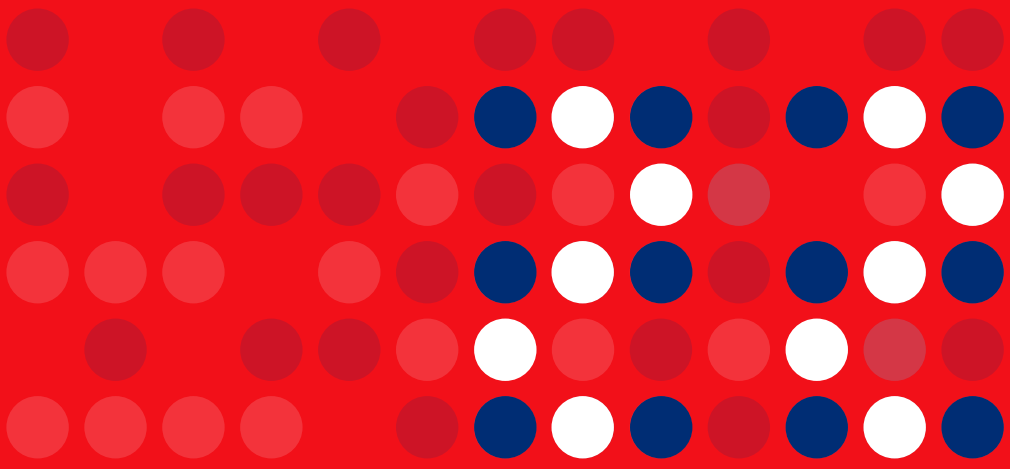
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2022



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 2022

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

Interactive PDF user guide

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

Links in this PDF

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

Reference numbers

Click on the reference numbers in the text to see the reference details on a web page (in a new window).

Guide to buttons

Content page

Next chapter

Preceding chapter

You can also navigate using the bookmarks.

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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 2022 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 2022 the following health institutes were recognized as centres for paediatric HIV care:

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

Table of contents

Introduction

HIV Monitoring Foundation (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.

The nationwide reach of our data collection, the extensiveness of the type of medical data we collect as well as our robust data infrastructure capabilities, allow us to provide the level of detail in the analyses as laid out in this report– the 21th edition in the series published by SHM.

Along with the many topics covered, such as latest counts in the continuum of care, analyses of treatment, morbidity and mortality trends in people with HIV and a review of the quality of care at the HIV treatment centres, more in-depth analyses can be found for key populations: children, adolescents, pregnant women, trans people and migrants. Special reports this year include: an extensive study on the prior use of pre-exposure prophylaxis (PrEP), COVID & HIV and a mapping of the HIV population in Curaçao.

With the data we aim to offer all those working in the space of HIV latest insights to enable more informed decision-making around HIV care and prevention programmes.

While the overall take-away of our report this year is positive and twofold– the total number of new HIV diagnoses continues to decline; a steep decline in the number of early-stage HIV infections among MSM, accounting for the effectiveness of PrEP– gaps in prevention programmes are also uncovered and a pressing need to dive deeper into the niche sockets of the HIV population in the Netherlands has become apparent.

Our report is the culmination of a great deal of hard work by many people both within and outside SHM. We would like to thank all the health care workers of the 24 HIV treatment centers across the country, along with the SHM data collection, data management and analytics teams.

Our thanks also go to all co-authors of the various chapters whose in-depth knowledge on relevant topics has helped shape the content to a large extent. Their input is highly valuable and improves the report's clinical and public health relevance.

Finally, we extend our gratitude to the people with HIV in the Netherlands who generously agree to provide their data to SHM. It is only through this partnership between professionals and impacted communities that we can further our insights.

Professor Marc van der Valk, MD, PHD
Sima Zaheri, MSc

Board of Directors, HIV Monitoring Foundation the Netherlands

1. HIV in the Netherlands

Ard van Sighem, Casper Rokx, Eline Op de Coul

Key findings

2021 at a glance

By the end of 2021, there were 24,110 people with HIV in the Netherlands, including 1,400 with an undiagnosed HIV infection. Altogether, 85% of this total, and 90% of those diagnosed and ever linked to care, had a suppressed viral load.

Of the approximately 427 people with a new HIV diagnosis, 250 (59%) were men who mostly likely acquired HIV through sex with men (MSM), 121 (28%) were men and women who acquired their HIV through heterosexual contact, while 56 (13%) acquired HIV through other or unknown modes of transmission. In total, 30% of all people newly diagnosed with HIV were aged 50 years or older at the time of diagnosis.

Of the 21,399 people with HIV-1 in care by the end of 2021, 55% were 50 years or older and 24% were 60 years or older. In total, 65% of people who are still in care have lived with HIV for more than 10 years.

Trends

2010–2021

The number of newly diagnosed HIV infections fell by 64% from 1,181 to 427, while among MSM this dropped by 68%, from 772 to 250.

The estimated annual number of newly acquired HIV infections decreased by 87%, from 920 to 120. For MSM this fell by 86%, from 660 to 90.

2002–2021

The proportion of MSM under the age of 30 at the time of diagnosis increased from 15% to 24%. For those aged 50 or older in this group, this figure rose from 12% to 27%.

2019–present

Of all people newly diagnosed in 2019 or later, 24% were diagnosed within 12 months of HIV infection; in MSM, this proportion was 34%.

In focus: PrEP

In 2021, 62% of MSM newly diagnosed with HIV had a previously negative test, down from 71% of MSM diagnosed in the period 2018-2020. This decrease suggests that in 2021 the risk of acquiring an HIV infection is lower for MSM who regularly test for HIV (and therefore have a previously negative test if they would be diagnosed with HIV). It may indicate that a significant proportion of men who regularly test for HIV are now protected by pre-exposure prophylaxis (PrEP). PrEP became available on a national level via the Sexual Health Centres (SHC) of the municipal Public Health Services (GGD) as part of the PrEP pilot programme, which started in August 2019 for those at highest risk of acquiring HIV[a]. More detailed PrEP analyses are presented in *Special Report: Prior use of pre-exposure prophylaxis*.

In focus: late-stage HIV from 2019 onwards

Since 2019, 740 (53%) individuals have been diagnosed with late-stage HIV infection. This figure comprises 367 MSM, 225 other men, and 148 women, which is 45%, 69% and 62%, respectively, of the total number diagnosed in each group.

Overall, late-stage HIV diagnoses increased from 51% in 2019 to 57% in 2021, mainly due to an increase in the proportion of MSM with late-stage HIV.

In the under-25 years of age category, late-stage HIV was detected in 32% of MSM, 50% of other men, and 46% of women. The proportion of individuals with late-stage HIV increased with age: it was found in 59% of MSM, 83% of other men and 75% of women diagnosed at 60 years of age or older.

Introduction

By May 2022, stichting hiv monitoring (SHM) had registered 32,832 individuals with HIV. The vast majority of these (31,989, or 97.4%) agreed to the collection of further clinical data once registered, whereas 843 (2.6%) declined to take part. Among those whose clinical data is collected, most (30,850) are registered with one of the HIV treatment centres in the Netherlands (*Figure 1.1*) while 1,365 are registered with the Curaçao Medical Center in Willemstad, Curaçao (see *Chapter 9*). A comparatively small group of 226 individuals are registered in both countries.

Of those registered in the Netherlands, the vast majority were diagnosed with HIV-1 (29,571, or 96%). Only 101 people were diagnosed with HIV-2, while 61 individuals were found to carry antibodies against both HIV-1 and HIV-2. Data is

a *https://www.rivm.nl/Soa-seksueel-overdraagbare-aandoening/prep*

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 1,117.

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 2021. 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

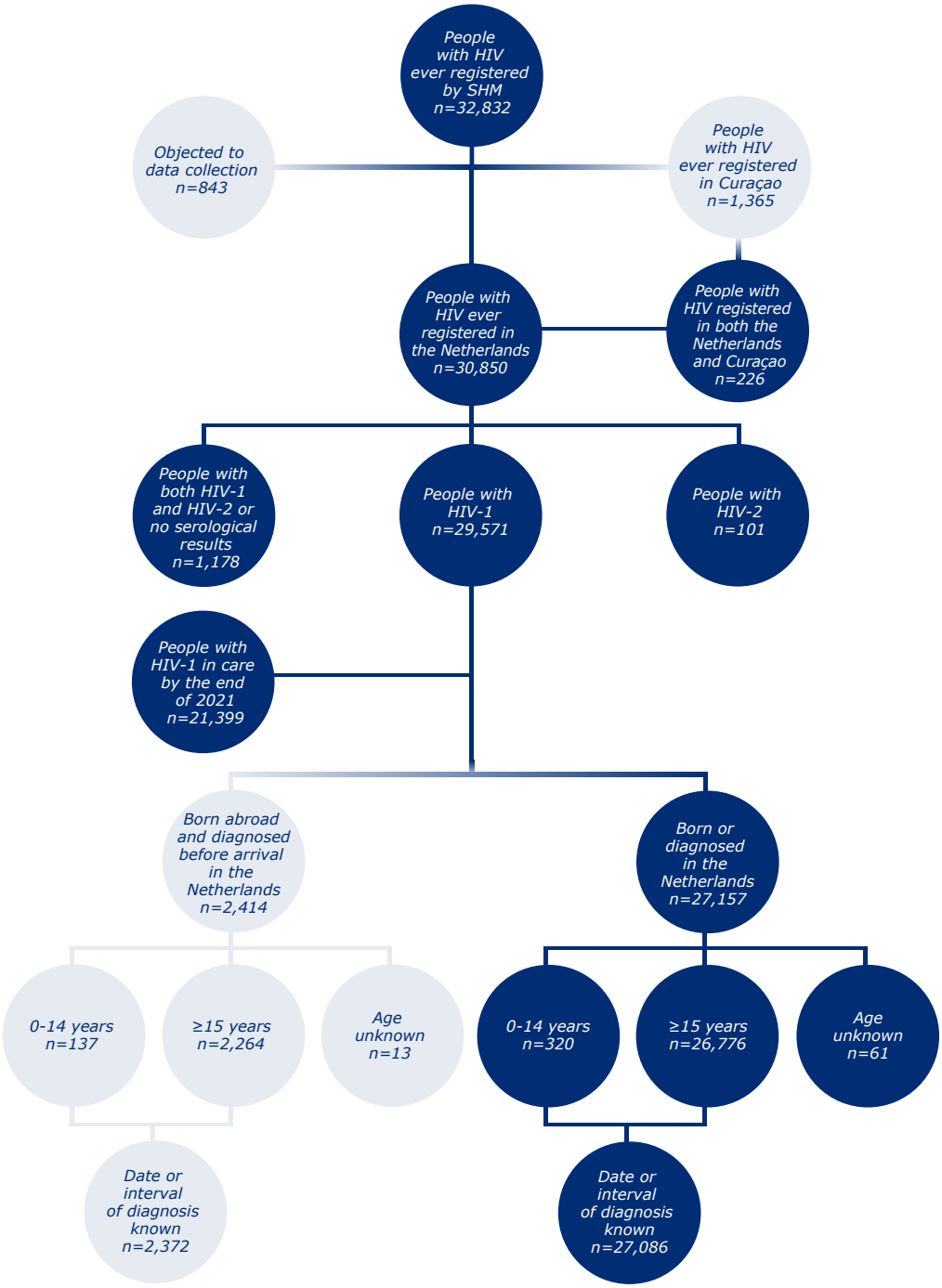
Infection	The moment an individual acquires HIV. The time of infection is often unknown.
Diagnosis	The moment an HIV infection is identified in an individual. The time of diagnosis can be weeks, months, or years after infection.
Entry into care	The moment an individual with HIV first receives care at 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.

HIV-1

Individuals with HIV-1

Of the 29,571 individuals in the Netherlands who were ever diagnosed with HIV-1, 2,414 (8%) were born abroad and had a documented HIV diagnosis prior to arrival in the Netherlands (*Figure 1.1*). These 2,414 individuals have been excluded from the analyses on newly diagnosed individuals later in this section. The remaining 27,157 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.

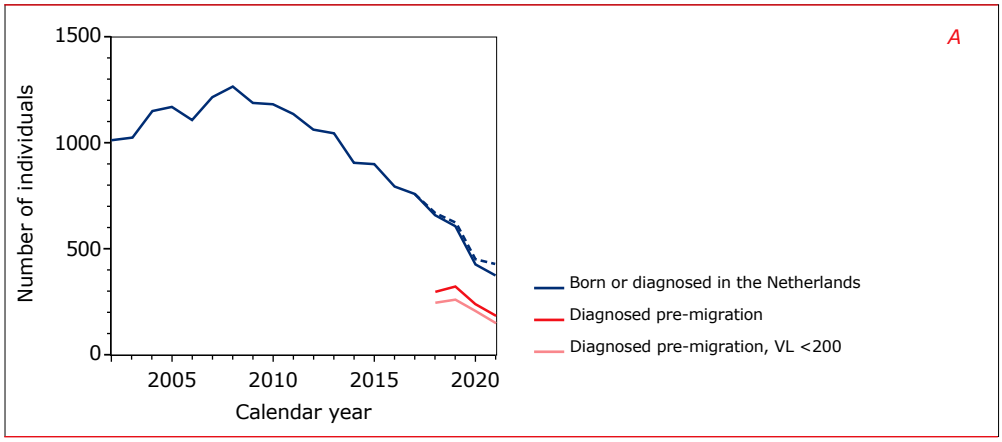
Figure 1.1: *Overview of the population with HIV registered by stichting hiv monitoring (SHM).*

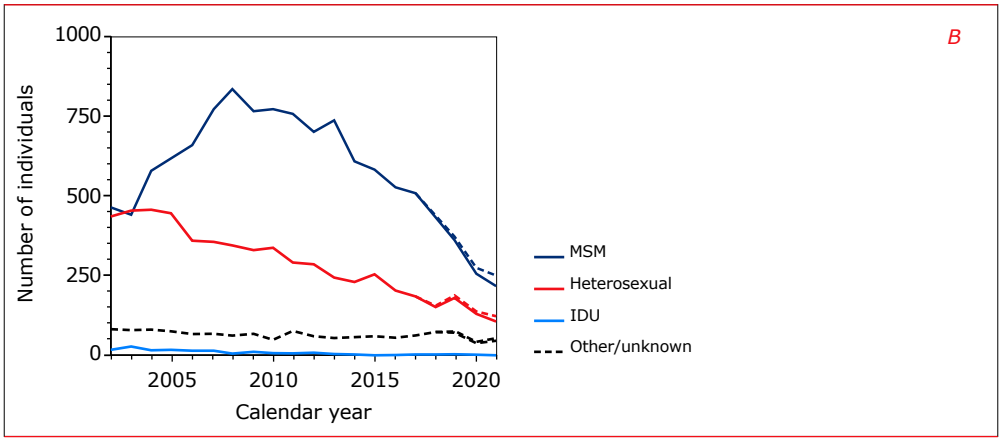


Individuals diagnosed before arriving in the Netherlands

In total, 2,414 individuals who were born abroad had a documented HIV-1 diagnosis before arriving in the Netherlands; 767 of them arrived in the Netherlands in 2019 or later (*Figure 1.2A*). So far, SHM has registered 183 migrants who arrived in 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.

Figure 1.2: *(A) Annual number of individuals newly diagnosed with HIV-1 in the Netherlands (by year of diagnosis) or with documented diagnosis abroad before moving to the Netherlands (by year of arrival), and (B) annual number of individuals newly diagnosed with HIV-1 in the Netherlands and aged 15 years or older at the time of diagnosis, according to the most likely mode of transmission. In 2021, infections via sex between men (MSM) accounted for 59% of the annual number of new diagnoses, infections via heterosexual sex for 28%, infections via injecting drug use (IDU) for 1%, and infections via other or unknown modes of transmission for 12%. 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 = sex between men; IDU = injecting drug use.*

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

Year of diagnosis	MSM	Heterosexual		IDU	
	Men	Men	Women	Men	Women
≤1995	2,151	269	394	276	132
1996	378	88	85	33	9
1997	433	113	126	38	10
1998	323	105	115	23	8
1999	345	110	139	19	7
2000	368	155	197	17	4
2001	440	167	232	14	6
2002	463	172	263	14	3
2003	442	179	274	22	5
2004	581	195	264	9	5
2005	620	191	252	14	3
2006	659	161	198	9	5
2007	767	156	201	11	4
2008	837	170	174	5	1
2009	767	160	172	9	0
2010	772	175	162	5	1
2011	757	142	146	5	1
2012	701	139	146	6	1
2013	738	117	125	1	2
2014	609	114	115	1	0
2015	582	128	124	1	0
2016	529	102	102	1	0
2017	508	97	87	3	0
*2017**	*509*	*97*	*87*	*3*	*0*
2018	433	78	72	1	1
*2018**	*439*	*79*	*73*	*1*	*1*
2019	354	89	91	2	0
*2019**	*365*	*92*	*94*	*2*	*0*
2020	256	65	65	0	0
*2020**	*271*	*69*	*69*	*0*	*0*
2021	218	51	54	2	0
*2021**	*250*	*59*	*62*	*2*	*0*
2022	35	10	12	3	0
Total	**16,066**	**3,698**	**4,387**	**544**	**208**

**Numbers adjusted for a delay in notification*

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

Blood or blood products		Other/unknown		<15 years of age		Total
Men	Women	Men	Women	Men	Women	
64	21	152	43	36	23	3,561
4	4	38	6	9	1	655
8	3	38	8	6	6	789
6	4	29	6	7	5	631
10	4	23	7	7	8	679
5	5	38	7	6	10	812
8	6	43	4	8	12	940
13	7	58	3	12	3	1,011
9	4	54	12	11	10	1,022
5	4	62	9	10	4	1,148
6	4	59	8	7	5	1,169
6	6	50	4	3	4	1,105
2	5	52	8	5	5	1,216
6	2	49	5	6	10	1,265
4	2	50	11	4	7	1,186
5	0	38	5	9	9	1,181
10	6	54	5	3	6	1,135
3	4	43	8	4	6	1,061
11	0	42	2	4	2	1,044
8	5	35	9	3	5	904
4	1	49	5	2	2	898
9	2	40	5	2	0	792
3	2	52	5	0	1	758
3	*2*	*52*	*5*	*0*	*1*	*760*
5	3	58	6	1	0	658
5	*3*	*59*	*6*	*1*	*0*	*666*
8	3	50	8	0	1	606
8	*3*	*52*	*8*	*0*	*1*	*625*
5	4	23	6	0	0	424
5	*4*	*24*	*6*	*0*	*0*	*450*
4	2	33	7	1	0	372
5	*2*	*38*	*8*	*1*	*0*	*427*
0	0	4	0	0	0	64
231	**113**	**1,316**	**212**	**166**	**145**	**27,086**

Of the 767 migrants who arrived in 2019 or later with a documented pre-arrival HIV diagnosis, 482 (63%) were men who reported sex with men (MSM) as the most likely mode of transmission, 152 (20%) were other men, and 133 (17%) were women. The median age at the time of arrival was 35 years (interquartile range [IQR] 29-41); 62 (8%) were below 25 years of age, including nine children under the age of 15, while 55 (7%) were 50 years of age or older. In terms of geographic origins, migrants arrived from:

- South America (170, or 22%);
- sub-Saharan Africa (139, or 18%);
- western Europe (108, or 14%);
- eastern Europe (100, or 13%);
- central Europe (75, or 10%); and
- South and southeast Asia (47, or 6%).

The most commonly reported countries of origin (from where at least 25 individuals with HIV arrived in the Netherlands) were Brazil (58, 8%), Poland (38, 5%), Russian Federation (36, 5%), and Colombia (26, 3%). In total, 23 (3%) people originated from Ukraine.

The majority (676, or 88%) of the 767 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 420-839) cells/mm^3, while 635 individuals had HIV RNA levels below 200 copies/ml (84% of the 759 who had an available viral load measurement).

Individuals newly diagnosed in the Netherlands

Of the 27,157 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, 320 (1%) were diagnosed as children under 15 years of age: they are described in more detail in *Chapter 5*. Among the 27,086 individuals for whom the date or period of diagnosis was known, 26,775 (99%) were diagnosed at 15 years of age or older. Of these, 16,066 (60%) were men who acquired their HIV infection through sex with men, while 3,698 (14%) other men and 4,387 (16%) women reported having acquired their infection through heterosexual sex (*Table 1.1*). For 752 (3%) individuals, the reported mode of transmission was injecting drug use, while for 344 (1%) individuals, infection occurred through exposure to contaminated blood. Other and unknown modes of transmission accounted for the remaining 1,528 (6%) HIV diagnoses.

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 2021, with an approximate number of 427 new HIV diagnoses. This number takes into account a projected backlog[b] in registration of HIV cases.

In MSM, the annual number of diagnoses rose to almost 840 in 2008 (*Figure 1.2B*), after which they gradually fell to approximately 250 in 2021. Among individuals who acquired their HIV infection via heterosexual sex, the annual number of new diagnoses has decreased to approximately 121 in 2021. Finally, injecting drug use is now rarely reported as the most likely mode of transmission, which reflects the decreasing popularity of injecting drugs.

Decreasing number of newly acquired infections

The observed changes over time in the number of HIV diagnoses are, in part, a consequence of changes in the annual number of newly acquired HIV infections. The estimated number of infections decreased from 920 (95% confidence interval [CI] 870-980) in 2010 to 120 (40-430) in 2021 (*Figure 1.3A*), which is a reduction of 87% (55-95). During the same period, the number of newly acquired HIV infections among MSM fell by 86% (48-97), from 660 (620-720) in 2010 to 90 (20-350) in 2021 (*Figure 1.3B*).

In other men, the estimated number of newly acquired infections in 2010 was 140 (95% CI 130-160), which was similar to the estimated number of 120 (100-130) in women. By 2021 this had dropped sharply in both groups, reaching 10 (10-20) in other men and 20 (10-110) in women; respective reductions of 90% (87-94) and 84% (11-95) (*Figure 1.3C* and *1.3D*).

It worth noting that the uncertainty around the estimated number of infections for the most recent calendar years is relatively large, as these are quite sensitive to the observed number of diagnoses in 2020 and 2021. In other men, the uncertainty appears to be smaller but this is due to far fewer observed diagnoses in 2020 and 2021 than in previous years. This may be a consequence of the COVID-19 pandemic and the partial lockdowns in 2020 and 2021, which disrupted testing services for HIV and possibly also delayed registration in the SHM database.

b *As it may take some time before people with HIV are registered in the SHM database by their treating physician, there is a backlog for the most recent calendar years. Based on past trends in registration, adjustment factors for 2017-2021 were estimated using the European Centre for Disease Prevention and Control (ECDC) HIV Platform Tool*[10].

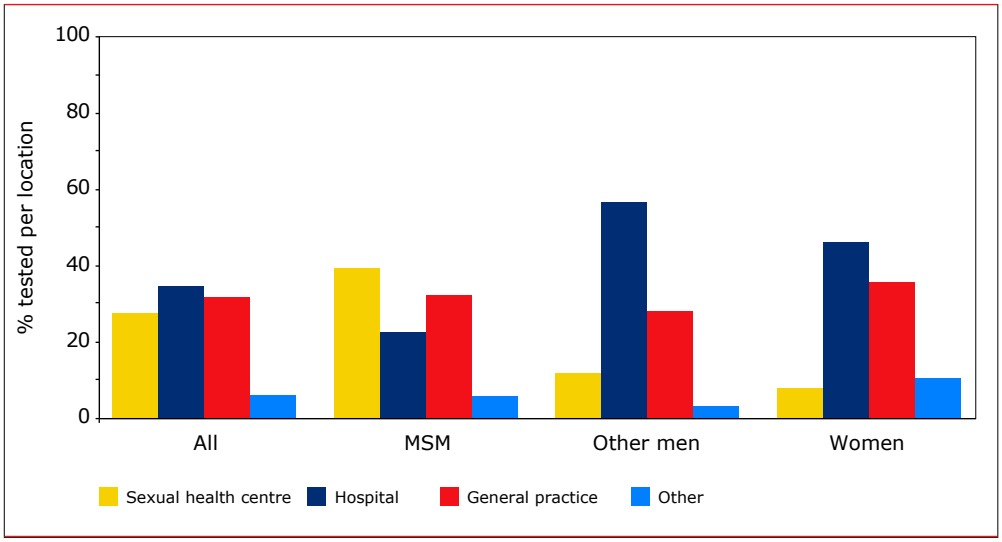
Figure 1.3: *Observed annual number of HIV diagnoses (red) and estimated annual number of newly acquired HIV infections (blue) in: the total population (A), in men who have sex with men (B), in other men (C), in women (D), according to the European Centre for Disease Prevention and Control (ECDC) HIV Platform Tool[10]. The red dashed lines represent the number of diagnoses after adjusting for the delay in notification to SHM, while the blue dashed lines indicate that estimates in 2019 and later are still uncertain.*

Legend: *MSM = sex between men.*

Setting in which HIV is diagnosed

Information on the setting in which HIV was diagnosed in the Netherlands was available for 1,396 (95%) of the 1,464 people diagnosed in 2019 or later, while 48 (3%) individuals were known to have been diagnosed abroad. Overall, 28% of these 1,396 individuals received their first HIV-positive test result at a sexual health centre, 35% at a hospital, 32% at a general practice, and 6% at another location (*Figure 1.4*). In 2021, the proportion diagnosed at a hospital increased to 41%, while the proportion diagnosed at a general practice decreased to 26%; the proportion diagnosed at a sexual health centre or at another location did not change. Among those diagnosed at sexual health centres in 2021, 84% were MSM, 10% were other men, and 6% were women, which was similar to the proportions directly reported by sexual health centres[1].

Figure 1.4: *Proportion of individuals diagnosed in 2019 or later, stratified by location of testing and transmission risk group.*

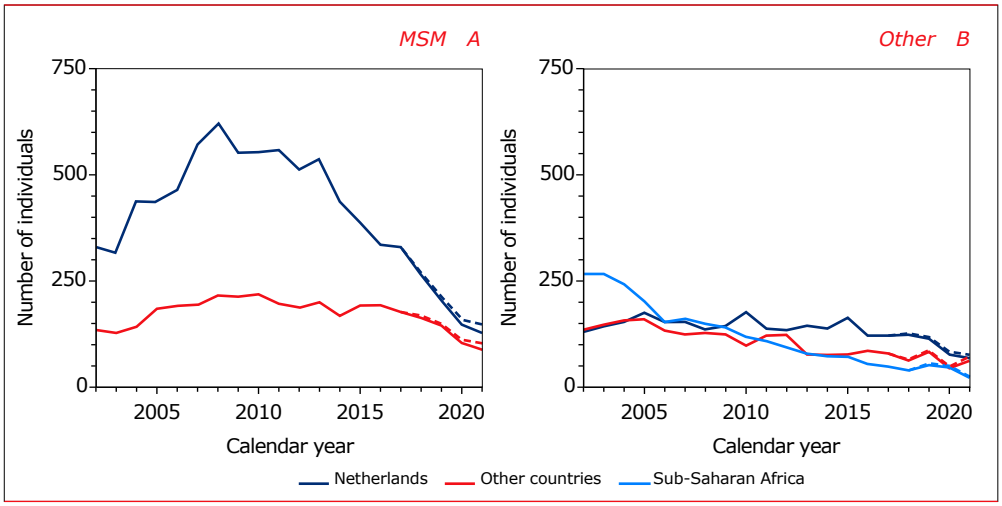


Legend: *MSM = sex between men.*

Geographical region of origin

In total, 11,176 (42%) people diagnosed with HIV-1 at 15 years of age or older were born outside the Netherlands. Of the men who acquired HIV via sex with men (MSM), 71% originated from the Netherlands, 10% from other European countries, 7% from South America, and 4% from the Caribbean (*Figure 1.5A*). In recent years (i.e. for diagnoses in, or after, 2019), the proportion of MSM of Dutch origin was 59%, while slight increases were observed in the proportion of MSM from central Europe, South America, and the Caribbean.

Figure 1.5: *Annual number of diagnoses by region of origin among: (A) men who acquired HIV via sex with men (MSM), and (B) other people aged 15 years or older at the time of diagnosis. Of the 863 MSM diagnosed in 2019 or later, 509 (59%) originated from the Netherlands, 126 (15%) from other European countries, 92 (11%) from South America, and 51 (6%) from the Caribbean. Of the other 601 people diagnosed in 2019 or later, 270 (45%) originated from the Netherlands, 75 (12%) from other European countries, 127 (21%) from sub-Saharan Africa, 44 (7%) from South America, 32 (5%) from the Caribbean, and 19 (3%) from south and southeast Asia.*



Legend: *MSM = sex between men.*

Among women and other men, only 39% originated from the Netherlands, while 31% originated from sub-Saharan Africa, 8% from South America, 5% from the Caribbean, and 4% from south and southeast Asia (*Figure 1.5B*). From 2019 onwards, 45% of the newly diagnosed women and other men were of Dutch origin, and 21% originated from sub-Saharan Africa.

Overall, 20% of individuals newly diagnosed since 2019 were living in the Amsterdam public health service (PHS) region at the time of diagnosis, and 15% were living in the Rotterdam- Rijnmond PHS region. Proportionally, people of Dutch origin accounted for 14% in each of the above PHS regions, with people of foreign origin amounting to 26% and 16%, respectively. Among MSM, 22% were living in Amsterdam at the time of diagnosis and 15% were living in Rotterdam-Rijnmond, while among other men and among women, 16% were living in Amsterdam and 15% in Rotterdam-Rijnmond. Other PHS regions with at least 5% of the new diagnoses since 2019 were Haaglanden (8%, including Den Haag) and Utrecht (6%).

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 2021, it was 40 years (IQR 31-52). In 2002-2021, 19% of individuals who received an HIV diagnosis were aged 50 years or older; in 2021, 30% were 50 years or older (*Figure 1.6*)[2].

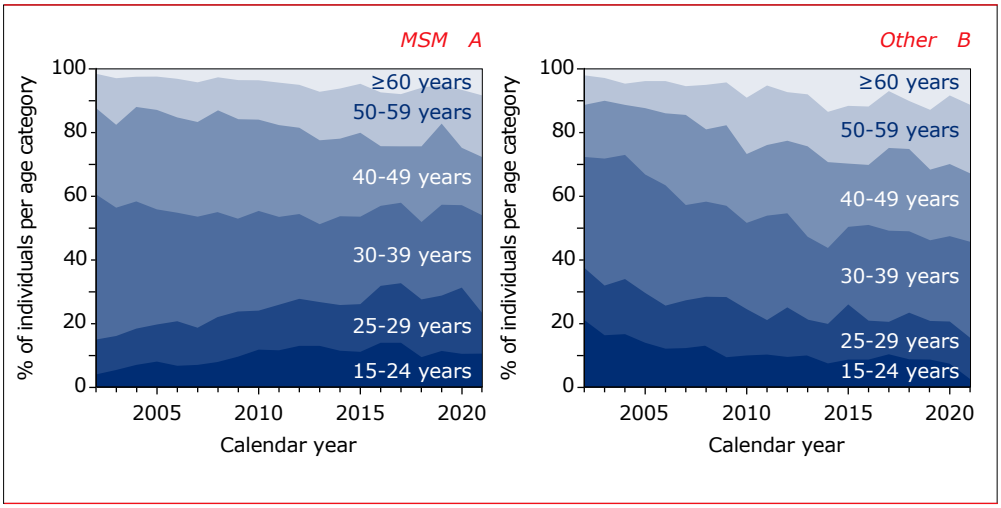
It is worth noting that although the median age at diagnosis in MSM (38 years) did not change between 2002 and 2021, both the proportion diagnosed below 30 years of age and the proportion diagnosed above 50 years of age increased during this period. In 2002, 15% of MSM were younger than 30 years at the time of their diagnosis while 12% were 50 years of age or older; these proportions were 24% and 27%, respectively, in 2021.

There were some age differences between MSM, other men, and women diagnosed in 2019 or later. MSM born in the Netherlands were diagnosed at a median age of 43 years (IQR 31-53), while MSM of foreign origin were diagnosed at a much younger median age of 32 years (27-41). Other men and women of Dutch origin were of similar age at the time of diagnosis as Dutch MSM: 44 years (33-56) for men and 42 years (30-56) for women. Foreign-born men other than MSM were 42 years (33-50) of age at the time diagnosis, which was somewhat older than the median age of 38 years (30-48) for foreign-born women. In 2021, 28% of MSM, 33% of other men, and 32% of women were 50 years or older at the time of diagnosis.

Young people

Between 2002 and 2021, 11% of the individuals who received an HIV diagnosis at 15 years of age or older were under 25 years of age (*Figure 1.6*). In 2021, 28 young people (all aged 18 or older) were diagnosed with HIV, which amounted to 8% of all people diagnosed with HIV that year. The number of young individuals diagnosed in 2021 was 23 (11%) among MSM, one (1%) among other men, and four (6%) among women. Of the 28 young people, 14 (50%) were born in the Netherlands, while five originated from central Europe, four from South America, three from the Caribbean, and two from elsewhere.

Figure 1.6: *Age distribution at the time of diagnosis among: (A) men who acquired HIV via sex with men (MSM), and (B) other men and women with HIV-1. In 2002-2021, the proportion of individuals between 15 and 29 years of age changed from 15% to 24% for MSM, and from 38% to 16% 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 28%, while these proportions were 11% and 33% for other individuals.*



Legend: *MSM = sex between men.*

Entry into care

Of the 1,396 individuals diagnosed with HIV in 2019 or later for whom the diagnosis setting was known, 81% entered HIV care within two weeks of diagnosis, 94% within four weeks, and 97% within six weeks. For individuals diagnosed in 2021, these proportions were 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 (97%), at a general practice (93%), or at other locations (93%). The proportion in care within four weeks did not differ between MSM, other men, and women, but increased with age at the time of diagnosis: 93% of individuals diagnosed at 15-24 years were in care within four weeks, compared to 93% of those diagnosed at 25-49 years of age, and 97% of those diagnosed at 50 years of age or older. The proportion in care within four weeks of diagnosis was larger among individuals born in the Netherlands (97%), than among those born abroad (92%).

Late diagnosis

Overall, 53% of the individuals diagnosed in 2019 or later had a late-stage HIV infection at the time of diagnosis; in other words, a CD4 count below 350 cells/mm^3 or an AIDS-defining event regardless of CD4 count[3]. Over time, the proportion of late-stage HIV diagnoses decreased from 58% in 2002 to a nadir of 43% in 2013, and then increased to 51% in 2019, 53% in 2020, and 57% in 2021 (*Figure 1.7*). This increase was mainly due to an increase in the proportion of MSM diagnosed with late-stage HIV (*Figure 1.8A*). The proportion of individuals diagnosed with advanced HIV disease (i.e. with a CD4 count below 200 cells/mm^3 or AIDS-defining event), has followed a similar pattern, and reached 41% in 2021. 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. It is worth noting that although newly diagnosed MSM had the lowest proportion of late-stage HIV infections, they accounted for 367 (50%) of all 740 individuals diagnosed with late-stage HIV in 2019 or later.

Figure 1.7: *Number and proportion of individuals classified as having: (A, B) late-stage, or (C, D) advanced-stage HIV infection at the time of diagnosis. In 2021, 200 (57%) individuals were diagnosed with late-stage HIV infection: 108 (52%) men who acquired HIV via sex with men (MSM), 58 (69%) other men, and 34 (58%) women; adjusting for reporting delay, 229 (57%) individuals: 123 (52%) MSM, 67 (69%) other men, and 39 (58%) women. During the same year, 145 (41%) individuals were diagnosed with advanced-stage HIV infection: 66 (32%) MSM, 49 (58%) other men, and 30 (51%) women; adjusting for reporting delay, 166 (41%) individuals: 75 (32%) MSM, 57 (58%) other men, and 35 (51%) 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. From 2019 onwards, the stage of infection was unknown for 77 (5%) individuals.*

Legend: *MSM = sex between men.*

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

Among individuals diagnosed with HIV in 2019 or later, 367 (45%) MSM, 225 (69%) other men, and 148 (62%) women had a late-stage HIV infection. Late-stage HIV infections, in relative terms, were most common among people originating from sub-Saharan Africa (72%, or 93 individuals), from central Europe (63%, or 72 individuals), or from south and southeast Asia (62%, 32 individuals). Among people who acquired their HIV infection via other routes than sex between men, late-stage HIV infection was also more common among those originating from the Netherlands (63%, or 162 individuals), from North Africa and the Middle East (67%, or 14 individuals), or from South America (66%, or 25 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 2019 or later, late-stage HIV was seen in 54% of MSM, 83% of other men, and 75% of women aged 50 years or older, compared with 32% of MSM, 50% of other men, and 46% of women diagnosed below the age of 30 years (*Table 1.2; Figure 1.8B*).

Figure 1.8A: *Number of new HIV diagnoses among men who reported sex with men (MSM) as the most likely mode of transmission, stratified by whether or not they had a late-stage HIV infection. Late-stage HIV infection: CD4 counts below 350 cells/mm3 or having AIDS, regardless of CD4 count. 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 78 (6%) MSM diagnosed in 2018–2021.*

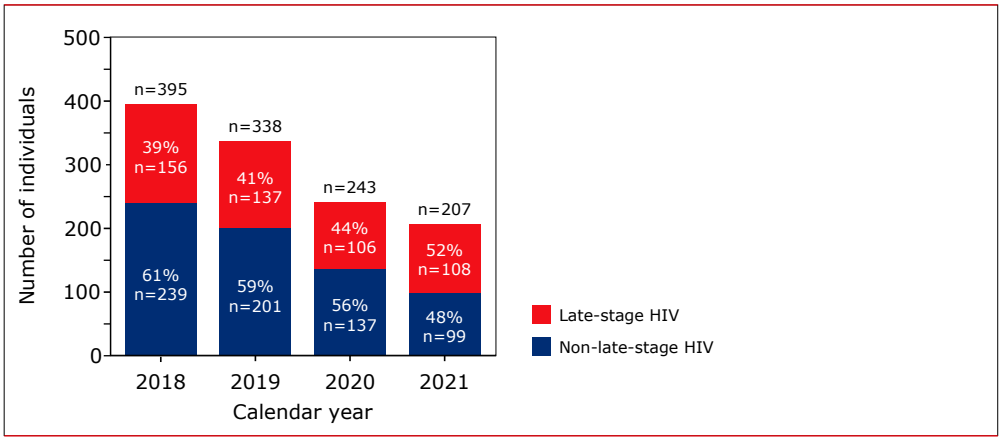
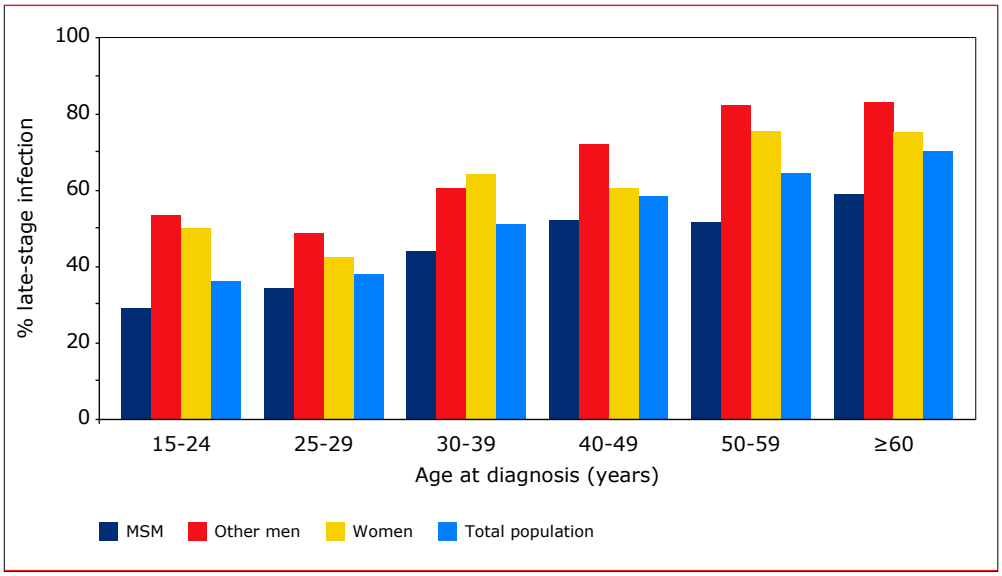


Figure 1.8B: Proportion of individuals diagnosed with late-stage HIV infection stratified by age category at the time of diagnosis for those diagnosed in 2019 or later.



Legend: MSM = sex between men.

Late-stage HIV was also observed more frequently in people who received their HIV diagnosis at a hospital (81%), than among those who were tested at a general practice (46%), a sexual health centre (30%), or another testing location (44%). These proportions did not change over time except for individuals diagnosed at a hospital, in whom the proportion with late-stage HIV increased from 70% in 2010 to 83% in 2021.

Impact of transient low CD4 cell counts early after infection

During the first few weeks after acquiring HIV, transient low levels of CD4 cell counts are common[4]. As a result, the stage of the infection may inadvertently be classified as late or advanced when individuals are diagnosed during this early phase of HIV infection. When people with a known HIV-negative test in the six months prior to HIV diagnosis were reclassified as not having a late-stage or advanced-stage HIV infection, the proportion of late-stage HIV infections among individuals diagnosed in 2019 or later changed from 53% to 50%. This decrease was mainly due to a drop in late-stage HIV among MSM (from 45% to 39%) whereas among other men and among women, the proportion decreased by a percentage

point at most. The change in the proportion of people diagnosed with advanced-stage HIV infection was more modest: 35% before and 34% after reclassification in people diagnosed in 2019 or later.

Table 1.2: *Characteristics of the 740 individuals with a late-stage HIV infection among the 1,464 individuals diagnosed with HIV in 2019 or later. In total, as a result of missing CD4 cell counts at diagnosis, it was not possible to classify whether 77 (5%) individuals (41 MSM, 23 other men, and 13 women) had a late-stage HIV infection. For each of the four groups (MSM, other men, women, and total) percentages represent the proportion with late-stage infection of the total number of individuals diagnosed in each category listed in the first column.*

	MSM (n=822)		Other men (n=326)		Women (n=239)		Total (n=1,387)	
	n	%	n	%	n	%	n	%
Overall	367	45	225	69	148	62	740	53
Age at diagnosis (years)								
15–24	25	29	8	53	13	50	46	36
25–29	49	34	18	49	14	42	81	38
30–39	100	44	52	60	43	64	195	51
40–49	92	52	57	72	29	60	178	59
50–59	68	52	56	82	34	76	158	64
≥60	33	59	34	83	15	75	82	70
Region of origin								
Western	*241*	*45*	*119*	*68*	*48*	*55*	*408*	*51*
The Netherlands	221	45	116	68	46	53	383	51
Western Europe	19	50	2	50	2	100	23	52
North America/Australia	1	25	1	100	0	0	2	40
Non-Western	*126*	*44*	*106*	*71*	*100*	*66*	*332*	*57*
Sub-Saharan Africa	5	50	38	84	50	68	93	72
Central Europe	38	58	23	70	11	69	72	63
South America	31	37	13	76	12	57	56	46
Caribbean	22	49	6	40	8	53	36	48
South and southeast Asia	17	52	6	75	9	82	32	62
North Africa and the Middle-East	7	33	12	67	2	67	21	50
Other/unknown	6	23	8	57	8	73	22	43
Location of HIV diagnosis								
Sexual health centre	87	28	15	43	8	44	110	30
Hospital	139	76	148	85	90	85	377	81
General practice	108	42	54	61	34	42	196	46
Other/unknown	33	49	8	30	16	47	57	44

Legend: *MSM = sex between men.*

Recent infection

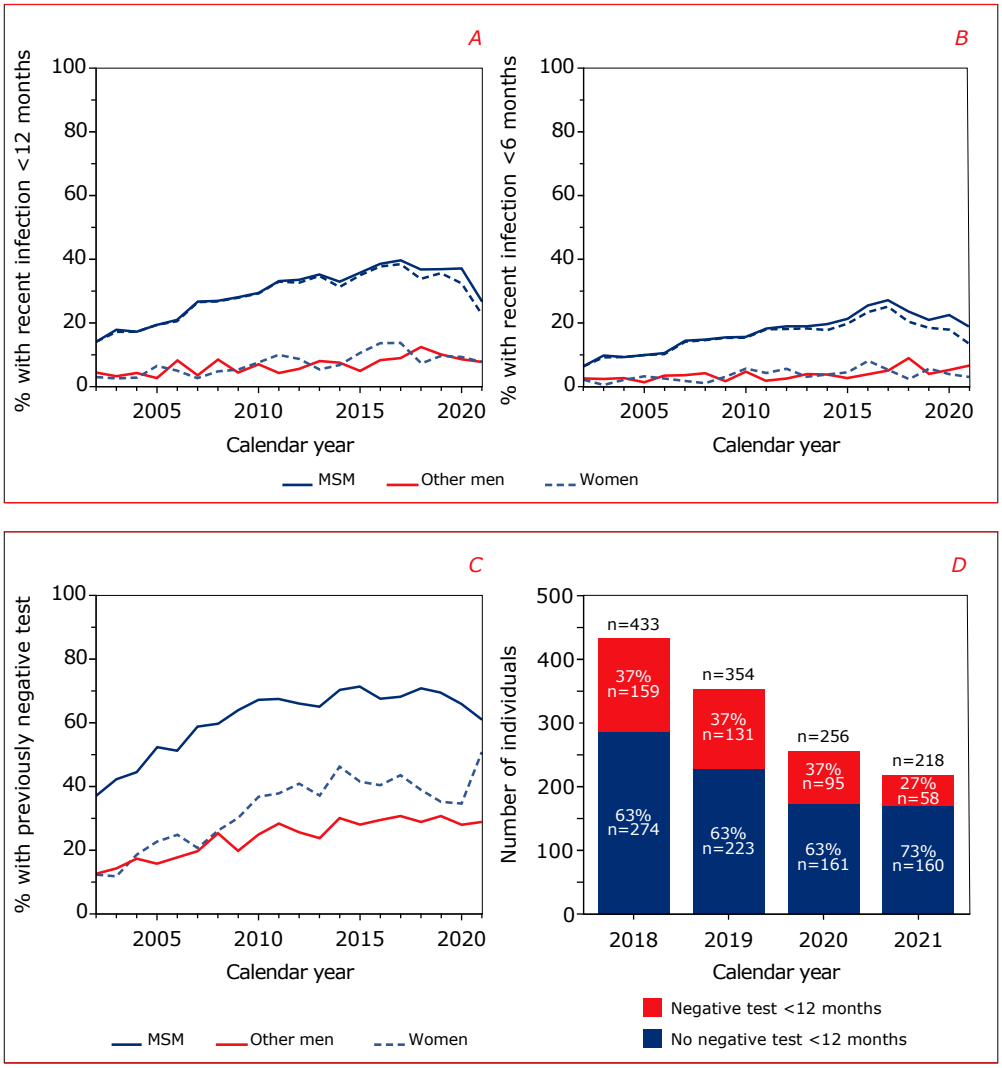
Although many individuals are diagnosed with a late-stage HIV infection, a considerable proportion of people receive their HIV diagnosis early in the course of their infection. In total, among the individuals diagnosed in 2019 or later, 24% had evidence of having acquired their HIV infection in the 12 months prior to diagnosis, while 14% had evidence of having acquired HIV in the six months prior to diagnosis (*Figure 1.9A* and *1.9B*). For MSM, these proportions were 34% and 21%, respectively, while they were considerably lower among other men and among women (9% and 5%, respectively).

It is worth noting that the proportion of MSM with evidence of having acquired their HIV infection in the 12 months prior to diagnosis was 37% in 2018-2020 and then appeared to be lower, 27%, in 2021 (*Figure 1.9D*). This decrease of approximately 10 percentage points remained when taking into account a previously negative test up to 24, 36, or 48 months prior to diagnosis. This makes it less likely that reduced testing for HIV during the COVID-19 pandemic is the only reason for the decrease.

The proportion of people with a recorded previously negative HIV test any time before their HIV diagnosis increased from 25% in 2002 to 53% in 2021. MSM were more likely to have a previously negative HIV test than other men and women. In 2021, 62% of MSM newly diagnosed with HIV had a previously negative test, which was lower than 71% of MSM diagnosed in the period 2018-2020 (*Figure 1.9C*). The proportion with a negative test among other men and women diagnosed in 2021 was 32% and 51%, respectively, which did not differ significantly from the proportions in 2018-2020 (32% and 39%, respectively). The proportion with a known previously negative test was highest among those diagnosed at a sexual health centre (79%), compared with 35% of those diagnosed in a hospital, 54% at a general practice, and 60% who were diagnosed elsewhere.

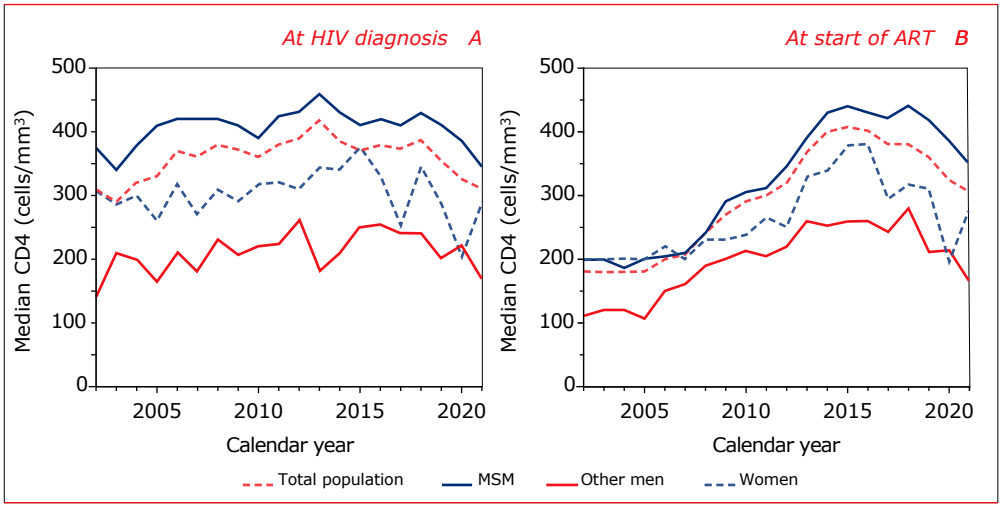
Between 2002 and 2018, median CD4 counts at the time of diagnosis increased from 308 to 387 cells/mm^3 (*Figure 1.10A*). This overall increase was mainly the result of a rise in CD4 counts in MSM, whereas CD4 counts in women and in other men showed more modest increases. After 2018, in conjunction with the increasing proportion of people diagnosed with late-stage HIV infection, median CD4 counts decreased and were 310 cells/mm^3 in 2021.

Figure 1.9: *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 and (D) number of new HIV diagnoses among men who acquired their HIV infection through sex with men (MSM), stratified by whether or not there was evidence of having acquired HIV at most 12 months 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. For MSM, the dashed lines represent the proportion with evidence of a recent infection based only on a last negative test. In total, 27% of MSM, 8% of other men, 8% of women, and 19% of all individuals diagnosed in 2021 had evidence of having acquired HIV at most 12 months before diagnosis, whereas 19% of MSM, 7% of other men, 3% of women, and 13% of all individuals had evidence of having acquired HIV at most six months before diagnosis.*



Legend: *MSM = sex between men.*

Figure 1.10: *Changes over calendar time in median CD4 counts: (A) at HIV diagnosis, and (B) at the start of antiretroviral therapy (ART). (A) From 2002 onwards, CD4 counts at the time of diagnosis initially increased, but this was followed by a decrease in most recent years. In 2021, CD4 counts were 310 (interquartile range [IQR] 120-520) cells/mm³ in the total population, 345 (160-570) cells/mm³ in MSM, 168 (50-420) cells/mm³ in other men, and 290 (117-455) cells/mm³ in women. (B) In the total population, CD4 counts at the start of ART were approximately 180 cells/mm³ between 2002 and 2005, and increased thereafter. Since 2015, treatment guidelines recommended immediate initiation of antiretroviral therapy, regardless of CD4 count, and since then CD4 counts at diagnosis and at start of ART are almost identical. In 2021, CD4 counts were 306 (127-546) cells/mm³ in the total population, 349 (160-580) cells/mm³ in MSM, 163 (20-420) cells/mm³ in other men, and 281 (123-454) cells/mm³ in women.*



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

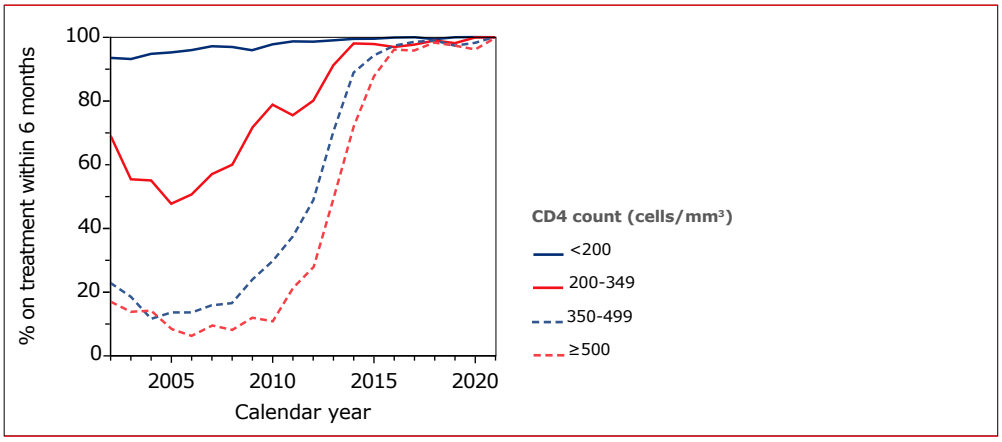
Altogether, our data show that the proportion of newly diagnosed MSM who had never tested before was larger in 2021 than in previous years. This suggests that in 2021 the risk of acquiring an HIV infection was lower for MSM who regularly test for HIV (and therefore have a previously negative test if they would be diagnosed with HIV). This may indicate that a significant proportion of men who regularly test for HIV are now protected by pre-exposure prophylaxis (PrEP). PrEP became available on a national level via the Sexual Health Centres (SHC) of the municipal Public Health Services (GGD) as part of the PrEP pilot programme, which started in August 2019 for those at highest risk of acquiring HIV[c]. More detailed PrEP analyses are presented in *Special Report: Prior use of pre-exposure prophylaxis*.

c https://www.rivm.nl/Soa-seksueel-overdraagbare-aandoening/prep

Antiretroviral therapy

Of the 26,775 individuals diagnosed at 15 years of age or older, 25,901 (97%) had started antiretroviral therapy (ART) by May 2022. Over the past two decades, ART has increasingly been initiated earlier in the course of an HIV infection, as evidenced by higher CD4 counts at the start of therapy since the mid-2000s (*Figure 1.10B*). This is a consequence of people being diagnosed sooner, on average, after acquiring their HIV infection, and of changes in treatment guidelines. These now recommend immediate initiation of ART, regardless of CD4 count[5]. 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 (*Figure 1.11*). In 2021, across all CD4 strata, at least 95% of people who were diagnosed with HIV that year started ART within six months.

Figure 1.11: *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 2019 or later, 100% of those with CD4 counts below 200 cells/mm³, 99% of those with CD4 counts between 200 and 349 cells/mm³, 98% of those with CD4 counts between 350 and 499 cells/mm³, and 97% of those with CD4 counts of 500 cells/mm³ or above had started ART within six months of diagnosis.*



Time between HIV infection and viral suppression

Individuals with a suppressed viral load do not transmit their virus to uninfected partners (undetectable equals untransmittable, or U=U)[6–8]. Hence it is crucial to minimise the time between the moment a person acquires HIV and the point at which they achieve viral suppression[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 2021, the median time from diagnosis to viral suppression decreased from 0.85 years (IQR 0.38-2.64) to 0.18 years (IQR 0.13-0.30), or from 10.2 months (IQR 4.5-31.7) to 2.1 months (IQR 1.5-3.6). This 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 2021, this was estimated to be a median of 3.2 years (IQR 1.5-5.8).

Population in care

In total, 21,399 (72%) of the 29,571 individuals with HIV-1 ever registered in the Netherlands were known to be in clinical care by the end of 2021 (*Figure 1.1*; *Table 1.3*). People were considered to be in clinical care if they had visited their treating physician in 2021, or had a CD4 count or HIV RNA measurement in that year, and were still living in the Netherlands. Of the 8,172 people who were not in care by the end of 2021, 3,731 (46%) had died, of whom 1,991 (53%) died before the end of 2011. Another 2,258 (28%) had moved abroad, including 784 (35%) who did so before the end of 2011. The remaining 2,183 (27%) individuals:

- were lost to care (2,046, 94%);
- were only diagnosed with HIV in 2022 (65, 3%);
- had only moved to the Netherlands in 2022 (31, 1%); or
- had newly entered care in 2022 (41, 2%).

Of the people who moved abroad, 1,760 (79%) had RNA levels below 200 copies/ml at their last viral load measurement; in those lost to care, that figure was 1,310 (65%).

Table 1.3: Characteristics of the 21,399 people with HIV-1 in clinical care by the end of 2021.

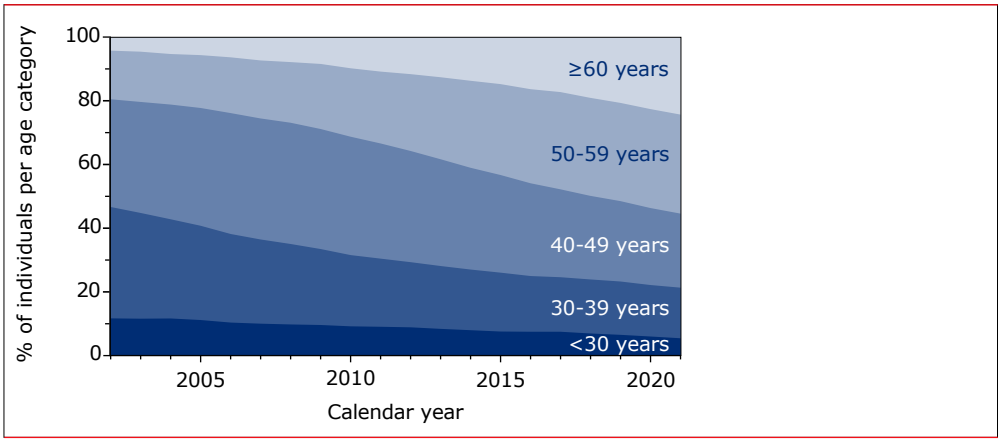
	Men (n= 17,445, 82%)		Women (n=3,954, 18%)		Total (n=21,399)	
	n	%	n	%	n	%
Transmission						
MSM	13,486	77	-	-	13,486	63
Heterosexual	2,556	15	3,449	87	6,005	28
IDU	186	1	79	2	265	1
Blood/blood products	179	1	106	3	285	1
Other/unknown	1,038	6	320	8	1,358	6
Current age (years)						
0–14	63	0	75	2	138	1
15–24	185	1	90	2	275	1
25–29	647	4	121	3	768	4
30–39	2,711	16	704	18	3,415	16
40–49	3,757	22	1,207	31	4,964	23
50–59	5,571	32	1,093	28	6,664	31
60–69	3,261	19	484	12	3,745	18
≥70	1,250	7	180	5	1,430	7
Region of origin						
The Netherlands	11,054	63	1,199	30	12,253	57
Sub-Saharan Africa	1,109	6	1,571	40	2,680	13
Western Europe	994	6	113	3	1,107	5
South America	1,345	8	356	9	1,701	8
Caribbean	787	5	188	5	975	5
South and southeast Asia	555	3	250	6	805	4
Other	1,506	9	262	7	1,767	8
Unknown	96	1	15	0	111	1
Years aware of HIV infection						
<1	309	2	57	1	366	2
1–2	841	5	184	5	1,025	5
3–4	1,281	7	196	5	1,477	7
5–9	3,870	22	647	16	4,517	21
10–19	7,268	42	1,776	45	9,044	42
≥20	3,845	22	1,078	27	4,923	23
Unknown	31	0	16	0	47	0

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

Ageing population

The median age of the population in clinical care by the end of 2021 was 52 years (IQR 42-60). This figure has been increasing since 2002 (*Figure 1.12*), 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 (55%) are 50 years or older (58% of men and 44% of women), and 24% 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 1.12: *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 19% were 50 years or older. In 2021, these proportions were 6% and 55%, respectively, while 24% 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 2021 were known to be HIV-positive for a median of 13.2 years (IQR 7.9-19.5). Therefore, a large group (65%) of those in care have been living with HIV for more than 10 years, including 23% who have done so for more than 20 years. The median time since diagnosis was 12.6 years for men who acquired HIV via sex with men (MSM), 13.5 years for other men, and 15.5 years for women. The majority of individuals who acquired their HIV infection via injecting drug use (94%) received their HIV diagnosis more than 10 years ago, which reflects how rare this mode of transmission has become since the Netherlands' rapid and early adoption of harm reduction strategies in the 1980s.

Treated population

By the end of 2021, almost all individuals in care had started ART, and 96% of them were using a once-daily regimen. Of the 100 individuals who had not yet started ART by the end of 2021, ten (10%) were known to have started therapy in 2022, while another 18 (18%) individuals were diagnosed with HIV in 2021, 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*.

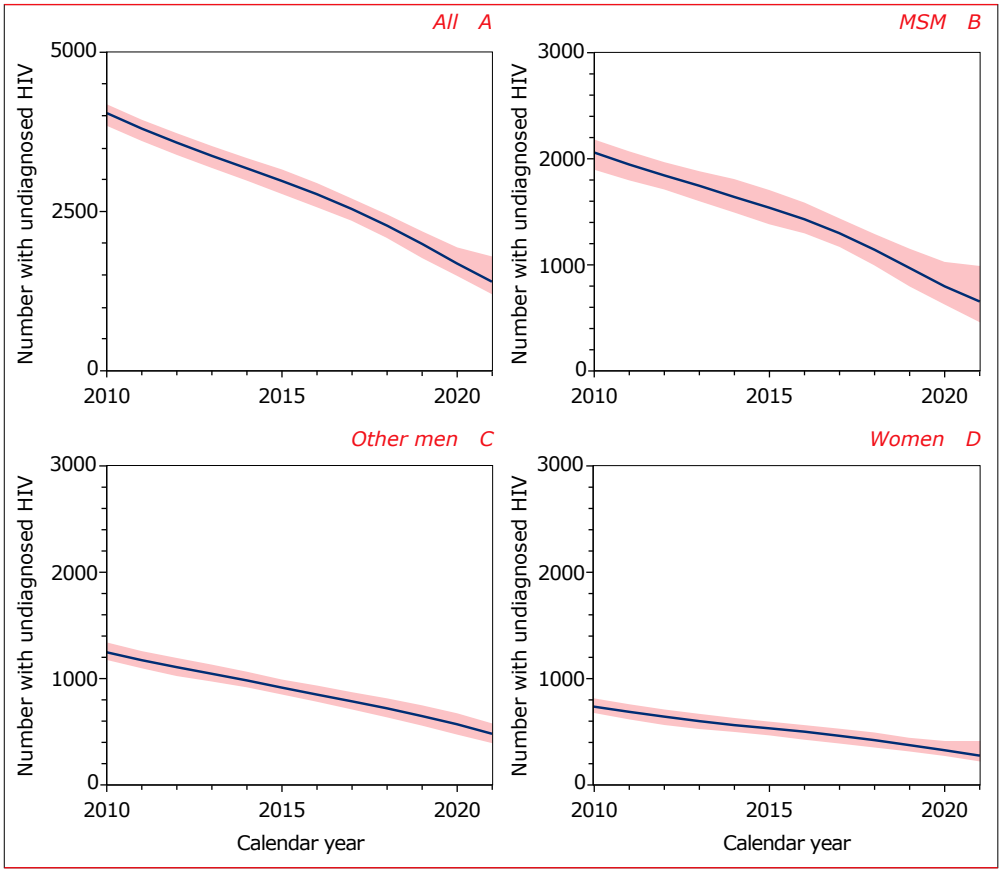
Clinical condition

The most recent 2019-2021 median CD4 count for people in care was 700 (IQR 518-920) cells/mm^3, which is mainly the result of effective ART. Most recent CD4 counts were largely similar between MSM and women, being 720 (IQR 540-930) and 710 (IQR 513-940) cells/mm^3, respectively. Men who acquired HIV via other modes of transmission had lower CD4 counts at a median of 617 (IQR 435-841) cells/mm^3. Of those in care with an HIV RNA measurement in 2021, 98% had a last measurement in that year below 200 copies/ml, and 96% had a last measurement below 50 copies/ml. More than one fifth (22%) of the individuals had ever been diagnosed with an AIDS-defining disease; 57% were diagnosed with AIDS concurrently with their HIV diagnosis.

Undiagnosed population

The estimated number of people with an undiagnosed HIV infection decreased from 4,050 (95% CI 3,840-4,190) in 2010 to 1,400 (1,190-1,790) in 2021, representing a reduction of 66% (56-70) (*Figure 1.13A*). This decrease was mostly driven by MSM, among whom the number of undiagnosed HIV cases fell by 68% (51-78) from 2,060 (1,890-2,180) in 2010 to 650 (460-990) by the end of 2021 (*Figure 1.13B*). Among other men, the estimated number with undiagnosed HIV was 1,250 (1,170-1,330) in 2010 and 480 (390-570) in 2021, while in women these numbers were 740 (670-810) and 270 (210-410), respectively (*Figures 1.13C* and *1.13D*).

Figure 1.13: *Estimated number of people with undiagnosed HIV in the Netherlands: (A) overall, (B) men who acquired HIV through sex with men (MSM), (C) other men, and (D) women, according to the European Centre for Disease Prevention and Control (ECDC) HIV Platform Tool[10].*



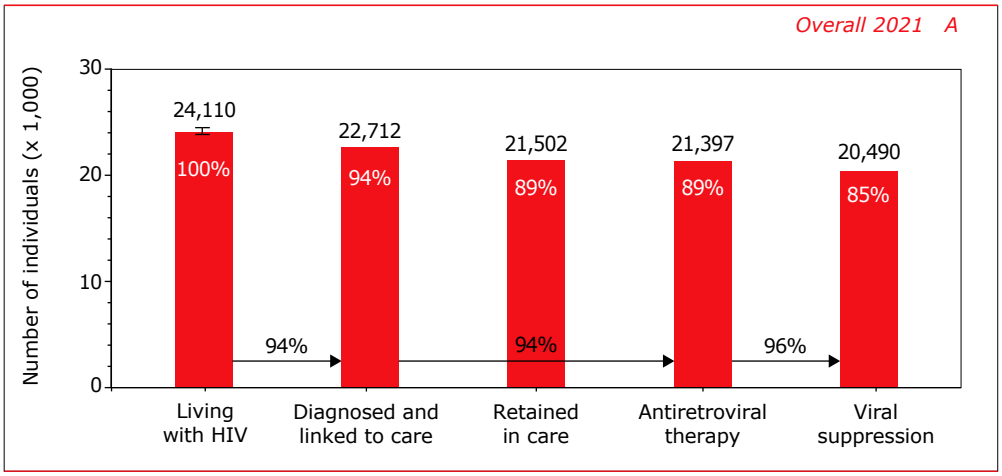
Legend: *MSM = sex between men.*

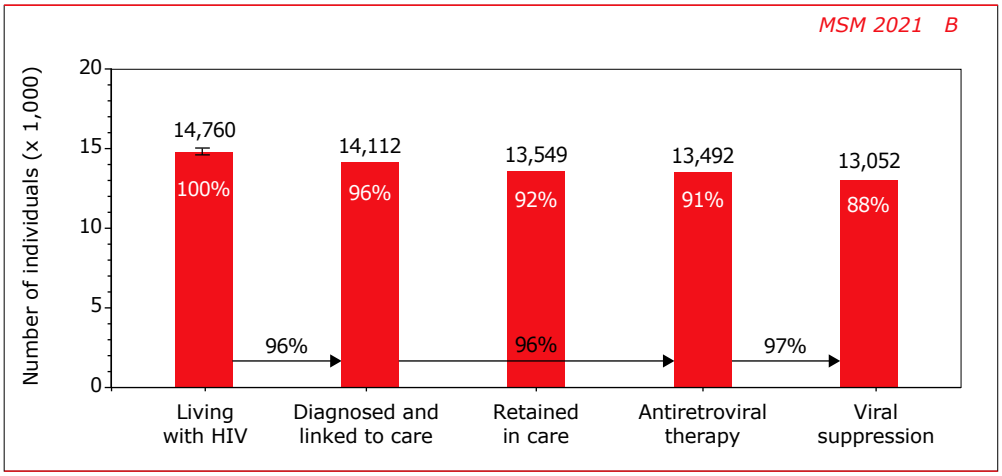
Continuum of HIV care – national level

The total number of people with HIV by the end of 2021 was 24,110 (95% CI 23,910-24,500), including the estimated 1,400 (1,190-1,790) who remained undiagnosed[10]. Adjusted for registration delays, of this total:

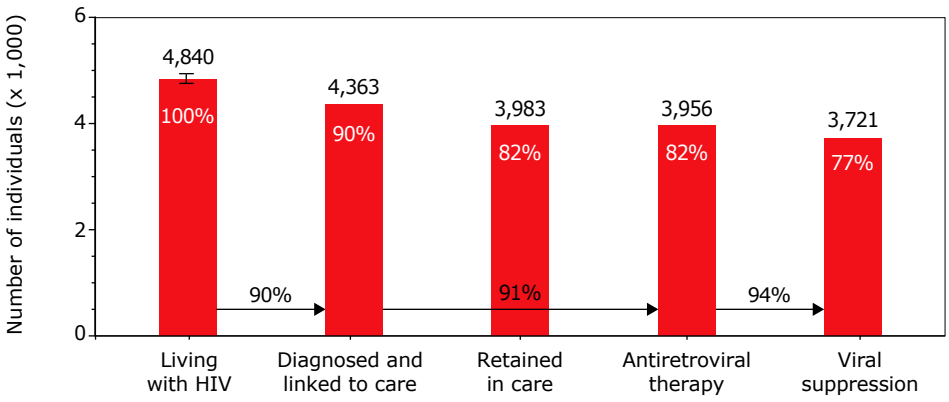
- 22,712 individuals (94% of the total number of people with HIV) had been diagnosed, linked to care, and registered by SHM;
- 21,502 (89%, or 95% of those diagnosed and linked to care) were retained in care (i.e. they had at least one documented HIV RNA or CD4 count measurement, or a clinic visit in 2021) (*Figure 1.14A*);
- 21,397 (89%, or 94% of those diagnosed and linked to care) had started ART;
- 20,490 (85%, or 96% of those treated) had a most recent HIV RNA measurement below 200 copies/ml; and
- 20,046 (83%, or 94% of those treated) had a most recent measurement below 50 copies/ml.

Figure 1.14: *Continuum of HIV care for people with HIV in the Netherlands by the end of 2021: (A) the total population with HIV-1, (B) men who acquired HIV via sex with men (MSM), (C) other men, and (D) women. Percentages at the top of the bars are calculated relative to the number with HIV, while percentages at the bottom correspond to the UNAIDS' 95-95-95 targets for 2025. Numbers were adjusted to reflect reporting delays.*

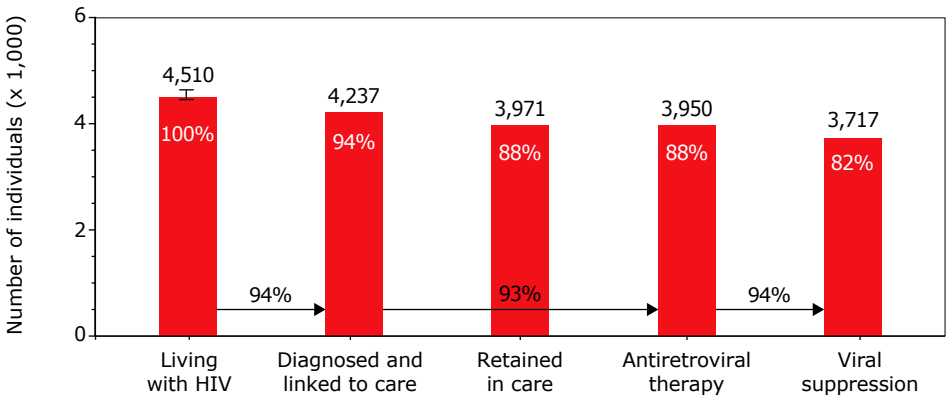




Other men 2021 C



Women 2021 D



Legend: *MSM = sex between men.*

Overall, 85% of the total estimated population with HIV and 90% of those diagnosed and ever linked to care had a suppressed viral load below 200 copies/ml. This means that by 2021 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 94-94-96, or 94-94-94 if 50 copies/ml is used as a threshold of viral suppression[11]. Of the people still in care by the end of 2021, 15,754 (73%, or 77% of those with a CD4 measurement) had a most recent CD4 count of 500 cells/mm^3 or higher, which was measured, at most, three years earlier.

Viral suppression

In total, 890 individuals (without adjusting for registration delays) had started therapy but did not have a suppressed viral load by the end of 2021. On closer inspection, 453 (51%) of these individuals did not have an HIV RNA measurement available in 2021; 339 (74%) of these 453 individuals had an RNA level below 200 copies/ml at their last measurement in 2020.

Of the 437 (49%) people with a viral load measurement and no viral suppression, 57 (13%) started therapy after their last available viral load measurement in 2021. Another 33 (8%) 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

In total, 2,046 individuals were lost to care by the end of 2021, and of these:

- 881 (43%) were last seen for care before the end of 2011;
- 571 (28%) in 2012-2017;
- 163 (8%) in 2018;
- 144 (7%) in 2019; and
- 287 (14%) in 2020[d].

The 881 individuals who were lost to care in or before 2011, 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 881 individuals were still living in the Netherlands by the end of 2021 without requiring care or ART during that ten-year period. Of the 1,165 individuals lost to care after 2011, 68% were born outside the Netherlands; this proportion was only 43% for those who were still in care by the end of 2021. This suggests that some of those lost to care may have moved abroad; in particular, back to their country of birth. It should be pointed out

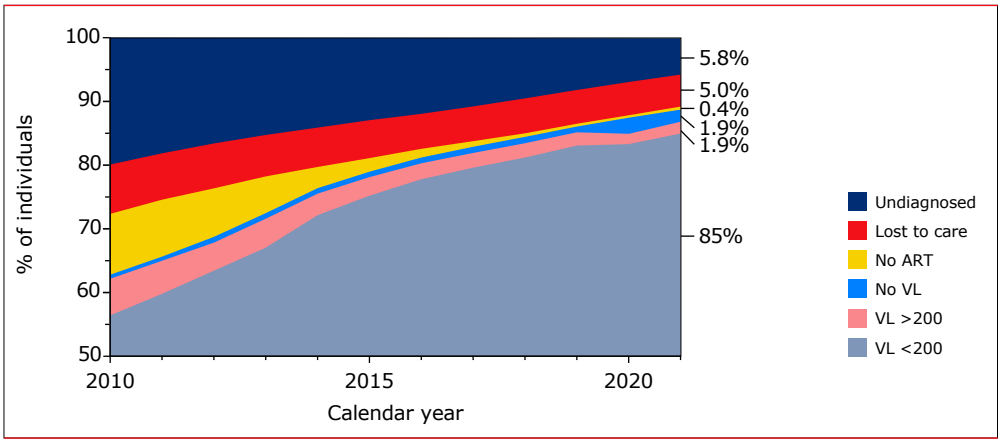
d *In addition to the 2,046 individuals lost to care there were 41 individuals who had already been diagnosed by the end of 2021 and were living in the Netherlands but entered care in 2022. These 41 individuals (44 with adjustment for registration delay), as well as the 1,165 lost to care after 2011 (1,166 with adjustment), are counted in the first and second stage of the continuum but not in the other stages.*

that 155 (13%) 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.

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 2021 (*Figure 1.15*). In 2010, 56% of the estimated 20,290 (95% CI 20,080-20,430) people with HIV had a suppressed viral load below 200 copies/ml, while this proportion was 85% in 2021. 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 2021, and, to a lesser extent, of a smaller proportion not yet on ART (10% in 2010, 0.4% in 2021).

Figure 1.15: *Estimated proportions of people with HIV across the various stages in the HIV care continuum. The numbers to the right of the graph are the proportions in 2021.*



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

The number of individuals with HIV who were likely to have an unsuppressed viral load by the end of 2021 was estimated to be 3,620, or 15% 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 2021 but it is likely that many now have viral load levels below 200 copies/ml, as they all started ART.

Continuum of care in MSM, other men, and women

The number of MSM with HIV at the end of 2021 was estimated at 14,760 (95% CI 14,570-15,100), of whom 650 (460-990) had yet to be diagnosed. Of these:

- 14,112 (96%) had been diagnosed and linked to care;
- 13,549 (92%) were still in care;
- 13,492 (91%) had started ART; and
- 13,052 (88%) had a most recent HIV RNA below 200 copies/ml.

In terms of the 2025 UNAIDS 95-95-95 target, this translates to 96-96-97, meaning that in MSM, the UNAIDS targets have already been met (*Figure 1.14B*). In total, 10,413 (77%, or 80% of those with a CD4 measurement) of MSM still in care by the end of 2021 had a CD4 count of 500 cells/mm^3 or higher at their last measurement in 2019-2021.

Among other men, the estimated number with HIV in 2021 was 4,840 (95% CI 4,750-4,940), including 480 (390-570) who were not yet diagnosed (*Figure 1.14C*). Of these:

- 4,363 (90%) men had been diagnosed and linked to care;
- 3,983 (82%) were still in care;
- 3,956 (82%) had started ART; and
- 3,721 (77%) had a suppressed viral load below 200 copies/ml.

The number of women with HIV was estimated to be 4,510 (4,590-45,210), of whom 270 (210-410) were not yet diagnosed (*Figure 1.14D*). Of these women:

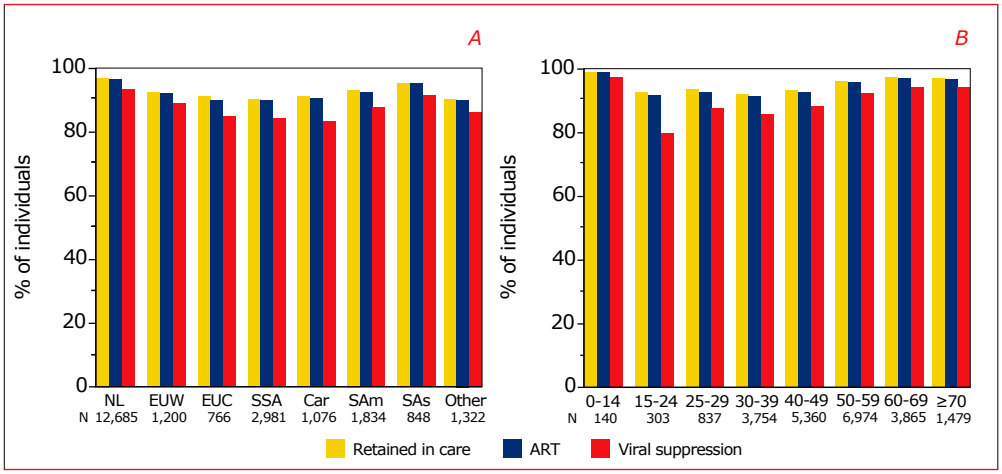
- 4,237 (94%) had been diagnosed and linked to care;
- 3,971 (88%) were still in care;
- 3,950 (88%) had started ART; and
- 3,717 (82%) had a suppressed viral load below 200 copies/ml.

Among women and other men still in care by the end of 2021, the proportion with viral suppression was 94%, which was somewhat lower than among MSM (96%).

Continuum of care by region of origin and age

Individuals of Dutch origin generally engaged more with the various stages of the care continuum than people from other countries (*Figure 1.16A*). Engagement with all stages of the care continuum was highest among the youngest age group. Levels of engagement were generally lower in the other age groups, but both the proportion of people who were still in care and the proportion who had started ART by the end of 2021, increased with age, and exceeded 95% in people aged 50 years or older (*Figure 1.16B*). As a consequence, the proportion of people with viral suppression also increased with age; rising from 80% among those aged 15 to 24 years, to more than 90% for people aged 50 years or older.

Figure 1.16: *Continuum of HIV care: (A) by region of origin, and (B) by age group for the total 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; 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 2020

We re-estimated the continuum of HIV care for 2020 and found that, by the end of that year, there were 24,130 (95% CI 23,930-24,380) people with HIV in the Netherlands, which was similar to the estimated 24,000 (23,700-24,500) outlined in last year's report[12]. While the number diagnosed (22,446 compared to 22,336), the number retained in care (21,195 compared to 21,155), and the number of those who started ART (21,097 compared to 21,027) were very similar to last year's report, the number with viral suppression (20,104 compared to 19,925) was somewhat higher in the re-estimation. This is because most of the backlog in the collection of 2020 data on viral load measurements has now been cleared.

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[e] in the Netherlands, and for the four largest cities in the country (*Table 1.4*). By the end of 2021, 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 530 (43%) 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 83% and 88%. 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 1.5*).

In total, 10,310 (95% CI 10,270-10,450) people with HIV were estimated to be living in the four largest cities in the Netherlands, which amounts to 43% of the total number of people in the country with HIV. Of these 10,310 people, 400 (350-540) were estimated to be undiagnosed (29% of the national estimate of 1,400 individuals with an undiagnosed HIV infection). Of the four cities, Amsterdam had the largest population of people with HIV; an estimated 6,350 (6,330-6,410) individuals, of whom 170 (140-230) were still undiagnosed (*Table 1.4*). Of the 10,310 people with HIV in the four largest cities:

- 9,913 (96%) had been diagnosed and linked to care;
- 9,359 (91%, or 94% of those diagnosed) had started ART; and
- 8,975 (87%, or 96% of those on therapy) had a suppressed viral load.

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

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 1.4* and *1.5*, 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 1,220 (95% CI 1,130-1,420) individuals living with undiagnosed HIV across the eight STI surveillance regions, is reasonably close to the number of 1,400 (1,190-1,790) 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 1.4: Continuum of care by the end of 2021 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 209 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	130	1,420	1,294	91
	80-200	1,380-1,500		*91*
Oost	160	2,690	2,526	94
	130-210	2,650-2,730		*94*
Noord-Holland/Flevoland	290	9,060	8,762	97
	250-360	9,000-9,120		*97*
Utrecht	60	1,380	1,314	95
	40-90	1,360-1,400		*95*
Zuid-Holland Noord	120	1,810	1,684	93
	90-200	1,770-1,880		*93*
Zuid-Holland Zuid	240	3,780	3,537	94
	200-330	3,730-3,860		*94*
Zeeland/Brabant	150	2,550	2,402	94
	110-200	2,510-2,600		*94*
Limburg	60	1,040	984	95
	30-100	1,020-1,080		*95*
Total	1,220	23,720	22,503	95
	1,130-1,420	23,630-23,920		*95*
City				
Amsterdam	170	6,350	6,181	97
	140-230	6,330-6,410		*97*
Rotterdam	110	2,090	1,980	95
	80-180	2,060-2,160		*95*
Den Haag	90	1,310	1,217	93
	50-160	1,270-1,380		*93*
Utrecht	30	570	535	95
	20-70	560-610		*95*
Total	400	10,310	9,913	96
	350-540	10,270-10,450		*96*

Retained in care		Antiretroviral therapy		Viral suppression	
n	%	n	%	n	%
1,235	87	1,228	86	1,175	83
			95		*96*
2,448	91	2,437	91	2,346	87
			96		*96*
8,272	91	8,240	91	7,892	87
			94		*96*
1,256	91	1,250	91	1,217	88
			95		*97*
1,604	89	1,594	88	1,494	83
			95		*94*
3,359	89	3,330	88	3,169	84
			94		*95*
2,265	89	2,260	89	2,179	85
			94		*96*
922	89	917	88	882	85
			93		*96*
21,360	90	21,257	90	20,354	86
			94		*96*
5,868	92	5,849	92	5,629	89
			95		*96*
1,869	90	1,851	89	1,772	85
			93		*96*
1,155	88	1,146	88	1,074	82
			94		*94*
516	91	513	91	499	88
			96		*97*
9,408	91	9,359	90	8,975	87
			94		*96*

Table 1.5: 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 2021. Proportions are given relative to the number of people diagnosed and linked to care.

	Diagnosed and linked to care	Retained in care	
Public health service region	**n**	**n**	**%**
Noord			
Groningen	613	586	96
Fryslân	382	367	96
Drenthe	298	281	94
Oost			
IJsselland	377	366	97
Twente	457	446	98
Noord- en Oost-Gelderland	516	505	98
Gelderland Midden	754	724	96
Gelderland-Zuid	421	406	96
Utrecht			
Regio Utrecht	1,314	1,256	96
Noord-Holland/Flevoland			
Flevoland	583	539	92
Gooi & Vechtstreek	302	286	95
Hollands Noorden	457	429	94
Zaanstreek-Waterland	388	364	94
Amsterdam	6,436	6,113	95
Kennemerland	595	540	91
Zuid-Holland Noord			
Haaglanden	1,684	1,604	95
Zuid-Holland Zuid			
Hollands Midden	573	547	95
Rotterdam-Rijnmond	2,649	2,508	95
Dienst Gezondheid & Jeugd ZHZ	314	303	96
Zeeland/Brabant			
Zeeland	247	230	93
West-Brabant	604	584	97
Hart voor Brabant	868	822	95
Brabant-Zuidoost	683	629	92
Limburg			
Limburg-Noord	412	383	93
Zuid Limburg	572	539	94
Unknown	209	142	68
Total	**22,712**	**21,502**	**95**

	Antiretroviral therapy		Viral suppression	
	n	%	n	%
	585	95	560	91
	365	96	352	92
	278	93	264	88
	364	97	352	93
	442	97	429	94
	503	97	489	95
	723	96	688	91
	405	96	389	92
	1,250	95	1,217	93
	536	92	512	88
	283	94	270	89
	428	94	403	88
	363	93	340	88
	6,090	95	5,861	91
	540	91	505	85
	1,594	95	1,494	89
	543	95	517	90
	2,486	94	2,364	89
	301	96	289	92
	229	93	214	86
	581	96	560	93
	822	95	794	91
	628	92	612	90
	381	92	366	89
	536	94	516	90
	140	67	135	65
	21,397	**94**	**20,490**	**90**

Trans people

Geographical region of origin

Of the 29,571 individuals with an HIV-1 infection, 285 were trans people; 272 (95%) trans women and 13 (5%) trans men. In this group of 285 individuals, the most commonly-reported regions of origin were South America (104, 36%), the Caribbean (59, 21%), the Netherlands (58, 20%) and south and southeast Asia (28, 10%). Interestingly, many of the trans people originated from only a few specific countries. Among the 104 individuals from South America, there were 28 people from Ecuador, 22 from Brazil, 14 from Colombia, 11 from Venezuela, and 11 from Suriname. Most frequently reported countries of origin in the Caribbean were the former Netherlands Antilles (23) and Cuba (14), while 13 people from south and southeast Asia originated from Thailand.

In total, 71 trans people, or 31% of those born abroad, had a documented HIV-1 diagnosis before moving to the Netherlands. The majority (52) of these 71 people had already started ART before arrival. By the time these 52 people entered HIV care in the Netherlands, 36 (69%) had HIV RNA levels below 200 copies/ml, which was lower than in cis people of whom 83%, or 1,441 out of 1,731, had RNA levels below 200 copies/ml.

Diagnosis

Among the 40 trans individuals diagnosed in 2019 or later while living in the Netherlands, 13 were diagnosed with a late-stage HIV infection, which is 39% of the 33 people for whom the stage of infection could be classified. In total, among the individuals diagnosed in 2019 or later, 13 had a negative HIV test in the 12 months prior to diagnosis, eight of them in the six months prior to diagnosis. The 40 trans people were relatively young at the time of their HIV diagnosis, with a median age of 31 years (IQR 28-41), and most of them (31) were born abroad.

Population in care

In total, 233 (82%) of the 285 trans individuals with HIV-1 were known to be in clinical care by the end of 2021. Of the 52 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 (18), were only diagnosed with HIV in 2022 (two), or only moved to the Netherlands in 2022 (one). In total, 13 of the people who moved abroad and ten 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 (228, or 98%), had started ART by the end of 2021. Of the 221 people in care with a viral load measurement in 2021, 212 (96%) had a last measurement in that year below 200 copies/ml; this proportion was 97% when considering individuals who had started therapy. The most recent CD4 count in 2019-2021 of those in care stood at a median of 729 (IQR 530-989) cells/mm^3, which was comparable to the CD4 counts in the total population in care.

HIV-2

In total, 101 of the 30,850 registered individuals with HIV acquired an HIV-2 infection (46 men and 55 women); 17 of these were diagnosed in 2011 or later. The majority (80, or 79%), acquired their infection via heterosexual sex. HIV-2 is endemic in West Africa, and 65 people originated from this region, mostly from Ghana (25 people) or Cape Verde (24 people). Twenty-two individuals were born in the Netherlands.

Population in care

By the end of 2021, a total of 61 people were still in clinical care, 21 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 62 years (IQR 56-66); 54 (89%) individuals were 50 years or older. The majority (82%) of those in care had been living with HIV-2 for more than 10 years, while 38% had been living with it for more than 20 years.

Clinical condition

Of the 61 people still in care, 51 had a most recent viral load measurement below 500 copies/ml, and 10 people had no available HIV-2 RNA result in 2021; there was no one with a viral load above 500 copies/ml. Most people in care (44, 66%) had started ART. Of the 17 individuals who were still in care but had yet to start therapy, 15 had a viral load measurement below 500 copies/ml, while the other two people had no RNA measurement in 2021. CD4 counts in the group of 61 people in care were a median of 635 (IQR 480-957) 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. This downward trend continued in 2021 with approximately 427 new diagnoses, although there is a degree of uncertainty around this figure because, at the time of writing, not all people diagnosed in 2021 have been registered in the SHM database. 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.

Although the number of consultations (excluding those that fall within the national PrEP pilot programme) at sexual health centres in 2020 were down 26% on 2019, and still 6% lower in 2021[1], our data did not show a reduction in the proportion diagnosed with HIV at these locations. One reason for this may be that decreased testing for HIV was partially offset by stricter triaging. In addition, testing for HIV at other locations – particularly at general practices – was also scaled back in 2020: for 2021 our data showed a proportional increase in those diagnosed at a hospital and a corresponding fall in those diagnosed at a general practice.

A large proportion (53%) of newly diagnosed individuals already had late-stage HIV infection (i.e. CD4 counts below 350 cells/mm^3 or AIDS) at the time of diagnosis. The downward trend in the proportion diagnosed with late-stage HIV 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 94-94-96[13].

National Action Plan on STIs, HIV and Sexual Health 2017–2022
One of the goals set by the National Action Plan on STIs, HIV and Sexual Health is to achieve a 50% reduction in the annual number of newly diagnosed HIV infections by 2022, compared with 2015 figures[14]. In 2021, there were approximately 427 newly diagnosed infections, which is a reduction of 52%, compared to the 898 diagnoses in 2015.

A second goal in the National Action Plan is to reach the Joint United Nations Programme on HIV/AIDS' (UNAIDS) 95-95-95 target by 2022, three years earlier than the UNAIDS' target year of 2025. By the end of 2021, the overall estimate in the Netherlands stood at 94-94-96, while in MSM the National Action Plan target had been reached (96-96-97). Earlier diagnosis of people with HIV, optimising indicator condition-driven testing, and retaining people in care will all be key to reaching and surpassing this specific goal in all groups affected by HIV.

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 2020 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, 1,165 individuals who were (1) diagnosed in or before 2021, (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 2021, 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. Worryingly, 13% 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. Unfortunately, current privacy regulations prohibit following-up on these individuals until SHM is notified of their arrival by their new centre.

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 1.16B* 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. In order to more fully achieve a sustained and steeper reduction in the number of new HIV infections, ART, prevention, and especially testing need to be scaled up even further. Major steps towards achieving this goal would be easy access to community-based or home-based HIV testing, promoting HIV indicator condition-guided testing by healthcare professionals, and increasing awareness of sexual risk behaviour.

A substantial number of individuals are still diagnosed with late-stage or advanced HIV infection. This is the case even among MSM, despite a high proportion of this group being diagnosed within a year of infection. Clearly, there are groups of MSM and other populations that the existing prevention and testing approaches do not reach. A recent study within the HIV Transmission Elimination Amsterdam

Initiative (H-TEAM) showed that important factors for receiving a late-stage HIV diagnosis were: people's personal relationship with health professionals; low-risk perceptions; fear related to the outcome of testing; institutional barriers and missed opportunities during client-provider interactions[15]. These findings will provide input for the design and implementation of integrated HIV testing and health check interventions aimed at, and developed together with, key affected populations.

References

1. van Wees DA, Visser M, van Aar F, et al. *Sexually Transmitted Infections in the Netherlands in 2021*. National Institute for Public Health and the Environment, Ministry of Health, Welfare and Sport; 2022. doi:10.21945/RIVM-2022-0023
2. Tavoschi L, Gomes Dias J, Pharris A, et al. New HIV diagnoses among adults aged 50 years or older in 31 European countries, 2004–15: an analysis of surveillance data. *Lancet HIV*. 2017;4(11):e514-e521. doi:10.1016/S2352-3018(17)30155-8
3. Antinori A, Coenen T, Costagiola D, et al. Late presentation of HIV infection: a consensus definition. *HIV Med*. 2011;12(1):61-64. doi:10.1111/j.1468-1293.2010.00857.x
4. Sasse A, Florence E, Pharris A, et al. Late presentation to HIV testing is overestimated when based on the consensus definition. *HIV Med*. 2016;17(3):231-234. doi:10.1111/hiv.12292
5. Nederlandse Vereniging van HIV Behandelaren. Hoofdstuk 2. Therapie bij volwassenen. Accessed August 8, 2022. http://richtlijnhiv.nvhb.nl/index.php/Hoofdstuk_2._Anti-retrovirale_therapie_bij_volwassenen
6. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *N Engl J Med*. 2011;365(6):493-505. doi:10.1056/NEJMoa1105243
7. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA*. 2016;316(2):171-181. doi:10.1001/jama.2016.5148
8. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *Lancet*. 2019;393(10189):2428-2438. doi:10.1016/S0140-6736(19)30418-0
9. Supervie V, Marty L, Lacombe JM, Dray-Spira R, Costagliola D, FHDH-ANRS CO4 study group. Looking Beyond the Cascade of HIV Care to End the AIDS Epidemic: Estimation of the Time Interval From HIV Infection to Viral Suppression. *J Acquir Immune Defic Syndr*. 2016;73(3):348-355. doi:10.1097/QAI.0000000000001120

10. *ECDC HIV Platform Tool [Software Application]. Version 2.0.1*. European Centre for Disease Prevention and Control; 2021. https://www.ecdc.europa.eu/en/publications-data/hiv-platform-tool
11. Gourlay AJ, Pharris AM, Noori T, et al. Towards standardized definitions for monitoring the continuum of HIV care in Europe. *AIDS*. 2017;31(15):2053-2058. doi:10.1097/QAD.0000000000001597
12. van Sighem AI, Wit FWNM, Boyd A, Smit C, Matser A, van der Valk M. *Monitoring Report 2021. Human Immunodeficiency Virus (HIV) Infection in the Netherlands*. stichting hiv monitoring; 2021.
13. Joint United Nations Programme on HIV/AIDS (UNAIDS). *End Inequalities. End AIDS. UNAIDS Global AIDS Strategy 2021-2026*.; 2021. https://www.unaids.org/sites/default/files/media_asset/global-AIDS-strategy-2021-2026_en.pdf
14. David S, van Benthem B, Deug F, van Haastrecht P. *Nationaal Actieplan Soa, Hiv En Seksuele Gezondheid 2017-2022*. National Institute for Public Health and the Environment, Ministry of Health, Welfare and Sport; 2018. doi:10.21945/RIVM-2018-0034
15. Bedert M, Davidovich U, de Bree G, et al. Understanding Reasons for HIV Late Diagnosis: A Qualitative Study Among HIV-Positive Individuals in Amsterdam, The Netherlands. *AIDS Behav*. 2021;25(9):2898-2906. doi:10.1007/s10461-021-03239-3

Special reports

1.1 COVID-19 in people living with HIV in the Netherlands

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Introduction

The first case of SARS-CoV-2 infection in the Netherlands was documented on 27 February 2020[1]. By December 2021 an estimated cumulative 3.1 million individuals had become infected and 20,897 had died of COVID-19[2]. The majority of SARS-CoV-2 infections result in a self-limiting disease with minor or mild symptoms, but certain people are at increased risk of developing severe COVID-19, hospitalisation and death[3–5]. These include individuals who:

- are older;
- are male;
- belong to certain ethnic groups;
- have a lower socio-economic status;
- have underlying health conditions such as obesity, hypertension, renal dysfunction, diabetes mellitus, and cardiovascular disease;
- have certain congenital immunodeficiency syndromes;
- have haematological malignancies;
- have had solid organ transplants;
- are receiving immune-suppressive/-modulatory therapy[6].

Populations at risk of severe COVID-19-related outcomes

Geographical region of origin

Many studies from general population COVID-19 cohorts in Western countries have reported migrants and individuals belonging to non-Western ethnic groups to be at increased risk of COVID-19-related hospitalisation and death[7–14], with possible explanations including lower socio-economic status and a higher prevalence (and severity) of comorbid conditions.

In the general Dutch population, migrant and ethnic groups (people with a non-Western migrant background; the largest groups being of Dutch Antillean, Moroccan, Surinamese, Turkish and Ghanaian descent) had a higher risk of COVID-19 hospitalisation compared to those of Dutch origin[15]. There were also significant ethnic disparities in the associations between the presence of comorbidities and risk of COVID-19 hospitalisation; the presence of certain comorbidities heightened the risk of a severe COVID-19-related outcome for some ethnic groups, more than for others[16].

Individuals living with HIV

At present, data to determine *if* people with HIV (PWH) – and if so, which particular groups – are at increased risk of severe COVID-19 are inconclusive[17]. Studies have suggested either a similar[18–23] or an increased risk of severe outcomes[24–29] in PWH. A meta-analysis looking at the risk of COVID-19-related mortality in PWH, mainly including studies from North-America and Europe, reported a pooled relative risk of 1.23[30], which is very similar to the adjusted odds ratio of 1.29 reported by a large cohort study from the USA[31].

Underlying comorbidities and other general risk factors for severe COVID-19-related outcomes appear to play a larger role than HIV-related factors in PWH on antiretroviral therapy with well-controlled HIV-replication and preserved CD4 cell counts[32,33]. However it is important to point out that while most of these studies adjusted their analyses for age, sex, ethnicity and comorbidities, many of them were conducted as part of general COVID-19 population-based studies. Consequently they often did not have detailed data available on potentially relevant HIV-related parameters, such as use and type of antiretroviral therapy, plasma HIV-RNA levels, prior AIDS diagnoses, and current and nadir CD4 cell counts. As a result it remains unclear which people with HIV in particular are at increased risk of severe COVID-19-related outcomes. Finally, many of the risk factors for severe COVID-19 in the general population are more prevalent in PWH, and more research is needed to clarify whether a potential increased risk in PWH is driven by (i) differences in demographic characteristics, (ii) a high prevalence of non-HIV-related comorbidities, and/or (iii) HIV-related factors.

We report on the incidence of COVID-19 and risk factors for severe outcomes in the nationally representative adult population of PWH in the Netherlands using all available data collected up to 1 December 2021.

Methods

Data collection

Stichting hiv monitoring (SHM) has prospectively been collecting relevant HIV and antiretroviral therapy (ART) related data on all consenting PWH in the Netherlands[34] since 2001. As of November 2020 this was supplemented with automated electronic queries of HIV treatment centre electronic medical records (EMR) to quickly identify new diagnoses of SARS-CoV-2 infection. SHM prioritises additional data collection regarding diagnosis, disease severity, hospitalisations and outcomes of COVID-19 events, but it should be noted that data collection does not happen in real time. Consequently, there are delays between the COVID-19 event itself, the recording of information in the EHR at the treatment centre, and the moment SHM captures the data for analysis.

SHM data collection of COVID-19 events is based on the Case Report Forms of the International Severe Acute Respiratory and emerging Infection Consortium and World Health Organisation, or ISARIC-WHO CRF[35]. The main focus of our data collection is on hospitalised patients, as individuals diagnosed with mild COVID-19 who are not admitted to hospital rarely have reliable, detailed information documented in their HIV treatment centre EHRs. SHM has not (yet) established links to other COVID-19 providers and cohorts/datasets, so direct comparisons with other patient populations cannot be made at present. Data on SARS-CoV-2 vaccination levels are also not yet available.

Measures of COVID-19 disease severity

It was often impossible to record objective measures of COVID-19 disease severity as these data were not systematically recorded in the HIV treatment centre EHRs. This was particularly the case for individuals who were not hospitalised or those who were hospitalised in a different facility to the one where they receive HIV care. Risk factors for COVID-19-related hospitalisation and death were investigated using multivariable logistic regression including:

- Relevant demographics (age, sex at birth, region of origin)
- Established other risk factors (comorbidities)
- HIV-related parameters

The presence of the following comorbidities and conditions known to increase the risk for severe COVID-19 were taken into account:

- **Cardiovascular disease** (myocardial infarction; coronary artery bypass grafting; coronary angioplasty or stenting; and carotid endarterectomy);
- Stroke;
- **Non-AIDS-defining malignancies** (excluding non-melanoma skin cancers and premalignant lesions found at cervical/anal screening;
- **Chronic kidney disease** (eGFR below 30 ml/min/1.73 m^2);
- **Diabetes mellitus** (defined as having glycated haemoglobin levels above 52 mmol/mol and/or the use of antidiabetic medication);
- **Hypertension** (defined as the use of antihypertensive drugs and/or measured grade 2 [or higher] hypertension with systolic pressure at or above 160 mmHg and/or diastolic pressure at or above 100 mmHg;
- **Obesity** (body mass index over 30 kg/mm^2).

The association between these comorbidities and the risk of developing severe COVID-19 were investigated by (i) entering them into the regression models separately, and (ii) as a multimorbidity covariate, i.e. the sum of all seven conditions listed above. All reported p-values are two-sided, with p-values below 0.05 considered statistically significant.

Results

Incidence of COVID-19

Between 27 February 2020 and 31 December 2021, 2,301 primary SARS-CoV-2 infections were registered among 21,289 adult PWH. Of these, 2,281 (99.1%) were found to be SARS-CoV-2 PCR-positive and an additional 20 (0.9%) were SARS-CoV-2 PCR-negative but clinical assessment indicated that infection was highly likely nonetheless (*Table 1*).

An additional 264 possible SARS-CoV-2 infections were self-reported by individuals who had experienced mild symptoms that could have been caused by SARS-CoV-2 infection, but without PCR confirmation. These had mostly occurred in the early months of the epidemic in 2020, when SARS-CoV-2 testing was not yet widely available for mild cases. None of these possible infections resulted in hospitalisation and therefore they are not included in this report.

Incidence of COVID-19 hospitalisation

Of the 2,301 individuals with a registered SARS-CoV-2 infection, 158 (6.9%) were hospitalised, with 27 (1.2%) requiring intensive care unit (ICU) admission. Of the remaining 2,143 (93.2%) individuals, 50 (2.2%) did present with COVID-19 at an emergency room, but did not require hospitalisation.

Those diagnosed with a SARS-CoV-2 infection who were not hospitalised were very similar to the total population of PWH in care in the Netherlands at the end of 2020 in terms of demographics, comorbidities and HIV-related characteristics. The only exception was that they were substantially more likely to be born in a non-Western country (*Table 1*).

Those who were hospitalised for COVID-19 however, were older, more likely to have acquired HIV through heterosexual contact (in men, and to a lesser extent women), and more likely to be born in sub-Saharan Africa or Latin America and the Caribbean, than the total population of PWH in care in the Netherlands at the end of 2020.

Overall, men were not more likely to be hospitalised for COVID-19 than women, as the percentage of men among hospitalised patients (77.2%) was slightly lower than in the total population of PWH (81.9%). Each investigated comorbidity was much more prevalent among those hospitalised compared to those not hospitalised for COVID-19, also resulting in a higher multimorbidity count in the hospitalised group (*Table 1*). The median duration of hospitalisation was 6 days (IQR 3-14). Individuals who were admitted to the ICU remained hospitalised for a median of 19 days (12-34).

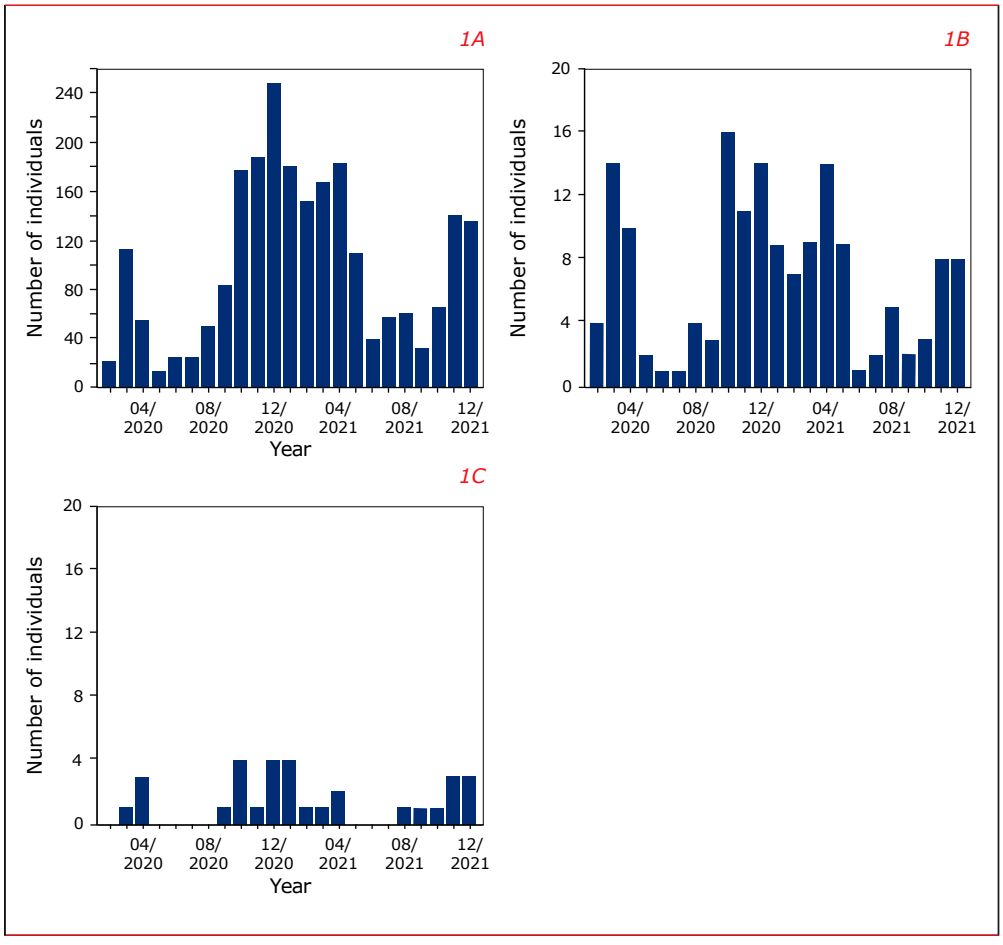
HIV-related characteristics

There were only minor differences between PWH who were diagnosed with COVID-19 but not hospitalised, and the total population of PWH, in terms of HIV-related characteristics. The vast majority of PWH receive ART, have a plasma HIV-1 viral load below 200 copies/ml and a high median CD4 cell count (above 500 cells/mm^3). There were, however, notable differences between PWH diagnosed with COVID-19 who *were* hospitalised and those who were not. Those who were hospitalised were on average 9.3 years older and, as a result, likely to have been living with HIV for longer. Furthermore, they had a lower median current and nadir CD4 cell count, and a higher prevalence of prior history of AIDS (*Table 1*).

Vaccinations

Figure 1 shows the number of registered SARS-CoV-2 infections, hospitalisations for COVID-19 and COVID-19-related deaths during the study period. The peaks and troughs of the epidemic waves in PWH largely resemble those observed for the general population of the Netherlands[1,2]. Vaccinations against SARS-CoV-2 in the Netherlands started in January 2021, with only the oldest PWH and those living in nursing homes initially eligible. From April 2021 all PWH became eligible for SARS-CoV-2 vaccination. Between June and December 2021 just 29 hospitalisations for COVID-19 were recorded, 16 of which occurred in individuals known to be vaccinated. Eight of these hospitalised patients died, four of which were known to be vaccinated.

Figure 1: *Incidence of COVID-19 diagnoses, hospitalisations and deaths over calendar time*



Risk factors for hospitalisation

Risk factors for COVID-19-related hospitalisation among PWH diagnosed with COVID-19, which were identified by multivariable logistic regression, included older age, migrant status (with higher risk for individuals originating from sub-Saharan Africa and to a lesser extent Latin America and the Caribbean), and a higher number of concomitant comorbidities. Additional factors identified as independently being associated with a higher risk of hospitalisation were (*Table 2*):

- a current CD4 count below 200 cells/mm^3
- a last measured HIV viral load of more than 200 copies/ml
- a history of prior AIDS

None of the other demographic, HIV and ART-related parameters were independently associated with a higher risk of being hospitalised following a diagnosis of SARS-CoV-2 infection. *Figure 2* shows the crude hospitalisation rates per age group, CD4 cell count category, and comorbidity count.

COVID-19-related mortality

In total, 31 (1.35%) out of the 2,301 PWH diagnosed with SARS-CoV-2 infection were reported to have died as a direct result of COVID-19. The observed mortality in the various age groups was (*Figure 2*):

- 0% (n=0) in 587 individuals aged 18-39 years;
- 0.2% (n=1) in 592 individuals aged 40-49 years;
- 0.7% (n=5) in 701 individuals aged 50-59 years;
- 3.1% (n=10) in 328 individuals aged 60-69 years;
- 13.0% (n=10) in 77 individuals aged 70-79 years; and
- 31.3% (n=5) in 16 individuals aged over 80 years.

COVID-19-related mortality was 13.9% (22) among the 158 who were hospitalised for COVID-19 and 37.0% (10) among the 27 who were admitted to the ICU.

Nine individuals (0.42%) died of COVID-19-related factors out of the 2,143 individuals who had *not* been hospitalised. Of those nine, eight were known to be living in a nursing home prior to being diagnosed with SARS-CoV-2 infection. The remaining individual was an unvaccinated 69-year-old Latin American man with a CD4 count below 500 cells/mm^3 and chronic renal failure due to HIV-related nephropathy.

Comorbidities and other risk factors for COVID-19-related mortality

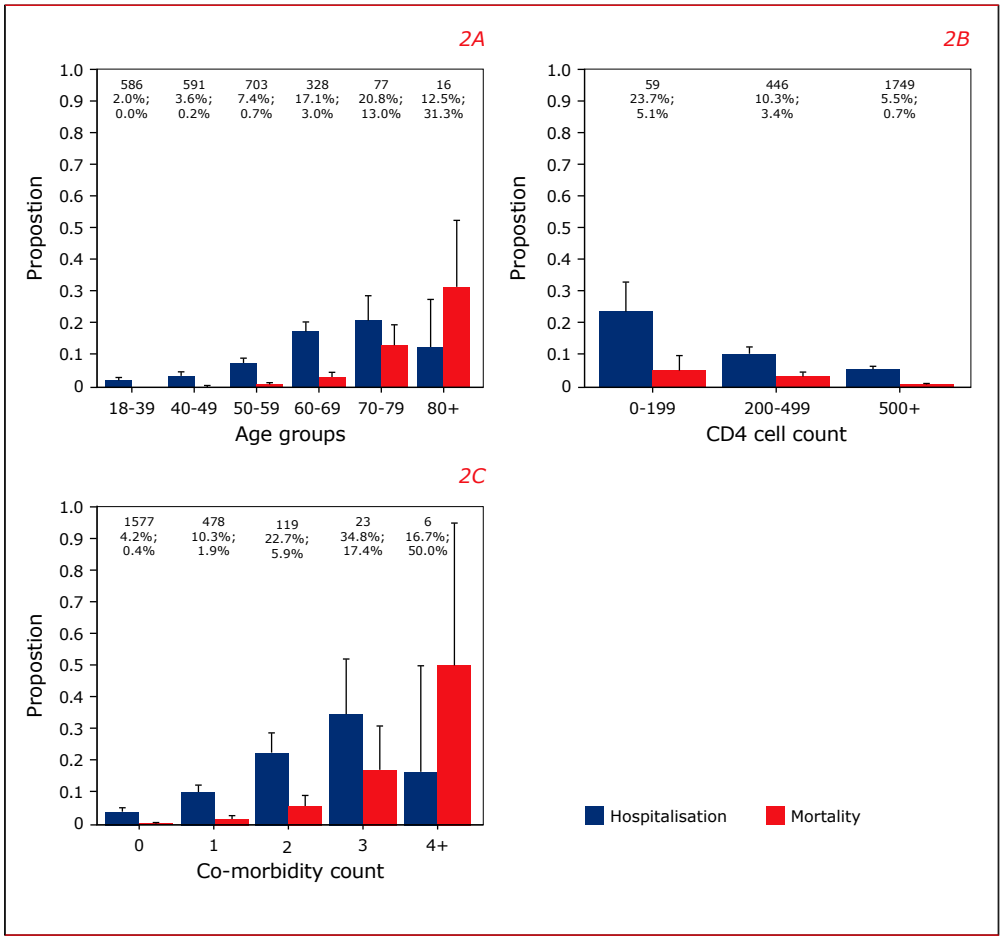
Table 3 shows the demographics, HIV-related characteristics and concomitant comorbidities of those who died of COVID-19 compared to those who recovered. As expected, there were very substantial differences between those who died of COVID-19 and those who survived, with the PWH who died of COVID-19 generally exhibiting poorer health at the onset of COVID-19, a higher number of concomitantly diagnosed comorbidities and less-favourable HIV-related parameters.

Because of the low number of COVID-19-related deaths, statistical power to formally explore risk factors using multivariable regression analysis was limited. Exploratory multivariable logistic regression models showed that independent risk factors for COVID-19-related mortality were (*Table 4*):

- Older age
- A Latin American origin
- A higher number of concomitantly diagnosed comorbidities
- A current CD4 cell count below 500/mm^3 (this risk increased further for CD4 cell counts below 200/mm^3)

Figure 2 shows the crude mortality rates per age group, CD4 cell count category, and comorbidity count.

Figure 2: Proportions of COVID-19-related hospitalisation and mortality by age group, CD4 cell count category, and comorbidity count



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

Ethnicity and severe COVID-19-related outcomes

We attempted to investigate possible differential associations between ethnicity and severity of COVID-19 for various comorbidities, but were limited by the low number of individuals diagnosed with each comorbidity. Only obesity, diabetes mellitus and hypertension were prevalent enough to allow for an exploratory analysis into hospitalisations for COVID-19. This consistently showed that people

of African origin diagnosed with one of these conditions were substantially more likely to be hospitalised for COVID-19, when compared with individuals from the other ethnic groups and native Dutch people diagnosed with the same conditions (data not shown). The number of COVID-19-related deaths in our cohort were too low to allow for any analysis of a possible interaction between ethnicity and comorbidities, even on an exploratory basis.

Discussion

Risk factors

Our analyses confirm that risk factors of severe COVID-19 in the general population also apply to PWH: older age; the presence of (multiple) comorbidities; and belonging to a non-Western migrant population all increase the risk of hospitalisation and/or death. The observed hospitalisation rates and mortality in PWH diagnosed with COVID-19 were very low in those aged below 50 years, but quickly increased in the older age strata. Independent of these general risk factors, having a low current CD4 cell count, and to a lesser extent uncontrolled HIV replication and a prior AIDS diagnosis, were also identified as risk factors. We did not observe an apparent protective effect of the concomitant use of tenofovir disoproxil, nor of any other commonly used antiretroviral agent, as has been reported by other cohorts[26]. Other Western COVID-19 cohorts of PWH found similar patterns of risk factors for severe COVID-19 outcomes[23,31,36–42].

Hospitalisation and mortality

The observed hospitalisation rate was 6.8% in all PWH diagnosed with COVID-19, and 1.2% were admitted to the ICU. The observed mortality rate in hospitalised individuals was 13.0%, and 31.3% for those admitted to the ICU. The mortality in PWH diagnosed with COVID-19 who were not hospitalised was very low (0.4%). Both the hospitalisation and mortality rates in non-hospitalised individuals is likely to represent an overestimation given that most cases of asymptomatic SARS-CoV-2 infection will have passed undiagnosed[43]. Furthermore eight of the nine PWH who were recorded as having died of COVID-19 without having been hospitalised, were already in poor health and living in nursing homes.

Migrant populations

In our study, migrants born in sub-Saharan Africa or Latin America and the Caribbean were at increased risk of hospitalisation and COVID-19-related mortality independent of age, comorbidities and HIV-related parameters. However, these findings should be interpreted with caution because of the limited number of events available for analysis, and the possibility of residual confounding. Migrant

populations in the Netherlands have been shown to be at greater risk of acquiring SARS-CoV-2 compared to the general population[44]. This may be related to a greater likelihood of a lower socio-economic status, which is associated with more crowded and multi-generational housing conditions, higher residential neighbourhood population density, and employment in front-line jobs where SARS-CoV-2 exposure is more likely[44]. Additionally, people with a migrant background with mild COVID-19 symptoms may be less willing to be tested and/or have more barriers to access testing, further increasing the estimates for the risk of serious outcomes in these populations[45].

Another factor that may contribute further to the observed higher risk of severe outcomes in PWH from non-Western migrant groups compared to PWH from the general Dutch population, could be a reduced willingness to be vaccinated against SARS-CoV-2[46–49]. However, it should be noted that most of the observed COVID-19-related mortality occurred before PWH became eligible for the national SARS-CoV-2 vaccination programme. Hence a lower vaccination rate could – at best – only partially explain the increased risk of hospitalisation and mortality in migrants.

Conclusions

We observed a low incidence of severe COVID-19 outcomes in the Dutch population of people living with HIV, very similar to what was observed in other Westerns cohorts of PWH. A major strength of our analysis is that we were able to account for both general and HIV-specific risk factors for severe COVID-19. As a result, we found that underlying comorbidities and other general risk factors for severe COVID-19-related outcomes play a larger role than HIV-related factors in PWH on antiretroviral therapy with well-controlled HIV infection and preserved CD4 cell counts.

Although in Western countries the risk of developing severe COVID-19 is slightly higher in the population of PWH as a whole compared to the general population, this risk is not distributed equally throughout the PWH population. It was found to be greater for:

- older people;
- those with (multiple) comorbidities;
- non-Western minority migrant groups; and
- those with less favourable HIV-related parameters (a small subgroup).

To illustrate this point, in the 707 PWH diagnosed with COVID-19 who were below the age of 50, with a CD4 cell count over 500, and no comorbidities, just 1.7% were hospitalised and none died of COVID-19.

Comorbidities are more prevalent in many populations of PWH than in the general population, either because of a higher prevalence of general risk factors for these comorbidities but possibly also because of the direct effects of HIV itself, as well as (prior) exposure to severe immune deficiency and antiretroviral therapy-related toxicities. As this higher comorbidity burden puts populations of well-treated PWH at increased risk for severe COVID-19 outcomes, HIV care providers should continue to prioritise addressing genuine concerns, misunderstandings, misinformation and other barriers to COVID-19 vaccination in PWH. This is important because vaccination (including timely application of boosters) remains a vitally important strategy for lowering the burden of severe COVID-19 disease in the population of PWH[50].

Table 1: Characteristics of all ATHENA cohort participants and individuals diagnosed with COVID-19

	All PWH	COVID-19, not hospitalised	Hospitalised with COVID-19
N	21,289	2,143	158
Age, years	51.2 (41.4-59.1)	48.8 (39.1-56.7)	58.1 (51.7-65.2)
Male sex	81.9%	80.0%	77.2%
HIV transmission category			
MSM	63.6%	63.6%	41.8%
Other men	18.3%	16.3%	35.4%
Women	18.1%	20.0%	22.8%
Region of origin			
Netherlands / Europe / North America	70.2%	59.6%	51.3%
Sub-Saharan Africa	12.0%	11.6%	20.3%
Latin America / Caribbean	12.6%	16.2%	18.4%
Other	5.2%	12.6%	10.1%
Years known to be living with HIV	12.5 (7.2-18.6)	11.9 (6.6-17.7)	16.0 (9.6-22.5)
On ART	97.9%	98.5%	99.3%
Current ART containing			
Tenofovir disoproxil	29.9%	29.6%	25.7%
Tenofovir alafenamide	42.8%	42.8%	44.7%
Abacavir	17.1%	15.0%	21.1%
Non-nucleoside RT inhibitor	31.1%	31.2%	29.6%
Protease inhibitor	15.7%	12.8%	23.0%
Integrase inhibitor	56.7%	59.9%	58.6%
HIV viral load >200 cps/mL	3.2%	2.2%	7.1%
Current CD4 count, mm^3	690 (510-908)	710 (533-901)	605 (400-830)
Nadir CD4 count, mm^3	248 (119-380)	260 (130-400)	160 (60-270)
Prior AIDS diagnosis	22.2%	18.1%	38.6%
Comorbidities			
Obesity (BMI>30 kg/m^2)	12.4%	13.8%	31.1%
Diabetes mellitus type 2	5.2%	4.6%	16.6%
Cardiovascular disease	3.6%	2.6%	8.6%
Stroke	1.8%	1.7%	7.3%
Hypertension (grade 2+ or on medication)	13.4%	11.8%	25.2%
Non-AIDS-defining malignancy	3.5%	2.4%	5.3%
Chronic kidney disease (eGFR<30 ml/min)	0.8%	0.6%	3.3%
Multimorbidity count			
0	69.0%	70.7%	37.8%
1	23.1%	22.4%	36.4%
2 or more	7.9%	6.9%	25.8%

Legend: *N (%) or median (IQR), as appropriate; MSM = men who have sex with men; eGFR = estimated glomerular filtration rate.*

Table 2: Independent predictors of hospitalisation among people living with HIV who were diagnosed with COVID-19

	Univariable		Multivariable	
Risk factor	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value
Male sex	0.78 (0.53-1.15)	0.21		
Age (per 10 years increase)	1.90 (1.64-2.20)	<0.0001	1.71 (1.44-2.03)	<0.0001
Region of birth				
Western	1.94 (1.24-3.04)	0.0036	-ref-	
Sub-Saharan Africa	1.41 (0.91-2.18)	0.12	2.06 (1.25-3.39)	0.0047
Latin America / Caribbean			1.31 (0.81-2.13)	0.28
Number diagnosed comorbidities (per 1 more)	2.29 (1.91-2.76)	<0.0001	1.73 (1.40-2.13)	<0.0001
Current CD4 cell count				
- 0 - 199	5.60 (2.88-1.10)	<0.0001	3.53 (1.65-7.57)	0.0012
- 200 - 499	2.07 (1.43-3.00)	0.0001	1.47 (0.98-2.20)	0.062
- 500+	-ref-		-ref-	
Nadir CD4 cell count (per 100 cells/mm^3 increase)	0.72 (0.64-0.80)	<0.0001		
HIV viral load >200 copies/mL	2.41 (1.49-3.92)	0.0004	1.98 (1.13-3.47)	0.017
Prior AIDS diagnosis	2.78 (1.97-3.93)	<0.0001	1.78 (1.16-2.72)	0.0010
Nucleoside-analogue RT inhibitor (NRTI)				
Tenofovir disoproxil	-ref-			
Tenofovir alafenamide	1.30 (0.86-1.97)	0.22		
Abacavir	1.63 (0.99-2.70)	0.058		
No NRTI	1.21 (0.67-2.16)	0.53		
Non-nucleoside RT inhibitor (NNRTI)				
EFV	-ref-			
DOR	0.43 (0.14-1.26)	0.12		
RPV	0.82 (0.35-1.96)	0.66		
Other	1.02 (0.47-2.22)	0.95		
No NNRTI	0.91 (4.8-1.73)	0.76		
Protease inhibitor (PI)				
DRV	-ref-			
ATV	0.36 (0.046-2.73)	0.32		
No PI	0.50 (0.33-0.76)	0.0010		
Integrase inhibitor (INSTI)				
DTG	-ref-			
BIC	1.06 (0.62-1.82)	0.82		
Other	1.02 (0.69-1.51)	0.19		
No INSTI	0.70 (0.41-1.20)	0.92		

Legend: 95% CI = 95% confidence interval.

Table 3: Characteristics of individuals diagnosed with COVID-19 who died of COVID-19 compared to those who survived

	Survived	Died of COVID-19
Number of individuals	2,270	31
Age, years	49.3 (39.6-57.0)	68.7 (60.9-78.2)
Male sex	79.8%	80.7%
HIV transmission category		
MSM	62.4%	45.2%
Other men	17.4%	35.5%
Women	20.2%	19.4%
Region of origin		
Netherlands / Europe / North America	59.3%	45.2%
Sub-Saharan Africa	12.2%	12.9%
Latin America / Caribbean	16.1%	32.3%
Other	12.5%	9.7%
Years known HIV-positive	12.1 (6.6-17.9)	22.1 (13.6-24.0)
On ART	98.6%	100%
HIV viral load >200 cps/mL	2.5%	3.3%
Current CD4 cell count, mm^3	710 (529-900)	417 (316-789)
Nadir CD4 cell count, mm^3	255 (130-390)	119 (62-220)
Prior AIDS diagnosis	19.3%	29.0%
Comorbidities		
Obesity (BMI>30)	15.0%	17.2%
Diabetes mellitus	5.2%	24.1%
Cardiovascular disease	2.9%	13.8%
Stroke	1.8%	27.6%
Hypertension (grade 2+ or on medication)	12.1%	55.2%
Non-AIDS-defining malignancy	2.5%	10.3%
Chronic kidney disease (eGFR<60 ml/min)	0.6%	20.7%
Multimorbidity count		
0	69.1%	17.2%
1	23.2%	31.0%
2	6.3%	27.6%
3	1.2%	13.8%
4 or more	0.2%	10.3%

Legend: N (%) or median (IQR), as appropriate; MSM = men who have sex with men; eGFR = estimated glomerular filtration rate.

Table 4: 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)	5.01 (3.18-8.17)	<0.0001
Region of birth		
Western	-ref-	
Sub-Saharan Africa	2.96 (0.72-12.1)	0.13
Latin America / Caribbean	3.32 (1.19-9.21)	0.021
Number of concomitantly diagnosed comorbidities (per 1 comorbidity increase)	2.11 (1.40-3.19)	<0.0001
Current CD4 cell count		
0-199	6.48 (1.22-34.54)	0.029
200-499	2.80 (1.15-6.84)	0.024
500+	-ref-	

Legend: 95% CI = 95% confidence interval.

References

1 Coronadashboard | COVID-19 | Rijksoverheid.nl. https://coronadashboard.rijksoverheid.nl/ (accessed 15 Jul 2022).

2 COVID-19 dataset. https://data.rivm.nl/covid-19/ (accessed 15 Jul 2022).

3 Wolff D, Nee S, Hickey NS, Marschollek M. **Risk factors for Covid-19 severity and fatality: a structured literature review**. *Infection* 2021; **49**:15–28.

4 Dessie ZG, Zewotir T. **Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients**. *BMC Infect Dis* 2021; **21**:1–28.

5 Li X, Zhong X, Wang Y, Zeng X, Luo T, Liu Q. **Clinical determinants of the severity of COVID-19: A systematic review and meta-analysis**. 2021; **16**:e0250602.

6 Fung M, Babik JM. **COVID-19 in Immunocompromised Hosts: What We Know So Far**. *Clin Infect Dis* 2021; **72**:340–350.

7 Sze S, Pan D, Nevill CR, Gray LJ, Martin CA, Nazareth J, *et al.* **Ethnicity and clinical outcomes in COVID-19: A systematic review and meta-analysis**.*EClinicalMedicine* 2020; **29–30**. doi:10.1016/J.ECLINM.2020.100630/ATTACHMENT/A9C41943-2A22-4676-9BD8-4DDD85B3FE05/MMC2.PDF

8 Passos-Castilho AM, Labbé A-C, Barkati S, Luong M-L, Dagher O, Maynard N, *et al.* **Outcomes of hospitalised COVID-19 patients in Canada: impact of ethnicity, migration status and country of birth**. *J Travel Med* 2022; **2022**:1–11.

9 Ramos-Rincon J-M, Cobos-Palacios L, López-Sampalo A, Ricci M, Rubio-Rivas M, Martos-Pérez F, *et al.* **Ethnicity and Clinical Outcomes in Patients Hospitalised for COVID-19 in Spain: Results from the Multicentre SEMI-COVID-19 Registry**. *J Clin Med 2022, Vol 11, Page 1949* 2022; **11**:1949.

10 Vanthomme K, Gadeyne S, Lusyne P, Vandenheede H. **A population-based study on mortality among Belgian immigrants during the first COVID-19 wave in Belgium. Can demographic and socioeconomic indicators explain differential mortality?** *SSM - Popul Heal* 2021; **14**. doi:10.1016/J.SSMPH.2021.100797

11 Rostila M, Cederström A, Wallace M, Brandén M, Malmberg B, Andersson G. **Disparities in Coronavirus Disease 2019 Mortality by Country of Birth in Stockholm, Sweden: A Total-Population–Based Cohort Study**. *Am J Epidemiol* 2021; **190**:1510–1518.

12 Indseth T, Grøsland M, Arnesen T, Skyrud K, Kløvstad H, Lamprini V, *et al.* **COVID-19 among immigrants in Norway, notified infections, related hospitalisations and associated mortality: A register-based study**. *Scand J Public Health* 2021; **49**:48–56.

13 Hayward SE, Deal A, Cheng C, Crawshaw A, Orcutt M, Vandrevala TF, *et al.* **Clinical outcomes and risk factors for COVID-19 among migrant populations in high-income countries: A systematic review**. *J Migr Heal* 2021; **3**. doi:10.1016/J.JMH.2021.100041

14 Price-Haywood EG, Burton J, Fort D, Seoane L. **Hospitalisation and Mortality among Black Patients and White Patients with Covid-19**. *N Engl J Med* 2020; **382**:2534–2543.

15 Coyer L, Wynberg E, Buster M, Wijffels C, Prins M, Schreijer A, *et al.* **Hospitalisation rates differed by city district and ethnicity during the first wave of COVID-19 in Amsterdam, The Netherlands**. *BMC Public Health* 2021; **21**:1–9.

16 Collard D, Stronks K, Harris V, Coyer L, Brinkman K, Beudel M, *et al.* **Ethnic Differences in Coronavirus Disease 2019 Hospitalisation and Hospital Outcomes in a Multiethnic Population in the Netherlands**. *Open Forum Infect Dis* 2022; **9**. doi:10.1093/OFID/OFAC257

17 Ambrosioni J, Blanco JL, Reyes-Urueña JM, Davies MA, Sued O, Marcos MA, *et al.* **Overview of SARS-CoV-2 infection in adults living with HIV**. *Lancet HIV* 2021; **8**:e294–e305.

18 Huang J, Xie N, Hu X, Yan H, Ding J, Liu P, *et al.* **Epidemiological, Virological and Serological Features of Coronavirus Disease 2019 (COVID-19) Cases in People Living With Human Immunodeficiency Virus in Wuhan: A Population-based Cohort Study**. *Clin Infect Dis* 2021; **73**:e2086–e2094.

19 Friedman EE, Devlin SA, McNulty MC, Ridgway JP. **SARS-CoV-2 percent positivity and risk factors among people with HIV at an urban academic medical centre**. *PLoS One* 2021; **16**. doi:10.1371/JOURNAL.PONE.0254994

20 Tesoriero JM, Swain CAE, Pierce JL, Zamboni L, Wu M, Holtgrave DR, *et al.* **COVID-19 Outcomes among Persons Living with or without Diagnosed HIV Infection in New York State**. *JAMA Netw Open* 2021; **4**.

21 Park LR, Sigel K R-BM. COVID-19 in the Largest US HIV Cohort. In: *AIDS 2020: 23rd International AIDS Conference Virtual; 6–10 July 2020.*; 2020. p. Abstract LBPEC23.

22 Inciarte A, Gonzalez-Cordon A, Rojas J, Torres B, de Lazzari E, de la Mora L, *et al.* **Clinical characteristics, risk factors, and incidence of symptomatic coronavirus disease 2019 in a large cohort of adults living with HIV: a single-centre, prospective observational study**. *AIDS* 2020; **34**:1775–1780.

23 Hadi YB, Naqvi SFZ, Kupec JT, Sarwari AR. Ch**aracteristics and outcomes of COVID-19 in patients with HIV: a multicentre research network study**. *AIDS* 2020; **34**:F3–F8.

24 Geretti AM, Stockdale AJ, Kelly SH, Cevik M, Collins S, Waters L, *et al.* **Outcomes of COVID-19 Related Hospitalisation Among People with HIV in the ISARIC WHO Clinical Characterisation Protocol UK Protocol: Prospective Observational Study**. *SSRN Electron J* 2020.

25 Boulle A, Davies M-A, Hussey H, Ismail M, Morden E, Vundle Z, *et al.* **Risk Factors for Coronavirus Disease 2019 (COVID-19) Death in a Population Cohort Study from the Western Cape Province, South Africa**. *Clin Infect Dis* 2021; **73**:e2005–e2015.

26 Del Amo J, Polo R, Moreno S, Díaz A, Martínez E, Arribas JR, *et al.* **Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy**. *Ann Intern Med* 2021; **174**:581–582.

27 Braunstein SL, Lazar R, Wahnich A, Daskalakis DC, Blackstock OJ. **Coronavirus Disease 2019 (COVID-19) Infection among People with Human Immunodeficiency Virus in New York City: A Population-Level Analysis of Linked Surveillance Data**. *Clin Infect Dis* 2021; **72**:E1021–E1029.

28 Sun J, Patel RC, Zheng Q, Madhira V, Olex AL, Islam JY, *et al.* **COVID-19 Disease Severity among People with HIV Infection or Solid Organ Transplant in the United States: A Nationally-representative, Multicentre, Observational Cohort Study**. *medRxiv Prepr Serv Heal Sci* Published Online First: 28 July 2021. doi:10.1101/2021.07.26.21261028

29 Hippisley-Cox J, Coupland CAC, Mehta N, Keogh RH, Diaz-Ordaz K, Khunti K, *et al.* **Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination: national prospective cohort study**. *BMJ* 2021; **374**. doi:10.1136/BMJ.N2244

30 Wang Y, Feng R, Xu J, Shi L, Feng H, Yang H. **An updated meta-analysis on the association between HIV infection and COVID-19 mortality**. *AIDS* 2021; **35**:1875–1878.

31 Yang X, Sun J, Patel RC, Zhang J, Guo S, Zheng Q, *et al.* **Associations between HIV infection and clinical spectrum of COVID-19: a population level analysis based on US National COVID Cohort Collaborative (N3C) data**. *Lancet HIV* 2021; **8**:e690–e700.

32 Johnston R. **The first 6 months of HIV-SARS-CoV-2 coinfection: outcomes for 6947 individuals**. *Curr Opin HIV AIDS* 2021; **16**:54–62.

33 Del Amo J, Polo R, Moreno S, Jarrin I, Hernan MA. **SARS-CoV-2 infection and coronavirus disease 2019 severity in persons with HIV on antiretroviral treatment**. *AIDS* 2022; **36**:161–168.

34 Boender TS, Smit C, Sighem A van, Bezemer D, Ester CJ, Zaheri S, *et al.* **AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort: cohort profile**. *BMJ Open* 2018; **8**:e022516.

35 WHO ISARIC COVID-19 Case Report Forms. https://isaric.org/research/covid-19-clinical-research-resources/covid-19-crf (accessed 15 Oct2021).

36 Dandachi D, Consortium HIVD 2019 (HIV–COVID-19), Geiger G, Consortium HIVD 2019 (HIV–COVID-19), Montgomery MW, Consortium HIVD 2019 (HIV–COVID-19), *et al.* **Characteristics, Comorbidities, and Outcomes in a Multicentre Registry of Patients With Human Immunodeficiency Virus and Coronavirus Disease 2019**. *Clin Infect Dis* 2021; **73**:e1964–e1972.

37 Hoffmann C, Casado JL, Härter G, Vizcarra P, Moreno A, Cattaneo D, *et al.* **Immune deficiency is a risk factor for severe COVID-19 in people living with HIV**. *HIV Med* 2021; **22**:372–378.

38 Kamis KF, Barbera L, Abdo M, Rowan SE, Hussain C, Gardner EM, *et al.* **Risk Factors for Hospitalisation in People With HIV and COVID-19**. *J Acquir Immune Defic Syndr* 2021; **88**:e22.

39 Virata MD, Shenoi S V., Ladines-Lim J, Villanueva MS, Barakat LA. **Cumulative burden of non-communicable diseases predicts COVID hospitalisation among people with HIV: A one-year retrospective cohort study**. *PLoS One* 2021; **16**:e0260251.

40 Shapiro AE, Bender Ignacio RA, Whitney BM, Delaney JA, Nance RM, Bamford L, *et al.* **Factors Associated With Severity of COVID-19 Disease in a Multicentre Cohort of People With HIV in the United States, March-December 2020**. *J Acquir Immune Defic Syndr* 2022; **90**:369–376.

41 Nomah DK, Reyes-Urueña J, Díaz Y, Moreno S, Aceiton J, Bruguera A, *et al.* **Sociodemographic, clinical, and immunological factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes in people living with HIV: a retrospective cohort study**. *Lancet HIV* 2021; **8**:e701–e710.

42 Varshney K, Ghosh P, Stiles H, Iriowen R. **Risk Factors for COVID-19 Mortality Among People Living with HIV: A Scoping Review**. *AIDS Behav* 2022; **26**:2256–2265.

43 Vos ERA, Den Hartog G, Schepp RM, Kaaijk P, Van Vliet J, Helm K, *et al.* **Nationwide seroprevalence of SARS-CoV-2 and identification of risk factors in the general population of the Netherlands during the first epidemic wave**. *J Epidemiol Community Heal* 2021; **75**:489–495.

44 Coyer L, Boyd A, Schinkel J, Agyemang C, Galenkamp H, Koopman ADM, *et al.* **Differences in SARS-CoV-2 infections during the first and second wave of SARS-CoV-2 between six ethnic groups in Amsterdam, the Netherlands: A population-based longitudinal serological study**. *Lancet Reg Heal - Eur* 2022; **13**:100284.

45 Embrett M, Sim SM, Caldwell HAT, Boulos L, Yu Z, Agarwal G, *et al.* **Barriers to and strategies to address COVID-19 testing hesitancy: a rapid scoping review**. *BMC Public Health* 2022; **22**:1–10.

46 Yousuf H, Van Der Linden S, Van Essen T, Gommers D, Scherder E, Narula J, *et al.* **Dutch Perspectives Toward Governmental Trust, Vaccination, Myths, and Knowledge About Vaccines and COVID-19**. *JAMA Netw Open* 2021; **4**:e2140529–e2140529.

47 Robinson E, Jones A, Lesser I, Daly M. **International estimates of intended uptake and refusal of COVID-19 vaccines: A rapid systematic review and meta-analysis of large nationally representative samples**. *Vaccine* 2021; **39**:2024–2034.

48 Neumann-Böhme S, Varghese NE, Sabat I, Barros PP, Brouwer W, van Exel J, *et al.* **Once we have it, will we use it? A European survey on willingness to be vaccinated against COVID-19**. *Eur J Heal Econ* 2020; **21**:977–982.
49 Abba-Aji M, Stuckler D, Galea S, McKee M. **Ethnic/racial minorities' and migrants' access to COVID-19 vaccines: A systematic review of barriers and facilitators**. *J Migr Heal* 2022; **5**:100086.
50 Boffito M, Waters L. **More evidence for worse COVID-19 outcomes in people with HIV**. *Lancet HIV* 2021; **8**:e661–e662.

Special reports

1.2 Prior use of pre-exposure prophylaxis

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Background

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs by people without HIV, to prevent HIV acquisition. Those at high risk of HIV acquisition in the Netherlands are eligible for the national PrEP pilot programme at the Sexual Health Centres (SHC) of the municipal Public Health Services (GGD), which was launched in September 2019. Prior to this, 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.

Data collection

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). SHM also retrospectively gathered information on prior use of PrEP by individuals who first entered into care between January 2018 and June 2019.

By 31 May 2022, data had been collected for 2,500 individuals. In 735 (29.4%) EMRs, information was available on prior use of PrEP. The proportion of individuals for whom this information was available increased from 10.6% in 2018, to 29.1% in 2019, 35.4% in 2020, 44.9% in 2021, and 56.6% in the first five months of 2022.

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 by MSM was slightly more likely to be available than it was for heterosexuals and other transmission categories. For transgender women however, this information was less likely to be available.

Main findings

Of the 735 individuals for whom information on prior use of PrEP was available, the majority (660, or 89.8%) reported no such use, whereas 75 (or 10.2%) reported prior PrEP use (*Table 2*). In terms of breakdown by gender:

- none of the 97 cisgender women reported prior PrEP use;
- none of the 17 transgender women reported prior PrEP use;
- 74 (12.0%) of the 616 cisgender men reported prior PrEP use; and
- one of the five transgender men reported prior PrEP use.

Of the 74 cisgender men and one transgender man, 71 men (94.7%) reported sexual contact with other men as the most likely mode of HIV acquisition. One man (1.3%) reported this to be sexual contact with women, while three men (4.0%) reported this to be another acquisition category or unknown.

The 75 individuals who reported prior use of PrEP were younger (median 31.2, IQR 26.2-40.9 years) than individuals who did not (median 38.0, IQR 29.7-49.7 years). They also had much higher median (IQR) CD4 counts (570 (360-740) vs. 360 (170-584) cells/mm^3). Individuals who had used PrEP were also less likely to be born outside of the Netherlands.

PrEP awareness and uptake

For 292 (44.3%) of the 660 individuals who reported no prior PrEP use, information was available on why they had not done so. 'Not knowing PrEP existed' (13.9%) and 'presumed to be at low risk for HIV' (13.2%) were the most commonly reported reasons.

Those who said that they did not know PrEP existed were of a similar age, but less likely to be of Dutch origin (33.7%) and more likely to have acquired HIV through heterosexual contact (52.2%).

In total, 39 (5.9%) individuals had wanted to start using PrEP but tested HIV-positive at screening before entry into a PrEP programme. Of these 39 individuals with high CD4 counts (median 510, IQR 370-770), 94.5% were MSM and 61.5% had evidence of recent HIV infection, as the majority frequently underwent HIV testing. Four individuals (0.6%) reported that they tested HIV-positive while on a PrEP programme waiting list.

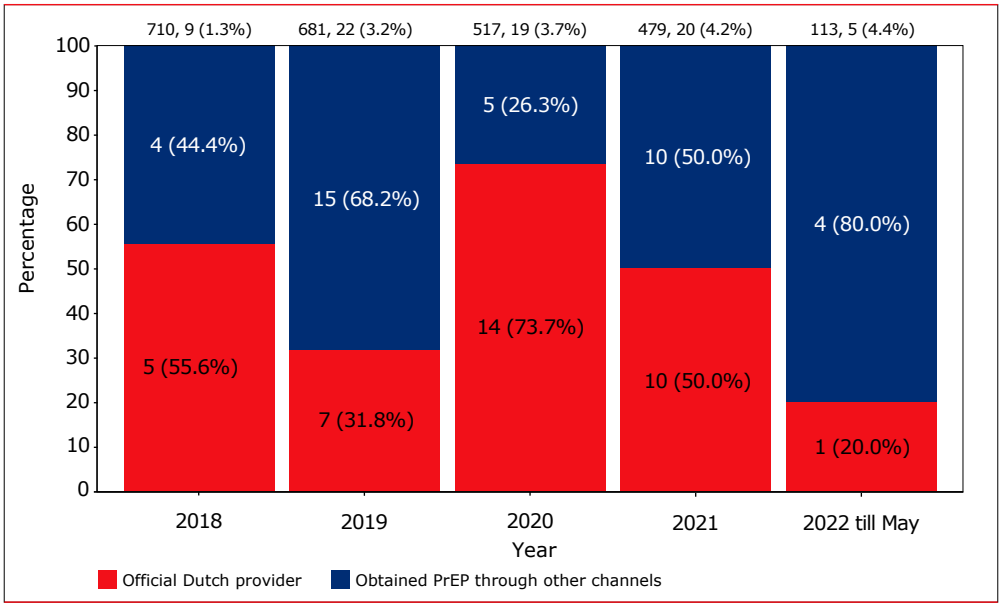
Prior use of PrEP upon entry into care

The percentage of people entering into care who reported prior PrEP use has remained stable since 2019 (P_{trend}=0.35, see Figure 1), with:

- 1.3%, or 9 out of 710 individuals, in 2018;
- 3.2%, or 22 out of 681 individuals, in 2019;
- 3.7%, or 19 out of 517 individuals, in 2020;
- 4.2%, or 20 out of 479 individuals, in 2021;
- 4.4%, or 5 out of 113 individuals, up to 31 May in 2022.

The characteristics of the 75 individuals who reported prior use of PrEP are shown in *Table 3*, with a stratification by calendar period. They do not differ significantly between those who entered into care before and after the start of the national PrEP pilot program.

Figure 1: *Time trends in the number and proportion of individuals with HIV first entering into care reporting prior use of PrEP, stratified by PrEP provider.*



Access to PrEP and usage patterns

Of the 75 individuals who reported prior PrEP use, 37 (49.3%) obtained it from a healthcare provider in the Netherlands, comprising:

- family practitioners (18, or 24.0%);
- the Municipal Health Service (15, or 20.0%); and
- HIV treatment centres (3, or 4.0%).

There was no further detailed information available for 1 individual (1.3%). The remaining individuals for whom this information was recorded, obtained their PrEP:

- from a buyers' club/internet/store outside of the Netherlands (16, or 21.3%);
- from a healthcare provider outside of the Netherlands (7, or 9.3%); or
- from a friend living with HIV who had donated some of their own medication (2, or 2.7%).

There was no information available for the remaining 13 (17.3%) individuals.

Just over half (40) of the 75 individuals who reported using PrEP, did so in the form of co-formulated tenofovir disoproxil / emtricitabine. One man used the drug Genvoya as PrEP (obtained through an unspecified route). For the remaining 34 men there was no further information available on the specific antiretrovirals used.

Dosage schedule information was available for 45 individuals (60.0%):

- 17 men (22.7%) reported on-demand use
- 20 men (27.7%) reported daily use
- 5 men (6.7%) reported intermittent use (i.e. a fixed schedule but not seven days a week)
- 3 men (4.0%) reported having used PrEP less than a week

For the remaining 30 men (40.0%), no dosage schedule information was available.

Of the 75 men who reported prior PrEP use, 19 (25.3%) had regular medical check-ups by the Public Health Service during that period. Five men (6.7%) attended an HIV treatment centre, 11 (14.7%) were seen by a family practitioner, and two men (2.7%) were checked by a medical specialist other than HIV treatment centre staff. Thirteen men (17.3%) did not have any medical check-ups, and there was no information available for the remaining 25 men (33.3%).

Forty-two (56.0%) of the 75 individuals were known or presumed to have HIV-seroconverted in the Netherlands, while 18 (24%) were known or presumed to have HIV-seroconverted before migrating to the Netherlands. For the remaining 18 (24%) this was unknown.

The median number of days between the last dose of PrEP and testing HIV-positive increased to 104 (0-232) days in the period after September 2019, up from a median of 39 (1.5-107) days in the period prior the September 2019. The number of individuals who tested HIV-positive while still using PrEP decreased from 14 (46.7%) in the period up to September 2019 to 14 (31.1%) in the period after September 2019.

In terms of demographic and HIV-related parameters, the 28 men who tested positive while still using PrEP were very similar to the total group of 75 men who reported prior PrEP use, although they were more likely to have evidence of HIV drug resistance. Of the 47 men who did not test HIV-positive while taking PrEP, 21 (44.7%) reported having tested HIV-seronegative after their last use of PrEP, while 22 (46.8%) did not have an HIV-test shortly after discontinuing the use of PrEP. There was no information available for 4 (8.5%) men.

PrEP and possible drug resistance

Genotypic resistance test results were available for 46 (or 61.3%) of the 75 men who reported having used PrEP when first entering HIV care. Reverse transcriptase (RT) resistance-associated mutations (RAM)[a] were detected in 14 (30.4%) cases. In nine men (19.6%), these may be associated with the use of PrEP:

- Nine individuals harboured an M184VI RT RAM (which decreases susceptibility to lamivudine and emtricitabine)
  - One of these also harboured a K65R RT RAM (which is selected for by tenofovir and decreases susceptibility to tenofovir, abacavir, lamivudine and emtricitabine)
- Four individuals harboured an E138A RT RAM (a known RT RAM that can be selected for by the use of rilpivirine but is also known to occur as a natural polymorphism, especially in non-B HIV-1 subtypes)
  - Two of the four were known to harbour HIV-1 subtype B and an M184V/I RT RAM[b]
    - One of these two individuals also harboured a K65R and a V108I RT RAM
- One individual was found to harbour a V103R (which may be a naturally occurring polymorphism) and no other RT RAM
- One individual was found to harbour an L74I (which decreases susceptibility to abacavir and didanosine) and no other RT RAM
- One individual was found to harbour an L74I, V103R, and V108I RT RAM (which is a non-polymorphic accessory mutation conferring decreased susceptibility to nevirapine and efavirenz)

It is worth noting that eight of the nine men in whom M184VI RT RAM (with or without K65R RT RAM) had been detected, said they had continued using PrEP for a while after their last HIV-negative test. Four of these men had acquired HIV in the Netherlands, three in another country in western Europe, and one in Colombia. The nine men last used PrEP in 2018 (n=2), 2019 (n=2), 2020 (n=3), and 2021 (n=2).

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.*

b *M184VI and M184V/I are used interchangeably here: they are a mixture of M184V and M184I in a single blood sample. They result in the same level of resistance as samples in which only M184V is detected.*

For the two individuals with HIV-1 subtype B and an M184V/I RT RAM, the results suggest that they may have acquired HIV from a person on a failing rilpivirine-containing regimen. However, it is not possible to determine whether the observed M184VI and K65R RAMs were also transmitted, or were selected for by their use of PrEP. One of the two tested HIV positive while still using on-demand PrEP. The other tested HIV positive on his first HIV test a few months after discontinuing on-demand PrEP. Both men are Europeans who tested HIV positive before migrating to the Netherlands.

The remaining 37 genotypic resistance tests exclusively yielded wild-type RT or naturally occurring polymorphisms that are probably unrelated to the prior use of PrEP. No major protease or integrase resistance-associated mutations were observed.

Prior use of PrEP and antiretroviral therapy (ART)

Data on the first-line ART and subsequent virological treatment response was available for 74 of the 75 individuals who reported prior use of PrEP. This includes the nine men with M184V/I (with or without K65R RT RAM), all of whom started a regimen containing an integrase inhibitor. Six of these combined the integrase inhibitor together with a protease inhibitor. The remaining three combined the integrase inhibitor with two nucleoside-analogue reverse transcriptase inhibitors, or NRTIs (tenofovir and emtricitabine, with either dolutegravir [n=2] or bictegravir [n=1]).

Of the remaining 65 individuals with no baseline resistance test results, or whose test showed no evidence of M184VI (with or without K65R RT RAM), 64 initiated a first-line regimen containing two NRTIs plus one of the following:

- an integrase inhibitor (n=39)
- a protease inhibitor (n=3)
- an integrase inhibitor plus a protease inhibitor (n=20)
- a non-nucleoside RT inhibitor (n=2)

Additionally, one individual initiated ART with lamivudine / dolutegravir.

In one of the nine individuals with an M184V (but without K65R) RT RAM, the first-line regimen was discontinued due to a persistent suboptimal virological efficacy. This individual's plasma viral load had initially become undetectable three months after starting on Biktarvy. However, in the following two-year period all eight recorded viral load measurements showed detectable viremia. The highest recorded value was 253 copies/ml. After this, ART was switched to another regimen, during which the viral load eventually became undetectable again.

For the 65 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 those with viral load measurements available at least four months after the initiation of ART showed an adequate initial virological treatment response. This is defined as a decrease to below 200 copies/ml. No subsequent viral breakthrough (above 200 copies/ml) was recorded, except in two individuals who temporarily interrupted the use of ART. They eventually re-suppressed after restarting the same ART regimen. The median duration of follow-up after the start of ART was 76.6 (IQR 33.4-126.3) weeks.

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	735 (29.4%)	1765 (70.6%)	
Age	37.6 (29.3-48.7)	38.1 (28.9-49.6)	0.975
Gender			<.001
Cisgender male	616 (83.8%)	1406 (79.7%)	
Cisgender female	97 (13.2%)	320 (18.1%)	
Transgender male	5 (0.7%)	1 (0.1%)	
Transgender female	17 (2.3%)	38 (2.2%)	
Dutch origin	370 (50.3%)	814 (46.1%)	0.059
Transmission category			<.001
MSM	505 (68.7%)	1033 (58.5%)	
Heterosexual transmission	176 (23.9%)	454 (25.7%)	
Other transmission categories	54 (7.3%)	278 (15.8%)	
Recent HIV inf. (<365 days after last neg. test)	206 (28.0%)	335 (19.0%)	<.001
CD4 at HIV diagnosis	376 (180-600)	360 (154-557)	0.012

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

	Prior use of PrEP	No prior use	p-value
Number of subjects	75 (10.2%)	660 (89.8%)	
Age	31.2 (26.2-40.9)	38 (29.7-49.7)	<.001
Gender			<.001
Cisgender male	74 (98.7%)	542 (82.1%)	
Cisgender female	0 (0.0%)	97 (14.7%)	
Transgender male	1 (1.3%)	4 (0.6%)	
Transgender female	0 (0.0%)	17 (2.6%)	
Dutch origin	34 (45.3%)	336 (50.9%)	0.395
Transmission category			<.001
MSM	71 (94.7%)	434 (65.8%)	
Heterosexual transmission	1 (1.3%)	175 (26.5%)	
Other transmission categories	3 (4.0%)	51 (7.7%)	
Recent HIV inf. (<365 days after last neg. test)	59 (78.7%)	147 (22.3%)	<.001
CD4 at HIV diagnosis	570 (360-740)	360 (170-584)	<.001
Reasons for not having used PrEP			
Did not know of PrEP		92 (13.9%)	
Wanted PrEP but had no access		44 (6.7%)	
Presumed to be at low risk for HIV		87 (13.2%)	
Knew of PrEP but did not want to use it		26 (3.9%)	
Tested positive at PrEP intake		39 (5.9%)	
Was on PrEP waiting list		4 (0.6%)	
Unknown		368 (55.8%)	

Table 3: characteristics of individuals who reported prior use of PrEP prior to or after the start of the national PrEP pilot program in September 2019

	2018-01 to 2019-09	2019-10 and later	p-value
Number of subjects	30 (40.0%)	45 (60.0%)	
Age	29.3 (25.6-36.3)	32.1 (27.4-46.4)	0.063
Gender			1.000
Cisgender male	30 (100%)	44 (97.8%)	
Transgender male	0 (0.0%)	1 (2.2%)	
Dutch origin	12 (40.0%)	22 (48.9%)	0.486
Transmission category			0.260
MSM	27 (90.0%)	44 (97.8%)	
Heterosexual transmission	1 (3.3%)	0 (0.0%)	
Other transmission categories	2 (6.7%)	1 (2.2%)	
Recent HIV inf. (<365 days after last neg. test)	23 (76.7%)	36 (80.0%)	0.778
Days between last neg. test and first CD4)	132 (55-216)	201 (95-347)	0.105
CD4 at HIV diagnosis	585 (420-750)	570 (347-740)	0.646
PrEP provider			0.201
Provider in the Netherlands	10 (33.3%)	27 (60.0%)	
- Public Health Service	4 (40.0%)	11 (40.7%)	
- HIV treatment center	0 (0.0%)	3 (11.1%)	
- Family practitioner	5 (50.0%)	13 (48.1%)	
- No info	1 (10.0%)	0 (0.0%)	
Provider outside of the Netherlands	4 (13.3%)	3 (6.7%)	
Buyers club/internet/store outside of the Netherlands	8 (26.7%)	8 (17.8%)	
From friend living with HIV	1 (3.3%)	1 (2.2%)	
No info	7 (23.3%)	6 (13.3%)	
ART used for PrEP			0.462
TDF/FTC	14 (46.7%)	26 (57.8%)	
Genvoya	0 (0.0%)	1 (2.2%)	
Unspecified	16 (53.3%)	18 (40.0%)	
ART schedule			0.786
On demand	5 (16.7%)	12 (26.7%)	
Daily	8 (26.7%)	12 (26.7%)	
Intermittent	3 (10.0%)	2 (4.4%)	
Unknown	13 (43.3%)	17 (37.8%)	
Used PrEP <1 week	1 (3.3%)	2 (4.4%)	

	2018-01 to 2019-09	2019-10 and later	p-value
Routine medical check-ups while on PrEP			0.754
Public Health Service	5 (16.7%)	14 (31.1%)	
Family practitioner	4 (13.3%)	7 (15.6%)	
HIV treatment center	2 (6.7%)	3 (6.7%)	
Other healthcare provider	1 (3.3%)	1 (2.2%)	
No medical check-ups	6 (20.0%)	7 (15.6%)	
No info	12 (40.0%)	13 (28.9%)	
Duration of PrEP use (days)	171 (36-428)	182 (30-599)	0.898
Days between last PrEP use and testing HIV-positive	39 (1.5-107)	104 (0-232)	0.200
Tested HIV-positive while on PrEP	14 (46.7%)	14 (31.1%)	0.225
HIV-negative test performed after last dose of PrEP			0.588
Yes	8 (50.0%)	13 (41.9%)	
No	6 (37.5%)	16 (51.6%)	
Unknown	2 (12.5%)	2 (6.5%)	
Seroconverted in the Netherlands or abroad			0.305
In the Netherlands	14 (46.7%)	27 (60.0%)	
Abroad	10 (33.3%)	8 (17.8%)	
Unknown	6 (20.0%)	10 (22.2%)	
Documented acute HIV infection (Fiebig 1-5)	2 (6.7%)	6 (13.3%)	0.464
Resistance test performed after testing HIV-positive	16 (53.3%)	30 (66.7%)	0.334
Resistance test findings in RT *			
M184V/I	4 (25.0%)	5 (16.7%)	
K65R	0 (0.0%)	1 (3.3%)	
V74I	0 (0.0%)	2 (14.3%)	
V103R	0 (0.0%)	2 (6.7%)	
V108I	0 (0.0%)	2 (6.7%)	
E138A	1 (6.3%)	3 (10.0%)	
No RT RAMs, only wild type or polymorphisms	12 (75.0%)	20 (66.7%)	
Resistance profile in RT **			
M184VI	3 (75.0%)	4 (40.0%)	
K65R,V108I,E138A,M184VI	0 (0.0%)	1 (10.0%)	
E138A,M184VI	1 (25.0%)	0 (0.0%)	
E138A	0 (0.0%)	2 (20.0%)	
V103R	0 (0.0%)	1 (10.0%)	
V74I	0 (0.0%)	1 (10.0%)	
V74I,V103R,V108I	0 (0.0%)	1 (10.0%)	

Legend: ** categories not mutually exclusive; ** complete RAM profile in RT.*

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 drug, even when combined with other drugs, cannot sufficiently prevent the selective pressures driving resistance. Over time, accumulation of mutations in the HIV genome that are associated with drug resistance can prevent sustained viral suppression, thereby increasing the risk of poor clinical outcomes[17-23].

In this chapter, we describe trends over time in the use of 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[24]. We also analyse the presence of transmitted and acquired HIV drug resistance. *Box 2.1* gives an overview of the number of people included in the various analyses described in this chapter.

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

Between 1996 and the end of 2021, a cumulative total of 29,128 individuals (aged 15 years or older at the time of diagnosis) were registered by SHM as with HIV-1 in the Netherlands

1. **Starting combination antiretroviral therapy**
   27,604 people were known to have initiated ART between January 1996 and December 2021.

2. **In care and on ART in the Netherlands in 2021**
   Of the 27,604 people who initiated ART between January 1996 and December 2021,
   ➔ 20,804 were in care by the end of 2021.

3. **Changes in the use of the initial ART regimen**
   Of the 27,604 people who initiated ART between January 1996 and December 2021,
   ➔ 4,767 initiated ART between January 2016 and December 2021.
   ➔ The most frequently used guideline-recommended initial regimens in 2016-21 were:

   - ABC/3TC/DTG (20.8%)
   - TAF/FTC/BIC (16.7%)
   - TDF/FTC/DTG (14.5%)
   - TAF/FTC/EVG/c (14.2%)
   - TDF/FTC/EFV (3.9%)
   - TDF/FTC/EVG/c (3.6%)
   - TAF/FTC/DRV/c (3.3%)
   - TDF/FTC/DRV/b (3.2%)
   - TAF/FTC/DTG (3.0%)

4. Virological response

Of the 27,604 people who initiated ART between January 1996 and December 2021,

➔ 23,443 people were ART-naïve, not pregnant at ART initiation, and had an HIV 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 2021, 8,637 HIV-1 sequences had been obtained from 8,327 ART-naïve people prior to initiation of ART in 2003-21.

➔ 8,627 reverse transcriptase sequences were available from 8,320 individuals.
➔ 8,133 protease sequences were available from 7,835 individuals.
➔ 202 integrase sequences were available from 201 individuals.

Acquired HIV drug resistance

As of December 2021, 4,587 HIV-1 sequences had been obtained from 2,757 people who received ART for at least four months in 2000-21.

➔ 3,225 sequences were from 2,021 people who had been ART-naïve before initiating ART.
➔ 4,511 reverse transcriptase sequences were available from 2,731 individuals.
➔ 4,343 protease sequences were available from 2,616 individuals.
➔ 371 integrase sequences were available from 295 individuals.

6. Immunological response

Of the 27,604 people who initiated ART between January 1996 and December 2021,

➔ 26,561 had CD4 cell count data available after initiating ART.

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, 27,604 individuals ever registered by SHM and monitored 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 2021 (*Box 2.1*). In *Table 2.1*, we have grouped people by calendar year of ART initiation: 9,578 started in 1996-2005, 6,084 in 2006-10, 7,175 in 2011-15, and 4,767 in 2016-21.

Of the 27,604 people known to have initiated ART since January 1996, 22,541 (81.7%) were men, of whom 16,760 (74.4%) were men who have sex with men (MSM). Overall, 15,123 (54.8%) originated from the Netherlands. Whereas the proportion of people from the Netherlands was stable over time, the region of origin for non-Dutch people changed. From 1996 onwards, there was a slight but steady increase in people from eastern and central Europe; from 2-3% prior to 2010, to 5.5% in 2011-15, and 10.3 in 2016-21. Simultaneously, the number of people from western Europe/North America/Australia decreased slightly from 10.0% in 1996-2005, to 5.4% in 2016-21. This was also true for sub-Saharan Africa; the number declined from 17.9% in 1996-2005, to 10.0% in 2016-21.

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 142 days (interquartile range [IQR] 33-731) for those who entered care in 2011, to:

- 36 days (IQR 17-83) in 2015;
- 25 days (IQR 11-48) in 2018;
- 23 days (IQR 9-47) in 2019;
- 19 days (IQR 8-42) in 2020; and
- 19 days (IQR 7-38) in 2021.

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 2021, 78.1% of this group initiated ART within one month, 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 (17.6%);
- between 6 and 12 months after diagnosis (1.7%); and
- more than one year after diagnosis (2.6%).

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 94.9% of people initiating ART in 2021 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 1996–2021.

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	1996–2021
Number of individuals		9,578	6,084	7,175	4,767	**27,604**
DEMOGRAPHIC						
Age at ART initiation (years)	Median	37.5	40.14	39.23	37.54	38.47
	Q1	31.76	32.85	30.79	29.15	31.3
	Q3	44.59	47.31	48.18	49.09	46.86
Male sex (at birth)	n	7,357	4,952	6,192	4,040	22,541
	%	76.7	81.4	86.4	85.1	81.6
Transmission risk group						
Missing	n	8	9	13	19	49
	%	0.1	0.1	0.1	0.3	0.1
Men who have sex with men	n	5,029	3,730	4,932	3,069	16,760
	%	52,5	61.3	68.7	64.4	60.7
Heterosexual contact	n	3,302	1,872	1,777	1,229	8,180
	%	34.5	30.8	24.8	25.8	29.6
Injecting drug use	n	539	110	44	35	728
	%	5.6	1.8	0.6	0.7	2.6
Blood or blood products*	n	170	48	61	54	333
	%	1.8	0.8	0.9	1.1	1.2
Vertical transmission	n	2	4	3	6	15
	%	0.02	0.1	0.04	0.1	0.1
Unknown	n	528	311	345	355	1,539
	%	5.5	5.1	4.8	7.5	5.6

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	1996–2021
Region of origin						
Missing	n	45	18	28	56	147
	%	0.5	0.3	0.4	1.2	0.5
The Netherlands	n	5,168	3,408	4,207	2,340	15,123
	%	54.0	56.0	58.6	49.1	54.8
Western Europe/North America/Australia	n	952	504	500	254	2,210
	%	9.9	8.3	7.0	5.3	8.0
Eastern/central Europe	n	179	210	391	483	1,263
	%	1.9	3.5	5.5	10.1	4.6
Latin America and the Caribbean	n	1,035	714	928	769	3,446
	%	10.8	11.7	12.9	16.1	12.5
Sub-Saharan Africa	n	1,705	881	671	469	3,726
	%	17.8	14.5	9.4	9.8	13.5
Other	n	494	349	450	396	1,689
	%	5.2	5.7	6.3	8.3	6.1
CLINICAL						
Recent infection (tested HIV-negative	n	580	939	1,721	1,146	4,386
<12 months before diagnosis)	%	6.1	15.4	24.0	24.0	15.9
Ever having tested HIV-negative	n	1,987	2,471	3,909	2,542	10,909
	%	20.8	40.6	54.5	53.3	39.5
CD4 cell count at start of ART	Median	190	243	353	379	270
	Q1	80	140	220	180	130
	Q3	320	330	500	570	410
HIV RNA (log_{10}) at start of ART	Median	4.9	5.0	4.8	4.8	4.9
	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	2,965	1,153	933	656	5,707
	%	31.0	19.0	13.0	13.8	20.7
Prior mono- or dual-NRTI treatment	n	2,027	54	26	31	2,138
at start of ART**	%	21.2	0.9	0.4	0.7	7.8
Hepatitis B status at start of ART						
HBV-negative (HBsAg-negative)	n	8,642	5,623	6,715	4,417	25,397
	%	90.2	92.4	93.6	92.7	92.0
HBV-positive (HBsAg-positive)	n	596	323	216	115	1,250
	%	6.2	5.3	3.0	2.4	4.5
Unknown	n	340	138	244	235	957
	%	3.6	2.3	3.4	4.9	3.5

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	1996–2021
Hepatitis C status at start of ART						
HCV-negative	n	8,669	5,773	6,903	4,509	25,854
	%	90.5	94.9	96.2	94.6	93.7
HCV RNA-positive	n	172	135	104	70	481
	%	1.8	2.2	1.5	1.5	1.7
HCV Ab seropositive	n	196	46	44	25	311
	%	2.1	0.8	0.6	0.5	1.1
Unknown	n	541	130	124	163	958
	%	5.7	2.1	1.7	3.4	3.5
ART started during pregnancy	n	403	231	140	85	859
	%	4.2	3.8	2.0	1.8	3.1

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 2012–21.

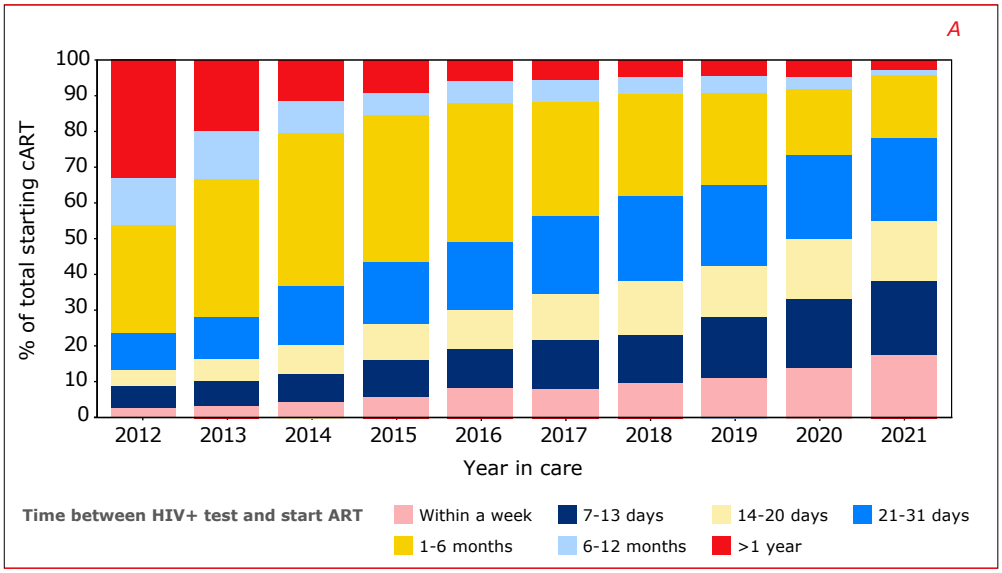
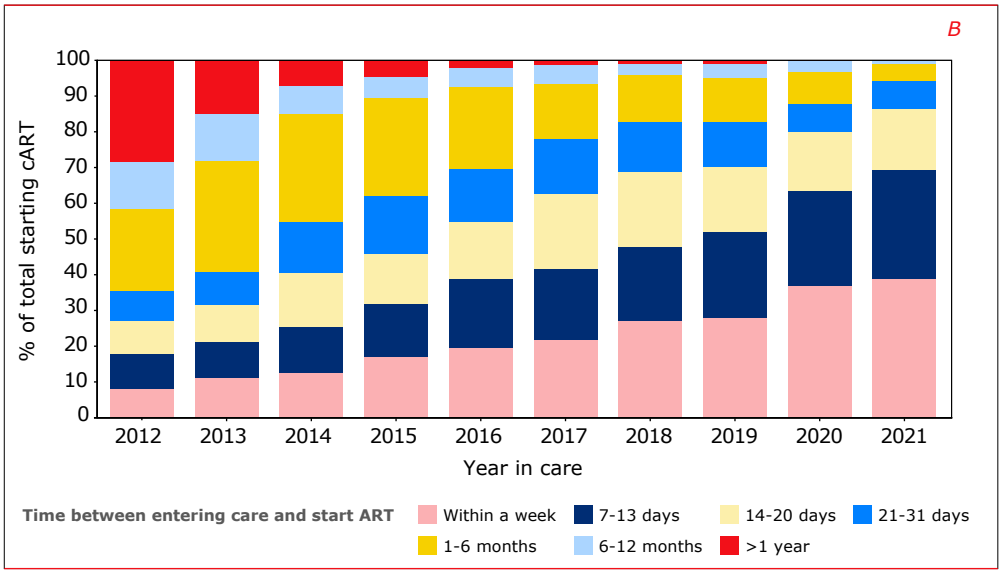


Figure 2.1B: Time between entry into HIV care and initiation of combination antiretroviral therapy (ART) for people starting ART in 2012–21.



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:

- 20.8% in the period 1996-2005;
- 40.6% in 2006-10;
- 54.5% in 2011-15; and
- 53.3% in 2016-21.

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 2006-10, 24.0% in 2011-15, and 24.0% in 2016-21.

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 2006-10;
- 353 cells/mm^3 (IQR 220-500) in 2011-15;
- 379 cells/mm^3 (IQR 180-570) in 2016-21

In 2015, the median CD4 cell count at ART initiation peaked at 415 (IQR 220-600) and has since continued to decrease slightly each year to 309 cells/mm^3 (IQR 130-551) in 2021. 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 2016-2021, at the start of ART, 14.6% of individuals had already been diagnosed with an AIDS-defining condition; 92.2% of those with prior AIDS diagnosis had a CD4 cell count below 350 cells/mm^3, and 84.5% had a CD4 cell count below 200 cells/mm^3.

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

In care and on ART in the Netherlands in 2021

Of the 27,604 people known to have initiated ART between January 1996 and December 2021, 20,804 (75.4%) were alive, still receiving ART, and had a recorded visit for HIV care in the Netherlands in 2021. A total of 238 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. They are expected to re-start ART once those issues are sufficiently resolved.

Table 2.2 shows the treatment and clinical characteristics of all 20,566 individuals on ART at the last clinic visit in 2021. Overall, 16,916 (82.3%) were men, and 13,236 (64.4%) were MSM. Their median age on 31 December 2021 was 52.2 (IQR 42.4-59.9) years. The majority (58.2%) originated from the Netherlands, followed by Latin America / the Caribbean (12.4%) and sub-Saharan Africa (11.7%).

Table 2.2: Characteristics of people receiving combination antiretroviral therapy and known to be in care in 2021.

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	All
Total	n	5,770	4,593	5,980	4,223	**20,566**
	%	**28.1**	**22.3**	**29.1**	**20.5**	**100**
Male sex	n	4,381	3,761	5,191	3,583	**16,916**
	%					
Age on 31 December 2021	Median	58.3	53.4	48.1	41.3	**52.2**
	Q1	52.4	46.3	39.5	32.8	**42.4**
	Q3	64.5	60.0	56.8	52.5	**59.9**
Transmission risk group						
No data	n	5	5	9	16	**35**
	%	0.1	0.1	0.2	0.4	**0.2**
Men who have sex with men	n	3,260	2,988	4,236	2,752	**13,236**
	%	56.5	65.1	70.8	65.2	**64.4**
Heterosexual contact	n	2,000	1,335	1,433	1,080	**5,848**
	%	34.7	29.1	24.0	25.6	**28.4**
Injecting drug use	n	163	49	17	20	**249**
	%	2.8	1.1	0.3	0.5	**1.2**
Blood or blood products	n	101	33	46	51	**231**
	%	1.8	0.7	0.8	1.2	**1.1**
Vertical transmission	n	1	3	2	5	**11**
	%	0.0	0.1	0.0	0.1	**0.1**
Other/unknown	n	240	180	237	299	**956**
	%	4.2	3.9	4.0	7.1	**4.6**
Region of origin						
No data	n	20	11	25	50	**106**
	%	0.3	0.2	0.4	1.2	**0.5**
The Netherlands	n	3,316	2,785	3,711	2,155	**11,967**
	%	57.5	60.6	62.1	51	**58.2**
Western Europe/North America/Australia	n	445	284	342	**193**	**1,264**
	%	7.7	6.2	5.7	4.6	**6.1**
Eastern/central Europe	n	101	141	291	396	**929**
	%	1.8	3.1	4.9	9.4	**4.5**
Latin America/the Caribbean	n	623	526	729	677	**2,555**
	%	10.8	11.5	12.2	16.0	**12.4**
Sub-Saharan Africa	n	938	568	508	399	**2,413**
	%	16.3	12.4	8.5	9.4	**11.7**
Other	n	327	278	374	353	**1,332**
	%	5.7	6.1	6.3	8.4	**6.5**

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	All
ART regimen						
TDF/FTC/EFV	n	365	484	316	51	**1,216**
	%	6.3	10.5	5.3	1.2	**5.9**
TDF/FTC/NVP	n	461	267	171	9	**908**
	%	8.0	5.8	2.9	0.2	**4.4**
TDF/FTC/RPV	n	114	84	248	27	**473**
	%	2.0	1.8	4.1	0.6	**2.3**
TDF/3TC/DOR	n	245	309	411	328	**1,293**
	%	4.2	6.7	6.9	7.8	**6.3**
TDF/FTC/DRV/b	n	105	108	129	51	**393**
	%	1.8	2.4	2.2	1.2	**1.9**
TDF/FTC/ATV/b	n	49	51	37	10	**147**
	%	0.8	1.1	0.6	0.2	**0.7**
TDF/FTC/LPV/r	n	7	8	1	.	**16**
	%	0.1	0.2	0.0	.	**0.1**
TDF/FTC/EVG/c	n	80	93	276	76	**525**
	%	1.4	2.0	4.6	1.8	**2.6**
TDF/FTC/DTG	n	111	89	181	356	**737**
	%	1.9	1.9	3.0	8.4	**3.6**
TDF/FTC/RAL	n	42	37	46	26	**151**
	%	0.7	0.8	0.8	0.6	**0.7**
ABC/3TC/DTG	n	417	424	721	598	**2,160**
	%	7.2	9.2	12.1	14.2	**10.5**
TAF/FTC/RPV	n	213	210	425	90	**938**
	%	3.7	4.6	7.1	2.1	**4.6**
TAF/FTC/DRV/c	n	342	296	372	226	**1,236**
	%	5.9	6.4	6.2	5.4	**6.0**
TAF/FTC/EVG/c	n	431	477	830	532	**2,270**
	%	7.5	10.4	13.9	12.6	**11.0**
TAF/FTC/DTG	n	110	102	133	154	**499**
	%	1.9	2.2	2.2	3.6	**2.4**
TAF/FTC/BIC	n	630	561	700	1,066	**2,957**
	%	10.9	12.2	11.7	25.2	**14.4**
TAF/FTC/NVP	n	386	219	89	4	**698**
	%	6.7	4.8	1.5	0.1	**3.4**
ABC/3TC/NVP	n	191	61	41	.	**293**
	%	3.3	1.3	0.7	.	**1.4**

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	All
DTG/3TC	n	308	300	520	441	**1,569**
	%	5.3	6.5	8.7	10.4	**7.6**
DTG/RPV	n	65	25	21	8	**119**
	%	1.1	0.5	0.4	0.2	**0.6**
CAB/RPV injectables *	n	16	14	22	28	**80**
	%	0.3	0.3	0.4	0.7	**0.4**
2DR: NNRTI + INST	n	7	.	2	1	**10**
	%	0.1	.	0.0	0.0	**0.0**
2DR: PI + INSTI	n	253	63	50	29	**395**
	%	4.4	1.4	0.8	0.7	**1.9**
2DR: NRTI + INSTI	n	3	1	.	.	**4**
	%	0.1	0.0	.	.	**0.0**
Other: 2NRTI + NNRTI	n	156	85	42	19	**302**
	%	2.7	1.9	0.7	0.4	**1.5**
Other: 2NRTI + PI	n	108	76	56	6	**246**
	%	1.9	1.7	0.9	0.1	**1.2**
Other: 2NRTI + INST	n	83	55	60	25	**223**
	%	1.4	1.2	1.0	0.6	**1.1**
Other: 2DR	n	55	14	12	7	**88**
	%	1.0	0.3	0.2	0.2	**0.4**
Other: NRTI + PI + INSTI (3ARVs)	n	48	2	4	3	**57**
	%	0.8	0.0	0.1	0.1	**0.3**
Other: NRTI + PI + INSTI (4ARVs)	n	129	35	27	32	**223**
	%	2.2	0.8	0.5	0.8	**1.1**
Other	n	240	43	37	20	**340**
	%	4.2	0.9	0.6	0.5	**1.7**
CD4: CD8 ratio						
No data	n	730	585	824	645	**2,784**
	%	12.7	12.7	13.8	15.3	**13.5**
<0.50	n	874	554	624	915	**2,967**
	%	15.1	12.1	10.4	21.7	**14.4**
≥0.50 to <1.00	n	2,458	2,078	2,635	1,586	**8,757**
	%	42.6	45.2	44.1	37.6	**42.6**
≥1.00	n	1,708	1,376	1,897	1,077	**6,058**
	%	29.6	30.0	31.7	25.5	**29.5**

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	All
CD4 count (cells/mm³)						
No data	n	22	17	21	37	**97**
	%	0.4	0.4	0.4	0.9	**0.5**
<50	n	6	8	7	22	**43**
	%	0.1	0.2	0.1	0.5	**0.2**
50–199	n	92	51	46	172	**361**
	%	1.6	1.1	0.8	4.1	**1.8**
200–349	n	362	235	257	428	**1,282**
	%	6.3	5.1	4.3	10.1	**6.2**
350–499	n	899	671	697	628	**2,895**
	%	15.6	14.6	11.7	14.9	**14.1**
500–749	n	2,020	1,666	1,991	1,287	**6,964**
	%	35.0	36.3	33.3	30.5	**33.9**
≥750	n	2,369	1,945	2,961	1,649	**8,924**
	%	41.1	42.3	49.5	39	**43.4**
Viral load <50 copies/ml						
No data	n	1	4	3	11	**19**
	%	0.0	0.1	0.1	0.3	**0.1**
Yes	n	5,596	4,425	5,796	3,900	**19,717**
	%	97.0	96.3	96.9	92.4	**95.9**
No	n	173	164	181	312	**830**
	%	3.0	3.6	3.0	7.4	**4.0**
Viral load <200 copies/ml						
No data	n	1	4	3	11	**19**
	%	0.0	.0.1	0.1	0.3	**0.1**
Yes	n	5,695	4,527	5,902	4,059	**20,183**
	%	98.7	98.6	98.7	96.1	**98.1**
No	n	74	62	75	153	**364**
	%	1.3	1.3	1.3	3.6	**1.8**

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 20,566 people in HIV care and on ART in 2021, the vast majority (85.9%) received a regimen based on two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with either:

- an integrase inhibitor (INSTI) (46.3%);
- a non-nucleoside reverse transcriptase inhibitor (NNRTI) (29.7%); or
- a protease inhibitor (PI) (9.9%).

The distribution of ART use among the population in care in 2021 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) (14.4%);
- tenofovir alafenamide (TAF)/ emtricitabine (FTC)/elvitegravir (EVG)/cobicistat (11.0%);
- abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (10.5%);
- dolutegravir (DTG)/lamivudine (3TC) (7.6%);
- tenofovir disoproxil fumarate (TDF)/ lamivudine (3TC)/doravirine (DOR) (6.3%);
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/darunavir (DRV)/cobicistat (6.0%); and
- tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/efavirenz (EFV) (5.9%).

The proportion of the population in care using TDF has slowly decreased in the last couple of years, with a percentage of:

- 46.4% in 2017;
- 35.3% in 2018;
- 31.9% in 2019;
- 30.8% in 2020;
- 29.7% in 2021.

The proportion of the population in care using TAF meanwhile, continued to slowly increase, with:

- 24.4% in 2017;
- 33.2% in 2018;
- 42.1% in 2019;
- 43.7% in 2020;
- 44.5% in 2021.

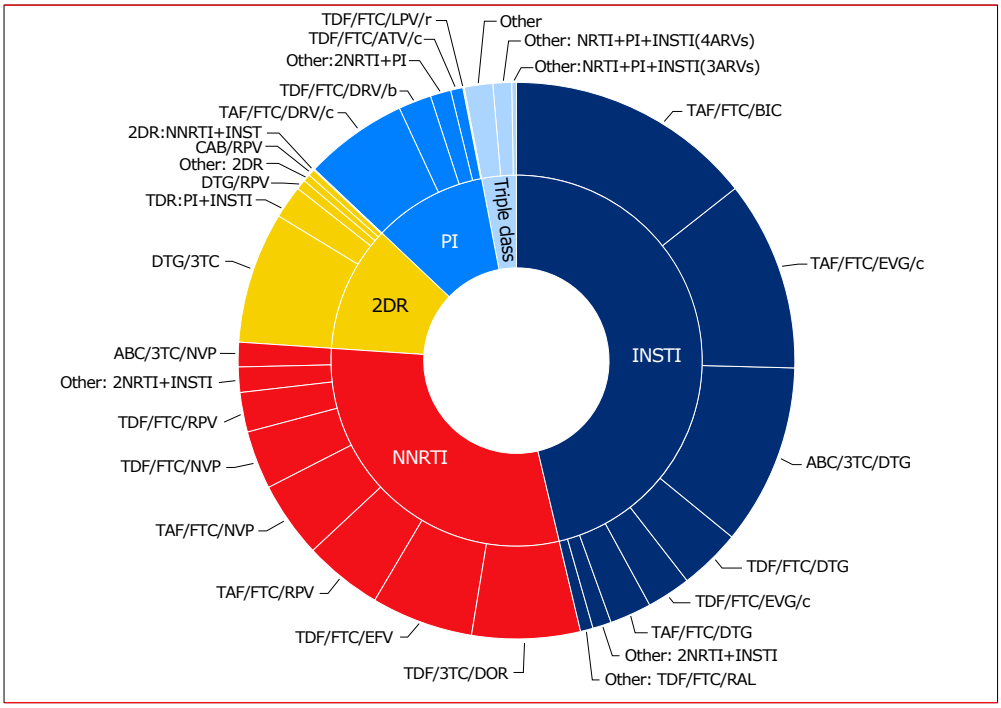
Zidovudine was still used by 97 individuals (0.5%, mostly in combination with lamivudine).

In 2021 the use of regimens not consisting of two NRTIs plus a third 'anchor drug' (an NNRTI, PI, or INSTI), continued to increase. In total, 745 (3.6%) individuals used an ART regimen without any NRTI and 1,748 (8.5%) individuals used one with just a single NRTI. There were 2,265 (11.0%) individuals who used a two-drug regimen (excluding pharmacological boosters). The most common of these regimens were a combination of:

- NRTI + INSTI (n=1,573 people or 69.5%) of which
  - 99.8% used lamivudine
  - 0.2% used TDF
  - 100% used dolutegravir;
- PI + INSTI (n=395 people, or 17.4%) of which
  - 98.2% used darunavir plus either dolutegravir (89.4%) or raltegravir (10.6%);
- NNRTI + INSTI (n=209 people, or 9.2%) of which
  - 95.2% used rilpivirine
  - 61.2% used dolutegravir
  - 38.3% used cabotegravir (intramuscularly);
- NNRTI + PI (n=22 people, or 1.0%).

Of those with a plasma HIV RNA measurement in 2021, 89.0% had a viral load below 50 copies/ml, and 98.1% had a viral load below 200 copies/ml. On the basis of the last available CD4 and CD8 cell count measurements in 2015-21, 77.3% had a CD4 cell count of 500 cells/mm^3 or higher, and 29.5% had a CD4: CD8 ratio of 1 or higher.

Figure 2.2: Combination antiretroviral therapy (ART) use in 2021.



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.*

Changes in the use of initial ART regimen

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

***Box 2.2:** Approval dates of new antiretroviral drugs/regimens for HIV treatment in the Netherlands in 2013–21.*

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 27,604 people known to have initiated ART between 1996 and 2021, 4,767 (17.3%) started ART between January 2016 and December 2021. *Figures 2.3* and *2.4* show the trends over time in third-drug additions to the NRTI backbone used as part of the initial ART regimen. The use of integrase inhibitors in combination with a dual-NRTI backbone as initial therapy, increased, with percentages reaching:

- 70.5% in 2016;
- 77.2% in 2017;
- 71.2% in 2018;
- 78.5% in 2019;
- 82.5% in 2020; and
- 80.8% in 2021 (90.9% including other INSTI-containing regimens).

Cobicistat-boosted elvitegravir was used in 25.2%, 30.7% and 23.8% of the initial regimens in 2016, 2017, and 2018, respectively, before its use dropped sharply to 3.2% in 2019, 1.3% in 2020, and 1.2% in 2021. Dolutegravir was used in:

- 50.7% of initial regimens in 2016;
- 50.7% of initial regimens in 2017;
- 43.8% of initial regimens in 2018;
- 35.1% of initial regimens in 2019;
- 43.5 of initial regimens in 2020; and
- 47.5% of initial regimens in 2021.

Bictegravir was introduced in the Netherlands in 2018 and was used in 7.0%, 44.3%, 44.5, and 41.1% of the initial regimens in 2018, 2019, 2020, and 2021, respectively. The use of NNRTIs in the initial regimen decreased from 13.6% in 2016 to:

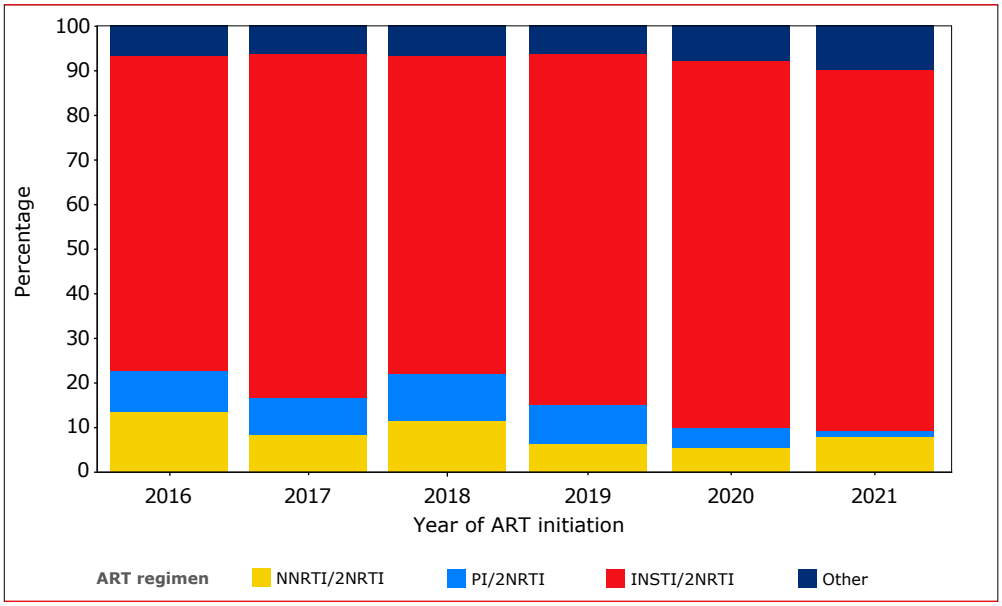
- 8.4% in 2017;
- 11.4% in 2018;
- 5.7% in 2019;
- 5.1% in 2020; and
- 7.6% in 2021.

The use of PIs in the initial regimen also decreased from 9.2% in 2016 to:

- 8.3% in 2017;
- 10.7% in 2018;
- 9.5% in 2019;
- 4.8% in 2020; and
- 1.5% in 2021.

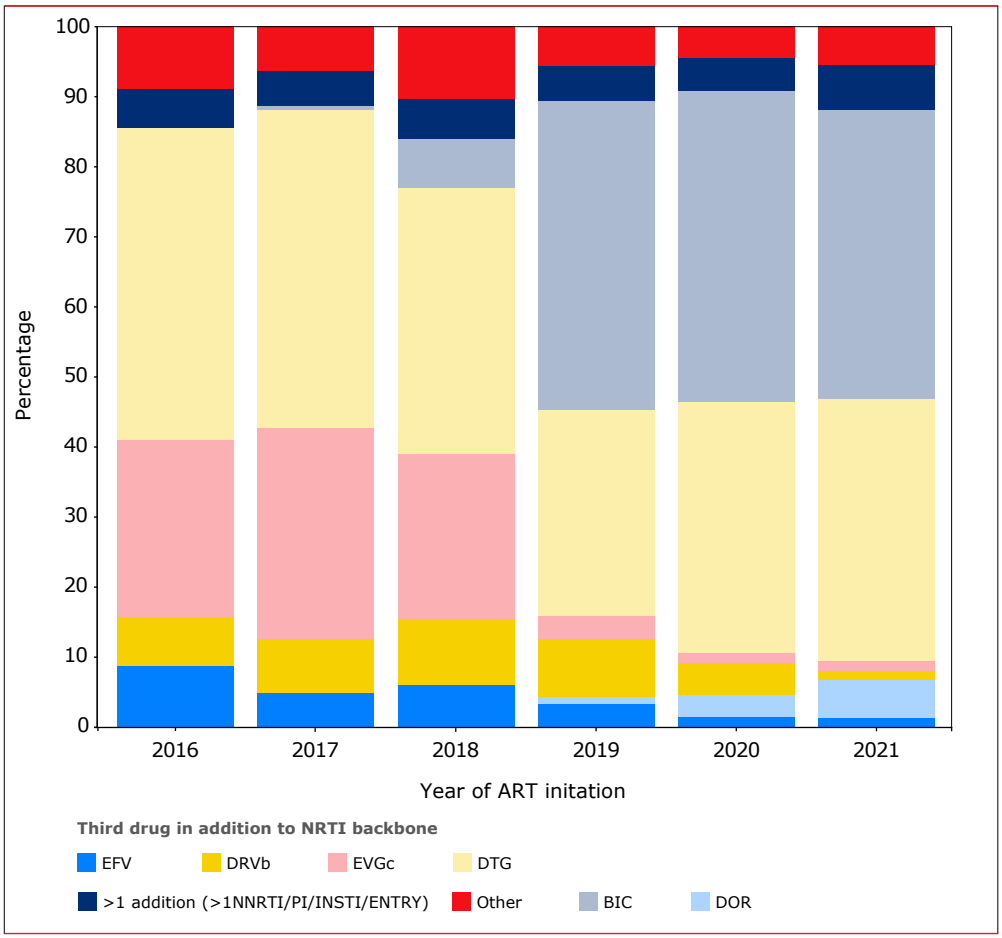
In the period 2016-21, 5.3% of individuals received more than one third-drug addition to the NRTI backbone in their initial ART regimen. The majority of these were people initiating ART during an acute HIV infection, with the regimen consisting of a PI (mainly boosted darunavir) plus an INSTI (mainly dolutegravir), plus two NRTIs. *Figure 2.4* shows all third-drug additions to the 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 2016-21. 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 2016-21. As a result, those regimens have been included in the category 'other' in *Figure 2.4*.

Figure 2.3: *Third-drug class additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2016-21.*



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 2016–21.



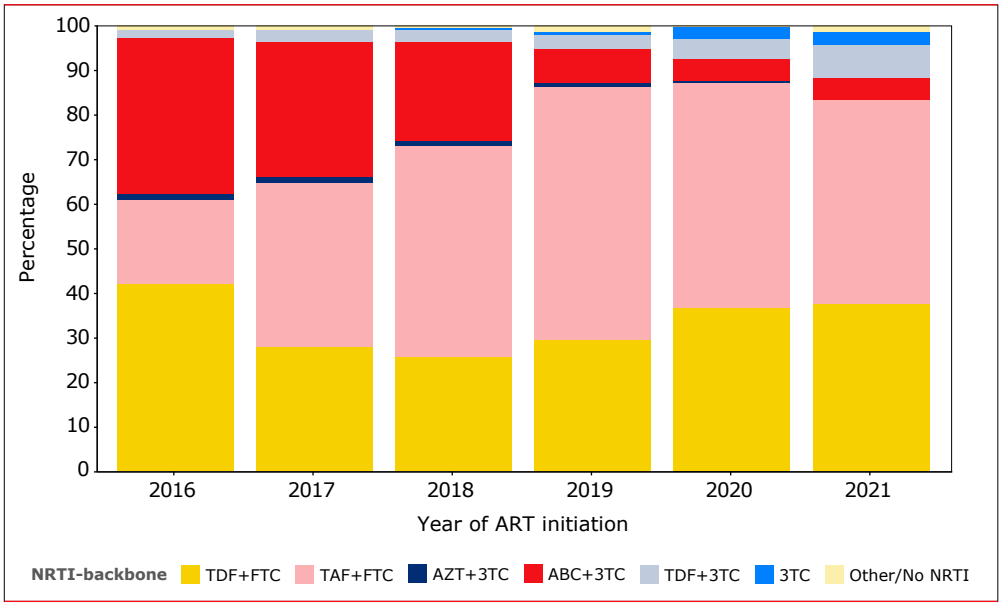
Legend: ART = combination antiretroviral therapy; b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; ENTRY = entry inhibitor; INSTI = integrase inhibitor; NRTI = nucleoside analogue 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 2016-21. The combination of tenofovir (TDF or TAF) and emtricitabine was the predominant backbone prescribed. Following its introduction at the end of 2015, TAF was prescribed in:

- 18.9% of the initial regimens in 2016;
- 37.2% of the initial regimens in 2017;
- 47.3% of the initial regimens in 2018;
- 57.1% of the initial regimens in 2019;
- 50.7% of the initial regimens in 2020; and
- 46.1% of the initial regimens in 2021.

At the same time, TDF use decreased from 43.6% in 2016 to 28.4% in 2018, before increasing to 33.1% in 2019, 41.4% in 2020, and 45.3% in 2021. The use of abacavir (in combination with lamivudine) decreased from 35.4% of all initial regimens in 2016 to 30.9% in 2017, and 22.3% in 2018, after which there was a sharp decrease to 8.1% in 2019, 4.8% in 2020, and 5.2% in 2021. The combination of zidovudine and lamivudine, which is still sometimes used by migrants who initiated ART before arriving in the Netherlands, has further decreased to less than 1% since 2017 (n=0 in 2021).

Figure 2.5: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2016-21.*



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 2016-21 are presented in *Figure 2.6* and *Table 2.3*. In 2021, the most frequently used initial regimen was TAF/FTC/bictegravir (41.1%). Dolutegravir-containing initial regimens were used in 38.4% of cases. Additionally, 5.4% initiated a doravirine-containing once-daily, fixed-dose combination with lamivudine and tenofovir (TDF). Elvitegravir/c, darunavir/b, or raltegravir use in an initial regimen was 1.2%, 1.5%, and 0.7%, respectively, in 2021. *Table 2.3* provides more detail on the 'other' initial regimens that are not further specified in *Figures 2.4-2.6*.

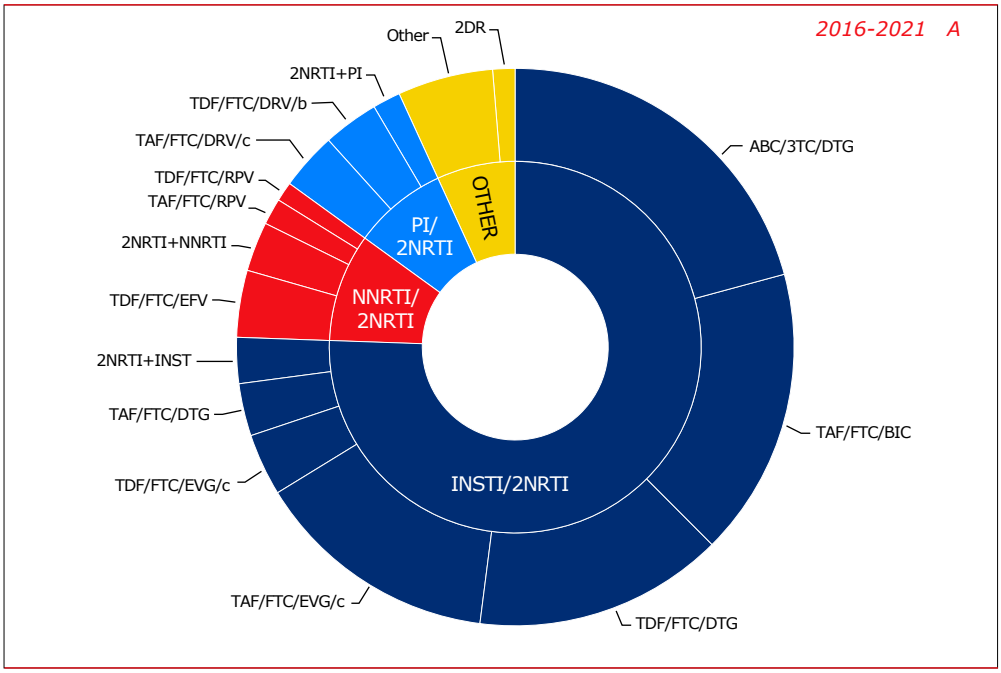
***Table 2.3:** Initial regimens in 2016–21.*

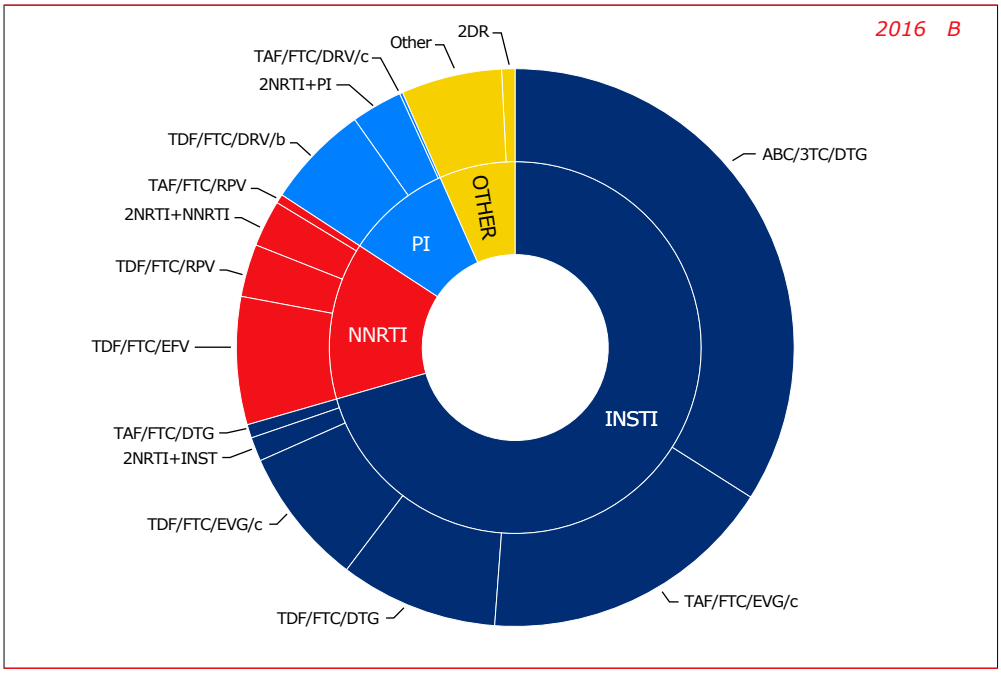
		2016	2017	2018	2019	2020	2021	2016–21
N		1,147	1038	900	750	526	406	4,767
Regimen								
TDF/FTC/EFV	n	85	33	39	19	6	3	185
	%	7.41	3.18	4.33	2.53	1.14	0.74	3.88
TDF/FTC/NVP	n	9	2	2	1	.	1	15
	%	0.78	0.19	0.22	0.13	.	0.25	0.31
TDF/FTC/RPV	n	35	10	4	3	.	2	54
	%	3.05	0.96	0.44	0.4	.	0.49	1.13
TDF/3TC/DOR	n	.	.	.	5	16	22	43
	%	.	.	.	0.67	3.04	5.42	0.9
TDF/FTC/DRV/b	n	69	42	15	16	9	3	154
	%	6.02	4.05	1.67	2.13	1.71	0.74	3.23
TDF/FTC/ATV/b	n	17	5	6	6	1	.	35
	%	1.48	0.48	0.67	0.8	0.19	.	0.73
TDF/FTC/LPV/r	n	2	1	.	.	.	.	3
	%	0.17	0.1	.	.	.	.	0.06
TDF/FTC/EVG/c	n	92	56	16	6	.	2	172
	%	8.02	5.39	1.78	0.8	.	0.49	3.61
TDF/FTC/DTG	n	105	92	92	132	152	118	691
	%	9.15	8.86	10.22	17.6	28.9	29.06	14.5
TDF/FTC/RAL	n	9	7	14	11	3	3	47
	%	0.78	0.67	1.56	1.47	0.57	0.74	0.99
ABC/3TC/DTG	n	390	311	190	56	25	19	991
	%	34	29.96	21.11	7.47	4.75	4.68	20.79
ABC/3TC/NVP	n	1	1	1	.	.	.	3
	%	0.09	0.1	0.11	.	.	.	0.06
TAF/FTC/RPV	n	6	20	37	6	3	1	73
	%	0.52	1.93	4.11	0.8	0.57	0.25	1.53

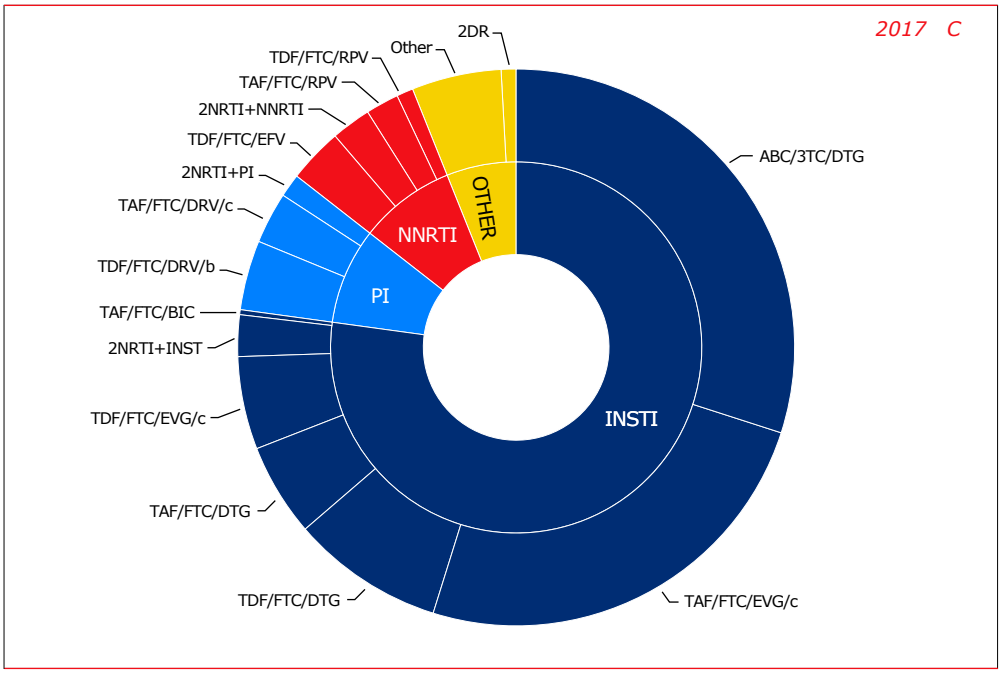
		2016	2017	2018	2019	2020	2021	2016–21
N		1,147	1038	900	750	526	406	4,767
Regimen								
TAF/FTC/DRV/c	n	2	31	65	46	12	3	159
	%	0.17	2.99	7.22	6.13	2.28	0.74	3.34
TAF/FTC/EVG/c	n	197	258	195	18	7	3	678
	%	17.18	24.86	21.67	2.4	1.33	0.74	14.22
TAF/FTC/DTG	n	9	56	48	18	6	8	145
	%	0.78	5.39	5.33	2.4	1.14	1.97	3.04
TAF/FTC/BIC	n	.	3	63	331	234	167	798
	%	.	0.29	7	44.13	44.49	41.13	16.74
DTG/3TC	n	1	1	3	4	13	11	33
	%	0.09	0.1	0.33	0.53	2.47	2.71	0.69
DTG/RPV	n	.	.	1	1	.	.	2
	%	.	.	0.11	0.13	.	.	0.04
2DR: PI + INSTI	n	8	8	3	3	1	3	26
	%	0.7	0.77	0.33	0.4	0.19	0.74	0.55
Other: 2NRTI + NNRTI	n	21	21	20	10	2	2	76
	%	1.83	2.02	2.22	1.33	0.38	0.49	1.59
Other: 2NRTI + PI	n	15	8	10	3	3	.	39
	%	1.31	0.77	1.11	0.4	0.57	.	0.82
Other: 2NRTI + INST	n	7	18	23	17	7	8	80
	%	0.61	1.73	2.56	2.27	1.33	1.97	1.68
Other: 2DR	n	.	.	1	.	.	.	1
	%	.	.	0.11	.	.	.	0.02
Other: NRTI + PI + INSTI (3ARVs)	n	1	1	1	1	.	1	5
	%	0.09	0.1	0.11	0.13	.	0.25	0.1
Other: NRTI + PI + INSTI (4ARVs)	n	57	52	50	33	24	23	239
	%	4.97	5.01	5.56	4.4	4.56	5.67	5.01
Other	n	9	1	1	4	2	3	20
	%	0.78	0.1	0.11	0.53	0.38	0.74	0.42

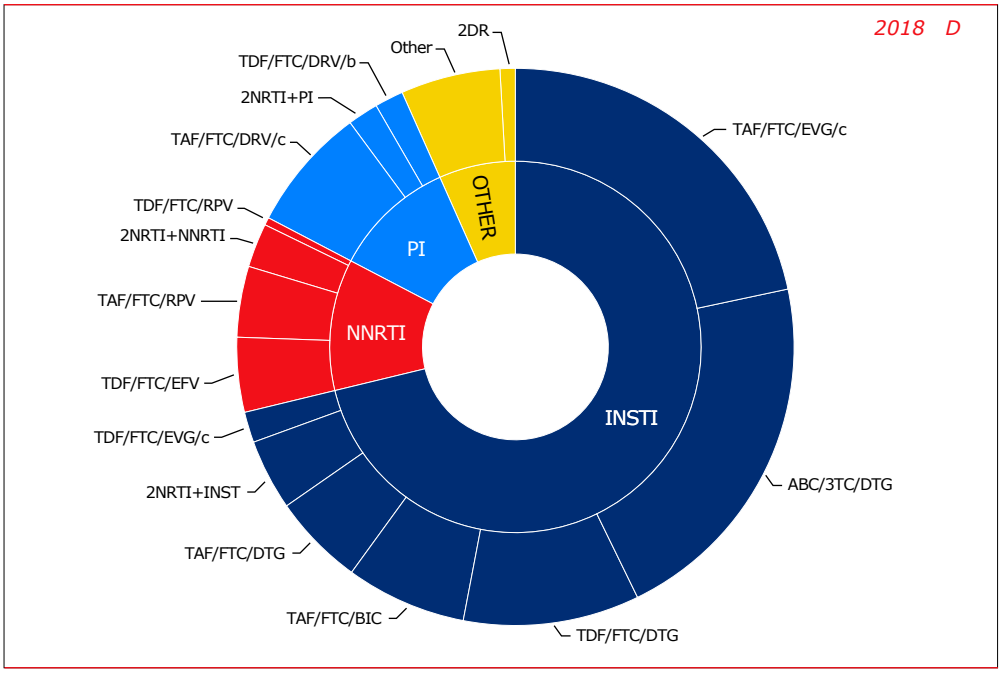
Legend: *ARVs = antiretroviral drugs; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; BIC = bictegravir; CI = confidence interval; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG =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

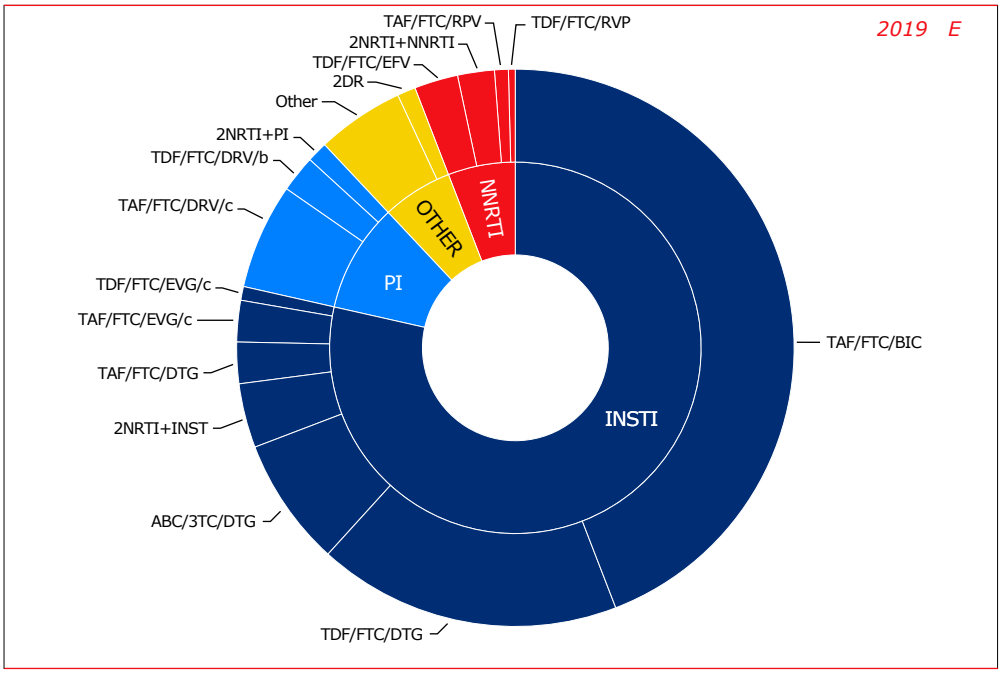
Figure 2.6: The initial combination antiretroviral therapy regimens given in 2016–21 A) in total and B) by year.

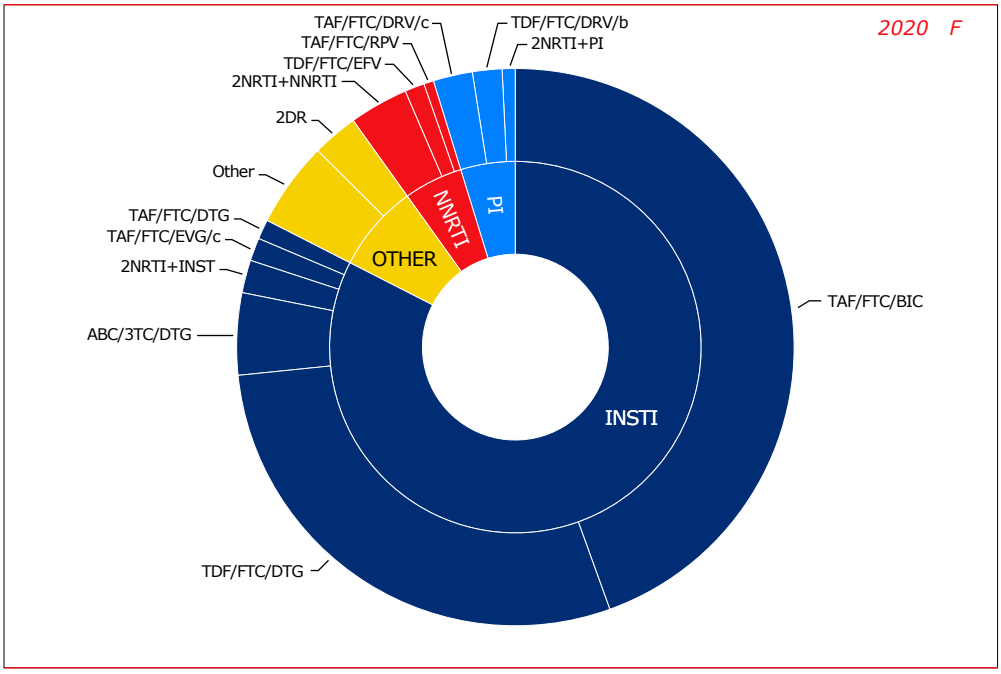


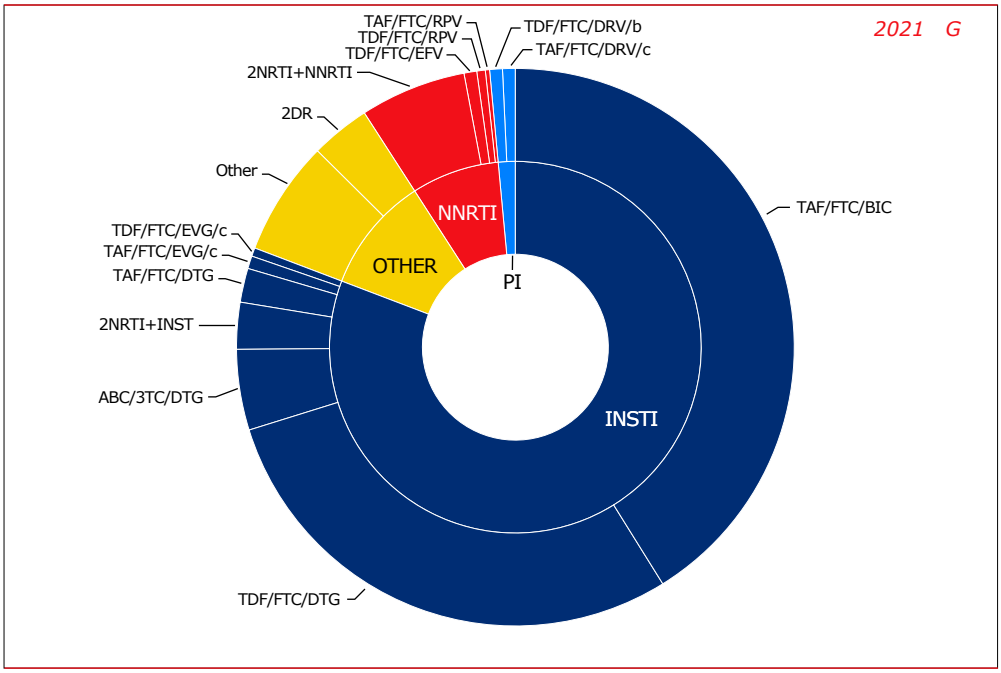



2017 C
2DR
Other
TDF/FTC/RPV
TAF/FTC/RPV
2NRTI+NNRTI
TDF/FTC/EFV
2NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/DRV/b
TAF/FTC/BIC
2NRTI+INST
TDF/FTC/EVG/c
TAF/FTC/DTG
TDF/FTC/DTG
ABC/3TC/DTG
TAF/FTC/EVG/c
OTHER
NNRTI
PI
INSTI


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


2020 F
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
2NRTI+INST
ABC/3TC/DTG
TDF/FTC/DTG
TAF/FTC/BIC
NNRTI
PI
OTHER
INSTI



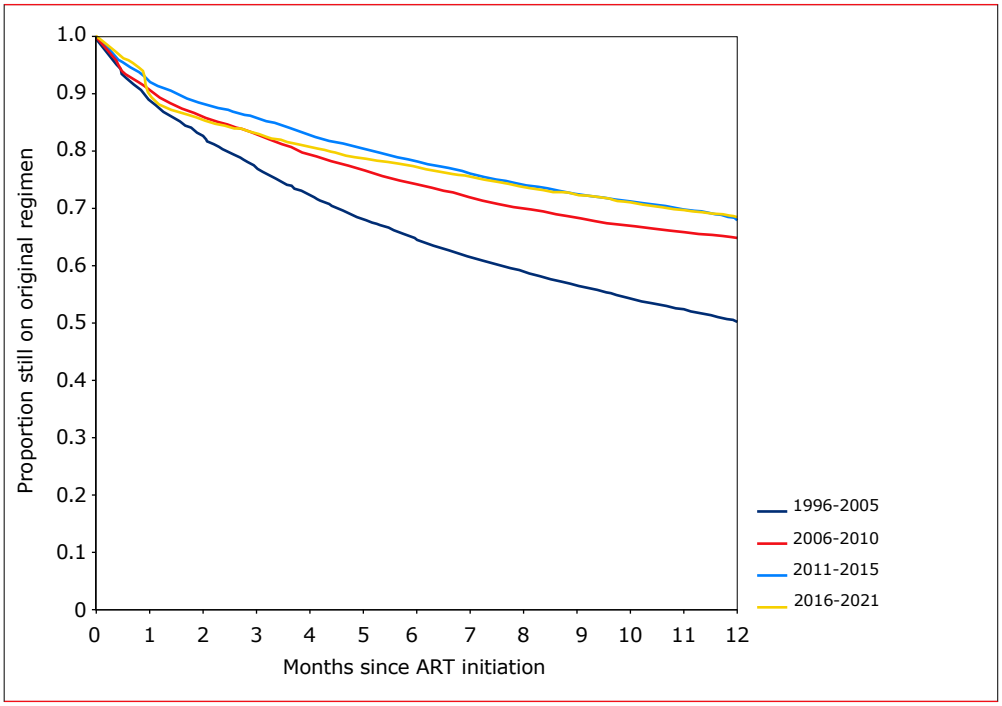
Legend: *3TC = lamivudine; ABC = abacavir; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; BIC = bictegravir; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase inhibitor; NNRTI = non-nucleoside reverse 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 27,604 people who started ART between 1996 and 2021, 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 1996-2021, 38.7% of individuals discontinued their initial regimen within one year; the length of time they remain on it has improved over the years: in 1996-2005, 49.9% discontinued it within a year, compared to 35.0% in 2006-10, 31.9% in 2011-15, and 31.0% in 2016-21. *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 regimen, by calendar year period of initiation (log-rank test p<0.001).*



Legend: *ART = combination antiretroviral therapy.*

Discontinuation of the initial ART regimen: 2016–21

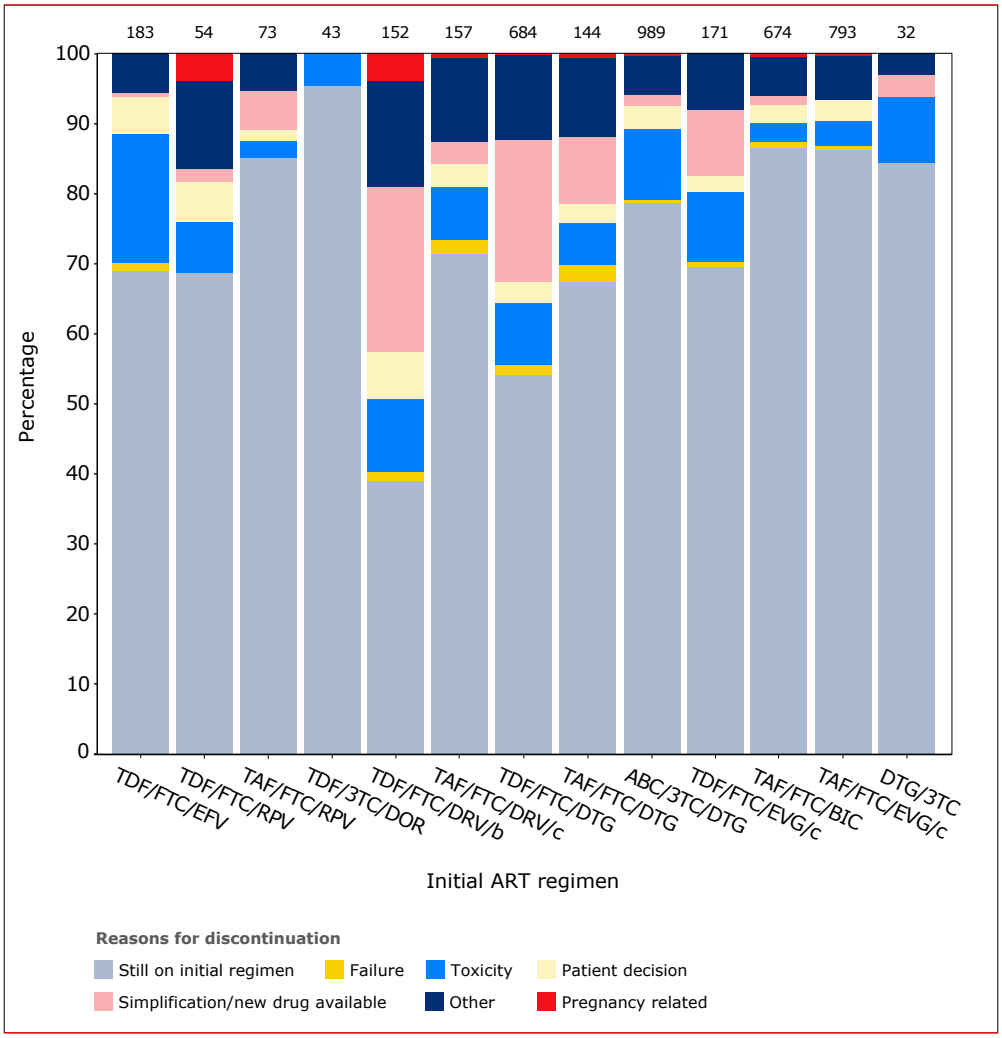
We further assessed the time to discontinuation of the initial regimen during the first year of treatment among the 4,149 people who started 'common' and guideline-recommended initial regimens in 2016-21. The regimens considered in this analysis were:

- tenofovir disoproxil fumarate/emtricitabine/efavirenz (TDF/FTC/EFV, 4.1%);
- tenofovir disoproxil fumarate/emtricitabine/rilpivirine (TDF/FTC/RPV, 1.3%);
- tenofovir disoproxil fumarate/emtricitabine/ritonavir-boosted or cobicistat-boosted darunavir (TDF/FTC/DRV/b, 3.7%);
- tenofovir disoproxil fumarate/emtricitabine/cobicistat-boosted elvitegravir (TDF/FTC/EVG/c, 4.1%);
- tenofovir disoproxil fumarate/emtricitabine/dolutegravir (TDF/FTC/DTG, 16.5%);
- tenofovir disoproxil fumarate/lamivudine/doravirine (TDF/3TC/DOR, 1.0%);
- abacavir-lamivudine/dolutegravir (ABC/3TC/DTG, 23.8%);
- tenofovir alafenamide/emtricitabine/cobicistat-boosted elvitegravir (TAF/FTC/EVG/c, 16.2%);
- tenofovir alafenamide/emtricitabine/rilpivirine (TAF/FTC/RPV, 1.8%);
- tenofovir alafenamide/emtricitabine/dolutegravir (TAF/FTC/DTG, 3.5%);
- tenofovir alafenamide/emtricitabine/cobicistat-boosted darunavir (TAF/FTC/DRV/c, 3.8%);
- tenofovir alafenamide/emtricitabine/bictegravir (TAF/FTC/BIC, 19.1%); and
- dolutegravir/lamivudine (DTG/3TC, 0.8%).

One year after ART initiation, 1,052 (25.4%) of the 4,149 individuals using one of these initial regimens had discontinued it. The main reason for this discontinuation was toxicity (306, 29.1%), followed by simplification and/or availability of new drugs (243, 23.1%). 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 2016–21, by regimen. Numbers above the bars represent the total number of individuals using that particular regimen.*

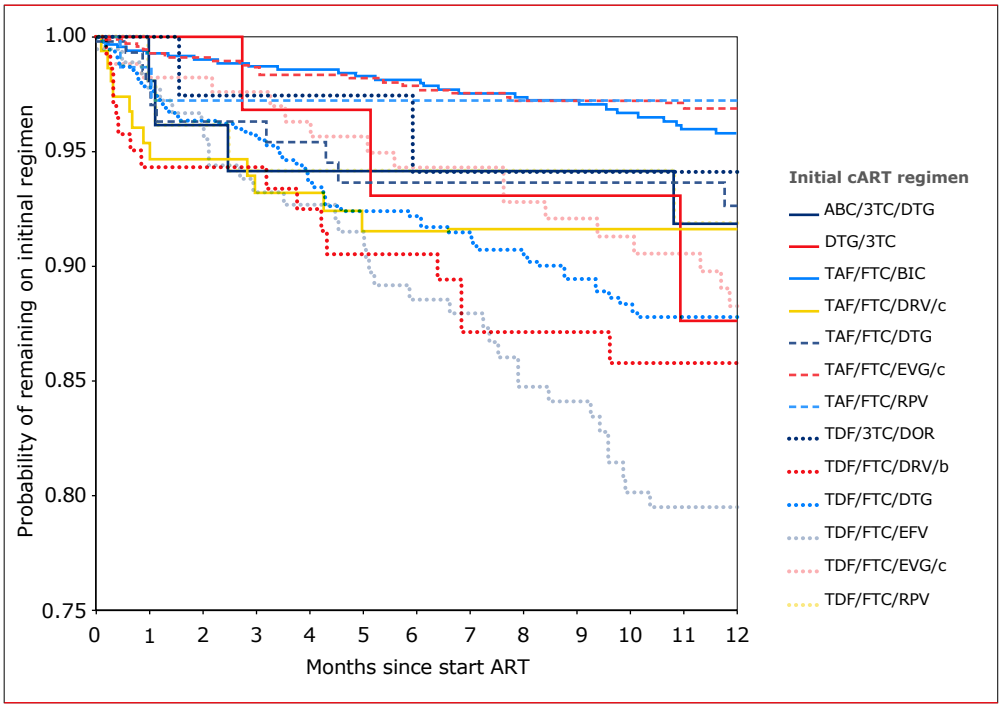


Legend: *ART = combination antiretroviral therapy; /b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; RPV = rilpivirine;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

Discontinuation of the initial ART regimen due to toxicity

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

Figure 2.9: *Kaplan-Meier estimate of the time on initial regimen until modification due to toxicity in 2016-21, by regimen. Time was censored when the initial regimen was discontinued due to reasons other than toxicity (log-rank p<0.001).*



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

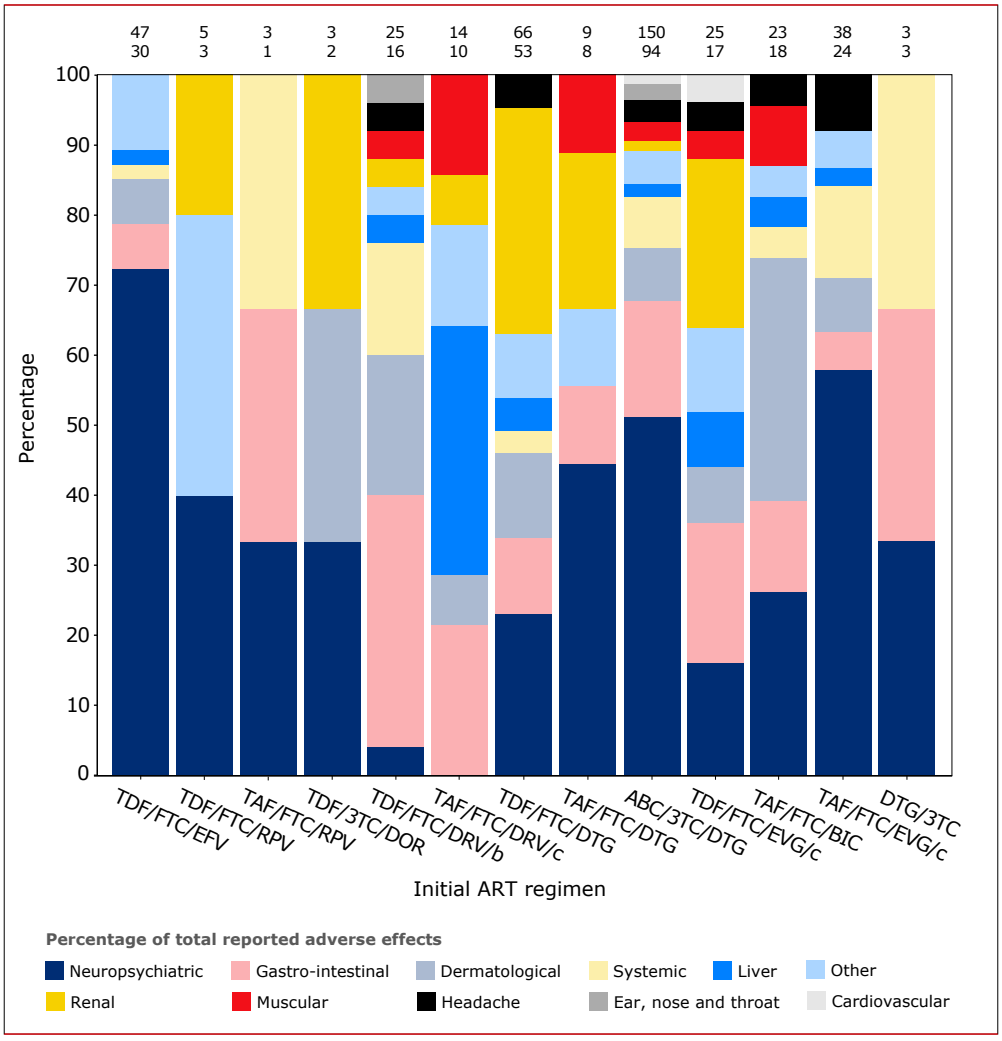
Adverse effects

Among the 306 individuals who discontinued their initial ART regimen within a year due to toxicity, 411 adverse effects were recorded. The predominant adverse effects were:

- neuropsychiatric (mainly insomnia, mood changes, dizziness, and depression) 40.6%;
- gastrointestinal (mainly diarrhoea and nausea) 14.6%;
- dermatological (rash due to medication, itching) 10.2%;
- renal (renal insufficiency and increased serum creatinine) 8.5%; and
- systemic (tiredness, apathy, and loss of appetite) 6.6%.

These adverse effects are stratified by ART regimen in *Figure 2.10*. Neuropsychiatric effects were associated with regimens containing efavirenz and dolutegravir, and, to a lesser extent, rilpivirine and elvitegravir. Renal effects were mainly, but not exclusively, reported by people who discontinued tenofovir disoproxil fumarate-based ART.

Figure 2.10: *Adverse effects associated with initial regimen discontinuation due to toxicity, during the first year of treatment in 2016–21. The bars represent the distribution of 411 reported effects among 306 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 27,604 adults started ART between January 1996 and December 2021. For the analysis of virological outcomes in this section, we have focused on the 23,443 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 an appropriate 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 100 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 2019 International Antiviral Society-USA (IAS-USA) HIV drug resistance mutation list was used to score major resistance-associated mutations[25].

Acquired HIV drug resistance
High-level resistance to at least one antiretroviral drug, detected at the time of an HIV viral load above 500 copies/ml, among people receiving 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[26,27].

Initial virological success

Of the 23,443 individuals with a viral load test result within at least three months of ART initiation, 20,207 (86.2%) had a viral load measurement six months (plus or minus three months) after ART initiation. Of these people, 17,155 (84.9%) achieved initial virological success (i.e. a plasma viral load below 100 HIV RNA copies/ml [*Box 2.3*]). That percentage has improved over time, from 68.3% in those starting ART between 1996 and 2005, to 87.9% in 2006-10, 92.3% in 2011-20, and 93.3% in those starting in 2021.

Initial virological success of common initial ART regimens (2013–21)

We analysed initial virological success among the 5,867 adults who started a common or guideline-recommended ART regimen in 2013-21, which was used frequently enough to allow for a meaningful analysis (TDF/FTC/EFV; TDF/FTC/RPV; TDF/FTC/DRV/b; TDF/FTC/DTG; TDF/FTC/EVG/c; TAF/FTC/RPV; TAF/FTC/DRV/c; TAF/FTC/BIC; TAF/FTC/DTG; TAF/FTC/EVG/c; and ABC/3TC/DTG), and had a viral load result within six months (plus or minus three months) of ART initiation. In total, 94.0% (95% confidence interval [CI] 93.4-94.6) of individuals achieved initial virological suppression, after a mean of 178 (standard deviation [SD] 39) days. Overall, people receiving an integrase inhibitor or NNRTI-based regimen showed significantly higher rates of initial virological success: 94.8% (CI 94.1-95.5) of those on an integrase inhibitor-based regimen and 94.0% (92.7-95.4) on a NNRTI-based regimen, compared to 89.4% (87.1-91.7) 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 (*Table 2.4*). However, there were no significant differences between the three regimen classes in people with a viral load below 100,000 copies/ml at ART initiation. Population characteristics, which may be associated with the initial prescribed regimen, were not taken into account in this analysis.

Table 2.4: *Initial virological success rates (see definition in Box 2.3), by initial regimen and initial viral load at ART initiation in 2013–2021.*

	Total		By initial viral load at ART initiation					
					<100,000 copies/ml			
	n	%	n	%	Initial viral success	95% CI low	95% CI high	p-value
ART regimen								
TDF/FTC/EFV	640	10.9	352	9.8	97.7	96.2	99.3	Ref.
TDF/FTC/RPV	465	7.9	465	12.9	95.3	93.4	97.2	0.070
TDF/FTC/DRV/b	549	9.4	226	6.3	95.6	92.9	98.3	0.15
TDF/FTC/EVG/c	769	13.1	531	14.8	97.4	96.0	98.7	0.73
TDF/FTC/DTG	711	12.1	338	9.4	96.5	94.5	98.4	0.32
ABC/3TC/DTG	1,254	21.4	839	23.4	97.0	95.9	98.2	0.50
TAF/FTC/RPV	52	0.9	52	1.5	100	100	100	0.99
TAF/FTC/DRV/c	122	2.1	54	1.5	100	100	100	0.99
TAF/FTC/EVG/c	561	9.6	348	9.7	97.4	95.7	99.1	0.79
TAF/FTC/DTG	105	1.8	48	1.3	95.8	90.2	100	0.44
TAF/FTC/BIC	639	10.9	340	9.5	98.2	96.8	99.6	0.64
Regimen class								
NNRTI/2NRTI	1,157	19.7	869	24.2	96.5	95.3	97.8	Ref.
PI/2NRTI	671	11.4	280	7.8	96.4	94.3	98.6	0.92
INSTI/2NRTI	4,039	68.8	2,444	68.0	97.2	96.6	97.9	0.32
All regimens	**5,867**	**100**	**3,593**	**61.2**	**97.0**	**96.4**	**97.6**	

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.*

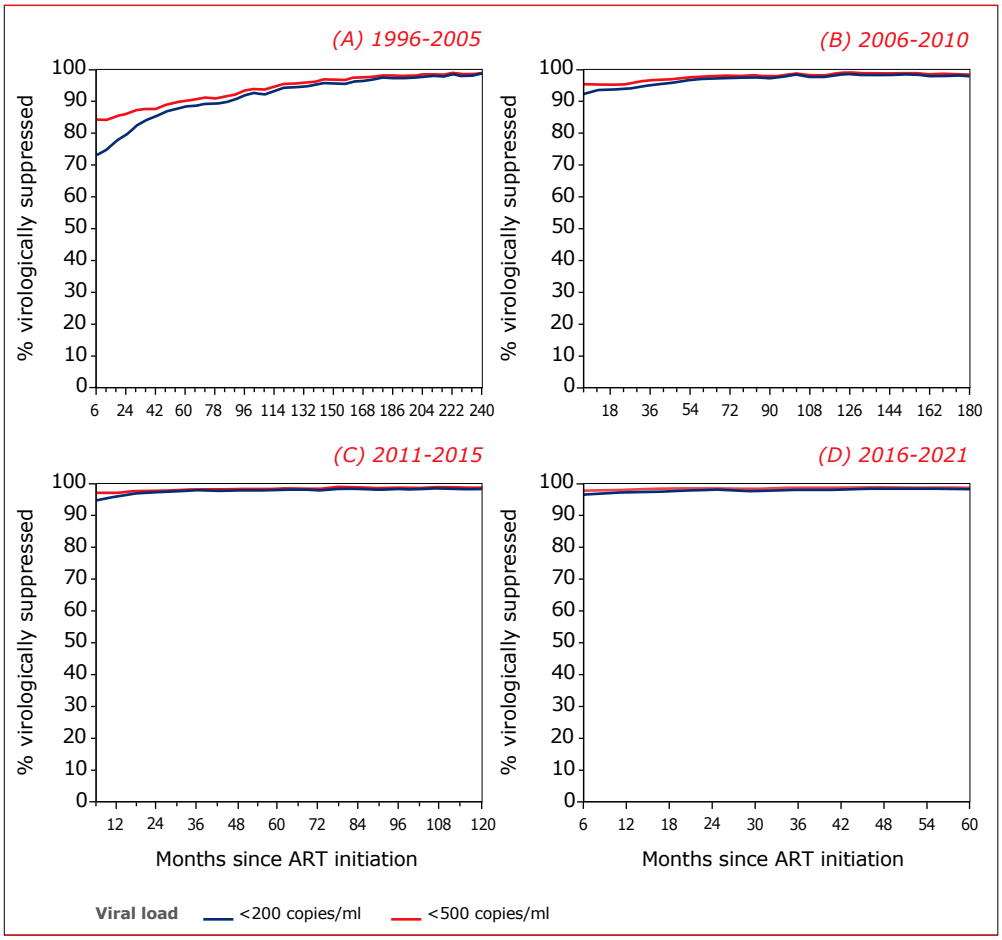
Viral suppression

We assessed long-term viral suppression rates (i.e. viral load below 200 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 2.11 shows viral suppression rates by calendar period of ART initiation: 1996-2005, 2006-10, 2011-15, and 2016-21. 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 96.8-97.9) after one year of ART use, to 98.4% (97.9-99.0) after four years.

		By initial viral load at ART initiation					
		≥100,000 copies/ml					
		n	%	Initial viral success	95% CI low	95% CI high	p-value
	ART regimen						
	TDF/FTC/EFV	288	12.7	86.5	82.5	90.4	Ref.
	TDF/FTC/RPV	not recommended					
	TDF/FTC/DRV/b	323	14.2	84.5	80.6	88.9	0.50
	TDF/FTC/EVG/c	238	10.5	89.5	85.6	93.4	0.29
	TDF/FTC/DTG	373	16.4	90.1	87.0	93.1	0.15
	ABC/3TC/DTG	415	18.3	92.0	89.4	94.7	0.017
	TAF/FTC/RPV	not recommended					
	TAF/FTC/DRV/c	68	3.0	83.8	75.1	92.6	0.57
	TAF/FTC/EVG/c	213	9.4	91.1	87.3	94.9	0.11
	TAF/FTC/DTG	57	2.5	91.2	83.9	98.6	0.33
	TAF/FTC/BIC	299	13.2	92.0	88.9	95.1	0.033
	Regimen class						
	NNRTI/2NRTI	288	12.7	86.5	82.5	90.4	Ref.
	PI/2NRTI	391	17.2	84.4	80.8	88.0	0.45
	INSTI/2NRTI	1,595	70.1	91.0	89.6	92.4	0.017
	All regimens	**2,274**	**38.8**	**89.3**	**88.0**	**90.6**	

Figure 2.11: *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 2016–21.*



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 2019 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[25].

Acquired HIV drug resistance
High-level resistance to at least one antiretroviral drug, detected at the time of an HIV viral load above 500 copies/ml, among people receiving ART for at least four months. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.0) was used to infer antiretroviral drug susceptibility and resistance scores[26,27].

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

We assessed the occurrence of HIV drug resistance in the Netherlands among adults for whom genotypic test results were available. The genotypic test results presented in this section relate to the HIV-1 reverse transcriptase and protease gene. HIV-1 sequences of the integrase gene were relatively rare, therefore results of testing for integrase inhibitor resistance are described separately. It is worth noting that SHM does not receive drug resistance data from all HIV treatment centres and laboratories, hence presented figures may not be representative of the entire population in HIV care.

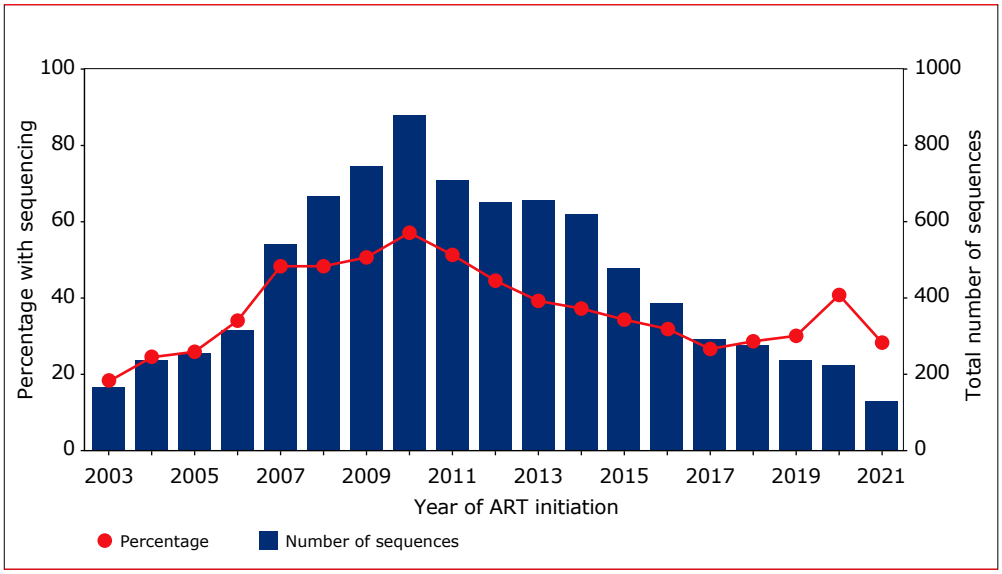
We evaluated the presence of mutations in the HIV genome that are associated with drug resistance. The 2019 International Antiviral Society-USA (IAS-USA) HIV drug resistance mutation list was used to score major resistance-associated mutations[25]. Furthermore, we assessed the association between these mutations and the susceptibility to antiretroviral drugs. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.0) was used to infer antiretroviral drug susceptibility scores for each sequence according to a five-level scheme: susceptible; potential low-level resistance; low-level resistance; intermediate resistance; and high-level resistance[26,27]. The definitions of transmitted and acquired-HIV drug resistance used in our analyses are summarised in *Box 2.3*. The number of sequences and people included in each of the analyses is outlined in *Box 2.1*.

Screening for drug-resistant HIV before treatment initiation

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

In total, 8,637 HIV-1 sequences were obtained between 2003 and 2021 from 8,327 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 2.12*). The decline in the number of sequences in 2021 is likely due to a backlog in relaying sequence data to SHM. 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 (67.4%), while (14.9%) were women. Most people with an available pre-treatment sequence originated from the Netherlands (59.5%), or sub-Saharan Africa (11.1%). The main HIV-1 subtype was B (74.7%), followed by non-B subtypes (25.3%), including recombinant form CRF_02AG (6.7%), subtype C (5.0%), and CRF_01AE (3.7%).

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

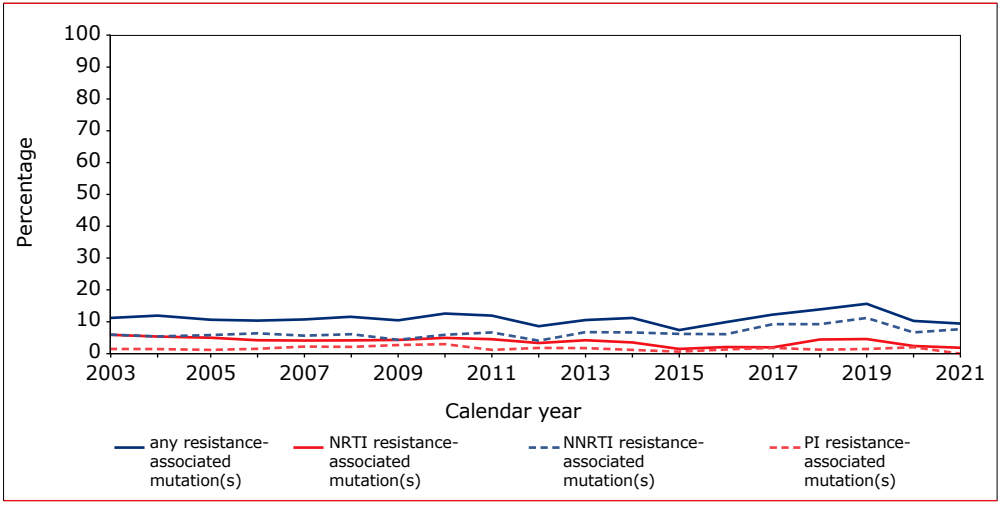


Legend: ART = combination antiretroviral therapy.

Transmitted HIV drug resistance

In total, at least one or more major resistance-associated mutation[25] was found in 909 (10.9%) of the people tested for resistance, including 334 (4.0%) with NRTI-associated resistance mutations, 509 (6.1%) with NNRTI-associated resistance mutations, and 144 (1.7%) with PI-associated resistance mutations. The prevalence of transmitted drug resistance was low and remained stable between 2003 and 2021 (*Figure 2.13*).

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



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

In total, 247 (3.0%) individuals screened for transmitted drug resistance harboured high-level resistance[26,27] to at least one antiretroviral drug: 45 (0.5%) to at least one NRTI; 182 (2.2%) to at least one NNRTI; and 34 (0.4%) to at least one PI. More information on transmitted resistance to NRTI and pre-exposure prophylaxis (PrEP) for HIV can be found in the special report on prior use of PrEP in this year's Monitoring Report. On the basis of the available resistance data, more than 97% were fully susceptible to all antiretroviral drugs: 2.6% (n=212) harboured high-level resistance in one drug class; 0.3% (n=24) in two drug classes; and less than 0.1% (n=5) to three drug classes (i.e. NRTIs, NNRTIs and PIs).

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

Integrase inhibitor resistance before HIV treatment initiation

In total, 201 people had an integrase sequence available prior to ART initiation, of whom all but three were ARV-naïve. No major or minor integrase resistance-associated mutations were detected in these individuals.

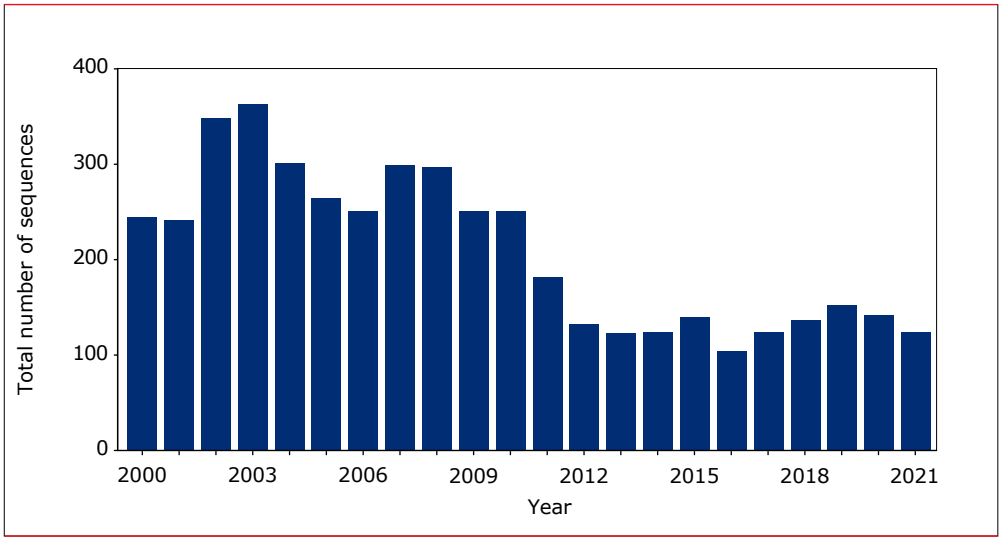
Acquired HIV drug resistance

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 2000-21. If ART had been interrupted more than two weeks before the test, the sequence was excluded from the analysis.

In total, 4,587 HIV-1 sequences were obtained from 2,757 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 remained at the same level until 2021 (*Figure 2.14*). The median time between initial start of ART and resistance testing was 5.7 years (IQR 3.1-9.2). The main HIV-1 subtype was B (67.5%), followed by recombinant form CRF_02AG (11.2%), and subtype C (5.7%).

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



Overall, sequences from people pre-treated with monotherapy or dual therapy were disproportionally represented: 1,362 (29.7%) sequences were obtained from 736 (26.7%) pre-treated people, and 3,225 (70.3%) sequences were obtained from 2,021 (73.3%) ARV-naïve people. However, over time this difference became less distinct: in 2000, 73.0% of sequences were obtained from pre-treated people, compared with 36.0% in 2005, and less than 14% from 2010 onwards.

Of the 4,587 sequences obtained when the HIV RNA was above 500 copies/ml, 2,828 (61.7%) harboured high-level resistance to at least one antiretroviral drug. High-level NRTI resistance was detected in 2,849 (62.1%) sequences; of those, 2,440 (85.6%) harboured high-level resistance to emtricitabine or lamivudine. Notably, of the 1,793 individuals ever identified as harbouring the M184V or M184I mutation who were still in care in 2021, 1,179 (65.8%) were still on ART containing lamivudine or emtricitabine, of whom 883 (74.9%) had undetectable HIV-RNA at their last visit. In addition, 1,693 (37.5%) harboured high-level resistance to at least one NNRTI, and 1,033 (23.8%) to at least one PI.

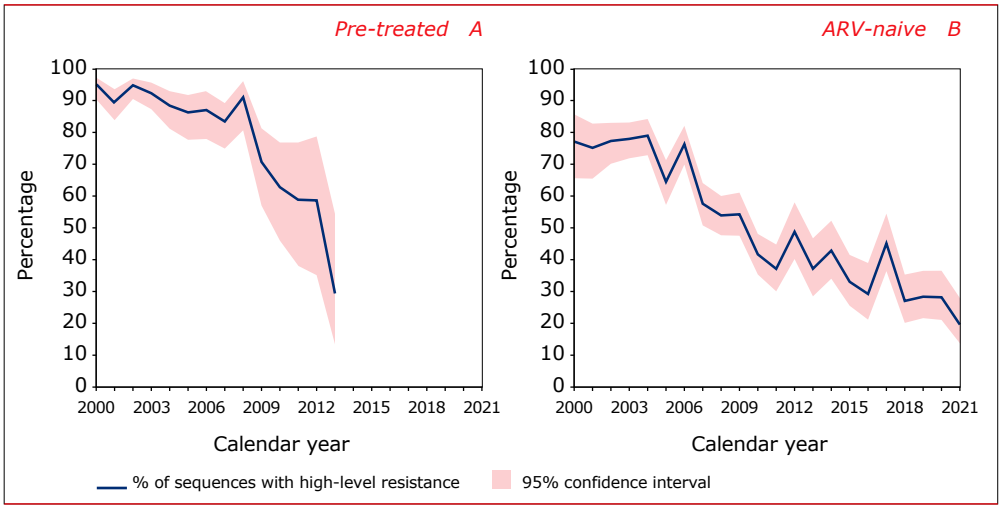
Previous antiretroviral drug exposure

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 90.6-97.4) in 2000, 62.9% (46.0-77.1) in 2010, and 29.4% (12.8-54.2) in 2013 (*Figure 2.15A*). The availability of new drugs, both in existing and new drug classes, largely explains the decline since 2008[33]. In recent years (2014-21), both the number of pre-treated people, and the number of sequences from pre-treated people, were too low to provide meaningful percentages.

Among previously ARV-naïve people, high-level resistance to at least one drug was detected among 77.3% (95% CI 65.7-85.8) of sequences in 2000, 49.1% (40.2-58.2) in 2012, and 19.7% (13.4-27.9) in 2021 (*Figure 2.15B*). Over time, the difference in acquired drug resistance detected among pre-treated and ARV-naïve people has disappeared.

Figure 2.15: *The annual percentage of sequences with evidence of high-level resistance to any antiretroviral drug, obtained at the time of virological failure when receiving combination antiretroviral therapy (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.*



Note: *The number of sequences from pre-treated people in 2014-21 was too low to give meaningful percentages.*

Acquired HIV drug resistance among previously ARV-naïve people

In the remainder of our analysis, we focus solely on the 2,021 people who were ARV-naïve before ART initiation. Overall, 1,849 (57.3%) of the 3,225 sequences from previously ARV-naïve people receiving ART harboured at least one major resistance mutation, which were associated with resistance to NRTI (n=1,461, or 45.3%), NNRTI (n=1,143, or 35.4%), or PI (n=370, or 11.5%).

In *Figure 2.16A*, the annual percentage of sequences harbouring high-level resistance is presented for each antiretroviral drug class. In 2000:

- 77.3% (95% CI 65.7-85.8) of sequences harboured high-level resistance to at least one NRTI;
- 27.7% (18.2-39.7) harboured high-level resistance to at least one NNRTI; and
- 49.2% (37.3-61.2) 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 2011:

- 37.1% (95% CI 30.0-44.9) of sequences harboured high-level resistance to at least one NRTI;
- 25.2% (19.0-32.5) harboured high-level resistance to at least one NNRTI; and
- 1.9% (0.6-5.8) harboured high-level resistance to at least one PI.

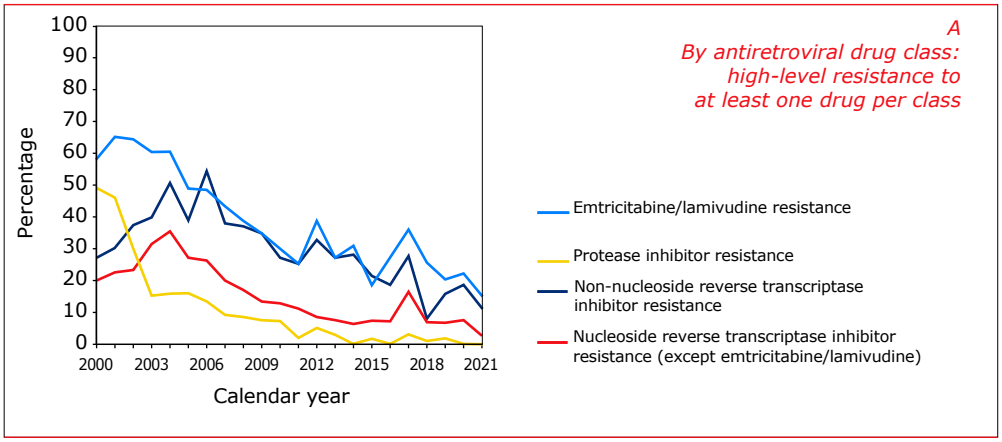
By 2021, these percentages were down to:

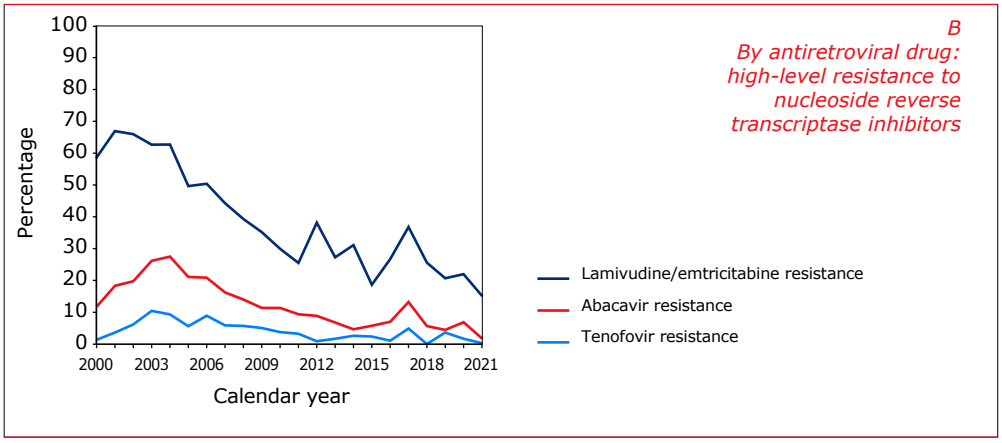
- 19.7% (95% CI 13.4-27.9) of sequences harbouring high-level resistance to at least one NRTI;
- 11.4% (6.6-19.1) harbouring high-level resistance to at least one NNRTI; and
- 0% harbouring high-level resistance to at least one PI.

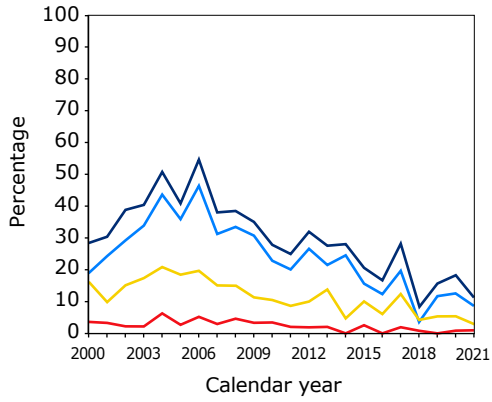
The percentage of sequences with at least one resistance mutation to all three drug classes (i.e. NRTI, NNRTI and PI) also declined over time: from 9.0% (4.1-18.8) in 2000 to 0% in 2014.

The annual percentage of sequences harbouring high-level resistance to individual antiretroviral drugs are presented in *Figure 2.16B-D*. The annual percentage of sequences harbouring major resistance mutations to specific drugs are outlined in *Appendix Table 2.1A-C*. *Figure 2.16E,* meanwhile, shows the annual percentage of sequences harbouring at least one high-level resistance mutation to all three drug classes. It should be pointed out that drug resistance does not disappear when viral replication is successfully suppressed or re-suppressed, but instead remains viably archived in the viral reservoir.

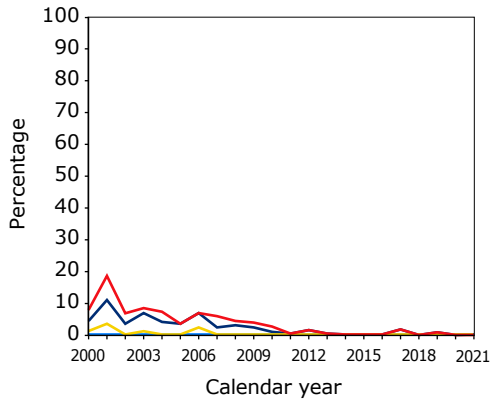
Figure 2.16: *The annual percentage of sequences with evidence of high-level resistance by drug class and antiretroviral drug, obtained at the time of virological failure when receiving combination antiretroviral therapy (ART), among previously antiretroviral drug-naïve people. Results are shown by A) 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.*



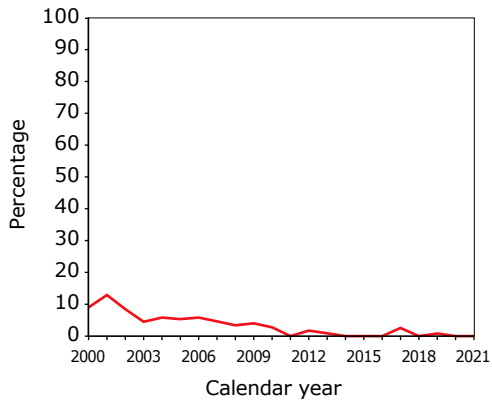




C
By antiretroviral drug: high-level resistance to non-nucleoside reverse transcriptase inhibitors



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



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

Legend: *NRTIs = nucleoside analogue reverse transcriptase inhibitors; NNRTIs = non-nucleoside reverse transcriptase inhibitors; PIs = protease inhibitors.*

Note: *The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.0) was used to infer antiretroviral drug susceptibility scores for each sequence, according to a five-level scheme: susceptible; potential low-level resistance; low-level resistance; intermediate resistance; and high-level resistance*[26,27].

Acquired integrase inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on ART was relatively rare. The available 371 integrase sequences originated from 295 people who received ART for at least four months; 32 were pre-treated with monotherapy or dual NRTI therapy before initiating ART, and 263 were ARV-naïve before initiating ART. Of the 295 people who received ART for at least four months and had integrase gene sequencing available, 288 (97.6%) had been treated with an INSTI-containing regimen. 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 4.6-15.7). For each person, we used the most recent sequence in our analysis.

At least one acquired major mutation associated with integrase inhibitor resistance was detected in 46 of the 295 individuals, which resulted in high-level resistance to at least one integrase inhibitor[25,26]. Among the 46, the following major INSTI resistance mutations were detected (numbers are given in parenthesis):

- N155H (n=16) and N155H/N (n=3);
- R263K (n=6) and R263R/K (n=3);
- E92Q (n=5) and E92E/Q (n=2);
- Y143R (n=2) and Y143Y/C (n=1);
- T66I (n=2) and T66T/I (n=1);
- Q148H (n=1) and Q148R (n=1); and
- S147G (n=1) and S147S/G (n=1).

Minor mutations detected were at position:

- T97 (any, n=6; T97A, n=6);
- T66 (any, n=5; T66T/A, n=3; T66T/K, n=1; T66K, n=1);
- L74 (any mutation, n=3; L74I/L/M, n=1; L74L/M, n=1; L74I/M, n=1);
- G140 (any, n=2; G140S, n=1; G140G/S, n=1); and
- E138 (any, n=1; E138K, n=1).

The 46 individuals who harboured major INSTI resistance mutations had been treated with the following INSTI drugs: raltegravir (n=23), elvitegravir (n=16), dolutegravir (n=33), and bictegravir (n=5). Seven of these 46 individuals 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[34,35]. 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[36]. Normal CD4 cell counts in people without HIV are on average approximately 800 cells/mm^3, but this varies according to factors such as age, ethnicity, sex, and smoking behaviour[37]. Furthermore, although the CD4 cell count is considered the key prognostic factor for mortality and AIDS-defining endpoints, some, but not all studies have suggested that the CD4: CD8 ratio may have additional prognostic value[38-43]. The clinical benefit of ART is strongly related to the level of recovery of the immune status (also see *Chapter 3*)[44-48].

Immunological response by calendar year

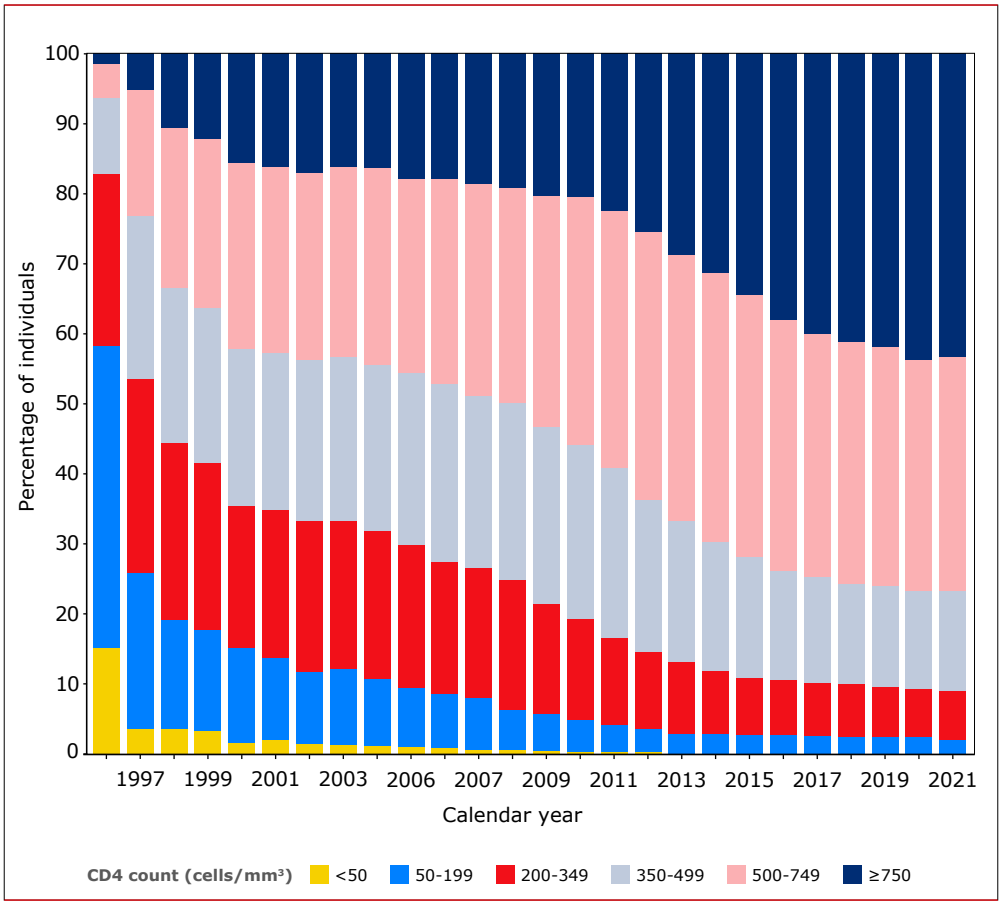
Of the 27,604 people known to have initiated ART between January 1996 and December 2020, CD4 cell count data after ART initiation were available for 26,561 (96.2%). *Figures 2.17* and *2.18* show the last known CD4 cell count and CD4: CD8 ratio of all people in HIV care for each calendar year. After starting ART, the percentage of people with CD4 cell counts below 350 cells/mm^3 dropped from 53.3% in 1997 to (*Figure 2.17*):

- 29.7% in 2005;
- 19.2% in 2010;
- 11.0% in 2015;
- 9.2% in 2020, and
- 8.9% in 2021.

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 2.17: Last available CD4 cell count of the treated population by calendar year (missing measurements/ data were not taken into account). Figures for 2021 may change slightly as data collection is not yet complete.



The percentage of those with a CD4: CD8 ratio of one or above increased from 1.2% in 1997 to (*Figure 2.18*):

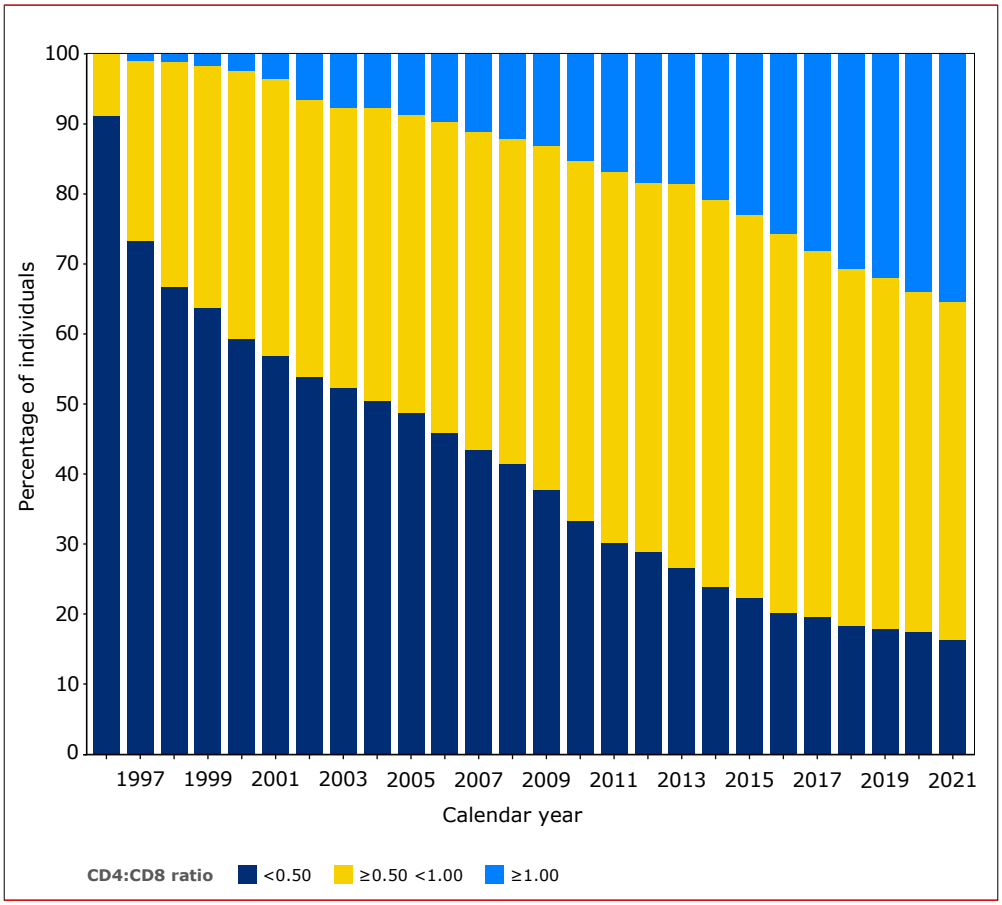
- 2.7% in 2000;
- 8.8% in 2005;
- 15.3% in 2010;
- 23.1% in 2015;
- 34.3% in 2020; and
- 35.6% in 2021.

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

- 10.1% had a CD4 cell count of less than 500 cells/mm^3;
- 31.6% had a CD4 cell count between 500-749 cells/mm^3; and
- 58.2% 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 802 cells/mm^3 (IQR 630-1,010).

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



Immunological response after ART initiation (2016–21)

We also assessed the immunological response in people who started ART more recently (i.e. in 2016-21), 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 3,690 people who started ART in 2016-21 and had sufficient immunological data available:

- 10.9% had CD4 cell counts below 50 cells/mm^3;
- 16.5% had CD4 cell counts between 50-199 cells/mm^3;
- 19.3% had CD4 cell counts between 200-349 cells/mm^3;
- 20.5% had CD4 cell counts between 350-499 cells/mm^3; and
- 32.8% 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 2.19* and *2.20* 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[49].

Figure 2.19: *CD4 cell count over time after the start of combination antiretroviral therapy (ART) in 2016–21.*

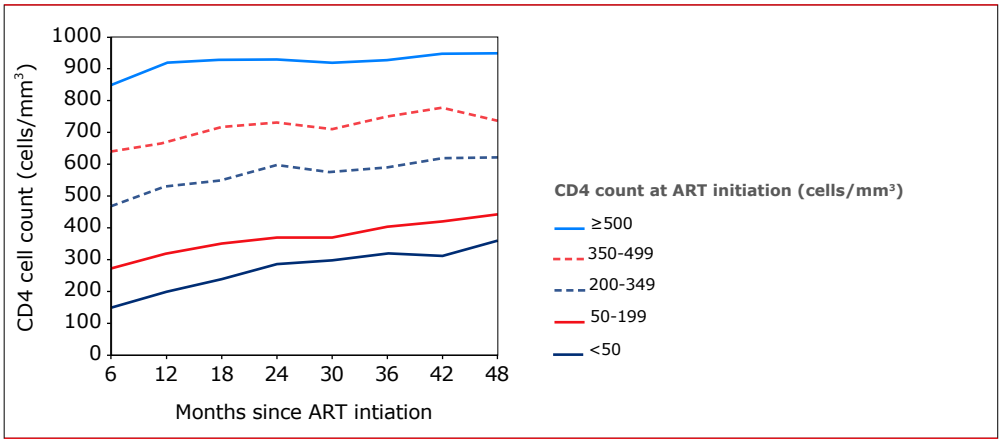
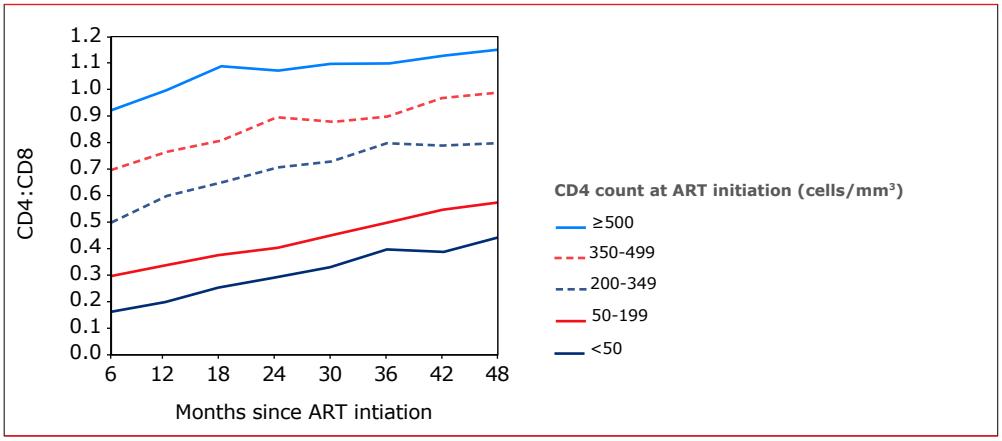


Figure 2.20: CD4: CD8 ratio over time after the start of combination antiretroviral therapy (ART) in 2016-21.



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[60]. 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.
- 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 2021, the median CD4 cell count was 200 cells/mm³ (IQR 51-398). *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 2021, 90.9% of initial regimens contained an integrase inhibitor. The most frequently used initial regimen was bictegravir/emtricitabine/tenofovir alafenamide (41.1%). Dolutegravir-containing initial regimens were used in 47.5% of cases.
- 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 2021

- ART containing two NRTIs plus an integrase inhibitor has been implemented on a large scale in the Netherlands and was used by 46.3% of all individuals. Integrase inhibitors were used by 59.4% of the total population receiving ART, if other integrase inhibitor-containing regimens are also considered.
- The nucleoside analogue backbone used contained TDF in 29.7% of cases, ABC in 13.8%, and TAF in 44.5% of cases.
- In 2021, 11.0% used a two-drug regimen.
- Of those receiving ART for at least 12 months (who had a plasma HIV RNA measurement in 2021) 98.1% had a viral load below 200 copies/ml, and 95.9% had a viral load equal to or below 50 copies/ml.

Virological response and drug resistance

- The overall viral suppression rates of the population 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[51,52].
- Transmitted drug resistance was rare, and the overall prevalence was low and stable over time, in line with rates reported by other European countries[53].
- Integrase inhibitor resistance data remain limited. No transmitted integrase inhibitor resistance was detected among the 201 people tested by the end of 2021. Detected rates of acquired integrase inhibitor resistance among available sequences remained very low, with only a few cases of significant resistance to dolutegravir.

- The number of sequences available in 2020 and 2021 were comparabe to other years, suggesting that the restricted capacity at virology departments during the COVID-19 pandemic did not affect sequencing for drug resistance.

Immunological response

- In individuals receiving ART, the percentage of people with CD4 cell counts below 350 cells/mm^3 dropped from 53.3% in 1997 to:
  - 29.7% in 2005;
  - 19.2% in 2010;
  - 11.0% in 2015;
  - 9.0% in 2020; and
  - 8.9% in 2021.
- The percentage of those with a CD4: CD8 ratio of one or above increased from 1.2% in 1997 to:
  - 8.8% in 2005;
  - 15.3% in 2010;
  - 23.1% in 2015;
  - 34.6% in 2020; and
  - 35.6% in 2021.

References

1. Cole, S. R. *et al.* Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. *Am. J. Epidemiol.* **158**, 687–694 (2003).
2. Rodger, A. J. *et al.* Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA* **316**, 171–81 (2016).
3. European AIDS Clinical Society. European AIDS Clinical Society (EACS) Guidelines. *Version 9* 72 (2017). doi: 10.1002/oby.21371.
4. Shilaih, M. *et al.* Genotypic resistance tests sequences reveal the role of marginalized populations in HIV-1 transmission in Switzerland. *Sci. Rep.* **6**, 27580 (2016).
5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. *Department of Health and Human Services* (2016). Available at: http: //aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. (Accessed: 14th July 2016)
6. World Health Organization. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.* (2016).

7. Ryom, L. *et al.* Highlights of the 2017 European AIDS Clinical Society (EACS) Guidelines for the treatment of adult HIV-positive persons version 9.0. *HIV Med.* 1–7 (2018). doi: 10.1111/hiv.12600
8. Richtlijn HIV - Nederlandse Vereniging van HIV Behandelaren (NVHB). Available at: https://richtlijnhiv.nvhb.nl/index.php/Inhoud. (Accessed: 5th October 2021)
9. Grinsztejn, B. *et al.* Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect. Dis.* **14**, 281–90 (2014).
10. Cohen, M. S. *et al.* Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *N. Engl. J. Med.* **365**, 493–505 (2011).
11. Prevention Access Campaign. Consensus Statement: Risk of sexual transmission of HIV from a person with HIV who has an undetectable viral load - Messaging Primer & Consensus Statement. *2017*
12. Nederlandse Vereniging van HIV Behandelaren. Het risico om hiv over te dragen is verwaarloosbaar klein indien de infectie goed behandeld wordt. *May 3* (2017). Available at: http://nvhb.nl/2017/05/03/wetenschappelijk-onderzoek-toont-aan-dat-het-risico-om-hiv-over-te-dragen-verwaarloosbaar-klein-is-indien-de-infectie-goed-behandeld-wordt/.
13. Quinn, T. C. *et al.* Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N. Engl. J. Med.* **342**, 921–9 (2000).
14. Tovanabutra, S. *et al.* Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. *J.Acquir.Immune.Defic.Syndr.* **29**, 275–283 (2002).
15. Reynolds, S. J. *et al.* HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. *AIDS* **25**, 473–477 (2011).
16. Rodger, A. J. *et al.* Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA* **316**, 171–81 (2016).
17. Raboud, J. M. *et al.* Consecutive rebounds in plasma viral load are associated with virological failure at 52 weeks among HIV-infected patients. *AIDS* **16**, 1627–1632 (2002).
18. Karlsson, A. C. *et al.* Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. *AIDS* **18**, 981–9 (2004).
19. Hughes, R. A. *et al.* Long-term trends in CD4 cell counts and impact of viral failure in individuals starting antiretroviral therapy: UK Collaborative HIV Cohort (CHIC) study. *HIV Med.* **12**, 583–593 (2011).

20. van Lelyveld, S. F. *et al.* Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS* **26**, 465–474 (2012).
21. Zhang, S. *et al.* Clinical significance of transient HIV type-1 viraemia and treatment interruptions during suppressive antiretroviral treatment. *Antivir. Ther.* **15**, 555–562 (2010).
22. Easterbrook, P. J. *et al.* The natural history and clinical significance of intermittent viraemia in patients with initial viral suppression to <400 copies/ml. *AIDS* **16**, 1521–1527 (2002).
23. Raffanti, S. P. *et al.* Effect of persistent moderate viremia on disease progression during HIV therapy. *J. Acquir. Immune Defic. Syndr.* **37**, 1147–1154 (2004).
24. Boender, T. S. *et al.* AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort: cohort profile. *BMJ Open* **8**, e022516 (2018).
25. Wensing, A. M. *et al.* 2019 update of the drug resistance mutations in HIV-1. *Top. Antivir. Med.* **27**, 111–121 (2019).
26. Stanford University. HIV Drug Resistance Database - Release Notes.
27. Liu, T. F. & Shafer, R. W. Web resources for HIV type 1 genotypic-resistance test interpretation. *Clin Infect Dis* **42**, 1608–18 (2006).
28. World Health Organization. *HIV Drug Resistance Report 2017*. (World Health Organization, 2017).
29. Little, S. J. *et al.* Persistence of Transmitted Drug Resistance among Subjects with Primary Human Immunodeficiency Virus Infection. *J. Virol.* **82**, 5510–5518 (2008).
30. Bezemer, D. *et al.* Evolution of transmitted HIV-1 with drug-resistance mutations in the absence of therapy: Effects on CD4 + T-cell count and HIV-1 RNA load. *Antivir. Ther.* **11**, 173–178 (2006).
31. Barbour, J. D. *et al.* Persistence of primary drug resistance among recently HIV-1 infected adults. *AIDS* **18**, 1683–9 (2004).
32. Boukli, N. *et al.* Utility of HIV-1 DNA genotype in determining antiretroviral resistance in patients with low or undetectable HIV RNA viral loads. *J. Antimicrob. Chemother.* **73**, 3129–3136 (2018).
33. Lange, J. M. & Ananworanich, J. The discovery and development of antiretroviral agents. *Antivir. Ther.* **19 Suppl 3**, 5–14 (2014).
34. Gras, L. *et al.* CD4 cell counts of 800 cells/mm^3 or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm^3 or greater. *J. Acquir. Immune Defic. Syndr.* **45**, 183–92 (2007).
35. Hughes, R. A. *et al.* Long-term trends in CD4 cell counts and impact of viral failure in individuals starting antiretroviral therapy: UK Collaborative HIV Cohort (CHIC) study. *HIV Med.* **12**, 583–593 (2011).

36. van Lelyveld, S. F. *et al.* Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS* **26**, 465–474 (2012).
37. Tsegaye, A. *et al.* Immunohematological reference ranges for adult Ethiopians. *Clin Diagn Lab Immunol* **6**, 410–414 (1999).
38. Serrano-Villar, S. *et al.* The CD4: CD8 ratio is associated with markers of age-associated disease in virally suppressed HIV-infected patients with immunological recovery. *HIV Med.* **15**, 40–49 (2014).
39. Serrano-Villar, S. *et al.* Increased risk of serious non-AIDS-related events in HIV-infected subjects on antiretroviral therapy associated with a low CD4/CD8 ratio. *PLoS One* **9**, (2014).
40. Serrano-Villar, S. *et al.* HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8 + T cell activation, and increased risk of non-AIDS morbidity and mortality. *PLoS Pathog.* **10**, e1004078 (2014).
41. Lo, J. *et al.* Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. *AIDS* **24**, 243–253 (2010).
42. O'Connor, J. *et al.* Durability of viral suppression with first-line antiretroviral therapy in patients with HIV in the UK: an observational cohort study. *Lancet HIV* **3018**, 1–8 (2017).
43. The Antiretroviral Therapy Cohort Collaboration (ART-CC). Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *Lancet HIV* **3018**, (2017).
44. Effros, R. B. *et al.* Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. *Clin Infect Dis* **47**, 542–53 (2008).
45. Baker, J. V *et al.* CD4 + count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS* **22**, 841–848 (2008).
46. Baker, J. V *et al.* Poor initial CD4 + recovery with antiretroviral therapy prolongs immune depletion and increases risk for AIDS and non-AIDS diseases. *JAIDS J. Acquir. Immune Defic. Syndr.* **48**, 541–546 (2008).
47. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* **372**, 293–299 (2008).
48. Lanoy, E. *et al.* Prognosis of patients treated with ART from 36 months after initiation, according to current and previous CD4 cell count and plasma HIV-1 RNA measurements. *AIDS* **23**, 2199–2208 (2009).
49. Hughes, R. A. *et al.* Long-term trends in CD4 cell counts, CD8 cell counts, and the CD4. *Aids* **32**, 1361–1367 (2018).

50. Nederlandse Vereniging van HIV Behandelaren. 4.1. Controles HIV-patiënten (polikliniek). *Richtlijn HIV*
51. Scherrer, A. U. *et al.* Emergence of acquired HIV-1 drug resistance almost stopped in Switzerland: A 15-year prospective cohort analysis. *Clin. Infect. Dis.* **62**, 1310–1317 (2016).
52. Buchacz, K. *et al.* Trends in decline of antiretroviral resistance among ARV-experienced patients in the HIV outpatient study: 1999-2008. *AIDS Res. Treat.* **2012**, (2012).
53. Hofstra, L. M. *et al.* Transmission of HIV drug resistance and the predicted effect on current first-line regimens in Europe. *Clin. Infect. Dis.* **62**, 655–663 (2016).

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									
	2017		2018		2019		2020		2021	
Treatment/mutation	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Emtricitabine/lamivudine										
K65R, E or N	5	4.8	4	3.3	3	2.3	5	4.5	1	1.1
M184V or I	39	37.1	31	25.8	27	20.9	25	22.7	14	15.9
Abacavir										
K65R, E or N	5	4.8	4	3.3	3	2.3	4	3.8	1	1.2
L74V	4	3.8	2	1.7	2	1.6	3	2.8	0	0
Y115F	4	3.8	1	0.8	2	1.6	3	2.8	0	0
M184V	36	34.6	26	21.7	20	15.6	18	17	8	9.4
Tenofovir										
K65R, E or N	5	4.9	0	0	4	3.1	2	1.9	0	0
K70R	0	0	1	0.9	1	0.8	0	0	1	1.2

B

	Calendar year									
	2017		2018		2019		2020		2021	
Treatment/mutation	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Nevirapine										
L100I	1	1.0	1	0.8	0	0	0	0	0	0
K101P	0	0	0	0	0	0	0	0	0	0
K103N or S	11	10.5	4	3.3	12	9.1	11	10.3	6	6.8
V106A or M	6	5.7	0	0	1	0.8	5	4.7	0	0
V108I	6	5.7	1	0.8	5	3.8	4	3.7	0	0
Y181C or I	12	11.4	5	4.2	7	5.3	8	7.5	4	4.5
Y188L, C or H	0	0	0	0	2	1.5	1	0.9	0	0
G190A	9	8.6	0	0	0	0	2	1.9	1	1.1
M230L	0	0	0	0	1	0.8	0	0	1	1.1
Etravirine										
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	2	2.1	1	0.9	0	0	0	0	1	1.2
Efavirenz										
L100I	1	1.0	1	0.9	0	0	0	0	0	0
K101P	0	0	0	0	0	0	0	0	0	0
K103N or S	12	12.5	4	3.5	12	9.5	11	10.8	6	7.1
V106M	2	2.1	0	0	1	0.8	2	2.0	0	0
V108I	5	5.2	0	0	2	1.6	1	1.0	0	0
Y181C or I	7	7.3	1	0.9	1	0.8	2	2.0	1	1.2
Y188L	0	0	0	0	1	0.8	0	0	0	0
G190S or A	8	8.3	0	0	0	0	2	2.0	1	1.2
P225H	0	0	0	0	1	0.8	0	0	1	1.2
M230L	1	1.0	1	0.9	0	0	0	0	1	1.2
Rilpivirine										
L100I	1	1.0	1	0.9	0	0	0	0	0	0
K101E or P	4	3.8	1	0.9	1	0.8	2	1.9	1	1.2
E138A, G, K, Q or R	7	6.7	6	5.1	7	5.5	10	9.7	4	4.7
V179L	1	1.0	0	0	0	0	0	0	0	0
Y181C, I or V	9	8.7	3	2.6	4	3.1	3	2.9	2	2.3
Y188L	0	0	0	0	1	0.8	0	0	0	0
H221Y	2	1.9	1	0.9	3	2.3	2	1.9	1	1.2
F227C	0	0	0	0	0	0	0	0	0	0
M230I or L	0	0	0	0	1	0.8	0	0	1	1.2

C

	Calendar year									
	2017		2018		2019		2020		2021	
Treatment/mutation	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Atazanavir										
I50L	0	0	0	0	0	0	0	0	0	0
I84V	0	0	0	0	1	1.0	0	0	0	0
N88S	0	0	0	0	0	0	0	0	0	0
Darunavir										
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										
V32I	1	1.1	1	1.1	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	2	2.1	0	0	1	1.0	0	0	0	0
L76V	0	0	0	0	1	1.0	0	0	0	0
V82A, F, T or S	0	0	0	0	0	0	0	0	0	0
I84V	0	0	0	0	1	1.0	0	0	0	0
Tipranavir										
I47V	0	0	0	0	0	0	0	0	0	0
Q58E	1	1.1	0	0	0	0	2	2.4	1	1.6
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 2016–21.*

Year of ART initiation	2016	2017	2018	2019	2020	2021	2016–2021
CD4 cell count available at ART initiation	936	843	710	605	404	192	**3,690**
CD4 cell count, median cells/mm³ (IQR)	410 (240–580)	380 (200–560)	376 (167–580)	360 (169–570)	300 (126–545)	200 (51–398)	**370 (173–566)**
CD4 cell count (cells/mm³)							
<50	8.9%	8.4%	11.1%	10.6%	14.3%	24.5%	**10.0%**
50–199	12.1%	16.3%	16.9%	18.5%	19.1%	25.5%	**16.0%**
200–349	18.3%	19.6%	18.6%	19.0%	22.3%	19.8%	**19.4%**
350–499	23.3%	22.8%	19.4%	19.5%	16.6%	13.0%	**21.0%**
≥500	37.5%	33.0%	33.9%	32.4%	27.7%	17.2%	**33.5%**

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

3. Morbidity and mortality

Ferdinand Wit, Berend van Welzen, Marc van der Valk

Introduction

Since the introduction of combined antiretroviral therapy (ART) in 1996, the life expectancy of people with HIV (PWH) has markedly improved; in a subgroup of recently-diagnosed, effectively-treated individuals, it was shown to be similar to that of the general population in the Netherlands[1]. Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased[2], morbidity and/or mortality associated with non-AIDS-related diseases has increased among PWH during the ART era[3–8]. 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 morbidity may be higher in individuals with HIV treated with ART, than in HIV-negative individuals of comparable age[9-11]. For example pulmonary hypertension[12], bone disease, and non-traumatic bone fractures[13-15] have each been reported to be more common in PWH. There is also a concern that HIV-related neurocognitive impairment may persist, or even progress, despite otherwise effective long-term ART[16-18]. Just as with HIV-negative individuals, traditional risk factors (such as tobacco use[19], alcohol abuse, and viral hepatitis co-infection[20]) also contribute to the increased risk of certain non-AIDS 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[21,22].

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 28,240 adult individuals ever registered by SHM – that breaks down as 27,760 adults and an additional 479 individuals who were diagnosed with HIV as children and have since become adults. In addition, we report on the incidence of AIDS and non-AIDS comorbidities, particularly diabetes mellitus, cardiovascular disease, chronic kidney disease (CKD), and non-AIDS malignancies in PWH.

Definitions

AIDS is defined as having experienced any of the United States' Centers for Disease Control (CDC) category C conditions[23]. 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 2016-20. We standardised these estimates according to the age distribution of the population during the period 2016-20 (divided into the following age classes: 18-29, 30-39, 40-49, 50-59, 60-69, and 70 years and over), using the indirect method[24]. Indirect standardisation compares the incidence rates in the study and reference (period: 2016-20) populations by applying the stratum-specific rates in the reference population to the study population. We investigated risk factors for AIDS, death,

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

The baseline for treated and untreated 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/mm3;
- 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 29,039 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 7.4-10.5) per 1,000 PYFU in 2010. It has since remained stable at that 2010 level up to 2020, but the observed mortality rate had increased slightly to 11.2 (9.8-12.9) in 2021 (*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 5.5 per 1,000 PYFU in 2021.

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 8.4 (7.2-9.9) per 1,000 PYFU in 2020, and 10.2 (8.7-11.9) in 2021. *Appendix Figure 3.1* shows the five-year survival curves after diagnosis of the first AIDS-defining condition, compared to survival for all people with HIV as well as survival after diagnosis of several common, non-AIDS-defining comorbidities.

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 HIV-positive individuals who present late for care with advanced immune deficiency. As such, the rate still falls short of the aim of zero AIDS-deaths by 2022, as stated in the Netherlands' National Action Plan on STIs, HIV and Sexual Health[25]. *Table 3.1* shows the characteristics of adults with HIV who died of AIDS, compared to those who died of non-AIDS causes in the period 2012-21. 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 62.9% 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 57% of cases, they did not have controlled viremia, and 15.5% 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 3.2*), primarily as a consequence of the ever increasing size and average age of the population of people with HIV in the Netherlands. People with HIV that were born in the Netherlands, MSM and men in general are overrepresented among those who died of non-AIDS causes, because people in these three (overlapping) categories have a higher average age compared to migrants, HIV transmission categories other than MSM, and women. Independent risk factors for death and for being diagnosed with an AIDS-defining condition are listed in *Appendix Table 3.2*.

Table 3.1: Characteristics of adults with HIV who died of AIDS compared to adults with HIV who died of non-AIDS causes in the period 2012-21.

	Died of non-AIDS causes	Died of AIDS	p-value
Number of subjects	1487 (86.5%)	232 (13.5%)	
Age	59.1 (51.2-67.9)	54 (45.1-61.8)	<.001
Male gender	1293 (87.0%)	188 (81.0%)	0.019
Dutch origin	1058 (71.1%)	143 (61.6%)	0.004
MSM	843 (56.7%)	106 (45.7%)	0.002
Heterosexual transmission	390 (26.2%)	78 (33.6%)	0.021
Other transmission categories	254 (17.1%)	48 (20.7%)	0.194
Years since HIV diagnosis	15 (8.26-21.6)	6.6 (0.69-13.6)	<.001
Years since start ART	12.3 (6.08-17.6)	2.87 (0.34-11.9)	<.001
CD4 at HIV diagnosis	290 (111-510)	115 (30-315)	<.001
Late presenter (CD4<350 at entry in care	831 (56.0%)	178 (78.1%)	<.001
Very late presenter (CD4<200)	545 (36.7%)	146 (62.9%)	<.001
CD4 nadir	140 (50-252)	50 (12-110)	<.001
Last CD4 measured before death	480 (290-690)	140 (43-310)	<.001
Not undetectable at date of death	228 (15.4%)	126 (56.5%)	<.001
Not on ART at date of death	102 (6.9%)	36 (15.5%)	<.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) Annual mortality and (B) incidence of AIDS in 29,039 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.*

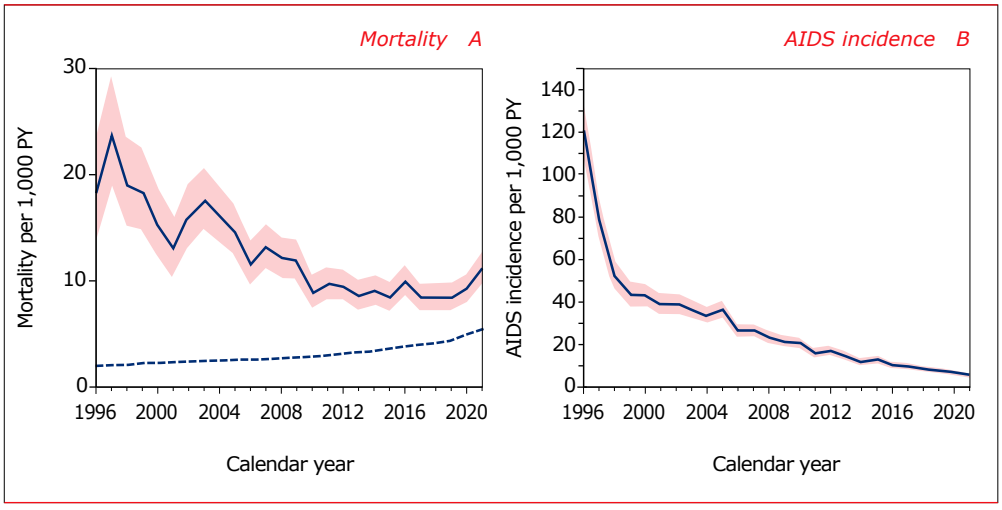
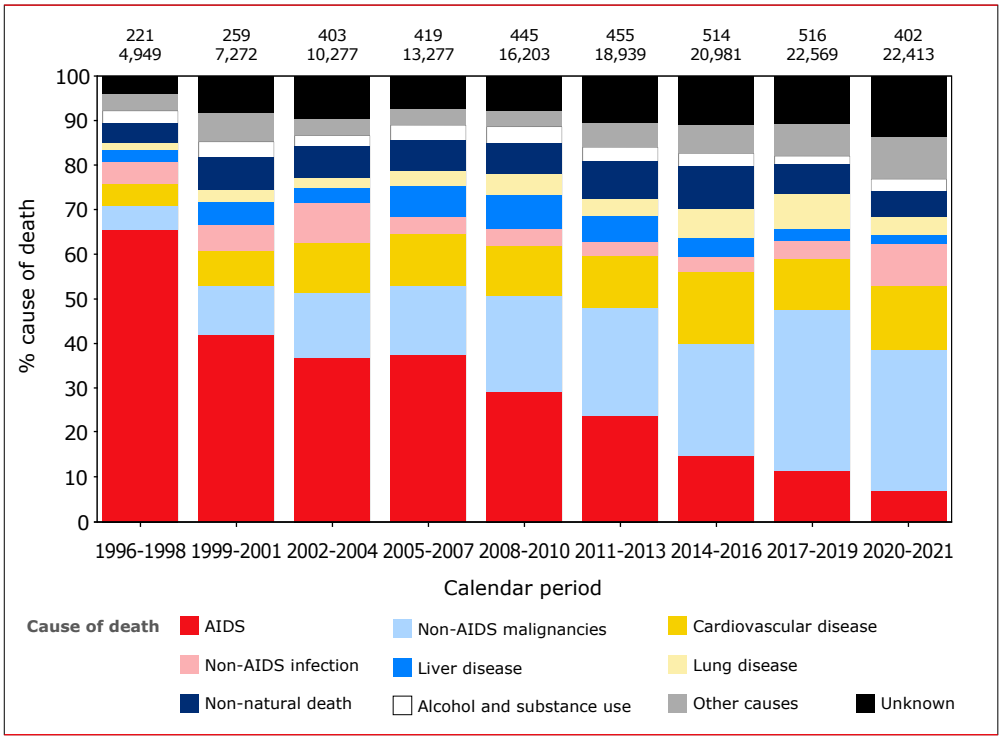


Figure 3.2: Relative changes in causes of death in different calendar periods since the introduction of combination antiretroviral therapy (ART) in the Netherlands. The numbers at the top of each bar represent the total number of deaths and the total number of individuals that were at risk during that 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 2021 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[26].

,

For patients with a serious somatic condition, who opted for euthanasia in the terminal disease stage, the underlying somatic condition was recorded as the cause of death. In the entire follow-up period from 1996 to 2021, a total of 151 instances of euthanasia were recorded; 30% of cases occurred in patients who died of AIDS, 40% in patients who died of non-AIDS-defining malignancies, and the remaining 30% in patients who died of other diseases. Our definition of euthanasia does not include the use of standard practice palliative care, such as palliative sedation in the terminal phase of the underlying disease.

AIDS-defining events

In the group of 29,039 adult PWH ever registered in the SHM database, the incidence of first AIDS-defining events decreased sharply from 121.0 (95% CI 108.5-134.6) in 1996 to 5.7 (4.7-6.9) cases per 1,000 PYFU in 2021 (*Figure 3.1B*). *Appendix Table 3.4* gives an overview of the first AIDS-defining events occurring between 1996 and 2021. The most common first AIDS-defining events between 2016 and 2021 were:

- *Pneumocystis jirovecii* pneumonia (21% of all events);
- oesophageal candidiasis (17%);
- Kaposi's sarcoma (11%);
- tuberculosis (pulmonary 8%, extrapulmonary 5%);
- lymphoma (6%);
- recurrent bacterial pneumonia (5%);
- AIDS-related wasting (5%);
- toxoplasmosis of the brain (4%);
- AIDS dementia complex/HIV encephalopathy (3%); and
- cytomegalovirus-associated end organ disease (3%).

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

In the present analyses, we concentrate on the first occurrence of any AIDS-defining event after the start of 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 2021, 25,684 individuals contributed a total of 224.9 thousand PYFU, during which 3,013 CDC-B and/or CDC-C (AIDS-defining events) were diagnosed. This resulted in an incidence rate of 12.4 events per 1,000 PYFU (1,647 CDC-B events, 6.8 events/1,000 PYFU; 1,366 CDC-C/AIDS events, 5.6 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 10.7 and 5.5 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 2.9 (95% CI 2.6-3.2) and 1.8 (1.5-2.1) events/1,000 PYFU, respectively. Note that the incidence in the over 750 cells/mm^3 stratum is statistically significantly lower than in the 500-749 cells/mm^3 stratum. In these highest CD4 strata, the main AIDS-defining events that still occurred were:

- recurrent bacterial pneumonia;
- Kaposi's sarcoma;
- oesophageal candidiasis;
- non-Hodgkin's lymphoma;
- tuberculosis (pulmonary and extrapulmonary);
- 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 2021 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)
0-49	252	101	151	0.6	456 (401-516)	183 (149-222)	273 (231-320)
50-199	581	304	277	8.6	67.7 (62.3-73.4)	35.4 (31.5-39.6)	32.3 (28.6-36.3)
200-349	636	341	295	27.6	23.0 (21.3-24.9)	12.4 (11.1-13.7)	10.7 (9.51-12.0)
350-499	563	295	268	48.4	11.6 (10.7-12.6)	6.10 (5.42-6.83)	5.54 (4.90-6.24)
500-749	623	375	248	85.4	7.30 (6.73-7.89)	4.39 (3.96-4.86)	2.90 (2.55-3.29)
750+	358	231	127	71.6	5.00 (4.49-5.54)	3.22 (2.82-3.67)	1.77 (1.48-2.11)
Total	**3013**	**1647**	**1366**	**242.2**	**12.4 (12.0-12.9)**	**6.80 (6.48-7.14)**	**5.64 (5.35-5.95)**

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 2021 a cumulative total of 1,125 cases of tuberculosis were diagnosed in 939 individuals, of which 656 (58.3%) were pulmonary cases and 469 (41.7%) were extrapulmonary/disseminated tuberculosis cases. During that same period, 531 cases of other mycobacterial infections were diagnosed in 473 individuals: 21 pulmonary and 304 extrapulmonary M. avium or M. kansasii cases, and 57 pulmonary and 149 extrapulmonary / disseminated cases of other atypical mycobacterial infections. *Figures 3.3A & 3.3B* 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 (50.4%) or from south(-east) Asia (8.9%) were strongly overrepresented among the tuberculosis cases, while those of Dutch origin (16.5%) and people from other western European countries (3.8%) were underrepresented. People originating from central and eastern European countries represented 3.4% and 1.6% of tuberculosis cases. Region of origin was not strongly associated with 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

Five per cent of the individuals diagnosed with pulmonary tuberculosis and 4.5% of the individuals diagnosed with extrapulmonary tuberculosis died within 365 days of the diagnosis, with the reported cause of death being 'AIDS' or 'infection'. The disease-related mortality rates within 365 days of diagnosis were:

- 0% for pulmonary and 16.8% for extrapulmonary M. avium / kansasii infections;
- 7.0% for pulmonary and 20.8% 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.

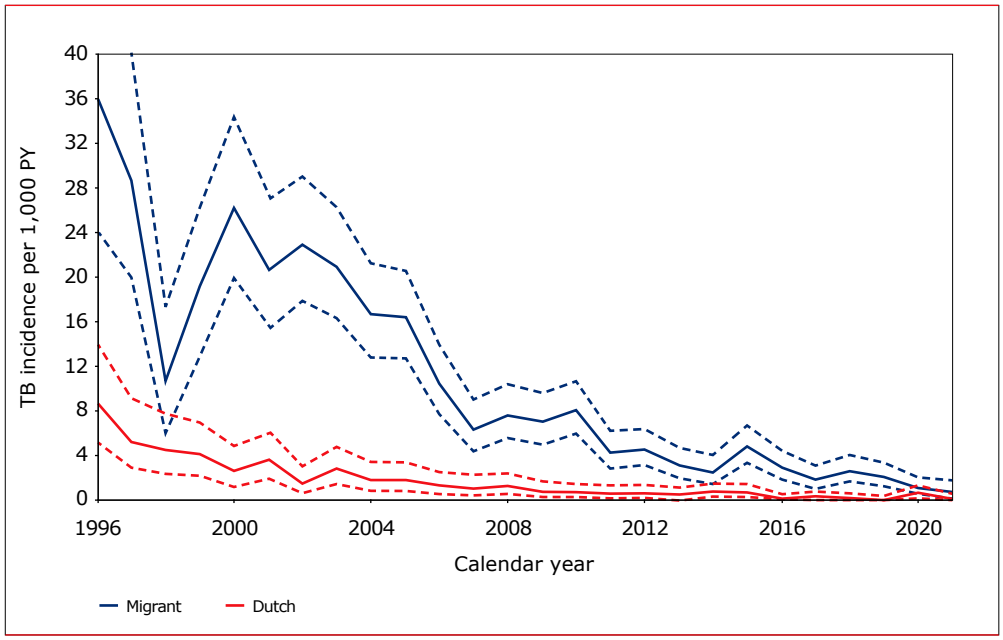
SHM has been collecting data on LTBI screening and treatment since 2018. IGRA testing during an episode in which active TB was diagnosed, was excluded from this dataset. A limitation of our analysis of LTBI screening is that we do not have data on whether, at the time of IGRA testing, the individual had complaints that may have been caused by tuberculosis, which then prompted the treating physician to perform IGRA testing. In 22.6% 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 1,534 individuals. In 142 (9.3%) of these individuals LTBI testing was positive, and 56 (39.4%) of those received a course of LTBI treatment. LTBI treatment consisted of:

- isoniazid plus rifampicin (typically for a duration of three months) in 15 individuals;
- isoniazid monotherapy (typically for a duration of six to nine months) in 32 individuals; and
- rifampicin monotherapy (typically for a duration of four months) in three individuals.

A further six individuals received another non-standard treatment. In the 142 individuals who tested positive on LTBI screening, one case of active extrapulmonary tuberculosis developed (four months after diagnosis) while that individual was receiving treatment consisting of rifampicin plus isoniazid. Of the 86 individuals with positive LTBI screening who did not receive LTBI treatment, 15 (17.4%) were known to have been diagnosed with and treated for active tuberculosis prior to the LTBI screening.

Figure 3.3A & 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).



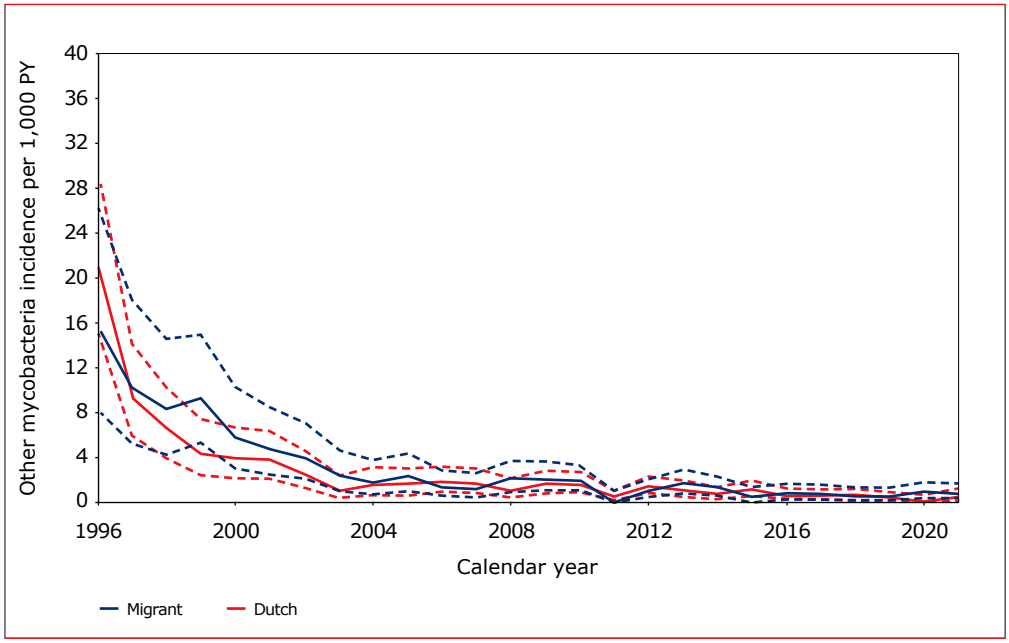


Table 3.3: Characteristics at the time individuals were diagnosed with tuberculosis or other mycobacterial infections for the first time.

	Tuberculosis	Other mycobacterial infections	p-value
Number of subjects	939 (66.5%)	473 (33.5%)	
Age	36.8 (30.5-44.6)	40 (34.5-47.5)	<.001
Male gender	625 (66.6%)	380 (80.3%)	<.001
Dutch origin	176 (18.7%)	270 (57.1%)	<.001
MSM	209 (22.3%)	218 (46.1%)	<.001
Heterosexuals	535 (57.0%)	182 (38.5%)	<.001
Other risk groups	195 (20.8%)	73 (15.4%)	0.018
Years since HIV diagnosis	0.91 (0.5- 4.5)	1.16 (0.61-6.55)	<.001
Years since start ART	0.41 (0-0.99)	0.63 (0.26- 1.3)	<.001
CD4 at HIV diagnosis	190 (60-400)	40 (10-197)	<.001
Late presenter (CD4<350 at entry in care	430 (69.0%)	356 (84.8%)	<.001
Very late presenter (CD4<200)	633 (67.4%)	368 (77.8%)	<.001
CD4 nadir	110 (40-242)	20 (10- 50)	<.001
Last CD4 measured before event	210 (100-370)	90 (23-180)	<.001
Not undetectable at date of event	774 (82.4%)	360 (76.1%)	0.006
Not on ART at date of event	682 (72.6%)	229 (48.4%)	<.001

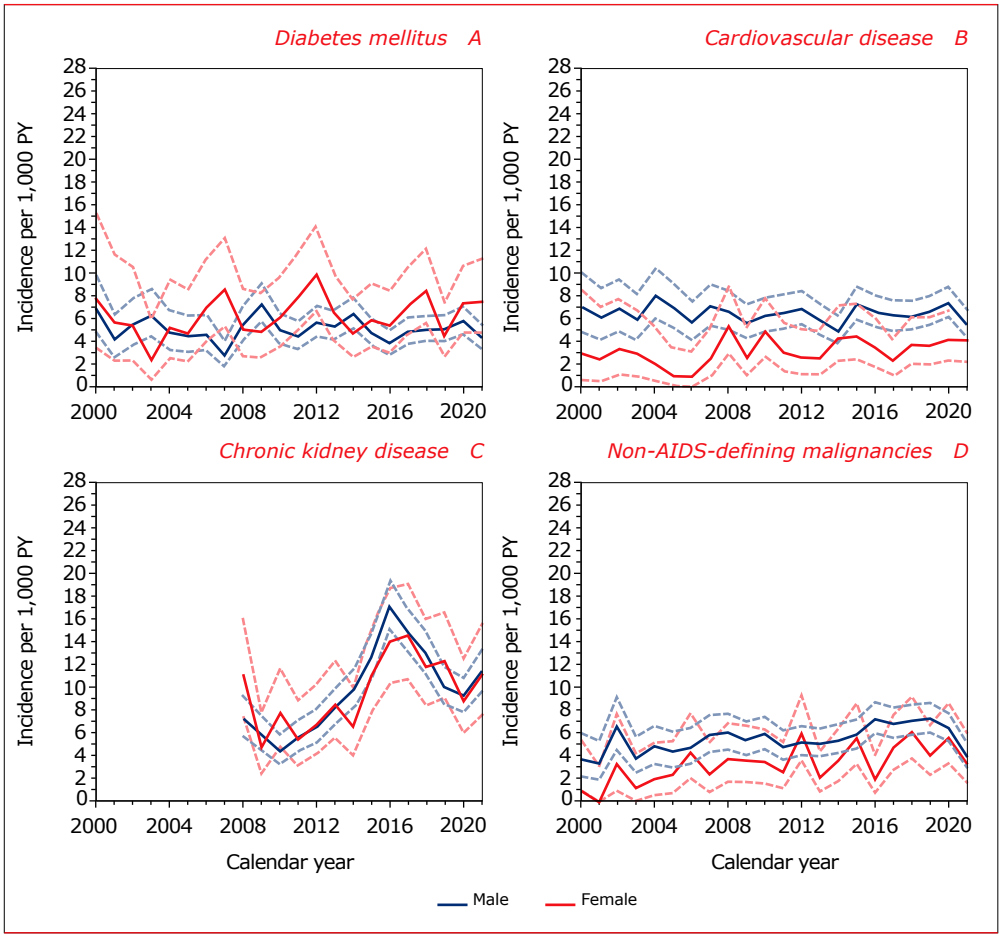
Non-AIDS-defining events

Of the 29,039 adult PWH ever registered with SHM, 28,695 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 (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 3.4*).

Figure 3.4: *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 28,695 individuals aged 18 years and over who were in follow up in, or after, January 2000, a total of 1,624 (n=1,248 men and n=376 women) were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.4A*), and in 2021 was 4.3 (95% CI 3.3-5.6) per 1,000 PYFU in men and 7.5 (4.7-11.2) per 1,000 PYFU in women. In men, the age-standardised incidence ratio declined over time and was significantly lower in 2016-21 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 2016-21 (*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; and
- a prior AIDS diagnosis (*Appendix Table 3.5*).

Moreover, the risk of new-onset diabetes in the periods 2000-10 and 2011-15 was significantly higher than in the period 2016-21. A longer time on didanosine was also significantly associated with an increased risk.

Table 3.4: *Crude incidence of diabetes mellitus per 1,000 person years of follow up in 2000–10, 2011–15 and 2016–21 and age-standardised incidence ratio (indirect method) with 95% confidence intervals.*

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)
2000–2010	5.2 (4.7–5.7)	1.40 (1.27–1.54)	5.8 (4.8–6.9)	0.99 (0.82–1.16)
2011–2015	5.3 (4.8–5.9)	1.24 (1.11–1.37)	6.9 (5.7–8.3)	1.09 (0.89–1.30)
2016–2021	4.9 (4.4–5.3)	1 (reference)	6.7 (5.7–8.0)	1 (reference)

**Standardised according to the observed age distribution between 2016–21.*

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

Cardiovascular disease

From January 2000 onwards, 1,759 individuals (n=1,566 men and n=193 women) had a fatal or non-fatal cardiovascular event. Of these:

- 874 had a myocardial infarction;
- 635 had a stroke;
- 134 had a coronary artery bypass graft;
- 630 had a coronary angioplasty or stenting; and
- 14 had a carotid endarterectomy.

The crude incidence over time remained stable and was lower in women than in men (*Figure 3.4B*). The 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 and past smoking; and
- the presence of hypertension.

Estimated cardiovascular risk using the D:A:D algorithm was also higher during 2000-10 and 2011-15 than during 2016-21, independent of other variables included in the analysis (*Appendix Table 3.5*). The strong positive association between use of abacavir and CVD was independent of renal function. When eGFR, estimated using the Cockcroft-Gault method (available from 2007 onwards), was included in the model the abacavir effect was only slightly attenuated, decreasing from an incidence risk ratio (IRR) of 1.58 to 1.43, $p<0.001$. 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 1.08 (95% CI 0.95-1.23), p = 0.22;
- at 30-60 ml/min the IRR was 1.65 (1.36-2.00), p<0.001;
- at 15-30 ml/min, the IRR was 4.82 (3.37-6.90), p<0.001; and
- at 0-15 ml/min the IRR was 3.80 (2.22-6.52), p<0.001.

From January 2000 onwards, 229 men and 23 women experienced a fatal or non-fatal secondary cardiovascular event (n=141 myocardial infarction, n=119 stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2021 in men and women with a prior cardiovascular event was 27.1 (23.7-30.8) and 19.9 (12.6-29.8), respectively. The crude rate and age-standardised incidence ratio (SIR; indirect method) of secondary myocardial infarction and stroke per 1,000 PYFU changed significantly during 2000-10 (crude rate: 30.1 events per 1,000 PYFU; SIR: 1.24, 95% CI 0.96-1.51), but not during 2011-15 (crude rate: 24.3 events per 1,000 PYFU; SIR: 0.98, 95% CI 0.74-1.22) compared with the reference period 2016-20 (crude rate: 25.1 events per 1,000 PYFU).

Table 3.5: *Crude incidence of cardiovascular disease per 1,000 person years of follow up in 2000–10, 2011–15, and 2016–21 and age-standardised incidence ratio with 95% confidence intervals.*

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)
2000–2010	6.5 (6.0–7.1)	1.52 (1.39–1.65)	2.9 (2.2–3.6)	1.40 (1.06–1.74)
2011–2015	6.3 (5.7–6.9)	1.19 (1.07–1.30)	3.3 (2.5–4.4)	1.18 (0.87–1.49)
2016–2021	6.4 (5.9–6.9)	1 (reference)	3.5 (2.7–4.4)	1 (reference)

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

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

Trends in cardiovascular risk factors

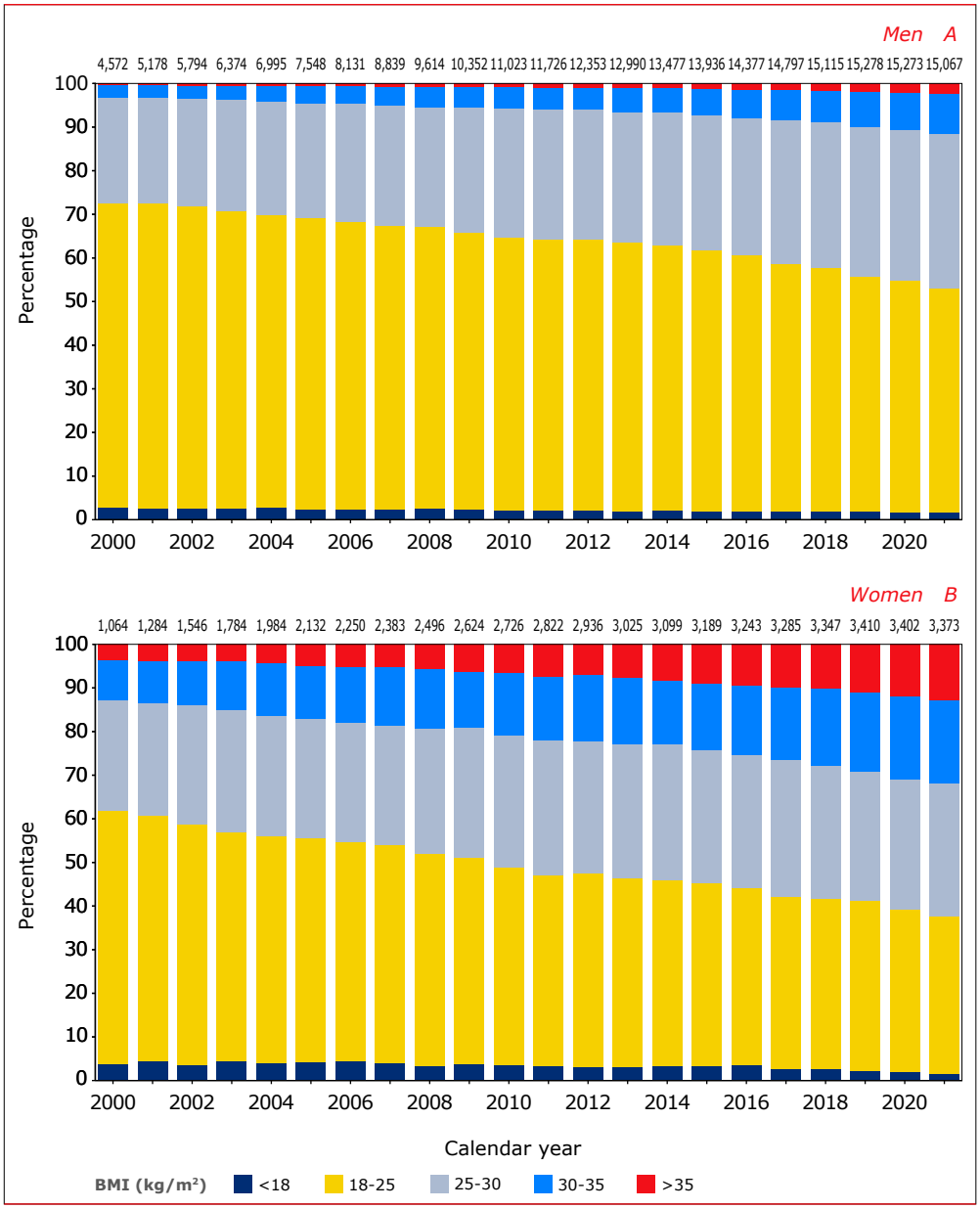
Figures 3.5A and *3.5B* show that the distribution of body mass index (BMI) of both men and women in the HIV-1-positive population has increased over time. In 2021, the proportion of men with available BMI data who were overweight (25-30 kg/m^2) or obese (WHO class I: 30-35 kg/m^2 and WHO class II/III: 35 kg/m^2 or over), was 35.6%, 9.3% and 2.3%, respectively. In women, these proportions were 30.6%, 18.9% and 12.8%, respectively.

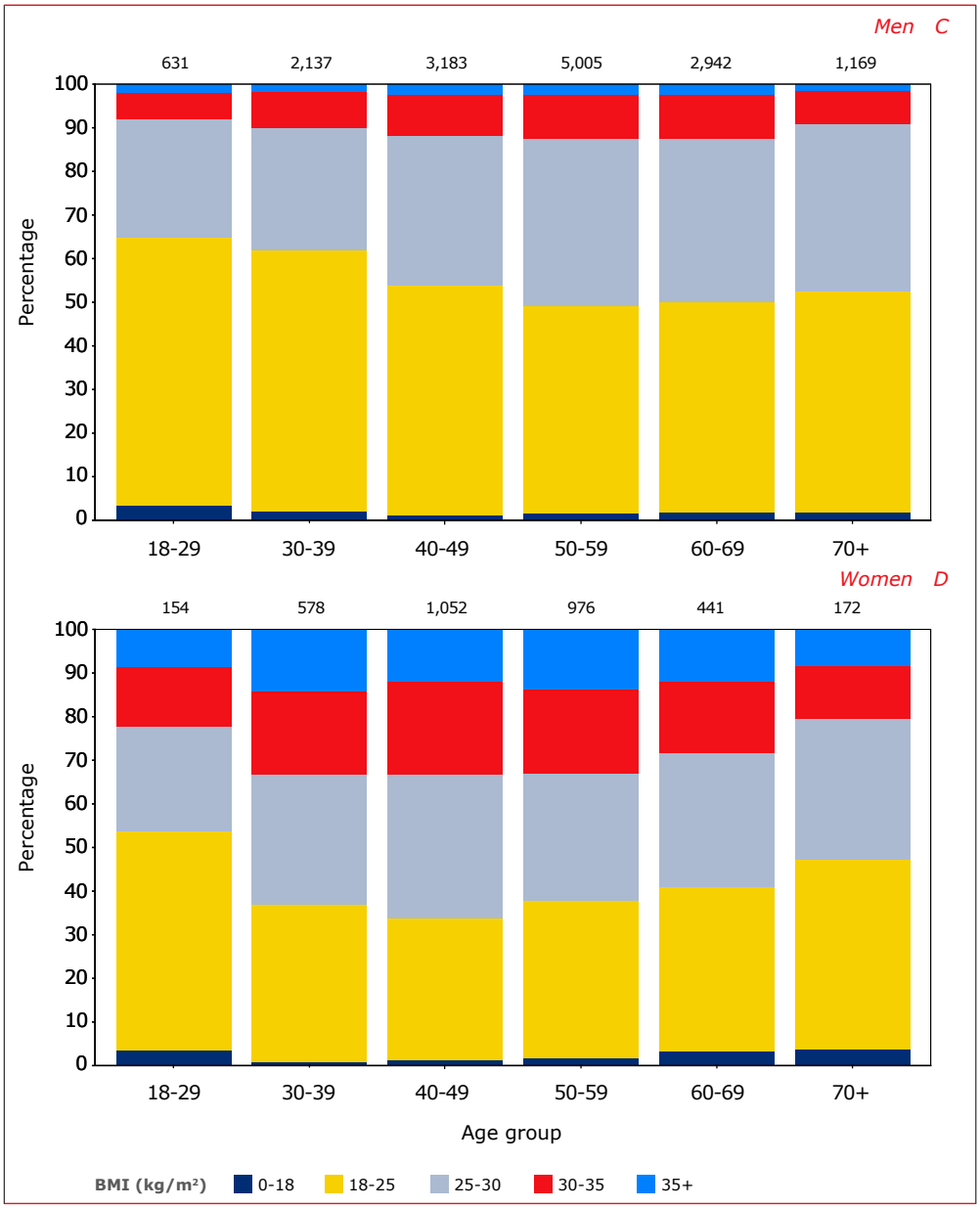
Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the population with HIV. This analysis revealed that the increase was at least partially driven by changes over time in population demographic 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. *Figures 3.5C* and *3.5D* show the distribution of BMI according to age groups in 2021 for men and women. Whereas in adult men of all age groups, the proportion classified as obese (11.6%) was somewhat lower than the proportion found in the general Dutch male population (12.3%), in women of all age groups there was more obesity (31.7%) than in the general Dutch female population (15.4%)[27]. There were substantial differences between those of Dutch origin, Western migrants and non-Western migrants: among males, 10.3% of Dutch men, 12.4% of Western migrants and 14.7% of non-Western migrants were obese. In females, however, those figures were 21.8%, 20.5%, and 38.4%, respectively. Being obese (a BMI over 30) was independently associated with an increased risk of diabetes (IRR 5.43, 95% CI 4.67-6.31, p<0.001), but that was not the case with CVD, CKD or non-AIDS-defining malignancies (*Appendix Table 3.5*).

Figure 3.6A shows that, in 2021, 51.3% of those treated with antihypertensives still had grade 1 hypertension or higher. In 2021, 27.3% (4,424) of individuals not using antihypertensives had grade 1-3 hypertension (*Figure 3.6B*). For 4,151 (93.8%) of these individuals, a five-year cardiovascular disease (CVD) risk could be calculated with the recalibrated D:A:D study algorithm[28]: 267 (6.4%) had a five-year CVD risk of 10% or more. According to the European AIDS Clinical Society (EACS) guidelines these individuals, in particular, should receive antihypertensive treatment[29]. *Figure 3.7* gives an overview of the ART-treated population's estimated risk of CVD over time. In 2000, the percentage of individuals at high (5-10%) or very high (10% or more) five-year risk were 12.0% and 5.8%, respectively, which steadily increased to 21.3% and 14.1%, respectively, in 2021. The increase in the percentage of individuals at high or very high risk likely reflects the increasing age of the study population.

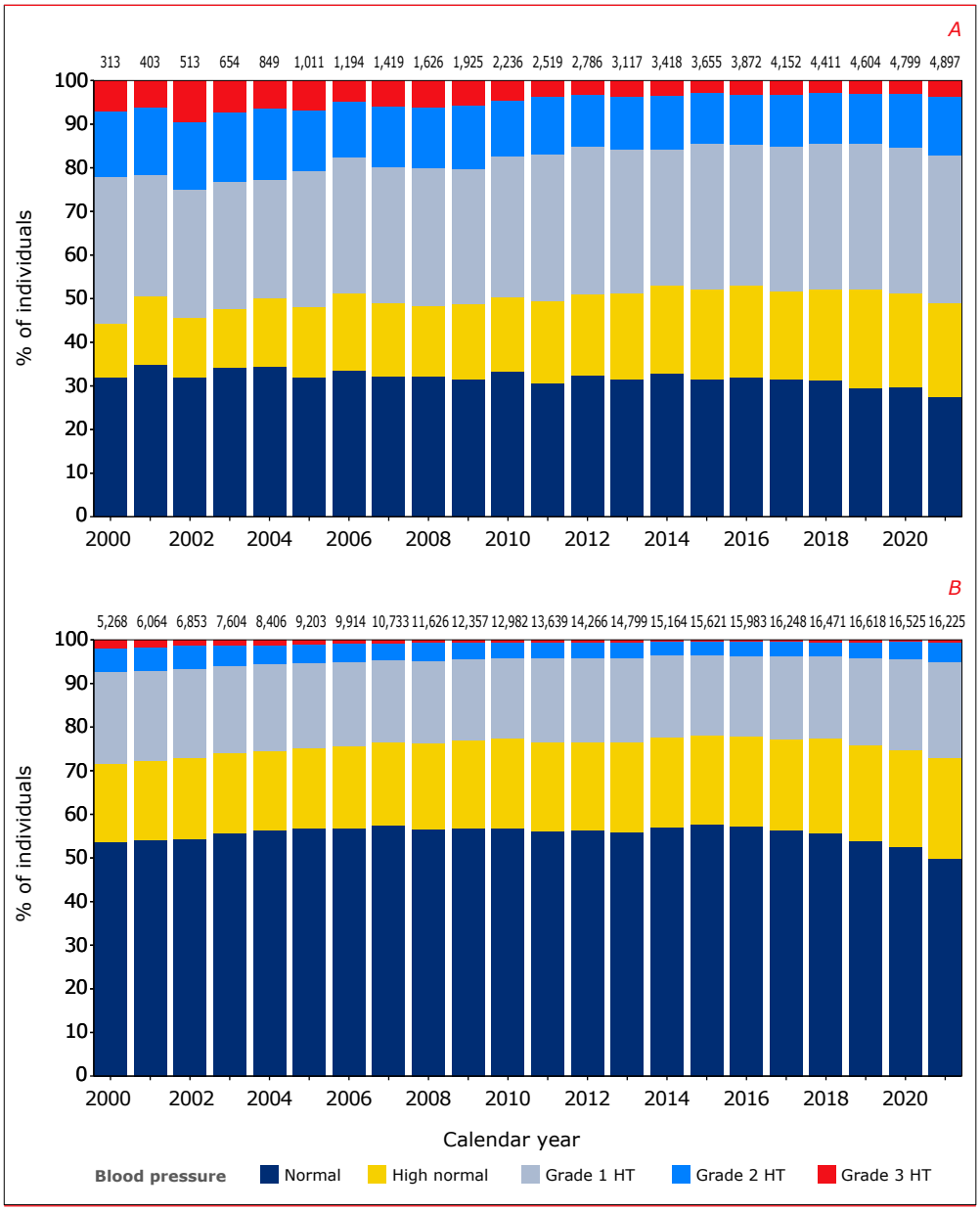
Figure 3.5: Distribution of the body mass index (BMI) at the end of each calendar year in (A) men, and (B) women, as a percentage of the total number of men and women with a known BMI in each year, and distribution of the BMI over the age groups for (C) men, and (D) women, in 2021. For each individual, the last available weight measurement in each year was selected. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year (A & B) or from that age group (C & D).





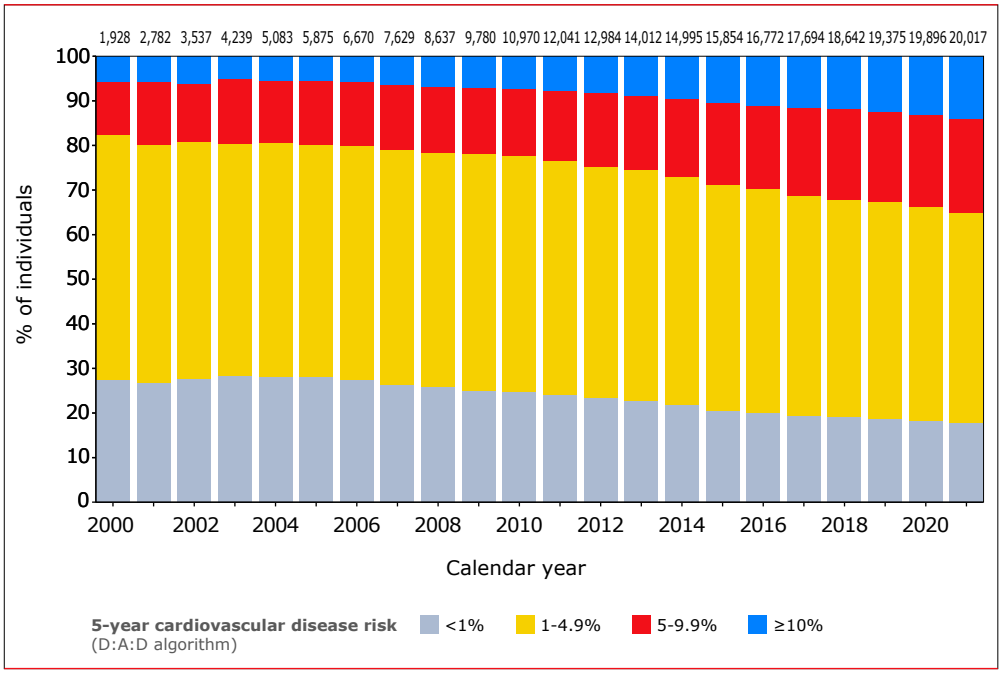
Legend: BMI = body mass index.

Figure 3.6: *Distribution of graded blood pressure at the end of each calendar year in (A) individuals known to be receiving antihypertensive treatment, and (B) those individuals not recorded as being treated for hypertension. For each individual, the last available systolic and diastolic blood pressure measurement in each year was selected. Blood pressure was graded according to the classification recommended in the guidelines for the management of arterial hypertension by the European Society of Hypertension and by the European Society of Cardiology[30]. Normal: systolic blood pressure (SBP) <130 mmHg or diastolic blood pressure (DBP) <85 mmHg; high normal: SBP 130–139 mmHg or DBP 85–89 mmHg; grade 1 hypertension SBP 140–159 mmHg or DBP 90–99 mmHg; grade 2 hypertension SBP 160–179 mmHg or DBP 100–109 mmHg; grade 3 hypertension SBP ≥ 180 mmHg or DBP ≥ 110 mmHg. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.*



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

Figure 3.7: Estimated five-year risk of coronary heart disease at the end of each calendar year according to the algorithm from the D:A:D: study[28]. Calculation of risk included variables such as total cholesterol, HDL cholesterol, and systolic blood pressure. Values for these variables were estimated on the basis of a 'last observation carried forward' approach. An accurate assessment of an individual's risk requires recent measurements of lipid levels and blood pressure. Recent HDL cholesterol measurements were often lacking or absent. Risk could not be estimated in younger individuals, in particular, because of missing data. Hence, the reported absolute number of individuals is smaller than the number of individuals in active follow up at the end of each calendar year, and older individuals are over-represented. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.



Use of preventive therapy for myocardial infarction or stroke

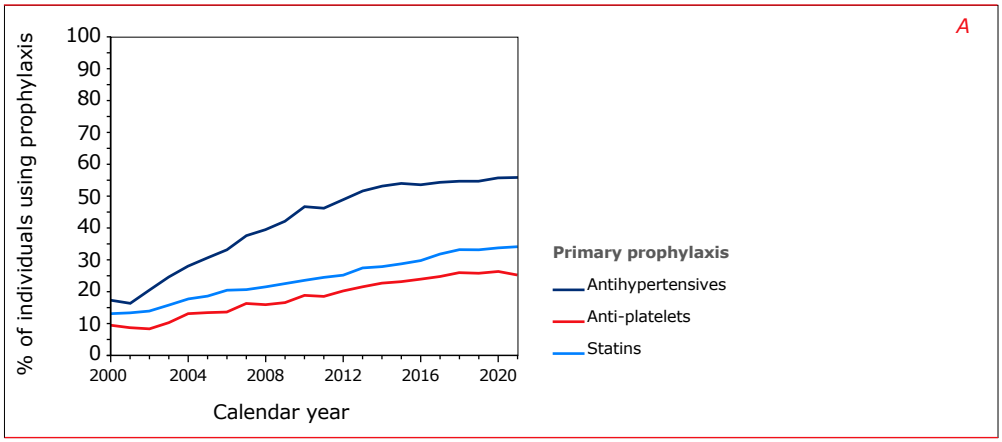
Primary prevention

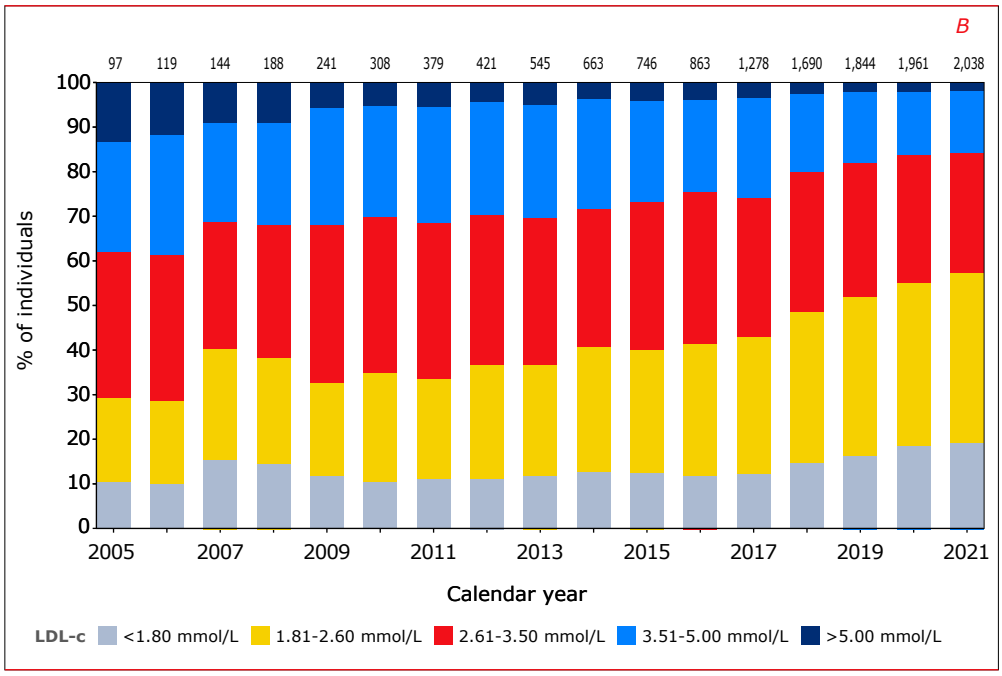
According to EACS guidelines, statin therapy should be offered to individuals with type 2 diabetes or a ten-year CVD risk ≥10%. They also recommend that angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers (CCB), (thiazide) diuretics, and non-dihydropyridine CCB (verapamil or diltiazem) should be offered to individuals with a systolic blood pressure ≥140 mmHg or diastolic blood pressure fff90 mmHg and a ten-year CVD risk ≥20%. For individuals aged 50 years and over with a ten-year CVD risk ≥20%, acetylsalicylic acid is recommended[31]. In general, the Dutch cardiovascular risk management (CVRM) guidelines closely resemble the EACS guidelines, with the

notable exception that the Dutch guidelines do not recommend the use of acetylsalicylic acid in older people with increased CVD risk, but without prior clinical CVD[32]. *Figure 3.8A* shows trends in the use of these medications in individuals without a prior stroke, myocardial infarction, or cardiovascular surgical procedure.

The percentage of individuals for whom primary prevention with statins and the above-mentioned antihypertensive drugs (referred to collectively hereafter as antihypertensives) is recommended, has increased over time, although the curve for antihypertensives has levelled off somewhat since 2013. Even though the percentage of individuals who were at high risk (aged 50 years and over, who used acetylsalicylic acid/clopidogrel as primary prevention) increased slowly prior to 2014, the overall proportion remained minimal and has remained stable during the last few years. Only about half of the individuals who received treatment with antihypertensive drugs or statins for the primary prophylaxis of myocardial infarction or stroke reached treatment targets (below 2.6 mmol/l). *Figure 3.6A* shows that of all individuals using antihypertensive drugs, only about half had a normal blood pressure in recent years. *Figure 3.8B* shows the distribution of LDL-cholesterol in subjects who use statins for primary CVD prophylaxis. The proportion of individuals with an LDL-c below 1.8 mmol/l or between 1.8 and 2.6 mmol/l was 10.3% and 18.6% respectively, in 2005. These increased to 19.2% and 38.0% respectively, in 2021.

Figure 3.8: (A) Percentage of individuals without a previous myocardial infarction, stroke, or cardiovascular surgical procedure who, according to European AIDS Clinical Society (EACS) guidelines, should be offered statin therapy, antiplatelet therapy, or antihypertensives for primary prevention of myocardial infarction or stroke. (B) Distribution of LDL-cholesterol in individuals using statins for primary prevention of myocardial infarction or stroke.

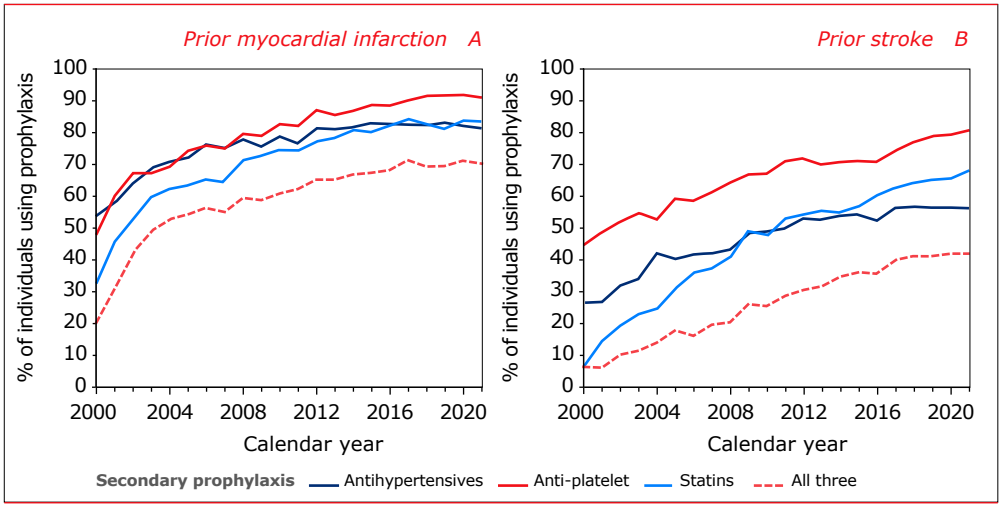




Secondary prophylaxis for myocardial infarction or stroke

According to all guidelines, individuals with a prior myocardial infarction or ischaemic stroke should receive lifelong treatment with statins, antihypertensives (ACE inhibitors, beta blockers or angiotensin receptor blockers), as well as low-dose acetylsalicylic acid/clopidogrel[33,34]. *Figure 3.9A* shows that the percentages of individuals using statins, acetylsalicylic acid/clopidogrel or antihypertensives after a myocardial infarction, increased between 2000 and 2021: in 2021, 83.5% of individuals with a prior myocardial infarction used statins, 81.5% used antihypertensives, and 91.1% used acetylsalicylic acid/clopidogrel. Although the use of statins and antihypertensives after an ischaemic stroke also increased over time, in 2021 these medications were used less frequently after a stroke than after a myocardial infarction (68.3% used statins, 56.4% used antihypertensives, and 80.8% used acetylsalicylic acid/clopidogrel) (*Figure 3.9B*).

Figure 3.9: *Percentage of individuals with (A) myocardial infarction or (B) ischaemic stroke using statin therapy, antiplatelet therapy, or antihypertensives.*



Chronic kidney disease

Glomerular filtration rate (GFR) is a marker of renal function and is commonly estimated by one of three formulae, namely the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD), or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations[35]. As all three equations used to estimate GFR (eGFR) are based on serum creatinine, they may be markedly affected by rapid changes in muscle mass, as is seen in some individuals with advanced HIV disease who commence ART. Of these equations, both the Cockcroft-Gault and the CKD-EPI equations have been validated in individuals with HIV[35,36]. However, because the CKD-EPI equation is the one most often used in clinical practice, we have chosen to report eGFR values as estimated by this equation. The distribution of eGFR categories in ml/min/1.73m^2 (90 or above, normal kidney function; 60-89, mildly reduced; 30-59, moderately reduced; 15-29, severely reduced; and below 15, very severely reduced kidney function) is shown in *Figures 3.10A* and *3.10B* for men and women. The percentage of men with normal kidney function decreased over time from 74.5% in 2007, to 44.9% in 2020, and this pattern was similar in women. Typically, eGFR decreases with increased age, as shown in *Figure 3.11*, 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

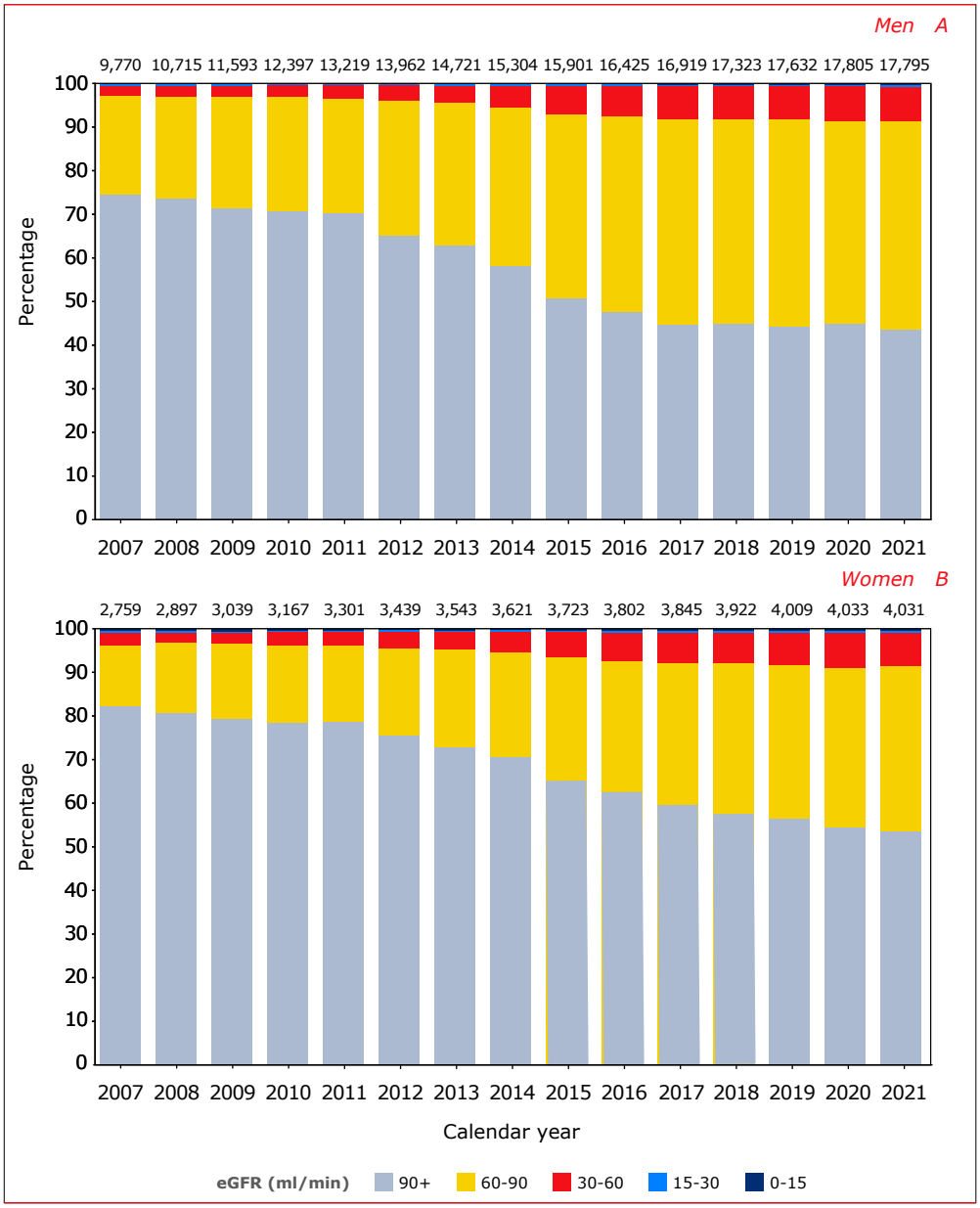
In individuals with an eGFR above 60ml/min/1.73m^2 at the time of inclusion in the analyses, who did not have a previously confirmed CKD, the crude incidence of CKD (defined as eGFR below 60ml/min/1.73m^2 confirmed by a second test at least 26 weeks later) varied over time (*Figure 3.4C*). Routine collection 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 2015-20. 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 2016-21 completely disappeared (even reversed) in comparison to 2008-10 and 2011-15. This strongly suggests that the increase in CKD seen in recent years is largely due to increases in serum creatinine caused by ARV-induced reversible inhibition of two transporters that mediate tubular secretion of creatinine, without affecting the true glomerular filtration rate (namely, organic cation transporter 2 [OCT2], and multidrug and toxin extrusion transporter [MATE1]) and is therefore not a true increase in CKD.

Figure 3.10: *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.*



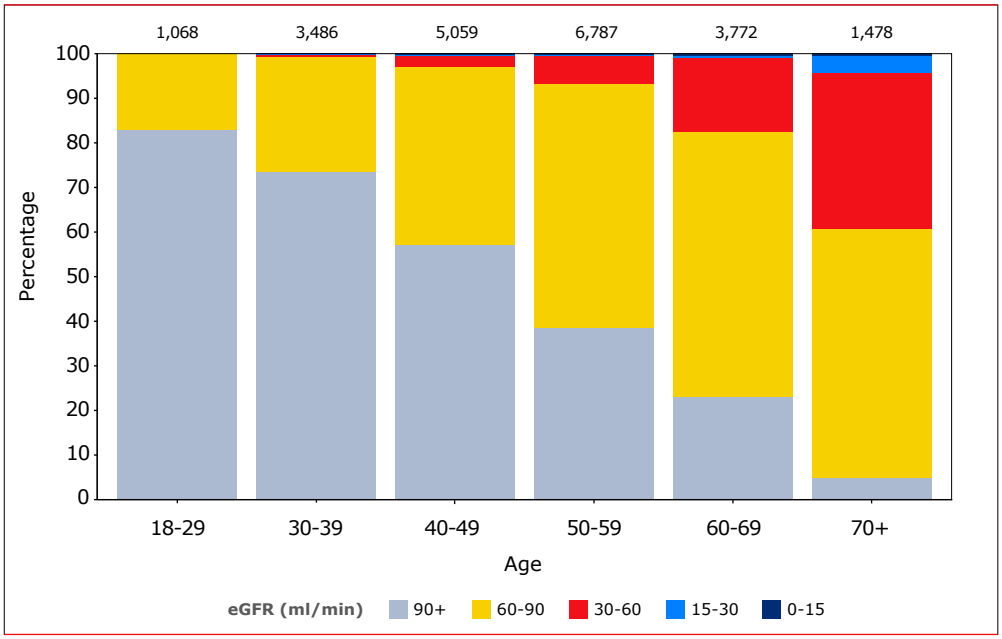
Legend: *eGFR = estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60–89 ml/min/1.73m²: mildly reduced; 30–59 ml/min/1.73m²: moderately reduced; 15–29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

Table 3.6: Crude chronic kidney disease incidence per 1,000 person years of follow up in 2008–14 and 2015–21, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)
2008–2014	7.1 (6.3–7.9)	0.78 (0.70–0.87)	7.4 (5.9–9.2)	0.90 (0.70–1.09)
2015–2021	11.6 (10.8–12.4)	1 (reference)	12.4 (10.7–14.3)	1 (reference)

**Standardised according to the observed age distribution in 2015–21.*
***Legend:** CI = confidence interval; PYFU = person years.*

Figure 3.11: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2021 for different age categories. For each individual, the last available measurement in 2021 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 2021, 2,108 diagnoses of non-AIDS-defining malignancies in 1,944 unique individuals were recorded in SHM's database. An additional 845 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 (16.4%);
- haematological malignancies (excluding AIDS-defining non-Hodgkin's lymphoma, 13.7%);
- intestinal cancer (mainly oesophageal, gastric, intestinal, and rectal cancers, but excluding liver cancer, 13.4%);
- invasive anal cancer (not AIN, 11.7%);
- prostate cancer (9.8%); and
- head and neck cancers (8.3%).

Figure 3.12 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: 3.13*, 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 3.4D*. The age-standardised incidence in men was statistically significantly lower in the period 2016-21, compared to 2000-10, and borderline significantly lower compared to 2011-15 (*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:

- older age group;
- acquiring HIV-1 through injecting drugs or contact with blood or blood products;
- lower current CD4 cell count (CD4 below 350 cells/mm^3);
- low body mass index;
- prior AIDS;
- chronic HBV co-infection; and
- current or past smoking (*Appendix Table 3.5*).

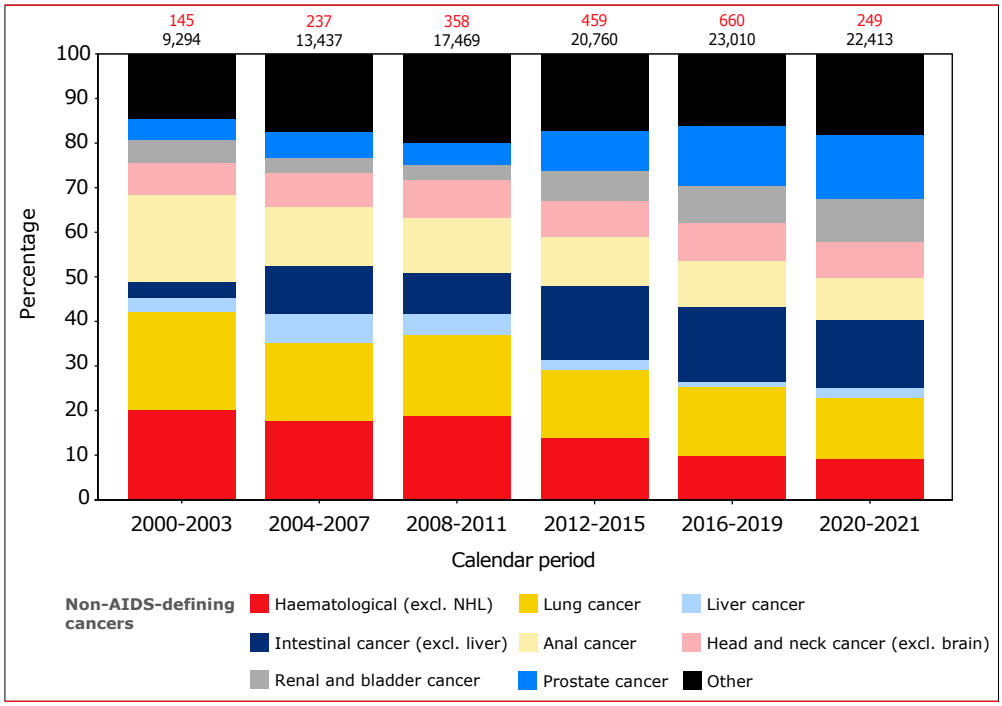
Furthermore, people who had been pre-treated with mono or dual-NRTI-based regimes prior to starting ART had an independently increased risk for NADM, compared with those who were therapy-naïve prior to starting ART (relative risk [RR] 1.18, 95% CI 1.02-1.36). Of note, independent of all other risk factors investigated, people who initiated ART within 12 months of their last negative HIV test had a significantly lower risk for NADM (RR 0.57, 95% CI 0.39-0.83) 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 2021, the overall five-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 50.0%, compared with 73.4% for CVD, 83.2% for DM, and 86.2% for CKD (*Appendix Figure 3.1*). In the same period, the five-year survival rate of all adults newly entering care in one of the Dutch HIV treatment centres was 95.7%, and 82.2% for those newly entering care with an AIDS diagnosis. The five-year survival rates following the most common non-AIDS-defining malignancies are shown in *Table 3.7* and *Appendix Figure 3.2*.

Anal cancer

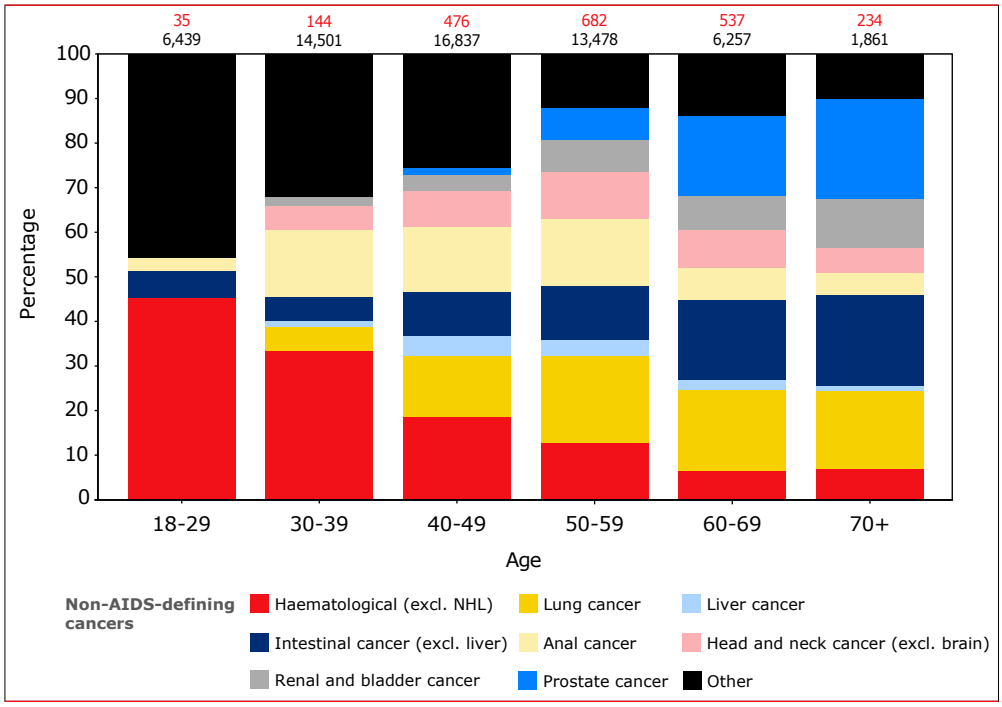
In total, 236 men with HIV and 11 women with HIV were diagnosed with anal cancer. Among men with HIV, the incidence of anal cancer fluctuated between 0.4 and 1.5 cases per 1,000 PYFU between 2000 and 2021 (*Figure 3.4G*). A 2015 study exploring the incidence of anal cancer among PWH in the Netherlands showed a significantly higher incidence of anal cancer in men who have sex with men (MSM), than in heterosexual men[37]. However, in this chapter, we will not report on the trend in anal cancer among heterosexual men over time, as the number of heterosexual men with anal cancer is too small (n = 25) to analyse.

Figure 3.12: Relative changes in non-AIDS-defining malignancies between 2000 and 2021 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 3.13: 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 2021.



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

Table 3.7: Most common non-AIDS-defining malignancies diagnosed in 2000-21, excluding non-melanoma skin cancer and pre-malignant lesions found by cervical and anal screening.

non-AIDS malignancy	# of malignancies	%	Five-year survival (%)
Lung cancer	345	16.4	15.3
Hematological (excl. NHL)	289	13.7	64.4
Intestinal cancer (excl. liver)	283	13.4	32.8
Anal cancer	247	11.7	66.3
Prostate cancer	206	9.8	80.1
Head and neck cancer (excl. brain)	174	8.3	57.3
Renal and bladder cancer	139	6.6	62.8
Other cancers	117	5.6	45.3
Malignant melanoma	91	4.3	73.6
Liver cancer	64	3.0	16.8
Breast cancer	57	2.7	79.1
Testicular cancer	39	1.9	88.4
Gynecological cancer (excl. cervical)	33	1.6	71.8
CNS cancer	24	1.1	54.9

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 2000-10, 2011-15, and 2016-21, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)
2000-2010	6.6 (6.0-7.1)	1.31 (1.20-1.42)	3.2 (2.5-4.0)	1.13 (0.88-1.39)
2011-2015	6.6 (6.0-7.2)	1.02 (0.93-1.11)	4.4 (3.4-5.5)	1.06 (0.82-1.31)
2016-2021	8.0 (7.5-8.6)	1 (reference)	5.2 (4.3-6.3)	1 (reference)

**Standardised according to the observed age distribution in 2011-21.*

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

Multimorbidity

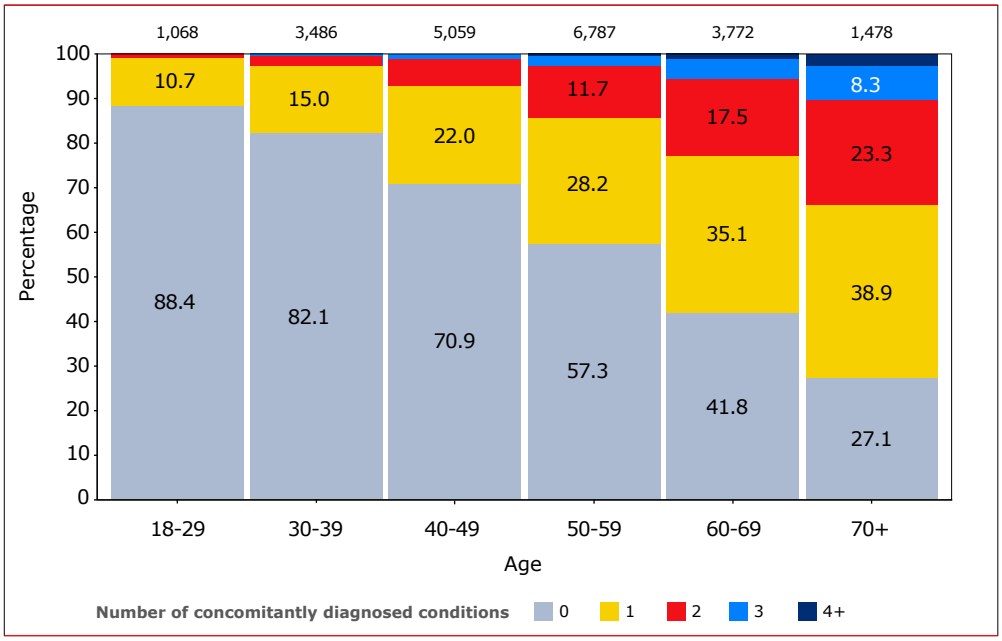
We investigated changes over time in the prevalence of non-AIDS multimorbidity. HIV infections and AIDS diagnoses did not contribute to the multimorbidity count. The following comorbidities and conditions were taken into account:

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 3.4 shows the prevalence of each individual comorbidity over calendar time. *Figure 3.14* shows the distribution of the number of concomitantly-diagnosed conditions in various age categories of the adult population in 2021. The number of concomitant conditions was slightly higher in women than in men for all age categories (*Appendix Figure 3.3*). Moreover, although the average number of concomitant conditions has steadily increased over the past ten years due to the increasing average age of the cohort, the prevalence of multimorbidity by age category has remained stable over the same period (*Appendix Figure 3.5*). After adjusting for the variables listed in *Appendix Table 3.2*, multimorbidity was independently associated with increased risk of mortality (RR 2.15, 95% CI 2.07-2.23, $p<0.001$, per additional comorbidity diagnosed).

Figure 3.14: Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2021. 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[aa]) 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 2021, our count revealed:

- 19.8% of adults in active follow up had no recorded comedication use
- 29.5% used one comedication;
- 16.2% used two comedications;
- 10.7% used three comedications; and
- 7.3% used four comedications.

A further 16.5% 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 3.15*): 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 3.16A*) and those with more comorbidities (*Figure 3.17*) 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 3.16B*). Finally, in adults receiving ART in the period 2007-21, polypharmacy was also associated with an increased risk of death (RR 2.23, 95% CI 2.01-2.47, $p<0.001$) 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 2021 are listed in *Table 3.9*.

Table 3.9: Use of comedications in 2021.

Comedication use in 2021	N	%
ATC group		
Vitamins	6184	12.0
Lipid modifying drugs	4360	8.5
Drugs for acid related disorders	3767	7.3
Drugs acting on the renin-angiotensin system	3247	6.3
Psycholeptics drugs (antipsychotics, anxiolytics, hypnotics, sedatives)	3089	6.0
Antithrombotic drugs	2711	5.3
Drugs for obstructive airway diseases	2437	4.7
Psychoanaleptics (antidepressants, psychostimulants)	2239	4.4
Drugs used in diabetes	2066	4.0
Mineral supplements	2056	4.0
Urological drugs	1694	3.3
Beta blocking drugs	1650	3.2
Calcium channel blockers	1484	2.9
Antianaemic drugs	1127	2.2
Diuretic drugs	1122	2.2
Antibacterial drugs	1102	2.1
Sex hormones and modulators of the genital system	1080	2.1
Corticosteroids systemic	918	1.8
Analgesic drugs	870	1.7
Antiepileptic drugs	791	1.5
Antiviral drugs	726	1.4
Cardiac therapy	696	1.4
Nasal preparations	643	1.3
Topical dermatological corticosteroids	640	1.2
Antidiarrheals, intestinal anti-inflammatory/anti-infective drugs	472	0.9
Antimycotic drugs	457	0.9
Drugs affecting bone structure and mineralisation	446	0.9
Thyroid therapy	359	0.7

Figure 3.15: 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.

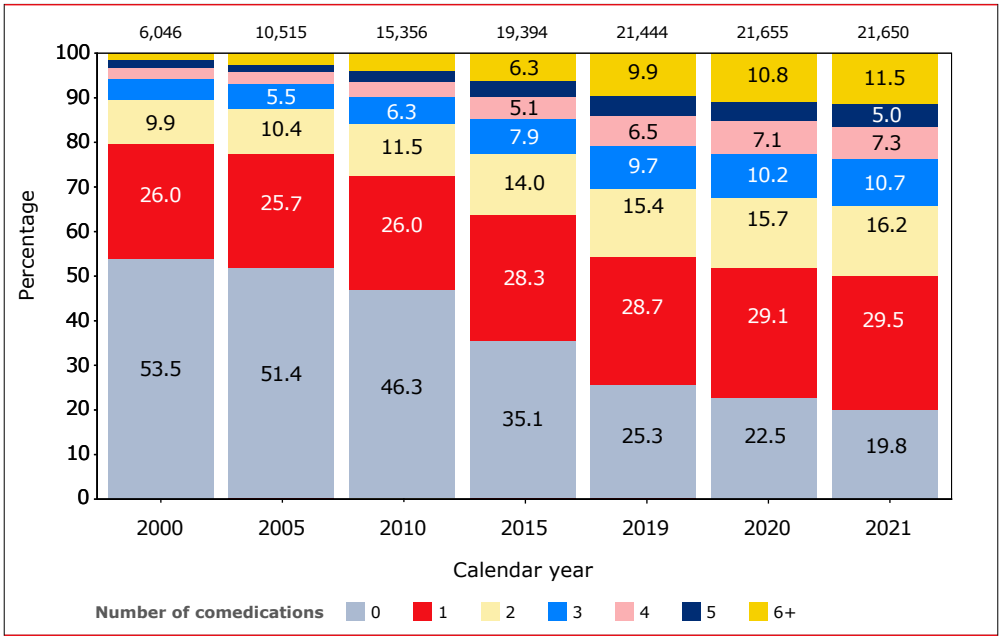
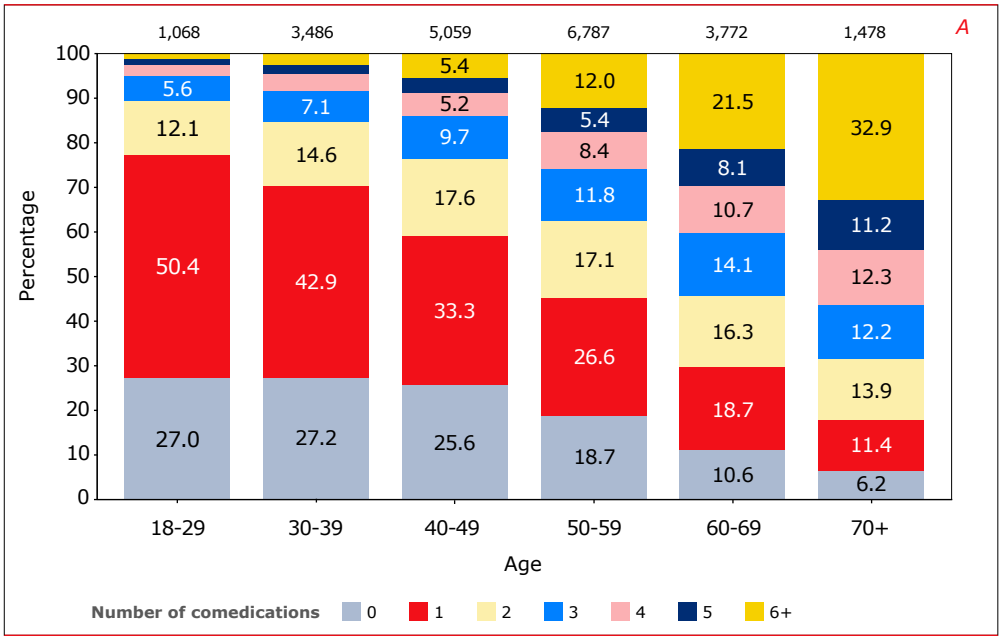


Figure 3.16: Number of comedications used by (A) age group, and (B) gender in 2021. The numbers at the top of each bar represent the number of individuals contributing data to that age/gender category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



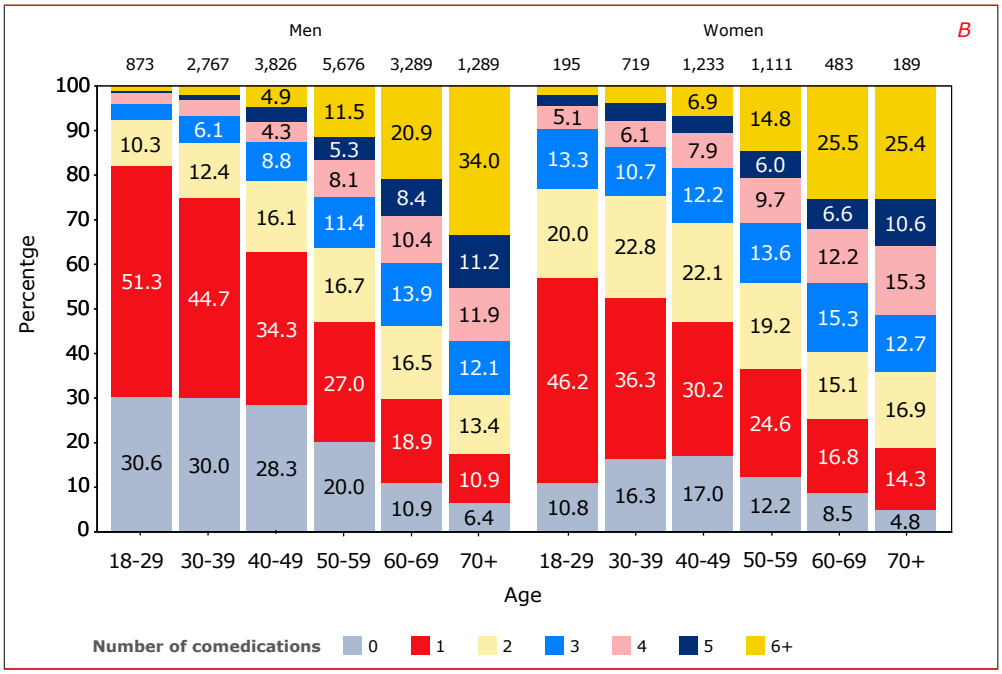
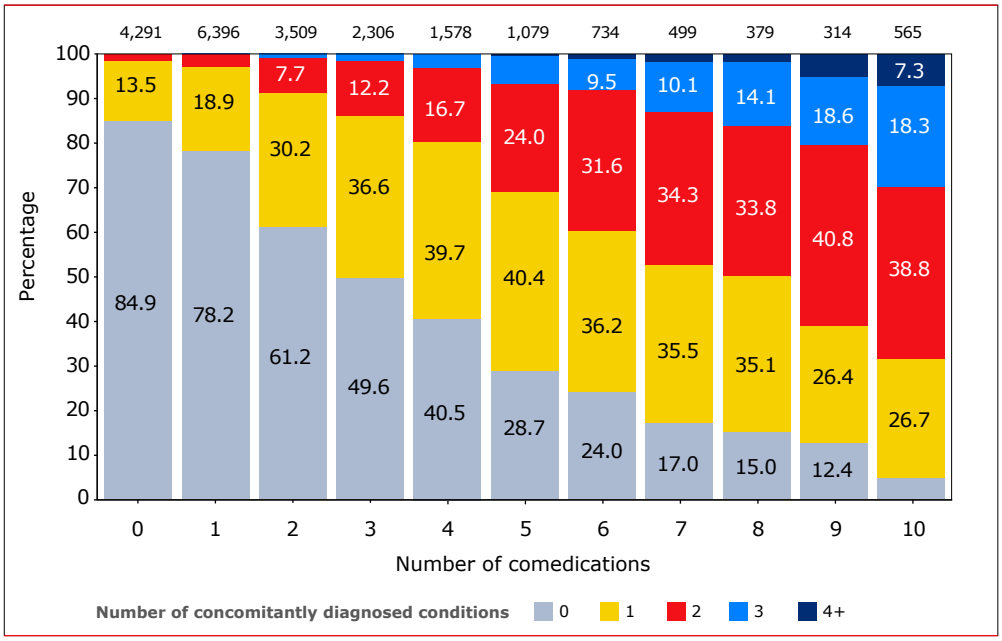


Figure 3.17: Number of comedications used in relation to the number of prevalent comorbidities. The numbers at the top of each bar represent the number of individuals contributing data to that category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per category.



Summary and conclusions

AIDS, mortality and causes of death

AIDS-related deaths have decreased dramatically since 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 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[38,39].

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 8.51 deaths per 1000 person years in 2019, to 9.30 in 2020 and 11.24 in 2021. The increase in 2020 and 2021 is 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[b].

Diabetes and cardiovascular disease

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

Cardiovascular risk factors

The proportion of adults with HIV at high (5-10%), or very high (more than 10%) cardiovascular risk slowly increased from 12.0% and 5.8% respectively in 2000, to 21.3% and 14.1% respectively in 2021. This increase largely reflects the increased average age of the population. We observed that cardiovascular risk management has improved over time, as illustrated by the increasing use of statins and antihypertensives, and the shift away from the use of antiretrovirals that have been demonstrated to be associated with increased cardiovascular risk, particularly

b Report "Sterfte en oversterfte in 2020 en 2021. Onderzoek door het CBS en het RIVM, in het kader van het ZonMw onderzoeksprogramma Oversterfte.", published by CBS and RIVM on 23 June 2022, accessed online at https://www.cbs.nl/nl-nl/longread/rapportages/2022/sterfte-en-oversterfte-in-2020-en-2021 [in Dutch].

in individuals with high underlying risk[45] (*Chapter 2*). Significant room for further improvement remains, however, particularly given the suboptimal use of statin therapy, antihypertensive therapy, and low-dose acetylsalicylic acid as secondary prevention following a myocardial infarction or ischaemic stroke, and the low, albeit slowly improving, uptake of these medications in the prevention of primary cardiovascular disease. The increased availability of preferred antiretroviral therapy options that do not contain pharmacological boosters that can interfere with these preventive medicines, has made it easier to implement proper cardiovascular risk management.

The clinical significance of the increase in BMI over time, especially in women, requires further study. Recent results suggest that weight gain after starting ART is associated with lower mortality for normal-weight individuals, but they show no clear benefit for overweight or obese individuals[46]. However, another study found that weight gain after starting 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[47]. Prospective longitudinal monitoring of lipid levels, smoking status, blood pressure, weight and other risk factors will be important to further optimise the assessment of cardiovascular risk in our increasingly ageing 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[48,49], and the use of tenofovir disoproxil

fumarate, atazanavir/ritonavir and lopinavir/ritonavir, to be additional independent predictors of chronic renal impairment[50]. Moreover, renal impairment in the population with HIV is associated with an increased risk of cardiovascular disease[51]. The increase in CKD in our population appears to be largely caused by the increased use of dolutegravir, bictegravir, rilpivirine, and cobicistat, all of which cause reversible inhibition of tubular excretion of creatinine, without causing a true decrease in glomerular filtration.

Non-AIDS-defining malignancies

The most common non-AIDS-defining malignancies (NADM) in the Netherlands are lung, intestinal, anal, and head and neck cancer, as well as Hodgkin's lymphoma. The crude incidence of NADM has remained stable over time, and we also observed a decline in age-standardised incidence of NADM in men, and to a lesser extent in women. In addition, our analyses showed that individuals diagnosed with NADM a more likely to be older. This is in line with data from other cohorts, including the Swiss HIV cohort[49-52]. Additional risk factors for NADM identified in our analyses were: current or past smoking; a CD4 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[56]. Importantly, individuals who had initiated ART earlier in infection (i.e. within 12 months of a last negative HIV test), had a significantly lower risk of NADM (RR 0.57, 95% CI 0.39-0.83, p = 0.004), independent of other traditional and HIV-related risk factors. The five-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 50.0%.

Multimorbidity and polypharmacy

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

Polypharmacy, defined as the concomitant use of five or more medications in addition to ART, is becoming more prevalent, mainly because of the increased age of the cohort and the associated rise in the prevalence of age-associated, non-AIDS comorbidities. In 2000, 3.3% of adults used five or more non-antiretroviral comedications alongside their ART regimen, and this steadily increased to 16.5% of adults in active follow up in 2021. 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 2007-21, polypharmacy was also strongly and independently associated with an increased risk of death, independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities.

Recommendations

The proportion of individuals dying of AIDS in the Netherlands has markedly declined throughout the ART era, but in order to reach the goal of zero AIDS-deaths by 2022, 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 such as the ongoing Comorbidity and Aging with HIV (AGEhIV) cohort study have provided further insights into the independent contribution of HIV and HIV-associated factors, such as innate and adaptive immune and coagulation activation, and inflammation. This will hopefully guide the development of interventions that target relevant pathophysiological mechanisms[9,60].

It is important to note that the risk of many, if not each, of the comorbidities frequently identified in people 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.

References

1. van Sighem, A. I. *et al.* Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. *AIDS* **24**, 1527–35 (2010).
2. Mocroft, A. *et al.* AIDS across Europe, 1994-98: the EuroSIDA study. *Lancet* **356**, 291–6 (2000).
3. The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* **372**, 293–299 (2008).
4. Emery, S. *et al.* Major clinical outcomes in antiretroviral therapy (ART)-naïve participants and in those not receiving ART at baseline in the SMART study. *J Infect Dis* **197**, 1133–1144 (2008).
5. Mocroft, A. *et al.* Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? *AIDS* **19**, 2117–25 (2005).
6. Bhaskaran, K. *et al.* Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA* **300**, 51–9 (2008).
7. Lohse, N. *et al.* Survival of persons with and without HIV infection in Denmark, 1995-2005. *Ann. Intern. Med.* **146**, 87–95 (2007).
8. Bonnet, F. *et al.* Changes in cancer mortality among HIV-infected patients: the Mortalité 2005 Survey. *Clin Infect Dis* **48**, 633–9 (2009).
9. Guaraldi, G. *et al.* Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* **53**, 1120–1126 (2011).
10. Freiberg, M. S. *et al.* The Risk of Incident Coronary Heart Disease Among Veterans With and Without HIV and Hepatitis C. *Circ. Cardiovasc. Qual. Outcomes* **4**, 425–432 (2011).
11. Schouten, J. *et al.* Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between hiv-infected and uninfected individuals: the AGEhIV cohort study. *Clin Infect Dis* **59**, 1787–1797 (2014).
12. Hsue, P. Y. *et al.* Role of HIV and human herpesvirus-8 infection in pulmonary arterial hypertension. *AIDS* **22**, 825–33 (2008).
13. Arnsten, J. H. *et al.* Decreased bone mineral density and increased fracture risk in aging men with or at risk for HIV infection. *AIDS* **21**, 617–623

14. Brown, T. T. & Qaqish, R. B. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS* **20**, 2165–2174 (2006).
15. Triant, V. A., Brown, T. T., Lee, H. & Grinspoon, S. K. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. *J.Clin.Endocrinol.Metab* **93**, 3499–3504
16. McCutchan, J. A. *et al.* HIV suppression by HAART preserves cognitive function in advanced, immune-reconstituted AIDS patients. *AIDS* **21**, 1109–17 (2007).
17. Robertson, K. R. *et al.* The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS* **21**, 1915–21 (2007).
18. Ances, B. M. *et al.* HIV infection and aging independently affect brain function as measured by functional magnetic resonance imaging. *J Infect Dis* **201**, 336–340
19. Clifford, G. M. *et al.* Cancer risk in the Swiss HIV cohort study: Associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J. Natl. Cancer Inst.* **97**, 425–432 (2005).
20. Grulich, A. E., van Leeuwen, M. T., Falster, M. O. & Vajdic, C. M. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* **370**, 59–67 (2007).
21. Baker, J. V *et al.* CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS* **22**, 841–848 (2008).
22. El-Sadr, W. M. *et al.* CD4+ count-guided interruption of antiretroviral treatment. *N. Engl. J. Med.* **355**, 2283–96 (2006).
23. Prevention, C. for D. C. and. *HIV/AIDS Surveillance Report, 2005*. **Vol. 17. R**, (U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2007).
24. Tripepi, G., Jager, K. J., Dekker, F. W. & Zoccali, C. Stratification for Confounding – Part 2: Direct and Indirect Standardization. *Nephron Clin. Pract.* **116**, c322–c325 (2010).
25. David S, van Benthem B, Deug F & van Haastrecht P. *National Action Plan on STIs, HIV and Sexual Health: 2017-2022*. (2018). doi:10.21945/RIVM-2017-0158
26. CBS. zelfdoding-in-nederland-een-overzicht-vanaf-1950. (2021). Available at: https://www.cbs.nl/nl-nl/longread/statistische-trends/2021/zelfdoding-in-nederland-een-overzicht-vanaf-1950.
27. Gezondheidsenquête/Leefstijlmonitor CBS i.s.m. RIVM. Volwassenen met overgewichtenobesitas2020.Availableat:https://www.volksgezondheidenzorg.info/onderwerp/overgewicht/cijfers-context/huidige-situatie#node-overgewicht-volwassenen. (Accessed: 26th August 2021)
28. Friis-Møller, N. *et al.* An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. *Eur. J. Prev. Cardiol.* **23**, 214–23 (2016).

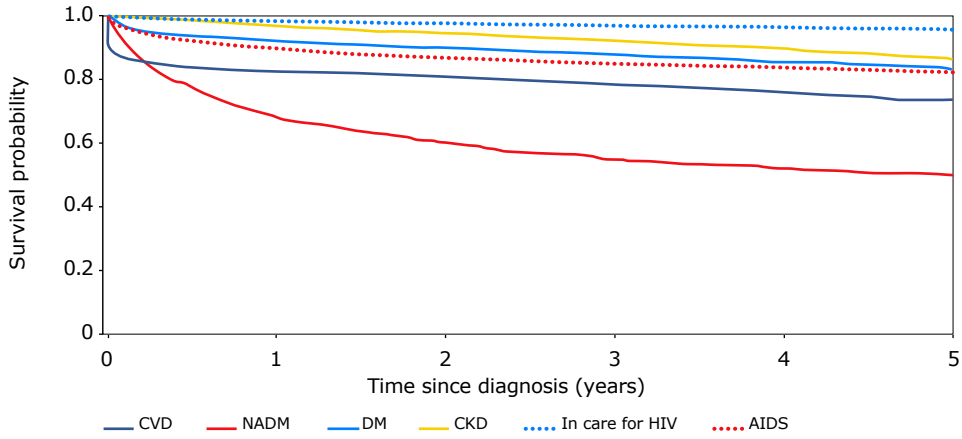
29. European AIDS Clinical Society. Guidelines. Version 8.0, October 2015. English edition. (2015).
30. Mancia, G. *et al.* 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur. Heart J.* **34**, 2159–2219 (2013).
31. Rockstroh, J. K. *et al.* European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. *HIV Med.* **9**, 82–88 (2008).
32. NHG-STANDAARD M84 - Cardiovasculair risicomanagement, Versie 4.0, Revisiedatum juni 2019. Available at: https://richtlijnen.nhg.org/standaarden/cardiovasculair-risicomanagement.
33. Genootschap, N. H. Beroerte. *Website Nederlands Huisartsen Genootschap* (2015).
34. Nederlands Huisartsen Genootschap Cardiovasculair Risicomanagement. (2016). Available at: https://www.nhg.org/standaarden/samenvatting/cardiovasculair-risicomanagement.
35. Mocroft, A. *et al.* A comparison of estimated glomerular filtration rates using cockcroft-gault and the chronic kidney disease epidemiology collaboration estimating equations in HIV infection. *HIV Med.* **15**, 144–152 (2014).
36. Vrouenraets, S. M. E. *et al.* A comparison of measured and estimated glomerular filtration rate in successfully treated HIV-patients with preserved renal function. *Clin. Nephrol.* **77**, 311–320 (2012).
37. Richel, O. *et al.* Anal Cancer in the HIV-Positive Population: Slowly Declining Incidence After a Decade of ART. *J. Acquir. Immune Defic. Syndr.* **69**, 602–605 (2015).
38. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord *et al.* All-cause mortality in treated HIV-infected adults with CD4 ≥500/mm^3 compared with the general population: evidence from a large European observational cohort collaboration. *Int. J. Epidemiol.* **41**, 433–45 (2012).
39. May, M. T. *et al.* Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. *AIDS* **28**, 1193–1202 (2014).
40. Capeau, J. *et al.* Ten-year diabetes incidence in 1046 HIV-infected patients started on a combination antiretroviral treatment. *AIDS* **26**, 303–14 (2012).
41. Worm, S. W. *et al.* High prevalence of the metabolic syndrome in HIV-infected patients: impact of different definitions of the metabolic syndrome. *AIDS* **24**, 427–435 (2010).
42. Sabin, C. A. *et al.* Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration. *BMC Med.* **14**, 61 (2016).

43. Ledergerber, B. *et al.* Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. *Clin Infect Dis* **45**, 111–119 (2007).
44. Brown, T. T. T. *et al.* Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch. Intern. Med.* **165**, 1179–84 (2005).
45. Kamara, D. A. *et al.* Longitudinal analysis of the associations between antiretroviral therapy, viraemia and immunosuppression with lipid levels: the D:A:D study. *Antivir. Ther.* (2016). doi:10.3851/IMP3051
46. Yuh, B. *et al.* Weight change after antiretroviral therapy and mortality. *Clin Infect Dis* **60**, 1852–1859
47. Achhra, A. C. *et al.* Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study. *HIV Med.* **17**, 255–68 (2016).
48. Mocroft, A. *et al.* Hepatitis B and C co-infection are independent predictors of progressive kidney disease in hiv-positive, antiretroviral-treated adults. *PLoS One* **7**, e40245- (2012).
49. Peters, L. *et al.* Hepatitis C virus viremia increases the incidence of chronic kidney disease in HIV-infected patients. *AIDS* **26**, 1917–1926 (2012).
50. Ryom, L. *et al.* Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: The D:A:D Study a. *J. Infect. Dis.* **207**, 1359–1369 (2013).
51. Ryom, L. *et al.* Renal Impairment and Cardiovascular Disease in HIV-Positive Individuals: The D:A:D Study. *J. Infect. Dis.* **214**, 1212–1220 (2016).
52. Krishnan, S. *et al.* Incidence of Non-AIDS-defining cancer in antiretroviral treatment-naïve subjects after antiretroviral treatment initiation: An ACTG longitudinal linked randomized trials analysis. *Oncology* **80**, 42–49 (2011).
53. Powles, T. *et al.* Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection. *J. Clin. Oncol.* **27**, 884–890 (2009).
54. Sigel, K. *et al.* HIV as an independent risk factor for incident lung cancer. *AIDS* **26**, 1017–25 (2012).
55. Hasse, B. *et al.* Morbidity and aging in HIV-infected persons: The swiss HIV cohort study. *Clin Infect Dis* **53**, 1130–1139 (2011).
56. Kesselring, A. *et al.* Immunodeficiency as a risk factor for non-AIDS-defining malignancies in HIV-1-infected patients receiving combination antiretroviral therapy. *Clin Infect Dis* **52**, 1458–1465 (2011).
57. Grinsztejn, B. *et al.* Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: Results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect. Dis.* **14**, 281–290 (2014).

58. The TEMPRANO ANRS 12136 Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N. Engl. J. Med.* **373**, 808–22 (2015).
59. Lundgren, J. D. *et al.* Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N. Engl. J. Med.* **373**, 795–807 (2015).
60. High, K. P. *et al.* HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. *J. Acquir. Immune Defic. Syndr.* **60 Suppl 1**, S1-18 (2012).

Appendix: supplementary figures and tables

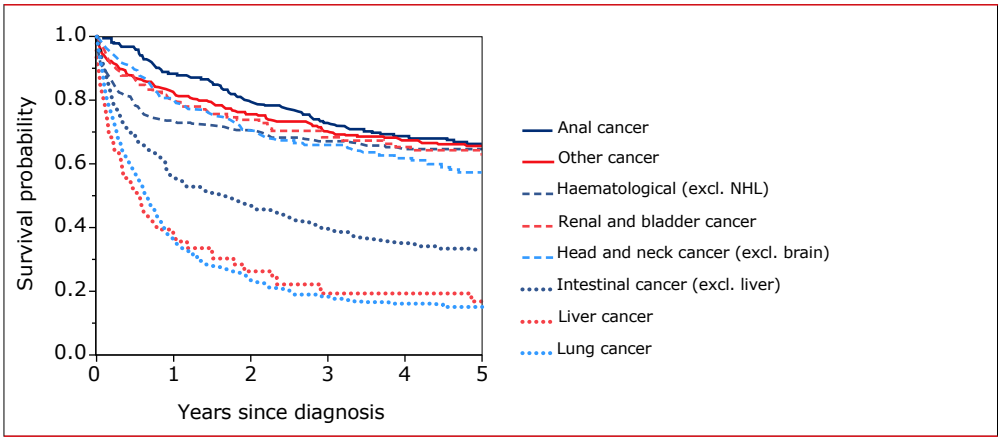
Appendix Figure 3.1: *Estimated five-year survival following the diagnosis of cardiovascular disease, non-AIDS-defining malignancy, diabetes mellitus, and chronic kidney disease. Two reference groups are included: survival from date of entry into HIV care (after 1 January 2000), and from date of first AIDS diagnosis (after 1 January 2000). The numbers below the graph represent the number of subjects per stratum at risk at each time point.*



Time since diagnosis (years)	0	1	2	3	4	5
CVD	1,757	1,376	1,224	1,084	954	819
NADM	1,639	1,063	845	695	581	491
DM	1,624	1,391	1,232	1,116	985	876
CKD	2,543	2,205	1,977	1,739	1,458	1,148
In care for HIV	23,134	21,233	20,081	18,898	17,732	16,560
AIDS	3,738	3,190	2,962	2,773	2,613	2,446

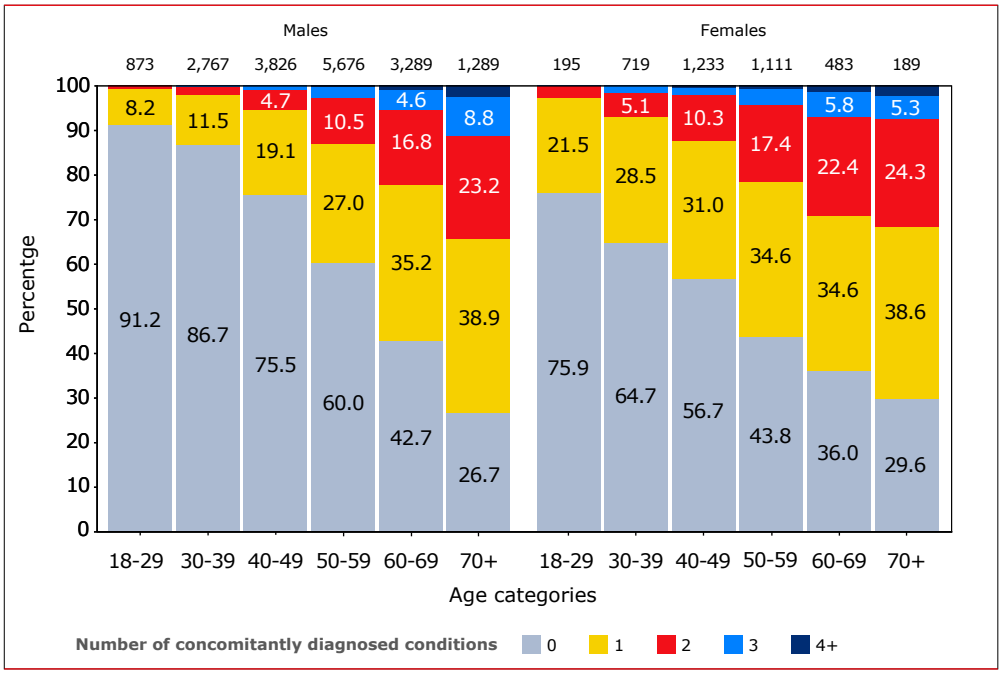
Legend: *KM = Kaplan-Meier; CVD = cardiovascular disease; NADM = non-AIDS defining malignancy; DM = diabetes mellitus; CKD = chronic kidney disease.*

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

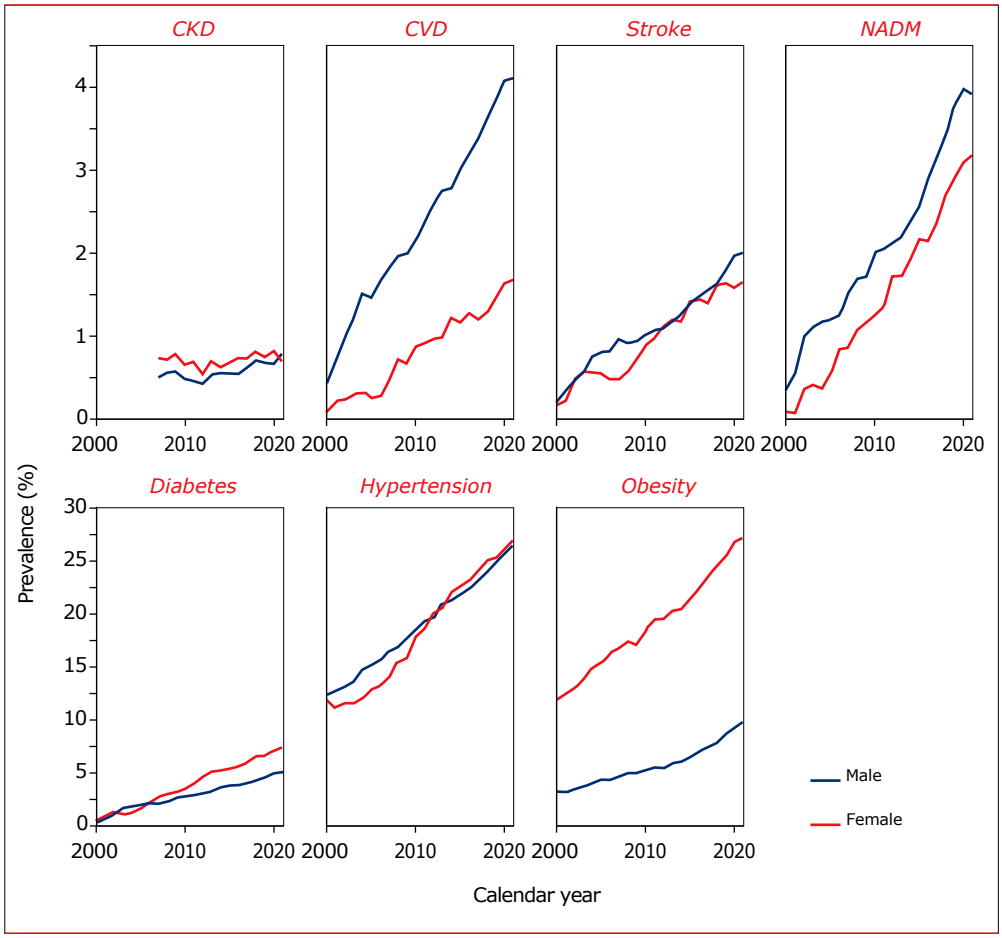


Legend: *KM = Kaplan-Meier; excl. = excluding; NHL = non-Hodgkin's lymphoma.*

Appendix Figure 3.3: *Prevalence of non-AIDS multimorbidity by gender in the adult population in 2021. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.*

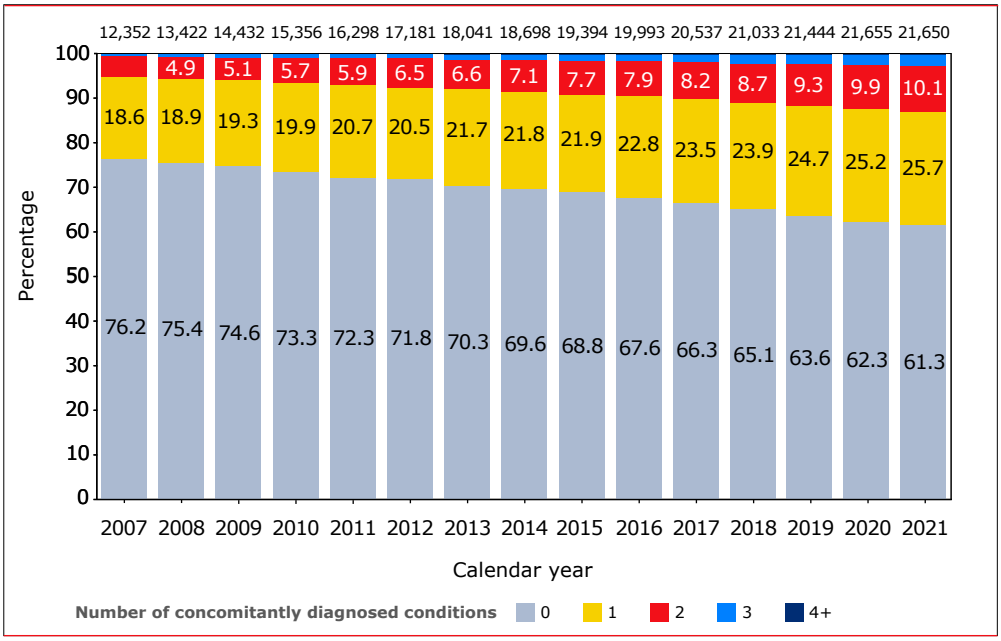


Appendix Figure 3.4: *Prevalence of non-AIDS comorbidities in the adult population between 2000 and 2021.*



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

Appendix Figure 3.5: *Prevalence of non-AIDS multimorbidity in the adult population. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per calendar year.*



Appendix Table 3.1: *Absolute number of causes of death among PWH during the periods 1996–2000, 2001–05, 2006–10, and 2011–21.*

	Calendar period										
Causes of death	**96–00**	**01–05**	**06–10**	**11–15**	**16–21**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
1. AIDS											
1.1 AIDS – infection	69	120	148	103	27	6	4	4	7	5	1
1.2 AIDS – malignancy	60	63	61	43	56	8	13	10	11	6	8
1.3 AIDS – unclassifiable	89	63	19	15	30	10	3	4	5	4	4
total	*218*	*246*	*228*	*161*	*113*	*24*	*20*	*18*	*23*	*15*	*13*
2. Non-AIDS malignancies	30	95	136	193	361	49	62	48	75	70	57
3. Cardiovascular disease											
3.1 Myocardial infarction	14	30	46	40	50	8	4	2	10	14	12
3.2 Stroke	3	11	13	11	23	7	3	3	2	3	5
3.3 Other CVD	6	24	26	50	76	16	10	16	10	11	13
total	*23*	*65*	*85*	*101*	*149*	*31*	*17*	*21*	*22*	*28*	*30*
4. Non-AIDS infection	23	42	32	27	66	7	3	10	7	16	23
5. Liver disease	15	28	55	43	27	6	7	8	.	2	4
6. Lung disease	7	11	30	38	69	13	14	9	16	7	10
7. Non-natural death											
7.1 Accident or violence	6	11	22	16	18	7	2	4	1	2	2
7.2 Suicide	12	30	30	52	59	10	12	11	5	14	7
7.3 Euthanasia	7	5	.	2	1	1	.	.	.	.	.
total	*25*	*46*	*52*	*70*	*78*	*18*	*14*	*15*	*6*	*16*	*9*
8. Alcohol and substance use	12	15	27	18	30	10	4	4	2	4	6
9. Other causes	21	24	23	43	86	13	8	18	10	14	23
10. Unknown	23	57	53	84	130	20	18	21	16	24	31
Total	**397**	**629**	**721**	**778**	**1,109**	**191**	**167**	**172**	**177**	**196**	**206**

Legend: *CVD = cardiovascular disease.*

Appendix Table 3.2: Adjusted risk factors for death and AIDS among PWH.

	Death			AIDS		
	RR (95%CI)	p-value	Overall p-value	RR (95%CI)	p-value	Overall p-value
Risk factors						
Male gender	1.24 (1.08-1.41)	0.002		0.99 (0.85-1.16)	0.900	
Region of birth						
Netherlands	1 (reference)		0.037	1 (reference)		0.112
Other	0.91 (0.83-0.99)	0.038		1.10 (0.98-1.23)	0.111	
HIV-1 transmission route						
Blood contact	0.85 (0.62-1.17)	0.317		0.81 (0.56-1.17)	0.261	
Heterosexual	1.08 (0.96-1.21)	0.188		0.92 (0.79-1.06)	0.257	
IDU	1.62 (1.36-1.94)	<.001		0.71 (0.55-0.92)	0.010	
MSM	1 (reference)		<.001	1 (reference)		0.031
Age *						
18-29	0.90 (0.66-1.24)	0.533	<.001	1.10 (0.89-1.35)	0.381	<.001
30-39	1 (reference)			1 (reference)		
40-49	1.53 (1.32-1.78)	<.001		1.09 (0.96-1.24)	0.206	
50-59	2.71 (2.34-3.14)	<.001		1.30 (1.13-1.50)	<.001	
60-69	4.90 (4.19-5.74)	<.001		1.37 (1.14-1.65)	<.001	
70+	11.58 (9.72-13.81)	<.001		2.01 (1.49-2.70)	<.001	
CD4 cell count **						
0-50	11.81 (9.88-14.12)	<.001	<.001	6.77 (5.46-8.39)	<.001	<.001
050-199	4.69 (4.11-5.34)	<.001		2.76 (2.35-3.25)	<.001	
200-349	1.98 (1.74-2.25)	<.001		1.53 (1.31-1.79)	<.001	
350-499	1.34 (1.18-1.53)	<.001		1.19 (1.01-1.39)	0.036	
500-749	1 (reference)			1 (reference)		
750+	0.86 (0.75-0.98)	0.027		1.04 (0.87-1.25)	0.662	
Per year longer on ART with HIV RNA>1000 cp/mL	1.06 (1.04-1.08)	<.001	<.001	1.04 (1.02-1.07)	0.002	0.002
Treatment status						
Treatment-experienced at start ART	0.95 (0.86-1.05)	0.290		0.64 (0.56-0.72)	<.001	
Treatment-naïve at start ART	1 (reference)			1 (reference)		
Prior AIDS event	1.71 (1.57-1.86)	<.001				

	Death			AIDS		
	RR (95%CI)	p-value	Overall p-value	RR (95%CI)	p-value	Overall p-value
Hepatitis B virus positive	1.27 (1.11–1.45)	<.001		1.10 (0.91–1.34)	0.308	
Hepatitis C virus positive	1.56 (1.36–1.79)	<.001		1.25 (1.04–1.50)	0.016	
Body mass index *						
0–18	3.07 (2.71–3.47)	<.001	<.001			
18–25	1 (reference)					
25–30	0.68 (0.61–0.75)	<.001				
30+	0.87 (0.75–1.02)	0.097				
Smoking status						
Current smoker	1.18 (1.04–1.33)	0.008	<.001	0.80 (0.71–0.90)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	2.00 (1.79–2.24)	<.001		0.99 (0.86–1.14)	0.859	
Early ART ***	0.88 (0.65–1.20)	0.425		1.26 (0.96–1.65)	0.093	

**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	48	2,741	17.5 (12.9–23.2)	3	159	18.9 (3.9–55.3)	8	161	49.8 (21.5–98.2)
050–199	198	10,305	19.2 (16.6–22.1)	11	842	13.1 (6.5–23.4)	38	1,034	36.7 (26.0–50.4)
200–349	411	22,830	18.0 (16.3–19.8)	16	1,052	15.2 (8.7–24.7)	83	2,062	40.3 (32.1–49.9)
350–499	528	45,789	11.5 (10.6–12.6)	36	1,788	20.1 (14.1–27.9)	120	3,640	33.0 (27.3–39.4)
500–749	772	99,502	7.8 (7.2–8.3)	58	5,063	11.5 (8.7–14.8)	198	8,099	24.4 (21.2–28.1)
750+	539	117025	4.6 (4.2–5.0)	42	6,047	6.9 (5.0–9.4)	170	10,447	16.3 (13.9–18.9)

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	1,832	2.2 (0.6–5.6)	27	491	54.9 (36.2–79.9)	6	99	60.5 (22.2–131.7)
	29	6,240	4.6 (3.1–6.7)	112	1,795	62.4 (51.4–75.1)	8	393	20.3 (8.8–40.1)
	78	14,382	5.4 (4.3–6.8)	208	4,491	46.3 (40.2–53.1)	26	844	30.8 (20.1–45.2)
	109	30,143	3.6 (3.0–4.4)	242	8,174	29.6 (26.0–33.6)	21	2,045	10.3 (6.4–15.7)
	233	67,274	3.5 (3.0–3.9)	262	14,891	17.6 (15.5–19.9)	21	4,175	5.0 (3.1–7.7)
	175	82,740	2.1 (1.8–2.5)	135	13,952	9.7 (8.1–11.5)	17	3,839	4.4 (2.6–7.1)

Appendix Table 3.4: *Absolute number of first AIDS events among PWH during the periods 1996–2000, 2001–05, 2006–10, 2011–15 and 2016–21.*

CDC event	1996–2000	2001–2005	2006–2010	2011–2015	2016–2019	2020–2021	Total	
	N	N	N	N	N	N	N	%
AIDS dementia complex – HIV encephalopathy	38	47	51	44	15	8	203	2.95
Bacterial pneumonia, recurring	48	64	67	78	76	21	354	5.15
CMV colitis/proctitis	1	.	1	2	3	.	7	0.10
CMV disease	27	34	29	33	3	.	126	1.83
CMV meningoencephalitis	.	.	.	.	1	.	1	0.01
CMV pneumonitis	.	.	.	.	9	9	18	0.26
CMV retinitis	31	20	12	12	10	.	85	1.24
Candidiasis oesophagitis	263	239	253	224	114	46	1139	16.57
Candidiasis lungs/bronchial/trachea	7	13	7	6	5	4	42	0.61
Cervical cancer, invasive	3	5	6	4	4	.	22	0.32
Coccidioidomycosis, extrapulmonary / disseminated	.	.	1	.	.	.	1	0.01
Cryptococcosis, extrapulmonary / disseminated	21	31	33	11	11	2	109	1.59
Cryptosporidiosis	22	12	11	12	2	1	60	0.87
Cystoisosporiasis	3	9	6	.	.	.	18	0.26
HIV wasting	48	56	77	77	52	17	327	4.76
HSV chronic ulcer	1	2	1	3	18	10	35	0.51
HSV oesophagitis	.	.	.	.	.	1	1	0.01
HSV pneumonitis	.	.	.	.	.	1	1	0.01
Herpes simplex virus	32	41	59	38	8	.	178	2.59
Histoplasmosis, extrapulmonary / disseminated	9	12	10	7	2	1	41	0.60
Kaposi sarcoma	154	153	188	139	77	24	735	10.69
Leishmaniasis visceral	.	1	2	2	2	.	7	0.10
Microsporidiosis	11	1	3	1	.	1	17	0.25
Mycobacterium avium/kansasii, extrapulmonary / disseminated	26	19	28	9	7	1	90	1.31
Mycobacterium avium/kansasii, pulmonary	1	2	.	1	8	2	14	0.20
Mycobacterium other / unspecified, extrapulmonary / disseminated	19	13	8	10	3	1	54	0.79
Mycobacterium other / unspecified, pulmonary	.	3	4	9	4	1	21	0.31
Non-Hodgkin's lymphoma (NHL)	57	87	80	96	55	23	398	5.79
Pneumocystis jirovecii extrapulmonary	1	1	3	.	1	.	6	0.09
Pneumocystis jirovecii pneumonia	333	300	326	265	164	59	1447	21.05
Primary CNS lymphoma	8	4	9	6	4	.	31	0.45

CDC event	1996–2000	2001–2005	2006–2010	2011–2015	2016–2019	2020–2021	Total	
	N	N	N	N	N	N	N	%
Progressive multifocal leukoencephalopathy	18	25	35	24	6	3	111	1.62
Salmonella sepsis, recurring	2	.	.	1	.	.	3	0.04
Talaromycosis	.	.	1	.	.	.	1	0.01
Toxoplasmosis of the brain	69	98	55	43	24	6	295	4.29
Tuberculosis, extrapulmonary / disseminated	79	113	80	54	19	11	356	5.18
Tuberculosis, pulmonary	105	174	118	74	44	4	519	7.55
Total	**1437**	**1579**	**1564**	**1285**	**751**	**257**	**6873**	**100.00**

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

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

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
Male gender	1.24 (1.11-1.37)	<.001	.	1.54 (1.26-1.88)	<.001	.
Region of birth						
Netherlands	1 (reference)	.	0.025	1 (reference)	.	0.731
Other	1.08 (1.01-1.16)	0.025	.	0.98 (0.86-1.11)	0.731	.
HIV-1 transmission route						
MSM	1 (reference)	.	<.001	1 (reference)	.	0.027
Heterosexual	1.20 (1.10-1.30)	<.001	.	1.19 (1.03-1.39)	0.021	.
IDU	1.31 (1.08-1.58)	0.005	.	1.40 (1.00-1.97)	0.048	.
Blood contact	1.21 (0.95-1.54)	0.114	.	1.06 (0.66-1.70)	0.806	.
Age *						
18-29	0.62 (0.47-0.81)	<.001	<.001	0.64 (0.32-1.26)	0.197	<.001
30-39	1 (reference)	.	.	1 (reference)	.	.
40-49	2.02 (1.79-2.29)	<.001	.	2.97 (2.20-4.02)	<.001	.
50-59	3.75 (3.31-4.24)	<.001	.	6.21 (4.62-8.34)	<.001	.
60-69	6.40 (5.60-7.31)	<.001	.	9.86 (7.27-13.39)	<.001	.
70+	10.21 (8.66-12.03)	<.001	.	16.41 (11.74-22.95)	<.001	.
CD4 cell count **						
0-50	3.94 (3.12-4.98)	<.001	<.001	3.24 (1.83-5.74)	<.001	<.001
050-199	1.79 (1.54-2.07)	<.001	.	1.70 (1.27-2.28)	<.001	.
200-349	1.25 (1.13-1.40)	<.001	.	1.40 (1.16-1.69)	<.001	.
350-499	1.04 (0.95-1.14)	0.392	.	1.00 (0.85-1.18)	0.984	.
500-749	1 (reference)	.	.	1 (reference)	.	.
750+	1.12 (1.03-1.22)	0.006	.	1.24 (1.08-1.42)	0.003	.
Per year longer with CD4<200 cells/mm^3	1.00 (0.98-1.02)	0.636	.	1.01 (0.98-1.04)	0.508	.
Prior AIDS event	1.21 (1.13-1.30)	<.001	.	1.17 (1.03-1.32)	0.013	.
Per year longer on ART while HIV RNA>1000 cp/mL	1.02 (1.00-1.04)	0.065	.	1.02 (0.98-1.05)	0.320	.
Treatment status						
Not (yet) started ART	1.17 (1.03-1.33)	0.019	<.001	1.33 (1.00-1.75)	0.047	0.032
Treatment-experienced at start ART	1.27 (1.16-1.39)	<.001	.	1.16 (0.98-1.37)	0.078	.
Treatment-naive at start	1 (reference)	.	.	1 (reference)	.	.
Per year longer on ART	1.01 (1.00-1.01)	0.054	.	1.00 (0.99-1.02)	0.477	.
Early ART within 12 months after last HIV-negat	0.81 (0.66-1.00)	0.051	.	1.18 (0.88-1.58)	0.268	.

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
1.05 (0.88-1.25)	0.605	.	1.28 (1.09-1.49)	0.002	.	0.62 (0.54-0.72)	<.001	.
1 (reference)	.	0.006	1 (reference)	.	<.001	1 (reference)	.	<.001
0.85 (0.75-0.96)	0.007	.	1.53 (1.36-1.71)	<.001	.	0.76 (0.69-0.85)	<.001	.
1 (reference)	.	0.135	1 (reference)	.	<.001	1 (reference)	.	0.057
1.00 (0.87-1.16)	0.964	.	1.44 (1.25-1.66)	<.001	.	0.99 (0.87-1.13)	0.899	.
1.33 (1.00-1.77)	0.053	.	1.50 (1.08-2.08)	0.015	.	1.43 (1.09-1.87)	0.010	.
1.43 (1.00-2.03)	0.049	.	1.53 (1.06-2.19)	0.022	.	1.27 (0.93-1.75)	0.136	.
0.78 (0.48-1.25)	0.296	<.001	0.62 (0.42-0.90)	0.012	<.001	0.26 (0.11-0.66)	0.005	<.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
2.27 (1.80-2.86)	<.001	.	1.53 (1.28-1.83)	<.001	.	3.20 (2.39-4.27)	<.001	.
4.26 (3.39-5.35)	<.001	.	2.42 (2.01-2.91)	<.001	.	8.84 (6.69-11.68)	<.001	.
8.88 (7.01-11.26)	<.001	.	3.87 (3.15-4.74)	<.001	.	24.19 (18.28-32.00)	<.001	.
15.81 (12.10-20.65)	<.001	.	4.36 (3.28-5.79)	<.001	.	45.37 (33.76-60.97)	<.001	.
3.17 (2.05-4.90)	<.001	<.001	6.10 (4.37-8.52)	<.001	<.001	1.47 (0.78-2.78)	0.229	<.001
2.04 (1.61-2.58)	<.001	.	1.74 (1.36-2.23)	<.001	.	1.66 (1.33-2.08)	<.001	.
1.39 (1.17-1.64)	<.001	.	1.12 (0.94-1.35)	0.210	.	1.16 (1.00-1.35)	0.054	.
1.11 (0.96-1.28)	0.171	.	0.99 (0.84-1.15)	0.861	.	1.07 (0.95-1.21)	0.246	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
0.92 (0.80-1.06)	0.236	.	1.28 (1.12-1.46)	<.001	.	0.96 (0.87-1.07)	0.500	.
0.99 (0.96-1.02)	0.347	.	1.00 (0.97-1.03)	0.931	.	0.99 (0.96-1.02)	0.385	.
1.18 (1.05-1.32)	0.004	.	1.29 (1.15-1.44)	<.001	.	1.14 (1.04-1.25)	0.006	.
1.01 (0.98-1.04)	0.681	.	1.02 (0.99-1.05)	0.256	.	0.98 (0.95-1.01)	0.151	.
1.20 (0.96-1.50)	0.102	0.030	1.38 (1.12-1.70)	0.002	<.001	0.41 (0.29-0.59)	<.001	<.001
1.18 (1.02-1.36)	0.029	.	1.27 (1.09-1.49)	0.003	.	1.19 (1.04-1.36)	0.011	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
1.00 (0.99-1.01)	0.640	.	1.00 (0.99-1.02)	0.682	.	0.98 (0.97-0.99)	<.001	.
0.57 (0.39-0.83)	0.004	.	0.66 (0.43-0.99)	0.047	.	0.94 (0.76-1.18)	0.603	.

	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	1.49 (1.24-1.80)	<.001	<.001	1.20 (0.85-1.70)	0.297	0.548
18-25	1 (reference)	.	.	1 (reference)	.	.
25-30	1.23 (1.14-1.33)	<.001	.	1.05 (0.92-1.19)	0.457	.
30+	2.03 (1.83-2.24)	<.001	.	1.14 (0.94-1.38)	0.197	.
Hepatitis B virus positive	1.22 (1.09-1.37)	<.001	.	1.02 (0.82-1.27)	0.872	.
Hepatitis C virus positive	1.05 (0.94-1.18)	0.391	.	1.00 (0.81-1.22)	0.962	.
Hypertension	1.13 (1.06-1.21)	<.001	.	1.30 (1.16-1.45)	<.001	.
Smoking status						
Current smoker	1.38 (1.27-1.49)	<.001	<.001	1.75 (1.52-2.00)	<.001	<.001
Never smoker	1 (reference)	.	.	1 (reference)	.	.
Past smoker	1.41 (1.30-1.54)	<.001	.	1.54 (1.34-1.78)	<.001	.
Calendar year period						
2000-2010	1.27 (1.15-1.39)	<.001	<.001	1.40 (1.19-1.65)	<.001	<.001
2011-2015	1.15 (1.06-1.25)	<.001	.	1.22 (1.07-1.39)	0.003	.
2016-2021	1 (reference)	.	.	1 (reference)	.	.
Recent use of ABC ***		.	.	1.58 (1.40-1.79)	<.001	.
Per year longer on LOP/r		.	.	1.01 (0.99-1.02)	0.278	.
Per year longer on IDV		.	.	1.00 (0.99-1.01)	0.919	.
Per year longer on ZDV		.	.		.	.
Per year longer on d4T		.	.		.	.
Per year longer on ddI		.	.		.	.
Per year longer on TAF		.	.		.	.
Per year longer on TDF		.	.		.	.
Prior cardiovascular event		.	.		.	.
Prior diabetes		.	.		.	.
Current use of cobicistat		.	.		.	.
Current use of dolutegravir		.	.		.	.
Current use of rilpivirine		.	.		.	.
Current use of bictegravir		.	.		.	.

**Time-updated.*

***Time-updated and lagged by 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 (1.53-2.51)	<.001	<.001	1.33 (0.91-1.94)	0.139	<.001	1.38 (1.05-1.83)	0.023	0.031
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
0.90 (0.79-1.01)	0.083	.	2.25 (1.97-2.58)	<.001	.	1.14 (1.03-1.25)	0.012	.
0.96 (0.78-1.16)	0.649	.	5.43 (4.67-6.31)	<.001	.	1.13 (0.98-1.30)	0.103	.
1.63 (1.38-1.94)	<.001	.	1.08 (0.88-1.32)	0.475	.	1.44 (1.23-1.69)	<.001	.
1.10 (0.91-1.33)	0.309	.	1.03 (0.84-1.26)	0.793	.	1.32 (1.15-1.53)	<.001	.
0.95 (0.85-1.06)	0.321	.	1.17 (1.05-1.31)	0.004	.	1.10 (1.01-1.20)	0.031	.
1.54 (1.34-1.76)	<.001	<.001	1.02 (0.90-1.17)	0.728	0.002	0.81 (0.73-0.91)	<.001	<.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
1.72 (1.50-1.97)	<.001	.	1.24 (1.09-1.42)	0.001	.	1.00 (0.91-1.11)	0.933	.
0.93 (0.80-1.09)	0.386	0.660	1.35 (1.14-1.59)	<.001	<.001	1.34 (1.13-1.58)	<.001	<.001
0.96 (0.84-1.09)	0.501	.	1.28 (1.11-1.47)	<.001	.	1.39 (1.24-1.56)	<.001	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	.	.		.	.		.	.
	.	.		.	.		.	.
	.	.		.	.		.	.
	.	.	1.02 (1.01-1.03)	0.005	.		.	.
	.	.	1.02 (1.00-1.05)	0.108	.		.	.
	.	.	1.06 (1.03-1.08)	<.001	.		.	.
	.	.		.	.	0.99 (0.98-1.01)	0.303	.
	.	.		.	.	1.01 (1.00-1.02)	0.042	.
	.	.		.	.	1.60 (1.39-1.84)	<.001	.
	.	.		.	.	1.33 (1.14-1.54)	<.001	.
	.	.		.	.	1.61 (1.42-1.84)	<.001	.
	.	.		.	.	3.17 (2.85-3.54)	<.001	.
	.	.		.	.	1.34 (1.13-1.59)	<.001	.
	.	.		.	.	2.25 (1.81-2.80)	<.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 2021.*

		All events		0-50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Aspergillosis, invasive pulmonary	9	0.3%	1	0.4%
	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis oropharyngeal	767	26.1%	69	27.9%
	Candidiasis vulvovaginal, frequent/persistent	54	1.8%	1	0.4%
	Cardiomyopathy, HIV-related	5	0.2%	0	0.0%
	Cardiomyopathy, with HIV-related component	17	0.6%	1	0.4%
	Diarrhoea, HIV-related > = 30 days	63	2.1%	1	0.4%
	Fever e.c.i. / HIV-related	6	0.2%	0	0.0%
	HIV-associated nephropathy (HIVAN)	21	0.7%	2	0.8%
	Herpes zoster, multidermatomal	19	0.6%	3	1.2%
	Herpes zoster, recurring / multidermatomal unspecified	211	7.2%	7	2.8%
	Herpes zoster, unidermatomal recurrent	17	0.6%	3	1.2%
	Listeriosis	1	0.0%	0	0.0%
	Myelopathy, HIV-related	10	0.3%	0	0.0%
	Neuropathy, HIV-related	108	3.7%	2	0.8%
	Neuropathy, with HIV-related component	79	2.7%	1	0.4%
	Nocardiosis	2	0.1%	1	0.4%
	Oral Hairy Leucoplakia (OHL)	53	1.8%	2	0.8%
	Pelvic inflammatory disease	9	0.3%	0	0.0%
	Thrombocytopenia, HIV-related	107	3.6%	3	1.2%
	Thrombocytopenia, with HIV-related component	14	0.5%	3	1.2%
	Weight loss >10%, HIV-related / unknown cause	36	1.2%	2	0.8%
Subtotal		**1609**	**54.7%**	**102**	**41.3%**
CDC-C events	AIDS dementia complex - HIV encephalopathy	44	1.5%	5	2.0%
	Bacterial pneumonia, recurring	311	10.6%	11	4.5%
	CMV disease	19	0.6%	4	1.6%
	CMV oesophagitis	1	0.0%	1	0.4%
	CMV retinitis	17	0.6%	4	1.6%
	Candidiasis oesophagitis	237	8.1%	26	10.5%
	Candidiasis lungs/bronchial/trachea	11	0.4%	2	0.8%
	Cervical cancer, invasive	10	0.3%	1	0.4%
	Coccidioidomycosis, extrapulmonary / disseminated	1	0.0%	0	0.0%

CD4 category									
050–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
3	0.5%	0	0.0%	1	0.2%	2	0.3%	2	0.6%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
183	32.2%	159	25.5%	121	21.9%	140	23.2%	95	27.4%
5	0.9%	9	1.4%	18	3.3%	16	2.6%	5	1.4%
1	0.2%	0	0.0%	2	0.4%	1	0.2%	1	0.3%
4	0.7%	2	0.3%	2	0.4%	6	1.0%	2	0.6%
5	0.9%	17	2.7%	10	1.8%	22	3.6%	8	2.3%
1	0.2%	2	0.3%	0	0.0%	1	0.2%	2	0.6%
4	0.7%	3	0.5%	4	0.7%	4	0.7%	4	1.2%
0	0.0%	4	0.6%	2	0.4%	6	1.0%	4	1.2%
25	4.4%	53	8.5%	44	8.0%	51	8.4%	31	8.9%
4	0.7%	0	0.0%	2	0.4%	4	0.7%	4	1.2%
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	0.9%
9	1.6%	17	2.7%	30	5.4%	29	4.8%	21	6.1%
10	1.8%	11	1.8%	18	3.3%	25	4.1%	14	4.0%
0	0.0%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
13	2.3%	11	1.8%	8	1.4%	11	1.8%	8	2.3%
0	0.0%	4	0.6%	0	0.0%	3	0.5%	2	0.6%
20	3.5%	23	3.7%	22	4.0%	27	4.5%	12	3.5%
0	0.0%	5	0.8%	0	0.0%	5	0.8%	1	0.3%
5	0.9%	9	1.4%	6	1.1%	8	1.3%	6	1.7%
297	**52.2%**	**333**	**53.4%**	**290**	**52.4%**	**362**	**59.9%**	**225**	**64.8%**
5	0.9%	8	1.3%	10	1.8%	9	1.5%	7	2.0%
52	9.1%	78	12.5%	80	14.5%	62	10.3%	28	8.1%
2	0.4%	3	0.5%	6	1.1%	1	0.2%	3	0.9%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
5	0.9%	1	0.2%	6	1.1%	1	0.2%	0	0.0%
55	9.7%	56	9.0%	39	7.1%	36	6.0%	25	7.2%
1	0.2%	5	0.8%	1	0.2%	1	0.2%	1	0.3%
2	0.4%	1	0.2%	2	0.4%	4	0.7%	0	0.0%
0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
	Cryptococcosis, extrapulmonary / disseminated	16	0.5%	6	2.4%
	Cryptosporidiosis	11	0.4%	4	1.6%
	Cystoisosporiasis	1	0.0%	0	0.0%
	HIV wasting	17	0.6%	7	2.8%
	HSV chronic ulcer	25	0.8%	1	0.4%
	HSV oesophagitis	1	0.0%	0	0.0%
	HSV pneumonitis	1	0.0%	0	0.0%
	Herpes simplex virus	61	2.1%	7	2.8%
	Histoplasmosis, extrapulmonary / disseminated	4	0.1%	3	1.2%
	Kaposi sarcoma	115	3.9%	7	2.8%
	Leishmaniasis visceral	5	0.2%	1	0.4%
	Microsporidiosis	5	0.2%	2	0.8%
	Mycobacterium avium/kansasii, extrapulmonary / disseminated	22	0.7%	4	1.6%
	Mycobacterium avium/kansasii, pulmonary	3	0.1%	0	0.0%
	Mycobacterium other / unspecified, extrapulmonary / disseminated	9	0.3%	3	1.2%
	Mycobacterium other / unspecified, pulmonary	5	0.2%	0	0.0%
	Non-Hodgkin's lymphoma (NHL)	153	5.2%	6	2.4%
	Pneumocystis jirovecii extrapulmonary	1	0.0%	0	0.0%
	Pneumocystis jirovecii pneumonia	69	2.3%	19	7.7%
	Primary CNS lymphoma	6	0.2%	1	0.4%
	Progressive multifocal leukoencephalopathy	18	0.6%	5	2.0%
	Toxoplasmosis of the brain	20	0.7%	8	3.2%
	Tuberculosis, extrapulmonary / disseminated	46	1.6%	3	1.2%
	Tuberculosis, pulmonary	70	2.4%	4	1.6%
Subtotal		**1335**	**45.3%**	**145**	**58.7%**
Total		**2944**	**100.0%**	**247**	**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	%
	7	1.2%	2	0.3%	0	0.0%	1	0.2%	0	0.0%
	0	0.0%	1	0.2%	3	0.5%	2	0.3%	1	0.3%
	0	0.0%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
	6	1.1%	1	0.2%	2	0.4%	1	0.2%	0	0.0%
	4	0.7%	1	0.2%	2	0.4%	12	2.0%	5	1.4%
	0	0.0%	0	0.0%	1	0.2%	0	0.0%	0	0.0%
	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
	6	1.1%	13	2.1%	16	2.9%	15	2.5%	4	1.2%
	0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
	11	1.9%	24	3.8%	28	5.1%	32	5.3%	13	3.7%
	3	0.5%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
	2	0.4%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
	9	1.6%	5	0.8%	2	0.4%	1	0.2%	1	0.3%
	0	0.0%	1	0.2%	0	0.0%	1	0.2%	1	0.3%
	2	0.4%	3	0.5%	0	0.0%	1	0.2%	0	0.0%
	2	0.4%	0	0.0%	2	0.4%	1	0.2%	0	0.0%
	40	7.0%	36	5.8%	32	5.8%	27	4.5%	12	3.5%
	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
	24	4.2%	11	1.8%	7	1.3%	7	1.2%	1	0.3%
	2	0.4%	2	0.3%	1	0.2%	0	0.0%	0	0.0%
	6	1.1%	4	0.6%	2	0.4%	1	0.2%	0	0.0%
	6	1.1%	4	0.6%	1	0.2%	1	0.2%	0	0.0%
	9	1.6%	7	1.1%	5	0.9%	12	2.0%	10	2.9%
	11	1.9%	22	3.5%	15	2.7%	11	1.8%	7	2.0%
	272	**47.8%**	**291**	**46.6%**	**263**	**47.6%**	**242**	**40.1%**	**122**	**35.2%**
	569	**100.0%**	**624**	**100.0%**	**553**	**100.0%**	**604**	**100.0%**	**347**	**100.0%**

4. Viral hepatitis

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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 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 non-alcoholic fatty liver disease (NAFLD) [7,8,9]. While progression of liver disease was faster in people 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 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 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.

Recent HCV infection[19,20]

1. Case definition of recent HCV according to *preferred* criteria[19]:
   Positive anti-HCV IgG with a documented negative anti-HCV IgG within the past 12 months,
   or:
   detectable HCV RNA in the presence of either a documented negative HCV RNA test, or a documented anti-HCV IgG seroconversion within the past 12 months.
2. Case definition of recent 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 recent or chronic HCV infection.

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

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

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

HCV screening over time

In the Netherlands the national guidelines for the treatment and monitoring of HIV recommend HCV screening during the first clinical visit after HIV diagnosis, and additional annual HCV screening for MSM who report HCV-related risk-taking behaviour[21]. Screening for HCV infection among individuals with HIV ever registered by stichting HIV monitoring (SHM), has increased over calendar time. Of the 29,040[a] individuals with HIV 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 2021, only 1.5% of the individuals in care had never been screened for HCV co-infection (*Figure 4.1A*). In 2021, unknown HCV status was relatively more common among individuals with heterosexually-acquired HIV (2.9%), or with another or unknown mode of HIV acquisition (3.1%), and relatively less common among MSM (0.8%) and people who inject drugs (PWID) or former PWID (0.4%).

Follow-up screening

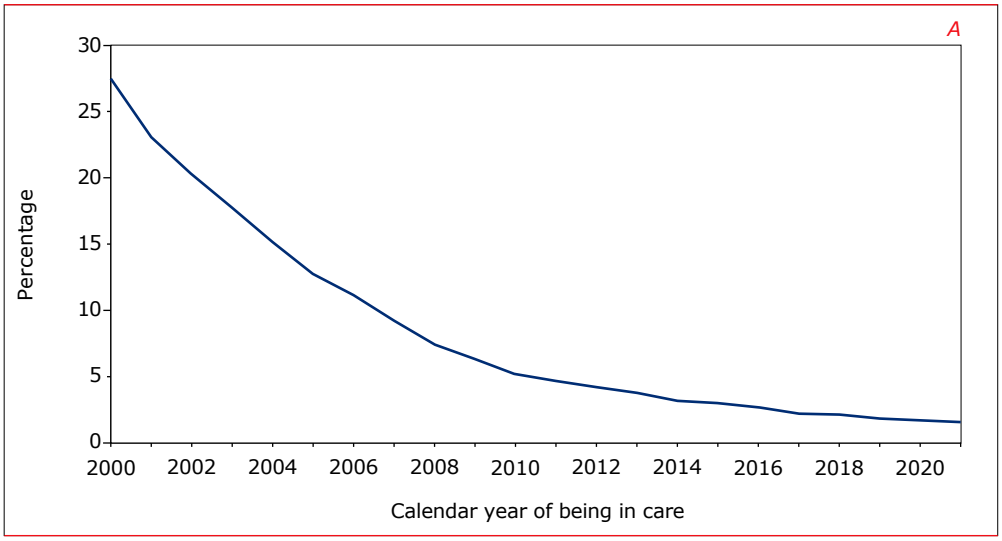
Among individuals who had a negative first HCV test and who remained in care, 78% had a second HCV test at some point during follow up. This proportion was highest for MSM, of whom 87% had at least a second HCV test, and lowest for individuals who acquired HIV through heterosexual contact (62%).

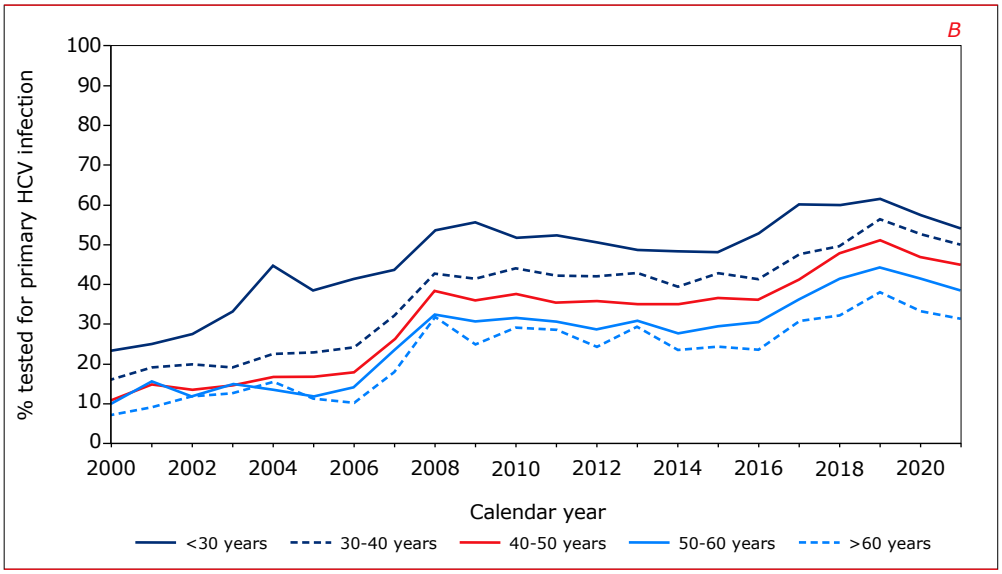
As most HCV infections are observed among MSM[22], the following analysis on testing frequency is reported for MSM only. Overall, the percentage of HCV seronegative MSM with at least one HCV test in a calendar year increased over time, from 13% in 2000 to 27% in 2007, and to 48% in 2019. However, testing frequency among HCV seronegative MSM decreased to 43% in 2020 and 41% in 2021. 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 36-46) *(Table 4.2*), while in the age range 40-50 years, 47% and 45% had at least one test in 2020 and 2021, respectively.

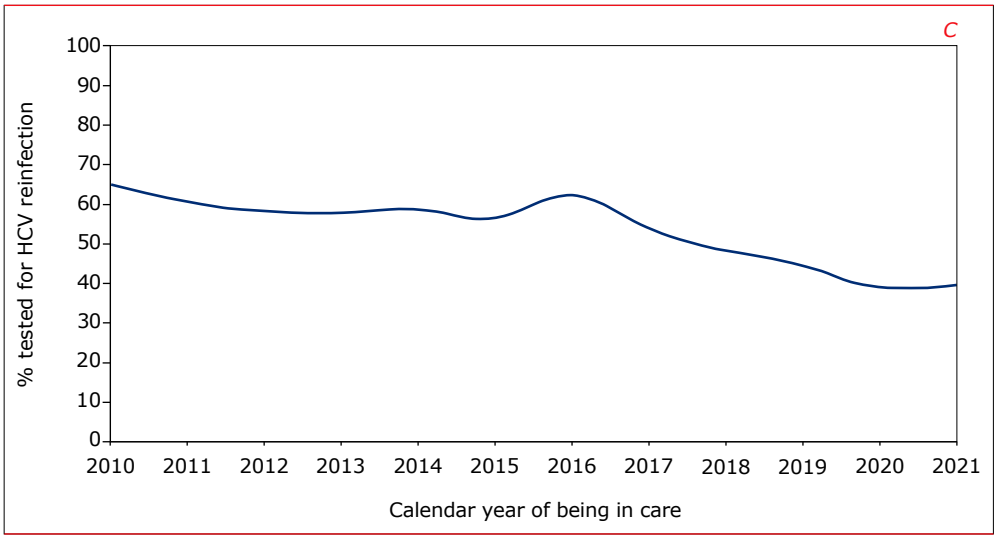
Screening for HCV RNA among those at risk of HCV reinfection is an important factor in identifying HCV reinfection. Among MSM with HIV at risk of reinfection after treatment-induced, or spontaneous clearance of HCV, the percentage of men with an HCV RNA test during a calendar year varied between 54% and 65% in 2010-16, but declined to 44% in 2019, and 39% in 2021 (*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 2012-2021[b] (*Figure 4.1D*).

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

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






C
% tested for HCV reinfection
100
90
80
70
60
50
40
30
20
10
0
2010
2011
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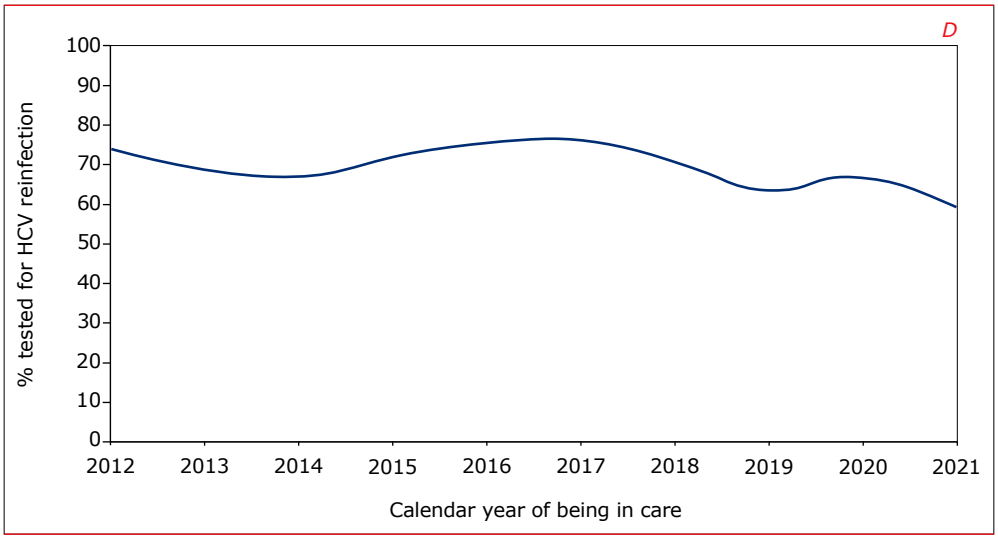
2021
Calendar year of being in care


D
% tested for HCV reinfection
100
90
80
70
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50
40
30
20
10
0
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Calendar year of being in care

HCV-positive individuals

As of May 2022, 29,040 HIV-1-positive adults (aged 15 years and over at the time of their HIV-1 diagnosis) had been registered by stichting HIV monitoring. Of those individuals, 27,833 (96%) were ever screened for HCV co-infection and had been in care at one of the HIV treatment centres: 3,154 (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 169 of the 3,154 cases (5%), of whom:

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

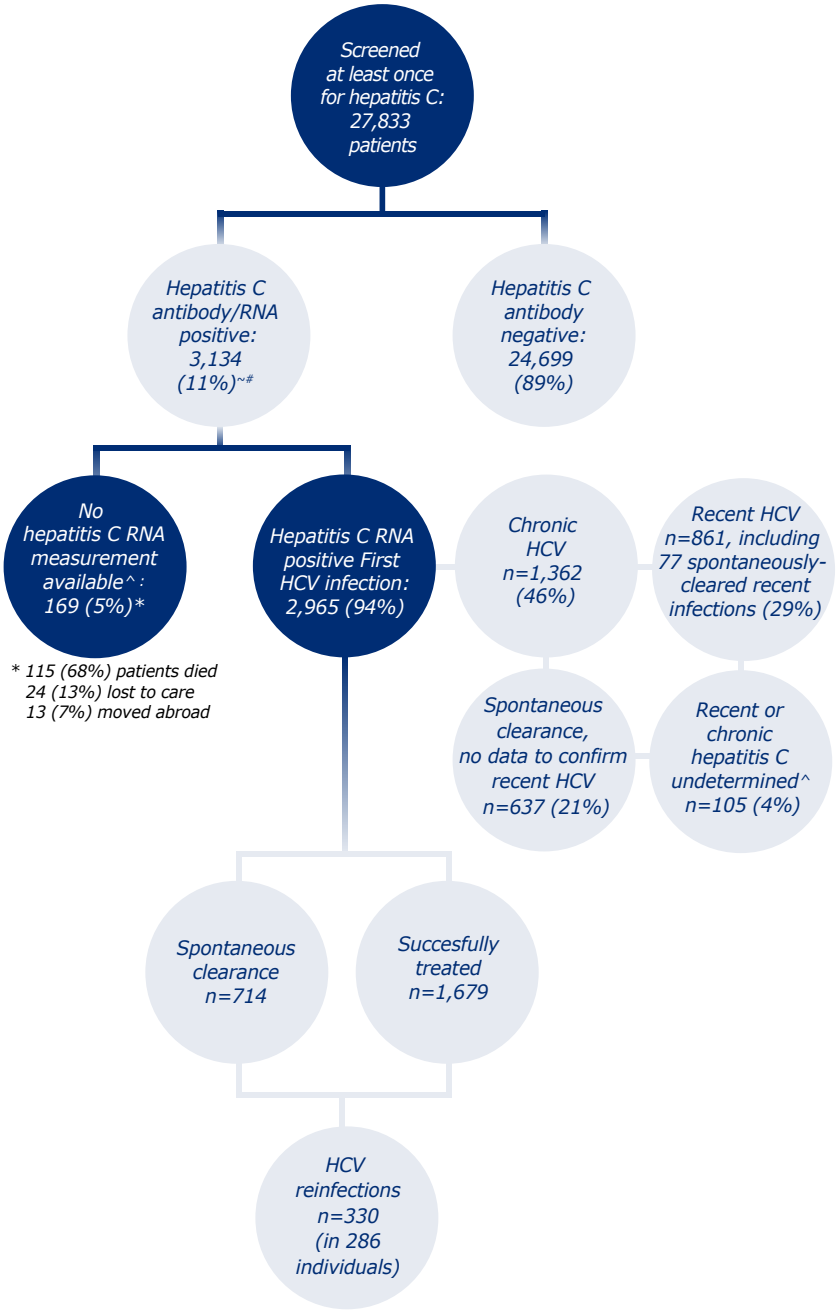
In total, 2,965 individuals were diagnosed with an HCV infection, with documented HCV RNA data for:

- 861 (29%) who were initially diagnosed with an recent HCV infection, of whom;
  - 77 spontaneously cleared their infection
  - 784 became chronic HCV infections or were treated within 6 months of diagnosis.
- 1,362 (46%) who were classified as having a chronic HCV infection at the time of their diagnosis.
- 637 (21%) 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 105 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 recent or chronic at the time of diagnosis. This group of individuals has therefore been excluded from the analysis. The majority (n=99) of individuals with no HCV follow-up data were no longer in care in 2021.

In total, 1,679 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 714 individuals spontaneously cleared their primary HCV infection. In total, 330 HCV reinfections after clearance occurred in 286 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 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, 714 individuals spontaneously cleared their HCV infection. Among the 861 individuals with primary recent hepatitis, 77 (9%) cases of spontaneous clearance were observed. Another 637 cases of spontaneous clearance were observed among individuals who could not be classified as having a primary recent 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, 1998-2021.*

	Total HCV co-infected	Spontaneous clearance
Total number of individuals	2,860	714 (25)
Age at HCV diagnosis (median, IQR)	40 (34-47)	41 (34-48)
HCV status		
Chronic HCV	1,362	
Recent HCV without spontaneous clearance	784	
Spontaneous clearance	714	
Definitive clearance		291
Possible clearance		364
Spontaneous clearance after confirmed primary recent infection		77
Male gender, n (%)	2462 (86)	580 (81)
Region, n (%)		
Netherlands	1723 (60)	363 (51)
Europe	366 (13)	91 (13)
Sub-Saharan Africa	120 (4)	61 (9)
Caribbean/South America	224 (8)	82 (11)
Southeast Asia	93 (3)	23 (3)
Other	334 (12)	94 (13)
HIV transmission route, n (%)		
Men who have sex with men	1,682 (59)	388 (54)
Heterosexual	325 (11)	126 (18)
People who use/used injecting drugs	592 (21)	126 (18)
Other	256 (9)	71 (10)
ART, n (%)	2775 (97)	689 (97)
Deaths, n (%)	513 (18%)	115 (16)

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

In total, 2,223 individuals could be definitively classified as having either chronic (n=1,362), or recent (n=861) 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: 760/1,362 [56%]; recent: 656/861 [76%]) (*Table 4.2*). Fifty-eight percent of the registered individuals who acquired HIV through injecting drug use (IDU), had chronic HCV (460 of the total 791 people who use/used injecting drugs [PWID]). In the MSM HIV transmission group (16,941), 3% (558) had chronic HCV and 5% (809) had documented recent HCV.

The HCV genotype was determined and documented in the clinical records of 1,216 of the 1,362 (89%) individuals with chronic HCV. Of the individuals with a genotype determination:

- 62% (n=751) harboured HCV genotype 1, spread across 61% (n=460) with type 1a and 14% (n=102) with type 1b. For 25% (n=189) of those with genotype 1, the subtype was not further specified.
- 5% (n=59) harboured HCV genotype 2
- 18% (214) harboured HCV genotype 3
- 16% (n=190) harboured HCV genotype 4
- 1 person harboured HCV genotype 5
- 1 person harboured HCV genotype 6

HCV genotype was also documented for 762 of the 861 (89%) individuals with recent HCV. They were most likely to harbour either genotype 1 (72%, n=545) or genotype 4 (21%, n=160). Of the 545 with genotype 1, 85% (n=461) harboured genotype 1a and 4% (n=23) with genotype 1b. For 11% of the people with genotype 1, the subtype was not further specified.

Table 4.2: *Demographic characteristics of individuals with HIV/hepatitis C virus (HCV) registered in the SHM database, 1998–2021.*

	Total	Chronic HCV	Recent HCV
Total number of individuals screened for HCV	27,833	1,362(5)	861 (3)
Age at baseline (median, IQR)	40 (34–47)	39 (33–45)	43 (36–46)
Male gender, n (%)	22,826 (82)	1,104 (81)	852 (99)
Region of origin, n (%)			
Netherlands	15,051 (54)	760 (56)	656 (76)
Europe	1,859 (7)	212 (16)	70 (8)
Sub-Saharan Africa	3,705 (13)	49 (4)	11 (1)
Caribbean/South America	3,617 (13)	92 (7)	53 (6)
Southeast Asia	999 (4)	45 (3)	27 (3)
Other	2,602 (9)	204 (14)	44 (5)
HIV transmission route, n (%)			
Men who have sex with men	16,941 (61)	558 (41)	809 (94)
Heterosexual	8,240 (30)	172 (13)	30 (3)
People who use/used injecting drugs	791 (3)	460 (34)	7(1)
Other	1,861 (6)	172 (12)	15 (2)
ART, n (%)	26,980 (97)	1,306 (96)	857 (99.5)
HCV genotype (GT), n (%*)			
Total determined		1,216 (89)	762 (89)
GT 1		751 (62)	545 (72)
1a		*460*	*461*
1b		*102*	*23*
1c, 1a/b or not further specified		*189*	*61*
GT 2		59 (5)	38 (5)
GT 3		214 (18)	18 (2)
GT 4		190 (16)	160 (21)
GT 5 & 6		2 (0.1)	1 (<1)
Deaths, n (%)	3,310(12)	349 (26)	49 (6)

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

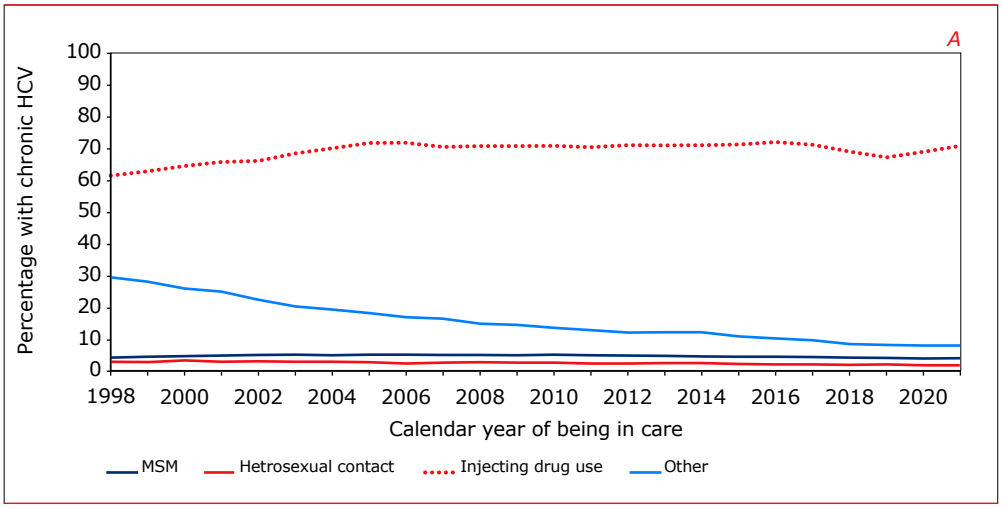
Legend: *n = total for each category; (%) = percentage of the total for each column; HCV = hepatitis C virus; ART = combination antiretroviral therapy; GT = genotype.*

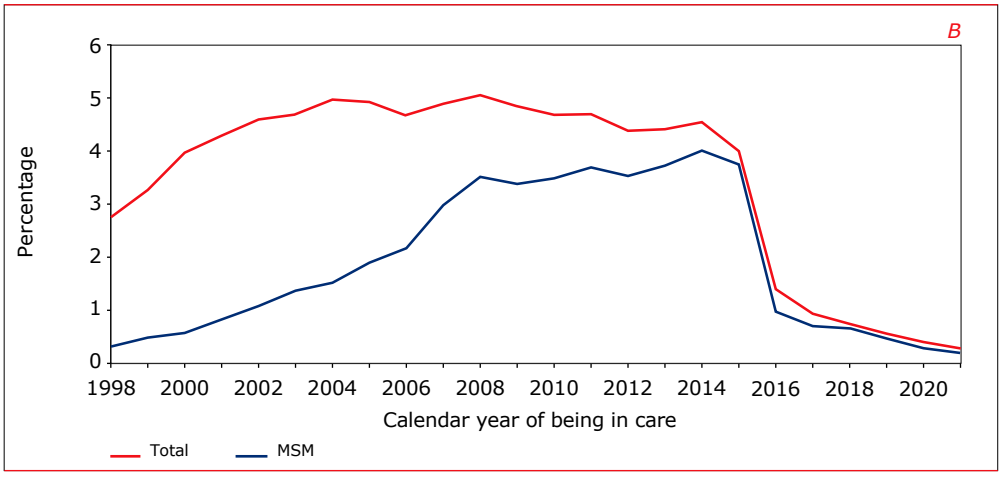
Changes over time

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 all individuals with HIV ever registered by SHM, decreased from 11.2% in 1998 to 4.3% in 2021, 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 being diagnosed with chronic hepatitis C virus (HCV) co-infection, and B) detectable HCV RNA, per calendar year.*





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 2021. In MSM, the highest percentage of HCV RNA positivity was 4% in 2014; by 2021, the percentage of positive HCV RNA tests in this group had decreased sharply to 0.20%. 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.

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.

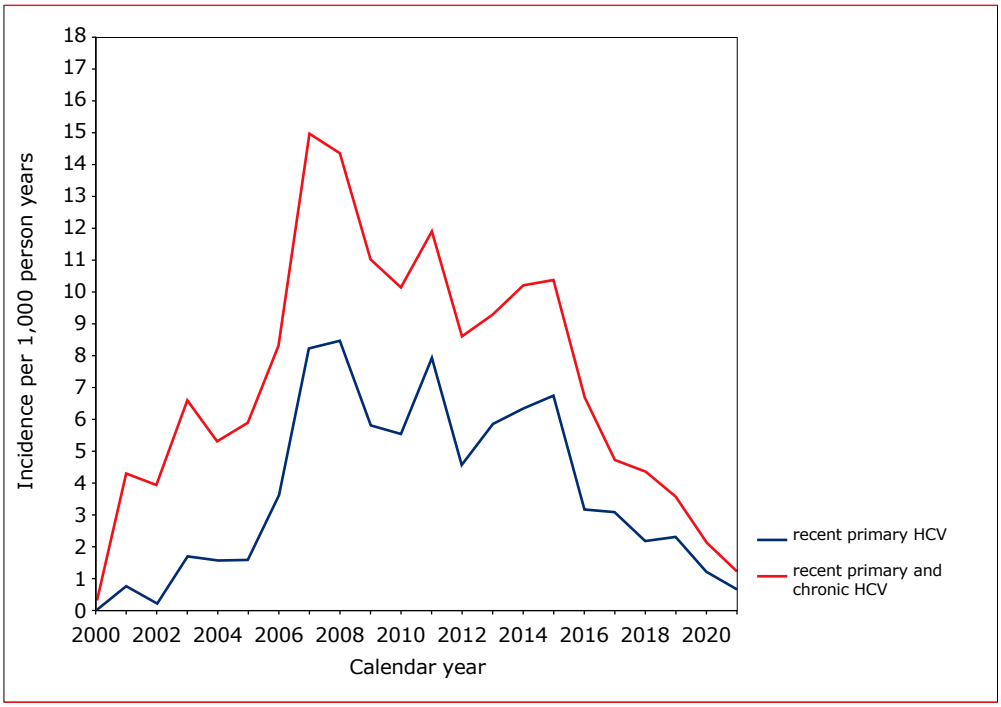
There were important differences in the incidence of the first diagnosis of recent HCV infection in terms of HIV transmission category. The vast majority of recent HCV infections occurred in MSM (n=809/861 [94%]). In contrast to the high prevalence of HCV in PWID or former PWID, the overall incidence 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 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 7.2 per 1,000 person years (PY) (95% confidence interval [CI] 6.9-7.6).

The incidence of primary infection increased from 0.28 per 1,000 PY (0.01-1.58) to a peak of 15.0 per 1,000 PY (12.2-18.2) in 2007 and decreased to 1.2 per 1,000 PY (0.7-2.1) in 2021. When including those with recent HCV, the overall rate of recent HCV infection among MSM was 4.0 per 1,000 PY (3.7-4.3). 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 8.2 and 8.5 per 1,000 PY in 2007 and 2008, respectively. By 2015, the incidence was 6.7 diagnoses per 1,000 PY. It then declined to 3.2 per 1,000 PY in 2016, before further decreasing to 1.2 diagnoses per 1,000 PY in 2020 and 0.7 per 1,000 PY in 2021.

As expected, incidence rates among MSM were higher when the preferred and alternative case definitions of recent HCV were combined, with incidence rates of 7.6 diagnoses per 1,000 PY in 2015, 4.1 per 1,000 PY in 2016, and 0.8 per 1,000 PY in 2021.

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

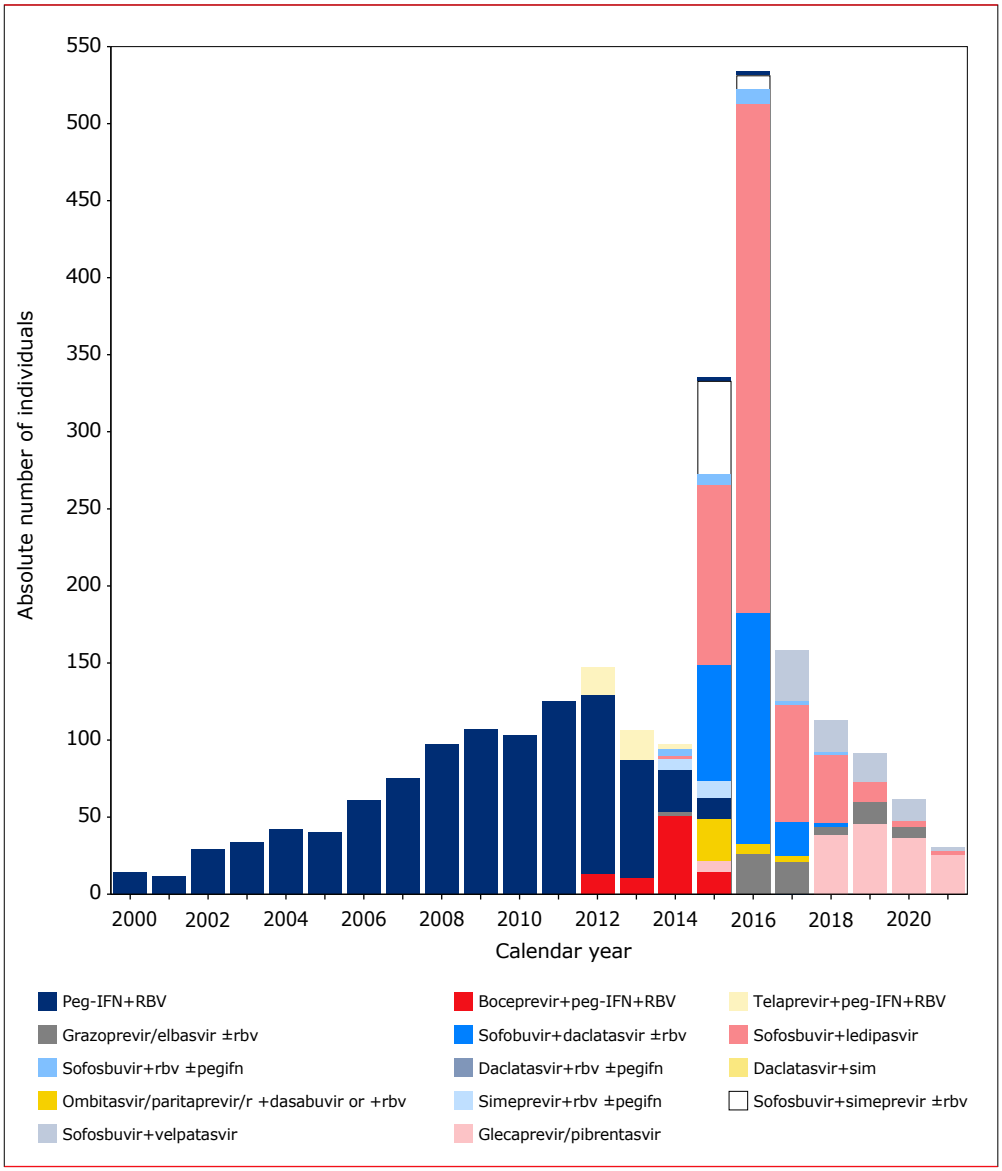
The primary aim of HCV treatment is to achieve a sustained virological response (SVR)[23] and the treatments used have changed markedly in recent years. In the past, treatment consisted of interferon alpha (IFN alpha), and subsequently pegylated interferon alpha (PEG-IFN alpha), in combination with ribavirin (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, 1,829 have ever received HCV treatment; of those, 571 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:

- 964 regimens with (peg-) interferon+ RBV;
- 130 regimens with first generation PI; and
- 1,306 regimens with all-oral 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 novel DAAs

In total, at the time of the database lock on 1 May 2022, 1,179 individuals were known to have started a DAA regimen; 111 of those had been treated more than once with a DAA regimen with, in total, 1,306 treatment episodes. The most common reasons for receiving DAA treatment more than once were: reinfection after earlier DAA treatment-induced clearance (n=53), 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 1,306 DAA treatment episodes, 15 occurred in 2014, 303 in 2015, and 532 in 2016. The number of treatment episodes subsequently decreased to 29 in 2021 (*Figure 4.5*).

The most frequently used DAA regimens were:

1. sofosbuvir plus ledipasvir +/- RBV (n=587);
2. sofosbuvir plus daclatasvir +/- RBV (n=255);
3. pibrentasvir/glecaprevir (n=151) (most commonly used regimen in 2021).

Sixty-two individuals who had previously been treated with DAAs are known to have died, with causes of death including:

- Liver disease (n=8)
- Non-AIDS-defining malignancies (n=14)
- Cardiovascular disease (n=3)
- Non-AIDS-defining infection (n=4)
- Non-natural death (n=6)

The remaining deaths (n=27) were related to alcohol and substance use, AIDS, lung disease, or the cause was unknown. The paragraph on mortality gives more details on mortality causes over time, including liver-related mortality.

Treatment outcomes

HCV RNA data were collected up to 1 May 2022. At that point, 1,248 out of 1,306 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 1,214 of the 1,248 treatment episodes (97%), SVR12 was achieved.
- No SVR was achieved in 29 treatment episodes among 27 individuals.
- For the remaining 5 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 two of the cases.

SVR rates were comparable for individuals who received HCV treatment for the first time and those with prior HCV treatment or severe liver disease. Higher SVR rates were found among MSM (98%), than among PWID or former PWID (94%), and individuals who acquired HIV through heterosexual contact (94%). Furthermore, no specific differences in SVR rates were observed regarding CD4 cell counts and HIV RNA at the time of DAA initiation.

Among the 27 individuals who did not achieve SVR:

- 22 were successfully retreated with a DAA regimen;
- three were not retreated; and
- two were unsuccessfully retreated.

HCV reinfection

Reinfection with HCV following successful treatment or spontaneous clearance has been reported mainly in MSM 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, 2,393 individuals were susceptible for HCV reinfection (1,679 after SVR, 714 after spontaneous clearance). Of those 2,393 individuals, 330 reinfections among 286 individuals (12%) were documented: 274 after SVR and 83 after spontaneous clearance. 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 (243 out of 286, or 85%). Another 29 were PWID or former PWID (10%). For the remaining 14 individuals, documented HIV transmission routes were heterosexual contact (six), blood-blood contact (three), and unknown (five).

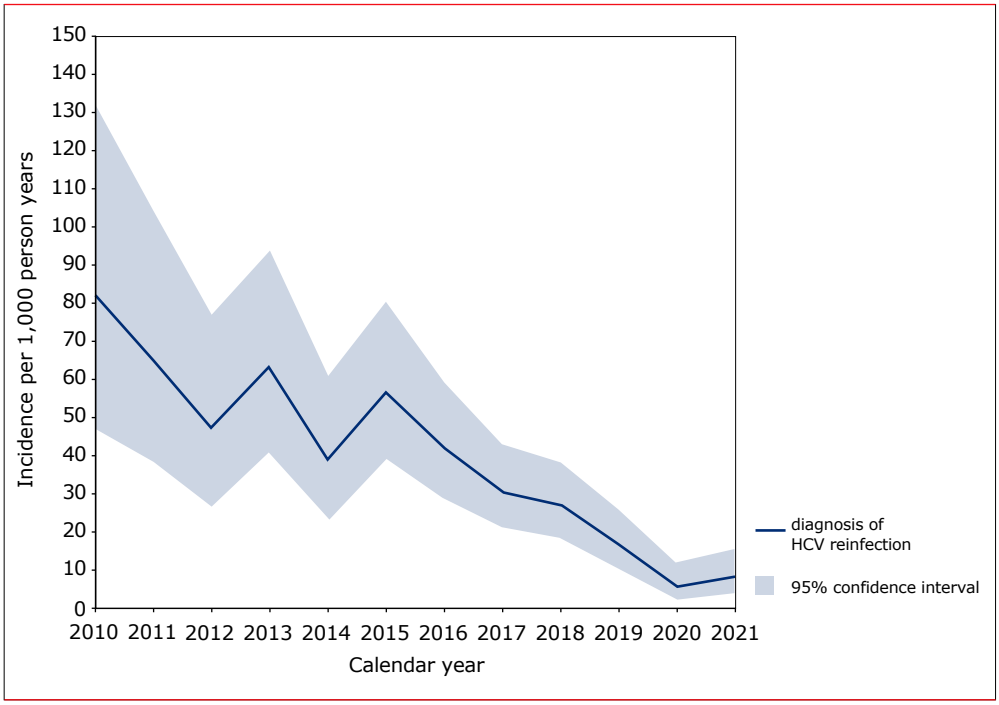
Of the 330 reinfections, 302 (92%) were retreated (232 with DAA, 70 with interferon+/- boceprevir/telaprevir). The median time to retreatment after reinfection diagnosis, stratified by calendar year of reinfection, was:

- Prior to 2015: 34.1 months (IQR 5.2-72.6)
- Between 2015 and 2017: 3.7 months (IQR 1.9-9.4)
- From 2018 onwards: 2.9 months (IQR 1.7-5.9)

We calculated the incidence of reinfection between 2010 and 2021. 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 22 reinfections per 1,000 PY (95% CI 19-24), and for MSM it was 29 reinfections per 1,000 PY (26-33).

Because most reinfections occurred among MSM, the incidence of HCV reinfection after achieving an SVR over time is shown only for MSM (*Figure 4.6*). This incidence decreased from 82 reinfections per 1,000 PY in 2010 to 57 per 1,000 PY in 2015, and then declined to 17 reinfections per 1,000 PY in 2019, and nine per 1,000 PY in 2021. A stable 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 or spontaneously clearance among men who have sex with men, per calendar year. Note, numbers in 2021 may be affected by a delay in data collection.



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 2021. Individuals were categorised according to their last documented HCV infection episode. In total 2,207 individuals were linked to HIV care, 1,921 individuals had a primary HCV infection, and 286 individuals had a reinfection.

Of the 2,207 individuals linked to HIV care:

- 1,529 (69%) were retained in care;
- 678 individuals were no longer in care (393 had died; 152 had moved abroad; and 133 were lost to care);

- 1,494 (98%) of those still alive and in care had received treatment for HCV (with DAAs or a pegylated interferon-containing regimen);
- 1,449 (97%) 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).

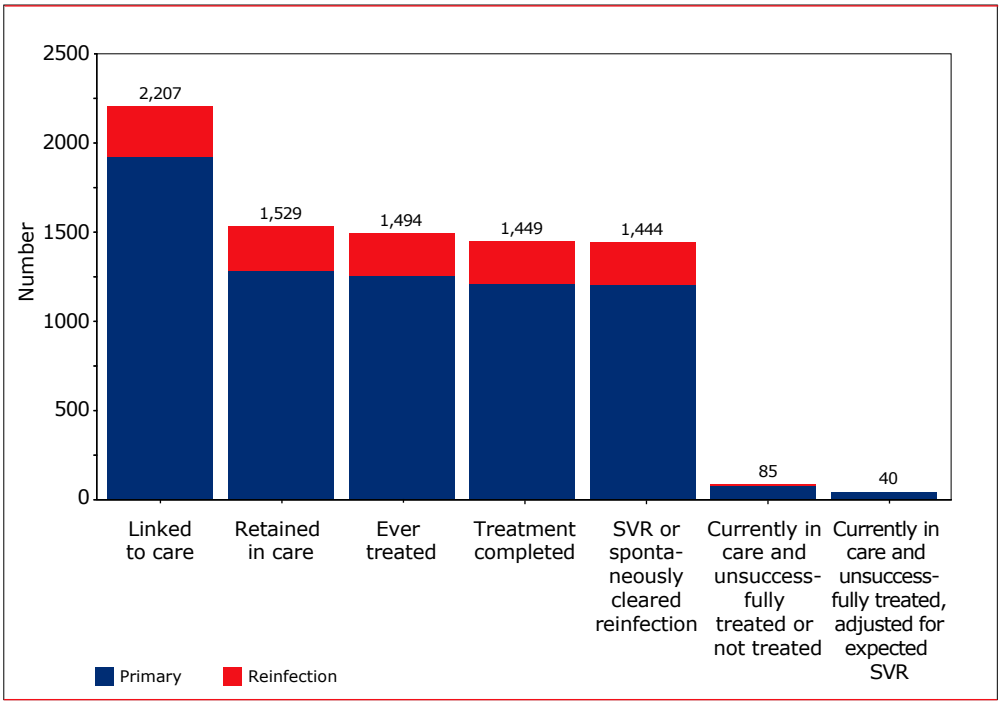
Overall, 1,429 of the 1,449 people who completed treatment (99%) had achieved an SVR, including those who had achieved an SVR on a pegylated interferon-containing regimen and those who were retreated after earlier treatment failure. Another 15 individuals with HCV reinfection had a negative last HCV 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 1,444.

As a result, 85 (6%) of the 1,529 individuals known to be alive and in care in one of the Dutch HIV treatment centres on 31 December 2021, were still in need of HCV treatment:

- 35 individuals had never been treated for HCV. The percentage untreated was higher among PWID (6%), people who acquired HIV through heterosexual contact (5%), and people with an unknown HIV transmission mode (4%), than among MSM (1%).
- Four had been unsuccessfully treated for HCV, including those who did not achieve an SVR on a pegylated interferon-containing regimen.
- 46 were still being treated or had insufficient time after treatment discontinuation to allow SVR calculation.

Of the 46 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 45 of the 46 (97%) will achieve SVR. This results in a more realistic estimate of individuals (85-45=40) 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 with HIV in follow up in the ATHENA cohort. In total, 1,206 cases of severe liver disease, according to our definition, were considered to be present (presumptive and definitive categories combined): 485 among individuals with HCV co-infection and 240 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 with HIV, therefore, further analyses in this section are limited to those with viral hepatitis.

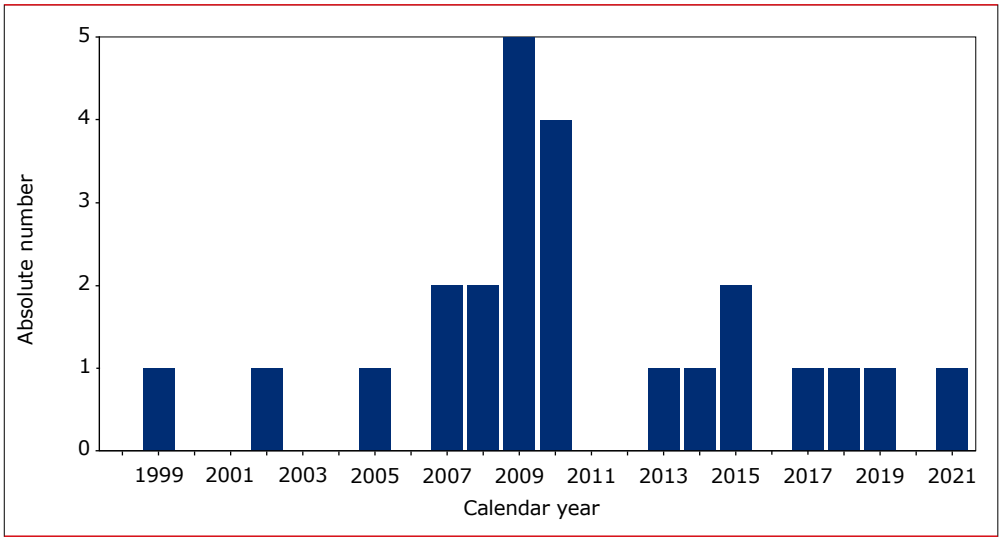
Liver-related morbidity in HCV

Additional data from liver biopsy pathology reports, transient elastography, radiology reports, or a combination of those sources, were available for 1,698 of the 2,007 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 485 (24%) of the 2007 individuals with HCV co-infection, and 29% of those with additional liver-related data. Definitive severe chronic liver disease was documented for 119 (6%) individuals with HCV co-infection.

Between 1998 and 2021, 24 (1.2%) cases of hepatocellular carcinoma (HCC) were reported among 2,007 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 2010 onwards. 15 of the 24 individuals with HCC were born in the Netherlands.

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

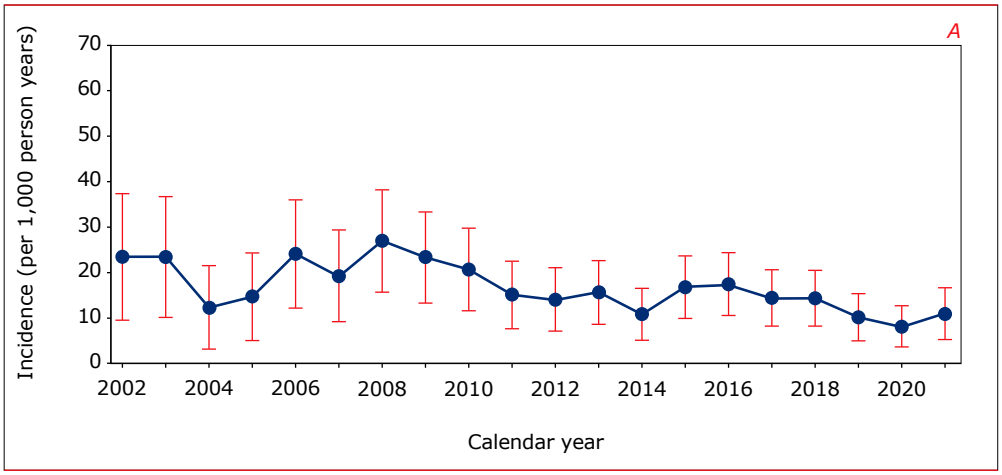


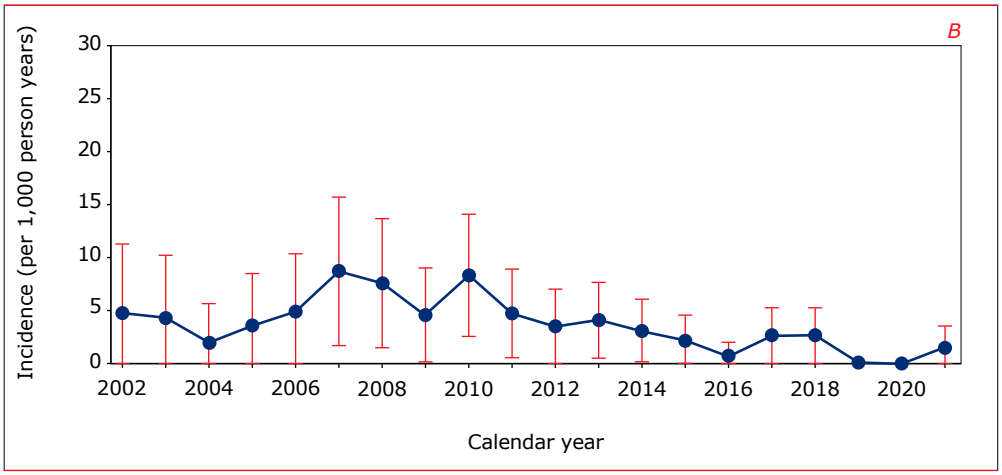
Mortality

All-cause mortality

Among the 2,007 individuals with HCV and without other viral hepatitis (i.e., HBV or HDV), 18% 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 20.3 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 9.1 per 1,000 PY in 2002-11, and 5.3 per 1,000 PY from 2012 onwards. In PWID with HCV, these incidence rates were 33.5 per 1,000 PY in the period 2002-11, and 37.9 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 2,007 HIV-1-positive individuals who were ever diagnosed with recent or chronic HCV and without other viral hepatitis (i.e., HBV or HDV).





Liver-related mortality

In total, 66 (3%) individuals with HCV and without other viral hepatitis (i.e., HBV or HDV) died of a liver-related cause between 2002 and 2021. For individuals with HCV, the incidence rate of death from a liver-related cause, adjusted for age and gender of the SHM population, was 5.6 per 1,000 PY in 2002-11. This decreased to 1.9 per 1,000 PY from 2012 onwards (*Figure 4.9B*). In MSM with HCV, these incidence

rates were 2.9 per 1,000 PY in 2002-11 and 0.7 per 1,000 PY from 2012 onwards. In PWID with HCV, these incidence rates were 7.5 per 1,000 PY in 2002-11 and 4.0 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; anti-HBc = anti-hepatitis B core; Pos = positive; Neg = negative; HBV = hepatitis B virus; ND = not determined.*

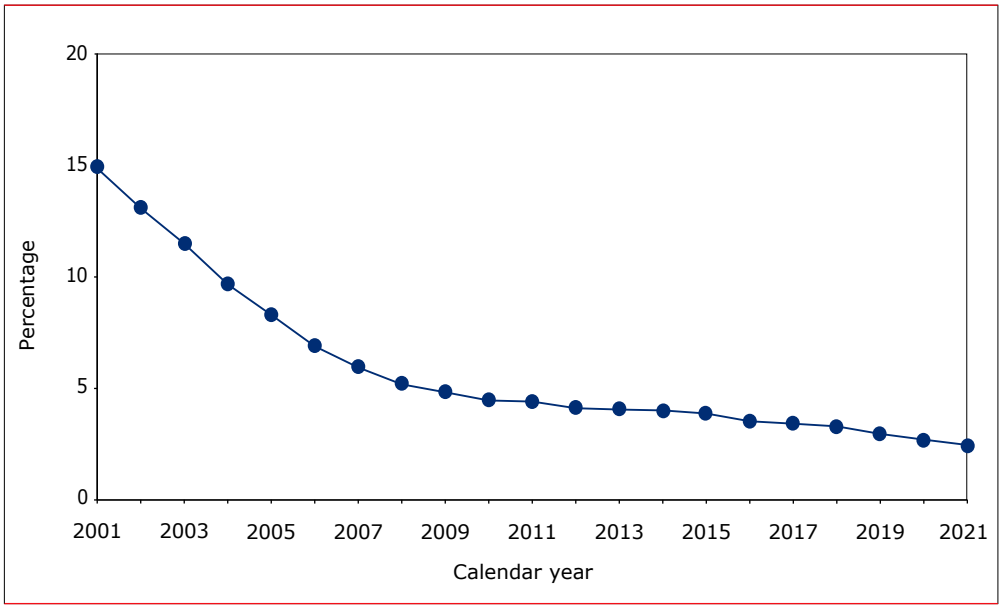
HBV screening

Ninety-seven percent of the 29,040 individuals 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 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 with HIV without HBV screening has decreased markedly, with 2% of all individuals with HIV in care having no measured HBV serological markers in 2021 (*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

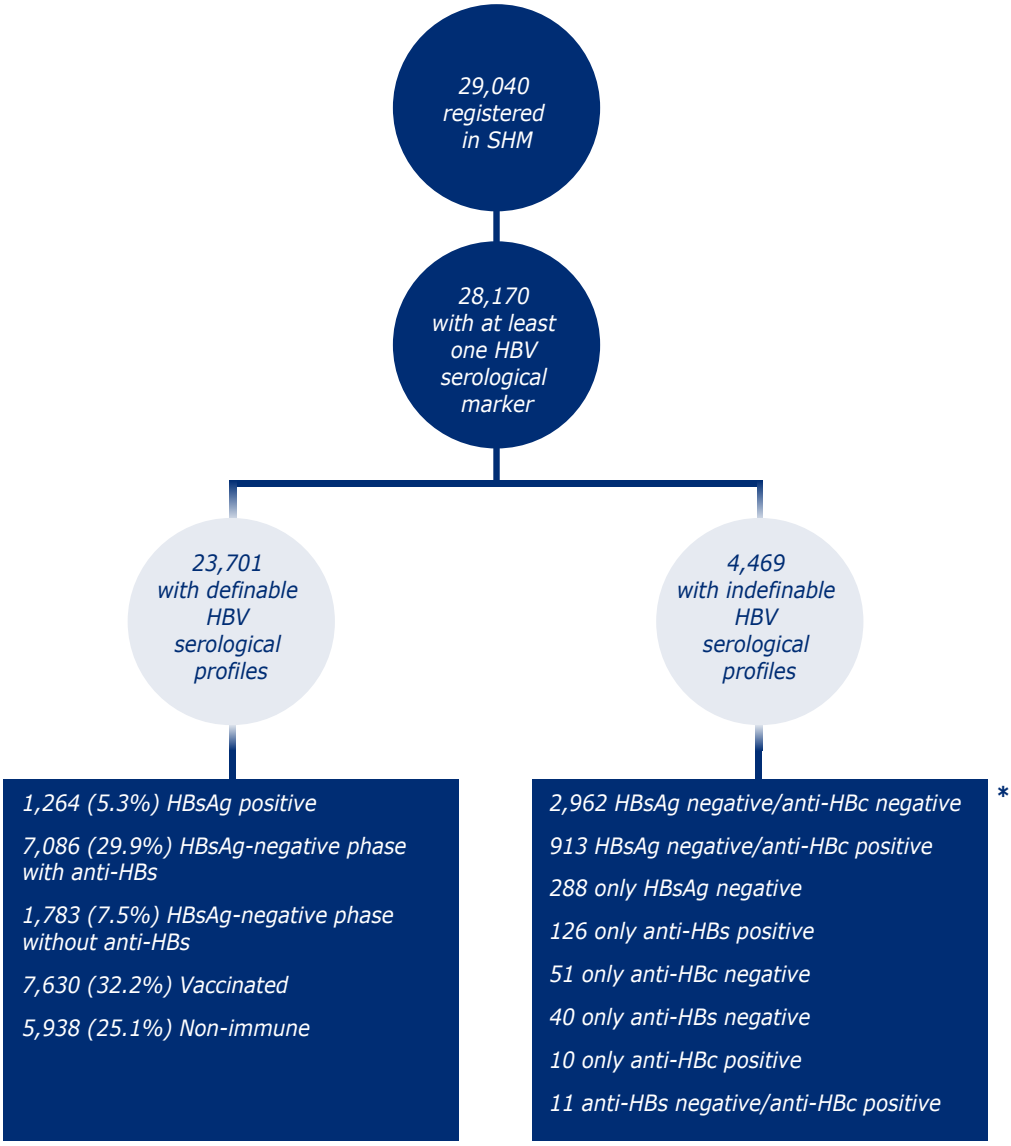
HBV serological profiles could be defined for 23,701 (84%) of the 28,170 screened individuals (*Figure 4.10*). A full HBV serological battery is not routinely performed in individuals with HIV; therefore, any results from an HBV serological test were assumed to remain the same over time until a new serological test was carried out. The distribution of HBV serological profiles at the last visit are given in *Figure 4.11*.

The remaining 4,469 (16%) individuals either:

- had insufficient information to establish an HBV serological profile (n=4,401); or
- were previously HBsAg-positive, no longer had anti-HBc antibodies and did not have anti-HBs antibodies (n=68)

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

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



**The 68 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 with HIV in care, according to their hepatitis B virus (HBV) serological profile as registered in the SHM database.

	HBV serological profile*, n (%)				
	Active HBV infection	HBsAg-negative phase with anti-HBs	HBsAg-negative phase without anti-HBs	Vaccinated	Non-immune
Total number	1,264	7,086	1,783	7,630	5,938
Male gender	1,076 (85%)	6,100 (86%)	1,357 (76%)	6,637 (87%)	4,371 (74%)
Region of origin					
The Netherlands	531 (42%)	3,752 (53%)	688 (39%)	4,402 (58%)	3,321 (56%)
Europe	77 (6%)	496 (7%)	123 (7%)	603 (8%)	331 (6%)
Sub-Saharan Africa	325 (26%)	1,082 (15%)	568 (32%)	529 (7%)	704 (12%)
Caribbean/South America	145 (11%)	906 (13%)	166 (9%)	1,016 (13%)	895 (15%)
Southeast Asia	72 (6%)	300 (4%)	72 (4%)	245 (3%)	161 (3%)
Other	114 (9%)	550 (8%)	166 (9%)	835 (11%)	526 (9%)
HIV transmission group					
Men who have sex with men	718 (57%)	4,888 (69%)	768 (43%)	5,635 (74%)	2,740 (46%)
Heterosexual	393 (31%)	1,551 (22%)	642 (36%)	1,566 (21%)	2,622 (44%)
Injecting drug use	52 (4%)	232 (3%)	195 (11%)	73 (1%)	115 (2%)
Other	101 (8%)	415 (6%)	178 (10%)	356 (5%)	461 (8%)
ART	1,218 (96%)	6,885 (97%)	1,712 (96%)	7,515 (98%)	5,773 (97%)
Deaths	266 (21%)	1,116 (16%)	326 (18%)	407 (5%)	739 (12%)

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

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

Individuals with active HBV

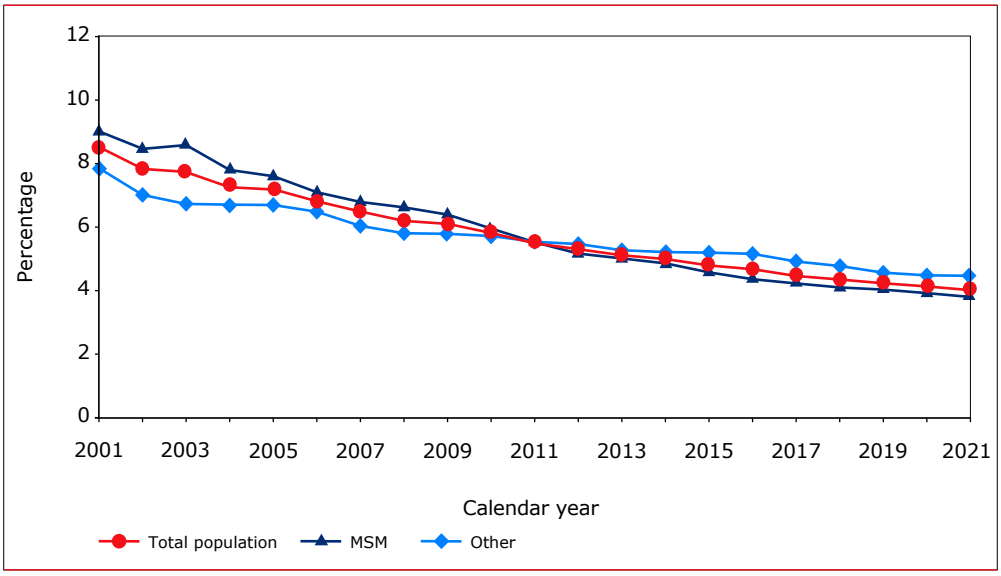
Prevalence of active HBV infection

Of the 28,170 individuals ever screened for at least one HBV serological marker, 27,827 had an HBsAg test. Of these, a total of 1,668 (6%) received a positive HBsAg test result. Over time, 195 (12%) of these individuals became HBsAg-negative and acquired anti-HBs antibodies (i.e., HBsAg-negative phase with anti-HBs) and an additional 209 (13%) became HBsAg-negative without acquiring anti-HBs antibodies (i.e., HBsAg-negative phase without anti-HBs). The remaining 1,264 (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 2021 (*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 therapy with an ART regimen that includes tenofovir disoproxil fumarate [TDF] / tenofovir alafenamide fumarate [TAF]), and a minority of individuals becoming HBsAg-negative during therapy[32].

As is the case for HCV co-infection, the percentage of individuals with HIV in care who have chronic HBV is considerably higher than the rate found in the general Dutch population. Individuals with HBV were predominantly male (1,076 out of a total 1,264, 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. Finally, HBV co-infection was less common than HCV co-infection among PWID.

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



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

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

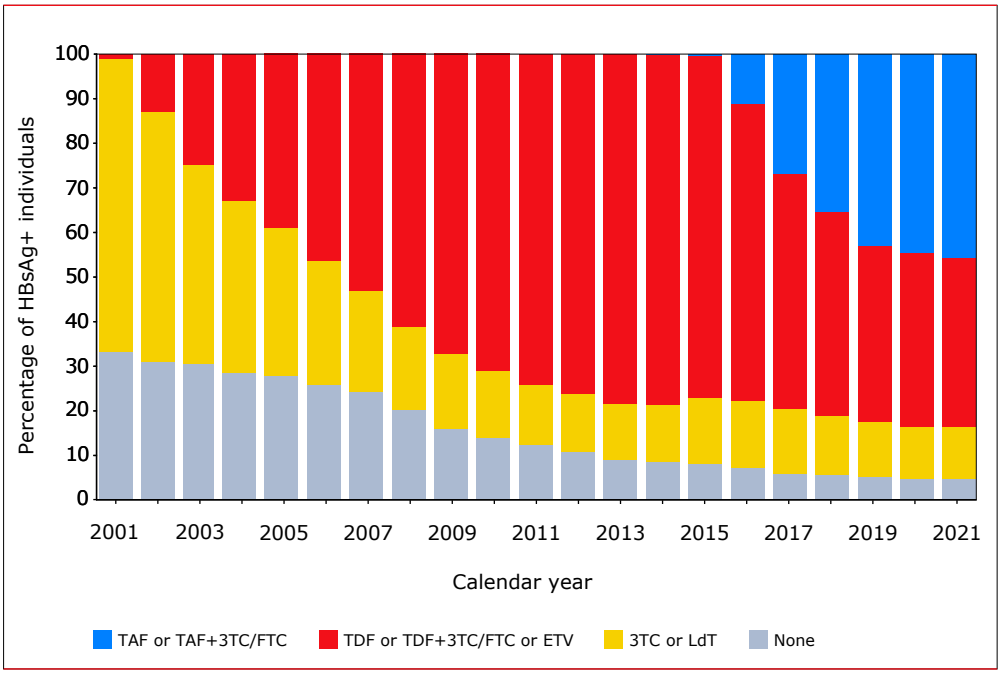
Of the 1,668 individuals with HIV in the SHM database who have ever had an HBsAg-positive serological test result, 1,605 (96%) received an ART regimen that included one or more agents with activity against both HIV and HBV. The reasons the remaining 63 individuals did not receive anti-HBV treatment included:

- death prior to start of treatment (n=16);
- recent entry into care (n=4);
- lost to care (n=40); or
- lack of sufficient information (n=3).

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 out of 642, 13%) and became more commonly used than lamivudine in 2005. TAF-based ART (with or without lamivudine or emtricitabine) was first used in 2016 (n=135 out of 1,239, 11%).

In 2021, most individuals with HBV were receiving TAF-based ART (n=590 out of 1,292, 46%), closely followed by TDF-based ART (n=494 out of 1,292, 38%), and lamivudine-based ART (n=147 out of 1,292, 11%), or no anti-HBV-containing ART (n=61 out of 1,292, 5%).

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.*

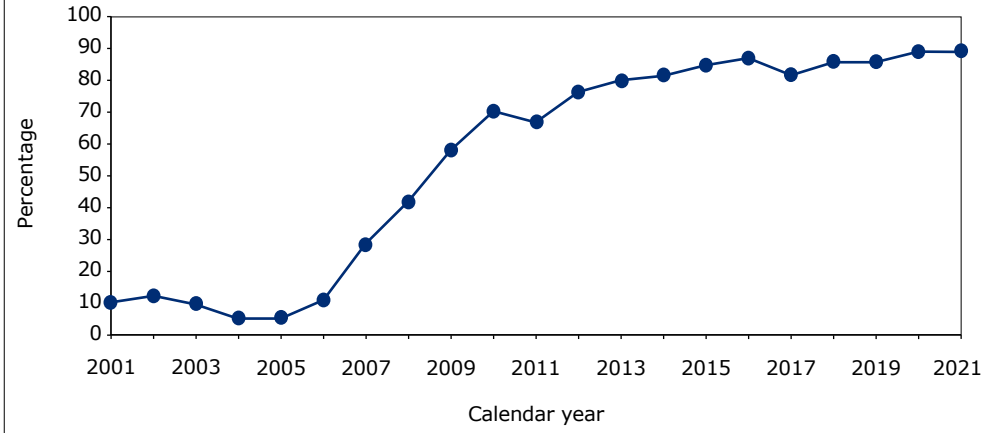
Note: *The categories of anti-HBV agents were: none, 3TC or LdT, TDF or TDF+3TC/FTC or ETV, and TAF or TAF+3TC/FTC. 3TC and LdT should not be combined and TDF and ETV can be combined under special circumstances[35].*

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. Therefore HBV DNA measurements were 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 2021, 89% 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.*



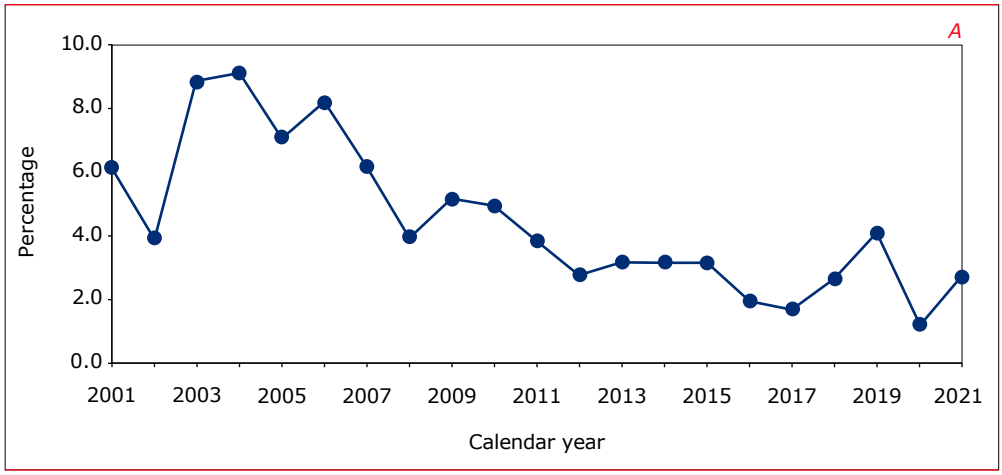
There are other serological outcomes associated with a more favourable prognosis in individuals with HBV[36]. Persistently negative hepatitis B "e" antigen (HBeAg) is associated with lower levels of HBV DNA replication. It also confers a favourable long-term outcome with low risk of cirrhosis and HCC,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

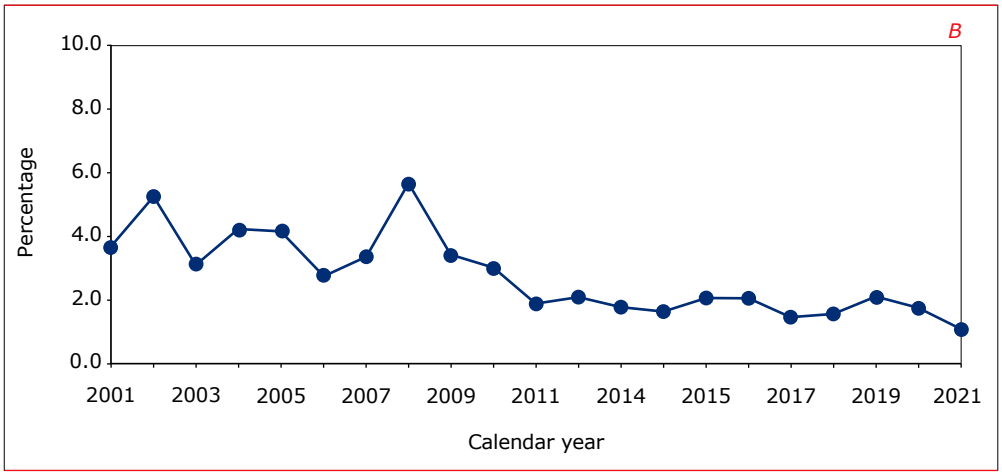
Persistently negative hepatitis B surface antigen (HBsAg) is associated with reduced viral activity, very low risk of developing HCC, and improved survival. For all individuals with HBV, the loss of HBsAg, known as HBsAg seroclearance or "functional" cure, is the penultimate goal of HBV therapy.

We examined the rates of HBeAg and functional cure per calendar year in the population of individuals with HIV and HBV. For these analyses, any results from an HBV serological test were assumed to remain the same over time until a new serological test was carried out. The percentage of individuals with HBeAg seroclearance ranged from 3.9% to 9.1% between 2001 and 2010, and slowly declined to 2.7% in 2021 (*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 1.1% in 2021 (*Figure 4.15B*).

Individuals with HIV-HBV who initiate ART at very low CD4+ cell counts, are more likely to have seroclearance due to an immuno-inflammatory reaction with accelerated CD4+ cell increases[38]. The higher percentages with seroclearance before 2010 could be due, in part, to the higher percentage of individuals with HIV and HBV initiating ART with severe immunosuppression during this period. It could also be due to the decrease in the number of individuals with recent HBV infection, who were more likely to clear their HBsAg, as TDF-containing ART became more widespread[32]. Furthermore, the number of HBeAg tests peaked in 2004 at 116, before slowly declining to 26 tests in 2021. The number of HBsAg tests peaked in 2008 at 230, before decreasing less dramatically to reach 118 tests in 2020, and 108 tests in 2021. 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.

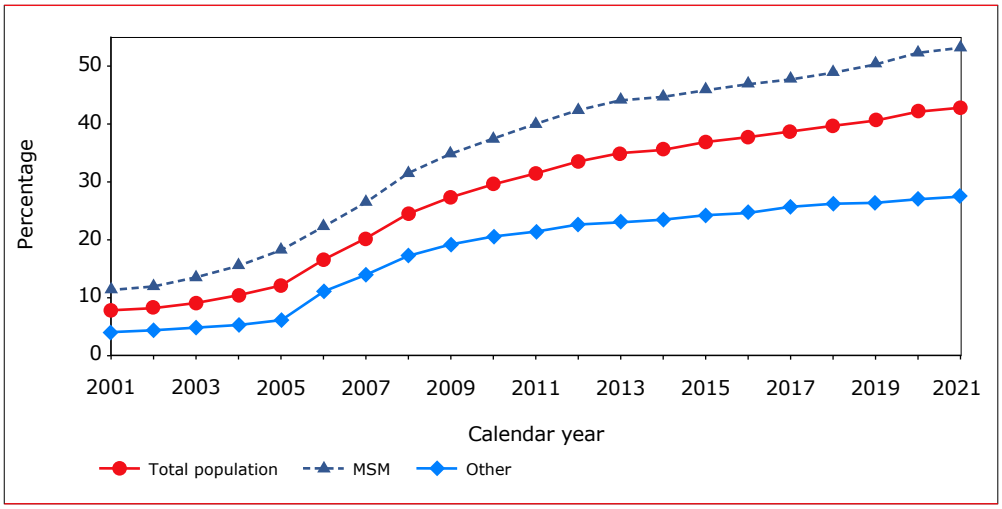




HBV vaccination in individuals with HIV

Of the 23,701 individuals with definable HBV serological profiles, 7,630 (32%) 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 2021 (*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 with HIV

Of the 23,701 individuals with definable HBV serological profiles, 5,938 (25%) had serological evidence of being non-immune and non-exposed to HBV at their last visit. When the 4,469 individuals with undefinable HBV serological profiles were considered, 80 of the 243 with an anti-HBs antibody test did not have detectable anti-HBs antibodies, and 3,703 of the 4,226 without an anti-HBs antibody test were not reported to have been vaccinated by their treating physician. Therefore, at most, 9,721 (35%) of the 28,170 individuals screened for HBV remained susceptible to infection at the time of their last visit (5,938 non-immune; 80 with an undefinable HBV profile and anti-HBs antibody negative; and 3,703 with an undefinable HBV profile and missing data on anti-HBs antibody status, and no physician-reported vaccination).

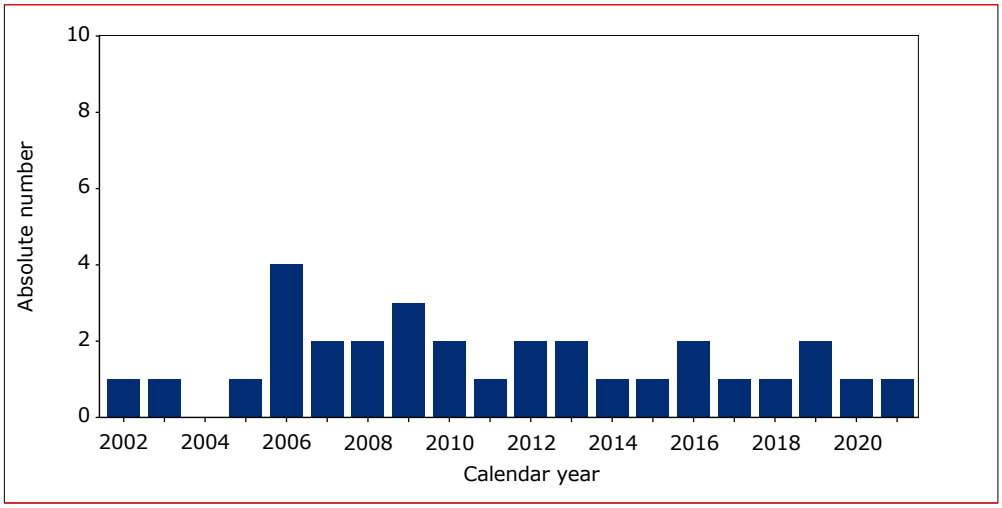
Individuals at risk, and MSM in particular, should be actively counselled about HBV vaccination. However, they may be protected from HBV infection by the use of tenofovir (TDF), or tenofovir alafenamide (TAF), as part of their ART regimen, according to findings reported by an international study, and one of the Dutch HIV treatment centres[39,40]. Data from SHM show that, of those people who remained at risk of acquiring HBV, 82% 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 1,174 of the 1,529 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 240 (16%) of the 1529 individuals with HBV. Definitive severe chronic liver disease was documented for 69 (4%) with HBV.

Figure 4.17 shows that the annual number of new HCC diagnoses declined from 2010 onwards. HCC was found in 31 (2.0%) individuals with HBV co-infection, 16 of whom were born in the Netherlands, nine in sub-Saharan Africa, two in South America, and one each in Asia, the United States, Australia, and western Europe.

Figure 4.17: Absolute number of annually-reported HCC cases among individuals with HBV and without other viral hepatitis (i.e., HCV or HDV) over time.



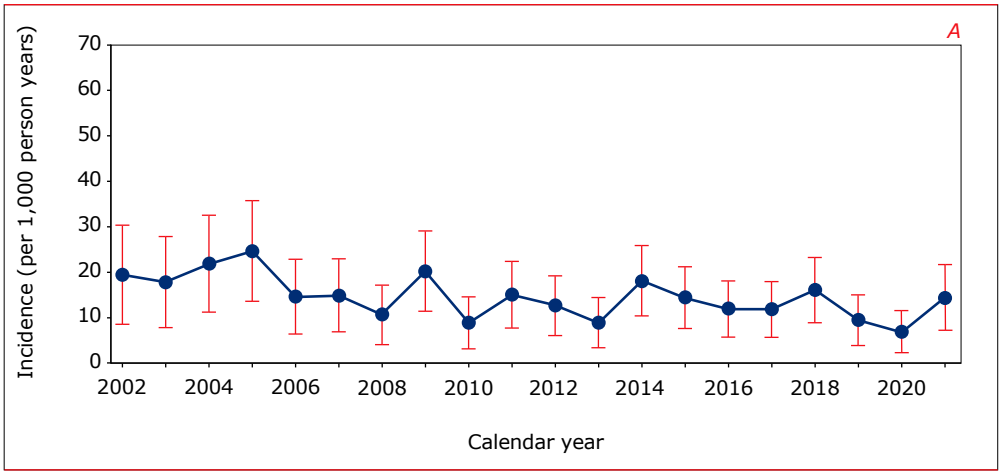
Legend: HBV=hepatitis B virus; HCC=hepatocellular carcinoma.

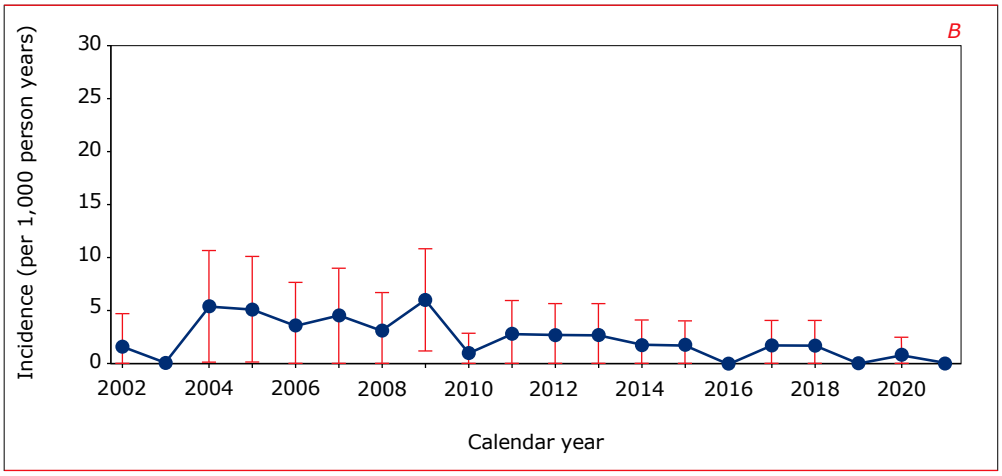
Mortality

All-cause mortality

Nineteen percent (n=294) of the 1,529 individuals with HBV and without other viral hepatitis (i.e., HCV or HDV) died of any cause. For individuals with an HBV infection the incidence rate of death from any cause, adjusted for age and gender of the SHM population, was 16.4 per 1,000 PY in 2002-11, and 12.4 per 1,000 PY from 2012 onwards (*Figure 4.18A*). In MSM with HBV, these incidence rates were 13.2 per 1,000 PY in 2002-11 and 10.7 per 1,000 PY from 2012 onwards. In PWID with HBV, these incidence rates were 33.3 per 1,000 PY in 2002-11 and 22.8 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 1,529 HIV-1-positive individuals who were ever diagnosed with active HBV and without other viral hepatitis (i.e., HCV or HDV).





Liver-related mortality

In total, 34 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 3.1 per 1,000 PY in 2002-11 and 1.2 per 1,000 PY from 2012 onwards. In PWID with HBV only, these incidence rates were 10.7 per 1,000 PY in 2002-11 and 10.8 per 1,000 PY from 2012 onwards.

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

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

Of the 29,040 individuals with HIV ever registered by SHM, 28,443 (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 2021, there were:

- 219 (0.8%) individuals who ever had HBV-HCV;
- 15 (0.1%) individuals who ever had HBV-HDV; and
- 7 (<0.1%) individuals with HBV-HCV-HDV.

It should be noted that by 2021:

- 198 of the 1,668 (12%) individuals who ever had HBV had been tested for HDV;
- 22 (11%) of the 198 were had either a past or current HDV infection;
- 12 of the 22 were tested for HDV RNA; and
- nine 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 241 individuals with multiple viral hepatitis, 69 (29%) had presumptive or definitive severe chronic liver disease: 59 with HBV-HCV, four with HBV-HDV and six with HBV-HCV-HDV.

HCC was found in 58 (24%) individuals with multiple viral hepatitis: 53 with HBV-HCV, four with HBV-HDV and one with HBV-HCV-HDV. In the individuals with multiple viral hepatitis, 76 deaths were observed, of which 13 (17%) were liver-related. The number of overall and liver-related deaths, respectively, were distributed across co-infection groups as follows: 71 and 12 with HBV-HCV, one and one with HBV-HDV and four and none with HBV-HCV-HDV.

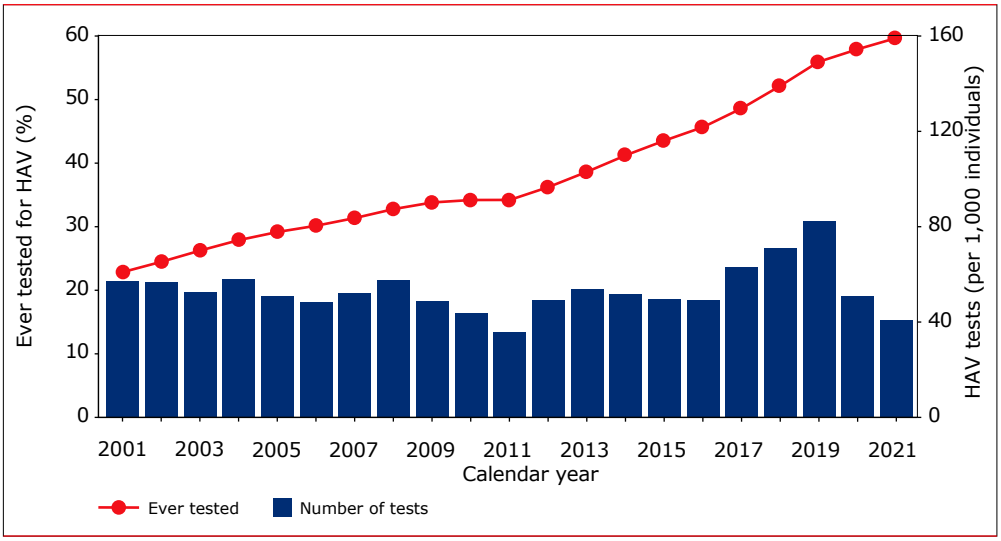
Hepatitis A virus (HAV)

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). Fifty-nine percent (n=17,222) of the 29,040 individuals with HIV ever registered in the SHM database have been screened for HAV. The frequency of screening for HAV in individuals with HIV has been consistent over the past two decades (*Figure 4.19*).

Between 2001 and 2017, roughly 40 to 60 HAV tests per 1,000 individuals were conducted each year. Between 2018 and 2019, screening frequency increased to 70 and 80 HAV tests per 1,000 individuals per year, respectively. In 2020, screening frequency returned to 50 HAV tests per 1,000 individuals and was 40 HAV tests per 1,000 individuals in 2021. The percentage of individuals who have ever been tested for HAV was 23% in 2001, and steadily increased to 60% in 2021 (*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.*

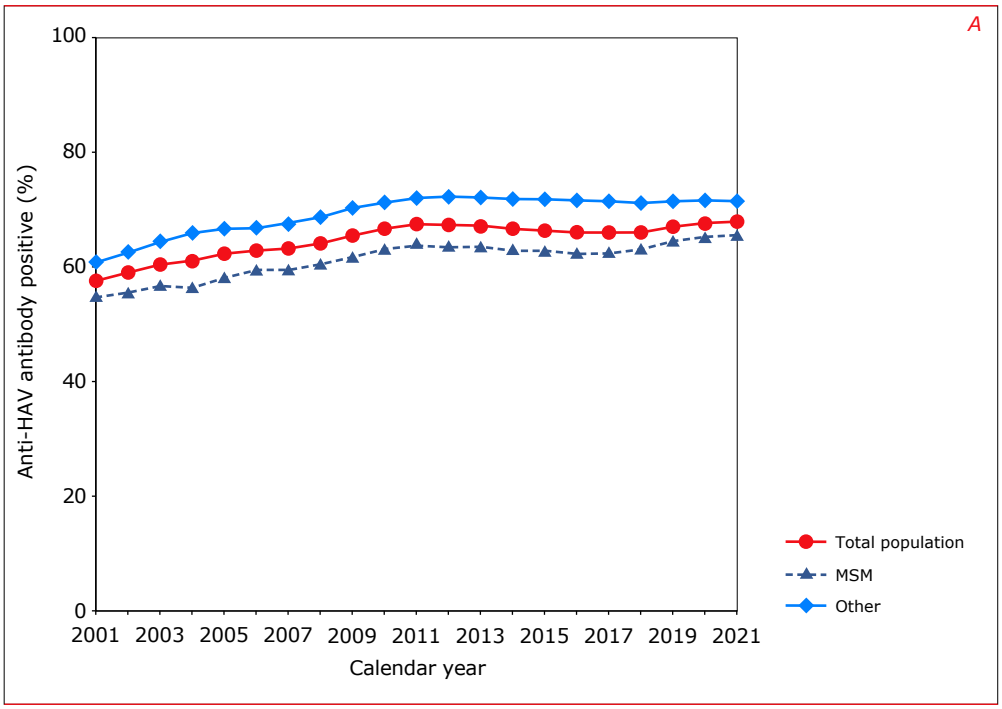
HAV seropositivity

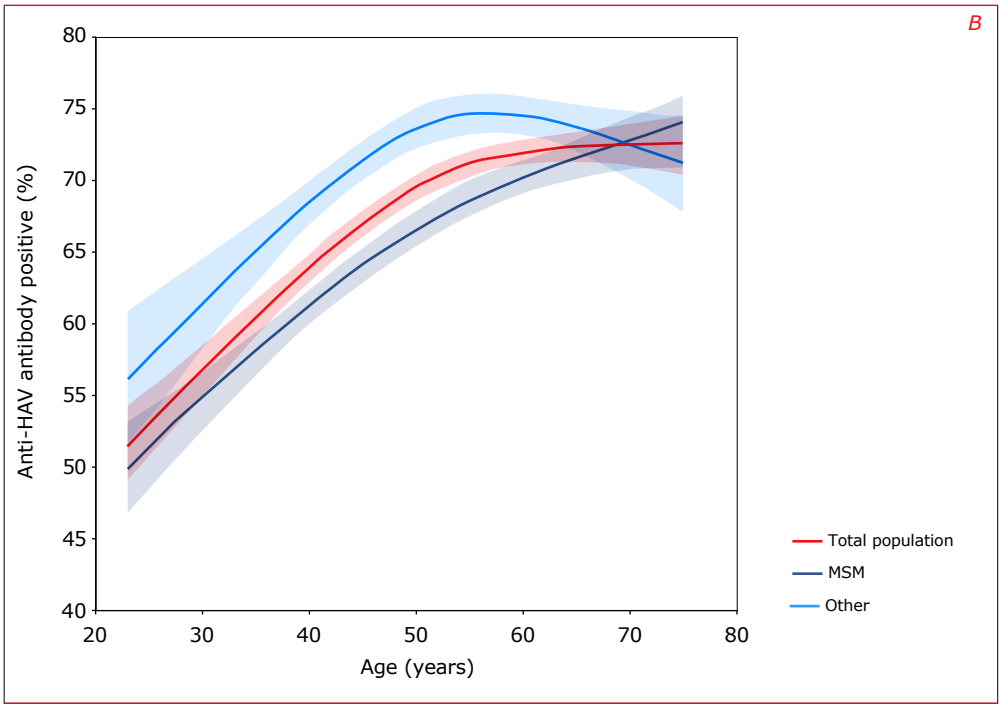
Of the 17,222 individuals ever screened for HAV, a total of 11,649 (68%) had a positive anti-HAV antibody test result:

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

The prevalence of anti-HAV antibody positivity was 58% in 2001 and then slowly increased to 68% in 2021 (*Figure 4.20A*). For MSM, the prevalence of anti-HAV antibody positivity was 55% in 2001, and it also slowly increased, reaching 65% in 2021. For all other transmission groups, the prevalence of anti-HAV antibody positivity was 61% in 2001 and 71% in 2021.

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.

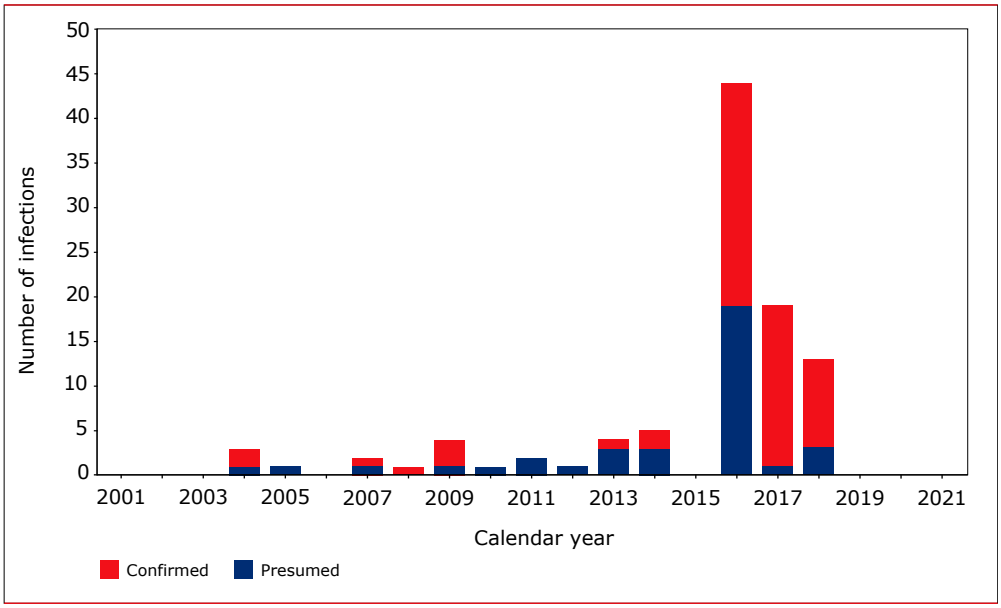
Epidemiological studies have highlighted the strong relationship between increasing anti-HAV antibody positivity and increasing age[41]. This age-dependent relationship was also observed in the 17,222 individuals ever screened for HAV (*Figure 4.20B*). Overall, anti-HAV antibody positivity was 59% for individuals below the age of 40, and 70% for those aged 40 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 62% 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 103 reported cases of acute HAV infection (n=66, presumed; n=37, confirmed), of which 83 (81%) were observed in MSM, 19 (18%) in heterosexuals, and one (1%) in PWIDs.

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 75 documented cases occurring between 2017 and 2019, 65 (87%) were observed in MSM. This increase in HAV infections was part of a European-wide outbreak of HAV among sexually-active MSM in 2017[42]. In 2021, there were no cases of acute HAV infection.

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



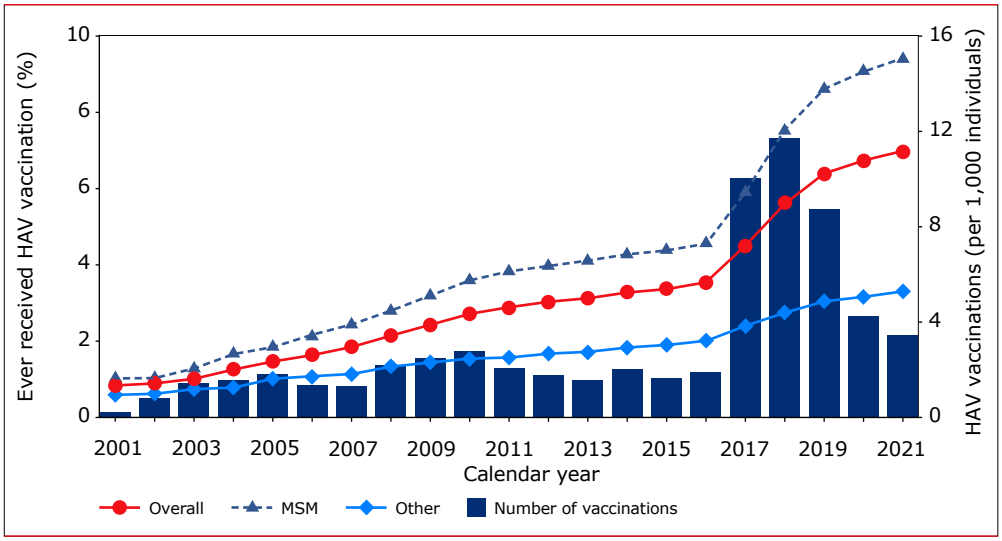
Of the 103 reported cases of acute HAV infection, 56 (54%) were recorded to have severe clinical symptoms. Severe chronic liver disease, according to our definition, was considered to be present (presumptive and definitive categories combined) in 17 (17%) of those with a reported acute HAV infection. 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 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 29,040 individuals with HIV ever registered in the SHM database, 2,039 (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 two vaccinations per 1,000 individuals 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 1.7% in 2000, 3.6% in 2016, and 7.0% in 2021. In MSM, this percentage was 2.2% in 2001, 4.6% in 2016, and 9.5% in 2021.

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



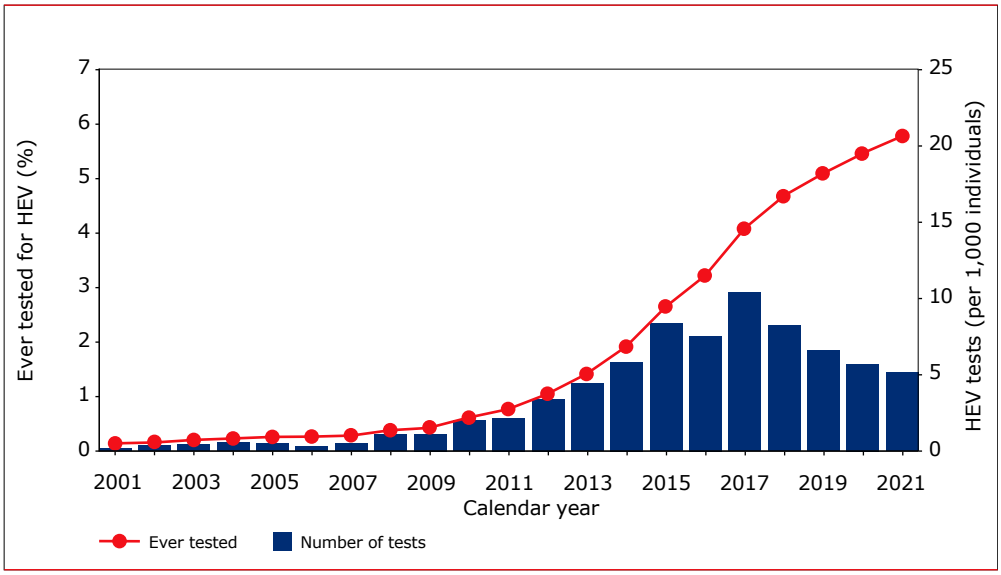
Legend: *HAV = hepatitis A virus; MSM = men who have sex with men.*

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 29,040 individuals with HIV ever registered in the SHM database have been screened for HEV. The screening frequency for HEV infection in individuals 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 2021, this frequency was five tests per 1,000 individuals.

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



Legend: HEV = hepatitis E virus.

Individuals with acute HEV diagnoses

Of the 1,669 individuals who were in care between 2001 and 2021, and who were ever screened for HEV, 226 (14%) were newly diagnosed as having past or current HEV infection. Of these individuals, 148 (66%) were MSM, 65 (29%) heterosexuals, six (3%) PWID, and seven (3%) were from other transmission groups. The largest number of new diagnoses were observed between 2013 and 2020 (*Figure 4.24*), mainly due to the higher frequency of HEV testing among individuals with HIV. The percentage of individuals newly diagnosed with past or current HEV infection ranged from 9% in 2004 to 14% in 2021 (*Figure 4.25*).

Of all individuals tested for HEV and in care between 2001 and 2021, there were 52 individuals diagnosed with acute HEV infection, of whom 38 were MSM and 14 heterosexuals. Only two of these cases were confirmed to have progressed to chronic infection (i.e., positive HEV RNA lasting more than three months). One of these individuals was treated with ribavirin and both were able to resolve their infection (i.e., achieve undetectable HEV RNA after chronic infection had been established).

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

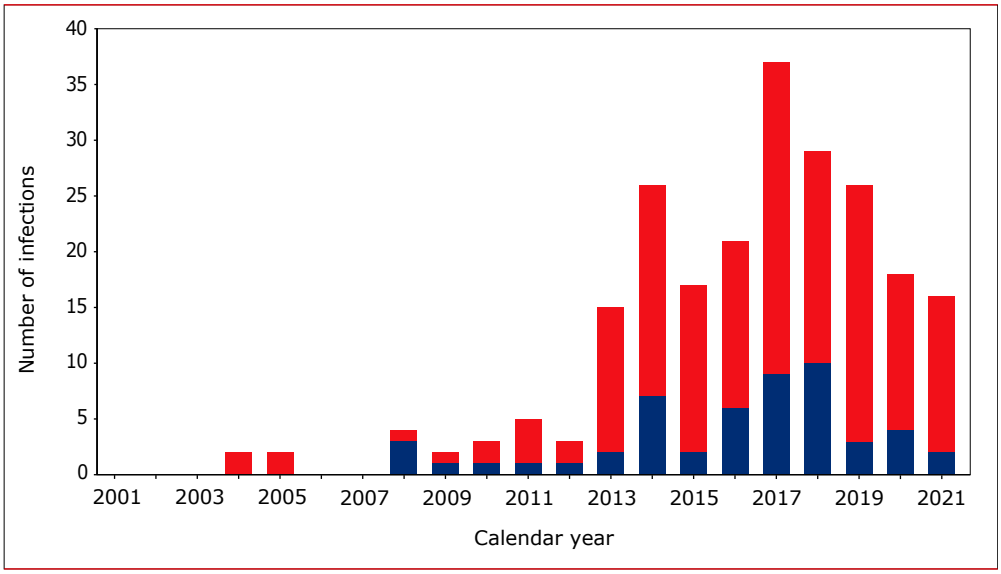
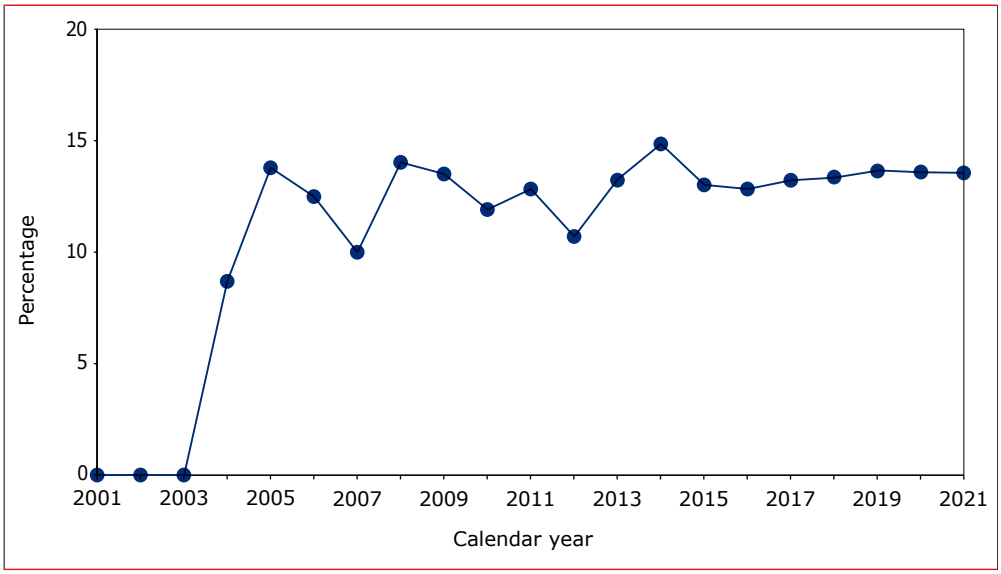


Figure 4.25: Percentage ever infected with HEV per calendar year.



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

Conclusions

Screening for HCV and HBV co-infection in the population with HIV in the Netherlands has continued to improve over time and is now almost universally documented. Five percent of individuals with HIV ever registered in the SHM database between 1998 and 2021, have been documented as having chronic HCV at some stage, and 3% have been documented as having had a recent HCV infection. Recent 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 with HIV receiving treatment for HCV has rapidly increased. More than 1,150 individuals have now received, or are currently receiving, treatment with novel DAAs. Overall, 97% of all individuals with sufficient follow-up data to calculate an SVR were found to have been cured. When retreatment was taken into account, the SVR for the last course of treatment was 99%. This high cure rate has reduced the number of individuals with HIV and HCV remaining in need of HCV treatment to 40 in 2021. Overall, a rapid reduction in the prevalence of active HCV infections was achieved, with prevalence in MSM having declined to 0.20% in 2021. 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]. However, in line with earlier reports[27,30,44], HCV reinfection after successful treatment has been observed. The rate of reinfections has declined substantially over the previous years, but new reinfections were nonetheless diagnosed in 2021, which indicates that continued awareness is needed. 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 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 2021 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 individuals receiving ART. Nonetheless, an estimated 25% of all individuals with HIV have either not been exposed to HBV, or have not been successfully vaccinated, and may remain at risk of acquiring HBV. Since 82% of all individuals still at risk of acquiring HBV infection receive an ART regimen that

includes TDF/TAF, their risk is probably very low due to sustained chemoprophylaxis. The remaining 18% of the individuals with HIV ever registered remain unprotected against HBV, which represents an estimated 7.0% of the total population of individuals 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 with HIV ever registered by SHM, 29% of those with chronic HCV and 22% of those with chronic HBV had evidence of severe chronic liver disease. However, the absolute number of HCC diagnoses has been decreasing since 2010, which can likely be attributed to the use of effective antiviral treatment for HBV and HCV co-infections. Overall, people with chronic HCV or HBV remained at increased risk of having a liver-related cause of death, although this risk has declined 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.

Almost half of the individuals ever registered by SHM have been tested for anti-HAV antibodies, with testing frequency consistent across calendar years. The percentage of tested individuals found to have anti-HAV antibodies was no different between MSM and other transmission groups, but it was more than double the percentage found in the general Dutch population[45]. The percentage of HIV-positive people 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 patients developed definitive severe chronic liver disease. Nevertheless, no individual died due to HAV infection.

The percentage of individuals reported to have received at least one HAV vaccination was low at 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 recent HCV (re)infection. In particular, efforts should continue to increase HBV vaccination rates among individuals 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 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.

HBV clinical practice guidelines from the European Association for the Study of the Liver suggest that individuals with chronic hepatitis B infection should be tested at least once for HDV[36]. In the Netherlands, 12% 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 HIV-positive individuals with HBV infection, as found in other settings[13].

Only half of the individuals ever registered by SHM have been screened for HAV and, among those tested, almost two-thirds had anti-HAV antibodies from either vaccination or cleared infection. Even though 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 with HIV[48], and only two individuals 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 with HIV.

References

1. Hahné SJM, De Melker HE, Kretzschmar M, et al. Prevalence of hepatitis B virus infection in The Netherlands in 1996 and 2007. Epidemiol Infect. 2012; 140(8):1469-1480. doi:10.1017/S095026881100224X
2. Van Dijk M, Kracht PAM, Arends JE, et al. Retrieval of Chronic Hepatitis C Patients. A Manifesto for Action to Eliminate Hepatitis C in the Netherlands: The CELINE Project. Neth J Med. 2019;77 (4):131-138.
3. Stockdale AJ, Kreuels B, Henrion MYR, et al. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. J Hepatol. 2020;73(3):523-532. doi:10.1016/j.jhep.2020.04.008
4. Gaeta GB, Precone DF, Cozzi-Lepri A, Cicconi P, D'Arminio Monforte A. Multiple viral infections. J Hepatol. 2006;44(1 Suppl):S108-13. doi:10.1016/j.jhep.2005.11.023
5. Heintges T, Wands J. Hepatitis C virus: epidemiology and transmission. Hepatology. 1997;26(3):1-6. doi:10.1002/hep.510260338
6. Lok AS. Chronic Hepatitis B. N Engl J Med. 2002;346(22).
7. Ikeda K, Saitoh S, Suzuki Y, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: A prospective observation of 2215 patients. J Hepatol. 1998;28(6):930-938. doi:10.1016/S0168-8278(98)80339-5
8. Posthouwer D, Makris M, Yee TT, et al. Progression to end-stage liver disease in patients with inherited bleeding disorders and hepatitis C: An international, multicenter cohort study. Blood. 2007;109(9):3667-3671. doi:10.1182/blood-2006-08-038349

9. Verna EC. Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis in Patients with HIV. Lancet Gastroenterol Hepatol. 2017 Mar;2(3):211-223. doi: 10.1016/S2468-1253(16)30120-0.
10. Arends JE, Lieveld FI, Boeijen LL, et al. Natural history and treatment of HCV/HIV coinfection: Is it time to change paradigms? J Hepatol. 2015;63(5):1254-1262. doi:10.1016/j.jhep.2015.06.034
11. Lieveld FI, Smit C, Richter C, et al. Liver decompensation in HIV/Hepatitis B coinfection in the combination antiretroviral therapy era does not seem increased compared to hepatitis B mono-infection. Liver Int. 2019;39(3):470-483. doi:10.1111/liv.14000
12. Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. In: The Lancet. Vol 378. Lancet; 2011:73-85. doi:10.1016/S0140-6736(10)61931-9
13. Béguelin C, Moradpour D, Sahli R, et al. Hepatitis delta-associated mortality in HIV/HBV-coinfected patients. J Hepatol. 2017;66(2):297-303. doi:10.1016/j.jhep.2016.10.007
14. Lemon SM, Walker CM. Hepatitis avirus and hepatitis E virus: Emerging and re-emerging enterically transmitted hepatitis viruses. Cold Spring Harb Perspect Med. 2019;9(6). doi:10.1101/cshperspect.a031823
15. Dalton HR, Bendall RP, Keane FE, Tedder RS, Ijaz S. Persistent carriage of hepatitis E virus in patients with HIV infection. N Engl J Med. 2009;361(10):1025-1027. doi:10.1056/NEJMc0903778
16. Friesema IHM, Sonder GJB, Petrignani MWF, et al. Spillover of a hepatitis A outbreak among men who have sex with men (MSM) to the general population, the Netherlands, 2017. Eurosurveillance. 2018;23(23). doi:10.2807/1560-7917.ES.2018.23.23.1800265
17. Alberts CJ, Schim van der Loeff MF, Sadik S, et al. Hepatitis E virus seroprevalence and determinants in various study populations in the Netherlands. PLoS One. 2018;13(12). doi:10.1371/journal.pone.0208522
18. Dalton HR, Kamar N, Baylis SA, Moradpour D, Wedemeyer H, Negro F. EASL Clinical Practice Guidelines on hepatitis E virus infection. J Hepatol. 2018;68(6):1256-1271. doi:10.1016/j.jhep.2018.03.005
19. Rockstroh JK. Acute hepatitis C in HIV-infected individuals - recommendations from the NEAT consensus conference. AIDS. 2011;25(4):399-409. doi:10.1097/QAD.0b013e328343443b
20. Arends JE, Lambers FAE, van der Meer JTM, et al. Treatment of acute hepatitis C virus infection in HIV+ patients: Dutch recommendations for management. Neth J Med. 2011;69(1):43-49. Accessed August 28, 2018.
21. Nederlandse Vereniging van HIV Behandelaren. Richtlijn HIV. Published 2017. http://richtlijnhiv.nvhb.nl/

22. Smit C, Boyd A, Rijnders BJA, et al. HCV micro-elimination in individuals with HIV in the Netherlands 4 years after universal access to direct-acting antivirals: a retrospective cohort study. lancet HIV. 2021;8(2):e96-e105. doi:10.1016/S2352-3018(20)30301-5
23. European AIDS Clinical Society. Guidelines. Version 8.0, October 2015. English edition. Published online 2015. http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html [Accessed: 15 September 2022]
24. Zorg intstituut Nederland. www.zorginstituutnederland.nl [Accessed: 29 October 2021]
25. Arends JE, van der Meer JTM, Posthouwer D, et al. Favourable SVR12 rates with boceprevir or telaprevir triple therapy in HIV/HCV coinfected patients. Neth J Med. 2015;73(7):324-330.
26. van Sighem AI, Boender TS, Wit FWNM, Smit C, Matser A, Reiss P. Monitoring Report 2016. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Stichting HIV Monitoring; 2016.
27. Lambers FAE, Prins M, Thomas X, et al. Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM. AIDS. 2011;25(17):F21-7. doi:10.1097/QAD.0b013e32834bac44
28. Berenguer J, Gil-Martin Á, Jarrin I, et al. Reinfection by hepatitis C virus following effective all-oral direct-acting antiviral drug therapy in HIV/hepatitis C virus coinfected individuals. AIDS. 2019;33(4):685-689. doi:10.1097/QAD.0000000000002103
29. Ingiliz P, Krznaric I, Stellbrink HJ, et al. Multiple hepatitis C virus (HCV) reinfections in HIV-positive men who have sex with men: no influence of HCV genotype switch or interleukin-28B genotype on spontaneous clearance. HIV Med. 2014;15(6):355-361. doi:10.1111/hiv.12127
30. Martin TCS, Martin NK, Hickman M, et al. Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM. AIDS. 2013;27(16):2551-2557. doi:10.1097/QAD.0b013e32836381cc
31. van Rijckevorsel G, Whelan J, Kretzschmar M, et al. Targeted vaccination programme successful in reducing acute hepatitis B in men having sex with men in Amsterdam, the Netherlands. J Hepatol. 2013;59(6):1177-1183. doi:10.1016/j.jhep.2013.08.002
32. Heuft MM, Houba SM, Van Den Berk GEL, et al. Protective effect of hepatitis B virus-active antiretroviral therapy against primary hepatitis B virus infection. AIDS. 2014;28(7):999-1005. doi:10.1097/QAD.0000000000000180
33. Kim HN, Newcomb CW, Carbonari DM, et al. Risk of HCC With Hepatitis B Viremia Among HIV/HBV-Coinfected Persons in North America. Hepatology. 2021;74(3):1190-1202. doi:10.1002/hep.31839

34. Dezanet LNC, Kassime R, Miailhes P, et al. Effect of Viral Replication and Liver Fibrosis on All-Cause Mortality in Human Immunodeficiency Virus-Hepatitis B Virus-Coinfected Individuals: A Retrospective Analysis of a 15-Year Longitudinal Cohort. Clin Infect Dis. 2022;74(6):1012-1021. doi:10.1093/cid/ciab594
35. Ratcliffe L, Beadsworth MB, Pennell A, Phillips M, Vilar FJ. Managing hepatitis B/HIV co-infected: adding entecavir to truvada (tenofovir disoproxil/emtricitabine) experienced patients. AIDS. 2011;25(8):1051-1056. doi:10.1097/QAD.0b013e328345ef5e
36. EASL. European Association for the Study of the Liver (EASL) 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-398. doi:10.1016/j.jhep.2017.03.021
37. Sharma SK, Saini N, Chwla Y. Hepatitis B virus: inactive carriers. Virol J. 2005;2:82. doi:10.1186/1743-422X-2-82
38. Boyd A, Dezanet LNC, Lacombe K. Functional Cure of Hepatitis B Virus Infection in Individuals With HIV-Coinfection: A Literature Review. Viruses. 2021;13(7):1341. doi:10.3390/v13071341
39. Quirk E, Graham H, Liu C, Rhee M, Piontkowsky D, Szwarcberg J. Reports of viral hepatitis B and C in HIV patients participating in clinical trials of elvitegravir/cobicistat/tenofovir DF/emtricitabine and cobicistat-boosted atazanavir plus tenofovir DF/emtricitabine. Antivir Ther. 2013;1 Suppl 38:A63.
40. Heuft MM, Houba SM, van den Berk GEL, et al. Protective effect of hepatitis B virus-active antiretroviral therapy against primary hepatitis B virus infection. AIDS. 2014;28(7):999-1005. doi:10.1097/QAD.0000000000000180
41. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine. 2010;28(41):6653-6657. doi:10.1016/j.vaccine.2010.08.037
42. Ndumbi P, Freidl GS, Williams CJ, et al. Hepatitis a outbreak disproportionately affecting men who have sex with men (MSM) in the european union and european economic area, june 2016 to may 2017. Eurosurveillance. 2018;23(33):1-12. doi:10.2807/1560-7917.ES.2018.23.33.1700641
43. LCI. No Title. www.lci.rivm.nl/richtlijnen/hepatitis-a#immunisatie [Accessed: 29 October 2021]
44. Newsum AM, Matser A, Schinkel J, et al. Incidence of HCV Reinfection Among HIV-Positive MSM and Its Association With Sexual Risk Behavior: A Longitudinal Analysis. Clin Infect Dis. 2021;73(3):460-467. doi:10.1093/cid/ciaa645
45. Verhoef L, Boot HJ, Koopmans M, et al. Changing risk profile of hepatitis A in the Netherlands: A comparison of seroprevalence in 1995-1996 and 2006-2007. Epidemiol Infect. 2011;139(8):1172-1180. doi:10.1017/S0950268810003043

46. Machiels JD, Braam EE, van Bentum P, et al. Vaccination with Fendrix of prior nonresponding patients with HIV has a high success rate. AIDS. 2019;33(3):503-507. doi:10.1097/QAD.0000000000002085
47. Wallace SJ, Webb GW, Madden RG, et al. Investigation of liver dysfunction: Who should we test for hepatitis E? Eur J Gastroenterol Hepatol. 2017;29(2):215-220. doi:10.1097/MEG.0000000000000781
48. Lopez-Lopez P, Frias M, Camacho A, Rivero A, Rivero-Juarez A. Human immunodeficiency virus infected patients are not at higher risk for hepatitis e virus infection: A systematic review and meta-analysis. Microorganisms. 2019;7(12). doi:10.3390/microorganisms7120618

5. Distinct populations: Children with HIV in the Netherlands

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Definitions

Box 5.1: Chapter definitions.

Child living with HIV	A child diagnosed with HIV before the age of 15[1,2], whose first visit to a Dutch HIV treatment centre was before the age of 18 years.
Infection	The moment a child acquires an HIV infection
Diagnosis	The moment an HIV infection is identified in a child.
Registration	The moment an HIV physician or nurse notifies SHM of a child with HIV (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 2021	Individuals with an HIV infection who had a documented clinical visit or lab measurement in 2021.
Vertically-acquired HIV	Transmission of HIV from a woman with the virus to a child during pregnancy, delivery, or breastfeeding.
Non-vertically-acquired HIV	Transmission of HIV through sexual contact or contact with contaminated blood or blood products.
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	Any viral load measurements below 200 copies/ml, except for time points in the past where tests had quantification limits higher than 200 copies/ml.

***Box 5.2:** Outline of the population: all children with HIV registered in the ATHENA cohort before 31 December 2021. (Children = individuals under the age of 15 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=397).
2. Population of those diagnosed as a child and in care in 2021:
   - under the age of 15 in 2021 (n=138); includes 119 adopted children.
   - aged 15-18 years in 2021 (n=36); includes 20 adopted children.
   - aged 18 years and over in 2021 (n=156); includes 10 adopted children.

Background

Combination 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
- therapy regimens
- long-term virological and immunological responses to therapy

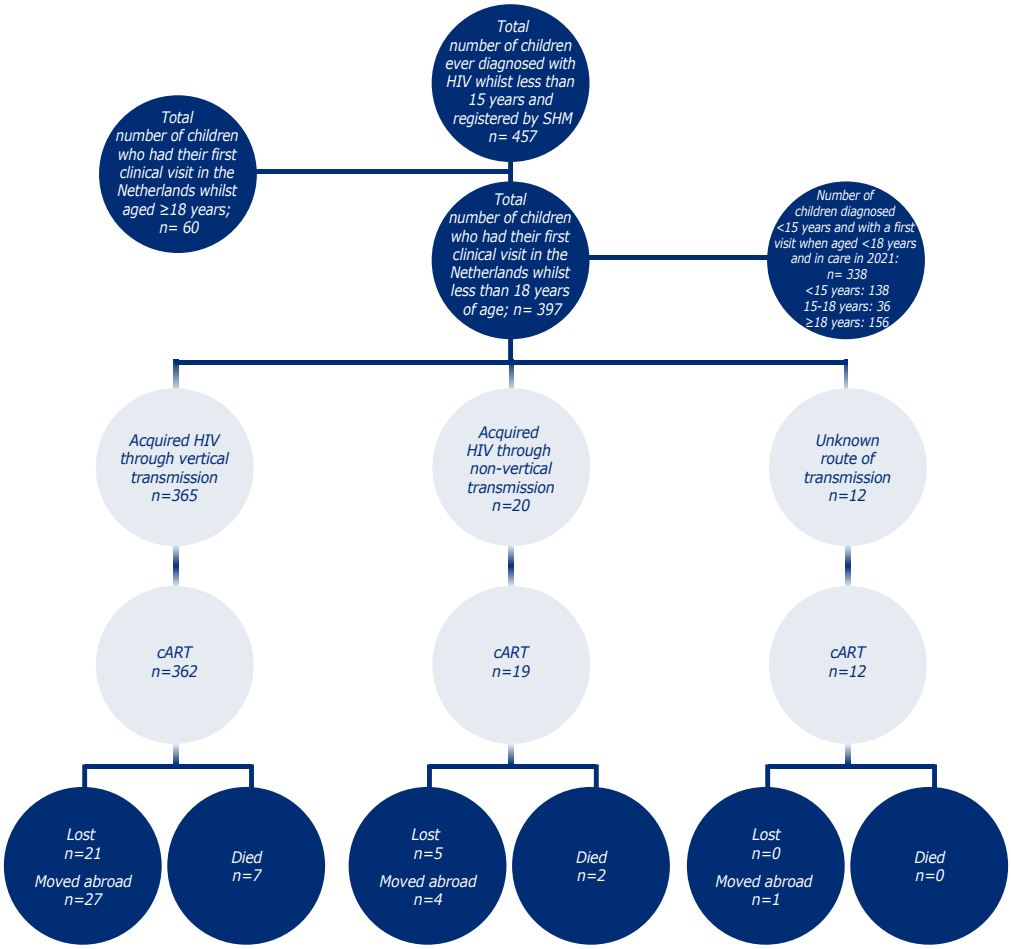
The limit of 15 years is aligned with the definition of children used by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO)[1,2].

a *The total number of children described in this analysis is lower compared to the 2019 SHM Monitoring Report. This is due to a change in definition: we now only include children who were diagnosed before the age of 15, whereas previously we also included adolescents who were diagnosed between the ages of 15 and 18.*

Children with HIV ever registered by SHM

As of 31 December 2021, SHM had registered 457 individuals who had ever been diagnosed with HIV while under 15 years of age (*Figure 5.1*). Of these, 137 were diagnosed with HIV before arriving in the Netherlands and 320 were newly diagnosed in the Netherlands. In total, 397 of the 457 children entered care in the Netherlands before the age of 18. Among the 60 children who entered care *after* the age of 18, 75% were born outside the Netherlands. Although the date of migration to the Netherlands is not available for all children, the median age at time of migration to the Netherlands was 28 years (IQR: 21-31) for those with an known date. Of those who were born in the Netherlands, all were diagnosed before 1995 and entered care after the age of 18 years.

Figure 5.1: *Overview of children with HIV registered by stichting HIV monitoring as of 31 December 2021.*



Legend: *ART = combination antiretroviral therapy.*

The majority (97%) of the children entered care at a paediatric HIV treatment centre. Ten entered care at an adult HIV treatment centre at a median age of 16.9 years (IQR 16.2-17.6) (*Table 5.1*).

Table 5.1: Demographic and HIV-related characteristics of 397 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	365 (92)	20 (5)	12 (3)
HIV treatment centre			
Paediatric care	362 (99)	15(75)	10 (83)
Adult care	3 (1)	5 (25)	2 (17)
Gender			
Male	175 (48)	8 (40)	9 (75)
Female	190 (52)	12 (60)	3 (25)
Child's country of origin			
The Netherlands	113 (31)	2 (10)	0
Sub-Saharan Africa	208 (57)	16 (80)	11 (92)
Other	44 (12)	3 (10)	1 (8)
Mother's country of origin			
The Netherlands	32 (9)	1 (5)	1 (8)
Sub-Saharan Africa	188 (51)	8 (40)	7 (58)
Other/unknown	145 (40)	11 (55)	4 (34)
Adopted	149 (41	0	3 (25)
Age at HIV diagnosis	1.1 (0.25-3.6)	11.5 (7.14-14.4)	10.5 (5.0-12.0)
ART-treated	362 (99)	19 (95)	12 (100)
Therapy-naïve at ART initiation	316(87)	16 (80)	12 (100)
CD4 at ART initiation	560 (286-1230)	324 (171-508)	330 (310-475)
CD4 Z-score at ART initiation	-0.6 (-1.0- -0.10)	-0.6 (-1.13- -0.01)	-0.50 (-0.8- -0.24)
VL (log copies/ml) at ART initiation	5.2 (4.5-5.8)	4.3 (4.0-5.5)	4.9 (4.6-5.0)

***Legend:** *Data are number (%) of children or median (interquartile range).*
ART = combination antiretroviral therapy; VL = viral load.

Mode of transmission

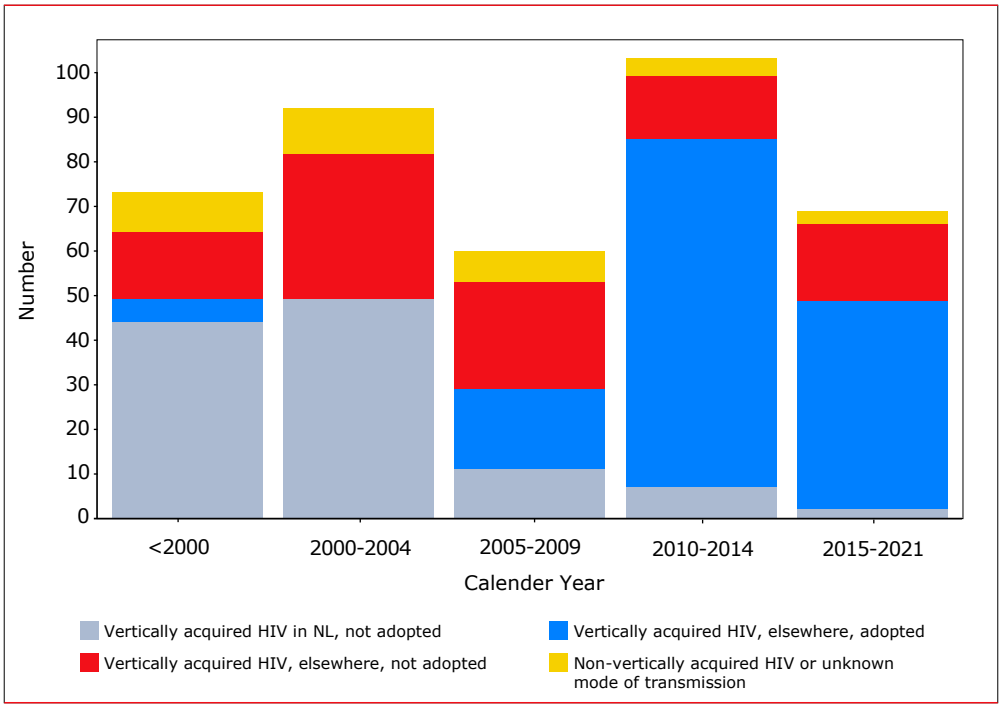
The majority (92%) of the children registered acquired HIV through vertical transmission. (*Figure 5.1*).

Vertical transmission

Between 1998 and 2021, 365 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). Of this total:

- 99% received care in a paediatric HIV treatment centre in the Netherlands;
- ART initiation was documented for 99% of the children;
- 57% (n = 208) of the children were born in sub-Saharan Africa;
- 31% (n = 113) of the children were born in the Netherlands; and
- 9% of the children born in the Netherlands (10 out of 113) 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 103 in 2010-14 to 69 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 2021, 20 children were registered as having acquired HIV through non-vertical transmission (*Table 5.1*); the reported modes 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. No further details are available regarding this category. It is also worth noting that some children only enter care a few years after their HIV diagnosis.

The median age at which they received their first reported HIV-positive test result was 11.5 years (IQR 7.14-14.4). However, the median age of HIV diagnosis for those who acquired HIV by sexual transmission was higher, at 14.7 years (IQR 13.8-14.9). In total:

- 95% of these children had started ART;
- 40% of children acquired HIV through heterosexual contact;
- 80% were born in sub-Saharan Africa; and
- 25% received care in an adult HIV treatment centre.

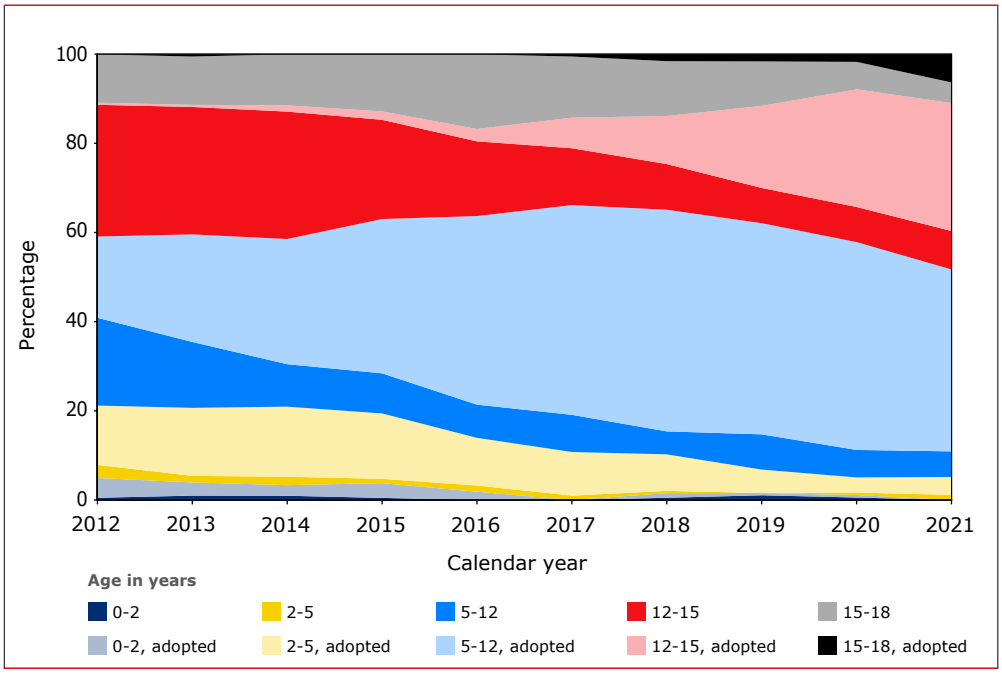
Unknown route of HIV transmission

For 12 children with HIV, the route of transmission remains unknown (*Table 5.1*). Their median age at diagnosis was 10.5 years (IQR 5-12), and all children had started ART.

Age distribution

Figure 5.3 shows the age distribution of children receiving HIV care in the last 10 years (2012-2021). 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 adopted children with HIV in those age groups. In 2021, approximately 83% of children with HIV aged between 5 and 15 years were adopted.

Figure 5.3: Time-dependent age distribution of children with HIV in care over time.



Low mortality rates

No children registered with SHM and in care were reported to have died before the age of 18 between 2012 and 2021. The mortality rate therefore remains very low, with a total of two deaths recorded since the start of registration. Both children died from AIDS before 2010. However, between 2012 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 therapy

Of the 397 children who entered care in the Netherlands before 18 years of age, 393 (99%) started ART; 344 (88%) of them were treatment-naïve at the start of ART and 49 (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-naïve children who initiated ART from 2012 onwards have been included. Children were grouped by calendar year of ART initiation: 76 children started an ART regimen in 2012-2016 and 23 in 2017-21. For 13 children, the year of ART initiation is not known. All these children were born outside the Netherlands.

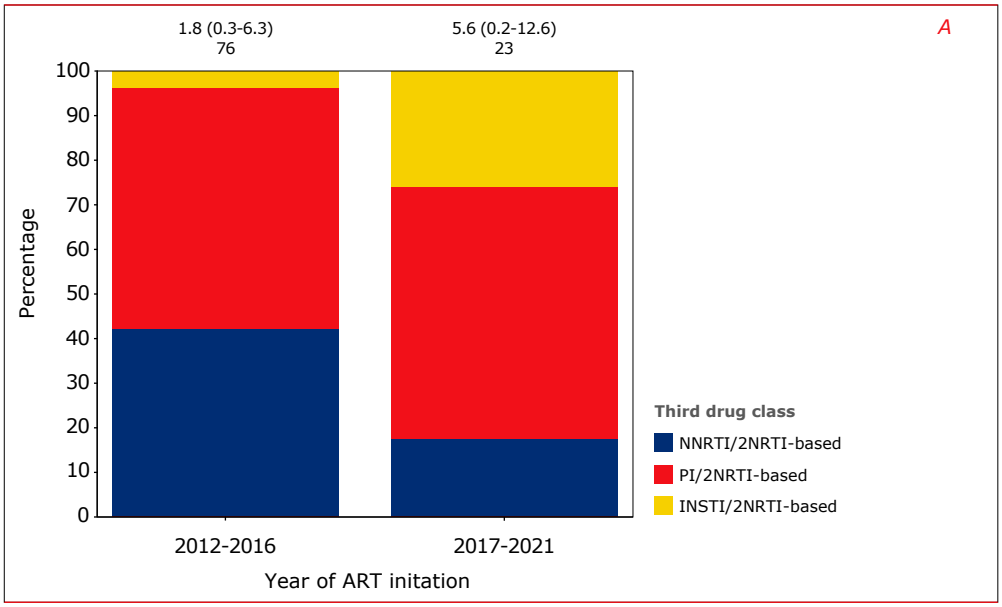
Initial ART regimen

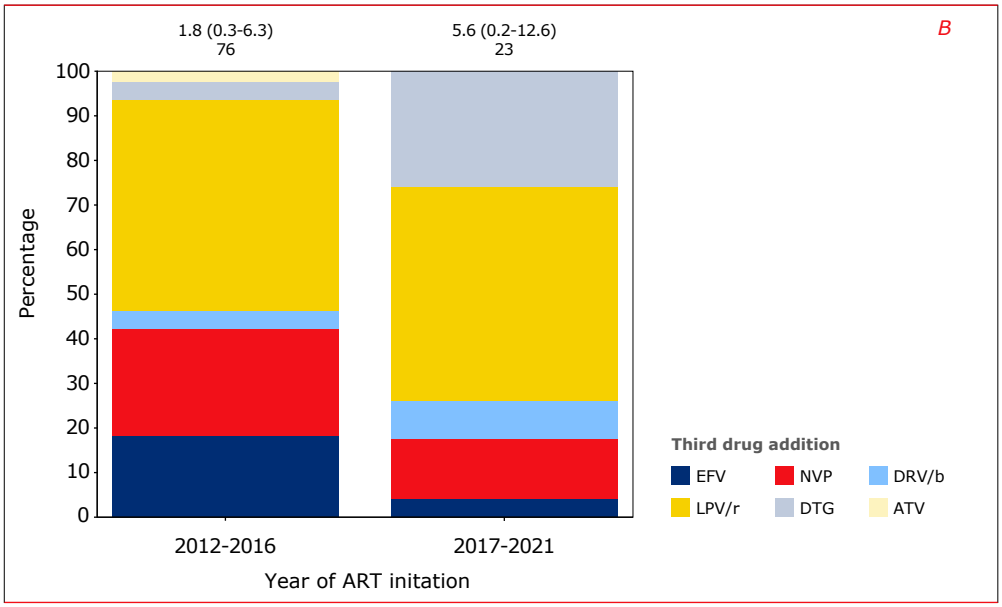
Of the 99 registered children known to have initiated ART between 2012 and 2021:

- 55% were treated with a first-line regimen that included a protease inhibitor (PI) and two or more nucleoside reverse transcriptase inhibitors (NRTIs);
- 36% were treated with a non-nucleoside reverse transcriptase inhibitor (NNRTI) with two or more NRTIs; and
- 9% were treated with an integrase inhibitor-based first-line 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, 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 26% of the children who initiated a first-line regimen between 2017-2021.

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 = combination antiretroviral therapy; ENTRY = entry inhibitor; INSTI = integrase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-NRTI; PI = protease inhibitor; EFV = efavirenz; NVP = nevirapine; LPV/r = ritonavir-boosted lopinavir; IDV = indinavir; SQV = saquinavir; NFV = nelfinavir; RAL = raltegravir; DRV/b = cobicistat- or ritonavir-boosted darunavir; ATV/r = ritonavir-boosted atazanavir; DTG = dolutegravir; EVG/c = cobicistat-boosted elvitegravir.*

Discontinuation of the initial ART regimen

The median time the 99 children who had started ART between 2012 and 2021 spent on an initial regimen was 22.0 months (IQR 7-39). Discounting weight-related dose changes, 65 children (66%) discontinued their first-line therapy regimen. The most important reasons for changing included simplification (42%) and toxicity (12%). Virological failure was the reason given in 11% of cases. Other reasons included parent or child decision, blood level-related issues, or unknown.

Virological response

Virological response to ART was assessed based on viral suppression (i.e. viral load below 200 copies/ml, [*Box 5.1*]). Initial virological response is reported for the first two years after starting ART between 2012-2021. Long-term virological response is reported by time-updated age for those who used ART for at least 24 months.

Initial response to ART

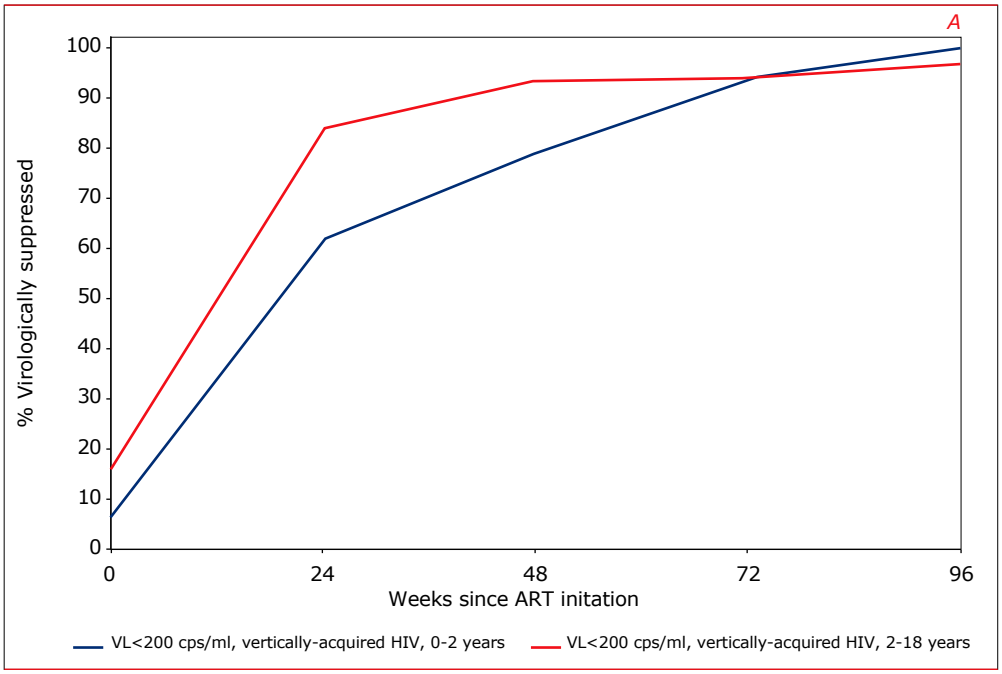
This analysis used data from the 90 children who were registered with SHM and had started ART between 2012-2021, and who had viral load data available in the first 24 months after ART initiation. Children were stratified by age at ART initiation, resulting in the following categories:

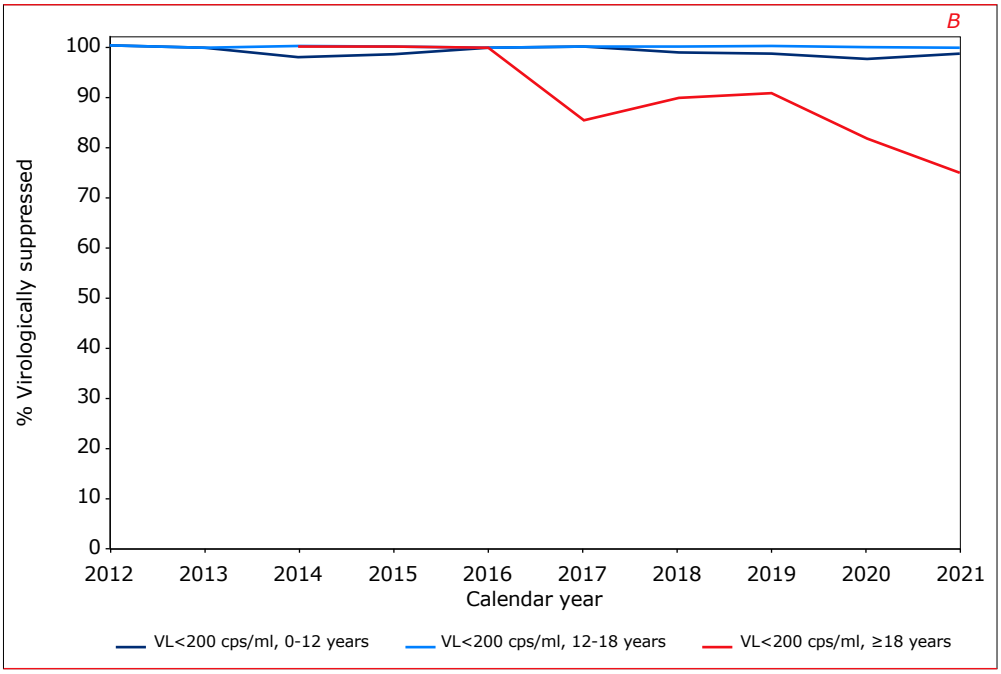
(1) 0-2 years, n=47
(2) 2-18 years, n=43

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 2012-2021 of ART initiation. *Figures 5.5A* shows viral suppression rates among children who initiated ART between 2012 and 2021:

- Among children who were aged 0-1 years at the time of ART initiation, viral suppression rates increased from 79% after one year of ART, to 100% after two years.
- Among children who were aged 2-18 years at ART initiation, viral suppression rates increased from 94% after one year of ART, to 97% after two years.

Figure 5.5: Viral suppression following combination antiretroviral therapy (ART) initiation: (A) during the first two years of ART 2012-2021, (B) time-dependent and age-dependent viral suppression rates for children in care between 2012 and 2021 after two years of ART with ART initiation from 2010 onwards. Viral suppression is defined as any viral load measurements below 200 copies/ml, except for time points in the past where tests were used with quantification limits above 200 copies/ml.





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

Long-term virological response

Among the children who were using ART for more than 24 months, we assessed viral suppression rates by calendar year of follow up. The latest viral load measurement in each calendar year was included in the analysis. Viral suppression rates were stratified by calendar period of ART initiation, to account for changes in the use of ART regimens.
Time-updated age of HIV RNA measurements was calculated, and children were stratified by the following time-updated age ranges:

(1) 0-12 years
(2) 12-18 years
(3) 18 years and over

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*).

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.

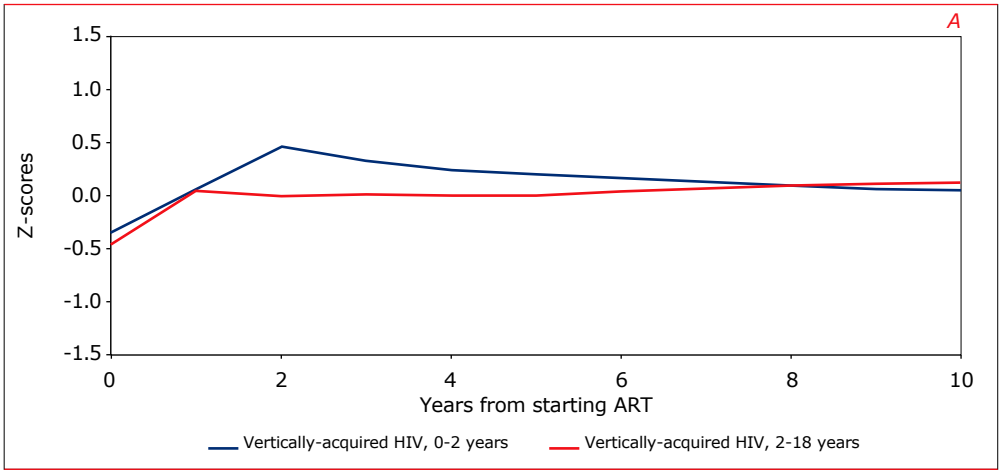
CD4 Z-scores represent the standard deviation from the reference values for HIV-negative children. They were calculated for CD4 cell counts to correct for age-related differences. All absolute CD4 T-cell counts were transformed into Z-scores by subtracting the age-related reference value for the age 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 2012 and 2021, 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 2012 and 2021.*



Legend: *ART = antiretroviral therapy.*

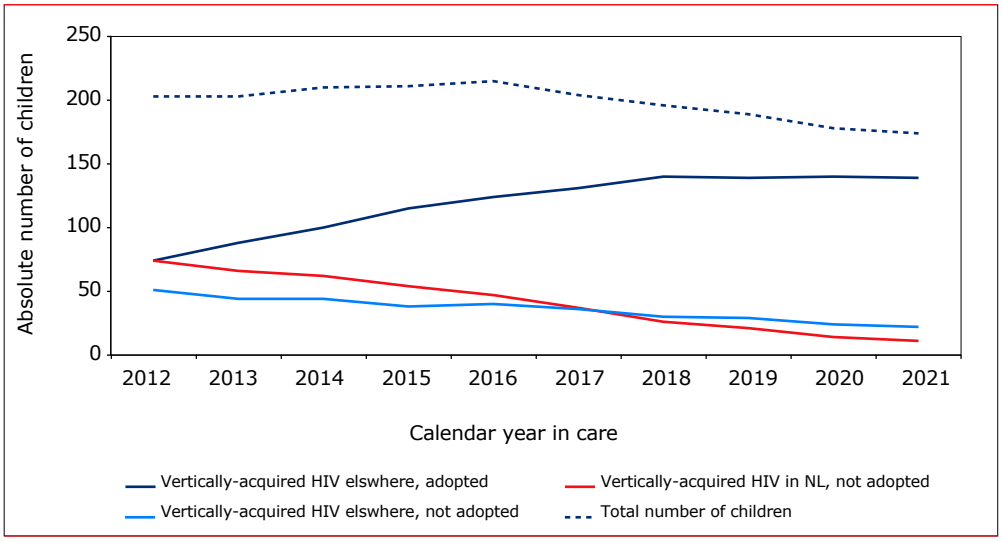
Currently in clinical care

Of the 397 children with HIV ever registered by SHM, and who entered care in the Netherlands before the age of 18, 330 (or 83%) were still in care in 2021. Of these, 174 were under the age of 18 (*Figure 5.1*). Of the 67 children no longer in care:

- Nine had died;
- 32 had moved abroad;
- 26 – a substantial number – were lost to care.

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 2021, this figure had declined to 174, mainly due to the fact that more children with vertically-acquired HIV who are not adopted are reaching the age of 18 years and, at the same time, fewer children are newly entering care.

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 clinical care: under 18 years of age

- 174 were younger than 18 years at the end of 2021
- 138 were younger than 15 years
- The median age was 12 years (IQR 10-15) as of 31 December 2021.

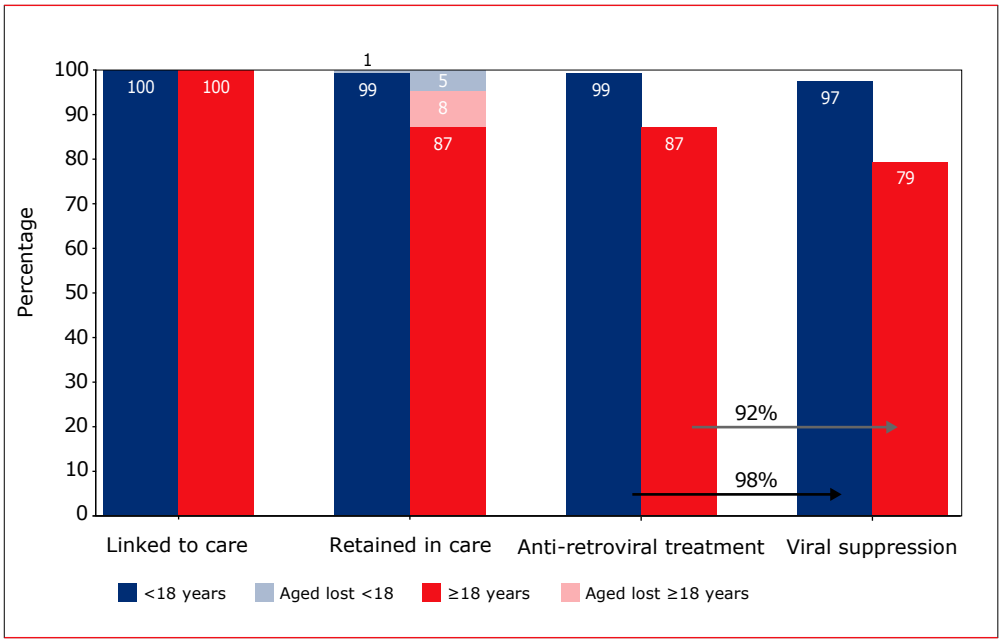
Currently in clinical care: aged 18 years and over

- 156 were older than 18 years of age at the end of 2021
- The median age was 25 years (IQR 22-29) as of 31 December 2021

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 2021 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 2021. The numbers in and above the bars indicate the proportion of individuals.



Individuals were stratified by age on 31 December 2021 and categorised as:
(1) current age, under the age of 18 years
(2) current age, 18 years and over

Continuum of care: current age under 18 years

In total, 176 children were linked to care, registered by SHM, still alive and not reported to have moved abroad. Of these:

- 99% (n=174) were retained in care;
- two children, both born outside the Netherlands, were lost to care;
- 99% (n=174) had ART during their last clinical visit in 2021; and
- 97% (n=170) had a most recent HIV RNA measurement below 200 copies/ml (98% of those on ART).

Continuum of care: current age 18 years and over

In total, 180 individuals were linked to care, registered by SHM, still alive and not reported to have moved abroad. Of these:

- 87% (n=156) were retained in care;
- 24 individuals (13 of whom were born outside the Netherlands) were lost to care, of whom
  - 10 before they turned 18
  - 14 when they were aged 18 and over;
- 87% (n=156) had ART during their last clinical visit in 2021; and
- 79% (n=143) had a most recent HIV RNA measurement below 200 copies/ml (92% of those on ART).

It is worth noting that 11 of the 24 young adults who were lost to care had their last clinical contact at a paediatric HIV treatment centre. They were deregistered and may have been lost during transition to adult care, or may be waiting to be re-registered at an adult treatment centre.

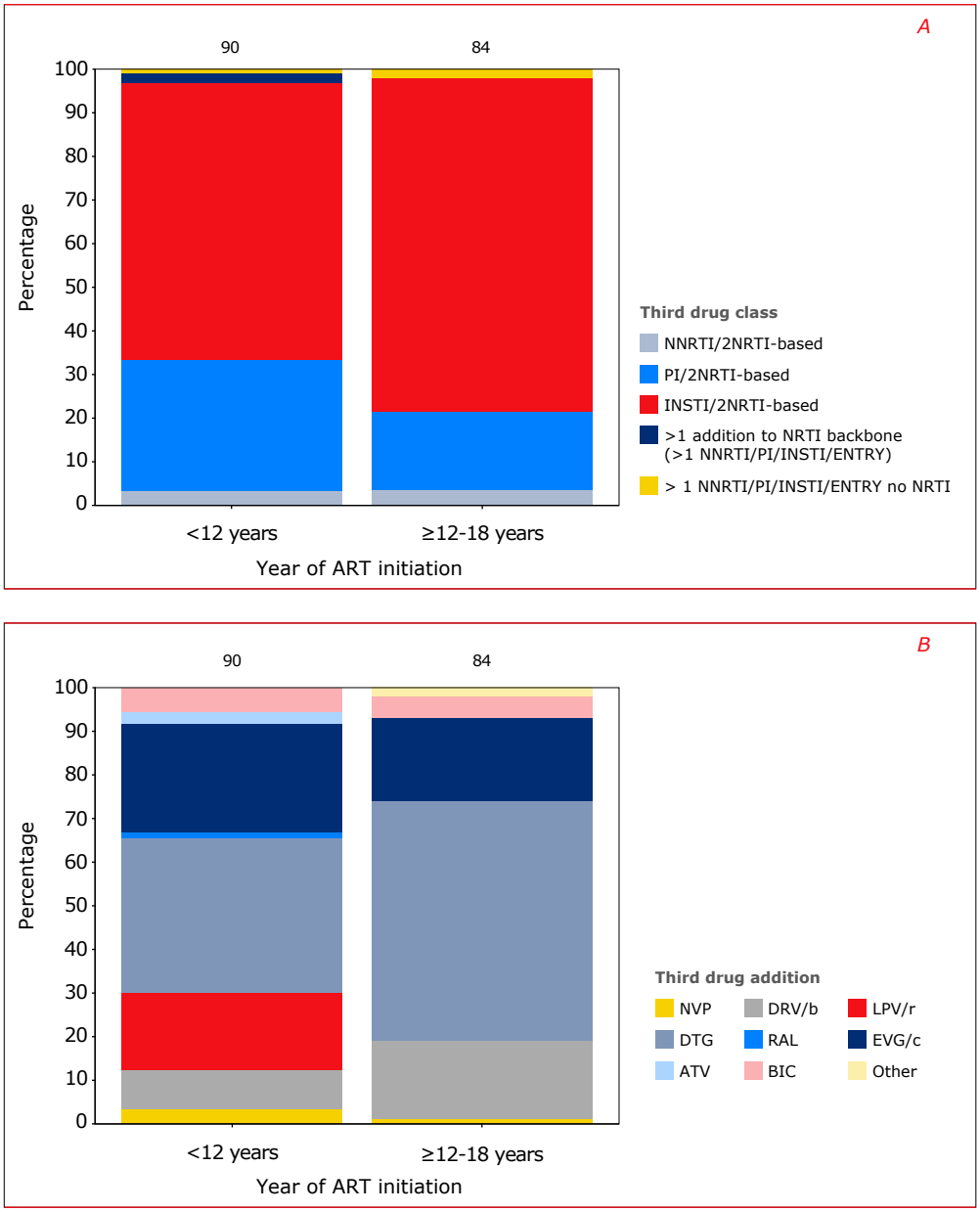
In care and on ART in 2021

Of the 174 children known to be in care in 2021 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 2021.

Among those under 12 years of age, PI-containing and INSTI-based regimens were the most commonly-used (30% and 63%), with dolutegravir (36%) and elvitegravir (24%) the most common individual third agents.

In children aged between 12 and 18 years, 76% were using an INSTI-based regimen and 18% a PI-containing regimen. Among those using an INSTI-based regimen, dolutegravir was most common (55%), followed by elvitegravir (19%). Overall, nine 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 397 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 1% in 2002 and 2001 to 86% in 2015 (*Figure 5.2*), with a median age at the time of entering care of 2.7 years (IQR 1.6-5.0). Overall:

- 108 (71%) children were already receiving ART before they were adopted;
- 18 (12%) 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;
- Three adopted children are no longer in care;
- All children known to be in care were still receiving therapy in 2021;
- 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.

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.

Figure 5.7 shows the number of adopted children still in care and under 18 years of age. As of 31 December 2021, 149 children were alive and in care and 139 of them were aged below 18 years. Their median age was 11.3 years (IQR 9.4-14.0).

Transfer to adult care

Of the 397 children ever registered by SHM who were under the age of 18 when they entered care in the Netherlands, 164 children had reached the age of 18 and above, and had transferred from paediatric care to adult care by 31 December 2021.

Figure 5.10: Follow up status, as of 31 December 2021, of children who transferred to adult care.

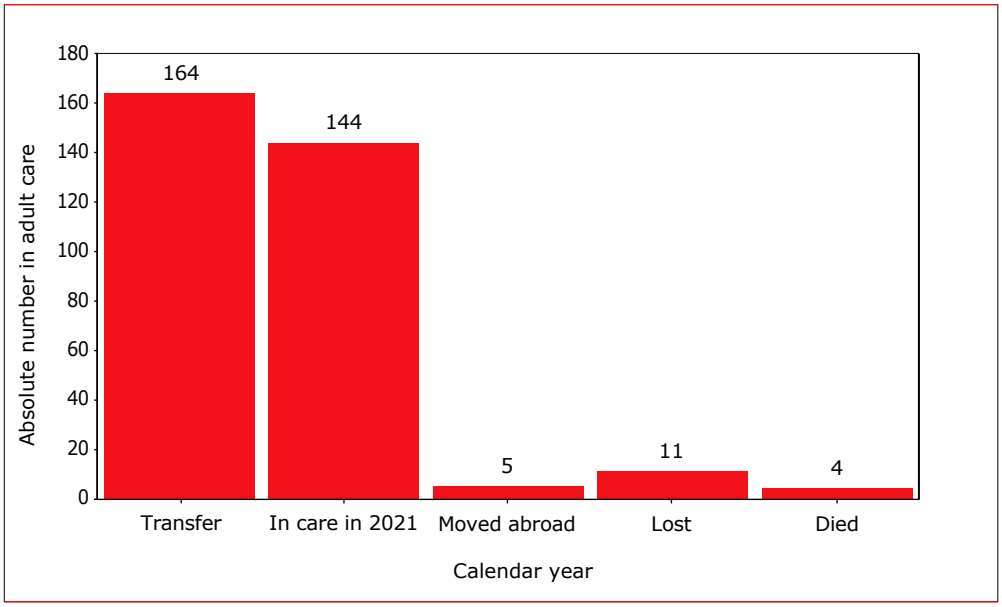
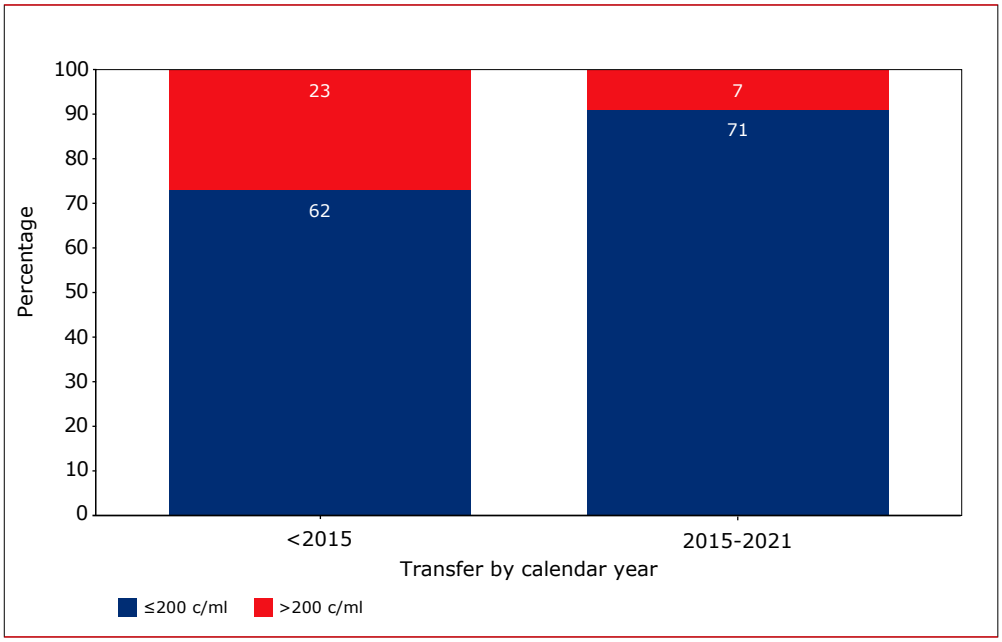
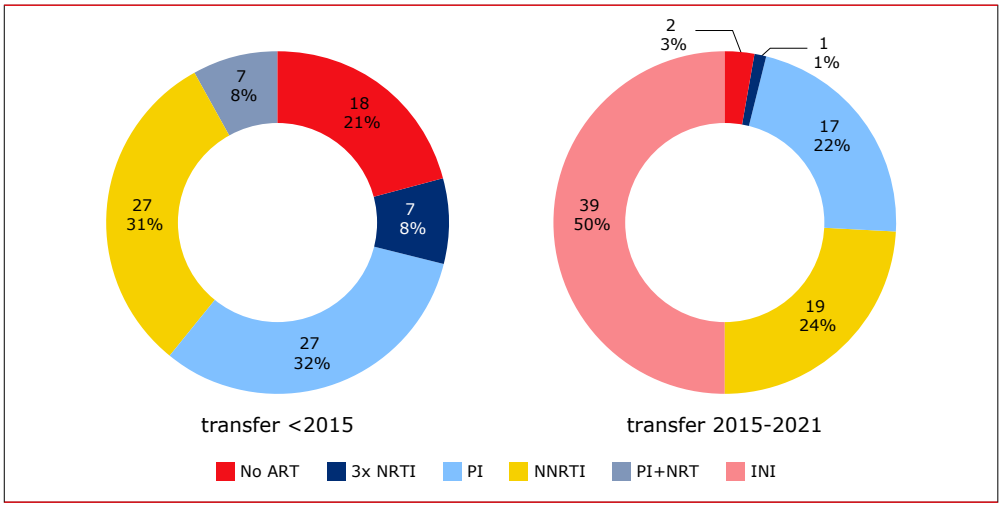


Figure 5.11: HIV RNA (A) and ART regimens (B) at last visit in paediatric care of children who transferred to adult care, stratified by calendar year of transfer (A).





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 2.6-5.8). Time in care after transfer until their last documented clinical visit was 6.7 years (IQR 3.1-9.9).

Figure 5.10 shows the follow up status of the 164 adolescents who transferred to adult care:

- 144(88%) were still in care in 2021;
- 11 (7%) were lost to care, of whom
- four 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
- four (2%) had died.

Overall, at the time of their last clinical visit to paediatric care, 30 adolescents (18%) had an HIV RNA level above 200 copies/ml (median 3443; IQR 1220-27065). This figure is more or less comparable to results from the UK, which found that 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 (9%), compared to those who transferred before 2015 (27%) (*Figure 5.11a*).

During their last visit to paediatric care, 88% of the 164 adolescents received ART, 3 adolescents (2%) 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 (21% and 3%, respectively, *Figure 5.11b*).

Among adolescents who transferred to adult care before 2015, 31% were on an NNRTI-based regimen and 32% on a PI-based regimen. These percentages differed for adolescents who transferred in or after 2015: 50% were on an integrase-based regimen, 24% on an NNRTI-based regimen and 22% on a PI-based regimen.

All 144 adolescents who transferred to adult care, and who were still in care in 2021, were receiving ART in 2021. Just over half of these were on an integrase inhibitor-based regimen (55%). In total, 92% of the 144 had HIV RNA levels below 200 copies/ml in 2021.

Summary

Of the 397 children with HIV ever registered by SHM who were under the age of 18 when they entered care in the Netherlands, 83% remain 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.
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].

None of the children who entered 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 ART for everyone with HIV, regardless of CD4 counts. All children in care in 2021 were receiving ART. Current regimens in use include an integrase inhibitor for 62% of young children and for 76% for children aged 12 years and over.

Although a less favourable *initial* virological response was seen in the youngest children, very high *long-term* viral suppression rates were observed in children with HIV who initiated ART in or after 2012. However, those response rates fell when children reached the age of 18. For example, overall detectable HIV RNA rates were 18% at the time of transition to adult care, which is typically the case around the age of 18. Nonetheless, transition to adult care with an undetectable viral load increased over time, from 73% to 91%.

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 2021, 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 therapy 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.

References

1. UNAIDS. Start Free, Stay Free, AID Free. Final report on 2020 targets. https://www.unaids.org/sites/default/files/media_asset/2021_start-free-stay-free-aids-free-final-report-on-2020-targets_en.pdf. Published 2021.
2. WHO. HIV/AIDS. https://www.who.int/news-room/fact-sheets/detail/hiv-aids. Published 2021.
3. Goetghebuer T, Haelterman E, Le Chenadec J, et al. Effect of early antiretroviral therapy on the risk of AIDS/death in HIV-infected infants. *AIDS*. 2009;23(5):597-604. doi:10.1097/QAD.0b013e328326ca37
4. Judd A, Chappell E, Turkova A, et al. Long-term trends in mortality and AIDS-defining events after combination ART initiation among children and adolescents with perinatal HIV infection in 17 middle- and high-income countries in Europe and Thailand: A cohort study. Deeks SG, ed. *PLOS Med*. 2018;15(1):e1002491. doi:10.1371/journal.pmed.1002491
5. Gibb DM. Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1infectedchildrenintheUnitedKingdomandIreland.*BMJ*.2003;327(7422):1019-0. doi:10.1136/bmj.327.7422.1019
6. Gortmaker SL, Hughes M, Cervia J, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med*. 2001;345(21):1522-1528. doi:10.1056/NEJMoa011157
7. de Martino M, Tovo PA, Balducci M, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Italian Register for HIV Infection in Children and the Italian National AIDS Registry. *JAMA*. 2000;284(2):190-197.
8. Foster C, Pace M, Kaye S, et al. Early antiretroviral therapy reduces HIV DNA following perinatal HIV infection. *AIDS*. 2017;31(13):1847-1851. doi:10.1097/QAD.0000000000001565

9. Shiau S, Strehlau R, Technau KG, et al. Early age at start of antiretroviral therapy associated with better virologic control after initial suppression in HIV-infected infants. *AIDS*. 2017;31(3):355-364. doi:10.1097/QAD.0000000000001312
10. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med*. 2008;359(21):2233-2244. doi:10.1056/NEJMoa0800971
11. Newell M-L, Patel D, Goetghebuer T, Thorne C. CD4 cell response to antiretroviral therapy in children with vertically acquired HIV infection: is it associated with age at initiation? *J Infect Dis*. 2006;193(7):954-962. doi:10.1086/500842
12. World Health Organization. Guidelines Guideline on When To Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV. *World Heal Organ*. 2015;(September):78. doi:978 92 4 150956 5
13. Boer K, Smit C, Van Der Flier M, De Wolf F. The comparison of the performance of two screening strategies identifying newly-diagnosed HIV during pregnancy. *Eur J Public Health*. 2011;21(5):632-637. doi:10.1093/eurpub/ckq157
14. Op de Coul ELM, Hahné S, van Weert YWM, et al. Antenatal screening for HIV, hepatitis B and syphilis in the Netherlands is effective. *BMC Infect Dis*. 2011;11(1):185. doi:10.1186/1471-2334-11-185
15. The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008;372(9635):293-299. doi:10.1016/S0140-6736(08)61113-7
16. Bunders M, Cortina-Borja M, Newell M-L, European Collaborative Study. Age-related standards for total lymphocyte, CD4+ and CD8+ T cell counts in children born in Europe. *Pediatr Infect Dis J*. 2005;24(7):595-600. http://www.ncbi.nlm.nih.gov/pubmed/15998999. Accessed September 16, 2016.
17. Comans-Bitter WM, De Groot R, Van den Beemd R, et al. Immunophenotyping of blood lymphocytes in childhood: Reference values for lymphocyte subpopulations. *J Pediatr*. 1997;130(3):388-393. doi:10.1016/S0022-3476(97)70200-2
18. Collins IJ, Foster C, Tostevin A, et al. Clinical Status of Adolescents with Perinatal HIV at Transfer to Adult Care in the UK/Ireland. *Clin Infect Dis*. 2017;64(8):1105-1112. doi:10.1093/cid/cix063

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 transmission from a mother with HIV[1]. Vertical transmission or mother-to-child-transmission of HIV mainly occurs perinatally during labour and delivery, or postnatally during breastfeeding. Less common is transplacental infection 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 2021, 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 478 women with HIV who had a registered pregnancy in the Netherlands between 2016 and 2021. Of these women, 341 (71%) were of non-Dutch origin and 137 (29%) were born in the Netherlands. The majority of women of non-Dutch origin were born in sub-Saharan Africa (n=214, 63%) or in the Caribbean/Latin America region (n=68, 20%). Fifty-nine (12%) women originated from other regions, including 24 women from Central or Eastern Europe, and 17 women from south and south-east Asia.

Diagnosis

The majority of the 478 women (n=409, 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, 69 women were newly diagnosed during their pregnancy. Among these:

- 19 (28%) women were born in the Netherlands;
- 29 (42%) women originated from Sub-Sahara Africa;
- 11 (16%) women originated from the Caribbean/Latin America region; and
- 10 (14%) women originated from other regions.

The median time between conception and diagnosis among newly diagnosed women was 13 weeks (IQR: 10-17). Of this total, 57% received their diagnosis during the first trimester of pregnancy, 36% in their second trimester, and 7% in their third trimester. Forty-three of the 69 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 eight 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 594 cells/mm^3 (IQR 400-770) 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 220-470). 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 measurement. These were also found to be lower than average among the group of women newly diagnosed during pregnancy (*Table 6.1*).

Mode of HIV acquisition

Among the 478 women, heterosexual contact was found to be the most common mode of HIV acquisition (90%). For eight women, the reported mode of HIV acquisition was exposure to contaminated blood, while, for two women of non-Dutch origin, infection occurred through injecting drug use. Nineteen pregnant women acquired HIV through vertical transmission themselves. For the remaining 17 women, the mode of acquisition remains unknown.

Population in care

Between 2016 and 2021, none of the mothers were documented to have died during follow up, this also includes following time after the pregnancy until the date of database closure. A total of 30 (6%) were no longer in care; of these, 12 (3%) were known to have moved abroad and 18 were lost to care (4%). No significant differences were observed between women of Dutch and non-Dutch origin in terms of those lost to care.

All 18 women were lost to care after their pregnancy ended; with a median time between delivery and last clinical visit of 8 months (IQR: 1-41). Of these:

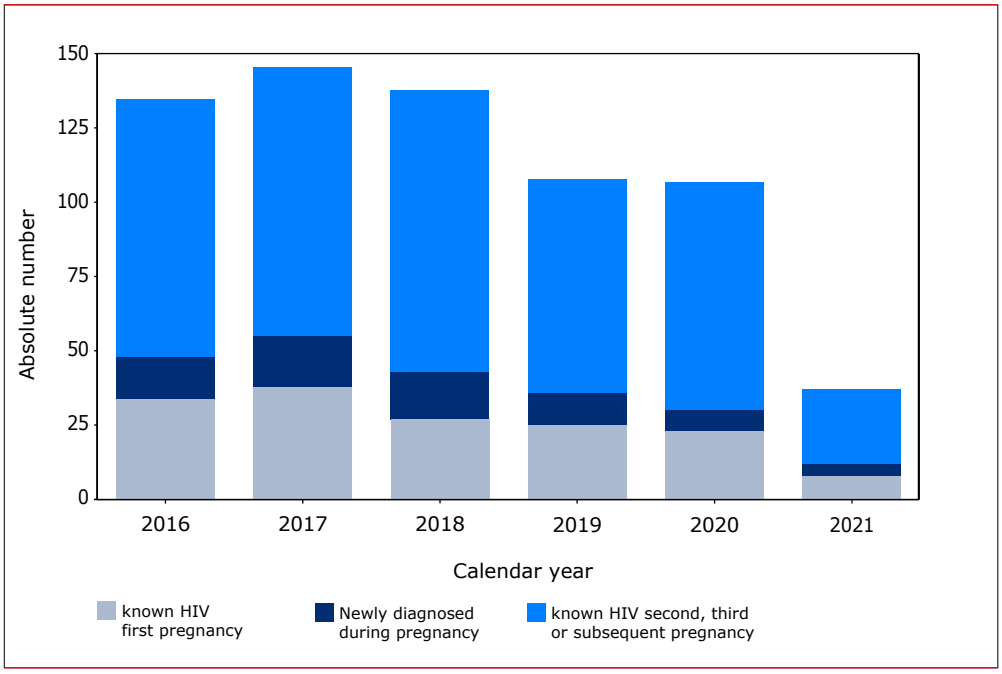
- four women started ART during their pregnancy, of whom three were newly diagnosed with HIV;
- all but one woman had a documented ART regimen reported during their last clinical visit; and
- two women had a detectable HIV RNA result during their last clinical visit.

In total, 16 of the 18 pregnancies resulted in a live-birth and two 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.

Trends in number of pregnancies in women with HIV

In total, 671 pregnancies among the 478 women were reported between 2016 and 2021. The absolute annual number of pregnancies in women with HIV in care in the Netherlands varied between 146 in 2017 and 37 in 2021[a] (*Figure 6.1*). The number of women newly diagnosed with HIV during pregnancy varied between 17 in 2017 and four in 2021[1], but remained relatively stable as a proportion of the total number of pregnancies per year, at 10-12%. The number of second, third or subsequent pregnancies in women already aware of their HIV status was approximately 75 annually. (*Figure 6.1*).

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



Pregnancy-related characteristics

Overall, 478 women accounted for 671 registered pregnancies: 32% of the women had one registered pregnancy, 29% had two registered pregnancies, and 38% of the women had three or more registered pregnancies (*Table 6.1*).

a *Data on the number of registered pregnancies in 2021 may be incomplete due to a delay in data collection.*

Table 6.1: Characteristics of pregnant women with HIV registered and monitored by stichting hiv monitoring between 2016-2021

	Total n (%)	Netherlands n (%)	Sub Saharan Africa n (%)	Latin America and the Caribbean n (%)	Other regions N (%)
Maternal characteristics	478	137 (29)	214 (45)	68 (14)	59 (12)
HIV diagnosis prior to pregnancy (%)	409 (86)	118 (86)	185 (86)	57 (84)	49 (83)
Newly diagnosed during pregnancy(%)	69 (14)	19 (14)	29 (14)	11 (16)	10 (17)
First CD4 cell count in pregnancy(cell/mm^3)*	594 (400-770)	641 (460-846)	570 (390-750)	570 (360-840)	550 (375-810)
CD4 percentage (%)	32 (25-40)	38 (32-41)	32 (23-38)	28 (18-38)	30 (24-37)
First CD4 cell count when newly diagnosed during pregnancy (cell/mm^3)*	350 (220-470)	355 (293-520)	270 (166-445)	408 (190-470)	340 (310-490)
CD4 percentage (%)	23 (16-26)	29 (23-37)	20 (15-23)	16 (12-27)	24 (21-25)
Age at start of first pregnancy following HIV diagnosis (years*)	33 (29-37)	32 (29-36)	34 (30-38)	34 (30-38)	34 (30-39)
HIV transmission route					
Heterosexual contact (%)	432 (90)	125 (91)	199 (93)	65 (96)	43 (73)
Vertical transmission	19 (4)	8 (6)	9 (4)	1 (2)	1 (2)
Other~ (%)	27 (6)	4 (3)	6 (3)	2 (3)	15 (25)
HBsAg positive/HBV co-infection					
Yes	21 (4)	3 (2)	15 (7)	1 (1)	2 (3)
No	453 (95)	133 (97)	197 (92)	67 (99)	56 (95)
Unknown	4 (1)	1 (1)	2 (1)	–	1 (2)
HCV Ab positive/HCV co-infection					
Yes	13 (3)	2 (1)	2 (1)	3 (4)	6 (10)
No	448 (94)	130 (95)	204 (95)	65 (96)	49 (83)
Unknown	17 (5)	5 (4)	8 (4)	–	4 (7)
Total number of pregnancies	671	188	311	89	83
Total number of pregnancies ever after HIV diagnosis among women with at least one pregnancy between 2016-2021**					
1	155 (32)	54 (39)	61 (29)	21 (31)	19 (32)
2	139 (29)	37 (27)	57 (27)	21 (31)	24 (41)
≥3	184 (38)	46 (33)	96 (45)	26 (38)	16 (27)

	Total n (%)	Netherlands n (%)	Sub Saharan Africa n (%)	Latin America and the Caribbean n (%)	Other regions N (%)
Pregnancy outcome					
Delivery after at least 24 weeks (%)	448(67)	132(70)	203 (65)	57 (64)	56 (67)
Spontaneous abortion					
<24 weeks (%)	144 (22)	32 (17)	72 (23)	16 (18)	24 (29)
induced abortion <24 weeks (%)	76 (11)	23 (12)	34 (11)	16 (18)	3 (4)
Unknown (%)	3 (<1)	1 (<1)	2 (1)	0	0
Total number of partus	448	132	203	57	56
Mode of delivery					
Vaginal	311 (69)	98 (74)	136 (67)	36 (63)	41 (73)
Caesarean, elective	63 (14)	12 (9)	30 (15)	12 (21)	9 (16)
Caesarean, secondary	71 (16)	21 (16)	35 (17)	9 (16)	6 (11)
Unknown	3 (<1)	1 (<1)	2 (1)	–	–
Pregnancy duration					
≥37 weeks	388 (87)	110 (83)	180 (89)	49 (86)	49 (88)
32–37 weeks	48 (11)	19 (14)	15 (7)	8 (14)	6 (11)
<32 weeks	11 (2)	3 (2)	7 (3)	0	1 (2)
Unknown	1 (<1)	0	1 (<1)	0	0
Birth weight (grams, IQR*)	3,130 (2,780–3,466)	3,130 (2,790–3,516)	3182 (2820–3531)	3035 (2720–3470)	3070 (2775–3577)
Perinatal deaths	4 (1)	2 (1)	2 (1)	0	0
Combination antiretroviral therapy started					
Before pregnancy	376 (84)	113 (86)	169 (83)	47 (82)	47 (84)
During pregnancy	72 (16)	19 (14)	34 (17)	10 (18)	9 (16)
No combination antiretroviral therapy during pregnancy	0	0	0	0	0
Latest available plasma HIV RNA level prior to delivery					
<50 copies/ml	429 (96)	128 (97)	191 (94)	55 (96)	55 (98)
50–500 copies/ml	16 (4)	4 (3)	9 (4)	2 (4)	1 (4)
>500 copies/m/	3 (<1)	0(0)	3 (1)	0	0
Time between delivery and latest HIV RNA measurement (weeks)*	3 (1–4)	3 (1–4)	2 (1–4)	3 (1–5)	3 (1–4)

**Median, Interquartile Range (IQR)*

~including blood or blood contact (n=8), injecting drug use (n=2) or unknown mode (n=17)

***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 2021 are included in the analyses of this chapter.*

Pregnancy outcome

The 671 pregnancies resulted in 448 (67%) births (including both live and stillbirths). A total of 220 (33%) pregnancies ended in miscarriage or abortion; 144 (22%) were miscarriages and 76 (11%) 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 448 pregnancies lasted at least 24 weeks and are therefore counted as a birth. The duration of these pregnancies is known in 447 cases. Overall, 388 (87%) pregnancies lasted at least 37 weeks, whereas 59 (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 nine 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 levels are 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 67% of women of non-Dutch 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 92% for women who delivered by elective Caesarean section, and 90% for those with a secondary (unplanned) Caesarean section (p=0.0002).

Combination antiretroviral therapy (ART) uptake and therapy response in pregnant women

Therapy uptake

From 2016 onwards, during the 448 pregnancies that lasted at least 24 weeks, all women involved received ART: in 376 (84%) pregnancies, women were already on ART at the time of conception, while in 72 (16%) pregnancies, ART began during pregnancy. This includes 63 women newly diagnosed with HIV. In 10 out these 72 pregnancies, ART was started during the first trimester.

Figure 6.2A shows the most commonly used third-drug additions to the nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone as part of ART in pregnant women and during delivery between 2016 and 2021. The most commonly used regimens contained darunavir (34%), atazanavir (17%) and raltegravir (13%). Dolutegravir was used in 11% of the pregnancies. The use of integrase inhibitors in pregnancy increased from 4% in 2016 to 41% in 2021. This increase coincides with a decrease in the use of NNRTI-containing regimens from 31% in 2016 to 14% in 2021 (*Figure 6.2C*).

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.*

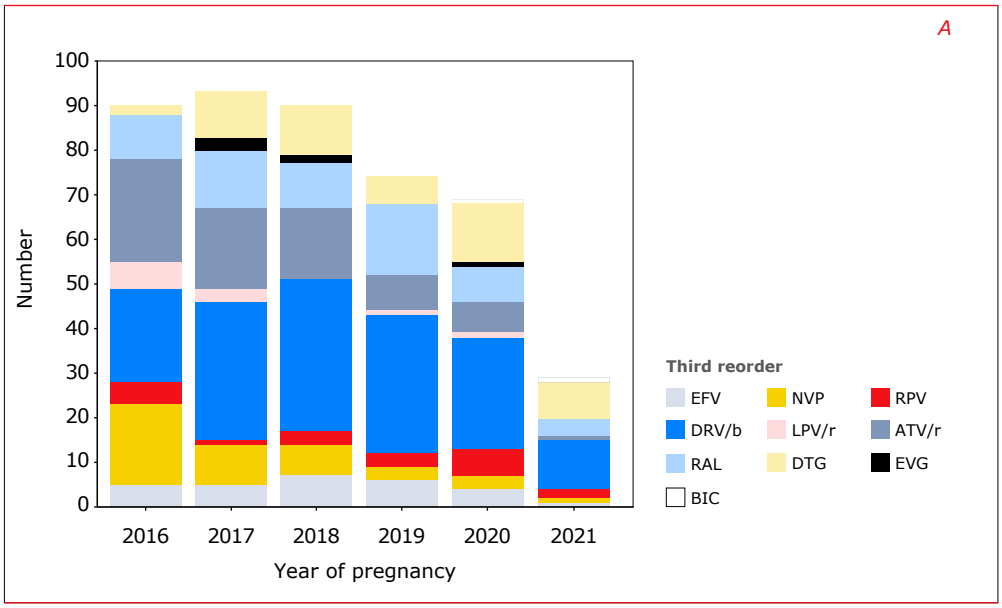


Figure 6.2B: The nucleoside reverse transcriptase (NRTI) backbone used as part of ART regimens during pregnancies in 2016-20.

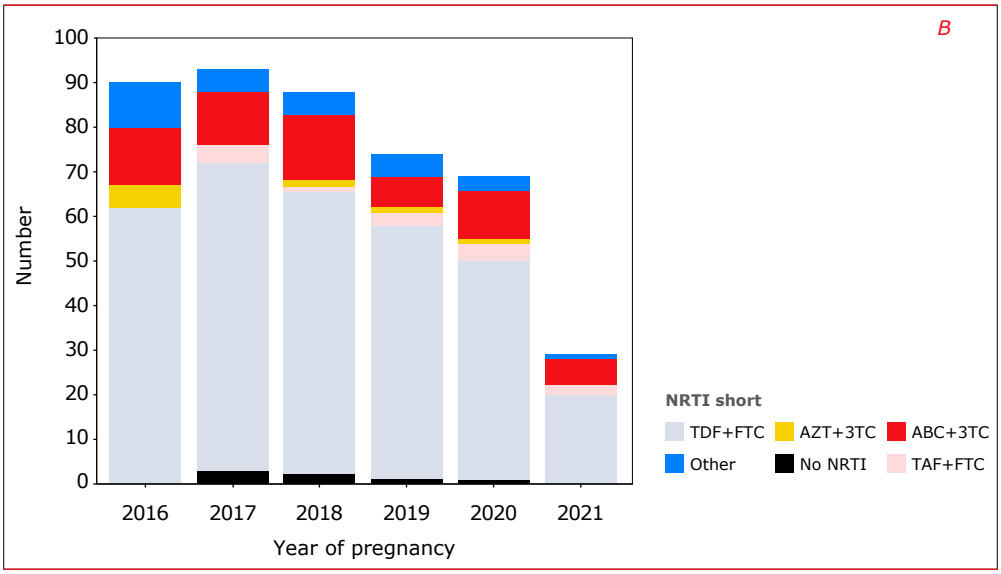
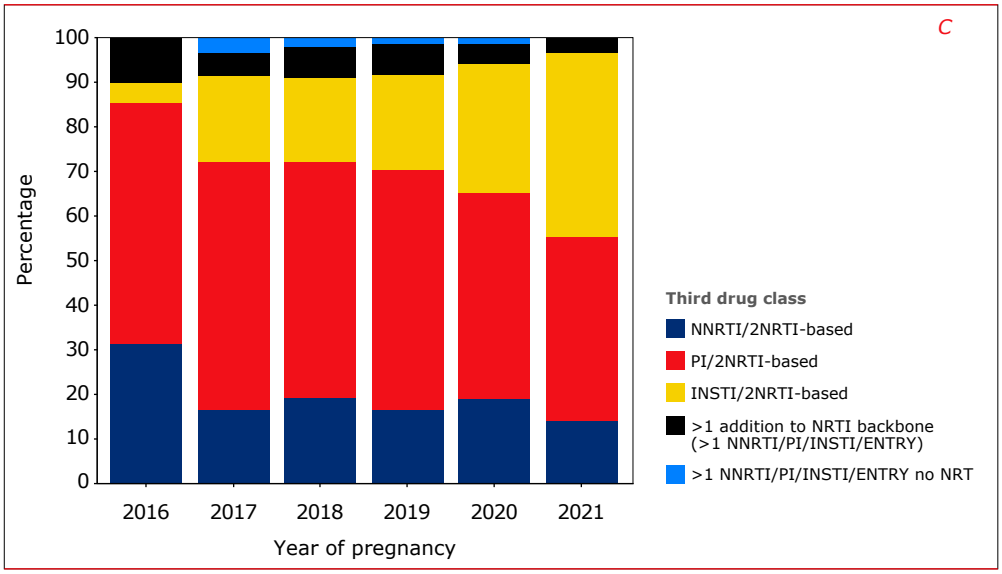


Figure 6.2C: Antiretroviral class stratified by calendar year period.



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, NNRTI=non-NRTI; PI=protease inhibitor; ENTRY=entry inhibitor; INSTI=integrase inhibitor.*

Figure 6.2B provides an overview of the components of the NRTI backbone used during pregnancy between 2016 and 2021. The most commonly prescribed backbone was the combination of tenofovir disoproxil fumarate and emtricitabine (TDF+FTC) (72%), followed by a combination of abacavir and lamivudine (ABC+3TC) (14%).

A switch in ART regimen was reported during 149 pregnancies. While no reason was documented in 14 cases, the most common documented reason for switching in the remaining pregnancies was pregnancy-related (n=95). In 43 pregnancies, ART was switched from an integrase-containing regimen to a protease inhibitor (mostly darunavir or atazanavir). Other common switches were within the class of integrase inhibitors, particularly from dolutegravir or elvitegravir to raltegravir. After switching, 4% of the women used a regimen which included a non-preferred antiretroviral (ARV) agent, except in the special circumstances outlined in the most recent guidelines[14].

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

Therapy response

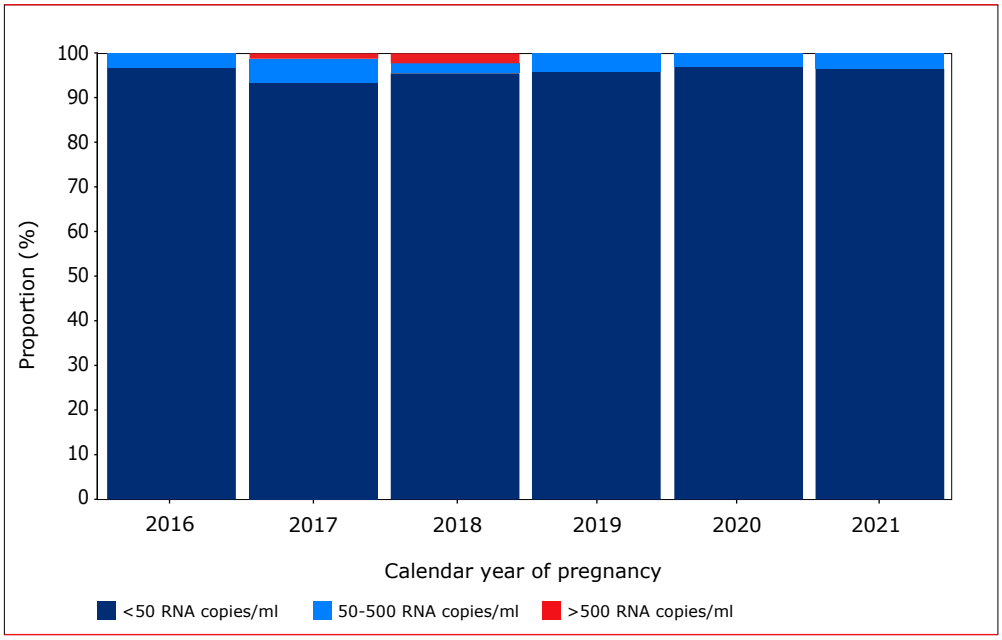
Figure 6.3 shows the percentage of women on ART and their latest available plasma HIV RNA level prior to delivery. HIV RNA levels were categorised as below 50 copies/ml, 50-500 copies/ml, and above 500 copies/ml.

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, 19 women had HIV RNA levels above 50 copies/ml (median RNA= 100 copies/ml; minimum=53, maximum=491) prior to delivery, of whom:

- Seven were first diagnosed with HIV during their pregnancy and had initiated ART during pregnancy as a result of that diagnosis;
- 12 were already on ART, and 10 of these had had earlier episodes of detectable HIV RNA levels while on ART (before conception);
- Five were found to have high-level drug-resistance to at least one NNTRI (the presence of HIV genome mutations associated with drug-resistance was evaluated; sequences were obtained for 14 women, or 74%);
- 12 women delivered by Caesarean section;
- Six women delivered vaginally; and
- One woman's mode of delivery was unknown.

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.*



Vertical transmission rate in the Netherlands

Between 2016 and 2021, 448 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 0.22% in pregnant women on ART in the Netherlands, which is in line with low reported vertical transmission rates in other western European countries[16,17,18,19].

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 448 pregnancies lasting 24 weeks or longer, 77 were excluded from this analysis: 67 because of insufficient follow up between delivery and the time of database closure; and 10 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 371 pregnancies in 326 women, ART was initiated before conception or during pregnancy in 81% and 19% of cases, respectively. The majority of women used an integrase inhibitor-containing regime during the postpartum period (43%). The use of integrase inhibitor increased from 25% in 2016, to 58% in 2020 and 38% in 2021.

In 39 of these 371 pregnancies, ART was discontinued postpartum:

- In 24 cases the documented reason was a decision by the patient.
- In three cases the documented reason was elite controller or long-term non-progressor[b].
- In three cases the documented reason was a decision by the treating physician, including other medical reasons or low treatment adherence.

b *Elite controller or long-term non-progressor refers to an individual who is infected with HIV, but able to control the infection without ART and maintain a CD4 cell count in the normal range indefinitely.*

In 24 out of the 39 cases, therapy was restarted after a median of eight weeks (IQR 4-13). In the remaining 15 cases, ART was not restarted postpartum, however eight women did start again after the postpartum period had ended. Seven women did not have a documented restart of ART at the time of database closure.

Virological outcome

Detectable viremia postpartum was defined as at least one HIV RNA measurement above 50 copies/ml during the postpartum period. On the basis of this definition:

- Detectable HIV RNA was observed in 15% of the 371 pregnancies analysed.
- For the subset of women with documented continued use of ART postpartum, 34 (10%) had an HIV RNA level above 50 copies/ml (median HIV RNA= 171 copies/ml, minimum=52 and maximum=17200 copies/ml), eight of whom had more than one episode of an HIV RNA level above 50 copies/ml during the postpartum period.

In the 39 women who discontinued the use of ART postpartum:

- 21 (54%) experienced viral rebound (median HIV RNA=15,511 copies/ml, minimum 617 and maximum 450000 copies/ml).
- 18 women had an undetectable HIV RNA level, even though they did not restart ART after discontinuing therapy during the postpartum period;
  - Three of these women continued to report high CD4 cell counts and low HIV RNA levels in the absence of ART (all three had previously low HIV RNA levels before starting ART);
  - Six experienced a viral rebound after the postpartum period;
  - Nine remained virally suppressed (six 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 328 of the 371 pregnancies, and was reported in 20 pregnancies (the duration of breastfeeding was not documented). It is noteworthy that all women had documented ART and HIV RNA levels below 100 copies/ml during the postpartum period, and no cases of vertical transmission were documented in any of these breastfeeding women.

Summary and conclusions

All women with a registered pregnancy since 2016 have received 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 0.22% during the period 2016 to 2021, 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 infection 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 these cases, the diagnosis was a result of the national pregnancy screening for HIV, syphilis and hepatitis B. 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 timely screening is only achieved in 76% of all women[20] in the general population. This may be a result of late booking of the first antenatal clinical visit or may be related to taking a single blood sample to test for HIV, HBV and syphilis as well as the NIPT test, at the same time. The latter is performed after the first trimester[20].

Finally, ART has been recommended for all individuals regardless of CD4 cell count since 2015, including postpartum. We observed an increasing proportion of women who received integrase inhibitors during pregnancy as well as during the postpartum period. From 2016 onwards, 10% 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[21,22,23,24,25,26].

The proportion 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%[27]). Other studies have found a high prevalence of caesarean sections in women with undetectable HIV RNA levels[28], or compared to women of the general population[29]. However as invasive perinatal procedures, such as foetal blood sampling or the placement of a foetal scalp electrode, are contraindicated in cases of HIV infection[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[30,31]. 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[32]. The association between various ARVs and adverse pregnancy outcomes, including low birthweight, has been evaluated in different studies, with conflicting results[33].

Recommendations

As a result of changes to guidelines concerning treatment of HIV infection in 2015, ART is more likely to be used at conception and continued post delivery. This is expected to result in a greater number of women with undetectable HIV RNA levels earlier in their pregnancy and around the time of delivery.

Women with HIV who start ART during pregnancy require a high degree of support; not only during the pregnancy itself to ensure suppressed HIV RNA levels at the time of delivery, but also post delivery to maintain adherence to ART, especially if they wish to breastfeed. As an alternative to formula feeding, some hospitals now discuss the option of breastfeeding (for a maximum period of six months) with women who have sustained undetectable viral loads 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[34,35]. In the Netherlands, this monitoring is described in the HIV exposure follow up protocol for newborns[36].

References

1. UNAIDS. *Global report: UNAIDS report on the global AIDS epidemic 2012*. vol. UNAIDS/JC2 (2012).
2. De Cock, K. M. *et al.* Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. *JAMA* **283**, 1175–82 (2000).
3. Coll, O. *et al.* Vertical HIV-1 Transmission Correlates with a High Maternal Viral Load at Delivery. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirology* **14**, 26–30 (1997).
4. Boer, K. *et al.* The AmRo study: pregnancy outcome in HIV-1-infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. *BJOG An Int. J. Obstet. Gynaecol.* **114**, 148–155 (2007).
5. Cooper, E. R. *et al.* Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J. Acquir. Immune Defic. Syndr.* **29**, 484–94 (2002).
6. DHHS. Perinatal, Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Transmission: Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1- Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in th. *August 6, 2015* http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. (2015).
7. Mulder-Folkerts, D. K. F. *et al.* [Less refusal to participate in HIV screening among pregnant women in the Amsterdam region since the introduction of standard HIV screening using the opting-out method]. *Ned. Tijdschr. Geneeskd.* **148**, 2035–2037 (2004).
8. van Sighem, A. I. *et al. Monitoring Report 2019. Human Immunodeficiency Virus (HIV) Infection in the Netherlands*. https://www.hiv-monitoring.nl/nl/resources/monitoring-report-2019 (2019).
9. Heffron, R. *et al.* A prospective study of the effect of pregnancy on CD4 counts and plasma HIV-1 RNA concentrations of antiretroviral-naive HIV-1-infected women. *J. Acquir. Immune Defic. Syndr.* **65**, 231–6 (2014).
10. Rowland, B. L., Vermillion, S. T. & Soper, D. E. Scheduled cesarean delivery and the prevention of human immunodeficiency virus transmission: A survey of practicing obstetricians. *Am. J. Obstet. Gynecol.* **185**, 327–331 (2001).
11. Stringer, J. S., Rouse, D. J. & Goldenberg, R. L. Prophylactic cesarean delivery for the prevention of perinatal human immunodeficiency virus transmission: the case for restraint. *JAMA* **281**, 1946–1949 (1999).
12. European Aids Clinical Society. Guidelines. Version 10.0, November 2019. (2019).
13. Nederlandse Vereniging van HIV Behandelaren. Richtlijn HIV. http://richtlijnhiv.nvhb.nl/ (2017).

14. Panel on treatment of pregnant women with HIV infection and prevention of perinatal transmission. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new-guidelines (2021).
15. Boyd, S. D. *et al.* Cobicistat-containing antiretroviral regimens are not recommended during pregnancy. *AIDS* **33**, 1089–1093 (2019).
16. Townsend, C. L. *et al.* Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS* **22**, 973–81 (2008).
17. Warszawski, J. *et al.* Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS* **22**, 289–99 (2008).
18. Prieto, L. M. *et al.* Low rates of mother-to-child transmission of HIV-1 and risk factors for infection in Spain: 2000-2007. *Pediatr. Infect. Dis. J.* **31**, 1053–8 (2012).
19. Mandelbrot, L. *et al.* No Perinatal HIV-1 Transmission From Women With Effective Antiretroviral Therapy Starting Before Conception. *Clin. Infect. Dis.* civ578 (2015) doi:10.1093/cid/civ578.
20. Rivm. *Prenatale Screening Infectieziekten en Erytrocyten-immunisatie (PSIE) 2019*.
21. Laine, C. *et al.* Adherence to antiretroviral therapy by pregnant women infected with human immunodeficiency virus: a pharmacy claims-based analysis. *Obstet. Gynecol.* **95**, 167–173 (2000).
22. Ickovics, J. R. *et al.* Prenatal and Postpartum Zidovudine Adherence Among Pregnant Women with HIV Results of a MEMS Substudy from the Perinatal Guidelines Evaluation Project. *J. Acquir. Immune Defic. Syndr.* **30**, 311–315 (2002).
23. Bardeguez, A. D. *et al.* Adherence to antiretrovirals among US women during and after pregnancy. *J. Acquir. Immune Defic. Syndr.* **48**, 408–17 (2008).
24. Mellins, C. a *et al.* Adherence to antiretroviral treatment among pregnant and postpartum HIV-infected women. *AIDS Care* **20**, 958–968 (2008).
25. Rana, A. I., Gillani, F. S., Flanigan, T. P., Nash, B. T. & Beckwith, C. G. Follow-up care among HIV-infected pregnant women in Mississippi. *J. Women's Heal.* **19**, 1863–7 (2010).
26. Huntington, S. *et al.* The risk of viral rebound in the year after delivery in women remaining on antiretroviral therapy. *AIDS* **29**, 2269–2278 (2015).
27. Perined | Home. https://www.perined.nl/.
28. Aebi-Popp, K. *et al.* Missed opportunities among HIV-positive women to control viral replication during pregnancy and to have a vaginal delivery. *J. Acquir. Immune Defic. Syndr.* **64**, 58–65 (2013).

29. Ørbaek, M. *et al.* Assessment of mode of delivery and predictors of emergency caesarean section among women living with HIV in a matched-pair setting with women from the general population in Denmark, 2002À2014. (2017) doi:10.1111/hiv.12519.
30. O'Brien, B. E. *et al.* Repeat Pregnancies Among US Women Living With HIV in the SMARTT Study: Temporal Changes in HIV Disease Status and Predictors of Preterm Birth. *J. Acquir. Immune Defic. Syndr.* **85**, 346–354 (2020).
31. Uthman, O. A. *et al.* Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis. *lancet. HIV* **4**, e21–e30 (2017).
32. Klumper, J., Ravelli, A. C. J., Roos, C., Abu-Hanna, A. & Oudijk, M. A. Deprived neighborhoods and spontaneous preterm birth: A national cohort study. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **274**, 88–95 (2022).
33. Saleska, J. L., Turner, A. N., Maierhofer, C., Clark, J. & Kwiek, J. J. Use of Antiretroviral Therapy During Pregnancy and Adverse Birth Outcomes Among Women Living With HIV-1 in Low- and Middle-Income Countries: A Systematic Review. *J. Acquir. Immune Defic. Syndr.* **79**, 1–9 (2018).
34. European Aids Clinical Society. No Title. http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf (2018).
35. Kahlert Christian, R. *et al.* Is breastfeeding an equipoise option in effectively treated HIV-infected mothers in a high-income setting? *Swiss Med. Wkly.* **148**, (2018).
36. PHON. *Update landelijk HIV expositie protocol neonaten, inclusief follow-up pasgeborene en kind*. (2019).

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.

HIV treatment guidelines are not only intended to help healthcare providers provide optimal care, but also to reduce the variation in care between different treatment centres. The Dutch Association of HIV-Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) has issued national guidelines for the treatment and monitoring of people living with HIV in the Netherlands[1]. In general, these guidelines follow the United States Department of Health and Human Services (DHHS) HIV/AIDS practice guidelines[1]. Using these guidelines as a basis, we defined a set of indicators that have been used in this analysis to explore the quality of care in Dutch HIV treatment centres, and provide insight into any potential variation between centres.

Our analysis is based on the data of individuals who were diagnosed with HIV, entered care and were registered with the SHM (*Box 7.1*). The indicators selected for this analysis fall into three categories: volume; outcome; or process. Each category contains a host of specific indicators, which are applicable to different focus populations. The details of the indicators used in this chapter, along with the focus populations to which they were applied, are defined in *Box 7.2*. Indicators are 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 used in this chapter.

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 living 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 living 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.
Patient	An individual living with HIV who is receiving, or has received, medical care at an HIV treatment centre. This term is specifically used in this chapter to denote the role of the individual in a medical context.

Box 7.2: Definitions of specific indicators and focus populations.

Specific indicator	Definition	Focus population
Volume indicator		
Newly entering care	The number of patients who entered care at one of the Dutch HIV treatment centres for the first time.	Entered care
Outcome indicators		
Retention in care		
Short-term retention	The percentage of patients who were still in care at least 18 months after entering care.	Entered care[1]
Overall retention	The percentage of all patients who had a documented clinical visit.	In care
Initiation of ART		
Early ART initiation	The percentage of patients who initiated ART within six months of entry into care.	Entered care[2]
Overall ART initiation	The percentage of patients who have initiated ART.	In care

Specific indicator	Definition	Focus population
Viral suppression		
Suppression after ART initiation	The percentage of patients with a plasma HIV RNA level <400 copies/ml within nine months of ART initiation.	Starting ART[3]
Suppression while on ART	The percentage of patients with a plasma HIV RNA level <100 copies/ml.	On ART[4]
Suppression while in care	The percentage of patients with a plasma HIV RNA level <100 copies/ml.	In care
Process indicators		
Lab measurements prior to ART	The percentage of patients for whom data were available on plasma HIV RNA or CD4 count within the six months prior to, or the one month following ART initiation.	Starting ART[3]
Lab measurements while in care	The percentage of patients for whom data were available on plasma HIV RNA or CD4 count.	In care

All indicators are reported within a given year.

Abbreviations: ART = (combination) antiretroviral therapy.

[1] This indicator is calculated for patients who entered care in the two years prior to a given year. It does not include individuals who moved abroad or died.

[2] Entered care and did not move abroad or die.

[3] Treatment-naive people who started ART in a given calendar year.

[4] On ART for at least six months and still in care in a given calendar year.

Volume indicator

As a volume indicator we quantified the number of patients *newly entering care* each year per treatment centre.

Outcome indicators

The outcome indicators include *retention in care*, *initiation of ART* and achievement of *viral suppression*.

For the purpose of the current analysis, we have defined short-term and overall retention in care as follows:

1. *Short-term retention in care*: The percentage of patients who entered care for the first time at one of the Dutch HIV treatment centres, after being diagnosed with HIV, who were still alive and in care at least 18 months after entering care. Patients known to have died or moved abroad were excluded from this retention-in-care indicator. Approximately 11% and 11% of patients who entered care in 2017 and 2018, respectively, switched treatment centres (mainly due to the closure of two treatment centres in 2018); we considered these to be retained in care, since they were not lost to follow up. However, to avoid double counting, they were assigned to their most recent treatment centre.
2. *Overall retention in care*: The percentage of all patients in care who did not move abroad or die, *and* had a documented clinical visit for a given year. Again, patients switching treatment centres were considered to be retained in care and were assigned to their most recent treatment centre.

Initiation of ART describes: (i) the patients entering care who started ART within six months of entry; and (ii) the percentage of patients still in care who have ever initiated ART.

Viral suppression was assessed by three indicators:

1. The percentage of treatment-naive patients, who started ART, with a plasma HIV RNA level below 400 copies/ml within nine months of starting ART;
2. The percentage of all patients on ART for at least six months who had a plasma HIV RNA level below 100 copies/ml; and
3. The percentage of all patients in care who had a last available HIV RNA level below 100 copies/ml.

Process indicators

Process indicators were calculated for two scenarios: (i) prior to starting ART and (ii) while in care.

To calculate indicators *prior to ART initiation,* we included all patients who had newly entered care in a given year. Patients who switched treatment centres were not counted as newly entering care, as they had already been in care elsewhere. Two separate indicators were defined as the percentage of individuals initiating ART for whom (i) plasma HIV RNA or (ii) CD4 count measurements were available in the six months prior to, or the one month following ART initiation. This period was selected as some patients may have initiated ART directly after entering care, in which case HIV RNA or CD4 count measurements will have been measured on the same day or directly after ART initiation.

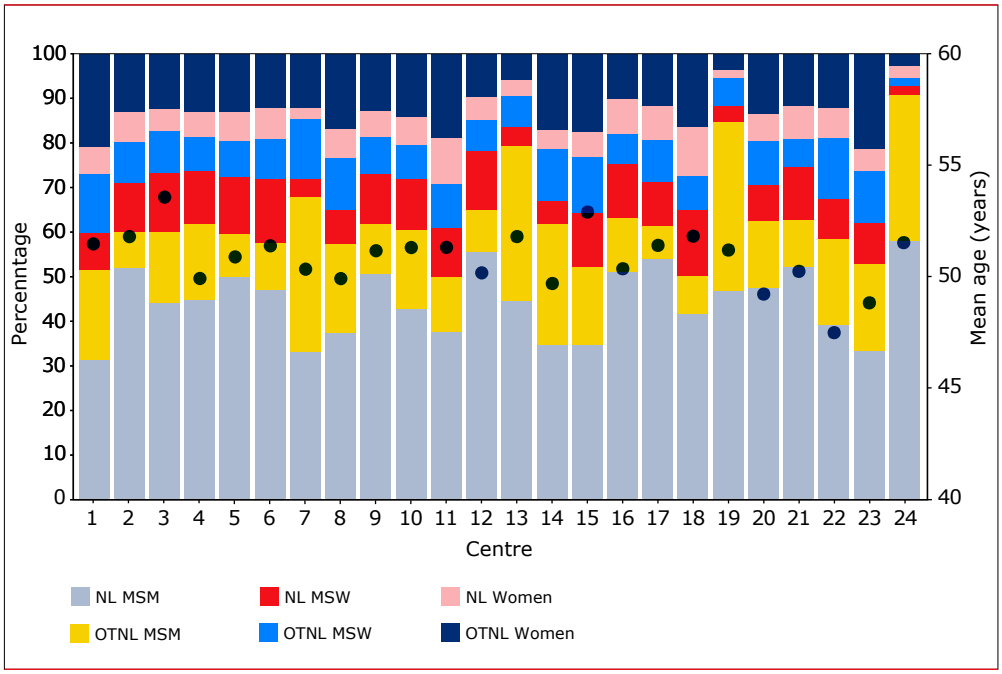
To calculate indicators *while in care*, we included all individuals who were in care and did not move abroad or die. Two separate indicators were defined as the percentage of patients in care for whom (i) plasma HIV RNA or (ii) CD4 count measurements were recorded at least once during a given calendar year.

Centre overview

The characteristics of patients in care in 2021 are described per HIV treatment centre in *Figure 7.1* (i.e., patient 'mix'). Overall, the mean within-centre age range was 47 to 54 years (median 51 years). The largest geographical origin/mode of transmission/gender group observed for almost all centres was Dutch men who have sex with men (MSM), ranging from 32% to 58% (median 45%) of patients per centre. Most individuals in the 'other than Dutch' groups originated from the Caribbean/South America (30%), sub-Saharan Africa (28%), other countries in Europe (12%), or southeast Asia (9%). The distribution of regions of birth for patients other than Dutch in care in 2021 are described per centre in *Appendix Figure 7.A*. There was substantial variation across centres in the other geographical origin/mode of transmission/gender groups:

- Other than Dutch MSM (median 17%, range 7-38%)
- Dutch men who exclusively have sex with women (MSW) (median 11%, range 2–15%)
- Other than Dutch MSW (median 9%, range 2–14%)
- Dutch women (median 6%, range 2–11%)
- Other than Dutch women (median 13%, range 2–21%).

Figure 7.1: Description of the patient 'mix' for patients in care in 2021 in the Netherlands.



***Note:** The bars in this chart show the percentage of individuals per centre according to geographical origin/ mode of transmission/gender group. Black dots represent the mean age of patients in care at each centre.*
***Legend:** MSM = men who have sex with men; MSW = men who exclusively have sex with women; NL = Dutch; OTNL = other than Dutch.*

Evolution of indicators over time

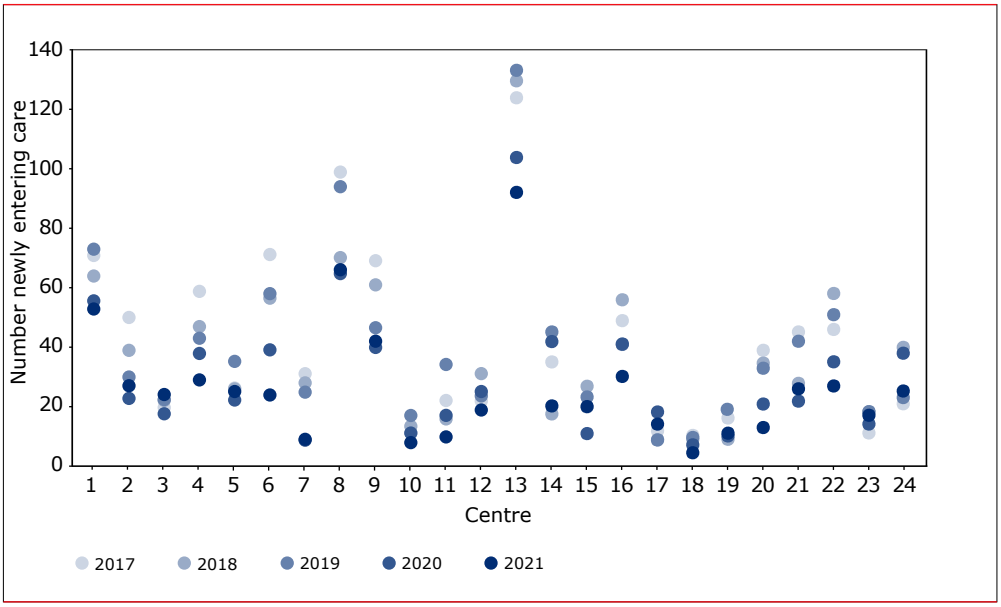
HIV testing and treatment guidelines have remained unchanged in the Netherlands since 2015. The distribution of patient 'mix' in care has also remained relatively stable over the past five years. As a result, increases in the percent of the indicators over time are likely to indicate organisational improvement in providing care to patients living with HIV, while decreases might indicate potential issues that require further assessment. To provide an understanding of how indicators have evolved, each indicator in *Box 7.2* has been reported for its corresponding focus population on an annual basis between 2017 and 2021. For example, the indicator 'overall ART initiation' has been provided for individuals who were in care in 2017, 2018, 2019, 2020, and 2021.

The first case of severe acute respiratory syndrome coronavirus 2, which causes the disease known as COVID-19, was detected in the Netherlands on 27 February 2020[2]. The rapidly evolving SARS-CoV-2 pandemic forced HIV treatment centres to reorganise their services at the end of March 2020. Visits that usually took place physically at the HIV treatment centres were, for the most part, replaced with other types of consultations, such as virtual consultations via a web camera or telephone, and blood had to be drawn at other locations. These reduced services continued during more severe epidemic waves of SARS-CoV-2 in 2020 and 2021, and may have affected many of the indicators for quality of care. Particular attention has thus been given to the changes in indicators between 2019 and 2021.

Volume indicator

The numbers of patients who newly entered care across the HIV treatment centres each year are shown in *Figure 7.2*; this number has steadily decreased for most centres over the past five years. The median number who newly entered care across centres was 23 in 2020 and 24 in 2021, with a minimum number of seven patients in 2020 and three in 2021. In 2021, nine HIV treatment centres had fewer than 20 patients newly entering care; all of these were of small patient size (i.e., fewer than 400 in care).

Figure 7.2: *Annual number of patients newly entering care per HIV treatment centre in the Netherlands between 2017 and 2021.*



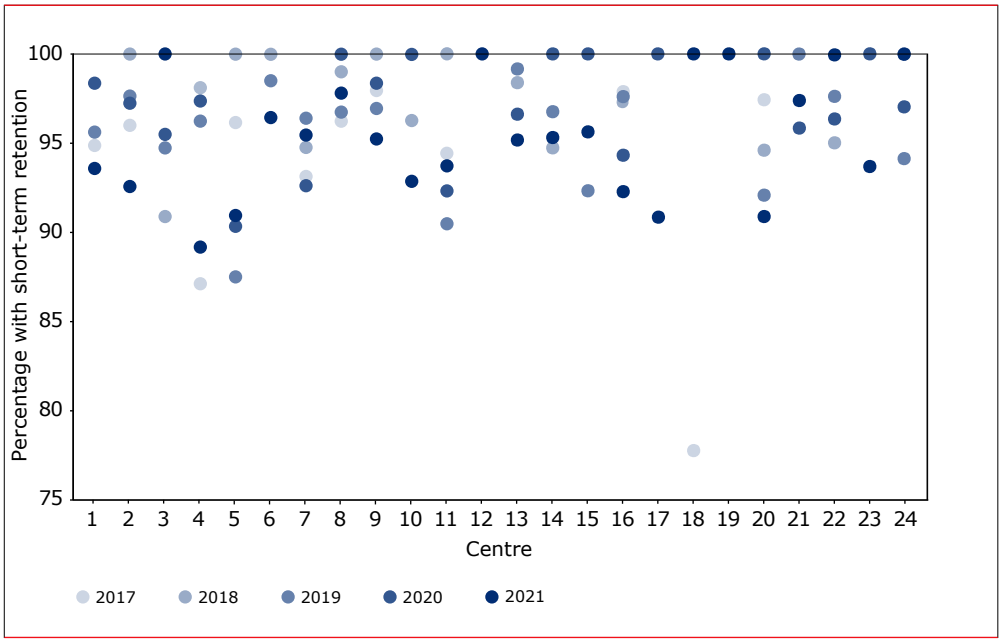
Legend: *Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

Outcome indicators

Retention in care

The annual percentage of patients with short-term retention has remained stable over the past five years and can be viewed per centre in *Figure 7.3*. The median percentage across centres was 98% (range 90–100%) in 2020, for patients entering care in 2018, and 95% (range 89–100%) in 2021, for those entering care in 2019. For most centres, the difference between 2021 and 2019 was within a margin of ±2%. A decrease of more than 5% was observed in five centres, all of which were of small patient size and thus more susceptible to having larger differences in percentages.

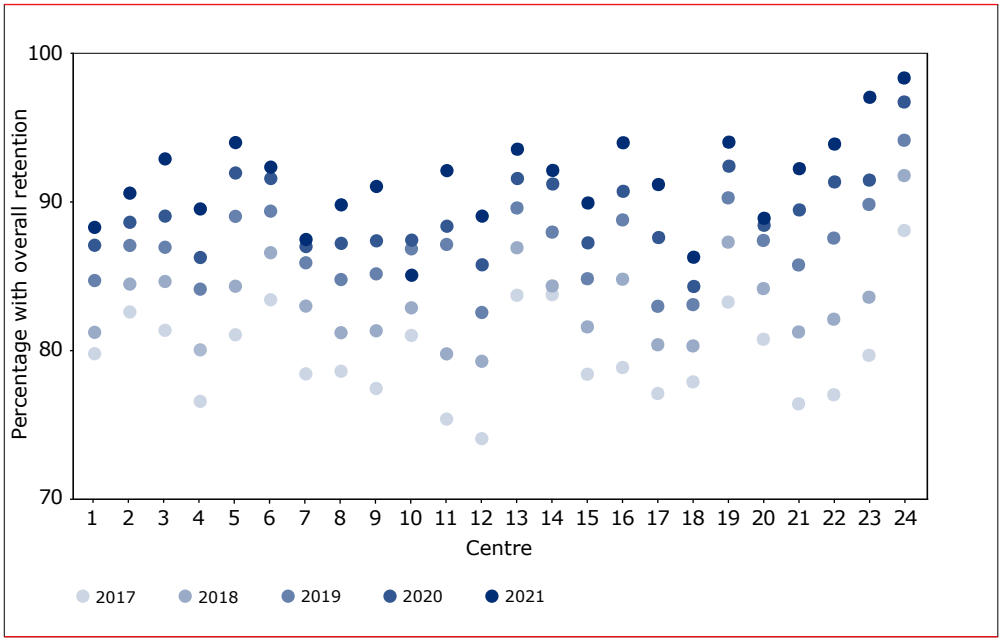
Figure 7.3: *Short-term retention in care; in other words, patients who entered care two years prior to 2017, 2018, 2019, 2020, or 2021, and were still in care 18 months later.*



Legend: *Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

The annual percentage of patients per centre with overall retention is given in *Figure 7.4*. This percentage has steadily increased for most centres over the past five years. The median increase from 2017 to 2021 across centres was 11% (range 4–17). It is worth noting that the median percentage with overall retention across centres was 89% (range 84–97%) in 2020 and 92% (range 85–98%) in 2021. No centre experienced a decrease of more than 2% between 2019 and 2021.

Figure 7.4: *Overall retention in care; in other words, patients in care who had a documented visit per calendar year between 2017 and 2021.*



Legend: *Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

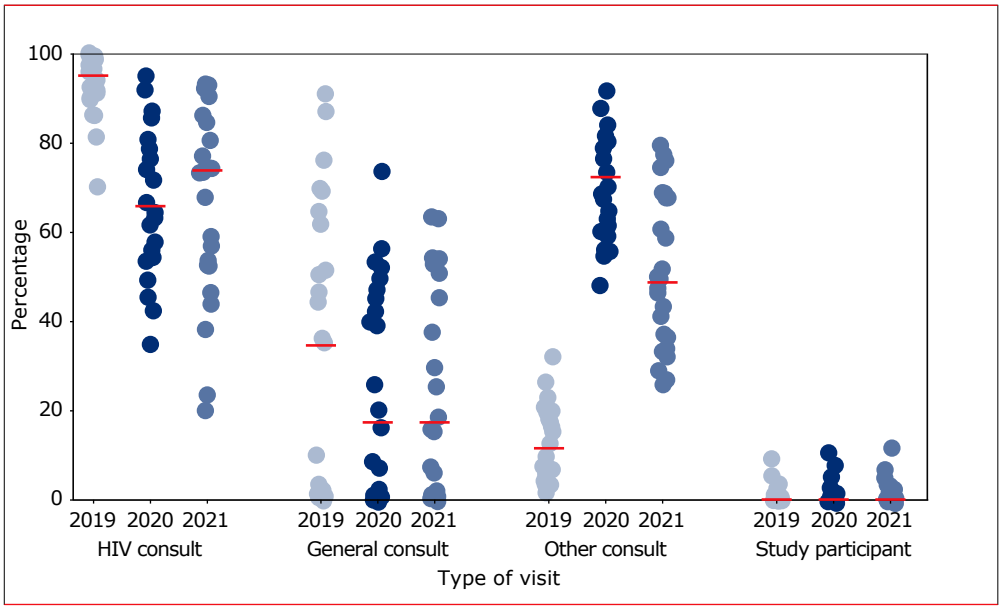
Overall retention is defined by whether a visit occurred during a given year. Since services at many of the HIV treatment centres were greatly reduced during the COVID-19 pandemic, alternative consultation options were required. *Figure 7.5* illustrates the change in visit types between 2019 and 2021 for those in care.

The median percentage of patients who had a physical consultation with an HIV specialist during the year decreased from 99% (range 97–100%) in 2019 to 80% (range 54–96%) in 2020 and remained comparable at 82% (range 48–95%) in 2021.

Similarly, the median percentage of patients who had a physical consultation with another specialist, consultant, or nurse consultant/specialist decreased from 35% (range 0–91%) in 2019 to 18% (range 0–74%) in 2020 and remained comparable at 17% (range 1–65%) in 2021.

In contrast, the percentage of patients who had a non-physical consultation with any type of healthcare professional increased from a median 12% (range 2–32%) in 2019 to 72% (range 47–91%) in 2020 and slightly decreased to 49% (range 25–81%) in 2021. Most of these consultations in 2021 occurred over the telephone or via email (97%) and few occurred virtually using video consultation (3%) or other means (3%). The proportion of patients who had a consultation as part of participating in a study remained comparable between 2019 and 2021. It should be noted that patients could have had more than one type of visit during the year and hence these percentages are not mutually exclusive.

Figure 7.5: *Distribution of visit types for patients in care between 2019 and 2021.*



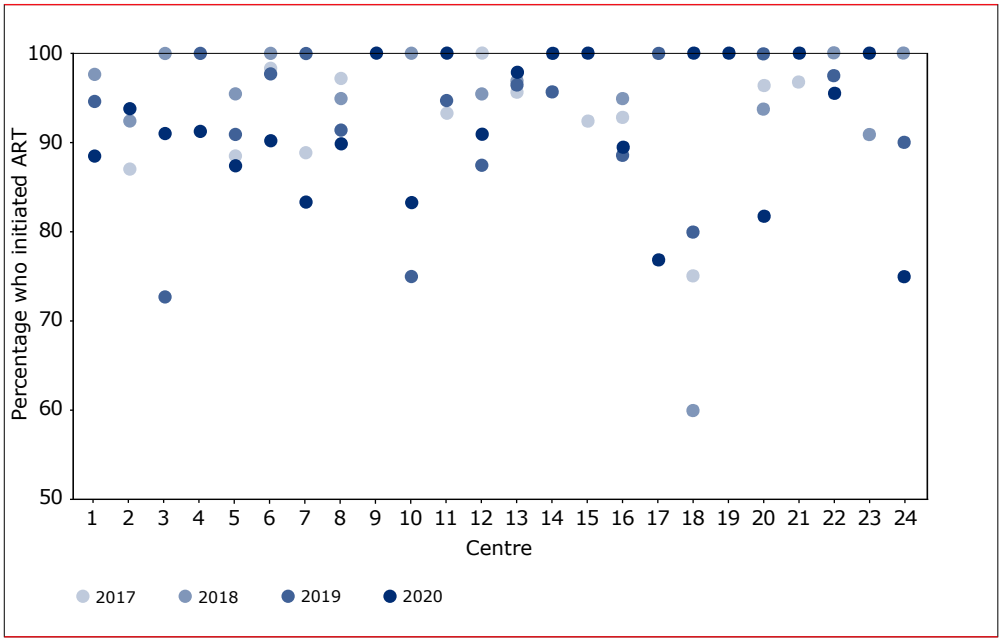
Legend: *"HIV consult" refers to a physical consultation with an HIV specialist. "General consult" refers to a physical consultation with another specialist, consultant, or nurse. "Other consult" refers to a consultation with any type of healthcare professional, which replaced what would have been a physical consultation. "Study participant" refers to a visit as part of participating in a biomedical study.*

Initiation of ART

The annual percentage of patients per centre who started ART within six months of entering care is given in *Figure 7.6*. This percentage varied only slightly at most centres over calendar years. Across centres, the median percentage was 96% (range 73–100%) in 2019 and 91% (range 75–100%) in 2020. Eight centres had a percentage lower than 90%, of which seven were small patient size and one was large patient size (i.e., more than 700 in care).

For individuals who started ART, the time between entering care in 2020 to starting their treatment, averaged within centres, was a median 13 days (range 3–35). No data are given for 2021 as there has not been enough follow-up time to calculate this indicator for patients who entered care in the latter half of 2021.

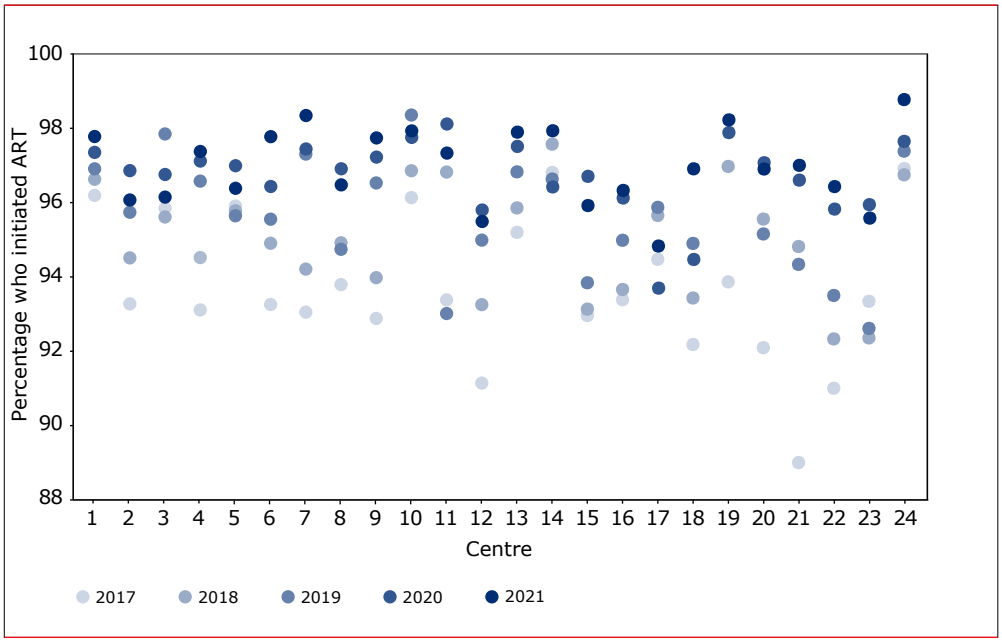
Figure 7.6: *The annual percentage of patients entering care between 2017 and 2020 who started combination antiretroviral therapy (ART) within six months of entry.*



Legend: *Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

The annual percentage of patients per centre remaining in care who ever initiated ART is given in *Figure 7.7*. This percentage has been steadily increasing for most centres over the past five years. The vast majority of patients in care in 2020 and 2021 initiated ART (across-centre median 97% and 97%, respectively). This figure reached or exceeded 95% in all centres in 2021.

Figure 7.7: *The annual percentage of patients in care between 2017 and 2021 who ever initiated combination antiretroviral therapy (ART).*



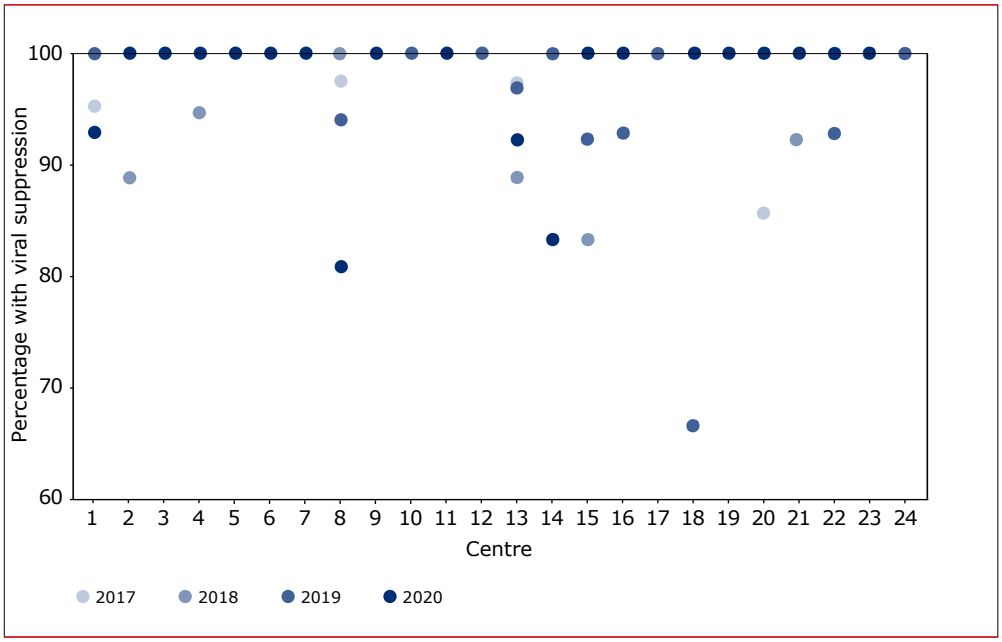
Legend: *Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

Viral suppression

Viral suppression was assessed using three indicators. The *first* of these is the percentage of treatment-naive patients newly initiating treatment who had an HIV RNA level below 100 copies/ml within nine months of starting ART. The annual percentage per centre is given in *Figure 7.8*, which shows consistently high proportions at most centres for individuals initiating ART between 2017 and 2020. The median percentage with viral suppression after ART initiation was 100% (range 93–100%) in 2019 and 100% (range 81–100%) in 2020; three centres with fewer than three patients were excluded from the calculation in both

2019 and 2020. No data are given for 2021 as there has not been enough follow-up time to calculate this indicator for patients who initiated ART in the latter half of 2021.

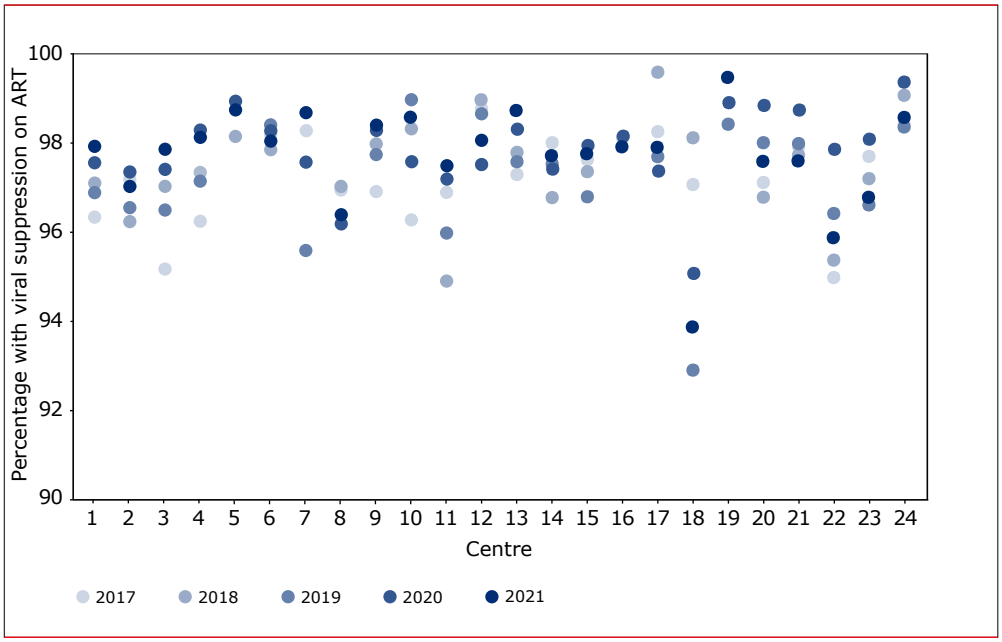
Figure 7.8: *The annual percentage of all patients who initiated combination antiretroviral therapy (ART) and stayed on it at least six months between 2017 and 2020, and who had an HIV RNA level <100 copies/ml within nine months of initiating treatment.*



Legend: *Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1. Three centres were excluded – three in 2019 (centres 11, 18, and 19) and three in 2020 (centre 12, 17, and 24) – as they had fewer than three patients included in the indicator.*

The *second* viral suppression indicator is the percentage of all patients in care who have been on ART for at least six months and have a last available HIV RNA level below 100 copies/ml. This annual percentage is given per centre in *Figure 7.9*, which shows rather high percentages with little variation over the past five years. The median percentage was 98% (range 95–99%) in 2020 and 98% (range 94–99%) in 2021.

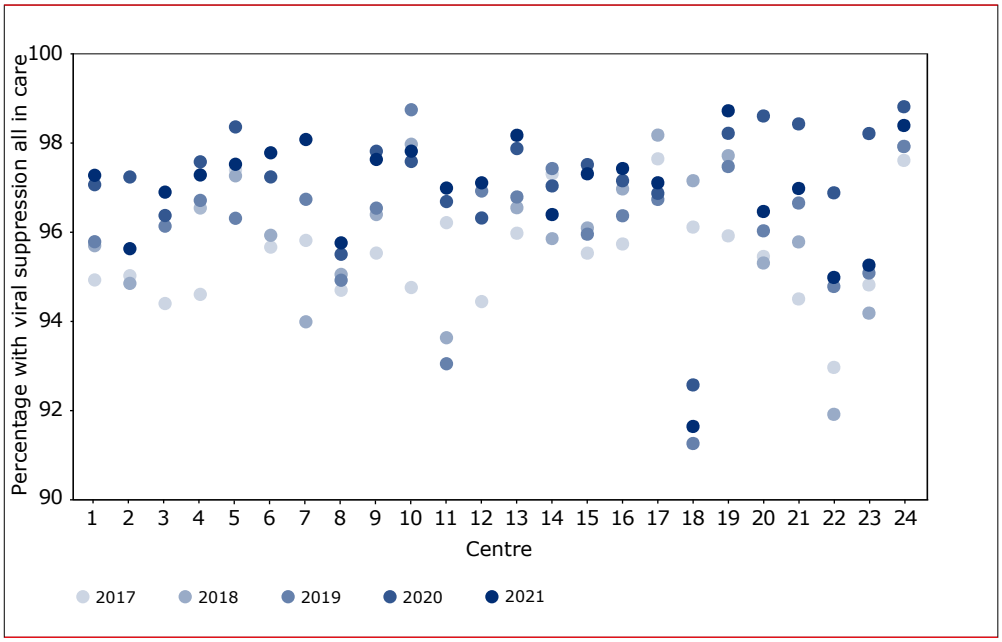
Figure 7.9: *The annual percentage of all patients on combination antiretroviral therapy (ART) for at least six months between 2017 and 2021 who had an HIV RNA level <100 copies/ml.*



Legend: *Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

The *third* viral suppression indicator is the percentage of all patients in care between 2017 and 2021 whose last available HIV RNA level was below 100 copies/ml (the percentage without HIV RNA measurements was 1.4% in 2017, 1.2% in 2018, 1.1% in 2019, 3.0% in 2020, and 2.2% in 2021). This annual percentage per centre is given in *Figure 7.10*, which again shows relatively high percentages of this indicator with little variation over the past five years. The median percentage was 97% (range 93–99%) in 2020 and 97% (range 92–99%) in 2021.

Figure 7.10: The annual percentage of all patients in care between 2017 and 2021 who had an HIV RNA level <100 copies/ml.



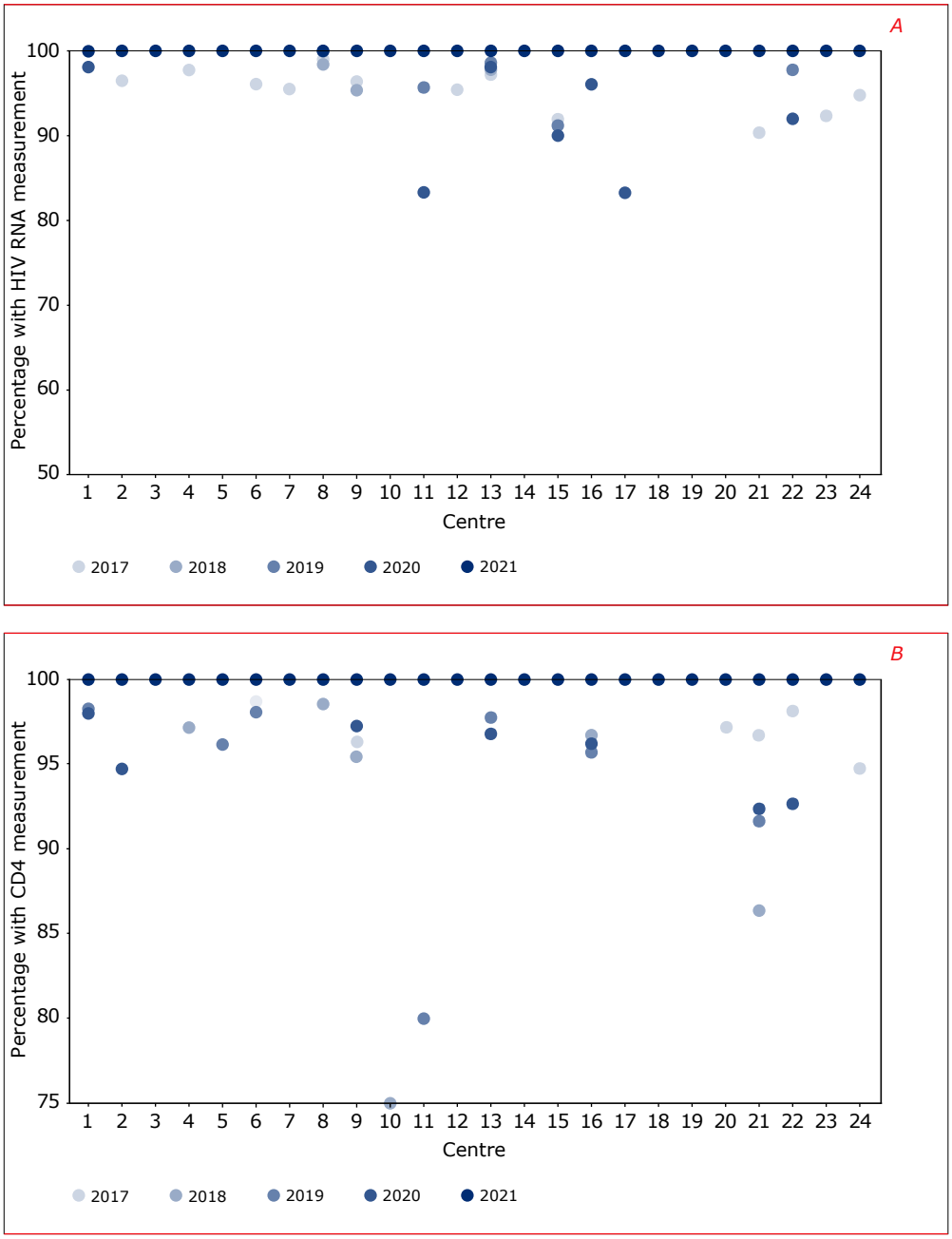
Legend: Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.

Process indicators

Prior to starting ART

Process indicators were evaluated in treatment-naïve patients who newly started ART. The annual percentages of patients who were tested for plasma HIV RNA or CD4 cell count within the six months prior to, or the one month following ART initiation are given per centre in *Figure 7.11A* (for plasma HIV RNA) and *Figure 7.11B* (for CD4 cell count). These percentages have been above 95% for most centres over the past five years. The median percentages tested for plasma HIV RNA were 100% (range 83–100%) in 2020 and 100% (range 100–100%) in 2021, and the median percentages tested for CD4 cell count were 100% (range 80–100%) in 2020 and 100% (range 100–100%) in 2021. For most centres, there were no differences in percentages between 2021 and 2019.

Figure 7.11: *The annual percentage of patients newly initiating combination antiretroviral therapy (ART) between 2017 and 2021 who had (A) a measurement of plasma HIV RNA or (B) CD4 cell count within the six months prior to initiating ART, or the one month following ART initiation.*

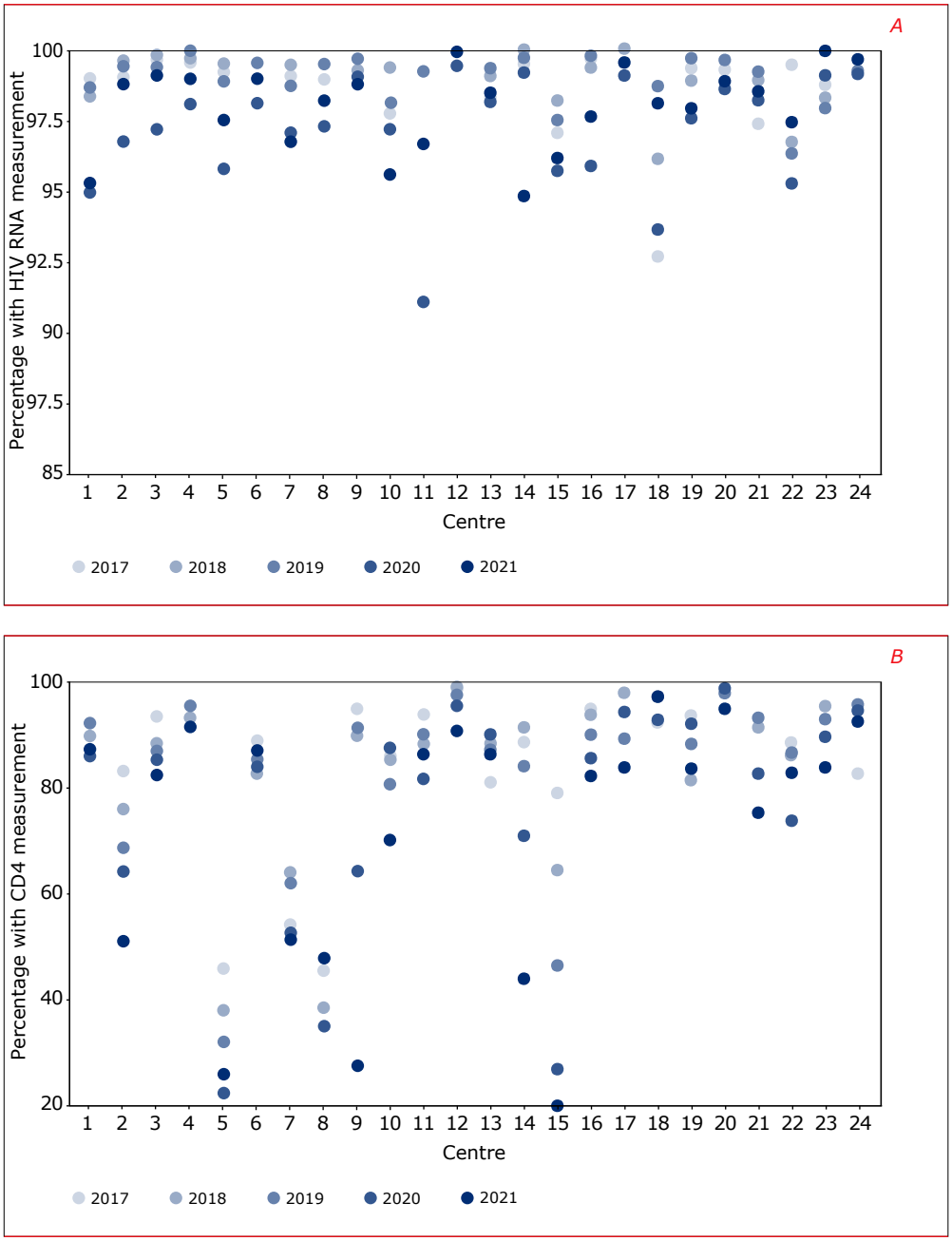


Legend: *Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

While in care

Process indicators were also evaluated for all patients who were in care. The annual percentages of patients who were tested for plasma HIV RNA or CD4 cell count while in care are given per centre in *Figure 7.12A* (for plasma HIV RNA) and *Figure 7.12B* (for CD4 cell count). These percentages have varied widely for some centres over the past five years, particularly in relation to CD4 cell count testing. The median percentages tested for plasma HIV RNA were 98% (range 91–99%) in 2020 and 98% (range 95–100%) in 2021, and the percentages tested for CD4 cell count were 86% (range 23–99%) in 2020 and 83% (range 19–98%) in 2021. For almost all centres, the percentages between 2021 and 2019 were comparable.

Figure 7.12: *The annual percentage of all patients in care between 2017 and 2021 who had (A) a measurement of plasma HIV RNA or (B) CD4 cell count.*



Legend: *Data points from multiple years can overlap with one another. Centre numbers correspond to those used in Figure 7.1.*

Centre performance

As reported in earlier studies, both the number of patients in care (i.e., the centre 'volume'), and the patient characteristics of a given centre (i.e., the patient 'mix'), may have an impact on the reported indicators[3,4,5,6].

Regarding centre volume, a smaller number of patients in an HIV treatment centre increases the chance that an indicator is more variable. When this occurs, it is difficult to distinguish whether a low-level indicator is the result of performing below expectations or having excessive variation. For this reason, we compare each centre's indicator to the national average and provide statistical guidance as to whether a given centre falls below the national average. This assessment depends on the number of patients included when calculating the indicator (an overview of this method is provided in *Box 7.3*). Given that statistical interpretation is unreliable when centre sizes are small, indicators whose focus population contains more than 40 patients have been considered in this analysis.

Regarding patient mix, individual-level factors, such as age and mode of transmission, are known to be associated with several indicators. If performance indicators are different across centres, it could be that the variation in the characteristics of patients attending those centres is driving these differences. We have therefore adjusted all indicators by year of birth and geographical origin/mode of transmission/gender (*Box 7.3*).

For this section, the indicators that we have used (defined in *Box 7.2*), while accounting for the issues described above, are:

- Overall retention for patients in care;
- Overall ART initiation for patients in care;
- Viral suppression while on ART and while in care; and
- HIV RNA and CD4 cell counts while in care.

Only indicators from 2021 were considered in this analysis.

Box 7.3: Funnel plots to compare centres to the national average.

What types of problems occur when evaluating indicators?	
Centres having 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).

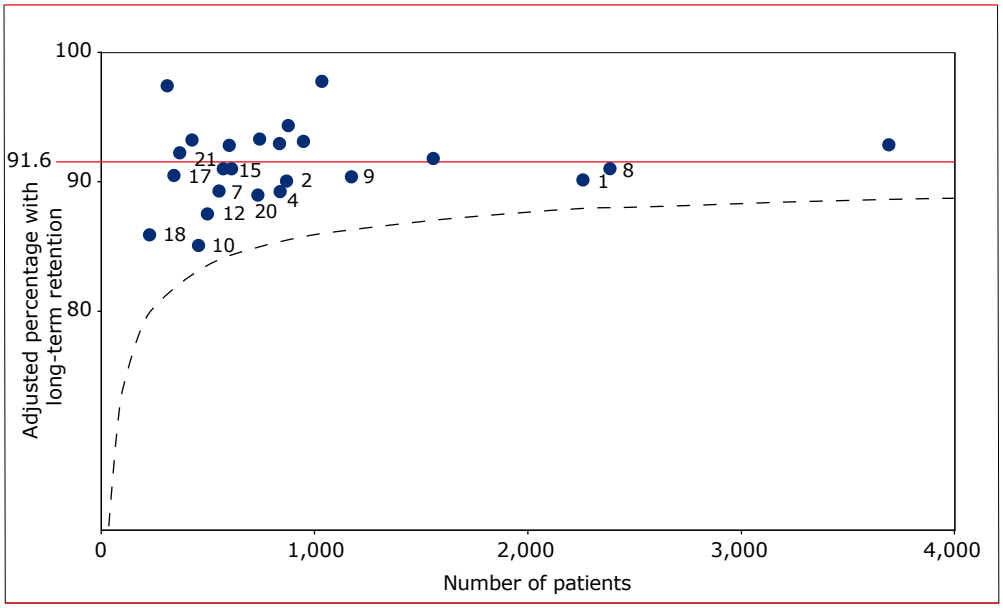
What is a funnel plot? A funnel plot is a graphical depiction that allows us to compare a centre's indicator to the national average. It can help account for the problems listed above. The following are key components of this plot:	
Patient size	The x-axis depicts the number of patients considered in a given indicator. For example, this number could be the total number of patients in care in 2021, etc.
Adjusted %	The y-axis depicts the percentage of patients who have achieved a given indicator. This indicator is adjusted for patient mix.
Centre's indicator	Dots depict each centre's indicator (adjusted %), which are plotted with respect to the number of patients included in the calculation of the indicator.
Comparison to the national average	A solid line depicts the national average. We can create boundaries that indicate (i) the highest indicator level a centre should achieve based on what we statistically expect from the national average ("upper" boundary), or (ii) the lowest indicator level a centre should achieve based on what we statistically expect from the national average ("lower" boundary). These boundaries make the form of a "funnel". The calculation of these boundaries is based on a statistical difference (±2 standard deviations) from the national average.
How is a funnel plot interpreted?	
When is an indicator lower than the national average?	If the centre's indicator falls below the "lower" boundary, then the centre has a lower-than-expected indicator compared to the national average.
When is an indicator higher than the national average?	This question will not be answered in this SHM report. The indicators will be high (ranging from 80-99%), making the "upper" boundary difficult to interpret. We will only provide the "lower" boundary.

Outcome indicators

Overall retention in care

Figure 7.13 shows the adjusted percentage of patients in care in 2021 with overall retention in care per centre. The median adjusted percentage across centres was 91% (range 85–98%). All centres had adjusted percentages of overall retention within the expected range, when compared to the national level.

Figure 7.13: *Overall retention in care; in other words, patients in care who had a documented visit in 2021. The percentage with overall retention in care has been adjusted for patient mix and is plotted as a function of the number of patients who entered care.*

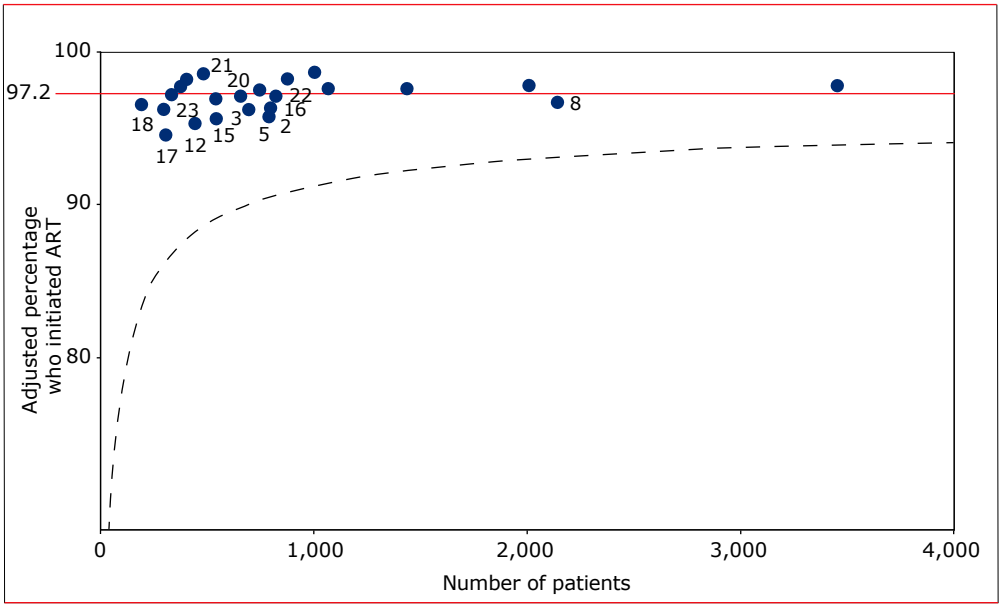


Legend: *Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The "lower" boundary of expected percentage retained in care (as compared to the national average) is indicated with a dashed line (Box 7.3).*

Overall initiation of ART in care

Figure 7.14 shows, per centre, the adjusted percentage of patients in care in 2021 who had ever initiated ART. The median adjusted percentage across centres was 97% (range 95–99%). All centres had adjusted percentages of overall ART initiation within the expected range, when compared to the national level.

Figure 7.14: The percentage of patients in care in 2021 who ever initiated combination antiretroviral therapy (ART). The percentage of overall ART initiation has been adjusted for patient mix and is plotted as a function of the number of patients still in care in 2021.

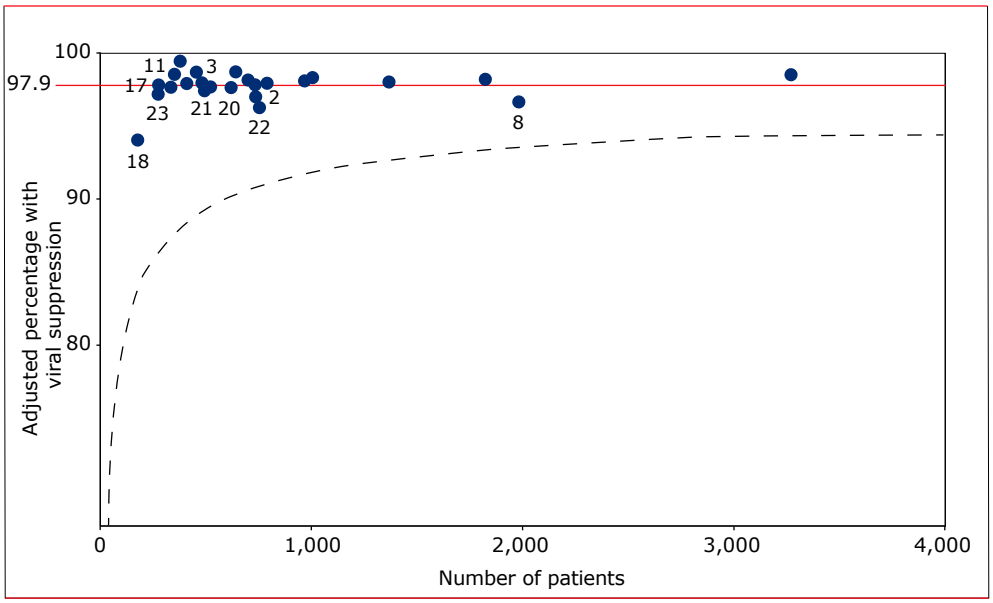


Legend: Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The "lower" boundary of expected percentage initiating ART (as compared to the national average) is indicated with a dashed line (Box 7.3).

Viral suppression

Figure 7.15 shows, per treatment centre, the adjusted percentage of patients on ART in 2021 who had a plasma HIV RNA viral load below 100 copies/ml (i.e., viral suppression while on ART). It illustrates the limited variation across centres of different patient volume in 2021. The median adjusted percentage across centres was 98% (range 94–99%). All centres had adjusted percentages within the expected range when compared to the national level.

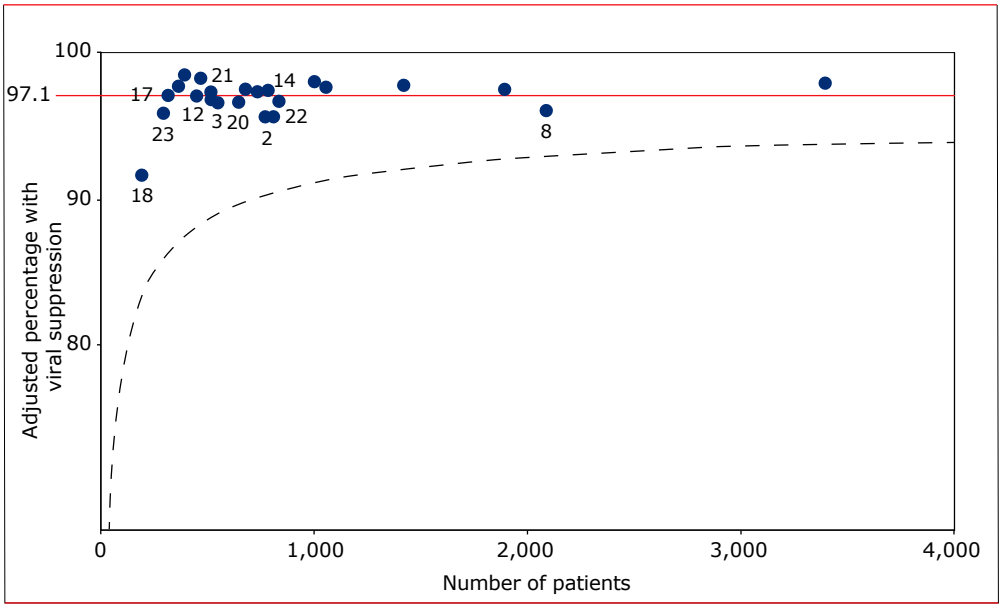
Figure 7.15: *The percentage of all patients on combination antiretroviral therapy (ART) for at least six months in 2021 who had an HIV RNA level <100 copies/ml. The percentage of individuals with viral suppression has been adjusted for patient mix and is plotted as a function of the number of patients in care in 2021 who had been on ART for at least six months.*



Legend: *Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The "lower" boundary of expected percentage with viral suppression (as compared to the national average) is indicated with a dashed line (Box 7.3).*

Figure 7.16 shows, per treatment centre, the adjusted percentage of patients in care in 2021 who had a plasma HIV RNA viral load below 100 copies/ml (i.e., viral suppression while in care). The median adjusted percentage across centres was 97% (range 92–99%), with slightly more variation across centres of different patient volume than for the indicator 'viral suppression while on ART'. All centres had adjusted percentages within the expected range when compared to the national level.

Figure 7.16: The percentage of all patients in care in 2021 who had an HIV RNA level <100 copies/ml. The percentage of individuals with viral suppression has been adjusted for patient mix and is plotted as a function of the number of patients in care in 2021.



Legend: Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The "lower" boundary of expected percentage with viral suppression (as compared to the national average) is indicated with a dashed line (Box 7.3).

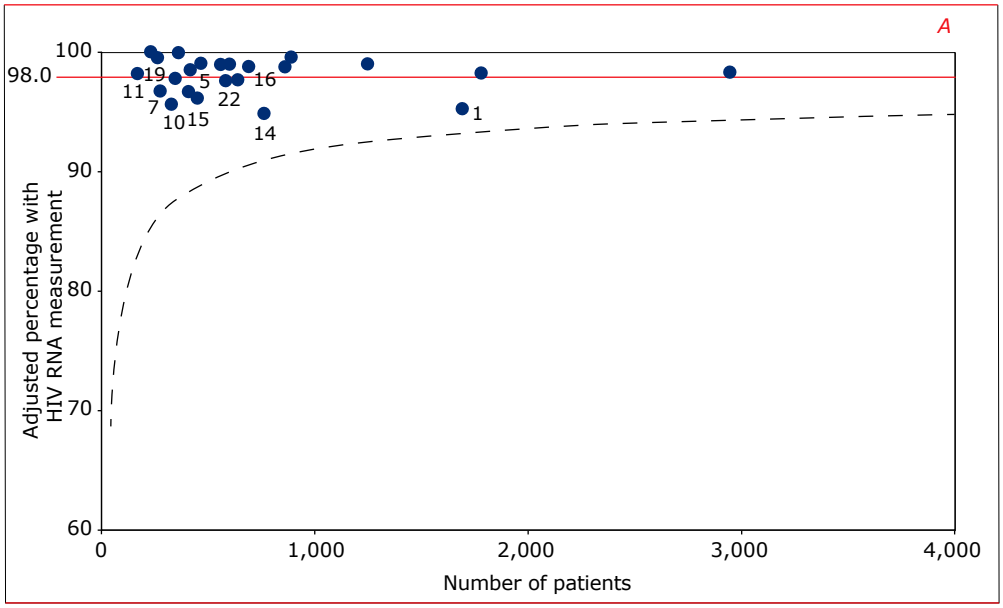
Process indicators

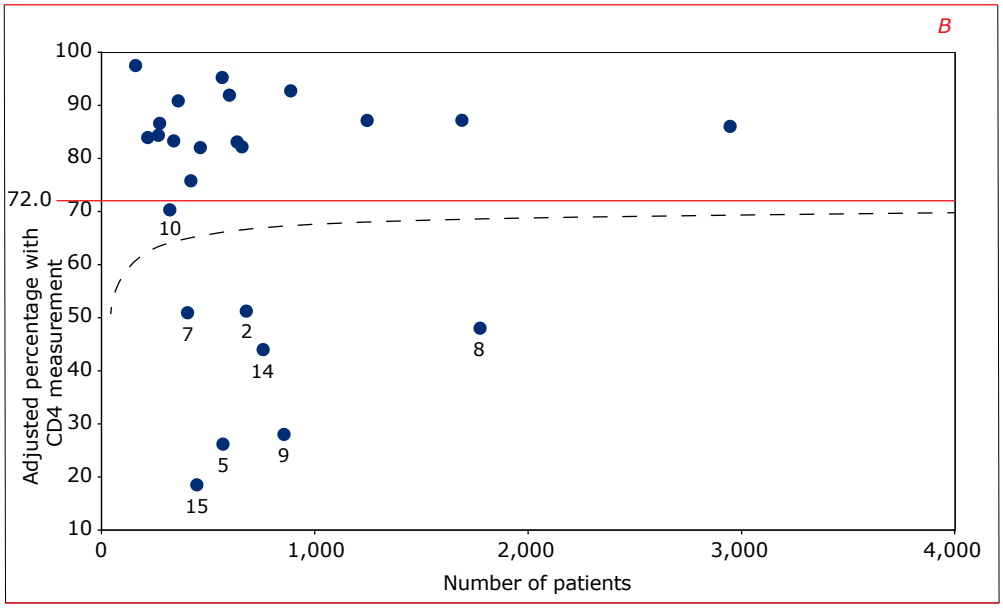
While in care

Process indicators were evaluated in patients who were in care in 2021. *Figure 7.17A and Figure 7.17B* show the across-centre variation in adjusted percentages of patients who had plasma HIV RNA or CD4 cell count measurements, respectively. Across centres, the median adjusted percentage of individuals tested for plasma HIV RNA was 98% (range 95–100%), with only slight variation observed across centres of different patient volume. All centres had adjusted percentages of plasma HIV RNA tested within the expected range when compared to the national level (*Figure 7.17A*).

Across centres, the median adjusted percentage of individuals tested for CD4 cell count was 83% (range 18–98%), with large variation observed across centres of different patient volume. Seven centres of varying patient volume had a lower-than-expected percentage of patients in care measured for CD4 cell count in 2021. However, some of the variation in this indicator could be due to differences in the CD4 measurement protocols between centres. It should be pointed out that there is no specific recommended frequency for CD4 cell count monitoring among patients with a CD4 level above 350 cells/mm^3 in the national guidelines[1].

Figure 7.17: The percentage of all patients in care in 2021 who had (A) a measurement of plasma HIV RNA or (B) a CD4 cell count. The percentages have been adjusted for patient mix and are plotted as a function of the number of patients in care in 2021.





Legend: Data points with centre numbers below the national average are labelled. Centre numbers correspond to those used in Figure 7.1. The "lower" boundary of expected percentage with measurements (as compared to the national average) is indicated with a dashed line (Box 7.3).

Indicators according to patient mix

In the previous analysis on centre performance, we accounted for the patient mix by adjusting each indicator using the six geographical origin/mode of transmission/gender groups. However, it remains difficult to determine whether indicators per centre are different across groups. We therefore explored centre-level differences for several indicators while stratifying on patient mix and accounting for age differences between groups.

For this section, the indicators that we have used (defined in *Box 7.2*) are:

- Overall retention for patients in care;
- Overall ART initiation for patients in care;
- Viral suppression while on ART and while in care; and
- HIV RNA and CD4 cell counts while in care.

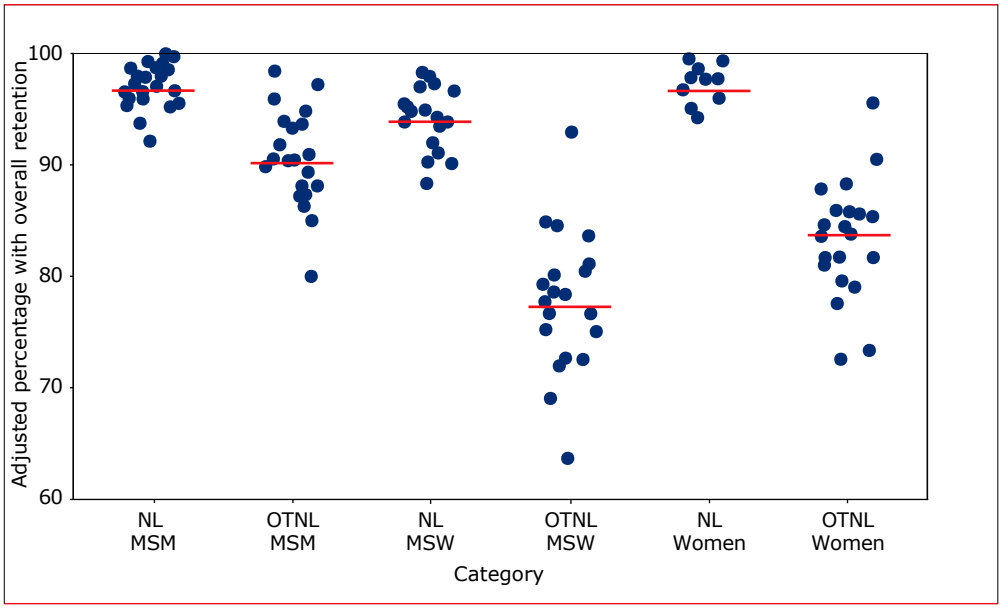
Given that statistical interpretation is unreliable when centre sizes are small, only centres where the focus population contains more than 40 patients have been considered in this analysis. In addition, only indicators from 2021 are considered.

Outcome indicators

Overall retention in care

Figure 7.18 shows the adjusted percentage of patients in care in 2021 with overall retention in care per centre, according to patient mix groups. The highest median percentages across centres were observed in Dutch MSM (97%, range 94–99%) and Dutch women (97%, range 96–98%), followed by Dutch MSW (94%, range 89–96%), and other than Dutch MSM (90%, range 82–97%). Two groups had median percentages below 90%: other than Dutch women (median 84%, range 74-95%) and other than Dutch MSW (median 77%, range 65-93%).

Figure 7.18: Overall retention in care; in other words, patients in care who had a documented visit in 2021. The percentage has been adjusted for patient age.



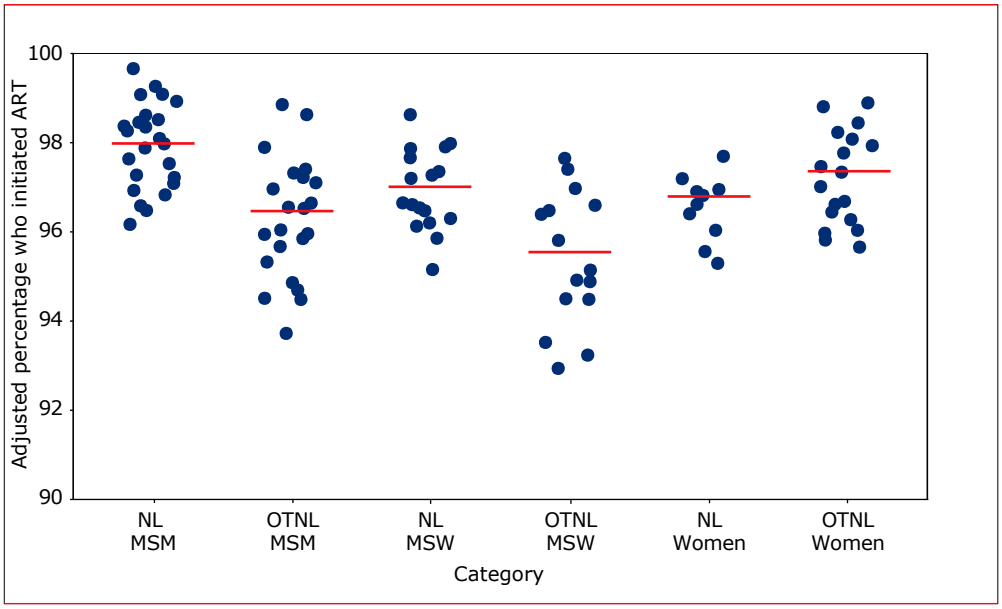
Legend: The median adjusted percentage across centres is indicated with a solid line for each patient mix group. MSM = men who have sex with men; MSW = men who exclusively have sex with women; NL = Dutch; OTNL = other than Dutch.

Overall initiation of ART in care

Figure 7.19 shows the adjusted percentage of patients in care in 2021 who ever initiated ART per centre, according to patient mix groups. All median percentages were above 95% for each of the patient mix groups. These median percentages were:

- 98% (range 96–99%) in Dutch MSM
- 96% (range 94–98%) in other than Dutch MSM
- 97% (range 95–98%) in Dutch MSW
- 96% (range 93–98%) in other than Dutch MSW
- 97% (range 95–97%) in Dutch women
- 97% (range 96–99%) in other than Dutch women

Figure 7.19: The percentage of patients in care in 2021 who ever initiated combination antiretroviral therapy (ART). The percentage has been adjusted for patient age.



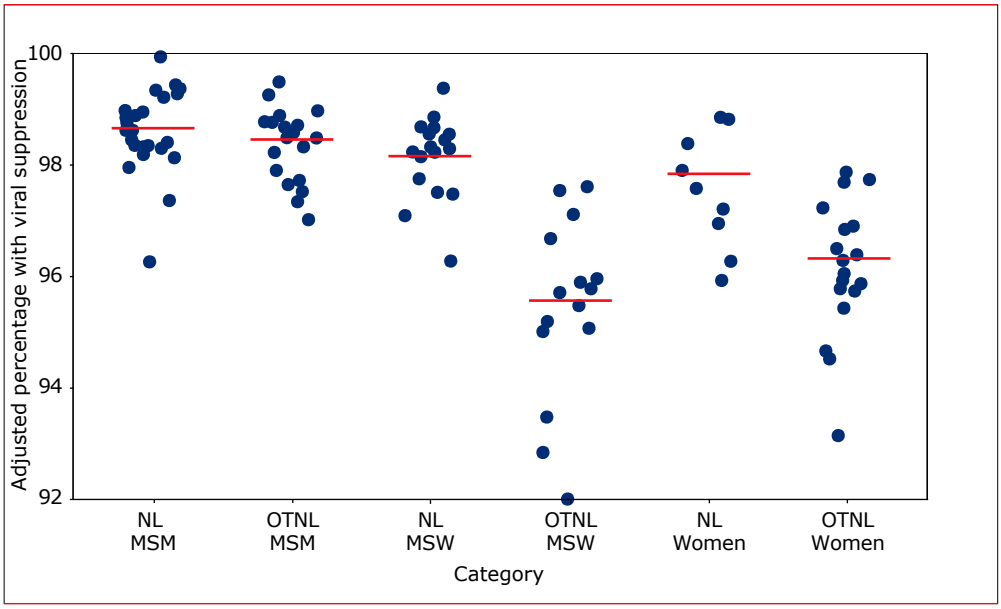
Legend: The median adjusted percentage across centres is indicated with a solid line for each patient mix group. MSM = men who have sex with men; MSW = men who exclusively have sex with women; NL = Dutch; OTNL = other than Dutch.

Viral suppression

Figure 7.20 shows the adjusted percentage of patients on ART in 2021 who had a plasma HIV RNA viral load below 100 copies/ml (i.e., viral suppression while on ART) per treatment centre, according to patient mix groups. All median percentages were above 95% for each of the patient mix groups. These median percentages were:

- 99% (range 96–100%) in Dutch MSM
- 98% (range 97–100%) in other than Dutch MSM
- 98% (range 97–99%) in Dutch MSW
- 96% (range 92–97%) in other than Dutch MSW
- 98% (range 96–99%) in Dutch women
- 96% (range 94–98%) in other than Dutch women

Figure 7.20: The percentage of all patients on combination antiretroviral therapy (ART) for at least six months in 2021 who had an HIV RNA level below 100 copies/ml. The percentage has been adjusted for patient age.

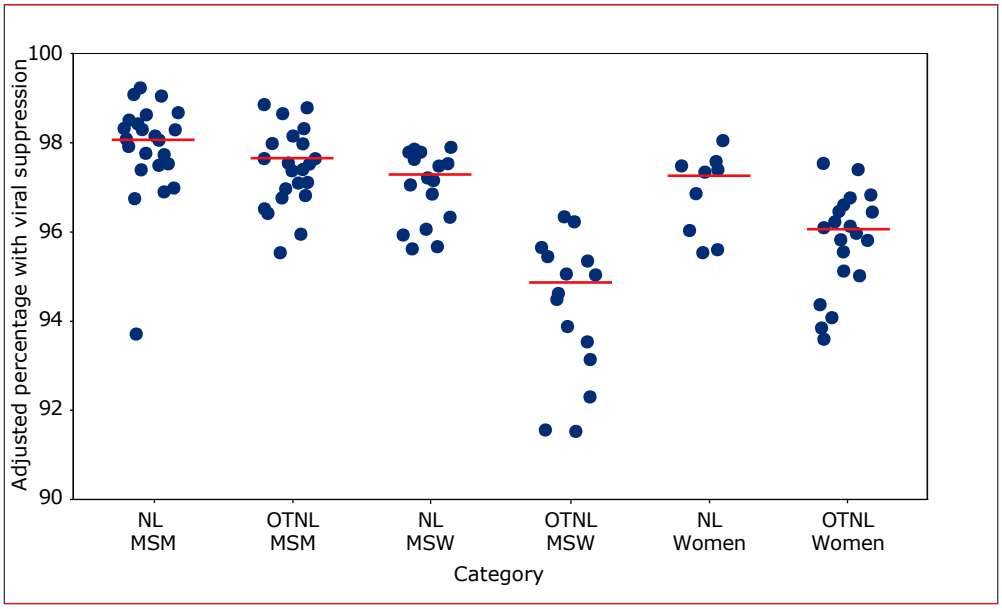


Legend: The median adjusted percentage across centres is indicated with a solid line for each patient mix group. MSM = men who have sex with men; MSW = men who exclusively have sex with women; NL = Dutch; OTNL = other than Dutch.

Figure 7.21 shows the adjusted percentage of patients in care in 2021 who had a plasma HIV RNA viral load below 100 copies/ml (i.e., viral suppression while in care) per treatment centre, according to patient mix groups. All median percentages were again above 95% for each of the patient mix groups. These median percentages were:

- 98% (range 94–99%) in Dutch MSM
- 98% (range 96–99%) in other than Dutch MSM
- 97% (range 95–98%) in Dutch MSW
- 95% (range 92–96%) in other than Dutch MSW
- 97% (range 95–98%) in Dutch women
- 96% (range 94–97%) in other than Dutch women

Figure 7.21: The percentage of all patients in care in 2021 who had an HIV RNA level <100 copies/ml. The percentage has been adjusted for patient age.



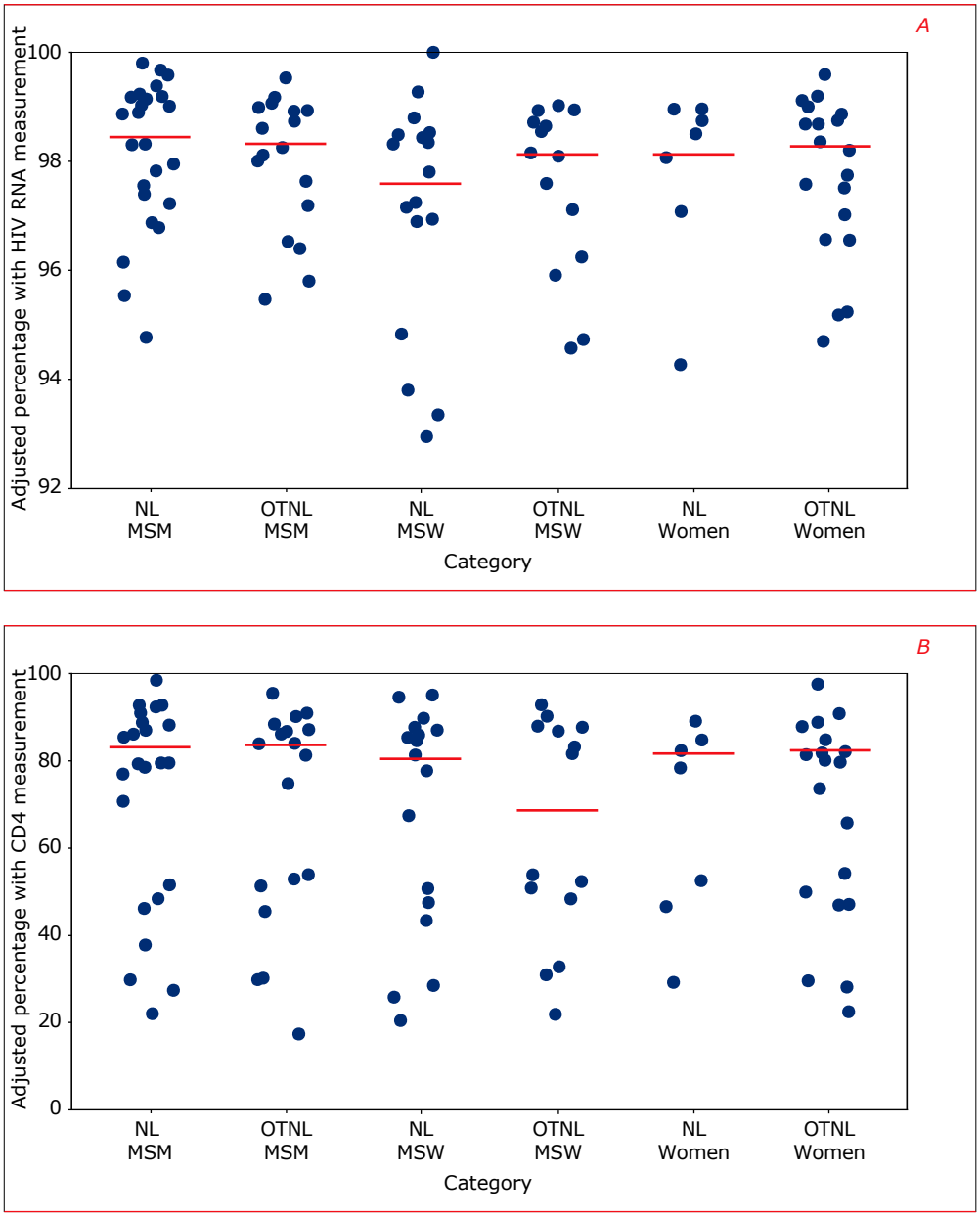
Legend: The median adjusted percentage across centres is indicated with a solid line for each patient mix group. MSM = men who have sex with men; MSW = men who exclusively have sex with women; NL = Dutch; OTNL = other than Dutch.

Process indicators

While in care

Process indicators were evaluated for patients who were in care in 2021. *Figure 7.22A and Figure 7.22B* show the across-centre variation, in adjusted percentages, of those who had plasma HIV RNA and CD4 cell count measurements, respectively, according to patient mix groups. All median adjusted percentages for HIV RNA measurements were high across patient mix groups, with the highest in Dutch MSM (99%, range 95–100%) and the lowest in Dutch MSW (98%, range 93–100%). All adjusted percentages for CD4 cell count measurements were highly variable across patient mix groups, with median percentages ranging from 83% (range 18–98%) in Dutch MSW and 69% in other than Dutch MSW (range 20–96%).

Figure 7.22: The percentage of all patients in care in 2021 who had (A) a measurement of plasma HIV RNA or (B) CD4 cell count. The percentage has been adjusted for patient age.



Legend: The median adjusted percentage across centres is indicated with a solid line for each patient mix group. MSM = men who have sex with men; MSW = men who exclusively have sex with women; NL = Dutch; OTNL = other than Dutch.

Indicators after centre closure

In 2018, two official HIV treatment centres closed (MC Slotervaart, Amsterdam, and MC Zuiderzee, Lelystad). At the time of closure, 662 patients were still in care at these centres. Of these patients:

- 574 (87%) transferred to another HIV treatment centre in the Netherlands (560 had a clinical visit in 2021);
- 15 (2%) moved abroad;
- 17 (3%) were lost to care;
- 36 (5%) died; and
- 20 (3%) patients had an unknown care status at the time of this analysis (i.e., their current status was not in the database).

The percentages who moved abroad or died are comparable to those recorded for the entire adult HIV-1 positive population in SHM in 2021 (*Chapter 1*). The slightly higher percentage of those lost to care could be due to an administrative backlog in re-registering those patients who have transferred to another centre.

The indicators most relevant to the group of patients who transferred care from a closed centre to another HIV treatment centre are:

- The percentage of all people living with HIV who ever initiated ART and were still in care in 2021;
- The percentage of people on ART for at least six months in 2021 with a plasma HIV RNA level below 100 copies/ml; and
- The percentage of all people living with HIV in care in 2021 with a plasma HIV RNA level below 100 copies/ml.

Table 7.1 summarises these indicators for individuals whose care was transferred from a closed centre, and compares them to the median indicators across centres: all were within range.

Table 7.1: Indicators in individuals whose care was transferred from a closed centre to another HIV treatment centre.

Indicator *(Box 7.2)*	Individuals transferred from a closed centre (n=574)	Median indicators (range) across all centres in the Netherlands in 2021
Overall ART initiation and still in care in 2021	99%	97% (95–99%)
Viral suppression while on ART in 2021	99%	98% (94–99%)
Viral suppression while in care in 2021	99%	97% (92–99%)

Key findings and conclusions

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

- The number of newly HIV-diagnosed individuals entering care has been slowly decreasing for the vast majority of centres, which is in line with the national trend of fewer newly diagnosed HIV infections.
- After exclusion of patients who either died or moved abroad, short-term retention has been high for individuals entering care, and the overall retention has witnessed a median increase of 11% over the past five years. No centre had an overall retention rate lower than the national average when adjusting for patient mix. Nevertheless, the overall retention rate for other than Dutch MSW and women was considerably lower than other groups after adjusting for age. The reasons for this finding need to be explored in future research.
- The overall percentage of individuals retained in care in 2019 was not substantially different from that of 2021 – the year after the beginning of the COVID-19 pandemic. This finding suggests that the COVID-19 pandemic had no major effect on current retention in care.
- The COVID-19 pandemic had drastically shifted how consultations were conducted at HIV treatment centres in 2020, with most centres opting for consultations via telephone or email over physical consultations. These trends continued in 2021. Nevertheless, the percentage of patients opting for another type of consultation decreased between 2020 and 2021.
- The percentage of patients initiating ART within six months of newly entering care remained high for those who entered care between 2017 and 2020. Nevertheless, some centres saw a considerable decline in this indicator for individuals entering care in 2019 and 2020. The overall percentage of patients in care who ever initiated ART has been slowly increasing over the past five years. In fact, no centre had an overall ART initiation figure lower than expected from the national average when adjusting for patient mix.

- Viral suppression rates in the first six months on ART, during longer-term use of ART, and while in care have been high across all HIV treatment centres in the Netherlands over the past five years. There was little variation in the percentage with viral suppression while on ART and in care across centres after adjusting for patient mix.
- The percentage of individuals with HIV RNA measurements prior to ART, or while in care, has been high across centres over the past five years, even during the COVID-19 pandemic in 2020 and 2021. However, several centres had a much lower-than-expected proportion with CD4 measurements while in care in 2021, as compared to the national average and after adjusting for patient mix.
- The ART and viral suppression indicators for individuals who were originally registered with the two HIV treatment centres that closed do not appear to have been affected by the transfer of their care to another HIV treatment centre.

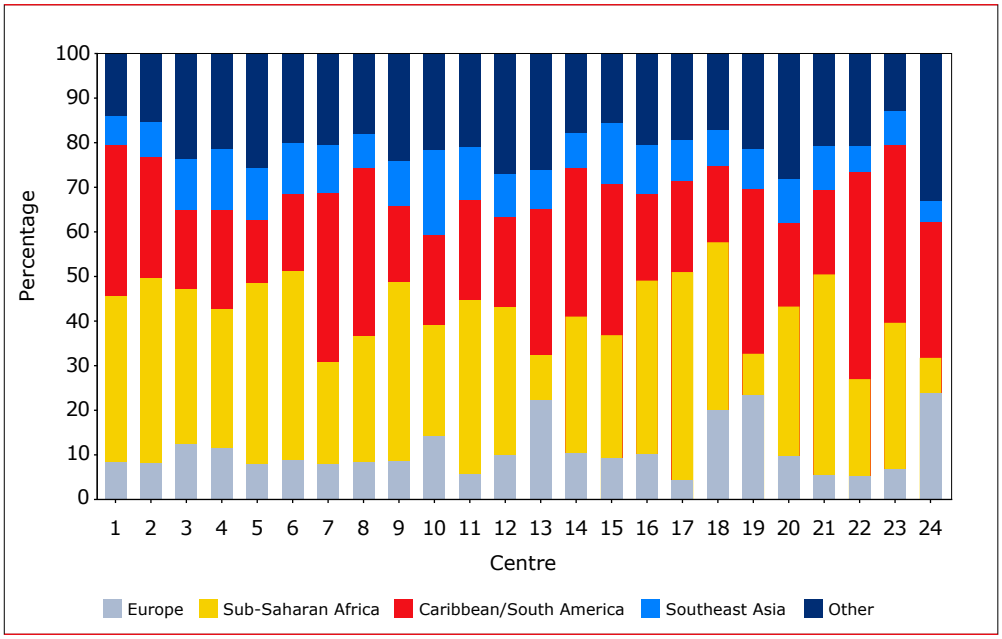
The wide range of indicators used in these analyses offers broad coverage of various aspects of HIV care and provides insight into care provision at the different treatment centres. These analyses also provide information on whether some of the 2022 targets of the Dutch National Action Plan for STIs, HIV and Sexual Health (*Nationaal Actieplan soa, hiv en seksuele gezondheid: 2017-2022*) will be met at the centre level. Nonetheless, data reliability remains an important issue, and it should be recognised that some of the reported variations may be due to missing data. Other important indicators reflecting the quality of care, such as quality of life, reduction in stigma, and discrimination, are difficult to obtain from patient files, and are therefore not collected in the SHM database.

References

1. Nederlandse Vereniging van HIV Behandelaren. Richtlijn HIV. http://richtlijnhiv.nvhb.nl/. Published 2017.
2. https://coronadashboard.rijksoverheid.nl/.
3. Engelhard EAN, Smit C, Van Sighem A, et al. Impact of HIV care facility characteristics on the cascade of care in HIV-infected patients in the Netherlands. *AIDS*. 2015;30(2):301-310. doi:10.1097/QAD.0000000000000938
4. Backus LI, Boothroyd DB, Phillips BR, et al. National Quality Forum Performance Measures for HIV/AIDS Care. *Arch Intern Med*. 2010;170(14):1239-1246. doi:10.1001/archinternmed.2010.234
5. Solomon L, Flynn C, Lavetsky G. Managed care for AIDS patients: is bigger better? *J Acquir Immune Defic Syndr*. 2005;38(3):342-347. http://www.ncbi.nlm.nih.gov/pubmed/15735455. Accessed August 22, 2016.
6. Gompels M, Michael S, Jose S, Hill T, Trevelion R S, CA MM. The use of funnel plots with regression as a tool to visually compare HIV treatment outcomes between centres adjusting for patient characteristics and size: a UK Collaborative HIV Cohort study. *HIV Med*. 2018;19(6).

Appendix

Figure 7.A: Distribution of region of origin for other than Dutch patients in care in 2021 in the Netherlands.



Note: Percentage of individuals per centre is given in the bar chart according to region of origin.

8. The Amsterdam Cohort Studies (ACS) on HIV Infection: annual report 2021

Amy Matser, Neeltje Kootstra, Lia van der Hoek, Maria Prins, Jeffrey Koole

Introduction

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS started shortly after the first cases of AIDS were diagnosed in the Netherlands. Since October 1984, men who have sex with men (MSM) have been enrolled in a prospective cohort study. A second cohort involving people who use/used injecting drugs (PWID) was initiated in 1985. In 2021, the cohorts reached 37 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 37 years, these aims have remained primarily the same, although the emphasis of the studies has changed. Early on, the primary focus was to elucidate the epidemiology of HIV-1 infection, whereas, later, more in-depth studies were performed to investigate the pathogenesis of HIV-1 infection. In the past decade, research on the epidemiology of other blood-borne and sexually-transmitted infections (STIs), and their interaction with HIV, has also become an important component of the ACS research programme.

From the outset, research in the ACS has taken a multidisciplinary approach, integrating epidemiology, social science, virology, immunology, and clinical medicine in one study team. This unique collaboration has been highly productive, significantly contributing to the knowledge and understanding of many different aspects of HIV-1 infection, as well as other infections such as viral hepatitis B and C (HBV and HCV) and human papillomavirus (HPV). This expertise, in turn, has contributed directly to advances in prevention, diagnosis, and management of these infections.

Collaborating institutes and funding

Within the ACS, different institutes collaborate to bring together data and biological sample collections, and to conduct research. These include the:

- **Public Health Service of Amsterdam** (*Gemeentelijke Gezondheidsdienst Amsterdam,* GGD Amsterdam): Department of Infectious Diseases, Research and Prevention;
- **Amsterdam University Medical Centres** (Academic Medical Centre [AMC] site): Departments of Medical Microbiology, Experimental Immunology, and Internal Medicine (Division of Infectious Disease);
- **Emma Kinderziekenhuis** (paediatric HIV treatment centre);
- **Stichting HIV Monitoring** (SHM);
- **MC Jan van Goyen**: Department of Internal Medicine; and
- **HIV Focus Centrum** (DC Klinieken Lairesse).

Sanquin Blood Supply Foundation has also been involved in the ACS from the very beginning; since 2007, it has provided financial support for the biobank of viable peripheral blood mononuclear cells (PBMC) at the AMC's Department of Experimental Immunology. In addition, there are numerous collaborations between the ACS and other research groups, both within and outside the Netherlands. The ACS is financially supported by the Centre for Infectious Disease Control Netherlands of the National Institute for Public Health and the Environment (*Centrum voor Infectieziektenbestrijding-Rijksinstituut voor Volksgezondheid en Milieu,* RIVM-CIb).

Ethics statement

The ACS has been conducted in accordance with the ethical principles set out in the Helsinki declaration. Participation in the ACS is voluntary and written informed consent is obtained from each participant. The most recent version was approved by the AMC medical ethics committee (METC) in 2007 for the MSM cohort, and in 2009 for the PWID cohort. In 2021, amendments – including the updated study protocol – were drafted for submission to the METC.

The ACS in 2021

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

As of 31 December 2021, 2,913 MSM were included in the ACS. Every three to six months, participants complete a standardised questionnaire designed to obtain data regarding: medical history, sexual behaviour and drug use, underlying psychosocial determinants, health care use, signs of depression and other psychological disorders, demographics.

Moreover, blood is collected for diagnostic tests and storage at the ACS biobank. Of the 2,913 MSM, 608 were HIV-positive at entry into the study and 264 seroconverted for HIV during follow up. In total, the GGD Amsterdam has been visited 64,664 times by MSM since 1984.

Between 1984 and 1985, men who had had sexual contact with a man in the preceding six months were enrolled, independent of their HIV status. From 1985 to 1988, HIV-negative men of all age groups were eligible to participate if they lived in, or around, Amsterdam and had had at least two male sexual partners in the preceding six months. Between 1988 and 1998, the cohort also included MSM with HIV. From 1995 to 2004, only men aged 30 years or younger, with at least one male sexual partner in the previous six months, could be included the study. Since 2005, HIV-negative men of all age groups have been eligible to participate in the ACS if they live in, or are closely connected to, the city of Amsterdam and have had at least one male sexual partner in the preceding six months. In line with the advice issued by the International Scientific Advisory Committee in 2013, the cohort continues to strive to recruit young HIV-negative MSM (aged 30 years or younger).

HIV-seroconverters within the ACS remained in the cohort until 1999, when follow up of a selection of MSM with HIV was transferred to the MC Jan van Goyen. In 2003, the HIV Research in Positive Individuals *(Hiv Onderzoek onder Positieven,* HOP) protocol was initiated. Individuals with a recent HIV infection when entering the study at the GGD Amsterdam, and those who seroconverted for HIV during follow up within the cohort, continue to return for study visits at the GGD Amsterdam, or at an HIV treatment centre. Blood samples from these participants are stored. All behavioural data are collected on a six-monthly basis by questionnaires, coordinated by the GGD Amsterdam, and clinical data are provided by SHM.

In the first half of 2021, data collection was affected by the COVID-19 pandemic, but overall a total of 699 HIV-negative and 52 MSM with HIV were active participants at the GGD Amsterdam in 2021. This is defined as visiting the cohort at least once in 2020 or 2021. All 52 MSM with HIV filled out behavioural questionnaires.

The group had the following characteristics:

- 12 new MSM with a median age at inclusion of 28.3 years (interquartile range [IQR]=26.5-31.0) were enrolled;
- The median age of the total group of MSM in active follow up was 45.1 years (IQR=34.9-52.6) at their last cohort visit;
- The majority were born in the Netherlands and were residents of Amsterdam (83.2% and 88.9%, respectively);
- 77.5% of the participants had a college degree or higher.

The cohort of people who use/used injecting drugs (PWID)

As of 31 December 2016, 1,680 PWID were included in the ACS and contributed 28,194 visits. In 2014, the cohort was closed to new participants. Regular follow up of PWID continued until February 2016. All PWID who had ever participated in the ACS were then invited for an end-of-study interview and follow up was successfully ended in July 2016. Of the 1,680 PWID, 323 were HIV-positive at entry, and 99 seroconverted during follow up. The last HIV seroconversion was seen in 2012. By 31 December 2016, 576 deaths had been confirmed among PWID. The median age of the PWID who visited the ACS in 2016 was 55 (IQR 49-59) years, 8.1% had attained a high level of education, and 63.4% were born in the Netherlands.

ACS biobank

The ACS visits, together with data collected from several subgroup studies and affiliated studies embedded in the ACS, have resulted in a large collection of stored samples. The ACS biobank includes plasma/serum and PBMC samples collected within the context of the ACS cohorts.

The biobank also contains samples collected during the Primo-SHM study: a national, randomised, study that started in 2003. It compares the effects of early, temporary antiviral therapy with that of no therapy among (1) patients who presented with primary HIV-1 infection at the AMC HIV outpatient clinic, and (2) ACS seroconverters. These samples are stored at the Amsterdam University Medical Centres' (AUMC) AMC location. Biological samples are still being collected prospectively for Primo-SHM participants visiting the AUMC's AMC clinic, up until one year after they have recommenced therapy.

The ACS biobank also contains plasma and PBMC samples collected from children with HIV and exposed to HIV, at the Emma Kinderziekenhuis in the AUMC's AMC clinic, before 2008. All stored samples are available for ACS research.

Subgroup studies and affiliated studies

AGE$_h$IV cohort study

The AGE$_h$IV cohort study is a collaboration between the Amsterdam UMC's AMC site Departments of Infectious Diseases and Global Health, the Amsterdam Institute of Global Health and Development, the GGD Amsterdam, and SHM. It 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 individuals 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 HIV-positive and HIV-negative groups. Participants undergo a comprehensive assessment for comorbidities and complete a questionnaire at intake plus follow-up research questionnaires every subsequent two years.

In total, 598 HIV-1-positive participants and 550 HIV-negative individuals completed a baseline visit between October 2010 and September 2012. People with HIV-1 (PWH) were included through the AUMC AMC site's HIV outpatient clinic, and HIV-negative participants from similar risk groups engaged via the Centre of Sexual Health Amsterdam (CSHA) (486) and the ACS (64). All participants were aged 45 years and over, and were as comparable as possible with respect to age, gender, ethnicity, and risk behaviour. In 2021, the sixth round was started; 59 HIV-negative participants came to the GGD for a sixth visit, which was lower than planned due to the COVID-19 pandemic. The sixth round of the AGE$_h$IV study will be completed in 2023.

In 2020, a two-year COVID-19 sub-study was started in this cohort, with five consecutive 6-monthly visits planned between September 2020 and October 2022. During each visit, participants completed a study questionnaire and provided a blood sample to measure SARS-CoV-2 immune responses. Additionally, in the four to 13 weeks after the last dose of the primary vaccination schedule, participants were invited for an additional blood draw to measure SARS-CoV-2 vaccine immune responses. In total, 567 participants (241 PWH and 326 HIV-negative people) were included in the COVID-19 sub-study, of whom 441 (195 PWH and 246 HIV-negative) participated in the additional post-vaccination blood draw[a].

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)*

AMPrEP project in H-TEAM

The Amsterdam pre-exposure prophylaxis (AMPrEP) project was a prospective, longitudinal, open-label demonstration study conducted between 2015 and 2020. The aim was to assess the uptake and acceptability of daily, versus event-driven, pre-exposure prophylaxis (PrEP) among MSM and transgender people (TGP) at increased risk of HIV infection. It formed part of a comprehensive HIV-reduction package offered at a large centre for sexual health.

In total, 374 MSM and two TGP were enrolled between August 2015 and May 2016 at GGD Amsterdam's sexual health centre, including 35 ACS participants who chose to participate in the AMPrEP project. Participants were asked to attend a follow-up visit one month after their PrEP initiation visit, and return every three months thereafter. At every visit, participants filled out questionnaires on risk behaviour, adherence, and general wellbeing, and were screened for STIs and HIV.

AMPrEP follow-up was completed on 1 December 2020. By then, all participants still in care and willing to continue PrEP were included in the national PrEP pilot scheme at a centre for sexual health of their choice.

The AMPrEP project was part of the HIV Transmission Elimination Amsterdam (H-TEAM) initiative, a multidisciplinary and integrative approach to reduce the spread of HIV[b].

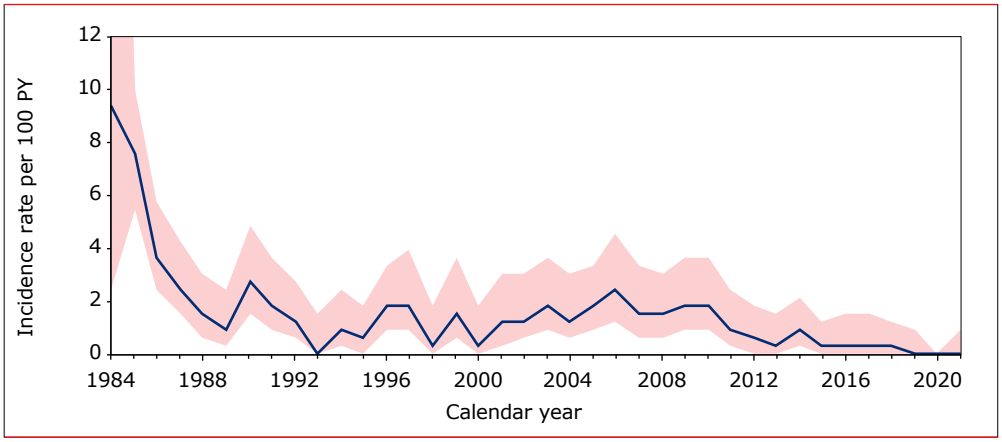
The HIV population

HIV incidence

The observed HIV incidence rate among MSM participating in the ACS has changed over time. 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 2021, two MSM participating in the ACS seroconverted for HIV. *Figure 8.1* shows the annually-observed HIV incidence rate for MSM from the start of the ACS through 2021.

b *www.hteam.nl*

Figure 8.1: HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984–2021.



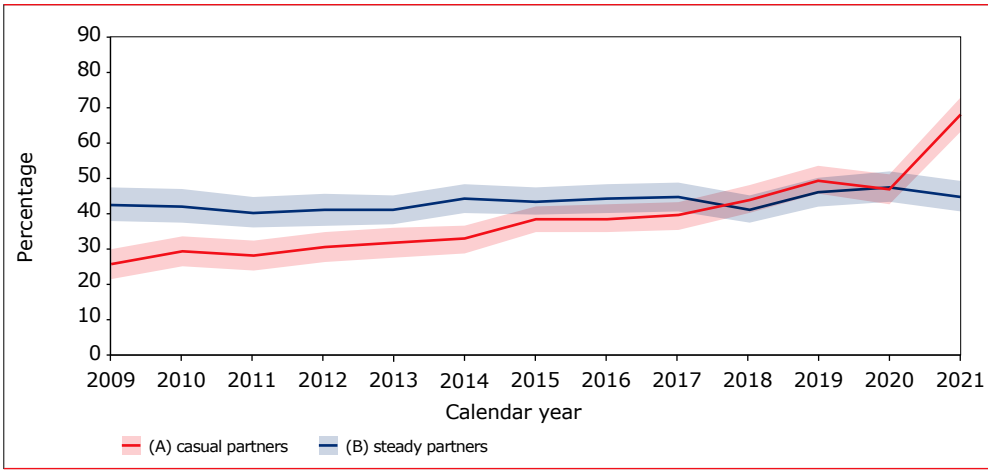
Transmission of therapy-resistant HIV strains

In 2021, there was no surveillance conducted of transmitted, drug-resistant HIV-1 strains.

Risk behaviour of MSM in ACS

Condomless anal sex (CAS) with a steady and casual partner was reported by 179 out of 440 (40.7%) and 183 out of 440 (41.5%) HIV-negative MSM, respectively, during their cohort visit in 2021. Trends in CAS among HIV-negative MSM participating in the ACS continued to show a gradual increase from 2009 onwards (*Figure 8.2*). Use of PrEP has also increased since 2015. In 2021, 322 of the 652 (49.4%) HIV-negative MSM actively participating in the ACS reported PrEP use in the preceding six months. CAS with a steady or casual partner was reported by 134 (41.6%) and 210 (65.2%) PrEP-using MSM, respectively. Among non-PrEP-using MSM, those figures were 119 (36.1%) and 75 (22.7%) respectively.

Figure 8.2: Trend in the proportion of condomless anal sex (CAS) with: (A) casual partners, and (B) steady partners, among HIV-negative men who have sex with men (MSM) in the Amsterdam Cohort Studies (ACS), 2009-21.



STI screening among MSM in ACS

Since October 2008 all MSM participating in the ACS have been routinely screened for bacterial STIs during their cohort visits. This conforms with the standard care offered by the Centre of Sexual Health Amsterdam (CSHA). Chlamydia and gonorrhoea were detected by polymerase chain reaction (PCR) techniques using urine samples and pharyngeal and rectal swabs. Syphilis was detected by Treponema pallidum haemagglutination assay (TPHA).

In 2021, 61 out of 577 (10.1%) MSM in the ACS tested positive for one of the bacterial STIs at least once during a cohort visit. For HIV-negative and HIV-positive MSM, these figures were 51 out of 541 (9.4%), and 10 out of 37 (27.0%), respectively. As the STI testing frequency differs between PrEP-using (quarter-annually) and non-PrEP-using participants (semi-annually), STI incidence rates of these groups cannot be compared and, therefore, are not reported. In general, the incidence rate of a bacterial STI significantly increased in the period 2009 to 2021.

Impact of COVID-19 on ACS

In the beginning of 2021 the COVID-19 pandemic was still ongoing and the ACS study visits continued only for participants who i) had been warned by a partner that they may have contracted an STI, ii) had run out of PrEP pills, or iii) had STD symptoms. In the first quarter, most governmental restrictions to prevent SARS-CoV-2 transmission were lifted. As per 1 April 2021, ACS study visits were scheduled according to the study protocol for all participants.

ACS 2021 research highlights

HIV-1 Nef sequences obtained from PWH show variations and mutations

Nef is a multifunctional viral protein that has the ability to downregulate cell surface molecules, including CD4 and major histocompatibility complex class I (MHC-I) and, as recently shown, also members of the serine incorporator family (SERINC). Natural occurring mutations in HIV-1 Nef may affect its function and as a consequence the clinical course of infection.

HIV-1 Nef sequences were obtained from 123 participants of the ACS and showed multiple amino acid variations and mutations. Most of the primary Nef proteins showed increased activity to counteract SERINC3 and SERINC5, as compared to NL4-3 Nef. Several mutations in Nef were associated with either an increased or decreased infectivity of the virus produced in the presence of SERINC3 or SERINC5. The 8R, 157N and R178G Nef mutations were shown to have an effect on disease progression[c].

Virological and immunological biomarkers among PWH

Incomplete restoration of CD4+ T-cell counts on antiretroviral therapy (ART) is a major predictor of HIV-related morbidity and mortality. To understand the possible mechanisms behind this poor immunological response despite viral suppression, virological and immunological biomarkers were measured among ACS participants with HIV.

Cell-associated HIV-1 unspliced-to-multiply-spliced (US/MS) RNA ratio at 12 weeks of ART positively correlated with markers of CD4+ T-cell activation and apoptosis, and negatively predicted both the absolute and relative CD4+ T-cell counts at 48 and 96 weeks. The fact that a virological biomarker performed better than any immunological biomarker in predicting an immunological outcome highlights the importance of considering the residual HIV activity on ART as a correlate and a possible cause of the residual immune dysfunction that frequently occurs despite virologically suppressive ART[d].

c *Kruize et. al. Viruses. 2021 Mar 6;13(3):423. (Kruize et al., 2021)*

d *Scherpenisse et.al. mBio. 2021 Mar 9;12(2):e00099-21. (Scherpenisse, Kootstra, Bakker, Berkhout & Pasternak, 2021)*

Afucosylated IgG characterises enveloped viral responses and correlates with COVID-19 severity

Immunoglobulin G (IgG) antibodies are crucial for protection against invading pathogens. A highly conserved N-linked glycan within the IgG-Fc tail, which is essential for IgG function, shows variable composition in humans. Afucosylated IgG (approximately 6% of total IgG in humans) are specifically formed against enveloped viruses including HIV-1 and SARS-CoV-2, but generally not against other antigens. Antibody glycosylation plays a critical role in immune responses to enveloped viruses via FcγRIIIa-expressing natural killer (NK) cells, monocytes, and macrophages as well as FcγRIIIb-expressing granulocytes. This may be desirable in some responses, such as against HIV, and can be achieved with available attenuated enveloped viral vaccine shuttles against targets for which vaccine-based approaches have failed. However, this phenomenon can also lead to an undesirable exaggerated response, as is the case for SARS-CoV-2[e].

Harm-reduction programmes for HIV, HCV and HBV among PWID

Major declines in HIV and HCV/HBV incidence among PWID have been attributed to early implementation of harm-reduction programmes (HRP) in the Netherlands. Using ACS data (1985-2014), we included 983 PWID who ever used opioids, had a recent history of injecting drug use (IDU) and tested negative for HIV, HCV or HBV. Intervention arms were: complete HRP participation [≥ 60 mg/day methadone and 100% needle and syringe programme (NSP) coverage, or any methadone dose if no recent injection drug use] versus no HRP and partial HRP participation combined (< 60 methadone mg/day and/or < 100% NSP coverage).

Compared with no/partial HRP participation, complete HRP participation led to lower risk of HIV [HR = 0.54, 95% confidence interval (CI) = 0.27-1.08], HCV (HR = 0.16, 0.06-0.40) and HBV (HR = 0.28, 0.13-0.61) acquisition[f].

Increase in sexualised drug use among HIV-negative MSM

There is a high prevalence of recreational drug use (RDU) among MSM. This study encompassed 976 ACS participants (HIV-negative MSM aged 18 and over) between 2008 and 2018, and evaluated changes in self-reported RDU (during sex: [SDU]) over time. It included the proportion of individuals and number of drugs, adjusted for current age, country of birth and education level.

The proportion of any RDU increased from 67.2% in 2008 to 69.5% in 2018 (aOR = 1.25; 95% CI = 1.03–1.51). Any SDU increased from 53.8% in 2008 to 59.8% in 2013 (aOR = 1.23; 1.07–1.42) and remained stable afterwards. The average number of

e *Larsen et.al. Science. 2021 Feb 26;371(6532):eabc8378. (Larsen et al., 2021)*

f *Van Santen-Addiction-2021 (van Santen et al., 2021)*

drugs used increased for those reporting any RDU and SDU (all P < 0.05). Among those engaging in sex, any SDU was associated with CAS (aOR = 1.36; 1.19–1.55), HIV (aOR = 5.86; 2.39–14.4) and STI (aOR = 2.31; 1.95–2.73).

Among HIV-negative MSM participating in the ACS, recreational drug use, including sexualized drug use, increased between 2008 and 2018. Sexualized drug use was strongly associated with condomless anal sex, HIV and sexually transmitted infections[g].

High carriage of ESBL-producing Enterobacteriaceae associated with sexual activity among men who have sex with men

Extended-spectrum β-lactamase Enterobacteriaceae (ESBL-E) may be sexually transmitted. MSM engage in different sexual behaviour than the general population, and thus may be at risk of ESBL-E carriage. For this study 583 HIV-positive and HIV-negative MSM from the Amsterdam Cohort Study were screened for rectal ESBL-E carriage between April and December 2018. Self-reported (sexual) behaviour and risk factors for antimicrobial resistance were also collected. The proportion of the study population with ESBL-E carriage was compared by number of sexual partners using logistic regression, and across clusters of sexual behaviours with steady and casual partners, separately, using latent class analyses. All results were adjusted for recent use of antibiotics, travel and hospitalisation.

Overall, 16.3% (95% CI 13.4-19.5) of the study population tested positive for ESBL-E. The odds of ESBL-E carriage increased as the number of sexual partners increased [aOR per ln(partner+1), 1.57, 95% CI 1.26-1.94; P<0.001]. There was no association between ESBL-E carriage and sexual behaviour with steady partner(s). Compared with participants in the 'no sex with casual partner(s)' cluster, adjusted odds of being ESBL-E positive were 2.95-fold higher (1.52-5.80) for participants in the 'rimming and frottage' cluster (P=0.001) and 2.28-fold higher (0.98-5.31) for participants in the 'toy use and fisting' cluster (P=0.056).

The prevalence of ESBL-E in MSM is higher compared with the overall Dutch population, which is likely due to sexual transmission with casual partners. This implies that sexually active MSM should be considered a risk group for ESBL-E carriage[h].

g *Coyer-Addiction-2021 (Coyer et al., 2022)*

h *van Bilsen-Int. J. Antimicrob. Agents-2021 (van Bilsen et al., 2021)*

Current and upcoming ACS research projects

Data collected within the ACS are used for multiple research projects at present. HCV-infection incidence and spontaneous-clearance rates, along with associated factors, are in the process of being estimated and identified. Additionally, blood samples of ACS participants, among others, are being analysed for SARS-CoV-2 antibodies to investigate the seroprevalence of SARS-CoV-2 antibodies and their determinants.

With PrEP widely available for eligible individuals since 2019, ACS data is also being used to optimise current PrEP eligibility criteria, uptake, and retention. Previously, trials on prophylactic use of antibiotics (before or after sex) to prevent bacterial STIs have been conducted outside the ACS cohort. At present the option to take antibiotics in this way is not offered in the Netherlands due to insufficient evidence regarding efficacy and safety. Hence this study aims to determine current informal use, intentions, and beliefs regarding prophylactic antibiotics among ACS participants. In particular, trials have found that long-acting oral and injectable PrEP are as safe and effective as the (short-acting oral) PrEP currently available in the Netherlands. Therefore attitudes towards, and intentions to switch to, long-acting PrEP among ACS participants are to be determined. Finally, qualitative research methods in the form of in-depth interviews on PrEP(-use) experience are used to identify missed opportunities, barriers and circumstances of PrEP use and care. These are held with MSM and TGP with HIV, who have a recent HIV-diagnosis from 2019 onwards.

Steering committee

In 2021 the steering committee gathered on five occasions. Seven proposals for use of data and/or samples (serum/PBMC) were submitted to the committee: three from Experimental Immunology (AUMC), three from Medical Microbiology and Infection Prevention (AUMC), and one from the GGD Amsterdam. One of the proposals was a collaboration with a group outside the ACS; RIVM in collaboration with the GGD Amsterdam. The ACS requested major revisions to three of the proposals, after which all requests were approved.

Publications in 2021 that included ACS data

1. Scherpenisse M, Kootstra NA, Bakker M, Berkhout B, Pasternak AO. Cell-Associated HIV-1 Unspliced-to-Multiply-Spliced RNA Ratio at 12 Weeks of ART Predicts Immune Reconstitution on Therapy. mBio. 2021 Mar 9;12(2):e00099-21. doi: 10.1128/mBio.00099-21. PMID: 33688002; PMCID: PMC8092199.
2. Kruize Z, van Nuenen AC, van Wijk SW, Girigorie AF, van Dort KA, Booiman T, Kootstra NA. Nef Obtained from Individuals with HIV-1 Vary in Their Ability to Antagonize SERINC3- and SERINC5-Mediated HIV-1 Restriction. Viruses. 2021 Mar 6;13(3):423. doi: 10.3390/v13030423. PMID: 33800773; PMCID: PMC8000780.
3. Larsen MD, de Graaf EL, Sonneveld ME, Plomp HR, Nouta J, Hoepel W, Chen HJ, Linty F, Visser R, Brinkhaus M, Šuštić T, de Taeye SW, Bentlage AEH, Toivonen S, Koeleman CAM, Sainio S, Kootstra NA, Brouwer PJM, Geyer CE, Derksen NIL, Wolbink G, de Winther M, Sanders RW, van Gils MJ, de Bruin S, Vlaar APJ; Amsterdam UMC COVID-19; biobank study group, Rispens T, den Dunnen J, Zaaijer HL, Wuhrer M, Ellen van der Schoot C, Vidarsson G. Afucosylated IgG characterizes enveloped viral responses and correlates with COVID-19 severity. Science. 2021 Feb 26;371(6532):eabc8378. doi: 10.1126/science.abc8378. Epub 2020 Dec 23. PMID: 33361116; PMCID: PMC7919849.
4. van Bilsen WPH, Zimmermann HML, Boyd A, Coyer L, van der Hoek L, Kootstra NA, Hoornenborg E, Prins M, Schim van der Loeff MF, Davidovich U, Matser A. Sexual Behavior and Its Determinants During COVID-19 Restrictions Among Men Who Have Sex With Men in Amsterdam. J Acquir Immune Defic Syndr. 2021 Mar 1;86(3):288-296. doi: 10.1097/QAI.0000000000002581. PMID: 33230027; PMCID: PMC7879601.
5. van Haaren MM, McCoy LE, Torres JL, Lee W, Cottrell CA, Copps JL, van der Woude P, Yasmeen A, de Taeye SW, Torrents de la Peña A, Moore JP, Burton DR, Klasse PJ, Ward AB, Sanders RW, van Gils MJ. Antibodies from Rabbits Immunized with HIV-1 Clade B SOSIP Trimers Can Neutralize Multiple Clade B Viruses by Destabilizing the Envelope Glycoprotein. J Virol. 2021 Aug 10;95(17):e0009421. doi: 10.1128/JVI.00094-21. Epub 2021 Aug 10. PMID: 34076487 Free PMC article.
6. Basten M, den Daas C, Heijne JCM, Boyd A, Davidovich U, Rozhnova G, Kretzschmar M, Matser A. The Rhythm of Risk: Sexual Behaviour, PrEP Use and HIV Risk Perception Between 1999 and 2018 Among Men Who Have Sex with Men in Amsterdam, The Netherlands.AIDS Behav. 2021; 2021 Jun;25(6):1800-1809.
7. Caby F, Guiguet M, Weiss L, Winston A, Miro JM, Konopnicki D, Le Moing V, Bonnet F, Reiss P, Mussini C, Poizot-Martin I, Taylor N, Skoutelis A, Meyer L, Goujard C, Bartmeyer B, Boesecke C, Antinori A, Quiros-Roldan E, Wittkop L, Frederiksen C, Castagna A, Thurnheer MC, Svedhem V, Jose S, Costagliola D,

Mary-Krause M, Grabar S; (CD4/CD8 ratio and cancer risk) project Working Group for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. CD4/CD8 Ratio and the Risk of Kaposi Sarcoma or Non-Hodgkin Lymphoma in the Context of Efficiently Treated Human Immunodeficiency Virus (HIV) Infection: A Collaborative Analysis of 20 European Cohort Studies. Clin Infect Dis. 2021 Jul 1;73(1):50-59.

8. Coyer L, Boyd A, Davidovich U, van Bilsen WPH, Prins M, Matser A. Increase in recreational drug use between 2008 and 2018: results from a prospective cohort study among HIV-negative men who have sex with men. Addiction. 2021 Aug 17.
9. van Bilsen WPH, van Dulm E, Matser DA, Linde I, van Duijnhoven DYTHP, Prins PJM, Prins PM, Boyd DA, van Dam DAP. High carriage of ESBL-producing Enterobacteriaceae associated with sexual activity among men who have sex with men. Int J Antimicrob Agents. 2021 Jan 9:106276. doi: 10.1016/j.ijantimicag.2021.106276. Online ahead of print.
10. van Bilsen WPH, Zimmermann HML, Boyd A, Coyer L, van der Hoek L, Kootstra NA, Hoornenborg E, Prins M, Schim van der Loeff MF, Davidovich U, Matser A. Sexual Behavior and its determinants during COVID-19 restrictions among men who have sex with men in Amsterdam. J Acquir Immune Defic Syndr. 2021 Mar 1;86(3):288-296.
11. van Santen DK, Coutinho RA, van den Hoek A, van Brussel G, Buster M, Prins M. Lessons learned from the Amsterdam Cohort Studies among people who use drugs: a historical perspective. Harm Reduct J. 2021 Jan 6;18(1):2.doi: 10.1186/s12954-020-00444-6.
12. van Santen DK, Boyd A, Matser A, Maher L, Hickman M, Lodi S, Prins M. The effect of needle and syringe programme and opioid agonist therapy on the risk of HIV, hepatitis B and C virus infection for people who inject drugs in Amsterdam, the Netherlands: findings from an emulated target trial. Addiction. 2021 Nov;116(11):3115-3126.
13. Xiridou M, Visser M, Urbanus A, Matser A, van Benthem B, Veldhuijzen I. Ending risk-group HBV vaccination for MSM after the introduction of universal infant HBV vaccination: A mathematical modelling study. Vaccine. 2021 May 18;39(21):2867-2875.
14. Zimmermann HML, Postma LR, Achterbergh RCA, Reyniers T, Schim van der Loeff MF, Prins M, de Vries HJC, Hoornenborg E, Davidovich U; Amsterdam PrEP Project Team in the HIV Transmission Elimination Amsterdam Initiative (H-TEAM). The Impact of Pre-exposure Prophylaxis on sexual well-being among men who have sex with men. Arch Sex Behav. 2021 May;50(4):1829-1841.

15. Zimmermann HM, van Bilsen WP, Boyd A, Prins M, van Harreveld F, Davidovich U; HIV Transmission Elimination Team Amsterdam. Prevention challenges with current perceptions of HIV burden among HIV-negative and never-tested men who have sex with men in the Netherlands: a mixed-methods study. J Int AIDS Soc. 2021 Aug;24(8):e25715. doi: 10.1002/jia2.25715.
16. Zimmermann HML, van Bilsen WPH, Boyd A, Matser A, van Harreveld F, Davidovich U; HIV Transmission Elimination Amsterdam Initiative (H-TEAM). The Burden of With HIV is Mostly Overestimated by HIV-Negative and Never-Tested Men Who Have Sex With Men. AIDS Behav. 2021 Nov;25(11):3804-3813.
17. Basten Maartje G J, van Wees Daphne A, Matser Amy, Boyd Anders, Rozhnova Ganna, den Daas Chantal, Kretzschmar Mirjam E E, Heijne Janneke C M; Time for change: transitions between HIV risk levels and determinants of behavior change in men who have sex with men; Dec 2021, In: PLoS ONE. 16 , p. 1-13

Theses in 2021 that included ACS data

Ward van Bilsen – HIV and other sexually transmitted infections among men who have sex with men. Promotor: prof. dr. M. Prins. Co-promotor: dr. A.A. Matser

Maartje Dijkstra – Early diagnosis and immediate treatment of HIV infection. Promotors: prof. dr. M. Prins & prof. dr. J.M. Prins. Co-promotors: dr. G.J. de Bree & prof. dr. M.F. Schim van der Loeff.

Vita Jongen – Studies on HPV and PrEP How People Vaccinate and Practices of responsible and Efficient Prevention. Promotors: prof. dr. M. Prins and prof. dr. M.F. Schim van der Loeff. Co-promotor: dr. E. Hoornenborg

Zita Kruize – HIV-1 infection: A complex interplay between virus and host
Promotor: N A Kootstra; copromotor: T Booiman

References

Coyer, L., Boyd, A., Davidovich, U., van Bilsen, W. P. H., Prins, M., & Matser, A. (2022). Increase in recreational drug use between 2008 and 2018: results from a prospective cohort study among HIV-negative men who have sex with men. *Addiction, 117*(3), 656-665. doi:10.1111/add.15666

Kruize, Z., van Nuenen, A. C., van Wijk, S. W., Girigorie, A. F., van Dort, K. A., Booiman, T., & Kootstra, N. A. (2021). Nef Obtained from Individuals with HIV-1 Vary in Their Ability to Antagonize SERINC3- and SERINC5-Mediated HIV-1 Restriction. *Viruses, 13*(3). doi:10.3390/v13030423

Larsen, M. D., de Graaf, E. L., Sonneveld, M. E., Plomp, H. R., Nouta, J., Hoepel, W., [...] Vidarsson, G. (2021). Afucosylated IgG characterizes enveloped viral responses and correlates with COVID-19 severity. *Science, 371*(6532). doi:10.1126/science.abc8378

Scherpenisse, M., Kootstra, N. A., Bakker, M., Berkhout, B., & Pasternak, A. O. (2021). Cell-Associated HIV-1 Unspliced-to-Multiply-Spliced RNA Ratio at 12 Weeks of ART Predicts Immune Reconstitution on Therapy. *mBio, 12*(2). doi:10.1128/mBio.00099-21

van Bilsen, W. P. H., van Dulm, E., Matser, A., Linde, I., van Duijnhoven, Y., Prins, J. M., [...] van Dam, A. P. (2021). High carriage of ESBL-producing Enterobacteriaceae associated with sexual activity among men who have sex with men. *Int J Antimicrob Agents*, 106276. doi:10.1016/j.ijantimicag.2021.106276

van Santen, D. K., Boyd, A., Matser, A., Maher, L., Hickman, M., Lodi, S., & Prins, M. (2021). The effect of needle and syringe programme and opioid agonist therapy on the risk of HIV, hepatitis B and C virus infection for people who inject drugs in Amsterdam, the Netherlands: findings from an emulated target trial. *Addiction, 116*(11), 3115-3126. doi:10.1111/add.15503

Verburgh, M. L., Boyd, A., Wit, F., Schim van der Loeff, M. F., van der Valk, M., Bakker, M., [...] Reiss, P. (2022). Similar Risk of Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Similar Nucleocapsid Antibody Levels in People With Well-Controlled Human Immunodeficiency Virus (HIV) and a Comparable Cohort of People Without HIV. *J Infect Dis, 225*(11), 1937-1947. doi:10.1093/infdis/jiab616

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.

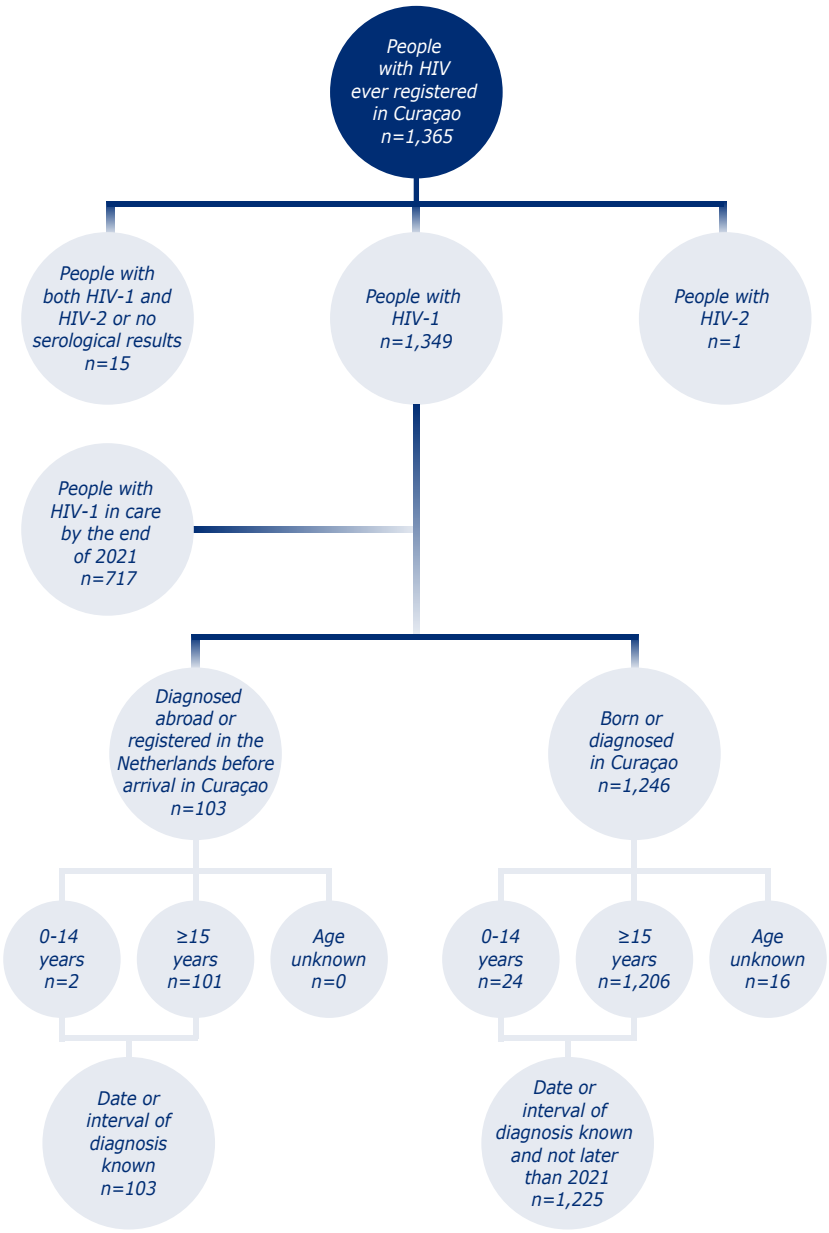
In total, 1,365 individuals with HIV recorded by SHM have been registered in Curaçao. Of these people, the majority were diagnosed with HIV-1 (n=1,349, or 99%), while one individual was diagnosed with HIV-2, and three had antibodies against both HIV-1 and HIV-2 (*Figure 9.1*). For 12 individuals, serological results on HIV type were not available in the SHM database.

The population with HIV in Curaçao

People newly diagnosed with HIV-1

Of the 1,349 individuals diagnosed with HIV-1, 96 (7%) were registered with an HIV treatment centre in the Netherlands prior to moving to Curaçao (*Figure 9.1*). The majority of these 96 individuals (n=70, or 73%) originated from the former Netherlands Antilles, while 21 (22%) were born in the Netherlands and five (5%) were born elsewhere. Another seven individuals were also born abroad, including four in Venezuela, and had a documented HIV diagnosis prior to migrating to Curaçao. The remaining 1,246 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 1,246 individuals, 931 (75%) were born in the former Netherlands Antilles, 112 (9%) originated from Haiti, and 90 (7%) from the Dominican Republic.

Figure 9.1: Overview of the population with HIV registered in Curaçao.



For 21 (2%) of the 1,246 individuals diagnosed while living in Curaçao, the date or interval of diagnosis was not recorded in the SHM database, or they were diagnosed in 2022. Among the remaining 1,225 individuals, 24 (2%) were diagnosed before the age of 15 years. The 1,201 individuals who were diagnosed at the age of 15 years and over comprised (*Table 9.1*):

- 249 (21%) men who reported sex with men (MSM) as the most likely mode of transmission;
- 515 (43%) other men,
  - 330 (64%) of whom reported sex with women as the most likely mode of transmission
  - 185 (36%) reported other or unknown modes of transmission;
- 437 (36%) women,
  - 417 (95%) of whom reported sex with men as the most likely mode of transmission
  - 20 (5%) reported other or unknown modes of transmission.

Between 2000 and 2018, the annual number of newly-diagnosed infections hovered around 50, before decreasing to below 30 in most recent calendar years.

Among the 83 individuals diagnosed in 2019 or later, the median age at diagnosis was 35 years (interquartile range [IQR] 27-50), with no differences between men and women. Of these 83 individuals:

- 26 (31%) were younger than 30 years of age at the time of diagnosis;
- 22 (27%) were aged between 30 and 39 years;
- 16 (19%) were aged between 40 and 49 years; and
- 19 (23%) were aged 50 years and over.

Table 9.1: Annual number of HIV-1 diagnoses in Curaçao among children under 15 years of age, and among men who acquired HIV via sex with men (MSM), other men, and women diagnosed at 15 years and over. Note: Data collection for 2021 may not have been finalised at the time of writing.

Year of diagnosis	MSM	Other men	Women	<15 years of age	Total
≤1999	31	105	77	17	230
2000	7	18	18	1	44
2001	3	13	14	1	31
2002	7	19	17	0	43
2003	8	28	19	0	55
2004	3	23	16	0	42
2005	12	19	17	0	48
2006	6	23	17	0	46
2007	12	18	10	0	40
2008	11	17	20	1	49
2009	9	17	21	1	48
2010	4	19	21	0	44
2011	12	19	24	0	55
2012	13	17	26	0	56
2013	19	31	22	1	73
2014	16	14	14	0	44
2015	16	22	12	1	51
2016	12	23	15	0	50
2017	14	17	13	0	44
2018	16	14	19	0	49
2019	7	11	7	0	25
2020	6	12	11	0	29
2021	5	16	7	1	29
Total	**249**	**515**	**437**	**24**	**1,225**

Legend: MSM = sex between men.

People in clinical care

In total, 717 (53%) of the 1,349 registered individuals with HIV-1 were known to be in clinical care in Curaçao by the end of 2021. People were considered to be in clinical care if they had visited their treating physician in 2021, or had a CD4 cell count or HIV RNA measurement during that year, and had not moved abroad. Of the 632 individuals who, according to this definition, were not in care by the end of 2021:

- 204 (32%) were known to have died;
- 159 (25%) had moved abroad; and
- 263 (42%) were lost to care

The remaining six individuals only entered HIV care in 2022. Of the 263 people lost to care, 59 (22%) had their last visit within a year of entering care, while another 31 (12%) had no follow-up visit after entering care. Of those lost to care:

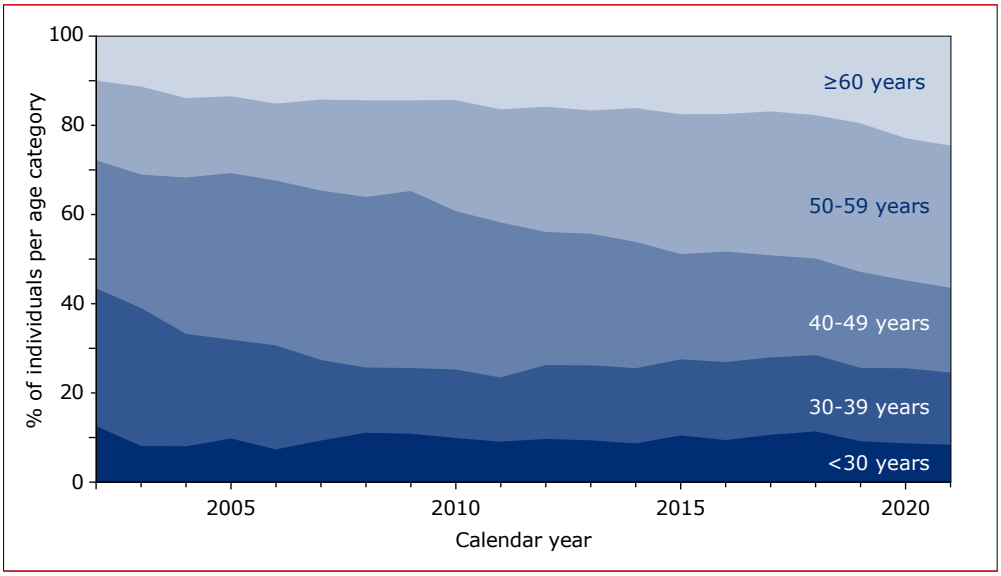
- 154 (59%) originated from the former Netherlands Antilles;
- 49 (19%) were from Haiti;
- 28 (11%) were from the Dominican Republic; and
- 32 (12%) were from other countries.

The 717 people in clinical care in 2021 included 14 individuals who did not have a clinical visit, CD4 cell count or HIV RNA measurement in 2020, but had previously received care for their HIV infection. Four of these individuals had not been in care for more than three years.

Ageing population

The median age of the population in care by the end of 2021 was 52 years (IQR 40-60), a figure which has been increasing since 2002 (*Figure 9.2*). 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 (56%) are aged 50 years and over, including 54% of men and 60% of women. A quarter of those in care (25%) are 60 years and over.

Figure 9.2: 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 2021, these proportions were 8% and 56%, respectively, while 25% 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 2021 had been diagnosed with HIV a median of 10.8 years (IQR 6.0-17.3) previously. Therefore, a large group (54%) has lived with HIV for more than 10 years; 17% for more than 20 years (*Table 9.2*). The median time since diagnosis was 10.4 years for MSM, 10.6 years for other men, and 11.6 years for women.

Table 9.2: Characteristics of the 717 individuals with an HIV-1 infection in clinical care in Curaçao by the end of 2021.

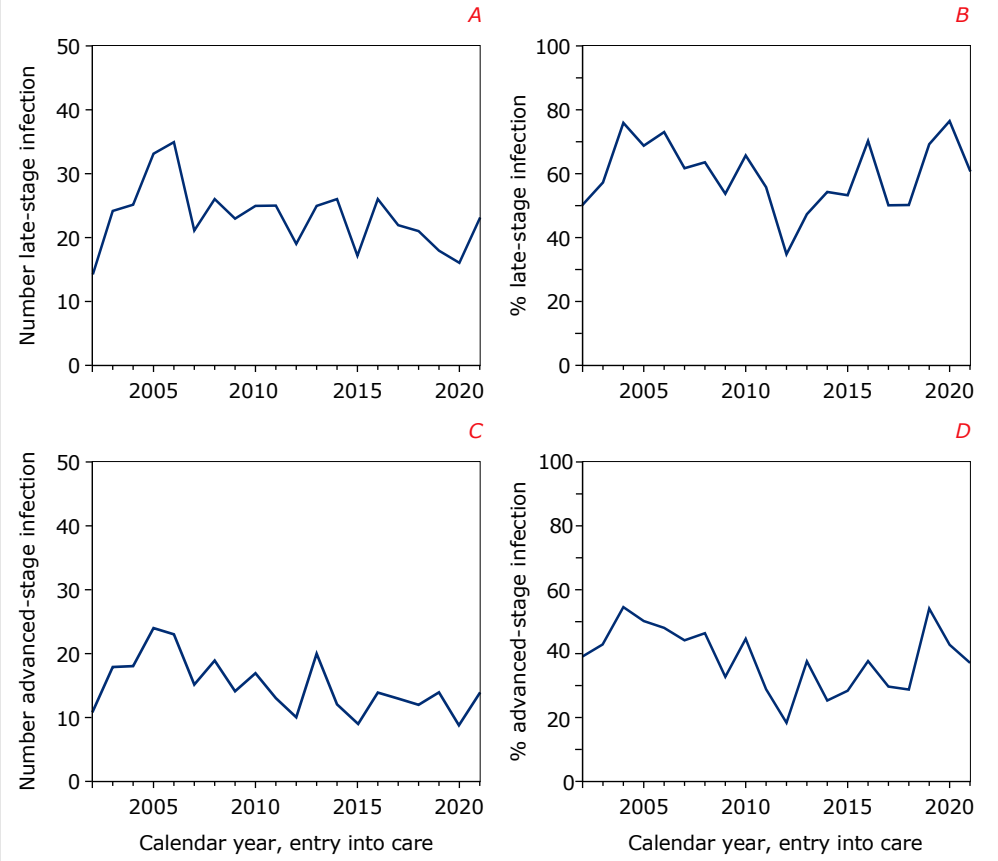
	Men (n=443, 62%)		Women (n=274, 38%)		Total (n=717)	
	n	%	n	%	n	%
Transmission						
MSM	166	37	-	-	166	23
Heterosexual	180	41	260	95	440	61
Other/unknown	97	22	14	5	111	15
Current age (years)						
0-14	2	1	2	1	4	1
15-24	10	2	7	3	17	2
25-29	23	5	16	6	39	5
30-39	77	17	39	14	116	16
40-49	90	20	46	17	136	19
50-59	138	31	91	33	229	32
60-69	71	16	51	19	122	17
≥70	32	7	22	8	54	8
Country of origin						
Former Netherlands Antilles	368	83	184	67	552	77
The Dominican Republic	9	2	41	15	50	7
Haiti	23	5	26	9	49	7
The Netherlands	10	2	0	0	10	1
Other	33	7	23	8	56	8
Years aware of HIV infection						
<1	22	5	8	3	30	4
1-2	35	8	17	6	52	7
3-4	41	9	23	8	64	9
5-9	113	26	67	24	180	25
10-19	159	36	106	39	265	37
≥20	71	16	51	19	122	17
Unknown	2	1	2	1	4	1

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

Late presentation

Among the 1,225 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[1]. The proportion of late presenters was 57% among individuals entering care in 2002-2018, and remained at a high level of 67% among those entering care in 2019 or later (*Figures 9.3A* and *9.3B*).

Figure 9.3: *Number and proportion of people classified as presenting with (A, B) late-stage, or (C, D) advanced-stage HIV infection at the time of entry into care. From 2019 onwards, 57 (67%) individuals presented with late HIV disease while 37 (44%) were advanced presenters. Late-stage HIV infection: CD4 cell counts below 350 cells/mm³ or having AIDS, regardless of CD4 cell count. Advanced-stage HIV infection: CD4 cell counts below 200 cells/mm³ or having AIDS. 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 2019 onwards, the stage of infection was unknown for 15 (15%) individuals.*



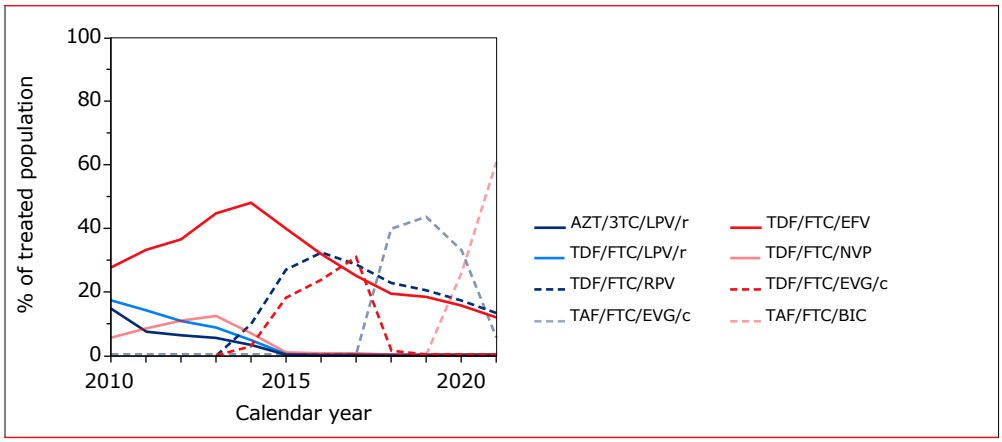
Advanced HIV infection (i.e. with a CD4 cell count below 200 cells/mm^3 or AIDS) was found in 37% in 2002-2018 and in 44% in 2019 or later (*Figures 9.3C* and *9.3D*). In total, 11 (11%) of the individuals who entered care since 2019 presented with an AIDS-defining disease. There were no significant differences in the proportion of individuals with late presentation in 2019 or later between MSM (71%), other men (67%), and women (65%).

Antiretroviral therapy (ART)

In total, 1,247 (92%) of the 1,349 registered individuals with HIV-1 had started antiretroviral therapy by the end of 2021. Of the 102 people who had not started therapy by that time, 93 were no longer in care, including 35 who had died. None of these 93 individuals had been seen for HIV care after 2017. Two of the 102 individuals who had not started therapy, managed to achieve HIV RNA levels below the lower limit of quantification without therapy. The other seven individuals started therapy in 2022, or their ART may not have been recorded yet.

Over time there have been clear shifts in the ART regimens prescribed in Curaçao (*Figure 9.4*). Of the 714 people who were still in care by the end of 2021 and had started ART:

Figure 9.4: *Percentage of individuals treated with antiretroviral therapy (ART) by specific regimens over calendar time. At the end of 2021, 61% were receiving TAF/FTC/BIC, 13% TDF/FTC/RPV, 12% TDF/FTC/EFV, and 6% TAF/FTC/EVG/c.*



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.*

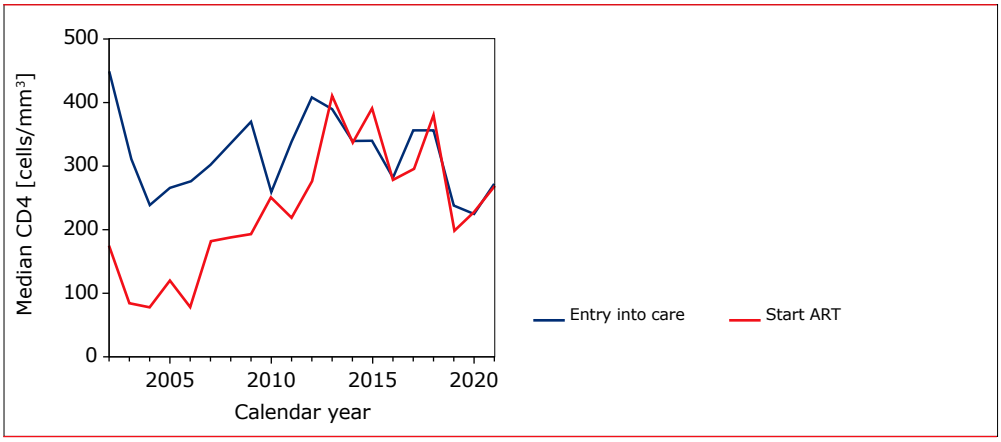
- 61% were being treated with a combination of tenofovir alafenamide, emtricitabine, and bictegravir;
- 13% with tenofovir disoproxil, emtricitabine, and rilpivirine;
- 12% with tenofovir disoproxil, emtricitabine, and efavirenz; and
- 6% with tenofovir alafenamide, emtricitabine, and cobicistat-boosted elvitegravir.

The majority (97%) used a once-daily regimen, with 92% being treated with a fixed-dose, single tablet regimen.

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 9.5*). 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 2019-2021, 96% 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:

- 45% had a measurement below 200 CD4 cells/mm^3;
- 21% had a measurement between 200 and 349 cells/mm^3;
- 16% had a measurement between 350 and 499 cells/mm^3; and
- 18% had CD4 cell counts of 500 cells/mm^3 or higher.

Figure 9.5: *Changes over calendar time in median CD4 cell counts at entry into care and at the start of antiretroviral therapy (ART). In 2019-2021, CD4 cell counts at entry into care were 250 cells/mm^3 (interquartile range [IQR] 130-418) and were similar, 232 cells/mm^3 (IQR 114-393), at the start of therapy.*

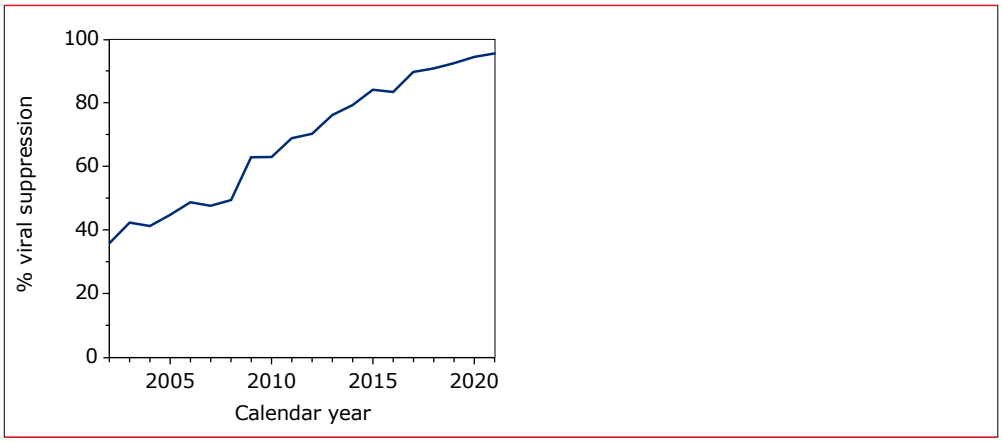


Legend: *ART = antiretroviral therapy.*

Therapy outcome

In the total population still in care by the end of 2021, the median current CD4 cell count was 501 cells/mm^3 (IQR 315-743). CD4 cell counts were highest in women (603 cells/mm^3; IQR 376-826) followed by MSM (502 cells/mm^3; IQR 356-726) and men who acquired their infection via other or unknown modes of transmission (403 cells/mm^3; IQR 244-618). 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 2021 (*Figure 9.6*).

Figure 9.6: *Proportion of people in care with HIV RNA <200 copies/ml at their last viral load measurement in each calendar year.*

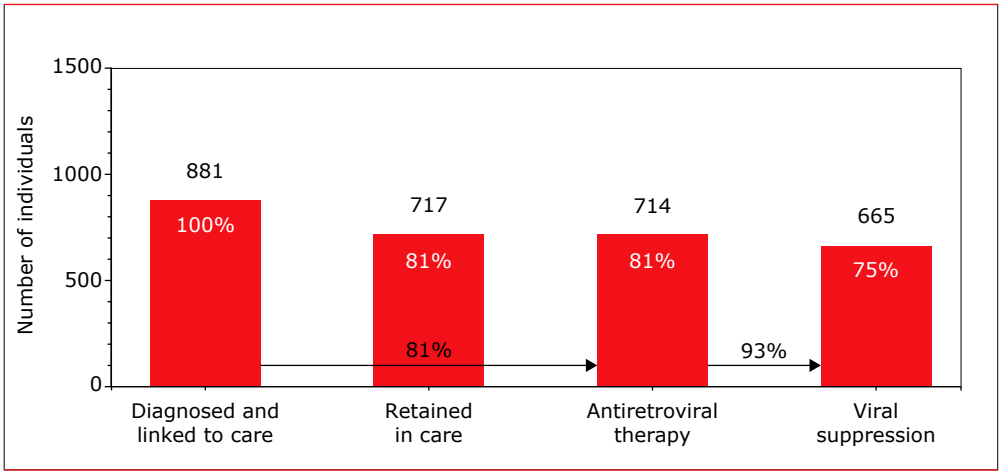


Continuum of HIV care

In total, 881 individuals had been diagnosed and linked to care, registered by SHM, had received HIV care in 2011 or later, and were not recorded in the SHM database as having died or moved abroad (*Figure 9.7*). Altogether:

- 717 people (or 81% 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 2021;
  - 714 (or 81% of those diagnosed and linked to care) of whom had started ART;
    - 695 (97% of those who started therapy) of whom had an HIV RNA measurement available in 2021; and
      ~665 (96%, or 93% of those treated) of those had a most recent HIV RNA level below 200 copies/ml.

Figure 9.7: Continuum of HIV care for the population with HIV-1 in Curaçao diagnosed and linked to care by the end of 2021. Percentages at the top of the bars are calculated relative to the number of people diagnosed and linked to care, while percentages at the bottom correspond to the second and third of UNAIDS' 95-95-95 targets.



Overall, 75% of the 881 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 81-93: 81% of all people diagnosed receive antiretroviral therapy, and 93% of people receiving ART have a suppressed viral load[2].

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 714 individuals who had started ART, 49 (7%) did not have a suppressed viral load. On closer inspection, 19 (39%) of these individuals were found to have no documented HIV RNA measurement in 2021. The remaining 30 (61%) had a viral load measurement in 2021, but with HIV RNA levels exceeding 200 copies/ml. Of these 30 individuals, two 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 28 individuals with HIV RNA levels above 200 copies/ml had been on ART for longer than six months.

Lost to care

In total, 263 individuals were lost to care by the end of 2021, of whom:

- 99 (38%) were last seen for care before the end of 2011;
- 104 (40%) between 2012 and 2017;
- 18 (7%) in 2018
- 30 (11%) in 2019; and
- 12 (5%) in 2020.

The 99 individuals who were lost to care before 2011 were excluded from the number of people diagnosed and linked to care. It is unlikely that these 99 individuals are still living in Curaçao without requiring care or ART. In total, 54 (33%) of the 164 individuals lost to care were born outside the former Netherlands Antilles, including 21 in Haiti and 11 in the Dominican Republic. For those still in care by the end of 2021, 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 relatively high proportion of people lost to care is worrisome and may result in underreporting of death and/or outmigration. Furthermore, the proportion of people entering care with late-stage HIV infection remained high in recent years.

The impact of the COVID-19 pandemic on HIV care in Curaçao appears to be limited. The number of individuals newly diagnosed with HIV in 2020 and 2021 was comparable with 2019, and in people who were receiving HIV care the proportion with a suppressed viral load remained high. There was, however, quite a substantial group of 30 individuals who were last seen for care in 2019 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. In respect of the latter, a crucial step has been taken with the addition of data on children with HIV. In 2021 three children below the age of 15 years were newly registered with SHM, including two who had already received HIV care for several years.

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.

References

1. Antinori A, Coenen T, Costagiola D, et al. Late presentation of HIV infection: a consensus definition. *HIV Med*. 2011;12(1):61-64.doi:10.1111/j.1468-1293.2010.00857.x
2. Joint United Nations Programme on HIV/AIDS (UNAIDS). *End Inequalities. End AIDS. UNAIDS Global AIDS Strategy 2021-2026*.; 2021. https://www.unaids.org/sites/default/files/media_asset/global-AIDS-strategy-2021-2026_en.pdf

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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