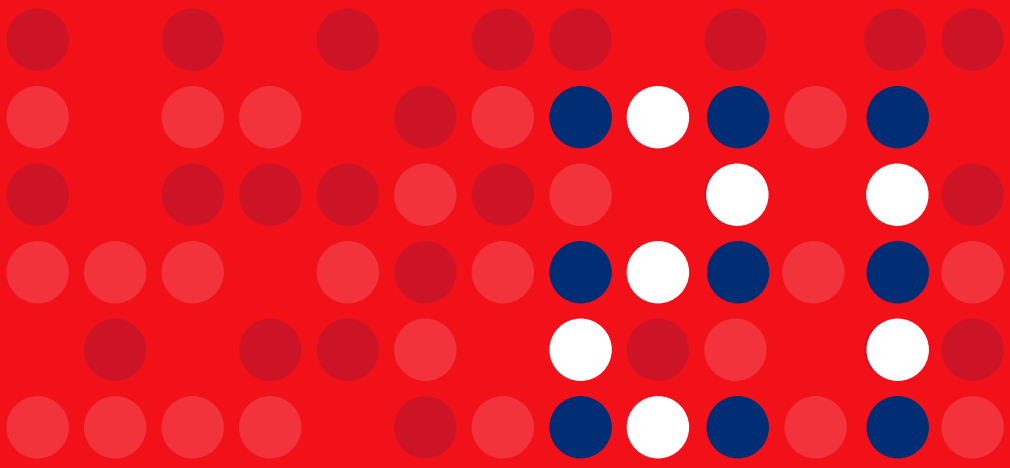
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2021

Chapter 4: Viral hepatitis



4. Viral hepatitis

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

Background

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

Individuals with chronic HCV and HBV infection 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 mono-infected with HCV or HBV[7,8]. While progression of liver disease was faster in HIV co-infected people prior to the availability of combination antiretroviral therapy (cART), the rate of such progression in those with optimally-managed HIV has since become increasingly similar to that in HCV or HBV mono-infected individuals[9,10]. Meanwhile, co-infection with HBV-HDV is known to be highly associated with severe liver-related outcomes compared to HBV mono-infection[11], with accelerated progression to end-stage liver disease in individuals living with HIV, despite effective cART[12].

Infection with hepatitis A virus (HAV) or hepatitis E virus (HEV) is more frequent in the Netherlands compared to HBV and HCV. Both are transmitted by way of the intestine and can cause acute inflammatory liver disease that can usually resolve without treatment[13,14]. 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[15], whereas markers of previous HEV infection can be detected in roughly 10% of the general population[16]. HAV and HEV infections rarely cause death in adults, yet a small minority of individuals infected with HEV will develop chronic infection and/or damage to tissues/organs outside the liver (e.g., neuralgic amyotrophy, Guillain-Barre syndrome, meningoencephalitis, glomerulonephritis, and thrombocytopenia)[17]. HEV infection more commonly persists and develops into chronic infection in immunocompromised individuals, who are then at increased risk of developing ongoing symptoms[14].

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

Hepatitis C virus (HCV)

***Box 4.1:** Definitions of hepatitis C infection.*

Primary HCV infection
First documented HCV infection.

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

Acute HCV infection[18,19]

1. Case definition of acute HCV according to *preferred* criteria[18]:
   Positive anti-HCV IgG with a documented negative anti-HCV IgG within the past 12 months,
   or:
   detectable HCV RNA in the presence of either a documented negative HCV RNA test, or a documented anti-HCV IgG seroconversion within the past 12 months.
2. Case definition of acute HCV according to *alternative* criteria[18]:
   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' (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 acute or chronic HCV infection.

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

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

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

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

HCV screening over time

In the Netherlands, the national guidelines for the treatment and monitoring of HIV recommend HCV screening during the first clinical visit after HIV diagnosis, and additional annual HCV screening for MSM who report HCV-related risk-taking behaviour[20]. Screening for HCV infection among the individuals living with HIV ever registered with SHM has increased over calendar time. Ninety-six percent of the 28,223[a] individuals living with HIV ever registered in the SHM database have been screened at least once for HCV; anti-HCV or HCV RNA. In 2000, 27% of the individuals living with HIV in care had never been screened for the presence of HCV infection in that 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 2020, only 1.6% of the individuals in care had never been screened for HCV co-infection (*Figure 4.1A*). In 2020, unknown HCV status was relatively more common among individuals with heterosexually-acquired

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.*

HIV (3.0%), or with another or unknown mode of HIV acquisition (4.5%), and relatively less common among MSM (0.8%) and people who inject drugs (PWID) or former PWID (0.4%).

Follow-up screening

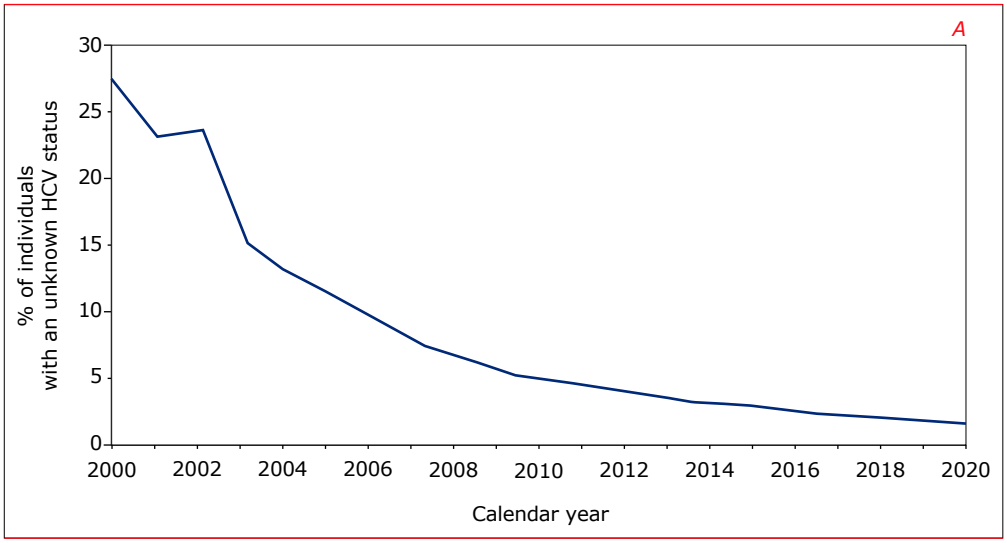
Among individuals who had a negative first HCV test and who remained in care, 77% had a second HCV test at some point during follow up. This proportion was highest for MSM, of whom 86% had at least a second HCV test, and lowest for individuals who acquired HIV through heterosexual contact (61%).

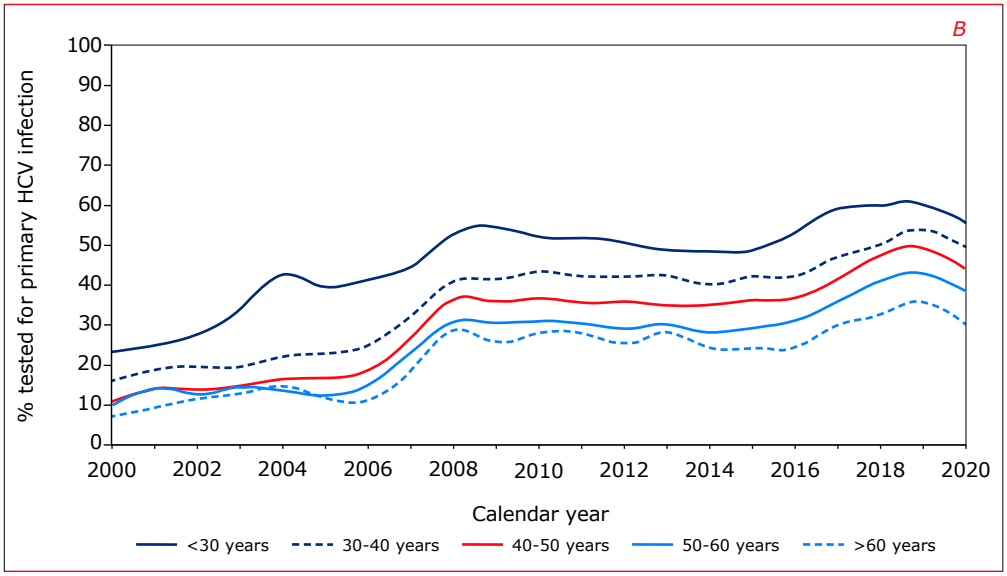
Most HCV infections are observed among MSM[21]; therefore, the following analysis on testing frequency is reported for MSM only. Overall, the percentage of HCV seronegative MSM with at least one HCV test in a calendar year increased over time, from 13% in 2000 to 27% in 2007, and 48% in 2019. However, testing frequency among HCV seronegative MSM decreased to 40% in 2020. 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 acute HCV was 43 years (IQR 36-39) (*Table 4.2*), while in the age range 40-50 years, 51% and 44% had at least one test in 2019 and 2020, respectively. Although reasons for screening or lack of screening are unknown, the lower testing frequency in 2020 may be related to the COVID-19 pandemic, which led to a reduction in services at many of the HIV treatment centres (*Chapter 7*).

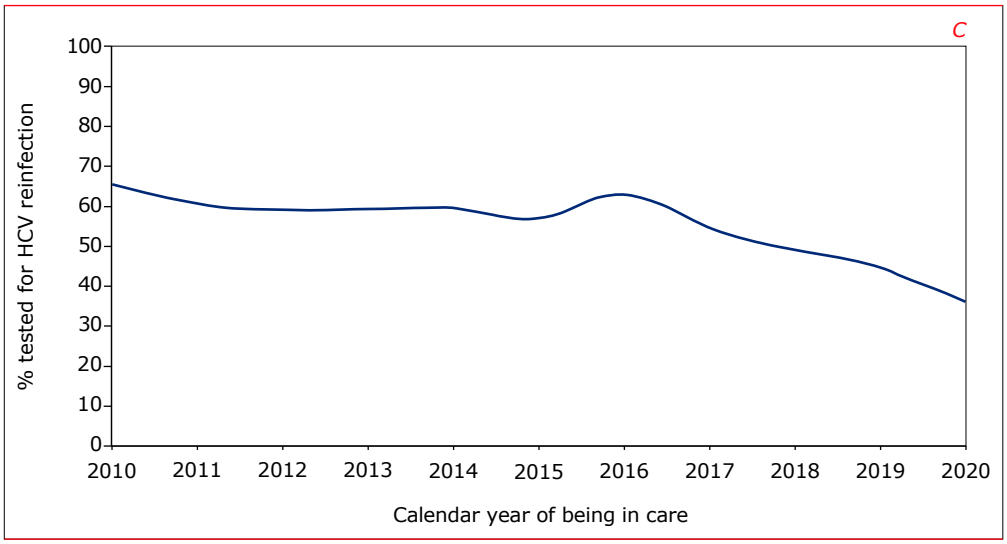
Screening for HCV RNA among those at risk of HCV reinfection is an important factor in identifying HCV reinfection. Among MSM living with HIV at risk of reinfection after treatment-induced, or spontaneous clearance of HCV, the percentage of men with an HCV RNA test during a calendar year varied between 55% and 66% in 2010-16, but declined to 45% in 2019, and 36% in 2020 (*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. 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 71% in 2012-2020[b]; unlike the observed decrease in testing in the total population of MSM at risk of reinfection, the testing frequency after an elevated transaminase level was higher in 2020 compared to 2019 (*Figure 4.1D*).

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

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



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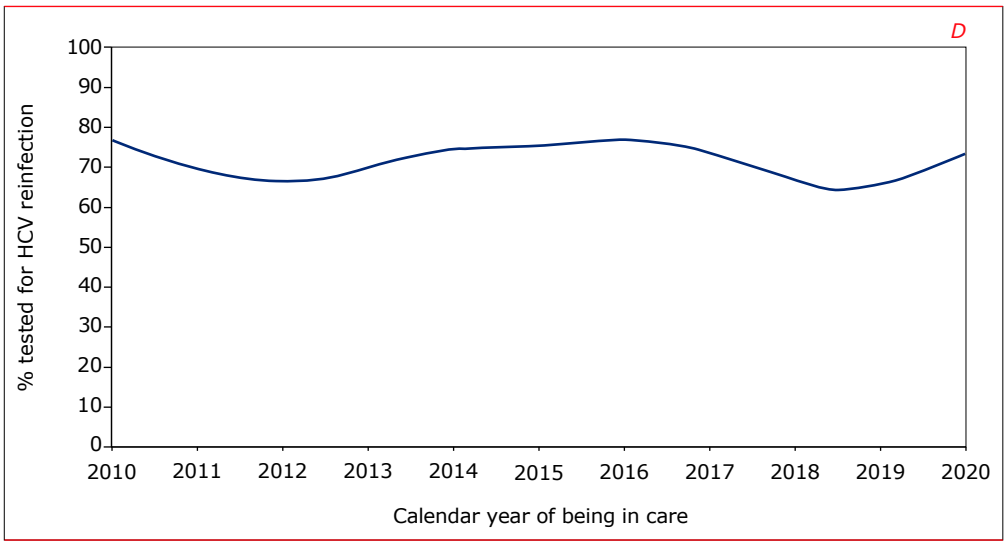
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Calendar year of being in care

HCV-positive individuals

As of May 2021, 28,223 HIV-1-positive adults (aged 15 years or older at the time of their HIV-1 diagnosis) had been registered by the stichting hiv monitoring (SHM). Of those individuals, 26,984 (96%) were ever screened for HCV co-infection and had been in care at one of the HIV treatment centres in the Netherlands: 3,051 (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 living with HIV than is estimated for the general Dutch population (*Figure 4.2*). HCV RNA data were not documented in 169 of the 3,051 cases (6%). Of these 169 individuals, 115 have died, 25 have been lost to care, and 11 have moved abroad; the reason for an undocumented HCV RNA in the remaining 18 individuals is unknown.

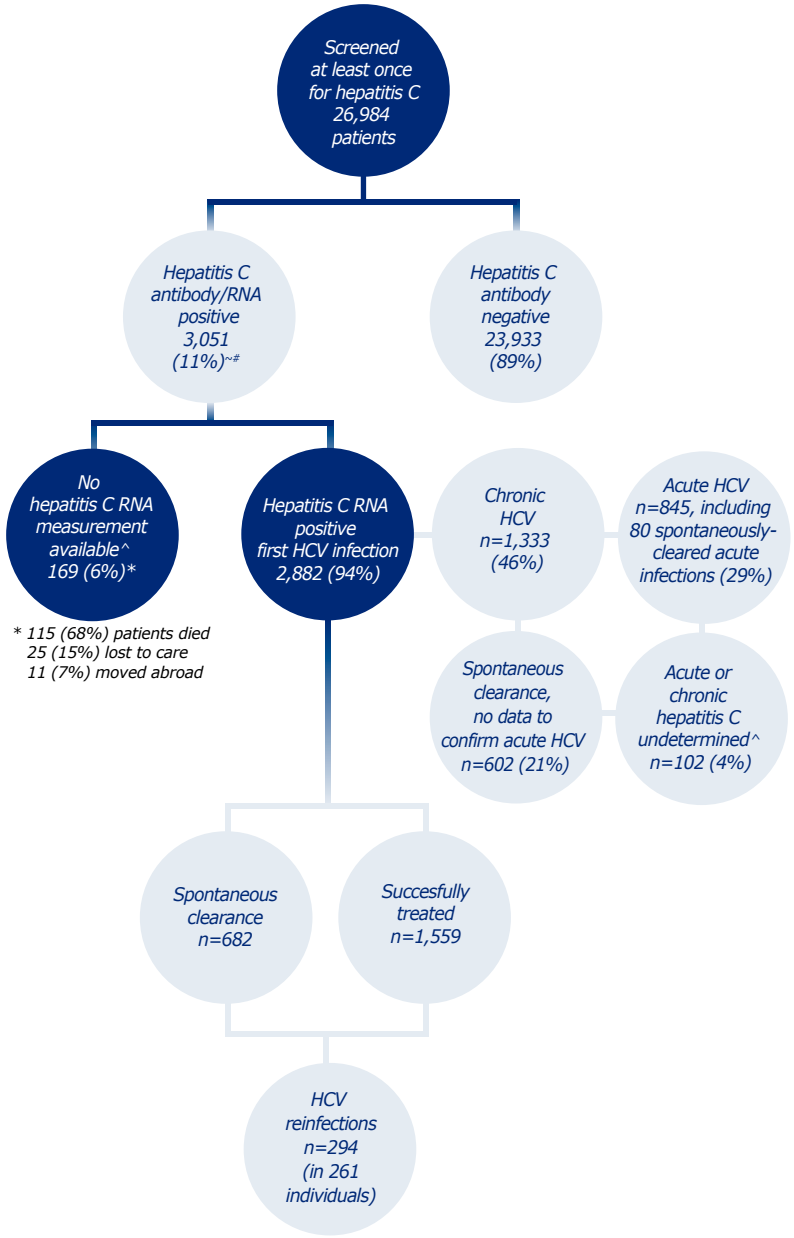
In total, 2,882 individuals were diagnosed with an HCV infection, confirmed by documented HCV RNA data:

- 845 (29%) were initially diagnosed with an acute HCV infection:
  - 80 spontaneously cleared their infection
  - 765 became chronic HCV infections, or were treated within six months of diagnosis.
- 1,333 (46%) were classified as having a chronic HCV infection at the time of their diagnosis.
- 602 (21%) had evidence of spontaneous clearance of HCV but could not be classified as having an acute HCV infection at the time of their HCV diagnosis.

The remaining 102 individuals with available HCV RNA data had one positive HCV RNA test result, but no registered follow-up results, rendering it impossible to determine whether their HCV infection was acute or chronic at the time of diagnosis. This group of individuals has therefore been excluded from the analysis. The majority (n=92) of individuals with no HCV follow-up data were no longer in care in 2020.

In total, 1,559 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 682 individuals spontaneously cleared their primary HCV infection. In total, 294 HCV reinfections after clearance occurred in 261 individuals. The majority (75%) of those with a primary infection who are not at risk of an HCV reinfection (i.e., those without SVR or spontaneous clearance of HCV) are no longer in care. The paragraph describing the continuum of HCV care gives more detail on those who remain in care, without clearance of their HCV infection.

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



* 115 (68%) patients died
25 (15%) lost to care
11 (7%) moved abroad

~ 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, 682 individuals spontaneously cleared their HCV infection. Among the 845 individuals with primary acute hepatitis, 80 (9%) cases of spontaneous clearance were observed. Another 602 cases of spontaneous clearance were observed among individuals who could not be classified as having a primary acute infection. Compared to all individuals with HCV co-infection, 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 HIV/hepatitis C virus (HCV) co-infected individuals and those who spontaneously cleared HCV registered in the SHM database, 1998-2020.*

	Total HCV co-infected	Spontaneous clearance
Total number of individuals	2,780	682 (25)
Age at HCV diagnosis (median, IQR)	40 (34-47)	41 (35-48)
HCV status		
Chronic HCV	1,333	
Acute HCV	765	
Definitive clearance	274	274
Possible clearance	328	328
Spontaneous clearance after confirmed primary acute infection	80	80
Male gender, n (%)	2394 (86)	557 (82)
Region, n (%)		
Netherlands	1694 (61)	354 (52)
Europe	358 (13)	89 (13)
Sub-Saharan Africa	120 (4)	61 (9)
Caribbean/South America	214 (8)	74 (11)
Southeast Asia	88 (3)	24 (4)
Other	306 (11)	80 (12)
HIV transmission route, n (%)		
Men who have sex with men	1,634 (59)	370 (54)
Heterosexual	310 (11)	116 (17)
People who use/used injecting drugs	579 (21)	124 (18)
Other	257 (9)	72 (11)
cART, n (%)	2696 (97)	657 (96)
Deaths, n (%)	479 (17%)	106 (16)

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

In total, 2,178 individuals could be definitively classified as having either chronic (n=1,333), or acute (n=845) 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: 751/1,333 [57%]; acute: 646/845 [76%]) (*Table 4.2*). Fifty-eight percent of the registered individuals who acquired HIV through injecting drug use (IDU), had a chronic HCV infection (449 of the total 773 PWID or former PWID). In the MSM HIV transmission group (16,432), 3% (546) had a chronic HCV infection and 5% (794) had a documented acute HCV infection.

The HCV genotype was determined and documented in the clinical records of 1,198 of the 1,333 (96%) individuals with a chronic HCV infection. Of the individuals with a genotype determination, the majority (62%, n=742) were infected with HCV genotype 1; 61% (n=451) with genotype 1a, and 14% (n=101) with genotype 1b. For 25% of the people infected with genotype 1, the subtype was not further specified. Five percent (n=59) were infected with HCV genotype 2, 17% (n=209) with genotype 3, and 16% (n=186) with genotype 4. One person was infected with genotype 5 and one with genotype 6.

HCV genotype was also documented for 739 of the 845 (88%) individuals with an acute HCV infection. They were most likely to be infected with either genotype 1 (72%, n=529) or genotype 4 (21%, n=155). Of the 529 infected with genotype 1, 84% (n=445) were infected with genotype 1a and 5% (n=23) with genotype 1b. For 14% of the people infected with genotype 1, the subtype was not further specified.

Table 4.2: Demographic characteristics of individuals co-infected with HIV/hepatitis C virus (HCV) registered in the SHM database, 1998-2020.

	Total	Chronic HCV	Acute HCV
Total number of individuals screened for HCV	26,984	1,333 (5)	845 (3)
Age at baseline (median, IQR)	40 (34-47)	39(33-45)	43 (36-49)
Male gender, n (%)	22,123(82)	1,078 (81)	838 (99)
Region of origin, n (%)			
Netherlands	14,809 (55)	751 (57)	646 (76)
Europe	1,802 (7)	207 (16)	69 (8)
Sub-Saharan Africa	3,636 (13)	49 (4)	11 (1)
Caribbean/South America	3,370 (12)	91(7)	52 (6)
Southeast Asia	960 (4)	44 (3)	24 (3)
Other	2,407 (9)	191 (14)	43 (5)
HIV transmission route, n (%)			
Men who have sex with men	16,432 (61)	546 (41)	794 (94)
Heterosexual	7,993 (30)	169 (13)	27 (3)
People who use/used injecting drugs	773 (3)	449 (34)	8 (1)
Other	1749 (6)	167 (12)	16 (2)
cART, n (%)	26,110 (97)	1,278(96)	841 (99)
HCV genotype (GT), n (%*)			
Total determined		1,198 (89)	739(87)
GT 1		742 (62)	529(72)
1a		451	445
1b		101	23
1c, 1a/b or not further specified		190	61
GT 2		59 (5)	38 (5)
GT 3		209 (17)	16 (2)
GT 4		186 (16)	155 (21)
GT 5 or 6		2 (0.1)	1 (<1)
Deaths, n (%)	3,067 (11)	333 (25)	45 (5)

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

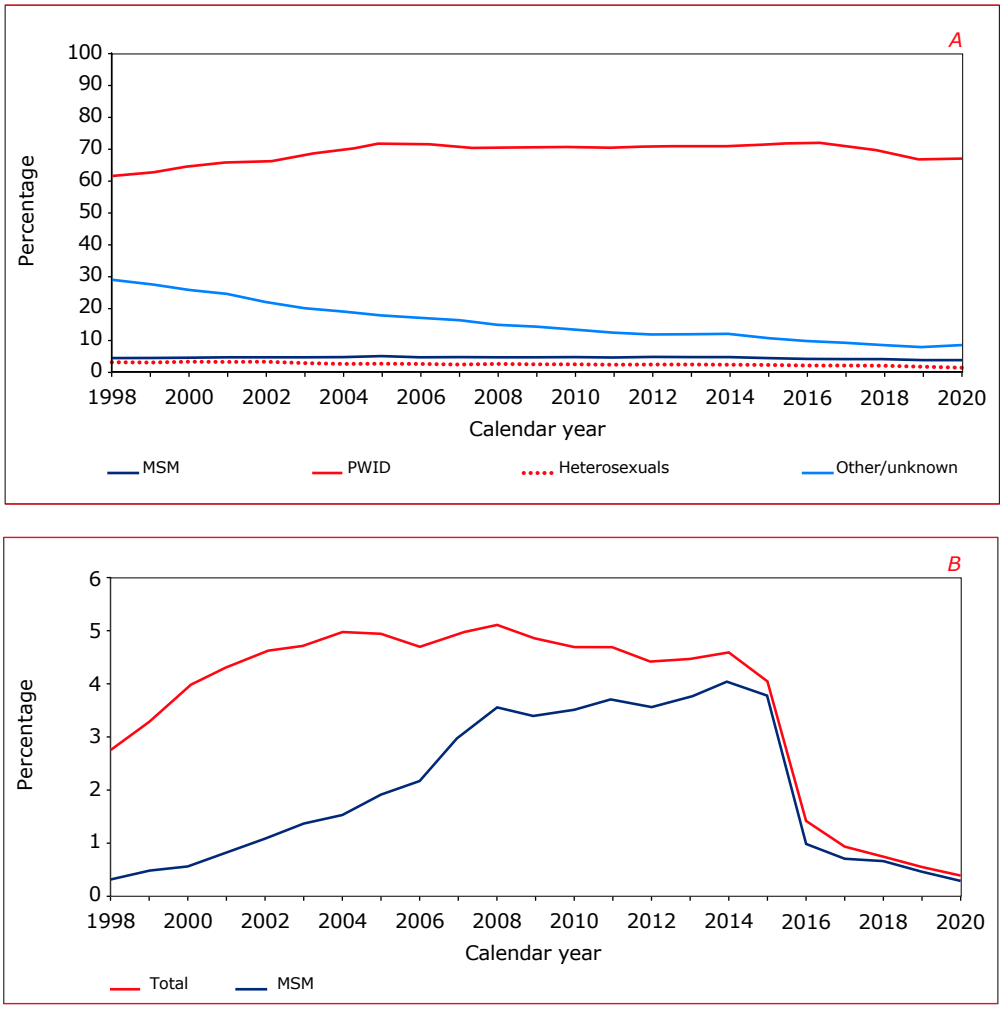
***Legend:** n=total for each category; (%)=percentage of the total for each column; HCV=hepatitis C virus; cART=combination antiretroviral therapy; GT=genotype.*

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 individuals living with HIV ever registered, decreased from 11.2% in 1998 to 4.3% in 2020, 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 61% and 72% over calendar years (*Figure 4.3A*).

Figure 4.3: *Prevalence of: A) chronic hepatitis C virus (HCV) co-infection, and B) detectable HCV RNA, per calendar year.*



Legend: *MSM: men who have sex with men; PWID: people who use/used injecting drugs.*

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 0.4% in 2020. In MSM, the highest percentage of HCV RNA positivity was 4% in 2014; by 2020, the percentage of positive HCV RNA tests in this group had decreased sharply to 0.29%.

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 acute HCV infection, including only cases of primary acute HCV infection (first diagnosis of HCV). The definition of acute HCV infection is consistent with the one given in the European AIDS Treatment Network (NEAT) preferred criteria[18]. We have also expanded this definition to include alternative criteria[18,19]. This alternative definition is based on detectable HCV RNA associated with an acute rise in alanine aminotransferase (ALT) greater than five times the upper limit of normal (above 200 IU/l), and a documented normal ALT within the past 12 months, together with 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.

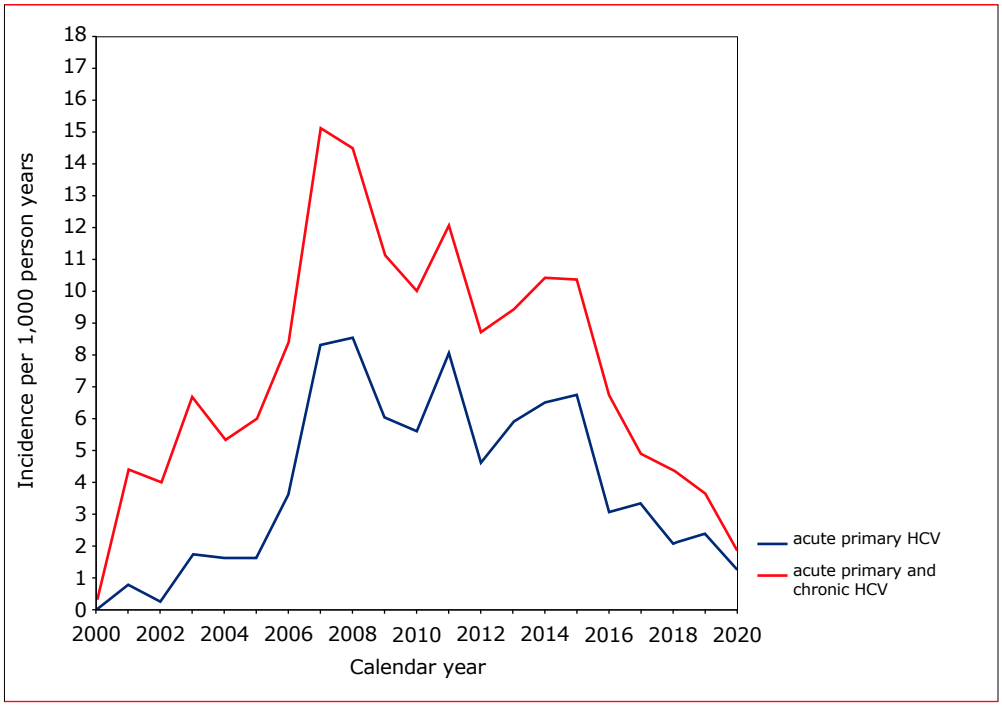
There were important differences in the incidence of the first diagnosis of acute HCV infection in terms of HIV transmission category. The vast majority of acute HCV infections occurred in MSM (n=794/845 [94%]). In contrast to the high prevalence of HCV in PWID or former PWID, the overall incidence of acute HCV in this group was low, occurring in only eight 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. Twenty-seven cases occurred among individuals who had acquired HIV hetero-sexually.

Figure 4.4 shows both the incidence of acute primary HCV infection and all primary HCV diagnoses among MSM over time. The overall rate of primary HCV infection was 7.7 per 1,000 person years (PY) (95% CI 7.3-8.1). The incidence of primary infection increased from 0.28 (95% CI 0.01-1.58) to a peak of 15.1 (CI 12.3-18.4) in 2007

and decreased to 1.8 (CI 1.1-2.9) in 2020. When including those with an acute HCV infection, the overall rate of acute HCV infection among MSM was 4.2 per 1,000 PY (95% CI 3.9-4.5). When the preferred NEAT acute HCV definition was used, the incidence increased from 0 diagnoses per 1,000 PY in 2000, to a peak of 8.3 and 8.5 per 1,000 PY in 2007 and 2008, respectively. By 2015, the incidence was 6.8 diagnoses per 1,000 PY. It then declined to 3.0 in 2016, before further decreasing to 1.3 diagnoses per 1,000 PY in 2020.

As expected, incidence rates among MSM were higher when the preferred and alternative case definitions of acute HCV were combined, with incidence rates of 7.6 diagnoses per 1,000 PY in 2015, 3.9 in 2016, and 1.5 in 2020.

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



Legend: *HCV=hepatitis C virus.*

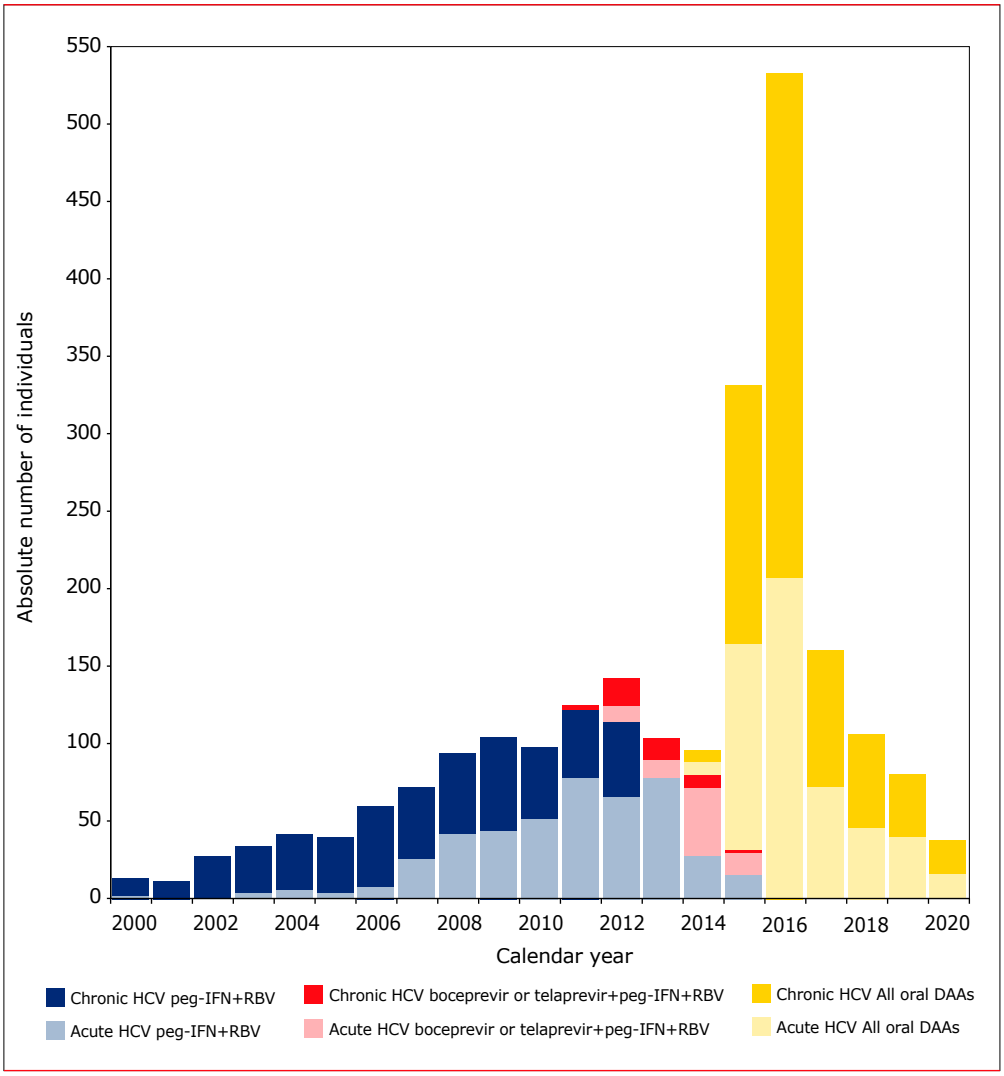
Treatment for HCV infection

The primary aim of HCV treatment is to achieve a sustained virological response (SVR)[22] 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[23,24]. 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 chronically infected with HCV, regardless of fibrosis state. Shortly thereafter, additional novel DAAs became available, such as new HCV NS3/4A protease inhibitors (simeprevir, paritaprevir, grazoprevir, glecaprevir, and voxilaprevir); NS5A inhibitors (daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir, and pibrentasvir); and an NS5B polymerase inhibitor (dasabuvir). 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 a primary chronic or acute HCV infection, or a reinfection, 1,769 have ever received HCV treatment; of those, 546 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, 955 regimens with (peg-)interferon+RBV, 125 regimens with first generation PI, and 1,235 regimens with all oral DAAs were documented.

Figure 4.5: Number of HIV/HCV co-infected individuals starting hepatitis C treatment per calendar year, according to acute or chronic HCV infection at the time of diagnosis.



Legend: HCV=hepatitis C virus; RBV=ribavirin; PEG-IFN=pegylated interferon; DAA direct-acting antiviral agent.

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[25]. 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 2021, 1,121 individuals were known to have started a DAA regimen; 100 of those had been treated more than once with a DAA regimen with, in total, 1,235 treatment episodes. The most common reasons for receiving DAA treatment more than once were: reinfection after earlier DAA treatment-induced clearance (n=52), and no SVR or discontinuation of first DAA treatment episode due to a lack of early virological response (n=29), or toxicity (n=6). Of the total 1,235 DAA treatment episodes, 17 occurred in 2014, 301 in 2015, and 532 in 2016. The number of treatment episodes has subsequently decreased to 38 in 2020 (*Figure 4.5*).

The most frequently used DAA regimens were 1) sofosbuvir plus ledipasvir +/- RBV (n=576); 2) sofosbuvir plus daclatasvir +/- RBV (n=253); and 3) pibrentasvir/glecaprevir (n=106). This last regimen was the one most commonly used in 2020. Forty-seven individuals who had previously been treated with DAAs are known to have died. The causes of death included liver disease (n=7), non-AIDS-defining malignancies (n=12), cardiovascular disease (n=5), non-AIDS-defining infection (n=4), and non-natural death (n=5). The remaining deaths (n=14) 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 2021. At that point, 1,178 out of 1,235 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 1,143 of the 1,178 treatment episodes (97%), SVR12 was achieved.
- No SVR was achieved in 29 treatment episodes among 27 individuals.
- For the remaining six 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 three 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 (93%), and individuals who acquired HIV through heterosexual contact (96%). 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:
- 17 were successfully retreated with a DAA regimen,
- eight 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 living with HIV[26,27], with high rates of reinfection found among MSM in the Netherlands, Germany[28], and the United Kingdom[29].

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

In total, 2,241 individuals were susceptible for HCV reinfection (1,559 after SVR, 682 after spontaneous clearance).

Of those 2,241 individuals, 294 reinfections among 261 individuals (12%) were documented: 179 after SVR and 115 after spontaneous clearance. The median time between SVR and HCV reinfection was 1.7 years (IQR 1.0-3.2), and between spontaneous clearance and reinfection it was 1.3 years (IQR 0.5-3.1).

Most individuals who became reinfected were MSM (225/261, 86%). Another 25 were PWID or former PWID (25/261, 10%). For the remaining 11 individuals, documented HIV transmission routes were heterosexual contact (three), blood-blood contact (three), and unknown (five).

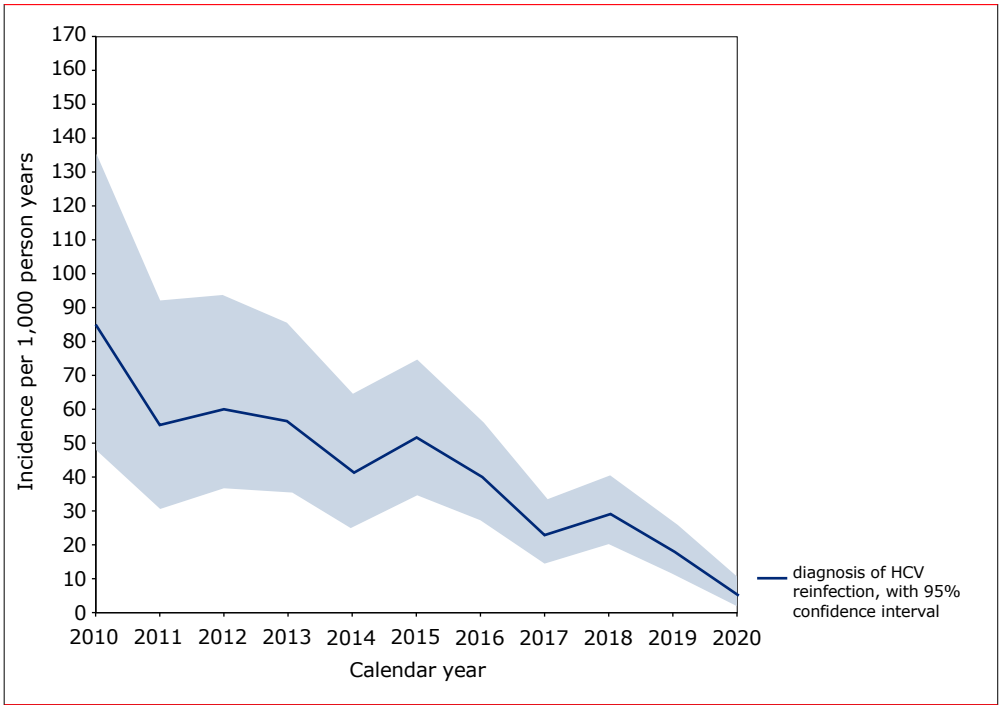
Of the 294 reinfections, 259 (88%) were retreated (193 with DAA, 66 with interferon+/-boceprevir/telaprevir) The median time to retreatment after reinfection diagnosis, stratified by calendar year of reinfection, was:
- Prior to 2015: 27.5 months (IQR 4.1-64.3).
- 2015-17: 3.1 months (IQR 1.6-7.6).
- From 2018: 2.5 months (IQR 1.5-4.0).

We calculated the incidence of reinfection between 2010 and 2020. 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 23 reinfections per 1,000 PY (95%, confidence interval [CI] 20-26), and for MSM it was 31 reinfections per 1,000 PY (95%, CI 27-36).

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 84 reinfections per 1,000 PY in 2010 to 52 in 2015, and then declined to 18 reinfections per 1,000 PY in 2019, and five in 2020. A stable decline in the incidence of reinfection in MSM has been seen since 2018. However, the effect of testing on the incidence of HCV reinfection cannot be completely excluded. Although HCV RNA testing after incident transaminase elevations showed an increase (*Figure 4.1D*), also during the beginning of the COVID-19 pandemic, the overall frequency of HCV RNA testing in MSM susceptible of reinfection has decreased (*Figure 4.1C*).

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



Note: numbers in 2020 may be affected by a delay in data collection.
Legend: HCV=hepatitis C virus.

Continuum of care for those with diagnosed HCV co-infection

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 2020. Individuals were categorised according to their last documented HCV infection episode. In total, 2,161 individuals were linked to HIV care, 1,900 individuals had a primary HCV infection, and 261 individuals had a reinfection. Of those 2,161 individuals, 1,528 (71%) were retained in care, while 633 individuals were no longer in care (374 had died, 139 had moved abroad, and 120 were lost to care). Of those still alive and in care, 1,464 (96%) had received treatment for HCV (with DAAs or a pegylated interferon-containing regimen), and 1,420 (97%) 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, 1,413 of the 1,420 people who completed treatment (99%) had achieved an SVR, including those who had achieved an SVR on a pegylated interferon-containing

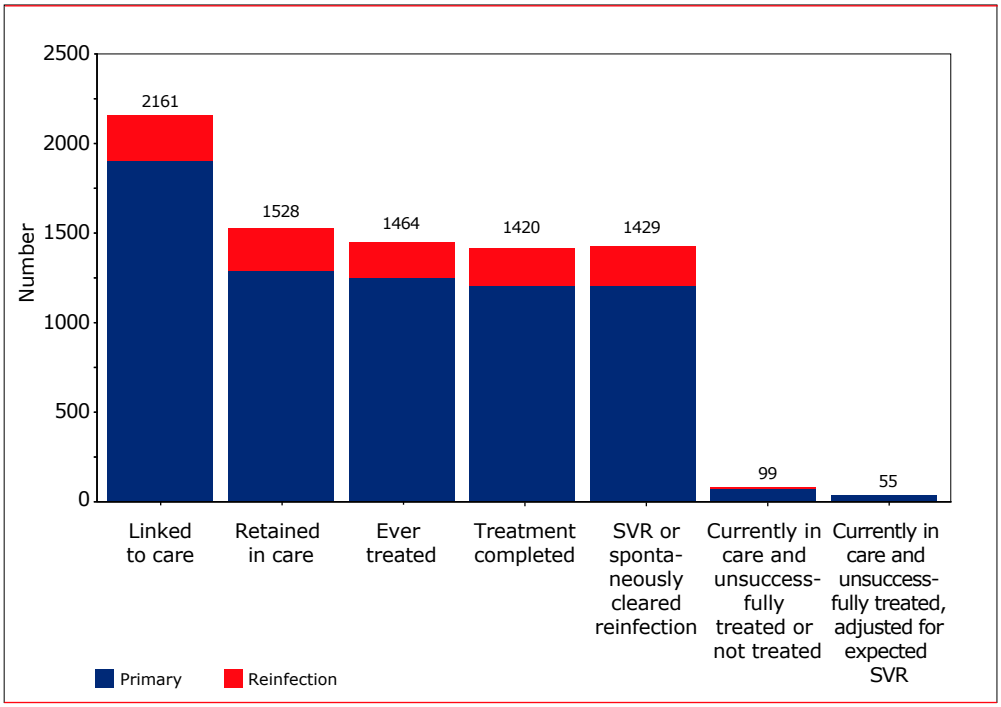
regimen and those who were retreated after earlier treatment failure. Another 16 individuals with HCV reinfection had a negative last HCV RNA test result, without documentation of HCV treatment. It is likely they spontaneously cleared their HCV infection, bringing the total of individuals with a treatment-induced or spontaneous clearance of their most recent HCV episode to 1,429.

As a result, 99 (6%) of the 1,528 individuals known to be alive and in care in one of the Dutch HIV treatment centres on 31 December 2020 were still in need of HCV treatment:

- 48 individuals had never been treated for HCV. The percentage untreated was higher among PWID (7%), people who acquired HIV through heterosexual contact (8%), and people with an unknown HIV transmission mode (7%), than among MSM (2%).
- Six had been unsuccessfully treated for HCV, including those who did not achieve an SVR on a pegylated interferon-containing regimen.
- 45 were still being treated or had insufficient time after treatment discontinuation to allow SVR calculation.

Of the 45 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 44 of the 45 (97%) will achieve SVR. This results in a more realistic estimate of individuals (99-44=55) who have yet to be treated or were unsuccessfully treated.

Figure 4.7: Hepatitis C continuum of care.



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

Liver-related morbidity

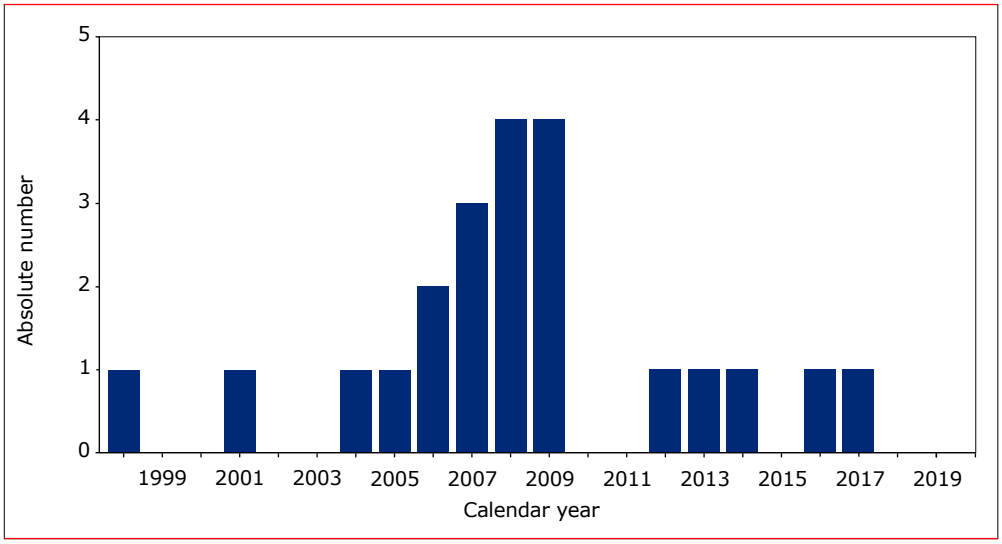
Data on liver-related morbidity are collected for all individuals living with HIV in follow up in the ATHENA cohort. In total, 1,149 cases of severe liver disease, according to our definition, were considered to be present (presumptive and definitive categories combined): 514 among individuals with HCV co-infection, 273 among individuals with HBV co-infection, 42 among individuals coinfected with HBV and HCV, and 404 among individuals living with HIV without documented HCV or HBV co-infection. This chapter reports on clinical characteristics and severe chronic liver disease with regards to HCV and/or HBV infection in individuals living with HIV; therefore, further analyses in this section are limited to those with viral hepatitis.

Liver-related morbidity in HCV

Additional data from liver biopsy pathology reports, transient elastography, radiology reports, or a combination of those sources, were available for 1,753 of the 2,098 individuals with HCV co-infection. Review of these additional data show that severe chronic liver disease was considered to be present (presumptive and definitive categories combined) in 514 (24%) of the individuals with HCV co-infection, and 29% of those with additional liver-related data. Definitive severe chronic liver disease was documented for 120 (7%) individuals with an HCV co-infection.

In total, 22 cases of hepatocellular carcinoma (HCC) were reported among individuals with HCV co-infection. *Figure 4.8* shows that the annual number of new HCC diagnoses declined from 2010 onwards. In 1998-2020, HCC was diagnosed in 22 of the 2,098 individuals (1.0%) with an HCV co-infection; 16 of those 22 were born in the Netherlands.

Figure 4.8: *Absolute number of annually-reported HCC cases among HCV co-infected individuals over time.*

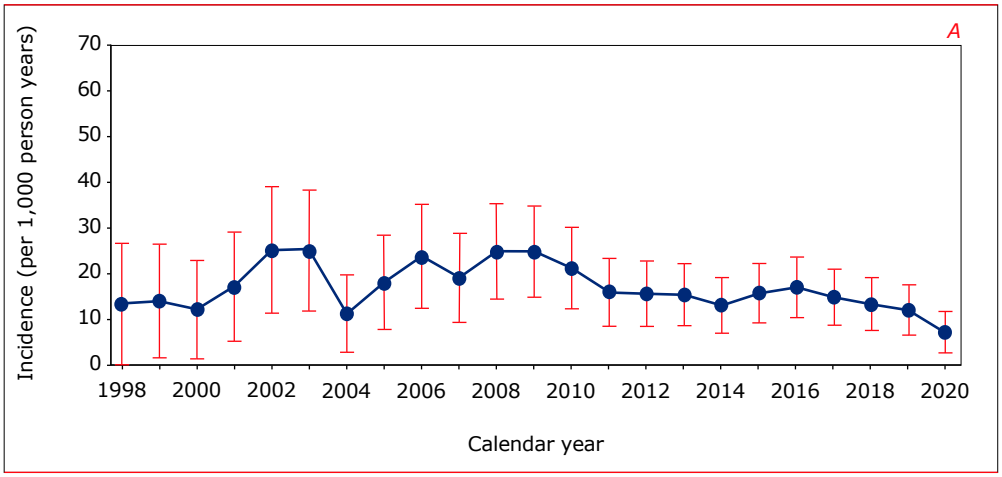


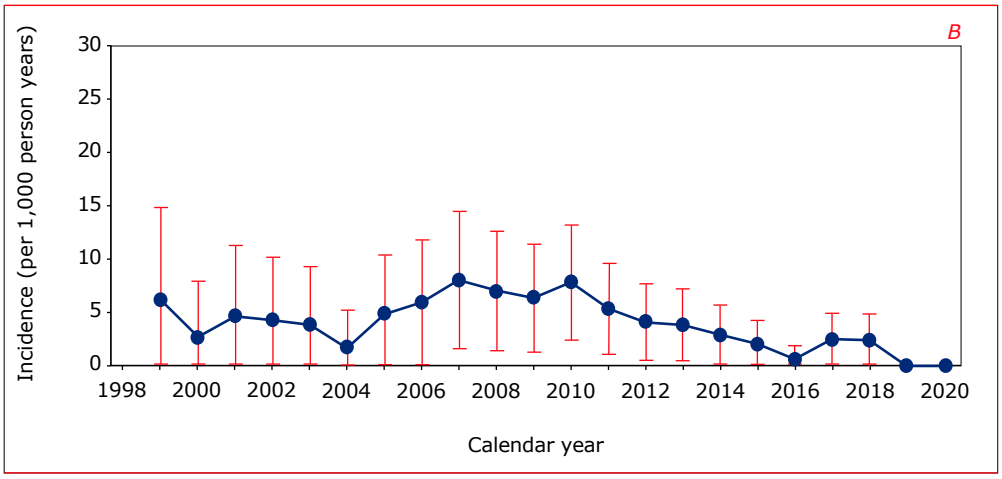
Mortality

All-cause mortality

Among the 2,098 individuals with an HCV infection, 18% died from any cause. For individuals with HCV infection, the incidence rate of death from any cause, adjusted for age and gender of the SHM population, was 17.2/1,000 PY in 1998-2002, 20.6 in 2003-11 and 13.9 from 2012 onwards (*Figure 4.9A*). In MSM with HCV infection, these incidence rates were 5.3/1,000 PY in 1998-2002, 8.9 in 2003-11, and 5.0 from 2012 onwards. In PWID with HCV infection, these incidence rates were 19.4/1,000 PY in 1998-2002, 38.4 in 2003-11, and 44.0 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 2,098 HIV-1-positive individuals who were ever diagnosed with an acute or chronic HCV infection.*





Note: *Individuals with acute or chronic HCV infection could be co-infected with HBV.*

Liver-related mortality

In total, 76 (4%) individuals co-infected with HCV died of a liver-related cause between 1998 and 2020. Other important causes of death among individuals with an HCV co-infection were non-AIDS malignancies (3%), AIDS (2%), and cardiovascular diseases (2%).

For individuals with HCV infection, the incidence rate of death from a liver-related cause, adjusted for age and gender of the SHM population, was 3.8/1,000 PY in 1998-2002, increasing to 5.9 in 2003-11, and decreasing to 2.0 from 2012 onwards (*Figure 4.9B*). In MSM with HCV infection, these incidence rates were 0/1,000 PY in 1998-2002, 3.5 in 2003-11, and 0.8 from 2012 onwards. In PWID with HCV infection, these incidence rates were 2.6/1,000 PY in 1998-2002, 8.5 in 2003-11, and 4.1 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**
HBsAg positive*	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.

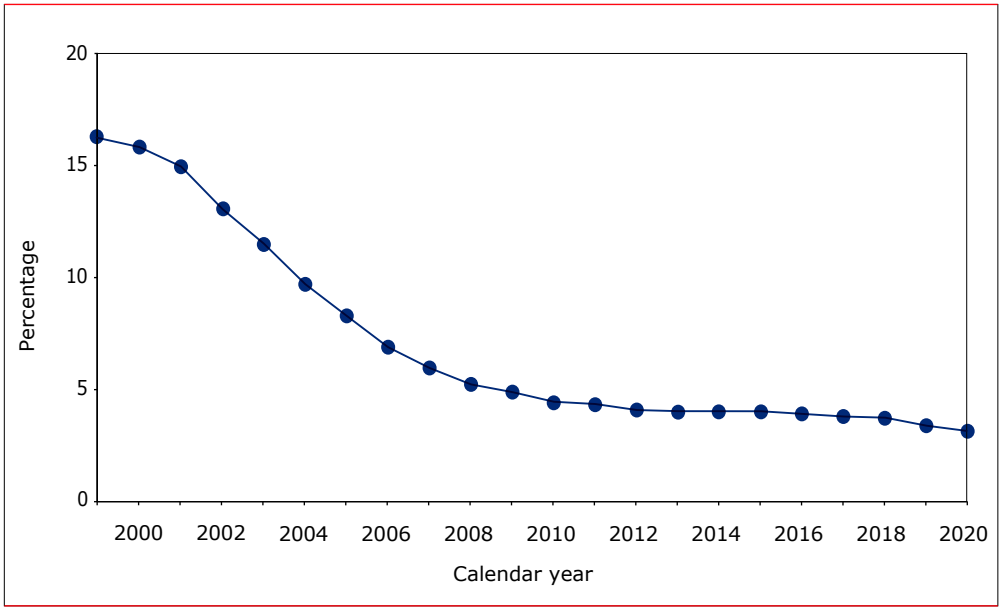
‡ Alternative definition: HBsAg-negative, anti-HBs antibody negative, and anti-HBc antibody not determined (and assumed to be negative).

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-six percent of the 28,223 individuals living with HIV ever registered in the SHM database have been screened for at least one serological marker of HBV (hepatitis B surface antigen [HBsAg], anti-hepatitis B surface [anti-HBs] antibodies, and/or anti-hepatitis B core [anti-HBc] antibodies). Screening for HBV infection in individuals living with HIV in care has improved over calendar time. In 1999, 16% of individuals had not been screened for HBV infection (*Figure 4.10*). Since then, the percentage of individuals living with HIV without HBV screening has decreased markedly, with 3% of all individuals living with HIV in care having no measured HBV serological markers in 2020 (*Figure 4.10*).

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

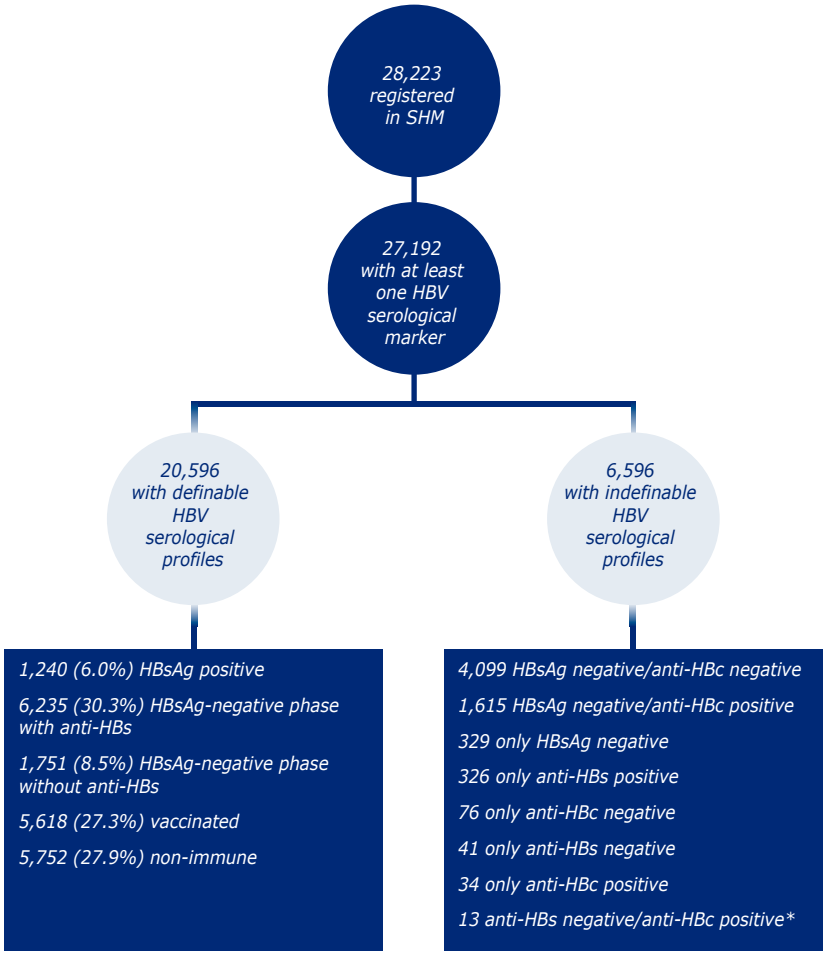


HBV serological profiles

HBV serological profiles could be defined for 20,596 (76%) of the 27,192 screened individuals (*Figure 4.11*). A full HBV serological battery is not routinely performed in individuals living with HIV; therefore, any results from an HBV serological test were assumed to remain the same over time until the performance of a new serological test. The distribution of HBV serological profiles at the last visit are given in *Figure 4.11*. The remaining 6,596 (24%) individuals either had insufficient information to establish an HBV serological profile (n=6,533), or were previously HBsAg-positive, no longer had anti-HBc antibodies, and did not have anti-HBs

antibodies (n=63). The demographic characteristics of people with definable HBV serological profiles are compared in *Table 4.3*.

Figure 4.11: *Flowchart of individuals living with HIV registered in the SHM database, 1999–2020, with testing for hepatitis B virus (HBV). Information was obtained from the most recent serological result.*



** The 63 individuals who were HBsAg-positive and then lost HBsAg without a definable profile are not included.*
Legend: *Anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus.*

Table 4.3: Demographic characteristics of individuals living with HIV in care, according to their hepatitis B virus (HBV) serological profile as registered in the SHM database, 1998–2020.

	HBV serological profile*, n (%)				
	HBsAg positive	HBsAg-negative phase with anti-HBs	HBsAg-negative phase without anti-HBs	Vaccinated	Non-immune
Total number	1,240	6,235	1,751	5,618	5,752
Male gender	1,056 (85%)	5,342 (86%)	1,340 (77%)	4,833 (86%)	4,245 (74%)
Region of origin					
The Netherlands	529 (43%)	3,351 (54%)	705 (40%)	3,328 (59%)	3,320 (58%)
Europe	75 (6%)	444 (7%)	122 (7%)	428 (8%)	300 (5%)
Sub-Saharan Africa	313 (25%)	978 (16%)	546 (31%)	425 (8%)	686 (12%)
Caribbean/South America	140 (11%)	752 (12%)	171 (10%)	720 (13%)	847 (15%)
Southeast Asia	69 (6%)	264 (4%)	62 (4%)	159 (3%)	149 (3%)
Other	114 (9%)	446 (7%)	145 (8%)	558 (10%)	450 (8%)
HIV transmission group					
Men who have sex with men	701 (57%)	4,287 (69%)	791 (45%)	4,088 (73%)	2,709 (47%)
Heterosexual	390 (31%)	1,380 (22%)	611 (35%)	1,215 (22%)	2,513 (44%)
Injecting drug use	52 (4%)	208 (3%)	183 (10%)	52 (1%)	110 (2%)
Other	97 (8%)	360 (6%)	166 (9%)	263 (5%)	420 (7%)
cART	1,193 (96%)	6,051 (97%)	1,684 (96%)	5,514 (98%)	5,583 (97%)
Deaths	255 (21%)	976 (16%)	317 (18%)	319 (6%)	665 (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; cART=combination antiretroviral therapy.*

Individuals with HBsAg-positive serology

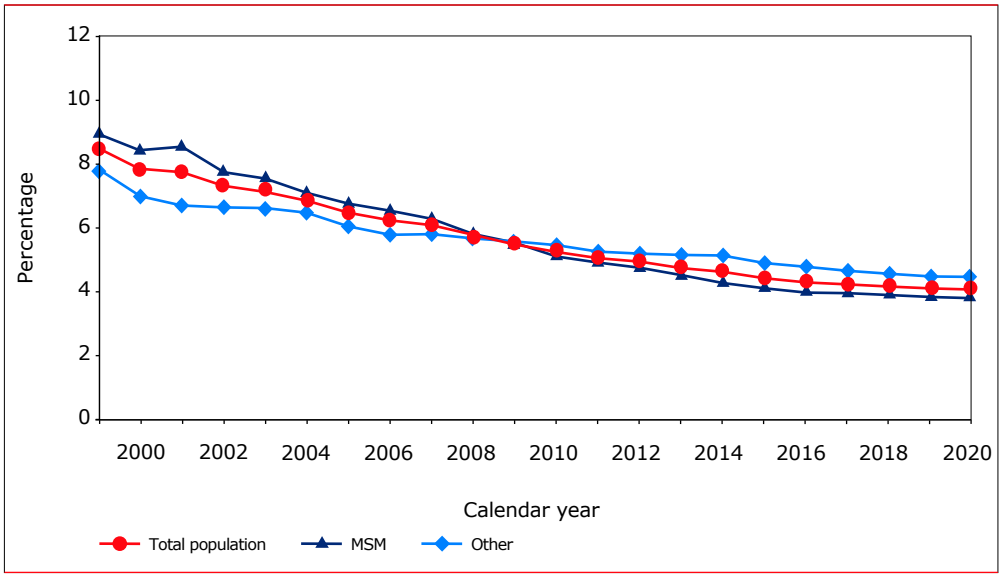
Prevalence of HBsAg-positive serology

Of the 27,192 individuals ever screened for at least one HBV serological marker, a total of 1,621 (6%) received a positive HBsAg test result. Over time, 183 (11%) of these individuals became HBsAg-negative and acquired anti-HBs antibodies (i.e., HBsAg-negative phase with anti-HBs) and an additional 198 (12%) became HBsAg-negative without acquiring anti-HBs antibodies (i.e., HBsAg-negative phase without anti-HBs). The remaining 1,240 (77%) individuals continued clinical care with HBsAg-positive serology.

The prevalence of HBsAg-positive serology was 8.5% in 1999, and slowly decreased to 4.1% in 2020 (*Figure 4.12*). This decline could be the result of several factors, including lower numbers of individuals with incident HBV infection (as a result of increased vaccination coverage among MSM[30], and the preventive effect of HIV treatment with a cART regimen that includes tenofovir disoproxil fumarate [TDF] / tenofovir alafenamide fumarate [TAF]); individuals becoming HBsAg-negative during treatment; and lower numbers of newly-diagnosed individuals living with HIV with HBsAg-positive serology[31].

As is the case for HCV co-infection, the percentage of individuals living with HIV in care and chronically co-infected with HBV is considerably higher than the rate found in the general Dutch population. Individuals co-infected with HBV were predominantly male (1,056/1,240; 85%), in line with those co-infected with HCV (*Table 4.3*). However, compared with people co-infected with HCV, those co-infected with HBV were more likely to have been born in sub-Saharan Africa and to have acquired HIV through heterosexual contact. HBV co-infection was also 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.*

Presence of HBV–HDV infection

By 2020, 216/1,621 (13%) individuals with HBV infection had been tested for HDV infection (i.e., IgG or IgM anti-HDV antibodies or presence of HDV RNA). Of those individuals, 24 (11%) were identified with either past or current HDV infection; 12 of these 24 were tested for HDV RNA and six were found to have detectable HDV RNA, indicating active HDV infection.

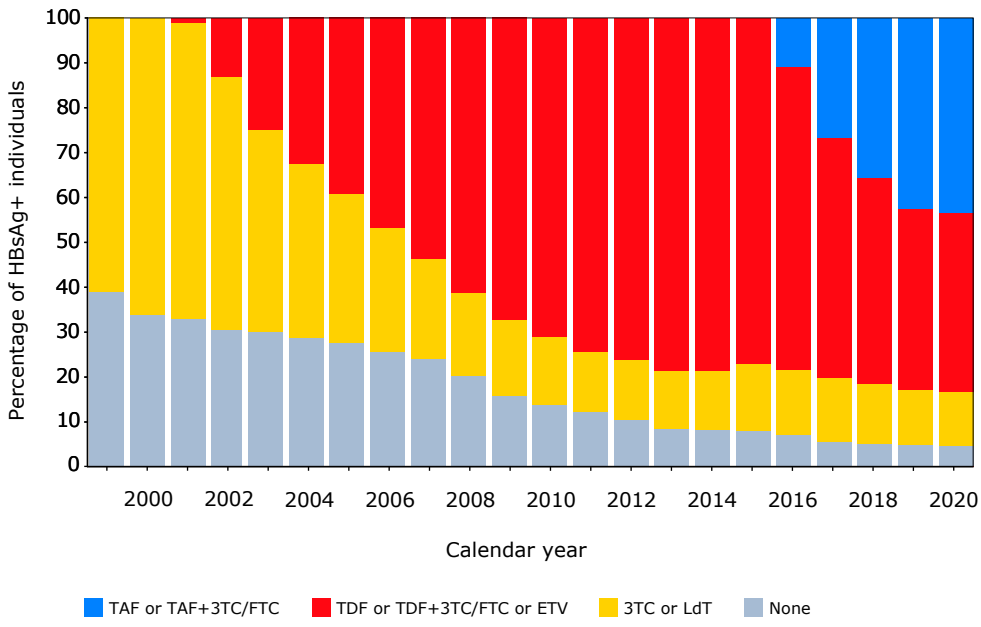
Treatment for chronic HBV infection

The treatment for chronic HBV infection aims to reduce viral replication of HBV. As HBV DNA is the parameter most directly influenced by therapy with either nucleoside or nucleotide analogues, HBV DNA undetectability is an appropriate surrogate marker for treatment response. Persistent lowering of HBV DNA levels has also been shown to reduce the risk of HCC and overall mortality in individuals with HIV-HBV co-infection[32,33]. A few antiviral agents used for treatment of HIV, such as lamivudine, and particularly TDF/TAF, are also active against HBV.

Of the 1,621 individuals with HIV in the SHM database who have ever had an HBsAg-positive serological test result, 1,557 (96%) received a cART regimen that included one or more agents with activity against both HIV and HBV. The reasons the remaining 64 individuals did not receive anti-HBV treatment included: death prior to start of treatment (n=16), recent entry into care (n=4), loss to follow up (n=40), or lack of sufficient information (n=4).

Most people with HBsAg-positive serology received treatment containing lamivudine in 1999-2000 (*Figure 4.13*). TDF-based cART (with or without lamivudine or emtricitabine) for combined HIV and HBV treatment was first used in 2002 (n=83/639, 13%) and became more commonly used than lamivudine in 2005. TAF-based cART (with or without lamivudine or emtricitabine) was first used in 2016 (n=132/1,215, 11%). In 2020, most HBV co-infected individuals were receiving TAF-based cART (n=550/1,264, 44%), closely followed by TDF-based cART (n=508/1,264, 40%), and lamivudine-based cART (n=149/1,264, 12%), or no anti-HBV-containing cART (n=57/1,264, 5%).

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



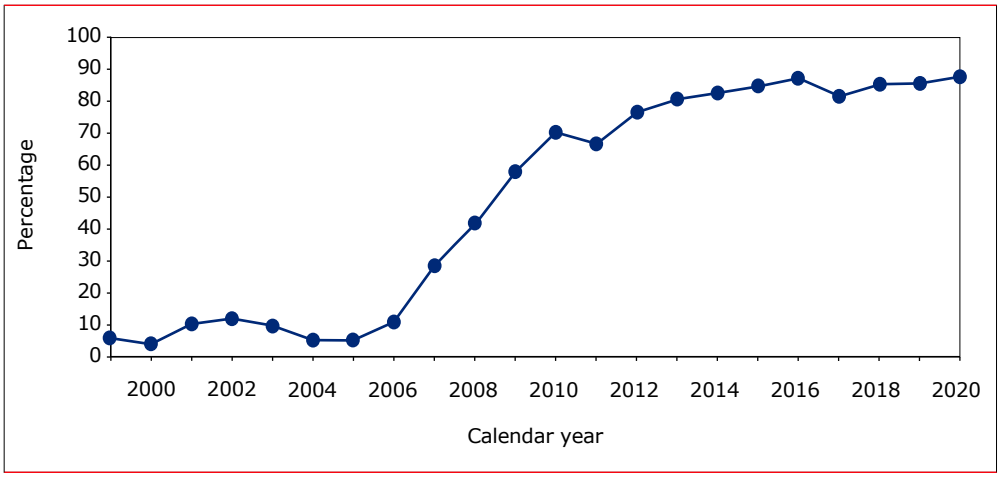
Note: *The categories of anti-HBV agents were: none, 3TC or LdT, TDF or TDF+3TC/FTC or ETV, and TAF or TAF+3TC/FTC. 3TC and LdT should not be combined and TDF and ETV can be combined under special circumstances[34].*

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

We examined the HBV DNA levels per calendar year in the population of individuals co-infected 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, for each year, HBV DNA measurements were available, on average, in 24% of individuals co-infected with HBV. *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 1999-2005, 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 cART, reaching 81% in 2013. In 2020, 88% of individuals co-infected with HIV and HBV had an undetectable HBV DNA level (*Figure 4.14*).

Figure 4.14: *Percentage of co-infected 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.*

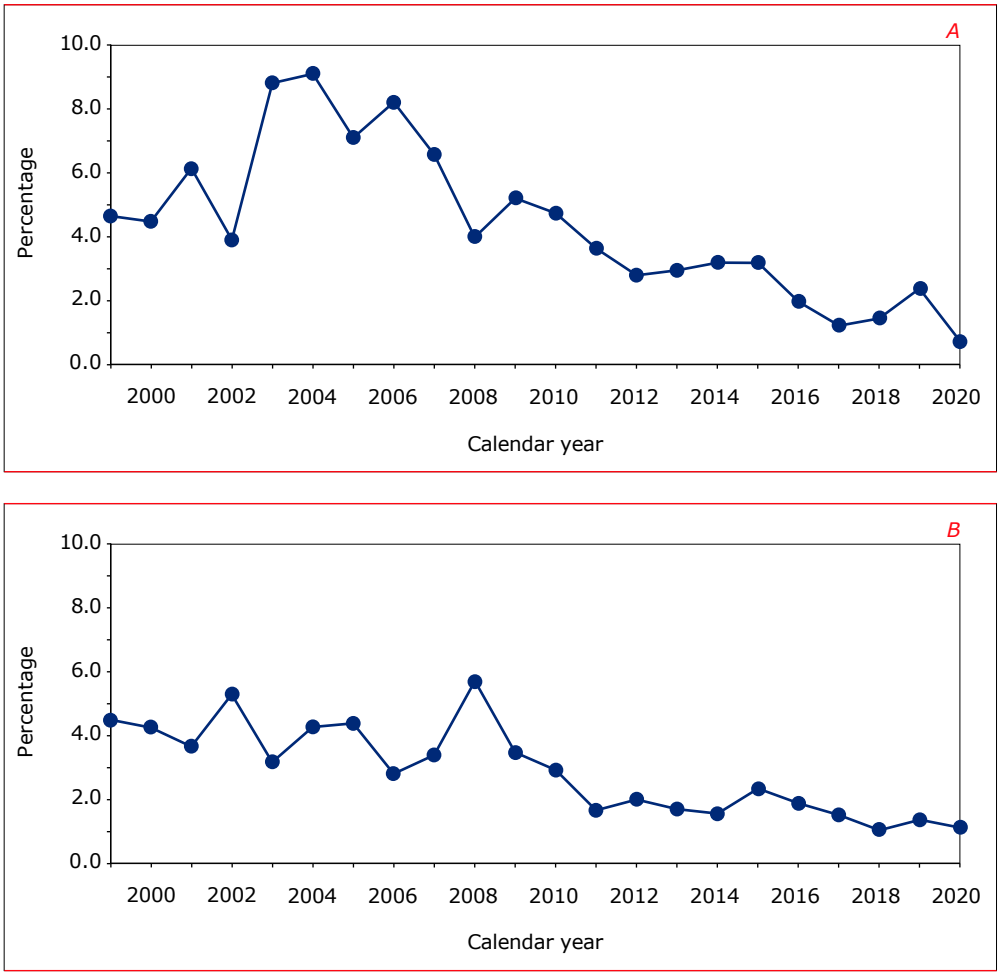


There are other serological outcomes associated with a more favourable prognosis in individuals with HBV infection[35]. Persistently negative hepatitis B "e" antigen (HBeAg) is associated with lower levels of HBV DNA replication. It also confers a favourable long-term outcome with low risk of cirrhosis and HCC, so long as transaminase and HBV DNA levels are low[36]. 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 infection, the loss of HBsAg, known as HBsAg seroclearance, is the penultimate goal of HBV therapy.

The percentage of individuals with HBeAg seroclearance ranged from 3.9% to 9.1% between 1999 and 2010, and slowly declined to 0.7% in 2020 (*Figure 4.15A*). Similarly, the percentage of individuals with HBsAg seroclearance was higher between 1999 and 2010, ranging from 2.8% to 5.7%, and slowly declined to 1.1% in 2020 (*Figure 4.15B*). Individuals with HIV-HBV co-infection, who initiate cART at very low CD4+ cell counts, are more likely to have seroclearance due to an immuno-inflammatory

reaction with accelerated CD4+ cell increases[37]. The higher percentages with seroclearance before 2010 could be due, in part, to the higher percentage of co-infected individuals initiating cART with severe immunosuppression during this period. Furthermore, the number of HBeAg tests peaked in 2004 at 116, before slowly declining to 23 tests in 2020. The number of HBsAg tests peaked in 2008 at 214, before less dramatically decreasing to 144 tests in 2019, and 105 tests in 2020. The lower percentage with seroclearance after 2010 might also be due to the lower testing rates in co-infected individuals.

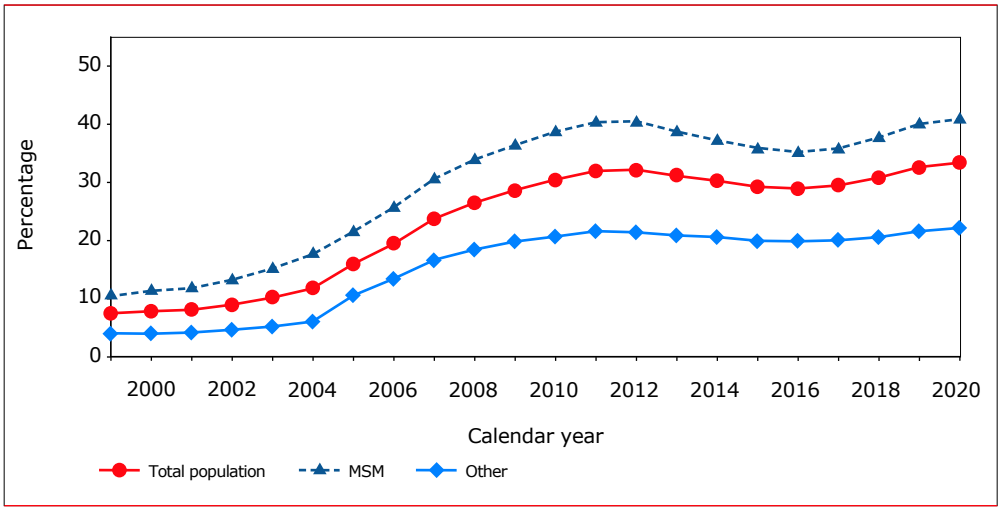
Figure 4.15: *(A) Percentage of hepatitis B "e" positive (HBeAg) co-infected individuals with HBeAg-seroclearance, and (B) percentage of all co-infected individuals with hepatitis B surface antigen-seroclearance. Both are shown by calendar year.*



HBV vaccination in individuals living with HIV

Of the 20,596 individuals with definable HBV serological profiles, 5,618 (27%) 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, and without previous evidence of HBsAg-positive serology, were considered, the prevalence of HBV vaccination status increased from 8% in 1999 to 33% in 2020 (*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[30].

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



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

HBV non-immune status in individuals living with HIV

Of the 20,596 individuals with definable HBV serological profiles, 5,752 (28%) had serological evidence of being non-immune and non-exposed to HBV at their last visit. When the 6,596 individuals with undefinable HBV serological profiles were considered, 84 of the 439 with an anti-HBs antibody test did not have detectable anti-HBs antibodies, and 5,528 of the 6,157 without an anti-HBs antibody test were not reported to have been vaccinated by their treating physician. Therefore, at most, 11,364 (42%) of the 27,192 individuals screened for HBV remained susceptible to infection at the time of their last visit (5,752 non-immune, 84 with an undefinable HBV profile and anti-HBs antibody negative, and 5,528 with an undefinable HBV profile and missing data on anti-HBs antibody status, and no physician-reported vaccination).

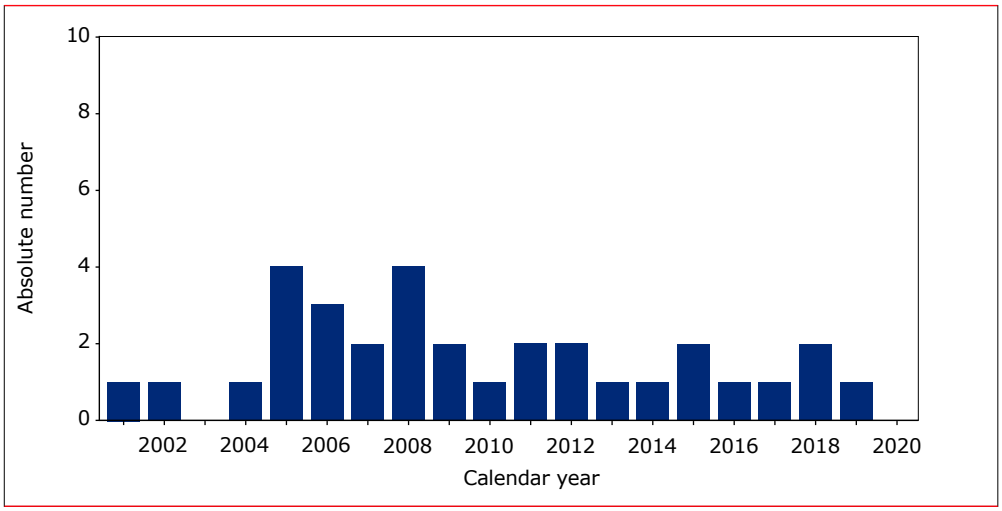
Individuals at risk, and MSM in particular, should be actively counselled about HBV vaccination. However, they may be protected from HBV infection by the use of tenofovir (TDF), or tenofovir alafenamide (TAF), as part of their cART regimen, according to findings reported by an international study, and one of the Dutch HIV treatment centres[38,39]. Data from SHM show that, of those people who remained at risk of acquiring HBV, 82% were being treated with a cART regimen that included TDF or TAF; for MSM, this percentage was 84%.

Liver-related morbidity in HBV

Additional data from liver biopsy pathology reports, transient elastography, radiology reports, or a combination of those sources, were available for 1,260 of the 1,621 individuals with an HBV co-infection. Review of these additional data show that severe chronic liver disease, according to our definition, was considered to be present (presumptive and definitive categories combined) in 273 (22%) of those with HBV co-infection. Definitive severe chronic liver disease was documented for 76 (6%) with an HBV co-infection. Of the 273 individuals with severe chronic liver disease, nine (3%) had past or current HDV infection.

Figure 4.17 shows that the annual number of new HCC diagnoses declined from 2010 onwards. HCC was found in 32 (2.1%) individuals with a chronic HBV co-infection, 18 of whom were born in the Netherlands, nine in sub-Saharan Africa, and one each in Asia, South America, the United States, Australia, and western Europe. One individual with newly-diagnosed HCC had either past or current HDV infection.

Figure 4.17: Absolute number of annually-reported HCC cases among HBV co-infected individuals over time.



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

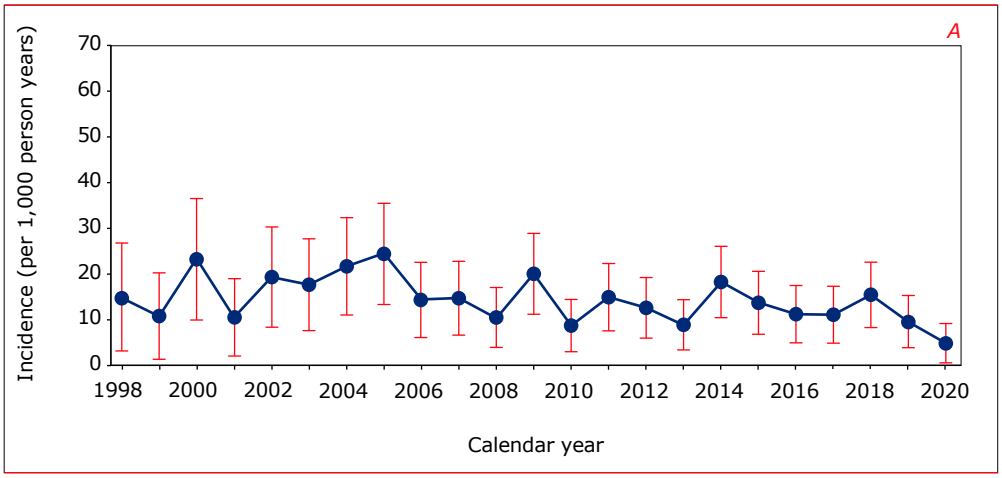
Mortality

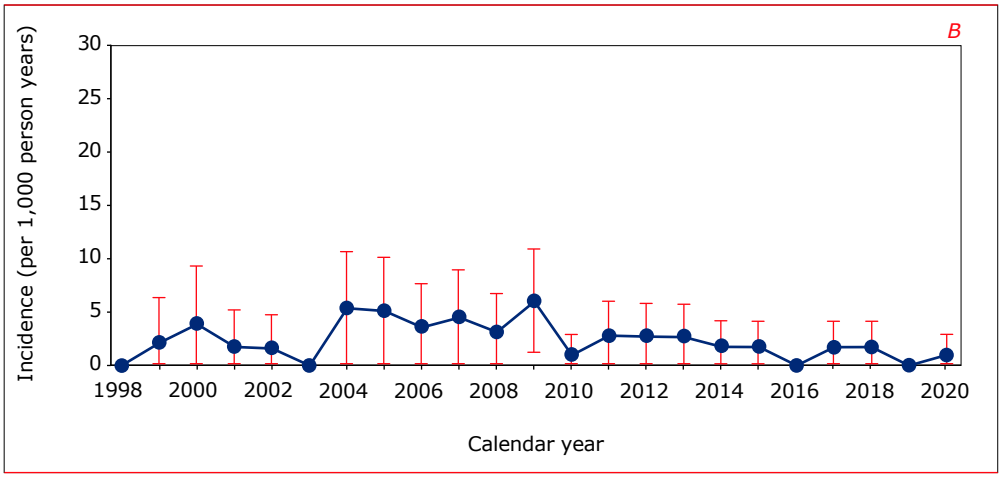
All-cause mortality

Nineteen percent (n=308) of the 1,621 individuals with an HBV infection died of any cause. For individuals with HBV infection, the incidence rate of death from any cause, adjusted for age and gender of the SHM population, was 16.0/1,000 PY in 1998-2002, 16.0 in 2003-11, and 11.9 from 2012 onwards (*Figure 4.18A*). In MSM with HBV infection, these incidence rates were 11.7/1,000 PY in 1998-2002, 13.5 in 2003-11, and 10.1 from 2012 onwards. In PWID with HBV infection, these incidence rates were 52.5/1,000 PY in 1998-2002, 60.4 in 2003-11, and 94.4 from 2012 onwards.

Of the 308 individuals with an HBV infection who died from any cause, five (1.6%) had either past or current HDV infection.

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 1,597 HIV-1-positive individuals who were ever diagnosed with HBV infection.





***Note:** Individuals who were diagnosed with HBV infection could be co-infected with HCV.*

Liver-related mortality

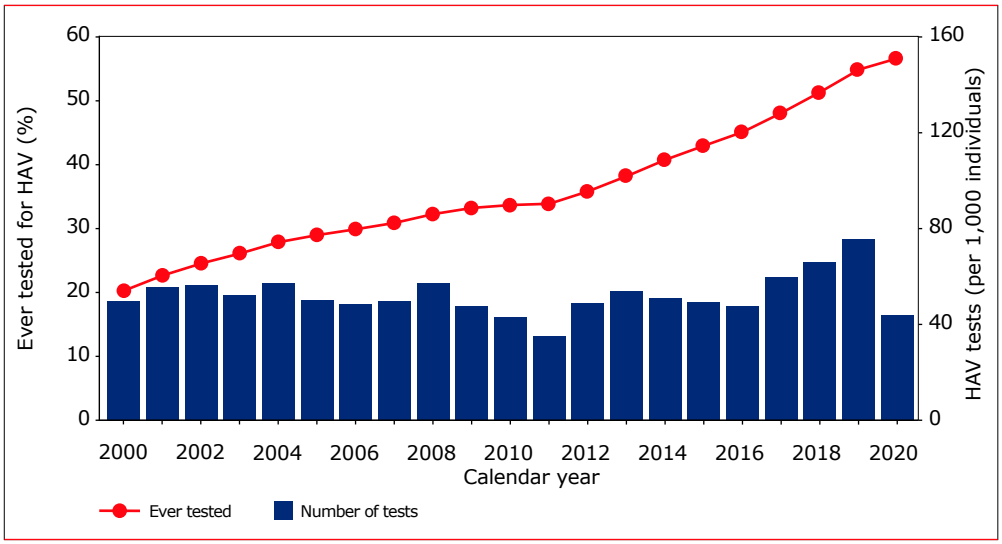
In total, 49 individuals co-infected with HBV died of a liver-related cause, only one of whom had either past or current HDV infection. For individuals with HBV infection, the incidence rate of liver-related death, adjusted for age and gender of the SHM population, was 1.9/1,000 PY in 1998-2002, increasing to 3.5 in 2003-11, and decreasing to 1.5 from 2012 onwards (*Figure 4.18B*). In MSM with HBV infection, these incidence rates were 2.4/1,000 PY in 1998-2002, 3.2 in 2003-11, and 1.4 from 2012 onwards. In PWID with HBV infection, these incidence rates were 3.4/1,000 PY in 1998-2002, 13.5 in 2003-11, and 11.9 from 2012 onwards.

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-six percent (n=15,918) of the 28,223 individuals living with HIV ever registered in the SHM database have been screened for HAV. The frequency of screening for HAV in individuals living with HIV has been consistent over the past two decades (*Figure 4.19*). Between 2000 and 2017, roughly 40 to 60 HAV tests per 1,000 individuals were conducted each year. Between 2018 and 2019, screening frequency increased to 68 and 76 HAV tests per 1,000 individuals per year, respectively. In 2020, screening frequency returned to 44 HAV tests per 1,000 individuals. The percentage of individuals who have ever been tested for HAV was 20% in 2000, and steadily increased to 57% in 2020 (*Figure 4.19*).

Figure 4.19: Percentage ever tested for anti-HAV antibodies and anti-HAV antibody testing frequency per calendar year.

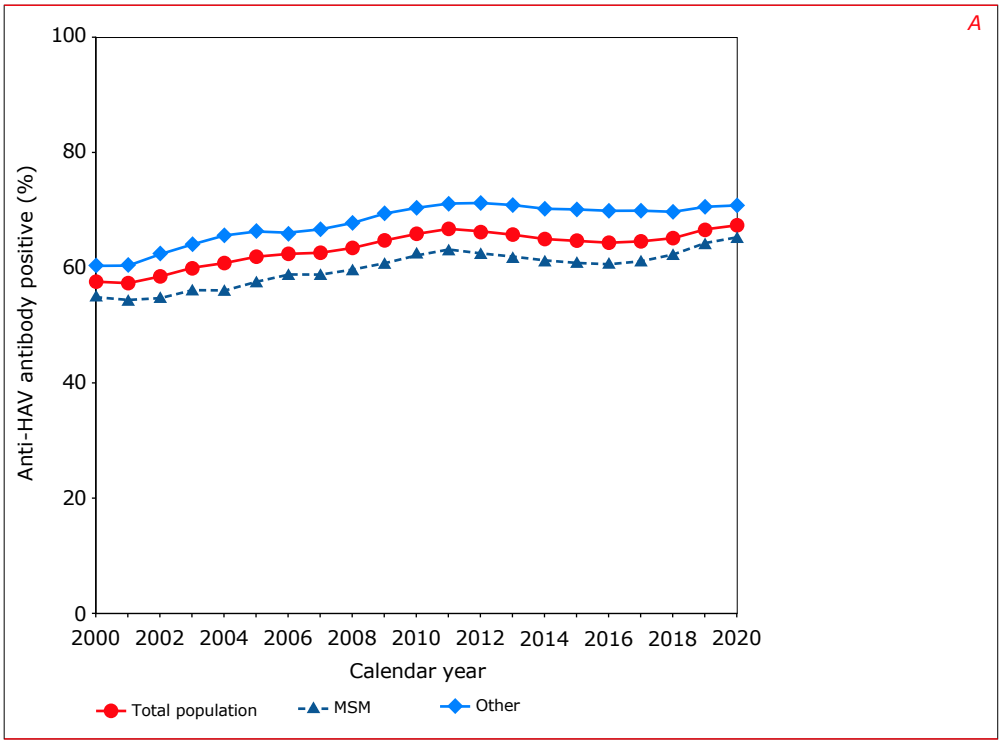


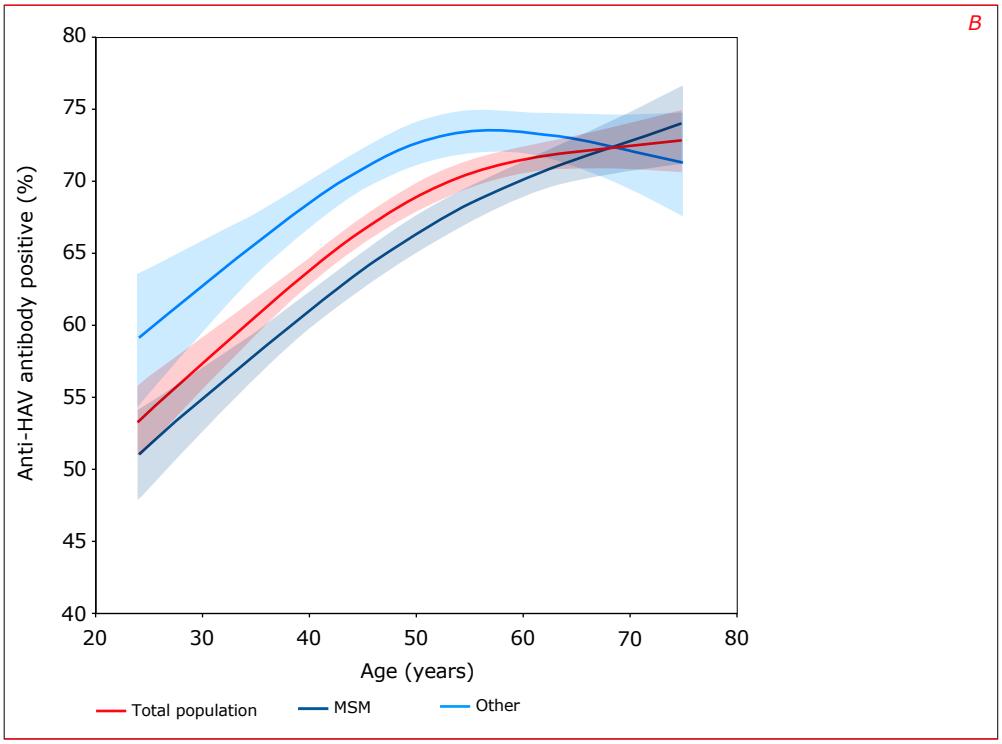
Legend: HAV=hepatitis A virus.

HAV seropositivity

Of the 15,918 individuals ever screened for HAV, a total of 10,711 (67%) had a positive anti-HAV antibody test result; 60% were observed in MSM, 3% in PWID, 35% in heterosexuals, and 2% in people from other transmission groups. The prevalence of anti-HAV antibody positivity was 58% in 2000 and then slowly increased to 67% in 2020 (*Figure 4.20A*). For MSM, the prevalence of anti-HAV antibody positivity was 55% in 2000, and it also slowly increased, reaching 65% in 2020. For all other transmission groups, the prevalence of anti-HAV antibody positivity was 60% in 2000 and 71% in 2020.

Figure 4.20: Percentage with anti-HAV antibodies per: A) calendar year, and B) age in years.





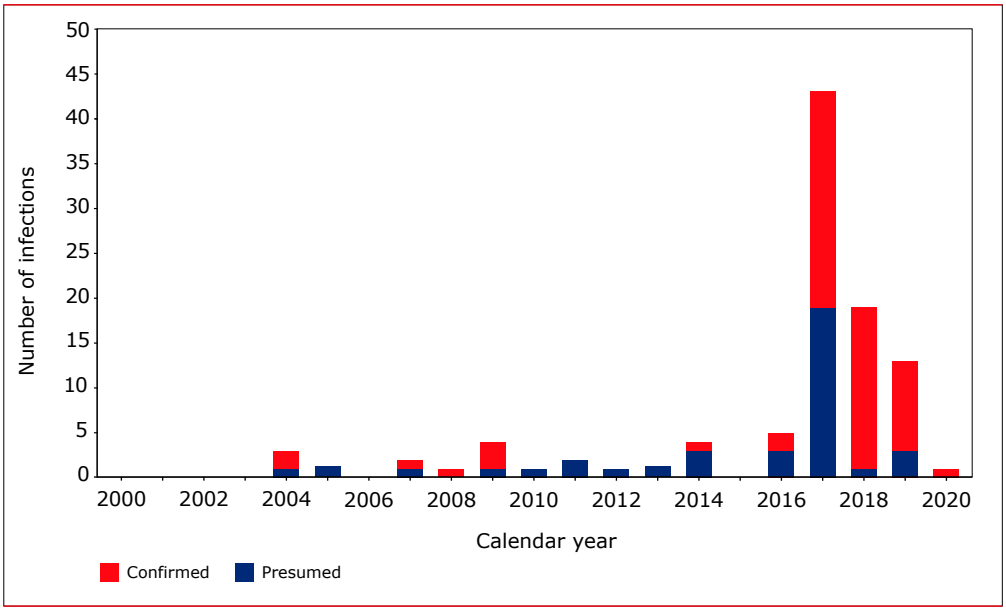
Legend: HAV=hepatitis A virus; MSM=men who have sex with men.

Epidemiological studies have highlighted the strong relationship between increasing anti-HAV antibody positivity and increasing age[40]. This age-dependent relationship was also observed in the 15,918 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 or older. For MSM, anti-HAV antibody positivity was 57% for individuals below the age of 40, and 68% for those aged 40 or older. For all other transmission categories, anti-HAV antibody seropositivity was 64% for individuals below the age of 40, and 73% for those aged 40 or older.

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 2000 and 2020, there were 105 reported cases of acute HAV infection (n=65, presumed; n=40, confirmed), of which 85 (81%) were observed in MSM, 19 (18%) in heterosexuals, and one (1%) in PWIDs. Cases of acute HAV were first documented in 2000, and the number of acute HAV cases were lower than five per year until 2017, when 43 cases of acute HAV infection were documented (n=24, presumed; n=19, confirmed) (*Figure 4.21*). This figure decreased to 19 in 2018 and 13 in 2019. Of the 76 documented cases occurring between 2017 and 2020, 66 (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[41]. In 2020, there was only one presumed case of acute HAV infection.

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

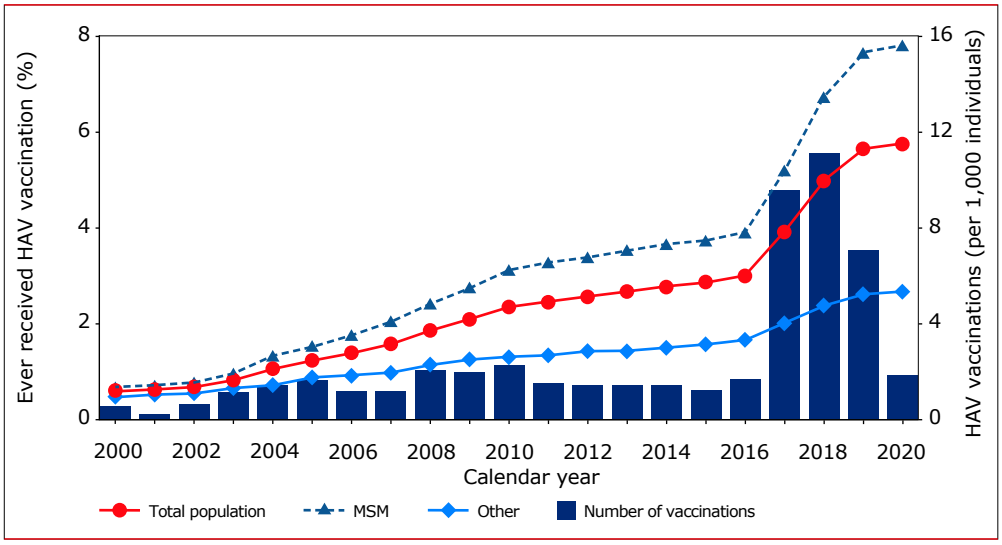


Of the 105 reported cases of acute HAV infection, 54 (51%) were recorded to have severe clinical symptoms. Severe chronic liver disease, according to our definition, was considered to be present (presumptive and definitive categories combined) in 16 (15%) of those with a reported acute HAV infection. Definitive severe chronic liver disease was documented for four (4%) with a reported HAV infection. No deaths due to acute HAV infection were reported.

HAV vaccination in individuals living with HIV

Information on HAV vaccination status was obtained from clinical files and was unknown for the majority of individuals ever registered by SHM. Of the 28,223 individuals living with HIV ever registered in the SHM database, 1,668 (6%) 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)[42]. HAV vaccination frequency was consistently lower than, or equal to two vaccinations per 1,000 individuals living with HIV from 2000 to 2016, and it increased substantially to nine and 11 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 1.5% in 2000, 3.1% in 2016, and 5.9% in 2020. In MSM, this percentage was 2.0% in 2000, 4.1% in 2016, and 8.0% in 2020.

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



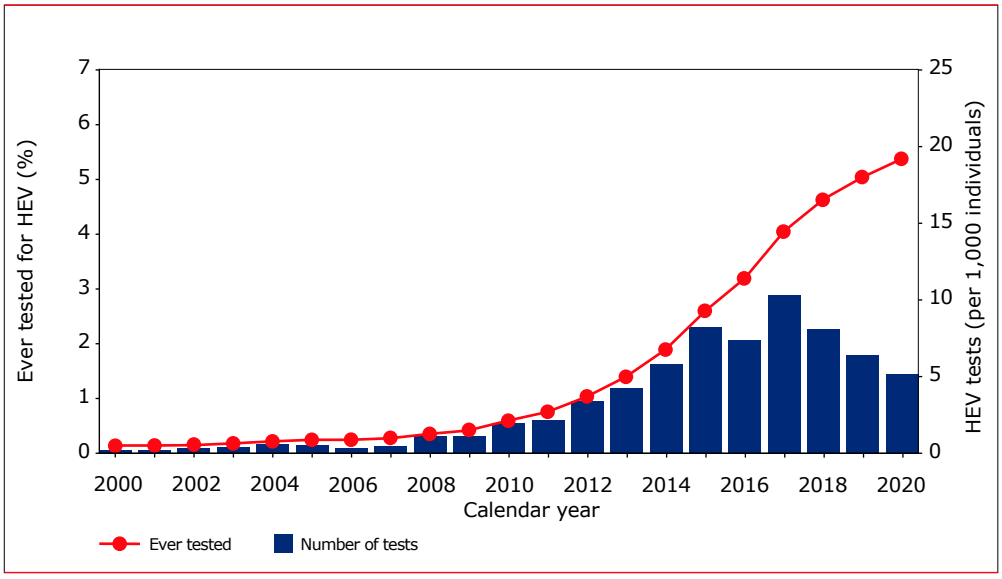
Legend: *HAV=hepatitis A virus; MSM=men who have sex with men.*

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). Five percent of the 28,223 individuals living with HIV ever registered in the SHM database have been screened for HEV. The screening frequency for HEV infection in individuals living with HIV in care was low between 2000 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 2020, 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 1,510 individuals who were in care between 2000 and 2020, and who were ever screened for HEV, 207 (14%) were newly diagnosed as having past or current HEV infection. Of these individuals, 136 (66%) were MSM, 59 (29%) heterosexuals, six (3%) PWID, and six (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 living with HIV. The percentage of individuals newly diagnosed with past or current HEV infection ranged from 9% in 2004 to 14% in 2020 (*Figure 4.25*).

Of all individuals tested for HEV and in care between 2000 and 2020, there were 49 individuals diagnosed with acute HEV infection, of whom 36 were MSM and 13 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.*

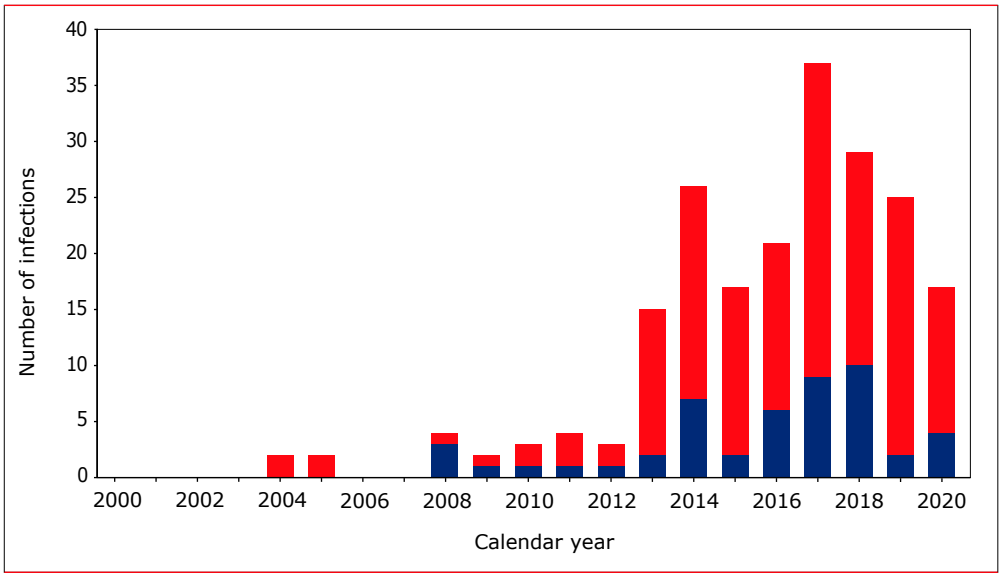
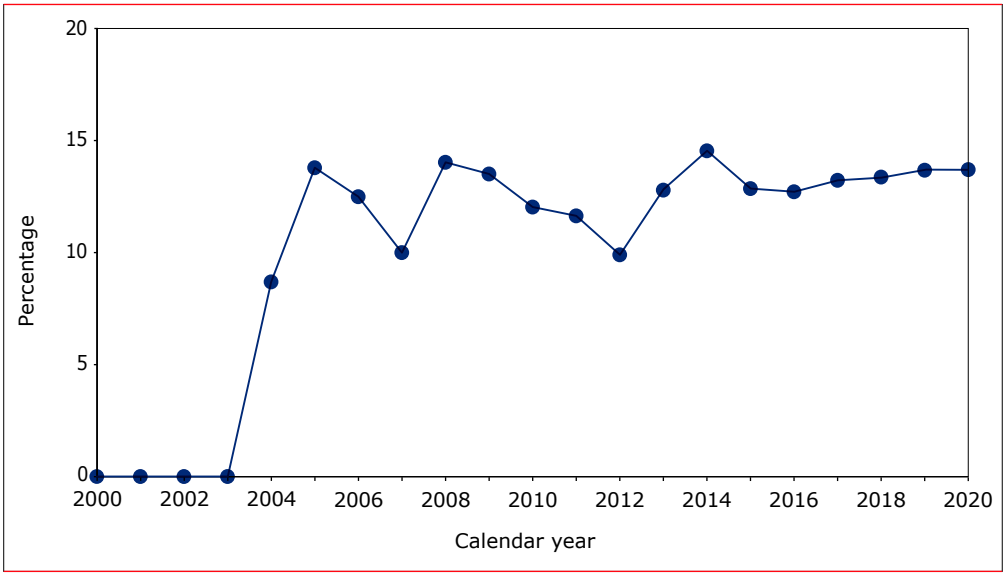


Figure 4.25: Percentage ever infected with HEV per calendar year.



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 living with HIV in the Netherlands has continued to improve over time and is now almost universally documented. Five percent of individuals living with HIV ever registered between 1998 and 2020 in the SHM database, have been documented as chronically infected with HCV at some stage, and 3% have been documented as having had an acute HCV infection. Acute HCV infection occurred more often among MSM (5%), while reinfection of HCV was documented in 17% of the MSM ever diagnosed with a primary HCV infection.

Our data clearly show that novel DAAs, which arrived in 2014, have entirely replaced PEG-IFN-containing regimens. In addition, the number of individuals living with HIV treated for HCV has rapidly increased. More than 1,100 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 HCV co-infected individuals remaining in need of HCV treatment to 55 in 2020. Overall, a rapid reduction in the prevalence of active HCV infections was achieved, with prevalence in MSM having declined to 0.29% in 2020. Successful treatment of HCV will also prevent onward transmission of HCV, which is possibly reflected in the lower incidence of acute HCV infections in recent years[21]. However, in line with earlier reports[26,29,43], HCV reinfection after successful treatment has been observed. Although the rate of reinfection has declined over the past few years, ongoing transmission of HCV persists.

Six percent of the individuals living with HIV ever in care have had HBV co-infection. The prevalence of HBsAg-positive serostatus has decreased over time for all transmission groups, mostly as a result of increased HBV vaccination rates[30], together with the HBV-prophylactic effect of TDF/TAF in cART-treated individuals. Nonetheless, an estimated 28% of all individuals living with HIV have either not been exposed to HBV, or have not been successfully vaccinated, and may remain at risk of acquiring HBV. Since 82% of all individuals still at risk of acquiring HBV infection use a cART regimen that includes TDF/TAF, their risk could be essentially nil due to sustained chemoprophylaxis. The remaining 18% of the individuals living with HIV ever registered remain unprotected against HBV, which represents an estimated 7.0% of the total population of individuals living with HIV screened for hepatitis B. Very few individuals were tested for HDV infection and, of those who were tested, a small percentage had evidence of active HDV infection.

Among the individuals living with HIV ever registered by SHM, 29% of the individuals chronically co-infected with HCV, and 17% of the individuals chronically co-infected with 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 co-infection 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 HCV and HBV co-infections since 2012, yet the rate remained much higher for co-infected PWIDs, 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[44]. The percentage of people living with HIV with anti-HAV antibodies was higher in older age groups, as would be expected from the general

epidemiology of HAV infection[40]. Among the individuals diagnosed with HAV, almost half reported having severe symptoms during their infection, while four 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 6%; 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[17]. 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[16]. 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 HCV reinfection. In particular, efforts should continue to increase HBV vaccination rates among individuals living with HIV who remain at increased risk of acquiring HBV, particularly those who are not receiving an antiretroviral regimen containing TDF or TAF, and those who previously failed to respond to vaccination[45]. Already, the provision of highly-effective DAA regimens for all known HCV co-infected individuals living with HIV 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 may 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, 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[35]. In the Netherlands, 13% of individuals who were ever infected with HBV had been tested for HDV infection; the reasons for this low percentage need to be elucidated. This information could help to establish whether HDV infection in the Netherlands is a substantial contributor to liver-related morbidity and mortality in individuals living with HIV with HBV infection, as found in other settings[12].

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[40] 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 yearly for HEV[46]. However, data from SHM and a meta-analysis found no noteworthy increase in HEV prevalence among individuals living with HIV[47], and only two patients in the SHM database were diagnosed with chronic HEV infection. We recommend following current European guidance, which states that individuals with persistently-elevated transaminase levels should be screened for HEV RNA[17]. Further data are needed to determine to what extent liver-related, and non-liver-related disease occurs as a result of HEV infection in individuals living with HIV.

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