Hepatitis C virus infection is uncommon at baseline and during follow-up among individuals using PrEP in the Dutch national PrEP programme between 2019 and 2022

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ABSTRACT

Objectives Studies showed that men who have sex with men (MSM), including those using pre-exposure prophylaxis (PrEP), are at increased risk of hepatitis C virus (HCV) infection. We evaluated HCV prevalence and incidence, along with their associated determinants, in a cohort of PrEP-using individuals in the Netherlands.

Methods In 2019, the Netherlands launched a 5-year national programme that offers subsidised PrEP to eligible individuals. We used prospectively collected data from individuals registered in this programme between 2019 and 2022. Individuals underwent annual testing for HCV antibodies and additional HCV-RNA testing when antibodies were present. We calculated the prevalence of past/current HCV infection at first visit and overall incidence rate (IR) during follow-up. Univariable logistic and Poisson regression models were used to identify determinants associated with past/current prevalent or incident HCV infection, respectively. Behavioural factors referred to those occurring in the previous 6 months.

Results A total of 10 563 (n=10 319, 97.7% MSM) were included. At first visit, 66 of 10 563 (0.6%) had a past/current HCV infection, which was associated with older age [odds ratio (OR) per 10 years=1.57, 95% confidence interval (CI)=1.31 to 1.88], the use of PrEP before first visit (OR=3.03, 95% CI=1.79 to 5.13), receptive condomless anal sex (CAS) (OR=2.73, 95% CI=1.25 to 5.98), chemsex (OR=2.44, 95% CI=1.49 to 3.99) and injecting drug use (IDU) (OR=6.61, 95% CI=2.35 to 18.61). Among 9851 individuals contributing to 17 150 person-years (PYs) of follow-up, 64 incident HCV infections (IR=0.37 per 100 PYs, 95% CI=0.29 to 0.48) were identified. Factors associated with incident HCV infection were receptive CAS [incidence rate ratio (IRR)=2.59, 95% CI=1.12 to 6.02], chemsex (IRR=1.78, 95% CI=1.06 to 2.98), sexually transmitted infection diagnosis (IRR=2.30, 95% CI=1.23 to 4.31) and IDU (IRR=6.15, 95% CI=2.20 to 17.18).

Conclusions Past/current prevalence and incidence of HCV were low among individuals in the Dutch PrEP programme. Infections were associated with behaviour known to be associated with HCV. Instead of annual HCV testing, as stated in most PrEP care guidelines, testing frequency for HCV could be based on behaviours associated with HCV acquisition.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early pre-exposure prophylaxis (PrEP) demonstration projects conducted in men who have sex with men (MSM), who were mostly early PrEP adopters with higher levels of behavioural risk, reported high prevalence and incidence of hepatitis C virus (HCV).

WHAT THIS STUDY ADDS

⇒ This study explores the past/current HCV prevalence at baseline and HCV incidence during follow-up in a larger and broader population of PrEP-using individuals, mostly MSM, in the Netherlands.

⇒ Low past/current prevalence and incidence of HCV were observed, while identified risk factors were similar to those found among MSM with HIV.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In a setting where (1) PrEP has been offered to a broader group of individuals with lower behavioural risk, (2) direct-acting antivirals have been implemented on a large scale and (3) yearly HCV testing is recommended, HCV past/current prevalence and incidence are low among the larger population of PrEP-users.

⇒ Given the low past/current prevalence and incidence of HCV, behaviourally driven testing for HCV could be considered instead of systematic annual HCV testing as is currently stated in most PrEP care guidelines.

INTRODUCTION

Since the early 2000s, hepatitis C virus (HCV) infection has emerged as a sexually transmitted infection (STI) among men who have sex with men (MSM), particularly among those with HIV.[1] Studies have shown that HCV acquisition is linked to receptive condomless anal sex (CAS), recent STI, unprotected fisting, sharing of sex toys and the use of recreational drugs before or during sex.[2 3]

Pre-exposure prophylaxis (PrEP) is a highly effective, biomedical HIV prevention strategy, and along with other biomedical strategies (ie, undetectable equals untransmittable), has supplanted previous

behavioural strategies, such as serosorting or condom use.[4–6] As a result, sexual networks between MSM with and without HIV more frequently overlap and increasingly involve sero-discordant CAS.[5 7 8] These changes could likely lead to an increased risk of HCV acquisition among PrEP-using MSM.[9 10]

Indeed, high prevalence and incidence of HCV among PrEP-using MSM have been reported between 2015 and 2018 in the Amsterdam PrEP demonstration project in the Netherlands.[11] These findings were confirmed by data from other European countries, including France, the United Kingdom and Belgium,[12–14] resulting in the recommendation across (inter) national HCV testing guidelines to test for HCV when starting PrEP and at least annually thereafter (while on PrEP).[15 16] Nevertheless, these early studies included early PrEP adopters, who were predominantly highly educated, middle-aged MSM who engaged frequently in behaviours associated with HCV acquisition.[4 13] In settings where PrEP use has expanded dramatically, low prevalence and incidence of HCV among PrEP-users have been observed.[17 18]

Since these studies, several countries have widened access to PrEP for individuals at risk of HIV. At the same time, restrictions to highly effective direct-acting antiviral (DAA) treatment were lifted, allowing nearly universal access to treatments against HCV. The sexual behaviours of MSM and transgender persons currently benefiting from PrEP might not reflect the behaviours of the population included in the previous studies, and thus, their risk of HCV acquisition could be different.[12 19] In 2019, the Netherlands launched a national PrEP programme (NPP) that offers PrEP to eligible individuals consulting at Public Health Services (PHS) around the country. The aim of this study is to assess the past/current prevalence, incidence and HCV-related risk in the broader population of PrEP-using MSM and transgender persons enrolled in the Dutch NPP.

METHODS

Study population and design

The NPP, launched in September 2019, is conducted by 23 PHS in the Netherlands, offering oral PrEP and related care to individuals who are eligible and will continue until August 2024. In the Netherlands, PrEP eligibility criteria pertain to MSM or transgender persons who report at least one of the following in the preceding 6 months: (1) insertive and/or receptive CAS with a male partner with unknown HIV status, or with a partner with a detectable HIV viral load; (2) an anal STI or infectious syphilis infection; or (3) use or indication of post-exposure prophylaxis.[16] The NPP has capacity to provide PrEP care to 8500 individuals. All regular STI/HIV test and PrEP consultations are routinely registered by the Center for Sexual Health (CSH) at the PHS in their electronic patient files. Routinely collected and pseudonymised surveillance data from CSH consultations are registered in the national STI surveillance database at the National Institute for Public Health and the Environment (RIVM). CSH visitors either provided verbal informed consent for sharing data with the RIVM or used an opt-out option. Data are secured in accordance with European privacy legislation. Multiple consultations of a unique individual can be linked using an ID of the electronic patient file.

For the current study, we included all MSM and transgender persons without HIV who were using PrEP within the NPP between July 2019 and December 2022 and had at least one visit with an HCV test result for past/current prevalence and at least two visits for the incidence estimations.

Study procedures

Individuals enrolled in the NPP had a PrEP initiation visit (for those who newly started PrEP) or commenced with a follow-up visit, indicating PrEP use before enrolment in the NPP. Follow-up visits continued every 3 months thereafter. Every visit consisted of PrEP counselling by a healthcare worker and the collection of data. Individuals could choose between daily or event-driven PrEP use and were able to switch regimens during follow-up. Individuals who reported both daily and event-driven PrEP during a visit were considered as daily PrEP users.

Demographic and behavioural characteristics were collected using computer-assisted self-administered questionnaires. Sociodemographic information (as reported at first visit) included age, key population, origin, place of residency and educational level. Behavioural characteristics were collected at all visits and included number of sexual partners, condom use, group sex and the use of drugs during sex.

At all visits, urine, blood and pharyngeal/anal samples were taken to test for HIV and STIs. HCV testing was performed at PrEP initiation and at least yearly thereafter, according to current testing guidelines.[16] Additional STI and HCV testing was performed if indicated (eg, receiving a partner notification or having STI-related symptoms). Furthermore, the interval between STI testing could be lengthened if the healthcare worker and PrEP user felt that STI risk was low.[16]

Study outcomes

Collected data on HCV infections were extended over time (see online supplemental appendix A for more detailed information about the collected data over time). Due to differences in data collection between the observed years, available data were reconstructed into anti-HCV antibody and HCV-RNA status. Online supplemental table 1 summarises the algorithm used to reconstruct data.

HCV status was initially assessed at the first visit in the NPP. We defined 'prevalent HCV infection' as having a past/current HCV infection at first visit, that is, a positive anti-HCV antibody and/or HCV-RNA test. If HCV status at first visit was missing, we used testing data at the 1-month follow-up visit (if available) or assumed negative status if an individual tested negative for anti-HCV antibodies at a subsequent visit.

HCV status was then assessed during follow-up. We defined 'primary HCV infection' as having a positive anti-HCV antibody and/or HCV-RNA test without evidence of a prior infection (ie, never had a previous positive anti-HCV antibody or HCV-RNA test). We defined 'HCV reinfection' as a positive HCV-RNA test following viral clearance from a previous HCV infection (ie, negative HCV-RNA test following a positive HCV-RNA or anti-HCV-antibody test). In the event of missing data, testing data from the last observation with available data were used (ie, last observation carried forward). The date of HCV (re)infection was estimated using the midpoint between the last negative and the first positive test. In individuals with a treated/cleared HCV infection at a visit, the date of infection was estimated as 24 weeks prior to the date of positive test (so long as no negative HCV test in the previous 24 weeks was found). This time interval was chosen as it represents the 12-week standard HCV treatment duration and subsequent 12 weeks needed to confirm sustained virological response.

Determinants

Determinants being evaluated of prevalent and incident HCV infection are summarised in online supplemental table 2, including whether they were time-fixed or time-updated.

Table 1 Characteristics at baseline and at the time of first incident HCV infection or at last visit among individuals without HCV enrolled in the Dutch national PrEP programme between July 2019 and December 2022

	Baseline	Follow-up*	
	Total (n=10 563)	Incident HCV infection (n=64)	No incident HCV infection (n=9788)
Sociodemographic characteristics			
Age in years, median (IQR)	34 (27–45)	40 (33–52)	36 (29–47)
≤34	5449 (51.6)	23 (35.9)	4538 (46.4)
35–44	2392 (22.6)	14 (21.9)	2367 (24.2)
≥45	2722 (25.8)	27 (42.2)	2883 (29.4)
Key population			
MSM	10 319 (97.7)	63 (98.4)	9548 (97.6)
Transgender person	244 (2.3)	1 (1.6)	240 (2.4)
Region of origin†			
Dutch	7143 (67.6)	42 (65.6)	6609 (67.5)
Non-Dutch	3413 (32.3)	22 (34.4)	3175 (32.4)
Residence			
Amsterdam	3676 (34.8)	32 (51.6)	3554 (36.3)
Other	6887 (65.2)	30 (48.4)	6230 (63.7)
Educational level‡			
Less than college degree	3268 (30.9)	14 (21.9)	2942 (30.1)
At least college degree	6752 (63.9)	44 (68.8)	6369 (65.1)
Choice of PrEP regimen			
Event driven	4381 (41.5)	25 (39.1)	4611 (47.1)
Daily	5608 (53.1)	39 (60.9)	5121 (52.3)
Missing	574 (5.4)	0 (0.0)	56 (0.6)
Self-reported sexual behaviour in the preceding 6 months			
Number of sex partners, median (IQR)	7 (3–15)	5 (3–10)	6 (3–12)
Receptive CAS§	7822 (74.1)	57 (89.1)	7540 (77.0)
Reporting chemsex¶/group sex**	4447 (42.1)	31 (48.4)	4382 (44.8)
Reporting sex work††	460 (4.4)	0 (0.0)	361 (3.7)
STI diagnosis‡‡	798 (7.6)	12 (18.8)	824 (8.4)
IDU§§	139 (1.3)	6 (9.4)	166 (1.7)

All statistics are n (%) or median (IQR).
*n=711 not included because they had only one visit with an HCV test result.
†Missing data; n=7 of which n=0 and n=4 among those with and without incident HCV infection, respectively.
‡Missing data; n=543 of which n=6 and n=477 among those with and without incident HCV infection, respectively.
§Missing data; n=220 of which n=1 and n=127 among those with and without incident HCV infection, respectively.
¶Defined as the use of methamphetamine, GHB/GBL and/or mephedrone before or during sex.
**Missing data; n=2372 of which n=16 and n=450 among those with and without incident HCV infection, respectively.
††Missing data; n=381 of which n=5 and n=202 among those with and without incident HCV infection, respectively.
‡‡Diagnosed with an anal chlamydia/gonorrhoea or a syphilis infection at visit.
§§Missing data; n=6438 of which n=36 and n=6062 among those with and without incident HCV infection, respectively.
CAS, condomless anal sex; GBL, γ-butyroactone; GHB, γ-hydroxybutyric acid; HCV, hepatitis C virus; IDU, injecting drug use; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

Statistical analyses

We examined the percentage of individuals tested for HCV at least once per year of follow-up overall and per region (within Amsterdam vs outside Amsterdam), where the denominator was restricted to those who had a follow-up visit during that year.

We then examined the past/current prevalence and determinants of HCV infection when entering the NPP using data obtained at the first visit. Characteristics of individuals at the first visit were described. HCV past/current prevalence was calculated by dividing the number of individuals with a positive anti-HCV antibody and/or HCV-RNA test by the total number of individuals included in analysis. We then modelled the probability of prevalent HCV infection using logistic regression. We estimated the univariable odds ratio (OR) and 95% confidence interval (CI) by including single covariates in the model. Multivariable analysis was precluded by the few outcomes expected.

To examine the incidence and determinants of HCV infection, we conducted a longitudinal analysis using data obtained at all visits. Follow-up began at the first visit with a negative anti-HCV antibody and HCV-RNA test result or a negative HCV-RNA and positive anti-HCV antibody test result and continued until the estimated date of HCV infection, last visit prior to HIV diagnosis (for those who acquired HIV) or last visit prior to administrative censoring (ie, 31 December 2022), whichever occurred first. Follow-up recommenced at the first HCV-RNA negative test following HCV infection.

We calculated the incidence rate (IR) of HCV per 100 person-years (PYs) by dividing the number of incident (re)infections with the total person-time at risk overall and per region. The 95% CIs were calculated using Poisson distribution. We then modelled the IR of HCV infection using Poisson regression. We estimated the univariable incidence rate ratio (IRR) and 95% CI

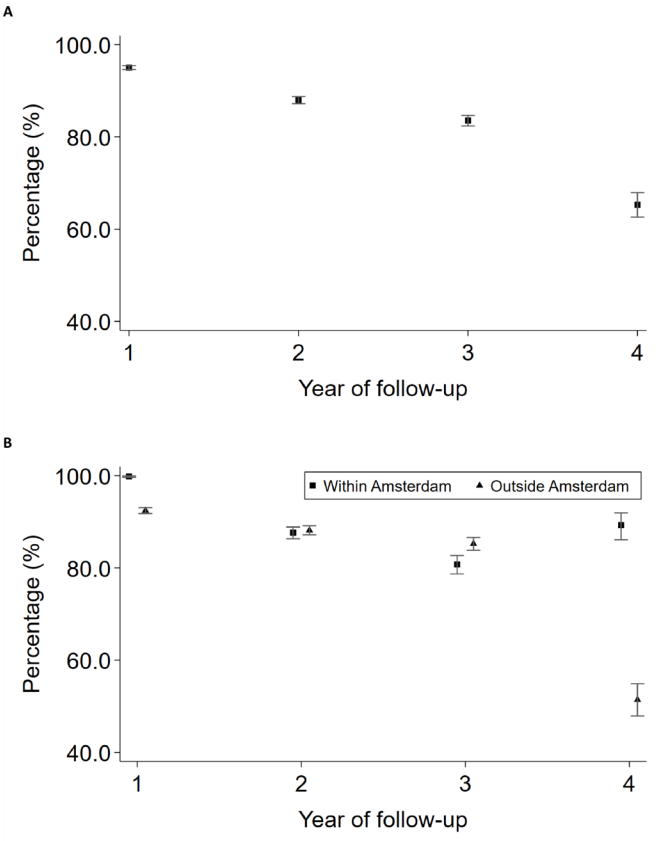

Figure 1 Percentage of individuals tested at least once for HCV year of follow-up in the total group (A) and stratified per region (B) in the Dutch national PrEP programme between July 2019 and December 2022. Boxes and whiskers represent the percentage of individuals tested for HCV during a year of follow-up and its 95% confidence intervals. HCV, hepatitis C virus; PrEP, pre-exposure prophylaxis.

by including single covariates in the model. Again, multivariable analysis was precluded by the few outcomes expected.[20]

Missing data were imputed using multivariate imputation by chained equations, assuming data were missing at random.[21] We used logistic regression to impute binary variables [ie, region of origin, educational level, receptive CAS, sex work and injecting drug use (IDU)] and produced 20 imputed datasets (see online supplemental table 3 for the number of missing values for each imputed variable).

We conducted three sensitivity analyses. First, information about group sex was not recorded at 2 of 23 CSH during a specific time frame and thus data were not missing at random for this variable. As chemsex is often highly correlated with group sex, we examined the combined effect of chemsex and group sex on prevalent and incident HCV infection using data from all centres. Second, we examined the effect of anal gonorrhoea/chlamydia and syphilis infection separately. Third, we restricted analyses to complete cases. All statistical analyses were performed using Stata (V.17.0, Statacorp, College Station, Texas, USA).

RESULTS

Of the 12 166 individuals registered in the NPP between July 2019 and December 2022, 1603 were excluded as they were diagnosed with HIV at PrEP initiation visit (n=28, 0.02%), never started PrEP (n=1169, 9.6%) or did not have at least one HCV test result (n=406, 3.3%). Of the 10 563 individuals included in analysis, 10 319 (97.7%) were MSM. At first visit, median age was 34 years [interquartile range (IQR)=27–45], 67.6% were of Dutch origin and 63.9% had a college degree or higher. Additionally, 5608 (53.1%) individuals chose daily and 4381 (41.5%) chose event-driven PrEP (table 1).

The per cent of individuals tested at least once for HCV per year of follow-up remained stable in the first 3 years (around 90%), but decreased to 65.3% in year 4 (figure 1A). As shown in figure 1B, the per cent of individuals tested for HCV in the Amsterdam region remained above 80.0% over time. At PHS outside the Amsterdam region, the per cent of individuals tested for HCV at least once per year of follow-up remained stable in year 1–3 of follow-up (around 90%), but decreased to 51.4% in year 4.

Past/current prevalent HCV infection was observed in 66 of 10 563 (0.6%) individuals. Of them, 8 were HCV-RNA positive, 47 had circulating antibodies but no HCV-RNA, and for 11 HCV-RNA data were lacking. In univariable analysis, older age (p<0.01), use of PrEP before enrolment in NPP (p<0.01), receptive CAS (p=0.01), chemsex (p<0.01) and IDU (p<0.01) significantly increased the odds of having a prevalent HCV infection (table 2). Sensitivity analyses yielded similar results (online supplemental table 4 for sensitivity analysis combining chemsex

Table 2 Univariable determinants of past/current prevalent HCV infection at baseline among individuals enrolled in the Dutch national PrEP programme between July 2019 and December 2022

	Total (n=10 563)		
	OR*	95% CI	P value
Age per 10 years, continuous	1.57	1.31 to 1.88	<0.01
Key population			
MSM	Ref		0.24
Transgender	2.03	0.63 to 6.49	
Region of origin			
Dutch	Ref		0.34
Non-Dutch	1.28	0.78 to 2.11	
Educational level			
At least college degree	Ref		0.41
Less than college degree	0.80	0.46 to 1.38	
Use of PrEP before enrolment	3.03	1.79 to 5.13	<0.01
Choice of PrEP regimen			
Daily	Ref		0.62
Event driven	1.12	0.68 to 1.86	
Missing	1.18	0.42 to 3.36	
Number of sex partners per ln(n+1) increase^{6M}	1.10	0.92 to 1.33	0.29
Receptive CAS^{6M}	2.73	1.25 to 5.98	0.01
Reporting chemsex†^{6M}	2.44	1.49 to 3.99	<0.01
Reporting sex work^{6M}	0.67	0.16 to 2.76	0.58
STI diagnosis‡	1.94	0.96 to 3.94	0.07
IDU^{6M}	6.61	2.35 to 18.61	<0.01

*Indicates the relative increase or decrease in odds for each socioeconomic characteristic or sexual behaviour when present at NPP consultation visit.
†Defined as the use of methamphetamine, GHB/GBL and/or mephedrone before or during sex.
‡Diagnosed with an anal chlamydia/gonorrhoea or a syphilis infection at visit.
CAS, condomless anal sex; CI, confidence interval; GBL, γ-butyroactone; GHB, γ-hydroxybutyric acid; HCV, hepatitis C virus; IDU, injecting drug use; ln, natural log; 6M, during the previous 6 months; MSM, men who have sex with men; NPP, national PrEP programme; OR, odds ratio; PrEP, pre-exposure prophylaxis; Ref, reference category; STI, sexually transmitted infection.

Table 3 Univariable determinants of incident HCV infection among individuals enrolled in the Dutch national PrEP programme between July 2019 and December 2022

	Total (n=9851)		
	IRR*	95% CI	P value
Age per 10 years, continuous	1.19	0.98 to 1.44	0.08
Key population			
MSM	Ref		0.81
Transgender	0.79	0.11 to 5.68	
Region of origin			
Dutch	Ref		0.45
Non-Dutch	1.22	0.73 to 2.05	
Educational level			
At least college degree	Ref		0.22
Less than college degree	0.68	0.37 to 1.26	
PrEP regimen^{12M}			
Daily	Ref		0.34
Event driven	0.79	0.48 to 1.31	
Missing	†		
Number of sex partners per ln(n+1) increase^{6M}	0.95	0.74 to 1.23	0.69
Receptive CAS^{6M}	2.59	1.12 to 6.02	0.03
Reporting chemsex‡^{6M}	1.78	1.06 to 2.98	0.03
Reporting sex work^{6M}	§		
STI diagnosis¶	2.30	1.23 to 4.31	0.01
IDU^{6M}	6.15	2.20 to 17.18	<0.01

*Indicates the relative increase or decrease in IR for each socioeconomic characteristic or sexual behaviour when present at visit.
†No incident HCV infections were among those whose PrEP regimen was missing at any visit.
‡Defined as the use of methamphetamine, GHB/GBL and/or mephedrone before or during sex.
§Sex work was excluded because all incident infections were among those who did not report sex work.
¶Diagnosed with an anal chlamydia/gonorrhoea or a syphilis infection at visit.
CAS, condomless anal sex; CI, confidence interval; GBL, γ-butyroactone; GHB, γ-hydroxybutyric acid; HCV, hepatitis C virus; IDU, injecting drug use; IR, incidence rate; IRR, incidence rate ratio; ln, natural log; 6M, during the previous 6 months; 12M, during the previous 12 months; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; Ref, reference category; STI, sexually transmitted infection.

and group sex; online supplemental table 5 for sensitivity analysis separating STIs; and online supplemental table 6 for sensitivity analysis restricted to complete cases).

A total of 9851 individuals were included in the longitudinal analysis with a median follow-up time of 1.7 years (IQR=0.9–2.7), totalling 17 152 PYs at risk. During follow-up, we identified 64 incident HCV infections among 64 individuals, corresponding to an overall IR of 0.37 per 100 PYs (95% CI=0.29 to 0.48). Of these 64 incident HCV infections, 41 only showed circulating antibodies, 13 showed HCV-RNA and 10 infections lacked HCV-RNA data. The overall IRs for individuals receiving care within and outside the Amsterdam region were 0.50 per 100 PYs (95% CI=0.35 to 0.70) and 0.30 per 100 PYs (95% CI=0.21 to 0.42), respectively. All incident infections were classified as primary infections. In univariable analysis, individuals reporting receptive CAS (p=0.03), chemsex (p=0.03), STI diagnosis (p=0.01) and IDU (p<0.01) were more likely to acquire HCV infection during follow-up (table 3). Sensitivity analysis separating STIs showed that a gonorrhoea/chlamydia infection increased the likelihood to acquire HCV (p=0.02) but syphilis did not (p=0.13) (online supplemental table 7). Other sensitivity analyses yielded similar results (online supplemental table 8 for sensitivity analysis combining chemsex and group sex and online supplemental table 9 for sensitivity analysis restricted to complete cases).

DISCUSSION

Past or current HCV infection was uncommon in the larger population of PrEP-using MSM and transgender persons between 2019 and 2022, with a prevalence of 0.6%. During follow-up, HCV incidence was 0.37 per 100 PYs. Determinants for prevalent and incident HCV infection included those previously known to be associated with HCV, namely receptive CAS, chemsex, STI diagnosis and IDU.

Percentage of individuals tested for HCV remained stable in the first 3 years of follow-up, but decreased in year 4. This might be explained by the low rate of HCV diagnoses in the early years of the NPP, which may have resulted in a more HCV risk-based testing approach among healthcare workers.[22] Post-hoc analyses revealed that type of PrEP regimen, increased number of casual partners, reporting chemsex/group sex and receptive CAS were related to increased HCV testing frequency (data not shown), supporting this hypothesis. The decrease was predominantly observed in regions outside Amsterdam, while in the Amsterdam area, the percentage of individuals being tested remained above 80%. The somewhat higher HCV IR in the Amsterdam area could reflect the stable high test rate. However, overall testing rates in both regions were high.

Early meta-analysis reported unexpectedly high pooled HCV prevalence and incidence among PrEP-using individuals, with a pooled prevalence of 1.5% and incidence of 1.5 per 100 PYs.[23] In a more recently published meta-analysis among PrEP-using MSM, including more recent and larger PrEP studies in the DAA era, the pooled HCV prevalence and incidence were lower (0.62% and 1.8 per 100 PYs), similar to our findings.[19] One explanation for this decrease could be that earlier PrEP studies included individuals who would benefit most from PrEP in terms of HIV prevention and as a result, were more likely to engage in behaviours associated with HCV. Indeed, previous studies in the Netherlands with high prevalence and incidence of HCV among PrEP-using individuals and MSM with HIV reported more IDU, chemsex and a higher number of sexual partners compared with individuals registered in the NPP.[11 24] Another contributing factor is that the Netherlands witnessed universal access to DAAs in 2015, which resulted in a steep decline in the number of individuals with HIV with active HCV infection,[25] which may explain the low number of individuals with HCV-RNA at baseline in our analysis. As the pool of individuals with HCV viraemia was reduced, the potential for ongoing HCV transmission also decreased.[26 27]

Determinants associated with HCV infection were comparable with other studies conducted among MSM without HIV and often using PrEP,[11 28] and were also largely comparable with determinants found among MSM with HIV.[24 29] The use of PrEP has made the use of other HIV prevention strategies, like serosorting and condom use, less common, resulting in more overlap in sexual networks of MSM with and without HIV, as has been demonstrated by HCV phylogenetic analysis.[10 11] In other countries, such as Canada, IDU is an important factor associated with HCV.[23] While we found an association between IDU and HCV infection, the percentage of individuals reporting IDU was 9.4% and unlikely to be the main driver of HCV transmission among this population.

One important strength of this study is that it is the first study reporting HCV past/current prevalence, incidence and

factors associated with HCV infection in the wider PrEP-using population in the Netherlands, providing a more representative understanding of the HCV epidemiology. However, this study has limitations. First, data on HCV infection had to be reconstructed. The distinction between primary and reinfections was therefore not entirely evident and some reinfections might have been missed or misclassified as primary infections. Second, several determinants associated with HCV, such as unprotected fisting, sharing of straws when snorting drugs and group sex, were not assessed or were not missing at random and thus, could not be evaluated. Possibly, there were other determinants missing not at random, such as IDU, which must be considered when interpreting the results. Third, for four individuals, no negative HCV test result was available before testing positive during any subsequent visit. These individuals were considered as missing for the prevalent analyses and were included in the incidence analysis where follow-up started from the moment of their first negative HCV test after the initial positive HCV test. It remains uncertain whether these individuals had a prevalent or incident HCV infection. Lastly, due to a small number of prevalent and incident HCV infections, we were unable to perform multivariable analysis. In addition, possible collinearity between determinants makes it challenging to disentangle the unique contribution of each determinant.[20]

In conclusion, from a setting where both DAAs and PrEP are implemented on a relatively large scale and where yearly HCV testing is included in PrEP care, the prevalence of past/current HCV infection at enrolment in a national PrEP programme and incidence of HCV infection during this programme were lower than observed in early PrEP demonstration projects, but comparable with more recent PrEP studies in the DAA era. Behaviours associated with HCV acquisition in this study population appear comparable with those found in previous studies among MSM. Instead of annual HCV testing, as stated in most PrEP care guidelines, testing frequency for HCV could be based on behaviours associated with HCV acquisition.

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Contributors KH contributed to the conception and design of the work, performed data management and data analysis and drafted the manuscript. AB contributed to the conception and design of the work, analysis of data and interpretation of the data. ELMOdC and EH contributed to the conception and design of the work. DS contributed to the conception and design of the work and data management. MP contributed to the conception and design of the work and interpretation of data. All authors critically revised the manuscript, and all approved the final version. MP was the guarantor, and therefore accept full responsibility for thw ork and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Patient consent for publication Not applicable.

Ethics approval According to the Dutch Medical Research (involving Human Subjects) Act, the study uses routinely collected, pseudonymised surveillance data and thus does not need ethical approval (Wet medisch-wetenschappelijk onderzoek met mensen 1998 §1 artikel 1).

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Data availability statement Data are available upon reasonable request. This study used data from the Dutch national registration of SHC consultations (SOAP). Pseudomised individual participant data can be requested for scientific use with a methodologically sound proposal submitted to the SOAP registration committee for approval. Proposal forms and additional information can be requested via soap@rivm.nl. Data requestors will need to sign a data access agreement.

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REFERENCES

1 Hagan H, Jordan AE, Neurer J, *et al*. Incidence of sexually transmitted hepatitis C virus infection in HIV-positive men who have sex with men: a systematic review and meta-analysis. *AIDS* 2015;29:2335–45.
2 Vanhommerig JW, Lambers FAE, Schinkel J, *et al*. Risk factors for sexual transmission of hepatitis C virus among human immunodeficiency virus-infected men who have sex with men: a case-control study. *Open Forum Infect Dis* 2015;2:ofv115.
3 Newsum AM, Stolte IG, van der Meer JT, *et al*. Development and validation of the HCV-MOSAIC risk score to assist testing for acute hepatitis C virus (HCV) infection in HIV-infected men who have sex with men (MSM). *Euro Surveill* 2017;22:30540.
4 Hoornenborg E, Coyer L, Achterbergh RCA, *et al*. Sexual behaviour and incidence of HIV and sexually transmitted infections among men who have sex with men using daily and event-driven pre-exposure prophylaxis in AMPrEP: 2 year results from a demonstration study. *Lancet HIV* 2019;6:e447–55.
5 Traeger MW, Schroeder SE, Wright EJ, *et al*. Effects of pre-exposure prophylaxis for the prevention of human immunodeficiency virus infection on sexual risk behavior in men who have sex with men: a systematic review and meta-analysis. *Clin Infect Dis* 2018;67:676–86.
6 Rodger AJ, Cambiano V, Bruun T, *et al*. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *Lancet* 2019;393:2428–38.
7 Van Dijk M, De Wit JBF, Guadamuz TE, *et al*. Bridging the Serodivide: attitudes of PrEP users towards sex partners living with HIV. *AIDS Care* 2022;34:349–52.
8 Paz-Bailey G, Mendoza MCB, Finlayson T, *et al*. Trends in condom use among MSM in the United States: the role of antiretroviral therapy and seroadaptive strategies. *AIDS* 2016;30:1985–90.
9 Bradshaw D, Vasylyeva TI, Davis C, *et al*. Transmission of hepatitis C virus in HIV-positive and PrEP-using MSM in England. *J Viral Hepat* 2020;27:721–30.
10 Charre C, Cotte L, Kramer R, *et al*. Hepatitis C virus spread from HIV-positive to HIV-negative men who have sex with men. *PLoS One* 2018;13:e0190340.
11 Hoornenborg E, Coyer L, Boyd A, *et al*. High incidence of HCV in HIV-negative men who have sex with men using pre-exposure prophylaxis. *J Hepatol* 2020;72:855–64.
12 Cotte L, Cua E, Reynes J, *et al*. Hepatitis C virus incidence in HIV-infected and in preexposure prophylaxis (PrEP)-using men having sex with men. *Liver Int* 2018;38:1736–40.
13 Vuylsteke B, Reyniers T, De Baetselier I, *et al*. Daily and event-driven pre-exposure prophylaxis for men who have sex with men in Belgium: results of a prospective cohort measuring adherence, sexual behaviour and STI incidence. *J Int AIDS Soc* 2019;22:e25407.
14 Desai M, White E, Vora N, *et al*. High incidence of hepatitis C virus infection observed in the PROUD study of HIV pre-exposure prophylaxis. *J Viral Hepat* 2020;27:852–7.
15 The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America Present. HCV guidance: recommendations for testing, managing, and treating hepatitis C. 2023. Available: www.hcvguidelines.org
16 Bierman WF, Hoornenborg E, Nellen J, *et al*. Nederlandse Multidisciplinaire Richtlijn pre-expositie profylaxe (PrEP) ter preventie van hiv update. 2022. Available: https://

www.soaaids.nl/files/2022-07/20220711-PrEP-richtlijn-Nederland-versie-3-update-2022.pdf
17 Harney BL, Sacks-Davis R, van Santen DK, *et al*. The incidence of hepatitis C among gay, bisexual, and other men who have sex with men in Australia, 2009-2019. *Clin Infect Dis* 2022;74:1804–11.
18 Thompson KA, Blank G, Toy J, *et al*. Prevalence and incidence of hepatitis C infection amongst men who have sex with men in a population-based pre-exposure prophylaxis program in British Columbia, Canada. *Liver Int* 2022;42:1528–35.
19 Traeger MW, Harney BL, Sacks-Davis R, *et al*. Incidence and prevalence of hepatitis C virus among HIV-negative gay and bisexual men using HIV pre-exposure prophylaxis (PrEP): a systematic review and meta-analysis. *Open Forum Infect Dis* 2023;10:ofad401.
20 Courvoisier DS, Combescure C, Agoritsas T, *et al*. Performance of logistic regression modeling: beyond the number of events per variable, the role of data structure. *J Clin Epidemiol* 2011;64:993–1000.
21 White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377–99.
22 European treatment network for HIV Hagidn-ICP. Recently acquired and early chronic hepatitis C in MSM: recommendations from the European treatment network for HIV, hepatitis and global infectious diseases consensus panel. *AIDS* 2020;34:1699–711.
23 Jin F, Dore GJ, Matthews G, *et al*. Prevalence and incidence of hepatitis C virus infection in men who have sex with men: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2021;6:39–56.
24 Newsum AM, Matser A, Schinkel J, *et al*. Incidence of HCV reinfection among HIV-positive MSM and its association with sexual risk behavior: a longitudinal analysis. *Clin Infect Dis* 2021;73:460–7.
25 Smit C, Boyd A, Rijnders BJA, *et al*. HCV micro-elimination in individuals with HIV in the Netherlands 4 years after universal access to direct-acting antivirals: a retrospective cohort study. *Lancet HIV* 2021;8:e96–105.
26 Isfordink CJ, Smit C, Boyd A, *et al*. Low hepatitis C virus-viremia prevalence yet continued barriers to direct-acting antiviral treatment in people living with HIV in the Netherlands. *AIDS* 2022;36:773–83.
27 Boerekamps A, van den Berk GE, Lauw FN, *et al*. Declining hepatitis C virus (HCV) incidence in Dutch human immunodeficiency virus-positive men who have sex with men after unrestricted access to HCV therapy. *Clin Infect Dis* 2018;66:1360–5.
28 Vaux S, Chevaliez S, Saboni L, *et al*. Prevalence of hepatitis C infection, screening and associated factors among men who have sex with men attending gay venues: a cross-sectional survey (PREVAGAY), France, 2015. *BMC Infect Dis* 2019;19:315.
29 Ireland G, Higgins S, Goorney B, *et al*. Evaluation of hepatitis C testing in men who have sex with men, and associated risk behaviours, in Manchester, UK. *Sex Transm Infect* 2017;93:404–9.