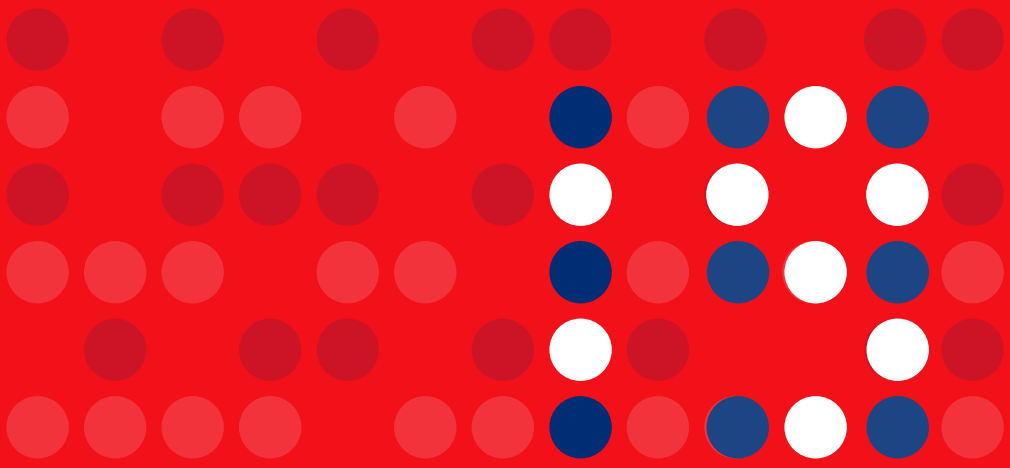
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2019

Chapter 4: Viral hepatitis



About Stichting HIV Monitoring

Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, was founded in 2001 and appointed by the Dutch minister of Health, Welfare and Sport as the executive organisation for the registration and monitoring of HIV-positive individuals in the Netherlands.

In collaboration with the HIV treatment centres in the Netherlands, SHM has developed a framework for systematically collecting HIV data for the long-term follow up of all registered individuals. The Netherlands is the only country in the world to have such a framework, which enables healthcare professionals to aspire to the highest standard of HIV care.

SHM contributes to the knowledge of HIV by studying the course of the infection and the effect of its treatment. To this end, SHM follows the treatment of every HIV-positive man, woman and child in care in the Netherlands and registered in the national observational HIV cohort, ATHENA. Continuous collection of data is carried out at 24 HIV treatment centres and subcentres and 4 paediatric HIV centres in the Netherlands. Patient data are collected and entered into the database in a pseudonymised form for storage and analysis. In this way SHM is able to comprehensively map the HIV epidemic and HIV treatment outcomes in the Netherlands.

Our mission

To further the knowledge and understanding of all relevant aspects of HIV infection, including comorbidities and co-infections (such as viral hepatitis), in HIV-positive persons in care in the Netherlands.

www.hiv-monitoring.nl

HIV Monitoring

Monitoring Report 2019

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

Interactive PDF user guide

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

Links in this PDF

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

Reference numbers

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

Guide to buttons

Content page

Next chapter

Preceding chapter

You can also navigate using the bookmarks.

Acknowledgements

Authors: Ard van Sighem, Ferdinand Wit, Anders Boyd, Colette Smit, Amy Matser, Peter Reiss

Co-authors: Joop Arends, Ward van Bilsen, Kees Brinkman, Ashley Duits, Suzanne Geerlings, Gonneke Hermanides, Jeroen van Kampen, Frank Kroon, Liesbeth van Leeuwen, Jeannine Nellen, Kees van Nieuwkoop, Eline Op de Coul, Jan Prins, Maria Prins, Annemarie van Rossum, Marc van der Valk, Anne Wensing, Diederik van de Wetering, Tom Wolfs

Production and support: Catriona Ester, Mireille Koenen, Yunka de Waart

Requests for digital copies: Stichting HIV Monitoring, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands
T +31 20 5664172
hiv.monitoring@amc.uva.nl, www.hiv-monitoring.nl

Visiting address: Stichting HIV Monitoring, Nicolaes Tulphuis, Tafelbergweg 51, 1105 BD Amsterdam, the Netherlands

Chamber of commerce no. 34160453

Correspondence to: Peter Reiss, hiv.monitoring@amc.uva.nl

To cite this report, please use: van Sighem A.I., Wit F.W.N.M., Boyd A., Smit C., Matser A., Reiss P. Monitoring Report 2019. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring, 2019. Available online at www.hiv-monitoring.nl

ISBN/EAN: 978-90-806415-0-1
First edition: 13 November 2019
Editing: Sally H. Ebeling, Boston, MA, USA

Art Direction & DTP: Studio Zest, Wormer, the Netherlands

4. Viral hepatitis

Colette Smit, Anders Boyd, Marc van der Valk, Joop Arends, Peter Reiss

Box 4.1: Definitions of hepatitis C infection.

Chronic hepatitis C virus (HCV) infection
Individuals who remain HCV RNA-positive for longer than 6 months after their first known positive HCV RNA test result.

Acute HCV infection[1,2]

1. Case definition of acute hepatitis C virus according to *preferred* criteria[1]
   Positive anti-HCV IgG with a documented negative anti-HCV IgG within the previous 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 previous 12 months.
2. Case definition of acute hepatitis C virus according to *alternative* criteria[1]
   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

1. Individuals with a documented positive test result for HCV antibody, a subsequent negative HCV RNA test result and no prior history of medical treatment.
2. Individuals who did not fulfil the definition of acute HCV infection, but had a positive HCV RNA test result that became negative within 6 months without 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 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 combined with a pathology, histology or transient elastography report documenting severe liver fibrosis or cirrhosis (Metavir score F3-F4 or transient elastography stiffness ≥8kPa).

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 percent of the general Dutch population has evidence of ever having been exposed to HCV and that the same percentage has ever been exposed to HBV[3,4,5]. In contrast, HCV and HBV co-infections are far more prevalent in HIV-positive individuals due to shared routes of transmission[6].

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 hepatocellular carcinoma (HCC)[7,8]. HBV infection can also directly lead to HCC without prior cirrhosis. Progression to severe liver disease takes, on average, 20 to 30 years in individuals mono-infected with HCV or HBV[9,10]. While liver fibrosis progression was faster in HIV co-infected persons 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[11,12].

This chapter reports on the demographic and clinical characteristics, severe chronic liver disease and mortality, as well as responses to treatment, in the population with HIV and HCV and/or HBV co-infection.

Box 4.2: Viral hepatitis data in the ATHENA cohort in the Netherlands.

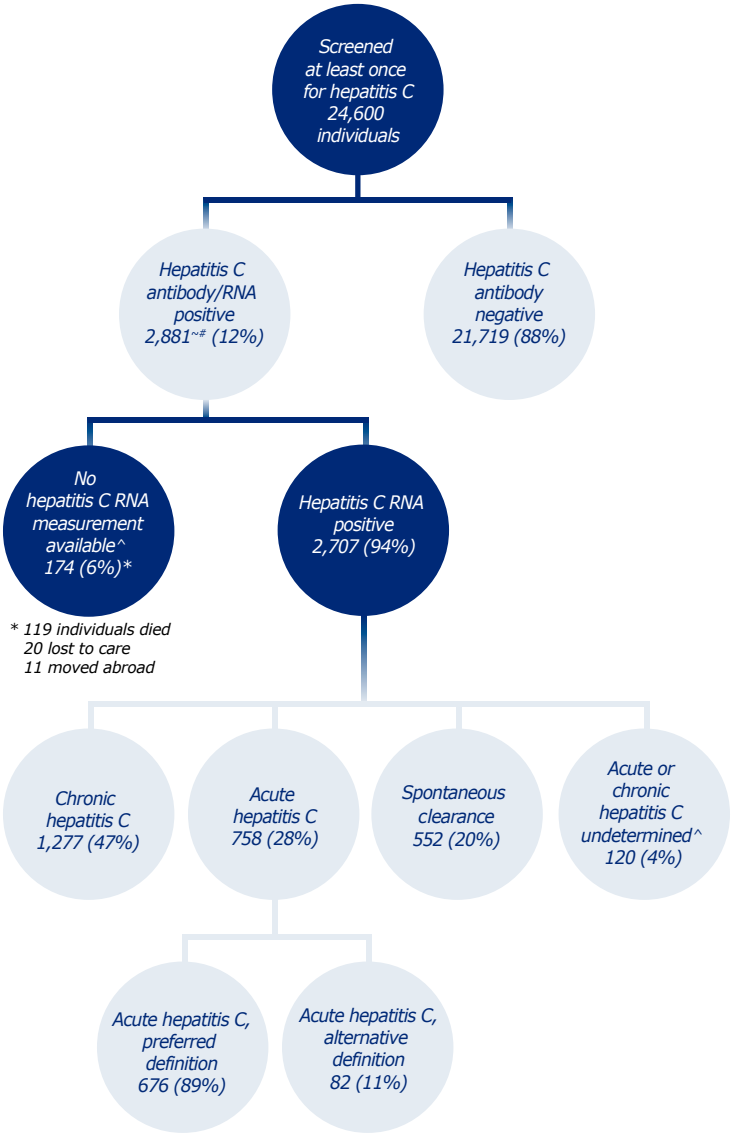
Population described in this chapter
All individuals ever registered up to 1 May 2019, based on the database lock in May 2019.

HCV

Demographic and clinical characteristics

As of May 2019, 26,247 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, 24,600 (94%) were ever screened for HCV co-infection and 2,881 (12%) had a positive result with an HCV antibody test and/or HCV RNA test. This confirms the far greater prevalence of HCV in the HIV-positive population than estimated for the general population in the Netherlands (*Figure 4.1*). HCV RNA data were not documented in 174 of these 2,881 individuals (6%). Of these 174 individuals, 119 are known to have died, 20 to have been lost to care, and 11 to have moved abroad; for the remaining 24 individuals with a positive HCV antibody test result, the reason for an undocumented HCV RNA was unknown. Of the remaining 2,707 individuals with positive HCV RNA test results, 758 (28%) were initially diagnosed with acute HCV infection that progressed to chronic infection and 1,277 (47%) were classified as already having chronic HCV infection (HCV RNA test result documented to have remained positive for more than 6 months after the first positive result at time of HCV diagnosis). Another 552 (20%) individuals had evidence of spontaneous clearance of HCV; the demographic characteristics of these are shown in *Appendix table 4.1*. The remaining 120 individuals of the 2,704 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 was therefore excluded from further analysis.

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



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

The analyses described in the remainder of this section on HCV are therefore limited to the 2,035 individuals who could be definitively classified as having either chronic (n=1,277) or acute (n=758) HCV infection at the time of the primary HCV diagnosis. Most of these were male (81% and 99%, respectively), and the majority originated from the Netherlands (chronic: 737/1,277 [58%]; acute: 583/758 [77%]) (*Table 4.1*). Fifty-nine percent of the individuals ever registered and who had acquired HIV through injecting drug use (IDU) had a chronic HCV infection (436 of the total 739 people who use/used injecting drugs [PWID]). In the men who have sex with men (MSM) HIV transmission group, 3% had a chronic HCV infection (521 of the total of 15,041 MSM) and 5% had a documented acute HCV infection (715 of the total of 15,041 MSM). Finally, compared with individuals without acute or chronic HCV, those with spontaneous clearance of HCV more often were female, and less often Dutch ($p<0.001$) (*Table 4.1*).

Table 4.1: Demographic characteristics of individuals co-infected with HIV/hepatitis C virus (HCV) registered in the SHM database, 1998-2018.

	Total	Chronic HCV	Acute HCV
Total number of individuals screened for HCV	24,600	1,277	758
Male gender, n (%)	20,204 (82)	1,038 (81)	749 (99)
Region, n (%)			
Netherlands	13,835 (56)	737 (58)	583 (77)
Europe	1,634 (7)	200 (16)	65 (9)
Sub-Saharan Africa	3,348 (14)	44 (3)	11 (1)
Caribbean/South America	3,005 (12)	84(7)	46 (6)
South-east Asia	862 (3)	43 ()	18 (2)
Other	1,916 (8)	169 (13)	35 (5)
HIV transmission route, n (%)			
Men who have sex with men	15,041 (61)	521 (41)	715 (94)
Heterosexual	7,299 (30)	160 (13)	24 (3)
People who use/used injecting drugs	739 (3)	436 (34)	7 (1)
Other	1,548 (6)	160 (12)	12 (2)
cART, n (%)	23,586 (96)	1,222 (96)	754 (99)
HCV genotype (GT), n (%*)			
Total determined		1,147 (90)	680 (90)
GT 1		704 (55)	485 (71)
1a		423 (60)	404 (83)
1b		94 (13)	21 (4)
1c, 1a/b or not further specified		187 (27)	60 (12)
GT 2		55 (5)	37 (5)
GT 3		205 (18)	15 (2)
GT 4		181 (16)	142 (21)
GT 5&6		2 (0.1)	1 (2)
Deaths, n (%)	2,679 (11)	303 (24)	27 (4)

**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.*

The HCV genotype was determined and documented in the clinical records of 1,147 of the 1,277 individuals (90%) with a chronic HCV infection. Of the individuals with a genotype determination, the majority (61%) were infected with HCV genotype 1 (n=704); of those persons, 60% were infected with genotype 1a (n=423) and 13% with genotype 1b (n=94). Five percent (n=55) were infected with HCV genotype 2, 18% (n=205) with genotype 3, and 16% (n=181) with genotype 4. One person was infected with genotype 5 and one with genotype 6.

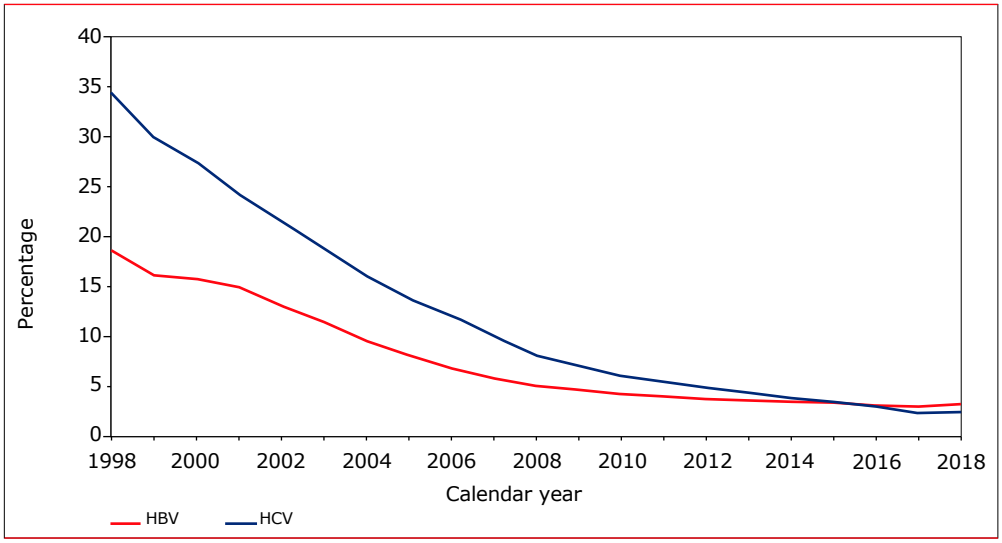
HCV genotype was also determined for 680 of the 758 individuals (90%) with an acute HCV infection. Individuals with an acute HCV infection were most likely to be infected with either genotype 1 (71%, n=485) or genotype 4 (21%, n=142). Of the 485 infected with genotype 1, 83% (404) were infected with genotype 1a and 4% (21) with genotype 1b.

Changes over time

Testing for HCV over time

Screening for HCV infection among HIV-positive individuals ever registered 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, with time, a strong and steady increase in the proportion of individuals with a known HCV status has been observed, and, in 2018, only 2% of the individuals in care had never been screened for HCV co-infection (*Figure 4.2*). In 2018, unknown HCV status was relatively more common among individuals with heterosexually acquired HIV (206/5,682, 3.6%) or with another or unknown mode of HIV acquisition (41/866, 4.7%) and relatively less common among MSM (1.8%) and PWID (0.3%).

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

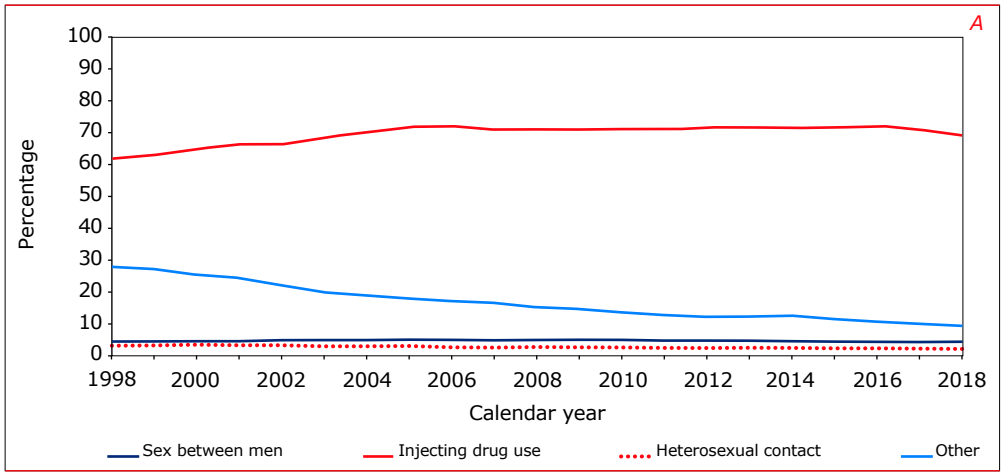


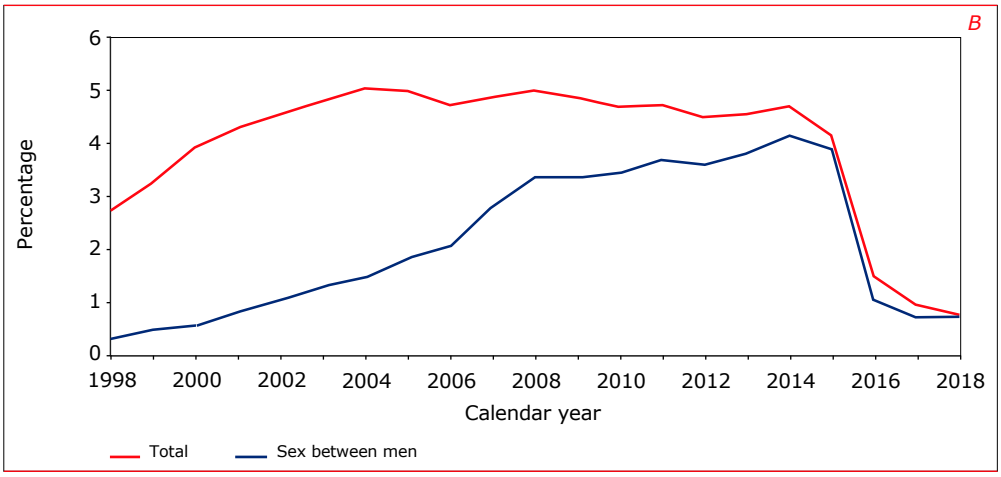
Legend: *HBV=hepatitis B virus; HCV=hepatitis C virus.*

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 11.1% in 1998 to 4.8% in 2018, 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.*





Prevalence of individuals with detectable HCV RNA

Figure 4.3B shows the proportion of individuals with an active HCV infection over calendar time (defined as a time-updated positive HCV RNA test result), regardless of a diagnosis of chronic or acute infection or re-infection. Individuals were included in follow-up time if they were in care in a specific calendar year and the HCV RNA positivity was based on a last available HCV RNA test result before the end of that calendar year. The overall proportion of individuals with detectable HCV RNA varied between 2.7% in 1998 and 5% in 2007, but it dropped to 0.8% in 2018. In MSM, the highest proportion of HCV RNA positivity was 4%; by 2018, the proportion of positive HCV RNA tests in this group had decreased sharply to 0.7%.

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). The definition of acute HCV is consistent with the definition according to the European AIDS Treatment Network (NEAT) preferred criteria[1]. In addition, we expanded this definition with alternative criteria[1,2]. In brief, 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 with a documented normal ALT within the past 12 months, together with no change in antiretroviral regimen in the last 6 months. As SHM has only routinely collected ALT levels since 2012, the incidence of acute HCV according to the alternative criteria is reported from 2012 onwards.

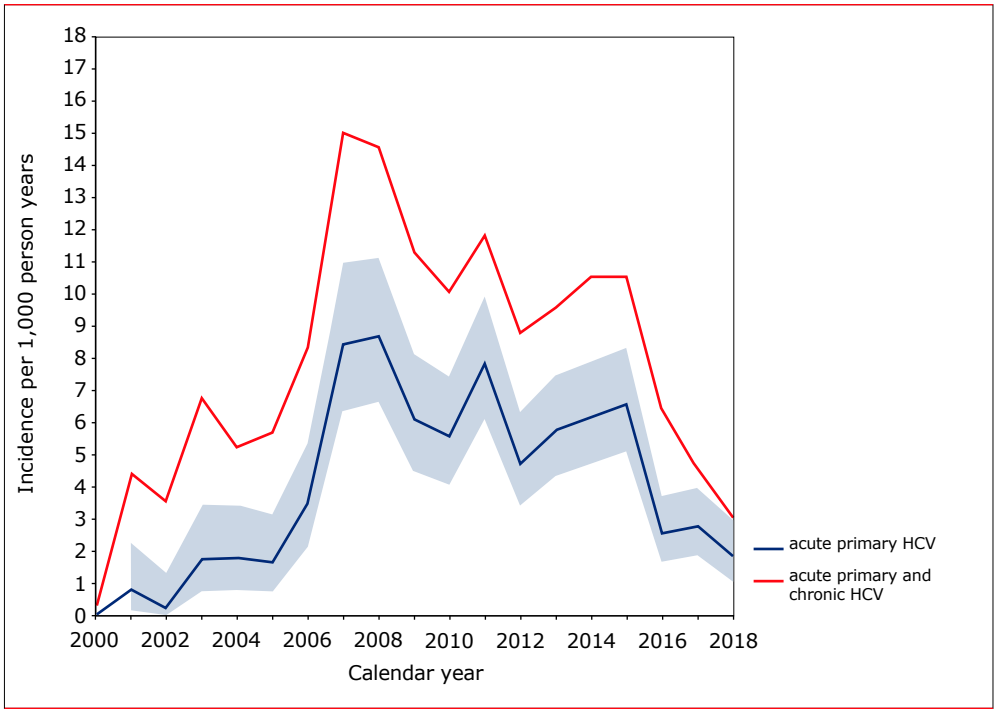
There were important differences in the incidence of the first diagnosis of acute HCV infection in terms of HIV transmission category. The vast majority of acute HCV infections occurred in MSM (715/758 [94%]). In PWID or former PWID, in contrast to the high prevalence of HCV, the overall incidence of acute HCV was low and occurred in only 7 cases. This is probably due to the high background prevalence of HCV infection in former PWID, together with injecting drug use having become very uncommon in the Netherlands. Twenty-four 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 1998 to a peak of 8.4 and 8.7 per 1,000 PY in 2007 and 2008, respectively. The incidence, which was 6.5 diagnoses per 1,000 PY in 2015, after the start of increasing direct-acting

antiviral agents (DAA) uptake in 2014, declined to 2.6 in 2016 and then stabilised at 2.8 diagnoses per 1,000 PY in 2017.

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, 3.7 in 2016 and 3.2 in 2017. The incidence of all newly-diagnosed HCV infections was higher during the overall observation period.

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. Note: Low numbers in 2018 may be due to a delay in data collection.*



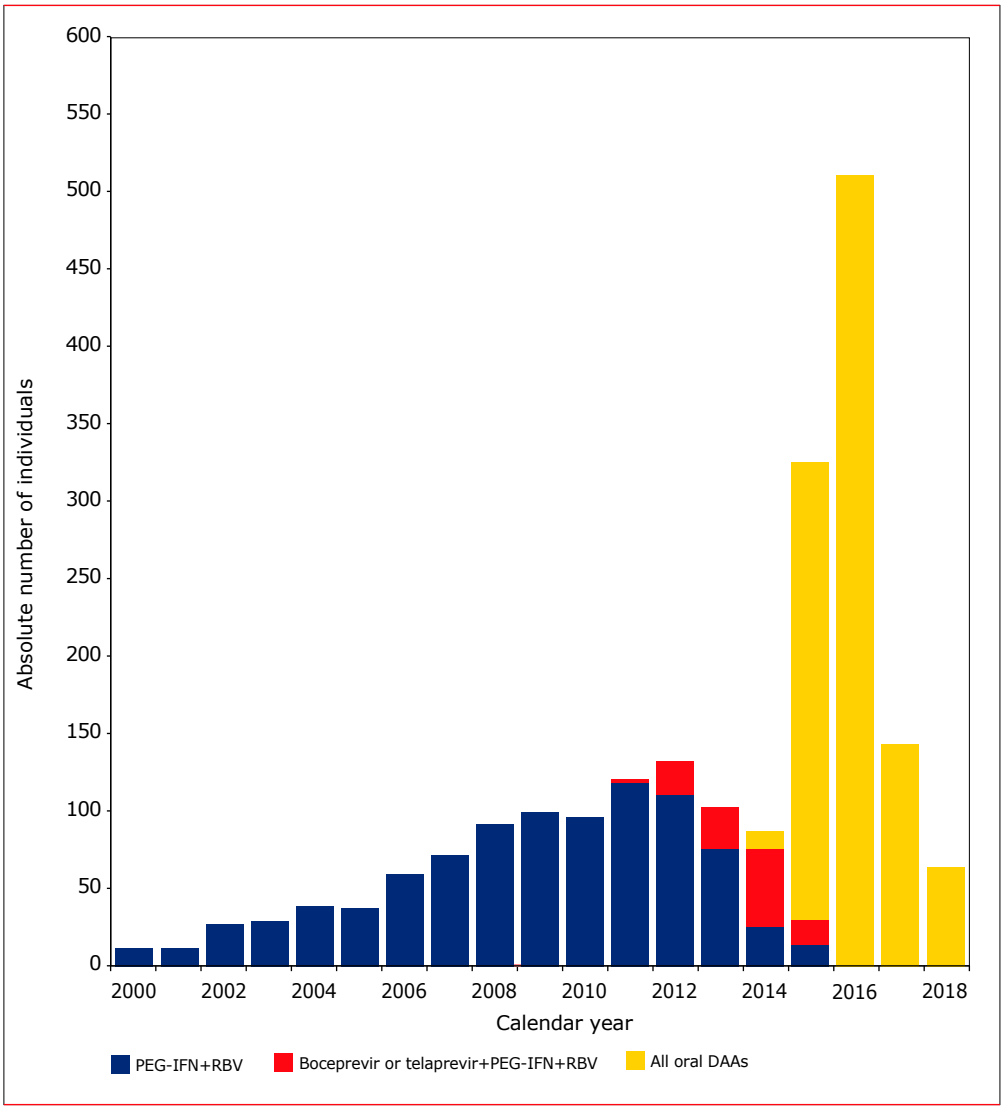
Legend: *HCV=hepatitis C virus; shaded area represents the 95% confidence interval.*

Treatment for HCV infection

The primary aim of HCV treatment is to achieve a sustained virological response (SVR)[13]. Treatment has 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. However, in April 2012, the first generation HCV NS3/4a protease inhibitors (PI) boceprevir and telaprevir, two DAAs active against HCV genotype 1, became available in the Netherlands[14,15]. These agents were subsequently used as part of triple therapy that included one of those two agents, together with PEG-IFN alpha and RBV. Subsequently, the HCV NS5B polymerase inhibitor sofosbuvir was introduced in the Netherlands in 2014. Initially, due to government restrictions, sofosbuvir was only reimbursed for a defined group of individuals infected with HCV, including those with severe liver fibrosis and cirrhosis. Later, in November 2015, sofosbuvir was made available for all individuals infected with HCV regardless of their fibrosis status, and shortly thereafter, additional novel DAAs became available such as new HCV NS3/4A protease inhibitors (simeprevir, paritaprevir and grazoprevir), 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 2,035 individuals ever diagnosed with chronic or acute HCV, 1,610 have ever received HCV treatment; of those, 448 have received HCV treatment more than once, including 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: low numbers in 2018 may be 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 the former PEG-IFN regimens was described in detail in SHM's 2016 monitoring report[16]. 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 2019, 961 individuals were known to have started a DAA regimen; 62 of those had been treated more than once with a DAA regimen. Reasons for receiving DAA treatment twice were: re-infection (n=26), no virologcial response during the first episode of DAA treatment (n=24), toxicity (n=2), and other reasons (n=6). Of the 1,026 DAA treatment episodes, 11 occurred in 2014, 296 in 2015, and 511 in 2016. The number of treatment episodes decreased to 143 in 2017 and 65 in 2018 (*Figure 4.5*).

The most frequently used DAA regimens were 1) sofosbuvir plus ledipasvir +/- RBV (n=532), and 2) sofosbuvir plus daclatasvir +/- RBV (n=245). Finally, 27 individuals who had previously been treated with DAAs are known to have died. The causes of death were liver disease (n=7), non-AIDS-defining malignancies (n=4), cardiovascular disease (n=3), non-AIDS-defining infection (n=3) and non-natural death (n=2); the remainder included alcohol and substance use, AIDS, lung disease, and unknown causes.

Outcome

HCV RNA data were collected up to 1 May 2019. At that point, 944 out of 1,026 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, 919 of these 944 individuals achieved an SVR12 (97%), with the same rate for both treatment-naive and pre-treated individuals and for those with severe liver disease. Twenty-five individuals failed to achieve an SVR12. This group was not specifically different from the group that did achieve an SVR regarding HIV transmission mode, region of origin, CD4 cell counts, and HIV RNA.

Continuum of care for those with diagnosed HCV co-infection

Figure 4.6 shows the HCV continuum of care based on the number of persons known to be in HIV care as of 31 December 2018, with data from previous monitoring reports for 2014-2018 shown for comparison. Out of a total of 2,035 individuals linked to HIV care and diagnosed with HCV, 1,533 (75%) were retained in care, and 502 individuals were no longer in care (330 had died, 88 moved abroad and 84

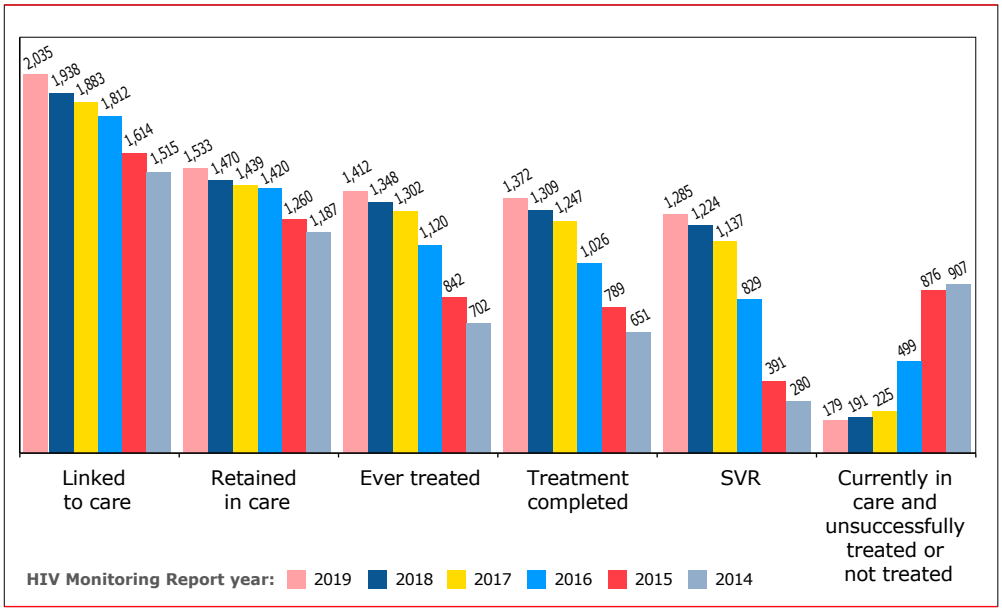
were lost to care). Of those still alive and in care, 1,412 (92%) had ever received treatment for HCV. Of the 1,412 individuals treated for HCV, 1,372 (97%) had completed HCV treatment, with enough data available to calculate the HCV treatment response (SVR12 for the DAAs and SVR24 for the older regimens). Overall, 1,285 of the 1,372 persons who completed treatment (94%) had achieved an SVR, including those who had achieved an SVR on a pegylated interferon-containing regimen.

As a result, 248 of the 1,533 individuals who were known to be alive and in care as of 31 December 2018 in one of the Dutch HIV treatment centres (16%) still needed HCV treatment:

- 121 individuals had never been treated for HCV; 116 of these were receiving cART for HIV during their last clinical visit, and 108 of these 121 individuals had an HIV RNA <100 copies/ml; the proportion untreated was higher among PWID (13%) or persons with an unknown HIV transmission mode (12%) compared to MSM (7%) (p=0.01).
- 56 had been unsuccessfully treated for HCV; 11 of these individuals had documented evidence of severe liver disease.
- 71 were still being treated or had insufficient time after treatment discontinuation to allow SVR calculation.

Of the 71 individuals for whom SVR could not yet be calculated due to insufficient time since treatment discontinuation, all had been treated with novel DAA combinations. For that reason, we extrapolated the observed DAA SVR rate of 97% to these individuals and assumed that 69 of the 71 will achieve SVR. This resulted in a more realistic estimate of individuals (248-69=179) 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 has been reported mainly in HIV-positive MSM[17,18,19], with high rates of re-infection found among MSM in the Netherlands, Germany[20] and the United Kingdom[21].

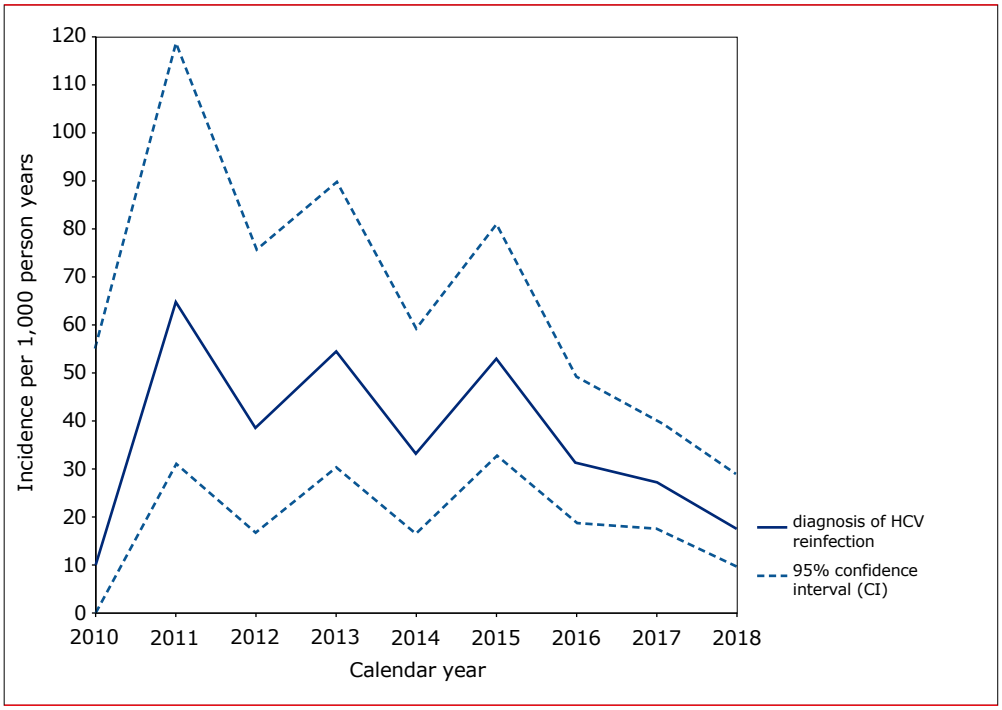
To identify possible HCV re-infection among HCV co-infected individuals, we selected the 1,450 individuals who had initially achieved an SVR after ever having received any type of HCV treatment. For these 1,450 individuals, the incidence of HCV re-infection was reported between 2010 and 2018. Follow-up time was calculated from the date of SVR, or if the SVR was achieved before 2010, from 1 January 2010 onward, until the earliest date of HCV re-infection, death, or last known contact.

Of these 1,450 individuals, 147 (10%) had documented detectable HCV RNA levels after having an earlier documented SVR, indicative of HCV re-infection. The median time between SVR and HCV re-infections that occurred from 2010 onwards was 1.6 years (IQR 0.9-3.5). For 49 of these 147 individuals (33%), an HCV genotype switch was reported, providing additional evidence of HCV re-infection.

Most individuals who became re-infected were MSM (131/147, 89%). Another five were PWID (5/147, 3%). For the remaining 8 individuals, documented HIV transmission routes were heterosexual contact (n=2) and unknown (n=6). Out of the 147 individuals with a re-infection, 126 were re-treated and the median time to re-treatment was 4.6 months (IQR; 2-16), with no difference between the pre- and post-DAA era; of those, 104 were re-treated with a DAA-containing regimen. In total, 110 of these 126 individuals achieved an SVR (96%). Among the 104 individuals who had been re-treated with a DAA-containing regimen, 93 achieved an SVR, and for 11 individuals SVR could not yet be determined.

The incidence of HCV re-infection was 26 re-infections per 1,000 PY (95%: 22-31) for the total population and 33 re-infections per 1,000 PY (95%: 27-39) for MSM. 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 10 to 53 re-infections per 1,000 PY between 2010 and 2015, respectively, and then declined to 27 re-infections per 1,000 PY in 2017.

Figure 4.7: *Incidence of hepatitis C re-infection after earlier treatment-induced clearance among men who have sex with men, per calendar year. Note: Numbers in 2018 may be affected by a delay in data collection.*



Legend: *HCV=hepatitis C virus.*

HBV

Ninety-six percent of the 26,247[b] HIV-positive individuals ever registered in the SHM database had 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 4.2*). Since then, the proportion of HIV-positive individuals without HBV screening has decreased markedly, with just 3% of all HIV-positive individuals in care having no measured HBV serological markers in 2018 (*Figure 4.2*).

***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)

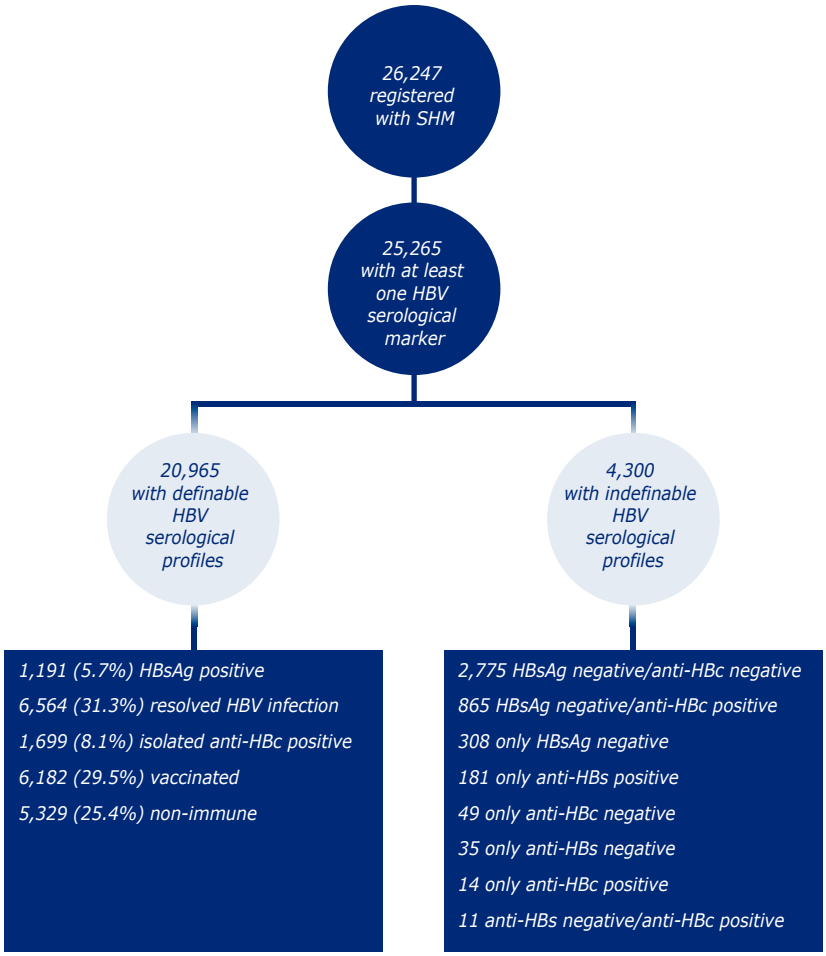
***Legend:** HBsAg=hepatitis B surface antigen; anti-HBs=anti-hepatitis B surface; anti-HBc=anti-hepatitis B core; Pos=positive; Neg=negative; HBV=hepatitis B virus; ND=not determined.*

HBV serological profiles

HBV serological profiles could be defined for 20,965 (83%) of the 25,265 screened individuals (*Figure 4.8*). 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 4.8*. The remaining 4,300 (17%) individuals either did not have sufficient information to establish HBV serological profile (n=4,238) or were previously HBsAg-positive and no longer had anti-HBc antibodies (n=62). Demographic characteristics are compared between persons with definable HBV serological profiles in *Table 4.2*.

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.*

Figure 4.8: *Flowchart of HIV-positive individuals registered in the SHM database, 1999-2018, with testing for hepatitis B virus (HBV).*



Information obtained from most recent serological result.

Legend: *Anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus.*

Table 4.2: Demographic characteristics of HIV-positive individuals in care according to their hepatitis B virus (HBV) serological profile as registered in the SHM database, 1998-2018.

	HBV serological profile*, n (%)				
	Active HBV infection	Resolved HBV infection	Isolated anti-HBc positive	Vaccinated	Non-immune
Total number	1,191	6,564	1,699	6,182	5,329
Male gender	1,027 (86%)	5,663 (86%)	1,302 (77%)	5,325 (86%)	3,984 (75%)
Region of origin					
Netherlands	531 (45%)	3,617 (55%)	669 (39%)	3,813 (62%)	3,110 (58%)
Europe	77 (6%)	459 (7%)	122 (7%)	476 (8%)	289 (5%)
Sub-Saharan Africa	304 (26%)	991 (15%)	541 (32%)	463 (7%)	616 (12%)
Caribbean/South America	123 (10%)	782 (12%)	167 (10%)	714 (12%)	790 (15%)
South-east Asia	63 (5%)	264 (4%)	67 (4%)	194 (3%)	138 (3%)
Other	93 (8%)	451 (7%)	133 (8%)	522 (8%)	386 (7%)
HIV transmission group					
Men who have sex with men	683 (57%)	4,566 (70%)	751 (44%)	4,523 (73%)	2,538 (48%)
Heterosexual	361 (30%)	1,398 (21%)	609 (36%)	1,340 (22%)	2,312 (43%)
Injecting drug use	50 (4%)	223 (3%)	190 (11%)	59 (1%)	101 (2%)
Other	97 (8%)	377 (6%)	149 (9%)	260 (4%)	378 (7%)
cART	1,143 (96%)	6,343 (97%)	1,623 (96%)	6,017 (97%)	5,116 (96%)
Deaths	242 (20%)	917 (14%)	284 (17%)	283 (5%)	583 (11%)

**Based on information obtained from 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.*

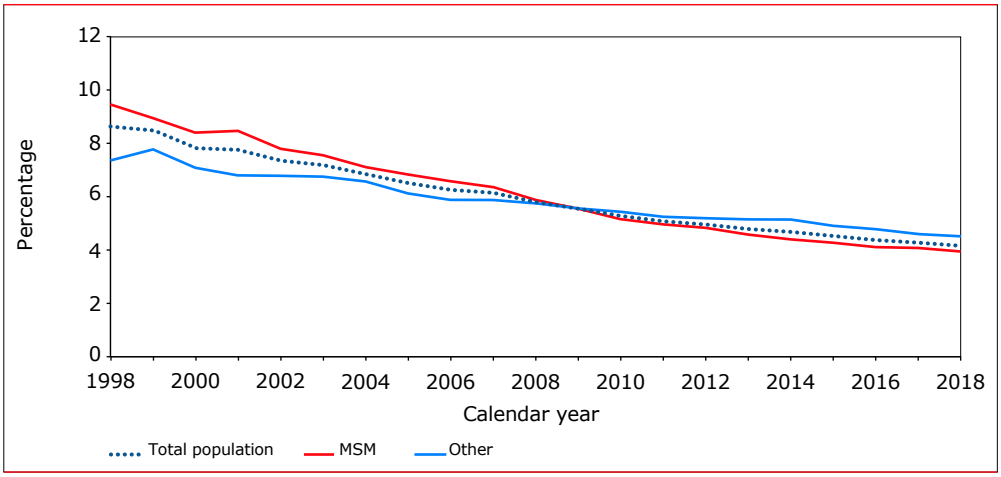
Individuals with active HBV infection

Of the 25,265 individuals screened for at least one HBV serological marker, a total of 1,551 (6%) ever had a positive HBsAg test result. Over time, 186 (12%) of these individuals resolved their HBV infection, i.e., they became HBsAg-negative and acquired anti-HBs antibodies; an additional 174 (11%) became HBsAg-negative without acquiring anti-HBs antibodies. The remaining 1,191 (77%) individuals continued clinical care with HBsAg-positive serology.

The prevalence of HBsAg-positive serology was 8.5% in 1998 and slowly decreased to 4.2% in 2018 (*Figure 4.9*). 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[22] 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[23]. As is the case for HCV co-infection, the proportion of HIV-positive individuals in care and chronically co-infected with HBV is considerably higher than that of the general Dutch population. Individuals co-infected with HBV were predominantly male (1,027/1,191, 86%), in line with those co-infected with HCV (*Table 4.2*). 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 4.9: *Prevalence of HBsAg-positive serology per calendar year.*



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

Treatment for chronic HBV infection

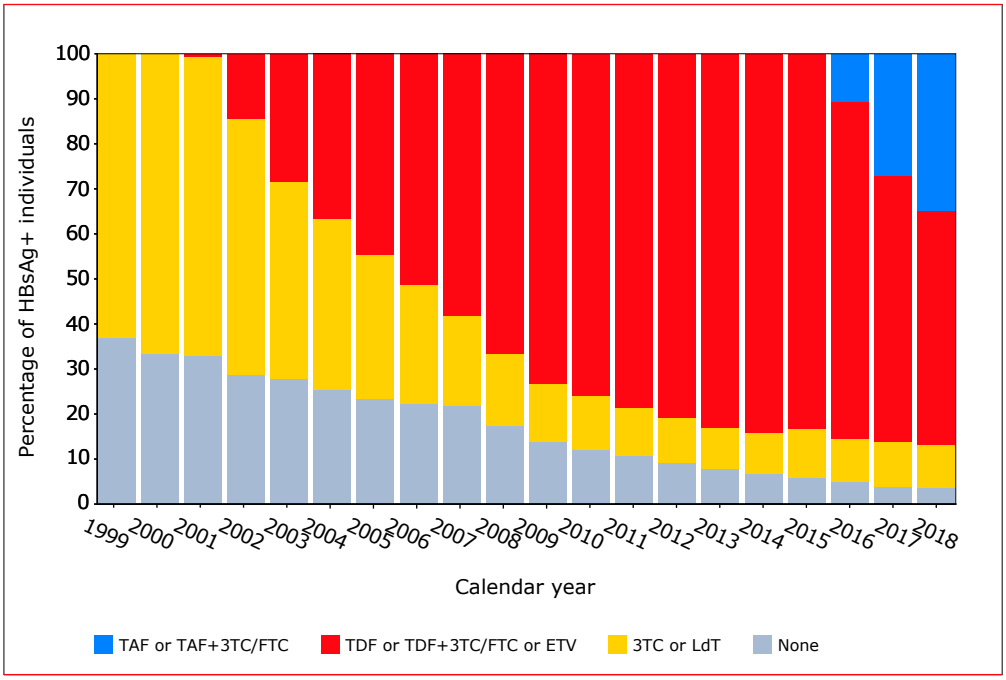
The treatment for chronic HBV infection aims to reduce viral replication. As HBV DNA is the parameter most directly influenced by therapy with either nucleoside or nucleotide analogues, HBV DNA undetectability is an appropriate surrogate marker for treatment response. Persistent lowering of HBV DNA levels to less than 20 IU/ml has also been shown to delay progression of liver fibrosis to cirrhosis[24]. 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 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 e-seroconversion is an important secondary treatment parameter, since studies have shown that it results in clinically important lowering of HBV DNA, thereby decreasing the risk of progression of liver fibrosis. A few antiviral agents used for treatment of HIV, such as lamivudine, emtricitabine and particularly TDF/TAF, are also active against HBV.

Of the 1,551 individuals with HIV in the SHM database who ever had an HBsAg-positive serological test result, 1,486 (96%) had ever received a cART regimen that included one or more agents with activity against both HIV and HBV. Reasons for the remaining 65 individuals not having received anti-HBV treatment included: death before being able to start treatment (n=16), recent entry into care (n=2), loss to follow up (n=41) and lack of sufficient information (n=6).

Most people with active HBV infection received treatment containing lamivudine in 1999-2000 (*Figure 4.10*). TDF-based cART (with or without lamivudine or emtricitabine) for combined HIV and HBV treatment was first used in 2002 (n=82/632, 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=130/1,206, 11%). In 2018, most co-infected individuals were receiving TDF-based cART (n=589/1,212, 49%), followed by TAF-based cART (n=399/1,212, 33%), lamivudine-based cART (n=171/1,212, 14%) or no anti-HBV-containing cART (n=53/1,212, 4%).

Figure 4.10: Anti-hepatitis B virus (HBV)-containing antiretroviral therapy per calendar year.



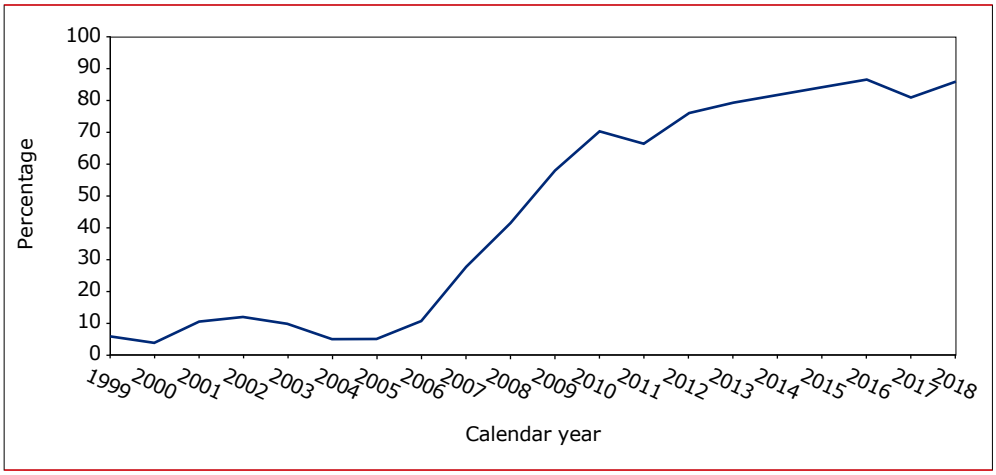
Legend: *TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; ETV=entecavir; 3TC=lamivudine; LdT=telbuvidine; FTC= emtricitabine.*

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[25].*

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[26]. 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 4.11* shows the proportion 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, 18% 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 2018, 86% of individuals co-infected with HIV and HBV had an undetectable HBV DNA level. (*Figure 4.11*).

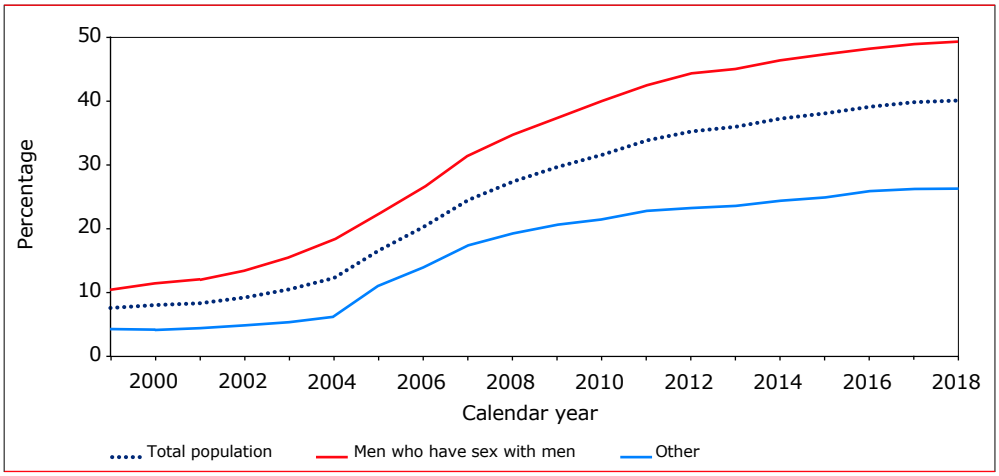
Figure 4.11: *Percentage of individuals with undetectable hepatitis B virus (HBV) DNA levels by assay with a detection limit of either <100, <200, <2000 IU/ml HBV DNA or <20 IU/ml per calendar year, regardless of HBeAg status.*



HBV vaccination in HIV-positive individuals

Of the 20,965 individuals with definable HBV serological profiles, 6,182 (29%) 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 40% in 2018 (*Figure 4.12*). The largest increase in HBV vaccination was observed in MSM compared to others, likely due to the national vaccination campaign targeting these individuals from 2002 onwards[22].

Figure 4.12: Prevalence of hepatitis B vaccination per calendar year.



Non-immune status in HIV-positive individuals

Of the 20,965 individuals with definable HBV serological profiles, 5,329 (25%) had serological evidence of being non-immune and non-exposed to HBV at their last visit. When the 4,300 individuals with indefinable HBV serological profiles were considered, 75 out of 287 with an anti-HBs antibody test did not have detectable anti-HBs antibodies, and 3,210 out of 4,013 without an anti-HBs antibody test were not reported to have been vaccinated by their treating physician. Thus, at most, 8,614 of 25,265 (34%) individuals screened for HBV remained susceptible to infection as of their last visit (*5,329* non-immune *plus 75* with indefinable HBV profile and anti-HBs antibody negative *plus 3,210* with indefinable 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 tenofovir (TDF) or tenofovir alafenamide (TAF) as part of their cART regimen, as suggested by findings reported by an international study and by one of the Dutch HIV treatment centres[27,28]. Data from SHM show that, of those people who remain at risk of acquiring HBV, 79% are currently being treated with a cART regimen that includes TDF or TAF; for MSM, this prevalence is 81%.

Morbidity and mortality in individuals co-infected with HIV and HCV and/or HBV

Liver-related morbidity

Additional data from liver biopsy pathology reports, transient elastography, radiology reports, or a combination of those sources, were available for 1,681 of the 2,035 individuals with HCV co-infection and for 1,180 of the 1,551 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 492 (29%) of the individuals with HCV co-infection and in 256 (22%) of those with HBV co-infection (*Table 4.3*). Definitive severe chronic liver disease was documented for 117 individuals with an HCV co-infection (7%) and 69 (6%) with an HBV co-infection.

Table 4.3: *Morbidity and mortality in HIV-positive individuals with hepatitis C virus (HCV) and/or hepatitis B virus (HBV) co-infection registered in the SHM database.*

	HCV infection, n (%)	HBV infection, n (%)
Total	2,035	1,551
Severe chronic liver disease#	494 (29)**	256 (22)***
HCC	20 (1)	32 (2.1)
Liver transplantation	2 (0.1)	1 (0.1)
Deaths from any cause*	330 (16)	290 (19)
Liver-related deaths	71 (3)	47 (3)

**including liver-related death*

***based on 1,681 individuals with data on liver disease*

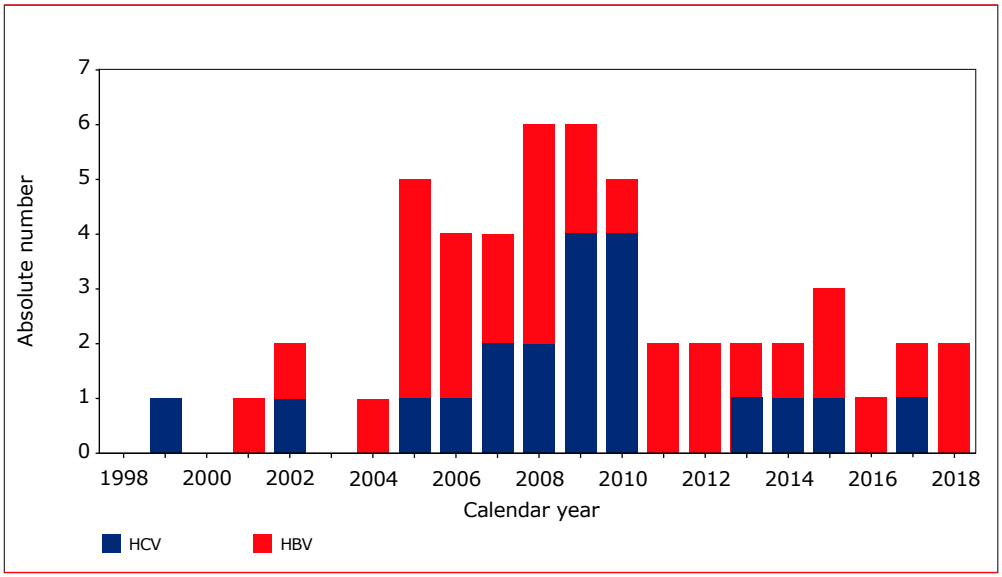
****based on 1,180 individuals with data on liver disease*

#including presumptive and definitive liver disease

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

Figure 4.13 shows that the annual number of new HCC diagnoses declined from 2010 onwards. HCC was diagnosed in 20 out of 1,362 individuals (1.4%) with a chronic HCV co-infection, 15 of whom were born in the Netherlands. HCC was found in 32 individuals (2.1%) with a chronic HBV co-infection, 18 of whom were born in the Netherlands, 9 in sub-Saharan Africa, 2 in Asia, and 1 each in South America, the United States, and Australia.

Figure 4.13: Absolute number of annually reported hepatocellular carcinoma cases over time.



Legend: HCV=hepatitis C virus; HBV=hepatitis B virus.

Mortality

All-cause mortality

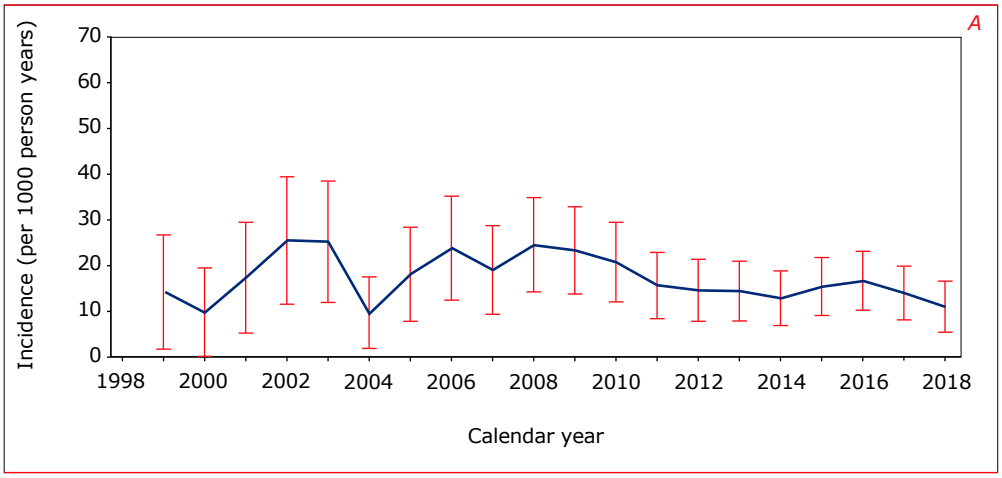
The overall proportion of those dying from any cause was 16% for the 2,035 individuals with an HCV infection and 19% for the 1,551 individuals with an HBV infection (*Table 4.3*). For individuals with HCV infection, the age- and gender-adjusted incidence rate of death from any cause was 16.4/1000 person years in 1998-2002, 20.1 in 2003-2011 and 14.2 from 2012 onwards (*Figure 4.14A*). In MSM with HCV infection, these incidence rates were 5.3/1000 person years in 1998-2002, 7.9 in 2003-2011, and 4.1 in 2012 onwards. In PWID with HCV infection, these incidence rates were 19.3/1000 person years in 1998-2002, 38.1 in 2003-2011, and 47.1 in 2012 onwards.

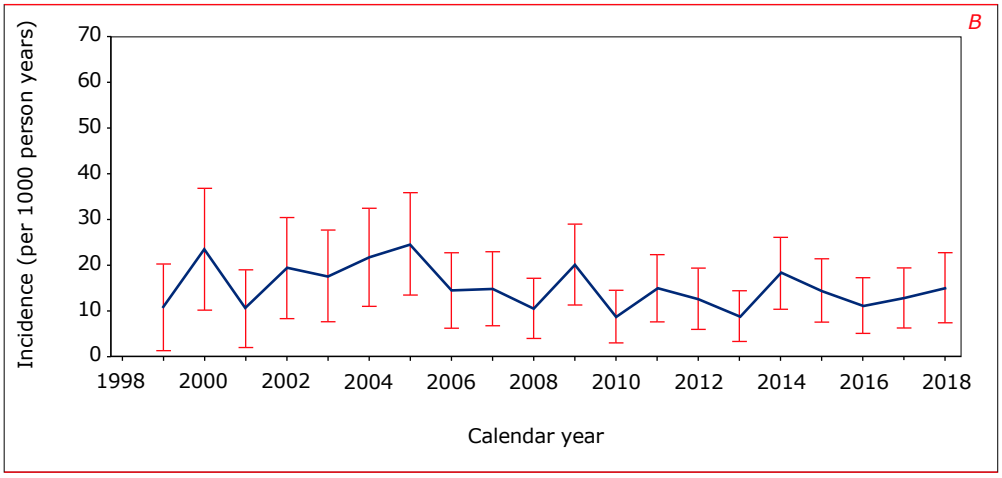
For individuals with HBV infection, the age- and gender-adjusted incidence rate of death from any cause was 16.0/1000 person years in 1998-2002, 16.1 in 2003-2011 and 13.4 from 2012 onwards (*Figure 4.14B*). In MSM with HBV infection, these incidence rates were 11.7/1000 person years in 1998-2002, 13.6 in 2003-2011, and 10.6 in 2012 onwards. In PWID with HCV infection, these incidence rates were 52.2/1000 person years in 1998-2002, 60.5 in 2003-2011, and 93.6 in 2012 onwards.

Liver-related mortality

In total, 118 individuals co-infected with hepatitis died of a liver-related cause (*Table 4.3*).

Figure 4.14: Annual age- and gender-adjusted all-cause mortality rate in individuals positive for HIV1 who were ever diagnosed with (A) an acute or chronic HCV infection and (B) active hepatitis B virus infection.

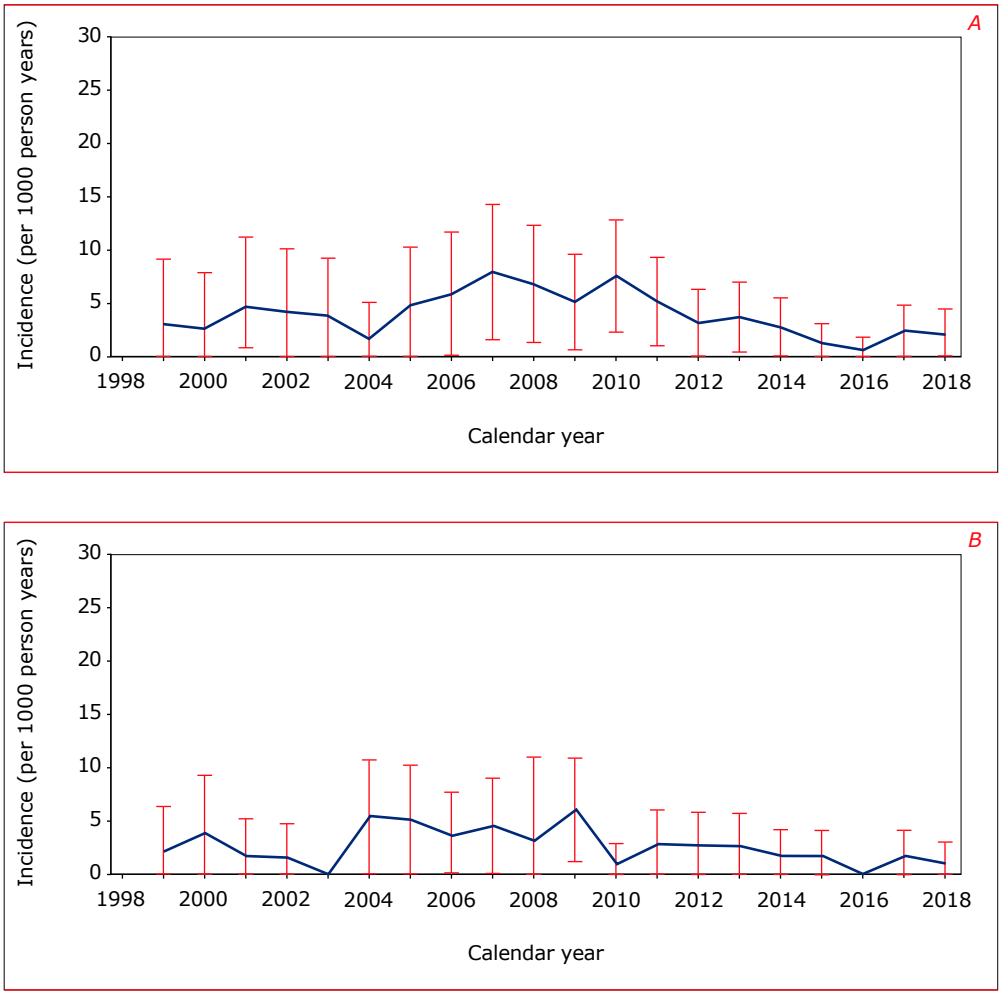




For individuals with HCV infection, the age- and gender-adjusted incidence rate of death from a liver-related cause was 3.2/1000 person years in 1998-2002, increasing to 5.7 in 2003-2011 and decreasing to 2.2 from 2012 onward (*Figure 4.15A*). In MSM with HCV infection, these incidence rates were 0/1000 person years in 1998-2002, 3.0 in 2003-2011, and 0.9 from 2012 onwards. In PWID with HCV infection, these incidence rates were 2.6/1000 person years in 1998-2002, 8.5 in 2003-2011, and 5.2 from 2012 onward.

For individuals with HBV infection, the age- and gender-adjusted incidence rate of liver-related death was 1.9/1000 person years in 1998-2002, increasing to 3.5 in 2003-2011 and decreasing to 1.7 from 2012 onward (*Figure 4.15B*). In MSM with HBV infection, these incidence rates were 2.4/1000 person years in 1998-2002, 3.2 in 2003-2011, and 1.6 from 2012 onward. In PWID with HBV infection, these incidence rates were 3.6/1000 person years in 1998-2002, 1.4 in 2003-2011, and 1.5 in 2012 onwards.

Figure 4.15: *Age- and gender-adjusted incidence rate of mortality related to liver disease for individuals infected with (A) hepatitis C virus or (B) hepatitis B virus, stratified by calendar year period.*



Conclusions

Screening for HCV and HBV co-infection in the HIV-positive population in the Netherlands continues to improve over time and nowadays is documented almost universally. Five percent of HIV-positive individuals ever registered between 1998 and 2018 in the SHM database were documented as being chronically infected with HCV and 3% were documented as having had an acute HCV infection.

Our data clearly show that, with the advent of novel DAAs from 2014 onwards, PEG-IFN-containing regimens largely have been replaced in clinical practice by various novel DAAs. 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 resulted in a decrease to 121 of HCV co-infected individuals remaining in need of HCV treatment. Overall, a rapid reduction in the prevalence of an active HCV infection has been achieved, with prevalence in MSM having declined to less than 1% in 2018. The rapidly increasing availability of novel interferon-free, highly effective combination antiviral regimens for HCV, together with optimised screening for HCV co-infection, with time will hopefully also limit the impact of HCV co-infection on liver-related morbidity and mortality. Successful treatment of HCV may 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[17,21], 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 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[22], together with the HBV-prophylactic effect of TDF/TAF in cART-treated individuals. Nonetheless, an estimated 32% of all HIV-positive individuals and 25% of MSM have either not been exposed to HBV or not been successfully vaccinated and may remain at risk of acquiring HBV. Since 79% of all individuals and 81% 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 21% of the HIV-positive individuals ever registered and 19% of the MSM remain unprotected against HBV, which represents an estimated 6.5% of the total population of HIV-positive individuals screened for hepatitis B.

Among the HIV-positive individuals ever registered by SHM, 29% 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 after 2012, yet the rate remains much higher for co-infected PWIDs compared to other transmission groups.

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 be ongoing 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[29]. In the long term, provision of highly effective DAA regimens for all known HCV co-infected HIV-positive individuals can be expected to contribute to reducing the burden of severe chronic liver disease, hepatocellular carcinoma, and mortality related to liver disease among persons 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 certain group of individuals shows that additional efforts are needed. This may include repeating an earlier approach by which SHM provides all HIV treatment centres with a pseudonymised list of untreated individuals, in order to draw specific attention to this group. Furthermore, additional research is recommended to provide more insight into 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 is recommended to ensure early detection of new HCV infections; this is in combination with preventive behavioural interventions aimed at MSM to reduce HCV re-infection after successful treatment of HCV. Continued monitoring of the population co-infected with HIV and hepatitis in the Netherlands will thus be key not only to monitoring the epidemiology of these infections and the response to existing and novel treatments but also to assessing the impact of treatment on reducing the burden of morbidity and mortality from chronic liver disease.

References

1. Rockstroh JK. Acute hepatitis C in HIV-infected individuals - recommendations from the NEAT consensus conference. *AIDS*. 2011;25(4):399-409. doi:10.1097/QAD.0b013e328343443b
2. Arends JE, Lambers FAE, van der Meer JTM, et al. Treatment of acute hepatitis C virus infection in HIV+ patients: Dutch recommendations for management. *Neth J Med*. 2011;69(1):43-49. http://www.ncbi.nlm.nih.gov/pubmed/21325703. Accessed August 28, 2018.
3. Hahné SJM, de Melker HE, Kretzschmar M, et al. Prevalence of hepatitis B virus infection in The Netherlands in 1996 and 2007. *Epidemiol Infect*. 2012;140(8):1469-1480. doi:10.1017/S095026881100224X
4. Nationaal Hepatitis Centrum. www.hepatitis.nl.
5. HepNed Study Group. Van Dijk M, Kracht PAM, Arends JE, et al. Retrieval of Chronic Hepatitis C Patients. A Manifesto for Action to Eliminate Hepatitis C in the Netherlands: The CELINE Project. *Neth J Med*. 2019;77(4):131-138.
6. Lincoln D, Petoumenos K, Dore GJ, Australian HIV Observational Database. HIV/HBV and HIV/HCV coinfection, and outcomes following highly active antiretroviral therapy. *HIV Med*. 2003;4(3):241-249. doi:10.1046/j.1468-1293.2003.00152.x
7. Heintges T, Wands J. Hepatitis C virus: epidemiology and transmission. *Hepatology*. 1997;26(3):1-6. doi:10.1002/hep.510260338
8. Lok AS. Chronic hepatitis B. *N Engl J Med*. 2002;346(22): 1682-3
9. Ikeda K, Saitoh S, Suzuki Y, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: A prospective observation of 2215 patients. *J Hepatol*. 1998;28(6):930-938. doi:10.1016/S0168-8278(98)80339-5
10. Posthouwer D, Makris M, Yee TT, et al. Progression to end-stage liver disease in patients with inherited bleeding disorders and hepatitis C: An international, multicenter cohort study. *Blood*. 2007;109(9):3667-3671. doi:10.1182/blood-2006-08-038349
11. Arends JE, Lieveld FI, Boeijen LL, et al. Natural history and treatment of HCV/HIV coinfection: Is it time to change paradigms? *J Hepatol*. 2015;63(5):1254-1262. doi:10.1016/j.jhep.2015.06.034
12. Lieveld FI, Smit C, Richter C, et al. Liver decompensation in HIV/Hepatitis B coinfection in the combination antiretroviral therapy era does not seem increased compared to hepatitis B mono-infection. *Liver Int*. 2019;39(3):470-483. doi:10.1111/liv.14000
13. European AIDS Clinical Society. Guidelines. Version 8.0, October 2015. English edition. 2015. http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html.
14. Zorg intstituut Nederland. www.zorginstituutnederland.nl.

15. Arends JE, van der Meer JTM, Posthouwer D, et al. Favourable SVR12 rates with boceprevir or telaprevir triple therapy in HIV/HCV coinfected patients. *Neth J Med*. 2015;73(7):324-330.
16. van Sighem AI, Boender TS, Wit FWNM, Smit C, Matser A, Reiss P. *Monitoring Report 2016. Human Immunodeficiency Virus (HIV) Infection in the Netherlands*. Amsterdam: Stichting HIV Monitoring; 2016.
17. Lambers FAE, Prins M, Thomas X, et al. Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM. *AIDS*. 2011;25(17):F21-7. doi:10.1097/QAD.0b013e32834bac44
18. den Hollander JG, Rijnders BJ, van Doornum GJJ, van der Ende ME. Sexually transmitted reinfection with a new hepatitis C genotype during pegylated interferon and ribavirin therapy. *AIDS*. 2005;19(6):639-640. http://www.ncbi.nlm.nih.gov/pubmed/15802989. Accessed August 26, 2016.
19. Berenguer J, Gil-Martin Á, Jarrin I, et al. Reinfection by HCV following effective all-oral DAA therapy in HIV/HCV-coinfected individuals. *AIDS*. December 2018. doi:10.1097/QAD.0000000000002103
20. Ingiliz P, Krznaric I, Stellbrink H-J, et al. Multiple hepatitis C virus (HCV) reinfections in HIV-positive men who have sex with men: no influence of HCV genotype switch or interleukin-28B genotype on spontaneous clearance. *HIV Med*. 2014;15(6):355-361. doi:10.1111/hiv.12127
21. Martin TCS, Martin NK, Hickman M, et al. Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM. *AIDS*. 2013;27(16):2551-2557. doi:10.1097/QAD.0b013e32836381cc
22. van Rijckevorsel G, Whelan J, Kretzschmar M, et al. Targeted vaccination programme successful in reducing acute hepatitis B in men having sex with men in Amsterdam, the Netherlands. *J Hepatol*. 2013;59(6):1177-1183. doi:10.1016/j.jhep.2013.08.002
23. Heuft MM, Houba SM, Van Den Berk GEL, et al. Protective effect of hepatitis B virus-active antiretroviral therapy against primary hepatitis B virus infection. *AIDS*. 2014;28(7):999-1005. doi:10.1097/QAD.0000000000000180
24. Xu B, Lin L, Xu G, et al. Long-term lamivudine treatment achieves regression of advanced liver fibrosis/cirrhosis in patients with chronic hepatitis B. *J Gastroenterol Hepatol*. 2015;30(2):372-378. doi:10.1111/jgh.12718
25. Ratcliffe L, Beadsworth MBJ, Pennell A, Phillips M, Vilar FJ. Managing hepatitis B/HIV co-infected: adding entecavir to truvada (tenofovir disoproxil/emtricitabine) experienced patients. *AIDS*. 2011;25(8):1051-1056. doi:10.1097/QAD.0b013e328345ef5e
26. Sharma SK, Saini N, Chwla Y. Hepatitis B virus: inactive carriers. *Virol J*. 2005;2:82. doi:10.1186/1743-422X-2-82

27. Quirk E, Graham H, Liu C, Rhee M, Piontkowsky D, Szwarcberg J. Reports of viral hepatitis B and C in HIV patients participating in clinical trials of elvitegravir/cobicistat/tenofovir DF/emtricitabine and cobicistat-boosted atazanavir plus tenofovir DF/emtricitabine. *Antivir Ther*. 2013;1 Suppl 38:A63.
28. Heuft MM, Houba SM, van den Berk GEL, et al. Protective effect of hepatitis B virus-active antiretroviral therapy against primary hepatitis B virus infection. *AIDS*. 2014;28(7):999-1005. doi:10.1097/QAD.0000000000000180
29. Machiels JD, Braam EE, van Bentum P, et al. Vaccination with Fendrix of prior nonresponding patients with HIV has a high success rate. *AIDS*. 2019;33(3):503-507. doi:10.1097/QAD.0000000000002085

Appendix: supplementary table

Appendix 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, 1998-2018.*

	Total HCV co-infected	Spontaneous clearance
Total number of individuals screened for HCV	2,035	552
Male gender, n (%)	1,787 (88)	437 (79)
Region of origin, n (%)		
Netherlands	1,320 (65)	281 (51)
Europe	265 (13)	78 (14)
Sub-Saharan Africa	55 (3)	58 (11)
Caribbean/South America	130(6)	67 (12)
South-east Asia	61 (3)	18 (32)
Other	204 (10)	50 (9)
HIV transmission route, n (%)		
Men who have sex with men	1,236 (60)	272 (49)
Heterosexual	184 (9)	101 (18)
People who use/used injecting drugs	443 (22)	114 (21)
Other	172 (8)	65 (12)
cART, n (%)	1,976(97)	524 (95)
Deaths, n (%)	330 (16)	86 (16)

< Back to page 206