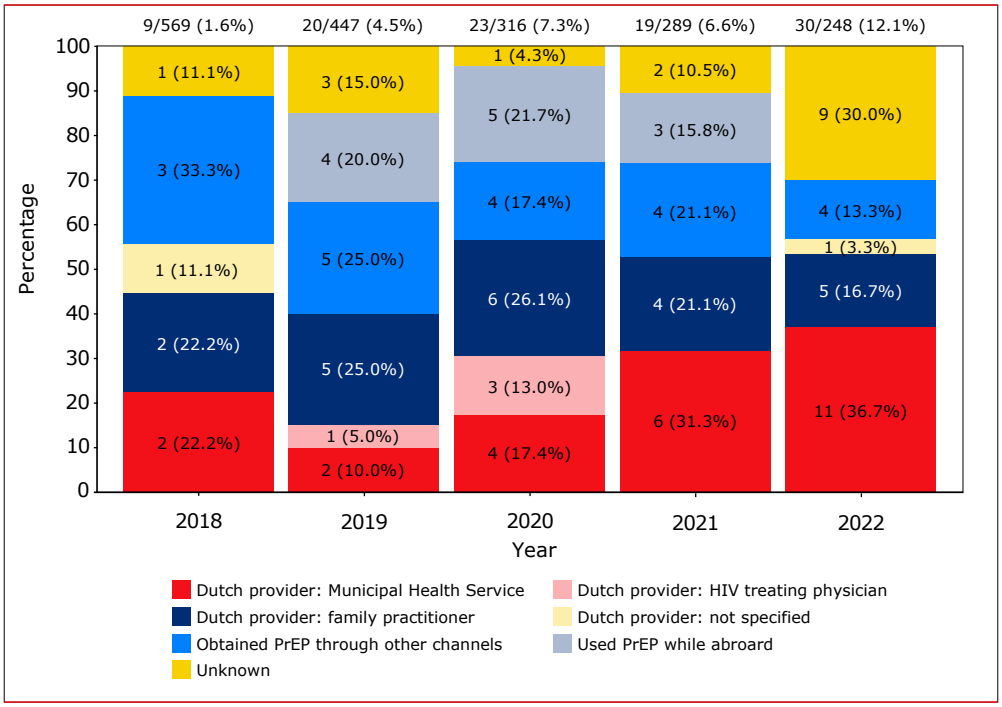


Table 1: Characteristics of individuals with and without available information on prior PrEP use.

	Info on PrEP available	No info available	p-value
Number of subjects	992 (33.9%)	1934 (66.1%)	
Age	37 (29.1-48.8)	38 (28.9-49.5)	0.367
Gender			0.004
Cisgender male	823 (83.0%)	1545 (79.9%)	
Cisgender female	134 (13.5%)	342 (17.7%)	
Transgender male	6 (0.6%)	3 (0.2%)	
Transgender female	29 (2.9%)	44 (2.3%)	
Region of birth			1.000
Born in the Netherlands	464 (46.8%)	906 (46.8%)	
Migrant	528 (53.2%)	1028 (53.2%)	
Documented seroconversion in NL or before migration *			0.109
In the Netherlands	125 (23.7%)	173 (16.8%)	
Before migration to the Netherlands	126 (23.9%)	292 (28.4%)	
Unknown / uncertain	277 (52.5%)	563 (54.8%)	
HIV acquisition category			<.001
MSM	676 (68.1%)	1124 (58.1%)	
Heterosexual acquisition	229 (23.1%)	519 (26.8%)	
Other acquisition categories	40 (4.0%)	104 (5.4%)	
Unknow acquisition route	55 (5.5%)	205 (10.6%)	
Recent HIV acquisition			
Tested pos. <365 days after last neg. test	263 (26.5%)	305 (15.8%)	<.001
Tested pos. <180 days after last neg. test	158 (15.9%)	145 (7.5%)	<.001
CD4 at HIV diagnosis	410 (209-630)	360 (154-570)	<.001

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

Table 2: Comparison of individuals with and without prior use of PrEP.

	Prior use of PrEP	No prior use, target group	No prior use, other groups	p-value
Number of subjects	106 (10.7%)	588 (59.3%)	298 (30.0%)	
Age	31.4 (26.9-40.9)	35 (28.4-47.8)	42.4 (33.3-52.1)	<.001
Gender				<.001
Cisgender male	103 (97.2%)	555 (94.4%)	165 (55.4%)	
Cisgender female	1 (0.9%)	0 (0.0%)	133 (44.6%)	
Transgender male	1 (0.9%)	5 (0.9%)	0 (0.0%)	
Transgender female	1 (0.9%)	28 (4.8%)	0 (0.0%)	
Region of birth				0.068
Born in the Netherlands	50 (47.2%)	291 (49.5%)	123 (41.3%)	
Migrant	56 (52.8%)	297 (50.5%)	175 (58.7%)	
Documented seroconversion in NL or before migration*				<.001
In the Netherlands	28 (50.0%)	70 (23.6%)	27 (15.4%)	
Before migration to the Netherlands	8 (14.3%)	99 (33.3%)	19 (10.9%)	
Unknown / uncertain	20 (35.7%)	128 (43.1%)	129 (73.7%)	
HIV acquisition category				<.001
MSM	97 (91.5%)	579 (98.5%)	0 (0.0%)	
Heterosexual acquisition	4 (3.8%)	5 (0.9%)	220 (73.8%)	
Other acquisition categories	3 (2.8%)	3 (0.5%)	34 (11.4%)	
Unknown acquisition route	2 (1.9%)	9 (1.5%)	44 (14.8%)	
Recent HIV acquisition				
Tested pos. <365 days after last neg. test	81 (76.4%)	165 (28.1%)	17 (5.7%)	<.001
Tested pos. <180 days after last neg. test	53 (50.0%)	99 (16.8%)	6 (2.0%)	<.001
CD4 at HIV diagnosis	570 (360-720)	440 (255-640)	257 (100-540)	<.001
Late presenter (CD4<350)	25 (23.8%)	221 (37.8%)	176 (59.1%)	<.001
Very late presenter (CD4<200 or AIDS)	8 (7.5%)	111 (18.9%)	121 (40.6%)	<.001
Reason known for not having used PrEP	106 (100%)	299 (50.9%)	119 (39.9%)	<.001
Reasons for not having used PrEP				
Did not know of PrEP	n.a.	63 (21.1%)	77 (64.7%)	
Presumed to be at low risk for HIV	n.a.	82 (27.4%)	33 (27.7%)	
Knew PrEP but did not want to use it	n.a.	34 (11.4%)	3 (2.5%)	
Tested positive at PrEP intake	n.a.	51 (17.1%)	0 (0.0%)	
Wanted PrEP but had no access	n.a.	65 (21.7%)	6 (5.0%)	
Was on PrEP waiting list	n.a.	4 (1.3%)	0 (0.0%)	

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

Table 3: socio-economic characteristics of those MSM and transgender persons with a known reason for not having used PrEP.

	Knowledge gap	Lack of access
Total group size	108	71
Age		
< 30 years	9.3%	19.7%
30 – 49 years	53.7%	54.9%
≥ 50 years	37.0%	25.4%
Scholarly attainment		
Higher / middle	44.4%	63.4%
Lower	19.4%	11.3%
Unknown	10.2%	18.3%
Income class		
≥ 140% of social minimum	71.3%	59.2%
< 140% of social minimum	18.5%	18.3%
unknown / institutionalized	10.2%	22.5%
Place of residence		
Amsterdam	33.3%	31.0%
Rotterdam / Utrecht / the Hague	10.2%	14.1%
Other	56.5%	54.9%
Ethnicity		
Dutch	64.8%	53.5%
Migrant, Western	25.9%	22.5%
Migrant, non-Western	10.2%	23.9%

Table 4: characteristics of individuals who reported use of PrEP.

	PrEP used in the Netherlands	PrEP used abroad	p-value
Number of subjects	89 (84.0%)	17 (16.0%)	
Age	32.1 (27- 43)	29.8 (25.7-33.6)	0.113
Gender			0.004
Cisgender male	89 (100%)	14 (82.4%)	
Cisgender female	0 (0.0%)	1 (5.9%)	
Transgender male	0 (0.0%)	1 (5.9%)	
Transgender female	0 (0.0%)	1 (5.9%)	
Region of birth			<.001
Born in the Netherlands	50 (56.2%)	0 (0.0%)	
Migrant	39 (43.8%)	17 (100%)	
Acquisition category			<.001
MSM	87 (97.8%)	10 (58.8%)	
Heterosexual acquisition	0 (0.0%)	4 (23.5%)	
Other acquisition categories	1 (1.1%)	2 (11.8%)	
Unknow acquisition route	1 (1.1%)	1 (5.9%)	
STD diagnosed at entry into care			
HBV (HBs antigen positive	1 (1.2%)	1 (6.7%)	0.169
HCV (positive antibodies)	3 (3.6%)	0 (0.0%)	0.455
Syphilis (positive RPR/VDRL)	22 (26.5%)	6 (40.0%)	0.287
PrEP started before migrating to the Netherlands	3 (3.4%)	17 (100%)	
PrEP provider			<.001
Provider in the Netherlands	53 (59.6%)	0 (0.0%)	
- Public Health Service	25 (28.1%)	0 (0.0%)	
- HIV treatment center	4 (4.5%)	0 (0.0%)	
- Family practitioner	22 (24.7%)	0 (0.0%)	
- No info	2 (2.2%)	0 (0.0%)	
Provider outside of the Netherlands	2 (2.2%)	7 (41.2%)	
Buyers club/internet/store outside of the Netherlands	14 (15.7%)	3 (17.6%)	
From friend living with HIV	2 (2.2%)	1 (5.9%)	
No info	18 (20.2%)	6 (35.3%)	
Seroconversion during PrEP use			
Tested HIV-positive while on PrEP	26 (29.2%)	2 (11.8%)	
HIV-negative test performed after last dose of PrEP	25 (39.7%)	2 (13.3%)	
No HIV-negative test performed after last dose of PrEP	24 (38.1%)	12 (80.0%)	
Unknown if HIV test was performed after last dose of PrEP	14 (22.2%)	1 (6.7%)	
Seroconverted in the Netherlands or before migration			<.001
In the Netherlands	76 (85.4%)	2 (11.8%)	
Before migration to the Netherlands	0 (0.0%)	8 (47.1%)	
Unknown / uncertain	13 (14.6%)	7 (41.2%)	

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

1.2 Identifying gaps in HIV care in the Netherlands using data from Statistics Netherlands

Vita Jongen, Rosan van Zoest, Mark Verhagen, Anders Boyd, Ard van Sighem, Marc van der Valk

Summary

To continue the path towards zero new HIV infections we need more focused insight into the circumstances of people who do not progress through the HIV care continuum and who, as a result, retain a detectable HIV-1 viral load. The results from this chapter are based on analyses made by SHM using non-public data from Statistics Netherlands (CBS). CBS is an independent organisation that collects, processes and publishes reliable statistical data on Dutch residents.

We combined all data from individuals with HIV registered by SHM with 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 postal code. We used all data up to and including 2021.

We were able to successfully combine the data of 20,996 individuals with data from CBS. That figure amounts to 94% of the 22,362 individuals ever linked to care and registered in the SHM database in 2021. Compared to the general Dutch population, individuals ever linked to HIV care were:

- younger (44% under 40 years of age vs. 34%);
- more often male (85% vs. 49%);
- more often living in a single-person household (52% vs. 29%);
- more often living in highly urban areas (49% vs. 25%); and
- more often in the lowest income level (16% vs. 9%) and receiving social welfare (13% vs. 4%)

Viral suppression among women and other men was below 95% regardless of socio-demographic characteristics and socio-economic status. Among MSM viral suppression was below 95% among those with an income of less than 120% of the social minimum, and among MSM with primary and secondary education. Further analyses will need be conducted to pinpoint the socio-demographic and socio-economic factors that affect optimal progression through the HIV care continuum.

Box 1: Definitions used in this chapter.

Term	Definition
Advanced HIV disease	Defined as a CD4 count below 200 cells/mm^3 or an AIDS-defining event, and no evidence of having acquired HIV in the 12 months before diagnosis.
Disengage-ment from care	Individuals ever linked to care who did not attend an HIV clinical visit in 2021 (but did attend visits prior to 2021).
Late-stage HIV diagnosis	Defined as a CD4 count between 200-350 cells/mm^3 or an AIDS-defining event regardless of CD4 count at the moment of diagnosis, and no evidence of having acquired HIV in the 12 months before diagnosis.*
Linked to care	All individuals with at least one HIV clinical visit in 2011-2021 and who did not pass away or move abroad.
On ART	All individuals who started ART before or in 2021.
Other/chronic HIV	Defined as a CD4 count above 350 cells/mm^3 at the moment of diagnosis.
Recent HIV infection	Defined as evidence of having acquired HIV in the 12 months before diagnosis, based on a negative or indeterminate Western blot at the time of diagnosis, or a reported last negative HIV test at most 12 months before diagnosis.
Retention in care	All individuals with a clinical visit or a CD4/viral load measurement in 2021.
Viral suppression	Defined as an HIV-1 RNA <200 copies/mL.

**Of note, this definition differs from the definition used in Chapter 1 to assure late-stage and advanced diagnoses are mutually exclusive and could be assessed separately.*

Aim

The Netherlands is on track to achieve the UNAIDS 95-95-95 targets before 2025 (see Chapter 1). In 2022, an estimated 24,400 individuals (95% CI 24,220-24,720) were living with HIV. Of these, 21,094 individuals (86%) had an undetectable viral load. While this proportion is high, it nonetheless means that approximately 3,311 individuals with HIV in the Netherlands (including individuals unaware of their HIV infection) are likely to have a detectable HIV-1 viral load. To continue on the path towards zero new HIV infections, we need more focused insight into the circumstances of people whose progression through the HIV care continuum is suboptimal.

Data from SHM provide information relating to socio-demographic factors of the population with HIV, such as date of birth and gender at birth. However, SHM lacks information on other societal factors that could indicate delayed progression through the HIV care continuum, such as an individual's socio-economic status or level of education. Moreover, SHM cannot provide information on the socio-demographic characteristics of people who disengage from HIV care in the Netherlands. Yet if these data are combined with external data from Statistics Netherlands (CBS), the resulting information could provide a basis for further improvements in specific gaps in care.

Method

The results in this chapter are based on analyses made by SHM using non-public data from CBS. CBS is an independent organisation that collects, processes and publishes reliable statistical data on Dutch residents. We combined all data from individuals with HIV registered by SHM with 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 postal code. As there is a delay in data registration at CBS, we used data for all individuals who were diagnosed with HIV up until 31 December 2021 (i.e. the most recent data available at CBS).

The following variables from the CBS database were included:

Box 2:. Description of variables included from Statistics Netherlands.

Variable	Description
Debt restructuring	Indicates whether an individual used the Debt Rescheduling Natural Persons Act (Wet Schuldsanering Natuurlijke Personen, WSNP).
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'). 1. Secondary: Completed secondary vocational education ('MBO'), senior general secondary education ('HAVO') or pre-university level ('VWO'). 1. College/University: completed higher vocational education (HBO) or university.
Migration background	Based on the country of birth of the parents and the individual. An individual was categorised as Dutch if the individual and both parents were born in the Netherlands or if both parents were born in the Netherlands, but the individual was not. If the individual and at least one parent were born outside of the Netherlands, migration background was determined by the country of birth of the mother. If in this case the country of birth of the mother was the Netherlands, migration background was determined based on the country of birth of the father.
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	Categorised as: single person household, living together with or without children, other (i.e. institutionalised, 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 annually by the Ministry of Social Affairs and Employment.
Mental health care (basic)	Defined as declared costs (more than 0 euro) for basic mental health care.
Mental health care (specialised)	Defined as declared costs (more than 0 euro) for specialised mental health care.
Social welfare	Defined as receiving social welfare within a given year.
Use of antipsychotics	Use of medication for psychosis.
Use of anti-depressants	Use of medication for depression.
Urbanisation	Based on the density of households per km^2 within a municipality. Classified as: very urban (≥2500 addresses per km^2), urban (1500-2499 addresses per km^2), not urban and not rural (1000-1500 addresses per km^2), and rural (<1000 addresses per km^2).

We used annual data concerning socio-demographic and socio-economic information for our analyses. Information from a given year (e.g. 2021) was based on data registered at the end of the previous calendar year (e.g. registered by 31 December 2020). Individuals who had migrated or passed away were excluded from the study population in the calendar year following migration or death.

To minimise the risk of personal data inadvertently leading to the identification of an individual, data involving fewer than ten people were not reported. When the number of individuals between steps in the HIV care continuum

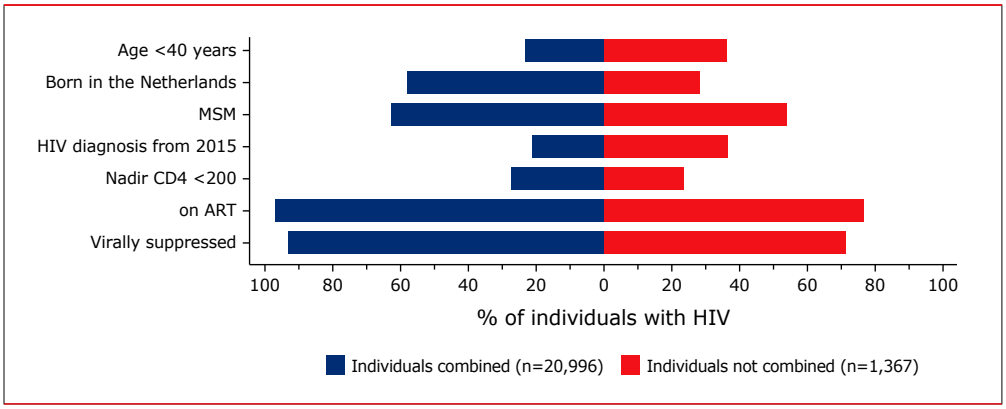
(e.g. between retention in care and using ART) amounted to fewer than five people, a range of values that included the minimum and maximum number of possible people was reported instead.

Description of the population sample

In 2021, there were 22,672 individuals ever registered in the SHM database. 310 (1%) individuals had migrated or died by 2021, according to CBS, and were subsequently excluded from the dataset. We were able to successfully combine the data of 20,996 individuals with data from CBS. That figure amounts to 94% of the 22,362 individuals registered in the SHM database in 2021 who were still living in the Netherlands.

SHM data show that individuals whose data could not be combined were younger, less often born in the Netherlands, less often MSM, and more often diagnosed with HIV after 2015 (Figure 1). Moreover, participants whose data could not be combined used ART less often and were subsequently less often virally suppressed.

Figure 1: *Socio-demographic and HIV-related characteristics of individuals whose data from SHM could be combined with Statistics Netherlands databases and those whose data could not.*



Note: *The percentage of virally suppressed people is calculated as the percentage of people prescribed ART with an HIV-1 RNA < 200 c/ml (individuals with combined SHM and CBS data, n=20,316; individuals without combined data, n=1,044).*

Abbreviations: *ART, antiretroviral therapy; HIV, human immunodeficiency virus; MSM, men who have sex with men.*

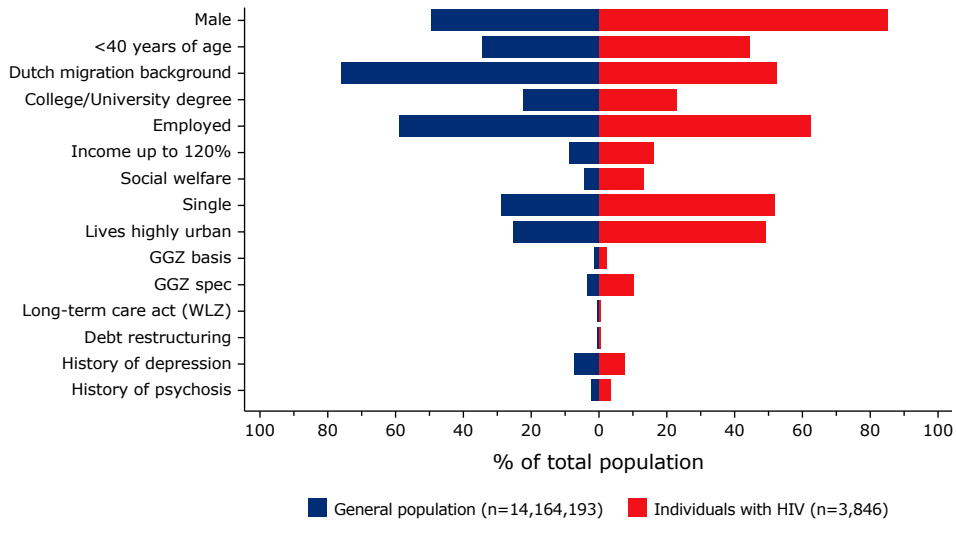
All individuals for whom demographic information was available and who were diagnosed with HIV from 2015 onwards (n = 3,846; 92% able to be combined with the CBS database) were compared (Figure 2a).

Compared to the general Dutch population, individuals ever linked to HIV care were:

- younger (44% under 40 years of age vs. 34%);
- more often male (85% vs. 49%);
- more often living in a single-person household (52% vs. 29%);
- more often living in highly urban areas (49% vs. 25%); and
- more often in the lowest income level (16% vs. 9%) and receiving social welfare (13% vs. 4%)

Moreover, people linked to HIV care also received specialist mental health care more often than the general Dutch population (10% vs. 4%).

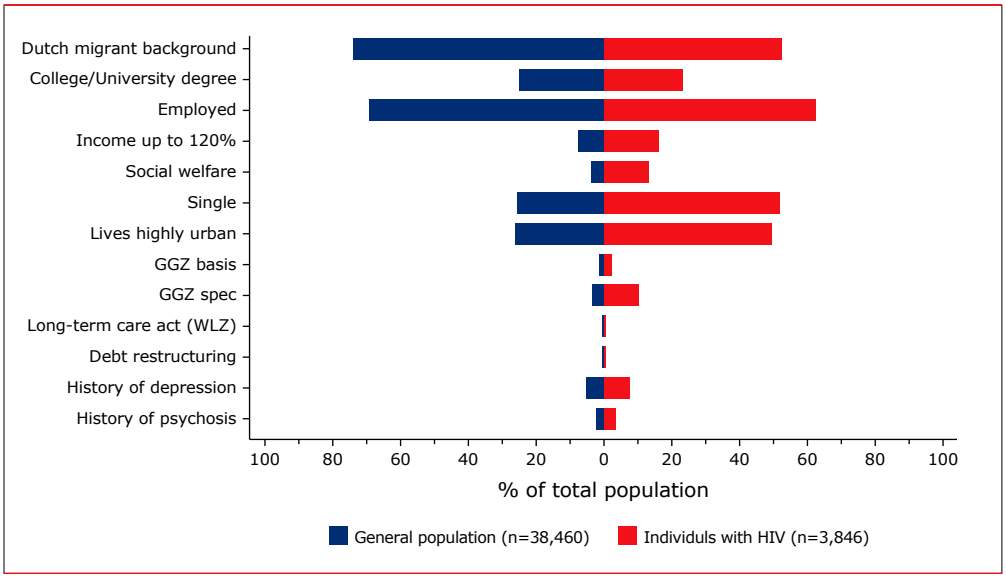
Figure 2a: *Socio-demographic and socio-economical description of the general Dutch population and individuals with HIV in care in the Netherlands.*



Abbreviations: *GGZ, geestelijke gezondheidszorg (i.e., mental health care); WLZ, wet langdurige zorg. The GGZ offers basic or specialized mental health care to people living in the Netherlands, which is covered by the mandatory Dutch insurance scheme.*

To minimize the effect of age and gender differences, we also matched each individual in the SHM database to 10 individuals in the CBS database based on age-groups and gender categories. We then compared individuals from SHM and CBS in these matched groups (Figure 2b). Results when populations were matched according to age and gender were similar to those including all individuals (Figure 2b).

Figure 2b: *Socio-demographic and socio-economical description of the general Dutch population and individuals with HIV in care in the Netherlands, matched according to age and gender.*



Note: *Populations matched on gender and age.*

Abbreviations: *GGZ, geestelijke gezondheidszorg (i.e., mental health care); WLZ, wet langdurige zorg.*

The GGZ offers basic or specialized mental health care to people living in the Netherlands which is covered by the mandatory Dutch insurance scheme.

Men who have sex with men

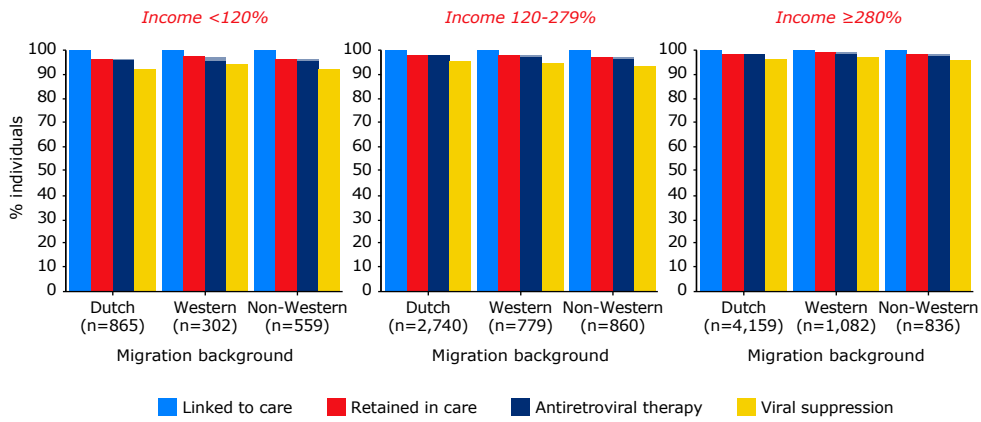
HIV care continuum by income and migration background, level of education, and level of urbanisation

Figure 3 shows the HIV care continua among MSM, stratified by income and migration background, level of education, and level of urbanisation. Viral suppression was less than 95% among MSM with a Dutch (92%) and other Western (94%) migration background who had an income lower than 120% of the social minimum (91%).

Among MSM with a non-Western migration background, viral suppression was less than 95% for those with an income lower than 120% (92%) of the social minimum and for those with an income of 120-280% (94%) of the social minimum. Moreover, viral suppression was less than 95% among MSM with primary (92%) and secondary education (94%).

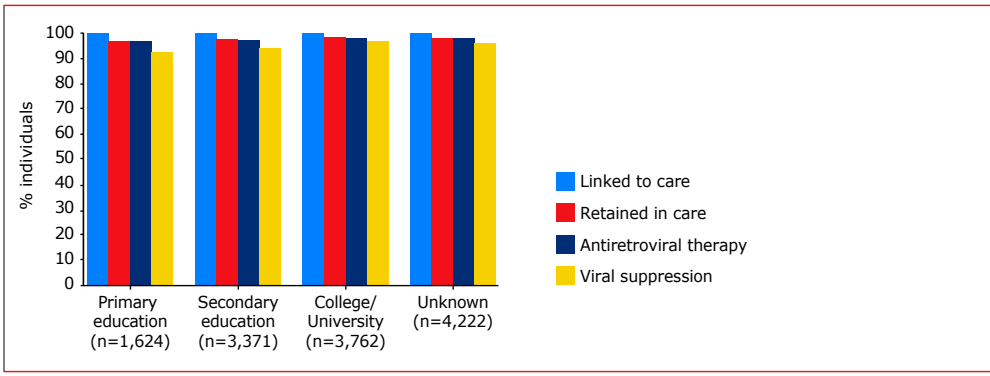
Figure 3: HIV care continuum in 2021 among men who have sex with men.

A: By migration background and income.

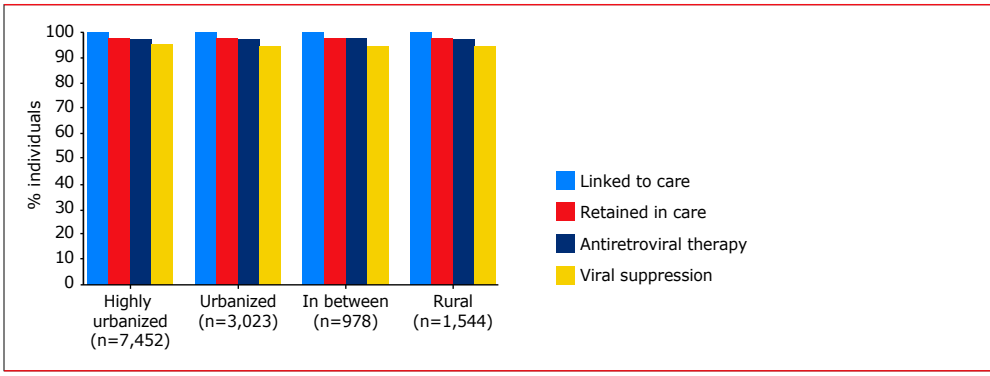


Light bars represent the possible range of values. Actual values could not be given due to less than 5 individuals lost from the previous step of care.

B: By education.



C: By level of urbanisation.

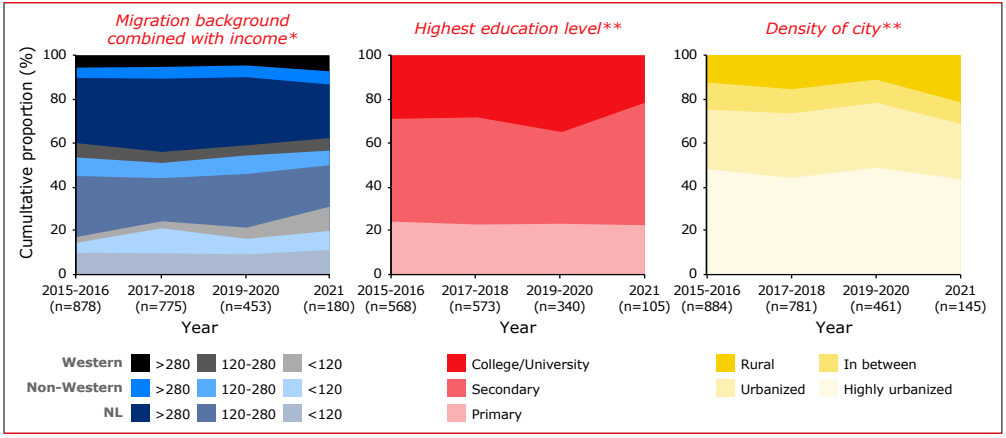


New diagnoses and late presentation from 2015 onwards

Between 2015 and 2021, 2,902 MSM with a new HIV diagnosis were registered with SHM. In recent years there was a slight decrease in the distribution of MSM with a new HIV diagnosis and a college/university education, and MSM newly diagnosed with HIV from 2015 onwards living in highly urbanised areas, between 2019 and 2021 (Figure 4a). No changes were observed in the distribution of migration background and income among MSM newly diagnosed with HIV (Figure 4a and 4b, respectively).

Figure 4: *Distribution of socio-demographic and socio-economical characteristics of MSM with a new HIV diagnosis between 2015-2021.*

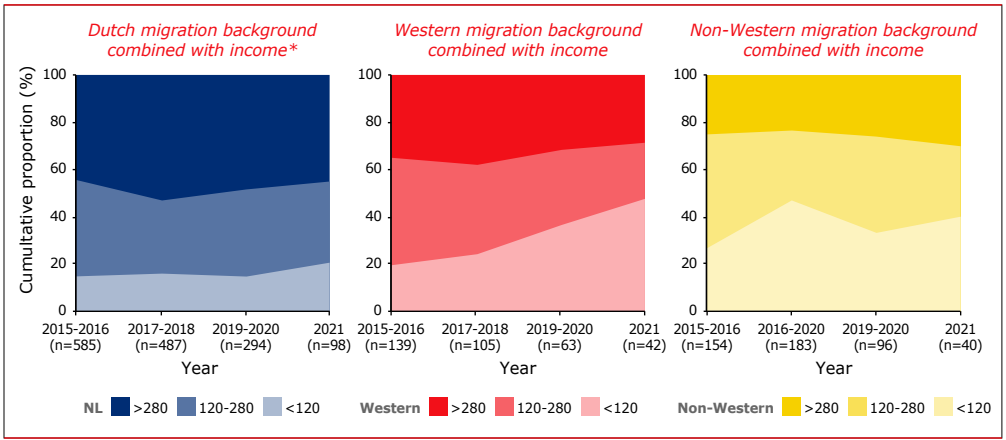
A: *Migration background combined with income, education level and level of urbanisation.*



* *Sum of new diagnoses do not add up to the total new HIV diagnoses among MSM. To provide an approximation of the percentage, data involving fewer than ten people were kept at ten people.*

** *Sum of new diagnoses do not add up to the total new HIV diagnoses among MSM due to missing data.*

B: *Income stratified by migration background.*



* *Sum of new diagnoses do not add up to the total new HIV diagnoses among MSM. To provide an approximation of the percentage, data involving fewer than ten people were kept at ten people.*

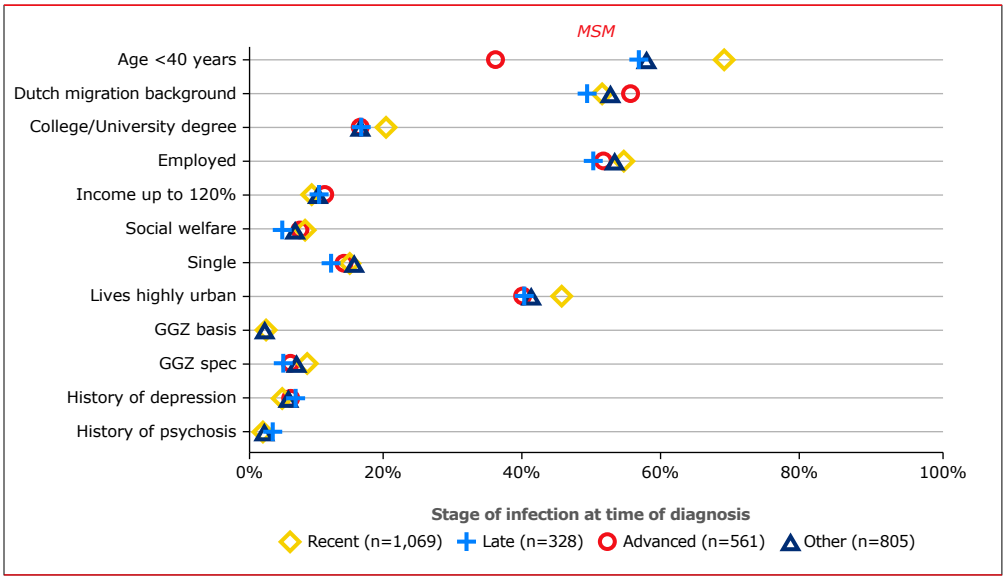
Of the 2,902 MSM newly registered with an HIV diagnosis between 2015-2021:

- 1,069 (37%) were diagnosed with a recent HIV infection;
- 328 (11%) were diagnosed with late-stage HIV infection;
- 561 (19%) were diagnosed with advanced HIV disease;
- 805 (28%) were diagnosed with other/chronic HIV; and
- 139 (5%) were diagnosed with an unclassified HIV stage.

MSM with an advanced diagnosis were less often under 40 years of age, while MSM with a recent infection were aged 40 years or younger in more than 60% of diagnoses (Figure 5).

MSM with a university education or living in highly-urbanised regions were diagnosed more often with a recent HIV infection compared to MSM diagnosed with an other/chronic-, late- or advanced HIV disease.

Figure 5: *Distribution of socio-demographic and socio-economical characteristics of MSM registered with a recent, late, advanced or other/chronic HIV diagnosis between 2015-2021.*



Abbreviations: *GGZ, geestelijke gezondheidszorg (i.e., menthal health care).*
The GGZ offers basic or specialized mental health care to people living in the Netherlands which is covered by the mandatory Dutch insurance scheme.

Women and other men

HIV care continuum by income and migration background, education level, and level of urbanisation

Figure 6 shows the HIV care continua among women and other men, stratified by income and migration background, level of education, and level of urbanisation. Viral suppression was 90%, 92%, and 90% for women of Dutch, other Western, and non-Western descent, respectively, who had an income lower than 120% of the social minimum (Figure 6a).

Among women with an income of between 120-279% of the social minimum, 91% and 92% of women of non-Western and other Western descent, respectively, were virally suppressed. Similarly, among women with an income equal to or more than 280% of the social minimum, viral suppression was 94% and 93% for women of Dutch and non-Western descent, respectively. For women of other-Western descent in this category, viral suppression was between 84-100%.

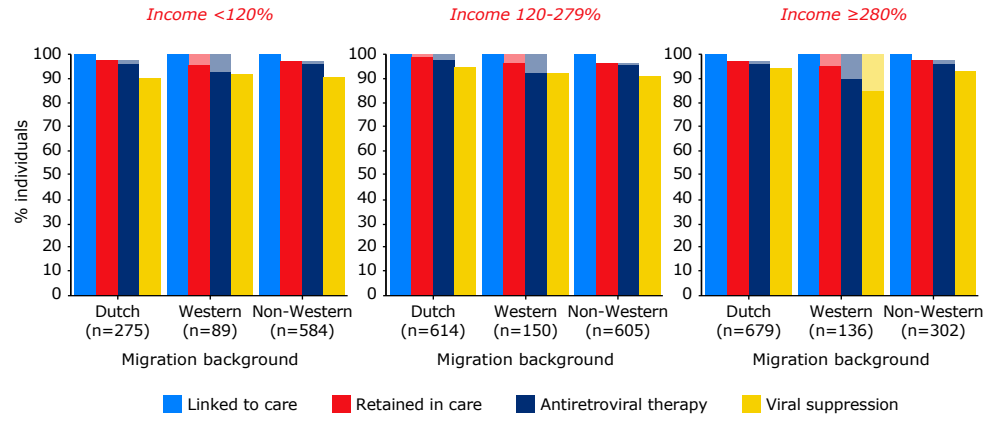
Among other men with an income lower than 120% of the social minimum, viral suppression was 90% for men of Dutch and non-Western descent, and 81% for men of other-Western descent (Figure 6b). Viral suppression was between 90%-93% for men with an income between 120-279% of the social minimum. Among men with an income equal to or greater than 280% of the social minimum, viral suppression was 89% for men who have sex with women (MSW) of other Western descent, 93% for MSW of non-Western descent and 95% for MSW of Dutch descent.

Viral suppression was below 95% for all women and other men, regardless of education level (Figure 6c). For other men with the highest level of education being primary education, only 88% were virally suppressed.

Among women, viral suppression was below 95% in rural (94%) and highly urban areas (90%, Figure 6d). For other men, viral suppression was below 95% in all areas, regardless of degree of urbanisation.

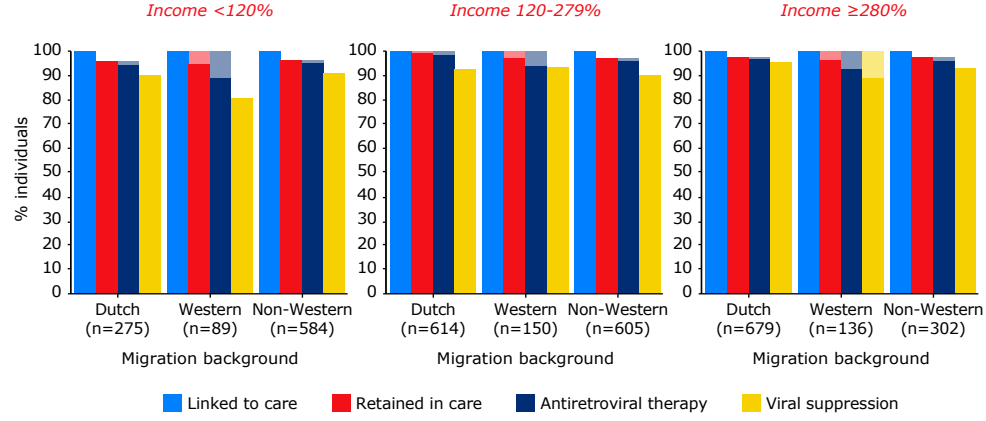
Figure 6: HIV care continuum in 2021 among women and other men.

A: Women by migration background and income.



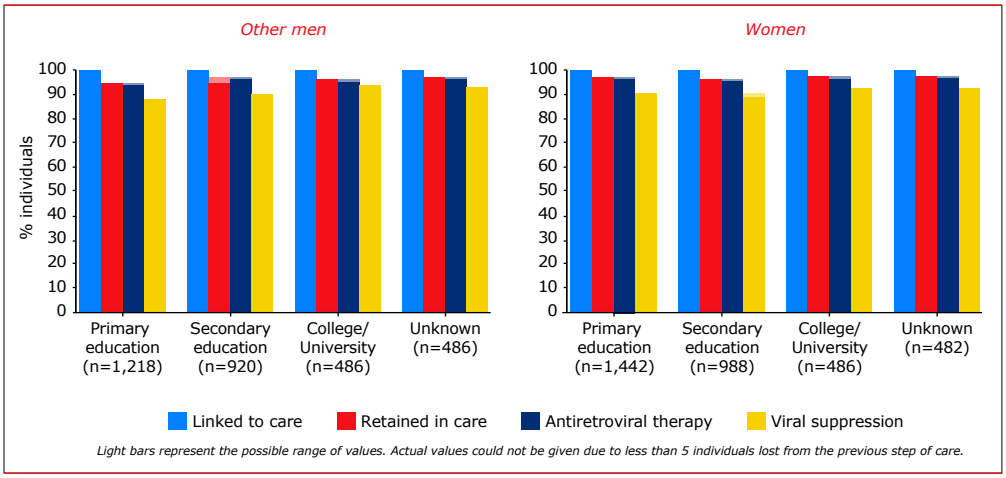
Light bars represent the possible range of values. Actual values could not be given due to less than 5 individuals lost from the previous step of care.

B: Other men by migration background and income.



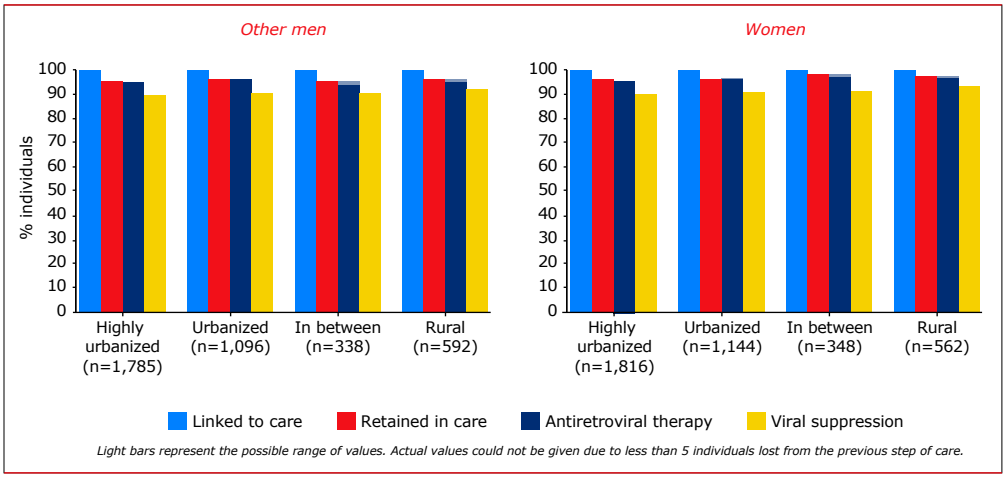
Light bars represent the possible range of values. Actual values could not be given due to less than 5 individuals lost from the previous step of care.

C: By education.



Light bars represent the possible range of values. Actual values could not be given due to less than 5 individuals lost from the previous step of care.

D: By level of urbanisation.



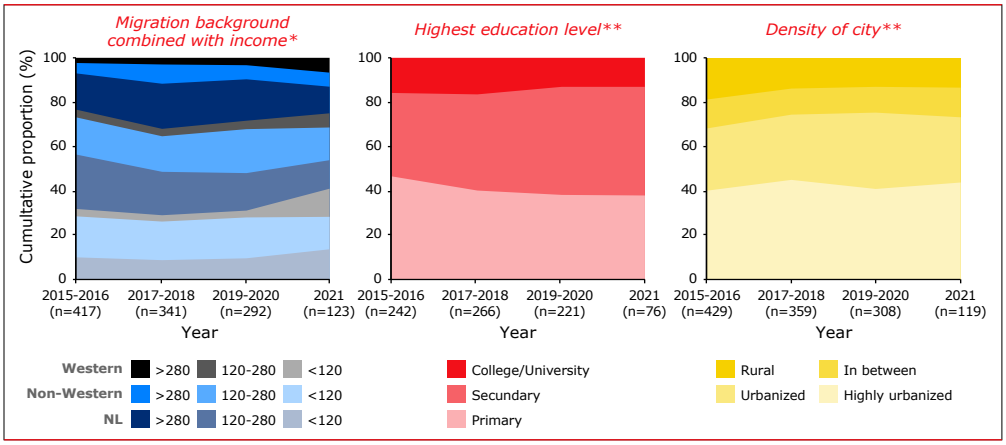
Light bars represent the possible range of values. Actual values could not be given due to less than 5 individuals lost from the previous step of care.

New diagnoses and late presentation from 2015 onwards

Between 2015 and 2021, 675 women and 991 other men were diagnosed with HIV. Only slight fluctuations in the distribution of socio-demographic characteristics over time were evident (Figure 7a and b).

Figure 7: *Distribution of socio-demographic and socio-economical characteristics of women and men who have sex with women newly diagnosed with HIV between 2015-2021.*

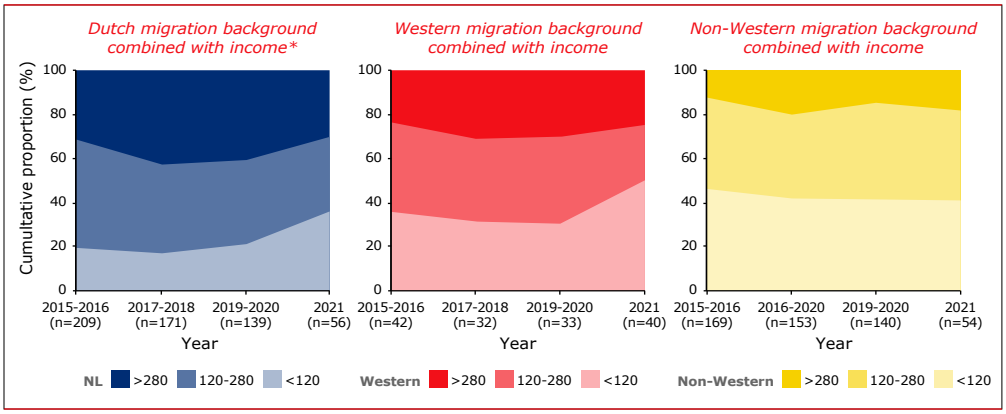
A: *Migration background combined with income, education level and level of urbanisation.*



* *Sum of new diagnoses do not add up to the total new HIV diagnoses among women and other men. To provide an approximation of the percentage, data involving fewer than ten people were kept at ten people.*

***Sum of new diagnoses do not add up to the total new HIV diagnoses among women and other men due to missing data.*

B: *Income stratified by migration background.*



* *Sum of new diagnoses do not add up to the total new HIV diagnoses among women and other men. To provide an approximation of the percentage, data involving fewer than ten people were kept at ten people.*

Of the 675 women newly diagnosed with HIV between 2015-2021:

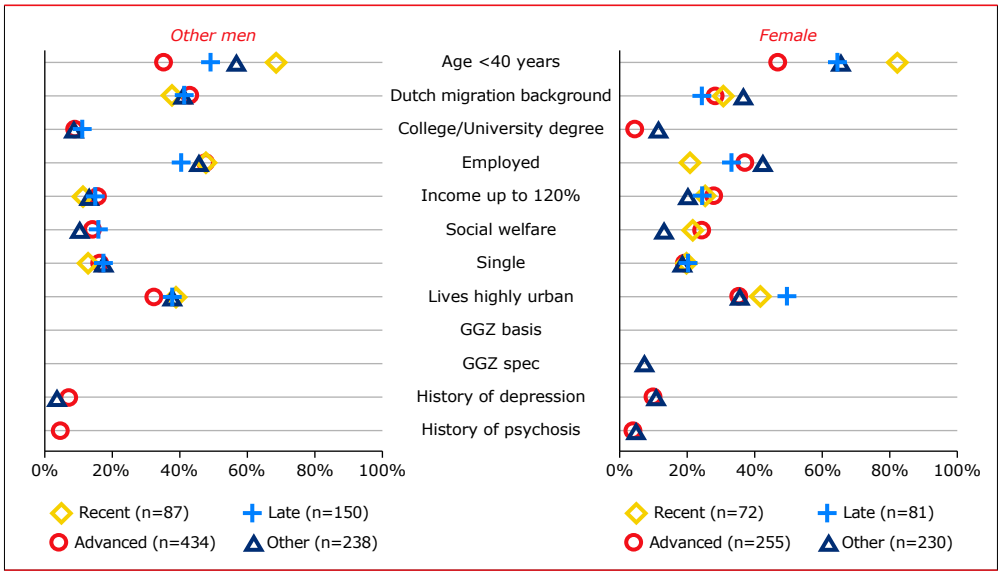
- 72 (11%) were diagnosed with a recent infection;
- 250 (34%) with other/chronic HIV; and
- 89 (12%) with late-stage HIV infection;
- 281 (38%) with advanced HIV disease;
- 37 (5%) with an unclassified HIV stage.

Of the 991 other men newly registered with an HIV diagnosis:

- 87 (9%) were diagnosed with a recent infection;
- 258 (24%) with other/chronic HIV; and
- 171 (16%) with late-stage HIV infection;
- 479 (44%) with advanced HIV disease;
- 85 (8%) with an unclassified HIV stage.

Women and other men with an advanced HIV diagnosis were older than those with a recent HIV diagnosis (Figure 8).

Figure 8: *Distribution of socio-demographic and socio-economical characteristics of other men and women registered with a recent, late, advanced or other/chronic HIV diagnosis between 2015-2021.*

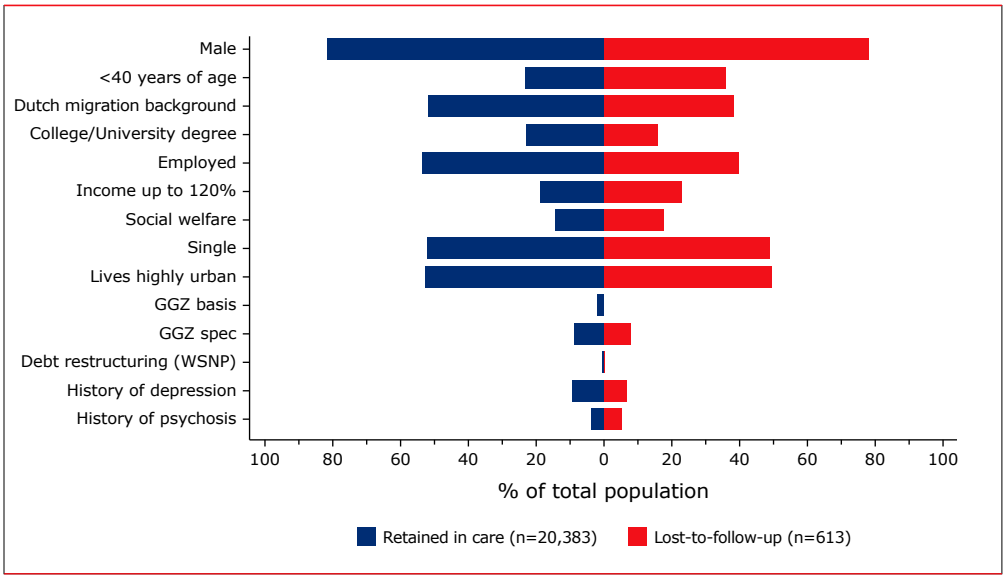


Abbreviations: *GGZ, geestelijke gezondheidszorg (i.e., menthal health care).*
The GGZ offers basic or specialized mental health care to people living in the Netherlands which is covered by the mandatory Dutch insurance scheme.

Disengagement from care

In total, 613 individuals disengaged from care before 2021 (Figure 9). Individuals who disengaged from care were less often male (78% vs. 81%), less often of a Dutch migration background (38% vs. 52%) and less often had a college or university degree (15% vs. 23%) compared to those who remained in care. They were also younger (36% vs. 23% younger than 40 years of age) and more often used debt restructuring (1% vs. 0.3%).

Figure 9: Socio-demographic and socio-economical characteristics of individuals who disengaged from care before 2021.



Abbreviations: *GGZ, geestelijke gezondheidszorg (i.e., mental health care).*
The GGZ offers basic or specialized mental health care to people living in the Netherlands which is covered by the mandatory Dutch insurance scheme.

Conclusions

Compared to the general Dutch population, individuals in HIV care were less often of a Dutch migration background and less often had a college/university degree. Moreover, individuals in HIV care more often lived in a single person household, had a lower household income and more often received social welfare and mental health care.

While the overall HIV care continuum mentioned in Chapter 1 almost reaches the 95-95-95 UNAIDS targets, the HIV care continuum among women and MSW was still suboptimal regardless of socio-demographics and socio-economic status. Among MSM, viral suppression was below 95% for MSM with an income lower than 120% of the social minimum and among MSM with primary and secondary education. Further analyses will need to be conducted to determine which socio-demographic and socio-economic factors, individually or in combination, contribute to suboptimal progression in the HIV care continuum.

2. Response to combination antiretroviral therapy

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Introduction

Since the introduction of combination antiretroviral therapy (ART) in 1996, there have been substantial advances in the use of antiretroviral drugs for the treatment and prevention of HIV infection. The primary goals of ART are to prevent HIV disease progression, improve clinical outcomes, and limit transmission[1,2]. Treatment guidelines across the globe recommend the initiation of ART as soon as possible in all people newly diagnosed with HIV, regardless of CD4 cell count. The decision to initiate ART should always include consideration of a person's comorbid conditions and willingness and readiness to initiate therapy[3-7]. In general, the guidelines of the Dutch Association of HIV Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) follow the US Department of Health and Human Services guidelines[8].

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

Treatment with ART generally results in sustained suppression of HIV viral load to levels below the reported threshold. Nevertheless, drug resistance mutations may develop if a given agent, even when combined with other agents, cannot sufficiently prevent the selective pressures driving resistance. Over time, accumulation of mutations in the HIV genome that are associated with drug resistance can prevent sustained viral suppression, thereby increasing the risk of poor clinical outcomes[16–22].

In this chapter, we describe trends over time in the use of ART, and trends in the virological and immunological responses to ART, in adults registered by stichting HIV monitoring (SHM) and enrolled in the ATHENA cohort[23]. We also analyse the presence of transmitted and acquired HIV drug resistance. *Box 2.1* gives an overview of the number of people included in the various analyses described in this chapter.

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

Between 1996 and the end of 2022, a cumulative total of 30,142 individuals (aged 15 years or older at the time of diagnosis) were registered by SHM as living with HIV-1 in the Netherlands

1. **Starting combination antiretroviral therapy**
   28,546 individuals were known to have initiated ART between January 1996 and December 2022.

2. **In care and on ART in the Netherlands in 2022**
   Of the 28,546 individuals who initiated ART between January 1996 and December 2022,
   ➔ 21,074 (73.8%) were in care and on ART by the end of 2022.

3. **Changes in the use of the initial ART regimen**
   Of the 28,546 individuals who initiated ART between January 1996 and December 2022,
   ➔ 5,578 (19.5%) initiated ART between January 2016 and December 2022.
   ➔ The most frequently used guideline-recommended initial regimens in 2016-22 were:

- TAF/FTC/BIC (1,034, 18.5%)
- ABC/3TC/DTG (1,030, 18.5%)
- TDF/FTC/DTG (878, 15.7%)
- TAF/FTC/EVG/c (693, 12.4%)
- TDF/FTC/EFV (230, 4.1%)
- TDF/FTC/EVG/c (179, 3.2%)
- TAF/FTC/DRV/c (171, 3.1%)
- TDF/FTC/DRV/b (158, 2.8%)
- TAF/FTC/DTG (157, 2.8%)

4. Virological response

Of the 28,546 individuals who initiated ART between January 1996 and December 2022,

➔ 24,277 people were ART-naïve, not pregnant at ART initiation, and had a baseline HIV viral load result. Of these 20,674 had a viral load result within six months (plus or minus three months) of ART initiation.

5. HIV drug resistance

Transmitted HIV drug resistance

As of December 2022, 9,125 HIV-1 sequences had been obtained from 8,806 ART-naïve people prior to initiation of ART in 2003-22.

➔ 9,111 reverse transcriptase sequences were available from 8,795 individuals.

➔ 8,572 protease sequences were available from 8,268 individuals.

➔ 412 integrase sequences were available from 411 individuals.

Acquired HIV drug resistance

As of December 2022, 4,905 HIV-1 sequences had been obtained from 2,933 people who received ART for at least four months in 2000-22.

➔ 3,518 sequences were from 2,185 people who had been ART-naïve before initiating ART.

➔ 4,819 reverse transcriptase sequences were available from 2,903 individuals.

➔ 4,582 protease sequences were available from 2,754 individuals.

➔ 563 integrase sequences were available from 437 individuals.

Legend: *ART = combination antiretroviral therapy (defined as a combination of three antiretroviral drugs from two different antiretroviral drugs classes, or the use of selected combinations of two antiretroviral drugs for which there is sufficient efficacy data to support its use); 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; /b = booster; /c = cobicistat; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.*

Starting combination antiretroviral therapy

In total, 28,546 individuals ever registered by SHM and followed in the ATHENA cohort were aged 15 years or above at the time of HIV-1 diagnosis, and were known to have initiated ART between January 1996 and December 2022 (*Box 2.1*). In *Table 2.1*, we have grouped people by calendar year of ART initiation: 9,578 started in 1996-2005, 6,119 in 2006-2010, 7,271 in 2011-2015, and 5,578 in 2016-22.

Of the 28,546 people known to have initiated ART since January 1996, 23,276 (81.5%) were men, of whom 17,259 (74.2%) were men who have sex with men (MSM). Overall, 15,354 (53.8%) originated from the Netherlands. Whereas the proportion of people born in the Netherlands was fairly stable over time until the mid-2010s, there has been a steady decline since than: 1996-2005 54.2%, 2006-2010 55.9%, 2011-2015: 58.1%, 2016-2022 46.6%. From 1996 onwards, there was a slight but steady increase in people from eastern and central Europe; from 2-4% prior to 2010, to 6.0% in 2011-2015, and 13.3 in 2016-2022. Simultaneously, the number of people from western Europe/North America/Australia decreased slightly from 10.1% in 1996-2005, to 5.2% in 2016-2022. This was also true for sub-Saharan Africa; the number declined from 17.9% in 1996-2005, to 9.9% in 2016-2022.

Prompt initiation of ART following the first seropositive HIV test has increased over time, reflecting implementation and uptake of evolving HIV treatment guidelines (*Figure 2.1A*). Among people with an accurate date of HIV diagnosis and who started ART in the Netherlands, the median time between an HIV-positive diagnosis and ART initiation shifted from 143 days (interquartile range [IQR] 33-731) for those who entered care in 2011, to:

- 36 days (IQR 17-84) in 2015;
- 25 days (IQR 11-47) in 2018;
- 23 days (IQR 9-47) in 2019;
- 19 days (IQR 8-44) in 2020;
- 20 days (IQR 7-41) in 2021; and
- 18 days (IQR 3-77) in 2022.

The time between entering care and starting ART decreased over time (*Figure 2.1B*). The majority of newly diagnosed, ART-naïve people entering care in the Netherlands initiated ART within one month. In 2022, 70.7% of this group initiated ART within one month of their HIV diagnosis, while the remainder of newly diagnosed, ART-naïve individuals who initiated ART in the Netherlands did so (*Figure 2.1A*):

- between 1 and 5 months after their HIV diagnosis (18.6%);
- between 6 and 12 months after diagnosis (3.1%); and
- more than one year after diagnosis (7.6%).

People originating from sub-Saharan Africa, the Caribbean, and central and eastern Europe were overrepresented among those starting more than six months after HIV diagnosis. The delay between testing HIV-positive and initiating ART was mostly driven by a long period between HIV diagnosis and entering care, as 94.1% of people initiating ART in 2022 did so within one month of entering care (*Figure 2.1B*). All designated HIV treatment centres in the Netherlands have a policy to arrange for the first consultation within a couple of days; usually just a single working day after being contacted by the newly diagnosed person or their referring healthcare provider.

Table 2.1 Characteristics of people starting combination antiretroviral therapy in 1996–2022.

Year of ART initiation		1996–2005	2006–10	2011–15	2016–22	1996–2022
Number of individuals		9,578	6,119	7,271	5,578	28,546
DEMOGRAPHICS						
Age at ART initiation (years)	Median	37.5	40.1	39.1	37.3	38.4
	Q1	31.8	32.8	30.7	29.1	31.2
	Q3	44.6	47.3	48.1	48.8	46.8
Male gender (at birth)	n	7,360	4,974	6,272	4,670	23,276
	%	76.8	81.3	86.3	83.7	81.5
Transmission risk group						
Missing	n	7	9	13	31	60
	%	0.1	0.2	0.2	0.6	0.2
Men who have sex with men	n	5,037	3,742	4,994	3,486	17,259
	%	52.6	61.2	68.7	62.5	60.5
Heterosexual contact	n	3,298	1,885	1,794	1,476	8,453
	%	34.4	30.8	24.7	26.46	29.6
Injecting drug use	n	539	115	48	64	766
	%	5.6	1.9	0.7	1.2	2.7
Blood or blood products*	n	169	50	62	72	353
	%	1.8	0.8	0.9	1.3	1.2
Vertical transmission	n	2	4	2	6	14
	%	0.02	0.07	0.03	0.1	0.1
Unknown	n	526	314	358	443	1,641
	%	5.5	5.1	4.9	7.9	5.8

Year of ART initiation		1996–2005	2006–10	2011–15	2016–22	1996–2022
Region of origin						
Missing	N	46	20	27	64	157
	%	0.5	0.3	0.4	1.2	0.6
The Netherlands	N	5,167	3,409	4,210	2,568	15,354
	%	54.0	55.7	57.9	46.0	53.8
Western Europe/North America/	n	958	508	510	287	2,263
Australia	%	10.0	8.3	7.0	5.2	7.9
Eastern/central Europe	n	182	224	432	732	1,570
	%	1.9	3.7	5.9	13.1	5.5
Latin America and the Caribbean	n	1,032	724	957	892	3,605
	%	10.8	11.8	13.2	16.0	12.6
Sub-Saharan Africa	n	1,702	882	681	548	3,813
	%	17.8	14.4	9.4	9.8	13.4
Other	n	491	352	454	487	1784
	%	5.1	5.8	6.2	8.7	6.3
CLINICAL						
Recent infection (within 12 months	n	580	940	1,726	1,275	4,521
of diagnosis)	%	6.1	15.4	23.7	22.9	15.8
Ever having tested HIV-negative	n	1,984	2,476	3,926	2,842	11,228
	%	20.7	40.5	54	51.0	39.3
CD4 cell count at start of ART	Median	190	243	350	370	270
	Q1	80	140	220	174	130
	Q3	320	330	500	570	420
HIV RNA (log10 cp/ml) at start of	Median	4.9	5.0	4.8	4.8	4.9
ART	Q1	4.3	4.4	4.3	4.2	4.3
	Q3	5.3	5.4	5.3	5.5	5.4
(Prior) AIDS at start of ART	n	2,963	1,157	939	758	5,817
	%	30.9	18.9	12.9	13.6	20.4
Prior mono or dual NRTI treatment	n	2,025	54	27	43	2,149
at start of ART**	%	21.1	0.9	0.4	0.8	7.5
Hepatitis B status at start of ART						
HBV-negative (HBsAg-negative)	n	8,644	5,654	6,813	5,143	26,254
	%	90.3	92.4	93.7	92.2	92.0
HBV-positive (HBsAg-positive)	n	598	323	216	140	1277
	%	6.2	5.3	3.0	2.5	4.5
Unknown	n	336	142	242	295	1015
	%	3.5	2.3	3.3	5.3	3.6

Year of ART initiation		1996–2005	2006–10	2011–15	2016–22	1996–2022
Hepatitis C status at start of ART						
HCV-negative	n	8,678	5,805	7,014	5,257	26,754
	%	90.6	94.9	96.5	94.3	93.7
HCV RNA-positive	n	171	136	104	88	499
	%	1.8	2.2	1.4	1.6	1.8
HCV Ab seropositive	n	197	48	44	28	317
	%	2.1	0.8	0.6	0.5	1.1
Unknown	n	532	130	109	205	976
	%	5.6	2.1	1.5	3.7	3.4
ART started during pregnancy	n	402	233	139	94	868
	%	4.2	3.8	1.9	1.7	3.0

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

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

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

Figure 2.1A: Time between HIV diagnosis and initiation of combination antiretroviral therapy (ART) in people starting ART in 2013–22.

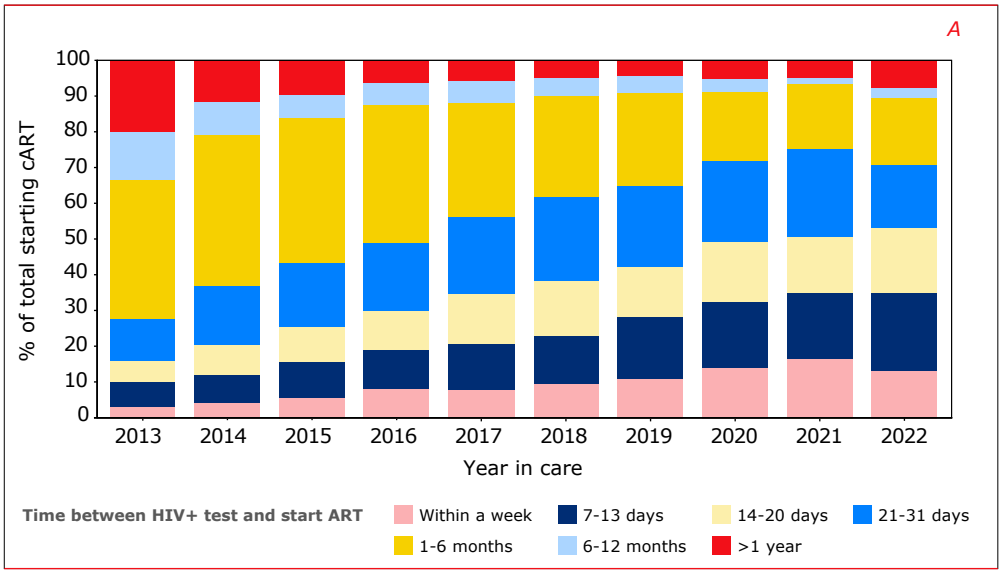
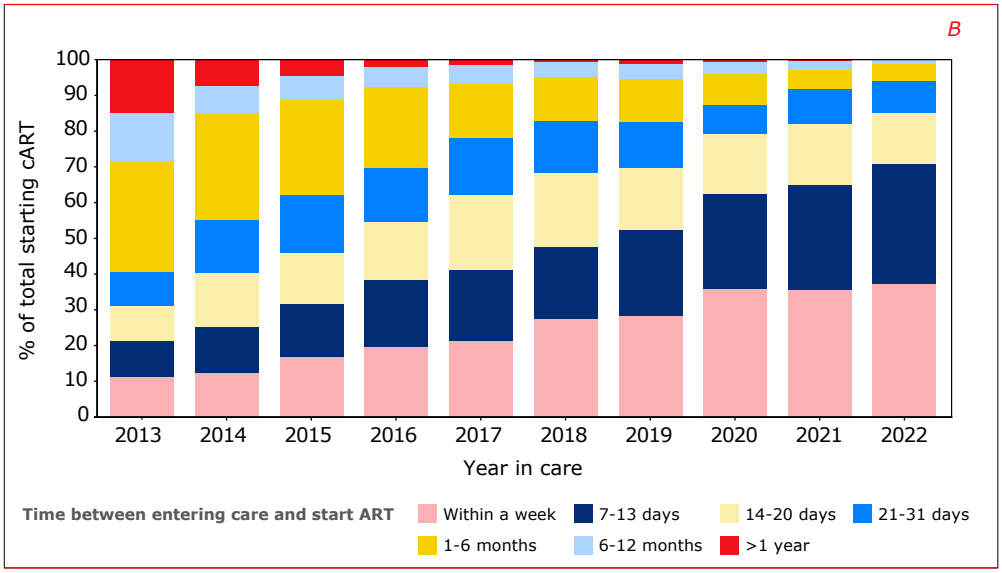


Figure 2.1B: Time between entry into HIV care and initiation of combination antiretroviral therapy (ART) for people starting ART in 2013–22.



Legend: ART = combination antiretroviral therapy.

The proportion of individuals newly diagnosed with HIV who have a known previous negative HIV test, has increased over the years, reaching:

- 20.7% in the period 1996-2005;
- 40.5% in 2006-2010;
- 54.0% in 2011-2015; and
- 51.0% in 2016-2022.

In addition, an increasing proportion of those starting ART showed evidence of recent infection (i.e. within 12 months of a last negative HIV test). The percentage of 6.1% in 1996-2005 rose to 15.4% in 2006-2010, 23.7% in 2011-2015, and has plateaued since at 22.9% in 2016-2022.

Over the same time period, there was an increase in the median CD4 cell count at the start of ART:

- 190 cells/mm^3 (IQR 80-320) in 1996-2005;
- 243 cells/mm^3 (IQR 140-330) in 2006-2010;
- 350 cells/mm^3 (IQR 220-500) in 2011-2015;
- 370 cells/mm^3 (IQR 174-570) in 2016-2020.

In 2015, the median CD4 cell count at ART initiation peaked at 410 (IQR 220-600) and has since continued to decrease slightly each year to a minimum of 302 cells/mm^3 (IQR 126-535) in 2021 but increased to 350 cells/mm^3 (IQR 150-550) in 2022. This trend is likely due to the substantial group already in care but not on ART (because of their high CD4 cells counts), who subsequently initiated ART en masse in 2015 and 2016, when the 2015 guideline change recommended ART for all, irrespective of CD4 count. In the period 2016-2022, at the start of ART, 14.9% of individuals had already been diagnosed with an AIDS-defining condition; 92.3% of those with prior AIDS diagnosis had a CD4 cell count below 350 cells/mm^3, and 87.7% had a CD4 cell count below 200 cells/mm^3.

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

In care and on ART in the Netherlands in 2022

Of the 28,546 people known to have initiated ART between January 1996 and December 2022, 21,074 (73.8%) were alive, still receiving ART, and had a recorded visit for HIV care in the Netherlands in 2022. A total of 252 people were still alive but (temporarily, and for various reasons) no longer on ART, and have therefore been excluded from the analyses in this section. Most of these individuals had medical, psychiatric, and/or psycho-social issues that temporarily prevented them from continuing ART, and are expected to re-start ART once those issues are sufficiently resolved.

Table 2.2 shows the treatment and clinical characteristics of all 21,074 individuals on ART at the last clinic visit in 2022. Overall, 17,269 (81.9%) were men, and 13,473 (63.9%) were MSM. Their median age on 31 December 2022 was 52.6 (IQR 42.7-60.6) years. The majority (56.9%) originated from the Netherlands, followed by Latin America / the Caribbean (12.6%) and sub-Saharan Africa (11.6%).

Table 2.2: Characteristics of people receiving combination antiretroviral therapy and known to be in care in 2022.

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2022	All
Total	n	5,648	4,562	5,990	4,874	21,074
	%	26.8	21.6	28.4	23.1	100
Male sex	n	4,285	3,726	5,184	4,074	17,269
	%	75.9	81.7	86.5	83.6	81.9
Age on 31 December 2021	Median	59.2	54.3	48.9	41.8	52.6
	Q1	53.3	47.1	40.3	33.4	42.7
	Q3	65.4	60.8	57.6	53.1	60.6
Transmission risk group						
No data	n	6	5	9	28	48
	%	0.1	0.1	0.2	0.6	0.2
Men who have sex with men	n	3,187	2,967	4,231	3,088	13,473
	%	56.4	65.0	70.6	63.4	63.9
Heterosexual contact	n	1,963	1,323	1,434	1,274	5,994
	%	34.8	29.0	23.9	26.1	28.4
Injecting drug use	n	160	54	20	45	279
	%	2.8	1.2	0.3	0.9	1.3
Blood or blood products	n	99	32	47	61	239
	%	1.8	0.7	0.8	1.3	1.1
Vertical transmission	n	1	3	2	5	11
	%	0.0	0.1	0.0	0.1	0.1
Other / unknown	n	232	178	247	373	1,030
	%	4.1	3.9	4.1	7.7	4.9
Region of origin						
No data	n	20	13	24	56	113
	%	0.4	0.3	0.4	1.1	0.5
The Netherlands	n	3,226	2,753	3,673	2,336	11,988
	%	57.1	60.3	61.3	47.9	56.9
Western Europe/North America/	n	439	277	340	219	1,275
Australia	%	7.8	6.1	5.7	4.5	6.1
Eastern/central Europe	n	102	159	325	601	1,187
	%	1.8	3.5	5.4	12.3	5.6
Latin America/the Caribbean	n	617	515	747	768	2,647
	%	10.9	11.3	12.5	15.8	12.6
Sub-Saharan Africa	n	918	568	508	460	2,454
	%	16.3	12.5	8.5	9.4	11.6
Other	n	326	277	373	434	1,410
	%	5.8	6.1	6.2	8.9	6.7

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2022	All
ART regimen						
TDF/FTC/EFV	n	316	404	269	63	1,052
	%	5.6	8.9	4.5	1.3	5.0
TDF/FTC/NVP	n	414	236	151	8	809
	%	7.3	5.2	2.5	0.2	3.8
TDF/FTC/RPV	n	101	67	192	23	383
	%	1.8	1.5	3.2	0.5	1.8
TDF/3TC/DOR	n	285	376	498	442	1,601
	%	5	8.2	8.3	9.1	7.6
TDF/FTC/DRV/b	n	90	102	110	44	346
	%	1.6	2.2	1.8	0.9	1.6
TDF/FTC/ATV/b	n	38	37	36	8	119
	%	0.7	0.8	0.6	0.2	0.6
TDF/FTC/LPV	n	4	6	1	0	11
	%	0.1	0.1	0.0	0.0	0.1
TDF/FTC/EVG/c	n	72	82	243	64	461
	%	1.3	1.8	4.1	1.3	2.2
TDF/FTC/DTG	n	117	92	185	485	879
	%	2.1	2.0	3.1	10.0	4.2
TDF/FTC/RAL	n	39	26	38	29	132
	%	0.7	0.6	0.6	0.6	0.6
ABC/3TC/DTG	n	370	368	620	527	1,885
	%	6.6	8.1	10.4	10.8	8.9
TAF/FTC/RPV	n	211	203	424	97	935
	%	3.7	4.4	7.1	2.0	4.4
TAF/FTC/DRV/c	n	335	300	354	235	1,224
	%	5.9	6.6	5.9	4.8	5.8
TAF/FTC/EVG/c	n	392	428	733	469	2,022
	%	6.9	9.4	12.2	9.6	9.6
TAF/FTC/DTG	n	110	100	120	142	472
	%	1.9	2.2	2.0	2.9	2.2
TAF/FTC/BIC	n	707	612	771	1,309	3,399
	%	12.5	13.4	12.9	26.9	16.1
TAF/FTC/NVP	n	384	212	93	4	693
	%	6.8	4.6	1.6	0.1	3.3
ABC/3TC/NVP	n	166	55	33	0	254
	%	2.9	1.2	0.6	0.0	1.2

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2022	All
DTG/3TC	n	384	432	678	629	2,123
	%	6.8	9.5	11.3	12.9	10.1
DTG/RPV	n	72	21	23	9	125
	%	1.3	0.5	0.4	0.2	0.6
CAB/RPV injectables *	n	56	71	132	123	382
	%	1.0	1.6	2.2	2.5	1.8
2DR: NNRTI + INST	n	13	0	2	3	18
	%	0.2	0.0	0.0	0.1	0.1
2DR: PI + INSTI	n	251	60	56	34	401
	%	4.4	1.3	0.9	0.7	1.9
2DR: NRTI + INSTI	n	2	1	0	0	3
	%	0.0	0.0	0.0	0.0	0.0
Other: 2NRTI + NNRTI	n	136	64	42	18	260
	%	2.4	1.4	0.7	0.4	1.2
Other: 2NRTI + PI	n	81	66	48	6	201
	%	1.4	1.4	0.8	0.1	1.0
Other: 2NRTI + INST	n	68	54	64	51	237
	%	1.2	1.2	1.1	1.0	1.1
Other: 2DR	n	52	12	12	7	83
	%	0.9	0.3	0.2	0.1	0.4
Other: NRTI + PI + INSTI (3ARVs)	n	43	2	4	3	52
	%	0.8	0.0	0.1	0.1	0.2
Other: NRTI + PI + INSTI (4ARVs)	n	120	35	26	25	206
	%	2.1	0.8	0.4	0.5	1
Other	n	219	38	32	17	306
	%	3.9	0.8	0.5	0.3	1.5
CD4: CD8 ratio						
No data	n	721	583	847	743	2,894
	%	12.8	12.8	14.1	15.2	13.7
<0.50	n	822	526	552	982	2,882
	%	14.6	11.5	9.2	20.1	13.7
> = 0.50 to <1.00	n	2,349	2,054	2,582	1,838	8,823
	%	41.6	45.0	43.1	37.7	41.9
> = 1.00	n	1,756	1,399	2,009	1,311	6,475
	%	31.1	30.7	33.5	26.9	30.7

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2022	All
CD4 count (cells/mm³)						
No data	n	26	17	27	43	113
	%	0.5	0.4	0.5	0.9	0.5
<50	n	9	8	6	26	49
	%	0.2	0.2	0.1	0.5	0.2
50–199	n	81	43	42	176	342
	%	1.4	0.9	0.7	3.6	1.6
200–349	n	362	234	245	511	1,352
	%	6.4	5.1	4.1	10.5	6.4
350–499	n	854	621	652	665	2,792
	%	15.1	13.6	10.9	13.6	13.2
500–749	n	1,960	1,654	1,968	1,467	7,049
	%	34.7	36.3	32.9	30.1	33.4
≥ 750	n	2,356	1,985	3,050	1,986	9,377
	%	41.7	43.5	50.9	40.7	44.5
Viral load <50 copies/ml						
No data	n	9	4	7	20	40
	%	0.2	0.1	0.1	0.4	0.2
Yes	n	5,416	4,396	5,794	4,498	20,104
	%	95.9	96.4	96.7	92.3	95.4
No	n	223	162	189	356	930
	%	3.9	3.6	3.2	7.3	4.4
Viral load <200 copies/ml						
No data	n	9	4	7	20	40
	%	0.2	0.1	0.1	0.4	0.2
Yes	n	5,554	4,488	5,901	4,686	20,629
	%	98.3	98.4	98.5	96.1	97.9
No	n	85	70	82	168	405
	%	1.5	1.5	1.4	3.4	1.9

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

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

Among the 21,074 people in HIV care and on ART in 2022, the vast majority (82.4%) received a regimen based on two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with either:

- an integrase inhibitor (INSTI) (45.0%);
- a non-nucleoside reverse transcriptase inhibitor (NNRTI) (28.4%); or
- a protease inhibitor (PI) (9.0%).

The distribution of ART use among the population in care in 2022 is presented in *Figure 2.2*. The most frequently used regimens (used by at least 5% of the population) were:

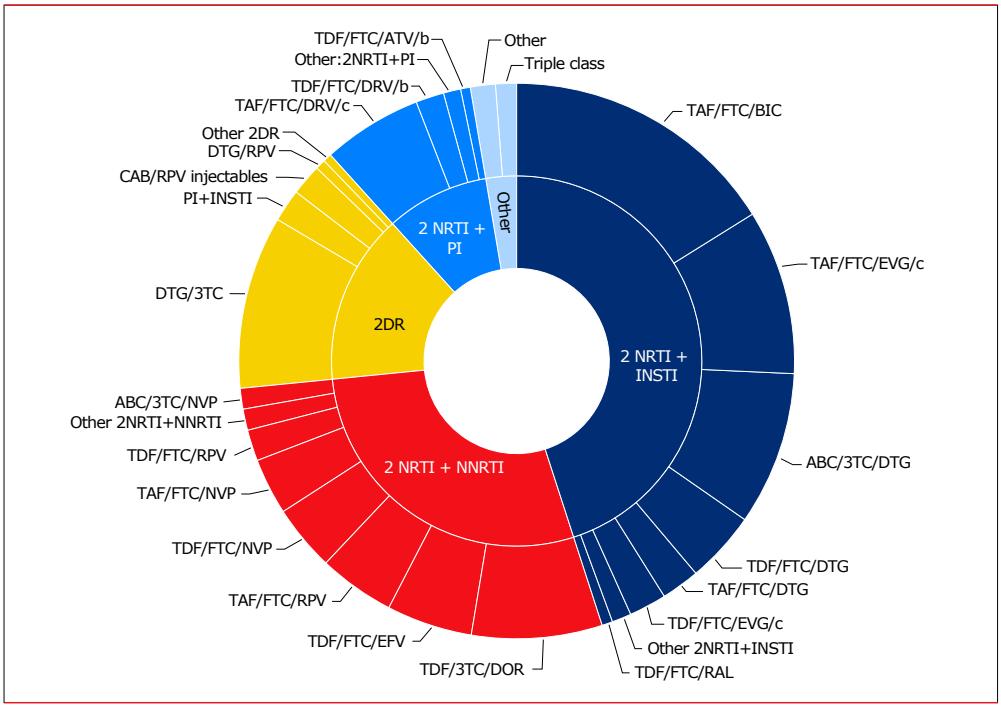
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/bictegravir (BIC) (16.1%);
- dolutegravir (DTG)/lamivudine (3TC) (10.1%);
- tenofovir alafenamide (TAF)/ emtricitabine (FTC)/elvitegravir (EVG)/cobicistat (9.6%);
- abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (8.9%);
- tenofovir disoproxil fumarate (TDF)/ lamivudine (3TC)/doravirine (DOR) (7.6%);
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/darunavir (DRV)/cobicistat (5.8%); and
- tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/efavirenz (EFV) (5.0%).

In 2022 the use of regimens not consisting of two NRTIs plus a third 'anchor drug' (an NNRTI, PI, or INSTI), continued to increase to 17.6% of which 14.9% used a two-drug regimen. The most common of these 2-drug regimens were a combination of:

- NRTI + INSTI (2,126 individuals or 67.8%) of which
  - 99.9% used lamivudine
  - 0.1% used TDF
  - 100% used dolutegravir;
- NNRTI + INSTI (525 individuals, or 16.8%) of which
  - 96.6% used rilpivirine
  - 27.1% used dolutegravir
  - 72.8% used cabotegravir (intramuscularly, long-acting);
- PI + INSTI (401 individuals, or 17.4%) of which
  - 98.3% used darunavir plus either dolutegravir (90.0%) or raltegravir (10.0%).

Of those with a plasma HIV RNA measurement in 2022, 95.4% had a viral load below 50 copies/ml, and 97.9% had a viral load below 200 copies/ml. On the basis of the last available CD4 and CD8 cell count measurements in the period 2015-22, 77.9% had a CD4 cell count of 500 cells/mm^3 or higher, and 30.7% had a CD4: CD8 ratio of 1 or higher.

Figure 2.2: Combination antiretroviral therapy (ART) use in 2022.



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

Changes in the use of initial ART regimen

Data from clinical trials on contemporary antiretroviral drugs have shown good outcomes in terms of viral suppression, convenience, tolerability, and toxicity. Over the past years, these new antiretroviral drugs and new, once-daily, fixed-dose combination regimens have been approved in the Netherlands (*Box 2.2*). In this section, we evaluate the post-approval implementation of these new drugs/regimens in HIV treatment.

Box 2.2: Approval dates of new antiretroviral drugs/regimens for HIV treatment in the Netherlands in 2013–22.

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

Legend: *3TC = lamivudine; ABC = abacavir; BIC = bictegravir; DTG = dolutegravir; DRV = darunavir; EVG = elvitegravir; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; RPV = rilpivirine.*
Source: *Medicines Evaluation Board http://english.cbg-meb.nl/ and European Medicines Agency http://www.ema.europa.eu/*

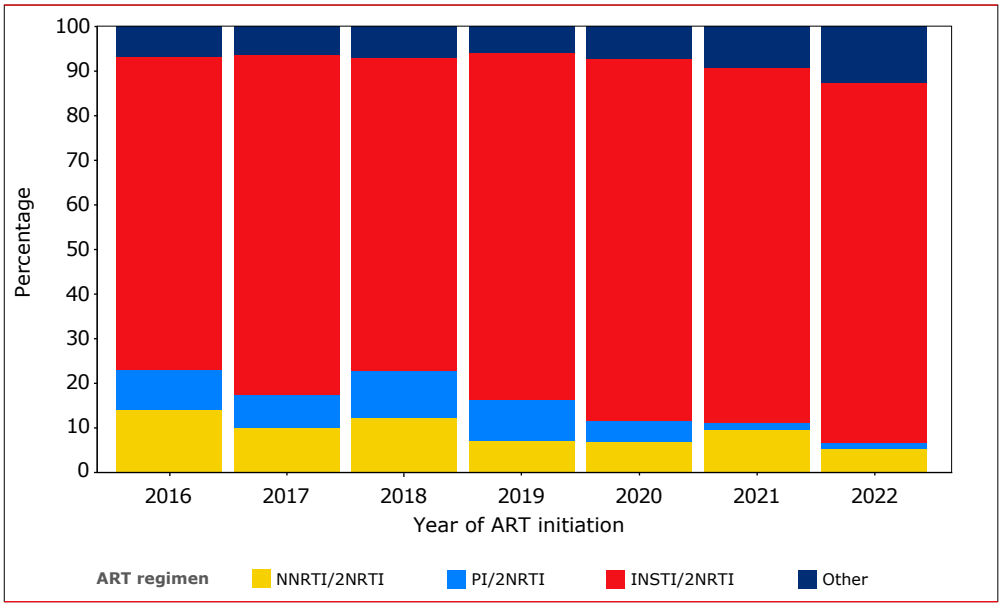
Initial ART regimen

Of the 28,546 people known to have initiated ART between 1996 and 2022, 5,578 (19.5%) started ART between January 2016 and December 2022. *Figures 2.3* and *2.4* show the trends over time in third-drug additions to the dual-NRTI backbone used as part of the initial ART regimen. The use of integrase inhibitors in combination with a dual-NRTI backbone as initial therapy, increased from 70.3% in 2016 to 80.4% in 2022 (93.1% including other INSTI-containing regimens). Cobicistat-boosted elvitegravir was used in 24.8%, 29.6% and 23.0% of the initial regimens in 2016, 2017, and 2018, respectively, before its use dropped sharply to 3.1% in 2019, 1.6% in 2020, 1.1% in 2021, and 0% in 2022. Dolutegravir was used in 50.7% of initial regimens in 2016, declined to 35.8% in 2019; after which it increased to 55.0% in 2022. Bictegravir was introduced in the Netherlands in 2018 and was used in 42.5% of initial regimens in 2019, which declined a little to 38.1% in 2022.

The use of NNRTIs in combination with a dual-NRTI backbone as the initial regimen decreased from 13.9% in 2016 to 4.9% in 2022. The use of PIs in combination with a dual-NRTI backbone as the initial regimen also decreased from 9.0% in 2016 to 1.8% in 2022.

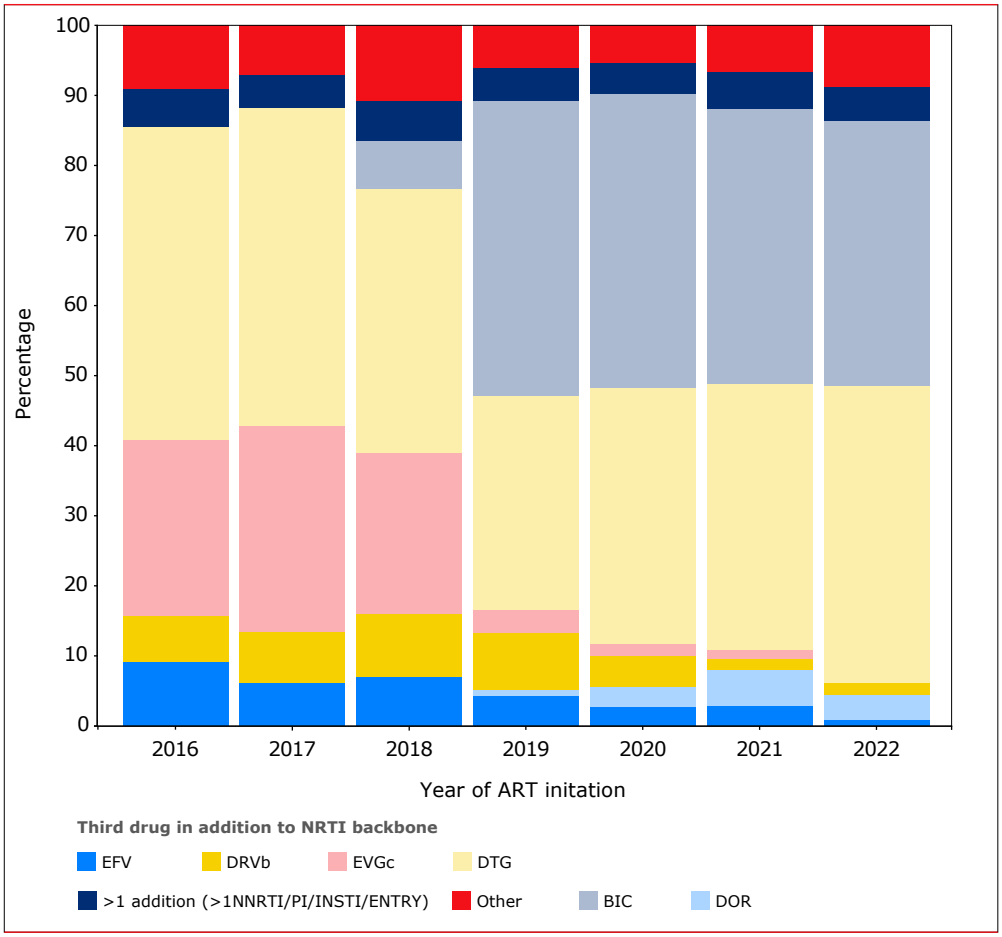
In the period 2016-22, a stable proportion of around 5% of individuals (4.5% in 2022) received more than one third-drug addition to the NRTI backbone in their initial ART regimen. The majority of these were people initiating ART during an acute HIV infection, with the regimen consisting of a PI (mainly boosted darunavir) plus an INSTI (mainly dolutegravir), plus two NRTIs. *Figure 2.4* shows all third-drug additions to the dual-nucleoside reverse transcriptase backbone that were used in at least 5% of individuals for one or more years as part of the initial regimen during the period 2016-22. The use of nevirapine, rilpivirine, atazanavir, lopinavir, and raltegravir as third-drug additions to initial regimens did not exceed 5% in any year in the period 2016-22. As a result, those regimens have been included in the category 'other' in *Figure 2.4*.

Figure 2.3: *Third-drug class additions to the dual-nucleoside reverse transcriptase backbone used as part of the initial regimen in 2016-22.*



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

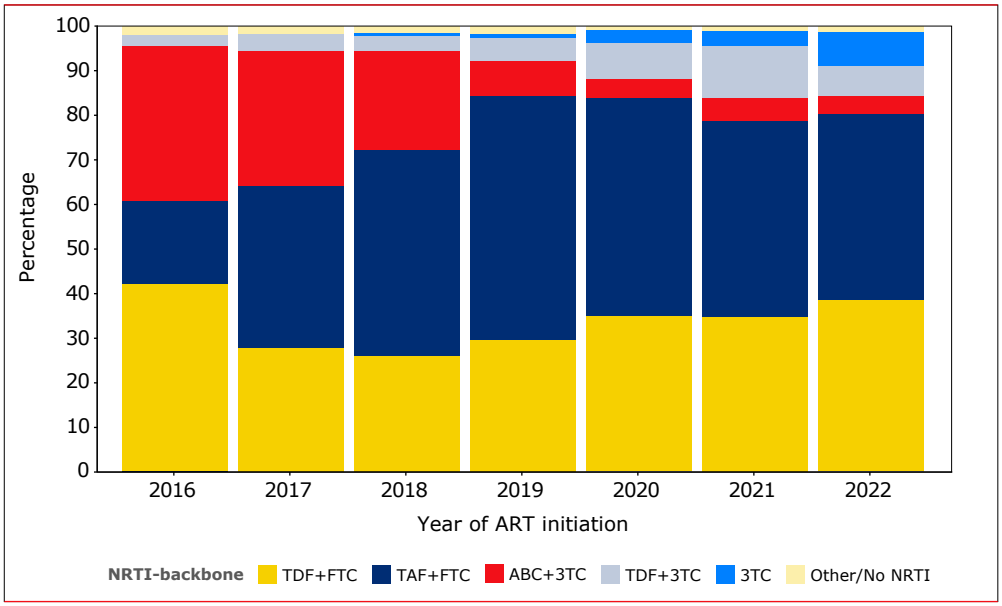
Figure 2.4: *Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2016–22.*



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

Figure 2.5 provides an overview of the NRTI backbone components of the initial ART regimens used in 2016-22. The combination of tenofovir (TDF or TAF) and emtricitabine 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 55.1% in 2019, but has since slowly declined to 41.8% in 2022. At the same time, TDF use decreased from 44.5% in 2016 to 29.7% in 2018, after which its use increased again to 45.4% in 2022. The use of abacavir steadily decreased from 34.8% of all initial regimens in 2016 to 4.0% in 2022.

Figure 2.5: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2016–22.*



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

The ART regimens initiated in 2016-22 are presented in *Figure 2.6* and *Table 2.3*. In 2022, the most frequently used initial regimen was TAF/FTC/bictegravir (38.1%). Dolutegravir-containing initial regimens were used in 46.3% of cases. Additionally, 3.6% initiated a doravirine-containing once-daily, fixed-dose combination with lamivudine and tenofovir (TDF). *Table 2.3* provides more detail on the 'other' initial regimens that are not further specified in *Figures 2.4-2.6*.

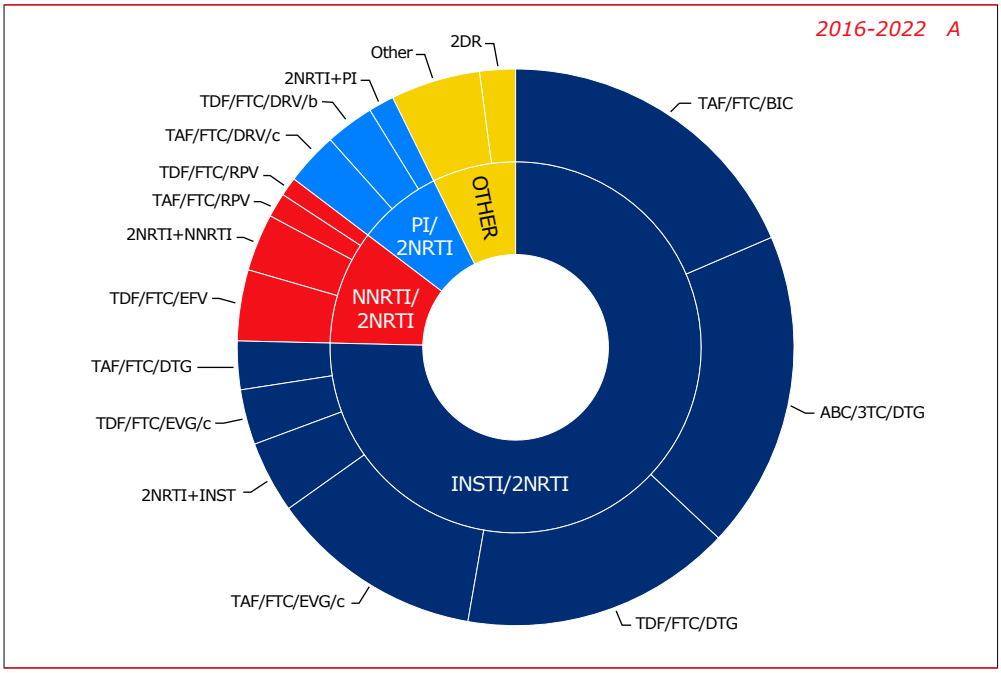
Table 2.3: Initial regimens in 2016–22.

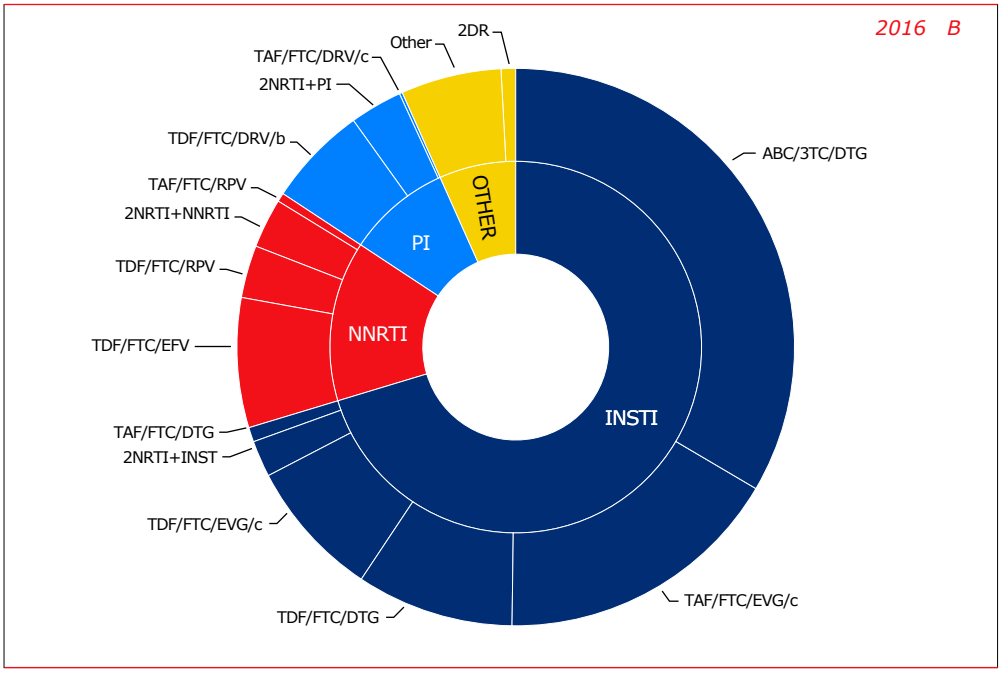
		2016	2017	2018	2019	2020	2021	2022	2016–22
N		1,183	1,079	956	802	579	530	449	5,578
Regimen									
TDF/FTC/EFV	n	89	42	48	25	10	13	3	230
	%	7.5	3.9	5	3.1	1.7	2.5	0.7	4.1
TDF/FTC/NVP	n	9	2	2	1	0	1	0	15
	%	0.8	0.2	0.2	0.1	0	0.2	0	0.3
TDF/FTC/RPV	n	36	10	5	5	2	3	0	61
	%	3	0.9	0.5	0.6	0.3	0.6	0	1.1
TDF/3TC/DOR	n	0	0	0	5	17	26	16	64
	%	0	0	0	0.6	2.9	4.9	3.6	1.1
TDF/FTC/DRV/b	n	69	40	16	16	11	3	3	158
	%	5.8	3.7	1.7	2	1.9	0.6	0.7	2.8
TDF/FTC/ATV/b	n	18	5	6	6	1	0	0	36
	%	1.5	0.5	0.6	0.7	0.2	0	0	0.6
TDF/FTC/LPV/r	n	2	1	0	0	0	0	0	3
	%	0.2	0.1	0	0	0	0	0	0.1
TDF/FTC/EVG/c	n	95	58	17	6	0	3	0	179
	%	8	5.4	1.8	0.7	0	0.6	0	3.2
TDF/FTC/DTG	n	108	96	96	138	154	136	150	878
	%	9.1	8.9	10	17.2	26.6	25.7	33.4	15.7
TDF/FTC/RAL	n	10	8	15	12	3	5	0	53
	%	0.8	0.7	1.6	1.5	0.5	0.9	0	1
ABC/3TC/DTG	n	396	314	195	58	24	25	18	1030
	%	33.5	29.1	20.4	7.2	4.1	4.7	4	18.5
ABC/3TC/NVP	n	1	1	1	0	0	0	0	3
	%	0.1	0.1	0.1	0	0	0	0	0.1
TAF/FTC/RPV	n	6	21	38	6	4	2	2	79
	%	0.5	1.9	4	0.7	0.7	0.4	0.4	1.4
TAF/FTC/DRV/c	n	2	31	67	49	12	6	4	171
	%	0.2	2.9	7	6.1	2.1	1.1	0.9	3.1
TAF/FTC/EVG/c	n	198	261	203	19	9	3	0	693
	%	16.7	24.2	21.2	2.4	1.6	0.6	0	12.4
TAF/FTC/DTG	n	10	56	49	18	7	9	8	157
	%	0.8	5.2	5.1	2.2	1.2	1.7	1.8	2.8
TAF/FTC/BIC	n	0	4	65	340	246	208	171	1,034
	%	0	0.4	6.8	42.4	42.5	39.2	38.1	18.5
DTG/3TC	n	1	2	8	5	15	18	32	81
	%	0.1	0.2	0.8	0.6	2.6	3.4	7.1	1.5

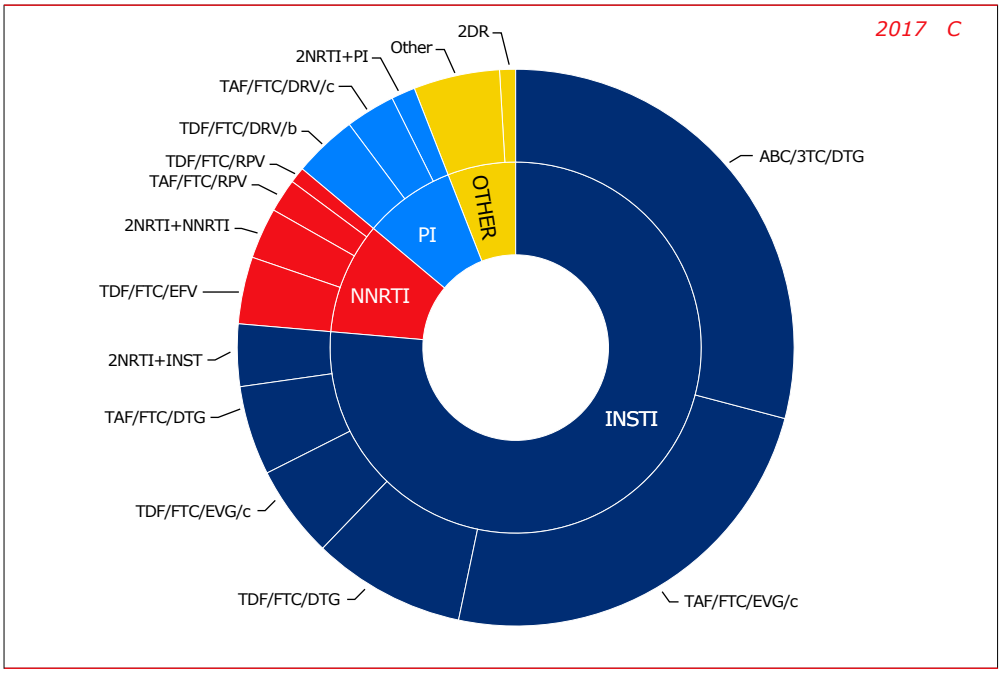
		2016	2017	2018	2019	2020	2021	2022	2016–22
N		1,183	1,079	956	802	579	530	449	5,578
Regimen									
DTG/RPV	n	0	0	1	1	0	0	0	2
	%	0	0	0.1	0.1	0	0	0	0
2DR: PI + INSTI	n	8	8	3	3	1	3	5	31
	%	0.7	0.7	0.3	0.4	0.2	0.6	1.1	0.6
Other: 2NRTI + NNRTI	n	24	29	24	15	6	4	2	104
	%	2	2.7	2.5	1.9	1	0.8	0.4	1.9
Other: 2NRTI + PI	n	16	9	10	3	4	1	1	44
	%	1.4	0.8	1	0.4	0.7	0.2	0.2	0.8
Other: 2NRTI + INST	n	15	27	31	33	27	33	14	180
	%	1.3	2.5	3.2	4.1	4.7	6.2	3.1	3.2
Other: 2DR	n	1	0	1	0	0	0	0	2
	%	0.1	0	0.1	0	0	0	0	0
Other: NRTI + PI + INSTI	n	1	1	1	1	0	1	1	6
(3ARVs)	%	0.1	0.1	0.1	0.1	0	0.2	0.2	0.1
Other: NRTI + PI + INSTI	n	57	52	51	33	24	24	17	258
(4ARVs)	%	4.8	4.8	5.3	4.1	4.1	4.5	3.8	4.6
Other	n	11	1	3	4	2	3	2	26
	%	0.9	0.1	0.3	0.5	0.3	0.6	0.4	0.5

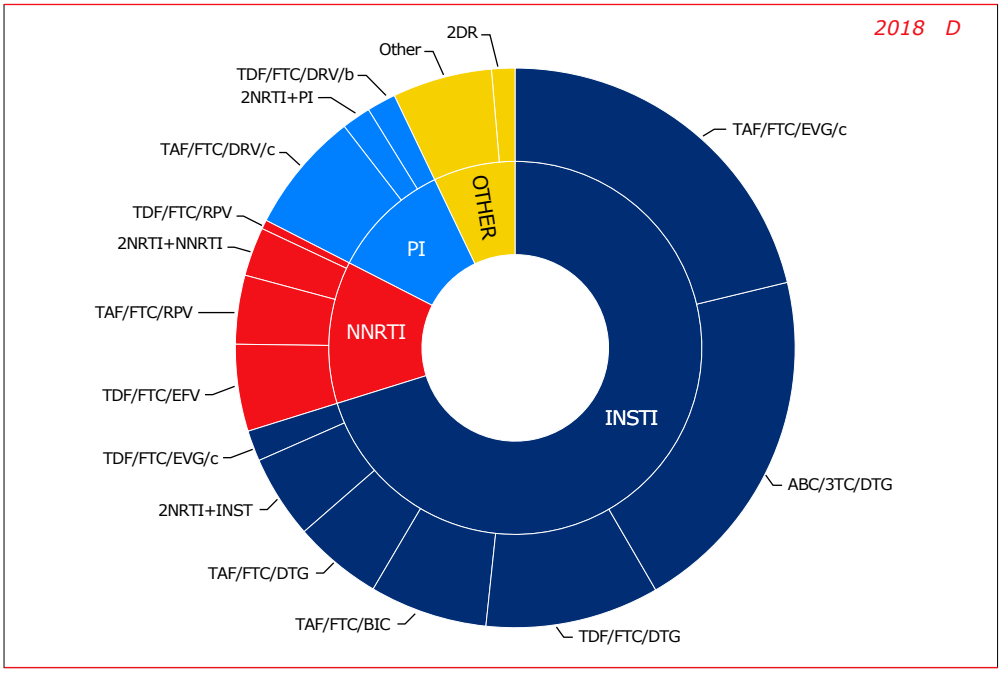
Legend: *ARVs = antiretroviral drugs; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; BIC = bictegravir; CI = confidence interval; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG =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

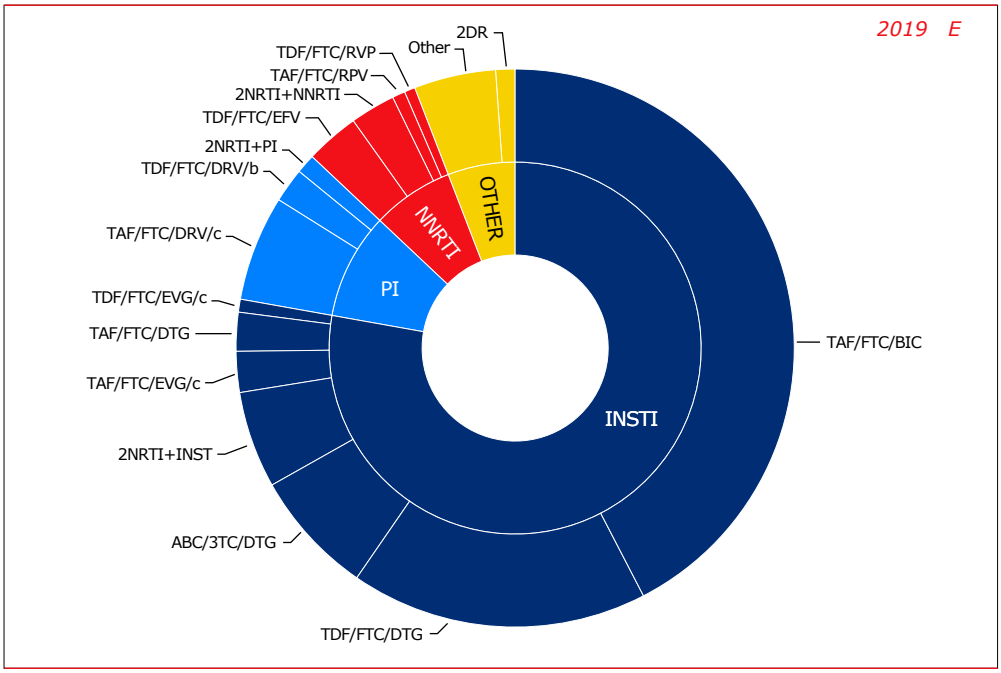
Figure 2.6: The initial combination antiretroviral therapy regimens given in 2016–22 A) in total and B) by year.

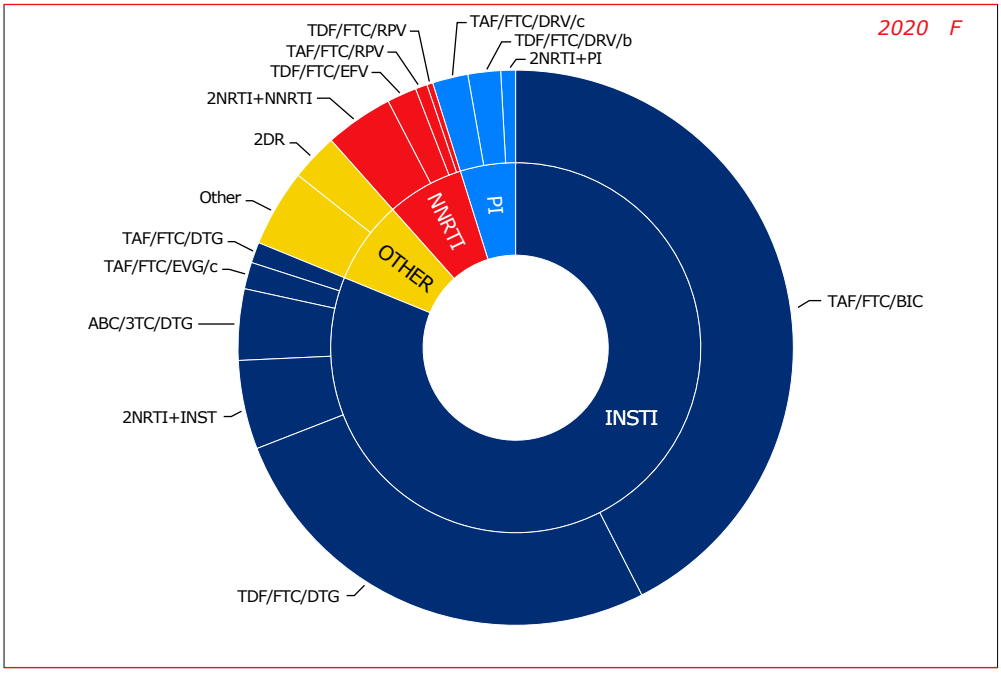


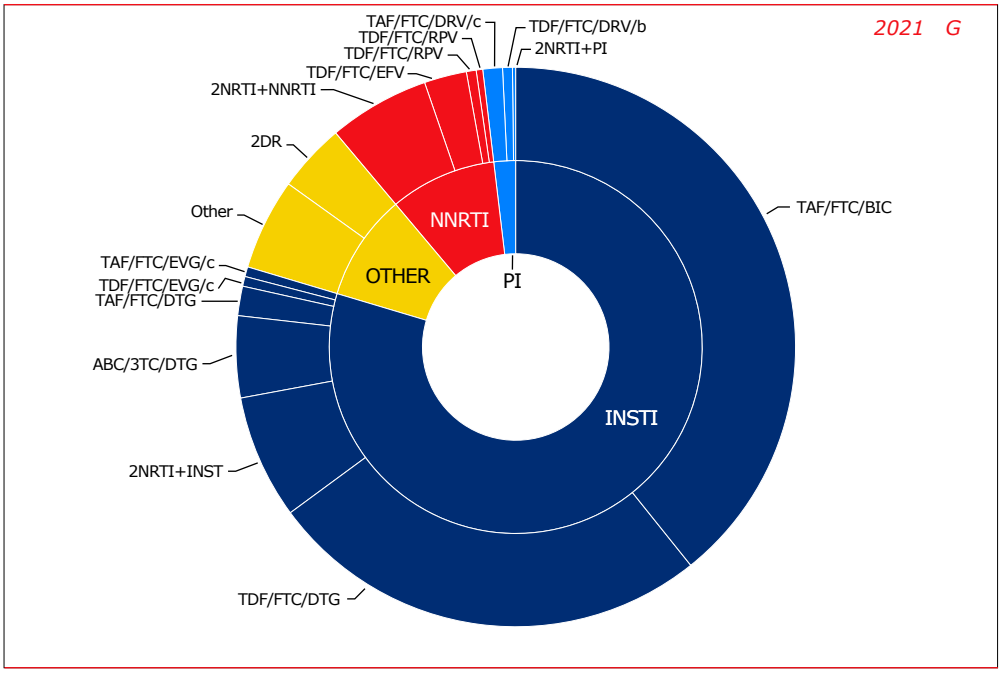


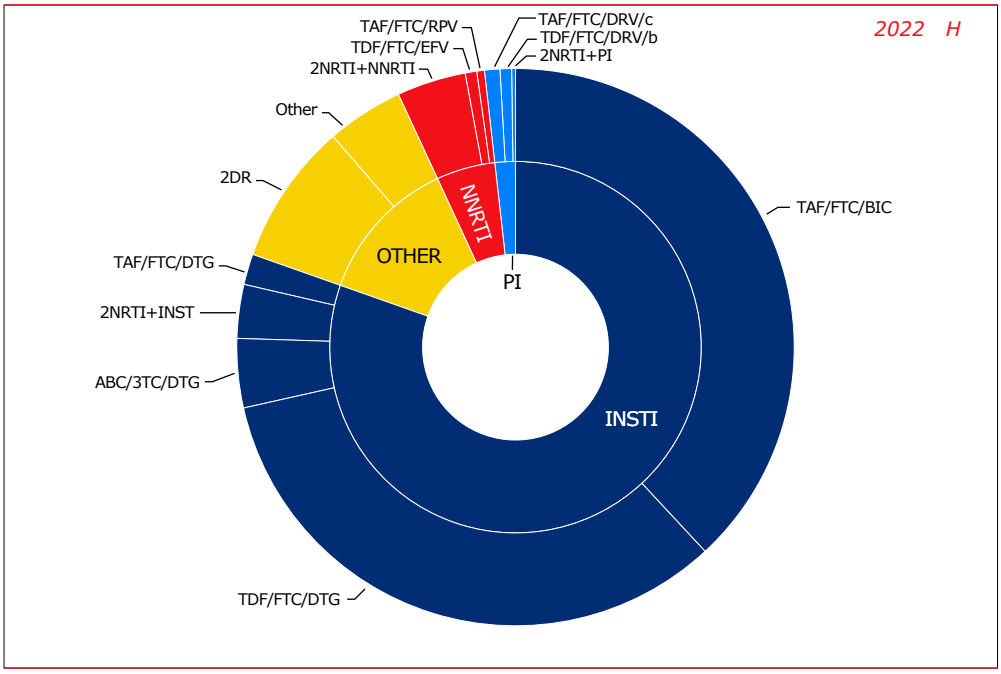

2017 C
2DR
Other
2NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/DRV/b
TDF/FTC/RPV
TAF/FTC/RPV
2NRTI+NNRTI
TDF/FTC/EFV
2NRTI+INST
TAF/FTC/DTG
TDF/FTC/EVG/c
TDF/FTC/DTG
ABC/3TC/DTG
TAF/FTC/EVG/c
OTHER
PI
NNRTI
INSTI


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


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


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





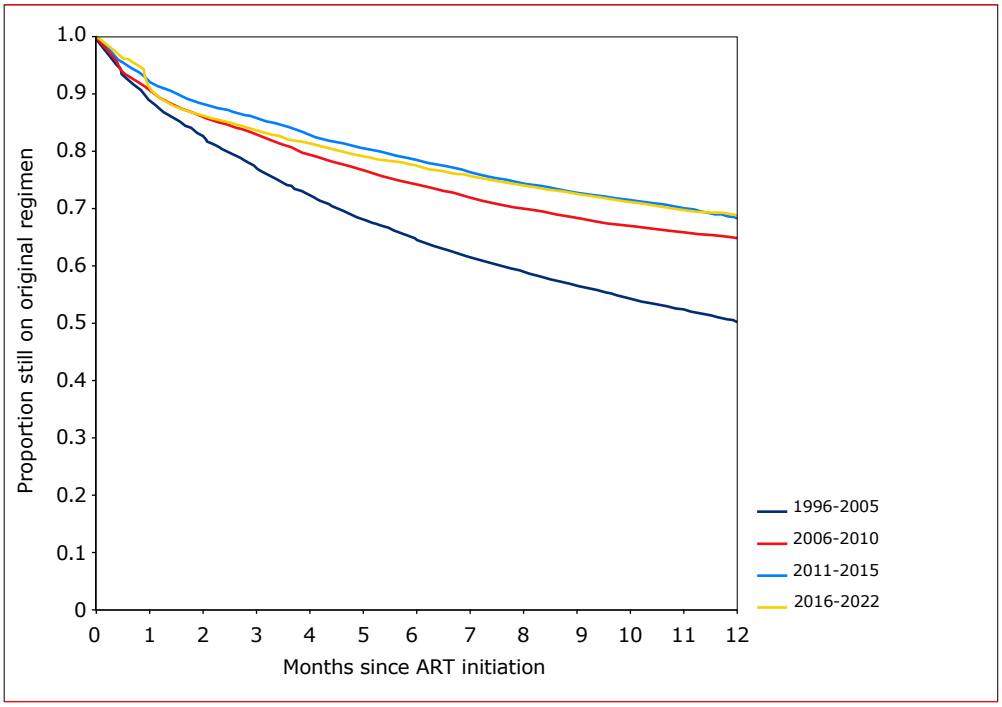
Legend: *3TC = lamivudine; ABC = abacavir; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; BIC = bictegravir; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase inhibitor; NNRTI = non-nucleoside reverse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

Discontinuation of the initial ART regimen

For the 28,546 people who started ART between 1996 and 2022, we assessed the time spent on that initial ART regimen. Discontinuation was defined as a change in, or discontinuation of, one or more of the drugs included in the regimen. Simplification to a fixed-drug combination formulation containing the same drugs was not considered a discontinuation. Likewise, the breakup of a (more expensive) single tablet regimen (STR) into (cheaper) generic components of the original STR, was also not considered a switch. A switch from one booster to another was also ignored; for example, a switch from efavirenz (EFV) with fixed-dose TDF/FTC to the fixed drug combination EFV/TDF/FTC was not considered discontinuation of the initial regimen, however, a change from EFV/TDF/FTC to EVG/c/TDF/FTC was. One-year discontinuation rates are based on the Kaplan-Meier estimates.

In the period 1996-2022, 38.3% of individuals discontinued their initial regimen within one year; the length of time they remain on it has improved over the years: in 1996-2005, 49.8% discontinued it within a year, compared to 35.0% in 2006-2010, 31.6% in 2011-2015, and 30.7% in 2016-2022. *Figure 2.7* shows the time to the first modification of the initial regimen during the first year of ART, stratified by five-year calendar periods.

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



Legend: *ART = combination antiretroviral therapy.*

Discontinuation of the initial ART regimen: 2016–22

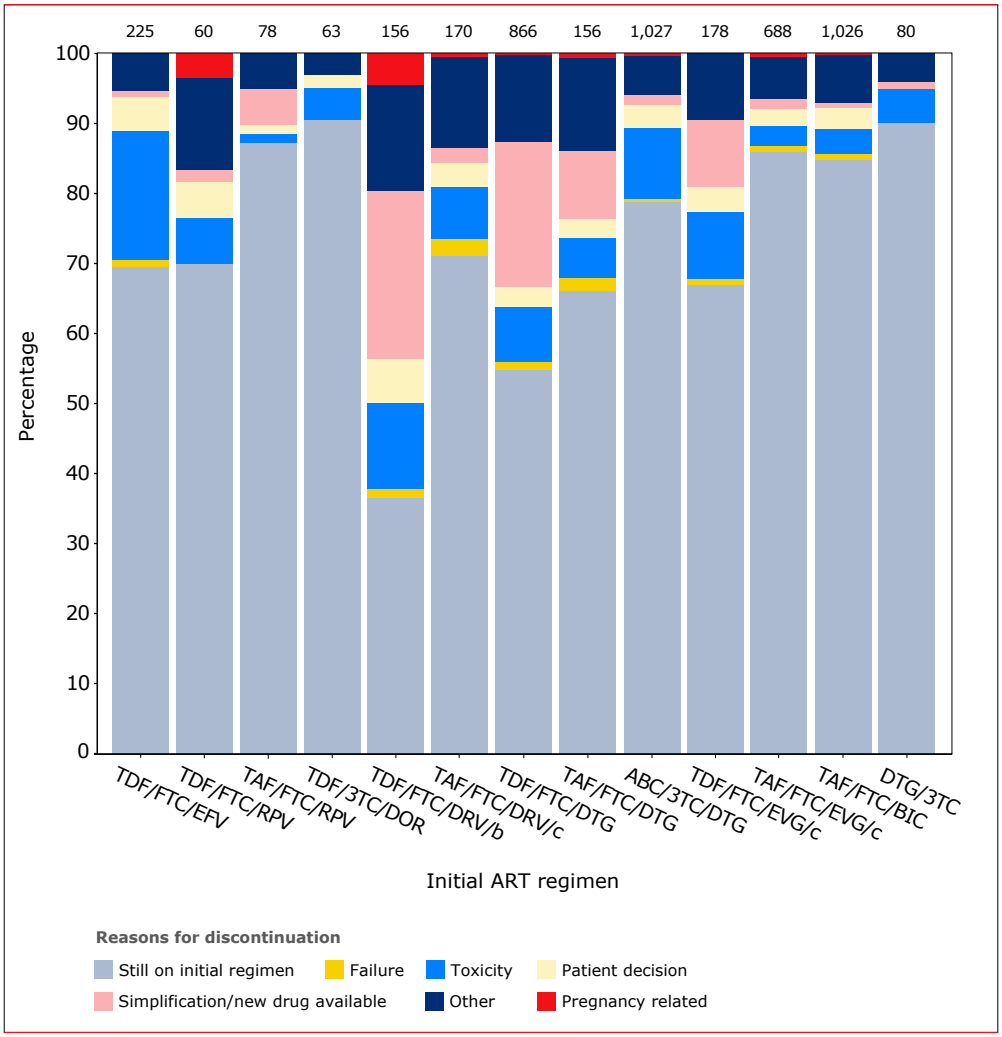
We further assessed the time to discontinuation of the initial regimen during the first year of treatment among the 4,473 people who started 'common' and guideline-recommended initial regimens in 2016-2022. The regimens considered in this analysis were:

- tenofovir disoproxil fumarate/emtricitabine combined with efavirenz (TDF/FTC/EFV, 4.7%);
- rilpivirine (TDF/FTC/RPV, 1.3%);
- ritonavir-boosted or cobicistat-boosted darunavir (TDF/FTC/DRV/b, 3.3%);
- cobicistat-boosted elvitegravir (TDF/FTC/EVG/c, 3.7%);
- dolutegravir (TDF/FTC/DTG, 18.1%);
- tenofovir disoproxil fumarate/lamivudine combined with doravirine (TDF/3TC/DOR, 1.3%);
- abacavir-lamivudine combined with dolutegravir (ABC/3TC/DTG, 21.5%);
- tenofovir alafenamide/emtricitabine combined with cobicistat-boosted elvitegravir (TAF/FTC/EVG/c, 14.4%);
- rilpivirine (TAF/FTC/RPV, 1.6%);
- dolutegravir (TAF/FTC/DTG, 3.3%);
- cobicistat-boosted darunavir (TAF/FTC/DRV/c, 3.6%);
- bictegravir (TAF/FTC/BIC, 21.5%); and
- dolutegravir/lamivudine (DTG/3TC, 1.7%).

One year after ART initiation, 1,221 (25.6%) of the 4,773 individuals using one of these initial regimens had discontinued it. The main reason for this discontinuation was toxicity (n=334, 27.4%), followed by simplification and/or availability of new drugs (293, 24.0%). The availability of new, once-daily, fixed-dose combinations contributed to an increase in initial regimen discontinuation due to simplification and/or availability of new drugs, especially for those receiving TDF/FTC/DTG, and TDF/FTC/DRV/b (*Figure 2.8*).

The nature and severity of toxicities leading to discontinuation have changed considerably over time. Because of the availability of a large number of potent and well-tolerated recommended and alternative regimens, as well as the very low risk of viral breakthrough following a switch, the threshold for modifying the initial (or any) regimen has become much lower over the years. Furthermore, in recent years, the regimens TDF/FTC/DTG and TDF/FTC/DRV/b have frequently been used as an initial 'induction' regimen in treatment-naïve patients because of their potent antiretroviral activity and high genetic barrier to resistance, with the explicit intention to quickly switch to a single tablet 'maintenance' regimen after the plasma HIV-1 viral load has become undetectable.

Figure 2.8: *Reasons for discontinuation of the initial regimen during the first year of treatment in 2016–2022, by regimen. Numbers above the bars represent the total number of individuals using that particular regimen.*



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

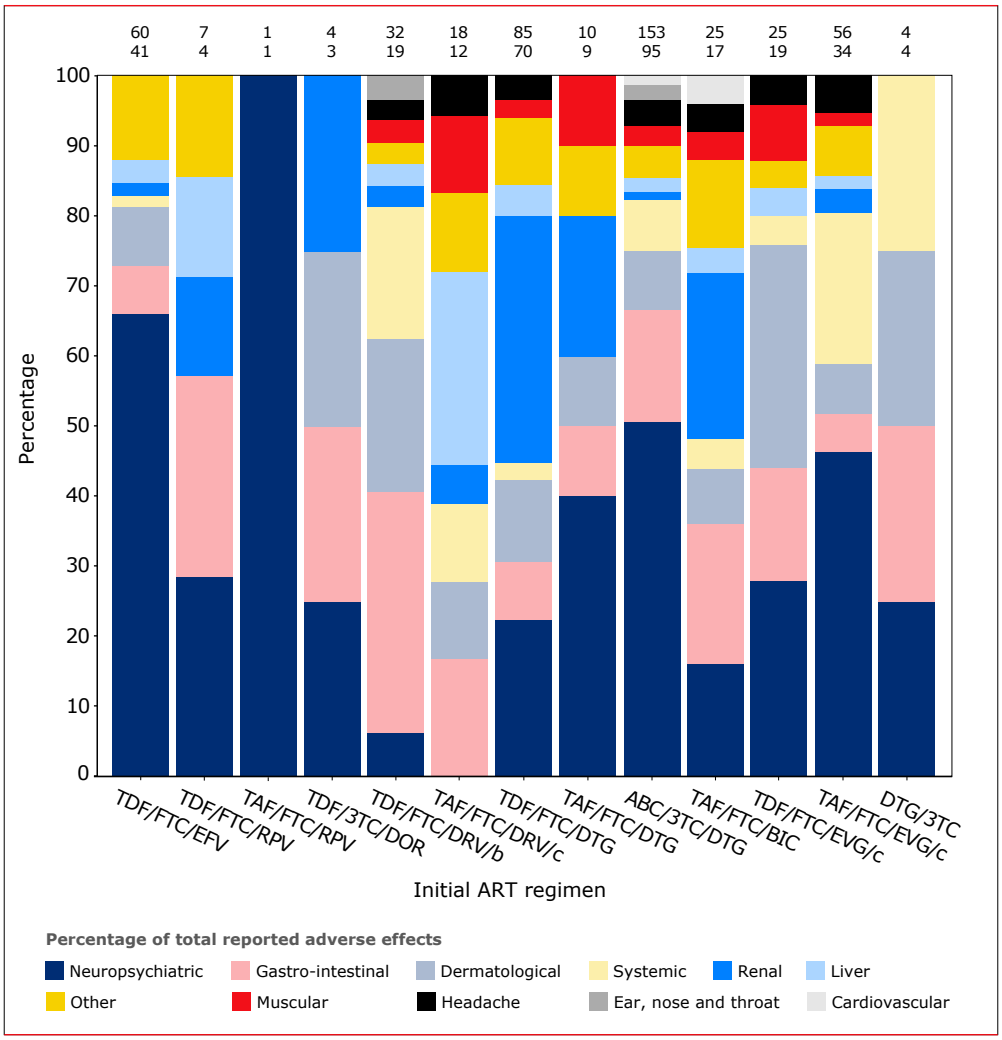
Adverse effects resulting in discontinuation

Among the 334 individuals who discontinued their initial ART regimen within a year due to toxicity, 480 adverse effects were recorded. The predominant adverse effects were:

- neuropsychiatric (mainly insomnia, mood changes, dizziness, and depression) 38.1%;
- gastrointestinal (mainly diarrhoea and nausea) 13.8%;
- dermatological (rash due to medication, itching) 11.3%;
- renal (renal insufficiency and increased serum creatinine) 9.8%; and
- systemic (tiredness, apathy, and loss of appetite) 7.7%.

These adverse effects are stratified by ART regimen in *Figure 2.9*. Neuropsychiatric effects were associated with regimens containing efavirenz and dolutegravir, and, to a lesser extent, rilpivirine and elvitegravir. Renal effects were mainly, but not exclusively, reported by people who discontinued tenofovir disoproxil fumarate-based ART.

Figure 2.9: *Adverse effects associated with initial regimen discontinuation due to toxicity, during the first year of treatment in 2016–2022. The bars represent the distribution of 480 reported effects among 334 individuals, by regimen. Numbers above the bars represent 1) the number of adverse events reported as reasons for discontinuing that particular regimen (top row), and 2) the number of individuals using that particular regimen who experienced those events (bottom row).*



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

Note: *The discontinuation rates and reasons for discontinuation are descriptive by nature and should be interpreted with caution. The choice of the initial ART regimen depends on personal characteristics, which might explain differences in discontinuation that are unrelated to the regimen (i.e. confounding by indication). Furthermore, follow-up time for some of the newer ART regimens was fairly short, which also influences discontinuation rates.*

Virological response

In the Netherlands, a total of 28,546 adults started ART between January 1996 and December 2022. For the analysis of virological outcomes in this section, we have focused on the 24,277 adults who were ART-naïve and not pregnant at the time of ART initiation (because ART may have been interrupted at the end of the pregnancy). We have also excluded people without a valid viral load test result within at least three months of ART initiation. The main definitions for virological outcomes used in this chapter are summarised in *Box 2.3*.

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

Virological response

Initial virological success
HIV viral load below 50 copies/ml within six months of starting combination antiretroviral therapy (ART).

The viral load measurement closest to six months (plus or minus three months) after ART initiation was included in the analysis, irrespective of the viral load level.

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

HIV drug resistance

Transmitted HIV drug resistance
At least one resistance-associated mutation detected among individuals who had never received antiretroviral drugs and had not started ART.
The 2022 International Antiviral Society-USA (IAS-USA) HIV drug resistance mutation list was used to score major resistance-associated mutations[24].

Acquired HIV drug resistance
High-level resistance to at least one antiretroviral drug, detected at the time of virological failure, among people receiving ART for at least four months.
The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.9-1) was used to infer antiretroviral drug susceptibility and resistance scores[25,26].

Initial virological success

Of the 24,277 individuals with a viral load test result within at least three months of ART initiation, 20,674 (85.2%) had a viral load measurement six months (plus or minus three months) after ART initiation. Of these people, 16,101 (77.9%) achieved initial virological success (i.e. a plasma viral load below 50 HIV RNA copies/ml [*Box 2.3*]). That percentage has improved over time, from 61.2% in those starting ART between 1996 and 2005, to 80.1% in 2006-10, 85.3% in 2011-21, and 88.1% in those starting in 2022.

Initial virological success of common initial ART regimens (2013–22)

We analysed initial virological success among the 6,323 adults who started a common or guideline-recommended ART regimen in 2013-22, which was used frequently enough to allow for a meaningful analysis (TDF/FTC/EFV; TDF/FTC/RPV; TDF/3TC/DOR; TDF/FTC/DRV/b; TDF/FTC/DTG; TDF/FTC/EVG/c; TAF/FTC/RPV; TAF/FTC/DRV/c; TAF/FTC/BIC; TAF/FTC/DTG; TAF/FTC/EVG/c; ABC/3TC/DTG; and 3TC/DTG), and had a viral load result within six months (plus or minus three months) of ART initiation. In total, 88.0% (95% confidence interval [CI] 87.2-88.8) of individuals achieved initial virological suppression. Overall, people receiving an integrase inhibitor or NNRTI-based regimen showed significantly higher rates of initial virological success: 89.6% (CI 88.7-90.5) of those on an integrase inhibitor-based regimen and 88.8% (87.1-90.6) on a NNRTI-based regimen, compared to 76.5% (73.3-79.7) on a protease inhibitor-based regimen.

Using logistic regression analysis, we further evaluated the initial virological success rates stratified by viral load at ART initiation (below, as well as equal to or above, 100,000 copies/ml), ART regimen, and regimen class. Stratified analysis of initial virological success based on viral load at ART initiation, showed superior virological outcomes for INSTI-based regimens, compared to both NNRTI-based and protease inhibitor-based regimens in people with a viral load at or above 100,000 copies/ml at ART initiation as well as in people with a viral load below 100,000 copies/ml at ART initiation (*Table 2.4*). Population characteristics, which may be associated with the initial prescribed regimen, were not taken into account in this analysis.

Table 2.4: *Initial virological success rates (see definition in Box 2.3), by initial regimen and initial viral load at ART initiation in 2013-2022.*

	Total		By initial viral load at ART initiation					
			<100,000 copies/ml					
	n	%	n	%	Initial virological success	95% CI low	95% CI high	p-value
ART regimen								
TDF/FTC/EFV	646	10.2	357	9.3	94.1	91.7	96.6	Ref.
TDF/FTC/RPV	466	7.4	466	12.1	91.8	89.4	94.3	0.21
TDF/3TC/DOR	53	0.8	39	1.0	97.4	92.5	100	0.41
TDF/FTC/DRV/b	553	8.8	228	5.9	89.0	95.0	93.1	0.028
TDF/FTC/EVG/c	771	12.2	531	13.8	96.2	94.6	97.9	0.14
TDF/FTC/DTG	829	13.1	400	10.4	94.8	92.6	96.9	0.70
ABC/3TC/DTG	1,274	20.2	848	22.1	95.8	94.4	97.1	0.22
TAF/FTC/RPV	53	0.8	53	1.4	100	100	100	0.98
TAF/FTC/DRV/c	128	2.0	56	1.5	96.4	91.6	100	0.49
TAF/FTC/EVG/c	562	8.9	348	9.1	97.1	95.4	98.9	0.056
TAF/FTC/DTG	112	1.8	50	1.3	94.0	87.4	100	0.97
TAF/FTC/BIC	824	13.0	425	11.1	96.9	95.3	98.6	0.058
3TC/DTG *	52	0.8	45	1.2	100	100	100	0.98
Regimen class								
NNRTI/2NRTI	1,218	19.3	915	23.8	93.4	91.8	95.0	Ref.
PI/2NRTI	681	10.8	284	7.4	90.5	87.1	93.9	0.096
INSTI/2NRTI **	4,424	70.0	2,647	68.8	96.1	95.4	96.8	0.0010
All regimens	6,323		3,846	60.8	95.1	94.4	95.7	

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

** excluding individuals with initial viral load > 500.000 copies/ml*

*** this class includes 3TC/DTG;*

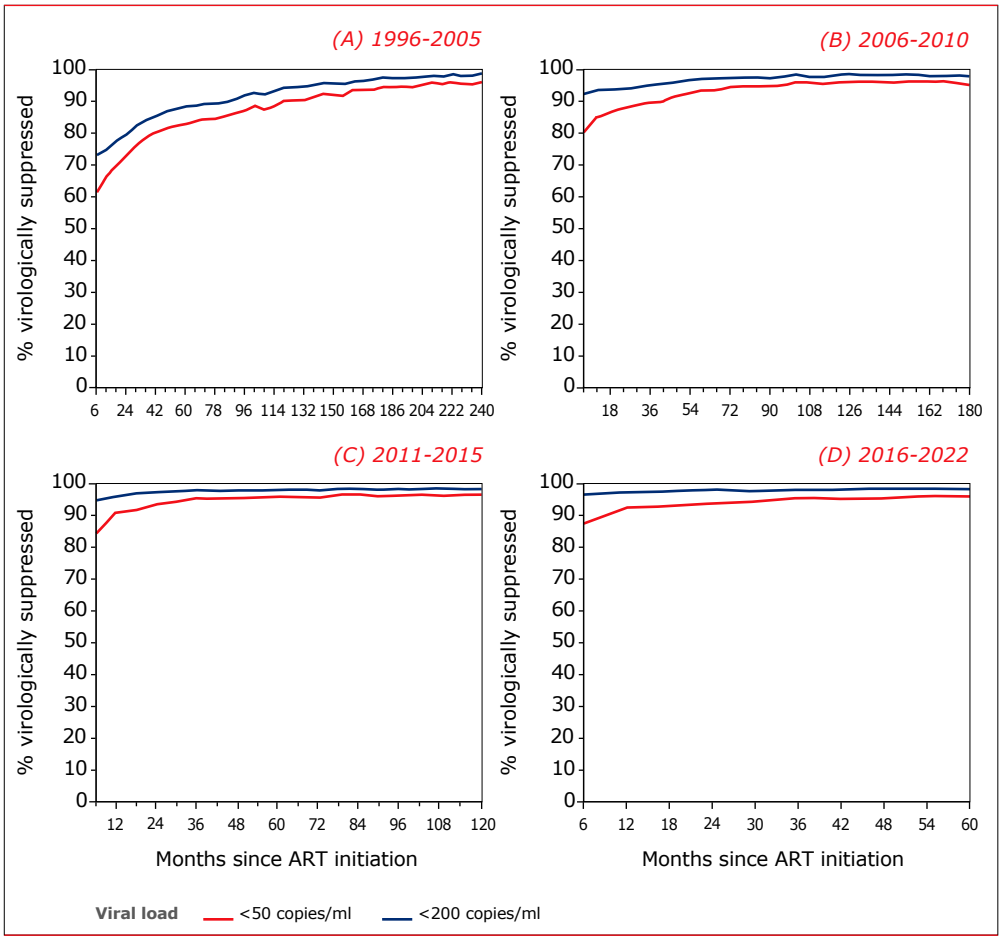
	By initial viral load at ART initiation					
	≥100,000 copies/ml					
	n	%	Initial virological success	95% CI low	95% CI high	p-value
ART regimen						
TDF/FTC/EFV	289	11.7	74.7	69.7	79.8	Ref.
TDF/FTC/RPV						
TDF/3TC/DOR	14	0.6	78.6	57.1	100	0.75
TDF/FTC/DRV/b	325	13.1	66.8	61.6	71.9	0.031
TDF/FTC/EVG/c	240	9.7	77.1	71.8	82.4	0.53
TDF/FTC/DTG	429	17.3	78.6	74.7	82.4	0.23
ABC/3TC/DTG	426	17.2	82.2	78.5	85.8	0.017
TAF/FTC/RPV						
TAF/FTC/DRV/c	72	2.9	65.3	54.3	76.3	0.11
TAF/FTC/EVG/c	214	8.6	79.4	74.0	84.9	0.22
TAF/FTC/DTG	62	2.5	77.4	67.0	87.8	0.66
TAF/FTC/BIC	399	16.1	80.5	76.6	84.3	0.075
3TC/DTG *	7	0.3	100	100	100	0.97
Regimen class						
NNRTI/2NRTI	303	12.2	74.9	70.0	79.8	Ref.
PI/2NRTI	397	16.0	66.5	61.9	71.1	0.054
INSTI/2NRTI **	1,777	71.7	79.8	77.9	81.7	0.016
All regimens	2,477	39.2	77.1	75.4	78.7	

Viral suppression

We assessed long-term viral suppression rates (i.e. viral load below 200 copies/ml) as well as the proportion of individuals with plasma viremia below 50 copies/ml, during six-month intervals among adults on ART with a viral load test result after ART initiation. The viral load measurement after at least three months of ART, closest to each six-month time point (plus or minus three months), was included in the analysis, irrespective of the viral load.

Figure 2.10 shows viral suppression rates by calendar period of ART initiation: 1996-2005, 2006-2010, 2011-2015, and 2016-2022. In line with the initial virological success rates, the long-term viral suppression rates improved over time. In people initiating ART in, or after 2016, suppression rates ranged from 97.4% (95% CI 96.9-97.9) after one year of ART use, to 98.5% (98.0-98.9) after four years.

Figure 2.10: *Viral suppression following combination antiretroviral therapy (ART) initiation, by calendar period of therapy initiation; A) 1996–2005, B) 2006–10, C) 2011–15, and D 2016–22.*



Legend: *ART = combination antiretroviral therapy.*

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

HIV drug resistance

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

HIV drug resistance

Transmitted HIV drug resistance
At least one resistance-associated mutation detected among individuals who had never received antiretroviral drugs and had not started ART. The 2022 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[24].

Acquired HIV drug resistance
High-level resistance to at least one antiretroviral drug, detected at the time of an HIV viral load above 500 copies/ml, among people receiving ART for at least four months. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.4) was used to infer antiretroviral drug susceptibility and resistance scores[25,26].

Preventing, monitoring and responding to HIV drug resistance is a key component of comprehensive and effective HIV care. When antiretroviral therapy does not result in complete suppression of viral replication, HIV drug resistance can occur: mutations in the genetic structure of HIV detrimentally affect the ability of a particular drug, or combination of drugs, to block replication of the virus. All current antiretroviral drugs, including newer classes, are at risk of becoming partially or fully inactive due to the emergence of drug-resistant HIV virus[27].

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

We evaluated the presence of mutations in the HIV genome that are associated with drug resistance. The 2022 International Antiviral Society-USA (IAS-USA) HIV drug resistance mutation list was used to score major resistance-associated mutations[24]. Furthermore, we assessed the association between these mutations and the susceptibility to antiretroviral drugs. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.4) was used to infer

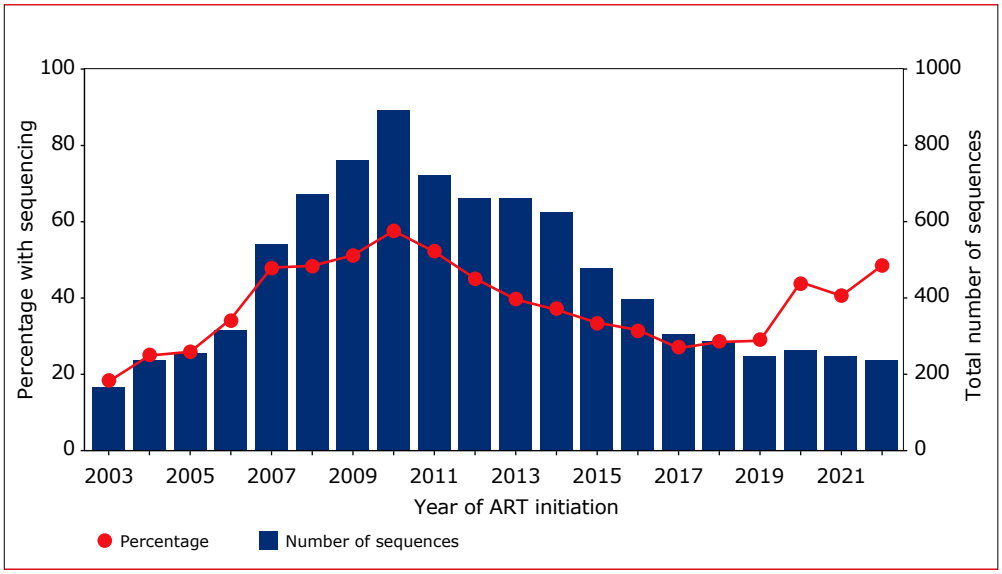
antiretroviral drug susceptibility scores for each sequence according to a five-level scheme: susceptible; potential low-level resistance; low-level resistance; intermediate resistance; and high-level resistance[25,26]. The definitions of transmitted and acquired-HIV drug resistance used in our analyses are summarised in *Box 2.3*. The number of sequences and people included in each of the analyses is outlined in *Box 2.1*.

Screening for drug-resistant HIV before treatment initiation

Since 2003 Dutch treatment guidelines have included a recommendation to screen for HIV drug resistance at the time of entry into care. Transmitted HIV drug resistance occurs when people acquire an HIV strain that harbours drug-resistant mutations. Drug-resistant variants of HIV may remain dormant in resting CD4 cells, awaiting more favourable replication conditions after treatment has started[28–30]. These dormant mutant variants may not be detected, which can make it difficult to distinguish between drug-susceptible and drug-resistant strains[31]. Ideally, the presence of transmitted resistance should be identified as close as possible to the moment of infection in people who are antiretroviral (ARV)-naïve before initiating ART.

In total, 9,125 HIV-1 sequences were obtained between 2003 and 2022 from 8,806 ARV-naïve people before they initiated ART. The number of sequences and the percentage of ARV-naïve people with sequencing before ART initiation peaked in 2010 and have steadily declined since then (*Figure 2.11*). If someone had more than one sequence available before ART initiation, we selected the first available sequence (closest to the date of HIV-1 diagnosis) for our analysis to limit the effect of back mutation. Of those with pre-treatment drug-resistance data, the majority were MSM (67.0%), while (15.1%) were women. Most people with an available pre-treatment sequence originated from the Netherlands (58.9%) or sub-Saharan Africa (11.1%). The main HIV-1 subtype was B (73.8%), followed by non-B subtypes (26.2%), including recombinant form CRF_02AG (6.8%), subtype C (5.0%), and CRF_01AE (3.7%).

Figure 2.11: The annual number of sequences and the percentage of ARV-naïve people with sequencing before ART.

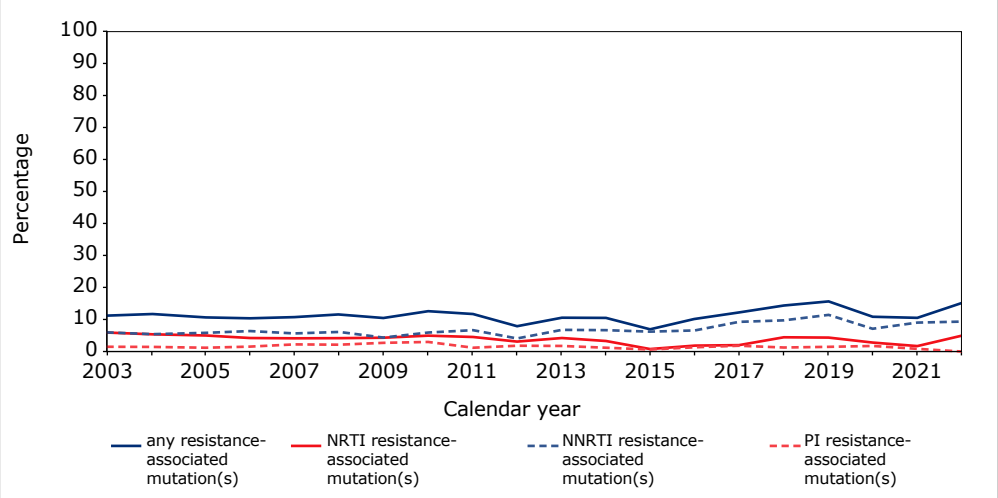


Legend: ART = combination antiretroviral therapy.

Transmitted HIV drug resistance

In total, at least one or more major resistance-associated mutation[32] was found in 980 (11.1%) of the ART-naïve people tested for resistance, including 352 (4.0%) with NRTI-associated resistance mutations, 559 (6.4%) with NNRTI-associated resistance mutations, and 152 (1.7%) with PI-associated resistance mutations. The prevalence of transmitted drug resistance was low and remained stable between 2003 and 2022 (*Figure 2.12*).

Figure 2.12: The annual percentage of people with evidence of transmitted HIV drug resistance over time. Transmitted drug resistance was defined as the presence of at least one resistance-associated mutation detected before initiation of ART. The 2022 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[24].



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

In total, 282 (3.2%) individuals screened for transmitted drug resistance harboured high-level resistance[25,26] to at least one antiretroviral drug: 73 (0.8%) to at least one NRTI; 209 (2.4%) to at least one NNRTI; and 36 (0.4%) to at least one PI. On the basis of the available resistance data, more than 97% were fully susceptible to all antiretroviral drugs: 2.8% (244) harboured high-level resistance in one drug class; 0.3% (27) in two drug classes; and less than 0.1% (five) to three drug classes (i.e., NRTIs, NNRTIs and PIs).

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

Integrase inhibitor resistance before HIV treatment initiation

In total, 411 people had an integrase sequence available prior to ART initiation, of whom all but 10 were ARV-naïve. Only one major integrase resistance-associated mutations was detected in these individuals (Y143Y/C).

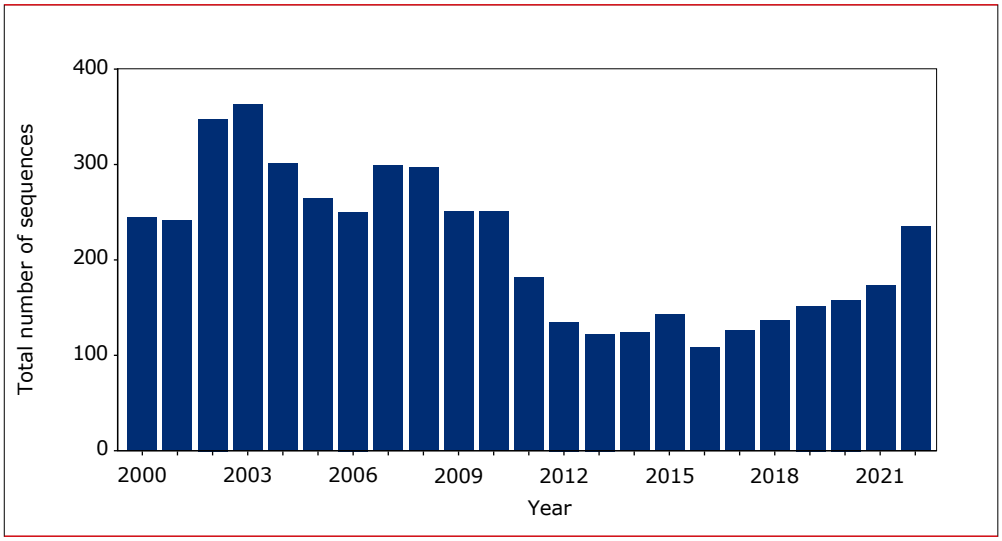
Acquired HIV drug resistance

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

In this section, we describe the level of acquired drug resistance detected among the treated population with a viral load above 500 copies/ml, and resistance test results available after at least four months of ART in 2000-2022. If ART had been interrupted more than two weeks before the test, the sequence was excluded from the analysis.

In total, 4,905 HIV-1 sequences were obtained from 2,933 people who received ART for at least four months. The number of sequences and people included in each subsequent analysis are outlined in *Box 2.1*. The number of sequences in this group was consistently above 200 between 2000 and 2010, substantially declined in 2011, then slightly increased until 2022 (*Figure 2.13*). The median time between initial start of ART and resistance testing was 5.8 years (IQR 3.2-9.6). The main HIV-1 subtype was B (67.0%), followed by recombinant form CRF_02AG (11.3%), and subtype C (5.9%).

Figure 2.13: *The annual number of HIV-1 sequences in people who received ART for at least four months.*



Overall, sequences from people pre-treated with monotherapy or dual therapy were disproportionally represented: 1,387 (28.3%) sequences were obtained from 748 (25.5%) pre-treated people, and 3,518 (71.7%) sequences were obtained from 2,185 (74.5%) people who had started ART while not being pre-treated with NRTI mono- or dual-therapy. However, over time this difference became less distinct: in 2000, 72.8% of sequences were obtained from pre-treated people, compared with 36.1% in 2005, and less than 14% from 2010 onwards.

Of the 4,905 sequences obtained when the HIV RNA was above 500 copies/ml, 2,939 (59.9%) harboured high-level resistance to at least one antiretroviral drug. High-level NRTI resistance was detected in 2,966 (60.5%) sequences; of those, 2,531 (85.3%) harboured high-level resistance to emtricitabine or lamivudine. Notably, of the 1,869 individuals ever identified as harbouring the M184V or M184I mutation who were still in care in 2022, 1,205 (64.5%) were still on ART containing lamivudine or emtricitabine, of whom 925 (76.8%) had undetectable HIV-RNA at their last visit. In addition, 1,764 (36.6%) harboured high-level resistance to at least one NNRTI, and 1,036 (22.6%) to at least one PI.

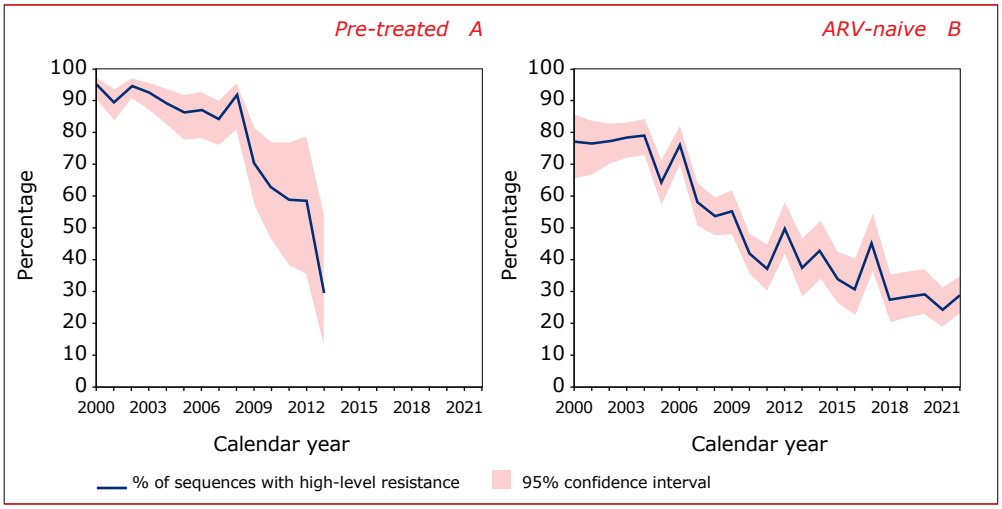
Previous antiretroviral drug exposure

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

Among pre-treated people, the annual percentage of sequences harbouring high-level resistance to at least one drug was 94.9% (95% CI 90.5-97.3) in 2000, 62.9% (46.0-77.1) in 2010, and 29.4% (12.8-54.2) in 2013 (*Figure 2.14A*). The availability of new drugs. both in existing and new drug classes. largely explains the decline since 2008[33]. In recent years (2014-22), both the number of pre-treated people, and the number of sequences from pre-treated people, were too low to provide meaningful percentages.

Among previously ARV-naïve people, high-level resistance to at least one drug was detected among 77.3% (95% CI 65.7-85.8) of sequences in 2000, 50.0% (41.1-58.9) in 2012, and 28.7% (23.1-35.1) in 2022 (*Figure 2.14B*). Over time, the difference in acquired drug resistance detected among pre-treated and ARV-naïve people has disappeared.

Figure 2.14: The annual percentage of sequences with evidence of high-level resistance to any antiretroviral drug. obtained at the time of virological failure when receiving combination antiretroviral therapy (ART), by prior antiretroviral (ARV) drug exposure, among A) people who were pre-treated with mono or dual nucleoside-analogue RT inhibitors (NRTIs), and B) previously antiretroviral drug-naïve people. The shaded area represents the 95% confidence interval.



Acquired HIV drug resistance among previously ARV-naïve people

In the remainder of our analysis, we focus solely on the 2,185 people who had not been pre-treated with NRTI mono- or dual-therapy before combination ART initiation. Overall, 1,963 (55.8%) of the 3,518 sequences from previously ARV-naïve people receiving ART harboured at least one major resistance mutation, which was associated with resistance to NRTI (1,536, or 43.7%), NNRTI (1,218, or 34.6%), or PI (373, or 10.6%).

In *Figure 2.15A*, the annual percentage of sequences harbouring high-level resistance is presented for each antiretroviral drug class. In ***2000***:

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

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

- 50.0% (95% CI 41.1-58.9) of sequences harboured high-level resistance to at least one NRTI;
- 33.9% (25.9-42.9) harboured high-level resistance to at least one NNRTI; and
- 5.1% (2.3-10.9) harboured high-level resistance to at least one PI.

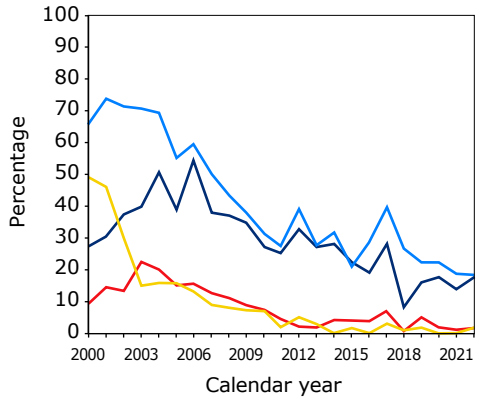
By ***2022***, these percentages were down to:

- 28.7% (95% CI 23.0-35.1) of sequences harbouring high-level resistance to at least one NRTI;
- 17.6% (13.0-23.4) harbouring high-level resistance to at least one NNRTI; and
- 2.0% (0.6-6.0) harbouring high-level resistance to at least one PI.

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

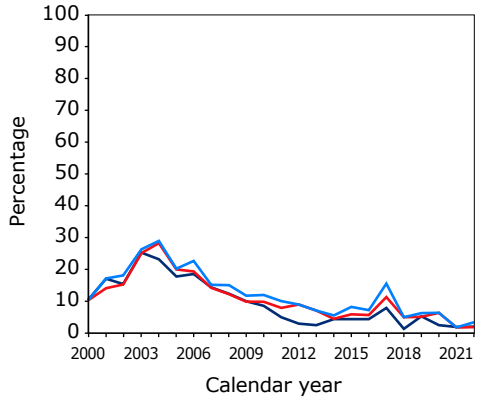
The annual percentage of sequences harbouring high-level resistance to individual antiretroviral drugs are presented in *Figure 2.15B-D*. The annual percentage of sequences harbouring major resistance mutations to specific drugs are outlined in *Appendix Table 2.1A-C*. *Figure 2.15E* meanwhile, shows the annual percentage of sequences harbouring at least one high-level resistance mutation to all three drug classes. It should be pointed out that drug resistance does not disappear when viral replication is successfully suppressed or re-suppressed, but instead remains viably archived in the viral reservoir.

Figure 2.15: *The annual percentage of sequences with evidence of high-level resistance by drug class and antiretroviral drug, obtained at the time of virological failure when receiving combination antiretroviral therapy (ART), among previously antiretroviral drug-naïve people. Results are shown by A) antiretroviral drug class: high-level resistance to at least one drug within class, B) antiretroviral drug: high-level resistance to nucleoside reverse transcriptase inhibitors, C) antiretroviral drug: high-level resistance to non-nucleoside reverse transcriptase inhibitors, D) antiretroviral drug: high-level resistance to protease inhibitors, and E) high-level resistance to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors.*



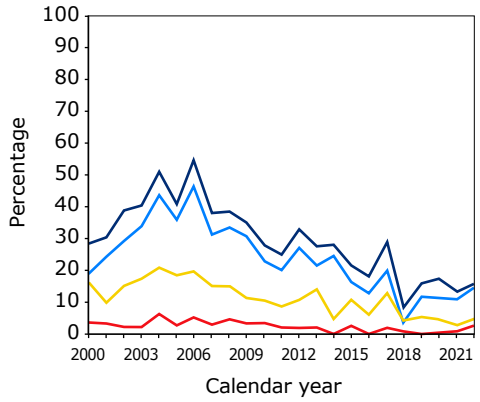
A
By antiretroviral drug class: high-level resistance to at least one drug per class

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

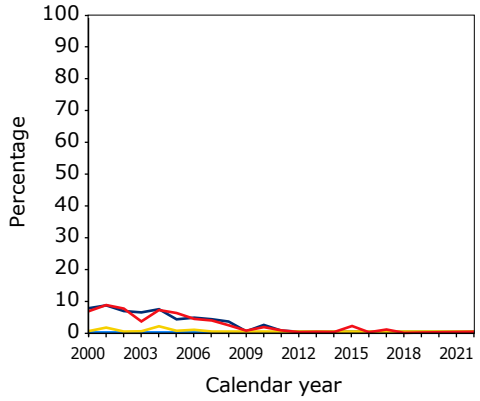


B
By antiretroviral drug: high-level resistance to nucleoside reverse transcriptase inhibitors

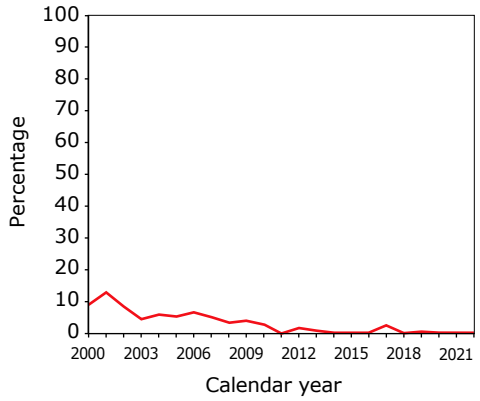
- Lamivudine/emtricitabine resistance
- Abacavir resistance
- Tenofovir resistance



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



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



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

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

Note: *The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.4) was used to infer antiretroviral drug susceptibility scores for each sequence, according to a five-level scheme: susceptible; potential low-level resistance; low-level resistance; intermediate resistance; and high-level resistance*[25,26].

Acquired integrase inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on ART was relatively rare. The available 563 integrase sequences originated from 437 people who received ART for at least four months; 43 were pre-treated with monotherapy or dual NRTI therapy before initiating ART, and 394 were ARV-naïve before initiating ART. Most people had initiated ART years before; the median time between initial ART initiation and testing for integrase inhibitor resistance was 10.4 years (IQR 4.8-15.8).

At least one acquired major mutation associated with integrase inhibitor resistance was detected in 52 of 437 individuals (observed in 67 of 563 sequences), which resulted in high-level resistance to at least one integrase inhibitor[25,32]. When assessing the last available integrase sequence of these 52 individuals, the following major INSTI resistance mutations were detected (numbers are given in parenthesis):

- N155H (18) and N155H/N (six);
- R263K (seven) and R263R/K (two);
- E92Q (five) and E92E/Q (three);
- Y143R (one) and Y143Y/C (two);
- T66I (two) and T66I/C (one);
- Q148H (one); and
- S147S/G (one).

Minor mutations detected were at position:

- T97 (any, eight; T97A, seven; T97T/A, one);
- T66 (any, nine; T66I, three; T66T/A, three; T66T/K, one; T66K, one; T66I/T, one);
- L74 (any mutation, two; L74I/L/M, one; L74I/M, one);
- G140 (any, two; G140S, one; G140G/S, one); and
- E138 (any, two; E138K, one; E138A, one).

Seven of the 52 patients who harboured major INSTI resistance mutations had ever received INSTI-monotherapy.

Immunological response

After initiation of ART, most people suppress HIV RNA to levels below the limit of detection, and this is accompanied by an increase in CD4 cell count. Failure to suppress viremia is associated with poorer recovery of CD4 cell count[18,34]. However, incomplete recovery of CD4 cell count (i.e. a CD4 cell count persistently below 350 cells/mm^3) may also occur, despite sustained viral suppression. This is a situation reported to be associated with an increased risk of progression to AIDS and development of non-AIDS-related diseases[19]. Normal CD4 cell counts in men without HIV are on average approximately 830 cells/mm^3 and around 1000 cells/mm^3 in women, but this varies according to factors such as age, ethnicity, and smoking behaviour[35,36]. Furthermore, although the CD4 cell count is considered the key prognostic factor for mortality and AIDS-defining endpoints, some, but not all studies have suggested that the CD4:CD8 ratio may have additional prognostic value[37–42]. The clinical benefit of ART is strongly related to the level of recovery of the immune status (also see *Chapter 3*)[43–47].

Immunological response by calendar year

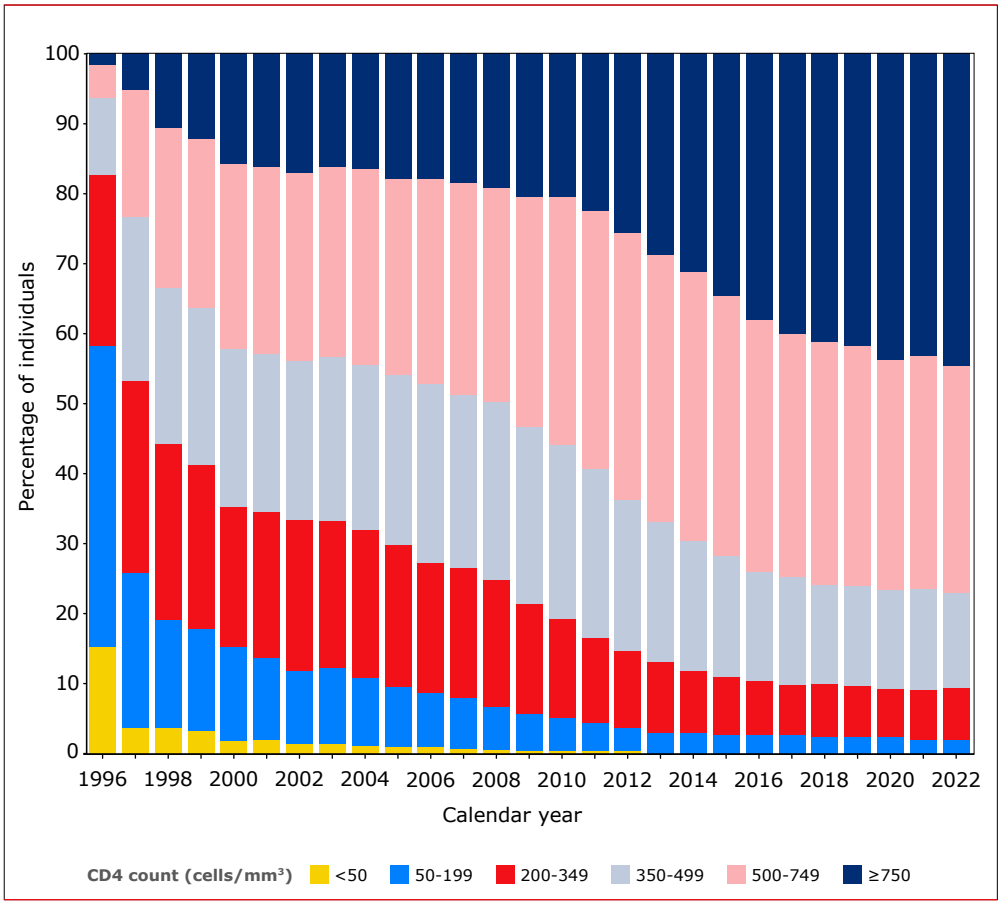
Of the 28,546 people known to have initiated ART between January 1996 and December 2022, CD4 cell count data after ART initiation were available for 27,446 (96.1%). *Figures 2.16* and *2.17* show the last known CD4 cell count and CD4:CD8 ratio of all people in HIV care for each calendar year. After starting ART, the percentage of people with CD4 cell counts below 350 cells/mm^3 dropped from 53.6% in 1997 to (*Figure 2.16*):

- 29.9% in 2005;
- 19.3% in 2010;
- 11.1% in 2015;
- 9.9% in 2020, and
- 9.8% in 2022.

The decrease in the percentage of people with low CD4 cell counts at the end of each calendar year is a consequence of:

- the trend of starting ART at higher CD4 cell counts;
- a more pronounced immune recovery with longer ART use;
- continually-declining virological failure rates; and
- attrition by the higher mortality rates in those with low CD4 counts.

Figure 2.16: Last available CD4 cell count of the treated population by calendar year (missing measurements/ data were not taken into account).



The percentage of those with a CD4:CD8 ratio of one or above increased from 1.2% in 1997 to (*Figure 2.17*):

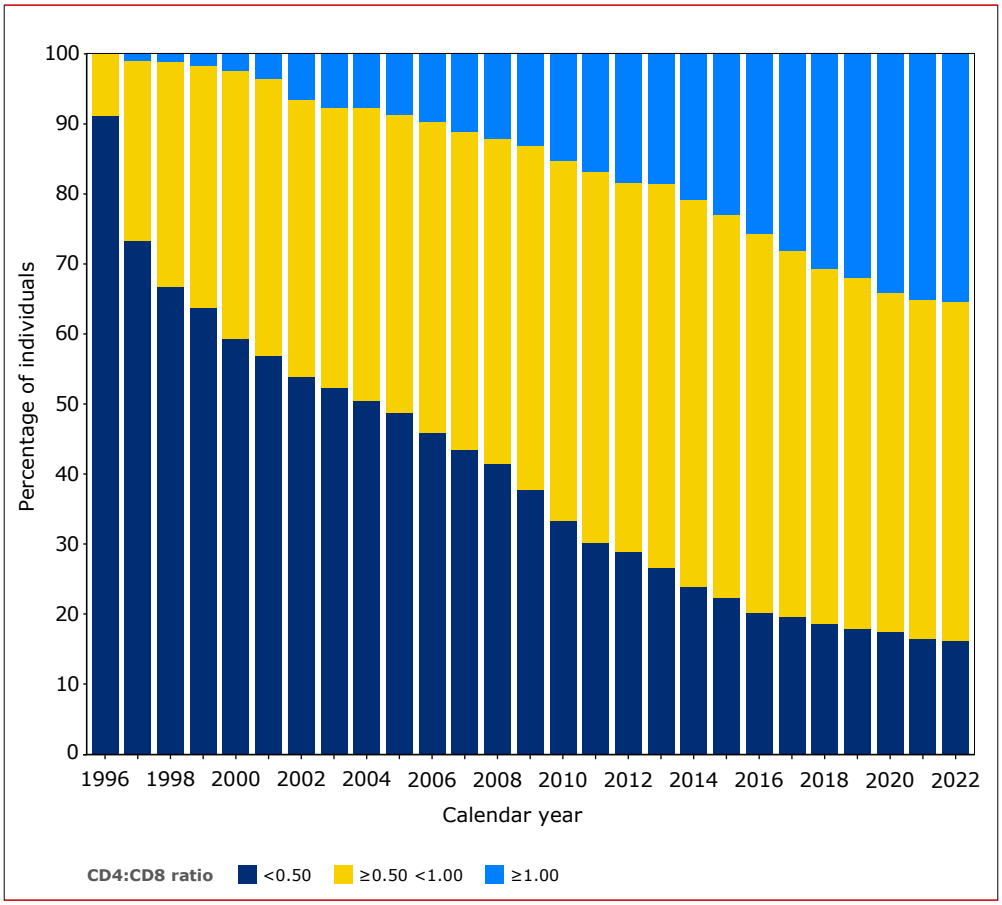
- 2.7% in 2000;
- 8.8% in 2005;
- 15.3% in 2010;
- 23.1% in 2015;
- 34.3% in 2020; and
- 35.5% in 2022.

Of all CD4:CD8 ratio measurements equal to or above one:

- 9.9% had a CD4 cell count of less than 500 cells/mm^3;
- 31.1% had a CD4 cell count between 500-749 cells/mm^3; and
- 59.1% had a CD4 cell count equal to or above 750 cells/mm^3.

When the CD4: CD8 ratio was equal to or above one, the median CD4 cell count was 810 cells/mm^3 (IQR 630-1,020).

Figure 2.17: Last available CD4: CD8 ratio in each calendar year after the start of combination antiretroviral therapy (ART).



Immunological response after ART initiation (2016–22)

We also assessed the immunological response in people who started ART more recently (i.e. in 2016-2022), and had CD4 cell count data available at, and after ART initiation. The level of viral suppression and treatment interruptions after initiating ART were not taken into account in this analysis. Of the 4,208 people who started ART in 2016-2022 and had sufficient immunological data available:

- 11.1% had CD4 cell counts below 50 cells/mm^3;
- 16.6% had CD4 cell counts between 50-199 cells/mm^3;
- 19.2% had CD4 cell counts between 200-349 cells/mm^3;
- 20.7% had CD4 cell counts between 350-499 cells/mm^3; and
- 32.4% had CD4 cell counts equal to or above 500 CD4 cells/mm^3 at the time of ART initiation.

The average CD4 cell count at ART initiation has decreased slightly in recent years (*Appendix Table 2.2*).

The CD4 cell count and CD4:CD8 ratio trajectories following ART initiation are plotted in *Figures 2.18* and *2.19* by CD4 cell count at ART initiation. The median CD4 cell counts and CD4: CD8 ratios increased after ART initiation. Both depended on the CD4 cell count at ART initiation and did not converge among the five baseline CD4 cell count strata. These observations are in line with a study by the Antiretroviral Therapy Cohort Collaboration (ART-CC), which included ATHENA data. It showed that the likelihood of normalisation of the CD4:CD8 ratio is strongly related to baseline CD4 cell count[48].

Figure 2.18: *CD4 cell count over time after the start of combination antiretroviral therapy (ART) in 2016–2022.*

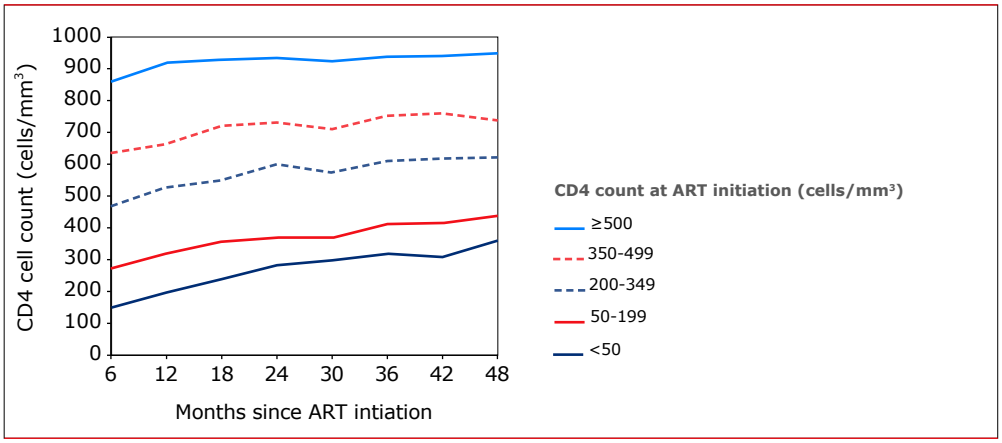
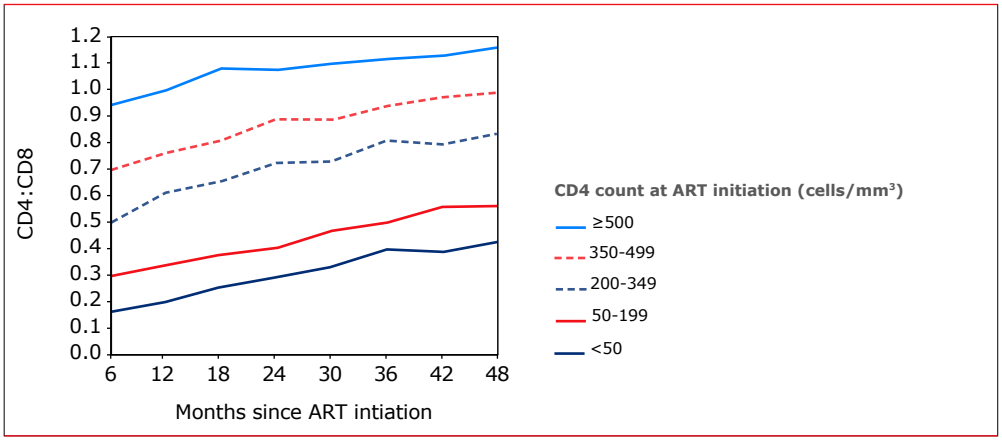


Figure 2.19: CD4: CD8 ratio over time after the start of combination antiretroviral therapy (ART) in 2016–22.



Note: The presented immunological outcomes are based on available test results. For people with a low-to-moderate CD4 cell count (below 350 cells/mm³), CD4 cell count testing is recommended at least twice a year[49]. When a person has a CD4 cell count above 350 cells/mm³, the testing frequency may be reduced. Therefore, CD4 data from people achieving higher CD4 cell counts are disproportionally underrepresented, and their true CD4 responses may be even better.

Summary and conclusions

Starting ART and the initial regimen

- Rapid initiation of ART following a diagnosis of HIV infection, irrespective of CD4 cell count, has generally resulted in a shorter median time to initiation of ART following diagnosis, which was 18 days in 2022.
- The CD4 cell count at ART initiation initially increased over time, peaking in the year 2015 at a median of 414 cells/mm³ (IQR 220-600). This was when new guidelines were issued that recommended rapid initiation of ART at any CD4 cell count. Those guidelines resulted in substantial numbers of individuals with preserved CD4 cell counts, who had postponed starting ART, deciding to initiate treatment. Since then, the median CD4 cell count at the start of ART has continued to decrease. Among individuals with HIV starting ART in 2022, the median CD4 cell count was 263 cells/mm³ (IQR 90-483). *Chapter 1* explores in greater detail the changes in the proportion of people with HIV (PWH) who are late presenters at the time of HIV diagnosis. It also considers possible reasons for the observed trends. Immunological recovery was better when ART was started at a higher CD4 cell count.

- In 2022, 93.1% of initial regimens contained an integrase inhibitor. The most frequently used initial regimen was bictegravir/emtricitabine/tenofovir alafenamide (38.1%). Dolutegravir-containing initial regimens were used in 55.0% of initial regimens in 2022.
- Compared to the first decade of the ART era, discontinuation of the initial regimen has become less common over time. In the past decade, the discontinuation rate has remained stable. However, the reasons for switching have continued to change, with virological failure a very rare event nowadays. In recent years, many switches were driven by the wish for regimen simplification and pre-emptive modifications because of the availability of new regimens that are perceived to have better long-term safety profiles.
- Toxicity-associated discontinuations of the initial regimen were often related to neuropsychiatric problems, problems involving the gastrointestinal tract or liver, or a rash due to medication.

In care and receiving ART in 2022

- Most (82.4%) individuals in care and on ART in 2022 used a combination of 2 NRTI plus either an integrase inhibitor (45.0%), an NNRTI (28.4%), or a PI (9.0%). Integrase inhibitors were used by 61.8% of the total population receiving ART, if other integrase inhibitor-containing regimens (2-DR, triple-class) are also considered.
- The proportion of individuals using a 2-drug regimen continunes to increase. In 2022, 14.9% used a two-drug regimen, with lamivudine/dolutegravir being the most frequently used (10.1%) which is now to second-most often used regimen in the Netherlands.
- In 2022, long-acting injectables (cabotegravir/rilpivirine) were used by 1.8%.
- Of those receiving ART and who were in care in 2022, 97.9% had a viral load below 200 copies/ml, and 95.4% had a viral load equal to or below 50 copies/ml.
- In individuals receiving ART, the percentage of people with CD4 cell counts below 350 cells/mm^3 decreased from 53.3% in 1997 to 9.4% in 2022.

Virological response and drug resistance

- The overall viral suppression rates of the population with HIV receiving ART is high and has continued to improve. Among the limited number of individuals who experienced virological failure, the annual percentage with acquired drug resistance remained low; this is in line with findings in other high-income settings[50,51].
- Transmitted drug resistance was rare, and the overall prevalence was low and stable over time, in line with rates reported by other European countries[52].

- Integrase inhibitor resistance data remain limited. Only one case of transmitted integrase inhibitor resistance was detected among the 411 people tested by the end of 2022. Detected rates of acquired integrase inhibitor resistance among available sequences remained very low, with only a handful of cases with significant resistance to dolutegravir or bictegravir.

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APPENDIX

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

A

	Calendar year									
	2018		2019		2020		2021		2022	
Treatment/mutation	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Emtricitabine/lamivudine	(N=117)		(N=128)		(N=116)		(N=127)		(N=187)	
K65R, E or N	0	0	4	3.1	2	1.7	1	0.8	3	1.6
M184V or I	28	23.9	26	20.3	26	22.4	20	15.7	33	17.6
Abacavir	(N=121)		(N=127)		(N=116)		(N=126)		(N=183)	
K65R, E or N	4	3.3	3	2.4	4	3.4	2	1.6	4	2.2
L74V	2	1.7	2	1.6	3	2.6	0	0	0	0
Y115F	1	0.8	2	1.6	3	2.6	0	0	0	0
M184V	25	20.7	20	15.7	22	19	12	9.5	22	12
Tenofovir	(N=120)		(N=129)		(N=116)		(N=125)		(N=189)	
K65R, E or N	4	3.3	5	3.9	4	3.4	2	1.6	5	2.6
K70R	1	0.8	1	0.8	0	0	1	0.8	1	0.5

B

	Calendar year									
	2018		2019		2020		2021		2022	
Treatment/mutation	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Nevirapine	(N=122)		(N=131)		(N=116)		(N=129)		(N=184)	
L100I	1	0.8	0	0	0	0	0	0	0	0
K101P	0	0	0	0	0	0	0	0	0	0
K103N or S	4	3.3	12	9.2	10	8.6	11	8.5	16	8.7
V106A or M	0	0	1	0.8	4	3.4	0	0	1	0.5
V108I	1	0.8	5	3.8	4	3.4	1	0.8	4	2.2
Y181C or I	5	4.1	7	5.3	9	7.8	5	3.9	6	3.3
Y188L, C or H	0	0	2	1.5	1	0.9	0	0	4	2.2
G190A	0	0	0	0	1	0.9	2	1.6	1	0.5
M230L	0	0	1	0.8	0	0	1	0.8	1	0.5
Etravirine	(N=115)		(N=122)		(N=111)		(N=126)		(N=184)	
L100I	0	0	0	0	0	0	0	0	0	0
L101P	0	0	0	0	0	0	0	0	0	0
Y181C, I or V	1	0.9	0	0	1	0.9	2	1.6	4	2.2
Efavirenz	(N=116)		(N=125)		(N=110)		(N=127)		(N=183)	
L100I	1	0.9	0	0	0	0	0	0	0	0
K101P	0	0	0	0	0	0	0	0	0	0
K103N or S	4	3.4	12	9.6	10	9.1	11	8.7	16	8.7
V106M	0	0	1	0.8	1	0.9	0	0	1	0.5
V108I	0	0	2	1.6	1	0.9	1	0.8	3	1.6
Y181C or I	1	0.9	1	0.8	3	2.7	2	1.6	4	2.2
Y188L	0	0	1	0.8	0	0	0	0	4	2.2
G190S or A	0	0	0	0	1	0.9	2	1.6	6	3.3
P225H	0	0	1	0.8	0	0	1	0.8	1	0.5
M230L	1	0.9	0	0	0	0	2	1.6	3	1.6
Rilpivirine	(N=119)		(N=127)		(N=112)		(N=127)		(N=185)	
L100I	1	0.8	0	0	0	0	0	0	0	0
K101E or P	1	0.8	1	0.8	2	1.8	2	1.6	4	2.2
E138A, G, K, Q or R	6	5.0	7	5.5	12	10.7	6	4.7	12	6.5
V179L	0	0	0	0	0	0	0	0	0	0
Y181C, I or V	3	2.5	4	3.1	4	3.6	3	2.4	4	2.2
Y188L	0	0	1	0.8	0	0	0	0	4	2.2
H221Y	1	0.8	3	2.4	3	2.7	2	1.6	6	3.2
F227C	0	0	0	0	0	0	0	0	0	0
M230I or L	0	0	1	0.8	0	0	1	0.8	1	0.5

C

	Calendar year									
	2017		2018		2019		2020		2021	
Treatment/mutation	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Atazanavir	(N=95)		(N=103)		(N=87)		(N=104)		(N=128)	
I50L	0	0	0	0	0	0	0	0	0	0
I84V	0	0	1	1.0	0	0	0	0	0	0
N88S	0	0	0	0	0	0	0	0	0	0
Darunavir	(N=95)		(N=102)		(N=87)		(N=104)		(N=128)	
I47V	0	0	0	0	0	0	0	0	0	0
I50V	0	0	0	0	0	0	0	0	0	0
I54M or L	0	0	0	0	0	0	0	0	0	0
L76V	0	0	0	0	0	0	0	0	0	0
I84V	0	0	0	0	0	0	0	0	0	0
Lopinavir	(N=95)		(N=103)		(N=87)		(N=104)		(N=128)	
V32I	1	1.1	0	0	0	0	0	0	0	0
I47V or A	0	0	0	0	0	0	0	0	0	0
I50V	0	0	0	0	0	0	0	0	0	0
I54V, L or M	0	0	1	1.0	0	0	0	0	0	0
L76V	0	0	1	1.0	0	0	0	0	0	0
V82A, F, T or S	0	0	0	0	0	0	0	0	0	0
I84V	0	0	1	1.0	0	0	0	0	0	0
Tipranavir	(N=95)		(N=102)		(N=87)		(N=104)		(N=128)	
I47V	0	0	0	0	0	0	0	0	0	0
Q58E	0	0	0	0	1	1.1	1	1	0	0
T74P	0	0	0	0	0	0	0	0	0	0
V82L or T	0	0	0	0	0	0	0	0	0	0
N83D	0	0	0	0	0	0	0	0	0	0
I84V	0	0	0	0	0	0	0	0	0	0

Appendix Table 2.2: *CD4 cell count at combination antiretroviral therapy (ART) initiation by calendar year in 2016–22.*

Year of ART initiation	2016	2017	2018	2019	2020	2021	2022	2016–2022
CD4 cell count available at ART initiation	941	856	732	625	439	379	236	4,208
CD4 cell count, median cells/mm³ (IQR)	410 (240–580)	384 (195–560)	379 (170–580)	361 (170–570)	312 (130–540)	287 (110–506)	263 (90–483)	368 (170–560)
CD4 cell count (cells/mm³)								
<50	8.8%	8.8%	10.8%	10.4%	14.2%	16.1%	18.2%	11.1%
50–199	12.0%	16.3%	16.8%	18.1%	18.2%	23.0%	19.1%	16.6%
200–349	18.4%	19.3%	18.9%	18.9%	21.2%	19.5%	20.3%	19.2%
350–499	23.2%	22.8%	19.7%	20.2%	18.5%	15.8%	19.0%	20.7%
≥500	37.6%	32.9%	33.9%	32.5%	28.0%	25.6%	23.3%	32.4%

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

3. Morbidity and mortality

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Introduction

Since the introduction of combined antiretroviral therapy (ART) in 1996, the life expectancy of people with HIV (PWH) has markedly improved[1]; in a subgroup of recently-diagnosed, effectively-treated individuals, it was shown to be similar to that of the general population in the Netherlands[2]. Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased[3], morbidity and/or mortality associated with non-AIDS-related diseases has increased among PWH during the ART era[4–9]. Examples of these include renal and liver disease, diabetes mellitus, myocardial infarction, stroke, osteoporosis, and non-AIDS-defining malignancies.

Various reports suggest that the risk of non-AIDS-related morbidity may be higher in individuals with HIV treated with ART, than in individuals without HIV of comparable age[9-11]. For example pulmonary hypertension[13], bone disease, and non-traumatic bone fractures[13-15] have each been reported to be more common in PWH. Just as with individuals without HIV, traditional risk factors (such as tobacco use[17], alcohol abuse, and viral hepatitis co-infection[18]) 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[19,20].

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 30,132 adult individuals ever registered by SHM – that breaks down as 29,521 adults and an additional 611 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[21]. 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 2000-10, 2011-15, and 2016-22. We standardised these estimates according to the age distribution of the population during the period 2016-22 (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[22]. Indirect standardisation compares the incidence rates in the study and reference (period: 2016-2022) 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;
- smoking; and
- calendar period.

Mortality

Mortality was investigated in all 30,132 adult PWH ever registered in the SHM database. The mortality rate was 18.2 (95% confidence interval [CI] 13.5-23.9) per 1,000 person years of follow up (PYFU) in 1996 and declined to 8.9 (95% CI 7.4-10.6) per 1,000 PYFU in 2010. It has since remained stable at that 2010 level up to 2022, but the observed mortality rate was noticeably higher in 2021 during the COVID-19 pandemic with 10.9 (9.6-12.4) (*Figure 3.1A*). Despite this 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 5.6 per 1,000 PYFU in 2022.

This excess mortality can be only partly ascribed to individuals who already had AIDS at the time of their HIV diagnosis, even less so in recent years. When these individuals were excluded from the analysis, the mortality rate decreased from 14.1 (9.8-19.6) per 1,000 PYFU in 1996 to 8.7 (7.3-10.2) per 1,000 PYFU in 2022.

Underlying causes of death

Observed underlying causes of death are presented in *Appendix Table 3.1*. Although the AIDS-related death rate has decreased significantly since the advent of 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[23]. *Table 3.1* shows the characteristics of adults with HIV who died of AIDS, compared to those who died of non-AIDS causes in the period 2013-2022. Individuals who died of AIDS were more frequently female, non-MSM and/or migrants, more recently diagnosed with HIV, had been on ART for a shorter period of time, and had much lower CD4 cell counts at diagnosis, with 61.2% qualifying as a very late presenter (CD4 cell count below 200 cells/mm^3). In addition, these individuals had much lower nadir CD4 cell counts. In 52.8% of cases, they did not have controlled viremia, and 18.1% of this group was not receiving any ART at the time of death, either because ART had not been started or had been discontinued (*Table 3.1*).

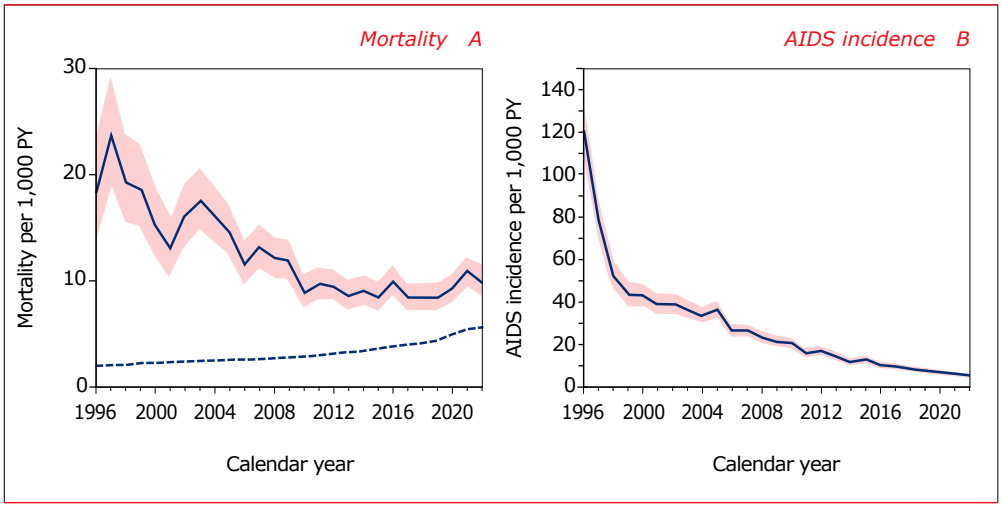
Among individuals who died of AIDS but did not classify as (very) late presenters (i.e. they had a CD4 cell count above 350 cells/mm^3 at diagnosis), the cause of death was relatively more likely to be an AIDS-related haematological malignancy, which are also known to occur in people on suppressive ART with high CD4 cell counts. The proportion and absolute number of deaths due to non-AIDS-defining conditions have increased significantly over time (*Figure 3.1.C*), primarily as a consequence of the ever increasing size and average age of the population of people with HIV in the Netherlands. People with HIV that were born in the Netherlands, MSM and men in general are overrepresented among those who died of non-AIDS causes, because people in these three (overlapping) categories have a higher average age compared to migrants, HIV transmission categories other than MSM, and women. Independent risk factors for death and for being diagnosed with an AIDS-defining condition are listed in *Appendix Table 3.2*.

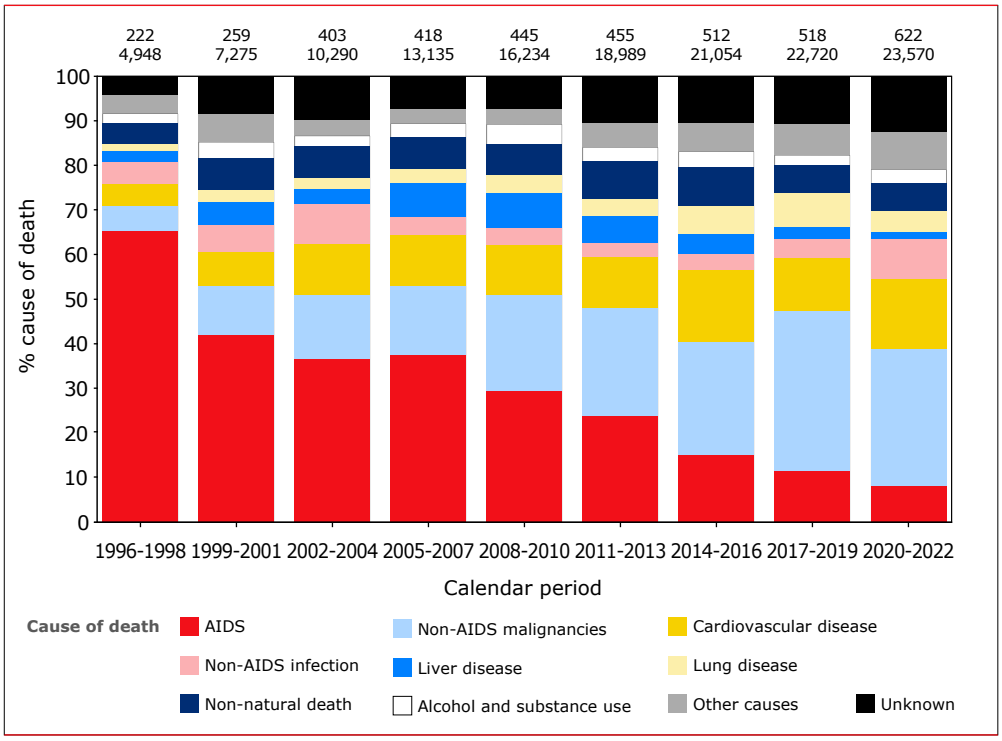
Table 3.1: *Characteristics of adults with HIV who died of AIDS compared to adults with HIV who died of non-AIDS causes in the period 2013-22.*

	Died of non-AIDS causes	Died of AIDS	p-value
Number of subjects	1561 (87.3%)	227 (12.7%)	
Age	60.1 (52.4-68.6)	55 (46-63.5)	<.001
Male gender	1355 (86.8%)	185 (81.5%)	0.039
Dutch origin	1113 (71.3%)	145 (63.9%)	0.024
MSM	892 (57.1%)	99 (43.6%)	<.001
Heterosexual transmission	417 (26.7%)	79 (34.8%)	0.014
Other transmission categories	252 (16.1%)	49 (21.6%)	0.046
Years since HIV diagnosis	15.6 (8.82-22.2)	7.95 (0.69-15.2)	<.001
Years since start cART	13 (6.8-18.4)	4.28 (0.34-12.4)	<.001
CD4 at HIV diagnosis	290 (110-510)	120 (40-322)	<.001
Late stage (CD4<350) at entry in care	878 (56.3%)	174 (77.3%)	<.001
Advanced stage (CD4<200) at entry in care	582 (37.3%)	139 (61.2%)	<.001
CD4 nadir	143 (50-260)	50 (17-130)	<.001
Last CD4 measured before death	500 (301-711)	150 (34-350)	<.001
Not undetectable at date of death	216 (13.9%)	115 (52.8%)	<.001
Not on cART at date of death	130 (8.3%)	41 (18.1%)	<.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/mm³.*

Figure 3.1.A-C: *(A) Annual mortality and (B) incidence of AIDS in 30,132 PWH in the Netherlands after entry into HIV care from 1996 onwards. Solid lines represent the incidence, while the shaded areas are the 95% confidence intervals. The dashed line is the mortality rate for age-matched and sex-matched individuals from the general population in the Netherlands. (C) 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.*





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 3.2*, including time-updated age and time-updated lagged CD4 cell counts, we found that, in general, risk of death was higher in men compared to women, and this risk increased as individuals grew older. It also increased if they:

- belonged to the HIV transmission risk group of people who use/used injecting drugs (PWID);
- had a prior AIDS diagnosis;
- were co-infected with the hepatitis B virus (HBV) or hepatitis C virus (HCV);
- were underweight;
- were current or past smokers;
- had spent more time with an HIV RNA level above 1,000 copies/ml while on ART; or
- had a current CD4 cell count less than 750 cells/mm^3, with the risk of death progressively increasing in lower CD4 strata.

Although a lower mortality risk was observed in individuals of non-Dutch origin, this is likely due to a larger proportion of people from sub-Saharan Africa, and other individuals not born in the Netherlands (with the exception of those born in Surinam or the Dutch Antilles), being lost to care (*Appendix Table 3.3*). In native Dutch individuals, and those from Surinam and the Dutch Antilles, 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 3.1*). The number of recorded suicides among people with HIV in the Netherlands in the period 2011 to 2022 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 10.5 instances per 100,000 individuals per year, compared to more than 40 instances per 100,000 person years in the population with HIV[24].

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 2022, a total of 165 instances of euthanasia were recorded; 30% of cases occurred in patients who died of AIDS, 39% in patients who died of non-AIDS-defining malignancies, and the remaining 31% 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 30,132 adult PWH ever registered in the SHM database, the incidence of first AIDS-defining events decreased sharply from 120.7 (95% CI 108.2-134.2) in 1996 to 5.2 (4.3-6.4) cases per 1,000 PYFU in 2022 (*Figure 3.1B*). *Appendix Table 3.4* gives an overview of the first AIDS-defining events occurring between 1996 and 2022. The most common first AIDS-defining events between 2016 and 2022 (n=1,168) were:

- *Pneumocystis jirovecii* pneumonia (22% of all events);
- oesophageal candidiasis (16%);
- Kaposi's sarcoma (10%);
- recurrent bacterial pneumonia (9%);
- tuberculosis (pulmonary 5%, extrapulmonary 3%);
- AIDS-defining lymphoma (7%);
- AIDS-related wasting (7%);
- cytomegalovirus-associated end organ disease (4%);
- toxoplasmosis of the brain (3%); and
- AIDS dementia complex/HIV encephalopathy (3%).

Risk factors for AIDS-defining events are shown in *Appendix Table 3.2*.

In the present analyses, we concentrate on the first occurrence of any AIDS-defining event after the start of ART. The results of these analyses show that individuals were more likely to experience their first AIDS-defining event if:

- they were older;
- had a current CD4 cell count below 500 cells/mm^3 (although the likelihood was even higher if their CD4 cell count was below 200 or 50 cells/mm^3);
- had more than 1,000 HIV RNA copies/ml for a longer period of time while on ART; or
- were co-infected with HCV.

Because the main findings of the analysis of AIDS events after the start of ART were heavily influenced by events occurring shortly after the start of ART and/or while HIV-1 RNA was still detectable, we also analysed the incidence of CDC-B (moderately symptomatic HIV disease) and AIDS-defining events in individuals who had started ART at least one year before and had undetectable viraemia or transient low-level viraemia (i.e. 'blips'; below 200 copies/ml) at the moment the HIV-related event was diagnosed. In other words, we focused on those individuals with an optimal response to ART. Events were classified into CD4 strata based on the current or previously measured CD4 cell count, whichever was the lowest. Use of opportunistic infection prophylaxis was not accounted for in this analysis. Only 'definitive' or 'probable' diagnoses were considered; 'possible' events or events with incomplete ascertainment were excluded. Cervical dysplasia was excluded from this analysis.

Between 1 January 2000 and 31 December 2022, 26,500 individuals contributed a total of 263.6 thousand PYFU, during which 3,185 CDC-B and/or CDC-C (AIDS-defining events) were diagnosed. This resulted in an incidence rate of 12.1 events per 1,000 PYFU (1,745 CDC-B events, 6.6 events/1,000 PYFU; 1,440 CDC-C/AIDS events, 5.5 events/1,000 PYFU) (*Table 3.2*). As expected, the incidence rates were highest in the CD4 strata below 200 cells/mm^3. Although the incidence rates declined sharply in the higher CD4 strata, the incidence rates in the 200-349 and 350-499 cells/mm^3 strata remained substantial, with 10.5 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 2.8 (95% CI 2.5-3.1) and 1.8 (1.6-2.2) events/1,000 PYFU, respectively. Note that the incidence in the over 750 cells/mm^3 stratum is statistically significantly lower than in the 500-749 cells/mm^3 stratum. In these highest CD4 strata, the main AIDS-defining events that still occurred were:

- recurrent bacterial pneumonia;
- Kaposi's sarcoma;
- oesophageal candidiasis;
- non-Hodgkin's lymphoma;
- tuberculosis (pulmonary and extrapulmonary);
- chronic genital Herpes simplex virus (HSV) ulcers; and
- AIDS dementia complex

Appendix Table 3.6 shows the type and number of HIV-related diagnoses by CD4 strata).

Table 3.2: CDC-B and CDC-C/AIDS events occurring between 2000 and 2022 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 (x1000)	Incidence rate CDC events (/1000 PY) (95%CI)	Incidence rate CDC-B events (/1000 PY) (95%CI)	Incidence rate CDC-C events (/1000 PY) (95%CI)
0-50	259	102	157	0.6	446 (393-503)	175 (143-213)	270 (230-316)
50-199	610	316	294	8.9	68.4 (63.1-74.1)	35.5 (31.7-39.6)	33.0 (29.3-37.0)
200-349	647	342	305	29.1	22.3 (20.6-24.1)	11.8 (10.6-13.1)	10.5 (9.35-11.7)
350-499	597	319	278	51.5	11.6 (10.7-12.6)	6.19 (5.53-6.91)	5.40 (4.78-6.07)
500-749	659	401	258	92.8	7.10 (6.57-7.66)	4.32 (3.91-4.76)	2.78 (2.45-3.14)
750+	413	265	148	80.7	5.12 (4.63-5.63)	3.28 (2.90-3.70)	1.83 (1.55-2.15)
Total	**3185**	**1745**	**1440**	**263.6**	**12.1 (11.7-12.5)**	**6.62 (6.31-6.94)**	**5.46 (5.18-5.75)**

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 other mycobacterial infections

Between 1 January 1996 and 31 December 2022 a cumulative total of 1,152 cases of tuberculosis were diagnosed in 961 individuals, of which 674 (58.5%) were pulmonary cases and 478 (41.5%) were extrapulmonary/disseminated tuberculosis cases. During that same period, 549 cases of other mycobacterial infections were diagnosed in 485 individuals: 28 pulmonary and 311 extrapulmonary M. avium or M. kansasii cases, and 58 pulmonary and 152 extrapulmonary / disseminated cases of other atypical mycobacterial infections. *Figures 3.2.A & B* and *Appendix Table 3.4* describe the incidence over calendar time of tuberculosis and other mycobacterial infections.

Geographical region of origin

People who originated from sub-Saharan Africa (49.9%) or from south(-east) Asia (9.2%) were strongly overrepresented among the tuberculosis cases, while those who were born in the Netherlands (15.9%) and people from other western European countries (3.7%) were underrepresented. People originating from central and eastern European countries represented 3.6% and 2.4% of tuberculosis cases. Region of origin was not strongly associated with the incidence of the other (atypical) mycobacterial infections. *Table 3.3* describes some key characteristics of the individuals diagnosed with either tuberculosis or another 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 4.4% 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:

- 0% for pulmonary and 16.7% for extrapulmonary M. avium / kansasii infections;
- 6.9% for pulmonary and 20.4% for extrapulmonary other 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.

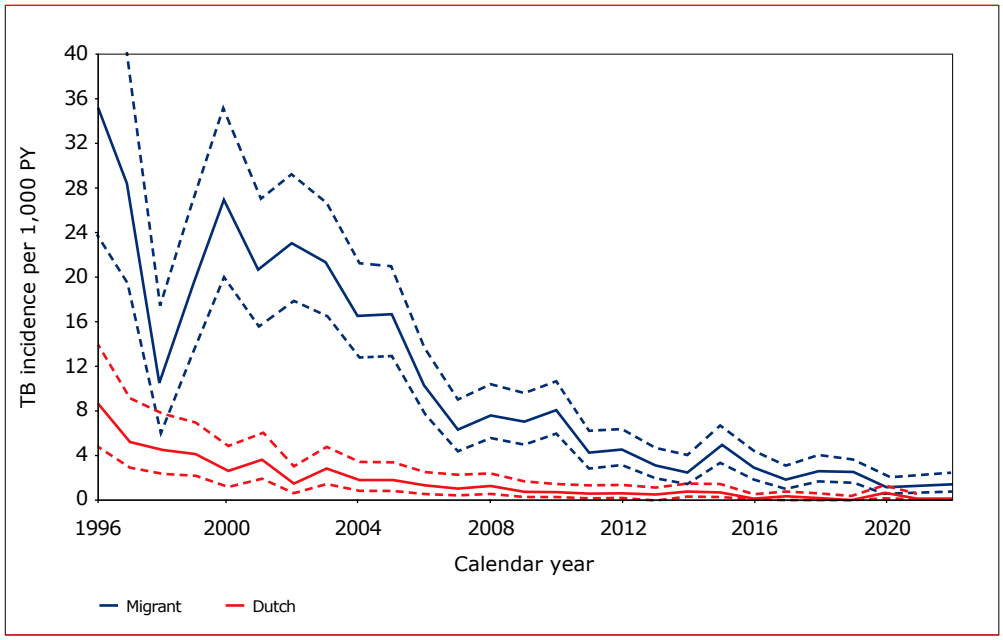
SHM has been collecting data on LTBI screening and treatment since 2018. IGRA testing during an episode in which active TB was diagnosed, was excluded from this dataset. A limitation of our analysis of LTBI screening is that we do not have data on whether, at the time of IGRA testing, the individual had complaints that may have been caused by tuberculosis, which then prompted the treating physician to perform IGRA testing. In 21.7% of cases an 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 1,906 individuals. In 184 (9.7%) of these individuals LTBI testing was positive, and 71 (38.6%) of those received a course of LTBI treatment. LTBI treatment consisted of:

- isoniazid plus rifampicin (typically for a duration of three months) in 22 individuals;
- isoniazid monotherapy (typically for a duration of six to nine months) in 39 individuals; and
- rifampicin monotherapy (typically for a duration of four months) in three individuals.

A further eight individuals received another non-standard treatment. In the 184 individuals who tested positive on LTBI screening, 3 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, one case of pulmonary tuberculosis was diagnosed 3 years after diagnosis of untreated LTBI, and one case of pulmonary tuberculosis was diagnosed about 3 months after completion of a course of 9 months of isoniazid monotherapy. Of the 113 individuals with positive LTBI screening who did not receive LTBI treatment, 18 (15.9%) were known to have been diagnosed with and treated for active tuberculosis prior to the LTBI screening.

Figure 3.2.A & B: Crude incidence rates of tuberculosis and nontuberculous mycobacterial infections in Dutch and migrants per 1,000 person years of follow up (solid lines) and 95% confidence intervals (dashed lines).



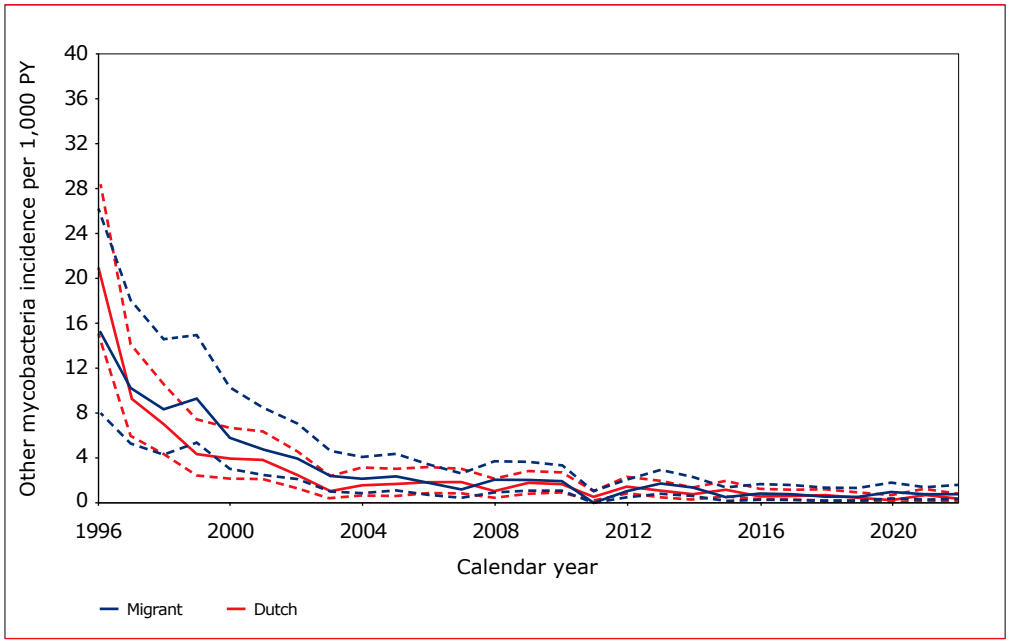


Table 3.3: Characteristics at the time individuals were diagnosed with tuberculosis or other mycobacterial infections for the first time.

	Tuberculosis	Other mycobacterial infections	p-value
Number of subjects	961 (66.5%)	485 (33.5%)	
Age	37 (30.7-44.6)	40.1 (34.6-47.8)	<.001
Male gender	638 (66.4%)	390 (80.4%)	<.001
Dutch origin	177 (18.4%)	275 (56.7%)	<.001
MSM	213 (22.2%)	219 (45.2%)	<.001
Heterosexuals	546 (56.8%)	186 (38.4%)	<.001
Other risk groups	202 (21.0%)	80 (16.5%)	0.042
Diagnosed before HIV diagnosis	222 (23.1%)	28 (5.8%)	<.001
Years since HIV diagnosis	0.91 (0.5- 4.5)	1.13 (0.59- 6.5)	0.004
Years since start cART	0.42 (0-1.09)	0.62 (0.25-1.24)	<.001
CD4 at HIV diagnosis	190 (60-400)	40 (10-190)	<.001
Late stage (CD4<350) at entry in care	439 (68.9%)	362 (85.0%)	<.001
Advanced stage (CD4<200) at entry in care	647 (67.3%)	380 (78.4%)	<.001
CD4 nadir	120 (40-243)	20 (10- 50)	<.001
Last CD4 measured before event	210 (100-367)	90 (25-180)	<.001
Not undetectable at date of event	792 (82.4%)	369 (76.1%)	0.005
Not on cART at date of event	690 (71.8%)	236 (48.7%)	<.001

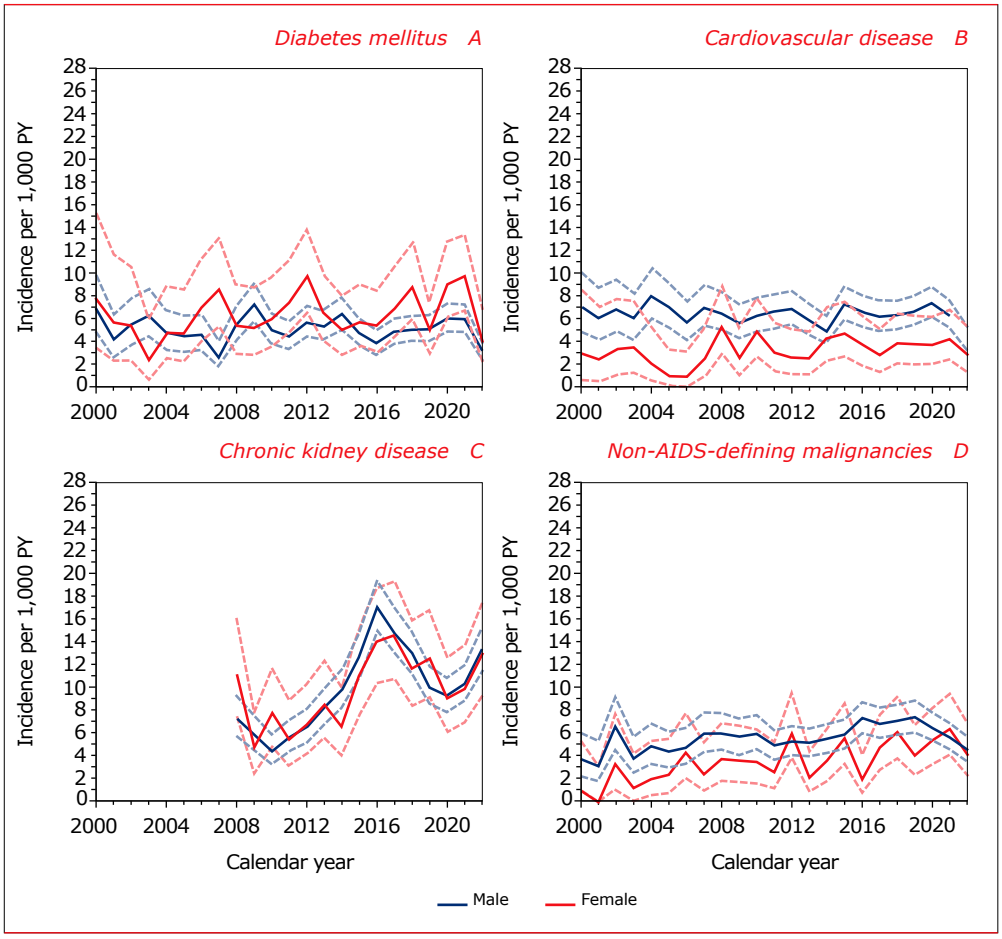
Non-AIDS-defining events

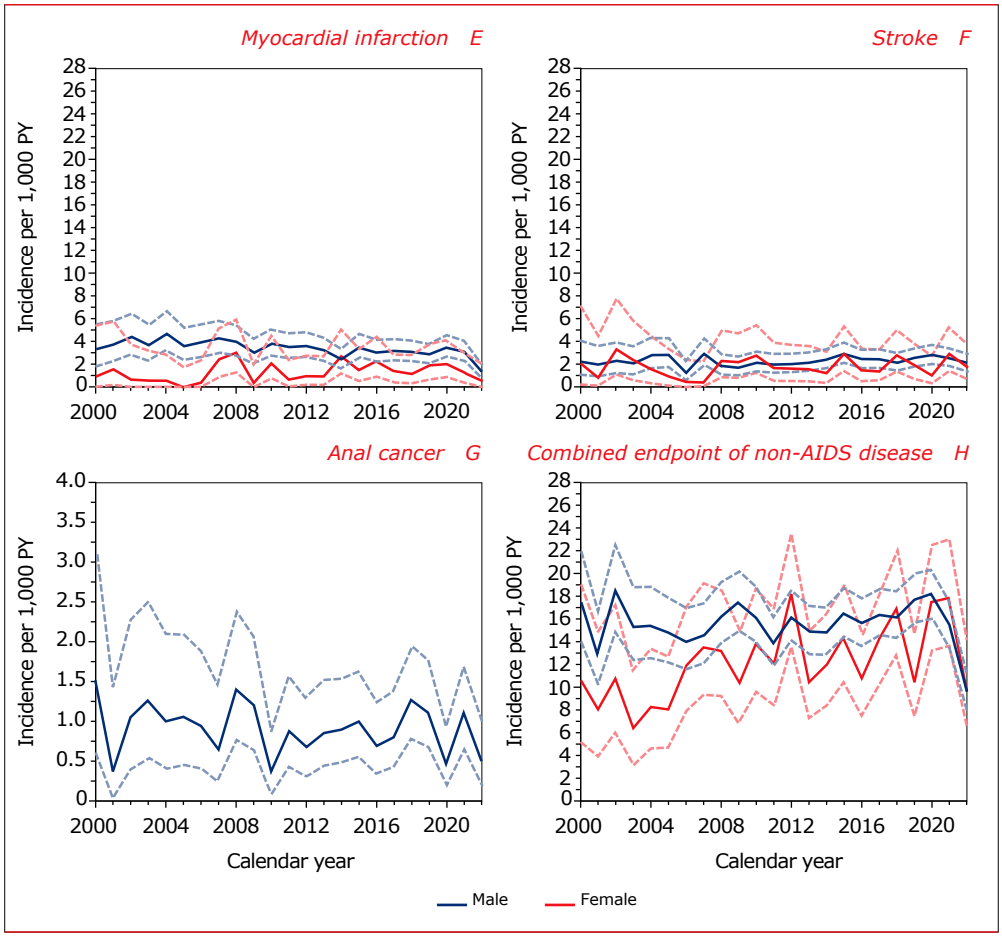
Of the 30,132 adult PWH ever registered with SHM, 29,786 were aged 18 years and over while in follow up in, or after January 2000. For these treated and untreated adults, we report incidence figures and risk factors for:

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

We also present the incidence of the first occurrence of diabetes mellitus, cardiovascular disease, or non-AIDS-defining malignancies as a combined non-AIDS disease endpoint (*Figure 3.3.A-H*).

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





Diabetes mellitus

Of the 29,786 individuals aged 18 years and over, who were in follow up in, or after January 2000, a total of 1,751 (1,341 men and 410 women) were diagnosed with type 2 diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.3A*), and in 2022 was 3.1 (95% CI 2.3-4.2) per 1,000 PYFU in men and 4.0 (2.1-6.8) per 1,000 PYFU in women. In men, the age-standardised incidence ratio declined over time and was significantly lower in 2016-22 than in 2000-10 and 2011-15. In women, however, the age standardised incidence in 2000-10 and 2011-15 was not significantly different from that in 2016-22 (*Table 3.4*).

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

- male gender;
- non-Dutch origin (in particular people born in sub-Saharan Africa, south Asia, and the Caribbean);
- older age group;
- acquiring HIV heterosexually or through injecting drug use;
- a BMI greater than 25 kg/m^2 or below 18 kg/m^2;
- hypertension;
- a latest CD4 cell count below 200 cells/mm^3;
- pre-treatment with nucleoside analogue reverse transcriptase inhibitors (NRTIs) prior to starting ART;
- treatment with the integrase inhibitors bictegravir, dolutegravir or raltegravir (but not elvitegravir) and
- a prior AIDS diagnosis (*Appendix Table 3.5*).

Moreover, the risk of new-onset diabetes in the periods 2000-2010 and 2011-2015 was significantly higher than in the period 2016-2022. Starting ART within 12 months of the last negative HIV test was also associated with a lower risk of new-onset diabetes.

Table 3.4: *Crude incidence of diabetes mellitus per 1,000 person years of follow up in 2000–2010, 2011–2015 and 2016–2022 and age-standardised incidence ratio (indirect method) with 95% confidence intervals.*

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000–2010	5.2 (4.7–5.7)	1.41 (1.27–1.54)	5.8 (4.8–6.8)	0.92 (0.76–1.08)
2011–2015	5.3 (4.7–5.9)	1.22 (1.09–1.35)	6.8 (5.6–8.2)	1.02 (0.83–1.22)
2016–2022	4.9 (4.5–5.4)	1 (reference)	7.1 (6.1–8.2)	1 (reference)

**Standardised according to the observed age distribution between 2016–2021.*

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

Cardiovascular disease

From January 2000 onwards, 1,879 individuals (1,667 men and 212 women) had a fatal or non-fatal cardiovascular event. Of these:

- 922 had a myocardial infarction;
- 692 had a stroke;
- 138 had a coronary artery bypass graft;
- 675 had a coronary angioplasty or stenting; and
- 15 had a carotid endarterectomy.

The crude incidence over time remained stable and was lower in women than in men (*Figure 3.3B*). The age-standardised incidence ratio in men and women declined over time (*Table 3.5*).

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

- male gender;
- Dutch origin;
- older age group;
- acquiring HIV through MSM contacts or through injecting drug use;
- a latest CD4 cell count below 350 cells/mm^3;
- a prior AIDS diagnosis;
- pre-treatment with NRTIs before starting ART;
- use of abacavir (either currently or in the last six months);
- current use of dolutegravir or raltegravir (but not elvitegravir or bictegravir);
- current and past smoking;
- a BMI > 30 (obesity); and
- the presence of hypertension.

Estimated cardiovascular risk using the D:A:D algorithm was also higher during 2000-2010 and 2011-2015 than during 2016-2022, independent of other variables included in the analysis (*Appendix Table 3.5*). The strong positive association between use of abacavir and CVD was independent of renal function. When eGFR, estimated using the Cockcroft-Gault method (available from 2007 onwards), was included in the model the abacavir effect was only slightly attenuated, decreasing from an incidence risk ratio (IRR) of 1.60 to 1.48, $p<0.001$. Compared to having an eGFR above 90 ml/min, having an eGFR below 60 ml/min was independently associated with a higher risk of CVD:

- at 60-90 ml/min, the IRR was 1.07 (95% CI 0.94-1.21);
- at 30-60 ml/min the IRR was 1.57 (1.31-1.89);
- at 15-30 ml/min, the IRR was 4.60 (3.27-6.49); and
- at 0-15 ml/min the IRR was 3.71 (2.20-6.24).

From January 2000 onwards, 252 men and 28 women experienced a fatal or non-fatal secondary cardiovascular event (156 had a myocardial infarction, 135 had a stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2022 in men and women with a prior cardiovascular event was 26.4 (23.3-29.9) and 21.5 (14.3-31.0), respectively. The crude rate and age-standardised incidence ratio (SIR; indirect method) of secondary myocardial infarction and stroke per 1,000 PYFU did not change significantly during 2000-2010 (crude rate: 29.7 events per 1,000 PYFU; SIR: 1.22, 95% CI 0.96-1.49), and 2011-2015 (crude rate: 23.7 events per 1,000 PYFU; SIR: 0.96, 95% CI 0.72-1.20) compared with the reference period 2016-2022 (crude rate: 25.0 events per 1,000 PYFU).

Table 3.5: *Crude incidence of cardiovascular disease per 1,000 person years of follow up in 2000–2010, 2011–2015, and 2016–2022 and age-standardised incidence ratio with 95% confidence intervals.*

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000–2010	6.5 (6.0–7.1)	1.60 (1.46–1.73)	2.9 (2.2–3.7)	1.40 (1.06–1.74)
2011–2015	6.3 (5.7–7.0)	1.23 (1.11–1.35)	3.4 (2.6–4.4)	1.19 (0.87–1.50)
2016–2022	6.3 (5.8–6.8)	1 (reference)	3.6 (2.9–4.4)	1 (reference)

**Standardised according to the observed age distribution in 2016–2022.*

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

Trends in cardiovascular risk factors

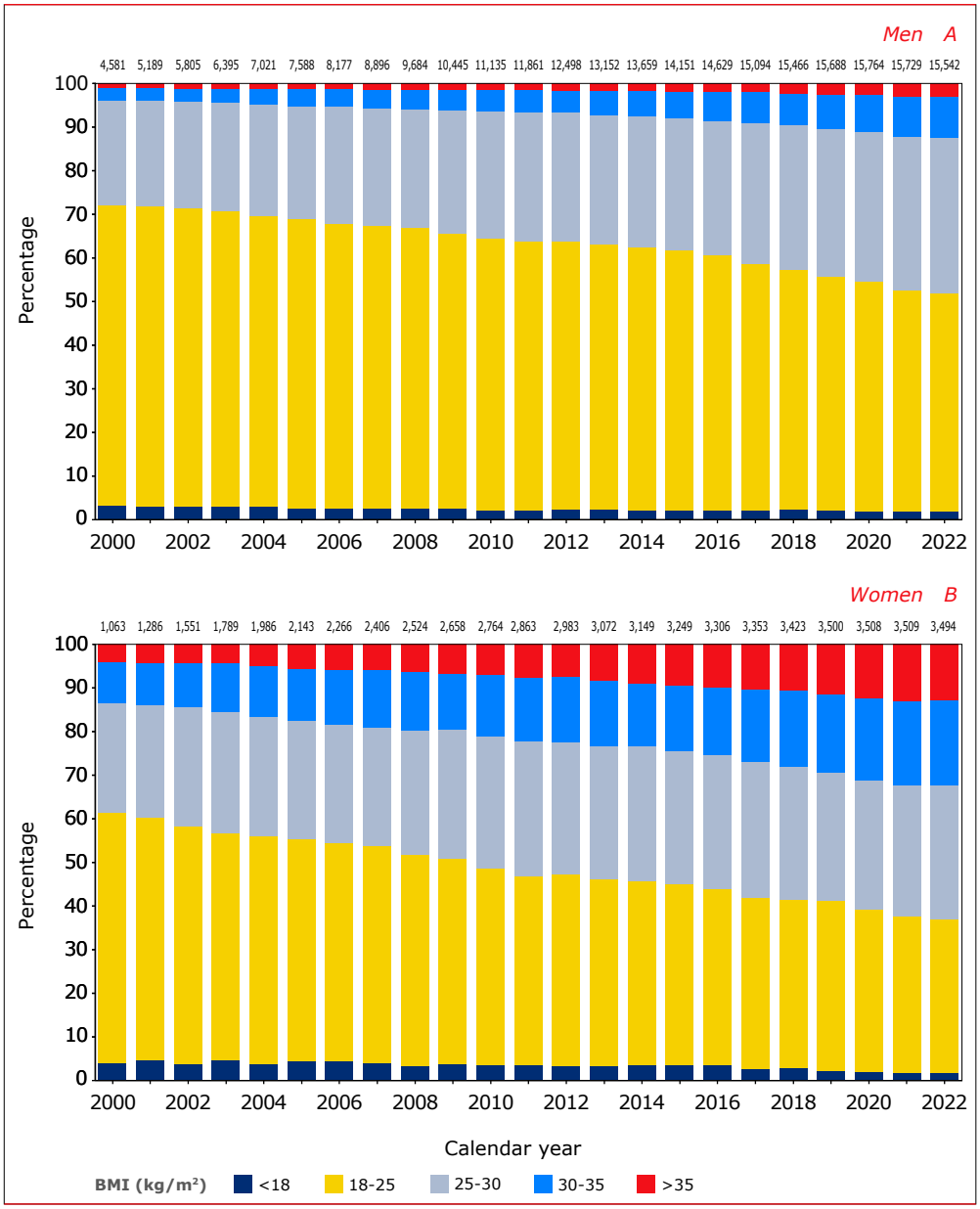
Figures 3.4A and *3.4B* show that the distribution of body mass index (BMI) of both men and women in the HIV-1-positive population has increased over time. In 2022, the proportion of men with available BMI data who were overweight (25-30 kg/m^2) or obese (WHO class I: 30-35 kg/m^2 and WHO class II/III: 35 kg/m^2 or over), was 36.1%, 9.6% and 2.4%, respectively. In women, these proportions were 30.9%, 19.6% and 12.4%, respectively.

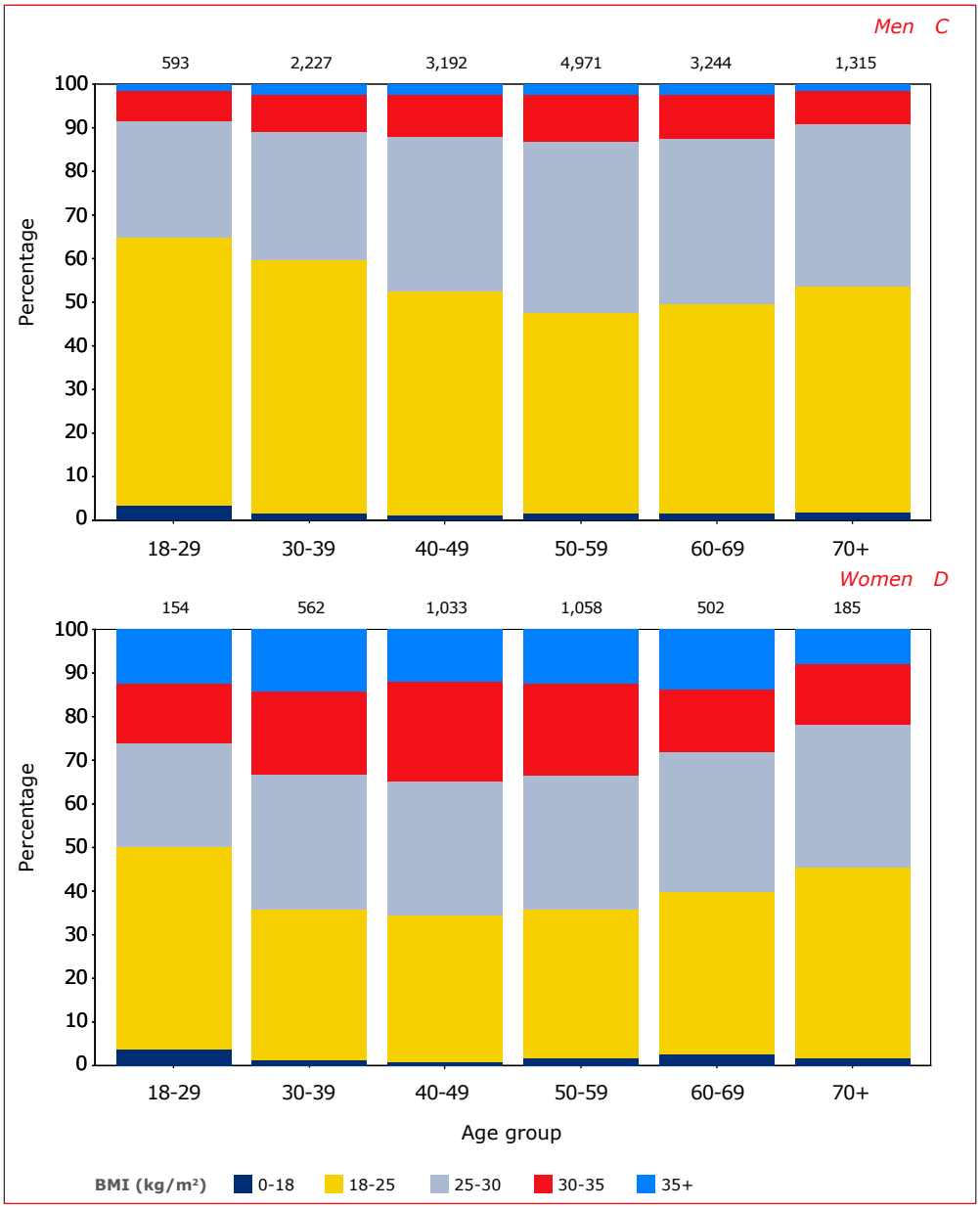
Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the population with HIV. This analysis revealed that the increase was at least partially driven by changes over time in population demographic characteristics (age, 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. A recent paper using data from the ATHENA cohort, demonstrated that rapid weight gain on these agents is not readily reversible after switching to alternative regimens[25].

Figures 3.4C and *3.4D* show the distribution of BMI according to age groups in 2022 for men and women. Whereas in adult men of all age groups, the proportion classified as obese (12.0%) was somewhat lower than the proportion found in the general Dutch male population (14.1%), in women of all age groups there was more obesity (32.0%) than in the general Dutch female population (16.1%)[26]. There were substantial differences between those of Dutch origin, Western migrants and non-Western migrants: among males, 10.9% of Dutch men, 12.5% of Western migrants and 14.7% of non-Western migrants were obese. In females, however, those figures were 23.6%, 20.4%, and 38.3%, 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 2.28, 95% CI 2.01-2.60, p<0.001; obese IRR 5.53, 95% CI 4.79-6.39, p<0.001), but that was not the case with CVD, CKD or non-AIDS-defining malignancies (*Appendix Table 3.5*).

Several topics that in previous editions of the SHM Monitoring Report were part of this Chapter are in this edition of the Monitoring Report included in Chapter 7 on Quality of Care: prevalence and treatment of hypertension; the proportion of treated hypertensive individuals attaining treatment goals; the proportion of individuals with a SCORE2 or SCORE2-OP predicted 10-year risk greater than 10%, without a history of CVD, that received a prescription for statins; the proportion of high-risk individuals receiving statins who attained treatment goals.

Figure 3.4: *Distribution of the body mass index (BMI) at the end of each calendar year in (A) men, and (B) women, as a percentage of the total number of men and women with a known BMI in each year, and distribution of the BMI over the age groups for (C) men, and (D) women, in 2022. For each individual, the last available weight measurement in each year was selected. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year (A & B) or from that age group (C & D).*





Legend: BMI = body mass index.

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[27]. 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[27,28]. However, because the CKD-EPI equation is the one most often used in clinical practice, we have chosen to report eGFR values as estimated by this equation. The distribution of eGFR categories in ml/min/1.73m^2 (90 or above, normal kidney function; 60-89, mildly reduced; 30-59, moderately reduced; 15-29, severely reduced; and below 15, very severely reduced kidney function) is shown in *Figures 3.5A* and *3.5B* for men and women. The percentage of men with normal kidney function decreased over time from 74.5% in 2007, to 42.2% in 2022, and this pattern was similar in women. Typically, eGFR decreases with increased age, as shown in *Figure 3.6*, and therefore the decrease in the proportion of individuals with normal function over time is likely due, in part, to the increasing age of individuals in care.

CKD incidence and risk factors

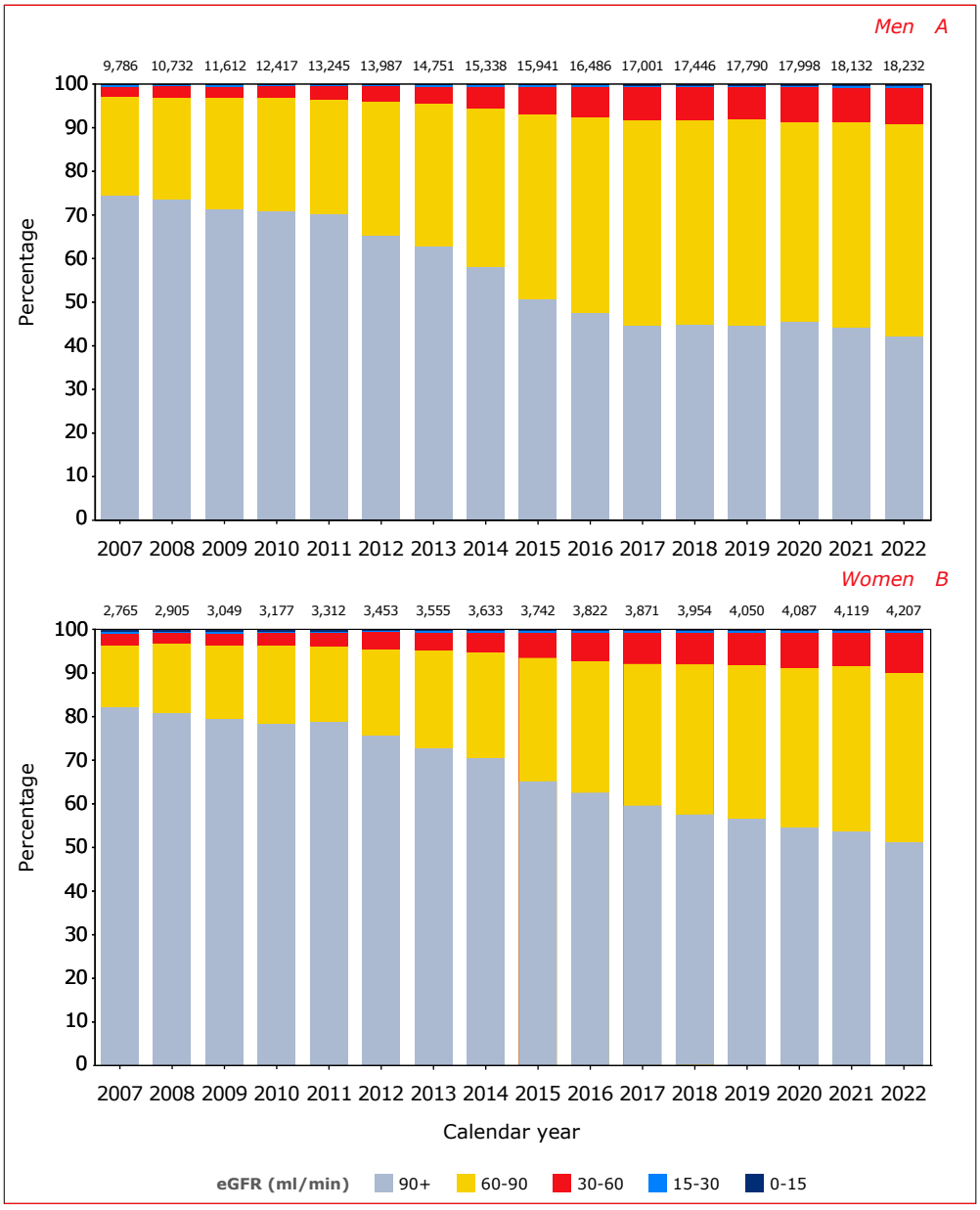
In individuals with an eGFR above 60ml/min/1.73m^2 at the time of inclusion in the analyses, who did not have a previously confirmed CKD, the crude incidence of CKD (defined as eGFR below 60ml/min/1.73m^2 confirmed by a second test at least 26 weeks later) varied over time (*Figure 3.3C*). Routine collection of serum creatinine measurements commenced in 2007. To avoid misclassifying prevalent CKD as incident CKD, we used serum creatinine levels measured in 2007 to distinguish between prevalent (i.e. CKD already present in 2007) versus new-onset incident cases of CKD (i.e. no CKD observed in 2007) from 2008 onwards. In men, the incidence rose from 7.1 cases per 1,000 PYFU in the period 2008-14 to 11.6 in 2015-22. In women, the incidence rose from 7.4 to 12.4 cases per 1,000 PYFU during the same periods (*Table 3.6*). The age-standardised incidence ratio in men and (to a lesser extent) women increased significantly over time (*Table 3.6*).

Risk factors for CKD included:

- female gender;
- Dutch origin;
- low current CD4 cell count (below 200 cells/mm^3);
- a prior AIDS diagnosis;
- belonging to the HIV transmission risk group of people who inject drugs;
- older age group;
- lower body mass index;
- hypertension;
- diabetes mellitus;
- cardiovascular disease;
- pre-treatment with monotherapy and dual therapy with nucleoside analogues before the start of ART; and
- chronic HBV and HCV co-infection (*Appendix Table 3.5*).

When current use of cobicistat, rilpivirine, dolutegravir, and bictegravir were added to the model, the increased risk of CKD in the calendar period 2016-2022 completely disappeared (even reversed) in comparison to 2008-2010 and 2011-2015. 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 3.5: *Distribution of categories of estimated glomerular filtration rate (eGFR) at the end of each calendar year in (A) men, and (B) women. For each individual, the last available measurement in each year was selected. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.*



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

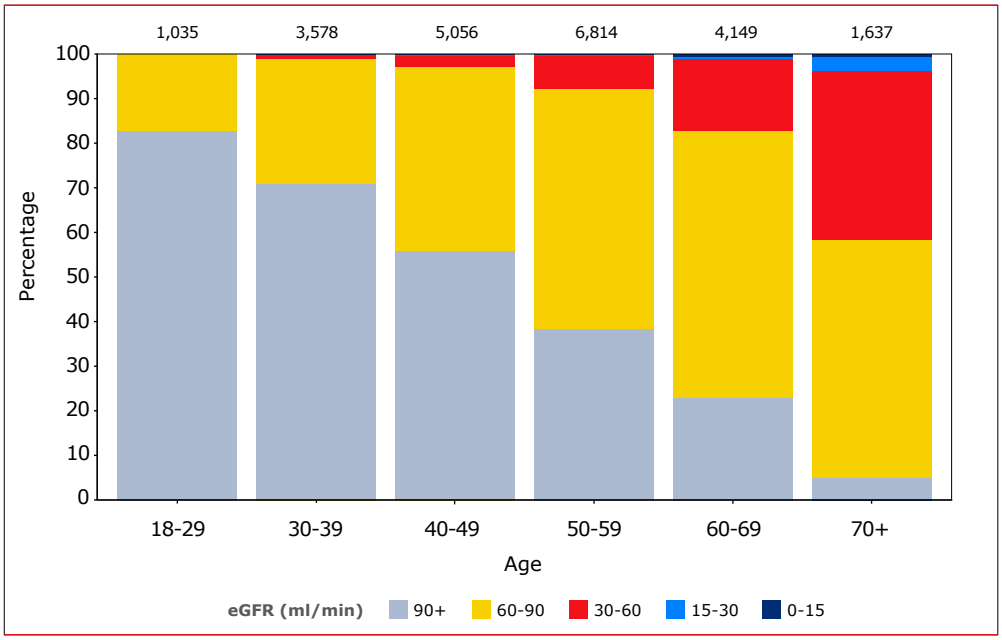
Table 3.6: Crude chronic kidney disease incidence per 1,000 person years of follow up in 2008-2014, and 2015-2022, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2008-2014	7.0 (6.3-7.8)	0.81 (0.72-0.90)	7.3 (5.7-9.0)	0.91 (0.71-1.11)
2015-2022	11.4 (10.7-12.2)	1 (reference)	12.1 (10.6-13.8)	1 (reference)

**Standardised according to the observed age distribution in 2015-2022.*

***Legend:** CI = confidence interval; PYFU = person years.*

Figure 3.6: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2022 for different age categories. For each individual, the last available measurement in 2022 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 2022, 2,293 diagnoses of non-AIDS-defining malignancies in 2,106 unique individuals were recorded in SHM's database. An additional 921 patients were diagnosed with one or more non-melanoma skin cancers, but these were not included in the present analysis. *Table 3.7* shows the most common types of non-AIDS-defining cancer:

- lung cancer (16.2%);
- intestinal cancer (mainly oesophageal, gastric, intestinal, and rectal cancers, but excluding hepato-cellular carcinoma, 13.5%);
- haematological malignancies (excluding AIDS-defining non-Hodgkin's lymphoma, 13.4%);
- invasive anal cancer (excluding pre-malignant AIN, 11.5%);
- prostate cancer (10.4%); and
- head and neck cancers (8.3%).

Figure 3.7 shows the changes in types of non-AIDS-defining cancers over time. The proportion of individuals with intestinal, prostate, and renal cancer has increased over time, likely reflecting the increasing age of the study population. This is further illustrated in *Figure 3.8*, which shows the distribution of non-AIDS-defining malignancies with increasing age at cancer diagnosis.

Risk factors for non-AIDS-defining malignancies

The crude incidence of non-AIDS-defining malignancies (NADM) in men and women is shown in *Figure 3.3D*. The age-standardised incidence in men was statistically significantly lower in the period 2016-2022, compared to 2000-2010, and borderline significantly lower compared to 2011-2015 (*Table 3.8*). This lower age-standardised incidence in men may be due to a reduction over time in risk factors such as smoking, and a higher proportion of individuals living with high CD4 cell counts. The temporal trend for women was similar – the age-standardised incidence decreased (although not significantly) over time (*Table 3.8*).

Demographic and clinical factors independently associated with an increased risk of a first non-AIDS-defining malignancy were (*Appendix Table 3.5*):

- older age group;
- acquiring HIV-1 through injecting drugs or contact with blood or blood products;
- lower current CD4 cell count (CD4 below 350 cells/mm^3);
- low body mass index;
- prior AIDS;
- chronic HBV co-infection; and
- current or past smoking.

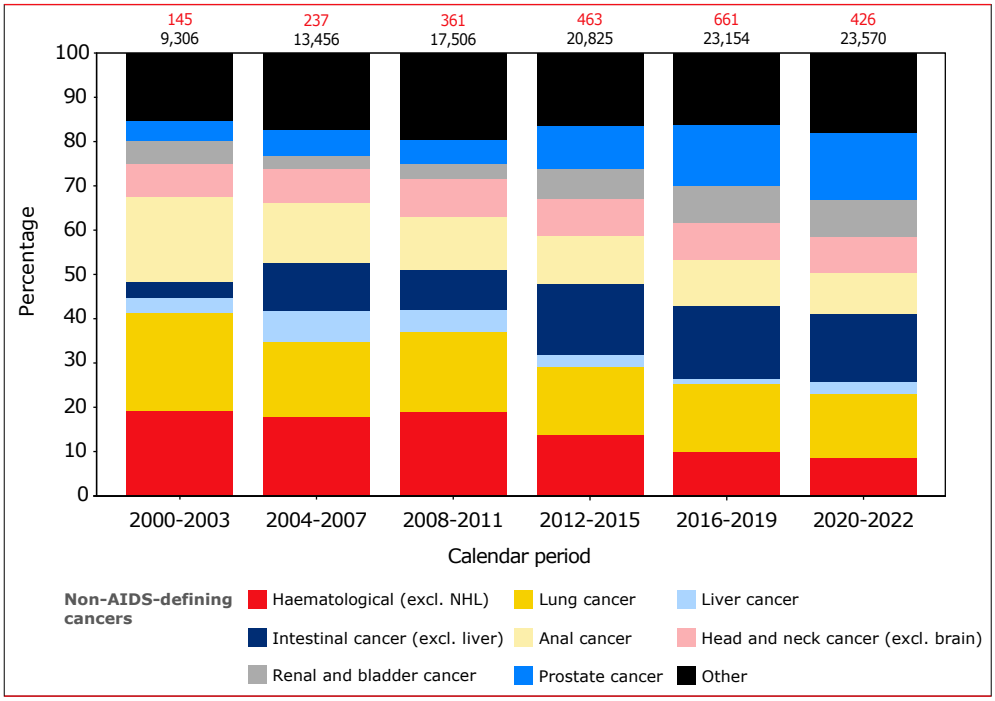
Furthermore, people who had been pre-treated with mono or dual-NRTI-based regimes prior to starting ART had an independently increased risk for NADM, compared with those who were therapy-naïve prior to starting ART (relative risk [RR] 1.17, 95% CI 1.01-1.34). Of note, independent of all other risk factors investigated, people who initiated ART within 12 months of their last negative HIV test had a significantly lower risk for NADM (RR 0.62, 95% CI 0.43-0.88) 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 2022, the overall five-year survival rate following the most common non-AIDS-defining malignancies are shown in *Table 3.7* and *Appendix Figure 3.1*. Table 3.7 also shows the distribution and crude 5-year survival rates of the sub-group of NADM diagnosed in the last 10 years of follow-up. The crude 5-year survival rates of liver cancer improved substantially from 18.9% in the period 2000-2022, to 50.7% in the period 2013-2022, however because of low numbers the uncertainty of this latter estimate is high. For nearly all other NADM we observed an improvement in the crude 5-year survival rates of a few percentage points (but with slightly better results for lung cancer and malignant melanoma).

Anal cancer

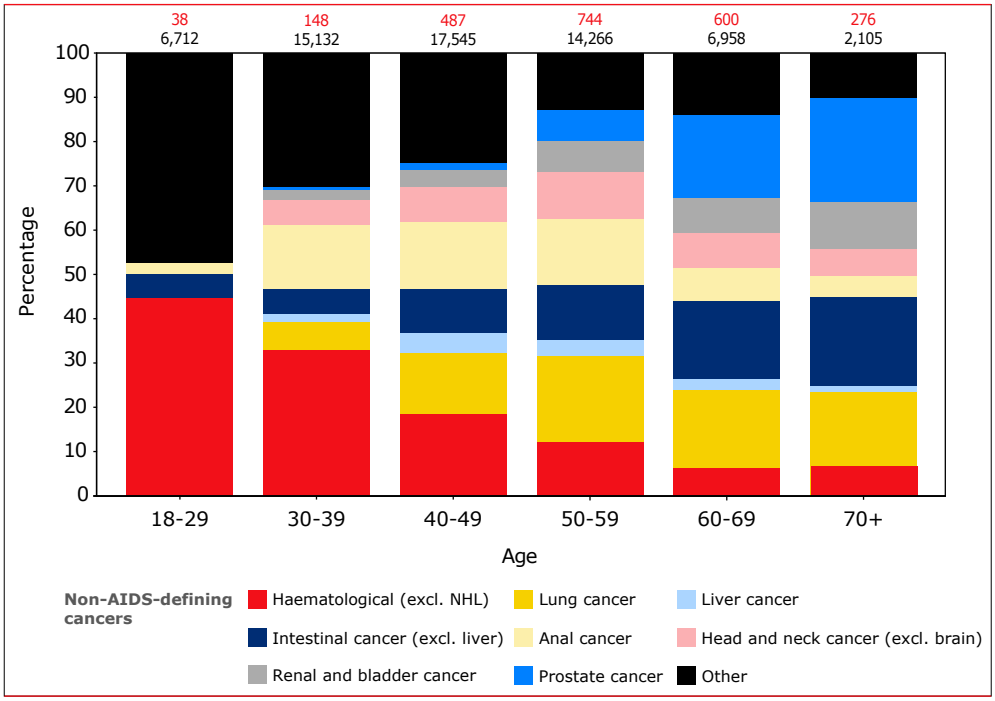
In total, 253 men with HIV and 11 women with HIV were diagnosed with anal cancer. Among men with HIV, the incidence of anal cancer fluctuated between 0.4 and 1.5 cases per 1,000 PYFU between 2000 and 2022 (*Figure 3.3G*). A 2023 study examined trends in incidence of and mortality after anal cancer diagnosis in people living with HIV, including the effect of AIN/anal cancer screening from 2007 onwards, in the Netherlands [29]. It found that anal cancer incidence slowly declined in MSM but not in non-MSM and women, and also that men diagnosed with anal cancer during screening had improved survival compared to those that were diagnosed while not participating in a screening program, probably because they were diagnosed at an earlier disease stage.

Figure 3.7: Relative changes in non-AIDS-defining malignancies between 2000 and 2022 in PWH in the Netherlands. The numbers at the top of each bar represent the number of non-AIDS-defining cancer diagnoses (top number) and the total number of individuals in care during that calendar period (bottom number).



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

Figure 3.8: Relative changes in non-AIDS-defining malignancies with increasing age in PWH with HIV in the Netherlands. The numbers at the top of each bar represent the number of individuals at risk and the number of cancer diagnoses in that age category between 2000 and 2022.



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

Table 3.7: Most common non-AIDS-defining malignancies diagnosed in 2000-2022, and a sub-group diagnosed between 2013-2022, excluding non-melanoma skin cancer and pre-malignant lesions found by cervical and anal screening.

			2000-2022			2013-2022
non-AIDS malignancy	**# of malignancies**	**%**	**Five-year survival (%)**	**# of malignancies**	**%**	**Five-year survival (%)**
Lung cancer	372	16.2	15.4	218	15.2	20.7
Intestinal cancer (excl. liver)	310	13.5	30.0	228	15.9	32.0
Hematological (excl. NHL)	307	13.4	61.8	156	10.8	64.7
Anal cancer	264	11.5	66.0	151	10.5	69.3
Prostate cancer	239	10.4	80.0	190	13.2	82.4
Head and neck cancer (excl. brain)	190	8.3	56.8	118	8.2	61.8
Renal and bladder cancer	149	6.5	61.1	116	8.1	62.3
Other cancers	120	5.2	40.8	70	4.9	41.3
Malignant melanoma	104	4.5	75.8	61	4.2	84.6
Liver cancer	70	3.1	18.9	29	2.0	50.7
Breast cancer	65	2.8	78.3	38	2.6	73.6
Testicular cancer	41	1.8	86.4	21	1.5	85.2
Gynecological cancer (excl. cervical)	34	1.5	69.9	17	1.2	74.6
CNS cancer	28	1.2	59.9	25	1.7	54.7

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

Table 3.8: Crude non-AIDS-defining malignancy incidence per 1,000 person years of follow up in 2000-2010, 2011-2015, and 2016-2022, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	**Male**		**Female**	
	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000-2010	6.6 (6.0-7.1)	1.34 (1.23-1.45)	3.2 (2.5-4.0)	1.20 (0.93-1.47)
2011-2015	6.6 (6.1-7.3)	1.05 (0.96-1.15)	4.4 (3.5-5.6)	1.10 (0.85-1.35)
2016-2022	8.0 (7.5-8.6)	1 (reference)	5.3 (4.4-6.2)	1 (reference)

**Standardised according to the observed age distribution in 2016-2022.*

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

Multimorbidity

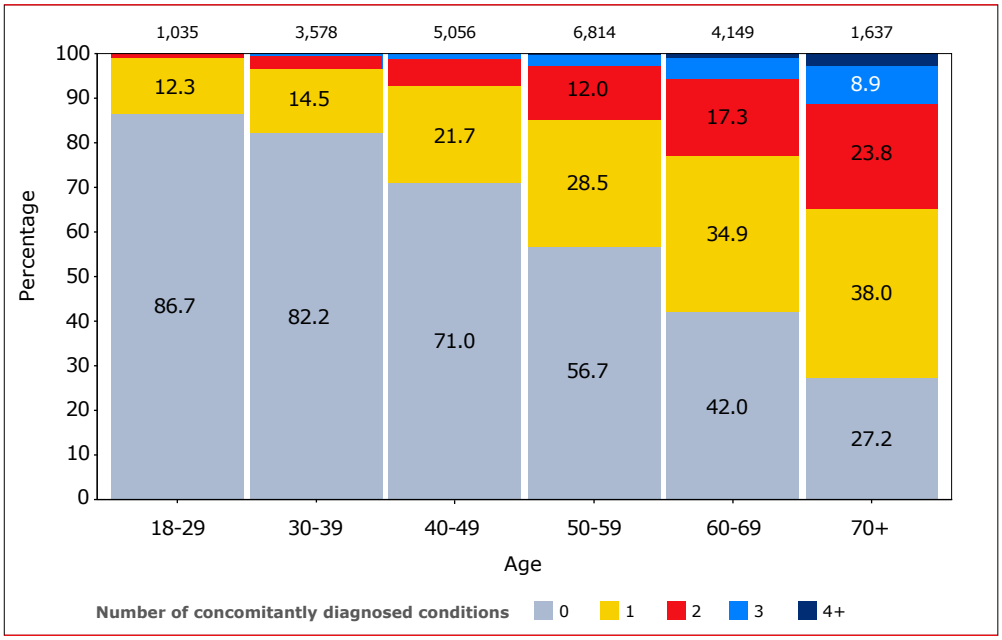
We investigated changes over time in the prevalence of non-AIDS multimorbidity. HIV infections and AIDS diagnoses did not contribute to the multimorbidity count. The following comorbidities and conditions were taken into account:

1. **Cardiovascular disease** (either myocardial infarction, coronary artery bypass grafting, coronary angioplasty or stenting, and carotid endarterectomy)
2. **Stroke**
3. **Non-AIDS-defining malignancies**, excluding non-melanoma skin cancers and pre-malignant lesions found at cervical/anal screening
4. **Chronic kidney disease** (eGFR below 30 ml/min/1.73 m^2)
5. **Diabetes mellitus** (according to D:A:D diagnostic criteria)
6. **Hypertension**, defined as the use of antihypertensive drugs and/or measured grade 2 (or higher) hypertension with systolic pressure at or above 60 mmHg and/or diastolic pressure at or above 100 mmHg
7. **Obesity** (BMI over 30).

Note that more stringent definitions of CKD and hypertension have been applied here than in the analyses presented earlier in this chapter; this is to avoid overdiagnosis of CKD in people using antiretroviral drugs that inhibit tubular secretion of creatinine, and hypertension in those with borderline hypertension. Recurrences and non-primary CVD, stroke, and non-AIDS-defining malignancy events were not considered. Finally, CKD, hypertension, and obesity could be reversible.

Appendix Figure 3.2 shows the prevalence of each individual comorbidity over calendar time. *Figure 3.13* shows the distribution of the number of concomitantly-diagnosed conditions in various age categories of the adult population in 2022. The number of concomitant conditions was slightly higher in women than in men for all age categories (*Appendix Figure 3.3*). After adjusting for the variables listed in *Appendix Table 3.2*, multimorbidity was independently associated with increased risk of mortality (RR 2.11, 95% CI 2.04-2.19, p<0.001, per additional comorbidity diagnosed).

Figure 3.9: Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2022. 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 counted individual ATC codes (Anatomical Therapeutic Chemical classification system[a] of the comedications. Note that coformulated combinations, such as cotrimoxazole, have a single ATC code and therefore increase the comedication count by one.

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

In 2022, our count revealed:

- 18.4% of adults in active follow up had no recorded comedication use
- 29.4% used one comedication;
- 16.4% used two comedications;
- 10.9% used three comedications; and
- 7.2% used four comedications.

A further 18.4% 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 3.14*): 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 3.15A*) and those with more comorbidities (*Figure 3.16*) used more comedications. There were some differences between men and women, with women using slightly more comedications than men, while the most pronounced differences were to be found in the youngest age groups (*Figure 3.15B*). Finally, in adults receiving ART in the period 2007-2022, polypharmacy was also associated with an increased risk of death (RR 2.17, 95% CI 1.96-2.39, $p<0.001$) 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 2022 are listed in *Table 3.9*.

Table 3.9: Use of comedications in 2022.

Comedication use in 2022	N	%
ATC group	6710	12.1
Vitamins		
Lipid modifying agents	4714	8.5
Drugs for acid related disorders	3954	7.2
Agents acting on the renin-angiotensin system	3462	6.3
Psycholeptics drugs (antipsychotics, anxiolytics, hypnotics, sedatives)	3355	6.1
Antithrombotic agents	2875	5.2
Drugs for obstructive airway diseases	2732	4.9
Psychoanaleptics (antidepressants, psychostimulants)	2360	4.3
Drugs used in diabetes	2268	4.1
Mineral supplements	2120	3.8
Urological drugs	1808	3.3
Beta blocking agents	1673	3.0
Calcium channel blockers	1585	2.9
Antianemic drugs	1235	2.2
Antibacterial drugs	1183	2.1
Diuretic drugs	1182	2.1
Sex hormones and modulators of the genital system	1120	2.0
Corticosteroids systemic	1010	1.8
Topical dermatological corticosteroids	885	1.6
Analgesic drugs	870	1.6
Antiepileptic drugs	842	1.5
Cardiac therapy	750	1.4
Nasal preparations	727	1.3
Antiviral drugs	711	1.3
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	506	0.9
Antimycotic drugs	505	0.9
Drugs affecting bone structure and mineralization	453	0.8
Thyroid therapy	379	0.7
Ophthalmological drugs	309	0.6
Immunosuppressants drugs	282	0.5
Other nervous system drugs	259	0.5

Figure 3.10: Number of comedications used over calendar time. The numbers at the top of each bar represent the number of individuals contributing data to that period. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per period.

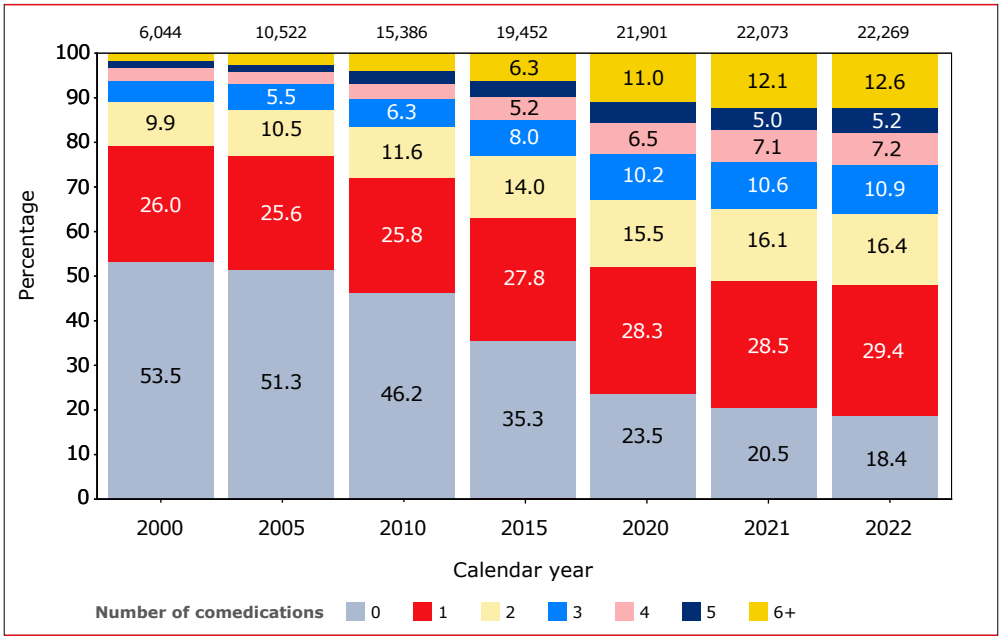
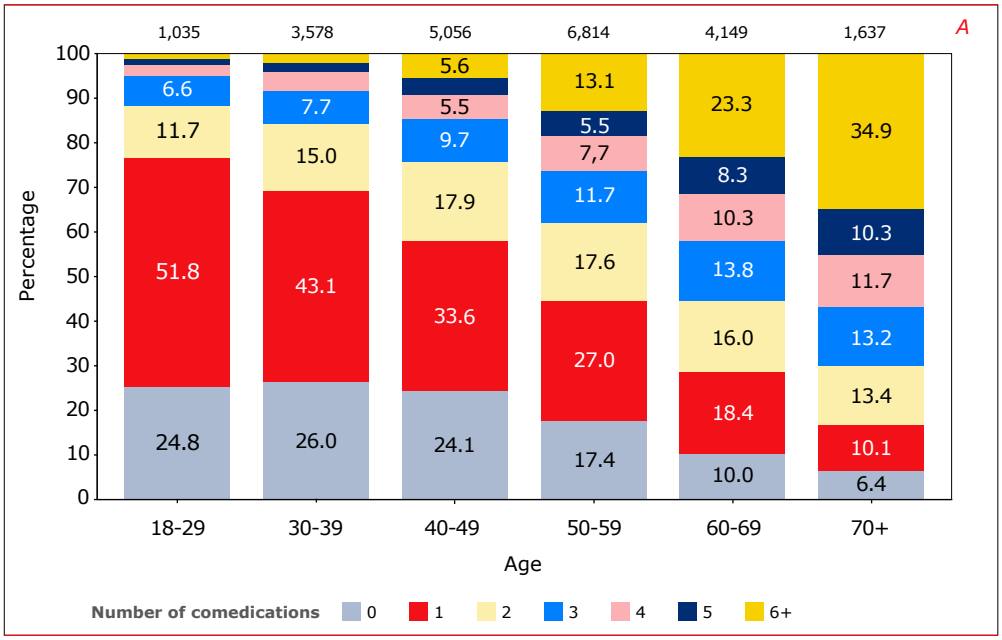


Figure 3.11: Number of comedications used by (A) age group, and (B) gender in 2022. The numbers at the top of each bar represent the number of individuals contributing data to that age/gender category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



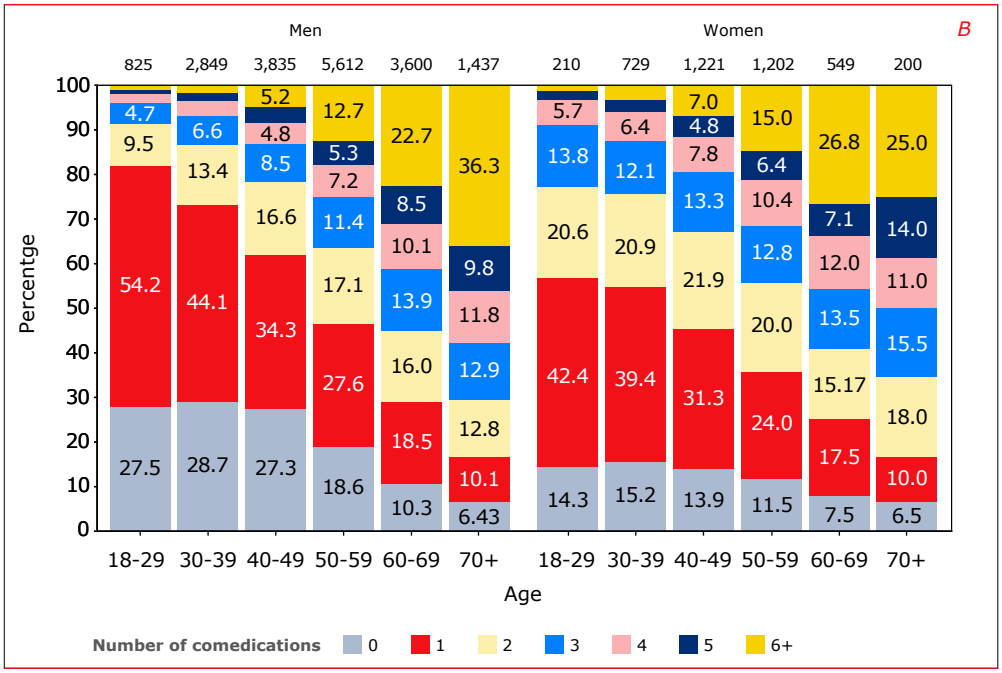
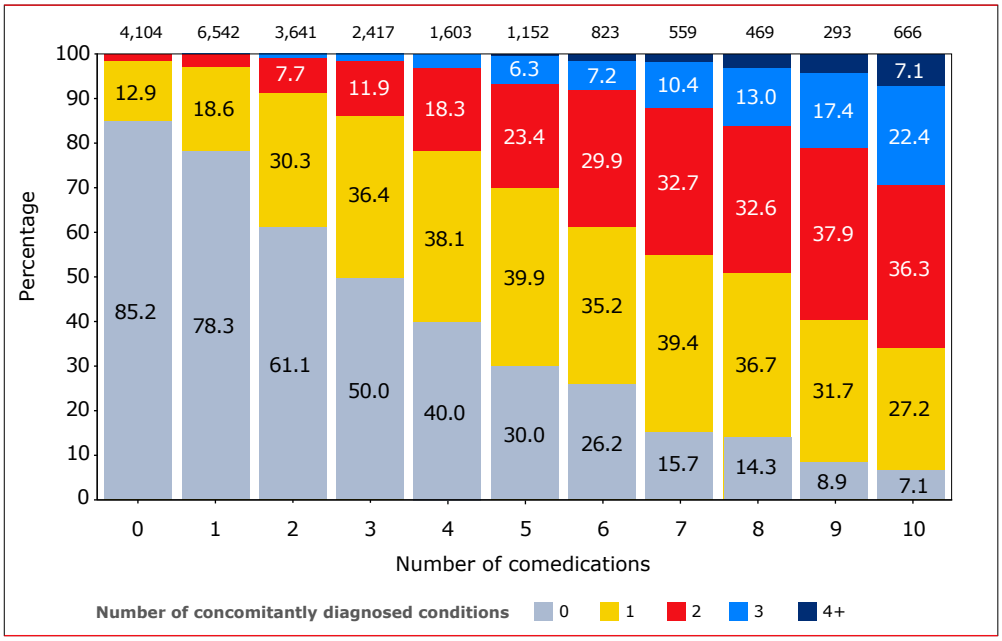


Figure 3.12: Number of comedications used in relation to the number of prevalent comorbidities. The numbers at the top of each bar represent the number of individuals contributing data to that category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per category.



SARS-CoV-2 and COVID-19

The first documented case of SARS-CoV-2 infection in the Netherlands was on 27 February 2020[30]. The majority of SARS-CoV-2 infections result in a self-limiting disease with minor or mild symptoms. In the Netherlands, the SARS-CoV-2 vaccination program started in January 2021. At the start of the SARS-CoV-2 vaccination program, PWH as a group were not prioritized, instead initially only the oldest PWH and those living in a nursing home were eligible. As of April 2021 all PWH became eligible for SARS-CoV-2 vaccination. National treatment guidelines for moderate and severe COVID-19 cases were continuously updated throughout the epidemic. These guidelines did not consider HIV status to be at strongly increased risk factor for severe COVID-19. Individuals however who are older, male, belong to non-Western ethnic groups, with lower socio-economic status, and those with certain underlying conditions like obesity, hypertension, renal dysfunction, diabetes mellitus, and cardiovascular disease, are at increased risk for severe COVID-19, hospitalization and death. Many of the risk factors for severe COVID-19 in the general population are more prevalent in people living with HIV. In a recent

study, we described the incidence, risk factors, and outcomes of COVID-19 in PWH in the Netherlands using data collected up to 31 December 2021. We found that risk of severe COVID-19 outcomes was increased in individuals with uncontrolled HIV replication, low CD4 count and prior AIDS diagnosis, independent of general risk factors like higher age, comorbidity burden and migrants originating from non-Western countries[31]. Here we present an updated analysis of the incidence, risk factors, and outcomes of COVID-19 in people living with HIV in the Netherlands using data collected up to 31 December 2022.

Stichting HIV Monitoring (SHM) records diagnosis of, and hospitalisations for COVID-19, using information available in the electronic medical records (EMRs) of the HIV treatment centers. Details regarding diagnosis, disease severity, hospitalisations, and outcomes of COVID-19 are also collected. SHM has not established links to other COVID-19 care providers and cohorts / datasets, nor to SARS-CoV-2 vaccination data repositories.
Objective measures of COVID-19 disease severity could often not be recorded by SHM, as these data were not systematically recorded in EMRs, especially for people who weren't hospitalised. In addition, detailed information on COVID-19 disease severity was often not available for patients who had been hospitalised for COVID-19, if the hospital differed from the one in which they received their HIV care. Therefore, we used data on hospitalisation for COVID-19 as a proxy for COVID-19 disease severity. Risk factors for severe COVID-19 (hospitalisation and death), were investigated using multivariable logistic regression including relevant demographics (age, sex, region of origin), general risk factors (comorbidities), and HIV-related parameters.

By the time of database closure for this analysis on 31 September 2023, SHM had collected data on 6,179 COVID-19 events diagnosed between 1 February 2020 and 31 December 2022 in 5,690 individuals (Figure 3.13.A). A total of 489 COVID-19 events occurred in individuals who had previously been diagnosed with COVID-19. Of the 6,147 recorded COVID-19 events, 243 (3.9%) resulted in hospitalisation (Figure 3.13.B); 39 (0.6%) of which required ICU admission. An additional 76 (1.2%) individuals presented with COVID-19 at an emergency room but required no hospitalisation, and the remaining 5,860 (94.8%) individuals remained at home. First COVID-19 events were slightly more likely to result in hospitalization (4.1%) compared to second COVID-19 events (2.0%). Table 3.10 describes the characteristics of the individuals that were diagnosed with (or hospitalized for) COVID-19, with individuals that had multiple COVID-19 events contributing only one (the most severe) event. The characteristics of the overall population living with HIV in care in the Netherlands in 2022 is also described in *Table 3.10*. Compared to the total

population living with HIV, those who were hospitalised for COVID-19 were older, were more likely to have acquired HIV through heterosexual contact (both men and women), and were more likely to be born in sub-Saharan Africa or Latin America (including the Caribbean). Overall, men were not more likely than women to be diagnosed with or hospitalised for COVID-19; however, MSM were much less likely while the other (mostly heterosexual) men were more likely.

Regarding HIV-related characteristics, there were only minor differences between people living with HIV who were diagnosed with COVID-19, and the total population living with HIV, with the overwhelming majority being on ART, with a plasma HIV-1 viral load below 200 cps/mL, and a high median CD4 cell count well above 500 cells/mm^3. There were, however, noticeable differences between people diagnosed with COVID-19 who were hospitalised and those who weren't hospitalised; for example, the former had generally been HIV-positive for longer, but this is most likely driven by the fact that those who were hospitalised were on average eight years older. Furthermore, those who were hospitalised had lower current and nadir CD4 cell counts, and had more frequently had a prior AIDS diagnosis, compared to those not hospitalised (*Table 3.10*).

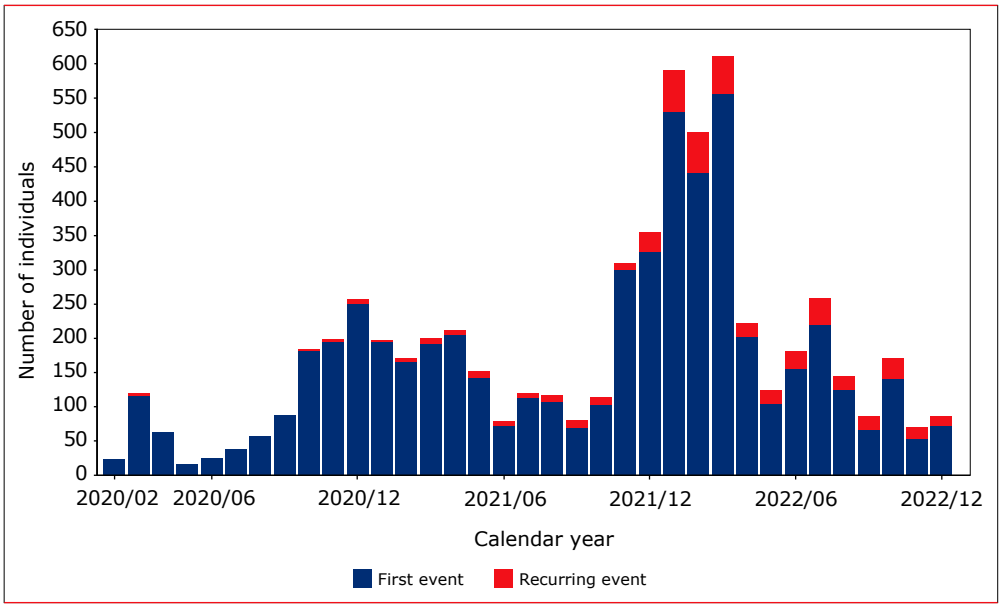
The bottom half of *Table 3.10* shows the distribution of selected comorbidities among individuals diagnosed with COVID-19. All investigated comorbidities were much more prevalent among the group that was hospitalised, resulting in a higher total multimorbidity count in the hospitalised group.

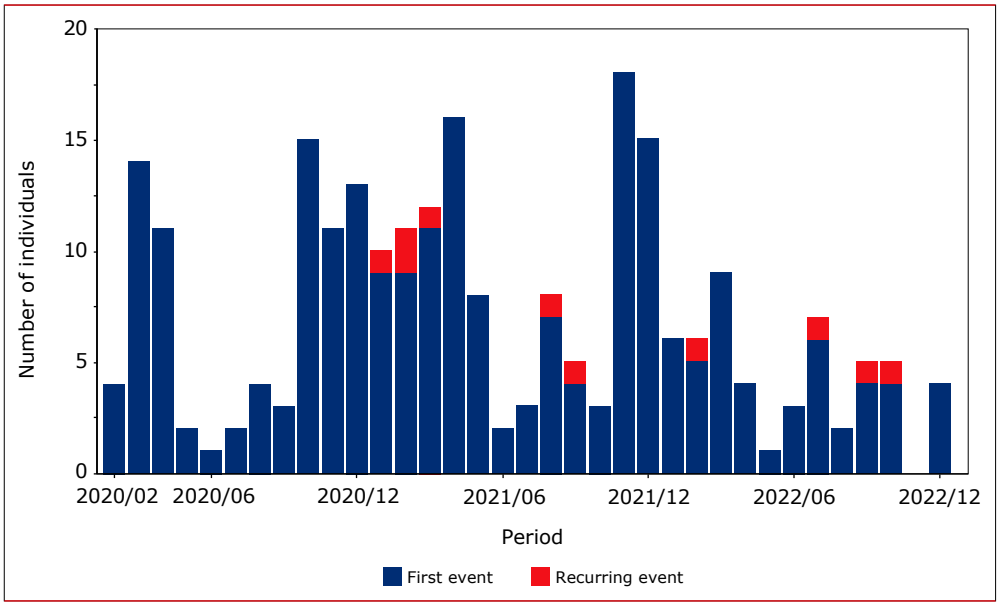
Multivariable logistic regression showed that independent risk factors for hospitalisation for COVID-19 among people living with HIV were higher age, migrant status (with higher risk in individuals originating from sub-Saharan Africa or, to a lesser extent, from Latin America), obesity (BMI over 30 kg/m^2), having a current CD4 count below 500 cells/mm^3 (the risk was even higher when the CD4 cell count was below 200 cells/mm^3), having a current viral load above 200 c/mL, and having had a prior AIDS-defining illness (*Table 3.11*). All other demographic, comorbidity, HIV-related and ART-related parameters investigated were not independently associated with a higher risk of being hospitalised following a diagnosis of COVID-19.

In total, 43 (0.76%) of the 5,690 individuals diagnosed with one (or more) COVID-19 event(s) were reported to have died as a direct result of COVID-19 (Figure 3.13.C). As is the case in the general population, the observed mortality rates increased strongly with increasing age (Figure 3.14.A) and in those diagnosed with co-morbidities (Figure 3.14.B). *Table 3.12* shows the demographics, HIV-related characteristics, and comorbidities of those who died from COVID-19, compared to those who survived. As expected, there were very substantial differences. Because of the low number of COVID-19-related deaths, statistical power to formally explore risk factors using regression analysis is low. Exploratory multivariable logistic regression models showed that independent risk factors for COVID-19-related mortality were higher age, having a sub-Saharan African or Latin American origin, having a higher number of concomitantly diagnosed comorbidities, and having a current CD4 count below 500/mm^3 (with the risk being even higher when the CD4 cell count was below 200/mm^3, Figure 3.14.C) (*Table 3.13*).

The SARS-CoV-2 Omicron strain has become the dominant circulating strain in the Netherlands since the end of December 2021. Comparing the pre-Omicron to the Omicron period, the hospitalization rate has decreased from 190 (6.04%) hospitalizations out of 3,146 COVID-19 events in the pre-Omicron period, down to 53 (1.75%) out of 3,033 COVID-19 events in the Omicron era. The COVID-19-related death rate has decreased from 34 (1.08%) out of 3,146 COVID-19 events in the pre-Omicron period, down to 9 (0.30%) out of 3,033 COVID-19 events in the Omicron period. Limiting the multivariable regression analyses of risk factors for COVID-19-related hospitalizations and deaths to the Omicron period, resulted in very similar findings indicating that the identified risk factors for severe COVID-19 outcomes have not changed since the Omicron period began, with older age and more comorbidities remaining to have the strongest associations with risk for hospitalization and death (data not shown).

Figure 3.13.A-C: Incidence of COVID-19 diagnoses (A), hospitalizations (B) and deaths (C) over calendar time.





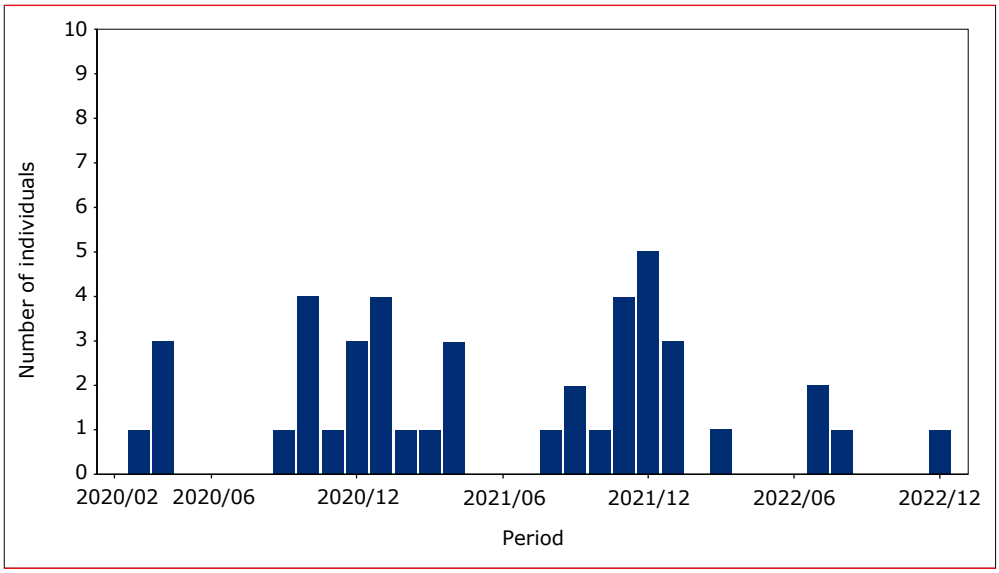
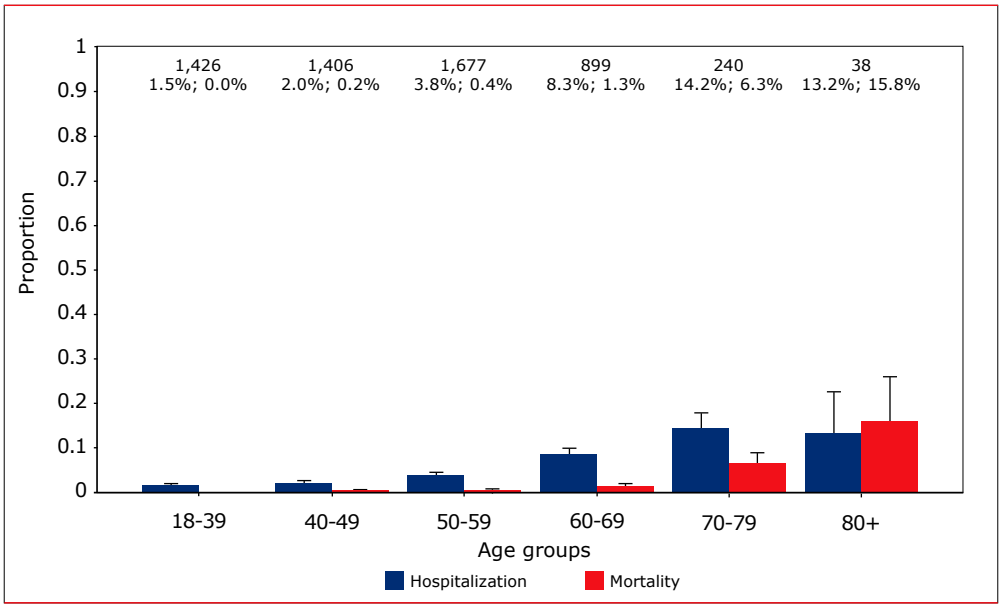
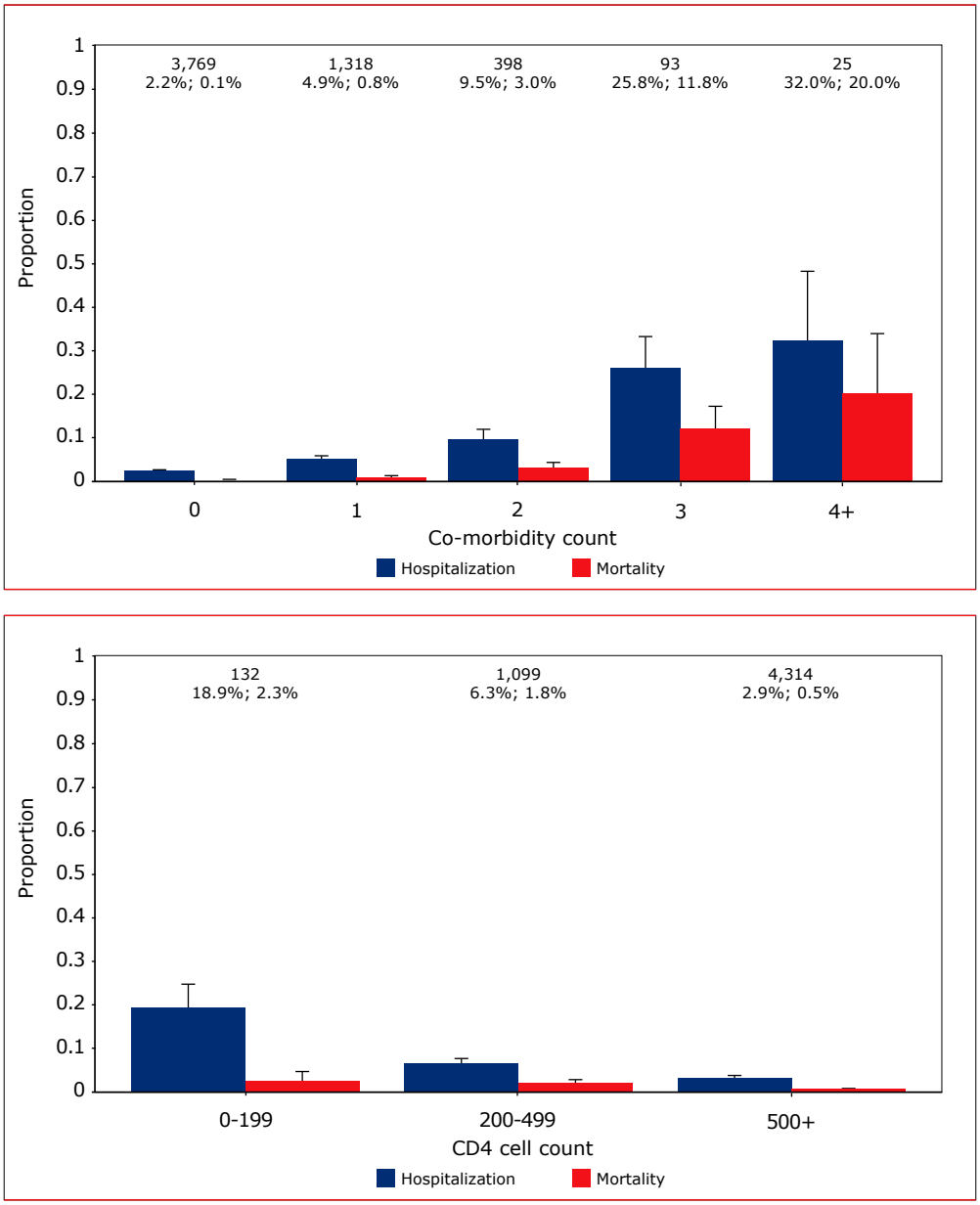


Figure 3.14.A-C: Proportions of COVID-19-related hospitalization and mortality by age group (A), co-morbidity count (B), and CD4 cell count category (C).





Legend: *The numbers at the top of the panels denote the number of individuals (top row) and the percentage of hospitalized and deceased individuals (bottom row) in each category.*

Table 3.10: Characteristics of individuals diagnosed with COVID-19.

	All PWH in 2022	Hospitalised	Not hospitalised
N	**21,901**	**233**	**5457**
Age, years	51.1 (41.3-59.0)	59.8 (51.4-66.7)	49.5 (39.4-57.9)
Male sex	81.8%	80.3%	81.6%
HIV transmission category			
MSM	63.5%	44.6%	66.2%
Other men	18.3%	35.6%	15.4%
Women	18.2%	19.7%	18.4%
Region of origin			
Netherlands / Europe / North America	69.8%	54.1%	63.9%
Sub-Saharan Africa	12.1%	16.7%	9.2%
Latin America / Caribbean	12.9%	18.0%	13.3%
Other regions	5.3%	11.1%	13.6%
Years known to be HIV positive	12.5 (7.2-18.6)	15.5 (8.8-22.0)	12.2 (6.6-18.4)
On ART	97.3%	96.9%	98.9%
HIV viral load >200 cps/mL	3.3%	8.4%	2.3%
Current CD4 count, mm^3	690 (507-905)	560 (360-790)	713 (530-920)
Nadir CD4 count, mm^3	250 (120-385)	160 (50-270)	263 (140-410)
Prior AIDS diagnosis	22.3%	40.3%	18.7%
Comorbidities			
Obesity (BMI>30 kg/m^2)	12.4%	26.8%	13.7%
Diabetes mellitus type 2	5.2%	20.5%	5.0%
Cardiovascular disease	3.6%	9.8%	3.3%
Stroke	1.8%	7.1%	1.8%
Hypertension (grade 2+ or on medication)	13.4%	30.4%	13.8%
Non-AIDS-defining malignancy	3.5%	9.8%	3.4%
Chronic kidney disease (eGFR<60 ml/min)	0.8%	6.3%	0.9%
Multimorbidity count			
0	62.2%	38.4%	68.5%
1	24.5%	30.4%	23.2%
2	9.9%	17.4%	6.7%
3 or more	3.4%	13.8%	1.6%

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

Table 3.11: Predictors of hospitalisation among people living with HIV who were diagnosed with COVID-19.

	Univariable analysis		Multivariable model	
Risk factor	**Odds ratio (95%CI)**	**P-value**	**Odds ratio (95%CI)**	**P-value**
Male sex	0.81 (0.61-1.18)	0.35		
Age (per 10 years increase)	1.79 (1.60-2.01)	<0.0001	1.59 (1.39-1.81)	<0.0001
Region of birth				
Western	-ref-			
Sub-Saharan Africa	2.36 (1.63-3.43)	<0.0001	2.52 (1.67-3.80)	<0.0001
Latin America / Caribbean	1.45 (1.00-2.11)	0.053	1.54 (1.023-2.32)	0.039
Other	0.96 (0.62-1.49)	0.87	1.14 (0.72-1.79)	0.58
Number diagnosed comorbidities (per 1 more)	2.25 (1.98-2.55)	<0.0001	1.73 (1.50-1.99)	<0.0001
Current CD4 cell count (cells/mm^3)				
0 – 199	7.72 (4.78-12.46)	<0.0001	4.95 (2.88-8.49)	<0.0001
200 – 499	2.25 (1.67-3.03)	<0.0001	1.75 (1.28-2.38)	0.0005
500+	-ref-			
Nadir CD4 cell count (cells/mm^3)				
0 – 199	6.00 (3.14-11.48)	<0.0001		
200 – 499	2.90 (1.50-5.62)	0.0015		
500+	-ref-			
HIV viral load >200 copies/mL	2.03 (1.38-2.99)	0.0004	1.52 (0.99-2.34)	0.054
Prior AIDS diagnosis	2.90 (2.20-3.82)	<0.0001	1.77 (1.32-2.38)	0.0001

Table 3.12: Characteristics of individuals diagnosed with COVID-19 who died from COVID-19 compared to those who survived.

	Survived	Died of COVID-19
Number of individuals	5,647	43
Age, years	49.8 (39.6-58.2)	68.7 (60.6-78.1)
Male sex	81.5%	79.1%
HIV transmission category		
MSM	65.5%	44.2%
Other men	16.1%	34.9%
Women	18.5%	20.9%
Region of origin		
Netherlands / Europe / North America	63.5%	53.5%
Sub-Saharan Africa	9.5%	11.6%
Latin America / Caribbean	13.4%	30.3%
Years known HIV-positive	12.3 (6.6-18.5)	18.1 (12.8-24.0)
On ART	98.8%	95.4%
HIV viral load >200 cps/mL	2.5%	4.7%
Current CD4 cell count, cells/mm^3	710 (520-913)	443 (232-750)
Nadir CD4 cell count, cells/mm^3	260 (130-404)	90 (30-200)
Prior AIDS diagnosis	19.4%	37.2%
Comorbidities		
Obesity (BMI>30)	14.2%	20.9%
Diabetes mellitus	5.4%	30.2%
Cardiovascular disease	3.4%	20.9%
Stroke	1.8%	23.3%
Hypertension (grade 2+ or on medication)	14.1%	67.4%
Non-AIDS-defining malignancy	3.5%	18.6%
Chronic kidney disease (eGFR<60 ml/min)	0.9%	23.3%
Multimorbidity count		
0	67.7%	9.3%
1	23.5%	25.6%
2	6.9%	27.9%
3	1.5%	25.6%
4 or more	0.4%	11.6%

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

Table 3.13: Independent predictors of mortality among people living with HIV who were diagnosed with COVID-19.

Risk factor	Odds ratio (95%CI)	P-value
Age (per 10 years increase)	3.16 (2.27-4.41)	<0.0001
Region of birth		
Western	-ref-	
Sub-Saharan Africa	3.01 (1.01-8.97)	0.048
Latin America / Caribbean	3.49 (1.56-7.83)	0.0024
Other	0.61 (0.14-2.71)	0.51
Number of concomitantly diagnosed comorbidities (per 1 comorbidity increase)	2.43 (1.85-3.2)	<0.0001
Current CD4 cell count		
0-199	1.90 (0.40-9.09)	0.42
200-499	2.90 (1.47-5.70)	0.0021
500+	-ref-	

Summary and conclusions

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. The five-year survival rate after a first AIDS-defining condition is far greater than after a diagnosis of cardiovascular disease (CVD), or a non-AIDS-defining malignancy. Death is increasingly 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, although it is slowly approaching the latter. Furthermore, several studies have 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[32,33].

In 2021, for the first time there was a substantial increase in the mortality rate in people with HIV in the Netherlands during the period 2019 to 2021; from 8.48 deaths per 1000 person years in 2019, to 9.23 in 2020 and 10.91 in 2021. The increase in 2020 and 2021 appears mostly driven by an increase in the number of non-AIDS infectious causes of death, which include COVID-19-related deaths. 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 2021 (as well as in other Western countries). It is thought to be mostly driven by COVID-19-related deaths and other indirect adverse health effects of the COVID-19 epidemic in the Netherlands[34]. However, in 2022 the observed mortality rate of 9.79 deaths per 1000 person years has returned to pre-COVID-19 levels.

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. This decline may suggest improved awareness, prevention (including switching from drugs associated with an increased risk of diabetes mellitus[35] and myocardial infarction[36,37] (MI), and increased attention to managing traditional risk factors for these conditions. It may also reflect an increasing proportion of individuals living at high CD4 cell counts (because of the trend over time to start ART at higher CD4 cell counts, but also due to an increase in the proportion of individuals who have used ART long enough to reach high CD4 cell counts). A recent paper from the RESPOND cohort study confirmed our own findings that also in the current era, a significant association between CVD incidence and recent abacavir use continues to be visible and is not explained by preferential use of abacavir in individuals at increased CVD or CKD risk[38]. Apart from the association of incident CVD with abacavir-use, another recent paper from the RESPOND cohort study confirmed our finding that the use of integrase inhibitors was associated with an increased risk of incident CVD, although statistical power was low and potential for unmeasured confounding and channelling bias cannot fully be excluded[39].

Importantly, individuals who had initiated ART earlier after HIV acquisition (i.e. within 12 months of a last negative HIV test), had a significantly lower risk of type 2 diabetes mellitus (RR 0.63, 95% CI 0.42-0.94, p=0.023), independent of other traditional and HIV-related risk factors. The observation that the age-standardised incidence ratios for diabetes mellitus do not decline as much in women remains unexplained and needs further study – but the observed increasing average BMI and high (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[35,40,41]. Several of these risk factors are more prevalent among people with HIV[17].

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. 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[42]. 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[43]. 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 and CKD, but not cardiovascular disease and non-AIDS malignancies. Obese and overweight adults had a significantly lower risk of death than those with an ideal body weight, although this is likely biased by reverse causality, as body weight was included as a time-updated variable in our regression analyses. Currently, analyses are underway in our cohort to look in depth at the relationship between weight gain on ART and the use of specific antiretroviral drugs (the integrase strand transfer inhibitors and tenofovir alafenamide, in particular) while controlling for demographic characteristics, traditional risk factors, and confounders.

Renal insufficiency

Since 2008, there has been a steady increase in the incidence of new-onset chronic kidney disease (CKD). As expected, older individuals and those with traditional risk factors such as hypertension were found to be at increased risk of CKD, as were individuals with advanced immunodeficiency. In addition, other studies have also reported hepatitis B and C virus co-infection[44,45], and the use of tenofovir disoproxil fumarate, atazanavir/ritonavir and lopinavir/ritonavir, to be additional independent predictors of chronic renal impairment[46]. Moreover, renal impairment in the population with HIV is associated with an increased risk of cardiovascular disease[47]. The increase in CKD in our population appears to be largely caused by the increased use of dolutegravir, bictegravir, rilpivirine, and cobicistat, all of which cause reversible inhibition of tubular excretion of creatinine, without causing a true decrease in glomerular filtration.

Non-AIDS-defining malignancies

The most common non-AIDS-defining malignancies (NADM) in the Netherlands are lung, intestinal, anal, prostate, and head and neck cancers, as well as Hodgkin's lymphoma. Despite the increasing average age of the cohort, the crude incidence of NADM has remained stable over time, and we even observed a decline in age-standardised incidence of NADM in men, and to a lesser extent in women. In addition, our analyses showed that individuals diagnosed with NADM a more likely to be older. This is in line with data from other cohorts, including the Swiss HIV cohort and RESPOND cohort [48–52]. 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[53]. Importantly, individuals who had initiated ART earlier after HIV acquisition (i.e. within 12 months of a last negative HIV test), had a significantly lower risk of NADM (RR 0.62, 95% CI 0.43-0.88, p = 0.008), independent of other traditional and HIV-related risk factors.

Multimorbidity and polypharmacy

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

Polypharmacy, defined as the concomitant use of five or more medications in addition to ART, is also slowly becoming more prevalent, mainly because of the increased age of the cohort and the associated rise in the prevalence of age-associated, non-AIDS comorbidities. In 2000, 3.3% of adults used five or more non-antiretroviral comedications alongside their ART regimen, and this steadily increased to 17.8% of adults in active follow up in 2022. The main drivers behind this increase in polypharmacy are the increasing age of the population and the increase in the number of chronic comorbidities per individual. In adults receiving ART in the period 2007-2021, polypharmacy was also strongly and independently associated with an increased risk of death, independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities.

SARS-CoV-2 and COVID-19

In the first months of 2022 the number of registered SARS-CoV-2 infections and COVID-19-related hospitalizations peaked as the SARS-CoV-2 Omicron variant became dominant in the Netherlands. After the initial Omicron wave the number of registered infections and hospitalizations came down considerably. In 2021, 8 people with HIV were reported to have died as a direct consequence of COVID-19 in the Netherlands. The observed risk factors for severe COVID-19 (hospitalizations and mortality) have remained similar to the risk factors observed in the preceding period: general risk factors, like age, ethnicity and comorbidity continued to be the strongest risk factors for severe COVID-19 in people with HIV in the Netherlands in the Omicron era.

Recommendations

The proportion of individuals dying of AIDS in the Netherlands has markedly declined throughout the ART era, but in order to reach the goal of zero AIDS-deaths by 2027, it is imperative that individuals are identified sooner following infection and rapidly linked to care for an immediate start of ART. This can also be expected to beneficially impact the incidence of comorbidities for which advanced immunodeficiency is a contributing risk factor[54-56]. Of note, our own analyses show a markedly lower risk for non-AIDS malignancies in those who initiate ART within the first year of infection.

The relatively poor five-year survival rates following the diagnosis of several of the analysed non-AIDS-defining comorbidities, compared with survival of all people newly entering care with an AIDS diagnosis, underlines the importance of primary prevention, early diagnosis and aggressive pursuit of treatment and secondary prevention of non-AIDS comorbidities in the population with HIV. Studies in the Netherlands such as the ongoing Comorbidity and Aging with HIV ($AGE_{h}IV$) cohort study[57] and the 2000HIV cohort study[58] have provided further insights into the independent contribution of HIV and HIV-associated factors, such as innate and adaptive immune and coagulation activation, and inflammation. This will hopefully guide the development of interventions that target relevant pathophysiological mechanisms[10,59].

It is important to note that the risk of many, if not each, of the comorbidities frequently identified in people with HIV, is determined by multiple factors. Besides immunodeficiency, additional key contributors for consideration include both well-known traditional, unmodifiable, risk factors such as age and genetic predisposition, and modifiable lifestyle-related factors. But known and potentially unknown effects of antiretroviral therapy and co-infection are risk factors too.

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

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

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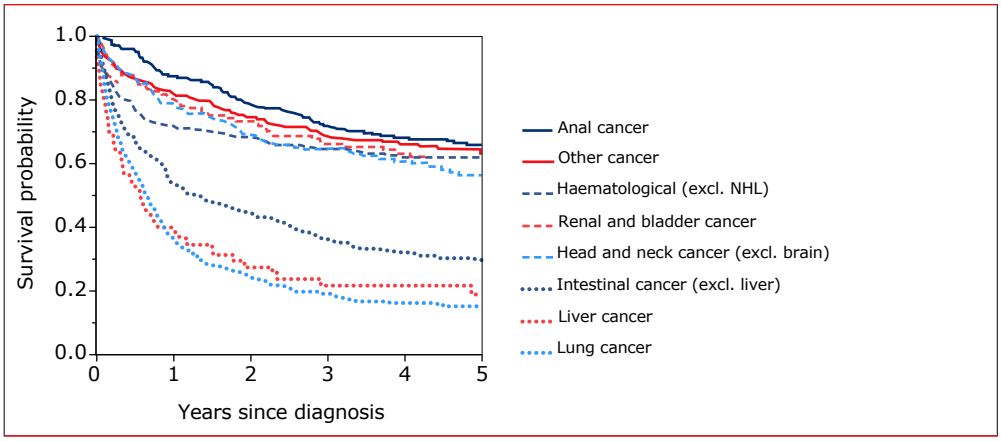
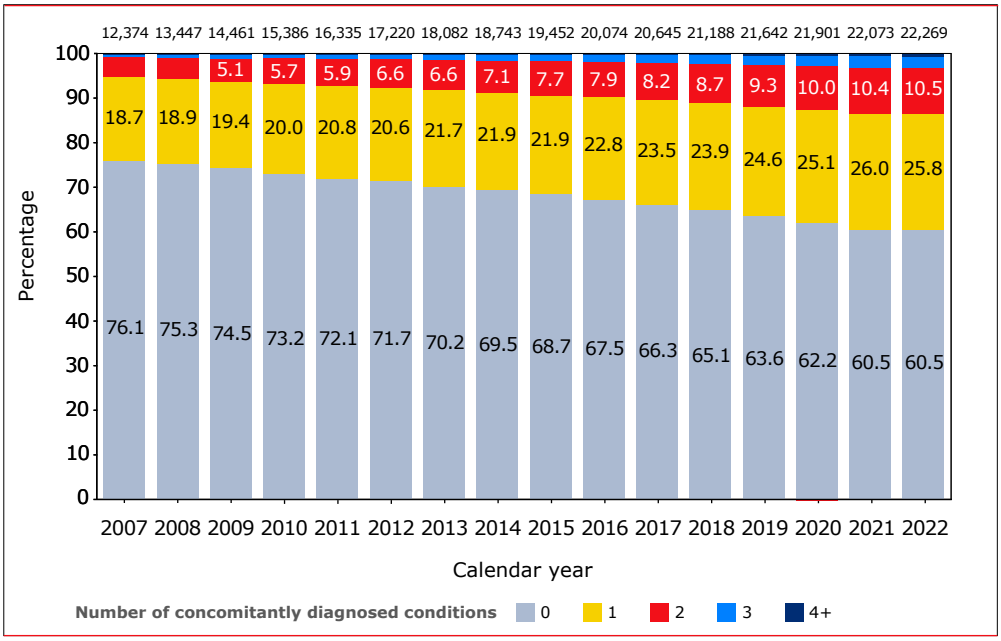
Appendix: supplementary figures and tables

Appendix Figure 3.1: Estimated five-year survival following the diagnosis of the most common non-AIDS-defining malignancies diagnosed between 1 January 2000 and 31 December 2022.

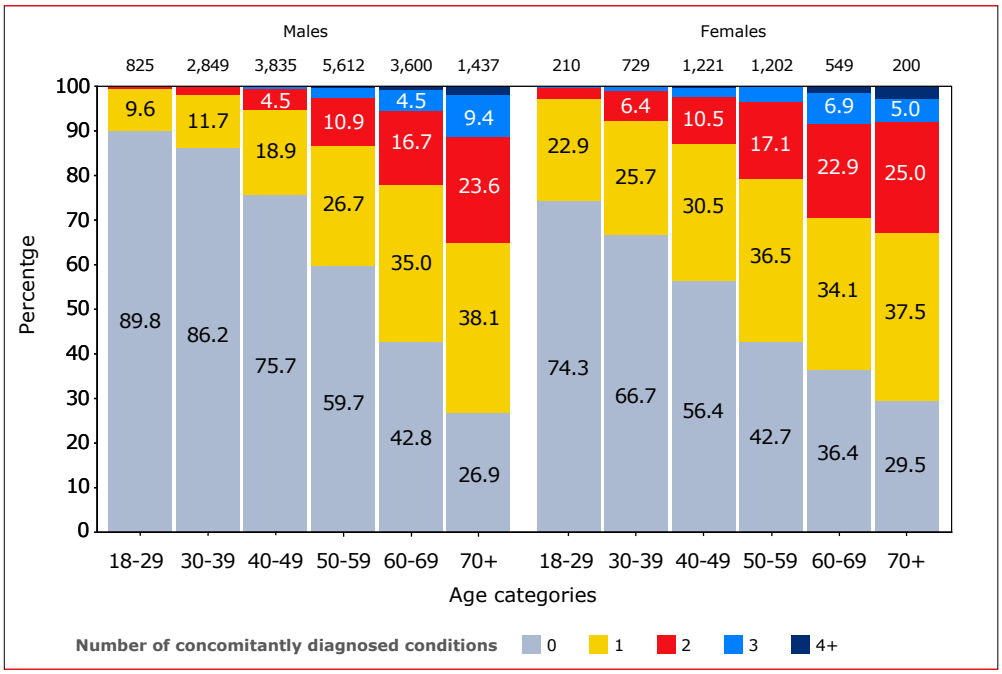


Legend: KM = Kaplan-Meier; excl. = excluding; NHL = non-Hodgkin's lymphoma.

Appendix Figure 3.2: Prevalence of non-AIDS multimorbidity in the adult population. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per calendar year.



Appendix Figure 3.3: *Prevalence of non-AIDS multimorbidity by gender in the adult population in 2022. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.*



Appendix Table 3.1: *Absolute number of causes of death among PWH during the periods 1996–2000, 2001–2005, 2006–2010, and 2011–2022.*

	Calendar period											
Causes of death	**96–00**	**01–05**	**06–10**	**11–15**	**16–22**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**
1. AIDS												
1.1 AIDS – infection	69	120	150	104	35	6	4	4	8	5	3	5
1.2 AIDS – malignancy	60	63	62	44	72	8	13	11	11	6	9	14
1.3 AIDS – unclassifiable	90	63	19	15	32	10	3	4	5	4	4	2
Subtotal	*219*	*246*	*231*	*163*	*139*	*24*	*20*	*19*	*24*	*15*	*16*	*21*
2. Non-AIDS malignancies	30	95	136	194	426	49	62	48	76	70	71	50
3. Cardiovascular disease												
3.1 Myocardial infarction	14	30	46	40	58	8	4	2	10	14	13	7
3.2 Stroke	3	11	13	11	34	7	3	3	2	3	7	9
3.3 Other CVD	6	24	26	50	98	16	10	16	10	11	16	19
Subtotal	*23*	*65*	*85*	*101*	*190*	*31*	*17*	*21*	*22*	*28*	*36*	*35*
4. Non-AIDS infection	23	42	32	27	83	7	3	10	8	16	30	9
5. Liver disease	15	28	55	43	31	6	7	8	.	2	4	4
6. Lung disease	7	11	30	38	80	13	14	9	16	7	11	10
7. Non-natural death												
7.1 Accident or violence	6	11	22	16	25	7	2	4	1	2	4	5
7.2 Suicide	12	30	30	52	67	10	12	11	5	14	8	7
7.3 Euthanasia	7	5	.	2	1	1	.	.	.	.	.	.
Subtotal	*25*	*46*	*52*	*70*	*93*	*18*	*14*	*15*	*6*	*16*	*12*	*12*
8. Alcohol and substance use	12	15	27	18	38	10	4	4	2	4	6	8
9. Other causes	21	24	23	43	101	13	8	18	10	14	21	17
10. Unknown	23	55	51	80	149	19	18	21	14	25	26	26
Total	**398**	**627**	**722**	**777**	**1,330**	**190**	**167**	**173**	**178**	**197**	**233**	**192**

Legend: *CVD = cardiovascular disease.*

Appendix Table 3.2: 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**
Male gender	1.25 (1.10-1.43)	<.001		1.03 (0.88-1.20)	0.753	
Region of birth						
Netherlands	1 (reference)		0.046	1 (reference)		0.106
Other	0.91 (0.83-1.00)	0.047		1.10 (0.98-1.23)	0.105	
HIV-1 transmission route						
Blood contact	0.88 (0.65-1.19)	0.408		0.78 (0.54-1.12)	0.173	
Heterosexual	1.12 (1.00-1.25)	0.043		0.93 (0.80-1.08)	0.338	
IDU	1.62 (1.36-1.93)	<.001		0.72 (0.56-0.92)	0.010	
MSM	1 (reference)		<.001	1 (reference)		0.045
Age *						
18-29	0.90 (0.66-1.23)	0.513	<.001	1.09 (0.89-1.34)	0.392	<.001
30-39	1 (reference)			1 (reference)		
40-49	1.57 (1.35-1.82)	<.001		1.08 (0.95-1.23)	0.229	
50-59	2.76 (2.39-3.20)	<.001		1.27 (1.10-1.46)	0.001	
60-69	5.01 (4.29-5.84)	<.001		1.32 (1.10-1.58)	0.003	
70+	11.62 (9.81-13.76)	<.001		2.02 (1.53-2.68)	<.001	
CD4 cell count **						
0-50	11.65 (9.78-13.87)	<.001	<.001	7.16 (5.80-8.84)	<.001	<.001
50-199	4.60 (4.05-5.21)	<.001		2.84 (2.42-3.33)	<.001	
200-349	1.92 (1.70-2.17)	<.001		1.52 (1.30-1.78)	<.001	
350-499	1.33 (1.17-1.50)	<.001		1.23 (1.05-1.44)	0.011	
500-749	1 (reference)			1 (reference)		
750+	0.84 (0.74-0.95)	0.007		1.07 (0.89-1.28)	0.457	
Per year longer on cART with HIV RNA>1000 cp/mL						
Treatment status	1.06 (1.04-1.07)	<.001	<.001	1.04 (1.02-1.07)	<.001	<.001
Treatment-experienced at start cART	0.95 (0.86-1.04)	0.265		0.64 (0.56-0.72)	<.001	
Treatment-naive at start	1 (reference)			1 (reference)		
Prior AIDS event	1.67 (1.54-1.81)	<.001				
Hepatitis B virus positive	1.23 (1.08-1.40)	0.002		1.08 (0.90-1.30)	0.398	
Hepatitis C virus positive	1.53 (1.34-1.75)	<.001		1.29 (1.08-1.55)	0.006	

			Death			AIDS
Risk factors	**RR (95%CI)**	**p-value**	**Overall p-value**	**RR (95%CI)**	**p-value**	**Overall p-value**
Body mass index *						
<18	3.14 (2.78-3.54)	<.001	<.001			
18-25	1 (reference)					
25-30	0.68 (0.62-0.75)	<.001				
30+	0.86 (0.74-1.00)	0.045				
Smoking status						
Current smoker	1.20 (1.07-1.34)	0.002	<.001	0.80 (0.71-0.90)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	1.96 (1.76-2.18)	<.001		1.02 (0.89-1.17)	0.762	
Early cART ***	0.79 (0.58-1.07)	0.124		1.21 (0.92-1.60)	0.181	

**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 3.3: *Lost to care (no follow up after 31 December 2020) by region of origin and time-updated CD4 cell count.*

	Total			Caribbean			Western Europe / North America		
Last CD4 count	**n**	**PY**	**Incidence/ 1,000 PY (95% CI)**	**n**	**PY**	**Incidence/ 1,000 PY (95% CI)**	**n**	**PY**	**Incidence/ 1,000 PY (95% CI)**
0–50	52	2,850	18.2 (13.6–23.9)	3	216	13.9 (2.9–40.6)	10	165	60.7 (29.1–111.7)
050–199	195	10,464	18.6 (16.1–21.4)	11	707	15.6 (7.8–27.9)	39	1,180	33.1 (23.5–45.2)
200–349	394	24,523	16.1 (14.5–17.7)	14	1,167	12.0 (6.6–20.1)	79	1,972	40.1 (31.7–49.9)
350–499	524	48,089	10.9 (10.0–11.9)	35	1,983	17.7 (12.3–24.6)	118	3,686	32.0 (26.5–38.3)
500–749	737	104908	7.0 (6.5–7.6)	54	5,387	10.0 (7.5–13.1)	194	8,502	22.8 (19.7–26.3)
750+	518	126974	4.1 (3.7–4.4)	31	6,747	4.6 (3.1–6.5)	168	11,429	14.7 (12.6–17.1)

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

	Netherlands			Sub-Saharan Africa			South and south-east Asia		
	n	PY	Incidence/ 1,000 PY (95% CI)	n	PY	Incidence/ 1,000 PY (95% CI)	n	PY	Incidence/ 1,000 PY (95% CI)
	4	1,750	2.3 (0.6–5.9)	29	593	48.9 (32.8–70.3)	6	127	47.4 (17.4–103.2)
	28	6,373	4.4 (2.9–6.3)	109	1,877	58.1 (47.7–70.1)	8	328	24.4 (10.5–48.0)
	74	15,685	4.7 (3.7–5.9)	202	4,721	42.8 (37.1–49.1)	25	979	25.5 (16.5–37.7)
	106	31,582	3.4 (2.7–4.1)	241	8,615	28.0 (24.6–31.7)	24	2,224	10.8 (6.9–16.1)
	211	71,148	3.0 (2.6–3.4)	258	15,525	16.6 (14.7–18.8)	20	4,346	4.6 (2.8–7.1)
	167	89,097	1.9 (1.6–2.2)	135	15,379	8.8 (7.4–10.4)	17	4,322	3.9 (2.3–6.3)

Appendix Table 3.4: *Absolute number of first AIDS events among PWH during the periods 1996–2000, 2001–2005, 2006–2010, 2011–2015 and 2016–2022.*

CDC event	1996–2000	2001–2005	2006–2010	2011–2015	2016–2019	2020–2022	Total	
	N	N	N	N	N	N	N	%
AIDS dementia complex – HIV encephalopathy	40	46	53	43	17	12	211	2.99
Bacterial pneumonia, recurring	48	66	67	78	81	27	367	5.19
CMV colitis/proctitis	1	.	1	2	3	1	8	0.11
CMV disease	27	34	29	34	3	.	127	1.80
CMV esophagitis	.	.	.	.	.	1	1	0.01
CMV meningo-encefalitis	.	.	.	.	1	.	1	0.01
CMV pneumonitis	.	.	.	.	11	15	26	0.37
CMV retinitis	30	20	12	13	11	1	87	1.23
Candidiasis esophagitis	264	237	254	224	114	73	1166	16.50
Candidiasis lungs/bronchial/trachea	7	13	7	6	5	4	42	0.59
Cervical cancer, invasive	3	5	6	4	4	1	23	0.33
Coccidioimycosis, extrapulmonary / disseminated	.	.	1	.	.	.	1	0.01
Cryptococcosis, extrapulmonary / disseminated	21	33	33	11	12	2	112	1.58
Cryptosporidiosis	22	12	11	13	2	2	62	0.88
Cystoisosporiasis	3	9	6	.	.	.	18	0.25
HIV wasting	48	54	76	77	53	24	332	4.70
HSV chronic ulcer	1	3	1	4	19	18	46	0.65
HSV esophagitis	.	.	.	.	.	2	2	0.03
HSV pneumonitis	.	.	.	.	.	1	1	0.01
Herpes simplex virus	32	41	59	38	8	.	178	2.52
Histoplasmosis, extrapulmonary / disseminated	9	12	10	7	2	1	41	0.58
Kaposi sarcoma	154	153	189	138	77	37	748	10.58
Leishmaniasis visceral	.	1	2	2	1	.	6	0.08
Microsporidiosis	11	1	3	1	.	1	17	0.24
Mycobacterium avium/kansasii, extrapulmonary / disseminated	26	20	28	9	7	1	91	1.29
Mycobacterium avium/kansasii, pulmonary	1	2	.	1	8	3	15	0.21
Mycobacterium other / unspecified, extrapulmonary / disseminated	20	13	8	10	2	1	54	0.76
Mycobacterium other / unspecified, pulmonary	.	3	5	9	4	1	22	0.31
Non-Hodgkin`s lymphoma (NHL)	57	88	79	99	55	28	406	5.75
Penicilliosis	.	.	1	.	.	.	1	0.01
Pneumocystis jirovecii extrapulmonary	1	1	3	.	1	.	6	0.08

CDC event	1996–2000	2001–2005	2006–2010	2011–2015	2016–2019	2020–2022	Total	
	N	N	N	N	N	N	N	%
Pneumocystis jirovecii pneumonia	331	302	327	268	165	96	1489	21.07
Primary CNS lymphoma	8	4	9	6	4	.	31	0.44
Progressive multifocal leukoencephalopathy	18	25	35	24	6	4	112	1.58
Salmonella sepsis, recurring	2	.	.	1	.	.	3	0.04
Toxoplasmosis of the brain	69	100	57	43	25	11	305	4.32
Tuberculosis, extrapulmonary / disseminated	80	114	81	55	22	15	367	5.19
Tuberculosis, pulmonary	105	177	118	80	47	15	542	7.67
Total	**1439**	**1589**	**1571**	**1300**	**770**	**398**	**7067**	**100**

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

Appendix Table 3.5: *Adjusted risk factors for non-AIDS-defining morbidity.*

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
Male gender	1.20 (1.08-1.32)	<.001	.	1.60 (1.34-1.90)	<.001	.
Region of birth						
Netherlands	1 (reference)	.	0.026	1 (reference)	.	0.466
Other	1.08 (1.01-1.16)	0.026	.	0.96 (0.86-1.07)	0.467	.
HIV-1 transmission route						
MSM	1 (reference)	.	<.001	1 (reference)	.	0.021
Heterosexual	1.17 (1.07-1.27)	<.001	.	1.18 (1.03-1.35)	0.014	.
IDU	1.30 (1.08-1.56)	0.005	.	1.21 (0.91-1.61)	0.188	.
Blood contact	1.16 (0.91-1.47)	0.227	.	1.15 (0.79-1.68)	0.458	.
Age *						
18-29	0.64 (0.49-0.83)	<.001	<.001	0.44 (0.23-0.82)	0.010	<.001
30-39	1 (reference)	.	.	1 (reference)	.	.
40-49	2.05 (1.81-2.31)	<.001	.	2.74 (2.17-3.46)	<.001	.
50-59	3.82 (3.38-4.31)	<.001	.	5.94 (4.73-7.46)	<.001	.
60-69	6.50 (5.70-7.41)	<.001	.	9.66 (7.60-12.28)	<.001	.
70+	10.27 (8.76-12.04)	<.001	.	16.21 (12.37-21.24)	<.001	.
CD4 cell count **						
0-50	3.95 (3.14-4.96)	<.001	<.001	2.79 (1.84-4.24)	<.001	<.001
050-199	1.71 (1.48-1.98)	<.001	.	1.42 (1.13-1.80)	0.003	.
200-349	1.23 (1.11-1.37)	<.001	.	1.25 (1.06-1.46)	0.008	.
350-499	1.04 (0.95-1.14)	0.396	.	1.02 (0.88-1.18)	0.789	.
500-749	1 (reference)	.	.	1 (reference)	.	.
750+	1.12 (1.04-1.22)	0.005	.	1.24 (1.10-1.40)	<.001	.
Per year longer with CD4<200 cells/mm^3	1.01 (0.99-1.03)	0.458	.	1.03 (1.00-1.06)	0.044	.
Prior AIDS event	1.21 (1.13-1.29)	<.001	.	1.16 (1.04-1.29)	0.007	.
Per year longer on cART while HIV RNA>1000 cp/mL	1.02 (1.00-1.03)	0.108	.	1.00 (0.97-1.03)	0.919	.
Treatment status						
Not (yet) started cART	1.19 (1.04-1.35)	0.009	<.001	1.06 (0.85-1.33)	0.605	0.031
Treatment-experienced at start cART	1.28 (1.17-1.40)	<.001	.	1.20 (1.05-1.37)	0.008	.
Treatment-naive at start	1 (reference)	.	.	1 (reference)	.	.
Per year longer on cART	1.00 (1.00-1.01)	0.196	.	1.00 (0.99-1.01)	0.995	.
Early cART within 12 months after last HIV-negat	0.80 (0.66-0.98)	0.030	.	1.06 (0.81-1.40)	0.669	.

Non-AIDS-defining malignancy			Diabetes mellitus			CKD		
IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
0.99 (0.84-1.18)	0.929	.	1.21 (1.04-1.40)	0.013	.	0.63 (0.55-0.72)	<.001	.
1 (reference)	.	0.004	1 (reference)	.	<.001	1 (reference)	.	<.001
0.84 (0.75-0.95)	0.004	.	1.53 (1.37-1.71)	<.001	.	0.77 (0.70-0.85)	<.001	.
1 (reference)	.	0.020	1 (reference)	.	<.001	1 (reference)	.	0.028
0.98 (0.85-1.13)	0.782	.	1.39 (1.22-1.60)	<.001	.	0.99 (0.88-1.12)	0.913	.
1.35 (1.02-1.78)	0.035	.	1.50 (1.08-2.07)	0.014	.	1.53 (1.18-1.98)	0.001	.
1.34 (0.95-1.90)	0.099	.	1.43 (1.00-2.04)	0.051	.	1.18 (0.87-1.62)	0.293	.
0.85 (0.53-1.35)	0.482	<.001	0.64 (0.45-0.93)	0.019	<.001	0.34 (0.15-0.74)	0.007	<.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
2.38 (1.89-3.00)	<.001	.	1.55 (1.30-1.84)	<.001	.	3.05 (2.32-4.02)	<.001	.
4.60 (3.66-5.78)	<.001	.	2.44 (2.04-2.92)	<.001	.	8.53 (6.55-11.12)	<.001	.
9.60 (7.58-12.16)	<.001	.	3.75 (3.07-4.58)	<.001	.	23.18 (17.77-30.24)	<.001	.
16.93 (13.02-22.01)	<.001	.	4.17 (3.18-5.48)	<.001	.	41.00 (30.95-54.30)	<.001	.
3.42 (2.27-5.16)	<.001	<.001	5.79 (4.15-8.06)	<.001	<.001	1.67 (0.94-2.98)	0.083	<.001
1.96 (1.56-2.47)	<.001	.	1.79 (1.42-2.27)	<.001	.	1.58 (1.27-1.97)	<.001	.
1.36 (1.16-1.60)	<.001	.	1.11 (0.93-1.32)	0.255	.	1.19 (1.03-1.38)	0.015	.
1.08 (0.94-1.24)	0.290	.	1.02 (0.88-1.19)	0.779	.	1.04 (0.93-1.17)	0.470	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
0.92 (0.81-1.05)	0.201	.	1.23 (1.08-1.40)	0.002	.	0.94 (0.85-1.04)	0.234	.
1.00 (0.97-1.02)	0.788	.	1.00 (0.97-1.03)	0.930	.	0.99 (0.97-1.02)	0.515	.
1.14 (1.03-1.28)	0.014	.	1.29 (1.15-1.44)	<.001	.	1.13 (1.04-1.24)	0.006	.
1.00 (0.97-1.03)	0.833	.	0.99 (0.96-1.02)	0.340	.	0.98 (0.95-1.01)	0.127	.
1.23 (0.99-1.53)	0.063	0.023	1.49 (1.21-1.83)	<.001	<.001	0.38 (0.27-0.55)	<.001	<.001
1.17 (1.01-1.34)	0.031	.	1.31 (1.13-1.52)	<.001	.	1.18 (1.04-1.34)	0.012	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
1.00 (0.99-1.01)	0.659	.	1.01 (1.00-1.02)	0.055	.	0.98 (0.97-0.99)	<.001	.
0.62 (0.43-0.88)	0.008	.	0.63 (0.42-0.94)	0.023	.	0.98 (0.80-1.21)	0.863	.

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
Body mass index *						
0-18	1.51 (1.26-1.81)	<.001	<.001	1.18 (0.88-1.59)	0.266	0.011
18-25	1 (reference)	.	.	1 (reference)	.	.
25-30	1.23 (1.14-1.32)	<.001	.	1.02 (0.91-1.14)	0.739	.
30+	2.07 (1.89-2.28)	<.001	.	1.25 (1.05-1.47)	0.010	.
Hepatitis B virus positive	1.22 (1.09-1.36)	<.001	.	0.98 (0.81-1.19)	0.844	.
Hepatitis C virus positive	1.05 (0.94-1.18)	0.399	.	1.05 (0.88-1.25)	0.595	.
Hypertension	1.14 (1.07-1.21)	<.001	.	1.23 (1.11-1.35)	<.001	.
Smoking status						
Current smoker	1.37 (1.27-1.48)	<.001	<.001	1.82 (1.61-2.06)	<.001	<.001
Never smoker	1 (reference)	.	.	1 (reference)	.	.
Past smoker	1.38 (1.28-1.50)	<.001	.	1.49 (1.31-1.70)	<.001	.
Calendar year period						
2000-2010	1.28 (1.17-1.40)	<.001	<.001	1.68 (1.43-1.98)	<.001	<.001
2011-2015	1.17 (1.08-1.26)	<.001	.	1.34 (1.16-1.55)	<.001	.
2016-2022	1 (reference)	.	.	1 (reference)	.	.
Recent use of ABC ***		.	.	1.49 (1.33-1.68)	<.001	.
Per year longer on LOP/r		.	.	1.00 (0.99-1.01)	0.425	.
Per year longer on IDV		.	.	1.00 (0.99-1.01)	0.828	.
Current use of bictegravir		.	.	1.24 (0.91-1.67)	0.171	.
Current use of dolutegravir		.	.	1.40 (1.19-1.64)	<.001	.
Current use of elvitegravir		.	.	1.03 (0.81-1.30)	0.828	.
Current use of raltegravir		.	.	1.82 (1.51-2.19)	<.001	.
Per year longer on ZDV		.	.		.	.
Per year longer on d4T		.	.		.	.
Per year longer on ddI		.	.		.	.
Per year longer on TAF		.	.		.	.
Per year longer on TDF		.	.		.	.
Prior cardiovascular event		.	.		.	.
Prior diabetes		.	.		.	.
Current use of cobicistat		.	.		.	.
Current use of rilpivirine		.	.		.	.

**Time-updated.*

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

****Current use or recently used in the past six months.*

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

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

Appendix Table 3.6: *Specific CDC-B and CDC-C (AIDS) events occurring in individuals on ART with undetectable viral load between 2000 and 2022.*

		All events		0-50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Aspergillosis, invasive pulmonary	12	0.4%	1	0.4%
	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis oropharyngeal	833	26.1%	71	27.3%
	Candidiasis vulvovaginal, frequent/persistent	56	1.8%	1	0.4%
	Cardiomyopathy, HIV-related	6	0.2%	0	0.0%
	Cardiomyopathy, with HIV-related component	21	0.7%	1	0.4%
	Diarrhea, HIV-related >=30 days	63	2.0%	1	0.4%
	Fever e.c.i. / HIV-related	6	0.2%	0	0.0%
	HIV-associated nephropathy (HIVAN)	22	0.7%	1	0.4%
	Herpes zoster, multidermatomal	24	0.8%	3	1.2%
	Herpes zoster, recurring / multidermatomal unspecified	202	6.3%	6	2.3%
	Herpes zoster, unidermatomal recurrent	45	1.4%	3	1.2%
	Listeriosis	1	0.0%	0	0.0%
	Myelopathy, HIV-related	10	0.3%	0	0.0%
	Neuropathy, HIV-related	117	3.7%	2	0.8%
	Neuropathy, with HIV-related component	101	3.2%	2	0.8%
	Nocardiosis	2	0.1%	1	0.4%
	Oral Hairy Leucoplakia (OHL)	55	1.7%	1	0.4%
	Pelvic inflammatory disease	9	0.3%	0	0.0%
	Thrombocytopenia, HIV-related	116	3.6%	4	1.5%
	Thrombocytopenia, with HIV-related component	20	0.6%	3	1.2%
	Weight loss >10%, HIV-related / unknown cause	35	1.1%	2	0.8%
Subtotal		1757	55.0%	103	39.6%

CD4 category										
	050–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
3	0.5%	1	0.2%	1	0.2%	3	0.5%	3	0.7%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
200	32.6%	162	25.0%	137	22.9%	152	23.0%	111	26.7%
5	0.8%	9	1.4%	18	3.0%	18	2.7%	5	1.2%
2	0.3%	0	0.0%	2	0.3%	1	0.2%	1	0.2%
4	0.7%	2	0.3%	2	0.3%	8	1.2%	4	1.0%
6	1.0%	16	2.5%	10	1.7%	22	3.3%	8	1.9%
1	0.2%	2	0.3%	0	0.0%	1	0.2%	2	0.5%
4	0.7%	3	0.5%	5	0.8%	4	0.6%	5	1.2%
0	0.0%	5	0.8%	2	0.3%	9	1.4%	5	1.2%
24	3.9%	50	7.7%	44	7.4%	48	7.3%	30	7.2%
6	1.0%	3	0.5%	4	0.7%	13	2.0%	16	3.8%
0	0.0%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
4	0.7%	2	0.3%	0	0.0%	1	0.2%	3	0.7%
8	1.3%	15	2.3%	29	4.8%	37	5.6%	26	6.3%
9	1.5%	11	1.7%	27	4.5%	33	5.0%	19	4.6%
0	0.0%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
13	2.1%	12	1.9%	9	1.5%	11	1.7%	9	2.2%
0	0.0%	4	0.6%	0	0.0%	3	0.5%	2	0.5%
22	3.6%	27	4.2%	24	4.0%	27	4.1%	12	2.9%
2	0.3%	9	1.4%	0	0.0%	5	0.8%	1	0.2%
5	0.8%	8	1.2%	6	1.0%	8	1.2%	6	1.4%
319	52.0%	343	52.9%	320	53.5%	404	61.0%	268	64.4%

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
CDC-C events	AIDS dementia complex – HIV encephalopathy	46	1.4%	5	1.9%
	Bacterial pneumonia, recurring	334	10.4%	14	5.4%
	CMV disease	19	0.6%	4	1.5%
	CMV esophagitis	2	0.1%	1	0.4%
	CMV pneumonitis	1	0.0%	0	0.0%
	CMV retinitis	19	0.6%	4	1.5%
	Candidiasis esophagitis	255	8.0%	25	9.6%
	Candidiasis lungs/bronchial/trachea	11	0.3%	2	0.8%
	Cervical cancer, invasive	13	0.4%	1	0.4%
	Coccidioimycosis, extrapulmonary / disseminated	1	0.0%	0	0.0%
	Cryptococcosis, extrapulmonary / disseminated	16	0.5%	6	2.3%
	Cryptosporidiosis	11	0.3%	4	1.5%
	Cystoisosporiasis	2	0.1%	0	0.0%
	HIV wasting	17	0.5%	5	1.9%
	HSV chronic ulcer	38	1.2%	2	0.8%
	HSV esophagitis	2	0.1%	0	0.0%
	HSV pneumonitis	2	0.1%	0	0.0%
	Herpes simplex virus	61	1.9%	6	2.3%
	Histoplasmosis, extrapulmonary / disseminated	4	0.1%	3	1.2%
	Kaposi sarcoma	122	3.8%	8	3.1%
	Leishmaniasis visceral	5	0.2%	1	0.4%
	Microsporidiosis	5	0.2%	2	0.8%
	Mycobacterium avium/kansasii, extrapulmonary / disseminated	25	0.8%	5	1.9%
	Mycobacterium avium/kansasii, pulmonary	3	0.1%	0	0.0%
	Mycobacterium other / unspecified, extrapulmonary / disseminated	10	0.3%	3	1.2%
	Mycobacterium other / unspecified, pulmonary	5	0.2%	0	0.0%
	Non-Hodgkin`s lymphoma (NHL)	164	5.1%	7	2.7%
	Pneumocystis jirovecii extrapulmonary	1	0.0%	0	0.0%
	Pneumocystis jirovecii pneumonia	73	2.3%	23	8.8%
	Primary CNS lymphoma	6	0.2%	1	0.4%
	Progressive multifocal leukoencephalopathy	20	0.6%	6	2.3%
	Toxoplasmosis of the brain	22	0.7%	9	3.5%
	Tuberculosis, extrapulmonary / disseminated	51	1.6%	4	1.5%
	Tuberculosis, pulmonary	74	2.3%	6	2.3%
Subtotal		**1440**	**45.0%**	**157**	**60.4%**
Total		**3197**	**100.0%**	**260**	**100.0%**

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

CD4 category									
050–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
6	1.0%	8	1.2%	11	1.8%	8	1.2%	8	1.9%
53	8.6%	79	12.2%	83	13.9%	68	10.3%	37	8.9%
1	0.2%	4	0.6%	6	1.0%	1	0.2%	3	0.7%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
4	0.7%	6	0.9%	4	0.7%	1	0.2%	0	0.0%
63	10.3%	55	8.5%	43	7.2%	41	6.2%	28	6.7%
1	0.2%	5	0.8%	1	0.2%	1	0.2%	1	0.2%
3	0.5%	1	0.2%	2	0.3%	5	0.8%	1	0.2%
0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
5	0.8%	3	0.5%	1	0.2%	1	0.2%	0	0.0%
0	0.0%	1	0.2%	3	0.5%	2	0.3%	1	0.2%
1	0.2%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
8	1.3%	1	0.2%	2	0.3%	1	0.2%	0	0.0%
7	1.1%	4	0.6%	3	0.5%	14	2.1%	8	1.9%
1	0.2%	0	0.0%	1	0.2%	0	0.0%	0	0.0%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	0.5%
6	1.0%	13	2.0%	17	2.8%	15	2.3%	4	1.0%
0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
11	1.8%	27	4.2%	28	4.7%	32	4.8%	16	3.8%
3	0.5%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
2	0.3%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
10	1.6%	5	0.8%	3	0.5%	1	0.2%	1	0.2%
0	0.0%	1	0.2%	0	0.0%	1	0.2%	1	0.2%
3	0.5%	3	0.5%	0	0.0%	1	0.2%	0	0.0%
2	0.3%	0	0.0%	2	0.3%	1	0.2%	0	0.0%
42	6.9%	39	6.0%	37	6.2%	27	4.1%	12	2.9%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
24	3.9%	11	1.7%	7	1.2%	6	0.9%	2	0.5%
2	0.3%	2	0.3%	1	0.2%	0	0.0%	0	0.0%
6	1.0%	4	0.6%	2	0.3%	2	0.3%	0	0.0%
7	1.1%	4	0.6%	1	0.2%	1	0.2%	0	0.0%
10	1.6%	7	1.1%	5	0.8%	13	2.0%	12	2.9%
13	2.1%	21	3.2%	15	2.5%	12	1.8%	7	1.7%
294	**48.0%**	**305**	**47.1%**	**278**	**46.5%**	**258**	**39.0%**	**148**	**35.6%**
613	**100.0%**	**648**	**100.0%**	**598**	**100.0%**	**662**	**100.0%**	**416**	**100.0%**

4. Viral hepatitis

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

Background

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

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

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

glomerulonephritis, and thrombocytopenia)[18]. HEV infection is thought to persist and develop into chronic infection in immunocompromised individuals, who are then at increased risk of developing ongoing symptoms[15].

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

Hepatitis C virus (HCV)

Box 4.1: Definitions of hepatitis C infection.

Primary HCV infection
First documented HCV infection.

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

Acute HCV infection[19,20]

1. Case definition of acute HCV according to preferred criteria[19]:
   Positive anti-HCV IgG with a documented negative anti-HCV IgG within the past 12 months,
   or:
   detectable HCV RNA in the presence of either a documented negative HCV RNA test, or a documented anti-HCV IgG seroconversion within the past 12 months.
2. Case definition of acute HCV according to alternative criteria[19]:
   Detectable HCV RNA in association with a rise in alanine aminotransferase (ALT) (above 200 IU/l) with a documented normal ALT within the past 12 months.

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

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

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

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

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

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

HCV screening over time

In the Netherlands the national guidelines for the treatment and monitoring of HIV recommend HCV screening during the first clinical visit after HIV diagnosis, and additional annual HCV screening for MSM who report behaviour associated with increased risk of acquiring HCV[21]. Screening for HCV among the individuals with HIV ever registered with stichting HIV monitoring (shm) has increased over calendar time. Of the 30,050[a] individuals ever registered in the shm database, 96% have been screened at least once for HCV; anti-HCV or HCV RNA. In 2000, 27% of the individuals with HIV in care had never been screened for the presence of HCV infection in that

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.

specific calendar year. However, over time, a strong and steady increase in the percentage of individuals with a known HCV status has been observed and in 2022, only 1.5% of the individuals in care had never been screened for HCV co-infection (Figure 4.1A). In all years, including 2022, unknown HCV status was relatively more common among individuals with heterosexually-acquired HIV (2.8%), or with another or unknown mode of HIV acquisition (3.4%), and relatively less common among MSM (0.7%) and people who inject drugs (PWID) or former PWID (1.8%).

Follow-up screening

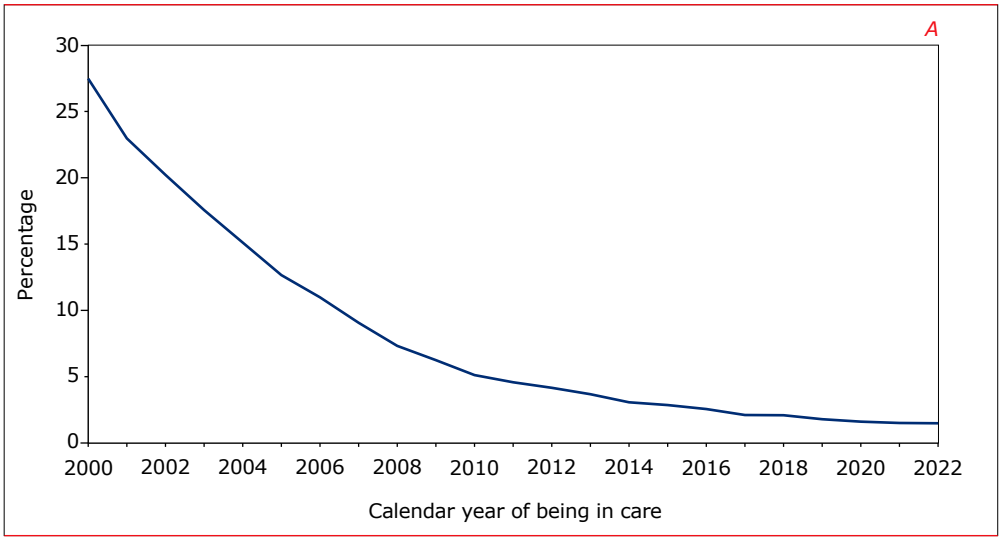
Among individuals who had a negative first HCV test and who remained in care for at least one year, 79% had a second HCV test at some point during follow up. This proportion was highest for MSM, of whom 87% had a second HCV test, and lowest for individuals who acquired HIV through heterosexual contact (63%).

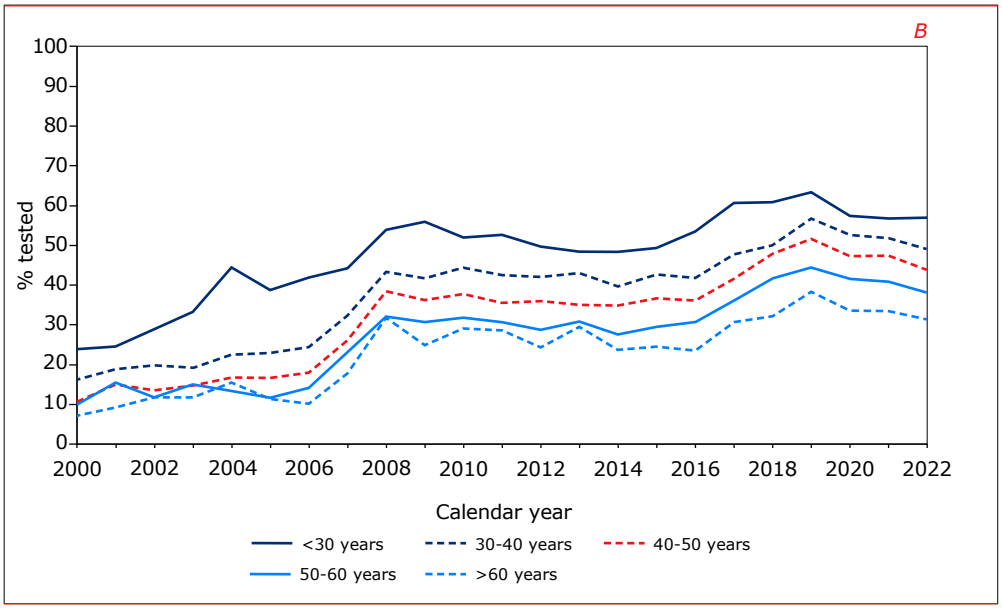
As most HCV infections are observed among MSM[22], the following analysis on testing frequency is reported for MSM only. Overall, the percentage of HCV seronegative MSM with at least one HCV test in a calendar year increased over time, from 13% in 2000 to 48% in 2019. However, testing frequency among HCV seronegative MSM decreased to 43% in 2021 and 40% in 2022. When testing was stratified by age, the highest percentage of testing was seen among MSM under 30 years of age, and testing decreased with increasing age (Figure 4.1B). Nevertheless, the median age for diagnosis of recent HCV was 43 years (IQR 36-50) (Table 4.2a), while in the age range 40-50 years, 44% had at least one test in 2022.

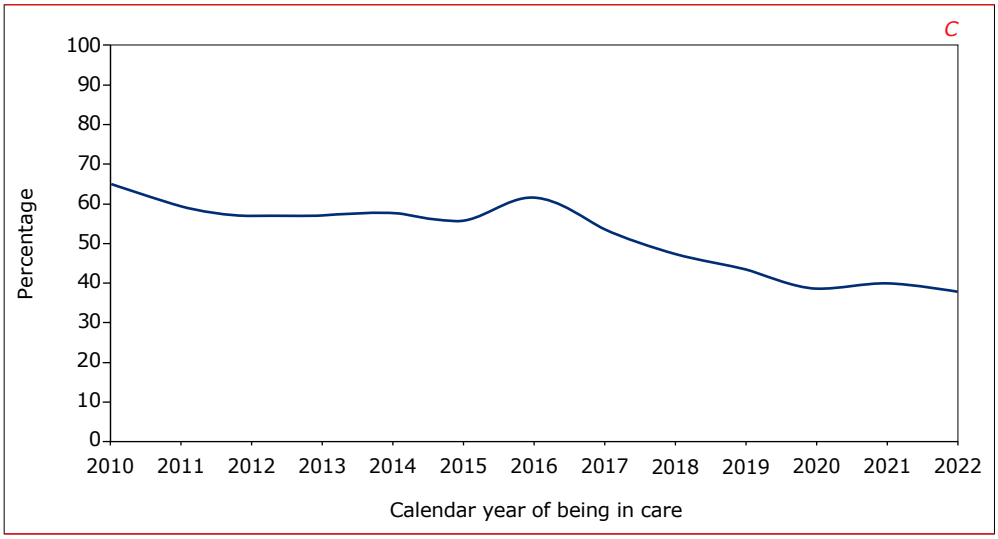
Screening for HCV RNA among those at risk of HCV reinfection is an important factor in identifying HCV reinfection. Among MSM with HIV at risk of reinfection after treatment-induced, or spontaneous clearance of HCV, the percentage of men with an HCV RNA test during a calendar year varied between 54% and 65% in 2010-16, but declined to 37% in 2020, and 38% in 2022 (Figure 4.1C). It is worth noting that these data may include MSM who are not considered at risk of HCV reinfection by their treating physician, as data on HCV-related risk-taking behaviour are not available to shm. Also of note is that repeated HCV screening among MSM at risk of HCV reinfection might be guided by a policy of targeted screening, based on the presence of incident transaminase elevations as an indicator of liver damage. This might be reflected by the observed higher proportion of repeated HCV screening among MSM with elevated transaminase levels (an increase of at least 50% compared to the last measured ALT value). In those at risk of HCV reinfection and incident transaminase elevations, the overall percentage of men with an HCV test following this elevated transaminase level was 70% in 2012-2022[b] (Figure 4.1D).

b Transaminase data became routinely available from 2012 onwards.

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



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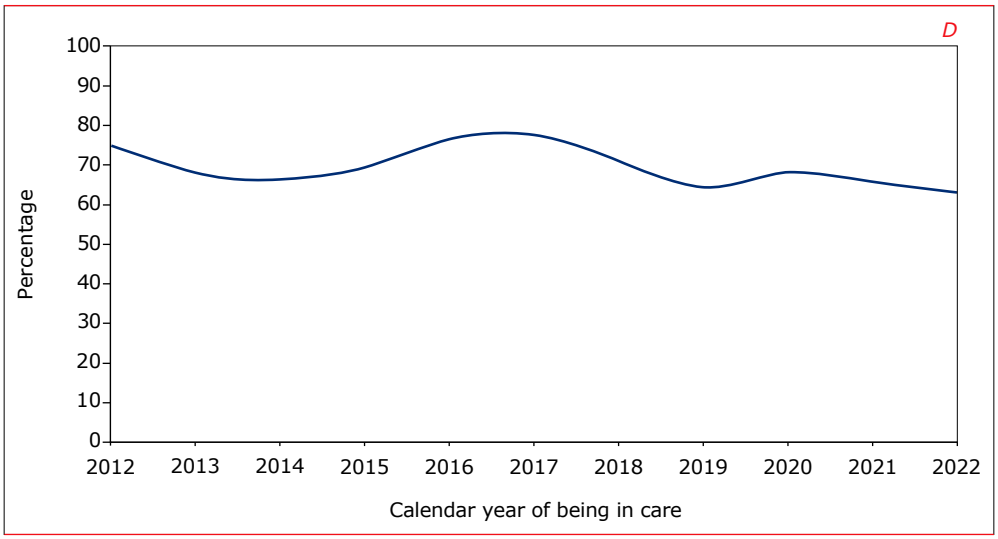
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Individuals with HCV

As of May 2023, 30,050 adults (aged 15 years or older at the time of their HIV-1 diagnosis) had been registered by stichting HIV monitoring. Of those individuals, 28,822 (96%) were ever screened for HCV co-infection and had been in care at one of the HIV treatment centres: 3,285 (11%) had a positive result with an HCV antibody test and/or HCV RNA test. This confirms that HCV is far more prevalent among the population with HIV than is estimated to be the case among the general Dutch population (Figure 4.2). HCV RNA data were not documented in 198 of the 3,285 cases (6%), of whom:

- 115 have died;
- 26 have been lost to care;
- 14 have moved abroad; and
- 43 do not have a known reason for an undocumented HCV RNA outcome.

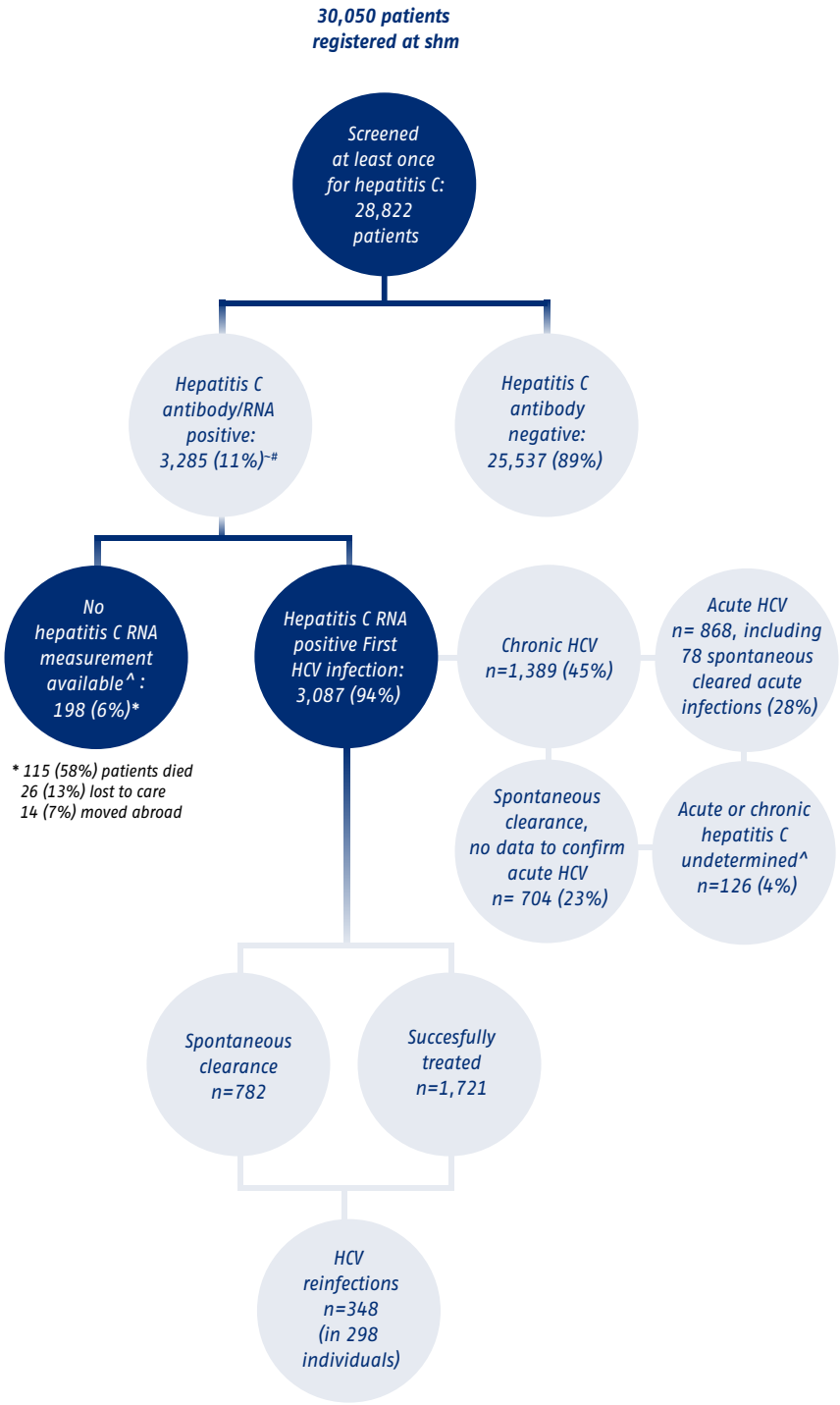
In total, 3,087 individuals were diagnosed with an HCV infection, with documented HCV RNA data for:

- 1,389 (44%) who were classified as having a chronic HCV infection at the time of their diagnosis.
- 868 (28%) who were initially diagnosed with an acute HCV infection, of whom;
  - 78 spontaneously cleared their infection
  - 790 became chronic HCV infections or were treated within 6 months of diagnosis.
- 704 (20%) who had evidence of spontaneous clearance of HCV but could not be classified as having an recent HCV infection at the time of their HCV diagnosis.

The remaining 126 individuals with available HCV RNA data had one positive HCV RNA test result, but no registered follow-up results, rendering it impossible to determine whether their HCV infection was acute or chronic at the time of diagnosis. This group of individuals has therefore been excluded from the analysis. The majority (n=97) of individuals with no HCV follow-up data were no longer in care in 2022. Of those still in care, 34% recently entered care in the Netherlands from Ukraine in 2022.

In total, 1,721 of the individuals with a primary HCV infection had a treatment-induced clearance of their primary HCV infection (including old and new treatment regimens). Another 782 individuals spontaneously cleared their primary HCV infection. In total, 348 HCV reinfections occurred in 298 individuals.
The majority (79%) of those with a primary infection who are not at risk of an HCV reinfection (i.e., those without SVR or spontaneous clearance of HCV) are no longer in care. The paragraph describing the continuum of HCV care gives more detail on those who remain in care, without clearance of their HCV infection.

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



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

Spontaneous clearance of HCV

In total, 782 individuals spontaneously cleared their HCV infection. Among the 868 individuals with primary recent hepatitis, 78 (9%) cases of spontaneous clearance were observed. Another 704 cases of spontaneous clearance were observed among individuals who could not be classified as having a primary acute infection. Compared to all individuals with HCV, those with spontaneous clearance of HCV were more likely to be female, less likely to be Dutch, and more likely to be from sub-Saharan Africa (p<0.001) (Table 4.1).

Table 4.1: *Demographic characteristics of individuals with HIV/hepatitis C virus (HCV) and those who spontaneously cleared HCV registered in the shm database, 1998-2022.*

	Total with HCV	Spontaneous clearance
Total number of individuals	2,961	782
Age at HCV diagnosis (median, IQR)	40 (34-47)	41 (35-48)
HCV status		
Chronic HCV	1,389	
Recent HCV without spontaneous clearance	790	
Spontaneous clearance	782	
Definitive clearance		312
Possible clearance		392
Spontaneous clearance after confirmed primary recent infection		78
Male gender, n (%)	2533 (86)	622 (80)
Region, n (%)		
The Netherlands	1741 (59)	374 (48)
Europe	366 (12)	93 (12)
Sub-Saharan Africa	124 (4)	64 (8)
Caribbean/South America	232 (8)	86 (11)
Southeast Asia	96 (3)	25 (3)
Other	402 (14)	140 (18)
HIV transmission route, n (%)		
Men who have sex with men	1,715 (58)	401(51)
Heterosexual	343 (12)	143 (18)
People who use/used injecting drugs	604 (20)	136 (17)
Other	299(10)	102 (13)
ART, n (%)	2874 (97)	756(97)
Deaths, n (%)	533 (18%)	118 (15)

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

In total, 2,257 individuals could be definitively classified as having either chronic (n=1,389), or recent (n=868) HCV infection at the time of their primary HCV diagnosis. Most of these were male (81% and 99%, respectively), and the majority originated from the Netherlands (chronic: 763/1,389 [55%]; recent: 661/868 [76%]) (Table 4.2a). Fifty-seven percent of the registered individuals who acquired HIV through injecting drug use (IDU), had chronic HCV (462 of the total 812 people who use/used injecting drugs [PWID]). Among MSM (17,314), 3% (571) had chronic HCV and 5% (816) had documented recent HCV.

The HCV genotype was determined and documented in the clinical records of 1,259 of the 1,389 (91%) individuals with chronic HCV. Of the individuals with a genotype determination:

- 62% (n=776) harboured HCV genotype 1, spread across 61% (n=474) with type 1a and 14% (n=111) with type 1b. For 25% (n=191) of those with genotype 1, the subtype was not further specified.
- 5% (n=59) harboured HCV genotype 2
- 18% (222) harboured HCV genotype 3
- 16% (n=200) harboured HCV genotype 4

HCV genotype was also documented for 796 of the 868 (92%) individuals with recent HCV. They were most likely to harbour either genotype 1 (71%, n=565) or genotype 4 (21%, n=169). Of the 565 with genotype 1, 85% (n=479) harboured genotype 1a and 4% (n=24) with genotype 1b. For 11% of the people with genotype 1, the subtype was not further specified.

New HCV diagnoses in 2022

In 2022, 57 individuals were newly diagnosed with primary HCV, of whom 49 (86%) had detectable HCV RNA (table 4.2b). Eight individuals had an HCV antibody positive test result, without an HCV RNA test result at time of database closure. Of these 57 individuals with a primary HCV diagnosis in 2022, 16% were born in the Netherlands and 68% were born in Eastern or central Europe.

In terms of HIV risk group for all 57 diagnoses of primary HCV in 2022, 28% were MSM, 26% acquired HIV through heterosexual contact, 26% were PWID and 19% of the individuals had an unknown or other reported mode of HIV transmission. The modes of HCV acquisition were mostly unknown for those who acquired HIV through heterosexual contact.

All PWID with a new HCV diagnosis in 2022 migrated from Eastern or Central Europe. The HCV genotype was determined and documented for 31 of the 57 (54%) individuals with a primary HCV diagnosis in 2022. Of the individuals with a genotype determination:

- 26% (n=8) had genotype 1a,
- 16% (n=5) had genotype 1b,
- 32% (n=10) had HCV genotype 3a, and
- 26% (n=8) had HCV genotype 4d.

At time of database closure, 19 individuals were known to have started HCV treatment, predominantly with glecaprevir/pibrentasvir.

Primary HCV diagnoses and entry into care in 2022

Forty-one of the 57 individuals with a primary HCV diagnosis in 2022 newly entered into HIV care in 2022, of whom 37 (90%) had an HCV RNA positive test result. The majority were male (71%), and all individuals were born abroad, the majority of migrants arrived from Eastern and Central Europe (n=33, 80%) (table 4.2b).

Table 4.2a: Demographic characteristics of individuals with HIV/hepatitis C virus (HCV) registered in the shm database, 1998-2022.

	Total	Chronic HCV	Recent HCV
Total number of individuals screened for HCV	28,822	1,389(5)	868 (3)
Age at HCV diagnosis (median, IQR)	40 (34-47)	39 (33-45)	43 (36-50)
Male gender, n (%)	23,594 (82)	1,128 (81)	858 (99)
Region of origin, n (%)			
Netherlands	15,297(53)	763 (55)	661 (76)
Europe	1,906 (7)	210 (15)	70 (8)
Sub-Saharan Africa	3,803 (13)	50 (4)	11 (1)
Caribbean/South America	3,784 (13)	94 (7)	55 (6)
Southeast Asia	1,044 (4)	47 (3)	26 (3)
Other	2,988 (10)	225 (16)	45 (5)
HIV transmission route, n (%)			
Men who have sex with men	17,314 (60)	571 (41)	816 (94)
Heterosexual	8,381 (29)	173 (13)	31 (3)
People who use/used injecting drugs	812 (3)	462 (33)	7(1)
Other	2,315 (8)	183 (13)	14 (2)
ART, n (%)	27,971 (97)	1,333 (96)	863 (99.4)
HCV genotype (GT), n (%*)			
Total determined		1,259 (91)	796 (92)
GT 1		776 (62)	565 (71)
1a		*474*	*479*
1b		*111*	*24*
1c, 1a/b or not further specified		*191*	*62*
GT 2		59 (5)	39 (5)
GT 3		222 (18)	22 (3)
GT 4		200 (16)	169 (21)
GT 5 & 6		2 (0.1)	1 (<1)
Deaths, n (%)	3,528(12)	363 (26)	58 (7)

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

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

Table 4.2b: Demographic characteristics of individuals with a primary HCV diagnosis in 2022.

	Primary HCV diagnoses in 2022	Primary HCV diagnoses with entry into care in 2022
Positive HCV test result	57	41
Positive HCV RNA test result	49 (86%)	37 (90%)
Acute or chronic hepatitis C undetermined		
Calendar year of entering HIV care		
Before 2022	16 (28%)	-
In 2022	41 (72%)	41
Age at HCV diagnosis (median, IQR)	44 (39-51)	41 (39-50)
Male gender, n (%)	42 (74%)	29 (71%)
Region of origin, n (%)		
The Netherlands	9 (16%)	*
Eastern & central Europe	39 (68%)	33 (80%)
Western Europe	0	0
Other	9 (16%)	8(20%%)*
HIV transmission route, n (%)		
Men who have sex with men	16 (28%)	6(15%)
Heterosexual	15 (26%)	11(27%)
People who use/used injecting drugs	15 (26%)	14 (34%)
Other or unknown	11 (19%)	10 (24%)
ART, n (%)	53 (93%)	37 (90%)
HCV genotype, n (%*)		
Total determined	31 (54%)	23 (56%)
1a	8	6
1b	5	3
3a	10	9
4d	8	5

**Due to small numbers the Netherlands is included in the category other.*

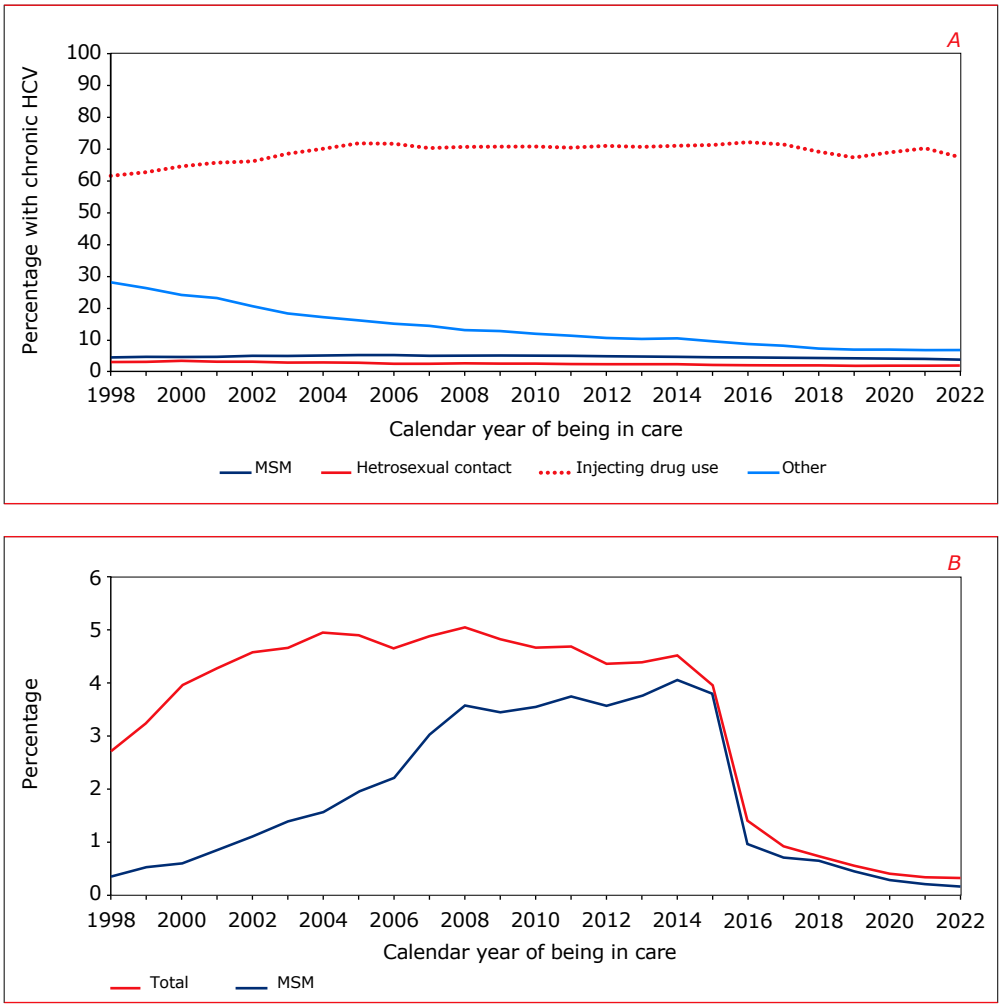
***Legend:** n = total for each category; (%) = percentage of the total for each column; HCV = hepatitis C virus; ART = combination antiretroviral therapy.*

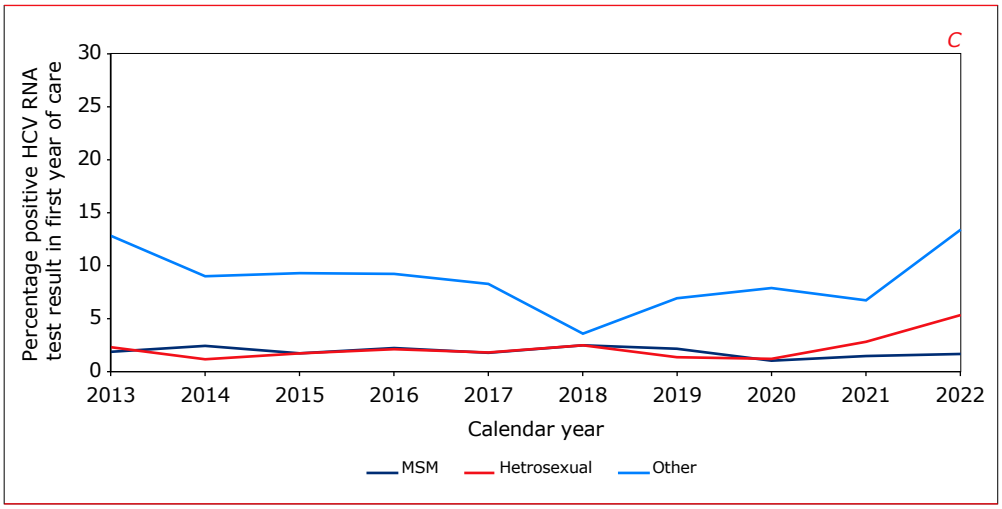
Changes over time

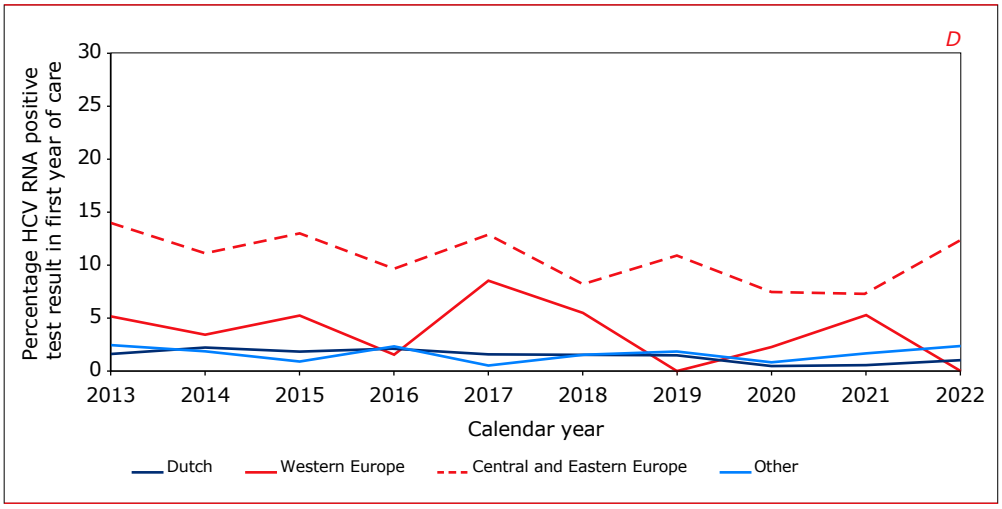
Prevalence of chronic HCV co-infection in individuals per calendar year

The overall prevalence of ever being diagnosed with a chronic HCV co-infection among individuals living with HIV ever registered, decreased from 11.0% in 1998 to 4.2% in 2022, but was not equally distributed among HIV transmission categories. The highest prevalence was found among individuals who had acquired HIV by injecting drug use, and this number varied between 62% and 72% over calendar years (Figure 4.3A).

Figure 4.3: *Prevalence of: A) ever chronic hepatitis C virus (HCV) co-infection, and B) detectable HCV RNA, per calendar year, C) primary HCV among individuals newly entering care in the Netherlands stratified by transmission risk group (the category PWID is combined with the category other modes of HIV transmission, because the small number of PWID newly entering into care per calendar year made this group more susceptible to having larger differences in the prevalence of detectable HCV RNA), D) primary HCV among individuals newly entering care in the Netherlands stratified by region of origin.*







Prevalence of individuals with detectable HCV RNA

Figure 4.3B shows the percentage of individuals with a positive HCV RNA over calendar time. Individuals contributed follow-up time to the analysis if they were in care in a specific calendar year. The HCV RNA positivity was based on a last available HCV RNA test result before the end of that calendar year. The overall percentage of individuals with detectable HCV RNA varied between 2.7% in 1998 and 5.1% in 2008, before dropping to 0.3% in 2022. In MSM, the highest percentage of HCV RNA positivity was 4% in 2014; by 2022, the percentage of positive HCV RNA tests in this

group had decreased sharply to 0.16%. Figures 4.1B and 4.1C show that HCV testing frequency among individuals in care is decreasing, which could have led to an underestimation of the prevalence of individuals with detectable HCV RNA.

Prevalence of individuals newly entering into care in the Netherlands

Figures 4.3C and D show percentage of individuals with detectable HCV RNA when newly entering into HIV care in the Netherlands. The prevalence of individual with detectable HCV RNA at time of newly entering into care remained stable over the last 10 years among MSM, between 1% and 3% (Figure 4.3C). However, in the most recent years an increase in the prevalence of detectable HCV RNA was seen among individuals who acquired HIV through heterosexual contact and other modes of transmission including PWID. Stratified prevalence of detectable HCV RNA by region of origin indicated that this increase was within individuals originating from European countries other than the Netherlands, mainly Eastern & Central Europe (Figure 4.3D).

Incidence of new HCV infections over time

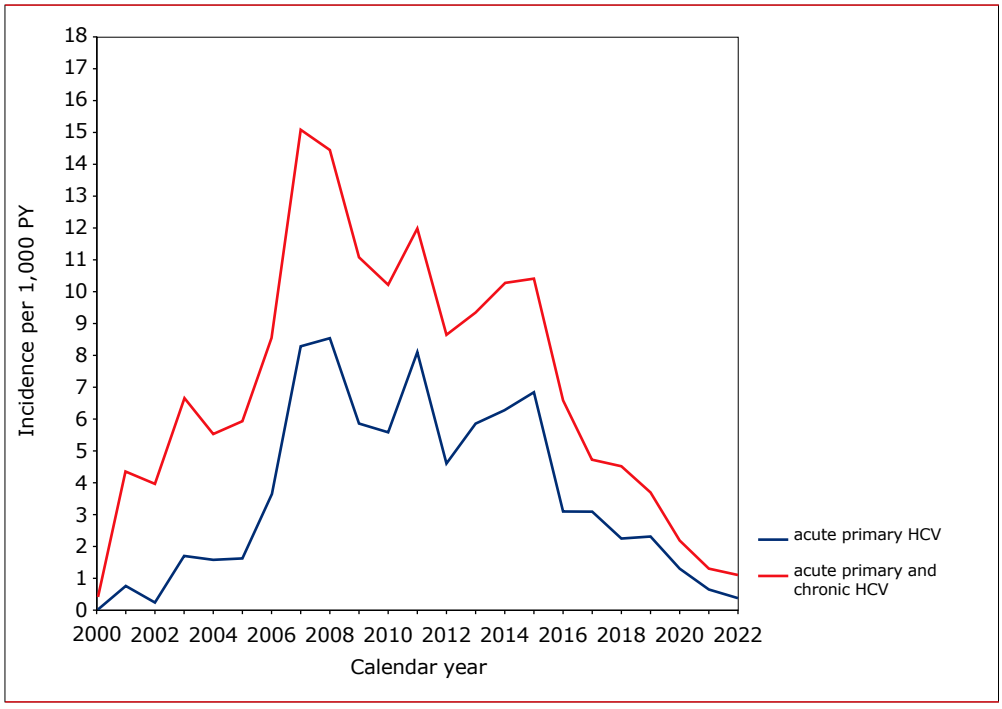
The incidence of primary infection is calculated for individuals with a first documented HCV infection, based on the date of their first positive HCV antibody or HCV RNA test result. This paragraph describes the incidence of recent HCV infection, including only cases of primary recent HCV infection (first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

There were important differences in the incidence of the first diagnosis of recent HCV infection in terms of HIV transmission category. The vast majority of recent HCV infections occurred in MSM (n=816/868 [94%]). In contrast to the high prevalence of HCV in PWID or former PWID, the overall incidence of recent HCV in this group was low, occurring in only seven cases. This is probably due to the high background prevalence of HCV infection in former PWID, the fact that injecting drug use has become very uncommon in the Netherlands, and the effective harm-reduction programmes implemented in addictive care centres in the Netherlands. Thirty-one cases occurred among individuals who had acquired HIV heterosexually.

Figure 4.4 shows both the incidence of recent primary HCV infection and all primary HCV diagnoses among MSM over time. The overall rate of primary HCV infection was 6.9 per 1,000 person years (PY) (95% confidence interval [CI] 6.5-7.3). The incidence of primary infection increased from 0.28 per 1,000 PY (95% CI 0.01-1.56) in 2000 to a peak of 15.1 per 1,000 PY (95% CI 12.2-18.3) in 2007 and decreased to 1.1 per 1,000 PY (95% CI 0.6-1.9) in 2022. When looking at those with recent HCV, the overall rate of recent HCV infection among MSM was 3.7 per 1,000 PY (95% CI 3.5-4.0). When the preferred NEAT recent HCV definition was used, the incidence increased from 0 diagnoses per 1,000 PY in 2000, to a peak of 8.3 and 8.5 per 1,000 PY in 2007 and 2008, respectively. By 2015, the incidence was 6.6 diagnoses per 1,000 PY. It then declined to 3.1 per 1,000 PY in 2016, before further decreasing to 1.3 diagnoses per 1,000 PY in 2020 and 0.4 per 1,000 PY in 2022.

As expected, incidence rates among MSM were higher when the preferred and alternative case definitions of recent HCV were combined, with incidence rates of 7.7 diagnoses per 1,000 PY in 2015, 4.0 per 1,000 PY in 2016, and 0.6 per 1,000 PY in 2022.

Figure 4.4: *Incidence of recent primary hepatitis C infection (blue line) and all recent primary and chronic HCV diagnoses (red line) among men who have sex with men per calendar year.*



Legend: *HCV = hepatitis C virus.*

Treatment for HCV infection

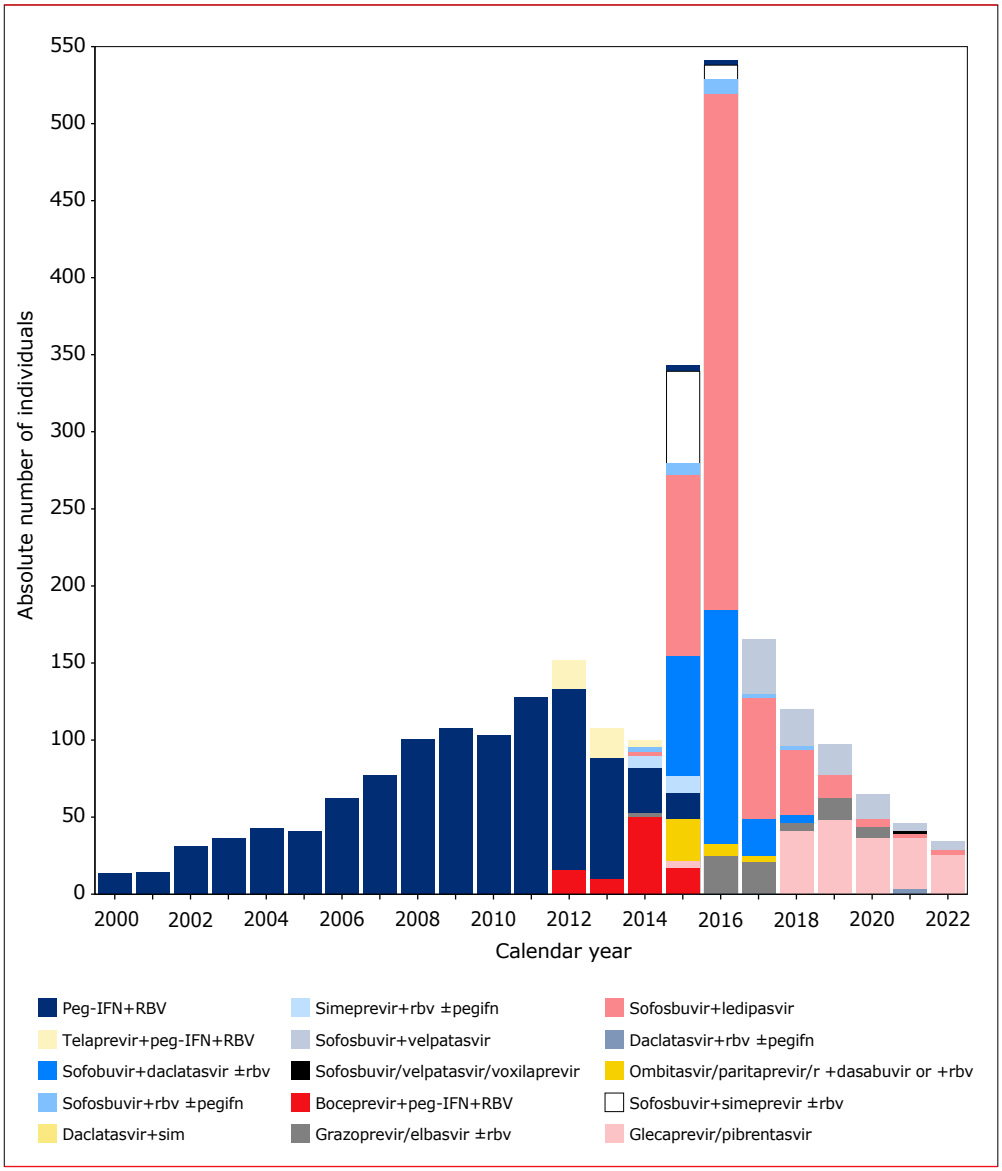
The primary aim of HCV treatment is to achieve a sustained virological response (SVR)[23] and the treatments used have changed markedly in recent years. In the past, treatment consisted of interferon alpha (IFN alpha), and subsequently pegylated interferon alpha (PEG-IFN alpha), in combination with ribavirin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

In April 2012, the first generation HCV NS3/4a protease inhibitors (PI) boceprevir and telaprevir (DAAs active against HCV genotype 1) became available in the Netherlands[24,25]. These agents were subsequently used as part of triple therapy that included one of those two agents, together with PEG-IFN alpha and RBV. In 2014, the HCV NS5B polymerase inhibitor sofosbuvir was introduced in the Netherlands. Initially, due to government restrictions, sofosbuvir was only reimbursed for a defined group of individuals with severe liver fibrosis and cirrhosis. In November 2015, sofosbuvir was made available for all individuals with chronic HCV, regardless of fibrosis state. Shortly thereafter, additional novel DAAs became available. An overview of DAA-containing HCV treatment combinations currently available in the Netherlands can be found at https://hcvrichtsnoer.nl/.

Figure 4.5 shows the absolute number of individuals who have started HCV treatment per calendar year. Of the individuals ever diagnosed with primary chronic or recent HCV, or a reinfection, 1,918 have ever received HCV treatment; of those, 601 have received HCV treatment more than once (this includes people who were unsuccessfully treated and those who reacquired HCV after prior successful treatment). In total, documented regimens comprised:

- 994 regimens with (peg-) interferon+ RBV;
- 135 regimens with first generation PI; and
- 1,390 regimens with all-oral direct-acting antiviral treatment (DAAs).

Figure 4.5: Number of individuals with HIV/HCV starting hepatitis C treatment per calendar year.



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

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

The outcome for people treated with PEG-IFN-based regimens was described in detail in shm's 2016 Monitoring Report[26]. As these regimens have not been used since 2016, due to the availability of more novel DAAs, they are no longer included in this report.

Treatment with DAAs

In total, at the time of the database lock on 1 May 2023, 1,250 individuals were known to have started a DAA regimen between 2014 and 2023; 140 of those had been treated more than once with a DAA regimen with, in total, 1,390 treatment episodes. The most common reasons for receiving DAA treatment more than once were: reinfection after earlier DAA treatment-induced clearance (n=60), and no SVR or discontinuation of first DAA treatment episode due to a lack of early virological response (n=32), or toxicity (n=8). Of the total 1,390 DAA treatment episodes, 16 occurred in 2014, 308 in 2015, and 540 in 2016. The number of treatment episodes subsequently decreased to 33 in 2022 (Figure 4.5).

The most frequently used DAA regimens were:

1. sofosbuvir plus ledipasvir +/- RBV (n=599);
2. sofosbuvir plus daclatasvir +/- RBV (n=263);
3. pibrentasvir/glecaprevir (n=188) (most commonly used regimen in 2021 and 2022);
4. sofosbuvir plus velpatasvir (n=106).

Treatment outcomes

HCV RNA data were collected up to 1 May 2023. At that point, 1,336 out of 1,390 treatment episodes had been completed with one of the DAA regimens, and sufficient time had elapsed since discontinuation of treatment to enable calculation of the SVR12 rate. In 1,327 treatment episodes, follow up HCV RNA data was available and for 9 there was no data after treatment discontinuation:

- In 1,295 of the 1,327 treatment episodes (98%), SVR12 was achieved.
- No SVR was achieved in 32 treatment episodes among 29 individuals.
- For the remaining 9 treatment episodes, no follow-up data on SVR were available: three people died shortly after being treated, and there were no reported HCV RNA tests available to assess treatment outcome in six of the cases.

SVR rates were comparable for individuals who received HCV treatment for the first time and those with prior HCV treatment or severe liver disease. In terms of HIV transmission risk groups, SVR rates were 98% among MSM (98%), 92% among PWID or former PWID, and 95% among individuals who acquired HIV through heterosexual contact.
Among the 29 individuals who did not achieve SVR:

- 21 were successfully retreated with another DAA regimen;
- five were not retreated, two individuals have died and one has moved abroad; and
- three were unsuccessfully retreated.

HCV reinfection

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

To identify possible HCV reinfection among individuals who previously had HCV, we selected people who initially achieved an SVR after receiving any type of HCV treatment, and individuals with spontaneous clearance of HCV.
In total, 2,503 individuals were susceptible for HCV reinfection (1,721 after SVR, 782 after spontaneous clearance). Of those 2,503 individuals, 348 reinfections among 298 individuals (12%) were documented. The median time between SVR or spontaneous clearance and HCV reinfection was 1.4 years (IQR 0.6-3.0).

Most individuals who became reinfected were MSM (252 out of 298, or 85%). Another 29 were PWID or former PWID (10%). For the remaining 17 individuals, documented HIV transmission routes were heterosexual contact (eight), blood-blood contact (three), and unknown (six).

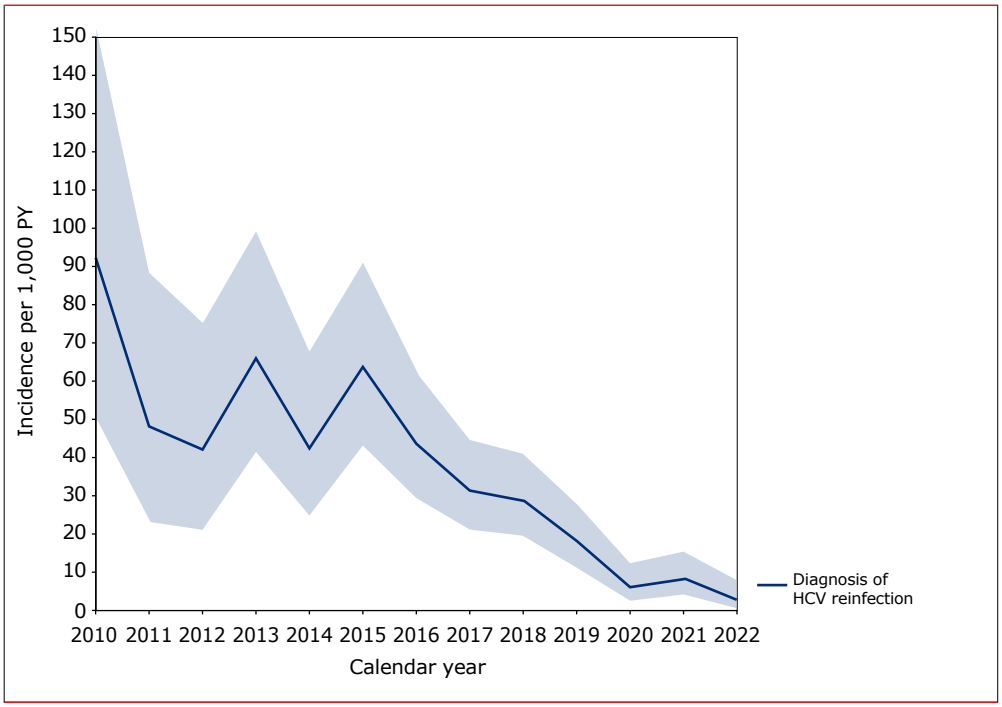
Of the 348 reinfections, 320 (92%) were retreated (246 with DAA, 74 with interferon+/-boceprevir/telaprevir). The median time to retreatment after reinfection diagnosis, stratified by calendar year of reinfection, was:

- Prior to 2015: 33.7 months (IQR 5.3-73.0)
- Between 2015 and 2017: 3.7 months (IQR 1.9-9.4)
- From 2018 onwards: 3.0 months (IQR 1.7-6.0)

We calculated the incidence of reinfection between 2010 and 2022. Follow-up time was from the date of SVR, date of spontaneous clearance, or from 1 January 2010 onwards, until the earliest date of HCV reinfection, death, or last known contact. The incidence of HCV reinfection for the total population was 20 reinfections per 1,000 PY (95% CI 18-22), and for MSM it was 26 reinfections per 1,000 PY (95% CI 23-30).

Because most reinfections occurred among MSM, the incidence of HCV reinfection over time is shown only for MSM (Figure 4.6). This incidence decreased from 82 reinfections per 1,000 PY in 2010 to 58 per 1,000 PY in 2015, and then declined to 18 reinfections per 1,000 PY in 2019, and 2.6 per 1,000 PY in 2022. A decline in the incidence of reinfection in MSM has been observed since 2015.

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



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

Continuum of care for those with diagnosed HCV

Figure 4.7 shows the HCV continuum of care, based on the number of people known to be in HIV care as of 31 December 2022. Individuals were categorised according to their last documented HCV infection episode. In total 2,240 individuals were linked to HIV care, 1,942 individuals had a primary HCV infection, and 298 individuals had a reinfection.

Of the 2,240 individuals linked to HIV care:

- 1,520 (68%) were retained in care;
- 720 individuals were no longer in care (415 had died; 170 had moved abroad; and 135 were lost to care);
- 1,488 (98%) of those still alive and in care had received treatment for HCV (with DAAs or a pegylated interferon-containing regimen);
- 1,449 (95%) of those still alive, in care and who had received treatment, had completed HCV treatment with enough data available to calculate the HCV treatment response (SVR12 for the DAAs and SVR24 for the older regimens).

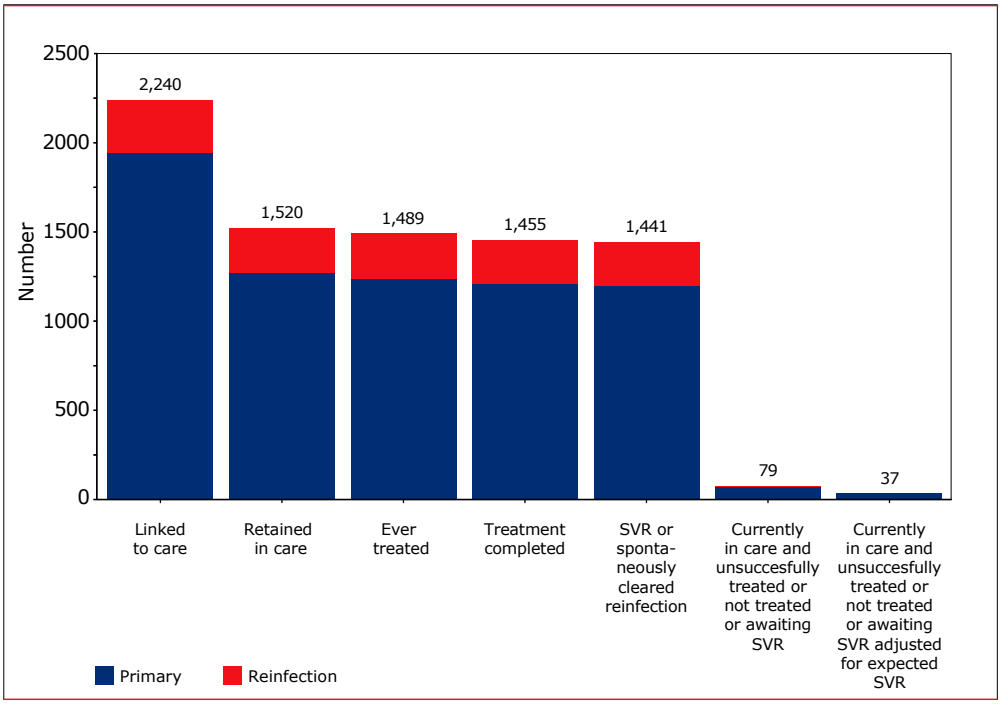
Overall, 1,426 of the 1,449 people in care in 2022 who completed treatment (98%) had achieved an SVR, including those who had achieved an SVR on a pegylated interferon-containing regimen and those who were retreated after earlier treatment failure. Another 15 individuals with HCV reinfection had a negative last HCV RNA test result, without documentation of HCV treatment. It is likely they spontaneously cleared their HCV infection, bringing the total of individuals with a treatment-induced or spontaneous clearance of their most recent HCV episode to 1,441.

As a result, 79 (5%) of the 1,520 individuals known to be alive and in care in one of the Dutch HIV treatment centres on 31 December 2022, were still in need of HCV treatment:

32 (2%) individuals had never been treated for HCV. Those who remained untreated at the time of database closure included 5 new HCV diagnoses (16%). Half of the individuals without treatment were born in the Netherlands, and 38% were born in Western, central or eastern Europe. All except two individuals had started ART, but 27% of the individuals who started ART, had detectable HIV RNA levels. The percentage untreated was higher among PWID (5%), people who acquired HIV through heterosexual contact (5%), and people with an unknown HIV transmission mode (5%), than among MSM (1%).Of the 43 individuals for whom SVR could not yet be calculated, all had been treated with novel DAA combinations.

For that reason, we have extrapolated the observed DAA SVR rate for these individuals and assumed that 42 of the 43 (98%) will achieve SVR. This results in a more realistic estimate of individuals (79-42=37) who have yet to be treated or were unsuccessfully treated.

Figure 4.7: Hepatitis C continuum of care.



Legend: SVR=sustained virological response.

Liver-related morbidity

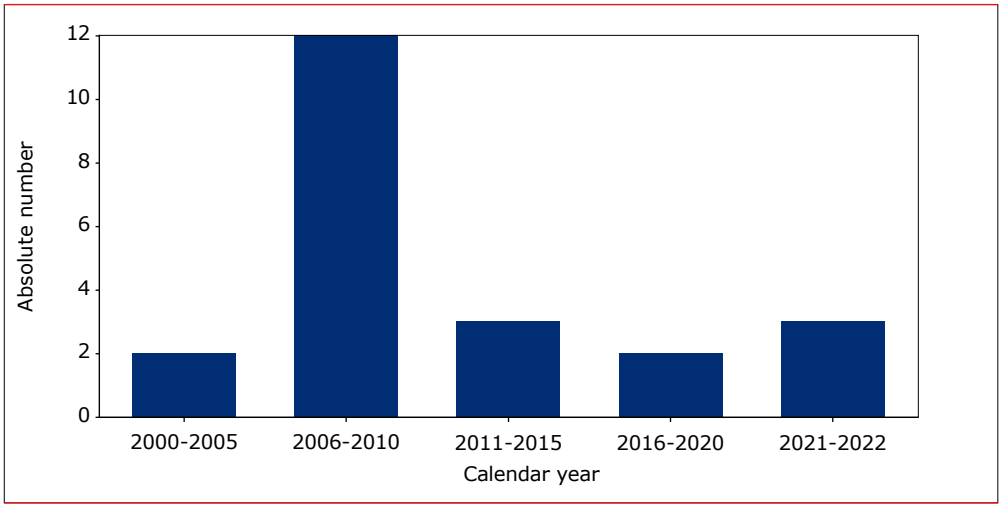
Data on liver-related morbidity are collected for all individuals living with HIV in follow up in the ATHENA cohort. In total, 1,273 cases of severe liver disease, according to our definition, were considered to be present (presumptive and definitive categories combined): 495 among individuals with HCV co-infection and 254 among individuals with HBV co-infection. This chapter reports on clinical characteristics and severe chronic liver disease with regards to HCV, HBV and HDV infection in individuals living with HIV, therefore, further analyses in this section are limited to those with viral hepatitis.

Liver-related morbidity in HCV

Additional data from liver biopsy pathology reports, transient elastography, radiology reports, or a combination of those sources were available for 1,698 of the 2,037 individuals with HCV and without other viral hepatitis (i.e., HBV or HDV). A review of these additional data shows that severe chronic liver disease was considered to be present (presumptive and definitive categories combined) in 495 (24%) of the 2,037 individuals with HCV co-infection, and 29% of those with additional liver-related data. Definitive severe chronic liver disease was documented for 122 (6%) individuals with HCV co-infection.

Between 1998 and 2022, 23 (1.1%) cases of hepatocellular carcinoma (HCC) were reported among 2,037 individuals with HCV and without other viral hepatitis (i.e., HBV or HDV). Figure 4.8 shows that the annual number of new HCC diagnoses declined from 2011 onwards. 15 of the 23 individuals with HCC were born in the Netherlands.

Figure 4.8: *Absolute number of reported HCC cases among individuals with HCV and without other chronic viral hepatitis coinfections (i.e., HBV and HDV) over time.*

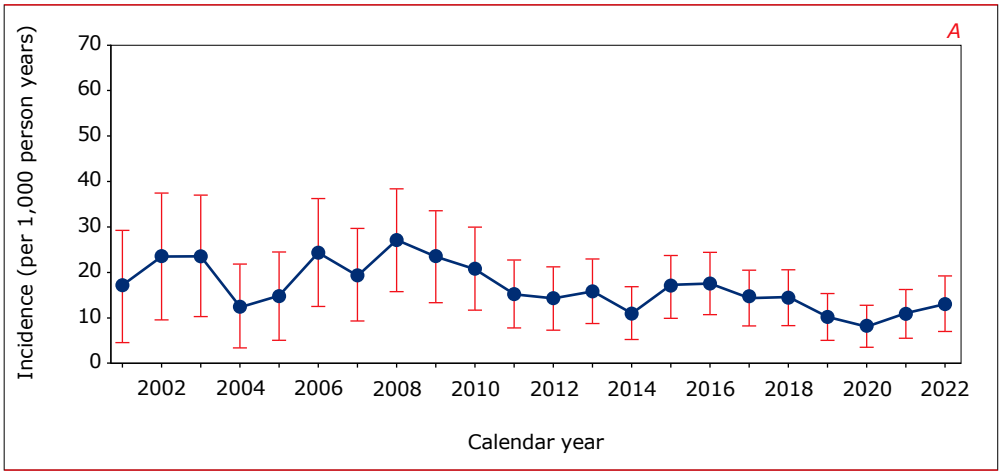


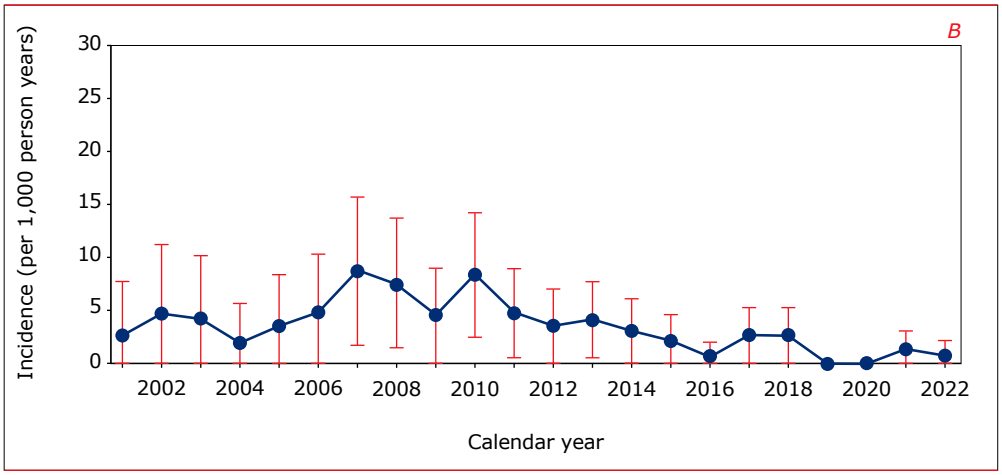
Mortality

All-cause mortality

Among the 2,037 individuals with HCV and without other viral hepatitis (i.e., HBV or HDV), 19% died from any cause. For individuals with HCV the incidence rate of death from any cause, adjusted for age and gender of the shm population, was 20.4 per 1,000 PY in 2002-11, and 13.3 per 1,000 PY from 2012 onwards (Figure 4.9A). In MSM with HCV, these incidence rates were 9.3 per 1,000 PY in 2002-11, and 5.9 per 1,000 PY from 2012 onwards. In PWID with HCV, these incidence rates were 33.8 per 1,000 PY in the period 2002-11, and 37.6 per 1,000 PY from 2012 onwards.

Figure 4.9: *Annual: (A) all-cause mortality rate, and (B) mortality related to liver disease (adjusted for age and gender of the shm population) in 2,037 individuals with HIV who were ever diagnosed with recent or chronic HCV and without other viral hepatitis (i.e., HBV or HDV).*





Liver-related mortality

In total, 71 (3%) individuals with HCV and without other viral hepatitis (i.e., HBV or HDV) died of a liver-related cause between 2002 and 2022. For individuals with HCV, the incidence rate of death from a liver-related cause, adjusted for age and gender of the shm population, was 5.7 per 1,000 PY in 2002-11. This decreased to 1.8 per 1,000 PY from 2012 onwards (Figure 4.9B). In MSM with HCV, these incidence rates were 3.3 per 1,000 PY in 2002-11 and 0.8 per 1,000 PY from 2012 onwards. In PWID with HCV, these incidence rates were 7.6 per 1,000 PY in 2002-11 and 4.2 per 1,000 PY from 2012 onwards.

Hepatitis B virus (HBV)

Box 4.2: Definitions of hepatitis B serological profiles.

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

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

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

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

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

HBV screening

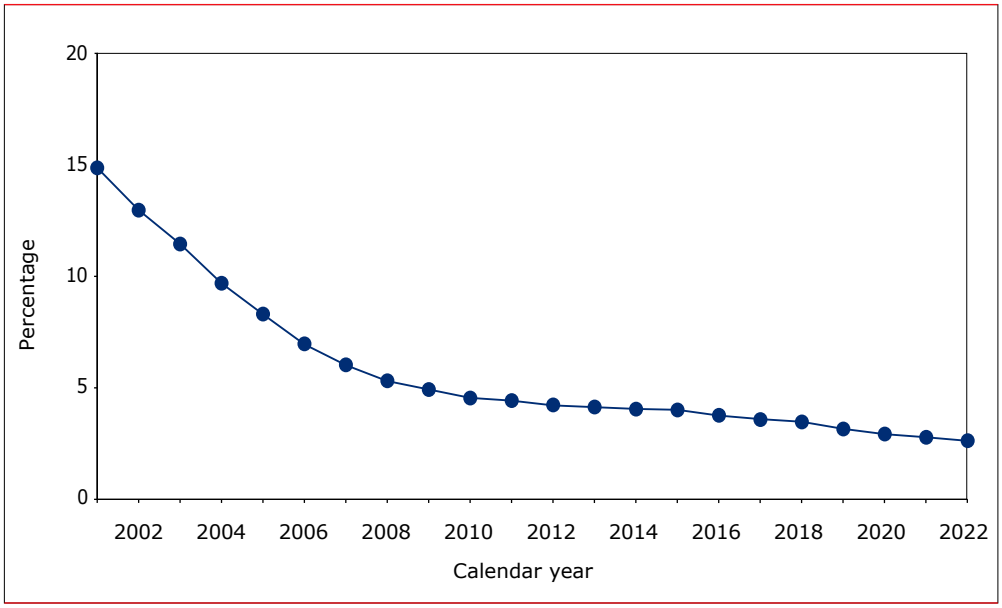
Ninety-seven percent of the 30,050 individuals living with HIV ever registered in the shm database have been screened for at least one serological marker of HBV, comprising:

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

Screening for HBV infection in individuals living with HIV in care has improved over calendar time. In 2001, 15% of individuals had not been screened for HBV infection (Figure 4.10). Since then, the percentage of individuals living with

HIV without HBV screening has decreased markedly, with 2.6% of all individuals living with HIV in care having no measured HBV serological markers in 2022 (Figure 4.10).

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



HBV serological profiles

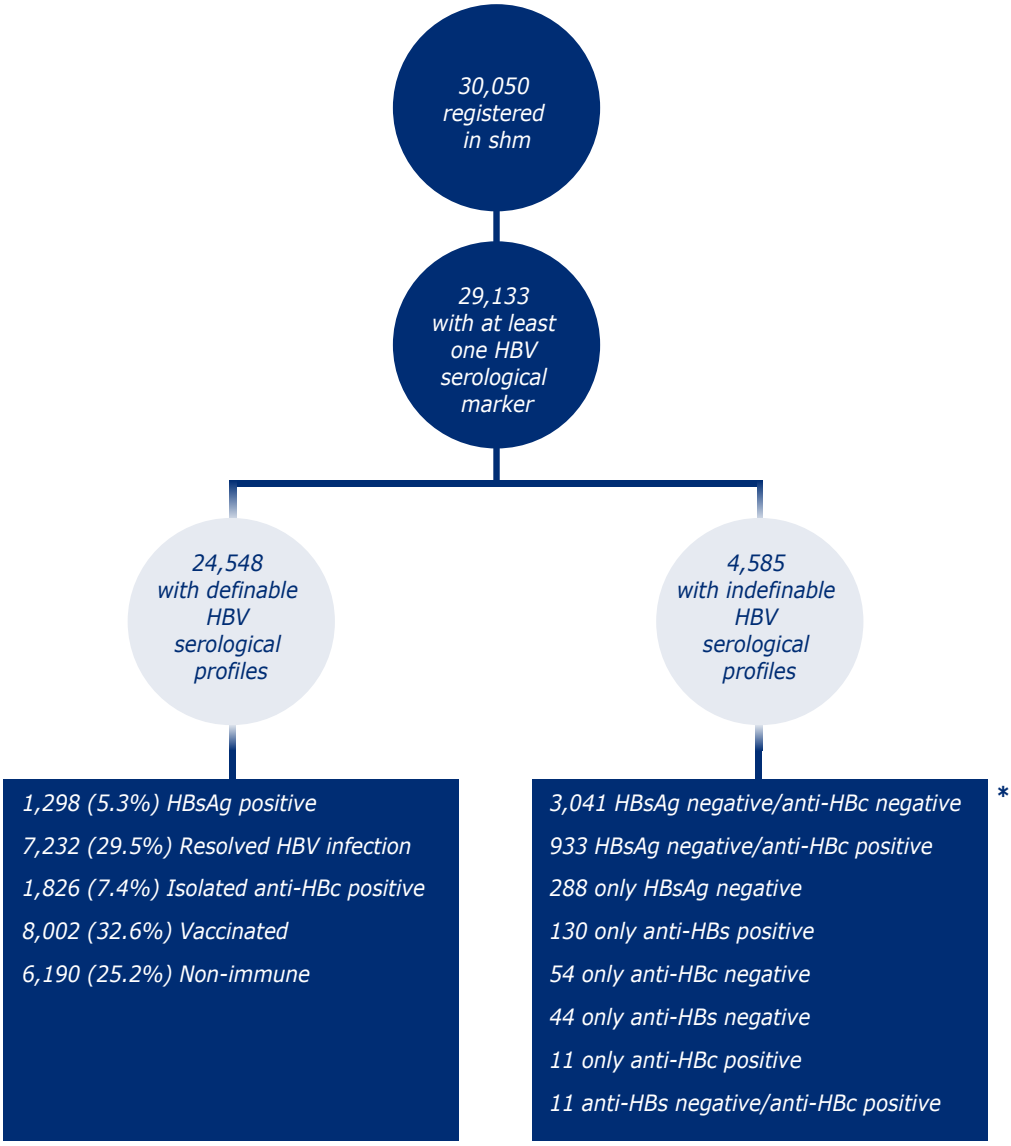
HBV serological profiles could be defined for 24,548 (84%) of the 29,133 screened individuals (Figure 4.10). A full HBV serological battery is not routinely performed in individuals living with HIV; therefore, any results from an HBV serological test were assumed to remain the same over time until a new serological test was carried out. The distribution of HBV serological profiles at the last visit are given in Figure 4.11.

The remaining 4,585 (16%) individuals either:

- had insufficient information to establish an HBV serological profile (n=4,512); or
- were previously HBsAg positive, no longer had anti-HBc antibodies and did not have anti-HBs antibodies (n=73)

The demographic characteristics of people with definable HBV serological profiles are compared in Table 4.3.

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



**The 73 individuals who were HBsAg positive and then lost HBsAg without a definable profile are not included.*
Legend: *Anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus.*

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

	HBV serological profile*, n (%)				
	HBV infection	HBsAg-negative phase with anti-HBs	HBsAg-negative phase without anti-HBs	Vaccinated	Non-immune
Total number	1,298	7,232	1,826	8,002	6,190
Gender at birth					
Male	1,105 (85%)	6,217 (86%)	1,382 (76%)	6,965 (87%)	4,546 (73%)
Female	193 (15%)	1,015 (14%)	444 (24%)	1,037 (13%)	1,644 (27%)
Region of origin					
The Netherlands	533 (41%)	3,780 (52%)	691 (38%)	4,516 (56%)	3,396 (55%)
Europe	79 (6%)	498 (7%)	123 (7%)	634 (8%)	338 (5%)
Sub-Saharan Africa	328 (25%)	1,111 (15%)	578 (32%)	548 (5%)	729 (12%)
Caribbean/South America	154 (12%)	932 (13%)	168 (9%)	1,104 (15%)	923 (15%)
Southeast Asia	74 (6%)	307 (4%)	74 (4%)	263 (3%)	162 (3%)
Other	130 (10%)	604 (8%)	192 (11%)	937 (12%)	642 (10%)
HIV transmission group					
Men who have sex with men	720 (55%)	4,918 (68%)	768 (42%)	5,871 (73%)	2,807 (45%)
Heterosexual	398 (31%)	1,568 (22%)	653 (36%)	1,581 (20%)	2,691 (44%)
Injecting drug use	57 (4%)	233 (3%)	201 (11%)	71 (1%)	117 (2%)
Other	123 (9%)	513 (7%)	204 (11%)	479 (6%)	575 (9%)
ART	1,248 (96%)	7,036 (97%)	1,756 (96%)	7,889 (99%)	6,025 (97%)
Deaths	271 (21%)	1,194 (17%)	341 (19%)	447 (6%)	787 (13%)

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

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

Individuals with an HBV infection

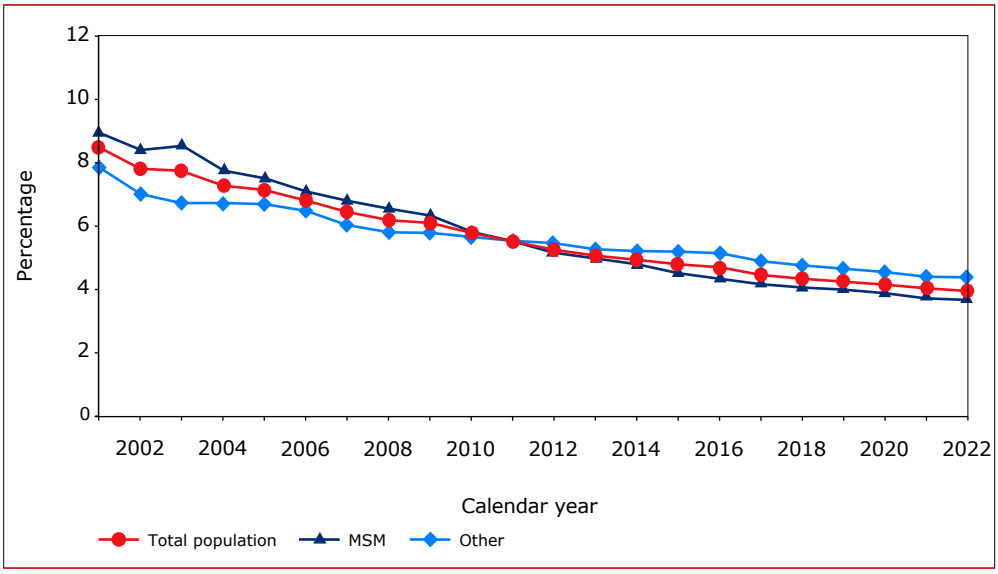
Prevalence of active HBV infection

Of the 29,133 individuals ever screened for at least one HBV serological marker, 28,778 had an HBsAg test. Of these, a total of 1,715 (6%) received a positive HBsAg test result. Over time, 215 (12%) of these individuals became HBsAg negative and acquired anti-HBs antibodies (i.e., HBsAg negative phase with anti-HBs) and an additional 202 (12%) became HBsAg negative without acquiring anti-HBs antibodies (i.e., HBsAg negative phase without anti-HBs). The remaining 1,298 (76%) individuals continued clinical care up until their last visit in care with HBsAg positive serology.

The prevalence of HBsAg positive serology was 7.8% in 2001, which slowly decreased to 3.9% in 2022 (Figure 4.12). This decline could be the result of several factors, including lower numbers of individuals with incident HBV (as a result of increased vaccination coverage among MSM[31], and the preventive effect of HIV treatment with an ART regimen that includes tenofovir disoproxil fumarate [TDF] / tenofovir alafenamide fumarate [TAF]), and a minority of individuals becoming HBsAg negative during treatment[32].

As is the case for HCV co-infection, the percentage of individuals living with HIV in care who have chronic HBV is considerably higher than that found in the general Dutch population. Individuals with HBV were predominantly male (1,105 out of a total 1,298, or 85%), in line with those with HCV (Table 4.3). However, compared with people with HCV, those with HBV were more likely to have been born in sub-Saharan Africa and to have acquired HIV through heterosexual contact.

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



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

Treatment for chronic HBV infection

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

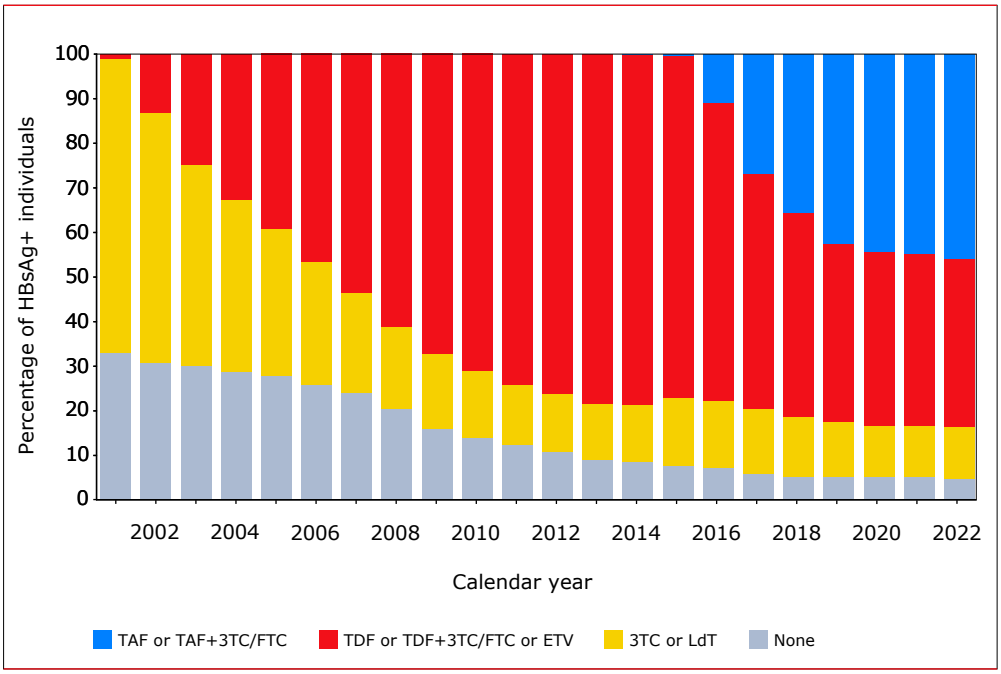
Of the 1,715 individuals with HIV in the shm database who have ever had an HBsAg positive serological test result, 1,650 (96%) ever received an ART regimen that included one or more agents with activity against both HIV and HBV. The reasons the remaining 63 individuals never received anti-HBV treatment included:

- death prior to start of treatment (n=16);
- recent entry into care (n=4);
- loss to follow up (n=43); or
- lack of sufficient information (n=2).

Most people with active HBV received treatment containing lamivudine in 2001 (Figure 4.13). TDF-based ART (with or without lamivudine or emtricitabine) for combined HIV and HBV treatment was first used in 2002 (n=84/646, 13%) and became more commonly used than lamivudine in 2004. TAF-based ART (with or without lamivudine or emtricitabine) was first used in 2016 (n=135/1,245, 11%).

In 2022, most individuals with HBV were receiving TAF-based ART (n=609/1,331, 46%), closely followed by TDF-based ART (n=504/1,331, 38%), and lamivudine-based ART (n=151/1,331, 11%), or no anti-HBV-containing ART (n=67/1,331, 5%). Of the 67 individuals who were not on an anti-HBV containing ART, 28 (41%) no longer had HBsAg positive serology.

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



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

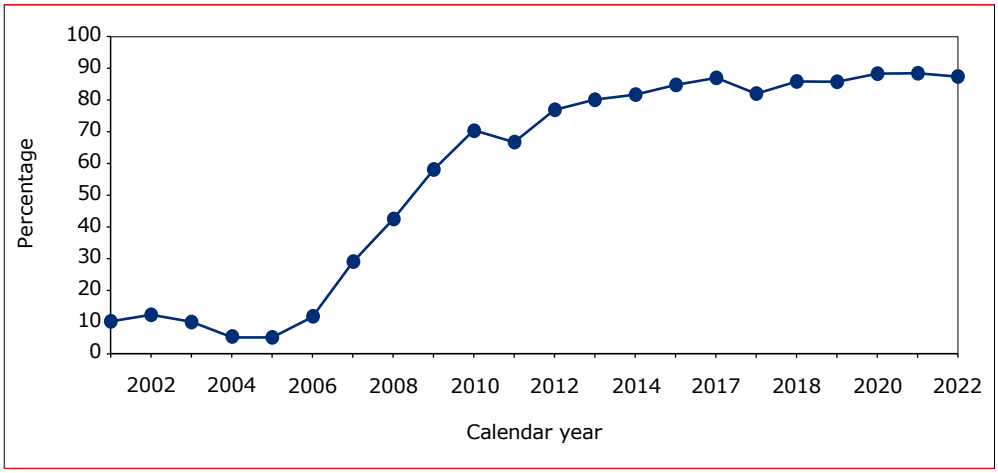
Note: *The categories of anti-HBV agents were: none, 3TC or LdT, TDF or TDF+3TC/FTC or ETV, and TAF or TAF+3TC/FTC. 3TC and LdT should not be combined and TDF and ETV can be combined under special circumstances[35].*

We examined the HBV DNA levels per calendar year in the population of individuals with HIV and HBV. In many treatment centres, HBV DNA is not routinely collected after the first negative HBV DNA result during treatment with TDF/TAF, so long as HIV RNA is undetectable. HBV DNA measurements were then available, on average, in 24% of individuals with HBV for each year.

Figure 4.14 shows the percentage of those over time with an undetectable HBV DNA level below 20 IU/ml, as a percentage of the total number of individuals with an HBV DNA measurement. For HBV DNA measurements with a detection limit other than 20 IU/ml, we used the detection limit of the specific assay (below 20, below 100, below 200, below 400, below 1,000, or below 2,000 IU/ml).

In 2001-2005, at most, 12% of the individuals had an undetectable HBV DNA level based on the detection limit of the assay used at the time of measurement. The percentage of individuals with an undetectable HBV DNA level became more common with increased use of TDF-containing ART, reaching 80% in 2013. In 2022, 87% of individuals with HIV and HBV had an undetectable HBV DNA level (Figure 4.14).

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

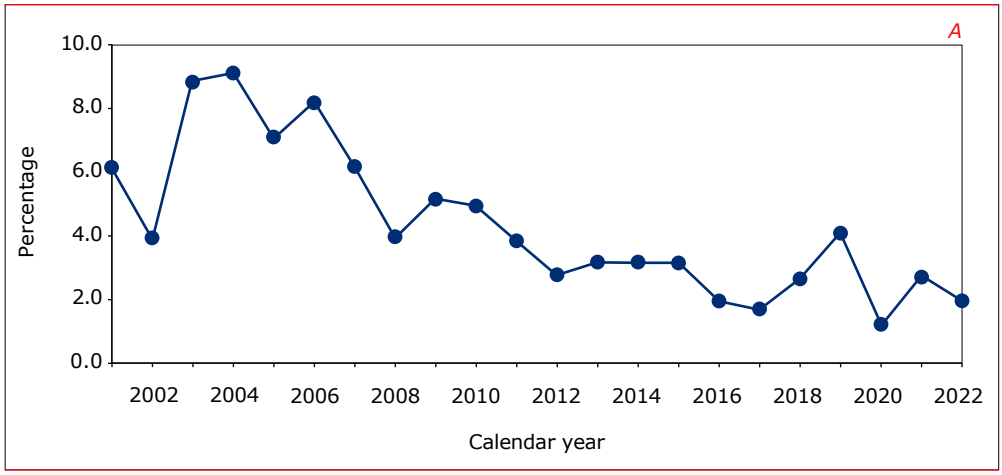


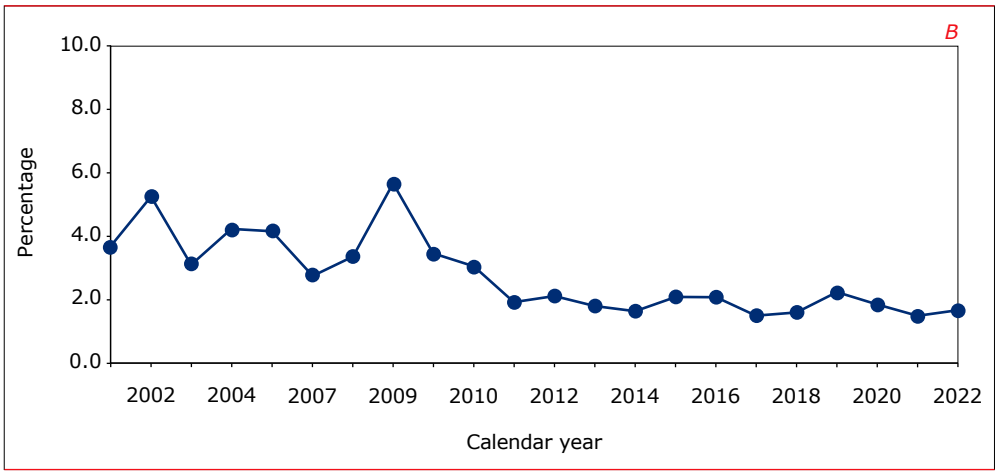
There are other serological outcomes associated with a more favourable prognosis in individuals with HBV[36]. Persistently negative hepatitis B "e" antigen (HBeAg) is associated with lower levels of HBV DNA replication. It also confers a favourable long-term outcome with low risk of cirrhosis and HCC, so long as transaminase and HBV DNA levels are low[37]. In those individuals with HBeAg-positive status, the loss of HBeAg, known as HBeAg seroclearance, is therefore a desired endpoint. Persistently negative HBsAg is associated with reduced viral activity, very low risk of developing HCC, and improved survival. For all individuals with HBV, the loss of HBsAg, known as HBsAg seroclearance or "functional" cure, is the penultimate goal of HBV therapy.

We examined the rates of HBeAg and functional cure per calendar year in the population of individuals with HIV and HBV. For these analyses, any results from an HBV serological test were assumed to remain the same over time until a new serological test was carried out. The percentage of individuals with HBeAg seroclearance ranged from 3.9% to 9.1% between 2001 and 2010, and slowly declined to 2.0% in 2022 (Figure 4.15A). Similarly, the percentage of individuals with HBsAg seroclearance was higher between 2001 and 2010, ranging from 2.8% to 5.7%, and slowly declined to 1.6% in 2022 (Figure 4.15B).

Individuals with HIV and HBV who initiate ART at very low CD4+ cell counts, are more likely to have seroclearance due to an immuno-inflammatory reaction with accelerated CD4+ cell increases[38]. The higher percentages with seroclearance before 2010 could be due, in part, to the higher percentage of individuals with HIV and HBV initiating ART with severe immunosuppression during this period. It could also be due to the decrease in the number of individuals with recent HBV infection, who were more likely to clear their HBsAg, as TDF-containing ART became more widespread[32]. Furthermore, the number of HBeAg tests peaked in 2004 at 116, before slowly declining to 26 tests in 2022. The number of HBsAg tests peaked in 2008 at 230, before decreasing less dramatically to reach 125 tests in 2022. The lower percentage with seroclearance after 2010 might also be due to the lower testing rates in individuals with HIV and HBV.

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



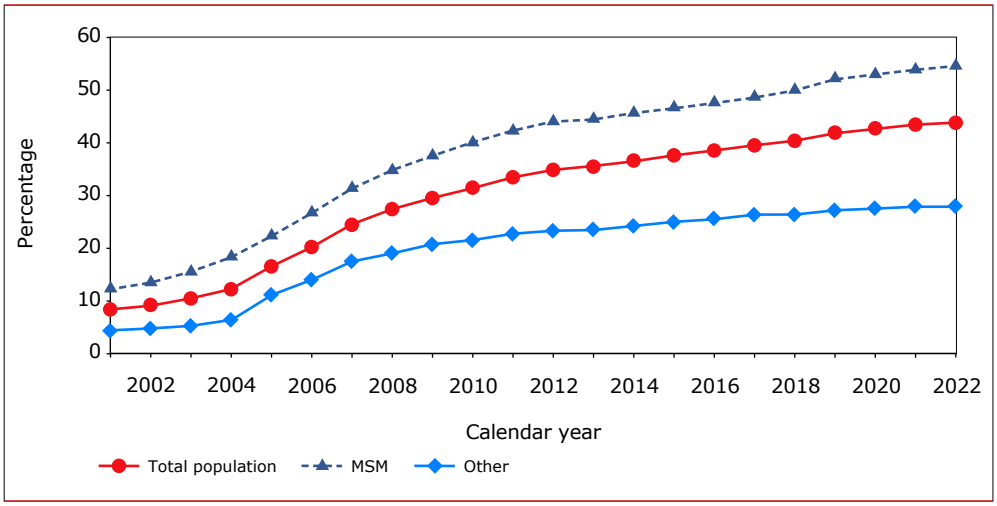


HBV vaccination in individuals living with HIV

Of the 24,548 individuals with definable HBV serological profiles, 8,002 (33%) had serological evidence of HBV vaccination status at their last visit. HBV vaccination is not recommended for individuals with HBsAg positive and/or anti-HBc antibody positive serology. When individuals with negative HBsAg and anti-HBc antibody serology (without previous evidence of HBsAg positive serology) were

considered, the prevalence of HBV vaccination status increased from 8% in 2001 to 44% in 2022 (Figure 4.16). The largest increase in HBV vaccination was observed in MSM, likely due to the national vaccination campaign targeting these individuals from 2002 onwards[31].

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



Legend: MSM = men who have sex with men.

HBV non-immune status in individuals living with HIV

Of the 24,548 individuals with definable HBV serological profiles, 6,190 (25%) had serological evidence of being non-immune and non-exposed to HBV at their last visit. When the 4,585 individuals with undefinable HBV serological profiles were considered, 84 of the 256 with an anti-HBs antibody test did not have detectable anti-HBs antibodies, and 3,776 of the 4,329 without an anti-HBs antibody test were not reported to have been vaccinated by their treating physician. Therefore, at most, 10,050 (34%) of the 29,133 individuals screened for HBV remained susceptible to infection at the time of their last visit (6,190 non-immune; 84 with an undefinable HBV profile and anti-HBs antibody negative; and 3,776 with an undefinable HBV profile and missing data on anti-HBs antibody status, and no physician-reported vaccination).

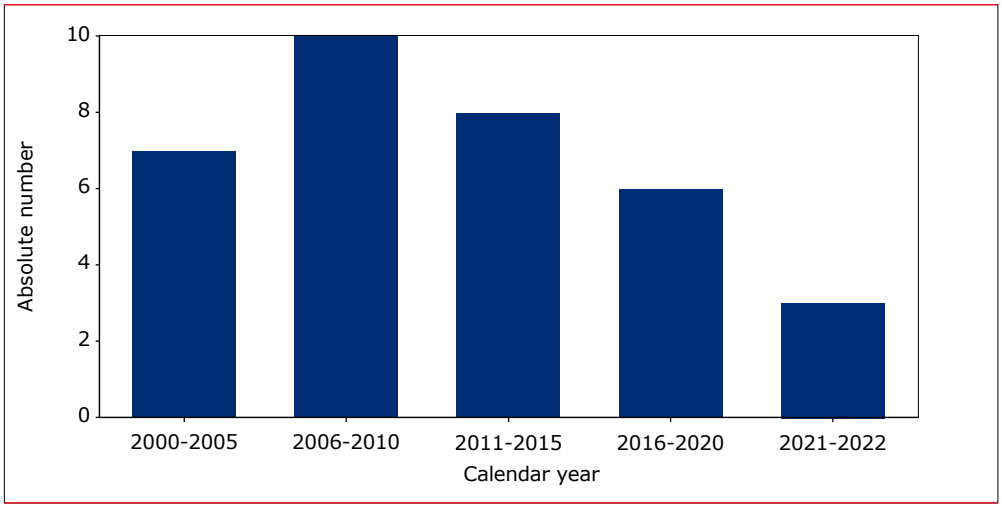
Individuals at risk, and MSM in particular, should be actively counselled about HBV vaccination. However, they may be protected from HBV infection by the use of tenofovir (TDF), or tenofovir alafenamide (TAF), as part of their ART regimen, according to findings reported by an international study, and one of the Dutch HIV treatment centres[39,40]. Data from shm show that, of those people who remained at risk of acquiring HBV, 83% were being treated with an ART regimen that included TDF or TAF; for MSM, this percentage was 85%.

Liver-related morbidity

Additional data from liver biopsy pathology reports, transient elastography, radiology reports, or a combination of those sources, were available for 1,273 of the 1,573 individuals with HBV and without other viral hepatitis (i.e., HCV or HDV). A review of these additional data shows that severe chronic liver disease, according to our definition, was considered to be present (presumptive and definitive categories combined) in 254 (16%) of the 1573 individuals with HBV. Definitive severe chronic liver disease was documented for 70 (4%) with HBV.

Figure 4.17 shows that the annual number of new HCC diagnoses declined from 2011 onwards. HCC was found in 34 (2.2%) individuals with HBV co-infection, 18 of whom were born in the Netherlands.

Figure 4.17: Absolute number of reported HCC cases among individuals with HBV and without other viral hepatitis (i.e., HCV or HDV) over time.

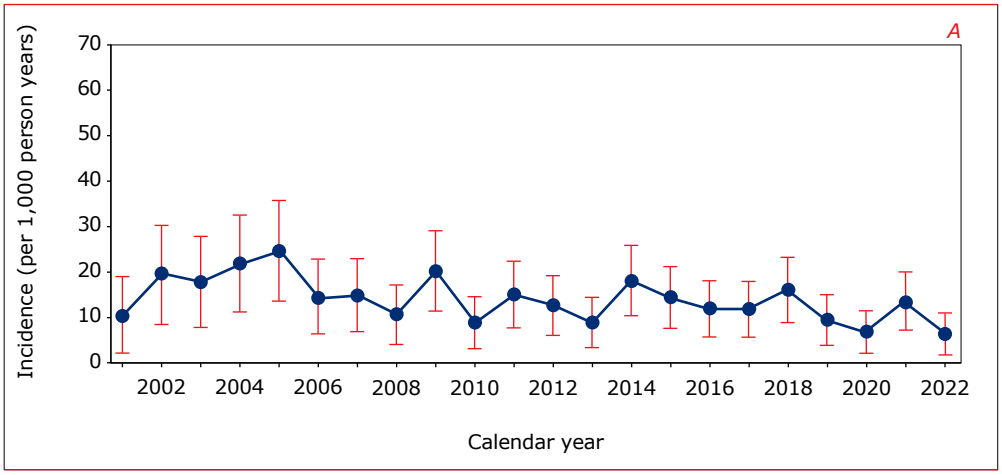


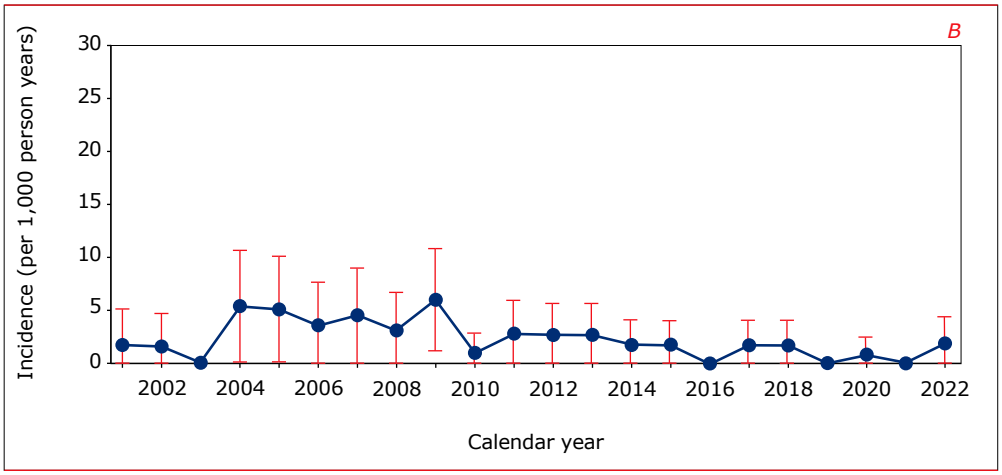
Mortality

All-cause mortality

Nineteen percent (n=300) of the 1,573 individuals with HBV and without other viral hepatitis (i.e., HCV or HDV) died of any cause. For individuals with an HBV infection the incidence rate of death from any cause, adjusted for age and gender of the shm population, was 16.3 per 1,000 PY in 2002-11, and 11.8 per 1,000 PY from 2012 onwards (Figure 4.18A). In MSM with HBV, these incidence rates were 13.3 per 1,000 PY in 2002-11 and 10.1 per 1,000 PY from 2012 onwards. In PWID with HBV, these incidence rates were 67.7 per 1,000 PY in 2002-11 and 88.0 per 1,000 PY from 2012 onwards.

Figure 4.18: *Annual: (A) all-cause mortality rate, and (B) mortality related to liver disease (adjusted for age and gender of the shm population), in 1,573 individuals with HIV who were ever diagnosed with active HBV and without other viral hepatitis (i.e., HCV or HDV).*





Liver-related mortality

In total, 35 individuals with HBV and without other viral hepatitis (i.e., HCV or HDV) died of a liver-related cause. For individuals with an HBV infection, the incidence rate of liver-related death, adjusted for age and gender of the shm population, was 3.4 per 1,000 PY in 2002-11 and decreased to 1.3 per 1,000 PY from 2012 onwards (Figure 4.18B). In MSM with HBV, these incidence rates were 3.2 per 1,000 PY in 2002-11 and 1.3 per 1,000 PY from 2012 onwards. In PWID with HBV only, these incidence rates were 10.7 per 1,000 PY in 2002-11 and 9.1 per 1,000 PY from 2012 onwards.

Multiple infections with HBV, HCV and HDV

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

Of the 30,050 individuals living with HIV ever registered by shm, 29,414 (98%) had been screened for HBV (i.e., HBsAg), HCV (i.e., anti-HCV antibodies) or HDV (i.e., IgG or IgM anti-HDV antibodies or presence of HDV RNA). Of those with HIV ever registered by 2022, there were:

- 225 (0.8%) individuals who ever had HBV-HCV;
- 16 (0.1%) individuals who ever had HBV-HDV; and
- 10 (<0.1%) individuals with HBV-HCV-HDV.

It should be noted that by 2022:

- 235 of the 1,715 (14%) individuals who ever had HBV had been tested for HDV;
- 26 (11%) of the 235 testing positive for HDV antibodies had an indication of past or current HDV infection;
- 15 of the 26 were tested for HDV RNA; and
- 11 of these were found to have detectable HDV RNA, indicating active HDV.

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

Of the 251 individuals with multiple viral hepatitis, 70 (28%) had presumptive or definitive severe chronic liver disease: 58 with HBV-HCV, three with HBV-HDV and seven with HBV-HCV-HDV.

HCC was found in 6 (2%) individuals with multiple viral hepatitis: 5 with HBV-HCV, one with HBV-HDV and none with HBV-HCV-HDV. In the individuals with multiple viral hepatitis, 77 deaths were observed, of which 14 (18%) were liver-related. The number of overall and liver-related deaths, respectively, were distributed across co-infection groups as follows: 72 and 13 with HBV-HCV, one and one with HBV-HDV and four and none with HBV-HCV-HDV.

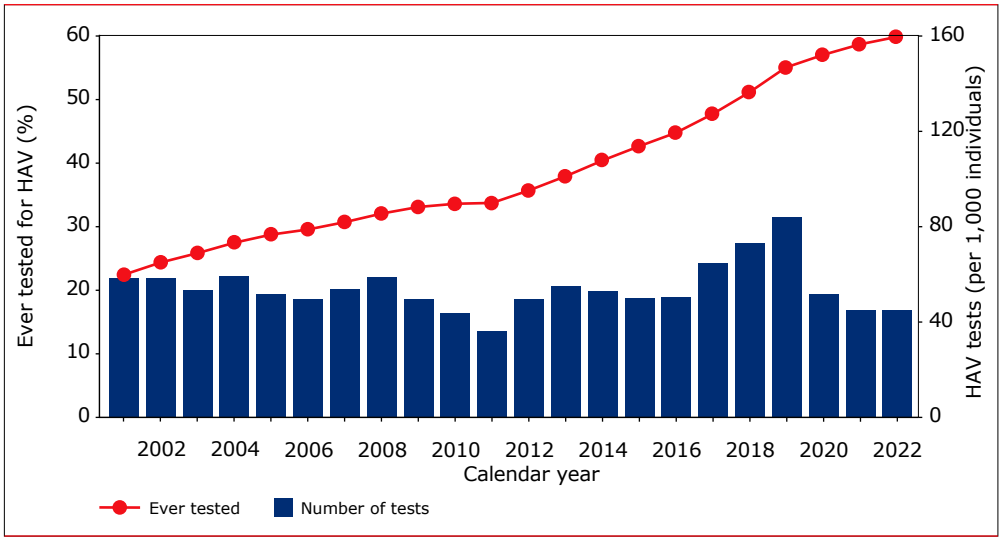
Hepatitis A virus (HAV)

HAV screening

Screening for HAV involves testing for IgG anti-HAV antibodies (to establish past or current HAV infection, or HAV vaccination response) and/or IgM anti-HAV antibodies (to establish acute HAV infection). Sixty-one percent (n=18,302) of the 30,050 individuals living with HIV ever registered in the shm database have been screened for HAV. The frequency of screening for HAV in individuals living with HIV has been consistent over the past two decades (Figure 4.19).

Between 2001 and 2017, roughly 35 to 63 HAV tests per 1,000 individuals were conducted each year. Between 2018 and 2019, screening frequency increased to 72 and 83 HAV tests per 1,000 individuals per year, respectively. In 2020, screening frequency returned to 52 HAV tests per 1,000 individuals and was 44 HAV tests per 1,000 individuals in 2022. The percentage of individuals who have ever been tested for HAV was 23% in 2001, and steadily increased to 61% in 2022 (Figure 4.19).

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



Legend: HAV = hepatitis A virus.

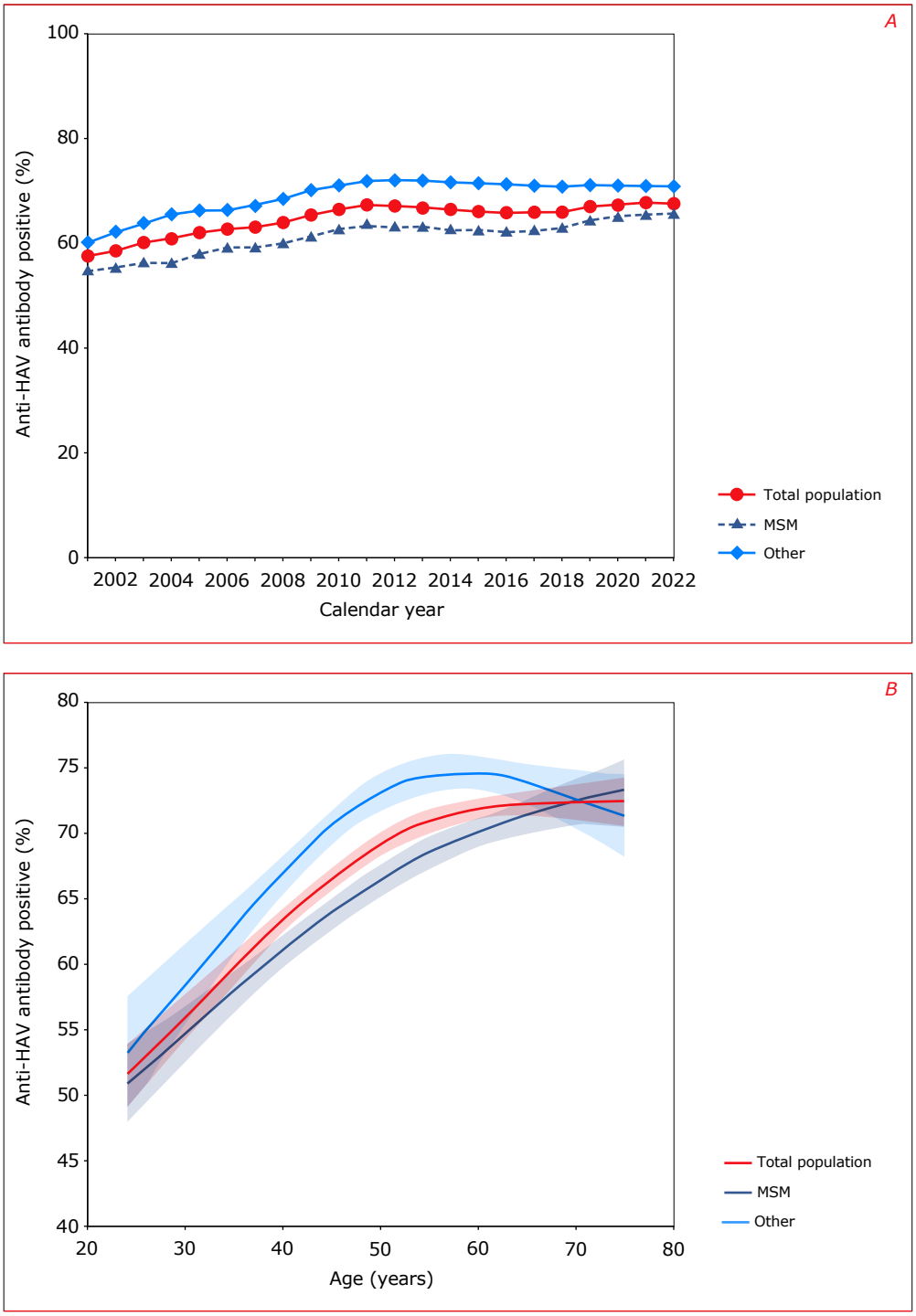
HAV seropositivity

Of the 18,302 individuals ever screened for HAV, a total of 12,353 (68%) had a positive anti-HAV antibody test result:

- 66% were observed in MSM;
- 66% in PWID;
- 73% in heterosexuals; and
- 66% in people from other transmission groups.

The prevalence of anti-HAV antibody positivity was 57% in 2001 and then slowly increased to 67% in 2022 (Figure 4.20A). For MSM, the prevalence of anti-HAV antibody positivity was 55% in 2001, and it also slowly increased, reaching 66% in 2022. For all other transmission groups, the prevalence of anti-HAV antibody positivity was 60% in 2001 and 71% in 2022.

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



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

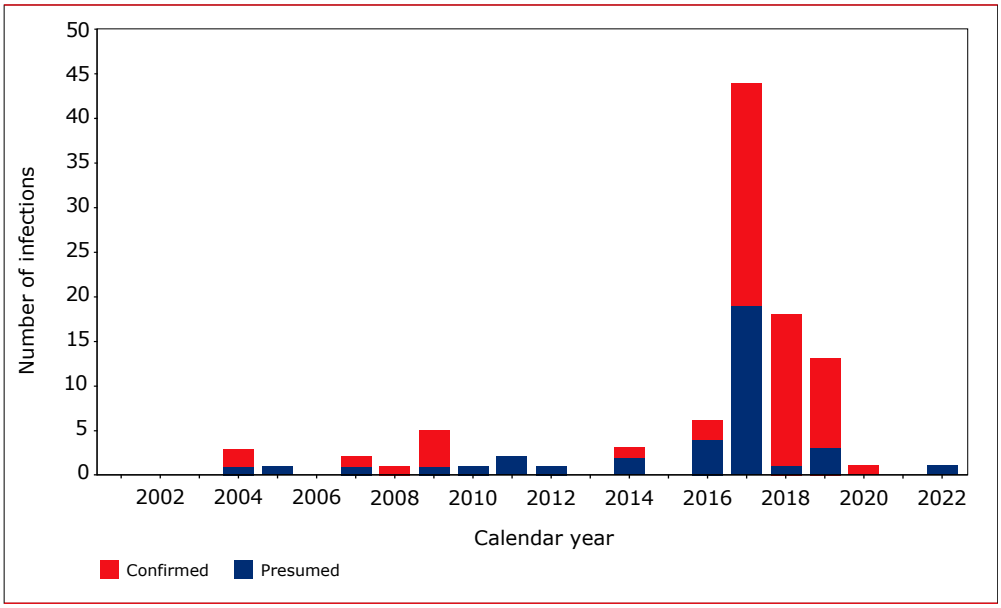
Epidemiological studies have highlighted the strong relationship between increasing anti-HAV antibody positivity and increasing age[41]. This age-dependent relationship was also observed in the 18,302 individuals ever screened for HAV (Figure 4.20B). Overall, anti-HAV antibody positivity was 58% for individuals below the age of 40, and 70% for those aged 40 and above. For MSM, anti-HAV antibody positivity was 57% for individuals below the age of 40, and 68% for those aged 40 and above. For all other transmission categories, anti-HAV antibody seropositivity was 60% for individuals below the age of 40, and 73% for those aged 40 and above.

Individuals with acute HAV diagnoses

Diagnoses of acute HAV infection were determined as either presumed (i.e., reported in the clinical file), or confirmed (i.e., detection of IgM anti-HAV antibodies or HAV RNA). Among the individuals who were in care between 2001 and 2021, there were 108 reported cases of acute HAV infection (n=69, presumed; n=39, confirmed), of which 86 (80%) were observed in MSM, 14 (13%) in heterosexuals, and 8 (7%) in those with other transmission categories.

Cases of acute HAV were first documented in 2001, and the number of acute HAV cases were lower than five per year until 2017, when 44 cases of acute HAV infection were documented (n=25, presumed; n=19, confirmed) (Figure 4.21). This figure decreased to 18 in 2018 and 13 in 2019. Of the 77 documented cases occurring between 2017 and 2019, 66 (86%) were observed in MSM. This increase in HAV infections was part of a European-wide outbreak of HAV among sexually-active MSM in 2017[42]. In 2022, there was only one case of acute HAV infection.

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

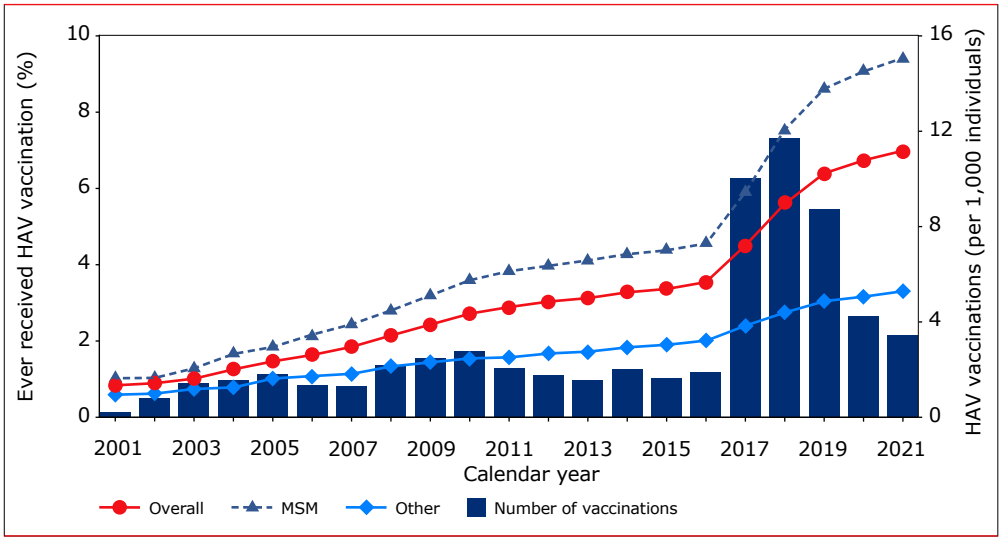


Of the 108 reported cases of acute HAV infection, 58 (54%) were recorded to have severe clinical symptoms. Severe chronic liver disease, according to our definition, was considered to be present (presumptive and definitive categories combined) in 18 (17%) of those with a reported acute HAV infection. Definitive severe chronic liver disease was documented for three (3%) with a reported HAV infection. No deaths due to acute HAV infection were reported.

HAV vaccination in individuals living with HIV

Information on HAV vaccination status was obtained from clinical files and was unknown for the majority of individuals ever registered by shm. Of the 30,050 individuals living with HIV ever registered in the shm database, 2,219 (7%) had received at least one HAV vaccination, according to their clinical file. The Netherlands has recommended HAV vaccination for any individual at risk of acquiring HAV infection (e.g., travellers to high-HAV endemic regions, professionals with potential exposure to HAV, and people with chronic hepatitis B or C)[43]. HAV vaccination frequency was consistently lower than or equal to three vaccinations per 1,000 individuals living with HIV from 2001 to 2016. It increased substantially to ten and 12 vaccinations per 1,000 individuals in 2017 and 2018, respectively (Figure 4.22). Accordingly, the percentage reported to have ever received an HAV vaccination was 0.9% in 2001, 3.8% in 2016, and 7.4% in 2022. In MSM, this percentage was 1.0% in 2001, 4.9% in 2016, and 10.0% in 2022.

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



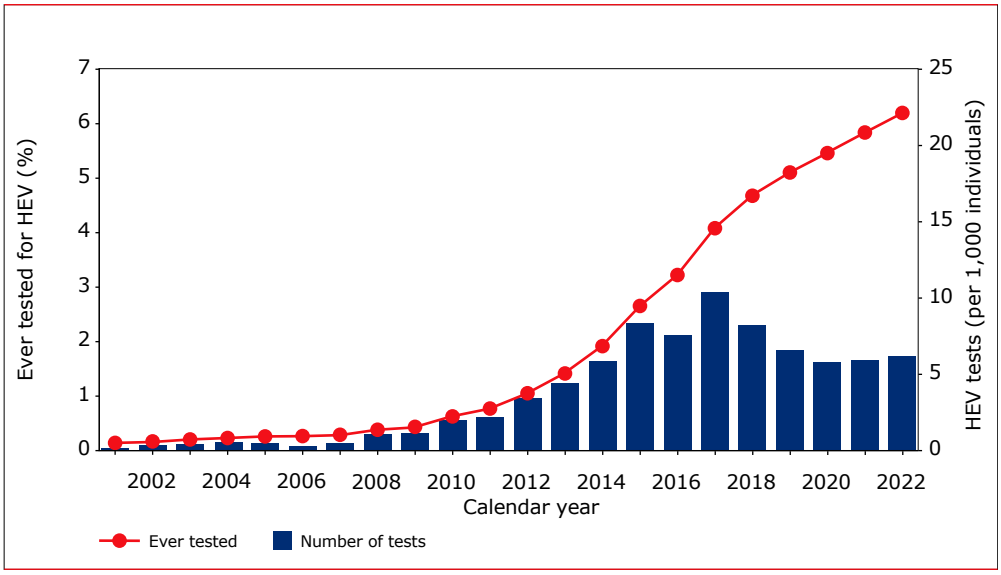
Legend: *HAV = hepatitis A virus; MSM = men who have sex with men.*

Hepatitis E virus (HEV)

HEV screening and seropositivity

Screening for HEV involves testing for IgG anti-HEV antibodies or HEV antigen (to establish past or current infection), or a combination of HEV RNA and/or IgM anti-HEV antibodies (to establish acute HEV infection). Six percent of the 30,050 individuals living with HIV ever registered in the shm database have been screened for HEV. The screening frequency for HEV infection in individuals living with HIV in care was low between 2001 and 2010, reaching a maximum of two tests per 1,000 individuals (Figure 4.23). HEV testing frequency rapidly increased from two tests per 1,000 individuals in 2011 to 10 tests per 1,000 individuals in 2017. In 2022, this frequency was six tests per 1,000 individuals.

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



Legend: HEV = hepatitis E virus.

Individuals with acute HEV diagnoses

Of the 1,852 individuals who were in care between 2001 and 2022, and who were ever screened for HEV, 252 (14%) were newly diagnosed as having past or current HEV infection. Of these individuals, 162 (64%) were MSM, 59 (23%) heterosexuals, six (2%) PWID, and 25 (10%) were from other transmission groups. The largest number of new diagnoses were observed between 2013 and 2020 (Figure 4.24), mainly due to the higher frequency of HEV testing among individuals living with HIV. The percentage of individuals newly diagnosed with past or current HEV infection ranged from 9% in 2004 to 14% in 2022 (Figure 4.25).

Of all individuals tested for HEV and in care between 2001 and 2022, there were 55 individuals diagnosed with acute HEV infection, of whom 40 were MSM and 9 heterosexuals. Only two of these cases were confirmed to have progressed to chronic infection (i.e., positive HEV RNA lasting more than three months). One of these individuals was treated with ribavirin and both were able to resolve their infection (i.e., achieve undetectable HEV RNA after chronic infection had been established).

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

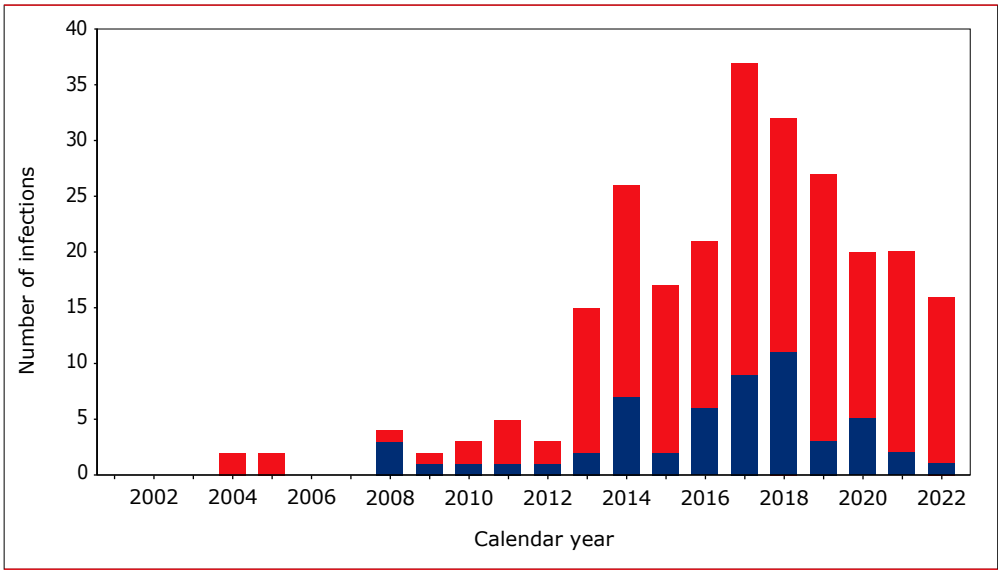
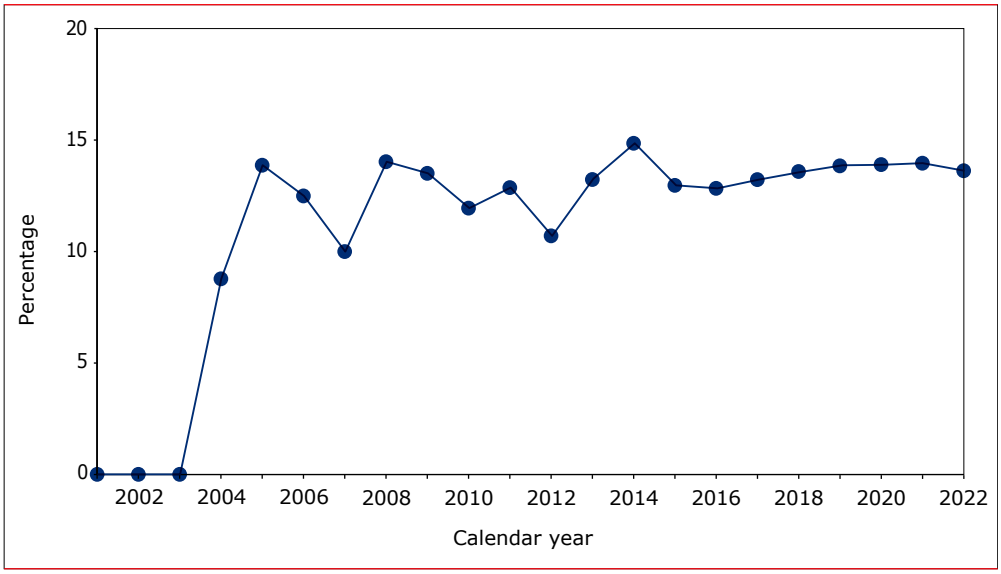


Figure 4.25: Percentage ever infected with HEV per calendar year.



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

Conclusions

Five percent of individuals living with HIV ever registered between 1998 and 2022 in the shm database, have been documented as having chronic HCV at some stage, and 3% have been documented as having had a recent HCV infection. Acute HCV infection occurred more often among MSM (5%), while reinfection of HCV was documented in 18% of the MSM ever diagnosed with primary HCV.

Our data clearly show that novel DAAs, which arrived in 2014, have entirely replaced PEG-IFN-containing regimens. In addition, the number of individuals living with HIV receiving treatment for HCV has rapidly increased. More than 1,250 individuals have now received, or are currently receiving, treatment with novel DAAs. Overall, 98% of all individuals with sufficient follow-up data to calculate an SVR were found to have been cured. When retreatment was taken into account, the SVR for the last course of treatment was 99%. This high cure rate has reduced the number of individuals with HIV and HCV remaining in need of HCV treatment to 37 in 2022. A recent Dutch study describing barriers to DAA treatment among people with HIV found that the appearing barriers were mostly patient-related,

and included a low frequency of clinical visits and refusal by patients[49]. Overall, a rapid reduction in the prevalence of active HCV infections was achieved, with prevalence in MSM having declined to 0.16% in 2022. Successful treatment of HCV has also prevented onward transmission of HCV, which is reflected in the lower incidence of recent HCV infections in recent years[22,50]. However, in line with earlier reports[27,30,44], HCV reinfection after successful treatment has been observed, but the rate of reinfections has strongly declined over the previous years. Our data showed a decrease in annual HCV testing, while screening for HCV RNA among those at risk of HCV reinfection is an important factor in identifying HCV reinfection. This might have led to an underestimation of the incidence of HCV reinfections.

Six percent of the individuals living with HIV ever in care had HBsAg positive serology. The prevalence of HBsAg positive serostatus has decreased over time from 7.8% in 2001 to 3.9% in 2022 overall, and across all transmission groups, mostly as a result of increased HBV vaccination rates[31], together with the treatment-as-prevention effect of TDF/TAF in ART-treated individuals. Nonetheless, an estimated 25% of all individuals living with HIV have either not been exposed to HBV, or have not been successfully vaccinated, and may remain at risk of acquiring HBV. Since 83% of all individuals still at risk of acquiring HBV infection use an ART regimen that includes TDF/TAF, their risk is probably very low, due to sustained chemoprophylaxis. The remaining 17% of the individuals living with HIV ever registered remain unprotected against HBV, which represents an estimated seven percent of the total population of individuals living with HIV screened for hepatitis B. Very few individuals were tested for HDV infection and, of those who were tested, a small percentage had evidence of active HDV.

Among the individuals living with HIV ever registered by shm, 24% of those with chronic HCV and 16% of those with chronic HBV had evidence of severe chronic liver disease. However, the absolute number of HCC diagnoses has been decreasing since 2011, which can likely be attributed to the use of effective antiviral treatment for HBV and HCV co-infections. Overall, people with chronic HCV or HBV remained at increased risk of having a liver-related cause of death, although this risk has declined substantially since 2012. The overall mortality rate has decreased in individuals with HIV/HCV and HIV/HBV co-infections since 2012, yet the rate remained much higher for PWIDs with HCV or HBV, compared to other transmission groups.

Over half of the individuals ever registered by shm have been tested for anti-HAV antibodies, with testing frequency consistent across calendar years. The percentage of tested individuals found to have anti-HAV antibodies was no different between MSM and other transmission groups, but it was more than double the percentage

found in the general Dutch population[45]. The percentage of people living with HIV with anti-HAV antibodies was higher in older age groups, as would be expected from the general epidemiology of HAV infection[41]. Among the individuals diagnosed with HAV, almost half reported having severe symptoms during their infection, while three individuals developed definitive severe chronic liver disease. Nevertheless, no individual died due to HAV infection.

The percentage of individuals reported to have received at least one HAV vaccination was low at 7%; this could be due to incomplete data on HAV vaccination. Despite the high prevalence of anti-HAV antibodies, the fact that only half of the individuals ever registered by shm were tested for anti-HAV immunity, and vaccine uptake was low, could signal that a substantial percentage of individuals remain at risk of HAV infection. Indeed, the majority of HAV diagnoses that were registered in the shm database were observed in HAV-susceptible MSM between 2017 and 2019.

Almost one in 20 individuals ever registered by shm have been screened for HEV. Testing frequency of HEV has increased substantially since 2014, probably due to awareness of HEV infection in Europe and its recognised role in hepatitis and liver-related disease[18]. With increased testing, the number of individuals newly diagnosed with past or current HEV infection, or with acute HEV infection, also increased from 2014 onwards. Nevertheless, the percentage of individuals ever identified as having an HEV infection has remained stable at between 9% and 15% over the past decade. This percentage is similar to figures found in the Dutch general population[17]. We were unable to determine whether any liver-related morbidity and mortality, or any extra-hepatic disease was associated with HEV infection.

Recommendations

Continued efforts must be made to ensure that all individuals with HIV are adequately assessed for the presence of HBV and HCV co-infection, or acute HCV (re)infection. In particular, efforts should continue to increase HBV vaccination rates among individuals living with HIV who remain at increased risk of acquiring HBV, particularly those who are not receiving an antiretroviral regimen containing TDF or TAF, and those who previously failed to respond to vaccination[46]. Already, the provision of highly-effective DAA regimens for all known individuals living with HIV and HCV has coincided with reductions in the burden of severe chronic liver disease, hepatocellular carcinoma, and mortality related to liver disease. In addition, these novel regimens have a beneficial impact on the risk of ongoing HCV transmission. Importantly, regular HCV RNA screening among individuals who have been successfully treated for HCV infection and who remain at risk of

reinfection, is recommended to ensure early detection of new HCV infections. This should be combined with behavioural interventions aimed at MSM to prevent HCV reinfection after successful treatment of HCV.

HDV clinical practice guidelines from the European Association for the Study of the Liver suggest that individuals with chronic hepatitis B infection should be tested at least once for HDV[36]. In the Netherlands, 14% of individuals who ever had HBV had been tested for HDV infection; the reasons for this low percentage need to be clarified. This information could help to establish whether HDV infection in the Netherlands is a substantial contributor to liver-related morbidity and mortality in individuals living with HIV with HBV infection, as found in other settings[13].

Only half of the individuals ever registered by shm have been screened for HAV and, among those tested, almost two-thirds had anti-HAV antibodies from either vaccination or cleared infection. Even though HAV infection reports have been uncommon over the last two decades, the recent HAV outbreak in MSM[41] brings strong evidence that clinicians need to assess HAV risk and, if present, recommend vaccination. Given that anti-HAV antibodies were less commonly detected in younger individuals, they should be particularly targeted for HAV vaccination.

Studies have suggested that individuals who are immunosuppressed should be tested annually for HEV[47]. However, data from shm and a meta-analysis found no noteworthy increase in HEV prevalence among individuals living with HIV[48], and only two patients in the shm database were diagnosed with chronic HEV infection. We recommend following current European guidance, which advises that individuals with persistently-elevated transaminase levels should be screened for HEV RNA[18]. Further data are needed to determine to what extent liver-related, and non-liver-related, disease occurs as a result of HEV infection in individuals living with HIV.

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5. Distinct populations: Children with HIV in the Netherlands

Colette Smit, Tom Wolfs, Annemarie van Rossum

Box 5.1: 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 2022	Individuals with HIV who had a documented clinic visit or lab measurement in 2022.
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 5.2: Outline of the paediatric ATHENA cohort in the Netherlands: all children with HIV registered in the ATHENA cohort before 31 December 2022. (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=400).
2. Population of those diagnosed as a child and in care in 2022:
   - under the age of 15 in 2022 (n=124); includes 104 adopted children.
   - aged 15-18 years in 2022 (n=44); includes 33 adopted children.
   - aged 18 years and over in 2022 (n=159); includes 11 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 5.2*)[a]:

- demographics
- clinical characteristics
- treatment regimens between 2013-2022.
- long-term virological and immunological responses to treatment between 2013-2022.

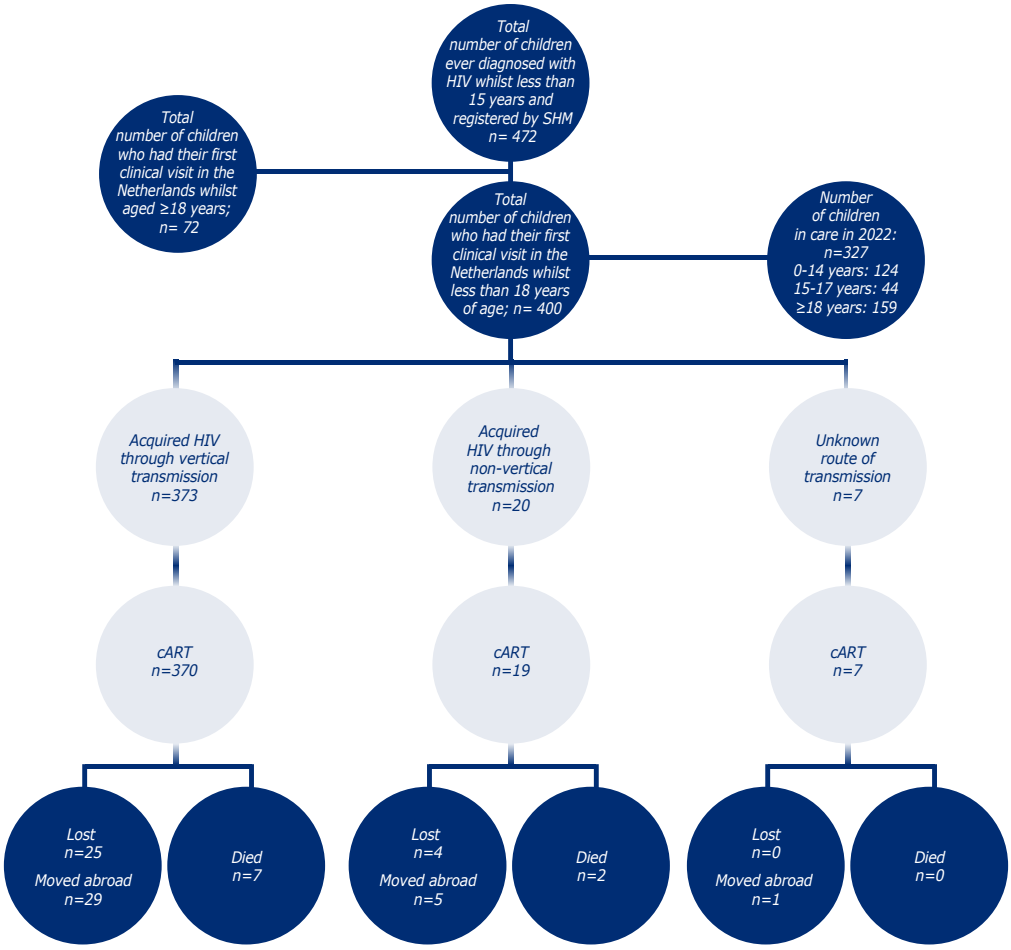
The limit of 15 years is aligned with the definition of children used by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO)[1,2].

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 2019 SHM Monitoring report.

Ever registered

As of 31 December 2022 the SHM database includes 472 individuals diagnosed with HIV while under 15 years of age (*Figure 5.1*). Of these, 400 children entered care in the Netherlands before the age of 18. The remaining 72 individuals who were diagnosed as a child, entered care in the Netherlands *after* the age of 18; 78% (n=56) of those were born outside the Netherlands. And the other 16 were born in the Netherlands.

Figure 5.1: *Overview of total population children with HIV registered in SHM database as of 31 December 2022.*



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

Legend: *ART = antiretroviral therapy.*

The remainder of this chapter will focus on the 400 children diagnosed under the age of 15 and entered care in the Netherlands before the age of 18.

The majority (98%) of this group entered HIV care at a paediatric HIV treatment centre in the Netherlands; nine children entered care at an adult HIV treatment centre at a median age of *16.9 years* (*IQR 16.2-17.6*) (*Table 5.1*). The most commonly reported region of birth was Sub Saharan Africa (n=235, 59%) and the Netherlands (n=114, 29%); 51 (13%) children were born in other regions, including the Caribbean, Latin America, Europe and Asia. Per 31 December 2022 4 children born in Ukraine were registered.

Table 5.1: *Demographic and HIV-related characteristics of 400 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	Vertical transmission*	Non-vertical transmission*	Route of transmission unknown*
Total	373 (93)	20 (5)	7 (2)
HIV treatment centre			
Paediatric care	368 (99)	16(80)	7 (100)
Adult care	5 (1)	4 (20)	0
Gender			
Male	181 (49)	8 (40)	5 (71)
Female	192 (51)	12 (60)	2 (29)
Child's country of origin			
The Netherlands	112 (30)	2 (10)	0
Sub-Saharan Africa	212 (57)	16 (80)	7 (100)
Other	49 (13)	2 (10)	0
Mother's country of origin			
The Netherlands	33 (9)	2 (10)	0
Sub-Saharan Africa	189 (51)	8 (40)	5 (72)
Other/unknown	151 (40)	10 (50)	2 (28)
Adopted	149 (41)	0	3 (25)
Age at HIV diagnosis	1.1 (0.25-3.6)	11.5 (7.14-14.4)	10.9 (10.1-11.7)
ART-treated	370 (99)	19 (95)	7 (100)
Therapy-naïve at ART initiation	325(87)	16 (80)	7 (100)
CD4 at ART initiation	550 (278-1220)	324 (171-508)	475 (320-570)
CD4 Z-score at ART initiation	-0.6 (-1.0- -0.10)	-0.6 (-1.13- -0.01)	-0.50 (-0.7- -0.19)
VL (log copies/ml) at ART initiation	5.2 (4.5-5.8)	4.3 (4.0-5.5)	4.9 (4.6-5.1)

Legend: **Data are number (%) of children or median (interquartile range).*
ART = antiretroviral therapy; VL = viral load.

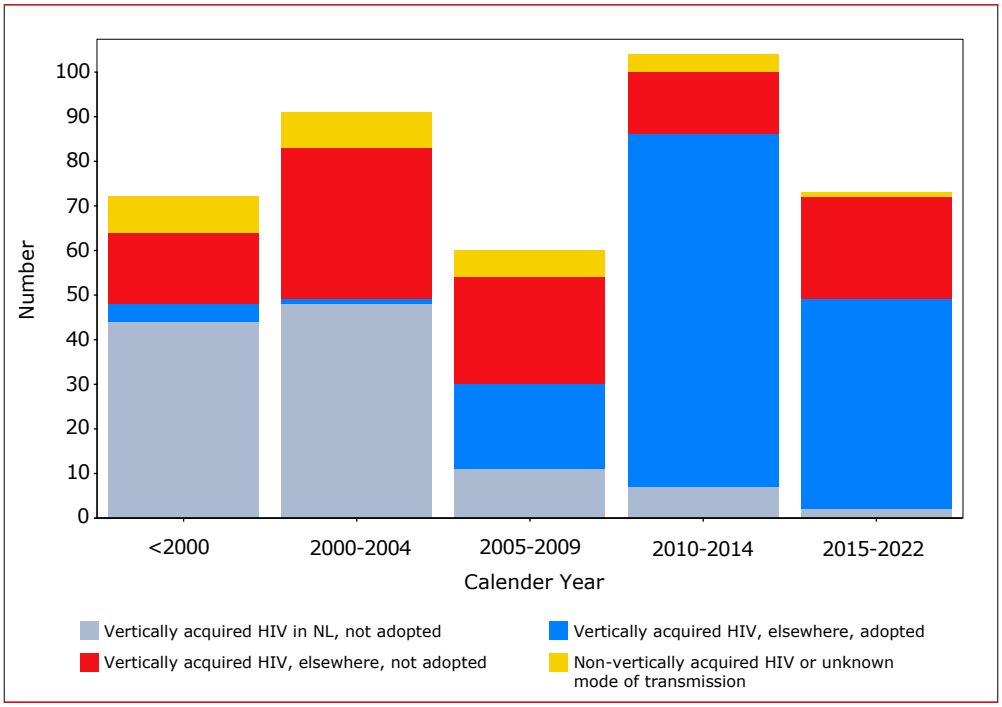
Mode of transmission

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

Vertical transmission

- Between 1998 and 2022, 373 children entered care after acquiring HIV through vertical transmission. (*Table 5.1*)
- 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] 0.3-3.6 years).
- 99% received care in a paediatric HIV treatment centre in the Netherlands.
- ART initiation was documented for 99% of the children.
- 57% (n=212) of the children were born in sub-Saharan Africa.
- 30% (n=112) of the children were born in the Netherlands.
- 9% of the children born in the Netherlands (10 out of 112), had two Dutch parents.

***Figure 5.2:** 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 5.2 shows the number of registered children by year of entering care, mode of transmission, and region of origin. The number newly entering care in the Netherlands has fallen over time from 104 in 2010-14 to 73 in 2015-22. 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 2022, 20 children were registered as having acquired HIV through non-vertical transmission (*Table 5.1*); the most likely modes (reported in the medical chart) were heterosexual transmission (n=8) and contact with contaminated blood and blood products or medical procedures (n=12). 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 7.14-14.4); 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.
- 40% of children acquired HIV through heterosexual contact.
- 80% were born in sub-Saharan Africa.
- 25% received care in an adult HIV treatment centre.

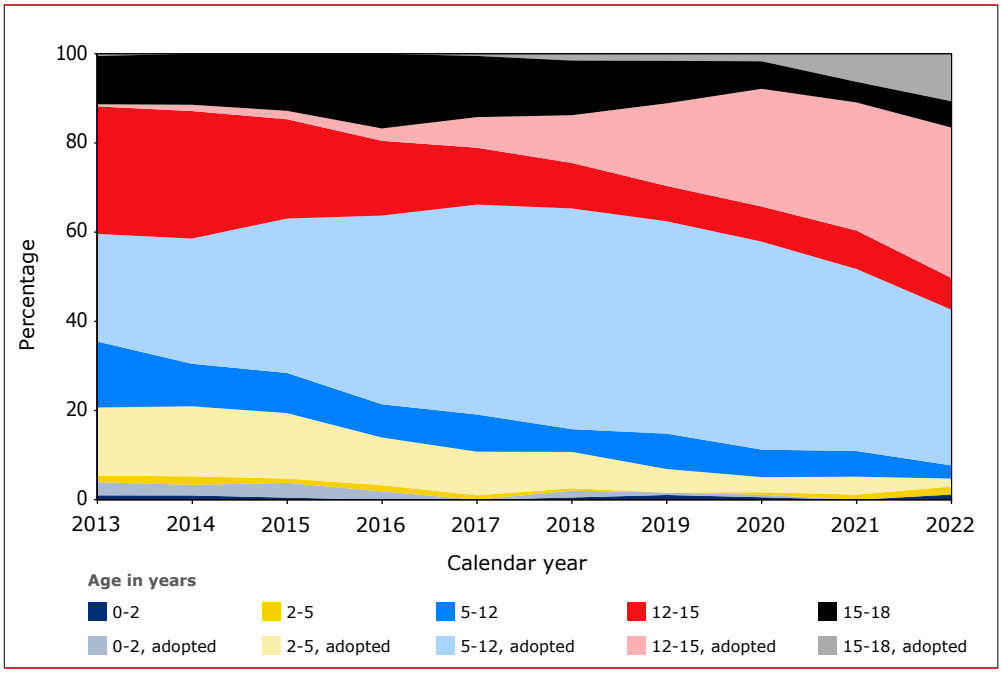
Unknown route of HIV transmission

- For 7 children with HIV, the route of transmission remains unknown (*Table 5.1*).
- Their median age at diagnosis was 10.9 years (IQR 10.1-11.7).
- All children had started ART.

Age distribution

Figure 5.3 shows the age distribution of children receiving HIV care in the last 10 years (2013-2022). Over time, the proportion of children aged 5-12 and 12-15 increased. This was mainly due to a relative increase in the rates of children adopted in those age groups. In 2022, 79% of children with HIV aged between 5 and 15 years was adopted.

Figure 5.3: Time-dependent age distribution of children with HIV in care over time.



Low mortality rates

No children registered with SHM were reported to have died before the age of 18 between 2013 and 2022. 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 2013 and 2022 seven young adults who had been diagnosed with HIV as children, died in adulthood; their median age at death was 26.8 years (IQR 24-30). Four of these young adults died from AIDS, two of a non-AIDS related cause and for one young adult the cause of death is unknown.

Antiretroviral treatment

Of the 400 children who entered care in the Netherlands before 18 years of age, 396 (99%) started ART; 348 (88%) of them were treatment-naive at the start of ART and 48 (12%) had previously been exposed to monotherapy or dual therapy (i.e. were pre-treated). In total, four children never received ART; all are no longer in care, and the last date of contact for them was between 1998 and 2010.

For the purposes of this analysis, both pre-treated and treatment-naive children who initiated ART from 2013 onwards have been included. Children were grouped by calendar year of ART initiation: 65 children started an ART regimen in 2013-2017 and 15 in 2018-22. For 14 children, the year of ART initiation is not known. All these children were born outside the Netherlands.

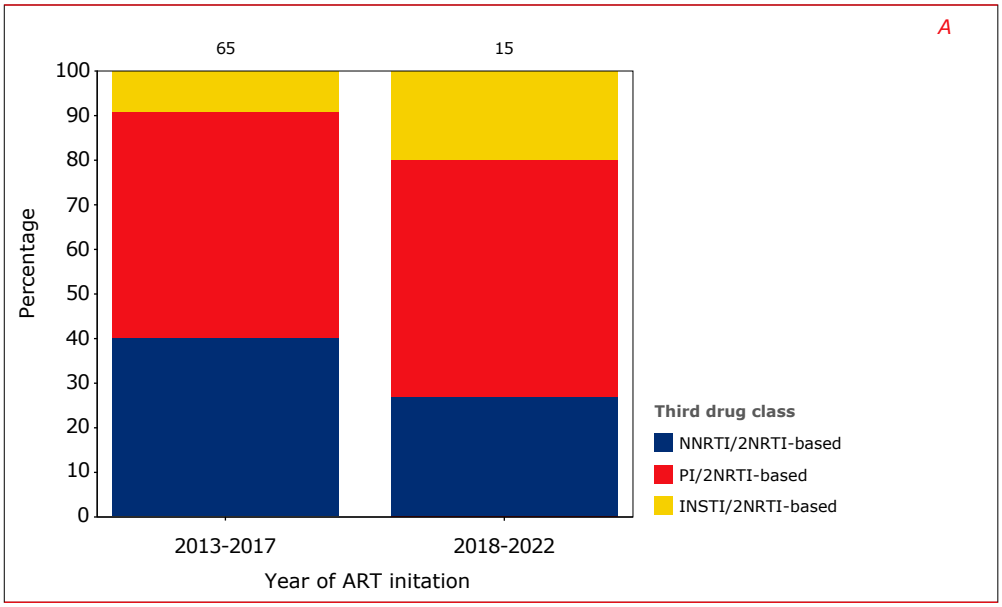
Initial antiretroviral regimen

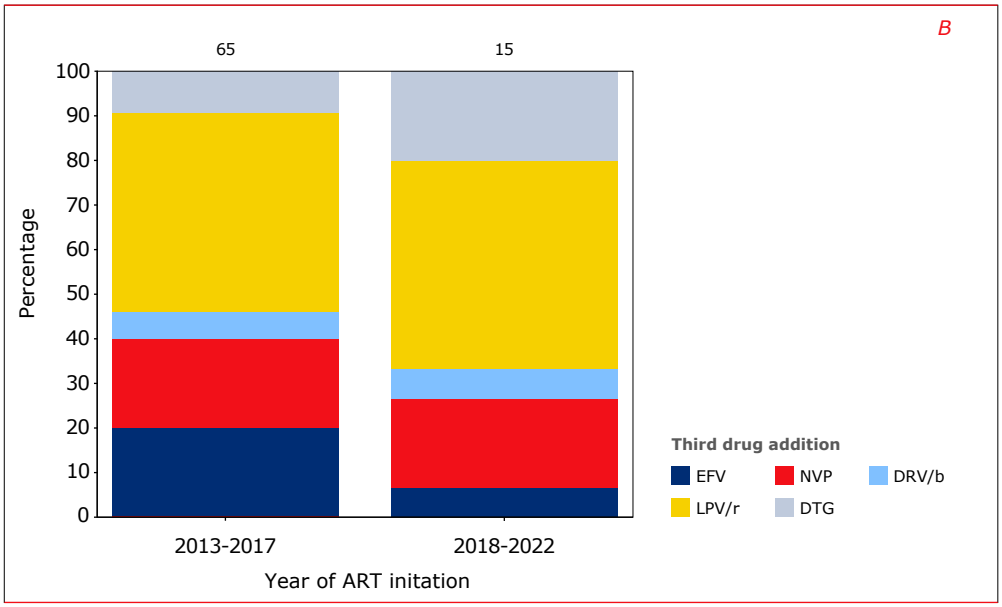
Of the 80 registered children known to have initiated ART between 2013 and 2022:

- 51% were treated with a first-line regimen that included a protease inhibitor (PI) and two or more nucleoside reverse transcriptase inhibitors (NRTIs);
- 38% were treated with a non-nucleoside reverse transcriptase inhibitor (NNRTI) with two or more NRTIs; and
- 11% were treated with an integrase inhibitor-based first-line with two or more NRTs regimen.

Figure 5.4 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 20% of the children who initiated a first-line regimen between 2018-2022.

Figure 5.4: *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.*





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.*

Discontinuation of the initial ART regimen

Among those who discontinued their first-line treatment regimen, the median time spent on first-line regimen among children who had started ART between 2013 and 2022 was 15.0 months (IQR 3-38). Discounting weight-related dose changes, 60 children (75%) discontinued their first-line treatment regimen. The most important reasons for changing included simplification (37%) and toxicity (13%). Virological failure was the reason given in 7% of cases and in 17% the reason was unknown.

Virological response

Virological response to ART was assessed based on viral suppression (i.e. viral load below 200 copies/ml and 50 copies/ml, [*Box 5.1*]). Initial virological response is reported for the first two years after starting ART between 2013-2022. Long-term virological response is reported by time-updated age for those who used ART for at least 24 months.

Initial response to ART

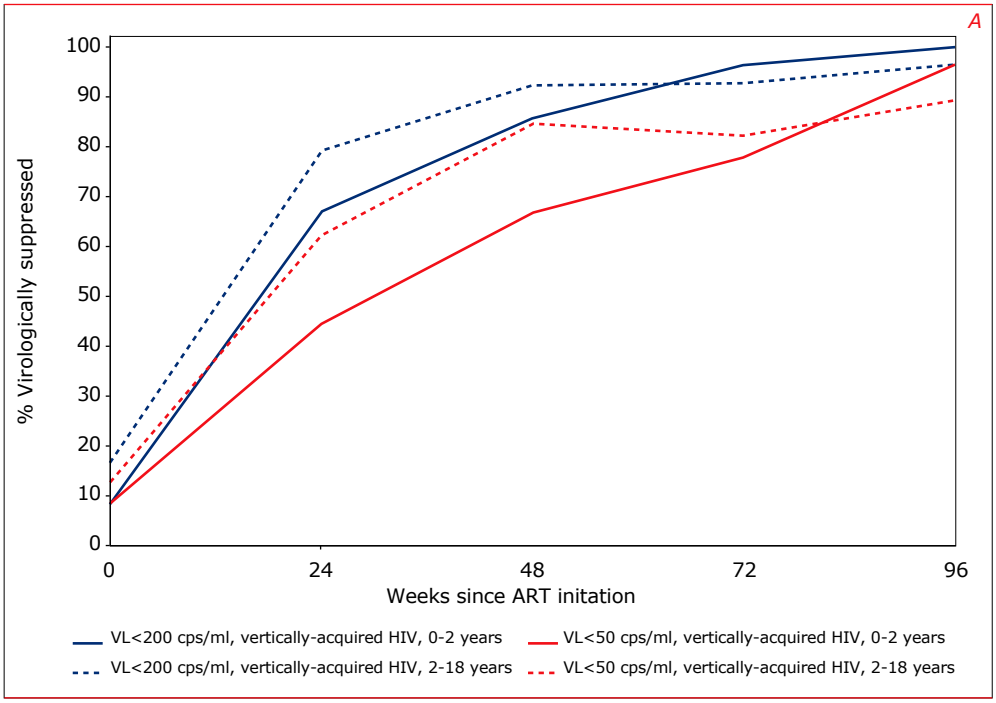
This analysis used data from the 80 children who were registered with SHM and had started ART between 2013-2022, and who had viral load data available in the first 24 months after ART initiation. Children were stratified by age at ART initiation, resulting in the following categories:

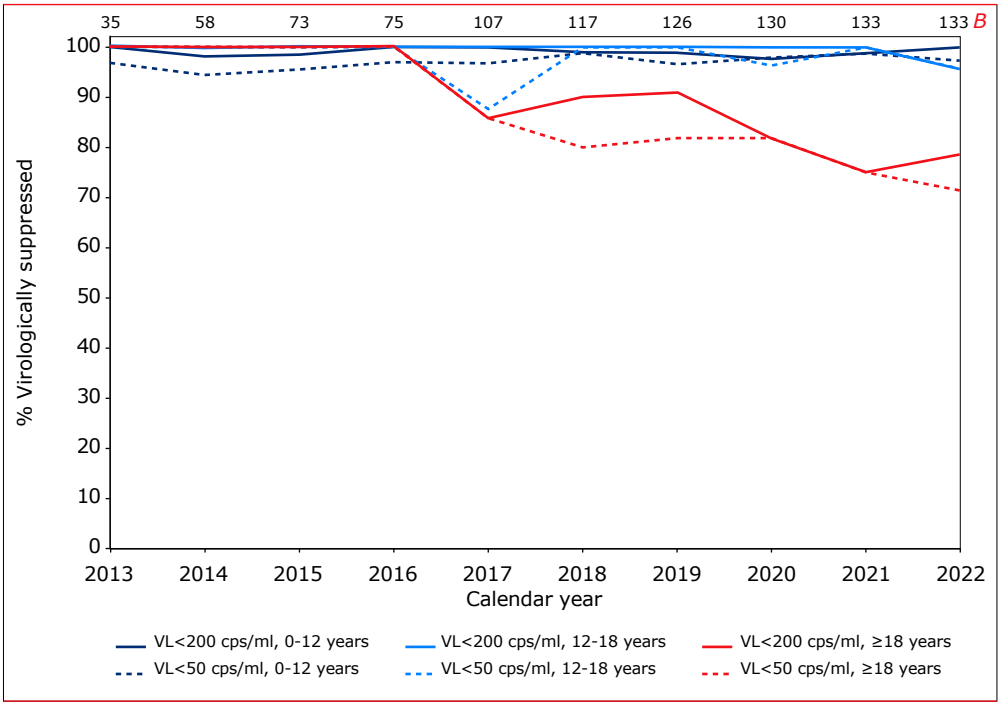
(1) 0-2 years
(2) 2-18 years

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 2013-2022 of ART initiation. *Figures 5.5A* shows viral suppression rates among children who initiated ART between 2013 and 2022:

- Among children who were aged 0-2 years at the time of ART initiation, viral suppression <200 copies/ml rates increased from 67% after 24 weeks, to 85% after one year of ART, to 100% after two years. Viral suppression <50 copies/ml rates were 44%, 67% and 96% after 24 weeks, one and two years.
- Among children who were aged 2-18 years at ART initiation, viral suppression <200 copies/ml rates increased from 79% after 24 weeks, to 92% after one year of ART, and 96% after two years, viral suppression <50 copies/ml rates were: 63%, 84% and 89% after 24 weeks, one and two years.

Figure 5.5: *Viral suppression following antiretroviral therapy (ART) initiation: (A) during the first two years of ART 2013–2022, (B) time-dependent and age-dependent viral suppression rates for children in care between 2013 and 2022 after two years of ART with ART initiation from 2010 onwards. Viral suppression is defined as any viral load measurements below 200 copies/ml and below 50 copies/ml, except for time points in the past where tests were used with quantification limits above 200 copies/ml or 50 copies/ml. The numbers above the bars represent the total number of individuals with an viral load measurement.*





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

Long-term virological response

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

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 5.5B*). 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.

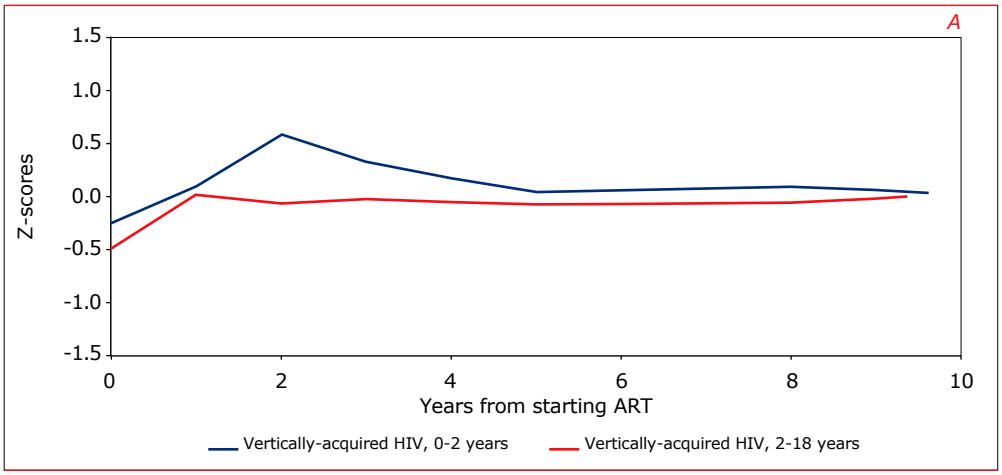
CD4 Z-scores represent the standard deviation from the reference values for HIV-negative children. They were calculated for CD4 cell counts to correct for age-related differences. All absolute CD4 T-cell counts were transformed into Z-scores by subtracting the age-related reference value for the age 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 5.6 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 2013 and 2022, CD4 Z-scores increased significantly for both age groups in the year following ART initiation. However, in the second year the increase in CD4 Z-scores was less pronounced for children aged between 2-18 years at time of ART initiation, resulting in higher CD4 Z-scores among the youngest children (*Figure 5.6*).

Figure 5.6: 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 2013 and 2022).



Legend: ART = antiretroviral therapy.

Currently in clinical care

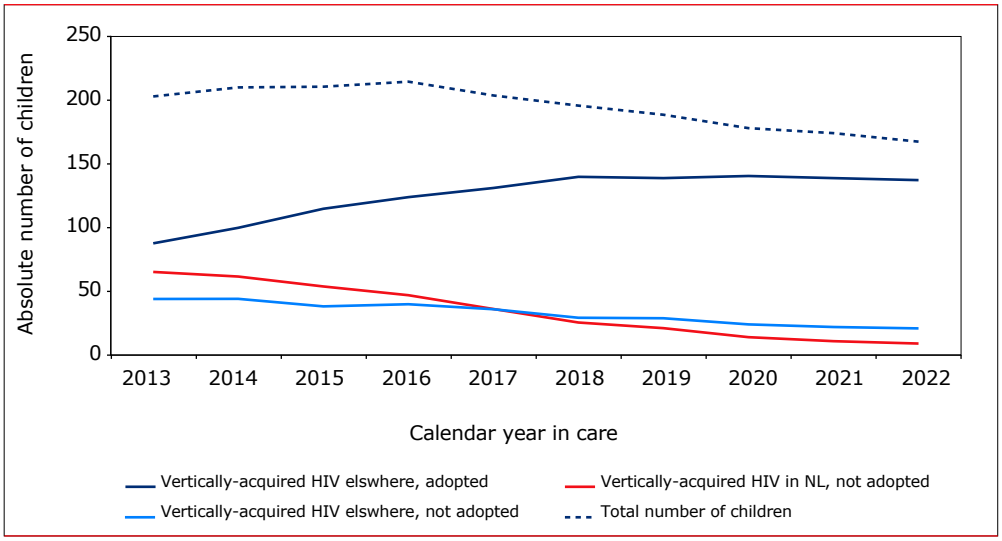
Of the 400 children with HIV ever registered by SHM, and who entered care in the Netherlands before the age of 18, 327 (82%) were still in care in 2022 and 73 were no longer in care. Of these 73 individuals :

- Nine had died;
- 35 had moved abroad;
- 29 were lost to care.

Of the 327 individuals still in care, 168 of them were under the age of 18 (*Figure 5.1*).

Figure 5.7 shows the number of children under 18 years of age in care, for each calendar year. This figure reached its peak in 2016, with 215 children. However by 2022, this figure had declined to 168, 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 5.7: Number of children aged <18 years known to be in care at the end of each calendar year shown by mode of HIV transmission and adoption status. Note: Children with non-vertically-acquired HIV are not reported as a separate category due to their small numbers, but they are included in the total number of children in care.



Currently in care and under 18 years of age

- 168 were younger than 18 years at the end of 2022
- 124 were younger than 15 years
- The median age was 13 years (IQR 10-15) as of 31 December 2022.

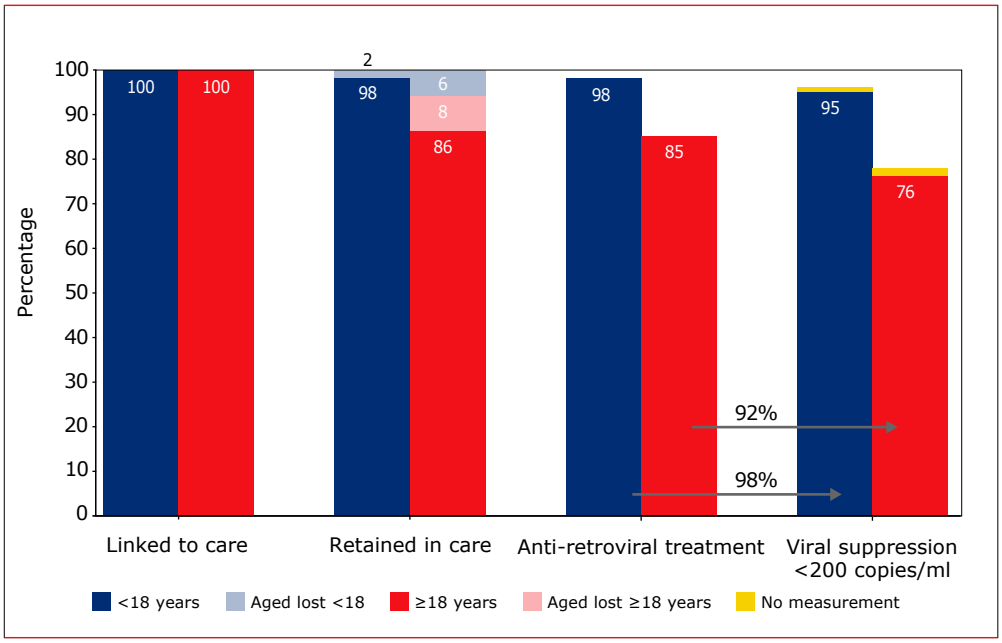
Currently in clinical care and 18 years or older

- 159 were older than 18 years at the end of 2022
- The median age was 25 years (IQR 22-29) as of 31 December 2022

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 2022 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 5.8*).

Figure 5.8: Continuum of care by age, as of 31 December 2022. The numbers in and above the bars indicate the proportion of individuals.



Individuals were stratified by age on 31 December 2022 and categorised as:
(1) current age, under 18 years
(2) current age, 18 years or older

Continuum of care: current age under 18 years

- 171 children were linked to care, registered by SHM, still alive and not reported to have moved abroad.
- 99% (168) were retained in care: three children, all were born outside the Netherlands, were lost to care.
- 98% (168) had ART during their last clinical visit in 2022.
- 95% (163) of all individuals linked to care had a most recent HIV RNA measurement below 200 copies/ml (98% of those on ART).

Continuum of care: current age 18 years or older

- 185 individuals were linked to care, registered by SHM, still alive and not reported to have moved abroad.
- 86% (159) were retained in care. The remaining 26 (15 of whom were born outside the Netherlands) were lost to care: 11 before they turned 18; 15 when they were older than 18 years of age.
- 85% (157) had ART during their last clinical visit in 2022.
- 76% (141) of all individuals linked to care had a most recent HIV RNA measurement below 200 copies/ml (92% of those on ART).

It is worth noting that 19 of the 26 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.

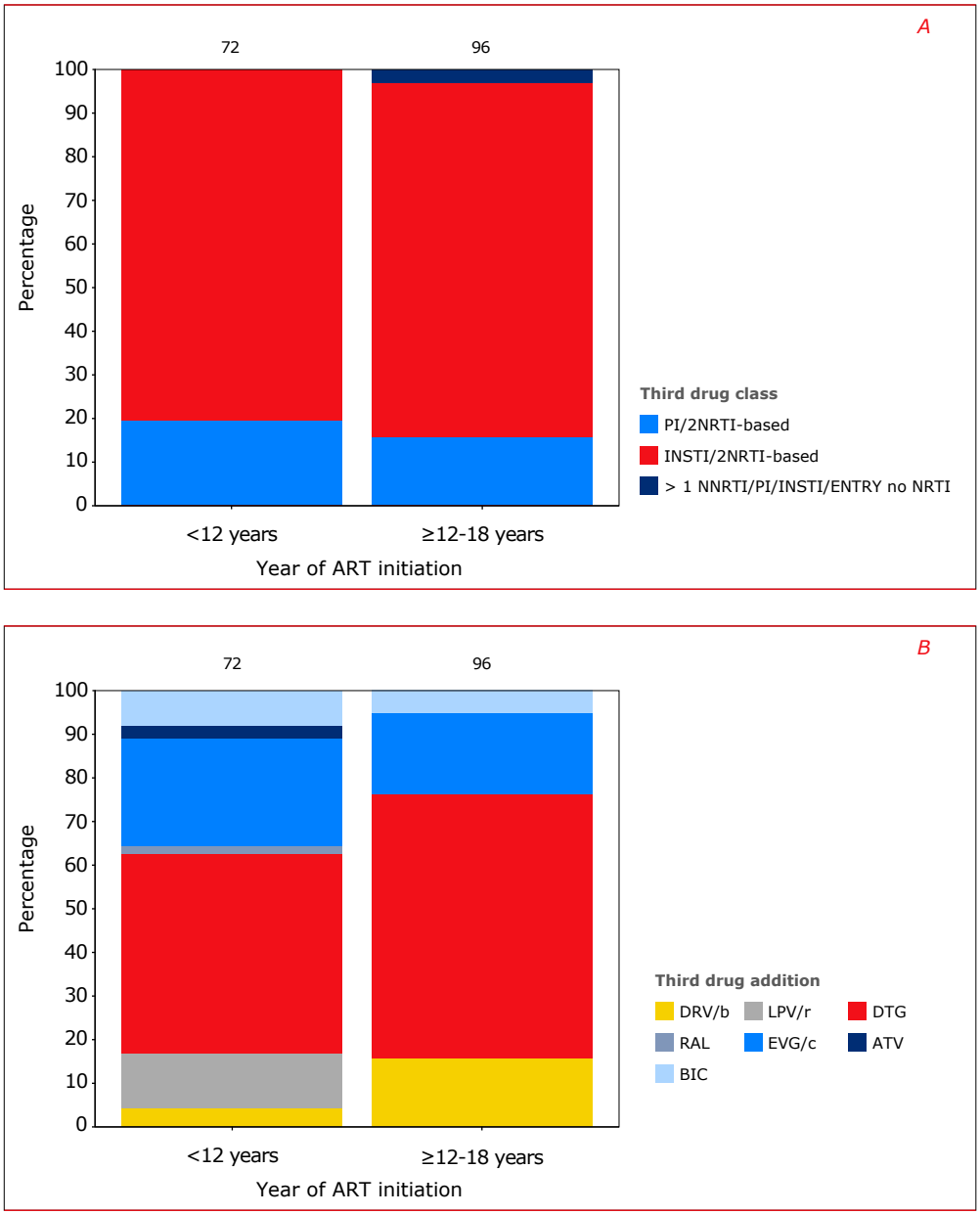
In care and on ART in 2022

Of the 168 children known to be in care in 2022 and under 18 years of age, all had ART during their last reported clinical visit. The distribution of current ART use is shown in *Figure 5.9*, according to age on 31 December 2022.

Among those under 12 years of age, INSTI-based regimens were the most commonly-used (81%), with dolutegravir (46%) and elvitegravir (25%) the most common individual third agents.

In children aged between 12 and 18 years, 81% were using an INSTI-based regimen and 18% a PI-containing regimen. Among those using an INSTI-based regimen, dolutegravir was most common (60%), followed by elvitegravir (19%). Overall, 11 children used bictegravir.

Figure 5.9: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the current regimen, stratified by current age: (A) antiretroviral class, and (B) specific drug. Numbers above the bars represent the total number of individuals initiating 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 400 children ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 152 (38%) had been adopted by Dutch parents. The percentage of adopted children newly entering care increased from 5% <2000 to 76% between 2010-2015, and was 64% between 2011-2022 (*Figure 5.2*), with a median age at the time of entering care of 2.7 years (IQR 1.6-5.0). Overall:

- 109 (72%) children were already receiving ART before they entered care in the Netherlands;
- 17 (11%) children were treated with monotherapy or dual therapy before the start of ART;
- All children had ART during follow up in clinical care at one of the Dutch HIV treatment centres;
- Four adopted children are no longer in care because of lost to follow up, moved abroad or died);
- All children known to be in care were still receiving treatment in 2022;
- 99% of those still in care had an undetectable viral load (equal to or below 200 copies/ml) in their most recent HIV RNA measurement and 95% had an undetectable viral load <50 copies/ml.

Initially, at the time of entering care in the Netherlands, only 66 (43%) of the 152 children had a viral load below 200 copies/ml and 27% below 50 copies/ml.

Figure 5.7 shows the number of adopted children still in care and under 18 years of age. As of 31 December 2022, 148 children were alive and in care and 137 of them were aged below 18 years. Their median age was 12.3 years (IQR 10.4-15.0).

Transfer to adult care

Of the 400 children ever registered by SHM who were under the age of 18 when they entered care in the Netherlands, 169 children had reached the age of 18 and above, and had transferred from paediatric care to adult care by 31 December 2022.

Figure 5.10: Follow up status, as of 31 December 2022, of children who transferred to adult care.

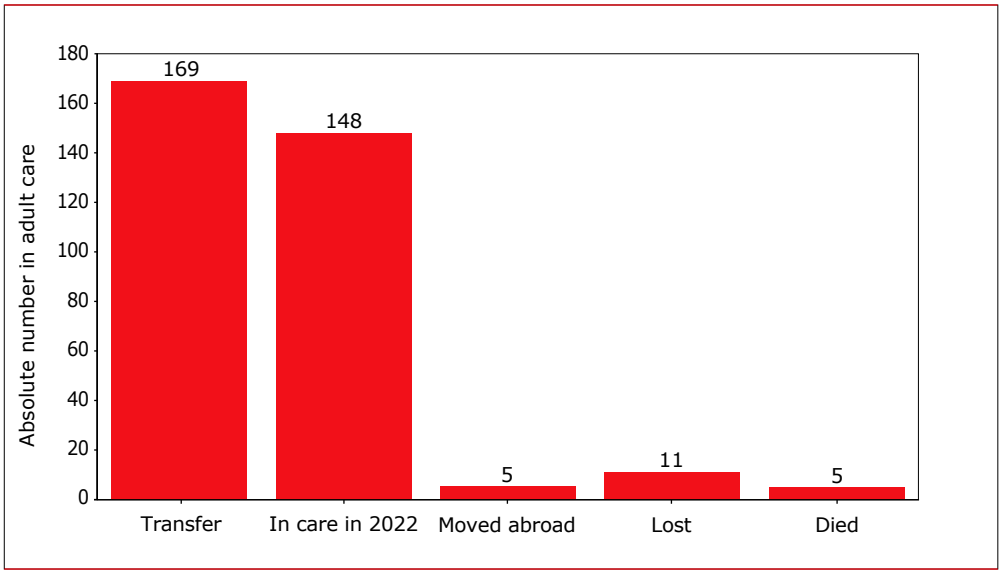
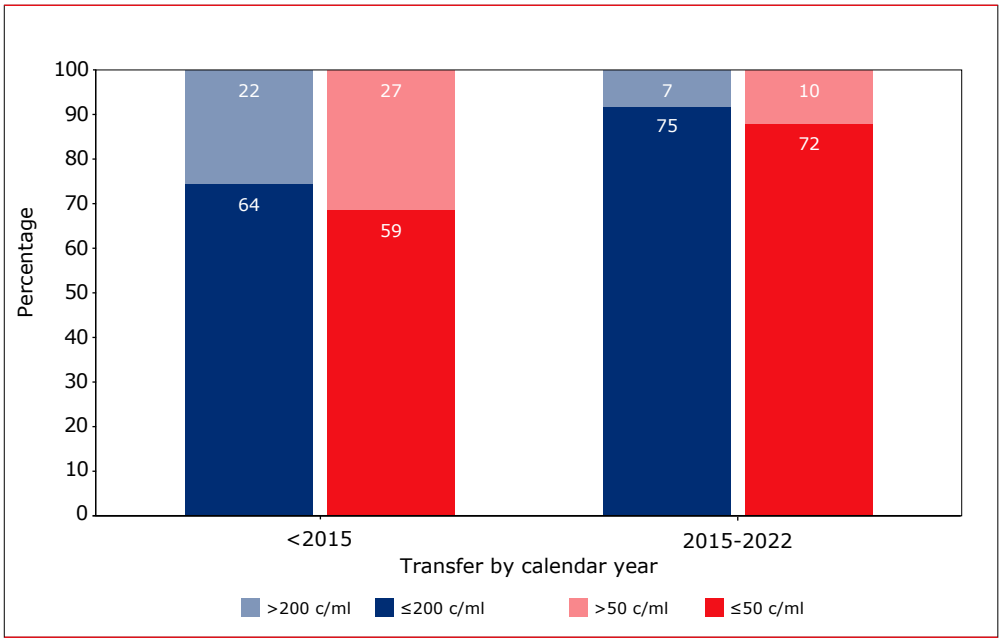
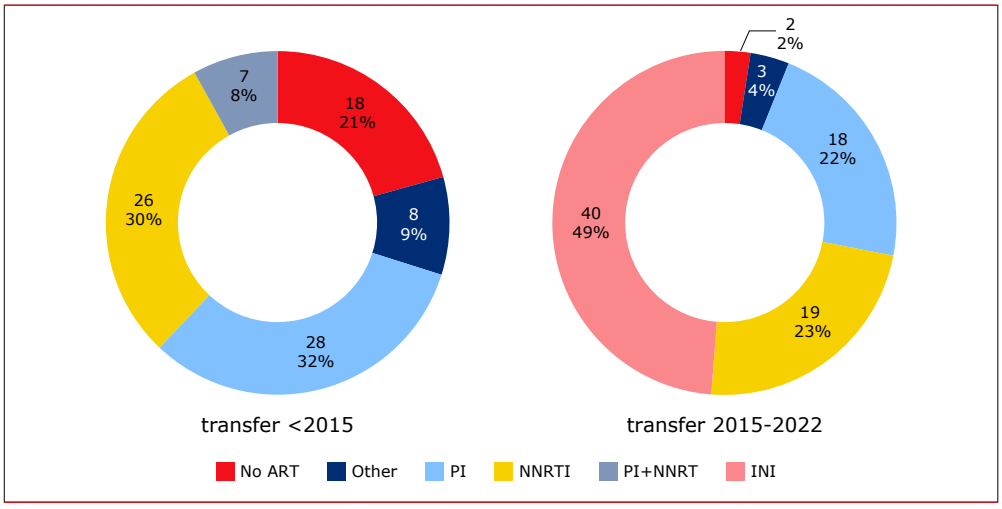


Figure 5.11: HIV RNA (A) and ART regimens (B) at last visit in paediatric care of children who transferred to adult care, stratified by calendar year of transfer (A).





The median age for their last visit to paediatric care was 18.3 years (IQR 18.0-19.0). The median time between their last visit to paediatric care and their first visit to adult care was 3.8 months (IQR 2.7-5.7). Time in care after transfer until their last documented clinical visit was 7.2 years (IQR 4.4-10.2).

Figure 5.10 shows the follow up status of the 169 adolescents who transferred to adult care:

- 148(88%) were still in care in 2022;
- 11 (7%) were lost to care – 5 of these 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);
- five (3%) had moved abroad; and
- five (3%) had died.

Overall, at the time of their last clinical visit to paediatric care, 29 adolescents (17%) had an HIV RNA level above 200 copies/ml (median 3444; IQR 1220-27065). When taking into account 50 copies/ml, 37 adolescents had an HIV RNA < 50 copies/ml (22%). This figure is more or less comparable to results from the UK and Ireland, where three quarters of adolescents were virologically suppressed at the time of transition[18]. However, we observed a lower proportion of detectable HIV RNA levels among young adolescents who made their transfer to adult care in or after 2015 compared to those who transferred before 2015, from 25% to 8% and from 31% to 12% for >200 copies/ml and 50 copies/ml respectively (Figure 5.11a).

During their last visit to paediatric care, 88% of the 169 adolescents received ART, 2% adolescents had not yet started ART and 10% had discontinued ART. Reported reasons for discontinuation were: decision by adolescent or parents; low adherence; or toxicity. Before 2015 there were more frequent occurrences of individuals not on ART at time of transfer, compared to 2015 or later (20% and 4%, respectively, Figure 5.11b).

Among adolescents who transferred to adult care before 2015, 31% were on an NNRTI-based regimen and 30% on a PI-based regimen. These percentages differed for adolescents who transferred in or after 2015: 49% were on an integrase-based regimen, 23% on an NNRTI-based regimen and 20% on a PI-based regimen.
Of the 148 adolescents who transferred to adult care, and who were still in care in 2022, 146 (99%) were receiving ART in 2022. Just over half of these were on an integrase inhibitor-based regimen (55%). In total, 90% of the 148 had HIV RNA levels below 200 copies/ml and 84% below 50 copies/ml in 2022.

Summary

Of the 400 children with HIV ever registered by SHM who were under the age of 18 when they entered care in the Netherlands, 82% 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 2016. In the last three years this has dropped to only a few cases, which has contributed to the decline in the overall number of newly registered children with HIV in the Netherlands since 2016.
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 in care over the last 10 years died before the age of 18. However seven 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. All children in care in 2022 were receiving ART. Current regimens in use include an integrase inhibitor for 81% of the children.

Very high long-term viral suppression rates were observed in children with HIV who initiated ART in or after 2013. However, those response rates fell when children reached the age of 18. We have seen overall viral suppression rates of 82% 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 75% to 92%.

The continuum of care showed a high retention-in-care rate among children under 18 years of age. Moreover, a substantially lower proportion of those aged 18 years and over had suppressed HIV RNA levels by the end of 2022, when compared to children under the age of 18 (92% versus 98% 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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6. Pregnancies in women with HIV in the Netherlands

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Introduction

The most common mode of HIV acquisition for children aged 0 to 15 years worldwide is vertical transmission[1]. Vertical transmission of HIV mainly occurs perinatally during labour and delivery, or postnatally during breastfeeding. Less common is transplacental transmission in utero. Without intervention, the risk of vertical transmission varies between 15% and 45%[2,3]. Since the introduction of combination antiretroviral therapy (ART) in pregnant women, the risk of vertical transmission has been dramatically reduced to less than 1%[4,5].

Recommendations for the treatment of HIV during pregnancy have changed over time. Previously, the initiation of ART was based on the maternal CD4 cell count. As a result, a substantial proportion of women who did not need to start ART according to their CD4 cell count, started it for the first time during pregnancy, with the sole purpose of reducing maternal HIV RNA to limit the risk of vertical transmission. In many of these cases, ART was discontinued after delivery. In 2015 general treatment guidelines were revised, and ART was recommended for all individuals regardless of their CD4 cell count[6]. As a result, most women with HIV are already receiving ART at the time of conception and are advised to continue therapy during pregnancy and postpartum.

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

This year's report focuses on women who were pregnant during the years 2016 to 2022, 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 6.1 shows the characteristics of the 529 women with HIV with a registered one or more pregnancies when receiving care in the Netherlands between 2016 and 2022. Of these women, 380 (72%) were of non-Dutch origin and 149 (28%) were born in the Netherlands. The majority of women of non-Dutch origin were born in sub-Saharan Africa (n=239, 45%) or in the Caribbean/Latin America region (n=74, 14%). Sixty-seven(13%) women originated from other regions, including 26 women from Central or Eastern Europe, and 21 women from south and south-east Asia.

Diagnosis

The majority of the 529 women (n=453, 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, 76 women were newly diagnosed during their pregnancy. The proportion of women newly diagnosed varied between 8% and 12% for the years 2016-2021. Among these:

- 19 (14%) women were born in the Netherlands;
- 34 (13%) women originated from Sub-Sahara Africa;
- 11 (14%) women originated from the Caribbean/Latin America region; and
- 12 (16%) women originated from other regions.

The median time between conception and diagnosis among newly diagnosed women was 13 weeks (IQR: 10-18). Of this total, 57% received their diagnosis during the first trimester of pregnancy, 34% in their second trimester, and 9% in their third trimester. Forty-seven of the 76 newly diagnosed women reported an earlier negative HIV antibody test. It is not known whether these earlier tests were part of the national pregnancy screening.

The median time between the date of the HIV test and first contact with one of the HIV treatment centres was eight days (interquartile range [IQR] 6-15). The median time between the first visit to a treatment centre and receiving antiretroviral therapy was also 8 days (IQR 1-16). While the database captures the date that blood is drawn for the HIV antibody test, the moment a woman receives her HIV diagnosis 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 547 cells/mm3 (IQR 380-750) for all women. A lower median CD4 cell count was seen among women who were newly diagnosed with HIV (and started ART) during pregnancy (350 cells/mms, IQR 220-456). However, as CD4 cell counts during pregnancy are affected by haemodilution, which results in lower CD4 cell counts[9], CD4 cell percentages may be a more reliable parameter. These were also found to be lower among the group of women newly diagnosed during pregnancy (*Table 6.1*).

Mode of HIV acquisition

Among the 529 women, heterosexual contact was the most common self-reported mode of HIV acquisition (90%). Nine women reported mode of exposure to contaminated blood, while, for two women of non-Dutch origin, the reported most likely mode of transmission was injecting drug use. Twenty-four pregnant women acquired HIV through vertical transmission themselves. For the remaining 18 women, the mode of acquisition was unknown.

Population no longer in care

Between 2016 and 2022, none of the mothers were documented to have died during follow up, this also includes follow-up time after the pregnancy until the end of 2022. A total of 30 (6%) were no longer in care; of these, 13 (3%) were known to have moved abroad and 17 were lost to care (3%). No significant differences were observed between women of Dutch and non-Dutch origin in terms of those lost to care.

All, except one, women were lost to care after their pregnancy ended; with a median time between delivery and last clinical visit of 8 months (IQR: 2-30). Of these:

- five women started ART during their pregnancy, of whom three were newly diagnosed with HIV;
- all but one woman had a documented ART regimen reported during their last clinical visit; and
- one women had a detectable HIV RNA result (RNA= 30,000 copies/ml) during the last clinical visit.

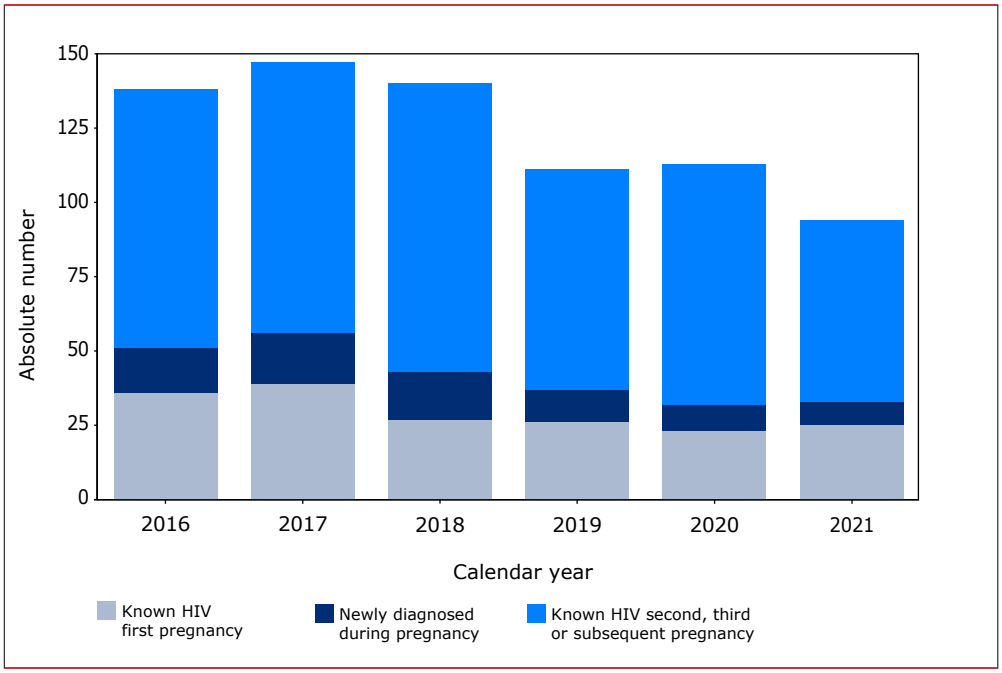
In total, 14 of the 17 pregnancies resulted in a live-birth and three in an abortion. All were singleton pregnancies. Vertical transmission or breastfeeding at the time of last clinical visit was not reported in any of the pregnancies.

Number of pregnancies in women with HIV over time

In total, 765 pregnancies among the 529 women were reported between 2016 and 2022. The absolute annual number of pregnancies in women with HIV in care in the Netherlands is following a downward trend from 147 in 2017 to 94 in 2021[a] (*Figure 6.1*). The number of women newly diagnosed with HIV during pregnancy varied between 17 in 2017 and eight in 2021[a], but varied as a proportion of the total number of pregnancies per year, between 8-12%. The number of second, third or subsequent pregnancies in women who had already received an HIV diagnosis was approximately 80 per year (*Figure 6.1*).

a Data on the number of registered pregnancies in 2022 is incomplete due to a delay in data collection.

Figure 6.1: 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 (2022). Therefore, the most recent calendar year is not shown in the figure.



Pregnancy-related characteristics

Overall, 529 women accounted for 765 registered pregnancies: 33% of the women had one registered pregnancy, 28% had two registered pregnancies, and 39% of the women had three or more registered pregnancies (*Table 6.1*).
Insert Table 6.1]

Table 6.1: Characteristics of pregnant women with HIV registered and monitored by stichting hiv monitoring between 2016-2022

	Total	Netherlands	Sub Saharan Africa	Latin America and the Caribbean	Other regions
	n (%)	n (%)	n (%)	n (%)	N (%)
Maternal characteristics	529	149 (28)	239 (45)	74 (14)	67 (13)
HIV diagnosis before pregnancy (%)	453 (86)	130 (87)	205 (86)	62 (84)	56 (84)
Newly diagnosed during pregnancy (%)	76 (14)	19 (14)	34 (14)	12 (16)	11 (16)
First CD4 cell count in pregnancy(cell/mm^3)*	547 (380-750)	600 (460-830)	490 (360-710)	570 (360-740)	510 (360-750)
CD4 percentage (%)*	31 (23-39)	37 (29-41)	29 (22-36)	27 (17-38)	30 (24-37)
First CD4 cell count when newly diagnosed during pregnancy (cell/mm^3)*	350 (220-456)	391 (293-520)	270 (170-430)	408 (190-470)	340 (310-490)
CD4 percentage (%)*	23 (16-26)	29 (23-37)	20 (13-24)	17 (12-27)	24 (21-25)
Age at start of first pregnancy following HIV diagnosis (years*)	33 (29-37)	32 (28-36)	34 (29-37)	34 (31-38)	34 (30-39)
HIV transmission route					
Heterosexual contact (%)	476 (90)	132 (89)	222 (93)	71 (96)	51 (76)
Vertical transmission (%)	24 (5)	9 (6)	12 (5)	2 (3)	1 (2)
Other~ (%)	29 (5)	8 (5)	5 (2)	1 (1)	15 (22)
Total number of pregnancies	765	209	353	101	102
Total number of pregnancies ever after HIV diagnosis among women with at least one pregnancy between 2016-2022**					
1	176 (33)	58 (39)	75 (31)	23 (31)	20 (30)
2	146 (28)	42 (28)	55 (23)	21 (28)	28 (42)
≥3	207 (39)	49 (32)	109 (46)	30 (41)	19 (28)
Pregnancy outcome					
Delivery after at least 24 weeks (%)	500(65)	143(68)	226 (64)	63 (62)	68 (67)
Miscarriage or stillbirth <24 weeks (%)	171 (22)	37 (18)	86 (24)	20 (20)	28 (27)
Induced abortion <24 weeks (%)	91 (12)	28 (13)	39 (11)	18 (18)	6 (6)
Unknown (%)	3 (<1)	1 (<1)	2 (1)	0	0

	Total	Netherlands	Sub Saharan Africa	Latin America and the Caribbean	Other regions
	n (%)	n (%)	n (%)	n (%)	N (%)
Total number of partus	500	143	226	63	68
Mode of delivery					
Vaginal	347 (69)	106 (74)	150 (66)	41 (65)	50 (74)
Caesarean, elective	70 (14)	15 (10)	33 (15)	12 (19)	10 (15)
Caesarean, secondary	80 (16)	21 (15)	41 (18)	10 (16)	8 (12)
Unknown	3 (<1)	1 (<1)	2 (1)	0	0
Pregnancy duration					
≥37 weeks	435 (87)	120 (84)	201 (89)	55 (87)	59 (87)
32–37 weeks	51 (10)	20 (14)	16 (7)	8 (13)	7 (10)
<32 weeks	13 (3)	3 (2)	8 (4)	0	2 (3)
Unknown	1 (<1)	0	1 (<1)	0	0
Birth weight (grams*)	3,142 (2,800–3,492)	3,150 (2,756–3,370)	3203 (2820–3535)	3038 (2780–3470)	3070 (2800–3595)
Perinatal deaths	4 (1)	2 (1)	2 (1)	0	0
Antiretroviral therapy started					
Before pregnancy	419 (84)	123 (86)	184 (81)	53 (84)	59 (87)
During pregnancy	81 (16)	20 (14)	42 (19)	10 (16)	9 (13)
No antiretroviral therapy during pregnancy	0	0	0	0	0
Latest available plasma HIV RNA level prior to delivery					
<50 copies/ml	480 (96)	139 (97)	213 (94)	61 (97)	67 (99)
50–500 copies/ml	16 (3)	4 (3)	9 (4)	2 (3)	1 (1)
>500 copies/m/	4 (1)	0(0)	4 (2)	0	0
Time between delivery and latest HIV RNA measurement (weeks)*	2.6 (1.0–4.2)	2.6 (1.1–4.3)	2.6 (0.9–4.0)	3.0 (1.4–4.7)	2.6 (0.8–4.1)

**Median, Interquartile Range (IQR)*

~including blood or blood contact (n=9), injecting drug use (n=2) or unknown mode (n=18)

***including all pregnancies ever after HIV diagnosis or in which HIV is diagnosed regardless of calendar time period or being in care in the Netherlands; only the pregnancies between 2016 and 2022 are included in the analyses of this chapter.*

Pregnancy outcome

The 765 pregnancies resulted in 500 (65%) births ≥24 weeks (including both live and stillbirths). A total of 262 (34%) pregnancies ended in miscarriage or still birth <24 weeks or abortion; 171 (22%) were miscarriages or still births<24 weeks and 91 (12%) were abortions. For the remaining three (<1%) pregnancies, the outcome is unknown due to missing data.

Pregnancy duration, preterm birth and perinatal death

A total of 500 pregnancies lasted at least 24 weeks and are therefore counted as a birth. The duration of these pregnancies is known in 499 cases. Overall, 435 (87%) pregnancies lasted at least 37 weeks, whereas 64 (13%) pregnancies resulted in preterm birth (defined as a pregnancy duration of 24-37 weeks). It is worth noting that 42% of the preterm births had a pregnancy duration of 36 weeks.
Perinatal death, including antepartum death, occurred in four (1%) births. Congenital disorders were registered for 11 infants.

Mode of delivery

If viral suppression during pregnancy can be achieved with ART, vaginal delivery is recommended for women with HIV [10,11]. However, in the presence of detectable HIV RNA levels at, or near the time of delivery, elective Caesarean section is recommended to minimise the risk of vertical transmission. The European AIDS Clinical Society (EACS) guidelines state that elective Caesarean section should be carried out if HIV RNA concentration is above 50 copies/ml in weeks 34-36 of pregnancy[12], whereas Dutch guidelines allow a vaginal delivery with HIV RNA below 500 copies/ml and declining viral loads[13]. In such cases intravenous zidovudine is given during labour.

Overall, 69% of newborns were delivered vaginally; 74% of the women of Dutch origin delivered vaginally, compared to 66% of women of SSA origin or 65% of women of Latin America or Caribbean origin. Fourteen percent of newborns were delivered by an elective Caesarean section and another 16% by a secondary Caesarean section.

In terms of mode of delivery, 98% of the women who delivered vaginally had an HIV RNA below 50 copies/ml. This figure was 93% for women who delivered by elective Caesarean section, and 90% for those with a secondary (unplanned) Caesarean section (p=0.0003).

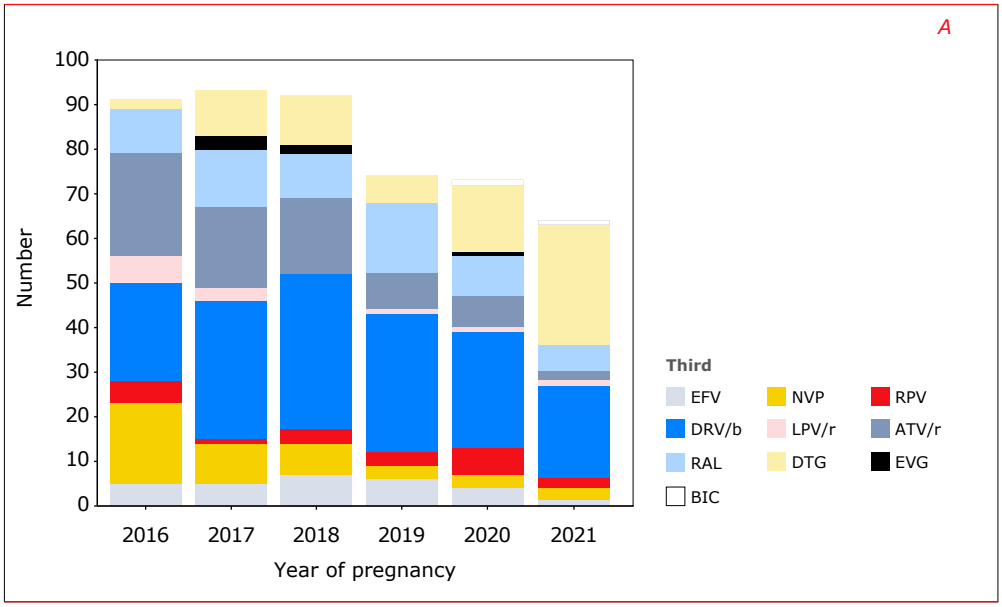
Therapy (ART) uptake and therapy response in pregnant women

Therapy uptake

From 2016 onwards, during the 500 pregnancies lasting at least 24 weeks, all women received ART: in 419 (84%) pregnancies, women were already on ART at the time of conception, while in 81 (16%) pregnancies, ART was started during pregnancy. This includes all women newly diagnosed with HIV. In 12 out of these 81 pregnancies, ART was started during the first trimester.

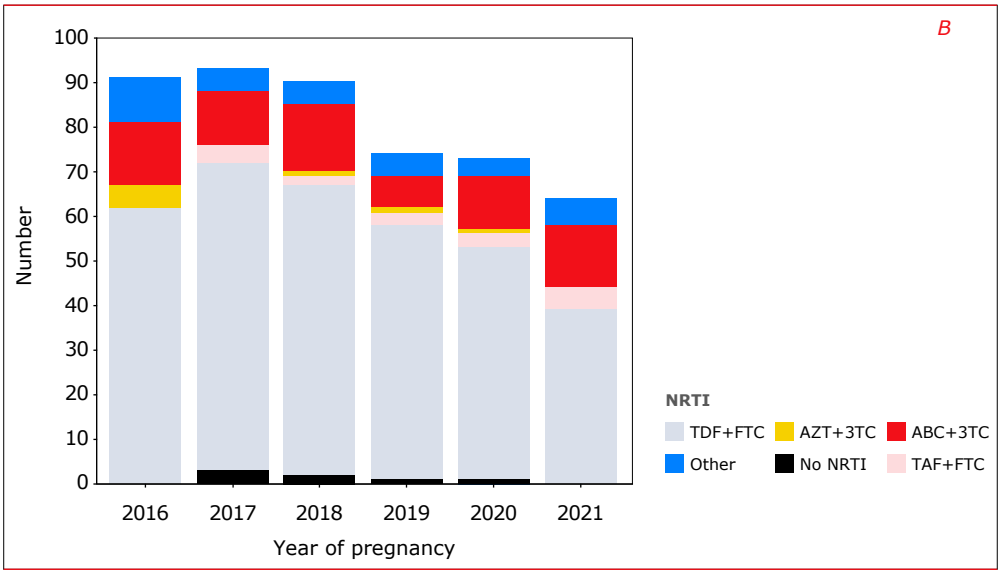
For 497 out of the 500 pregnancies, information on ART regimens was available. *Figure 6.2A* shows the most commonly used third-drug additions to the nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone as part of ART in pregnant women and during delivery between 2016 and 2022. The most commonly used regimens contained darunavir (34%), dolutegravir (15%), atazanavir (15%) and raltegravir (12%). The use of integrase inhibitors (INSTI) in pregnancy increased from 4% in 2016 to 60% in 2022. This increase coincides with a decrease in the use of NNRTI-containing regimens from 31% in 2016 to 9% in 2021(*Figure 6.2C*). In eight pregnancies a two-drug regimen was used, which were combinations of NRTI+INSTI or PI+INSTI

Figure 6.2A: *The most commonly used third-drug additions to the nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone used as part of ART regimens during pregnancies in 2016-21 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 6.2B: *The nucleoside reverse transcriptase (NRTI) backbone used as part of ART regimens during pregnancies in 2016-2021 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 (2022). 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 6.2C: Antiretroviral class use stratified by calendar year period regimens during pregnancies in 2016–2021, 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 (2022). Therefore, the most recent calendar year is not shown in the figure.

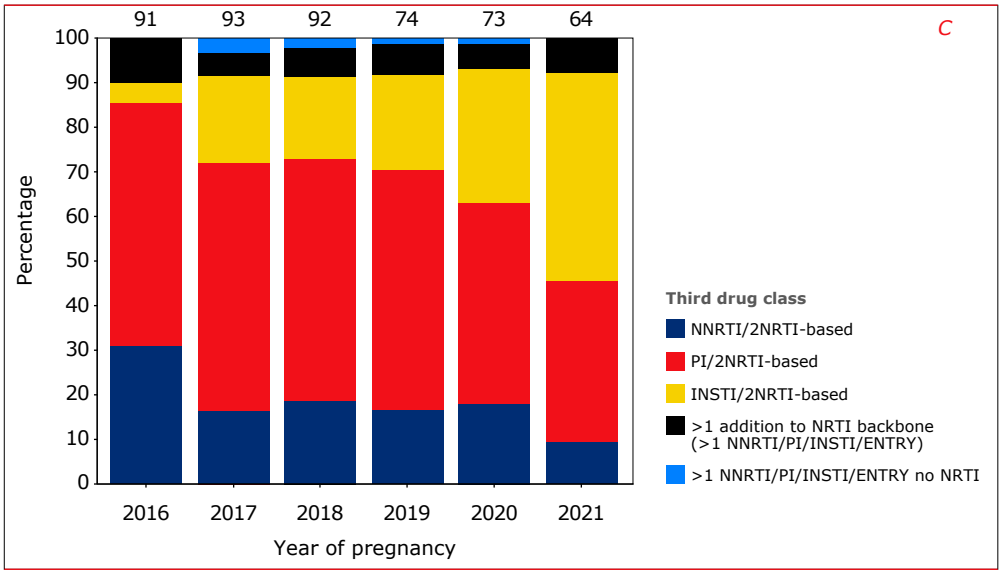


Figure 6.2B provides an overview of the components of the NRTI backbone used during pregnancy between 2016 and 2022. The most commonly prescribed backbone was the combination of tenofovir disoproxil fumarate and emtricitabine (TDF+FTC) (71%), followed by a combination of abacavir and lamivudine (ABC+3TC) (15%).

A switch in ART regimen was reported during 155 pregnancies. While no reason was documented in 4 cases, the most common documented reason for switching in the remaining pregnancies was pregnancy-related, for example as a precaution due to possible teratogenicity (n=102). In 34 pregnancies, ART was switched from an integrase-containing regimen to a protease inhibitor (darunavir or atazanavir). Other common switches were within the class of integrase inhibitors, particularly from dolutegravir or elvitegravir to raltegravir. After switching, 3% 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 five pregnancies between 2018 and 2022. All women had an HIV RNA level below 50 copies/ml at the time of delivery.

Therapy response

Figure 6.3 shows the percentage of women on ART and their latest available plasma HIV RNA level prior to delivery. HIV RNA levels were categorised as below 50 copies/ml, 50-500 copies/ml, and above 500 copies/ml.[b]

In 96% of the overall births, the mothers had an HIV RNA level below 50 copies/ml at the time of delivery, and 4% had an HIV RNA level above 50 copies/ml. The proportion of women with an HIV RNA below 50 copies/ml at the time of delivery was above 95% in all years, with exception of 2017.
In total, 20 women had HIV RNA levels above 50 copies/ml (50-500 copies/ml n=16, >500 copies/ml, n=4, median RNA=128 copies/ml; minimum=53, maximum=15500) prior to delivery, of whom:

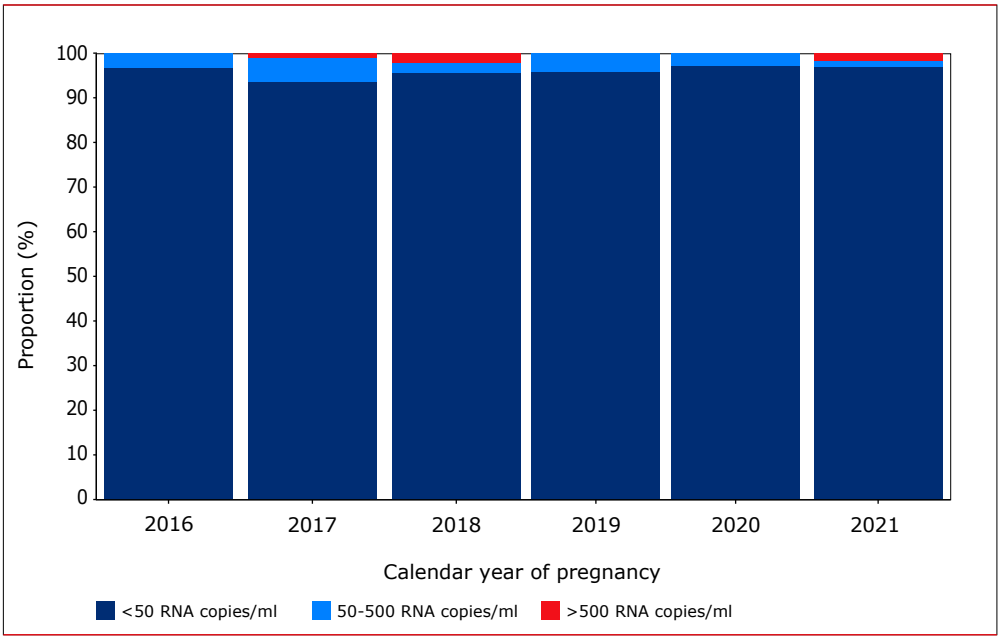
- Eight were first diagnosed with HIV during their pregnancy and had initiated ART during pregnancy;
- 12 women were already on ART, and 10 of these had had earlier episodes of detectable HIV RNA levels while on ART (before conception);
- The presence of HIV genome mutations associated with drug-resistance was evaluated; sequences were obtained for 14 women (70%);
  - Five were found to have high-level drug-resistance;
    ~ Four women to at least one NNTRI;
    ~ Two women for at least one NRT.
  - Of these five women, three were already diagnosed before pregnancy, in two of them at least one major resistance mutation was found before pregnancy and one women was screened for resistance for the first time while pregnant.
  - The remaining two women were newly diagnosed during pregnancy and at least one resistant associated mutation was found before the start of ART or in the first four months after the start of ART.
- 13 women delivered by Caesarean section (RNA minimum 53, maximum 15500 copies/ml);
- Six women delivered vaginally (RNA minimum 70, maximum 1003 copies/ml); and

b 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.

- One woman's mode of delivery was unknown.
- Thirteen women received zidovudine during partus, and 5 women did not, but zidovudine use was unknown in two cases.

At time of database closure, no vertical transmission was reported among the infants born to mothers who had HIV RNA levels above 50 copies/ml at the time of delivery.

Figure 6.3: *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 (2022). Therefore, the most recent calendar year is not shown in the figure.*

Vertical transmission rate in the Netherlands

Between 2016 and 2022, 500 births were registered in the Netherlands among mothers who knew they had HIV prior to conception, or were first diagnosed during pregnancy. All mothers received ART during their pregnancy. This resulted in a vertical transmission rate of <0.5% in pregnant women on ART in the Netherlands[c], which is in line with low reported vertical transmission rates in other western European countries[16,17,18,19].

c Due too small numbers, absolute numbers are not reported

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 500 pregnancies lasting 24 weeks or longer, 52 were excluded from this analysis: 41 because of insufficient follow up between delivery and the time of database closure; and 11 because the women were no longer in care (one had moved abroad and nine were reported as lost to care during the postpartum period).

For the remaining 448 pregnancies in 376 women, ART was initiated before conception or during pregnancy in 80% and 20% of cases, respectively. The majority of women used an integrase inhibitor-containing regimen during the postpartum period (45%). The use of integrase inhibitor increased from 25% in 2016, to 59% in 2020 and 67% in 2022.

In 28 of these 448 pregnancies, ART was discontinued postpartum:

- The most common documented reason was a decision by the patient (n=17).
- In two cases the documented reason was elite controller or long-term non-progressor[d].
- In 2 cases the documented reason was toxicity.

In 11 out of the 28 cases, therapy was restarted after a median of seven weeks (IQR 4-11). In the remaining 17 cases, ART was not restarted postpartum, however eight women did start again after the postpartum period had ended. Eight women (accounting for 9 post-partum pregnancies) 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 was observed in 14% of the 448 pregnancies analysed.
- For the subset of women with documented continued use of ART postpartum, 46 (11%) had an HIV RNA level above 50 copies/ml (median HIV RNA=238 copies/ml, minimum=52 and maximum=85900 copies/ml), 18 of whom had more than one episode of an HIV RNA level above 50 copies/ml during the postpartum

d 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.

period. Nine of the 46 women were newly diagnosed with HIV during the pregnancy, whilst 37 women were diagnosed before the onset of the pregnancy and had also already started ART. 68% (n=25) had earlier episodes of detectable HIV RNA levels more than 6 months after the start of ART.

In the 28 women who discontinued the use of ART postpartum:

- 17 (62%) experienced viral rebound (median HIV RNA=21,000 copies/ml, minimum 617 and maximum 450000 copies/ml).
- 11 women had an undetectable HIV RNA level during the post-partum period, including 8 women who did not restart ART after discontinuing therapy during the postpartum period;
  - Three of these 8 women continued to have reported high CD4 cell counts and low HIV RNA levels in the absence of ART;
  - Three experienced a viral rebound after the postpartum period;
  - Five cases remained virally suppressed (two of whom eventually restarted ART).

Breastfeeding

The option of breastfeeding for women with sustained virological suppression is discussed based on shared decision-making in the Netherlands. Breastfeeding in such cases is recommended for a maximum of six months.

Breastfeeding data were available for 389 of the 448 pregnancies, and was reported in 28 pregnancies (the duration of breastfeeding was not documented). It is noteworthy that all women had documented use of ART and HIV RNA levels below 50 copies/ml or below the detection limit of the used HIV RNA assay during the postpartum period. The median number of HIV RNA measurements during the first 6 months after partus among the 28 pregnancies with reported breastfeeding was 3 HIV RNA measurements (IQR 2-6 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 96% 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. The vertical transmission rate in pregnant women using ART was less than 0.5% during the period 2016 to 2022, which is comparable to the low figures reported in other western European countries[16,17,18,19].

A small proportion of women had detectable HIV RNA levels near the time of delivery. This included women who were newly diagnosed with HIV and thus started ART during the pregnancy, and women who were already using ART at conception but had earlier episodes of detectable HIV RNA levels. To maintain a low rate of vertical transmission of HIV, it is important to provide multidisciplinary care for – and close monitoring of – women newly diagnosed with HIV after conception, as well as those with a history of virological failure.

Although most women were aware of their HIV status prior to their pregnancy, 14% were newly diagnosed during pregnancy. Twenty-eight percent of the women originated from the Netherlands and 72% 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 will be offered from 10 weeks pregnancy onwards as from April 2023 as part of the national pre- and neonatal screening programme[20].

The proportions of preterm births and Caesarean sections among women with HIV were higher than those observed in the general population (13% and 30% compared to 7% and 17%[29]). Other studies have found a high prevalence of caesarean sections in women with undetectable HIV RNA levels[30], and compared to the general population[31]. However as invasive perinatal procedures, such as foetal blood sampling or the placement of a foetal scalp electrode, are contraindicated in women with HIV[13] the threshold to perform a Caesarean section is generally lower. It is not clear whether this lower threshold contributed to the higher number of Caesarean sections observed. In addition, premature delivery has been

linked to ART use, especially in the first 12 weeks of pregnancy[32,33,34]. As the aetiology of preterm delivery is complex and multifactorial, it is unclear whether this or other, for example socio-economic factors, can explain the high proportion of preterm births[35]. The association between various ARVs and adverse pregnancy outcomes, including low birthweight, has been evaluated in different studies, with conflicting results[36].

Finally, ART has been recommended for all individuals regardless of CD4 cell count since 2015, including postpartum. We observed an increasing proportion of women who received integrase inhibitors during pregnancy as well as during the postpartum period. From 2016 onwards, 11% of women who continued to use ART postpartum had at least one episode of viraemia. In earlier studies, adherence to therapy has been reported to deteriorate during the postpartum period[23,24,25,26,27,28].

Recommendations

As a result of changes in the guidelines concerning treatment of HIV in 2015, ART is more likely to be used at conception and continued post-delivery. This is expected to result in a greater number of women with undetectable HIV RNA levels earlier in their pregnancy and around the time of delivery.

Women with HIV who start ART during pregnancy require a high degree of support; not only during the pregnancy itself to ensure suppressed HIV RNA levels at the time of delivery, but also postpartum 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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7. Quality of care

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Introduction

One of the missions of stichting hiv monitoring (shm) is to contribute to the quality of HIV care in the Netherlands. Via the collection of pseudonymised data from patients in outpatient care at the 24 dedicated treatment centres, shm can provide a nationwide overview of the outcome of care for patients. This unique overview allows shm to facilitate assessment of the quality of HIV care in the Netherlands.

The Dutch Association of HIV-Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) has issued a variety of indicators to reflect the quality of health care provided to individuals with HIV. These include, for example, HIV outcome indicators (e.g., the percentage with HIV viral suppression), and hepatitis B and C virus and syphilis screening for men who have sex with men (MSM). 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 a result, we have decided to bring more focus to primary and secondary prevention of cardiovascular disease. These include whether or not centres have provided information on smoking and other items that are needed for cardiovascular disease screening, such as total cholesterol, HDL- and LDL-cholesterol and blood pressure. The SCORE-2 for individuals aged 40-69 years old and the SCORE2-OP for individuals 70 years old or older are often used in clinical care to understand the 10-year risk of developing a cardiovascular disease event among those who have not yet had such an event[3,4]. We also provide information on whether the SCORE2 or SCORE2-OP were able to be calculated for these age groups. For individuals with a 10-year risk of a cardiovascular disease event of 10% or higher, we report the percentage who received a prescription for statins and those with an LDL cholesterol at or below the recommended limits in European guidelines (i.e., target LDL cholesterol)[5]. Finally, we report the percentage of individuals who had high blood pressure and received a prescription for antihypertensive medication and, subsequently, the percentage of individuals who received an antihypertensive medication and had a blood pressure at or below the recommended limits

in European 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 7.1.

This analysis relates to all individuals who were diagnosed with HIV and who are currently in care at one of the 24 HIV treatment centres in the Netherlands. Considering that this chapter describes the role of the individual in a medical context, we describe all individuals with HIV who are receiving, or have received, medical care at an HIV treatment centre as patients. To facilitate presentation, we have decided to provide mostly figures describing changes over the last 5 years and comparison of indicators between individual centres and the national average. Indicators are reported for the 24 HIV treatment centres individually. Each HIV treatment centre is referenced by a number, which is used consistently across all figures in this chapter.

Box 7.1: Definitions of specific indicators and focus populations.

Indicator	Definition	Focus population
Information on smoking status		
Known smoking status	The percentage of patients who ever gave information on their smoking. status.	In care and by age group[1]
Information needed for cardiovascular disease screening		
Total cholesterol	The percentage of patients who had a total cholesterol measurement during the calendar year.	In care and by age group[1]
HDL cholesterol	The percentage of patients who had an HDL cholesterol measurement during the calendar year.	
LDL cholesterol	The percentage of patients who had an LDL cholesterol measurement during the calendar year.	
Blood pressure	The percentage of patients who had at least one blood pressure measurement during the calendar year.	

All cardiovascular parameters	The percentage of patients who had total, HDL and LDL cholesterol and blood pressure measurement during the calendar year.	
Information on cardiovascular event risk		
SCORE2	The percentage of patients who had enough information to have their SCORE2 cardiovascular risk assessment during the calendar year.	40-69 year olds without a history of CVD
SCORE2-OP	The percentage of patients who had enough information to have their SCORE2-OP cardiovascular risk assessment during the calendar year.	70 year old or older, without a history of CVD
Statin use	The percentage of patients who received a prescription for statins during the calendar year.	SCORE2 or SCORE2-OP predicted 10-year risk greater than 10%, without a history of CVD[2]
Target LDL cholesterol	The percentage of patients who had an LDL cholesterol level ≤1.8 mmol/mL during the calendar year.	SCORE2 or SCORE2-OP predicted 10-year risk greater than 10%, without a history of CVD[2]
Antihypertensive medication use	The percentage of patients who received a prescription for antihypertensive medication during the calendar year.	All patients with high blood pressure[3]
Target blood pressure	The percentage of patients who had a systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg (for those 18-64 years old), or a systolic blood pressure <140 mmHg and diastolic blood pressure <80 mmHg (for those 65 years old or older).	All patients on antihypertensive medication

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

[1]Age groups refer to the following: 18-39 year olds, 40-69 year olds and 70 year old or older.

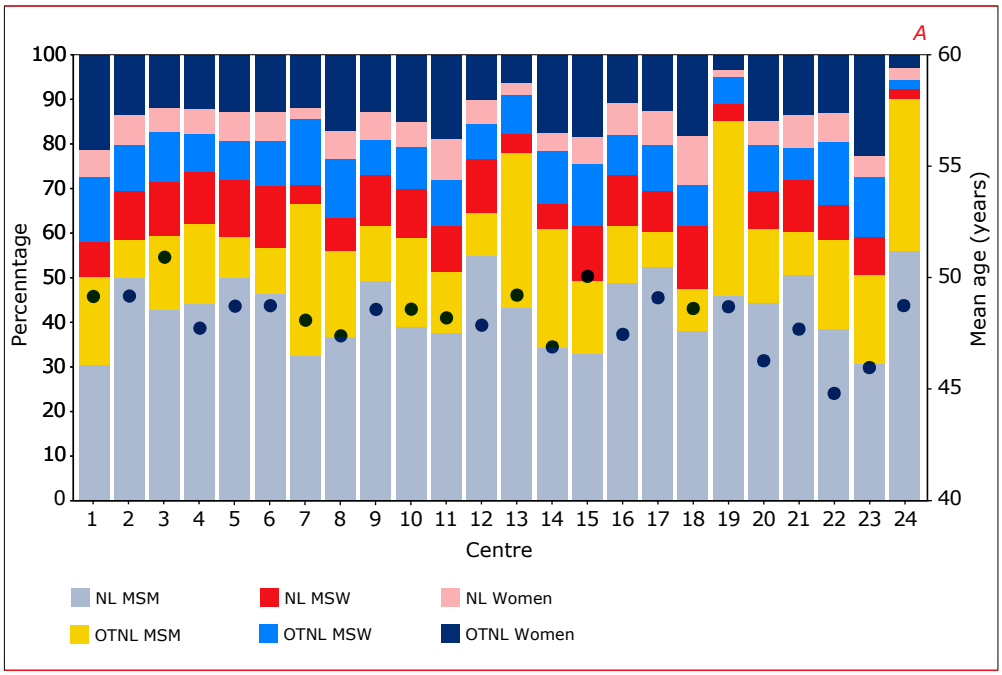
[2]Details on these scores can be found in the following website: https://u-prevent.com and also ref.[3,4]

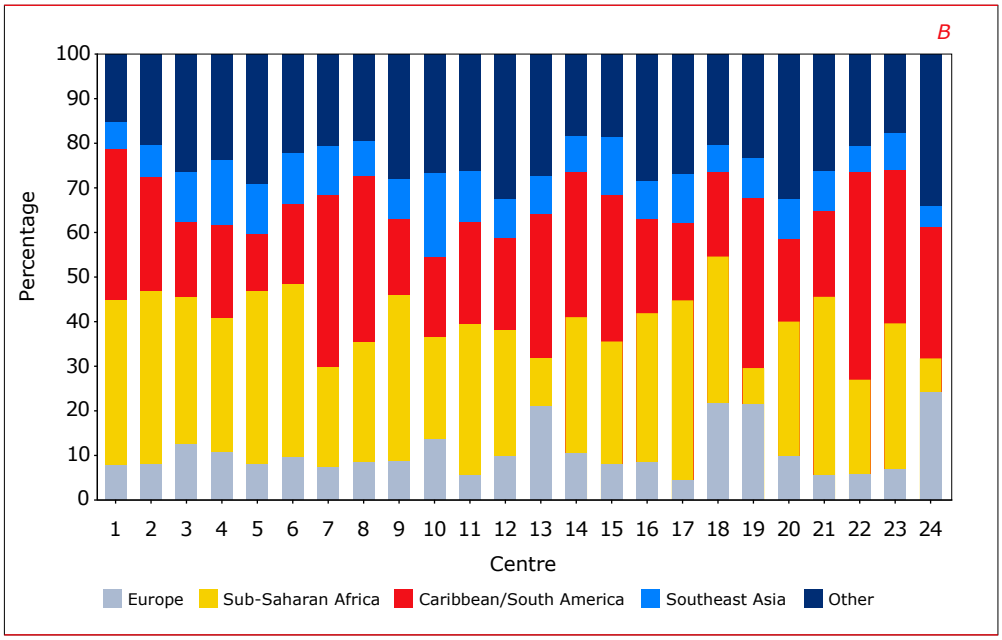
[3]Defined as a diastolic blood pressure ≥90 mmHg.

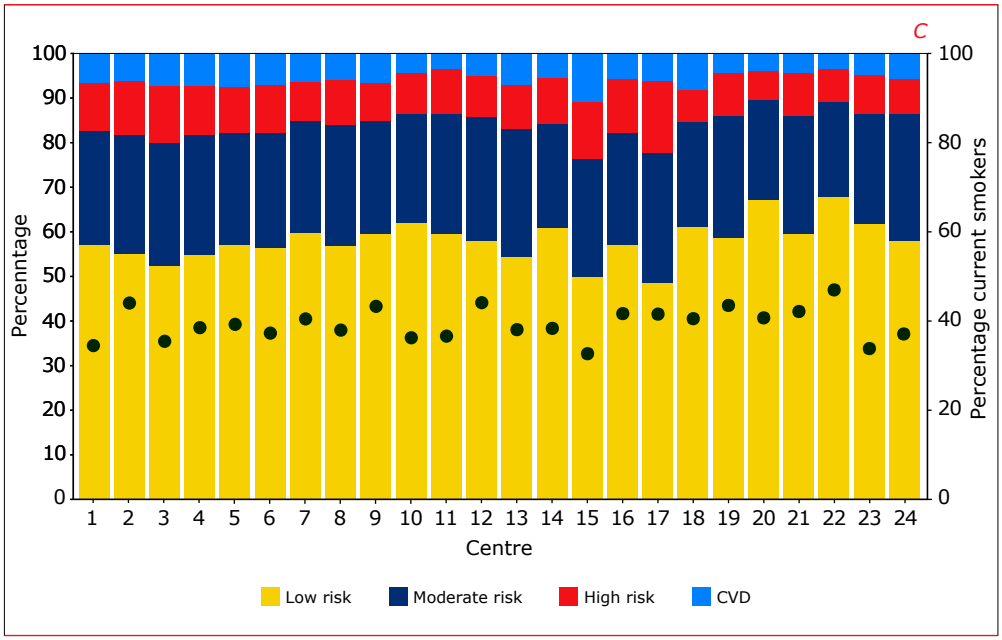
Centre overview

To provide an understanding of the patient 'mix' across centres, the distribution of geographical origin/mode of HIV acquisition/gender groups and age are provided for each centre (Figure 1A). For patients who are other than Dutch, the distribution of region of origin is also given for each treatment centre (Figure 1B). Finally, the distribution of patients with low (<5%), moderate (5-10%), and high (>10%) predicted 10-year risk of cardiovascular disease, for those who have not had a cardiovascular disease event, and the percentage with cardiovascular disease are also provided for each treatment centre (Figure 1C). Predicted 10-year cardiovascular risk was assessed with SCORE2 (for 40-69 year olds) or SCORE2-OP (for 70 year olds or older). These are presented alongside the percentage of patients who are currently smoking.

Figure 7.1: Description of the patient 'mix' (A), as well as distribution of region of origin for other than Dutch individuals (B), and cardiovascular disease risk and smoking status (C) among patients in care in 2022 in the Netherlands.







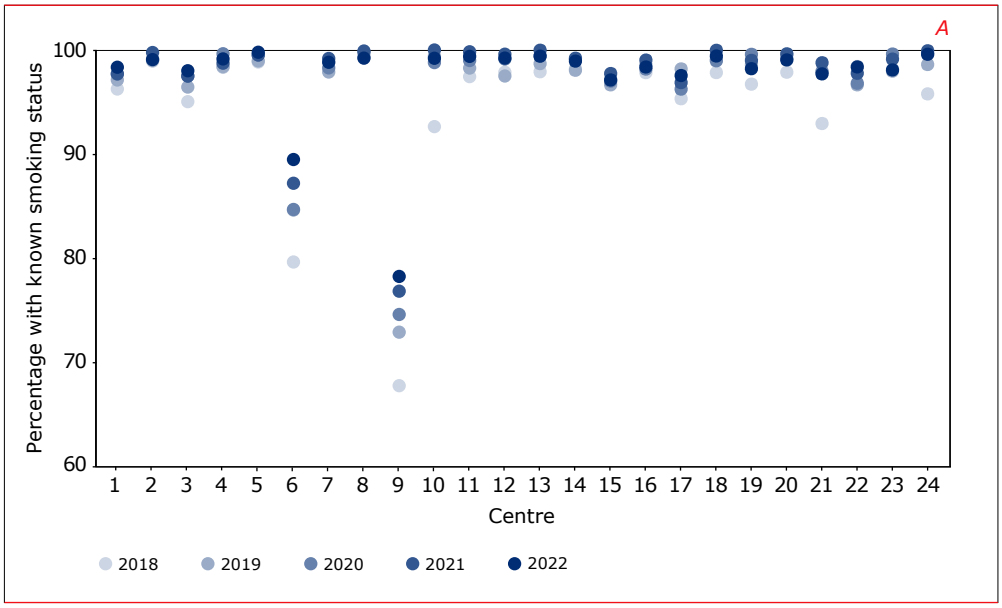
Note: *The bars in this chart show the percentage of individuals per centre. In A, black dots represent the mean age of patients in care at each centre. In C, black dots represent the percentage of current smokers of patients in care at each centre. This panel distinguishes those who already have cardiovascular disease (CVD) and those who have low, moderate or high risk according to the predicted 10-year cardiovascular risk were assessed with SCORE2 (for 40-69 year olds) or SCORE2-OP (for 70 year olds or older).*

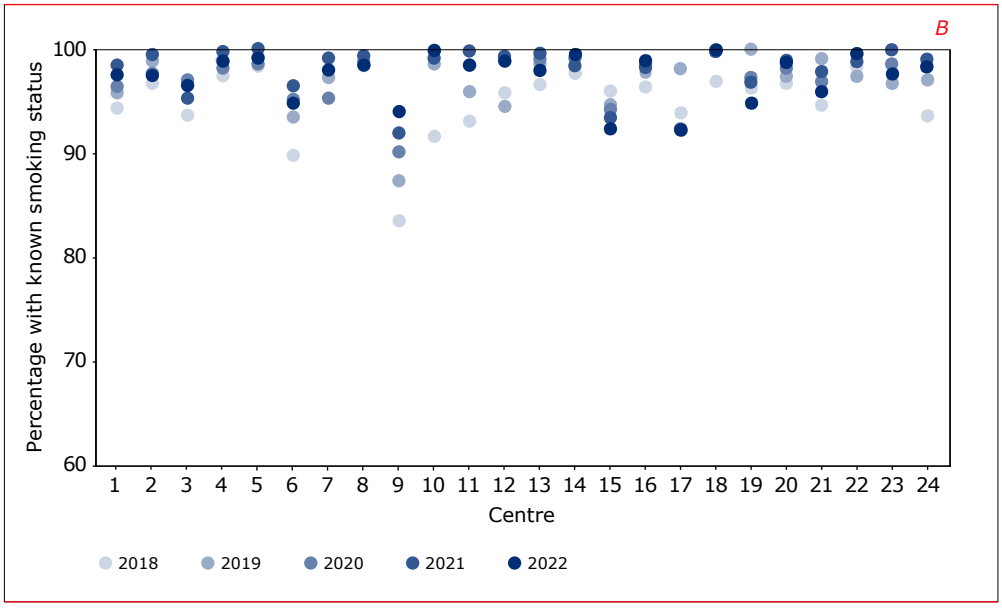
Legend: *CVD=cardiovascular disease; MSM = men who have sex with men; MSW = men who exclusively have sex with women; NL = Dutch; OTNL = other than Dutch.*

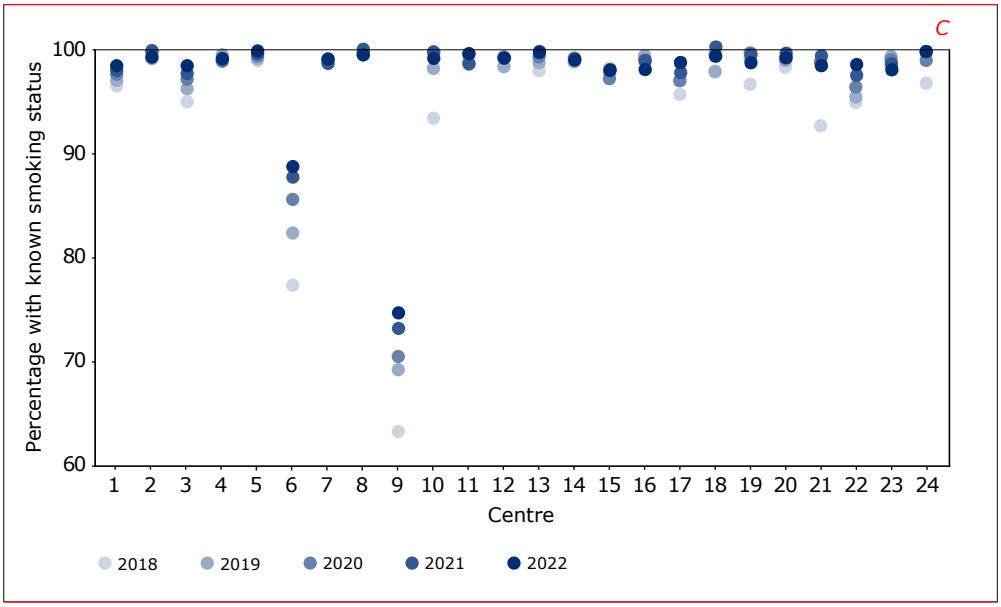
Evolution of indicators over time

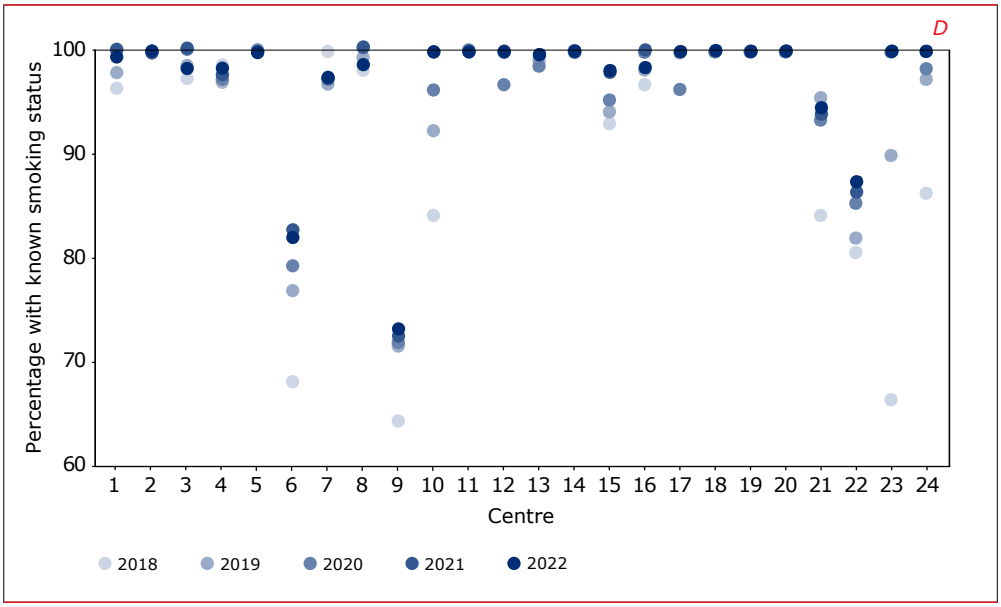
To provide an understanding of how indicators have evolved, each indicator in *Box 7.1* is reported for its corresponding focus population on an annual basis between 2018 and 2022. For example, the indicator 'information on smoking' is provided for individuals who were in care in 2018, 2019, 2020, 2021 and 2022.

Figure 7.2: Known smoking status; in other words, patients who ever had information on their smoking status during each year between 2018 and 2022.



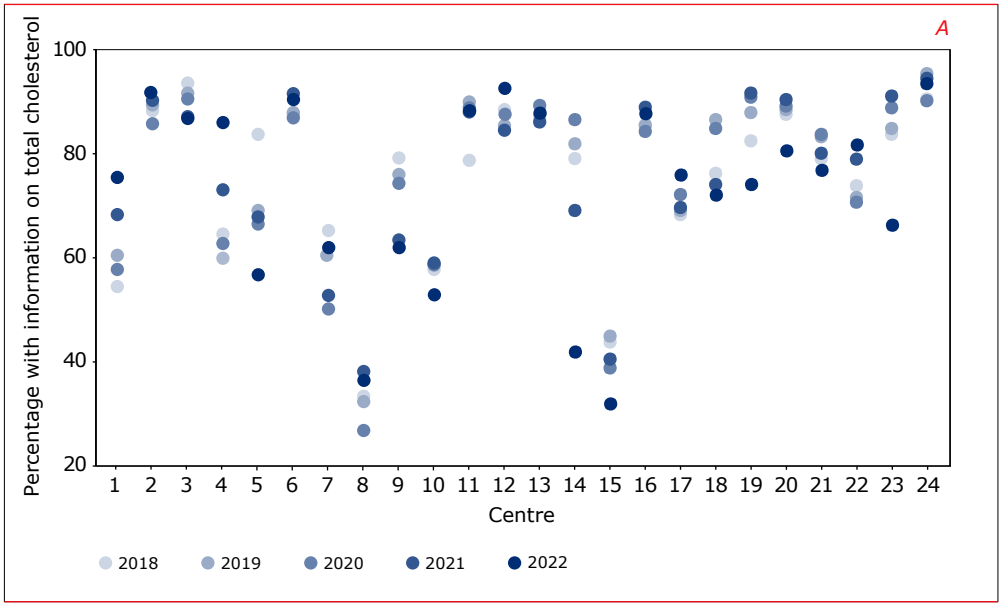


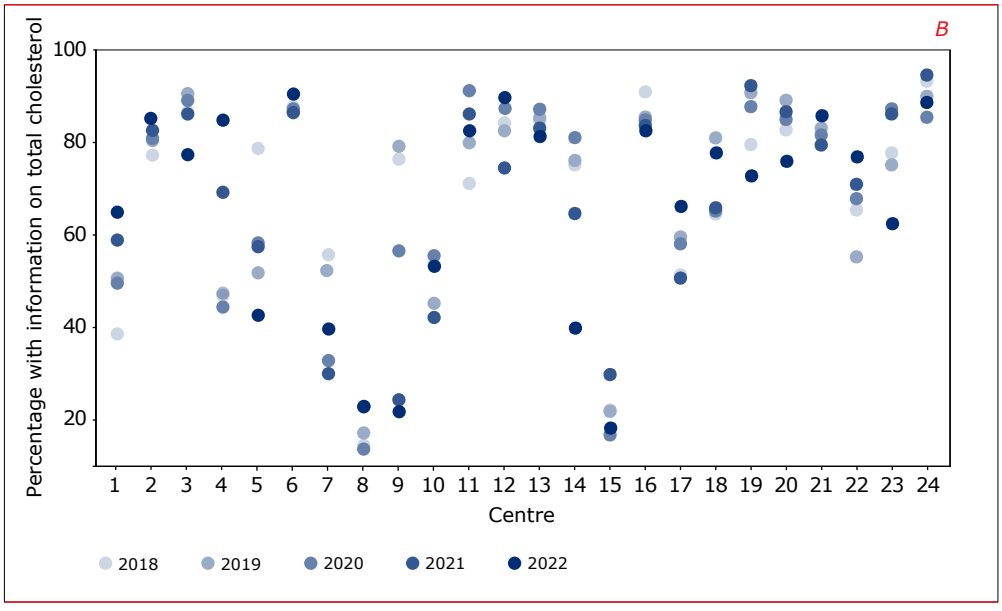


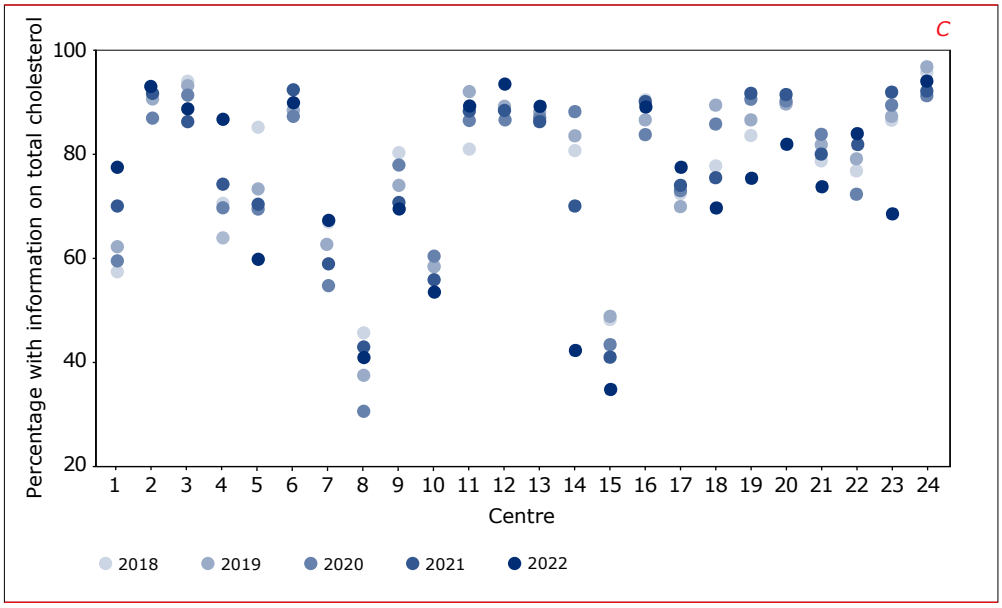


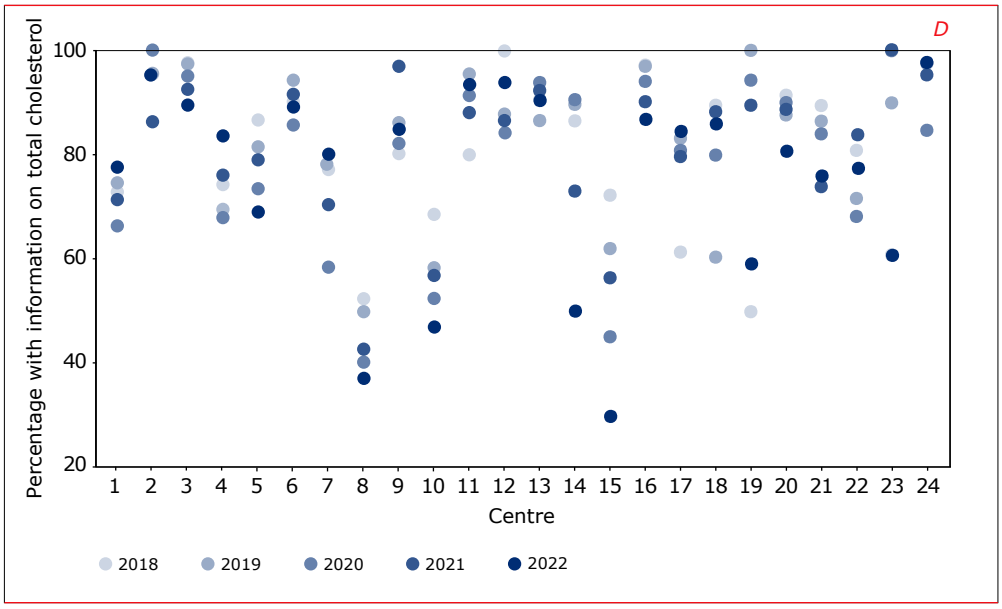
Legend: *Data are provided overall (A) and by age group: 18–39 year olds (B), 40–69 year olds (C) and 70 years old or older (D). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

Figure 7.3: Information on total cholesterol; in other words, patients who had a total cholesterol measurement during each year between 2018 and 2022. .



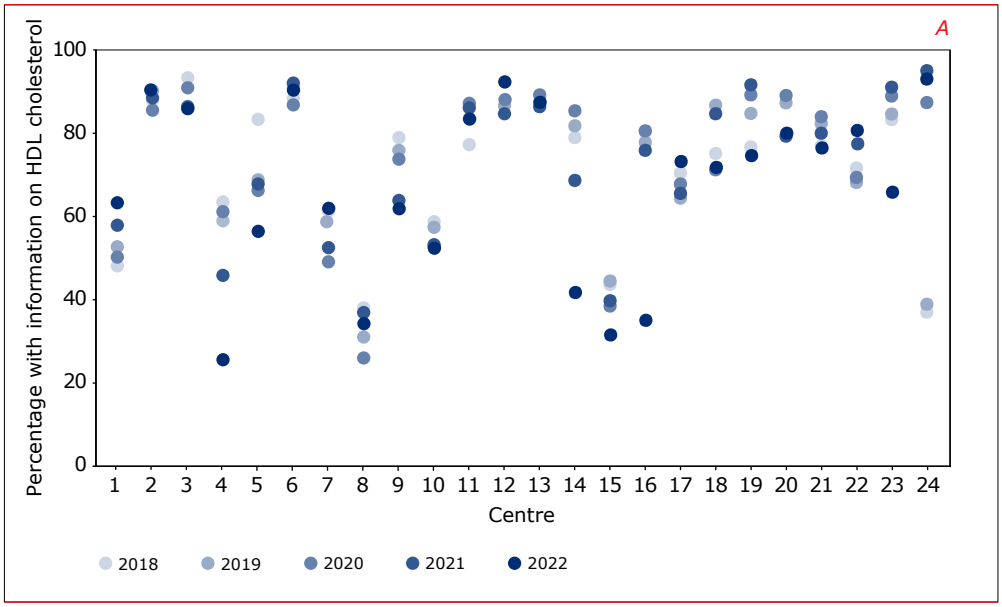


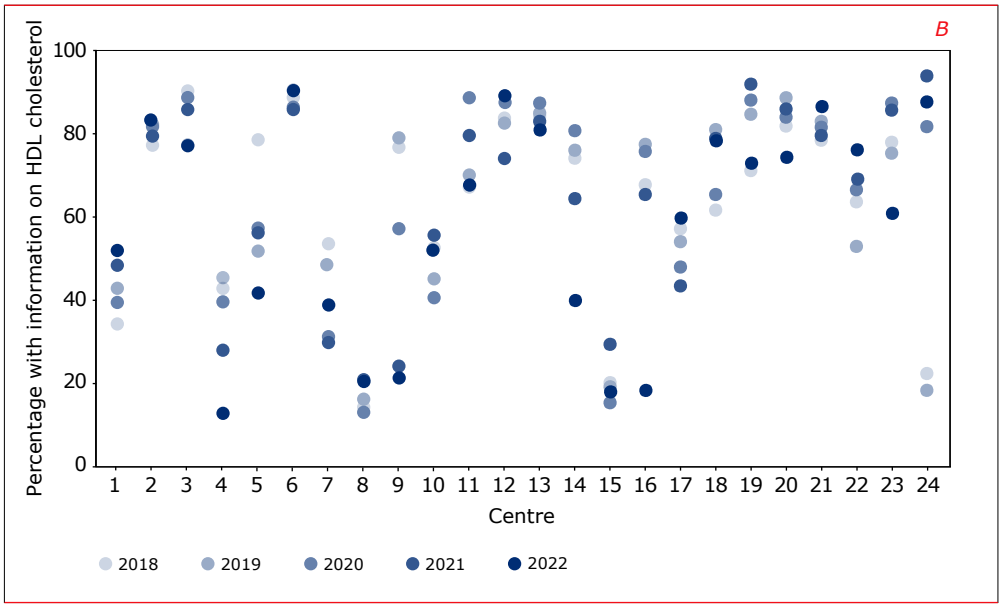


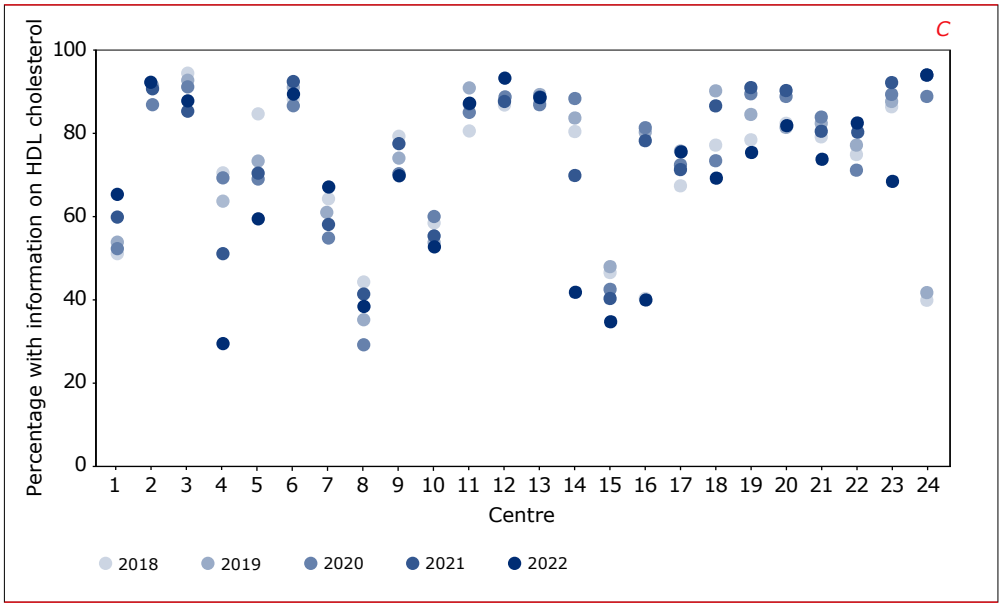


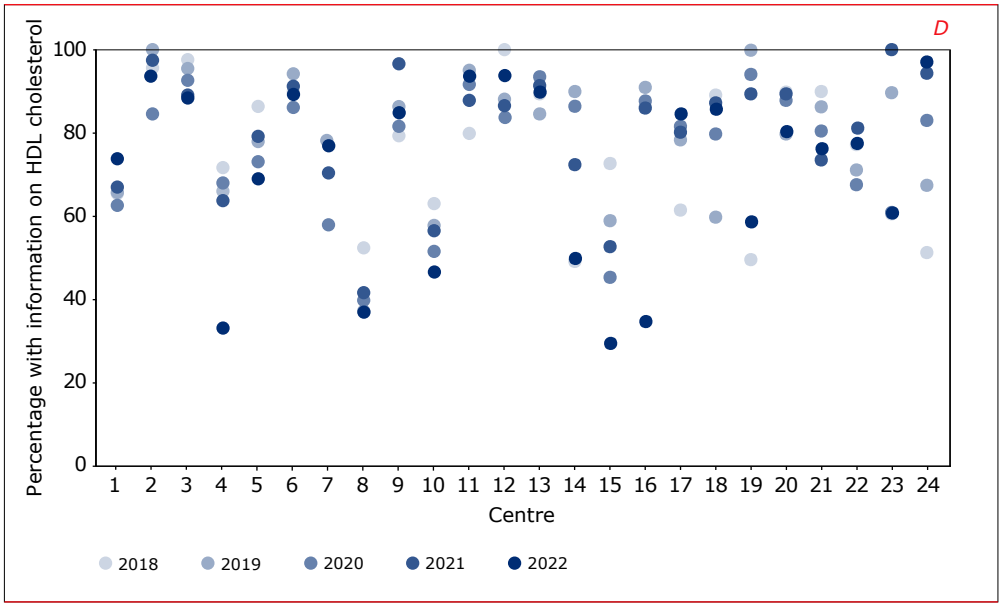
Legend: *Data are provided overall (A) and by age group: 18–39 year olds (B), 40–69 year olds (C) and 70 years old or older (D). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

Figure 7.4: Information on HDL cholesterol; in other words, patients who had an HDL cholesterol measurement during each year between 2018 and 2022.



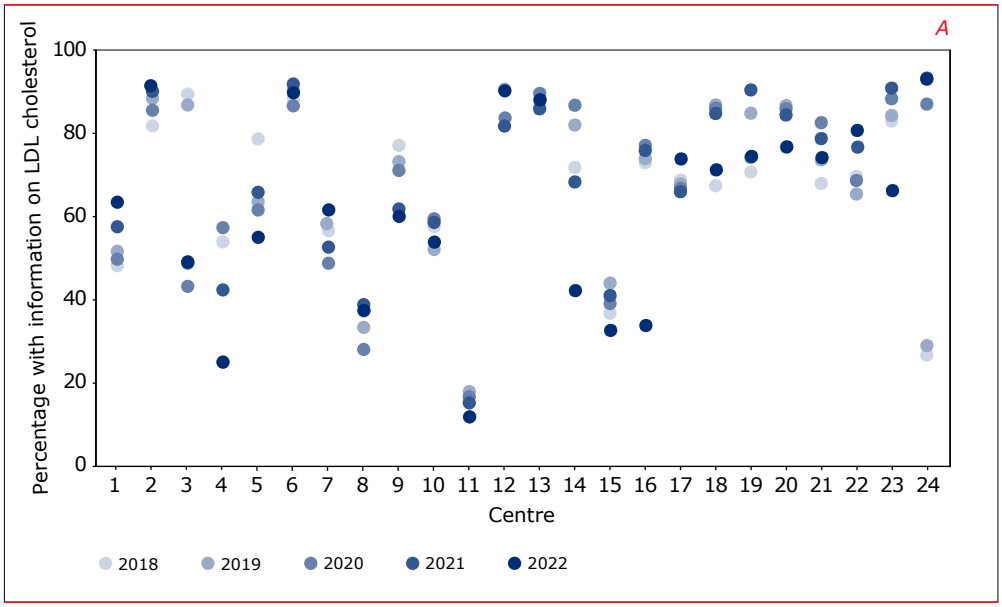


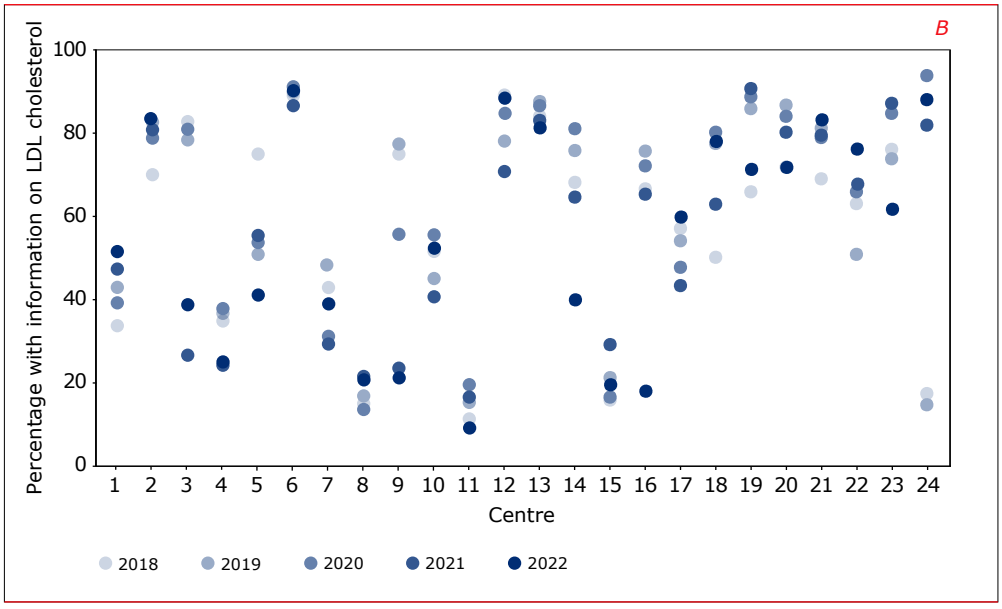


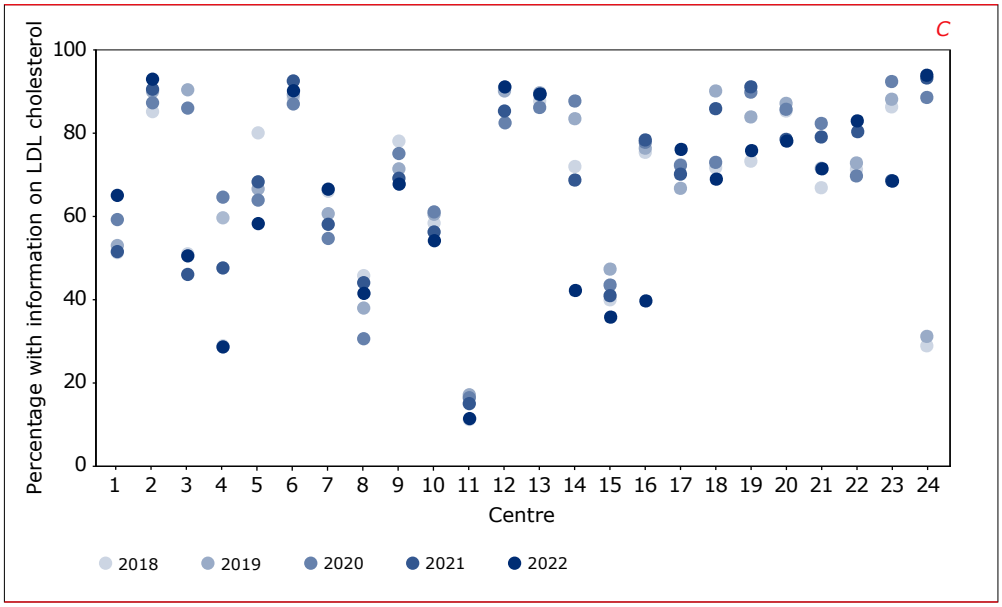


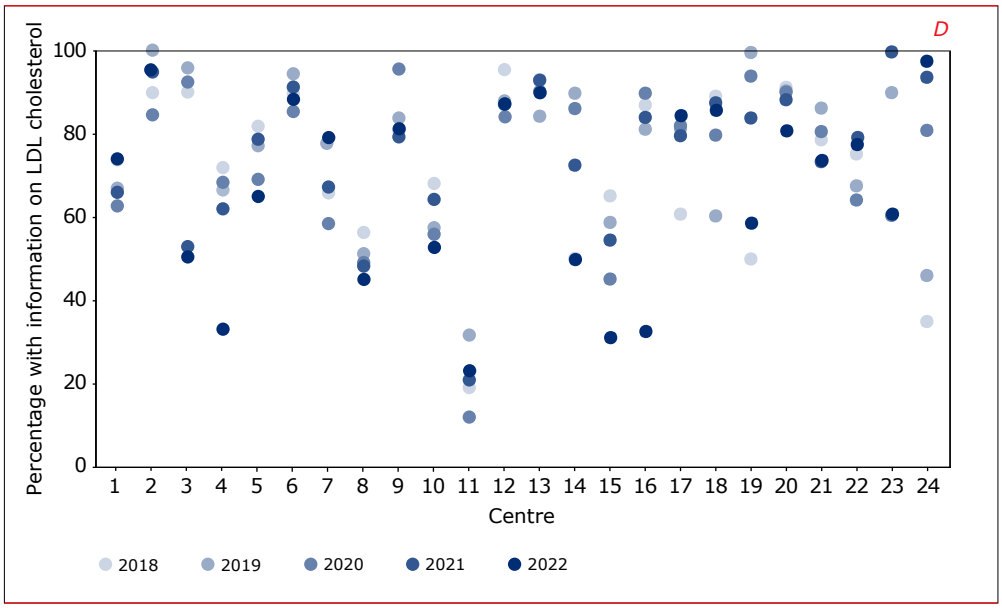
Legend: *Data are provided overall (A) and by age group: 18–39 year olds (B), 40–69 year olds (C) and 70 years old or older (D). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

Figure 7.5: Information on LDL cholesterol; in other words, patients who had an LDL cholesterol measurement during each year between 2018 and 2022.



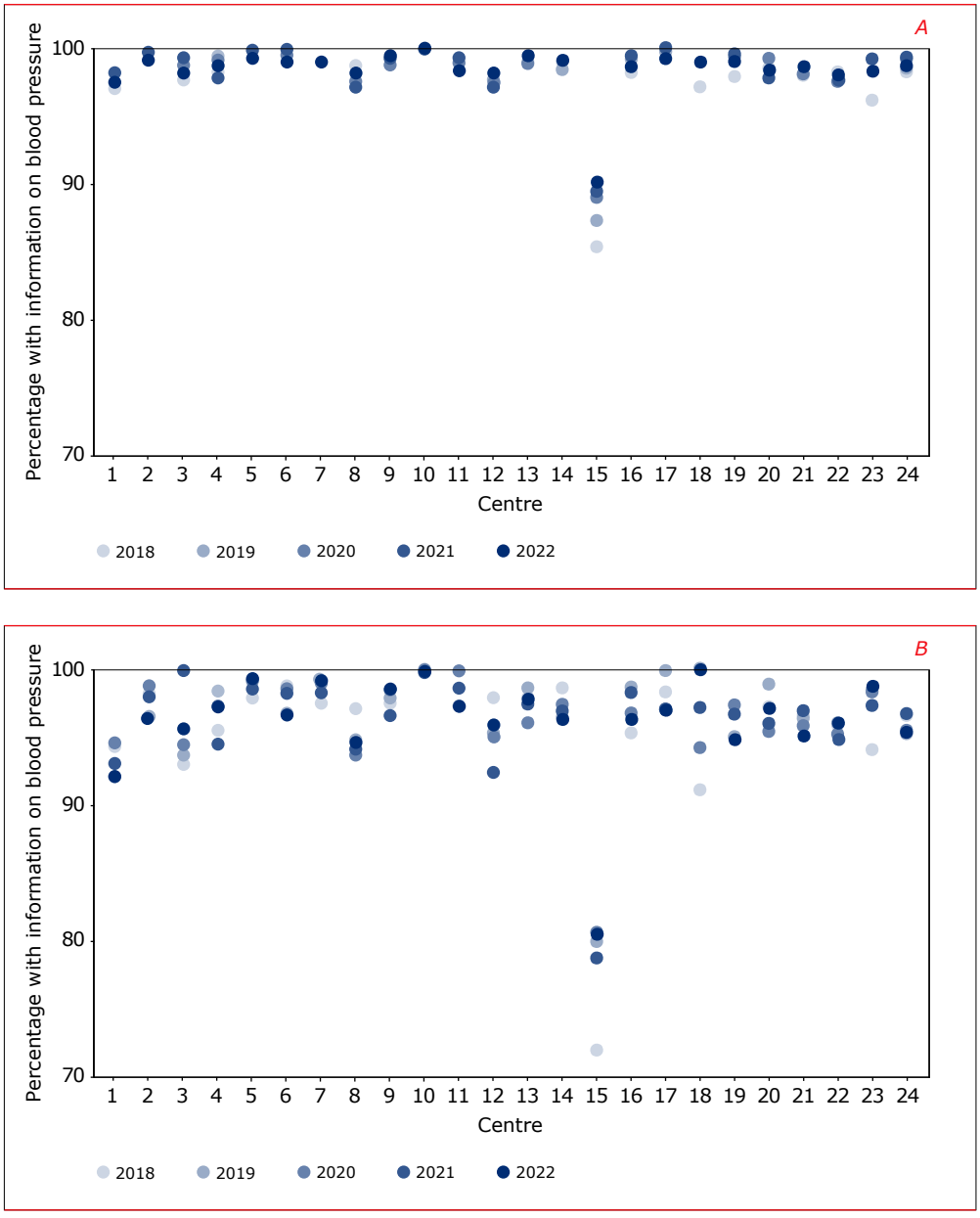


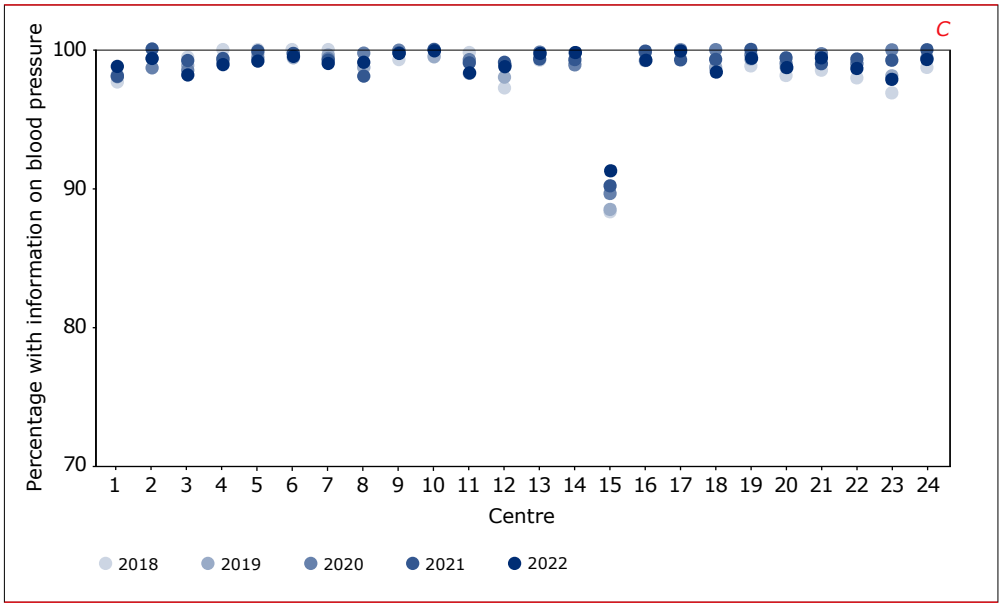


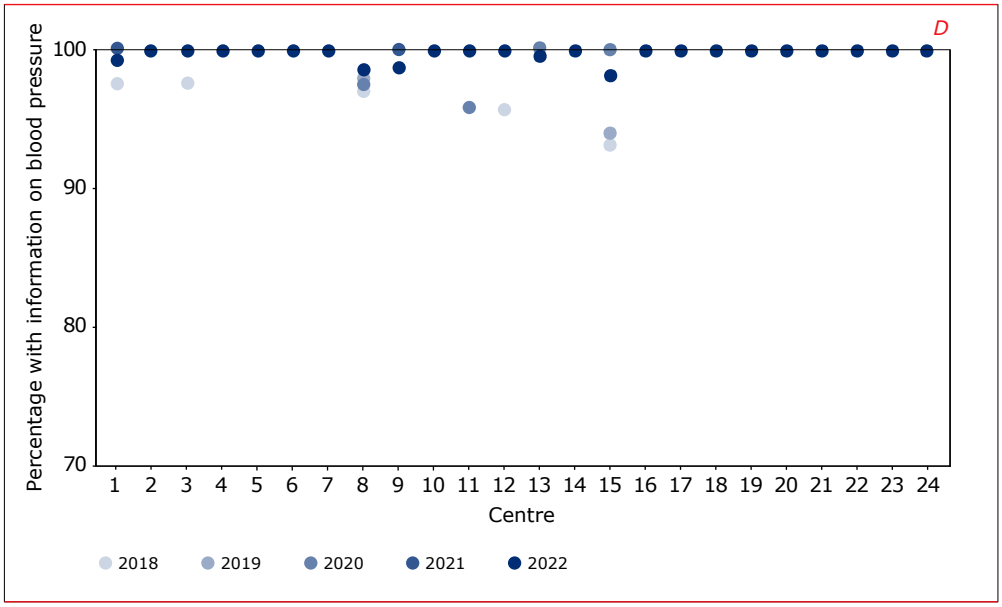


Legend: *Data are provided overall (A) and by age group: 18–39 year olds (B), 40–69 year olds (C) and 70 years old or older (D). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

Figure 7.6: Information on blood pressure; in other words, patients who had a blood pressure measurement during each year between 2018 and 2022.

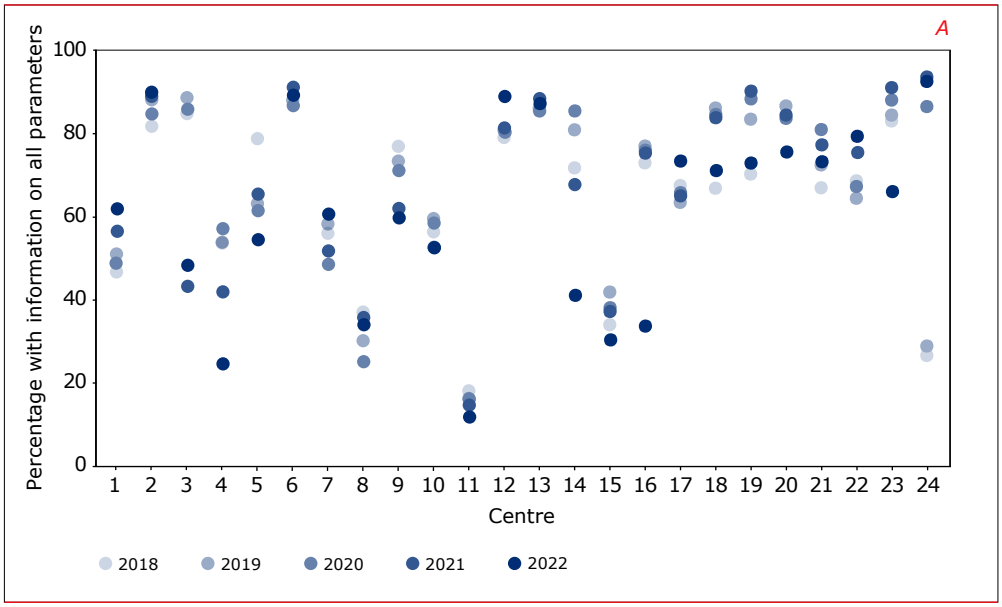


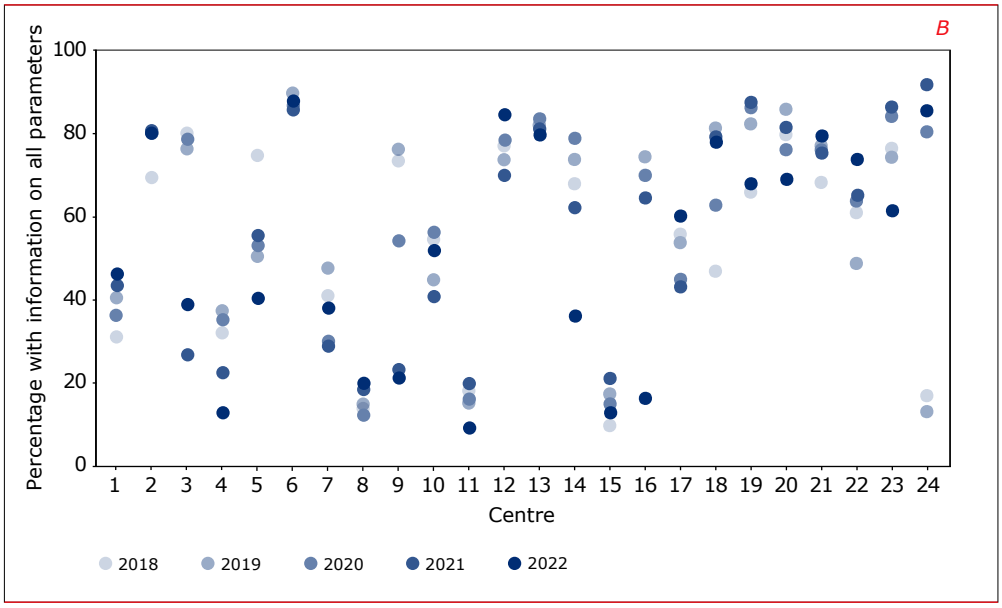


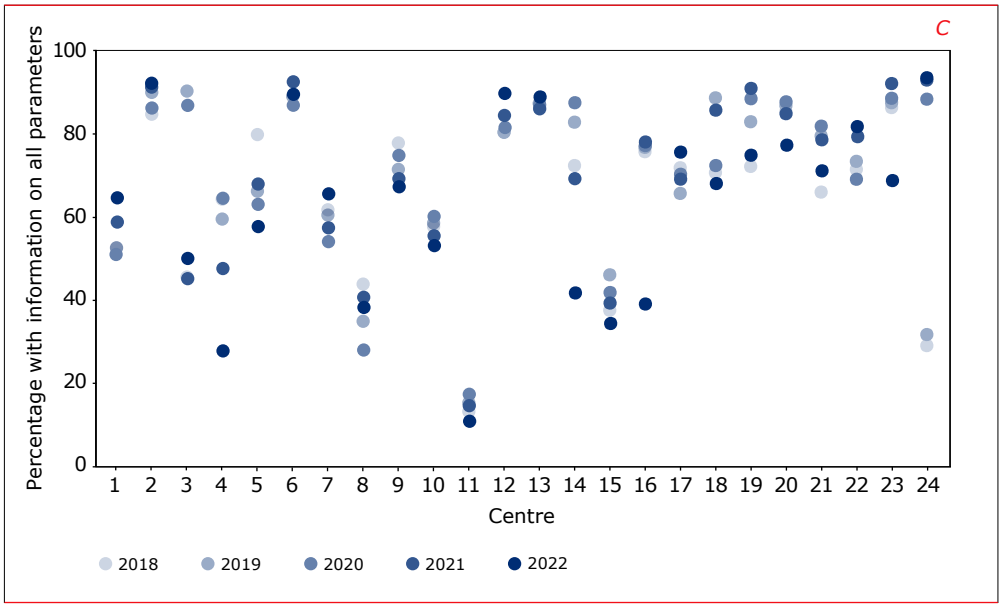


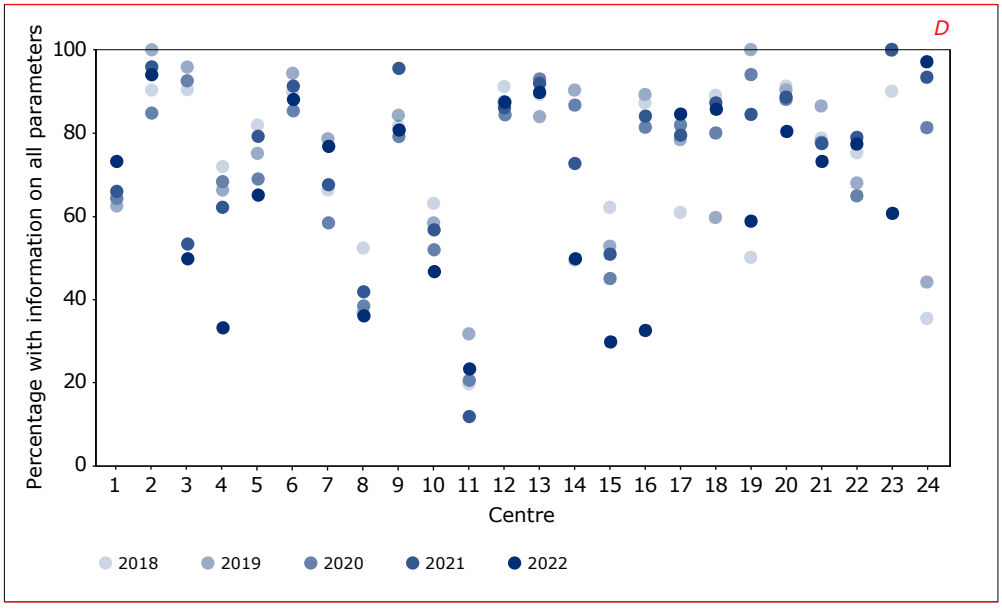
Legend: *Data are provided overall (A) and by age group: 18-39 year olds (B), 40-69 year olds (C) and 70 years old or older (D). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

Figure 7.7: Information on all cardiovascular parameters; in other words, patients who had total, HDL and LDL cholesterol and blood pressure measurement during each year between 2018 and 2022.



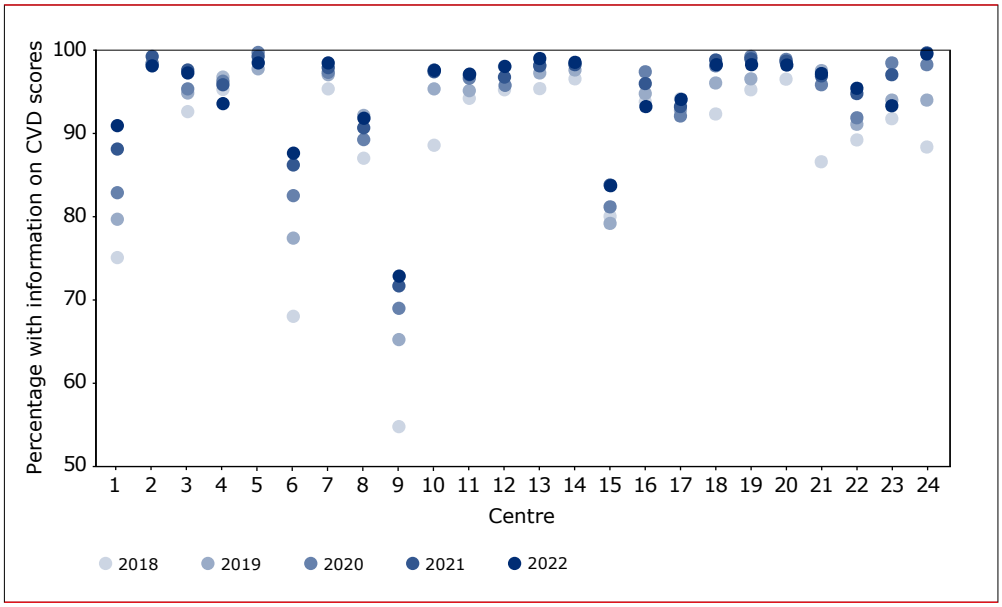






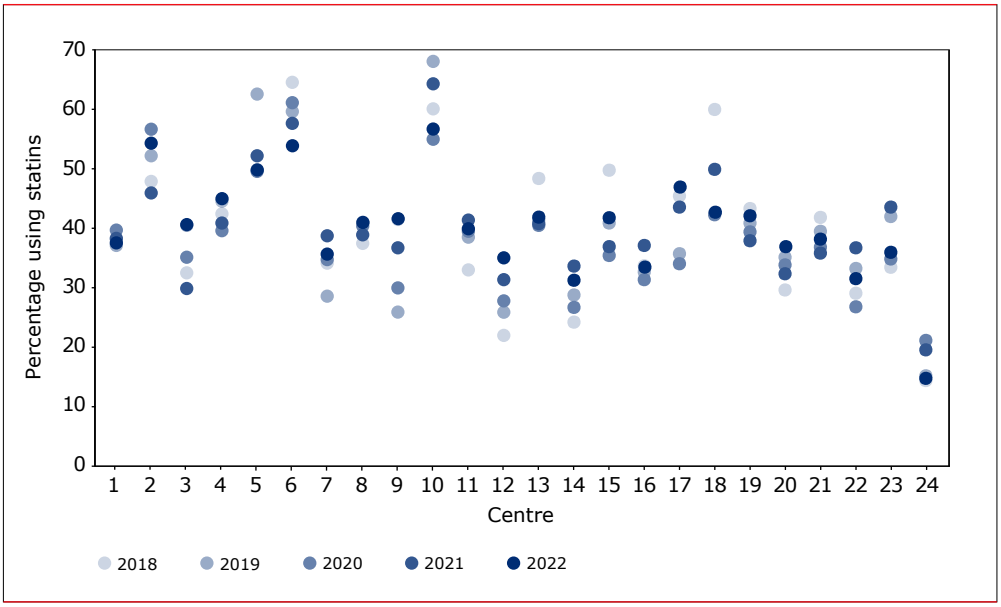
Legend: *Data are provided overall (A) and by age group: 18–39 year olds (B), 40–69 year olds (C) and 70 years old or older (D). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

Figure 7.8: *Information on cardiovascular event risk; in other words, patients who had enough information to have their SCORE2 (40–69 year olds) or SCORE2-OP (70 year olds or older) cardiovascular risk assessment during each year between 2018 and 2022.*



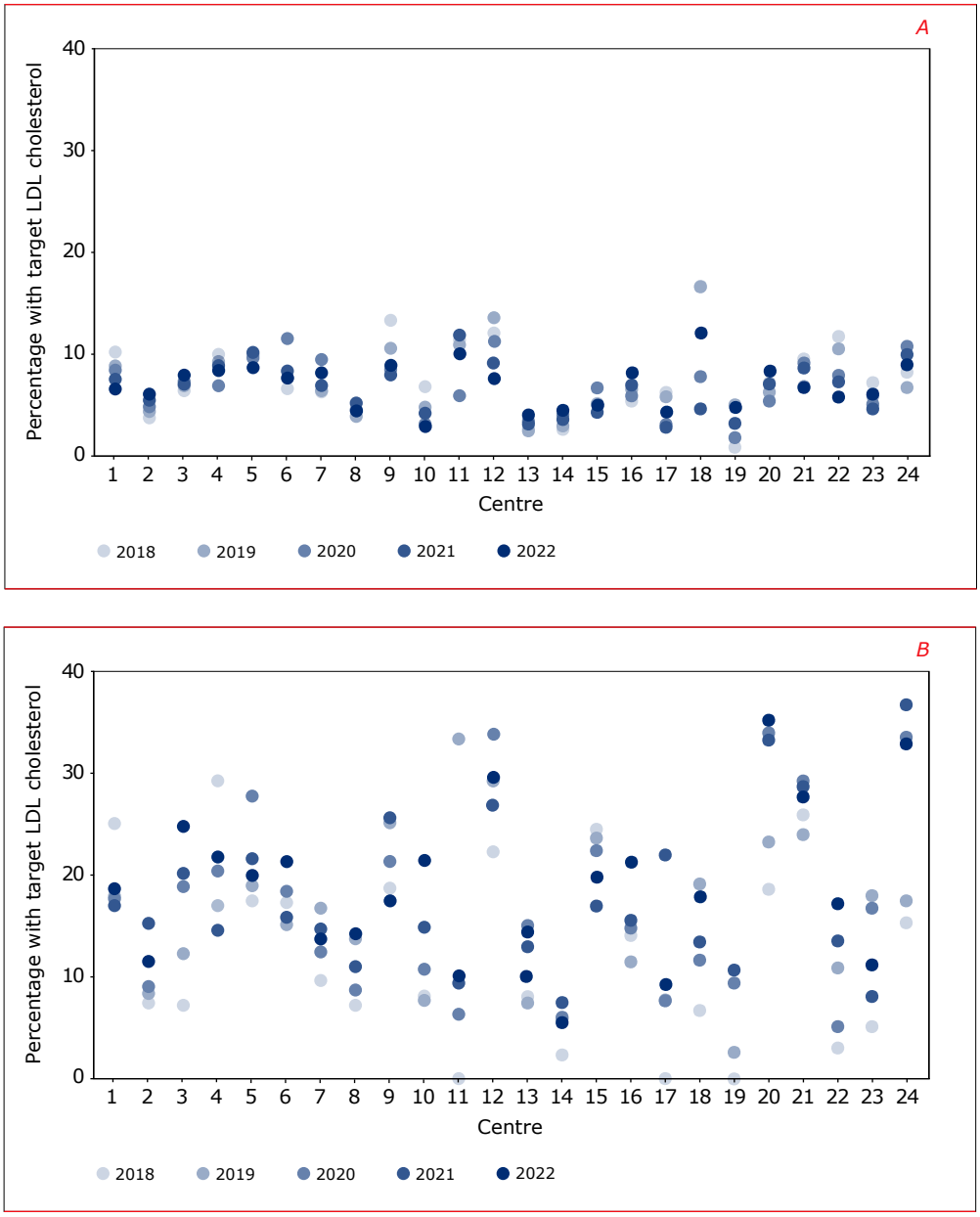
Legend: *Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

Figure 7.9: *Statin use; in other words, patients who had a predicted 10-year cardiovascular event risk-score greater than 10% and received a prescription for statins during each year between 2018 and 2022.*



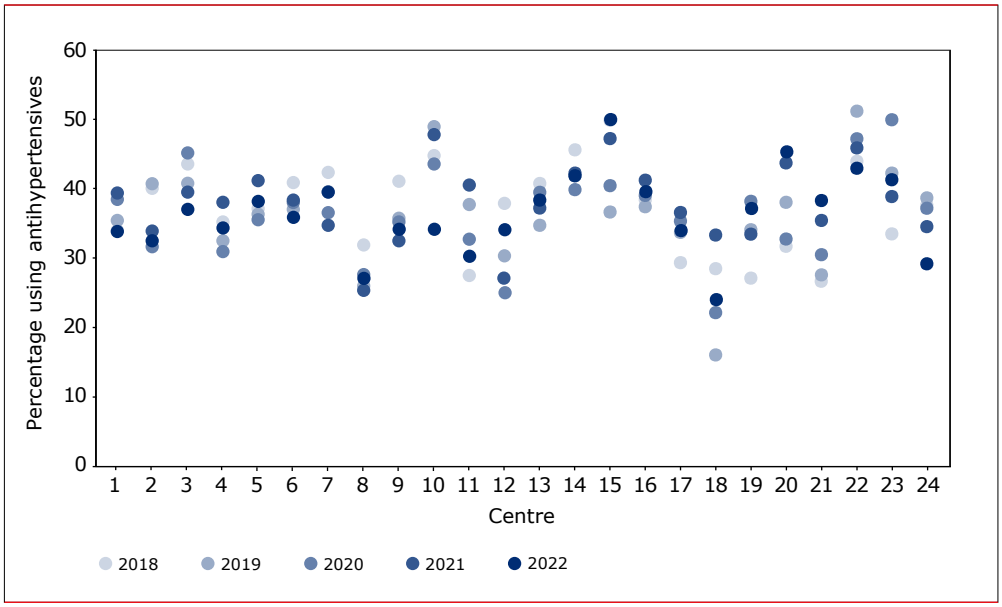
Legend: *Data are provided for those whose predicted 10-year cardiovascular risk were assessed with SCORE2 (for 40-69 year olds) or SCORE2-OP (for 70 year olds or older). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

Figure 7.10: *Target LDL cholesterol; in other words, patients who had a predicted 10-year cardiovascular event risk-score greater than 10% and had an LDL cholesterol level ≤1.8 mmol/mL during each year between 2018 and 2022.*



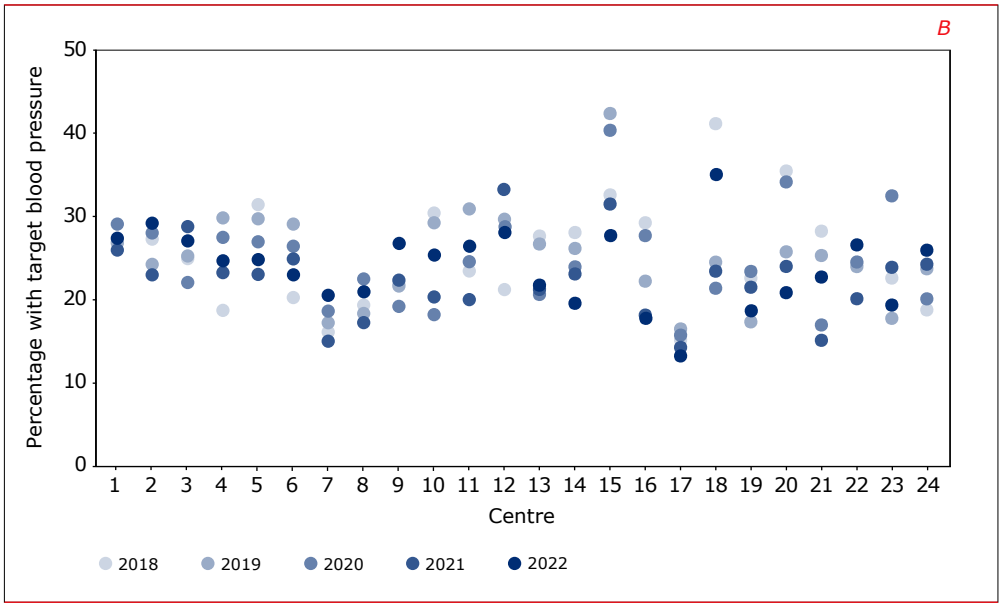
Legend: *Data are separated for those without and with a prescription for statins (A and B, respectively). Data are provided for those whose 10-year cardiovascular risk were assessed with SCORE2 (for 40-69 year olds) or SCORE2-OP (for 70 year olds or older). Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

Figure 7.11: *Antihypertensive medication use; in other words, patients who had high blood pressure and received a prescription for antihypertensive medication during each year between 2018 and 2022.*



Legend: *Data are provided for those who had high blood pressure, defined as ever having a diastolic blood pressure ≥90 mmHg. Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

Figure 7.12: *Target blood pressure; in other words, patients who were receiving antihypertensive medication and had a blood pressure below age-specific thresholds during each year between 2018 and 2022*



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 7.1.*

Centre performance

As reported in earlier studies, both the number of patients in care (i.e., the centre 'volume'), and the patient characteristics of a given centre (i.e., the patient 'mix'), may have an impact on the reported indicators[6–9].

Regarding centre volume, a smaller number of patients in an HIV treatment centre can increase the chance that an indicator is more variable. When this occurs, it is difficult to distinguish whether a low-level indicator is the result of performing below expectations or having excessive variation. For this reason, we compare each centre's indicator to the national average and provide statistical guidance as to whether a given centre falls below the national average. This assessment depends on the number of patients included when calculating the indicator (an overview of this method is provided in *Box 7.2*). Statistical interpretation is unreliable when centre sizes are small, hence we do not draw conclusions on whether these particular centres fall below the national average.

Regarding patient mix, individual-level factors, such as age and mode of transmission, are known to be associated with several indicators. If performance indicators are different across centres, it could be that the variation in the characteristics of patients attending those centres is driving these differences. We have therefore adjusted all indicators by year of birth and geographical origin/mode of transmission/gender (*Box 7.2*). For this section, we have used all the indicators and populations defined in *Box 7.1*, while accounting for the issues described above. Only indicators from 2022 were considered in this analysis.

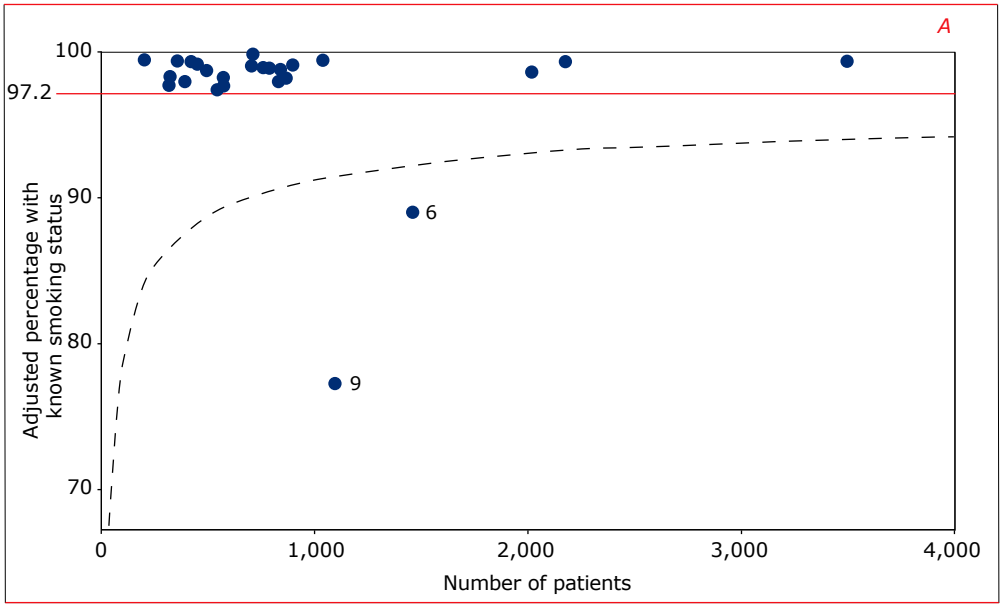
Box 7.2: Funnel plots to compare centres to the national average.

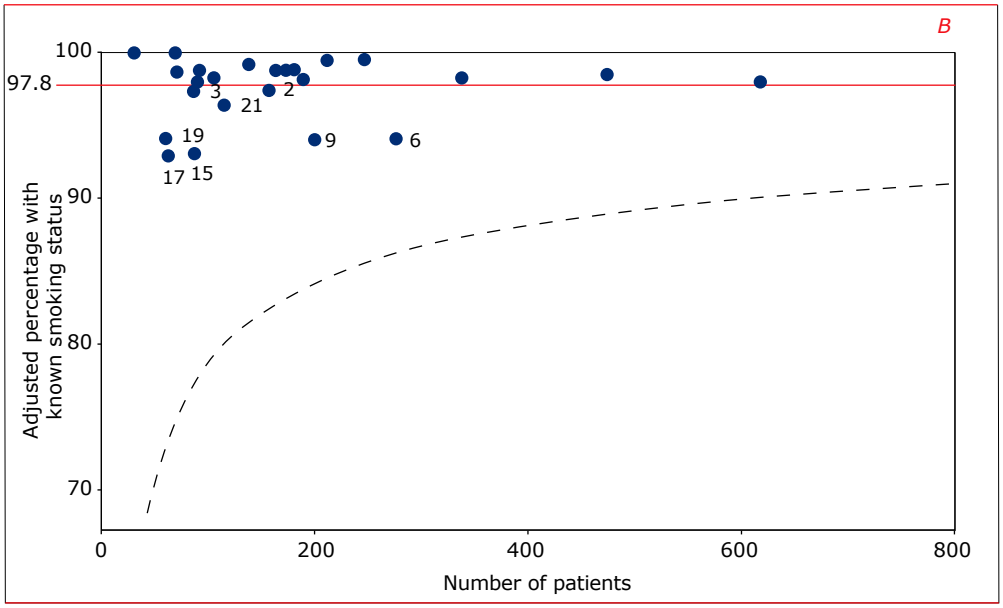
What types of problems occur when evaluating indicators?	
Centres with fewer patients	Centres of a smaller size are expected to have a wider variation in any given indicator. This variation makes it difficult to determine if the indicator is truly higher or lower than expected.
Patient mix	Individual-level 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).

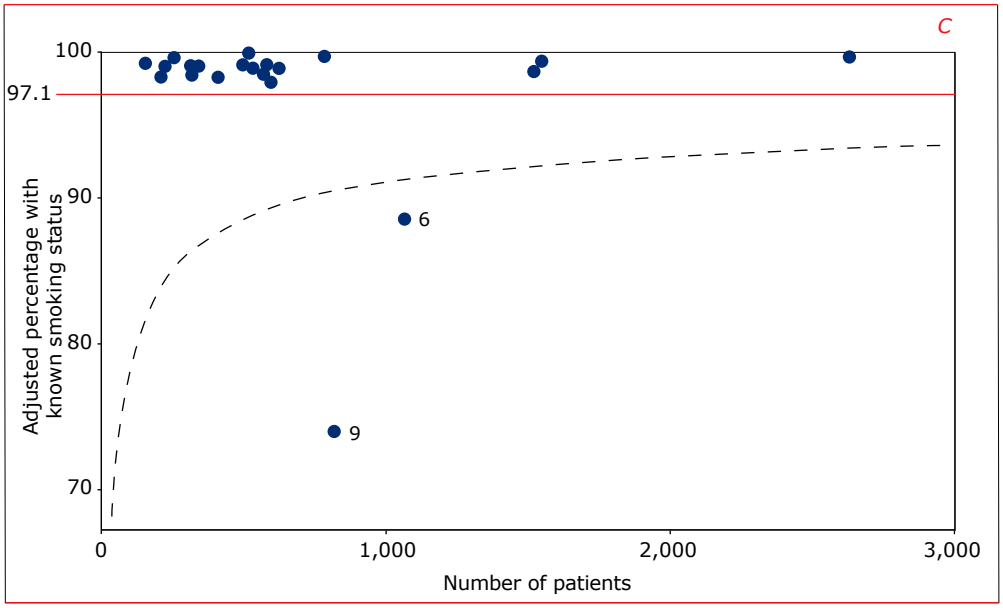
What is a funnel plot?
A funnel plot is a graphical depiction that allows us to compare a centre's indicator to the national average. It can help account for the problems listed above. The following are key components of this plot:

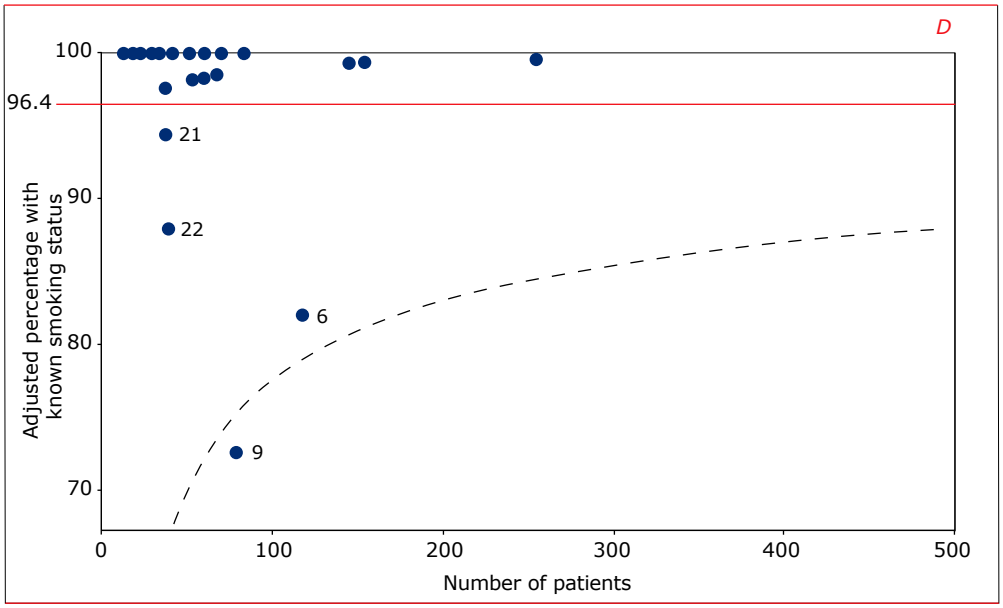
Patient size	The *x*-axis depicts the number of patients considered in a given indicator. For example, this number could be the total number of patients in care in 2022, etc.
Adjusted %	The *y*-axis depicts the percentage of patients who have achieved a given indicator. This indicator is adjusted for patient mix.
Centre's indicator	Dots depict each centre's indicator (adjusted %), which are plotted with respect to the number of patients included in the calculation of the indicator.
Comparison to the national average	A solid line depicts the national average. We can create boundaries that indicate (i) the highest indicator level a centre should achieve based on what we statistically expect from the national average ("upper" boundary), or (ii) the lowest indicator level a centre should achieve based on what we statistically expect from the national average ("lower" boundary). These boundaries make the form of a "funnel". The calculation of these boundaries is based on a statistical difference (±2 standard deviations) from the national average.
How is a funnel plot interpreted?	
When is an indicator lower than the national average?	If the centre's indicator falls below the "lower" boundary, then the centre has a lower-than-expected indicator compared to the national average.
When is an indicator higher than the national average?	This question will not be answered in this shm report. The indicators will be high (ranging from 80-100%), making the "upper" boundary difficult to interpret. We will only provide the "lower" boundary.

Figure 7.13: Known smoking status; in other words, patients who ever had information on their smoking status in 2022. The percentage with information on smoking has been adjusted for patient mix and is plotted as a function of the number of patients in care.



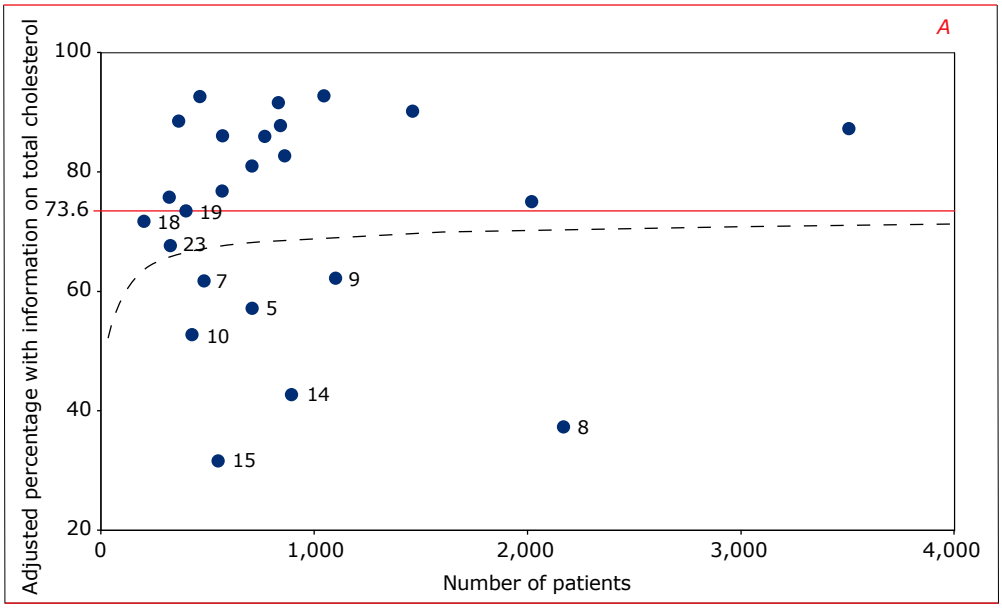


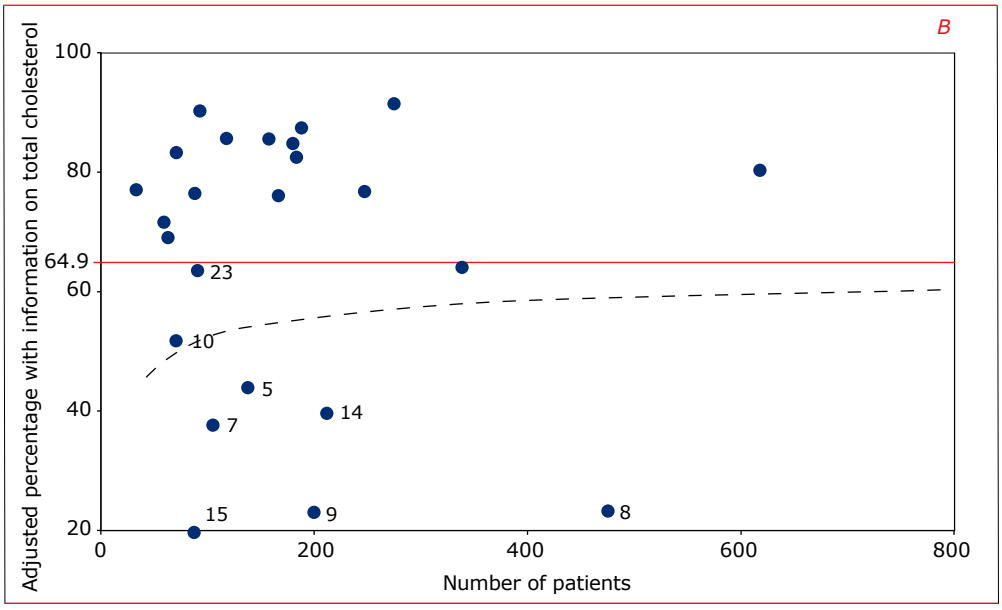


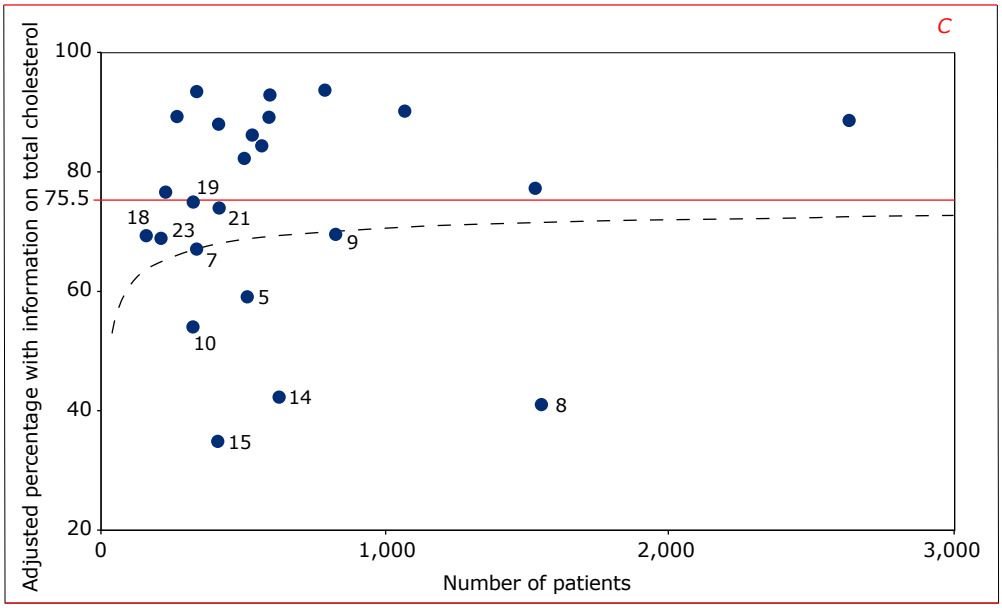


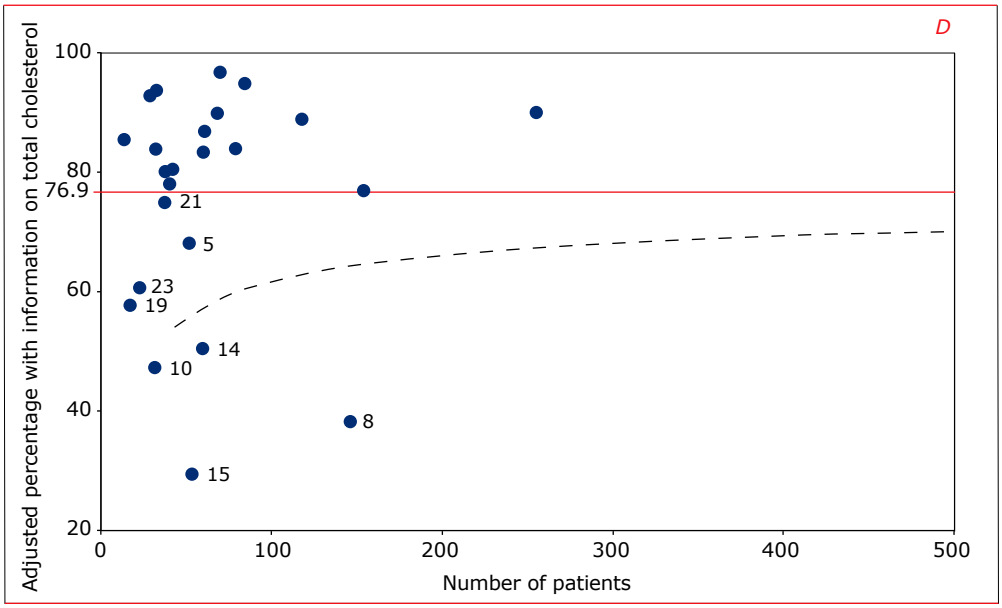
Legend: *Data are provided overall (A) and by age group: 18-39 year olds (B), 40-69 year olds (C) and 70 years old or older (D). Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The "lower" boundary of expected percentage (as compared to the national average) is indicated with a dashed line (Box 7.2).*

Figure 7.14: Information on total cholesterol; in other words, patients who had a total cholesterol measurement in 2022. The percentage with information on total cholesterol has been adjusted for patient mix and is plotted as a function of the number of patients in care.



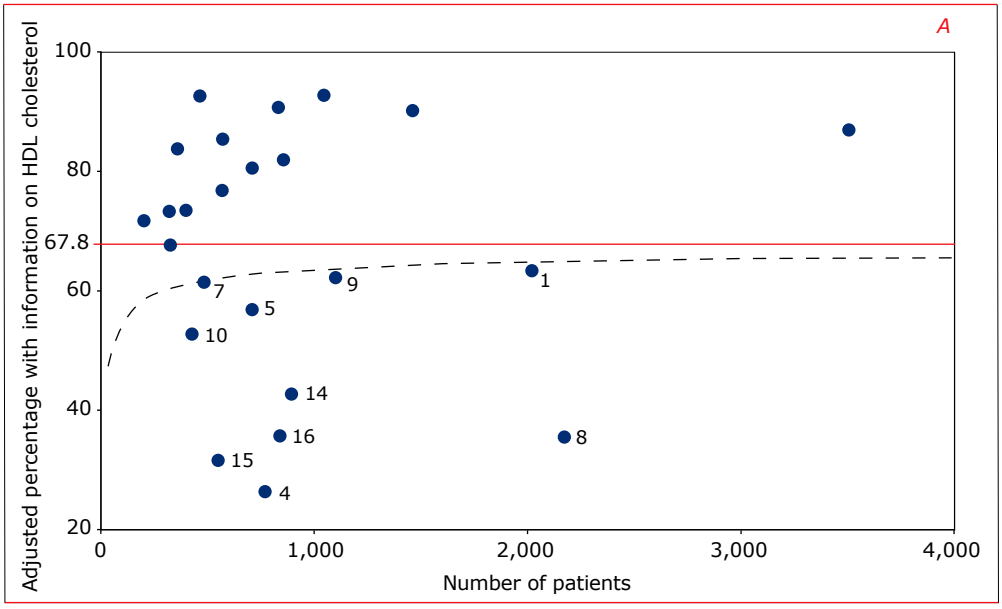


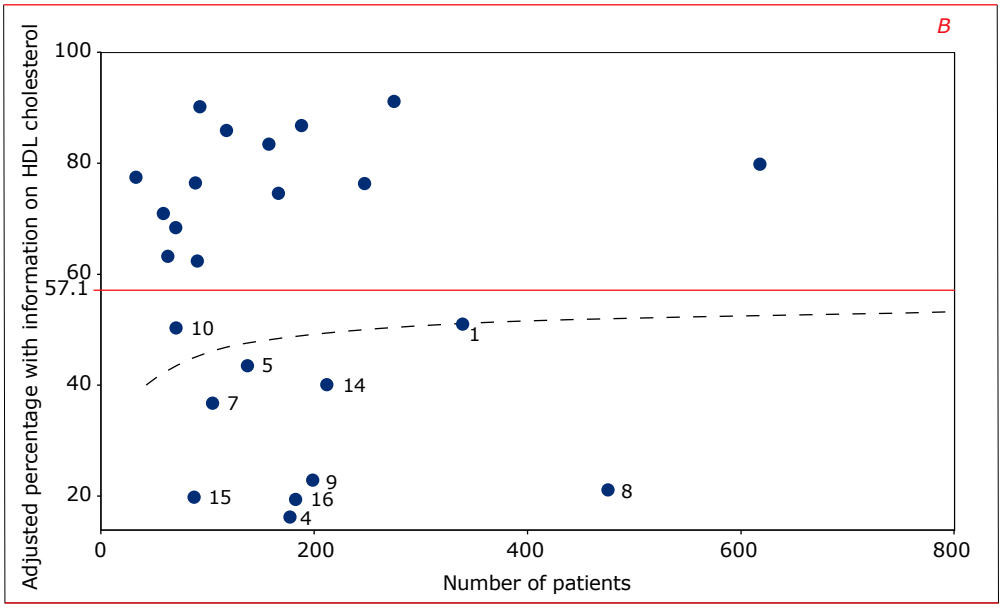


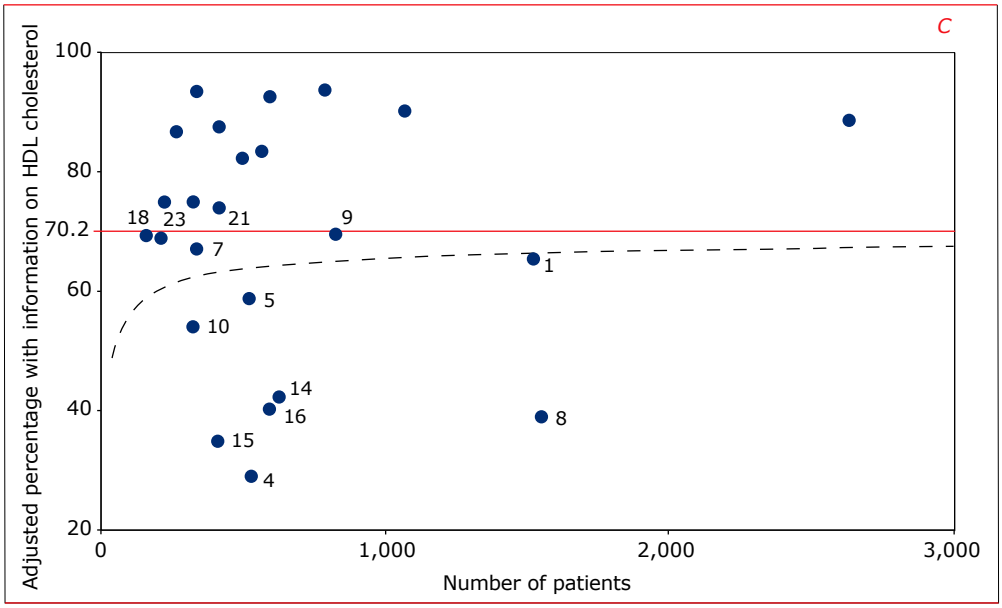


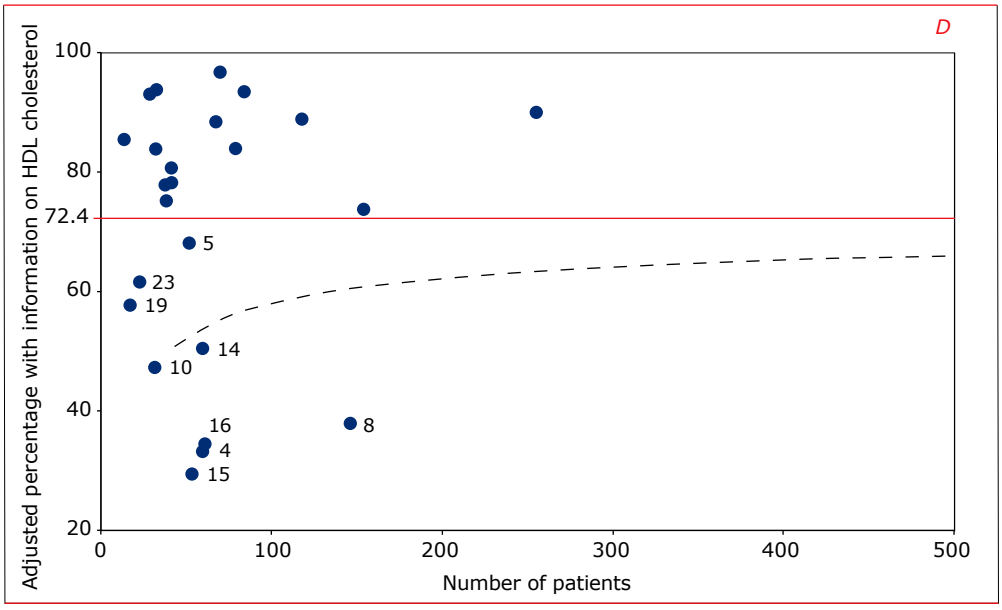
Legend: *Data are provided overall (A) and by age group: 18-39 year olds (B), 40-69 year olds (C) and 70 years old or older (D). Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The "lower" boundary of expected percentage (as compared to the national average) is indicated with a dashed line (Box 7.2).*

Figure 7.15: Information on HDL cholesterol; in other words, patients who had an HDL cholesterol measurement in 2022. The percentage with information on HDL cholesterol has been adjusted for patient mix and is plotted as a function of the number of patients in care.



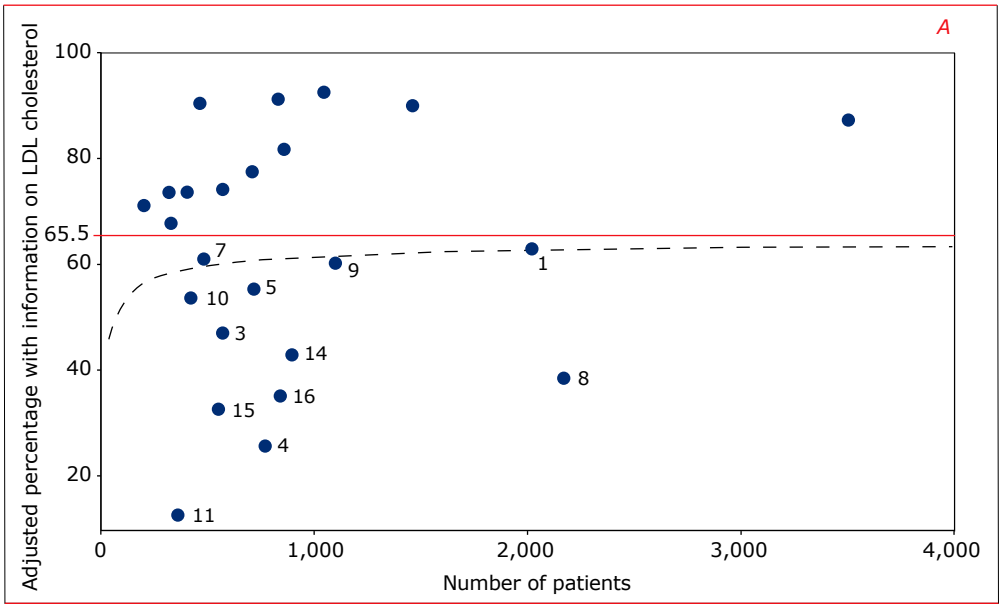


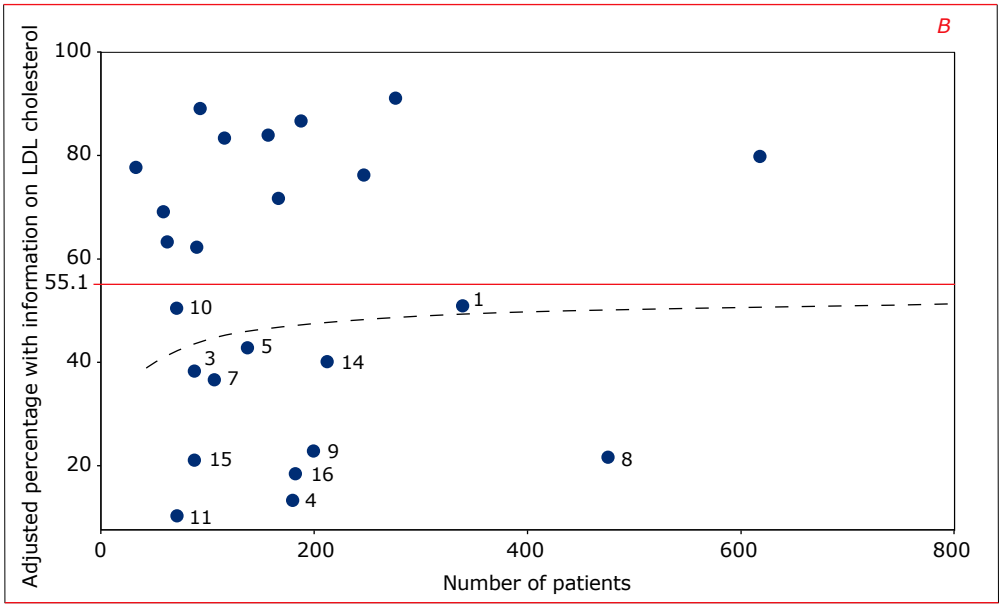


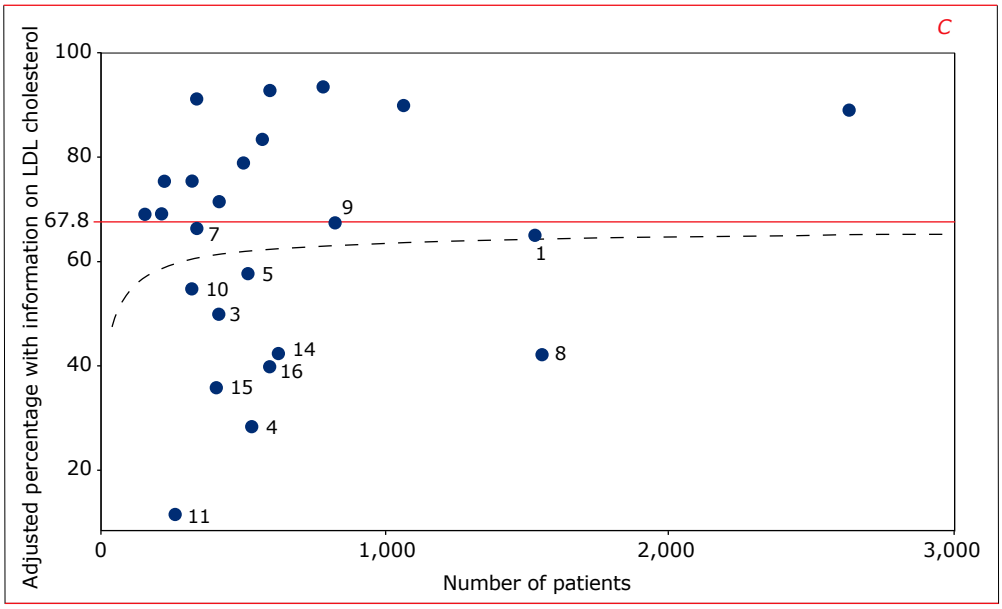


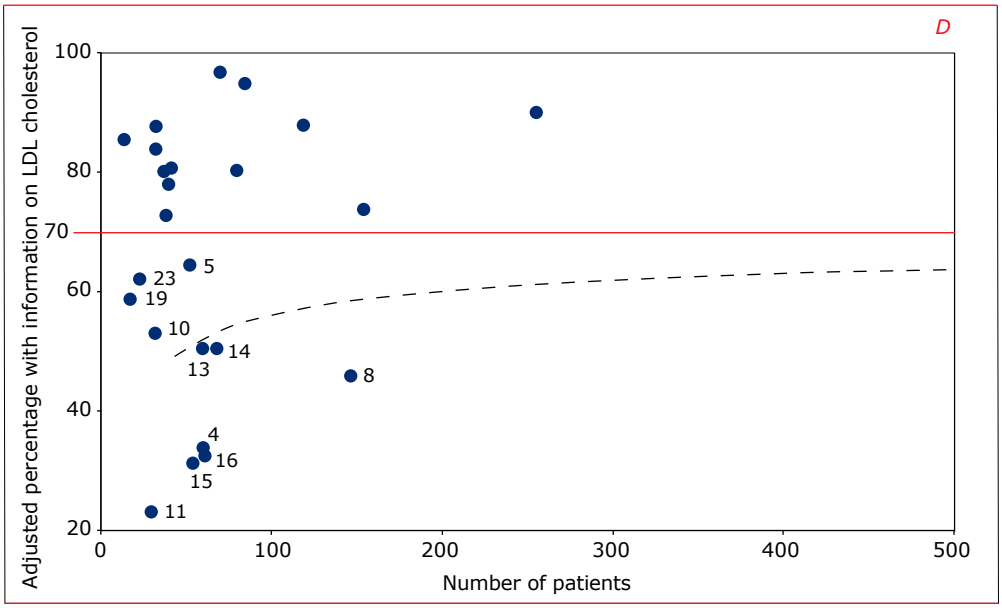
Legend: *Data are provided overall (A) and by age group: 18-39 year olds (B), 40-69 year olds (C) and 70 years old or older (D). Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The "lower" boundary of expected percentage (as compared to the national average) is indicated with a dashed line (Box 7.2).*

Figure 7.16: Information on LDL cholesterol; in other words, patients who had an LDL cholesterol measurement in 2022. The percentage with information on LDL cholesterol has been adjusted for patient mix and is plotted as a function of the number of patients in care.



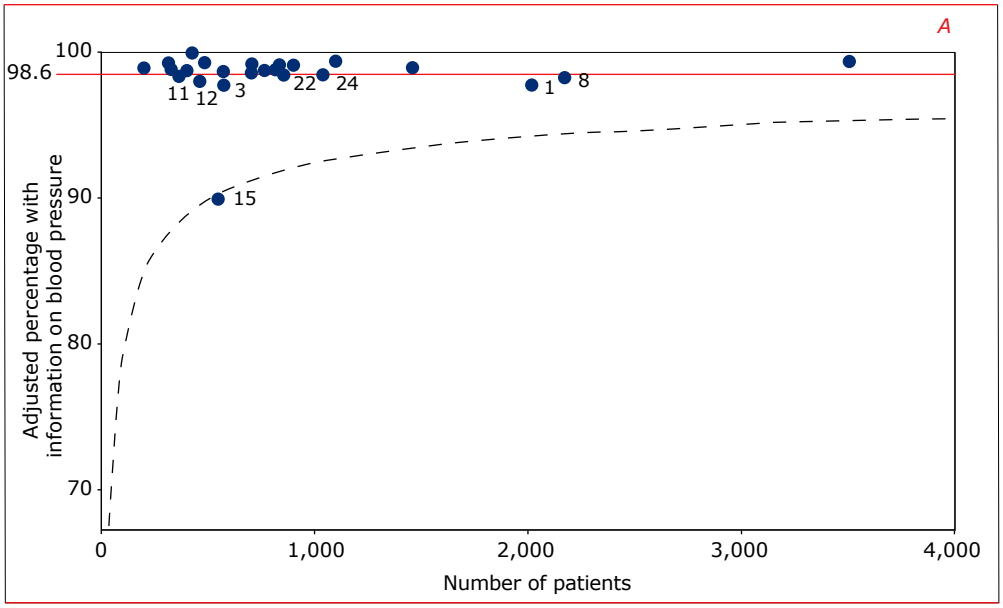


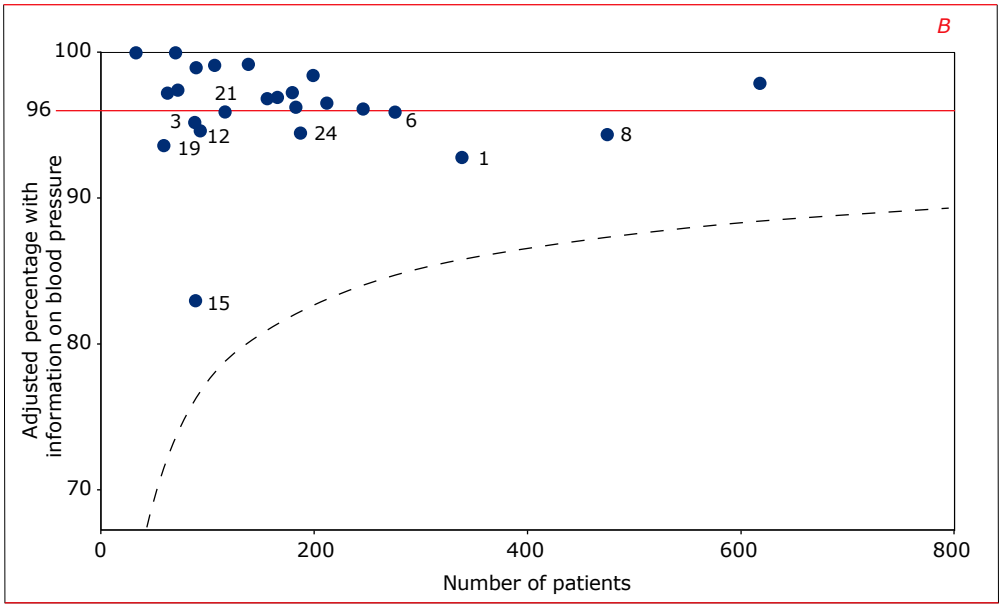


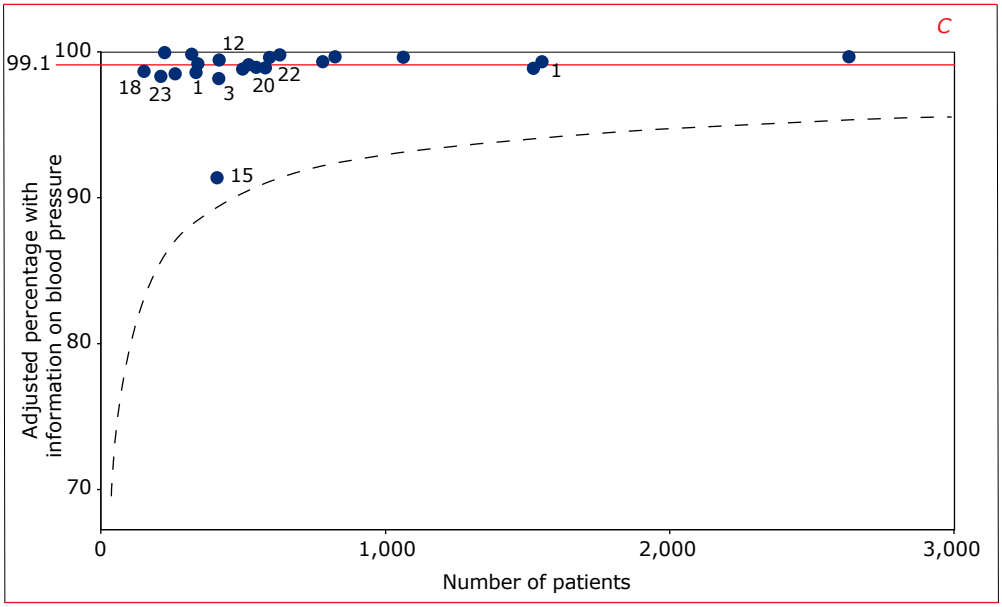


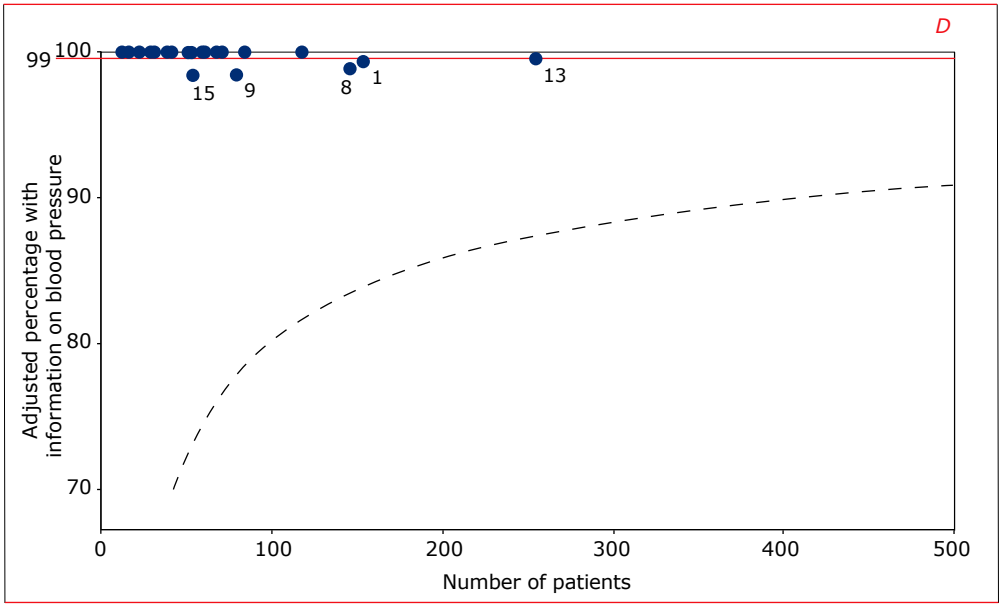
Legend: *Data are provided overall (A) and by age group: 18-39 year olds (B), 40-69 year olds (C) and 70 years old or older (D). Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The "lower" boundary of expected percentage (as compared to the national average) is indicated with a dashed line (Box 7.2).*

Figure 7.17: Information on blood pressure; in other words, patients who had a blood pressure measurement in 2022. The percentage with information on blood pressure has been adjusted for patient mix and is plotted as a function of the number of patients in care.



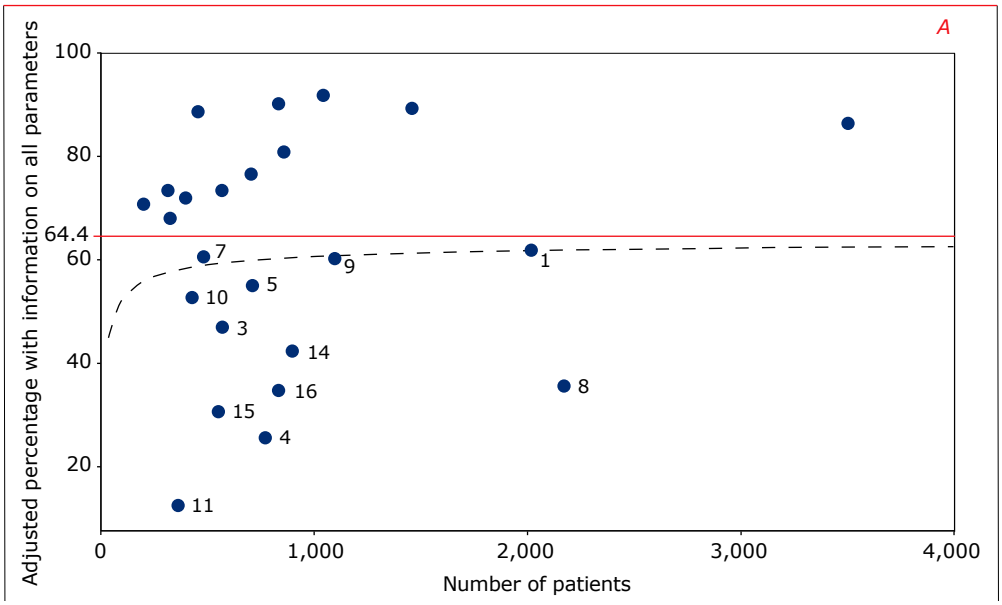


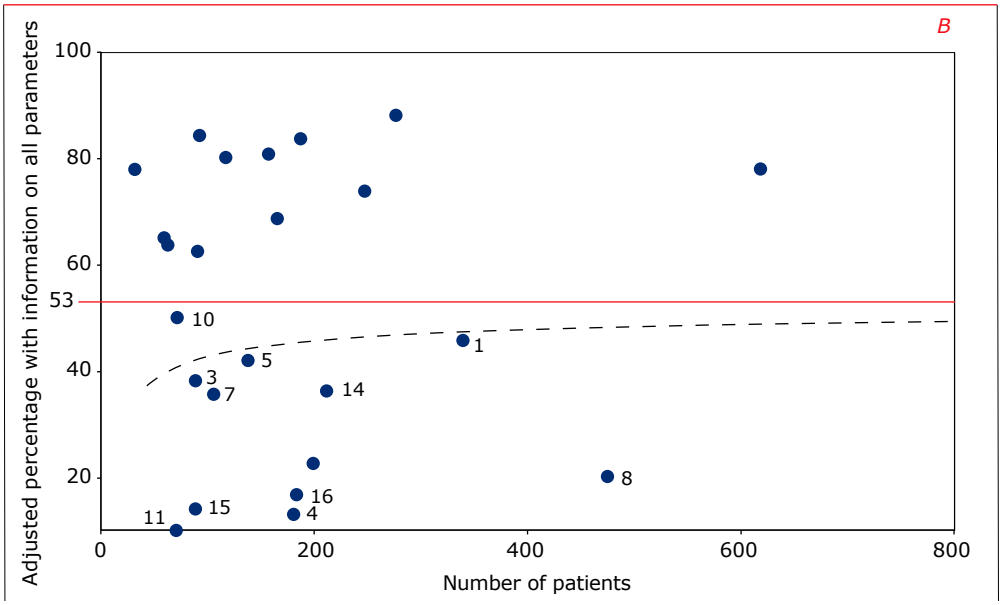


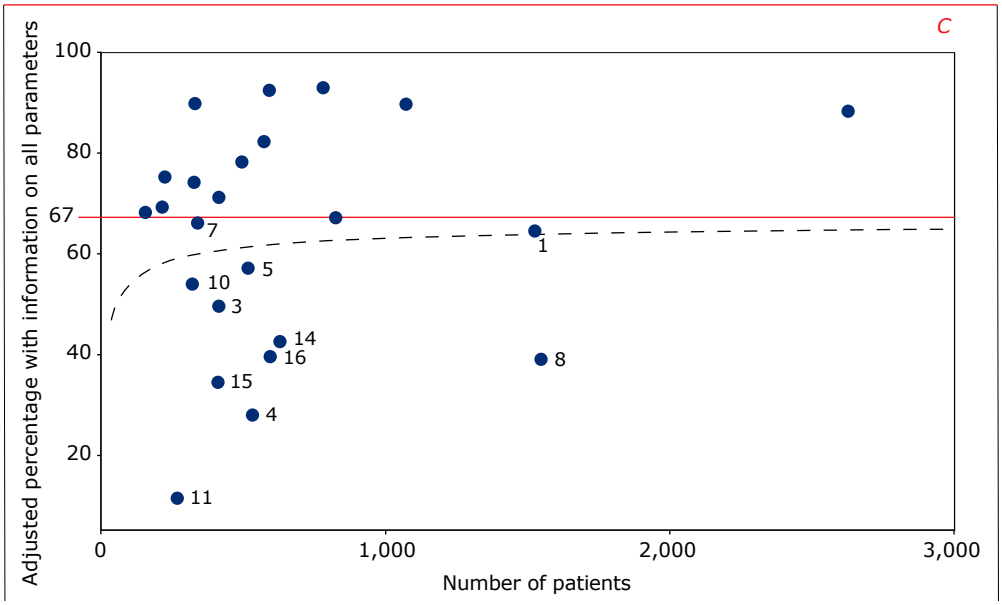


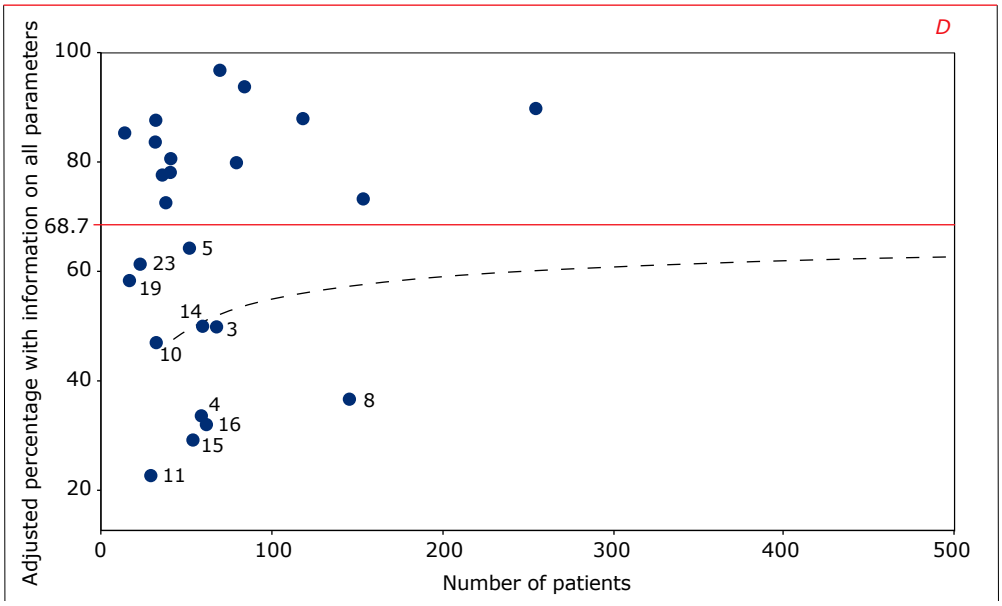
Legend: *Data are provided overall (A) and by age group: 18-39 year olds (B), 40-69 year olds (C) and 70 years old or older (D). Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The "lower" boundary of expected percentage (as compared to the national average) is indicated with a dashed line (Box 7.2).*

Figure 7.18: Information on all cardiovascular parameters; in other words, patients who had total, HDL and LDL cholesterol and blood pressure measurement in 2022. The percentage with information on all cardiovascular parameters has been adjusted for patient mix and is plotted as a function of the number of patients in care.



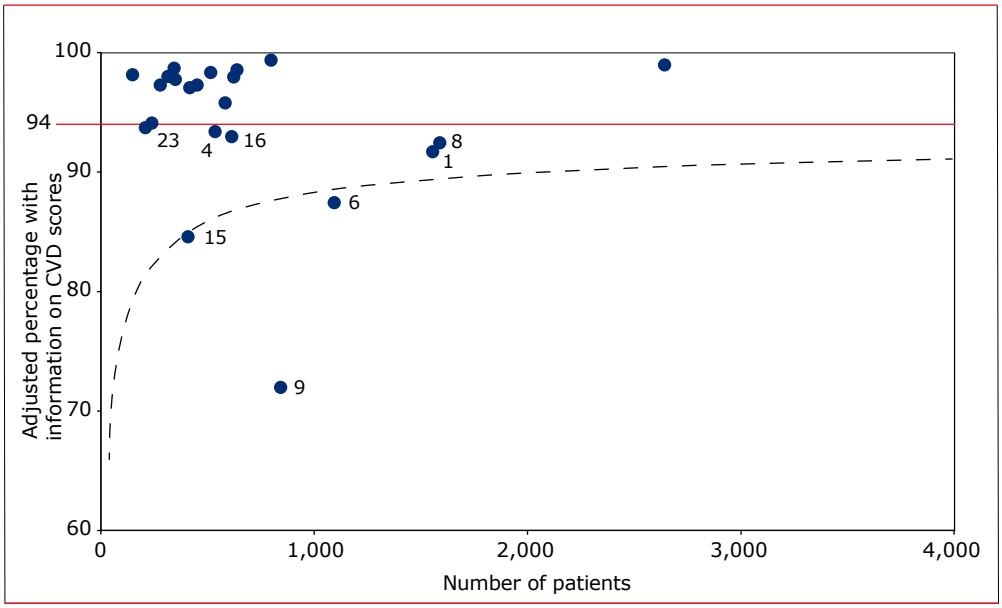






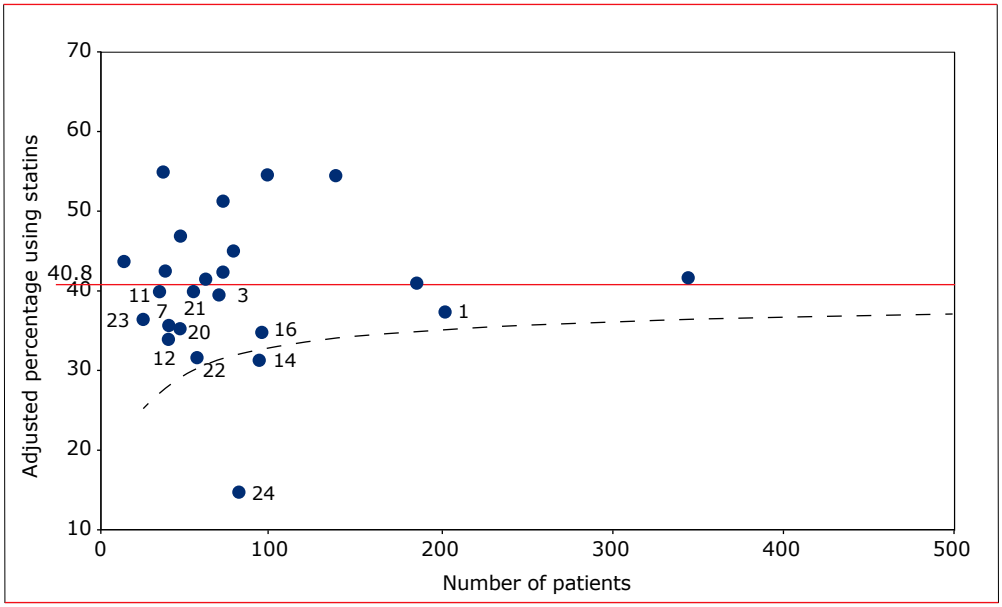
Legend: *Data are provided overall (A) and by age group: 18-39 year olds (B), 40-69 year olds (C) and 70 years old or older (D). Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The "lower" boundary of expected percentage (as compared to the national average) is indicated with a dashed line (Box 7.2).*

Figure 7.19: *Information on cardiovascular event risk; in other words, patients who had enough information to have their SCORE2 (40-69 year olds) or SCORE2-OP (70 year olds or older) cardiovascular risk assessment in 2022. The percentage with information on cardiovascular event risk assessment has been adjusted for patient mix and is plotted as a function of the number of patients in care.*



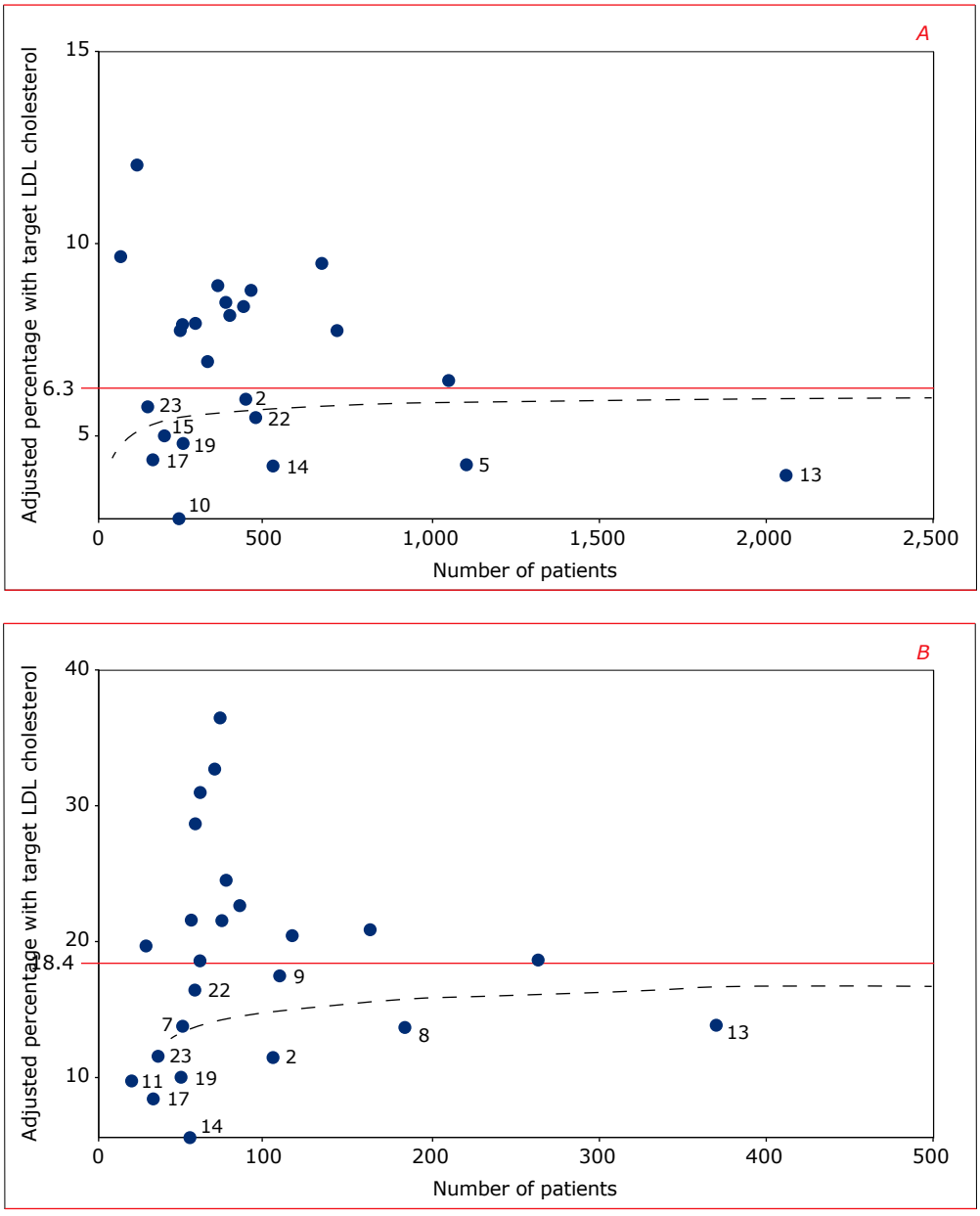
Legend: *Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The "lower" boundary of expected percentage (as compared to the national average) is indicated with a dashed line (Box 7.2).*

Figure 7.20: *Statin use; in other words, patients who had a predicted 10-year cardiovascular event risk-score greater than 10% and received a prescription for statins in 2022. The percentage with statin use has been adjusted for patient mix and is plotted as a function of the number of patients in care.*



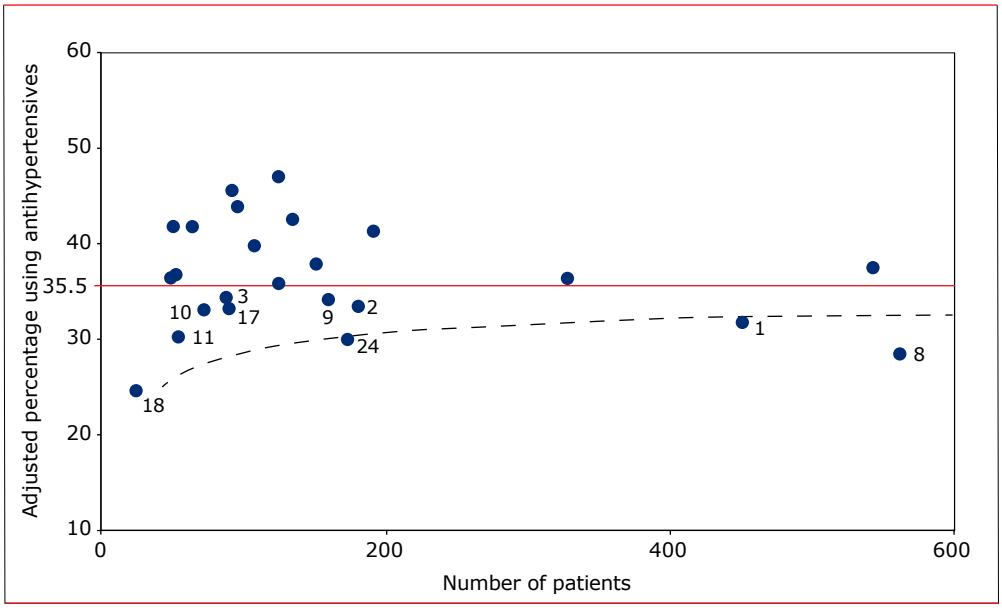
Legend: *Data are provided for those whose cardiovascular risk were assessed with SCORE2 (for 40-69 year olds) or SCORE2-OP (for 70 year olds or older). The "lower" boundary of expected percentage (as compared to the national average) is indicated with a dashed line (Box 7.2).*

Figure 7.21: *Target LDL cholesterol; in other words, patients who had a predicted 10-year cardiovascular event risk-score greater than 10% and had an LDL cholesterol level ≤1.8 mmol/mL in 2022. The percentage with target HDL cholesterol has been adjusted for patient mix and is plotted as a function of the number of patients in care.*



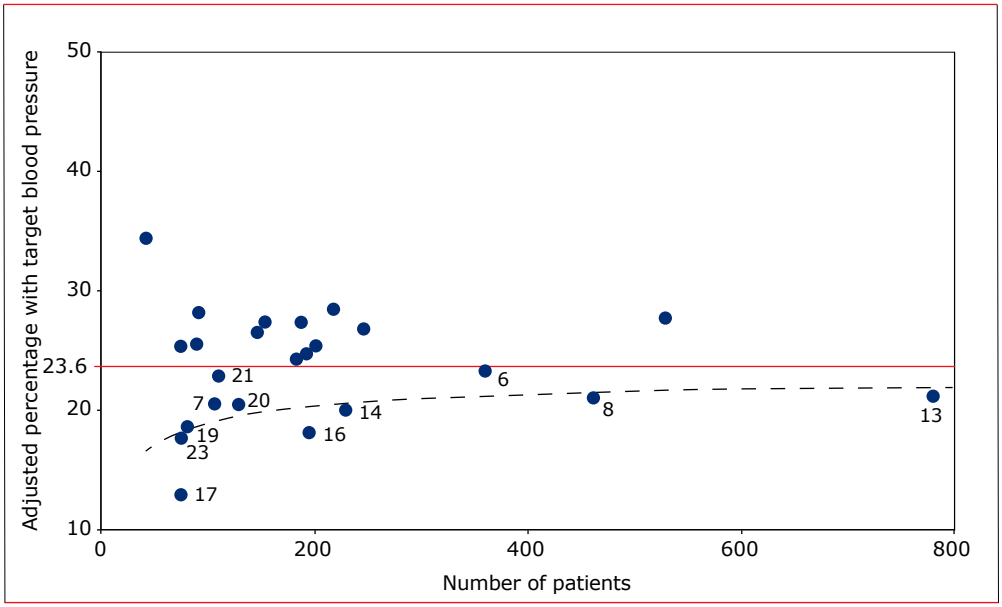
Legend: *Data are separated for those without and with a prescription for statins (A and B, respectively). Data are provided for those whose cardiovascular risk were assessed with SCORE2 (for 40-69 year olds) or SCORE2-OP (for 70 year olds or older). The "lower" boundary of expected percentage (as compared to the national average) is indicated with a dashed line (Box 7.2).*

Figure 7.22: *Antihypertensive medication use; in other words, patients who had high blood pressure and received a prescription for antihypertensive medication in 2022. The percentage with antihypertensive medication use has been adjusted for patient mix and is plotted as a function of the number of patients in 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 (as compared to the national average) is indicated with a dashed line (Box 7.2).*

Figure 7.23: *Target blood pressure; in other words, patients who were receiving antihypertensive medication and had a blood pressure below age-specific thresholds in 2022. The percentage with target blood pressure has been adjusted for patient mix and is plotted as a function of the number of patients in 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 (as compared to the national average) is indicated with a dashed line (Box 7.2).*

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:

- Most centres had information on smoking status and blood pressure both overall and in older age groups. However, there was substantial variation in the percentage of patients with information on total-, HDL- and LDL- cholesterol. This led to a number of centres with percentages of information needed for cardiovascular disease screening that were much lower-than-expected compared to the national average. It should be noted that much of this variation was observed in individuals between the ages of 18 and 39. Screening for cholesterol is not necessarily warranted in this age group, and differences between centres more likely reflect centre-specific preferences.
- More than 80% of patients 40 years or older had information on their predicted 10-year risk of a cardiovascular disease event for all but one centre. For three centres, this percentage was much lower-than-expected compared to the national average. Nevertheless, many of the centres demonstrated marked improvement in this indicator over the past five years.
- Among those with a high (i.e., 10%) predicted 10-year risk of a cardiovascular disease event, there was substantial variation in the percentage who received a prescription for statins. Although some centres have shown increases in the percentage with high cardiovascular disease risk who received statins over the past five years, this percentage remains low nationally.
- Among those with a high predicted 10-year risk of a cardiovascular disease event, there was some variation in the percentage with target LDL cholesterol when patients had a prescription for statins. No centre, however, had a much lower-than-expected percentage with target LDL for this specific group. There was less variation in the percentage with target LDL cholesterol when patients did not receive a prescription for statins, but this percentage was high across all centres.
- There was also substantial between-centre variation in the percentage of patients with high blood pressure who received an antihypertensive prescription. Likewise, there was between-centre variation in the percentage of patients taking antihypertensive medication who had achieved a target blood pressure. For most centres, these percentages were similar over the last five years. Some of the larger HIV treatment centres had levels of these indicators that were much lower-than-expected when compared to the national average.

Care related to cardiovascular disease does have some variation across centres. Nevertheless, certain centres should strive to increase the percentage of patients with information on cholesterol measurements and risk assessment of cardiovascular disease events. Some centres may also want to think about increasing the percentage of patients on statins or antihypertensive medication, especially those who are at higher risk of a cardiovascular disease event. This analysis provides insight into the provision of cardiovascular diseases care at the different treatment centres. Nonetheless, data reliability remains an important issue, and it should be recognised that some of the reported variations may be due to missing data.

During a meeting of the NVHB in 2020-2021, it was decided that the monitoring of patient quality of care needed to be changed. The NVHB established several quality of care indicators based on the NVHB guidelines (https://nvhb.nl), which included aspects of care related to cardiovascular diseases. HIV treatment centres are expected to use these indicators as guidance for higher quality of care. The shm is responsible for providing information on these indicators to individual centres. In collaboration with *V&VN Verpleegkundig Consulenten HIV*, the NVHB organizes yearly audits with 3 different HIV treatment centres during which two auditors discuss aspects of quality of care, and results of the indicator report generated by the shm. These audits also serve as an opportunity to discuss difficulties in delivering care and best practices. HIV treatment centres are re-audited every 5 years. The data presented in this chapter are included in these audits and may additionally serve as a useful benchmark that centres can use to identify potential aspects for improvement.

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8. The Amsterdam Cohort Studies (ACS) on HIV infection: annual report 2022

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Introduction

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS started shortly after the first cases of AIDS were diagnosed in the Netherlands. Since October 1984, men who have sex with men (MSM) have been enrolled in a prospective cohort study. A second cohort involving people who use/used (injecting) drugs (PWUD/PWID) was initiated in 1985 and discontinued in 2016.

In 2022, the cohorts reached 38 years of follow-up. The initial aim of the ACS was to investigate the prevalence and incidence of HIV-1 infection and AIDS, the associated risk factors, the natural history and pathogenesis of HIV-1 infection, and the effects of interventions. During the past 38 years, these aims have remained primarily the same, although the emphasis of the studies has changed. Early on, the primary focus was to elucidate the epidemiology of HIV-1 infection, whereas, later, more in-depth studies were performed to investigate the pathogenesis of HIV-1 infection. In the past years, investigating the epidemiology, determinants, course of infections and pathogenesis of HIV, sexually transmitted (STI), blood-borne and other infections, and to evaluate the effect of interventions have become an important component of the ACS research programme.

From the outset, research in the ACS has taken a multidisciplinary approach, integrating epidemiology, social science, virology, immunology, and clinical medicine in one study team. This unique collaboration has been highly productive, significantly contributing to the knowledge and understanding of many different aspects of HIV-1 infection, as well as other infections such as STI [e.g., viral hepatitis B and C (HBV and HCV) and human papillomavirus (HPV)]. This expertise, in turn, has contributed directly to advances in prevention, diagnosis, and management of these infections.

Collaborating institutes and funding

Within the ACS, the following different institutes collaborate 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, Research and Prevention;
- **Amsterdam University Medical Centres, location Academic Medical Centre (AMC)** (Amsterdam UMC): Departments of Medical Microbiology, Experimental Immunology, and Internal Medicine (Division of Infectious Disease);
- **Emma Kinderziekenhuis** (Paediatric HIV treatment centre);
- **Stichting HIV Monitoring** (HIV Monitoring Foundation, SHM);
- **MC Jan van Goyen** Department of Internal Medicine; and
- **HIV Focus Centrum** (DC Klinieken Lairesse)

In addition, there are numerous collaborations between the ACS and other research groups, both within and outside the Netherlands. The ACS is financially supported by the Centre for Infectious Disease Control Netherlands of the National Institute for Public Health and the Environment (*Centrum voor Infectieziektenbestrijding-Rijksinstituut voor Volksgezondheid en Milieu,* RIVM-CIb).

Ethics statement

The ACS has been conducted in accordance with the ethical principles set out in the Helsinki declaration. Participation in the ACS is voluntary and written informed consent is obtained from each participant. The most recent version was approved by the Amsterdam UMC medical ethics committee in 2022 for the MSM cohort, and in 2009 for the PWID cohort.

ACS in 2022

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

Between 1984 and 1985, men who had had sexual contact with at least one other man in the preceding six months were enrolled, independent of their HIV status. In the first 6 months of the recruitment period, 750 MSM, of which one-third with HIV, were enrolled. From 1985 to 1988, men without HIV of all age groups were eligible to participate if they lived in or around Amsterdam and had had at least two male sexual partners in the preceding six months. Between 1988 and 1998, MSM with HIV were also enrolled because of the cohort involvement in HIV treatment trials. From 1995 to 2004, only men aged 30 years or younger, with at least one male sexual partner in the previous six months, could be included the study. From 2005 to 2022 men without HIV of all age groups were eligible

to participate in the ACS if they live in or are closely connected to the city of Amsterdam and have had at least one male sexual partner in the preceding six months. In line with the advice issued by the International Scientific Advisory Committee in 2013, the cohort continues to strive to recruit young MSM (aged 30 years or younger). From 2022 onwards, we aim to actively follow 825 MSM (750 without HIV and 75 with HIV). Individuals of at least 16 years old, who were assigned male sex at birth and not having undergone gender reassignment surgery, live in the Amsterdam area or are involved in MSM-related activities in Amsterdam, and having had sex with at least one man in the preceding six months are eligible for enrolment. Active recruitment campaigns (e.g., online advertisements, promotional activities in gay venues in Amsterdam) are organized approximately once every two years.

Men who seroconverted for HIV within the ACS remained in the cohort until 1999, when follow-up of a selection of MSM with HIV was transferred to the MC Jan van Goyen. In 2003, the 'HIV Research in Positive Individuals' (*Hiv Onderzoek onder Positieven,* HOP) protocol was initiated. Individuals with a recent HIV infection when entering the study at the GGD Amsterdam, and those who seroconverted for HIV during follow-up within the cohort, continued to return for study visits at the GGD Amsterdam, or at an HIV treatment centre. Blood samples from these participants are stored at the ACS Biobank long-term storage and analyses. All (sexual) behavioural data are collected on a six-monthly basis by questionnaires, coordinated by the GGD Amsterdam, and clinical data are provided by SHM.

As of 31 December 2022, 2,950 MSM have been included in the ACS since its initiation in 1984. Every three to six months, participants complete a standardised questionnaire designed to obtain data regarding: medical history, (sexual) behaviour and substance use, underlying psychosocial determinants, health care use, signs of depression and other psychological disorders, and demographics. In total, the GGD Amsterdam has been visited 67,636 times by MSM since 1984. Moreover, blood is collected for diagnostic tests and storage at the ACS biobank. Of the 2,950 MSM, 607 were living with HIV at entry into the study and 265 seroconverted for HIV during follow-up.

In 2022, the cohort had 615 active participants: 578 MSM without HIV and 37 MSM with HIV.
Active participation is defined as having had at least one study visit in the year 2021 or 2022. The total group of MSM in active follow-up had the following characteristics:

- 30 newly enrolled MSM without HIV, with a median age at inclusion of 32 years [interquartile range (IQR)=25-37];
- The median age was 46 years (IQR=35-53) at their last cohort visit in 2022;
- The majority was born in the Netherlands and was a resident of Amsterdam (83.7% and 89.4%, respectively);
- 78.4% had a college degree or higher.

The cohort of people who use/used (injecting) drugs (PWUD/PWID)

Between 1984-2016, 1,680 PWUD/PWID were included and followed in the ACS, who contributed 28,194 visits. Study enrolment and data collection continued until 2014 and February 2016, respectively. An end-of-study interview was offered to those who had ever participated in the ACS. Median age of the PWUD/PWID cohort was 55 (IQR=49-59) years in 2016, 8.1% had attained a high level of education, and 63.4% were born in the Netherlands. Of the 1,680 PWUD/PWID, 323 were living with HIV at entry, and 99 HIV seroconverted during follow-up. The last HIV seroconversion was seen in 2012. In total, 576 deaths had been confirmed among PWID.

ACS biobank

The ACS biobank stores all samples [plasma/serum, peripheral blood mononuclear cells (PBMC)] taken in the context of the ACS study, at the Amsterdam UMC, location AMC. In addition to samples taken at routine ACS study visits, it also includes samples collected for sub-studies and affiliated studies embedded in the ACS.

Subgroup studies and affiliated studies

AGE$_h$IV cohort study

The AGE$_h$IV cohort study is a collaboration between the Amsterdam UMC, location AMC, Departments of Infectious Diseases and Global Health, the Amsterdam Institute of Global Health and Development, the GGD Amsterdam, and SHM. The AGE$_h$IV study was started in October 2010 and aims to assess the prevalence and incidence of a broad range of comorbidities, along with known risk factors for these comorbidities, in people with HIV aged 45 years and over. It also strives to determine the extent to which comorbidities, their risk factors and

their relation to quality of life, differ between groups of people with and without HIV. Participants undergo a comprehensive assessment for comorbidities and completed a questionnaire at intake. Every two years, participants complete follow-up research questionnaires.

In total, 598 participants with HIV-1 and 550 individuals without HIV were enrolled between October 2010 and September 2012. People with HIV-1 were included through the Amsterdam UMC, location AMC, HIV outpatient clinic, and participants without HIV from similar risk groups engaged via the Centre of Sexual Health Amsterdam (n=486) and the ACS (n=64). All participants were aged 45 years and over, and participants without HIV were as comparable as possible to participants with HIV with respect to age, gender, ethnicity, and risk behaviour. In 2021, the sixth study round was started, and during 2022, 206 participants without HIV came for a sixth round visit. The sixth round will be completed in 2023.

In 2020, a two-year COVID-19 sub-study was initiated within the AGE$_h$IV cohort, with as main aim to assess whether the risk for SARS-CoV-2 infection, the immune response to natural infection and to vaccination, and the disease burden (including mental health) differed between participants with and those without HIV. Five consecutive 6-monthly visits were conducted between September 2020 and October 2022. During each visit, participants completed a questionnaire and provided a blood sample to measure SARS-CoV-2 immune responses. Additionally, in the four to 13 weeks after their last dose of the primary COVID-19 vaccination, participants were invited for an additional blood draw to measure SARS-CoV-2 vaccine immune responses. In total, 567 participants (241 participants with HIV-1 and 326 participants without HIV) were included in this COVID-19 sub-study, of whom 441 (195 with and 246 without HIV) participated in the additional post-vaccination blood draw[a]. This sub-study has now been completed. Three papers have been published and a fourth is in preparation; the results are discussed below.

In the first paper using data collected within the AGEhIV COVID-19 sub-study, B-cell and T-cell responses to SARS-CoV-2 vaccines among 195 participants with HIV-1 and 246 controls without HIV were compared. Participants with HIV-1 showed strong immune responses, similar to controls, with no significant differences in key markers. Factors like prior SARS-CoV-2 infection, mRNA vaccine type, and demographics influenced vaccine response, but HIV status did not, offering reassurance about vaccine effectiveness in participants with HIV-1 with access and a good response to HIV treatment (Verburgh-2023-Microbiol Spectr). In the second paper, the impact of social distancing on health-related quality of

a The first manuscript on the cumulative SARS-CoV-2 incidence in this cohort was published in December 2021: https://academic.oup.com/jid/article/225/11/1937/6470931; (Verburgh et al., 2022)

life and depressive symptoms among 214 participants with HIV-1 and 285 controls without HIV was examined. The majority of both groups reported social distancing important and adhered to these measures. Irrespective of HIV status, concerns about contracting COVID-19 negatively affected participants' perceived current health and increased risk of depressive symptoms (Schaaf-2022-JAIDS). Lastly, in the third paper, the incidence of SARS-CoV-2 infection, risk factors and SARS-CoV-2 nucleocapsid antibody levels between 241 participants with HIV-1 (99.2% virally suppressed) and 326 participants without HIV were compared. The cumulative incidence of SARS-CoV-2 infection by April 2021 was similar in both groups (13.4% in HIV-positive and 11.6% in HIV-negative individuals). Younger age and African origin were associated with a higher risk of COVID-19 infection, but HIV status did not impact this risk. Moreover, among those with COVID-19 infection, HIV status did not affect antibody levels, with only self-reported fever being associated with higher antibody levels. To conclude, participants with HIV-1 with suppressed HIV-viremia and adequate CD4 counts, defined as ≥500/μL and no clinically relevant immunodeficiency, had similar risk of SARS-CoV-2 acquisition and antibody levels with comparable controls (Verburgh-2022-J Infect Dis).

Primo-SHM Trial

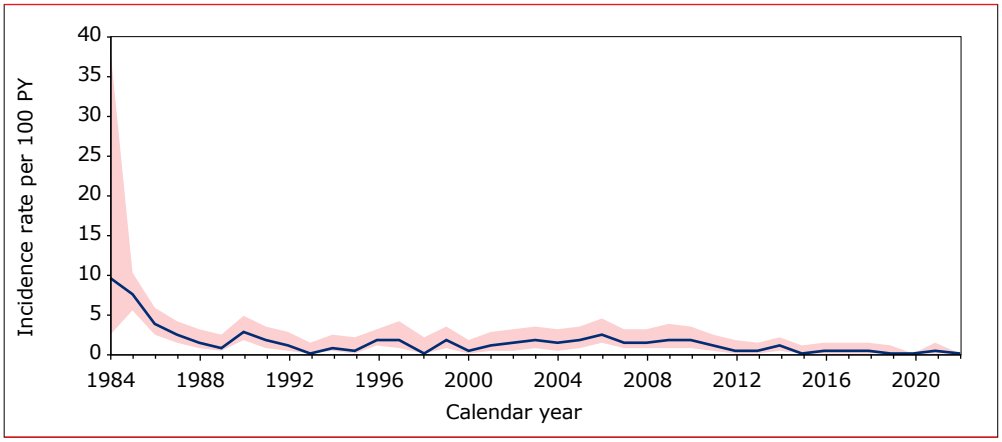
The Primo-SHM study is a national, randomised study that started in 2003. It compares the effects of early, temporary antiviral therapy with that of no therapy among (1) individuals presented with primary HIV-1 infection at the Amsterdam UMC HIV outpatient clinic, and (2) ACS participants who seroconverted for HIV during follow-up. Samples collected within the Primo-SHM study are stored at the ACS biobank at the Amsterdam UMC.

ACS in 2022: HIV/STI and sexual behaviour among MSM

HIV incidence

The estimated HIV incidence rate among MSM participating in the ACS has declined over time (*Figure 8.1*). Between 1985 and 1993 it declined significantly, then stabilised between 1993 and 1996, before rising in the period 1996 to 2009. Since 2009, the HIV incidence has decreased significantly. In 2022, no MSM participating in the ACS seroconverted for HIV.

Figure 8.1: *HIV incidence rate among men who have sex with men participating in the Amsterdam Cohort Studies (ACS), 1984–2022*



Sexual behaviour

Condomless anal sex with a steady and casual partner was reported by 176 out of 416 (42.3%) and 191 out of 292 (65.4%) MSM without HIV, respectively, during their cohort visit in 2022. Trends in recent (i.e., in preceding 6 months) condomless anal sex among MSM without HIV participating in the ACS continued to show an increase from 2009 onwards (*Figure 8.2*). More specifically, proportion of MSM reporting condomless anal sex showed a higher increase for casual partners than for steady partners in recent years. Use of PrEP has also increased since 2015. Data on recent PrEP use was available for 539 MSM without HIV actively participating in the ACS, of whom 199 (36.9%) reported PrEP use in the preceding six months. Of these 199 PrEP users, 80 (40.2%) obtained PrEP through the national PrEP program at the Centre of Sexual Health, 68 (34.2%) through their general practitioner; 18 (9.1%) through a PrEP study (e.g., *AmPrEP, DISCOVER*), 5 (2.5%) through an Internal Medicine specialist or another PrEP prescribing physician, and 5 (2.5%) obtained their pills through informal routes (e.g., *sexual or social networks, or online offered pills*). Of the remaining 23 PrEP users, data on PrEP uptake route were not available. Of the 199 MSM using PrEP, 174 (87.4%) reporting recent anal sex with either steady or casual partners (*Figure 8.3*). Among those, condomless anal sex with a steady and casual partner was reported by 74 (42.5%) and 138 (79.3%), respectively. Among the 379 MSM not using PrEP, 278 (81.2%) reported recent anal sex. Of these, 115 (41.4%) and 62 (22.3%) reported condomless anal sex with a steady and a casual partner, respectively.

Figure 8.2: Trends in the proportion of condomless anal sex with (A) casual and (B) steady sexual partners among men who have sex with men without HIV participating the Amsterdam Cohort Studies (ACS), 2009-2022

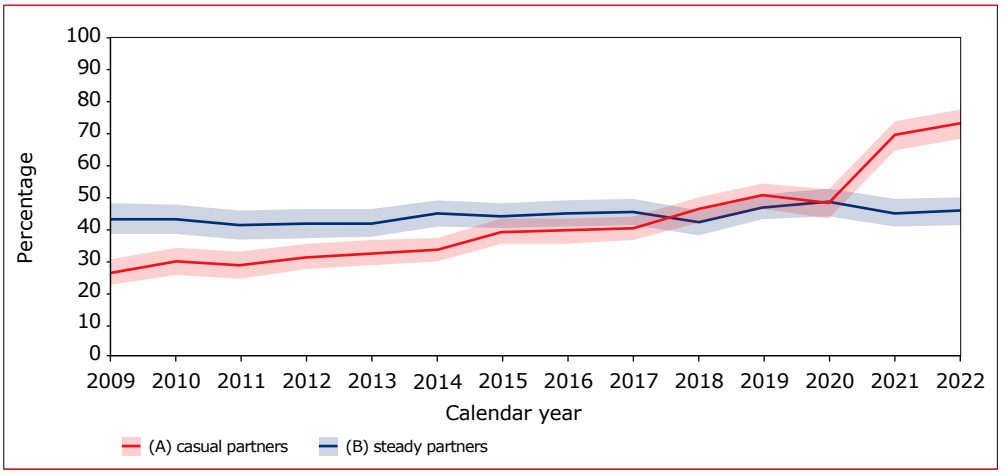
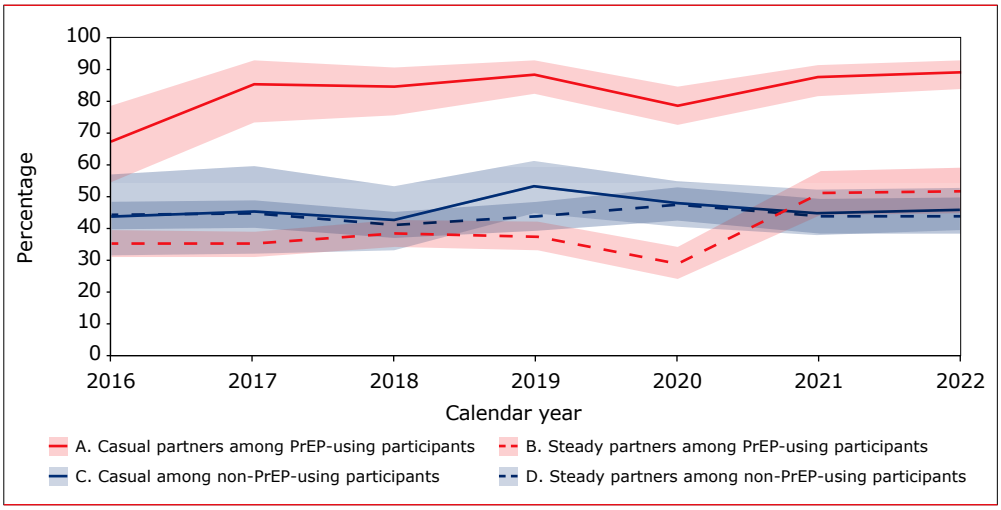


Figure 8.3: Trends in the proportion of condomless anal sex with casual and steady sexual partners among PrEP-using and non-PrEP-using men who have sex with men without HIV participating the Amsterdam Cohort Studies (ACS), 2016-2022



STI screening

Since October 2008, all MSM participating in the ACS are routinely screened for bacterial STIs during their cohort visits (in addition to HIV testing). This conforms with the standard care offered by the Centre of Sexual Health Amsterdam. Chlamydia and gonorrhoea were detected by polymerase chain reaction techniques using urine samples and pharyngeal and rectal swabs. Syphilis was detected by *Treponema pallidum* haemagglutination assay.

Following national PrEP guidelines, those who use PrEP are screened for STIs more often (i.e., 3-monthly) compared to those not using PrEP (i.e., 6-monthly). As the STI testing frequency differ between PrEP using and non-PrEP using participants, STI incidence rates cannot be compared and, therefore, are not reported here. In general, the incidence rate of a bacterial STI among MSM in the ACS significantly increased in the period 2009 to 2019. In 2022, STI data were available for 556 MSM actively participating in the ACS. Of these 566 MSM, 43 (7.7%) MSM had at least one positive bacterial STI test. For MSM with and without HIV, these figures were 3 out of 34 (8.9%), and 40 out of 522 (7.7%), respectively.

ACS 2022 research highlights

A highly virulent variant of HIV-1 circulating in the Netherlands

HIV-1 virulence is most commonly measured by the concentration of viral particles in blood plasma and the dynamics of CD4+ T cell decline in peripheral blood. Successful treatment with antiretroviral drugs suppresses viral load and interrupts the decline in CD4 counts that would otherwise lead to AIDS. Viral load dynamics and CD4 cell decline could however change with the emergence of a new viral variant(s). We screened for new viral variants and found a distinct, new subtype-B HIV-1 variant. Within two Dutch studies (the BEEHIVE project and the ATHENA project, among the participants also ACS with HIV-1), we identified 107 individuals with this distinct subtype-B viral variant, among 7,272 Dutch participants with HIV tested in total, and this variant was rarely found in countries outside the Netherlands. The variant is more virulent as participants with HIV carrying this variant experienced double the rate of CD4+ cell count declines than expected. Fortunately, upon HIV-1 treatment these individuals showed the same CD4 cell recovery as participants with HIV not carrying the more virulent variant of HIV-1 (Wymant-2022-Science).

Trends in sexual behaviour and STI after initiating PrEP in MSM from Amsterdam

MSM who initiate PrEP may report increased condomless anal sex and number of partners, and, consequently, more often acquire STIs. Using data from the ACS, sexual behavior and STI incidence among MSM after PrEP-initiation were compared with controls not initiating PrEP. MSM who initiated PrEP between January 1, 2015 and December 31, 2019 were compared to MSM who did not use PrEP. This study found that 228 out of the 858 (26.6%) MSM initiated PrEP; and 198 out of 228 (86.8%) were matched to a control. Before PrEP-initiation, end-points increased over time in both groups, although not significantly. Among MSM who initiated PrEP, casual partner number as well as odds of condomless anal sex, receptive condomless anal sex and anal STI were higher post- than pre-PrEP-initiation. These differences were not found among the controls. These findings support frequent STI screening and counseling in MSM who use PrEP (Coyer-2022-AIDS Patient Care STDS).

Eligibility criteria vs. need for PrEP: a reappraisal among MSM in Amsterdam

To reconsider PrEP eligibility criteria towards MSM with highest HIV-risk, PrEP need (in other words: risk of acquiring HIV infection) was assessed using ACS data from 2011-2017 for all MSM not using PrEP. Among 810 MSM, 22 HIV-infections and 436 anal STIs were diagnosed during follow-up. Chemsex, condomless anal sex with a casual partner and anal STI were significantly associated with the highest risk for acquiring HIV. Chemsex and condomless anal sex with a casual partner were also significantly associated with anal STI, as was younger age and group sex. This study shows that chemsex should be an additional PrEP eligibility criterion in order to further optimizing HIV prevention (De La Court-2022-Epidemiol Infect).

Current and upcoming ACS research projects

Data collected within the ACS are used for multiple research projects at present. Estimates of HCV-infection incidence and spontaneous-clearance rates, along with associated factors, are in the process of being updated. Data on PrEP surfing, defined as using the PrEP status of sexual partners as HIV prevention strategy, are being collected and will be analysed thereafter. From May 2022, the first mpox cases were reported in Europe, and over half of those diagnosed with mpox in the Netherlands were found in Amsterdam. Since vaccine campaigns are commonly leveraged by high vaccine intention, ACS data are being used to assess the impact of intention to vaccinate and other factors on mpox vaccination uptake. Also, those who were vaccinated against mpox were invited for additional blood drawl in order to assess the immune response post-vaccination. Moreover, data on alcohol and other substance use have been collected in the ACS over the preceding years. Analysis of these data have been initiated in order to estimate the frequency and its determinants of problematic and non-problematic substance use in the context

of the COVID-19 pandemic. Furthermore, qualitative data collection and analysis in order to identify barriers and missed opportunities of PrEP-uptake, PrEP-care and PrEP-use among MSM with HIV and previous PrEP experience are ongoing. Additionally, ACS participants can participate in a qualitative study on sexualized drug use (i.e., chemsex) among MSM, conducted by GGD Amsterdam.

Steering committee

In 2022 the steering committee gathered on four occasions. On March 22, a meeting with Amsterdam UMC and GGD Amsterdam researchers was held to discuss the future of the ACS, and how ACS fits in the ongoing and future research lines of the research groups. Ten proposals for use of ACS data or samples (serum/PBMC) were submitted to the committee: three from Experimental Immunology (Amsterdam UMC, location AMC), four from Medical Microbiology and Infection Prevention (Amsterdam UMC, location AMC), and one from the GGD Amsterdam. Two proposals were a collaboration with a group outside the ACS; National Institute for Public Health and the Environment (RIVM) and UMC Utrecht in collaboration with the GGD Amsterdam. The ACS reviewed the proposal and suggested minor revisions in some cases, after which all requests were approved.

Publications in 2022 that included ACS data

1. Romijnders KAGJ, de Groot L, Vervoort SCJM, Basten MGJ, van Welzen BJ, Kretzschmar ME, Reiss P, Davidovich U, Rozhnova G. The perceived impact of an HIV cure by people living with HIV and key populations vulnerable to HIV in the Netherlands: A qualitative study. Journal of virus eradication. Mar 2022. 8 , p. 1-7
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7. Timmerman AL, Kaczorowska J, Deijs M, Bakker M, van der Hoek L. Control of Human Anelloviruses by Cytosine to Uracil Genome Editing. mSphere. 2022 Dec 21;7(6):e0050622. doi: 10.1128/msphere.00506-22. Epub 2022 Nov 14. PMID: 36374042; PMCID: PMC9769745.
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14. van Schooten J, Schorcht A, Farokhi E, Umotoy JC, Gao H, van den Kerkhof TLGM, Dorning J, Rijkhold Meesters TG, van der Woude P, Burger JA, Bijl T, Ghalaiyini R, Torrents de la Peña A, Turner HL, Labranche CC, Stanfield RL, Sok D, Schuitemaker H, Montefiori DC, Burton DR, Ozorowski G, Seaman MS, Wilson IA, Sanders RW, Ward AB, van Gils MJ. Complementary antibody lineages achieve neutralization breadth in an HIV-1 infected elite neutralizer. PLoS Pathog. 2022 Nov 17;18(11):e1010945. doi: 10.1371/journal.ppat.1010945. eCollection 2022 Nov. PMID: 36395347
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16. Kaczorowska J, Cicilionytė A, Wahdaty AF, Deijs M, Jebbink MF, Bakker M, van der Hoek L. Transmission of anelloviruses to HIV-1 infected children. Front Microbiol. 2022 Sep 16;13:951040. doi: 10.3389/fmicb.2022.951040. PMID: 36187966; PMCID: PMC9523257.
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PhD theses in 2022 that included ACS data

1. Hanne M.L. Zimmermann, HIV prevention in the biomedical era: A psychosocial investigation among men who have sex with men, 9 February 2022
2. Eline van Dulm-Freriks, Antibiotic resistance in specific sociodemographic groups: Implications for public health, 21 January 2022
3. Anna Schorcht, HIV-1 vaccine candidates based on envelope glycoproteins from infected individuals in Amsterdam, 9 June 2022
4. Jelle van Schooten, Fine-mapping HIV-1 antibody responses to guide vaccine design, 9 September 2022
5. Marlies van Haaren, Antiviral monoclonal antibodies inform vaccine design, 14 September 2022

9. Curaçao

Diederik van de Wetering, Esther Rooijakkers, Gonneke Hermanides, Marije Hofstra, Ashley Duits, Ard van Sighem

Introduction

Since 2005, stichting hiv monitoring (SHM) has assisted in collecting demographic and clinical data on individuals with HIV receiving care at the now-closed St. Elisabeth Hospital or at the 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 special report presents a concise overview of the current situation for people with HIV in Curaçao.

In total, 1,418 individuals with HIV recorded by SHM have been registered in Curaçao. Of these people, the majority were diagnosed with HIV-1 (n=1,403, or 99%), while one individual was diagnosed with HIV-2, and three had antibodies against both HIV-1 and HIV-2 (*Figure 9.1*). For 11 individuals, serological results on HIV type were not available in the SHM database.

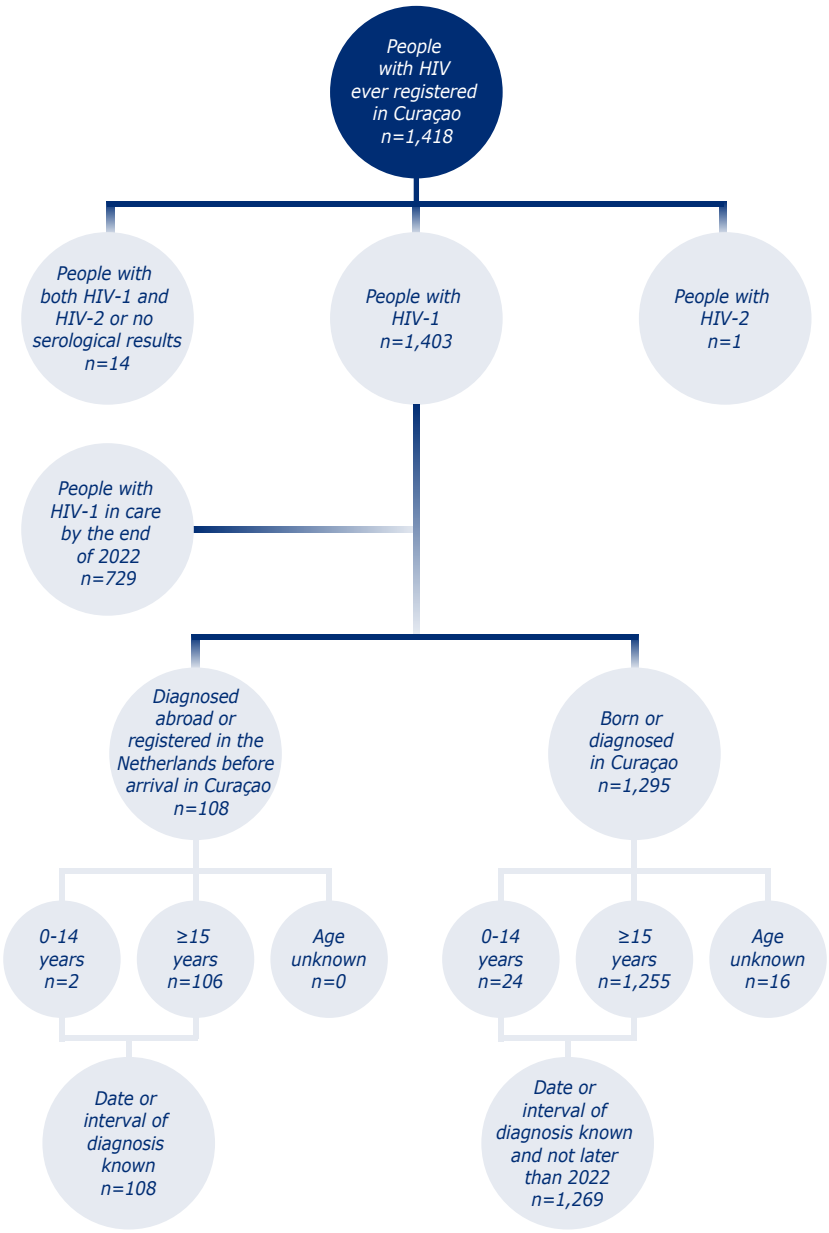
The population with HIV-1 in Curaçao

Of the 1,403 individuals in Curaçao with HIV-1, 108 (8%) had a documented HIV diagnosis prior to arrival in Curaçao (*Figure 9.1*). The remaining 1,295 individuals were newly diagnosed while living in Curaçao, or their date of arrival in Curaçao has not yet been recorded in the SHM database.

Individuals diagnosed before arriving in Curaçao

The 108 individuals with a documented HIV-1 diagnosis prior to arrival in Curaçao included 97 (90%) people who were registered with an HIV treatment centre in the Netherlands prior to moving to Curaçao (*Figure 9.1*). The majority of these 97 individuals (n=71, or 73%) originated from the former Netherlands Antilles, while 21 (22%) were born in the Netherlands and five (5%) were born elsewhere. The other 11 individuals with pre-migration diagnosis were also born abroad, including 5 in Venezuela. Of the 11 people arriving in Curaçao in 2020-2022 with a documented HIV-1 diagnosis prior to arrival, 8 had a suppressed viral load below 200 copies/ml (*Figure 9.2*).

Figure 9.1: Overview of the population with HIV registered in Curaçao.



Individuals newly diagnosed in Curaçao

Altogether, 1,295 individuals were newly diagnosed while living in Curaçao, or information on where they lived at the time of diagnosis was not yet available (*Figure 9.1*). Of these 1,295 individuals, 970 (75%) were born in the former Netherlands Antilles, 114 (9%) originated from Haiti, 93 (7%) from the Dominican Republic, 28 (2%) from Jamaica, 20 (2%) from Venezuela, and 70 (5%) from other countries.

For 26 (2%) of the 1,295 individuals diagnosed while living in Curaçao, the date or interval of diagnosis was not recorded in the SHM database, or they were diagnosed in 2023. The remaining 1,269 individuals comprised (*Table 9.1*):

- 249 (20%) men who have sex with men (MSM);
- 535 (42%) other men,
  - 330 (62%) of whom reported sex with women as the most likely mode of transmission
  - 205 (38%) reported other or unknown modes of transmission;
- 456 (36%) women,
  - 434 (95%) of whom reported sex with men as the most likely mode of transmission
  - 22 (5%) reported other or unknown modes of transmission;
- 5 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 below 30 in most recent calendar years (*Table 9.1*; *Figure 9.2*).

Among the 97 individuals diagnosed in 2020 or later, the median age at diagnosis was 38 years (interquartile range [IQR] 28-50), with no differences between men and women. Of these 97 individuals:

- 28 (29%) were younger than 30 years of age at the time of diagnosis;
- 23 (24%) were aged between 30 and 39 years;
- 22 (23%) were aged between 40 and 49 years; and
- 24 (25%) were aged 50 years and over.

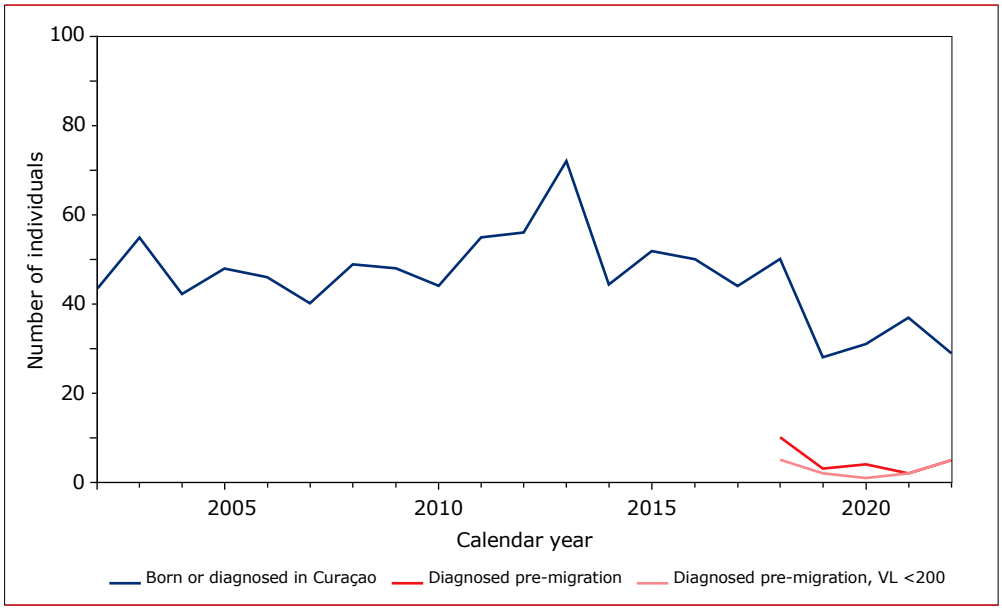
Table 9.1: Annual number of HIV-1 diagnoses in Curaçao among men who have sex with men, other men, women, and trans men and women diagnosed at 15 years of age and over, and children under 15 years.

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	23	17	0	0	46
2007	12	18	10	0	0	40
2008	10	17	20	1	1	49
2009	9	17	21	0	1	48
2010	4	19	21	0	0	44
2011	12	19	24	0	0	55
2012	13	17	26	0	0	56
2013	18	30	22	1	1	72
2014	16	14	14	0	0	44
2015	16	22	12	1	1	52
2016	12	23	15	0	0	50
2017	14	17	13	0	0	44
2018	17	13	19	1	0	50
2019	7	13	8	0	0	28
2020	7	12	12	0	0	31
2021	5	21	10	0	1	37
2022	0	15	14	0	0	29
Total	**249**	**535**	**456**	**5**	**24**	**1,269**

Note: *Data collection for 2022 may not have been finalised at the time of writing.*

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

Figure 9.2: 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.



People in clinical care

In total, 729 (52%) of the 1,403 registered individuals with HIV-1 were known to be in clinical care in Curaçao by the end of 2022. People were considered to be in clinical care if they had visited their treating physician in 2022, or had a CD4 cell count or HIV RNA measurement during that year, and had not moved abroad. Of the 674 individuals who, according to this definition, were not in care by the end of 2022:

- 212 (32%) were known to have died;
- 169 (25%) had moved abroad; and
- 281 (42%) were lost to care

The remaining 12 individuals only entered HIV care in 2023. Of the 281 people lost to care, 56 (20%) 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:

- 167 (59%) originated from the former Netherlands Antilles;
- 49 (17%) were from Haiti;
- 29 (10%) were from the Dominican Republic; and
- 36 (13%) were from other countries.

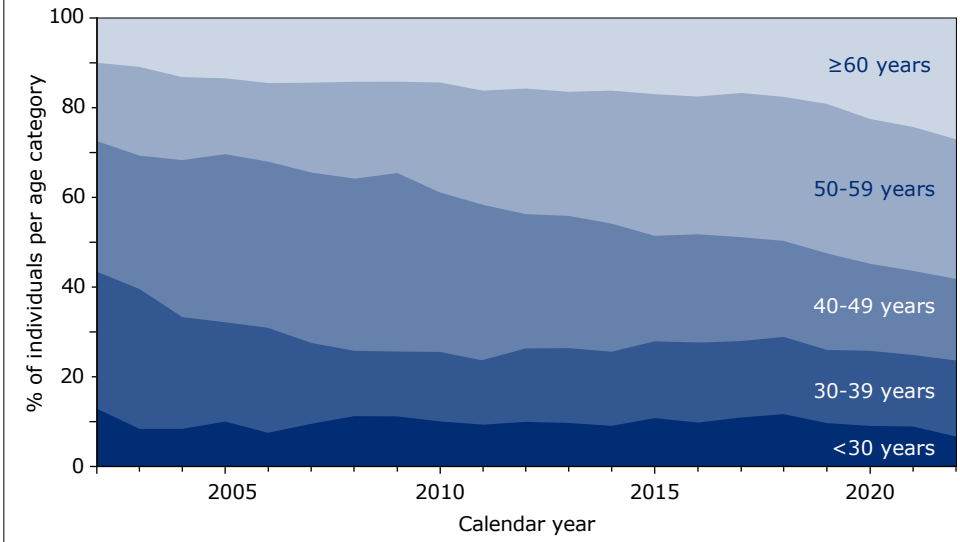
The 729 people in clinical care in 2022 included 8 individuals who did not have a clinical visit, CD4 cell count or HIV RNA measurement in 2021, but had previously received care for their HIV infection. Five of these individuals had not been in care for more than three years.

Of the 695 people who were still in care by the end of 2019, 39 (6%) did not have a clinical visit or HIV RNA or CD4 measurement in 2020. Of these 39 people, 3 had died and 8 were back in care in 2022 (including one individual who had moved to the Netherlands), while the remaining 28 individuals were still lost to care.

Ageing population

The median age of the population in care by the end of 2022 was 53 years (IQR 41-61), a figure which has been increasing since 2002 (*Figure 9.3*). This increase is mainly a result of the improved life expectancy of individuals with HIV following the introduction of combination antiretroviral therapy (ART). As a result, more than half of all people currently in care (58%) are aged 50 years and over, including 57% of men and 61% of women. More than a quarter of those in care (27%) are 60 years and over.

Figure 9.3: 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 2022, these proportions were 6% and 58%, respectively, while 27% 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 2022 had been diagnosed with HIV a median of 11.4 years (IQR 6.1-18.1) previously. Therefore, a large group (56%) has lived with HIV for more than 10 years; 20% for more than 20 years (*Table 9.2*). The median time since diagnosis was 11.6 years for MSM, 10.5 years for other men, and 12.0 years for women.

Table 9.2: Characteristics of the 729 individuals with an HIV-1 infection in clinical care in Curaçao by the end of 2022.

	MSM (n=155, 21%)		Other men (n=293, 40%)		Women (n=279, 38%)		Total* (n=729)	
	n	%	n	%	n	%	n	%
Transmission								
Sex with men	113	73	–	–	263	94	378	52
Sex with women	0	0	177	60	0	0	177	24
Sex, partner unspecified	41	26	6	2	0	0	47	6
Other/unknown	1	1	110	38	16	6	127	17
Current age (years)								
0–15	0	0	2	1	2	1	4	1
15–24	4	3	2	1	7	3	13	2
25–29	10	6	11	4	9	3	30	4
30–39	31	20	50	17	41	15	124	17
40–49	38	25	45	15	50	18	133	18
50–59	44	28	91	31	91	33	226	31
60–69	18	12	64	22	58	21	140	19
≥70	10	6	28	10	21	8	59	8
Country of origin								
Former Netherlands Antilles	133	86	239	82	187	67	560	77
The Dominican Republic	2	1	8	3	40	14	50	7
Haiti	0	0	24	8	26	9	50	7
Venezuela	7	5	7	2	2	1	17	2
Jamaica	0	0	4	1	10	4	14	2
The Netherlands	7	5	3	1	0	0	10	1
Other	6	4	8	3	14	5	28	4
Years aware of HIV infection								
<1	0	0	13	4	13	5	26	4
1–2	11	7	34	12	20	7	65	9
3–4	16	10	21	7	22	8	60	8
5–9	39	25	72	25	56	20	168	23
10–19	56	36	99	34	108	39	263	36
≥20	33	21	53	18	59	21	145	20
Unknown	0	0	1	0	1	0	2	0

** Includes two trans individuals*

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

Late presentation

Among the 1,269 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 2002-2019, and remained at a high level of 61% among those entering care in 2020 or later (*Figures 9.4A* and *9.4B*). There were no significant differences in the proportion of individuals with late presentation in 2020 or later between MSM (57%), other men (67%), and women (55%).

Advanced HIV infection (i.e. with a CD4 cell count below 200 cells/mm^3 or AIDS) was found in 37% in 2002-2019 and in 34% in 2020 or later (*Figures 9.4C* and *9.4D*). In total, 8 (7%) of the individuals who entered care since 2020 presented with an AIDS-defining disease.

Figure 9.4: *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. From 2020 onwards, 57 (61%) individuals presented with late HIV disease while 32 (34%) 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. From 2020 onwards, the stage of infection was unknown for 18 (16%) individuals.*

Antiretroviral therapy (ART)

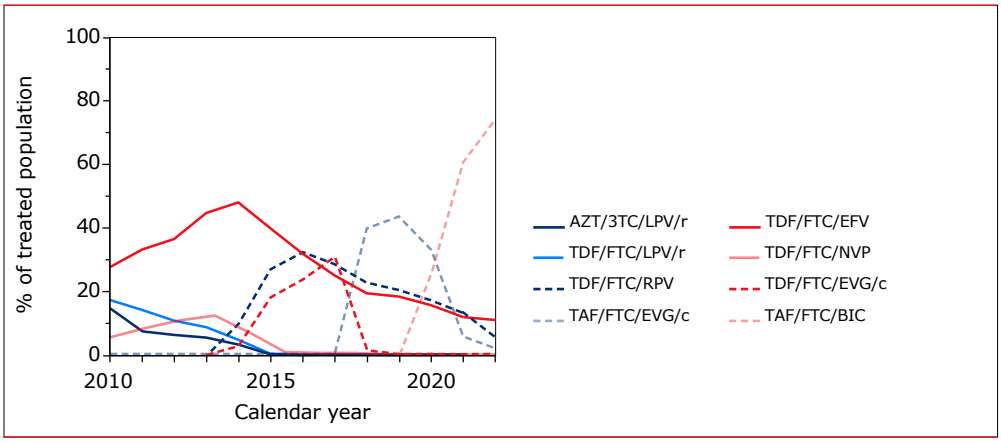
In total, 1,292 (92%) of the 1,403 registered individuals with HIV-1 had started antiretroviral therapy by the end of 2022. Of the 111 people who had not started therapy by that time, two managed to achieve HIV RNA levels below the lower limit of quantification without therapy, while 92 people were no longer in care, including 35 who had died. The other 17 individuals started therapy in 2023, or their ART may not have been recorded yet.

Over time there have been clear shifts in the ART regimens prescribed in Curaçao (*Figure 9.5*). Of the 723 people who were still in care by the end of 2022 and had started ART:

- 75% were being treated with a combination of tenofovir alafenamide, emtricitabine, and bictegravir;
- 11% with tenofovir disoproxil, emtricitabine, and efavirenz; and
- 6% with tenofovir disoproxil, emtricitabine, and rilpivirine.

The majority (98%) used a once-daily regimen, with 94% being treated with a fixed-dose, single tablet regimen.

Figure 9.5: *Percentage of individuals treated with antiretroviral therapy (ART) by specific regimens over calendar time. At the end of 2022, 75% were receiving TAF/FTC/BIC, 11% TDF/FTC/EFV, and 6% TDF/FTC/RPV.*

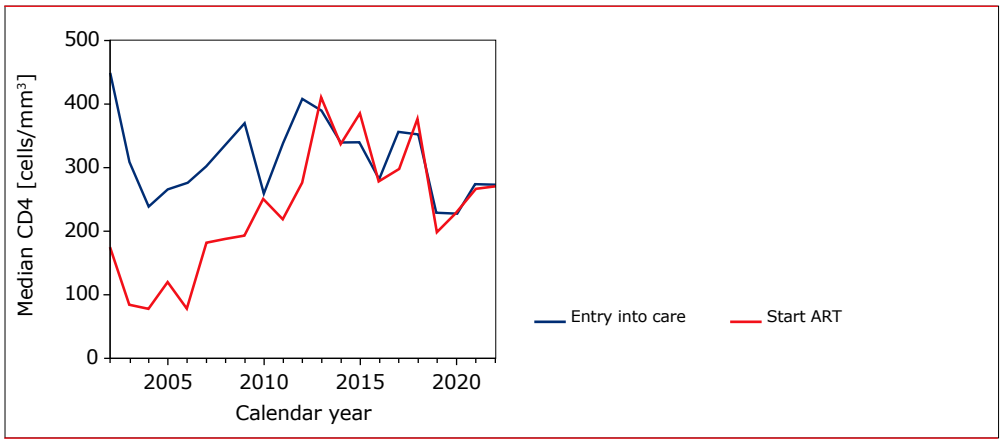


Legend: *AZT = zidovudine; 3TC = lamivudine; LPV/r = ritonavir-boosted lopinavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; RPV = rilpivirine; EFV = efavirenz; NVP = nevirapine; EVG/c = cobicistat-boosted elvitegravir; BIC = bictegravir.*

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 9.6*). 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 2020-2022, 91% 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:

- 40% had a measurement below 200 CD4 cells/mm^3;
- 24% had a measurement between 200 and 349 cells/mm^3;
- 12% had a measurement between 350 and 499 cells/mm^3; and
- 24% had CD4 cell counts of 500 cells/mm^3 or higher.

Figure 9.6: *Changes over calendar time in median CD4 cell counts at entry into care and at the start of antiretroviral therapy (ART). In 2020-2022, CD4 cell counts at entry into care were 267 cells/mm^3 (interquartile range [IQR] 130-473) and were similar, 251 cells/mm^3 (IQR 114-477), at the start of therapy.*

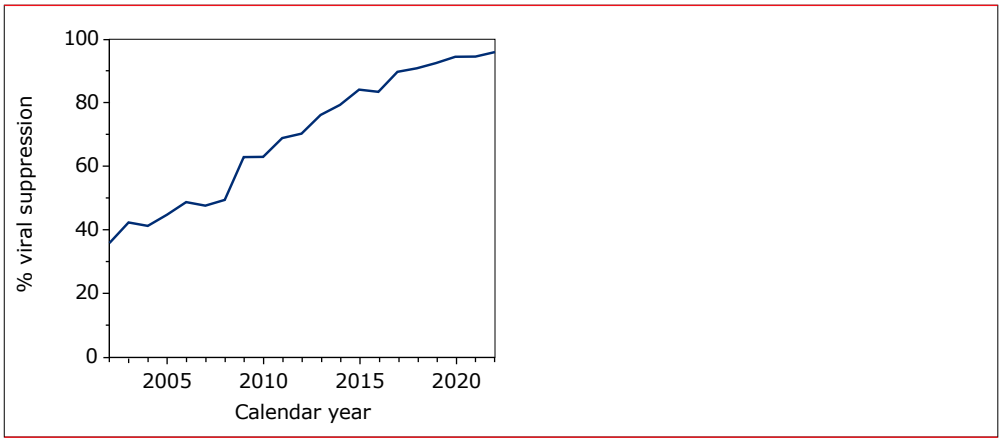


Legend: *ART = antiretroviral therapy.*

Therapy outcome

In the total population still in care by the end of 2022, the median current CD4 cell count was 528 cells/mm^3 (IQR 328-747). CD4 cell counts were highest in women (634 cells/mm^3; IQR 411-889) followed by MSM (549 cells/mm^3; IQR 366-741) and other men (439 cells/mm^3; IQR 265-664). Among individuals with a viral load measurement, the proportion with HIV RNA levels lower than 200 copies/ml increased from 36% in 2002 to 96% in 2022 (*Figure 9.7*).

Figure 9.7: Proportion of people in care with HIV RNA <200 copies/ml at their last viral load measurement in each calendar year.



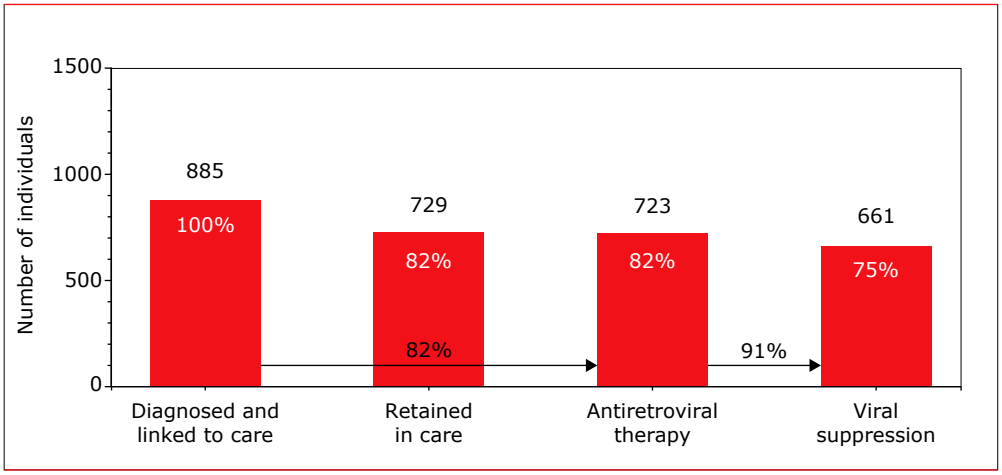
Continuum of HIV care

In total, 885 individuals had been diagnosed and linked to care, registered by SHM, had received HIV care in 2012 or later, and were not recorded in the SHM database as having died or moved abroad (*Figure 9.8*). Altogether:

- 729 people (or 82% 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 2022;
- 723 (or 82% of those diagnosed and linked to care) of whom had started ART;
- 689 (95% of those who started therapy) of whom had an HIV RNA measurement available in 2022; and
- 661 (96%, or 91% of those treated) of those had a most recent HIV RNA level below 200 copies/ml.

Overall, 75% of the 885 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 82-91: 82% of all people diagnosed receive antiretroviral therapy, and 91% of people receiving ART have a suppressed viral load[2].

Figure 9.8: Continuum of HIV care for the population with HIV-1 in Curaçao diagnosed and linked to care by the end of 2022. 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 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 this year, 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 723 individuals who had started ART, 62 (9%) did not have a suppressed viral load. On closer inspection, 34 (55%) of these individuals were found to have no documented HIV RNA measurement in 2022. The remaining 28 (45%) had a viral load measurement in 2022, but with HIV RNA levels exceeding 200 copies/ml. Of these 28 individuals, five 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 23 individuals with HIV RNA levels above 200 copies/ml had been on ART for longer than six months.

Lost to care

In total, 281 individuals were lost to care by the end of 2022, of whom:

- 125 (44%) were last seen for care before the end of 2012;
- 90 (32%) between 2013 and 2018;
- 28 (10%) in 2019;
- 10 (4%) in 2020; and
- 28 (10%) in 2021.

The 125 individuals who were lost to care before 2012 were excluded from the number of people diagnosed and linked to care. It is unlikely that these 125 individuals are still living in Curaçao without requiring care or ART. In total, 54 (35%) of the 156 individuals lost to care after 2012 were born outside the former Netherlands Antilles, including 19 in Haiti and 12 in the Dominican Republic. For those still in care by the end of 2022, the percentage of people born outside the former Netherlands Antilles falls to 23%. This suggests that some of those lost to care may have moved abroad; in particular, back to their country of birth. It also shows that, overall, a considerable proportion was not retained in care.

Conclusion

Over the years, the quality of 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/or outmigration. Among those lost to care is a substantial group of 28 individuals who were last seen for care in 2019 (i.e. the last year before the COVID-19 pandemic) and have not yet returned.

Recommendations

Curaçao is in a unique position in the Caribbean, in that data on individuals with HIV in care are regularly collected and monitored. However, it is important that the quality of these data is maintained and that the collected data remain representative of the population with HIV.

Early start of ART in adults appears possible, but long-term, continuous follow up should be guaranteed to optimise its effect. The continuum of care for Curaçao illustrates that while almost everyone who is still in care has started antiretroviral therapy, too many individuals are lost to care. In part, this may be explained by people who, unknown to SHM, have died or moved abroad. To address this issue, efforts have recently been stepped up to trace people who miss their scheduled appointment at the hospital. It is hoped that this will improve retention in care in the near future.

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

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Terminology

Acute infection
Any infection that begins suddenly, with intense or severe symptoms, is called acute (or primary). If the illness lasts longer, such as more than a couple of weeks, it is called chronic.

Adherence
Adherence measures how regularly a person takes all their antiretroviral medications at the right time. Poor adherence is one of the main reasons that antiretroviral combinations fail.

AIDS
Acquired Immunodeficiency Syndrome. A disease caused by a retrovirus, HIV (human immunodeficiency virus), and characterised by the immune system's failure to protect against infections and certain cancers.

AIGHD
Amsterdam Institute for Global Health and Development.

Antibody
An immune system protein formed in response to invading disease agents, such as viruses, fungi, bacteria, and parasites. Usually antibodies defend the body against invading disease agents, however, the HIV antibody does not give such protection.

Antigen
An invading substance that may be the target of antibodies.

Antiretroviral therapy (ART)
A treatment that may prevent HIV from further damaging the immune system by blocking or hampering the reproduction of the virus.

Antiviral
A substance that stops or suppresses the reproduction of a virus.

ATHENA
AIDS Therapy Evaluation in the Netherlands project (ATHENA). Stichting hiv monitoring was founded in 2001 as a result of the successful ATHENA project.

Baseline
An initial measurement used as the basis for future comparisons. For people infected with HIV, baseline testing includes CD4 count, viral load (HIV RNA), and resistance testing. Baseline test results are used to guide HIV treatment choices, and to monitor the effectiveness of antiretroviral therapy (ART).

ART
Combination antiretroviral treatment.

CD4 (T4) cell
CD4+ T-lymphocyte, or T4 cell or T-helper cell. A white blood cell that plays a vital role within the immune system and can be infected by HIV. In the course of the HIV infection, the number of CD4 cells may drop from normal levels (above 500 per mm^3) to dangerously low levels (below 200 CD4 cells per mm^3 blood).

CDC
US Centres for Disease Control and Prevention.

CIb
Centre for Infectious Disease Control Netherlands, National Institute for Public Health and Environment (www.rivm.nl/cib).

Co-infection
When a person has two or more infections at the same time. For example, a person infected with HIV may be co-infected with hepatitis C (HCV), tuberculosis (TBn), or both.

Comorbidity
When a person has two or more diseases or conditions at the same time. For example, a person with high blood pressure may also have heart disease.

COVID-19
COVID-19 is an infectious disease caused by the SARS-CoV-2 virus (coronavirus).

DAAs
Direct-acting antivirals (DAAs) are new-generation drugs that treat hepatitis C virus infection by targeting specific steps in the hepatitis C virus lifecycle. There are different classes of DAAs, defined by their mechanism of action and therapeutic target.

DNA
Deoxyribonucleic acid. A complex protein that carries genetic information. HIV can insert its own genetic material into the DNA molecules inside human cells and establish dormant infection.

EASL
European Association for the Study of the Liver.

ECDC
European Centre for Disease Prevention and Control.

Epidemiology
The study of the distribution, causes, and clinical characteristics of disease or health status in a population.

Genotype
The genotype is the underlying genetic makeup of an organism.

GGD
Dutch public health service (Geneeskundige en Gezondheidsdienst).

Half-life
The time it takes a drug to lose half its original concentration or activity after being introduced into the body. Drug half-life is considered when determining drug dosing.

Hepatic
Pertaining to the liver.

Hepatitis A virus (HAV)
A viral infection that affects the liver and is acquired predominately through faecal-oral transmission.

Hepatitis B virus (HBV)
A viral infection that affects the liver and is transmitted only through blood-to-blood and sexual contact.

Hepatitis C virus (HCV)
A viral infection that affects the liver and is transmitted primarily by blood, and blood products – as in blood transfusions or injecting drug use – and sometimes through sexual contact.

Hepatitis D virus (HDV)
A viral infection that affects the liver and requires infection with hepatitis B virus (HBV). It is transmitted by the same routes as HBV.

Hepatitis E virus (HEV)
A viral infection that affects the liver and is transmitted by indirect, or direct contact with animals.

HIV
Human Immunodeficiency Virus; the virus that causes Acquired Immunodeficiency Syndrome (AIDS). HIV enters and destroys the cells that control and support the immune response system.

HIV type 1 (HIV-1)
The HIV type responsible for the majority of HIV infections worldwide.

HIV type 2 (HIV-2)
An HIV type endemic to West Africa. HIV-2 infections generally take longer to progress to AIDS than HIV-1.

HIV Vereniging
Dutch HIV association.

HIVdb genotypic resistance interpretation algorithm
A tool developed by Stanford University to determine the level of treatment resistance that is found in HIV circulating in the blood.

IAS
International AIDS Society

Immunoglobulin G (IgG)
A type of antibody molecule that develops as a result of an infection and is often continuously produced in the body well after infection.

Immunoglobulin M (IgM)
A type of antibody molecule that often develops immediately as a result of an infection and is no longer produced within a short time after infection.

Immunological failure
A type of HIV treatment failure. There is no consensus on the definition of immunological failure; however, some experts define it as the failure to achieve and maintain adequate CD4 counts, despite viral suppression.

Integrase
A type of enzyme that helps the virus insert its viral genome into the genome of a cell (integration). HIV inserts a double-stranded DNA copy of its viral genome using this enzyme. Blocking integrase activity helps decrease HIV replication.

Interferon
Interferons are naturally-occurring proteins (cytokines) produced by immune cells in response to an antigen, usually a virus. Although they do not directly kill viral cells, they boost the immune response by signalling neighbouring cells into action and inhibiting the growth of malignant cells. There are three types of interferons: alpha, beta, and gamma. Laboratory-made interferons are used to treat certain cancers and opportunistic infections. Addition of polyethylene glycol to interferons prolongs their half-life. Pegylated interferon alpha was formally used to treat chronic hepatitis C infection.

Mono-infection
When a person has only one infection.

Mortality
Mortality rate is a measure of the frequency of occurrence of death among a defined population during a specified time period.

MSM
Men who have sex with men.

Nederlandse Federatie Universitair Medische Centra (NFU)
Dutch Federation of University Medical Centres.

Non-AIDS event
Diseases and clinical events that are not related to AIDS (i.e., they are not listed as being associated with AIDS by the Centres for Disease Control and Prevention). These include conditions such as malignancies, end-stage renal disease, liver failure, pancreatitis, and cardiovascular disease.

Non-nucleoside reverse transcriptase inhibitor (NNRTI)
An antiretroviral HIV drug class. NNRTIs bind to and block HIV reverse transcriptase; an enzyme that HIV uses to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

Nucleoside reverse transcriptase inhibitor (NRTI)
An antiretroviral HIV drug class. NRTIs block reverse transcriptase; an enzyme that HIV uses to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

Nucleotide
A building block of nucleic acids. DNA and RNA are nucleic acids.

Nucleotide reverse transcriptase inhibitor (NtRTI)
A type of antiretroviral (ARV) HIV drug included in the NRTI drug class. NtRTIs interfere with the HIV lifecycle in the same way as NRTIs; both block reverse transcription.

NVHB
Dutch Association of HIV-Treating Physicians (Nederlandse Vereniging van HIV Behandelaren).

Person year
A measure of time used in medical studies. It combines the number of people and their time contribution (e.g., in years) to the study. In the ATHENA cohort, person years generally refer to the cumulative number of years that individuals were followed by SHM.

Perinatal transmission
Perinatal transmission of HIV refers to the transfer of HIV from a pregnant person with HIV to their child during pregnancy, labour and delivery, or via breastfeeding (through breast milk).

PrEP
Pre-Exposure Profylaxis. A treatment to avoid an infection with hiv.

Protease
A type of enzyme that breaks proteins down into smaller proteins or protein units, such as peptides or amino acids. In the case of HIV, these smaller proteins combine with HIV's genetic material to form a new HIV virus. Protease inhibitors (PIs) prevent HIV from replicating by blocking protease.

Protease inhibitor (PI)
An antiretroviral HIV drug class. In people with HIV, PIs block protease from forming new HIV viruses (see Protease definition).

Pseudonymisation
Pseudonymisation is a privacy-enhancing technique that replaces personal identifiers with coded data. Certain identifiers (such as gender and age), are included in the record, but personal information is removed or replaced by a randomised string of characters. The data collected from people living with HIV are stored in SHM's database in a pseudonymised form. Pseudonymisation takes place within the HIV treatment centre and the key to the code is only available to the HIV treating physician.

Retrovirus
A class of viruses that includes HIV. Retroviruses are so named because they carry their genetic information in RNA, rather than DNA, and then translate that RNA information "backwards" into DNA.

Reverse transcriptase
After infecting a cell, HIV uses an enzyme called reverse transcriptase to convert its RNA into DNA. It then replicates itself using the cell's machinery.

RIVM
The Netherlands' National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu).

RNA
Ribonucleic acid. A complex protein that carries genetic information.

Seroconversion
The change from an absence of HIV antibodies in the blood to the presence of those antibodies.

SHM
The Dutch HIV Monitoring Foundation (stichting hiv monitoring).

Sustained virologic response (SVR12 or SVR24)
A measure of the response to hepatitis C virus (HCV) treatment. SVR12 or SVR24 indicates an undetectable level of HCV in blood in the 12 or 24 weeks, respectively, following completion of antiviral therapy for chronic HVC infection.

Sustained viral suppression
The continuous, long-term suppression of a person's viral load (HIV RNA), generally to undetectable levels, as the result of treatment with antiretroviral drugs.

Tolerability
The extent to which a drug's side effects can be tolerated by the patient.

UNAIDS
The Joint United Nations Programme on HIV/AIDS

Viraemia
The presence of a virus in the blood.

Virological failure
A type of HIV treatment failure. Virological failure occurs when antiretroviral therapy (ART) fails to suppress and sustain a person's viral load to less than 200 copies/ml. Factors that can contribute to virological failure include drug resistance, drug toxicity, and poor treatment adherence.

Viral load
The number of HIV particles in a millilitre of blood or other bodily fluid, such as semen or cerebrospinal fluid.

Viral suppression or virological control
When antiretroviral therapy (ART) reduces a person's viral load (HIV RNA) to an undetectable level. Viral suppression does not mean a person is cured; HIV still remains in the body.

V&VN VCH
Dutch Association for HIV nursing consultants (Verpleegkundigen & Verzorgenden Nederland Verpleegkundig Consulenten HIV).

VWS
Dutch ministry of Health, Welfare and Sport (Ministerie van Volksgezondheid, Welzijn en Sport).

Some of the above definitions were taken from hivinfo.nih.gov