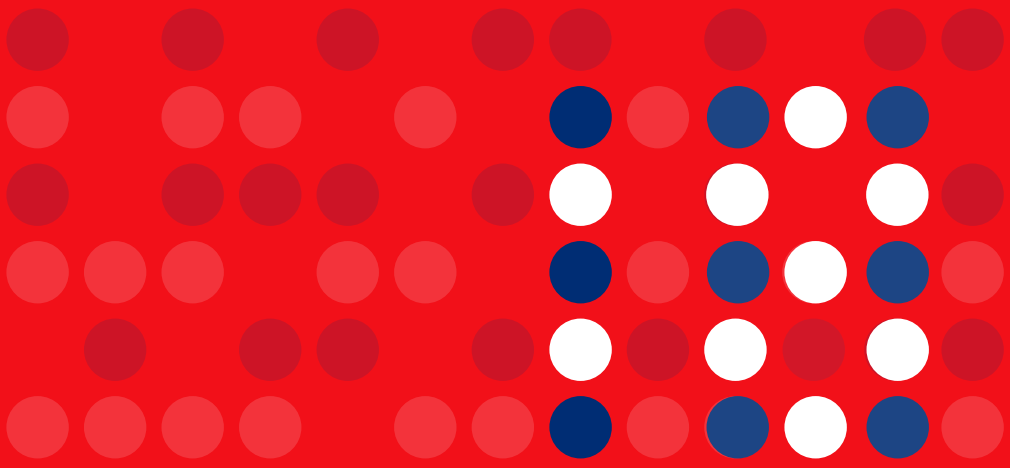
Human Immunodeficiency Virus (HIV)
infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2018

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.

SHM comprehensively maps the HIV epidemic and HIV treatment outcomes in the Netherlands, thereby contributing to the knowledge of HIV. 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.

In addition to national reports, healthcare professionals are provided with treatment centre-specific reports to enable them to monitor and optimise care provided in their centres. Moreover, upon request, SHM data are also made available for use in HIV-related research, both in the Netherlands and internationally. The outcome of SHM's research and international collaborations provides tangible input into policy guidelines and further improves HIV care 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.

HIV Monitoring

Monitoring Report 2018

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

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4. Viral hepatitis

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Box 4.1: Definitions of hepatitis B and C co-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*
   Positive anti-HCV IgG and 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*
   Detectable HCV-RNA in association with a rise in alanine aminotransferase (ALT) (>200 U/l) with a documented normal ALT within the past 12 months and no changes in antiretroviral regimens within the last 6 months.

Spontaneously cleared HCV infection

1. Individuals with a documented positive test result for HCV antibody with a subsequent negative HCV RNA test result.
2. Individuals who fulfilled the above criteria for acute HCV and who subsequently had a negative HCV RNA test without having received HCV treatment.
3. Individuals who did not fulfil the definition of acute HCV infection, but had a positive HCV RNA test result and became negative within 6 months without treatment.

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.

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.

Hepatitis C re-infection
Detectable HCV RNA more than 6 months after an SVR12 or SVR24, or spontaneous HCV clearance or documentation of a genotype switch.

Chronic hepatitis B virus (HBV) infection
Two or more consecutive positive test results for hepatitis B surface antigen (HBsAg) over a period of at least 6 consecutive months.

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 radiographic or endoscopic documentation of the presence of portal hypertension by oesophageal varices, ascites, splenomegaly and reversal of portal blood flow and/or cirrhosis.

Definitive if:
- combined with a pathology 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]. In contrast, HCV and HBV co-infections are far more prevalent in HIV-positive individuals due to shared routes of transmission[5].

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)[6,7]. HBV infection can also directly lead to HCC without cirrhosis. Progression to severe liver disease takes, on average, 20 to 30 years in HCV or HBV mono-infected individuals[8,9]. Although 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 become increasingly similar to that in HCV or HBV mono-infected individuals[10].

In the era when treatment for HIV infection was either unavailable or insufficiently effective to achieve sustained suppression of viral replication, most individuals progressed to AIDS and died before the effects of co-infection with HCV or HBV were able to clinically manifest as severe chronic liver disease. However, now that the incidence of AIDS and its associated mortality rate have markedly declined with the widespread use of cART, liver disease has become an increasingly frequent cause of morbidity and mortality in persons living with HIV[11].

This chapter reports on the demographic and clinical characteristics, progression to 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

Data used in this chapter
In 2018, Stichting HIV Monitoring launched a new data entry system, DataCapTree, which went live in February 2018 with an initial set of approved data collection protocols. However, the protocol for the collection of viral hepatitis data was delayed until the second half of 2018. For this reason, data used in this chapter are based on the database lock on 31 December 2017, rather than May 2018 as in from previous years.

Population described in this chapter
All individuals ever registered up to 31 December 2017.

HCV

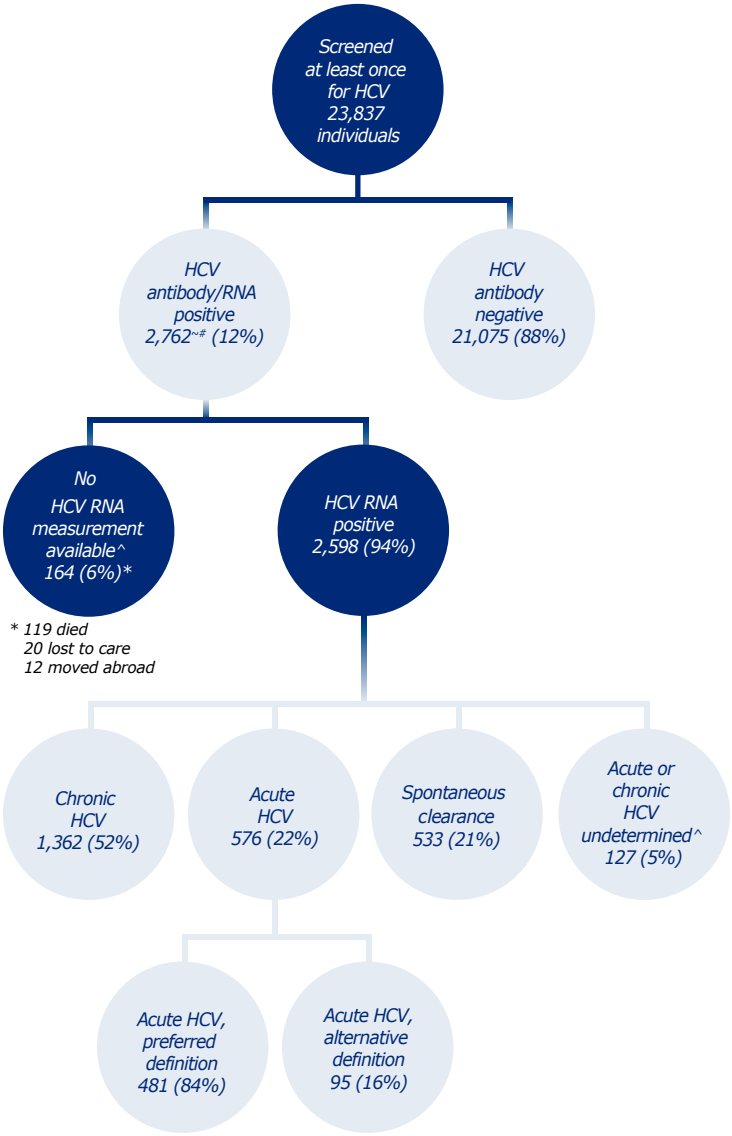
Demographic and clinical characteristics

In total, 2,762 (12%) of the 23,837 HIV-1-positive adults (≥18 years of age at time of HIV-1 diagnosis) in care who were ever screened for HCV co-infection had a positive result with an HCV antibody test 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 164 of the 2,762 individuals (6%). Of these 164 individuals, 119 had died, 20 were lost to care, and 12 had moved abroad; for the remaining 13 individuals with a positive HCV antibody test result, the reason for an undocumented HCV RNA was unknown. Of the remaining 2,598 individuals with positive HCV RNA test results, 1,362 (52%) were classified as having a chronic HCV infection (HCV RNA test result documented to have remained positive for more than six months after the first positive result), and 576 (22%) were diagnosed with acute HCV infection (481 individuals were classified as having been diagnosed with an acute HCV infection based on the

preferred NEAT definition: documented anti-HCV IgG seroconversion or HCV RNA conversion within 12 months, and 95 individuals were classified based on the alternative definition: detectable HCV RNA with an acute rise in alanine amino-transferase [ALT]). Another 533 (21%) individuals had evidence of spontaneous clearance of HCV (documented positive test result for HCV antibody or HCV RNA followed by a subsequent negative HCV RNA test result, without having received HCV treatment); the demographic characteristics of these are shown in *Table 4.1*. The remaining 123 individuals of the 2,598 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.

The analyses described in the remainder of this section on HCV are therefore limited to those individuals who could be definitively classified as having either chronic (n=1,362) or acute (n=576) HCV infection at the time of the primary HCV diagnosis. Most of these people with chronic or acute HCV infection were male (83% and 99%, respectively) and the majority originated from the Netherlands (chronic: 814/1,362 [60%]; acute: 451/576 [78%]) (*Table 4.1*). Sixty-two percent of the individuals ever registered and who had acquired HIV through injecting drug use (IDU) had a chronic HCV infection (450 of the total 728 people who use/used injecting drugs [PWUID]). In the men who have sex with men (MSM) HIV transmission group, 4% had a chronic HCV infection (617 of the total of 14,541 MSM) and 4% had a documented acute HCV infection (543 of the total of 14,541 MSM). Finally, compared with individuals with an acute primary HCV infection, those with spontaneous clearance of HCV were less likely to be male, originate from the Netherlands or belong to the MSM group (*Table 4.1*).

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



The HCV genotype was determined and documented in the clinical records of 1,232 of the 1,362 individuals (90%) with a chronic HCV infection. For 25 of these 1,232 genotype determinations, the genotype could not be successfully identified. Of those individuals for whom genotype determination was successful, the majority (61%) were infected with HCV genotype 1 (n=755); 61% were infected with genotype 1a (n=462) and 13% with genotype 1b (n=96). Five percent were infected with HCV genotype 2 (n=61), 16% were infected with genotype 3 (n=195), and 16% with genotype 4 (n=195). One person was infected with genotype 6.

HCV genotype was also determined for 537 of the 576 individuals (93%) with an acute HCV infection, with unsuccessful genotype identification in 22 out of these 537 individuals. Individuals with an acute HCV infection were most likely to be infected with either genotype 1 (67%) (n=359) or genotype 4 (21%, n=114). Of the 359 infected with genotype 1, 295 (82%) were infected with genotype 1a and 15 (4%) with genotype 1b. For the remaining 49 individuals with genotype 1, no differentiation between genotype 1a or 1b was available.

Table 4.1: Demographic characteristics of HIV/hepatitis C virus (HCV) co-infected individuals registered in the SHM database, 1998-2017.

	Total	Chronic HCV	Acute HCV	Spontaneous clearance
Total number of individuals screened for HCV	23,837	1,362	576	533
Male gender, n (%)	19,554 (82)	1,127 (83)	568 (99)	417 (78)
Region, n (%)				
Netherlands	13,590 (57)	814 (60)	451 (78)	274 (51)
Europe	1,578 (7)	208 (15)	46 (8)	75 (14)
Sub-Saharan Africa	3,279 (14)	45 (3)	8 (1)	57 (11)
Caribbean/South America	2,797 (12)	87 (6)	34 (6)	65 (12)
South-east Asia	828 (3)	44 (3)	12 (2)	16 (3)
Other	1,765 (7)	164 (12)	25 (4)	46 (9)
HIV transmission route, n (%)				
Men who have sex with men	14,541 (61)	617 (45)	543 (94)	255 (48)
Heterosexual	7,044 (30)	155 (11)	18 (3)	99 (19)
People who use/used injecting drugs	728 (3)	432 (32)	6 (1)	111 (21)
Other	1,524 (6)	158 (12)	9 (2)	68 (13)
cART, n (%)	22,645 (95)	1,307 (96)	571 (99)	507 (95)
HCV genotype (GT), n (%*)				
Total determined		1,232	537	
GT 1		755 (61)	359 (67)	
1a		*462*	*295*	
1b		*96*	*15*	
1c, 1a/b or not further specified		*197*	*49*	
GT 2		61 (5)	7 (5)	
GT 3		195 (16)	14 (3)	
GT 4		195 (16)	114 (21)	
Other		1 (0.1)	1 (0.2)	
Indeterminate		25 (2)	22 (4)	
Deaths, n (%)	2,489 (10)	291 (21)	21 (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.*

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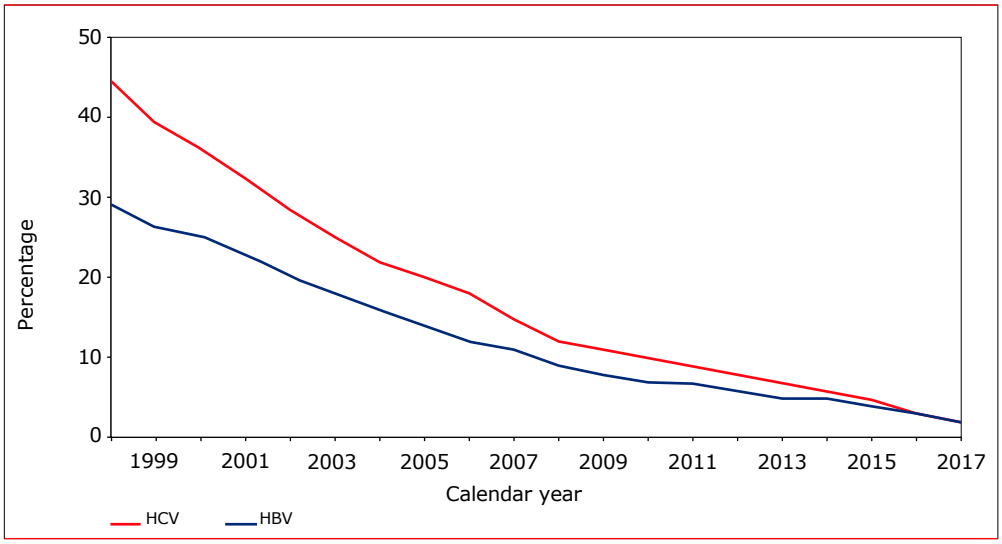
Changes over time

Testing for HCV over time

Screening for HCV infection among HIV-positive individuals ever registered has increased over calendar time. In 1998, 44% of the HIV-positive individuals in care had not 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 2017, only 2% of the individuals in care had not been screened for HCV co-infection (*Figure 4.2*). Unknown HCV status was relatively more common among individuals with heterosexually acquired HIV (4.1%) or with an unknown route of HIV acquisition (4.5%) and relatively less common among MSM (1.8%). Additionally, the HCV co-infection status was known for all individuals with injecting drug use as the reported mode of HIV acquisition.

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



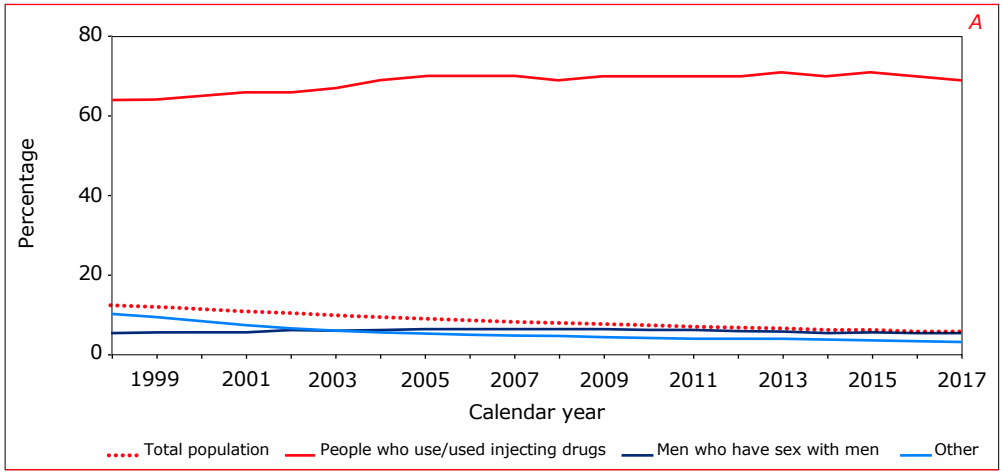
Legend: HBV=hepatitis B virus; HCV=hepatitis C virus.

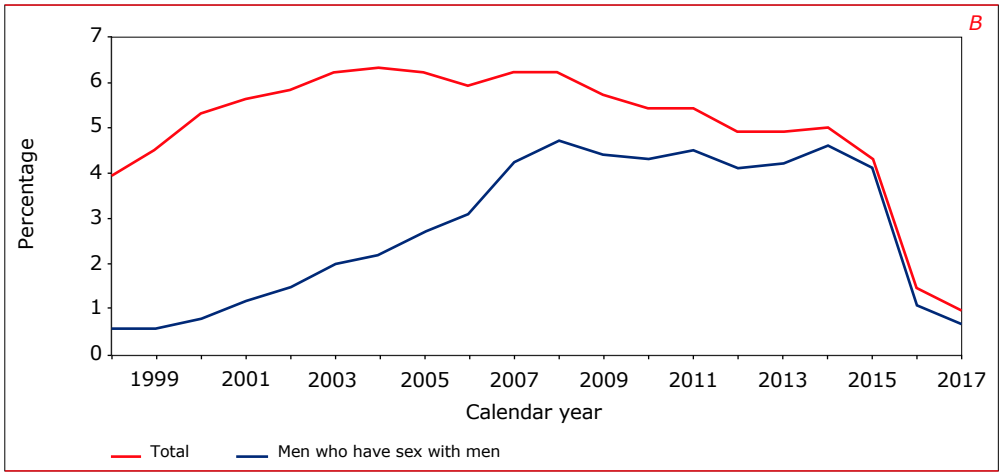
Prevalence of chronic HCV co-infection in individuals per calendar year

The overall prevalence of ever being diagnosed with a chronic HCV co-infection (defined as the proportion of individuals who tested positive for HCV RNA for at least six months) among HIV-positive individuals ever registered decreased

from 12.5% in 1998 to 5.8% in 2017, 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 64% and 71% (*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 whether the diagnosis was 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 3.9% in 1998 and 6.2% in 2007, but dropped to 1.0% in 2017. In MSM, the highest proportion of HCV RNA positivity was observed in 2008, when 4.7% of the men had a positive HCV RNA test result; by 2017, the proportion of positive HCV RNA tests in this group had decreased sharply to 0.7%.

Incidence of acute HCV infection over time

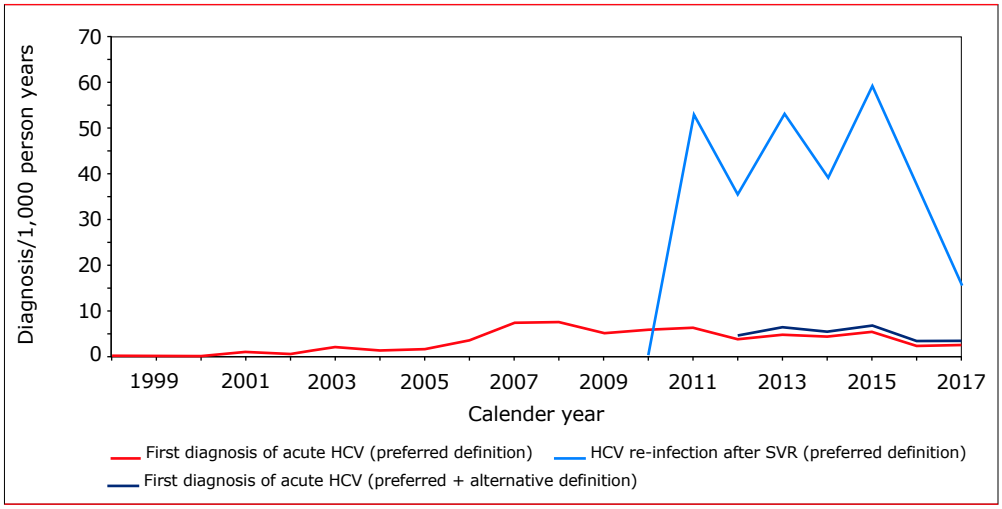
For the purpose of this analysis, the definition of acute HCV infection included cases of both primary acute HCV infection (first diagnosis of HCV) and HCV re-infection. The definition of acute HCV is consistent with the definition according to the NEAT preferred criteria[1]. In addition, in this year's report, we expanded this definition with alternative criteria[1,2]. In brief, this definition is based on detectable HCV-RNA in association with an acute rise in 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 regimens in the last 6 months. Since SHM has routinely collected ALT levels since 2012, the incidence of acute HCV according to the alternative criteria is reported from 2012 onwards.

Appendix *Table 4.1* presents the number of acute HCV infections and re-infections per calendar year. There were important differences in the incidence of the first diagnosis of acute HCV infection in terms of HIV transmission categories. The vast majority of acute HCV infections occurred in MSM (543/576 [94%]). In IDU or former IDU, in contrast to the high prevalence of HCV, the overall incidence was low (3.6/1,000 person years [PY], 95% confidence interval [CI] 1.60-7.20). This is probably due to the high background prevalence of HCV infection in former IDU, together with injecting drug use having become very uncommon in the Netherlands. Among individuals who acquired HIV heterosexually, the overall incidence of acute HCV was 0.3/1000 PY (0.2-0.5).

Figure 4.4 shows the incidence of acute HCV infection among MSM over time. The overall rate of acute HCV infection in this group was 4.2 per 1,000 PY (95% CI 3.9-4.6). Based on the preferred NEAT acute HCV definition, this incidence increased from 0 diagnoses per 1,000 PY in 1998 to 5.2 diagnoses per 1,000 PY in 2015, with a peak in 2007 and 2008 of 7.3 and 7.4 acute HCV infections per 1,000 PY, respectively.

In 2017, the incidence of the first diagnosis of acute HCV infection was 2.4 per 1,000 PY. As expected, incidence rates among MSM were higher when the preferred and alternative acute HCV case definitions were combined, the incidence rate was 4.5 diagnoses per 1000 PY in 2012, 6.6 in 2015 and 3.3 in 2017.

Figure 4.4: *Incidence of acute hepatitis C infection among men who have sex with men, per calendar year. Note: Low numbers in 2017 may be due to a delay in data collection.*



Legend: *HCV=hepatitis C virus; SVR=sustained virological response.*

Treatment for HCV infection

The primary aim of HCV treatment is to achieve a sustained virological response (SVR)[12]. Treatment for HCV infection has changed markedly in recent years. In the past, HCV 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 direct-acting antivirals (DAAs) active against HCV genotype 1, became available in the Netherlands[13,14]. These agents were subsequently used as part of triple therapy that included one of these 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 HCV-infected individuals, including those with severe liver fibrosis and cirrhosis. Later, in November 2015, sofosbuvir was made available for all HCV-infected individuals regardless of their fibrosis

status, and shortly after additional novel DAAs became available such as new HCV NS3/4A protease inhibitors (simeprevir, paritaprevir and grazoprevir), NS5A inhibitors (daclatasvir, ledipasvir, ombitasvir, elbasvir and velpatasvir) and an NS5B polymerase inhibitor (dasabuvir). *Table 4.2* provides an overview of all DAA-containing HCV treatment combinations currently available in the Netherlands[15].

Table 4.2: *Overview of treatment regimens available as of 31 December 2017, including direct-acting antivirals (DAAs), active against hepatitis C virus (HCV) in the Netherlands.*

DAA/HCV treatment combination*	Available since	HCV genotypes covered	Treatment duration
Sofosbuvir+RBV+PEG-IFN	2014	All	12 weeks
Sofosbuvir+RBV	2014	2+3	12-24 weeks
Simeprevir+RBV+ PEG-IFN	2014	1+4	24-48 weeks
Simeprevir+sofosbuvir +/- RBV	2014	1+4	12-24 weeks
Daclatasvir+sofosbuvir+/- RBV	2015	1,2,3,4	12-24 weeks
Daclatasvir+RBV+PEG-IFN	2015	1,2,3, 4	24-48 weeks
Ledipasvir/sofosbuvir+/- RBV	2015	1, 3, 4	12-24 weeks
Paritaprevir/r/ombitasvir	2015	1,4	12-24 weeks
Paritaprevir/r/ombitasvir /dasabuvir	2015	1	12-24 weeks
Elbasvir/grazoprevir	2016	1,4	12 weeks
Sofosbuvir/velpatasvir	2016	All	12 weeks

**Boceprevir and telaprevir were only temporarily available and therefore not included in this table.*

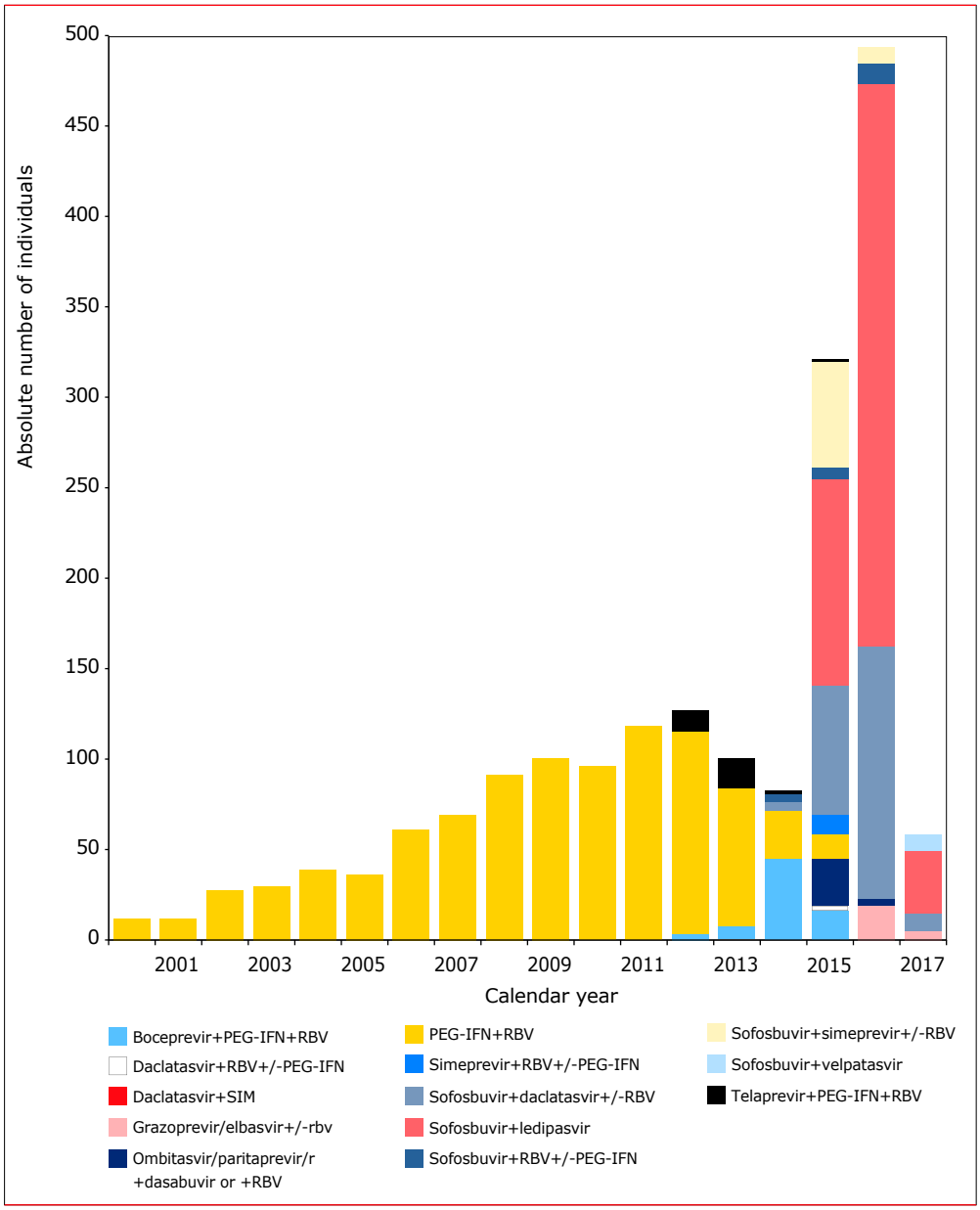
Legend: *DAA=direct-acting antiviral agent; HCV=hepatitis C; RBV=ribavirin; PEG-IFN=pegylated interferon; r=ritonavir.*

Figure 4.5 shows the absolute number of individuals who have started HCV treatment per calendar year. In total, 1,507 individuals have ever received HCV treatment; of those, 323 have received HCV treatment more than once, including people who were unsuccessfully treated and those who re-acquired HCV after previously successful treatment.

Treatment with IFN alpha/PEG-IFN alpha plus ribavirin and boceprevir or telaprevir

The outcome of 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 will no longer be included in the current report.

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



Note: Low numbers in 2017 may be due to the use of data from the database lock of 31 December 2017, rather than that of May 2018 as in previous years, possibly resulting in a larger backlog in data collection.

***Legend:** RBV=ribavirin; PEG-IFN=pegylated interferon; r=ritonavir.*

Treatment with novel DAAs

In total, at the time of database lock on 31 December 2017, 838 individuals were known to have started a DAA regimen, 13 of whom had been treated twice with a DAA regimen. Reasons for receiving DAA treatment twice were: re-infection (n=3), no SVR achieved during the first episode of DAA treatment (n=8), and patient's decision to discontinue the first episode of DAA treatment (n=2). Of these 838 individuals, 9 had started their treatment in 2014, 292 in 2015, and the remaining 537 had started in either 2016 or 2017.

Table 4.3 provides an overview of the DAAs used. The most frequently-used DAA regimens were 1) sofosbuvir plus ledipasvir +/- RBV (n=461), which was prescribed to 311 individuals with HCV genotype 1 and 114 with genotype 4, and 2) sofosbuvir plus daclatasvir +/- RBV (n=228), which was prescribed to 128 individuals with genotype 1 and 51 with genotype 3. Finally, 16 individuals who had previously been treated with DAAs had died, with liver disease being the reported underlying cause of death in 4 individuals.

Table 4.3: Overview of responses (SVR12) to regimens containing novel direct-acting antivirals (DAAs) used by hepatitis C/HIV co-infected individuals in care in the Netherlands, based on data available as of 31 December 2017.

Regimen	n	HCV genotype (GT)	Severe chronic liver disease (see definition)	Treatment completed and SVR12* (n/total number individuals with available HCV RNA test results)	Treatment completed and SVR12* among individuals with severe chronic liver disease (n/total number individuals with available HCV RNA test results)
Sofosbuvir+ledipasvir+/-RBV	461		130	418/430 (97%)	119/123 (97%)
GT 1		311			
GT 2		5			
GT 3		6			
GT 4		114			
other		11			
unknown		14			
Sofosbuvir+daclatasvir+/-RBV	228		103	206/213 (97%)	91/93 (98%)
GT 1		128			
GT 2		9			
GT 3		51			
GT 4		23			
other		6			
unknown		11			
Sofosbuvir+simeprevir +/-RBV	66		53	64/64 (100%)	52/52 (100%)
GT 1		51			
GT 3		1			
GT 4		13			
other		1			
Sofosbuvir++RBV+/- PEG-IFN	19		8	17/17 (100%)	7/7 (100%)
GT 1		1			
GT 2		12			
GT 3		2			
GT 4		2			
other		1			
unknown		1			

Regimen	n	HCV genotype (GT)	Severe chronic liver disease (see definition)	Treatment completed and SVR12* (n/total number individuals with available HCV RNA test results)	Treatment completed and SVR12* among individuals with severe chronic liver disease (n/total number individuals with available HCV RNA test results)
Paritaprevir/r/ombitasvir +/- dasabuvir or RBV	32		9	30/32 (94%)	9/9 (100%)
GT 1		14			
GT 4		5			
other		3			
unknown		10			
Simeprevir+PEG-IFN+RBV	10		2	10/10 (100%)	2/2 (100%)
GT 1		4			
GT 4		5			
unknown		1			
Daclatasvir+RBV +/- PEG-IFN	4		2	3/3 (100%)	1/1 (100%)
GT 1		2			
GT 3		1			
unknown		1			
Simeprevir+daclatasvir	1		1	1/1 (100%)	1/1 (100%)
GT 1		1			
Grazoprevir/elbasvir	22		5	18/19 (95%)	5/5 (100%)
GT 1		13			
GT 4		8			
unknown		1			
Sofosbuvir/velpatasvir	8		3	1/1 (100%)	0
GT 1		2			
GT 2		1			
GT 3		2			
GT 4		2			
unknown		1			
Total	**851**		**316**	**768/790 (97%)**	**287/293 (98%)**

**SVR12=sustained virological response defined as a negative HCV RNA test result 12 weeks after treatment discontinuation.*

***Legend:** PEG-IFN=pegylated interferon; RBV=ribavirin; r=ritonavir; GT=HCV genotype; DAA=direct-acting antiviral agent; SVR12=sustained virological response result 12 weeks after treatment discontinuation.*

Outcome

HCV RNA data were collected up to 31 December 2017. At that point, 790 individuals had completed treatment with one of these regimens, and sufficient time had elapsed since discontinuation of treatment to enable calculation of the SVR12 (sustained virological response defined as a negative HCV RNA test result 12 weeks after treatment discontinuation) rate (*Table 4.3*). In total, 768 of these 790 individuals achieved an SVR12 (97%), with the same rate for both treatment-naive and pre-treated individuals. The SVR rate was 98% in people with chronic liver disease. Twenty-two individuals failed to achieve an SVR12, and failure occurred among all genotypes. This group was not specifically different from the group that did achieve an SVR and, due to the small group size, it is not possible to draw any further conclusions regarding failure to achieve an SVR.

Continuum of care for those with diagnosed HCV co-infection

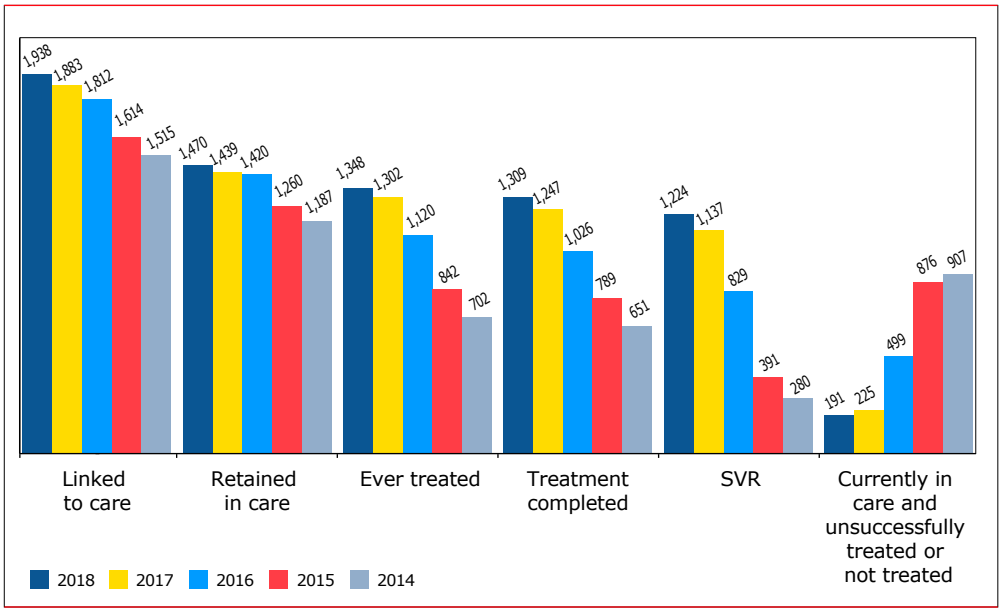
Figure 4.6 shows the continuum of care for individuals with an HCV co-infection, based on the number known to be in care as of 31 December 2017, with data from previous monitoring reports for 2014 (data cut-off 1 June 2014), 2015 (data cut-off 15 September 2015), 2016 (data cut-off 1 May 2016) and 2017 (data cut-off 1 May 2017) shown for comparison. Out of a total of 1,938 individuals linked to HIV care and diagnosed with HCV, 1,470 (76%) were retained in care, and of these, 1,348 (92%) had ever received treatment for HCV. Of the 1,348 individuals treated for HCV, 1,309 (97%) had completed HCV treatment and had data available with which HCV treatment response could be calculated (SVR12 for the DAAs and SVR24 for the older regimens). Overall, 1,224 of the 1,309 (94%) people who completed treatment had achieved an SVR, including those who had achieved an SVR on a pegylated interferon-containing regimen.

As a result, 246 of the 1,470 individuals (21%) who were alive and in care as of 31 December 2017 in one of the Dutch HIV treatment centres were still in need of treatment:

- 122 individuals had not been not treated for HCV; 90% of these were receiving cART for HIV, and 87% of these 122 individuals had an HIV RNA <100 copies/ml;
- 67 had been unsuccessfully treated for HCV;
- 57 were still being treated or had insufficient time after treatment discontinuation to allow SVR calculation.

All 57 individuals in whom SVR could not yet be calculated due to insufficient time since treatment discontinuation had been treated with novel DAA combinations. For that reason, we extrapolated the observed DAA SVR rate of 97% and assumed that 97% of these 57 individuals (n=55 individuals) will eventually be successfully treated. This resulted in an estimated number of 246-55=191 individuals who remain untreated or unsuccessfully treated.

Figure 4.6: Hepatitis C continuum of care.



Legend: SVR=sustained virological response.

Compared with the continuum of care presented in SHM's 2017 monitoring report, the continuum of care in this year's report shows that an additional 46 individuals have received HCV treatment, resulting in an increase in HCV/HIV co-infected individuals ever having been treated for HCV from 59% in 2014 to 92% in this year's report. Furthermore, since last year's report, an additional 87 individuals have documented evidence of cure. Finally, the total number of individuals who remain in need of HCV treatment has decreased from 225 in the 2017 monitoring report to 191 in the present report.

HCV re-infection

Re-infection with HCV following successful treatment has been reported mainly in HIV-positive MSM[17,18], with high rates of re-infection found among MSM in the Netherlands, Germany[19] and the United Kingdom[20].

To identify possible HCV re-infection among HCV co-infected individuals, we selected the 1,333 individuals who had initially achieved an SVR after ever having received any type of HCV treatment. For these 1,333 individuals, the incidence of HCV reinfection was reported between 2010 and 2017. Follow-up time was calculated from the date of SVR, or if the SVR had been achieved before 2010, from 1 January 2010 onward, until the earliest date of HCV re-infection, death, or last known contact.

Of these 1,333 individuals, 151 (11%) had documented detectable HCV RNA levels after having an earlier documented SVR (*Appendix Table 4.1*), indicative of HCV re-infection. For 61 of these 151 individuals (40%), an HCV genotype switch was reported, providing additional evidence of HCV re-infection.

The majority of individuals who became newly HCV RNA-positive after successful treatment for HCV (based on SVR) were MSM (134/151, 89%). A further six were PWUID (6/151, 4%). For the remaining 11 individuals, the HCV transmission route was unknown. However, documented HIV transmission routes were heterosexual contact (n=2), blood-blood contact (n=5) and unknown (n=4). Out of the 151 individuals with a re-infection, 108 were re-treated; of those, 83 were re-treated with a DAA-containing regimen. In total, 89 of these 108 individuals achieved an SVR. Among the 83 individuals who had been re-treated with a DAA-containing regimen, 79 achieved an SVR and for four individuals the SVR was not yet available.

The incidence of HCV reinfection was 31 re-infections per 1,000 PY (95%: 25-37) for the total population and 40 infections per 1,000 PY (95%: 33-48) for MSM. Because the majority of re-infections occurred among MSM, the incidence of HCV re-infection after achieving an SVR over time is shown only for MSM (*Figure 4.4*). This incidence increased from 0 to 59 infections per 1,000 PY between in 2010 and 2015 and then declined to 15 re-infections per 1,000 PY in 2017. All re-infections that were documented in 2016 and 2017 occurred in MSM.

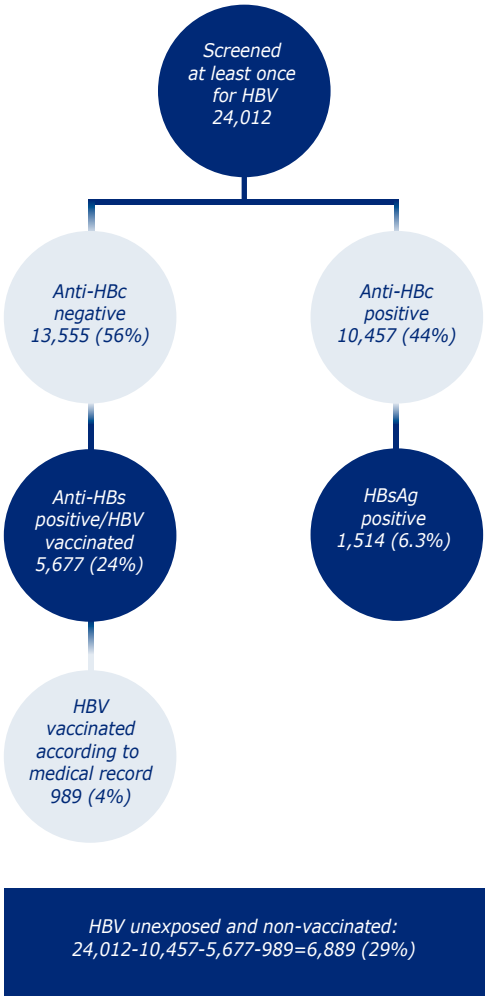
HBV

Forty-four percent of the 24,012[b] HIV-positive individuals ever registered in the SHM database and ever screened for hepatitis B core antibody (anti-HBc) tested positive during screening and thus had been exposed to HBV. The remaining 56%

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.

(n=13,555) tested negative for anti-HBc. Of these individuals, 24% (5,677) were anti-hepatitis B surface antigen-positive (anti-HBs+), indicating that they had been successfully vaccinated against HBV (*Figure 4.7*). In terms of route of HIV acquisition, this rate was 28% for MSM, 17% for heterosexuals and only 7% for PWUID. For 989 individuals (4%) who had not been tested for anti-HBs, the HIV-treating physician had noted HBV vaccination in the medical record; 751 of these individuals were MSM.

Figure 4.7: *Flowchart of HIV-positive individuals tested at least once for hepatitis B.*



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

Overall, therefore, approximately 29% of the HIV-positive individuals ever registered remain at risk of HBV infection because they have not been exposed to HBV, have not been vaccinated, or have been unsuccessfully vaccinated (24,012 minus 10,457 exposed minus 5,677 with serological evidence of successful vaccination minus 989 former successful vaccination otherwise documented=6,889 [29% of 24,012]).

Furthermore, 21% of HIV-positive MSM remain at risk (100% minus 45.3% exposed minus 28.5% serological evidence of successful vaccination minus 5.2% former successful vaccination otherwise documented=21%). MSM, in particular, should be offered 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[21,22]. Data from SHM show that, of those people who remain at risk of acquiring HBV, 56% are currently being treated with a cART regimen that includes TDF or TAF; for MSM this prevalence is 63%.

HBV co-infection (defined as two or more consecutive positive test results for HBsAg over a period of at least six consecutive months) was found in 1,514 of the 24,012 (6.3%) HIV-positive individuals ever screened for HBV. As for HCV co-infection, this rate is considerably higher than that of HBV infection in the general Dutch population. Individuals co-infected with HBV were predominantly male (1,306/1,514, 86%), in line with those co-infected with HCV (*Table 4.4*). However, compared to 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 PWUID.

Table 4.4: Demographic characteristics of HIV-positive individuals with an active chronic hepatitis B virus (HBV) co-infection registered in the SHM database, 1998-2017.

	Total, n (%)	Hepatitis B surface antigen (HBsAg) positive, n (%)
Total number of individuals screened for HBV	24,012	1,514
Male gender	19,576 (82%)	1,306 (86%)
Region		
Netherlands	13,641 (57%)	748 (49%)
Europe	1,579 (7%)	9 (6%)
Sub-Saharan Africa	3,400 (14%)	343 (23%)
Caribbean/South America	2,807 (12%)	161 (11%)
South-east Asia	842 (4%)	66 (4%)
Other	1,743 (7%)	104 (7%)
HIV transmission group		
Men who have sex with men	14,475 (60%)	899 (59%)
Heterosexual	7,253 (30%)	436 (29%)
Injecting drug use	730 (3%)	69 (5%)
Other	1,554 (6%)	110 (7%)
cART	22,774 (95%)	1,441 (95%)
Deaths	2,646 (11%)	268 (18%)

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

Testing for HBV infection over time

Screening for HBV infection in HIV-positive individuals in care has improved over calendar time. In 1998, 29% of the individuals had not been screened for the presence of HBV infection (*Figure 4.2*). Since then, the proportion of HIV-positive individuals with an unknown HBV status has decreased markedly, with just 2% of all HIV-positive individuals in care having an unknown HBV status in 2017 (*Figure 4.2*).

Prevalence

The overall prevalence of chronic HBV co-infection among HIV-positive individuals in care decreased from 9.8% in 1998 to 5.8% in 2017. The highest prevalence was found in MSM: in 1998, 11% of MSM had chronic HBV co-infection, and this figure decreased to 6.0% in 2017 (*Figure 4.8*). This decreasing prevalence of chronic HBV co-infection could be the result of increasing HBV vaccination rates (*Figure 4.9*), together with the preventive effect of HIV treatment with a cART regimen that includes TDF/TAF.

Figure 4.8: Prevalence of chronic active hepatitis B co-infection per calendar year.

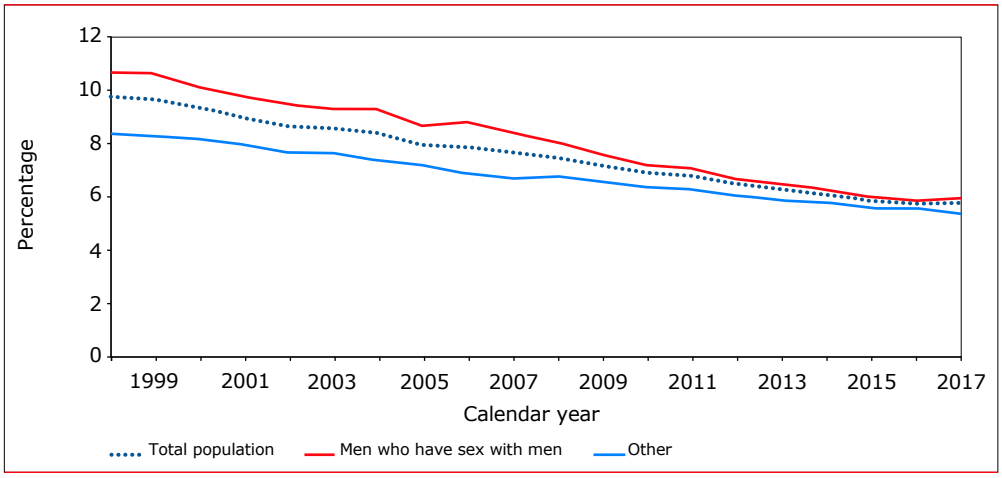
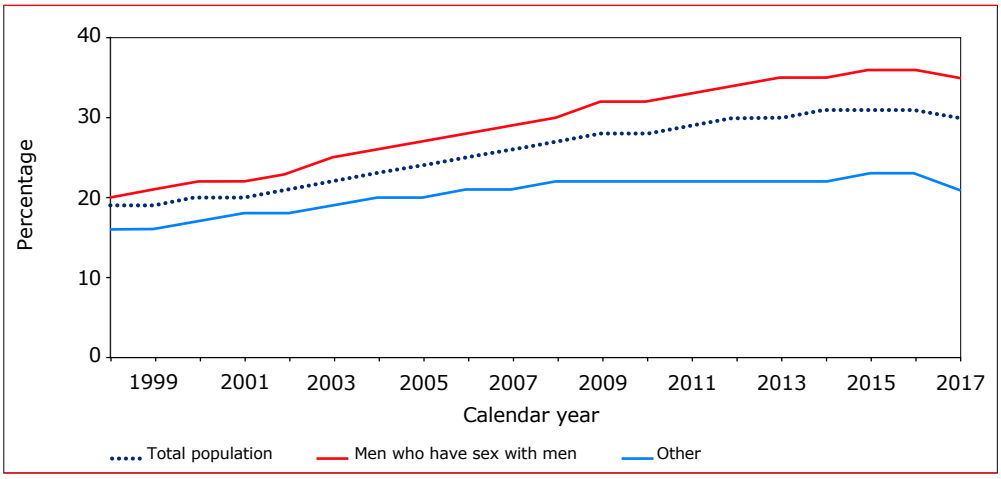


Figure 4.9: Prevalence of hepatitis B vaccination per calendar year.



Treatment for chronic HBV infection

The aim of treatment for chronic HBV infection is to reduce virus replication. As HBV DNA is the parameter most directly influenced by therapy with either nucleoside or nucleotide analogues, HBV DNA undetectability is the best surrogate marker for treatment response, and persistent lowering of HBV DNA levels to less than 20 IU/ml has also been shown to delay progression of liver fibrosis to

cirrhosis[23]. Chronic HBV infection is defined by the presence of hepatitis B surface antigen (HBsAg+). Lowering HBV DNA levels may result in HBsAg negativity in a 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 HBeAg 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 a clinically important lowering of HBV DNA, thereby lowering the risk of progression of liver fibrosis. Several antiviral agents used for treatment of HIV, such as lamivudine, emtricitabine and particularly TDF/TAF, are also active against HBV.

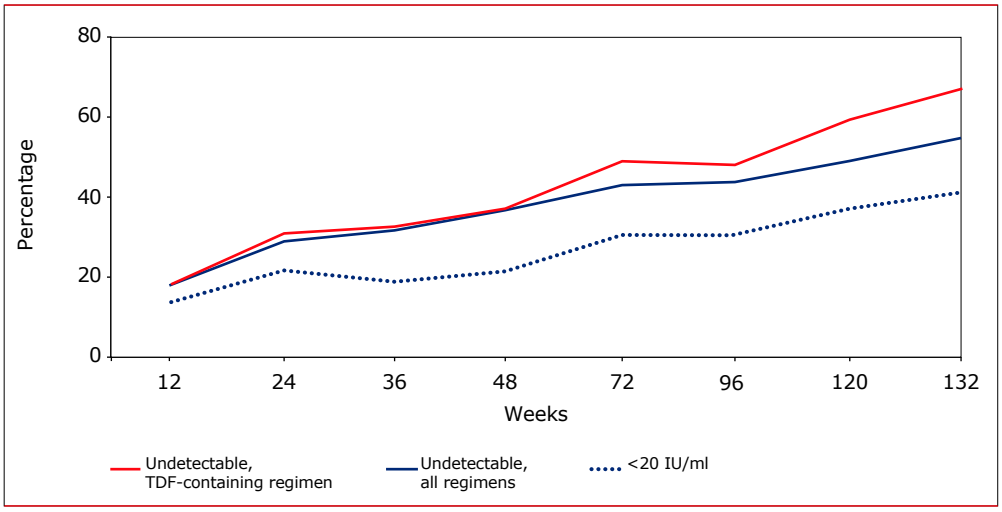
Of the 1,514 individuals with HIV in the SHM database who were co-infected with chronic HBV, 1,438 (95%) had ever received a cART regimen that included one or more agents with activity against both HIV and HBV. Reasons for the remaining 76 individuals not having received anti-HBV treatment included: death before being able to start treatment (n=16), recent entry into care (n=4), loss to follow up (n=42) and lack of sufficient information (n=14).

Most people treated for HBV (n=756/1,438, 53%) initially received lamivudine. Of those treated with lamivudine, 294 (39%) switched to a regimen containing tenofovir plus lamivudine after a median of 1.7 years (IQR 0.5-4.2) of prior exposure to lamivudine monotherapy for HBV and 222 (29%) switched to a regimen containing tenofovir plus emtricitabine after a median of 1.5 years (IQR 0.5-4.0). The remaining 240 individuals did not have a documented switch to a regimen containing TDF or TAF, 169 of whom were still in care in 2017. For 666 of 1,438 individuals (46%), their initial cART regimen included TDF and one additional agent with activity against HBV; for 114 of these 666 individuals (17%), the additional agent was lamivudine, and for 552 individuals (83%) the additional agent was emtricitabine; another 16 individuals started with a TAF-containing regimen.

In most HBV mono-infected individuals, a persistently HBeAg-negative chronic HBV infection with undetectable HBV DNA confers a favourable long-term outcome, with low risk of cirrhosis and HCC[24]. We therefore examined the HBV DNA levels in the population of individuals co-infected with HIV and HBV. HBV DNA measurements were available for 1,063 (74%) out of the 1,438 treated HBV co-infected individuals. *Figure 4.10* shows the proportion 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). Twelve weeks after the start of HBV treatment, 18% of the individuals had an undetectable HBV DNA level based on the detection limit of the assay used at the time of measurement, and 14% had an HBV DNA level less than 20 IU/ml. The percentage of individuals with an undetectable HBV DNA level was 37% after the first year of treatment, with an increase to 44% two years after the start of treatment and 55% three years after the start of treatment. The percentage of people with an HBV DNA level less than 20 IU/ml was 22% one year after the start of treatment, 31% after two years, and 41% after three years. In terms of individuals who were using a tenofovir-containing cART regimen, 67% of individuals with HBV DNA follow-up data had an undetectable HBV DNA level after three years of receiving treatment (*Figure 4.10*).

Figure 4.10: *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 since the start of HBV treatment, regardless of HBeAg status.*



Legend: *TDF=tenofovir.*

Among the 1,438 individuals whose cART regimen ever included one or more agents with activity against HBV, 533 of the 1,052 people with an available test result (51%) had a documented positive test result for HBeAg. Of these 533 individuals, 368 (69%) were re-tested, with 188 (51%) converting from HBeAg positivity to HBeAg negativity and 107 (29%) developing HBe antibodies. In total,

520 (53%) of the 982 individuals with HBsAg serology available during HBV treatment and who were HBsAg positive at time of treatment initiation became HBsAg negative. In addition, 136 (15%) of the 882 individuals with a documented negative HBs-antibody test result became HBs-antibody-positive, i.e., underwent an HBs seroconversion.

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, were available for 1,600 of the 1,938 individuals with chronic or acute HCV co-infection and for 1,149 of the 1,514 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 667 (34%) of the individuals with HCV co-infection, and in 396 (26%) of those with HBV co-infection (*Table 4.5*). Definitive severe chronic liver disease was documented for 165 individuals with an HCV co-infection and 75 with an HBV co-infection.

Table 4.5: *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	1,983	1,514
Severe chronic liver disease#	667 (34)	396 (26)
HCC	20 (1.0)	26 (1.7)
Liver transplantation	2 (0.1)	1 (0.07)
Deaths from any cause*	312 (16)	268 (18)
Liver-related deaths	69 (3.5)	47 (3.1)

**including liver-related death*

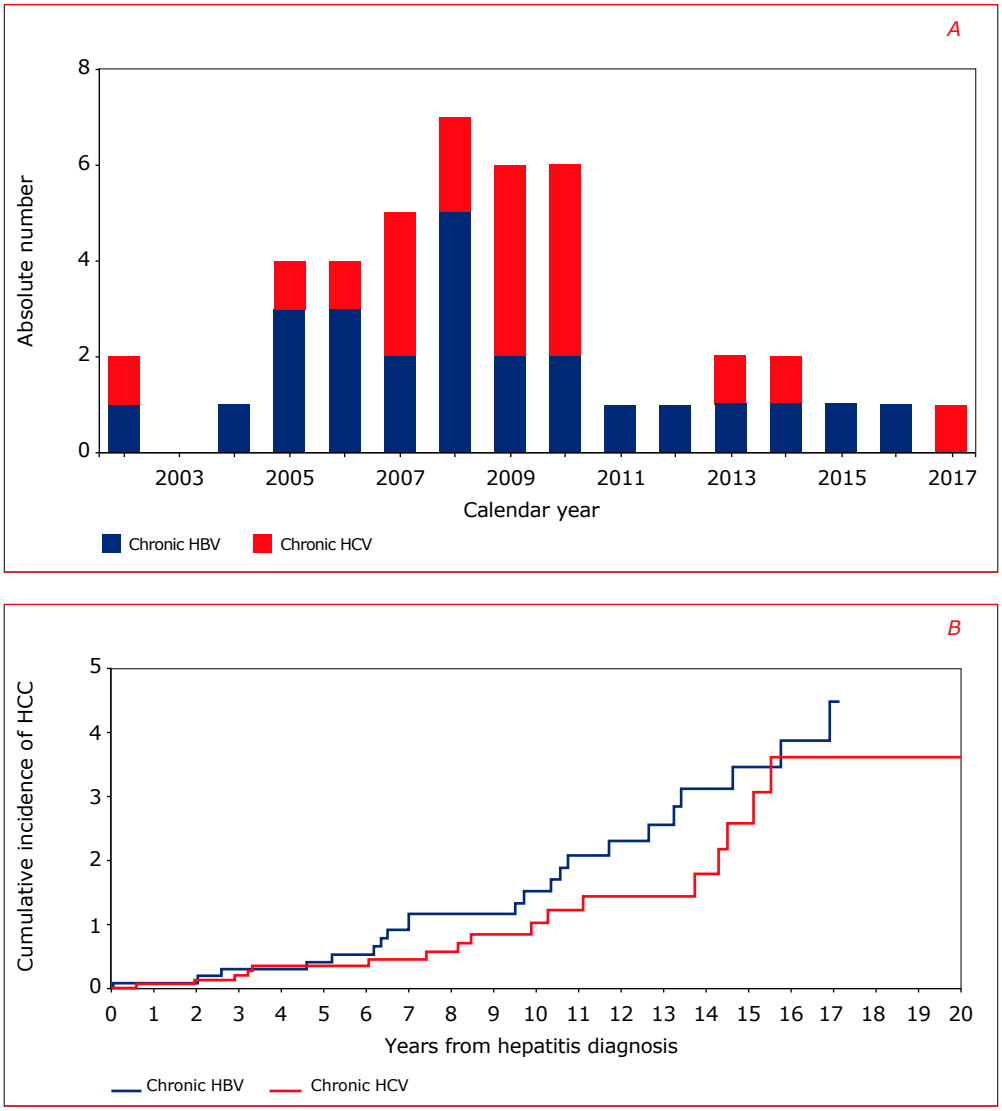
#including presumptive and definitive liver disease

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

Figure 4.11A 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, of whom 15 were born in the Netherlands. HCC was found in 26 individuals (1.7%) with a chronic HBV co-infection, 15 of whom were born in the Netherlands, 7 in sub-Saharan Africa, and 1 each in South America, Asia, the United States, and Australia.

Figure 4.11B shows the cumulative incidence of HCC. It should be noted, however, that the time between diagnosis of hepatitis co-infection and HCC was not significantly different between individuals with an HCV co-infection and those with an HBV co-infection. Ten years after a known diagnosis of viral hepatitis, HCC had developed in 1.7% (95% CI 0.9-2.7%) of individuals with HCV co-infection and in 1.2% (95% CI 0.6-2.3%) of those with chronic HBV co-infection. It should be noted that the exact moment of acquiring the hepatitis infection is unknown and that the infection with HBV or HCV could have existed for a longer period of time than was accounted for in these analyses.

Figure 4.11: A) Absolute number of reported HCC cases over time and B) cumulative incidence of hepatocellular carcinoma (HCC) among individuals co-infected with HIV and hepatitis C (HCV) or hepatitis B (HBV), from date of hepatitis diagnosis onwards. The Kaplan-Meier estimate was used to determine the time to HCC. Follow-up time was measured from the date of hepatitis diagnosis to the date of last contact, diagnosis of HCC, or 31 December 2017.



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

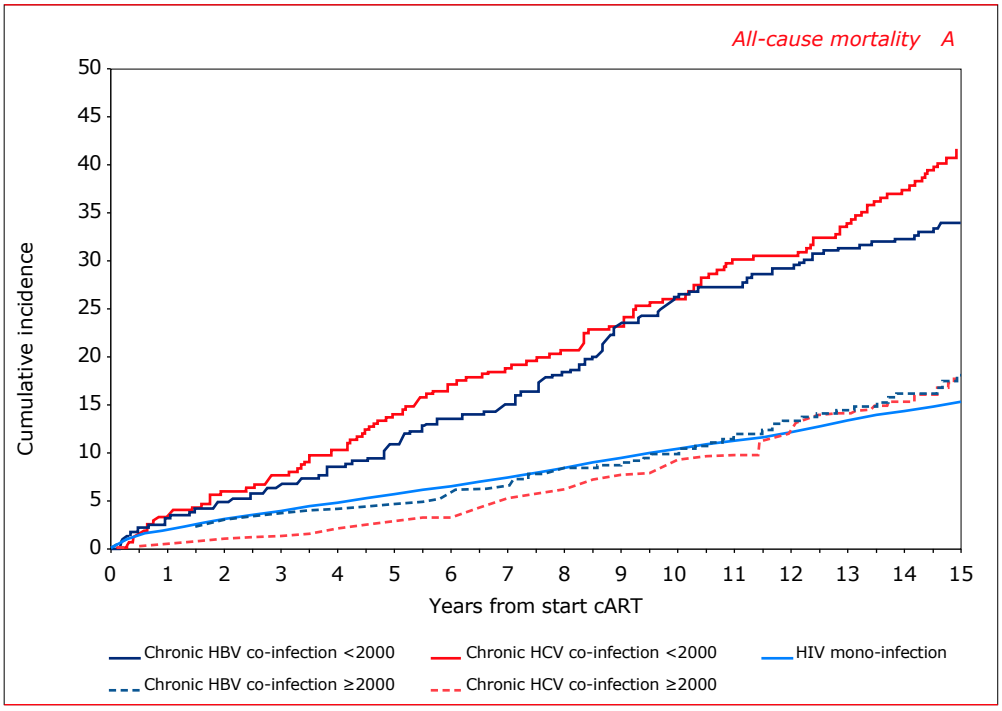
Mortality

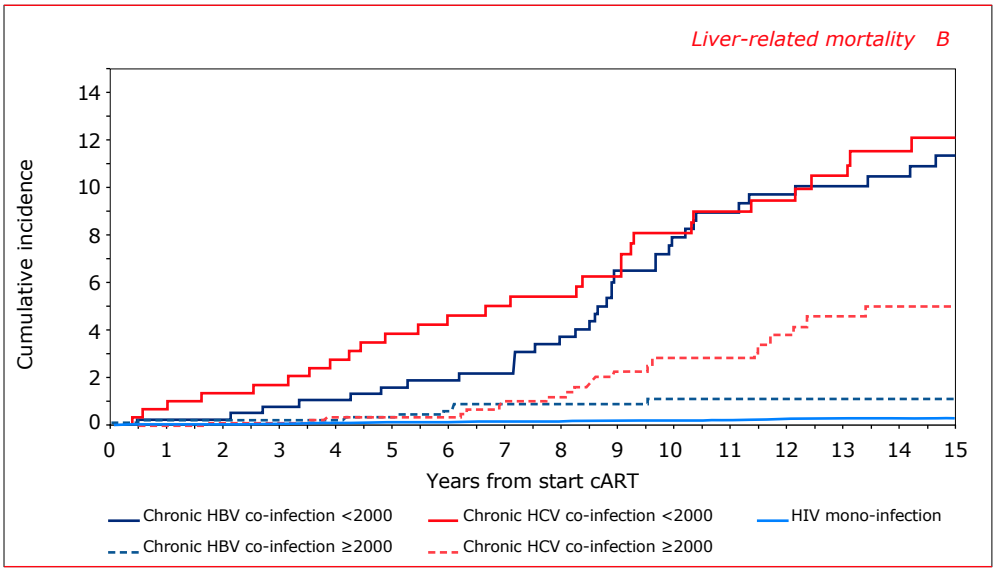
All-cause mortality

The overall rate of death from any cause was 16% for the 1,938 individuals with an HCV infection and 18% for the 1,514 individuals with an HBV infection (*Table 4.5*). The cumulative incidence of death from any cause was higher among people who were diagnosed with HCV or HBV before 2000 compared with those who were diagnosed in later calendar years (*Figure 4.12A*). When the risk of death from any cause was adjusted for differences in demographic and clinical characteristics (age at HIV diagnosis, gender, region of origin, HIV transmission risk group, calendar year of cART initiation, CD4 count and HIV RNA level at time of cART initiation, alcohol use and smoking and time since HIV diagnosis), the overall risk of death was significantly higher in individuals with HIV and HCV co-infection diagnosed before 2000 than in HIV mono-infected individuals. For people with an HCV co-infection diagnosed after 2000, the adjusted overall risk of death was non-significantly higher than in HIV mono-infected individuals.

Moreover, after adjustment for differences in demographic and clinical characteristics, the overall risk of death was significantly higher for both individuals with a chronic HBV co-infection diagnosed before 2000 and those diagnosed with HBV after 2000 than for HIV mono-infected individuals (*Table 4.6*).

Figure 4.12: Cumulative incidence of (A) all-cause mortality and (B) liver-related mortality, stratified by calendar year period. The Kaplan-Meier estimate was used to determine the time to death. The follow-up time was measured from the date of HIV diagnosis to the date of last contact, death or 31 December 2017.





Legend: cART=combination antiretroviral therapy; HCV=hepatitis C virus; HBV=hepatitis B virus.

Liver-related mortality

In total, 116 individuals co-infected with hepatitis died of a liver-related cause (*Table 4.5*). Ten years after cART initiation, 8% (95% CI 5-12) of chronically HCV co-infected individuals who were diagnosed with HCV before 2000 had died of a liver-related cause. This proportion was lower (3%; 95% CI 2-5) among individuals with an HCV diagnosis after 2000. Among those with HBV co-infection, 8% of individuals diagnosed before 2000 died of a liver-related cause (95% CI 6-12), which dropped to 3% (95% CI 2-5) in those diagnosed after 2000 (*Figure 4.12B*).

After adjustment for demographic and clinical characteristics, HBV co-infected individuals and HCV co-infected individuals diagnosed both before and after 2000 remained more likely to have a liver-related cause of death than HIV mono-infected individuals (*Table 4.6*). However, the adjusted risk of death from a liver-related cause strongly decreased in HBV co-infected individuals from a hazard ratio (HR) of 26.9 (95%: 16.0-45.2) in individuals diagnosed with HBV before 2000 to an HR of 4.09 (95%: 1.90-8.82) in individuals diagnosed from 2000 onwards. In HCV co-infected individuals, the adjusted risk of death from a liver-related cause decreased from an HR of 17.7 (95% CI: 9.30-33.5) in individuals diagnosed with HCV before 2000 to an HR of 8.75 (95%CI: 4.95-15.5) in individuals diagnosed with HCV from 2000 onwards.

Table 4.6: Adjusted hazard ratios of time from start of combination antiretroviral therapy (cART) to all-cause mortality and liver-related mortality in HIV-positive individuals with hepatitis co-infection compared with HIV mono-infected individuals. To evaluate the impact of HBV and HCV co-infection on risk of death, time on cART to death was estimated by a Cox proportional hazard model. The follow-up time was measured from the date of cART initiation until date of last contact, most recent follow-up visit, death, or 31 December 2017.

	Risk of death from any cause: hazard ratio* (95% CI)	p-value	Risk of liver-related death: hazard ratio* (95% CI)	p-value
HIV	1	<0.0001	1	<0.0001
HIV/chronic HCV, <2000	1.94 (1.58-2.40)		17.6 (9.29-33.5)	
HIV/chronic HCV, ≥2000	1.23 (0.99-1.54)		8.74 (4.95-15.48)	
HIV/chronic HBV, <2000	1.90 (1.59- 2.27)		26.9 (16.0-45.2)	
HIV/chronic HBV, ≥2000	1.27 (1.04-1.56)		4.09 (1.90-8.82)	

**adjusted for age, gender, region of origin, transmission risk group, calendar year of cART initiation, baseline CD4 and HIV RNA levels, alcohol use and smoking, and duration of HIV infection.*

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

Conclusion

Screening for HCV and HBV co-infection in the HIV-positive population in the Netherlands continues to improve over time. While, in 1998, approximately 39% of the individuals in care had not been screened for HBV or HCV co-infection, today the presence or absence of these co-infections is documented for almost all HIV-positive individuals. Six percent of HIV-positive individuals ever registered in the SHM database were documented as being chronically infected with HCV and 2.0% 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 have largely been replaced in clinical practice by a variety of novel DAAs. The number of HIV-positive individuals treated for HCV has rapidly increased. More than 800 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 lower number of HCV co-infected individuals remaining in need of HCV treatment, despite an increase in the total number of individuals currently in care compared with the numbers reported last year[16]. 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 2017. 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 probably 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 number of acute HCV infections in the past year. However, in line with earlier reports[17,20], 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 a chronic HBV co-infection. The prevalence of HBV has decreased over time as a result of increased HBV vaccination rates, together with the HBV-prophylactic effect of TDF/TAF in cART-treated individuals. Nonetheless, an estimated 29% of all HIV-positive individuals and 21% of MSM have either not been exposed to HBV or not been successfully vaccinated and may remain at risk of acquiring HBV. However, 56% of all individuals and 63% of MSM still at risk of acquiring HBV infection use a cART regimen that includes TDF/TAF and may therefore be at a substantially lower risk due to sustained chemoprophylaxis. The remaining 44% of the HIV-positive individuals ever registered and 37% of the MSM remain unprotected against HBV, which represents an estimated 12.6% of the total population of HIV-positive individuals.

In general, HIV-positive individuals co-infected with HCV or HBV are at increased risk of progression to severe liver disease[6,7]. Among the HIV-positive individuals ever registered by SHM, 34% of the chronically HCV co-infected individuals and 26% of the chronically HBV co-infected individuals had evidence of severe chronic liver disease. In both HCV and HBV co-infected individuals, we observed an increase in the proportion of individuals with hepatocellular carcinoma in relation to the duration of hepatitis infection. 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 significantly for people diagnosed after 2000.

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, there should be ongoing efforts to increase HBV vaccination rates among HIV-positive individuals who are at increased risk of acquiring HBV, particularly those who are not receiving an antiretroviral regimen containing TDF or TAF. 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 liver-related mortality among persons living with HIV. In addition, these novel regimens may have a beneficial impact on the risk of ongoing HCV transmission.

Nevertheless, regular HCV RNA screening among individuals who have been successfully treated for HCV infection is recommended to ensure early detection of new HCV infections, 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 monitor the epidemiology of these infections and the response to existing and novel treatments, but also to assess the impact of treatment on reducing the burden of morbidity and mortality from chronic liver disease.

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Appendix: supplementary table

Appendix Table 4.1: Absolute number of acute HCV diagnoses per calendar year among HIV-1 positive individuals ever registered.

	Acute primary HCV, preferred criteria	Acute primary HCV, alternative criteria	HCV re-infection	Total
≤2002	16	2	0	**18**
2003	5	0	0	**5**
2004	7	0	1	**8**
2005	8	1	1	**10**
2006	20	2	4	**26**
2007	41	1	2	**44**
2008	56	3	5	**64**
2009	41	1	7	**49**
2010	44	4	7	**55**
2011	50	6	23	**79**
2012	27	9	14	**50**
2013	44	16	18	**78**
2014	38	12	18	**68**
2015	49	17	29	**95**
2016	20	13	20	**53**
2017	15	8	8	**31**
total	**481**	**95**	**157**	**733**

Legend: HCV=hepatitis C virus

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