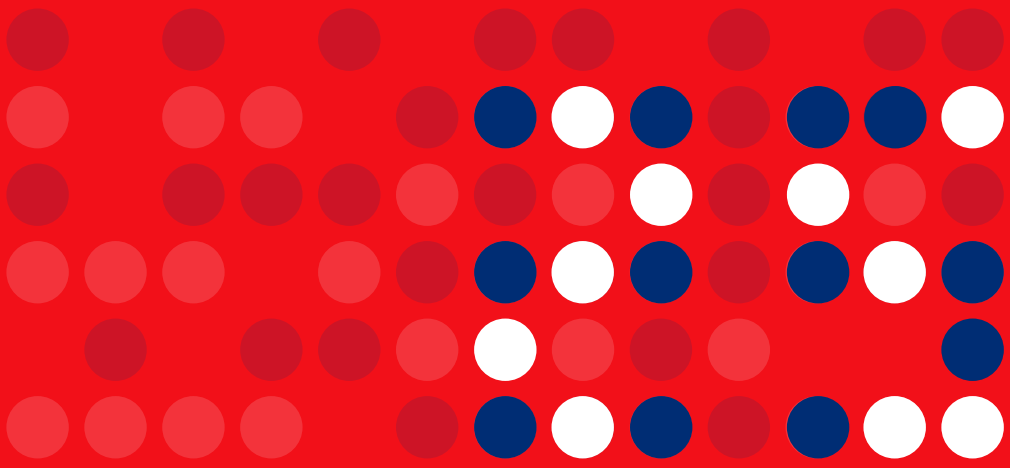
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2025

Chapter 7: Viral hepatitis



7. Viral hepatitis

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Key findings

Hepatitis C (2015–2024)

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

Hepatitis B

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

Hepatitis A

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

Introduction

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

Hepatitis C virus (HCV)

Box 7.1: Definitions of hepatitis C infection.

Primary HCV infection
First documented HCV infection.

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

Recent HCV infection[3,4]

1. Case definition of recent HCV according to preferred criteria[3]:
   Positive anti-HCV IgG with a documented negative anti-HCV IgG within the past 12 months,
   or:
   detectable HCV RNA in the presence with either a documented negative HCV RNA test, or a negative anti-HCV IgG within the past 12 months.
2. Case definition of acute HCV according to alternative criteria[3]:
   Detectable HCV RNA in association with a rise in alanine aminotransferase (ALT) (above 200 IU/l) with a documented normal ALT within the past 12 months.

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

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

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

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

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

HCV screening over time

In the Netherlands the national guidelines for the treatment and monitoring of HIV recommend HCV screening during the first clinical visit after HIV diagnosis, and additional annual HCV screening for MSM who report behaviour associated with increased risk of acquiring HCV[5].

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

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

Follow-up screening

Individuals with a negative first HCV test

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

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

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

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

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

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

When testing was stratified by age, the highest percentage of testing was seen among MSM under 30 years of age, and testing decreased with increasing age (*Figure 7.1*). From the diagnosis data we known that the median age at diagnosis of recent HCV was 44 years (IQR 36-50) (*Table 7.2A*), while in the age range 40-50 years, 42% had at least one test in 2024.

Individuals with a history of HCV infection

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

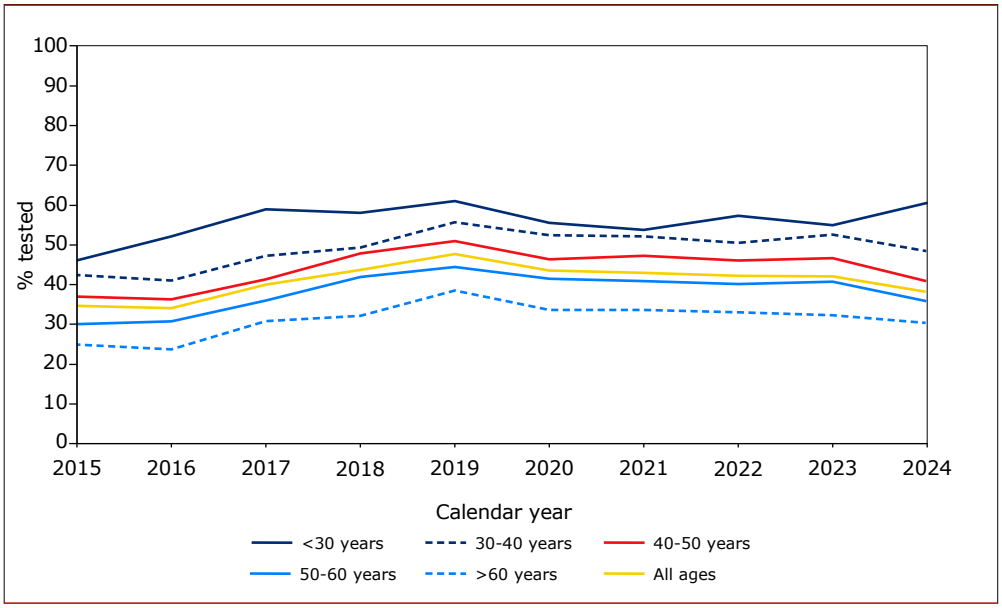
Among MSM with HIV at risk of reinfection after treatment-induced or spontaneous clearance of HCV, the percentage of MSM with repeated HCV RNA testing declined from 53% in 2015 to 37% in 2024. The median cumulative number of repeated HCV RNA tests among MSM with a history of HCV was 10 (IQR: 5-16).

Targeted screening, based on the presence of incident transaminase elevations

National guidelines advice additional annual HCV screening for MSM who report behaviour associated with increased risk of acquiring HCV[5]. The above-described HCV RNA follow up testing data may include MSM who are not considered at risk of HCV reinfection anymore by their treating physician. However, we cannot exclude these individuals as data on HCV-related risk-taking behaviour are not available to SHM. Also of note is that repeated HCV screening among MSM at risk

of HCV reinfection might be guided by a policy of targeted screening, based on the presence of incident transaminase elevations as an indicator of liver inflammation. This might be reflected by the observed higher proportion of repeat HCV screening among MSM with elevated transaminase levels (defined as an increase of at least 50% compared to the last measured ALT value). In those at risk of HCV reinfection and incident transaminase elevations, the overall percentage of men with an HCV test following elevated transaminase level varied between 60% and 77% in 2015-2024.

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



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

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

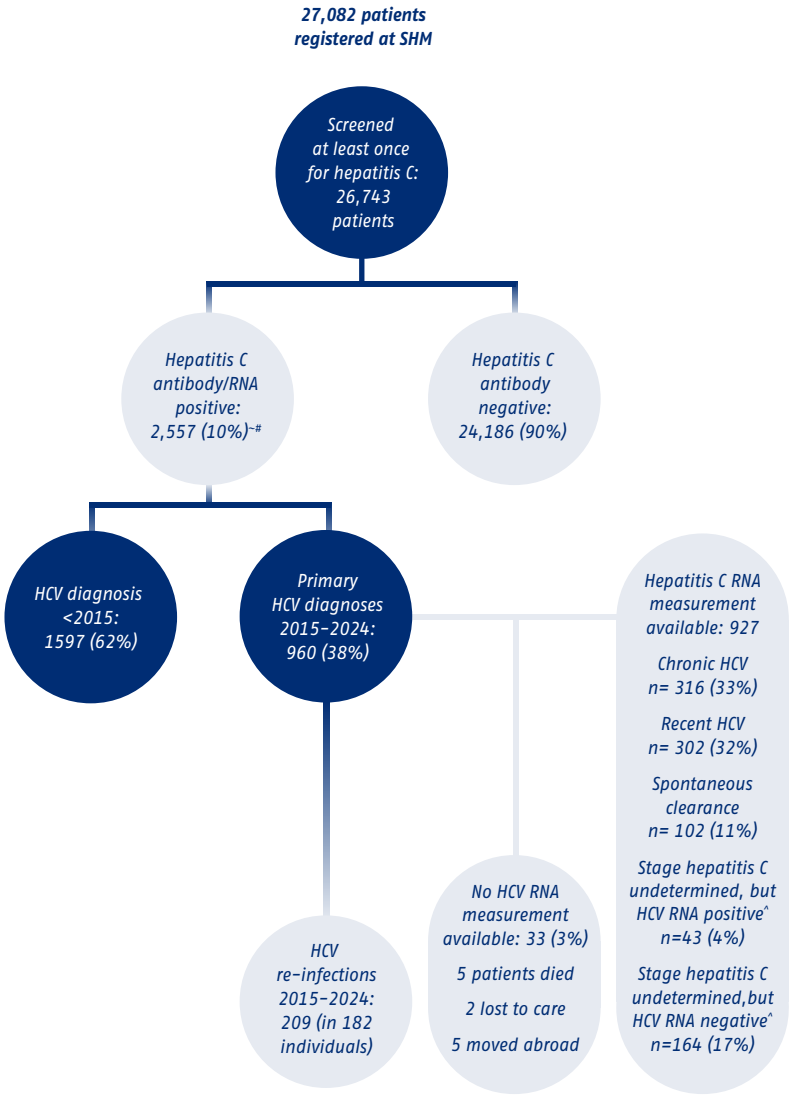
- 5 had died;
- 2 had been lost to care;
- 5 had moved abroad; and
- 21 do not have a known reason for an undocumented HCV RNA outcome.

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

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

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

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



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

Spontaneous clearance of HCV

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Changes over time

Number of diagnoses of primary HCV and reinfection

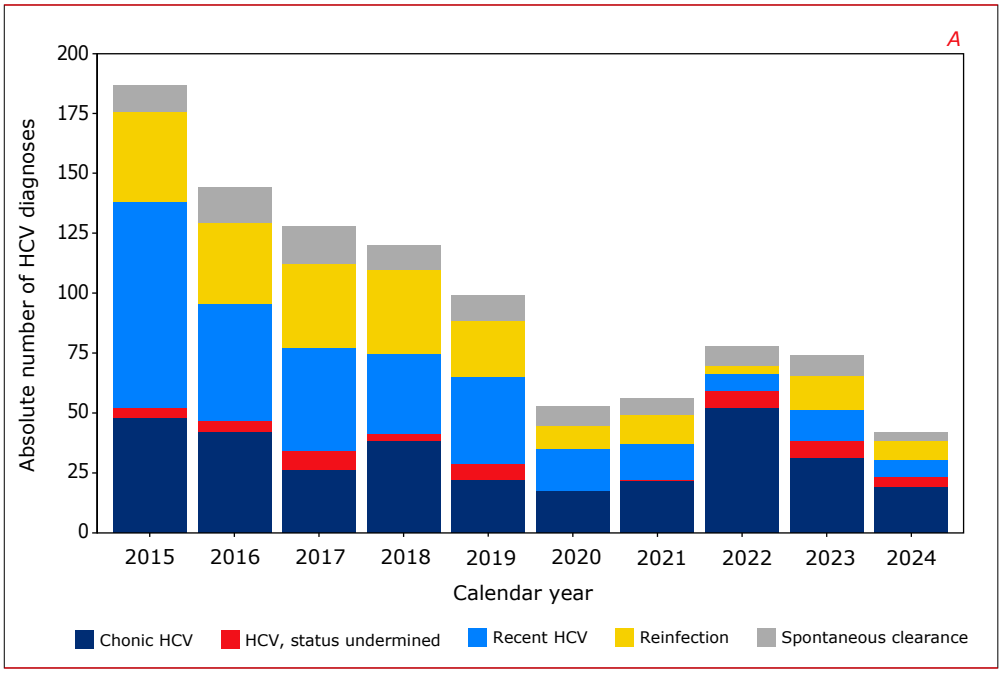
Between 2015 and 2024, 972 HCV diagnoses with detectable HCV RNA occurred (763 primary infections and 209 reinfections). The annual number of primary HCV diagnoses (ie with detectable HCV RNA) and HCV reinfection decreased from 187 cases in 2015 to 78 and 74 in 2022 and 2023, respectively. The decreasing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

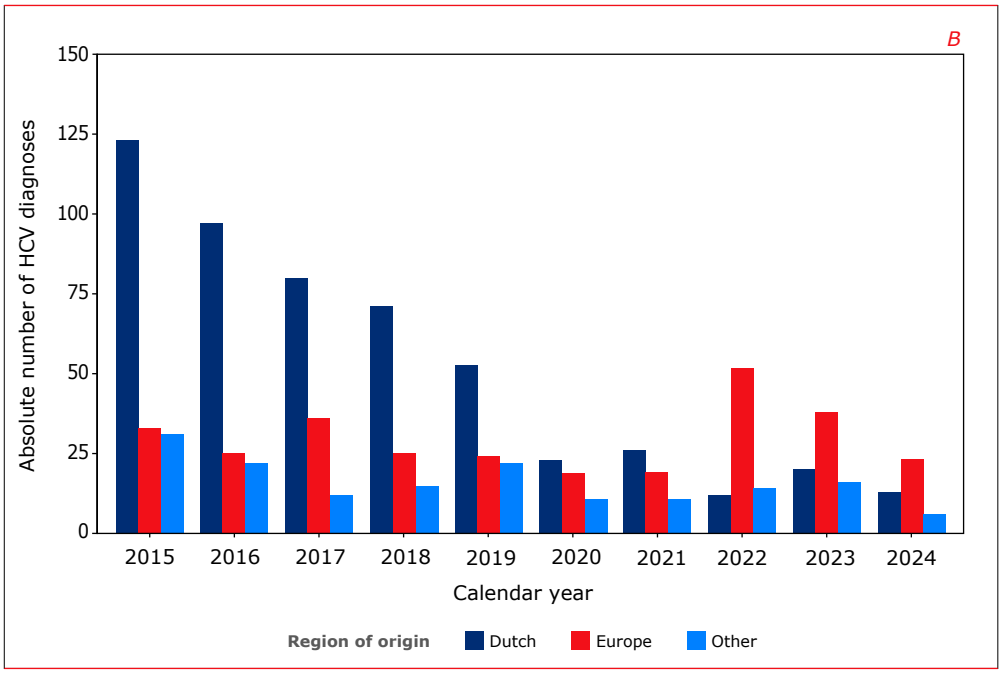
Of the HCV diagnoses with detectable HCV RNA between 2015 and 2024, 518 (53%) originated from the Netherlands, 14% from Eastern Europe, 9% from Western Europe and 8% from Central Europe. Between 2015 and 2021, the majority of individuals with an HCV diagnosis originated from the Netherlands. But the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

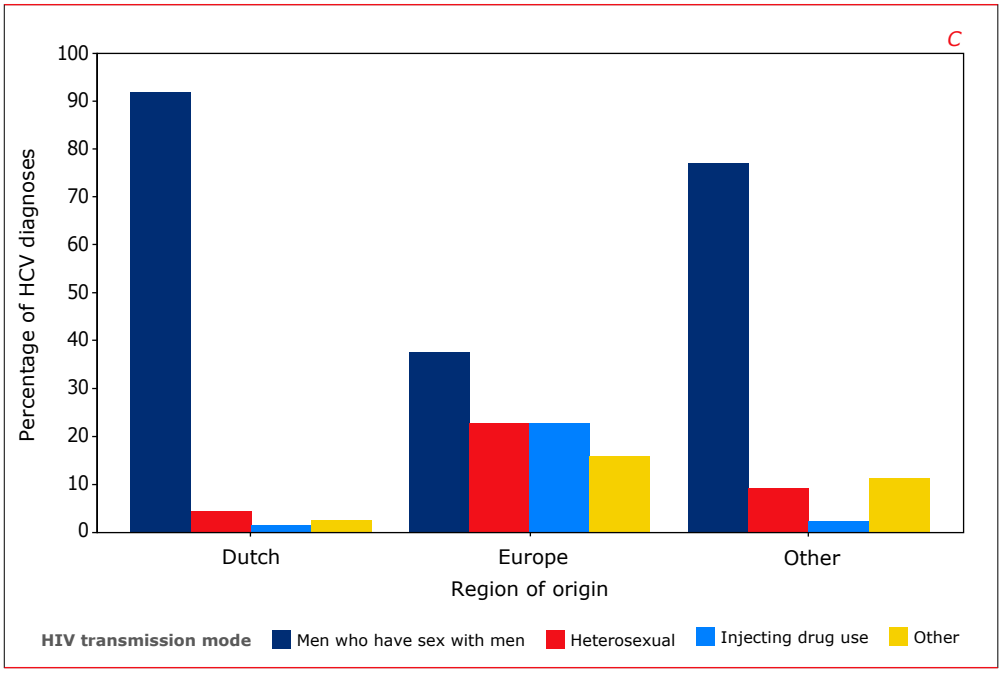
Prevalence of detectable HCV RNA

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

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



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Percentage of HCV diagnoses
Dutch
Europe
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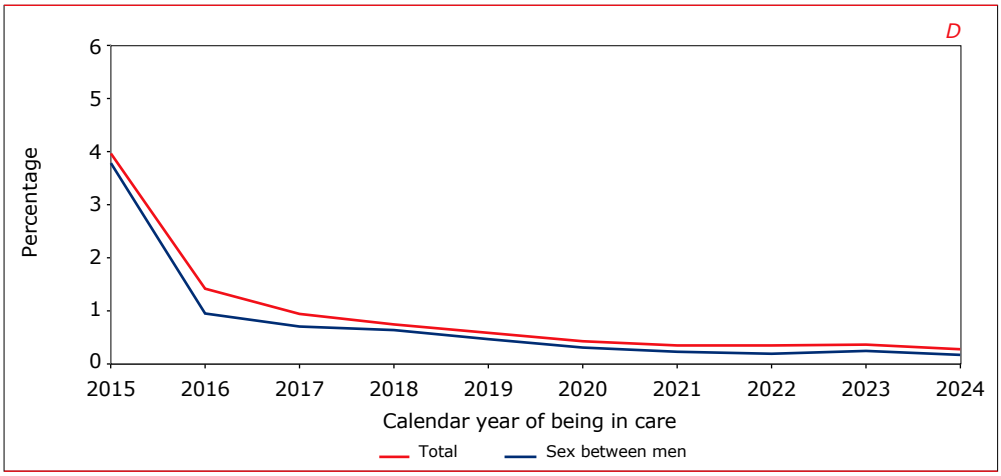
HIV transmission mode
Men who have sex with men
Heterosexual
Injecting drug use
Other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2020
2021
2022
2023
2024
Calendar year of being in care
Total
Sex between men

Incidence of new HCV infections

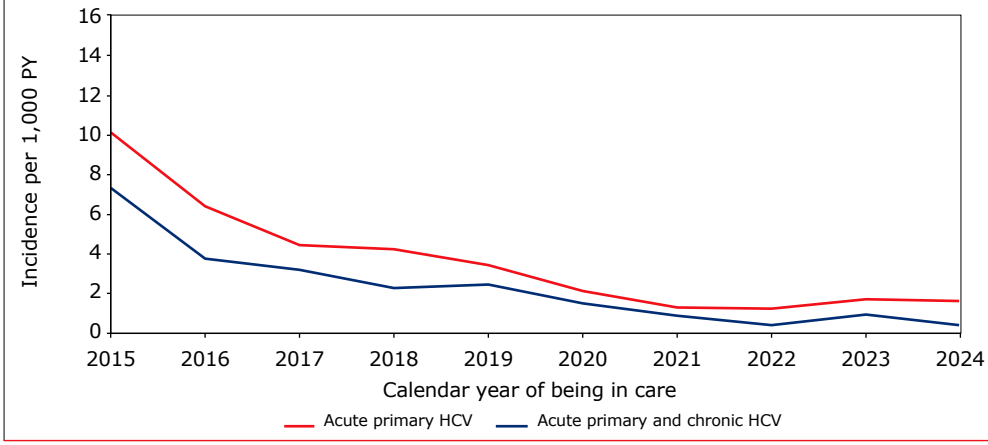
The incidence of primary infection is calculated for individuals with a first documented HCV infection, based on the date of their first positive HCV antibody or HCV RNA test result. The definition of recent HCV infection is consistent with the one given in the European AIDS Treatment Network's (NEAT) preferred criteria[7]. We have expanded this definition to include alternative criteria[3,4]. This alternative definition is based on (i) detectable HCV RNA associated with an acute rise in alanine aminotransferase (ALT) greater than five times the upper limit of normal (above 200 U/l), and (ii) a documented normal ALT within the past 12 months, together with (iii) no change in antiretroviral regimen in the last six months.

There were important differences in the incidence of primary recent HCV infection in terms of HIV transmission category. Between 2015 and 2024, the majority of recent HCV infections occurred in MSM (n=280/302 [93%]). In contrast to the high prevalence of HCV in PWID or former PWID, the overall incidence of recent HCV in this group was low, occurring in only two out of the 490 PWID or former PWID. This is probably due to the high background prevalence of HCV infection in former PWID, the fact that injecting drug use has become very uncommon in the Netherlands, and the effective harm-reduction programmes implemented in addictive care centres in the Netherlands. Twelve cases occurred among individuals who had acquired HIV heterosexually (*Table 7.2*).

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

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

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



Legend: HCV = hepatitis C virus.

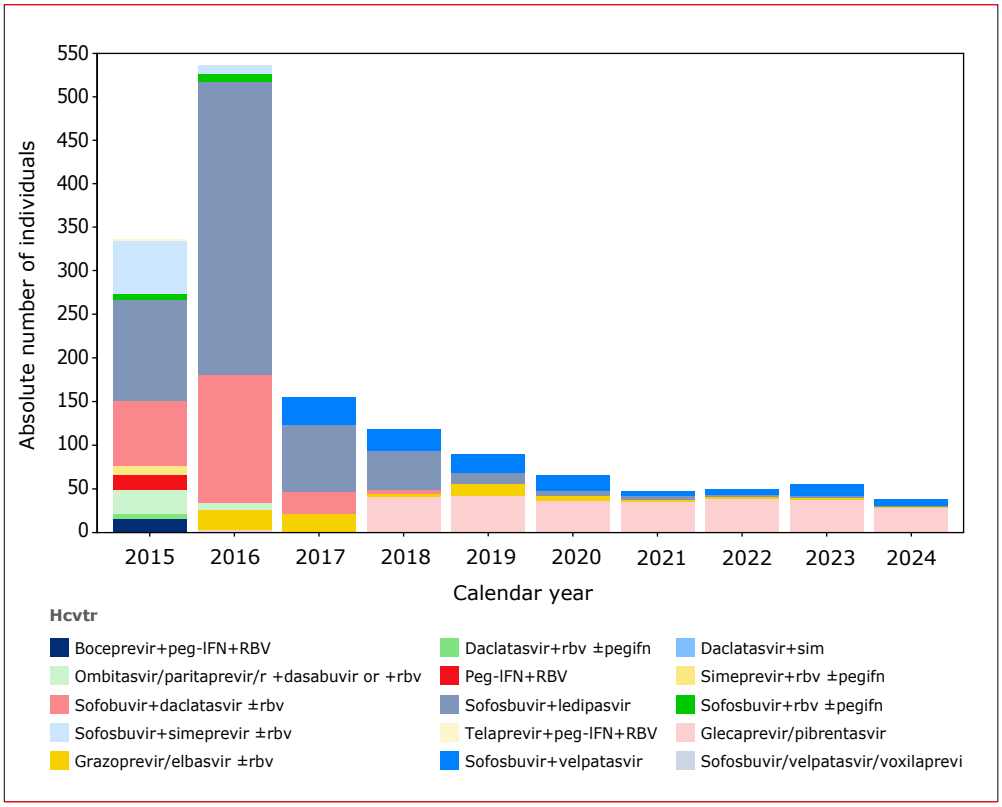
HCV treatment

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

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

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

Figure 7.5: Number of individuals with HIV/HCV starting hepatitis C treatment per calendar year.



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

Treatment with DAAs

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

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

The most frequently used DAA regimens were:

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

Treatment outcomes

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

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

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

Among the 43 individuals who did not achieve SVR:

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

HCV reinfection

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

To identify possible HCV reinfection among individuals who previously had HCV, we selected people who initially achieved an SVR after receiving any type of HCV treatment, and individuals with spontaneous clearance of HCV.

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

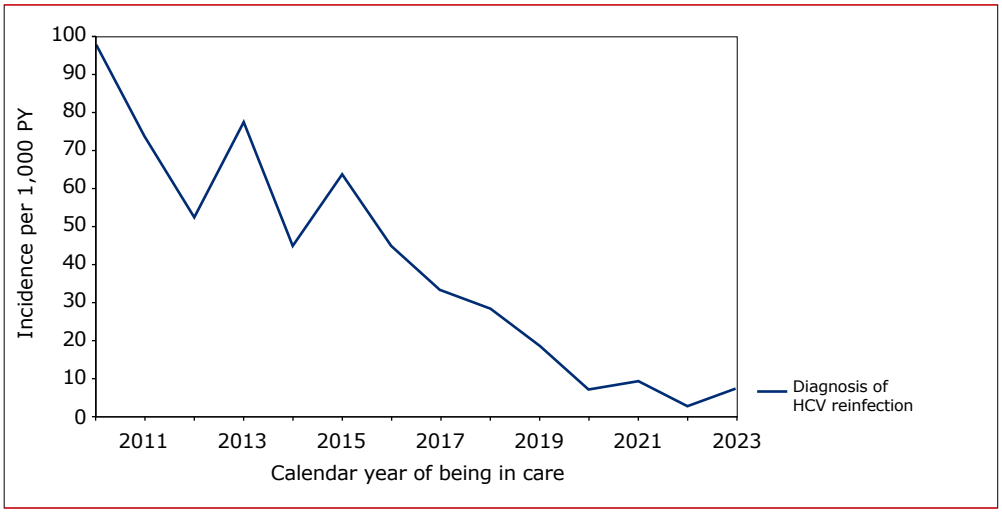
Most individuals who became reinfected were MSM (163 out of 182, 90%). Another 4 were PWID or former PWID (2%). For the remaining 15 individuals, documented HIV transmission routes were heterosexual contact (n=6) and another or unknown (n=9).

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

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

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

Figure 7.6: Incidence of hepatitis C reinfection after earlier treatment-induced and spontaneous clearance among men who have sex with men, per calendar year.



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

Continuum of care for those with diagnosed HCV

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

Of the 1,604 individuals linked to HIV care:

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

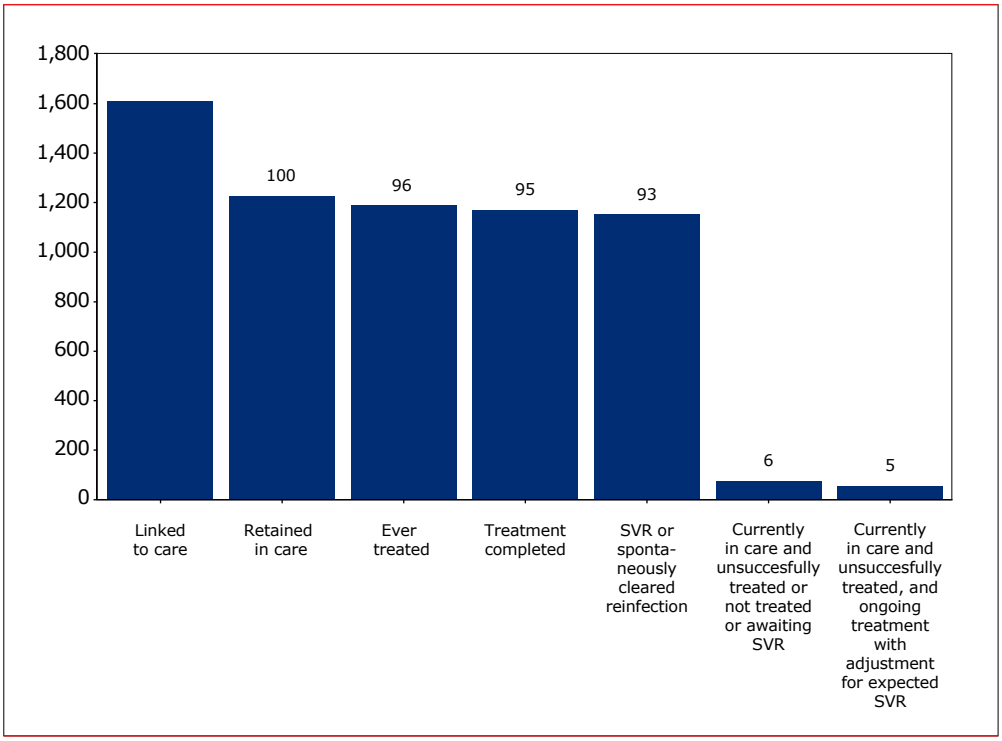
Overall, 1,146 of the 1,166 people in care in 2024 who completed treatment (98%) achieved SVR, including those who were retreated after earlier treatment failure. Another 5 individuals with HCV reinfection had a negative last HCV RNA test result, without documentation of HCV treatment. It is likely these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

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

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

For 20/75 individuals SVR could not yet be determined, all had been treated with novel DAA combinations. For that reason, we have extrapolated the observed DAA SVR rate for these individuals and assumed that 19 of the 20 (96%) will achieve SVR. This results in an estimate of individuals 56 (75-19=56) who have yet to be treated or were unsuccessfully treated.

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



Legend: SVR=sustained virological response.

Liver-related morbidity and mortality in individuals with HCV

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

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

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

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

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

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

Hepatitis B virus

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

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

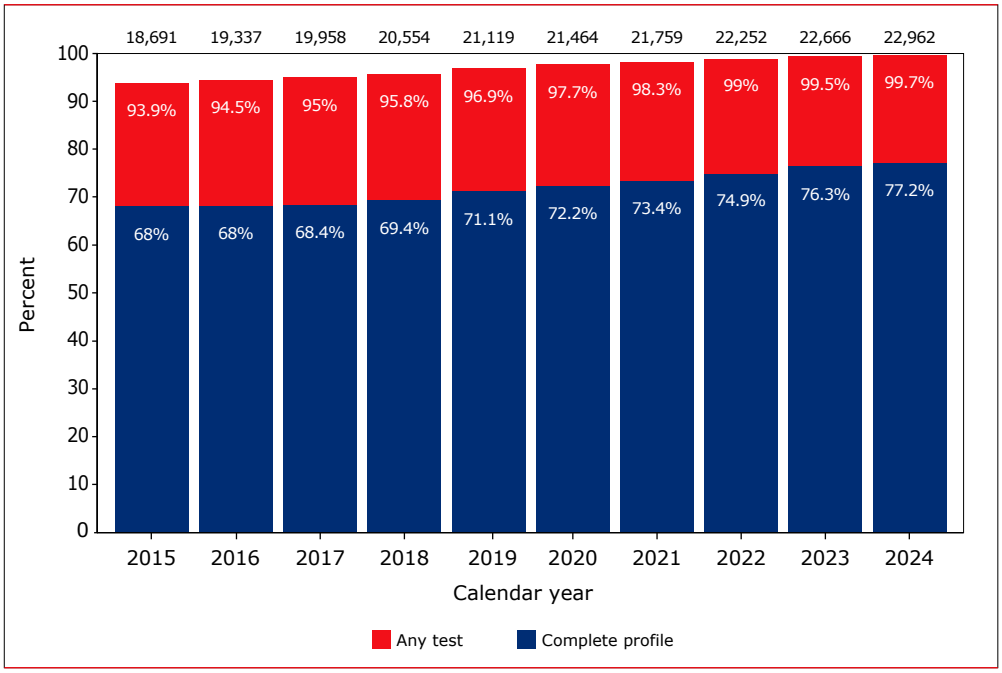
Box 7B: Interpretation of HBV serological profiles.

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

HBV testing

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

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

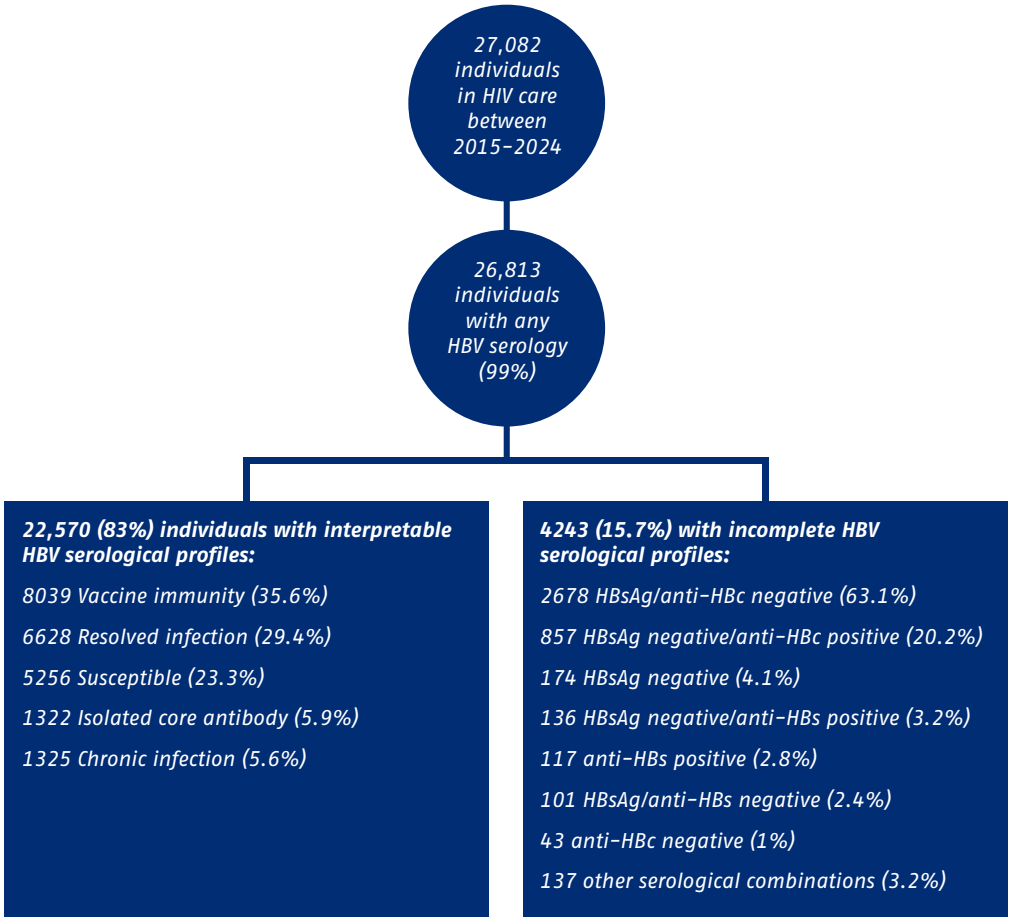


Numbers above bars represent the number of participants in care.

HBV serological profiles

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

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



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

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

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

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

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

Chronic HBV

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

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

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

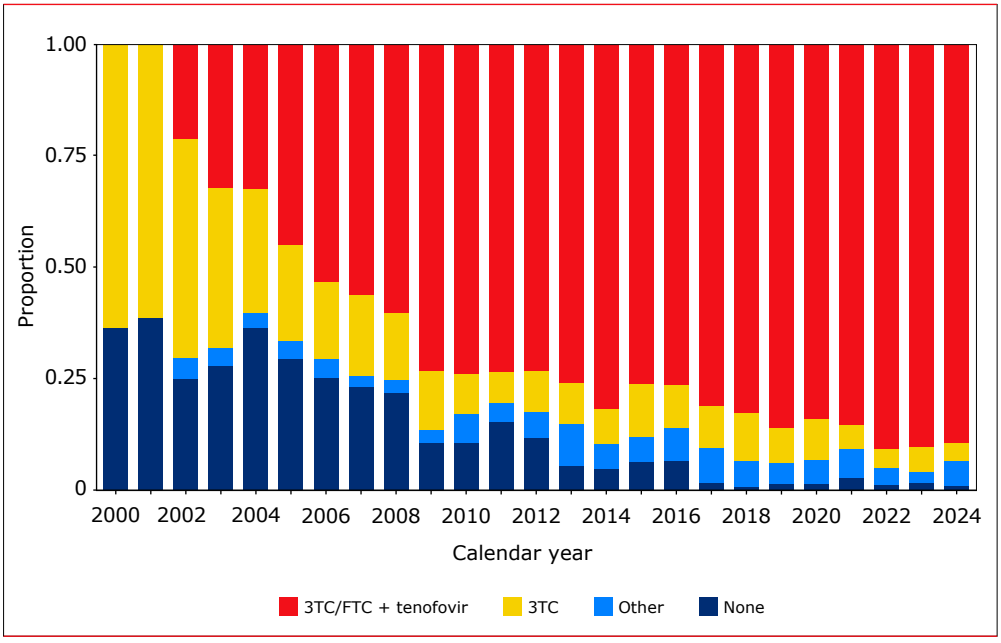
	HBsAg+ (N=879)	HBsAg−/anti-HBs+ (N=245)	HBsAg−/anti-HBs− (N=201)	Total (N=1,325)
HBV DNA <500 copies/ml				
No	90 (11.2%)	25 (16.8%)	19 (13.7%)	134 (12.3%)
Yes	714 (88.8%)	124 (83.2%)	120 (86.3%)	958 (87.7%)
NA	75	96	62	233
Cirrhosis				
No	803 (91.4%)	234 (95.5%)	186 (92.5%)	1,223 (92.3%)
Yes	76 (8.6%)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

Treatment of chronic hepatitis B

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

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

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



Coinfection with other hepatitis viruses

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

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

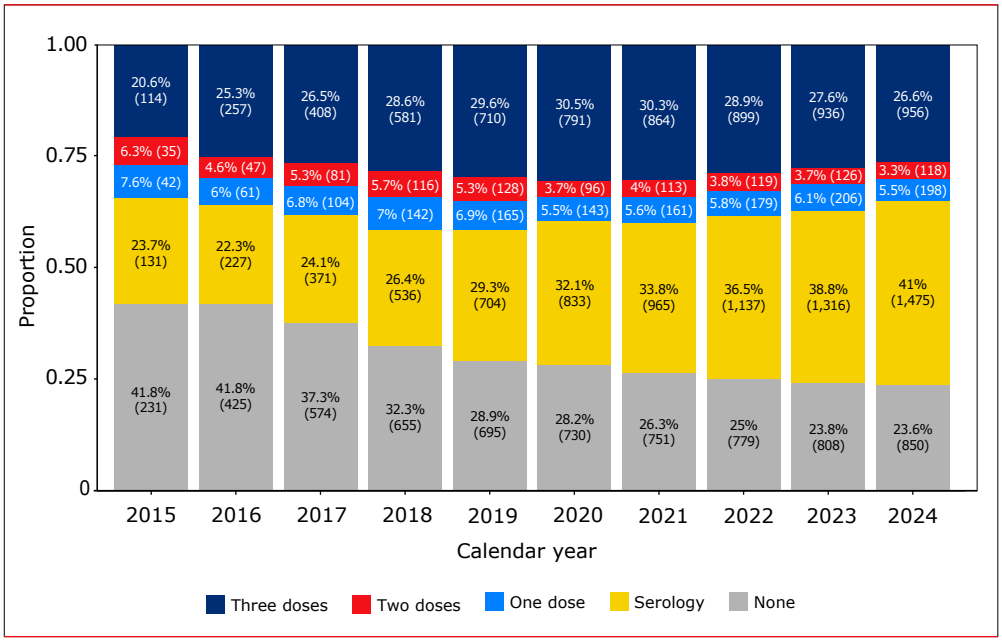
HBV vaccination

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

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

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

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



Hepatitis A virus

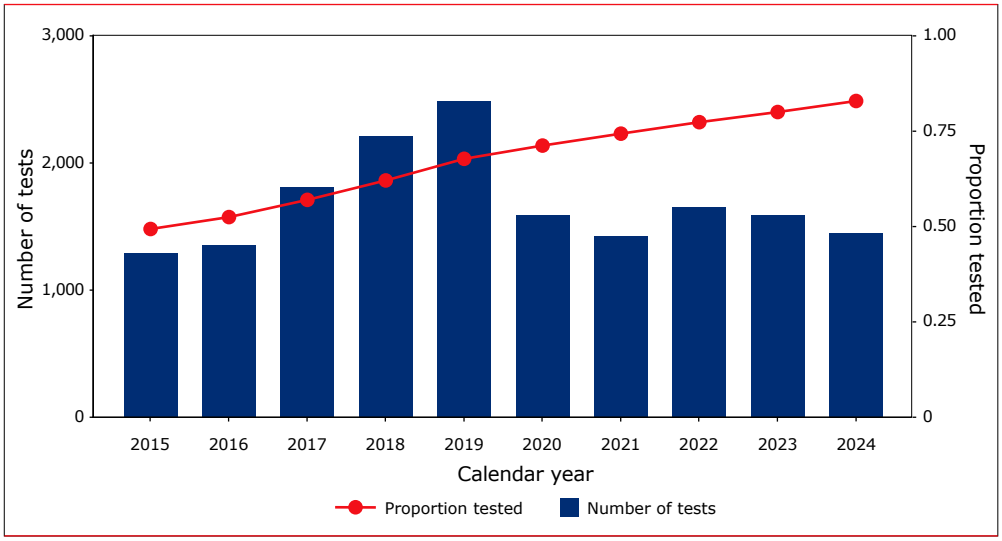
Hepatitis A is a vaccine-preventable infection caused by the hepatitis A virus (HAV). HAV is transmitted via the fecal-oral route, including through anal-oral sexual contact. HAV causes acute hepatitis without establishing chronicity.

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

HAV testing

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

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



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

Acute HAV

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

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

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

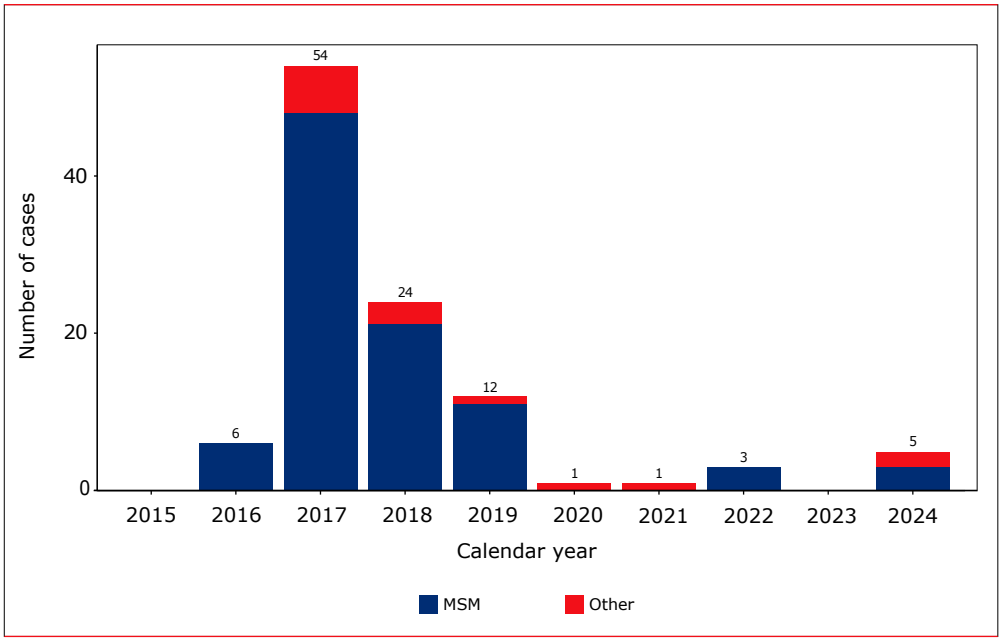
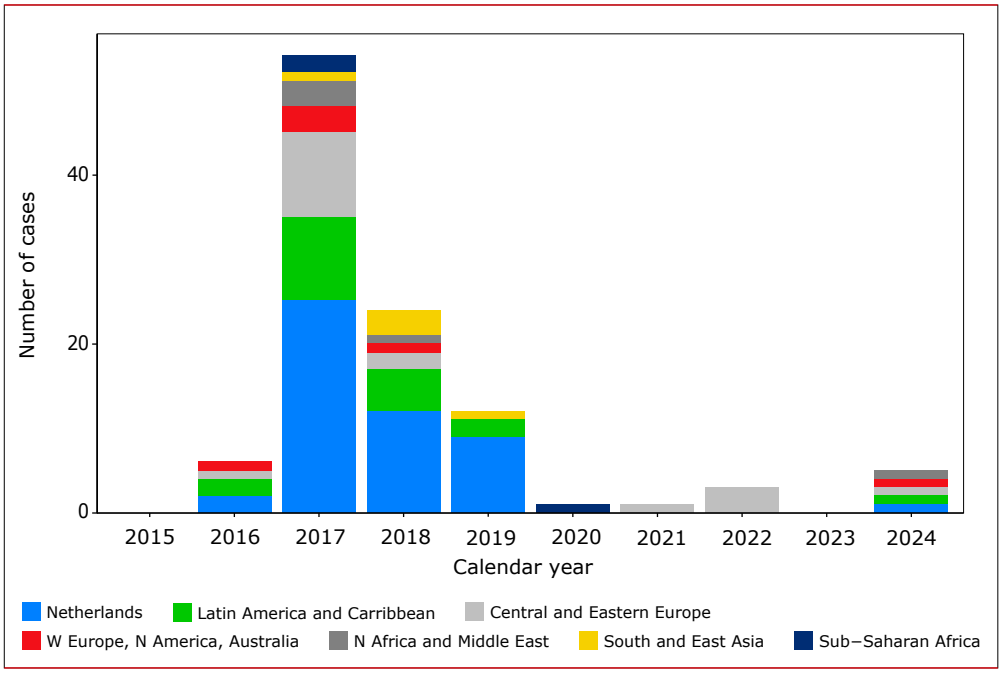


Figure 7.14: Number of acute HAV cases by year and birth region, 2015–2024 (n=106).



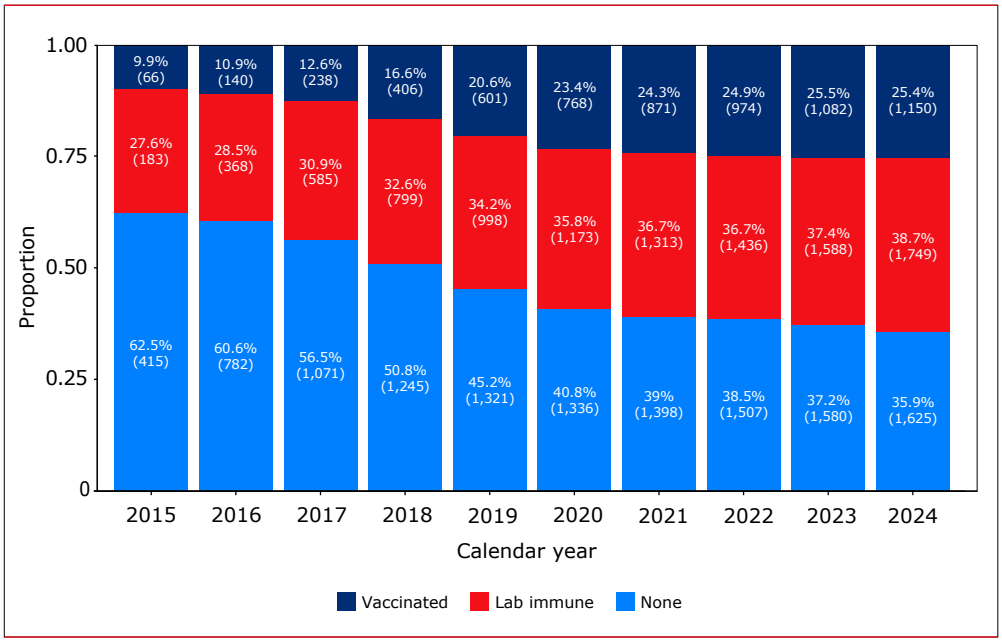
HAV vaccination

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

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

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

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



Hepatitis E virus

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

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

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

Conclusions

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

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

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

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

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

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