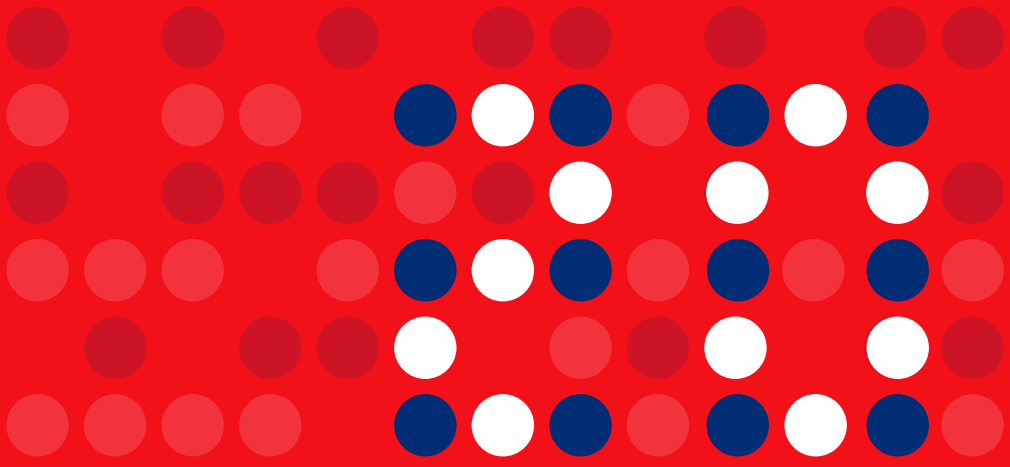
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2020



4. Viral hepatitis

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Box 4.1: Viral hepatitis data in the ATHENA cohort in the Netherlands.

Population described in this chapter
All individuals ever registered with Stichting HIV Monitoring (SHM) by 1 May 2020 – the date the SHM database was locked for the purposes of this report.

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 ever having been exposed 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 HIV-positive individuals 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 can ultimately result in end-stage liver disease and/or hepatocellular carcinoma (HCC)[6,7]. Progression to severe liver disease takes, on average, 20 to 30 years in individuals mono-infected with HCV or HBV[8,9]. While liver fibrosis progression 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[10,11]. Meanwhile, co-infection with HBV/HDV is known to be highly associated with severe liver-related outcomes compared to HBV mono-infection[12], with accelerated progression to end-stage liver disease in HIV-positive individuals, despite effective cART[13].

Infection with hepatitis A virus (HAV) and hepatitis E virus (HEV) is more frequent in the Netherlands compared to HBV and HCV. Both are enterically transmitted and can cause acute, self-limited inflammatory liver disease[14,15]. In the Netherlands, outbreaks of HAV infection are mostly observed in specific groups, such as men who have sex with men (MSM), with some onward transmission[16], whereas markers of previous HEV infection can be detected in roughly 10% of the general population[17]. HAV and HEV infection 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)[18]. HEV infection more commonly persists and develops into chronic infection in immunocompromised individuals, who are then at increased risk of developing ongoing symptoms[15].

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

HCV

Box 4.2: Definitions of hepatitis C infection.

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

Acute HCV infection[19,20]

1. Case definition of acute hepatitis C virus according to preferred criteria[19]
   Positive anti-HCV IgG with a documented negative anti-HCV IgG within the past 12 months.
   or:
   Detectable HCV RNA in the presence of either a documented negative HCV RNA test, or a documented anti-HCV IgG sero-conversion within the past 12 months.
2. Case definition of acute hepatitis C virus according to alternative criteria[19]
   Detectable HCV RNA in association with a rise in alanine aminotransferase (ALT) (>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.

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 re-infection
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- 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:
- 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).

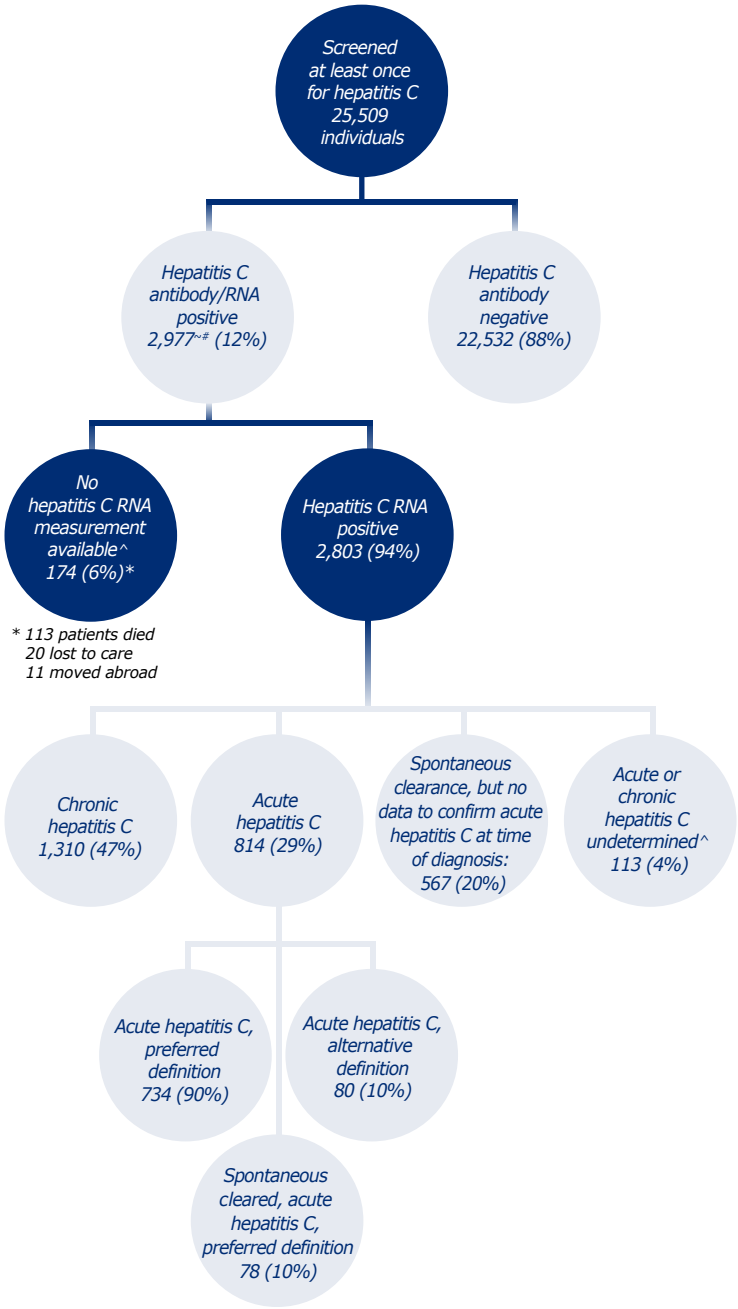
HCV positive individuals

As of May 2020, 27,093[a] HIV-1-positive adults (≥18 years of age at time of HIV-1 diagnosis) had ever been registered by Stichting HIV Monitoring (SHM) and in care in one of the HIV treatment centres in the Netherlands. Of those individuals, 25,509 (94%) were ever screened for HCV co-infection and 2,977 (12%) had a positive result with an HCV antibody test and/or HCV RNA test. This confirms that HCV is far more prevalent among the HIV-positive population, than is estimated for the general Dutch population (*Figure 4.1*). HCV RNA data were not documented in 174 of the 2,977 cases (6%). Of these 174 individuals, 113 have died, 20 have been lost to care, and 11 have moved abroad; the reason for an undocumented HCV RNA in the remaining 30 individuals is unknown. Of the 2,803 individuals with documented HCV RNA data, 814 (29%) were initially diagnosed with acute HCV infection; 78 spontaneously cleared their infection; and 736 became chronic HCV infections, or were treated within six months of diagnosis. Another 1,310 (47%) individuals were classified as having chronic HCV infection at the time of diagnosis. In total,

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

567 (20%) individuals had evidence of spontaneous clearance of HCV, but could not be classified as acute HCV infection at the time of HCV diagnosis. The remaining 113 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 have therefore been excluded from the analysis.

Figure 4.1: Flowchart of HIV-positive individuals tested at least once for hepatitis C virus (HCV).



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

Spontaneous clearance of HCV

In total, 645 individuals spontaneously cleared their HCV infection. Among the 814 individuals with primary acute hepatitis, 78 cases of spontaneous clearance were observed (10%). Another 567 cases of spontaneous clearance were observed among individuals who could not be classified as having a primary acute infection: 258 infections were classified as a definitive spontaneous clearance (i.e., two negative HCV RNA test results after a positive HCV test result), and 309 as possible spontaneous clearance (i.e., one negative HCV RNA test). 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 (*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, 1998-2019.*

	Total HCV co-infected	Spontaneous clearance
Total number of individuals	2,691	645 (24%)
Age at HCV diagnosis (median, IQR)	40 (34-47)	40 (35-47)
HCV status		
Chronic HCV	1,310	
Acute HCV	736	
Definitive clearance	258	258
Possible clearance	309	309
Spontaneous clearance after confirmed primary acute infection	78	78
Male gender, n (%)	2,318 (86)	525 (81)
Region, n (%)		
Netherlands	1,657 (62)	337 (52)
Europe	350 (13)	86 (13)
Sub-Saharan Africa	116 (4)	59 (9)
Caribbean/South America	202 (8)	72 (11)
Southeast Asia	87 (3)	22 (3)
Other	279 (10)	69 (11)
HIV transmission route, n (%)		
Men who have sex with men	1,581 (59)	350 (54)
Heterosexual	303 (11)	111 (17)
People who use/used injecting drugs	565 (21)	116 (18)
Other	242 (9)	68 (11)
cART, n (%)	2,606 (97%)	617 (96)
Deaths, n (%)	454 (22%)	98 (15)

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

The analyses described in the remainder of this section on HCV are limited to the individuals who could be definitively classified as having either chronic (n=1,310), or acute (n=814) HCV infection at the time of their primary HCV diagnosis (*Appendix Figure 4.1*). Most of these were male (81% and 99%, respectively), and the majority originated from the Netherlands (chronic: 753/1,310 [57%]; acute: 621/814 [76%]) (*Table 4.2*). Fifty-nine percent of the registered individuals who had acquired HIV through injecting drug use (IDU), had a chronic HCV infection (442 of the total 752 people who use/used injecting drugs [PWID]). In the MSM HIV transmission group (15,602), 3% (541) had a chronic HCV infection and 5% (765) had a documented acute HCV infection.

The HCV genotype was determined and documented in the clinical records of 1,176 of the 1,310 (89%) individuals with a chronic HCV infection. Of the individuals with a genotype determination, the majority (61%, n=725) were infected with HCV genotype 1; 61% (n=441) with genotype 1a, and 13% (n=94) with genotype 1b. For 26% of the people infected with genotype 1, the subtype was not further specified. Five percent (n=57) were infected with HCV genotype 2, 18% (n=206) 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 714 of the 814 (88%) individuals with an acute HCV infection. They were most likely to be infected with either genotype 1 (71%, n=514) or genotype 4 (20%, n=146). Of the 514 infected with genotype 1, 84% (n=430) were infected with genotype 1a and 5% (n=24) with genotype 1b. For 12% 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, 1998-2019.

	Total	Chronic HCV	Acute HCV
Total number of individuals screened for HCV	25,509	1,310	814
Age at baseline (median, IQR)	40 (34-47)	39 (32-45)	43 (36-49)
Male gender, n (%)	20,985 (82)	1,063 (81)	806 (99)
Region of origin, n (%)			
Netherlands	14,199 (55)	753 (57)	621 (76)
Europe	1,709 (7)	204 (16)	68 (9)
Sub-Saharan Africa	3,456 (14)	47 (4)	11 (1)
Caribbean/South America	3,144 (12)	87 (7)	49 (6)
Southeast Asia	912 (4)	43 (3)	24 (3)
Other	2,089 (8)	176 (13)	41 (5)
HIV transmission route, n (%)			
Men who have sex with men	15,602 (61)	541 (41)	765 (94)
Heterosexual	7,517 (30)	66 (13)	28 (3)
People who use/used injecting drugs	752 (3)	442 (34)	8 (1)
Other	609 (6)	159 (12)	13 (2)
cART, n (%)	24,554 (96)	1,256 (96)	809 (99)
HCV genotype (GT), n (%*)			
Total determined		1,176 (90)	714 (88)
GT 1		725 (62)	514 (71)
1a		441	430
1b		94	24
1c, 1a/b or not further specified		190	60
GT 2		57 (5)	37 (5)
GT 3		206 (18)	16 (2)
GT 4		186 (16)	146 (20)
GT 5&6		2 (0.1)	1 (<1)
Deaths, n (%)	2,833 (11)	320 (24)	39 (5)

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

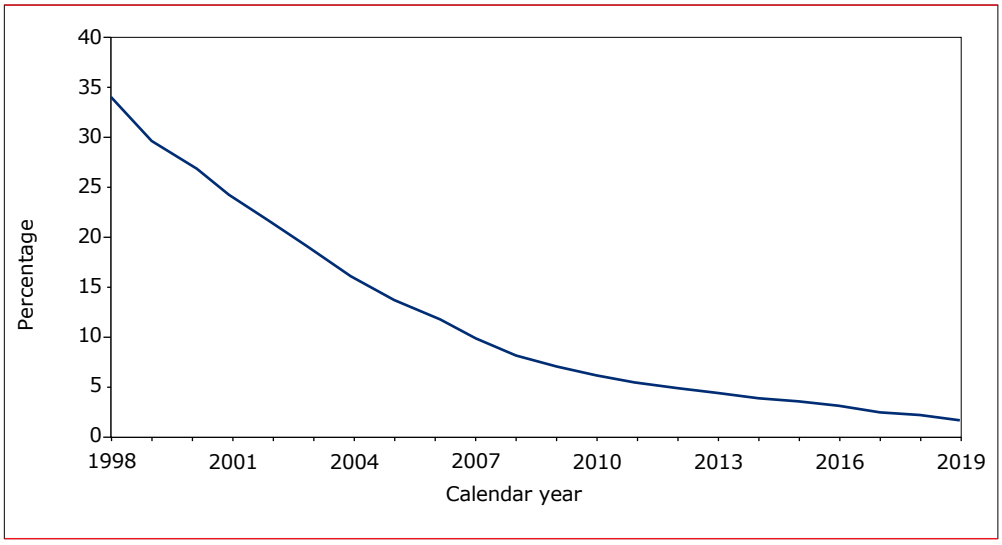
***Legend:** n=total for each category; (%)=percentage of the total for each column; HCV=hepatitis C virus; cART= combination antiretroviral therapy; GT= genotype.*

Changes over time

Testing for HCV over time

In the Netherlands, the national guidelines for the treatment and monitoring of HIV recommend HCV screening at first clinical visit after HIV diagnosis, and additional annual HCV screening for MSM who report HCV-related risk-taking behaviour[21]. Screening for HCV infection among the HIV-positive individuals ever registered with SHM has increased over calendar time. In 1998, 34% of the HIV-positive individuals 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 was observed, and, in 2019, only 1.8% of the individuals in care had never been screened for HCV co-infection (*Figure 4.2*). In 2019, unknown HCV status was relatively more common among individuals with heterosexually-acquired HIV (n=187/5,821, 3.2%) or with another or unknown mode of HIV acquisition (n=36/853, 4.2%), and relatively less common among MSM (0.9%) and PWID or former PWID (0.7%).

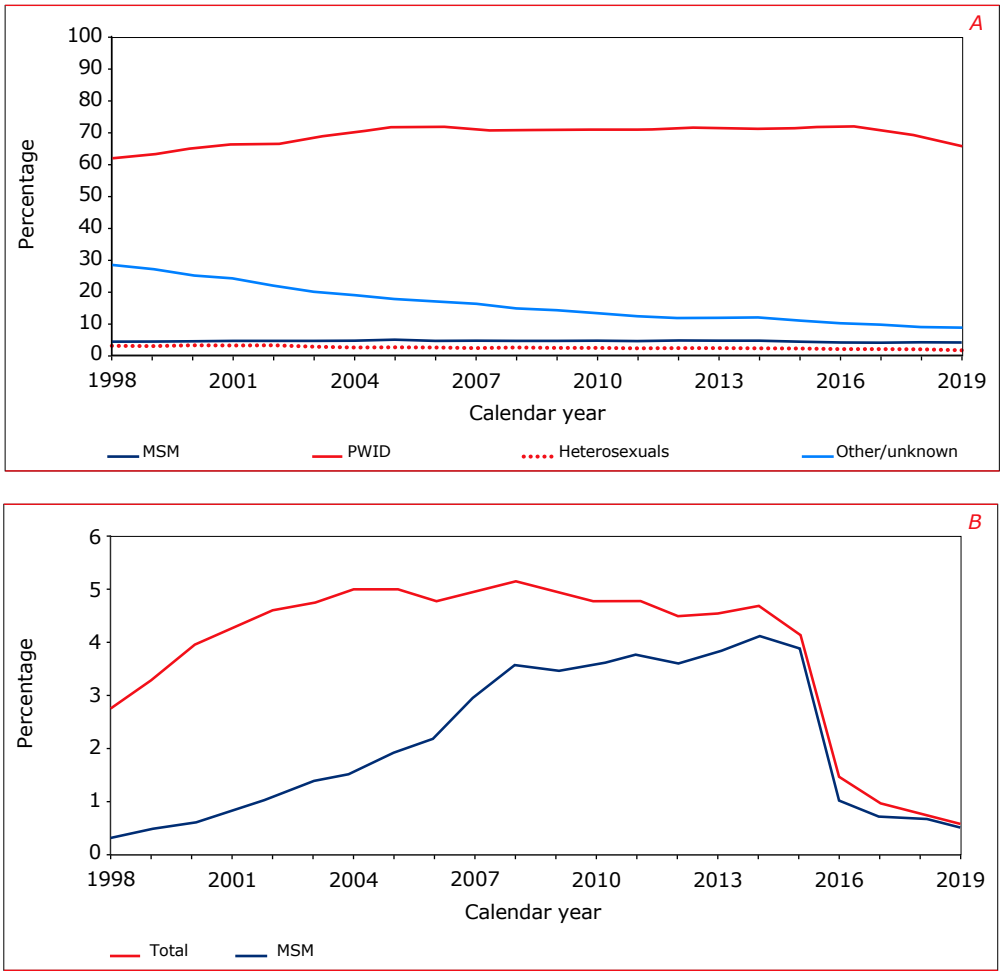
Figure 4.2: Percentage of individuals in care with an unknown hepatitis C status per calendar year of care.



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 HIV-positive individuals ever registered, decreased from 11.2% in 1998 to 4.6% in 2019, but was not equally distributed across HIV transmission categories. The highest prevalence was found among individuals who had acquired HIV by injecting drug use, and this number varied between 62% and 72% over calendar years (*Figure 4.3A*).

Figure 4.3: Prevalence of A) 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 2.8% in 1998 and 5.1% in 2008, before dropping to 0.6% in 2019. In MSM, the highest percentage of HCV RNA positivity was 4% in 2014; by 2019, the percentage of positive HCV RNA tests in this group decreased sharply to 0.5%.

Incidence of acute HCV infection over time

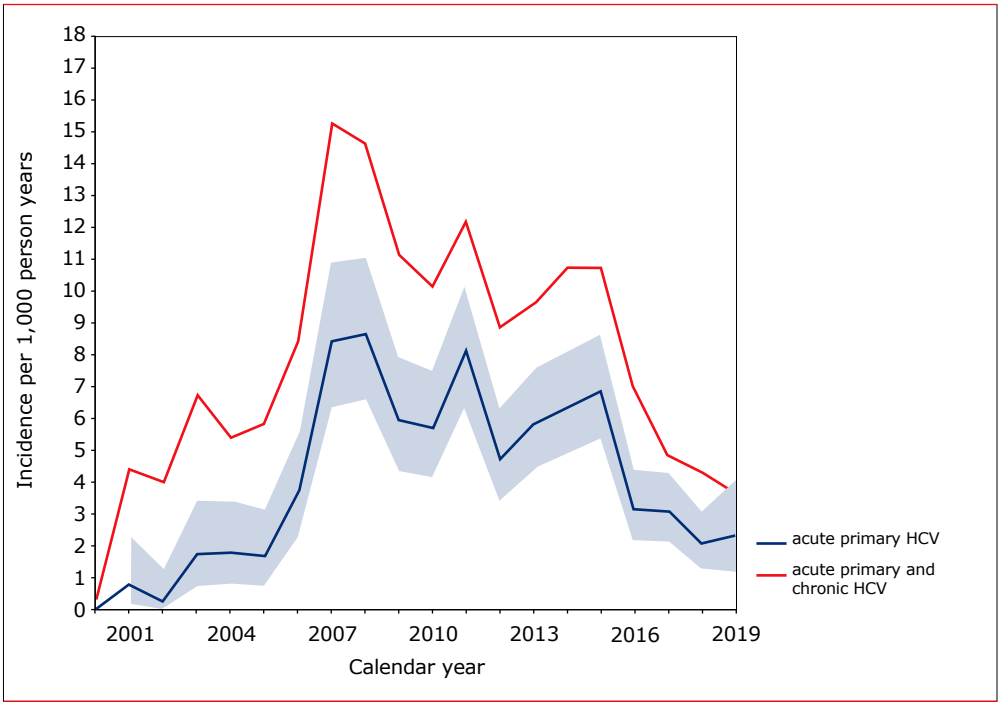
For the purpose of this analysis, the definition of acute HCV infection includes only cases of primary acute HCV infection (first diagnosis of HCV). This definition is consistent with the one given in the European AIDS Treatment Network (NEAT) preferred criteria[19]. In addition, we have expanded this definition to include alternative criteria[19,20]. 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 (>200 U/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=765/814 [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 programs implemented in addictive care centres in the Netherlands. Twenty-eight cases occurred among individuals who had acquired HIV heterosexually.

Figure 4.4 shows both the incidence of acute primary HCV infection and all newly-diagnosed acute primary and chronic HCV diagnoses among MSM over time. The overall rate of acute HCV infection in this group was 4.5 per 1,000 person years (PY) (95% CI, 4.2-4.9). 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 8.4 and 8.7 per 1,000 PY in 2007 and 2008, respectively. The incidence, which was 6.9 diagnoses per 1,000 PY in 2015, declined to 3.2 in 2016, before stabilising at 2.3 diagnoses per 1,000 PY in 2019.

As expected, incidence rates among MSM were higher when the preferred and alternative case definitions of acute HCV were combined, with incidence rates of 7.9 diagnoses per 1,000 PY in 2015, 4.2 in 2016, and 2.7 in 2019.

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; shaded area represents the 95% confidence interval.

Treatment for HCV infection

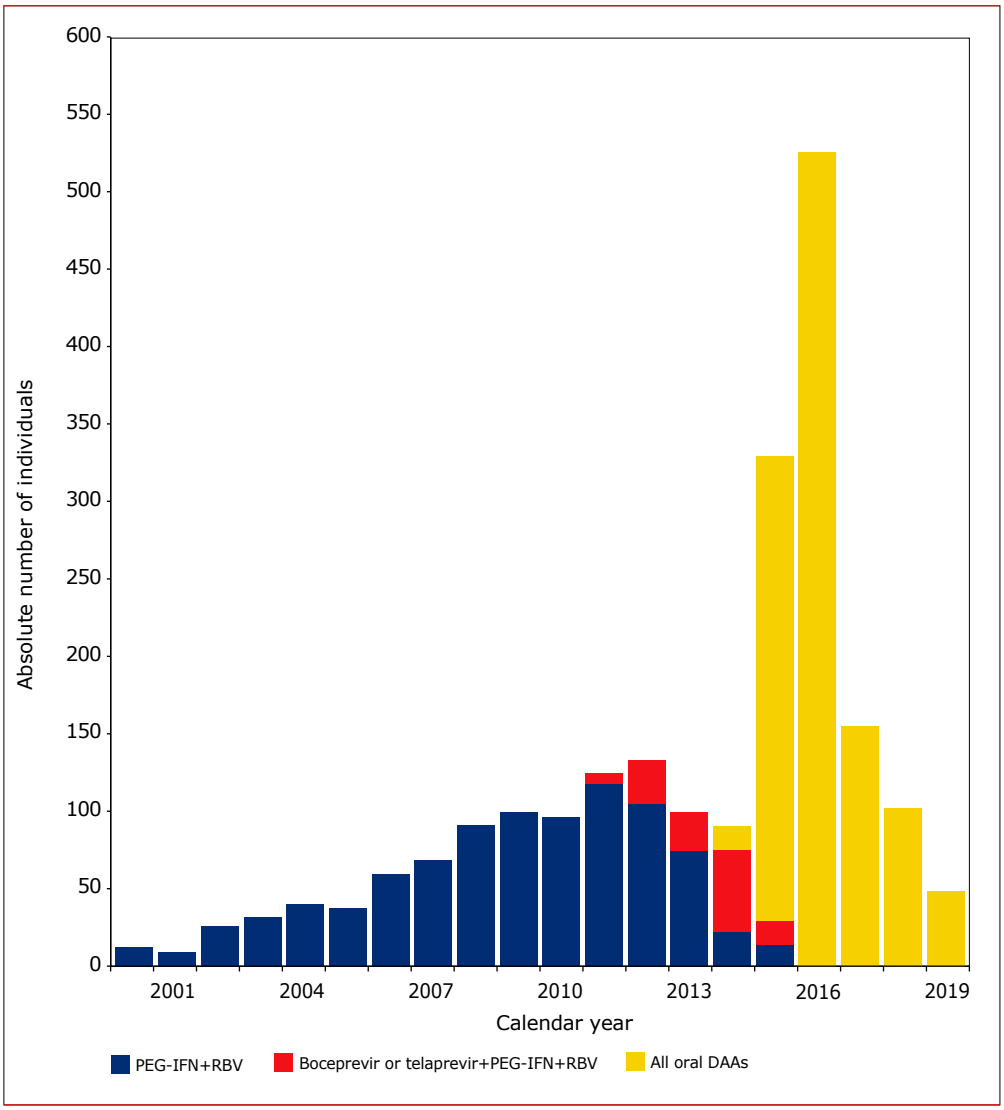
The primary aim of HCV treatment is to achieve a sustained virological response (SVR)[22] and the treatment used have changed markedly in recent years. In the past, treatment consisted of interferon alpha (IFN alpha), and subsequently pegylated interferon alpha (PEG-IFN alpha) in combination with ribavirin (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. Among the 2,046 individuals ever diagnosed with chronic or acute HCV, 1,707 have ever received HCV treatment; of those, 415 have received HCV treatment more than once (this includes people who were unsuccessfully treated and those who re-acquired HCV after prior successful treatment).

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



Note: *numbers in 2019 may be underreported, due to a delay in data collection.*

Legend: *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 2020, 1,060 individuals were known to have started a DAA regimen; 86 of those had been treated more than once with a DAA regimen. The most common reasons for receiving DAA treatment more than once were: re-infection after earlier DAA treatment-induced clearance (n=40); no SVR or discontinuation of first treatment episode due to lack of early virological response during the first episode of DAA treatment (n=24), or toxicity (n=5). Of the total 1,156 DAA treatment episodes, 15 occurred in 2014, 299 in 2015, and 526 in 2016. The number of treatment episodes has subsequently decreased to 155 in 2017, 104 in 2018, and 51 in 2019 (*Figure 4.5*).

The most frequently used DAA regimens were 1) sofosbuvir plus ledipasvir +/- RBV (n=568); 2) sofosbuvir plus daclatasvir +/- RBV (n=247); and 3) pibrentasvir/glecaprevir (n=75). Thirty seven individuals who had previously been treated with DAAs are known to have died. The causes of death were liver disease (n=6), non-AIDS-defining malignancies (n=7), cardiovascular disease (n=4), non-AIDS-defining infection (n=3), and non-natural death (n=3); the remaining deaths (n=14) were related to alcohol and substance use, AIDS, lung disease, or the cause was unknown.

Treatment outcomes

HCV RNA data were collected up to 1 May 2020. At that point, 1,100 out of 1,156 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 total:

- In 1,065 of the 1,100 treatment episodes SVR12 (97%) was achieved.
- No SVR was achieved in 30 treatment episodes.
- For the remaining five treatment episodes, no follow-up data on SVR was available; because persons had died shortly after being treated (n=4) or no reported HCV RNA tests were available to assess treatment outcome (n=1).

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 (92%). 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:
- 15 were successfully retreated with a DAA regimen
- Nine were not retreated
- Three were unsuccessfully retreated

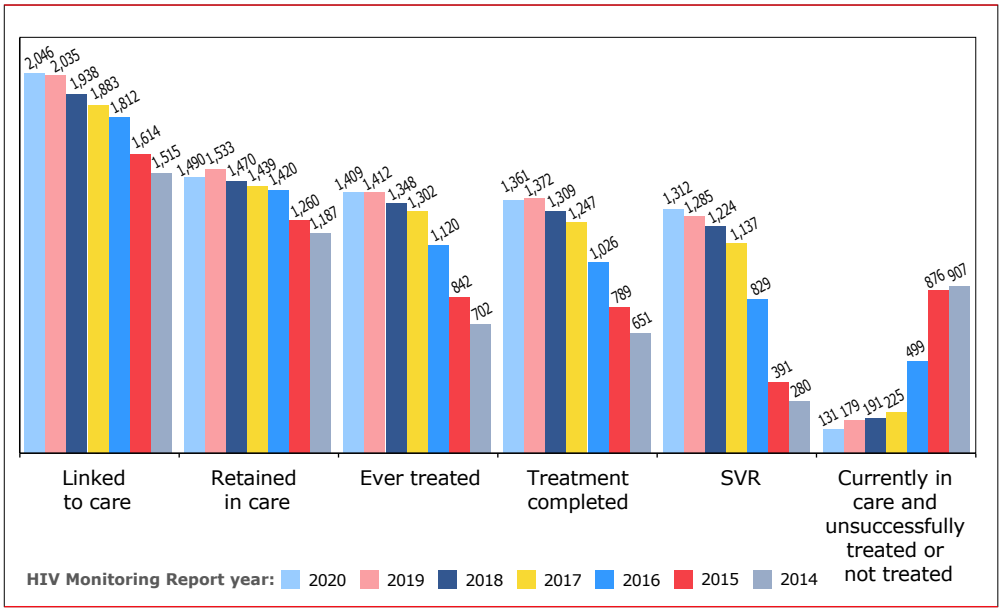
Continuum of care for those with diagnosed HCV co-infection

Figure 4.6 shows the HCV continuum of care, based on the number of people known to be in HIV care as of 31 December 2019, with data from previous monitoring reports for 2014-18 shown for comparison. A total of 2,046 individuals linked to HIV care were diagnosed with HCV (1,310 with a chronic HCV infection and 736 with an acute HCV infection [814 minus 78 with spontaneous clearance] at diagnosis). Of these, 1,490 (73%) were retained in care, while 556 individuals were no longer in care (356 had died, 106 had moved abroad, and 94 were lost to care). Of those still alive and in care, 1,409 (95%) had received treatment for HCV (with DAAs or a pegylated interferon-containing regimen) and 1,361 (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, 1,312 of the 1,361 people who completed treatment (96%) achieved an SVR, including those who achieved an SVR on a pegylated interferon-containing regimen.

As a result, 178 (11%) of the 1,490 individuals known to be alive and in care in one of the Dutch HIV treatment centres on 31 December 2019, were still in need of HCV treatment:
- 81 individuals had never been treated for HCV; 75 of these were receiving cART for HIV during their last clinical visit, and 71 of these 81 individuals had an HIV RNA <100 copies/ml; the percentage untreated was higher among PWID (11%) and people with an unknown HIV transmission mode (6%), compared to MSM (4%) (P=0.01).
- 49 had been unsuccessfully treated for HCV, including those who had not achieved an SVR on a pegylated interferon-containing regimen; eight of these individuals had documented evidence of severe liver disease.
- 48 were still being treated or had insufficient time after treatment discontinuation to allow SVR calculation.

Of the 48 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 of 97% to these individuals and assumed that 47 of the 48 will achieve SVR. This results in a more realistic estimate of individuals (178-47=131) who remained untreated or unsuccessfully treated.

Figure 4.6: Hepatitis C continuum of care.



Legend: SVR=sustained virological response.

HCV re-infection

Re-infection with HCV following successful treatment or spontaneous clearance has been reported mainly in HIV-positive MSM[26,27], with high rates of re-infection found among MSM in the Netherlands, Germany[28], and the United Kingdom[29].

To identify possible HCV re-infection among HCV co-infected individuals, we selected people who had initially achieved an SVR after having received any type of HCV treatment, and individuals with spontaneous clearance of HCV.

In total 1,866 individuals were susceptible for HCV re-infection (1,329 after SVR, 537 after spontaneous clearance).

Of these 1,866 individuals, 271 re-infections among 240 individuals (13%) were documented (*Appendix Figure 4.1*): 144 after SVR and 127 after spontaneous clearance. The median time between SVR and HCV re-infection was 1.6 years (IQR: 0.9-3.0) and between spontaneous clearance and re-infection it was 1.2 years (IQR: 0.5-3.2).

Most individuals who became re-infected were MSM (210/240, 88%). Another 21 were PWID or former PWID (21/240, 9%). For the remaining nine individuals, documented HIV transmission routes were heterosexual contact (three), blood-blood contact (two) and unknown (four).

Out of the 271 re-infections, 228 (84%) were re-treated (171 with DAA, 57 with interferon+/-boceprevir/telaprevir) The median time to re-treatment after re-infection diagnosis, stratified by calendar year of treatment initiation, was:

- <2014: 3.1 months (IQR: 1.2-7.1)
- 2014-18: 11.6 months (IQR: 3.2-34.8)
- ≥2018: 3.6 months (IQR: 2.0-15.3).

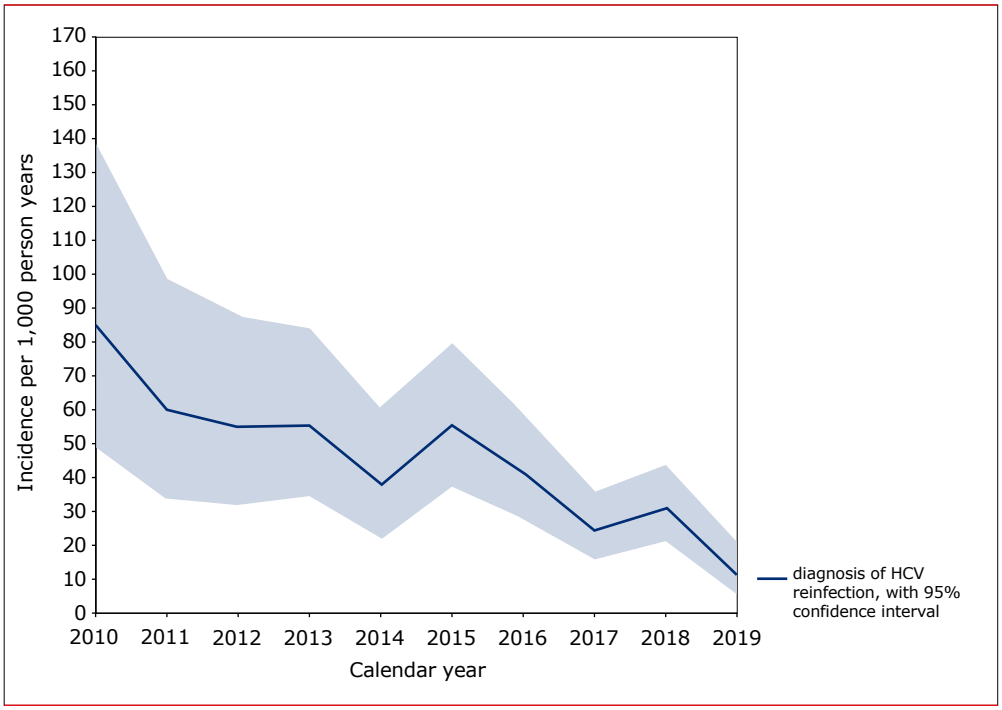
We calculated the incidence of re-infection between 2010 and 2019 for these 1,866 individuals. Follow-up time was from the date of SVR, date of spontaneous clearance, or from 1 January 2010 onward, until the earliest date of HCV re-infection, death, or last known contact.

The incidence of HCV re-infection for the total population was 20 re-infections per 1,000 PY (95% CI: 17-23), and for MSM it was 29 re-infections per 1,000 PY (95% CI: 25-33).

Because most re-infections occurred among MSM, the incidence of HCV re-infection after achieving an SVR over time is shown only for MSM (*Figure 4.7*). This incidence increased from 35 re-infections per 1,000 PY in 2010 to 49 in 2015, and then declined to 27 re-infections per 1,000 PY in 2018, and 11 in 2019.

Screening for HCV RNA among those at risk for HCV re-infection is an important factor in identifying HCV re-infection. The national guidelines for the treatment and monitoring of HIV recommend annual HCV screening for MSM who report HCV-related risk-taking behaviour[21]. In the Netherlands, among HIV-positive MSM at risk of re-infection, the percentage of men with an HCV RNA test during a calendar year varied between 55% and 65% for 2010-16, but showed a decline to 45% in 2018, and 40% in 2019. It is worth noting that these data might include MSM who are not considered at risk for HCV re-infection by the treating physician, as data on HCV-related risk-taking behaviour are not available to SHM.

Figure 4.7: Incidence of hepatitis C re-infection after earlier treatment-induced clearance or spontaneous clearance among men who have sex with men, per calendar year. Note, numbers in 2019 may be affected by a delay in data collection.



Liver-related morbidity

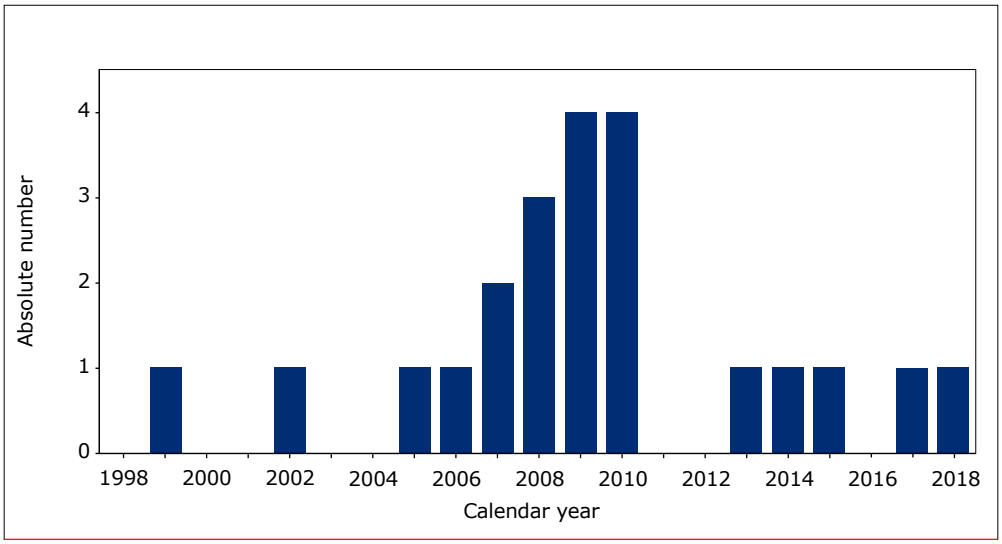
Data on liver-related morbidity are collected for all HIV-positive individuals in follow up in the ATHENA cohort. In total 1,112 cases of severe liver disease according to our definition were considered to be present (presumptive and definitive categories combined); 502 among individuals with HCV co-infection, 265 among individuals with HBV co-infection, and 345 among HIV-positive individuals 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 are limited to those with viral hepatitis. Findings are first discussed for HCV infection, and then for HBV infection in the corresponding section of this chapter.

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 1,702 of the 2,046 individuals with HCV co-infection. Review of these additional data showed that severe chronic liver disease was considered to be present (presumptive and definitive categories combined) in 502 (25%) of the individuals with HCV co-infection. Definitive severe chronic liver disease was documented for 120 individuals with an HCV co-infection (6%).

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. Between 1998-2019, HCC was diagnosed in 22 out of 2,046 individuals (1.1%) with an HCV co-infection, 16 of whom were born in the Netherlands.

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



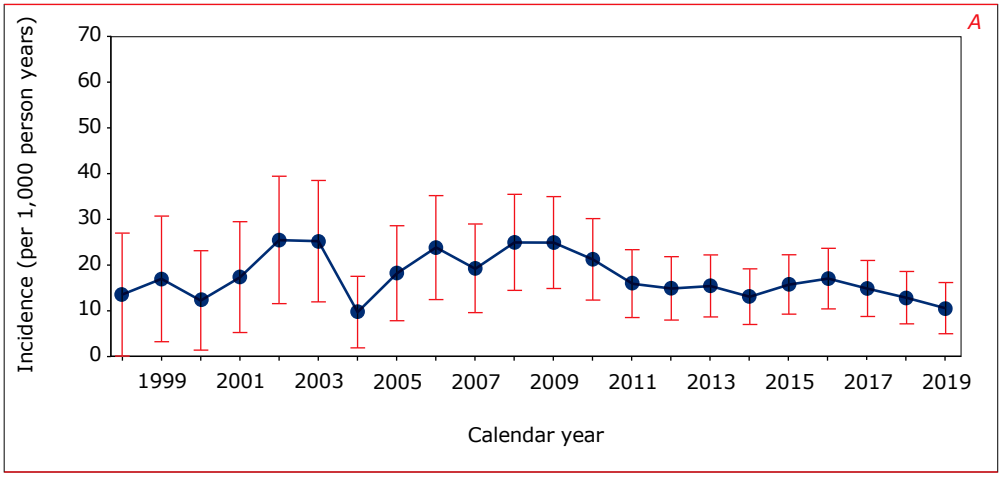
Mortality

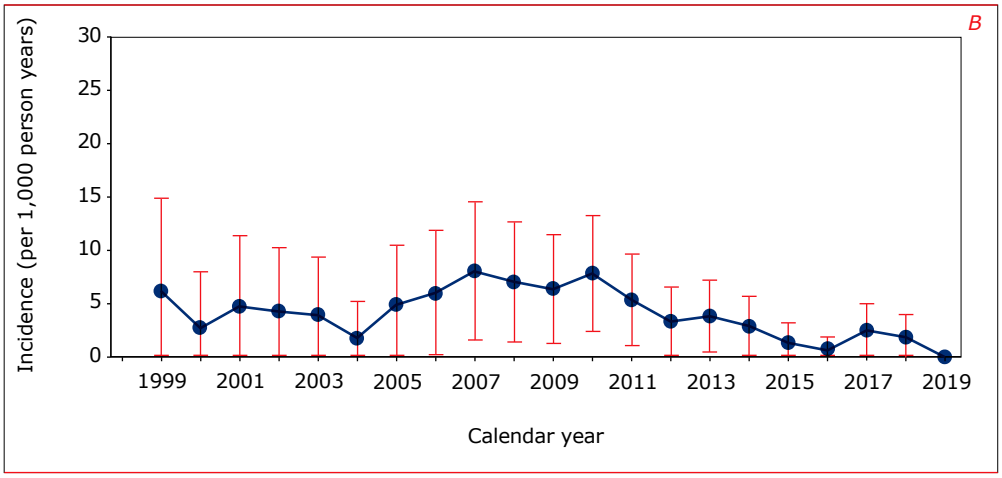
All-cause mortality

The percentage of the 2,046 individuals with an HCV infection who died from any cause was 17%. For individuals with HCV infection, the incidence-rate of death from any cause, adjusted for age and gender of the SHM population, was 17.8/1000

person years in 1998-2002, 20.5 in 2003-11 and 14.4 from 2012 onwards (*Figure 4.9A*). In MSM with HCV infection, these incidence rates were 5.3/1000 person years in 1998-2002, 8.9 in 2003-11, and 4.7 from 2012 onwards. In PWID with HCV infection, these incidence rates were 20.3/1000 person years in 1998-2002, 38.0 in 2003-11, and 46.2 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 2,046 HIV-1-positive individuals who were ever diagnosed with an acute or chronic HCV infection.*





Liver-related mortality

In total, 72 individuals co-infected with HCV died of a liver-related cause between 1998 and 2019. Other important causes of death among individuals with an HCV co-infection were non-AIDS malignancies (2%), 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 3.8/1000 person years 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 0/1000 person years in 1998-2002, 2.5 in 2003-11, and 0.7 from 2012 onwards. In PWID with HCV infection, these incidence rates were 2.6/1000 person years in 1998-2002, 8.5 in 2003-11, and 4.6 from 2012 onwards.

HBV

Box 4.3: Definitions of hepatitis B serological profiles.

	HBV serological results		
	HBsAg	Anti-HBs antibody	Anti-HBc antibody
Active HBV infection*	Pos	–	–
Resolved HBV infection	Neg/ND	Pos	Pos
Isolated anti-HBc positive	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.*

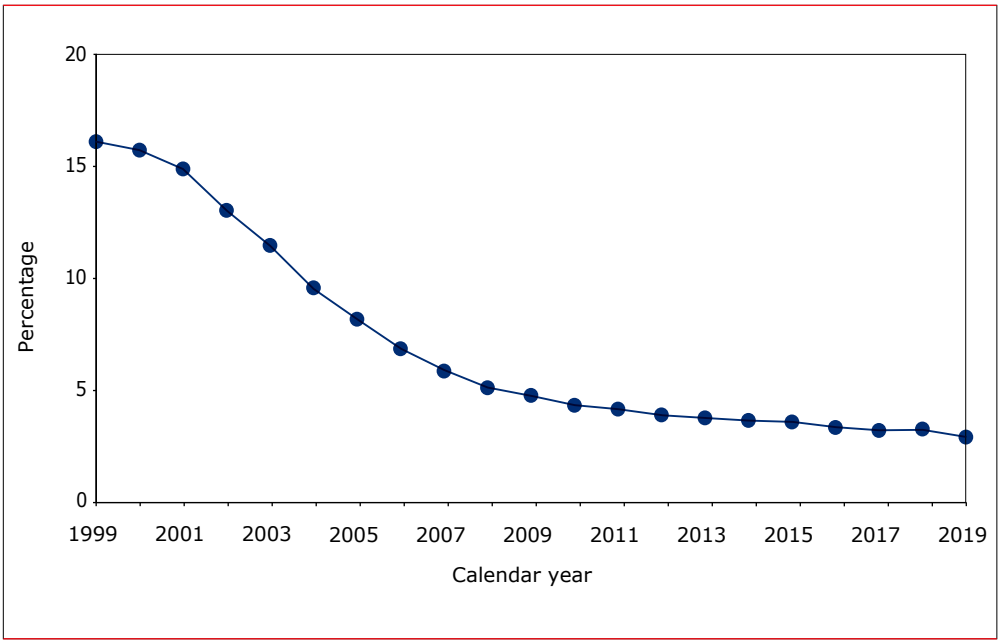
HBV screening

Ninety-six percent of the 27,167[b] HIV-positive individuals 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 HIV-positive individuals in care has improved over calendar time. In 1999, 16% of individuals had not been screened for HBV infection (*Figure 4.10*). Since then,

b *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.*

the percentage of HIV-positive individuals without HBV screening has decreased markedly, with just under 3% of all HIV-positive individuals in care having no measured HBV serological markers in 2019 (*Figure 4.10*).

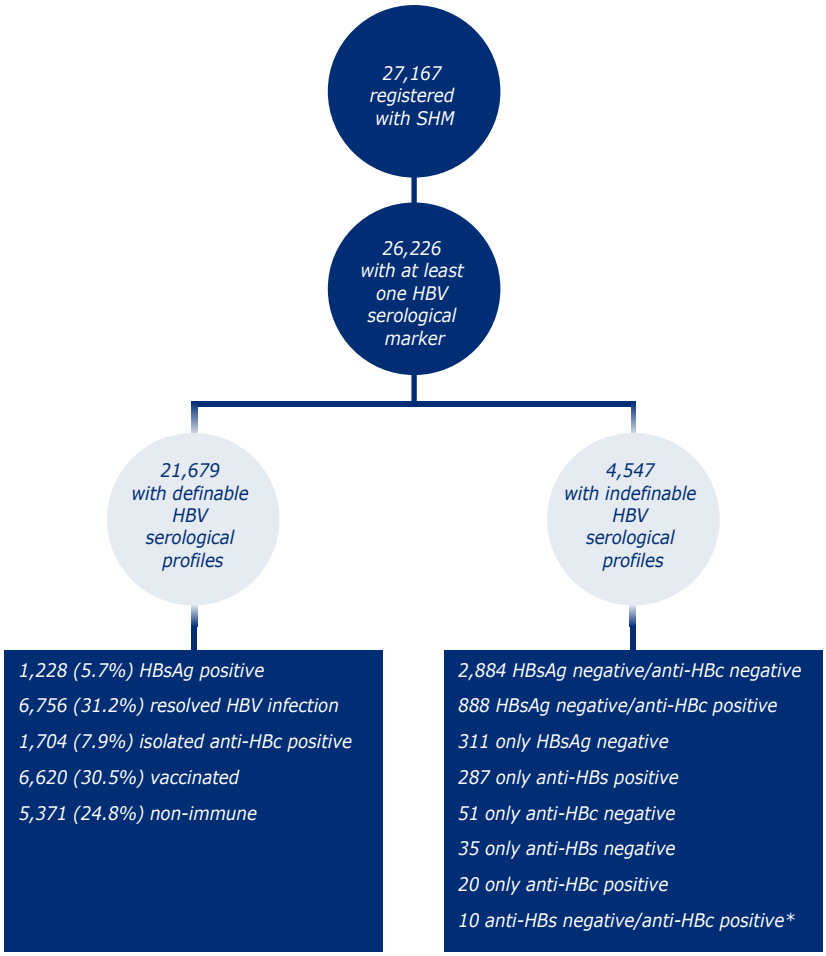
Figure 4.10: *Percentage of individuals in care without any hepatitis B virus serological test per calendar year of care.*



HBV serological profiles

HBV serological profiles could be defined for 21,680 (83%) of the 26,226 screened individuals (*Figure 4.10*). A full HBV serological battery is not routinely performed in HIV-positive individuals; 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 4,546 (17%) individuals either had insufficient information to establish HBV serological profile (n=4,485) or were previously HBsAg-positive, no longer had anti-HBc antibodies and did not have anti-HBs antibodies (n=61). The demographic characteristics of people with definable HBV serological profiles are compared in *Table 4.3*.

Figure 4.11: *Flowchart of HIV-positive individuals registered in the SHM database, 1999-2019, with testing for hepatitis B virus (HBV).*



Information obtained from the most recent serological result.

**The 61 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 HIV-positive individuals in care, according to their hepatitis B virus (HBV) serological profile as registered in the SHM database, 1998-2019.

	HBV serological profile*, n (%)				
	Active HBV infection	Resolved HBV infection	Isolated anti-HBc positive	Vaccinated	Non-immune
Total number	1,228	6,756	1,704	6,620	5,371
Male gender	1,056 (86%)	5,832 (86%)	1,305 (77%)	5,724 (86%)	3,981 (74%)
Region of origin					
Netherlands	534 (43%)	3,676 (54%)	676 (40%)	4,037 (61%)	3,095 (58%)
Europe	79 (6%)	479 (7%)	117 (7%)	497 (8%)	293 (5%)
Sub-Saharan Africa	315 (26%)	1,020 (15%)	545 (32%)	487 (7%)	640 (12%)
Caribbean/South America	133 (11%)	824 (12%)	166 (10%)	797 (12%)	800 (15%)
Southeast Asia	65 (5%)	281 (4%)	66 (4%)	206 (3%)	143 (3%)
Other	102 (8%)	476 (7%)	134 (8%)	596 (9%)	400 (7%)
HIV transmission group					
Men who have sex with men	704 (57%)	4,692 (69%)	755 (44%)	4,856 (73%)	2,491 (46%)
Heterosexual	377 (31%)	1,442 (21%)	605 (36%)	1,412 (21%)	2,382 (44%)
Injecting drug use	50 (4%)	229 (3%)	190 (11%)	61 (1%)	105 (2%)
Other	97 (8%)	393 (6%)	154 (9%)	291 (4%)	393 (7%)
cART	1,176 (96%)	6,537 (97%)	1,629 (96%)	6,477 (98%)	5,186 (97%)
Deaths	247 (20%)	962 (14%)	298 (17%)	311 (5%)	626 (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 active HBV infection

Prevalence of active HBV infection

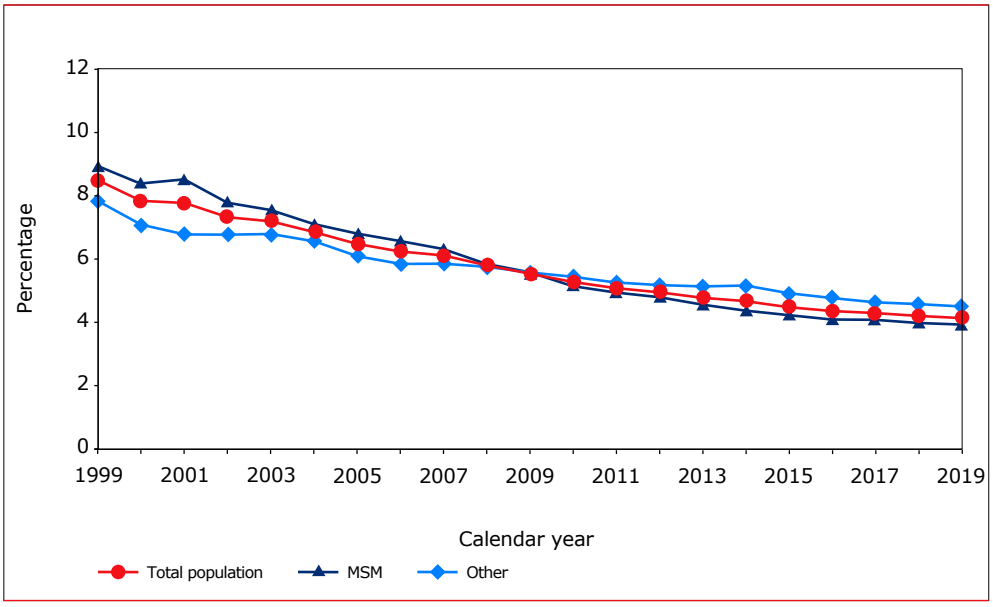
Of the 26,226 individuals ever screened for at least one HBV serological marker, a total of 1,597 (6%) received a positive HBsAg test result. Over time, 190 (12%) of these individuals resolved their HBV infection (i.e., they became HBsAg-negative and acquired anti-HBs antibodies); an additional 178 (11%) became HBsAg-negative without acquiring anti-HBs antibodies. The remaining 1,229 (77%) individuals continued clinical care with HBsAg-positive serology.

The prevalence of HBsAg-positive serology was 8.5% in 1999, and it slowly decreased to 4.2% in 2019 (*Figure 4.12*). This decreasing prevalence 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 HIV-positive individuals with HBsAg-positive serology[31].

As is the case for HCV co-infection, the percentage of HIV-positive individuals in care and chronically co-infected with HBV is considerably higher than the percentage found in the general Dutch population. Individuals co-infected with HBV were predominantly male (1,057/1,229; 86%), 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. Finally, HBV co-infection was less common than HCV co-infection among PWID.

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



Presence of HBV/HDV infection

By 2019, 190/1,597 (11.9%) 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 (12%) were identified with either past or current HDV infection; nine of which were tested for HDV RNA, which found that six had detectable HDV RNA, indicating active HDV infection.

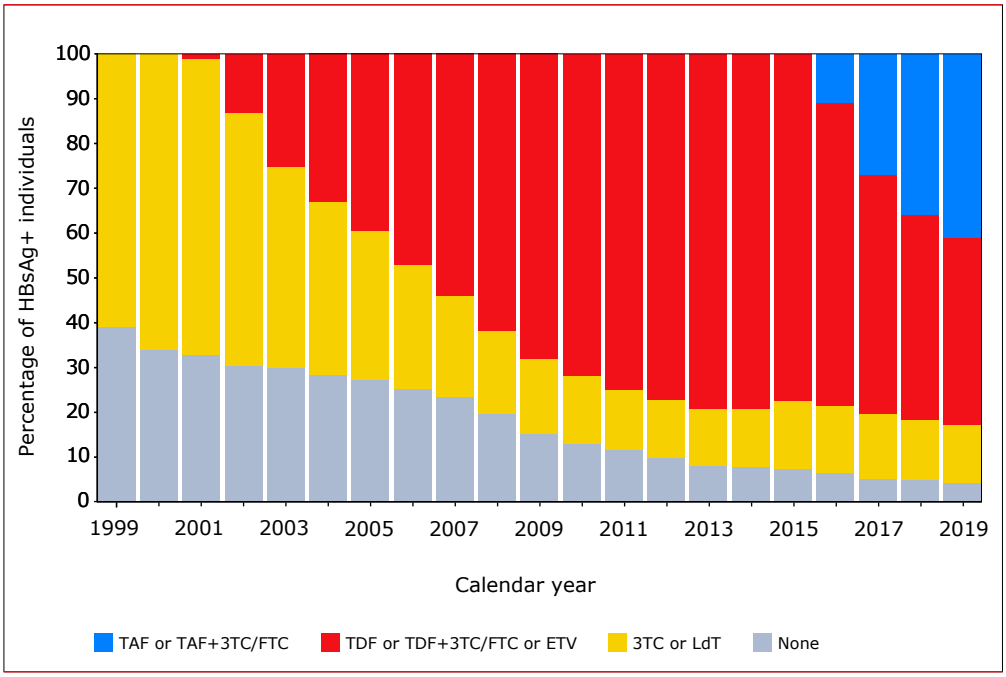
Treatment for chronic HBV infection

The treatment for chronic HBV infection aims to reduce viral replication. 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 to less than 20 IU/ml has also been shown to delay progression of liver fibrosis to cirrhosis[32]. Lowering HBV DNA levels may result in HBsAg negativity in a small subgroup of individuals. Persistent HBsAg negativity, together with the development of anti-HBs antibodies, is known as HBs Ag- seroconversion and is the penultimate goal of HBV therapy. In those individuals who are also e-antigen positive (HBeAg+), a similar seroconversion from HBeAg positivity to negativity can occur, with subsequent development of anti-hepatitis B e-antigen (anti-HBe) antibodies. This so-called HBeAg-seroconversion is an important secondary treatment parameter, since studies have shown that it is associated with reduced viral activity in the liver, thereby decreasing the risk of progression of liver fibrosis. A few antiviral agents used for treatment of HIV, such as lamivudine, and particularly TDF/TAF, are also active against HBV.

Of the 1,597 individuals with HIV in the SHM database who have ever had an HBsAg-positive serological test result, 1,529 (96%) received a cART regimen that included one or more agents with activity against both HIV and HBV. The reasons for the remaining 68 individuals not receiving anti-HBV treatment included: death before being able to start treatment (n=16), recent entry into care (n=3), loss to follow up (n=44), and lack of sufficient information (n=5).

Most people with active HBV infection 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=83/634, 13%) and became more commonly used than lamivudine in 2006. TAF-based cART (with or without lamivudine or emtricitabine) was first used in 2016 (n=132/1,214, 11%). In 2019, most HBV co-infected individuals were receiving TDF-based cART (n=522/1,247, 42%), closely followed by TAF-based cART (n=513/1,247, 41%), and lamivudine-based cART (n=159/1,247, 13%), or no anti-HBV-containing cART (n=53/1,247, 4%)

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



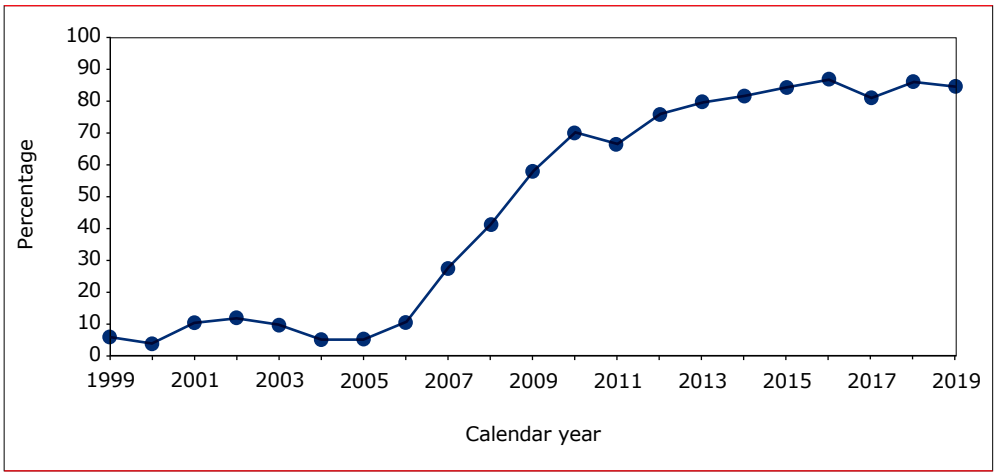
Legend: *TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; ETV=entecavir; 3TC=lamivudine; LdT=telbuvidine; FTC=emtricitabine.*

Note: *Anti-HBV agents were divided as 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[33].*

In most individuals mono-infected with HBV, a persistently HBeAg-negative chronic HBV infection with undetectable HBV DNA confers a favourable long-term outcome, with low risk of cirrhosis and HCC[34]. We therefore 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, provided that 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 less than 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 (<100, <200, <400, <1000

or <2000 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, and reached 80% in 2013. In 2019, 85% of individuals co-infected with HIV and HBV had an undetectable HBV DNA level (*Figure 4.14*).

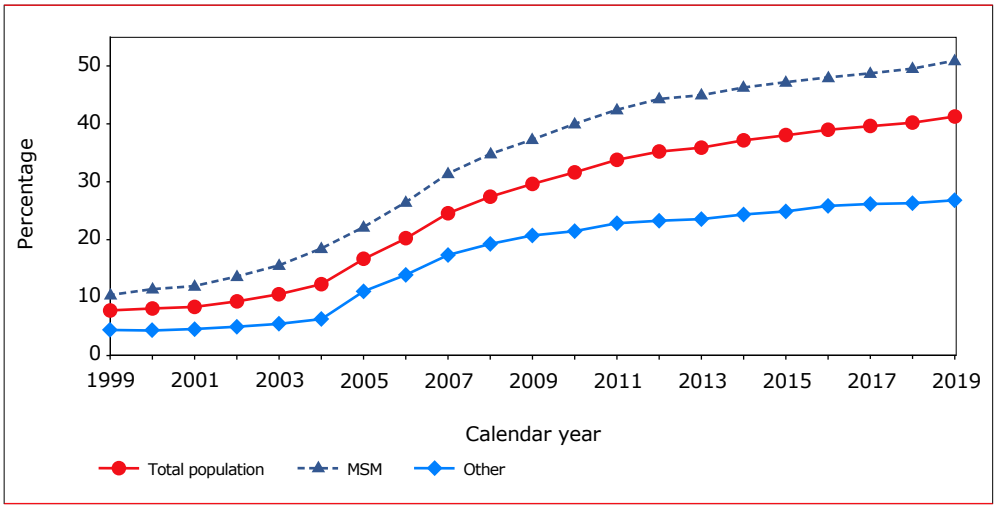
Figure 4.14: *Percentage of individuals with undetectable hepatitis B virus (HBV) DNA levels by assay, with a detection limit of <20, <100, <200 or <2000 IU/ml HBV DNA per calendar year, regardless of HBeAg status.*



HBV vaccination in HIV-positive individuals

Of the 21,680 individuals with definable HBV serological profiles, 6,619 (31%) 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 41% in 2019 (*Figure 4.15*). 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 4.15: Prevalence of hepatitis B vaccination per calendar year.



HBV non-immune status in HIV-positive individuals

Of the 21,680 individuals with definable HBV serological profiles, 5,371 (25%) had serological evidence of being non-immune and non-exposed to HBV at their last visit. When the 4,546 individuals with undefinable HBV serological profiles were considered, 72 out of 391 with an anti-HBs antibody test did not have detectable anti-HBs antibodies, and 3,810 out of 4,155 without an anti-HBs antibody test were not reported to have been vaccinated by their treating physician. Therefore, at most, 9,253 of 27,167 (34%) individuals screened for HBV remained susceptible to infection at the time of their last visit [5,371 non-immune *plus* 72 with undefinable HBV profile and anti-HBs antibody negative *plus* 3,810 with undefinable HBV profile and missing data on anti-HBs antibody status and no physician-reported vaccination].

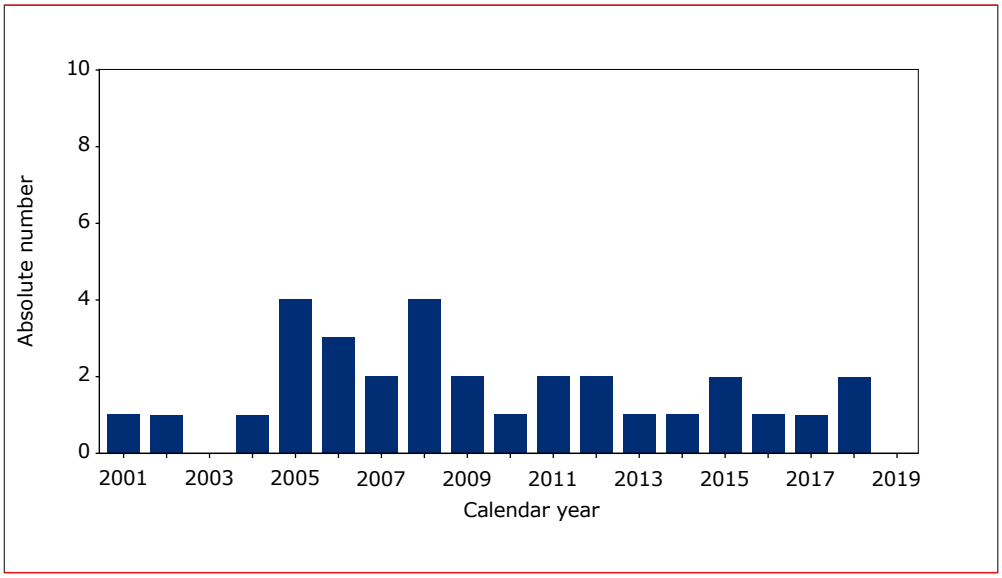
Individuals at risk, and MSM in particular, should be actively counselled about HBV vaccination, although they may be protected from HBV infection by the use of TDF or TAF as part of their cART regimen, according to the findings reported by an international study and by one of the Dutch HIV treatment centres[35,36]. Data from SHM show that, of those people who remain at risk of acquiring HBV, 80% are currently being treated with a cART regimen that includes TDF or TAF; for MSM, this percentage is 82%.

Liver-related morbidity

Additional data from liver biopsy pathology reports, transient elastography, radiology reports, or a combination of those sources, were available for 1,223 of the 1,597 individuals with an HBV co-infection. Review of these additional data showed that severe chronic liver disease, according to our definition, was considered to be present (presumptive and definitive categories combined) in 265 (22%) of those with HBV co-infection. Definitive severe chronic liver disease was documented for 72 (6%) with an HBV co-infection. Of the 256 individuals with severe chronic liver disease, nine (3%) had past or current HDV infection.

Figure 4.16 shows that the annual number of new HCC diagnoses declined from 2010 onwards. HCC was found in 33 (2.1%) individuals with a chronic HBV co-infection, 18 of whom were born in the Netherlands, nine in sub-Saharan Africa, two in Asia, and one each in South America, the United States, Australia, and western Europe. One individual with newly diagnosed HCC had either past or current HDV infection.

Figure 4.16: *Absolute number of annually-reported HCC cases among HBV co-infected individuals over time.*



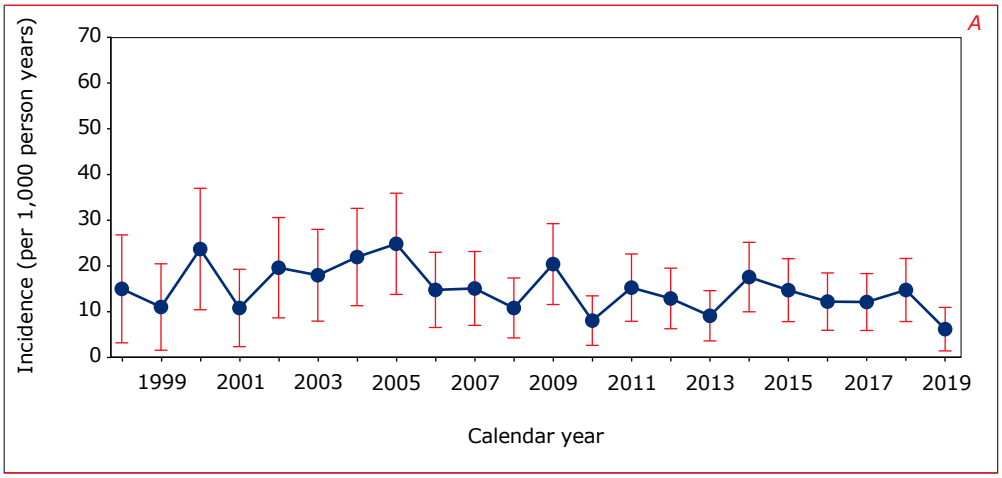
Mortality

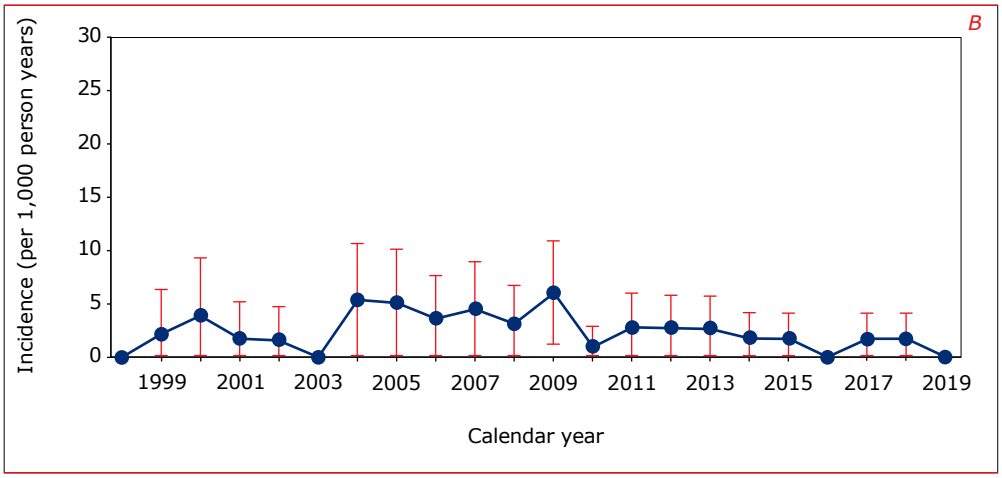
All-cause mortality

Nineteen percent (n=298) of the 1,597 individuals with an HBV infection died of any cause (*Table 4.3*). For individuals with HBV infection, the incidence rate of death from any cause, adjusted for age and gender of the SHM population, was 16.1/1000 person years in 1998-2002, 16.0 in 2003-11 and 12.4 from 2012 onwards (*Figure 4.17A*). In MSM with HBV infection, these incidence rates were 11.7/1000 person years in 1998-2002, 13.3 in 2003-11, and 10.0 from 2012 onwards. In PWID with HCV infection, these incidence rates were 52.4/1000 person years in 1998-2002, 60.6 in 2003-11, and 89.2 from 2012 onwards.

Of the 298 individuals with an HBV infection who died from any cause, five (1.7%) had either past or current HDV infection.

Figure 4.17: 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 individuals positive for HIV-1 who were ever diagnosed with an acute or chronic HBV infection.





Liver-related mortality

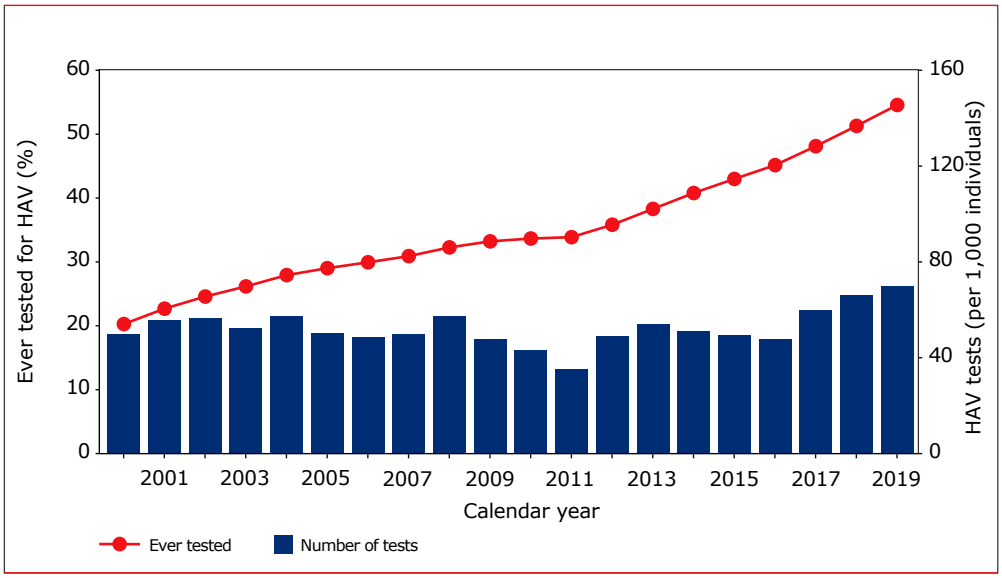
In total, 48 individuals co-infected with HBV died of a liver-related cause, only one of whom had either past or current HDV infection. For individuals with HBV infection, the incidence rate of liver-related death, adjusted for age and gender of the SHM population, was 1.9/1000 person years in 1998-2002, increasing to 3.5 in 2003-11, and decreasing to 1.6 from 2012 onwards (*Figure 4.17B*). In MSM with HBV infection, these incidence rates were 2.4/1000 person years in 1998-2002, 3.2 in 2003-11, and 1.4 from 2012 onwards. In PWID with HBV infection, these incidence rates were 0.4/1000 person years in 1998-2002, 1.4 in 2003-11, and 1.3 in 2012 onwards.

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-four percent (n=14,777) of the 27,167 HIV-positive individuals ever registered in the SHM database have been screened for HAV. The frequency of screening for HAV in HIV-positive individuals has been consistent over the past two decades (*Figure 4.18*). Between 2000 and 2017, roughly four to six HAV tests per 1000 individuals were conducted each year. Between 2018 and 2019, screening frequency increased to almost seven HAV tests per 1000 individuals per year. Accordingly, the percentage of individuals who have ever been tested for HAV was 20% in 2000 and steadily increased to 55% in 2019 (*Figure 4.18*).

Figure 4.18: Percentage ever tested for anti-HAV antibodies and anti-HAV antibody testing, frequency per calendar year.

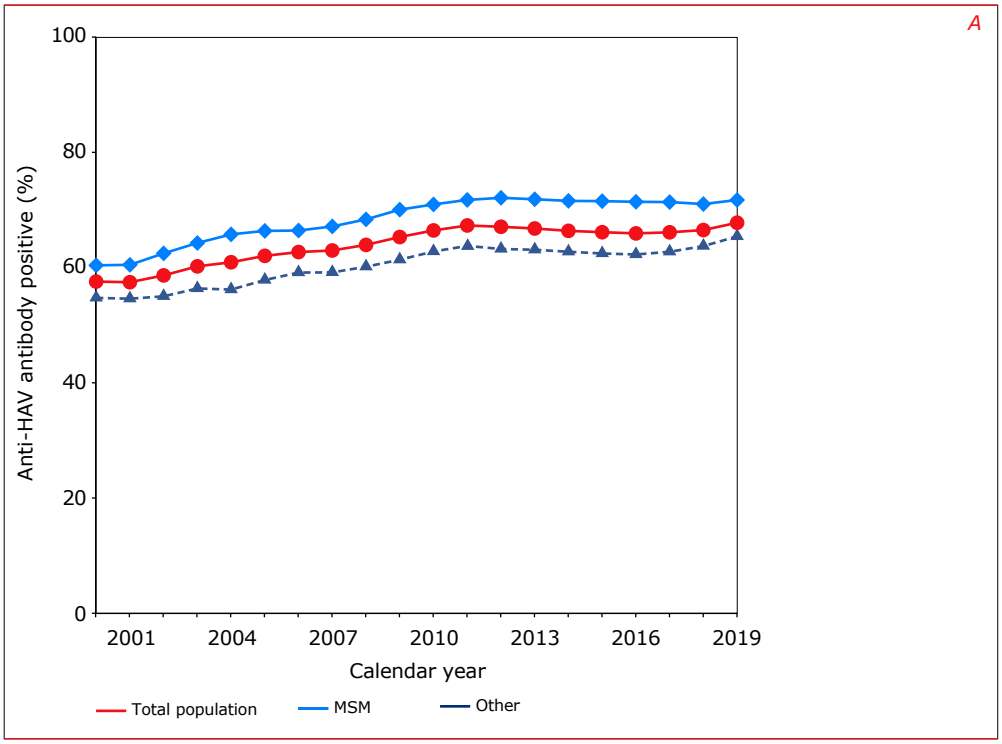


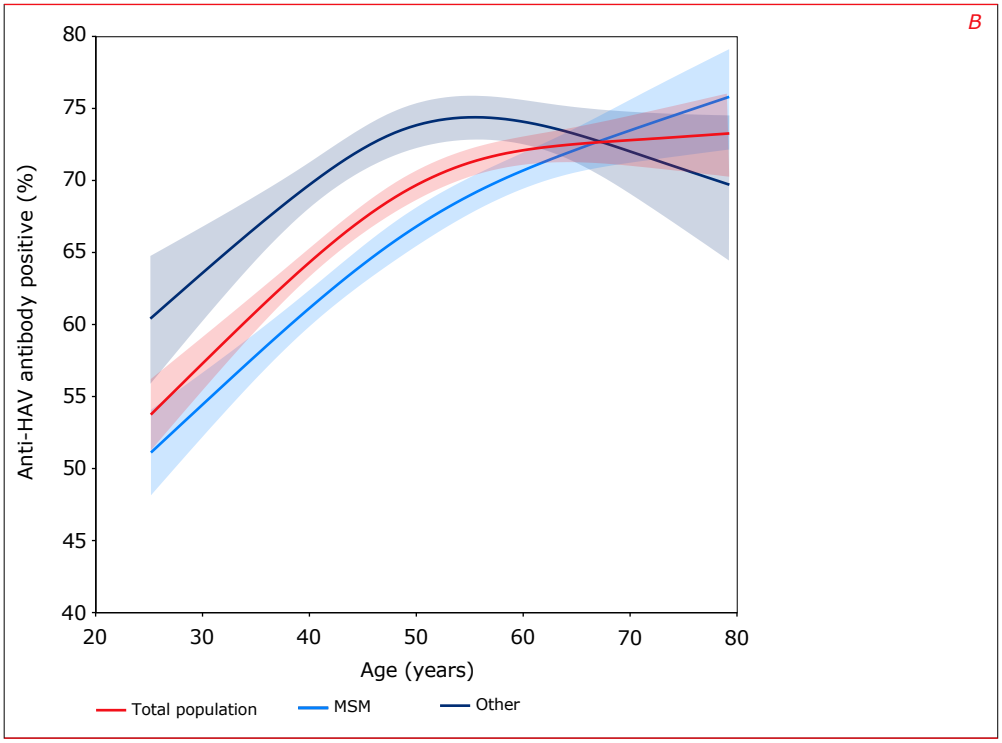
Legend: HAV=hepatitis A virus.

HAV seropositivity

Of the 14,777 individuals ever screened for HAV, a total of 10,002 (68%) had a positive anti-HAV antibody test result; 65% were observed in MSM, 67% in PWID, 72% in heterosexuals, and 73% in people from other transmission groups. The prevalence of anti-HAV antibody positivity was 57% in 1999 and it slowly increased to 68% in 2019 (*Figure 4.19A*). For MSM, the prevalence of anti-HAV antibody positivity was 55% in 1999 and it also slowly increased to 65% in 2019. For all other transmission groups, the prevalence of anti-HAV antibody positivity was 60% in 1999 and it slowly increased to 72% in 2019.

Figure 4.19: 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.*

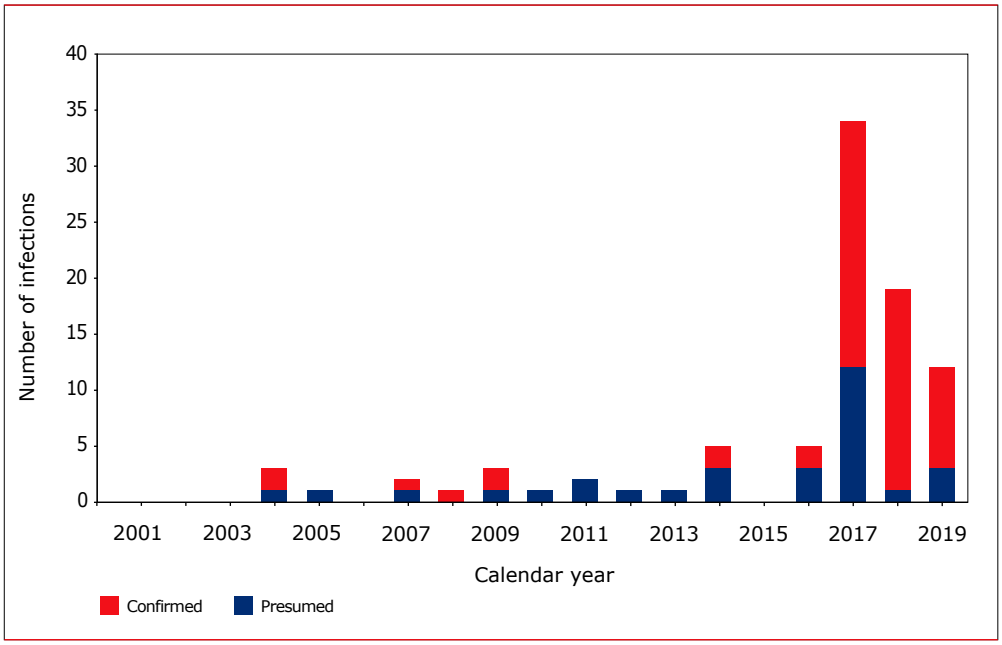
Epidemiological studies have highlighted the strong relationship between increasing anti-HAV antibody positivity and increasing age[37]. This age-dependent relationship was also observed in the 14,777 individuals ever screened for HAV (*Figure 4.19B*). Overall, anti-HAV antibody positivity was 60% for individuals below the age of 40, and 70% for those aged 40 or older. For MSM, anti-HAV antibody positivity was 56% for individuals below the age of 40, and 68% for those aged 40 or older. For all other transmission categories, anti-HAV seropositivity was 65% 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 2019, there were 90 reported cases of acute HAV infection (n=59, presumed; n=31, confirmed), of which 72 (80%) were observed in MSM, 17 (19%) in heterosexuals,

and one (1%) in PWIDs. Cases of acute HAV were first documented in 2004 and the number of acute HAV cases remained between 0 to 5 cases per year until 2016 (*Figure 4.20*). In 2017, 34 cases of acute HAV infection were documented (*n*=22, presumed; *n*=12, confirmed). The number of cases of acute HAV infection decreased to 19 in 2018 and 12 in 2019. Of the 65 documented cases occurring between 2017 and 2019, 55 (85%) were observed in MSM. This increase in HAV infections was part of a European-wide outbreak of HAV among sexually-active MSM in 2017[38].

Figure 4.20: *Number of reported cases of confirmed and presumed acute HAV infection per calendar year.*

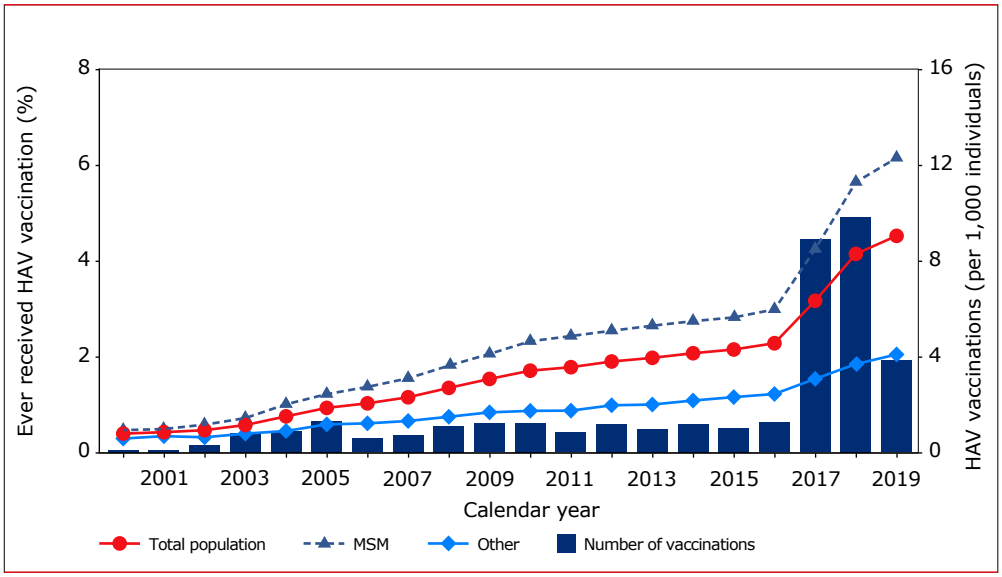


Of the 90 reported cases of acute HAV infection, 47 (52%) reported having severe clinical symptoms due to infection. Severe chronic liver disease, according to our definition, was considered to be present (presumptive and definitive categories combined) in 14 (16%) of those with a reported acute HAV infection. Definitive severe chronic liver disease was documented for three (3%) with a reported HAV infection. No deaths due to acute HAV infection were reported.

HAV vaccination in HIV-positive individuals

Information on HAV vaccination status was obtained from clinical files and was unknown for the majority of individuals ever registered by SHM. Of the 27,167 HIV-positive individuals ever registered in the SHM database, 1,231 (5%) 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)[39]. HAV vaccination frequency was consistently lower than two vaccinations per 1000 HIV-positive individuals from 2000 to 2016, and it increased substantially to 9 and 10 vaccinations per 1000 individuals in 2017 and 2018, respectively (*Figure 4.21*). Accordingly, the percentage reported to have ever received an HAV vaccination was 1.3% in 2000, increasing to 2.5% in 2016, and then 4.5% in 2019. In MSM, this percentage was 1.7% in 2000, 3.3% in 2016, and 6.2% in 2019.

Figure 4.21: *Percentage that ever received an HAV vaccination and HAV vaccination frequency per calendar year.*



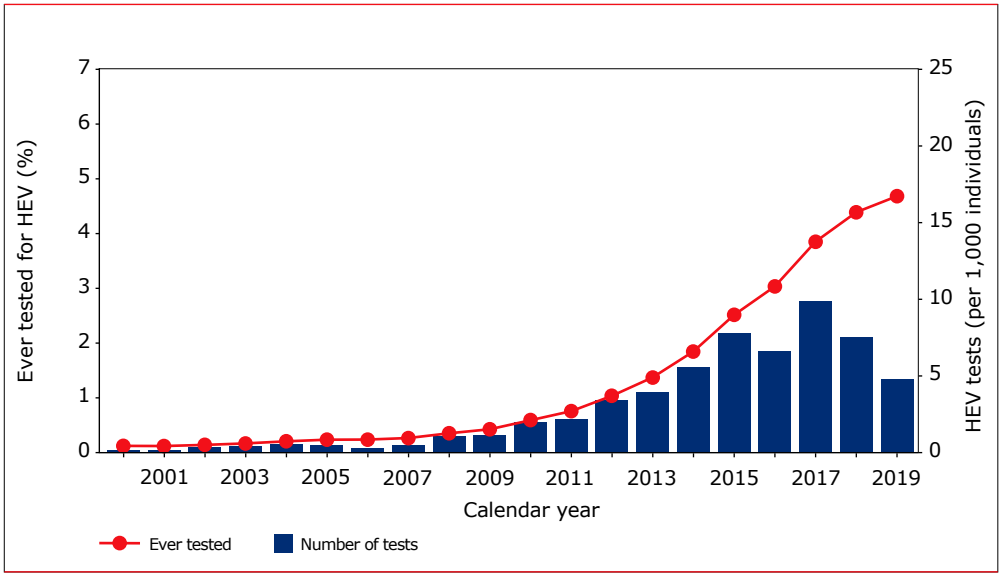
Legend: *HAV=hepatitis A virus; MSM=men who have sex with men.*

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 27,167 HIV-positive individuals ever registered in the SHM database have been screened for HEV. The screening frequency for HEV infection in HIV-positive individuals in care was low between 2000 and 2010, ranging between fewer than one and two tests per 1000 individuals (*Figure 4.22*). HEV testing frequency rapidly increased from two tests per 1000 individuals in 2011, to 10 tests per 1000 individuals in 2017. In 2019, this frequency was five tests per 1000 individuals.

***Figure 4.22:** 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 1,268 individuals who were in care between 2000 and 2019 and who were ever screened for HEV, 181 (14%) were newly diagnosed as having past or current HEV infection. Of these individuals, 122 (67%) were MSM, 48 (27%) heterosexuals, six (3%) PWID, and five (3%) were from other transmission groups. The largest number of new diagnoses were observed between 2013 and 2019 (*Figure 4.23*), mainly due to the higher frequency of HEV testing among HIV-positive individuals. The percentage of individuals newly diagnosed with past or current HEV infection ranged from 9% to 15% between 2004 and 2019 (*Figure 4.24*).

Of all individuals tested for HEV and in care between 2000 and 2019, there were 43 individuals diagnosed with acute HEV infection, of whom 33 were MSM and 10 heterosexuals. Only one of these cases was confirmed to have progressed to chronic infection (i.e., positive HEV RNA lasting more than three months).

Figure 4.23: *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.*

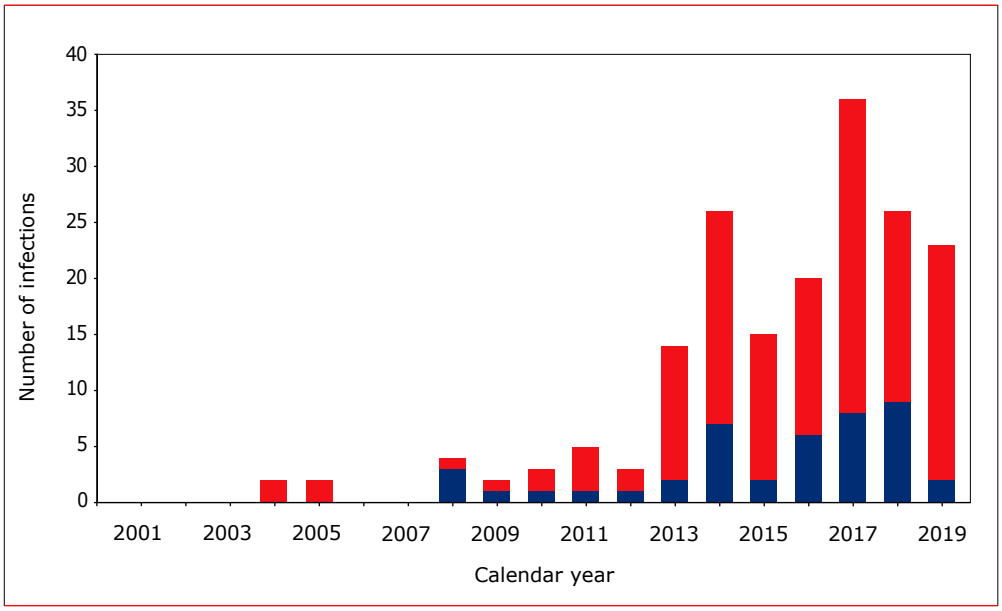
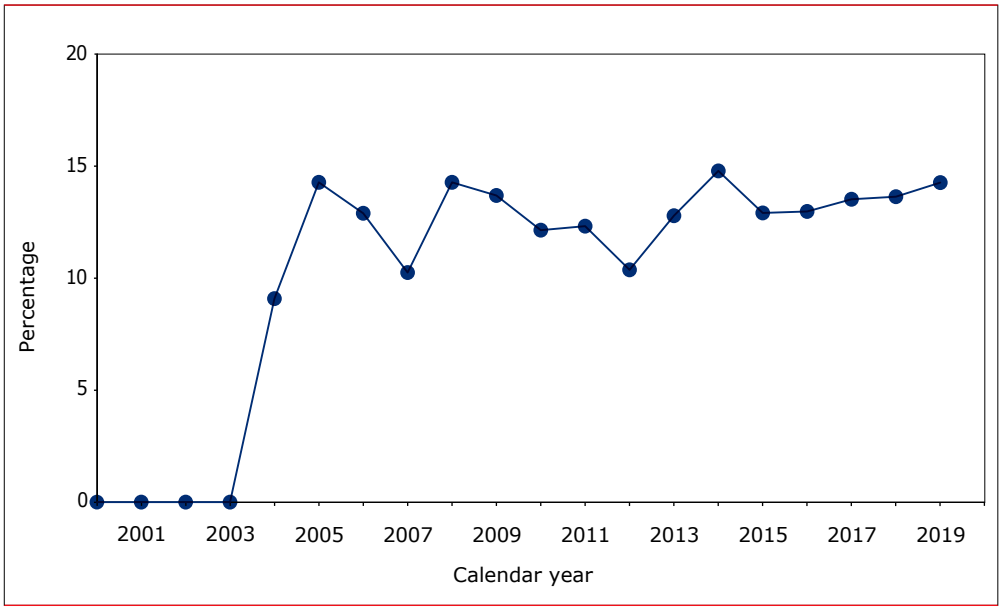


Figure 4.24: Percentage ever infected with HEV per calendar year.



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 HIV-positive population in the Netherlands has continued to improve over time and nowadays is documented almost universally. Five percent of HIV-positive individuals ever registered between 1998 and 2019 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, with 5% of the MSM ever being diagnosed with an acute HCV infection.

Our data clearly show that since the arrival of novel DAAs in 2014, they have entirely replaced PEG-IFN-containing regimens. The number of HIV-positive individuals treated for HCV has rapidly increased. More than 1,000 individuals have 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. This high cure rate has seen the number of HCV co-infected individuals remaining in need of HCV treatment fall to 131. Overall, a rapid reduction

in the prevalence of active HCV infections has been achieved, with prevalence in MSM having declined to 0.5% in 2019. The rapidly increasing availability of novel interferon-free, highly-effective combination antiviral regimens for HCV, together with optimised screening for HCV co-infection, will also limit the impact of HCV co-infection on liver-related morbidity and mortality. Successful treatment of HCV will also prevent onward transmission of HCV, which is possibly reflected in a lower incidence of acute HCV infections in recent years. However, in line with earlier reports[26,29], HCV re-infection after successful treatment has been observed. Although the rate of re-infection has declined in the most recent years, ongoing transmission of HCV persists.

Six percent of the HIV-positive individuals 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 34% of all HIV-positive individuals, and 27% of MSM, have either not been exposed to HBV, or have not been successfully vaccinated, and may remain at risk of acquiring HBV. Since 80% of all individuals, and 82% of MSM, 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 20% of the HIV-positive individuals ever registered, and 18% of the MSM, remain unprotected against HBV, which represents an estimated 7.0% of the total population of HIV-positive individuals 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 HIV-positive individuals ever registered by SHM, 25% of the individuals chronically co-infected with HCV, and 22% 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 remain 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 remains 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 and testing frequency of anti-HAV antibodies was consistent across calendar years. The percentage of tested individuals found to have anti-HAV

antibodies is no different between MSM and other transmission groups, and it is over twice as high as that of the general Dutch population[40]. The percentage with anti-HAV antibodies was also higher with increasing age, as would be expected from the general epidemiology of HAV infection[37]. Among the individuals diagnosed with HAV, almost half reported having severe symptoms during their infection, while one patient 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 5%. This low percentage of vaccine uptake 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 were tested for anti-HAV immunity, and vaccine uptake was low, could signal a substantial percentage of individuals who 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. This increase was likely due to awareness of HEV infection in Europe and its recognised role in hepatitis and liver-related disease[18]. With increased testing, the number of individuals newly diagnosed with past or current HEV infection, or who had acute HEV infection, also increased from 2014. 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 what would be expected in the Dutch general population[17]. We were unable to determine whether any liver-related morbidity and mortality, or any extra-hepatic disease was associated with HEV infection.

Recommendations

Continued efforts must be made to ensure that all individuals with HIV are adequately assessed for the presence of HBV and HCV co-infection, or HCV re-infection. In particular, efforts should continue to increase HBV vaccination rates among HIV-positive individuals who remain at increased risk of acquiring HBV, particularly those who are not receiving an antiretroviral regimen containing TDF or TAF, or those previously not responding to vaccination[41]. In the long term, provision of highly-effective DAA regimens for all known HCV co-infected HIV-positive individuals is expected to further contribute to reducing the burden of severe chronic liver disease, hepatocellular carcinoma, and mortality related to liver disease among people living with HIV. In addition, these novel regimens may

have a beneficial impact on the risk of ongoing HCV transmission. The fact that DAA treatment uptake is lagging behind for a small group of individuals, shows that additional research is required to establish the underlying reasons why treatment may be delayed in some individuals. Importantly, regular HCV RNA screening among individuals who have been successfully treated for HCV infection, and remain at risk of re-infection, is recommended to ensure early detection of new HCV infections; this is in combination with behavioural interventions aimed at MSM to prevent HCV re-infection after successful treatment of HCV.

HBV clinical practice guidelines from the European Association for the Study of the Liver suggest that HDV should be tested at least once for all individuals with chronic hepatitis B infection[42]. In the Netherlands, roughly 12% 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 of liver-related morbidity and mortality in HIV-positive individuals with HBV infection, as found in other settings[13].

Only half of the individuals ever registered by SHM have been screened for HAV and, among those tested, almost two-thirds had anti-HAV antibodies from either vaccination or cleared infection. Even though reports of HAV infections were uncommon in the last two decades, the recent HAV outbreak in MSM 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[43]. However, data from SHM and data from a recent meta-analysis, support no noteworthy increase in HEV prevalence among HIV-positive individuals[44], and only one patient in the database was diagnosed with chronic HEV infection. We recommend following current European guidance, which recommends that individuals with persistently elevated transaminase levels should be screened for HEV-RNA[18]. Further data are needed to determine to what extent liver-related and non-liver-related disease occurs as a result of HEV infection in HIV-positive individuals.

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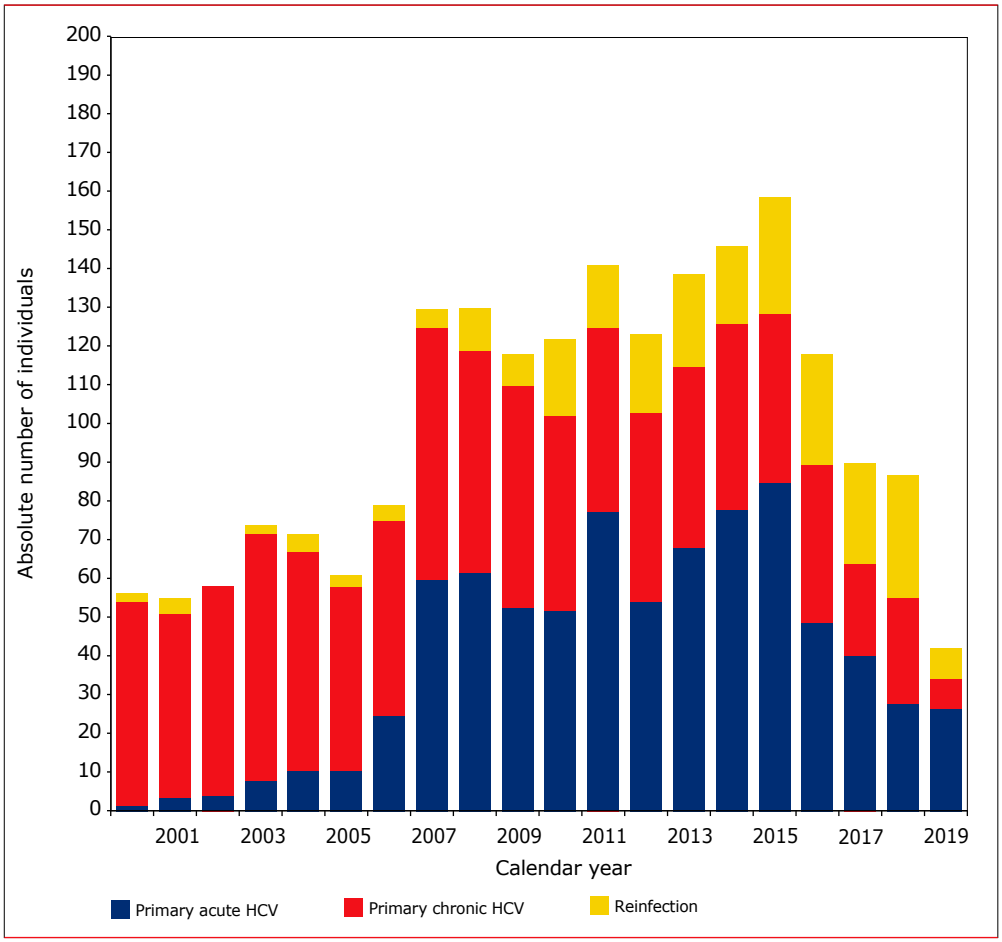
Appendix:

Appendix Figure 4.1: Total number of primary and chronic infections, and re-infections with hepatitis C among HIV-positive individuals in care from 2000-2019, by year of HCV diagnosis.



Legend: HCV=hepatitis C virus