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HCV micro-elimination in individuals with HIV in the Netherlands 4 years after universal access to direct-acting antivirals: a retrospective cohort study

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Summary

Background In the Netherlands, access to direct-acting antivirals (DAAs) against hepatitis C virus (HCV) has been unrestricted for chronic infection since 2015. We evaluated whether the nationwide incidence of HCV infections in individuals with HIV has changed since 2015.

Methods In this retrospective cohort study, data from the ATHENA cohort of people with HIV aged 18 years or older attending any of the 24 HIV treatment centres in the Netherlands between 2000 and 2019 were assessed. We used parametric proportional hazards models with a piecewise exponential survival function to model HCV primary infection and reinfection incidence per 1000 person-years.

Findings Of the 23 590 individuals without previous HCV infection, 1269 cases of HCV primary infection were documented (incidence 5·2 per 1000 person-years [95% CI 5·0–5·5]). The highest incidence was observed in men who have sex with men (MSM; 7·7 per 1000 person-years [7·3–8·2]) and was lower in people who inject drugs (PWID; 1·7 per 1000 person-years [0·7–4·1]) and other key populations (1·0 per 1000 person-years [0·8–1·2]). In MSM, incidence increased in 2007 to 14·3 per 1000 person-years and fluctuated between 8·7 and 13·0 per 1000 person-years from 2008 to 2015. In 2016, incidence declined to 6·1 cases per 1000 person-years and remained steady between 4·1 and 4·9 per 1000 person-years from 2017 to 2019. Of the 1866 individuals with a previous HCV infection, 274 reinfections were documented (incidence 26·9 per 1000 person-years [95% CI 23·9–30·3]). The highest incidence rate was observed in MSM (38·5 per 1000 person-years [33·9–43·7]) and was lower in PWID (10·9 per 1000 person-years [3·5–33·8]) and other key populations (8·9 per 1000 person-years [6·3–12·5]). In MSM, reinfection incidence fluctuated between 38·0 and 88·9 per 1000 person-years from 2006 to 2015, reaching 55·6 per 1000 person-years in 2015. In 2016, reinfection incidence declined to 41·4 per 1000 person-years, followed by further decreases to 24·4 per 1000 person-years in 2017 and 11·4 per 1000 person-years in 2019.

Interpretation The sharp decline in HCV incidence in MSM with HIV shortly after restrictions on DAAs were lifted suggests a treatment-as-prevention effect. HCV incidence was already low in PWID and other groups before unrestricted access. Ongoing HCV transmission is occurring in MSM, as illustrated by a declining but high rate of reinfection, stressing the need for additional preventive measures.

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Introduction

During the 2000s, the incidence rate of hepatitis C virus (HCV) infections rapidly increased in individuals with HIV across most of Europe.[1] Treatment at the time was confined to interferon-based regimens with sub-optimal sustained virological response rates.[2] Coupled with the low rates of spontaneous clearance after infection[3] and a prolonged, clinically asymptomatic disease course, a substantial proportion of individuals co-infected with HIV and HCV had active HCV replication and were thereby causing onward transmission of HCV.[4]

With the advent of potent direct-acting antivirals (DAAs), sustained virological response has become attainable for most individuals with HCV.[5] This led WHO to set targets to eliminate HCV as a public health threat by 2030, including an 80% reduction in HCV incidence from that reported in 2015.[6] Because HCV infection is more prevalent in some individuals with HIV, such as people who inject drugs (PWID) and men who have sex with men (MSM), elimination targets need to be met for these key populations (ie, micro-elimination). For HCV micro-elimination to occur, treatment uptake must be widespread. Modelling studies specific to PWID and MSM with HIV have shown that reductions in the incidence and prevalence of HCV could be obtained for most settings when treatment coverage substantially increases.[7,8] However, data from observational studies confirming these reports are few in number and most have short follow-up.

Research in context

Evidence before this study

We searched PubMed and the databases of the International AIDS Society Conference (2018–20) and the Conference on Retroviruses and Opportunistic Infections (2018–20) without language restrictions from their inception to April 23, 2020, for articles or abstracts, using the search terms "HCV", "incidence", "HIV", "direct acting antivirals", and "DAA". Our initial search yielded 120 articles. We selected studies that included individuals with HIV and provided hepatitis C virus (HCV) incidence estimates before and after access to DAAs was broadened. Studies focusing on primary HCV incidence after universal DAA access reported a stable or decreasing incidence of HCV in men who have sex with men (MSM) and people who inject drugs (PWID), immediate decreases in HCV incidence in MSM, decreases in HCV incidence rates even before universal access to direct-acting antivirals in MSM, or even increases in HCV incidence. Studies focusing on HCV reinfection after universal DAA access reported low infection rates overall, mostly in MSM, low prevalence of viraemic HIV-positive and HIV-negative PWID, and no change in reinfection rates between interferon and DAA eras. Differences in treatment uptake could partly explain these discrepancies. Most studies assumed that HCV testing rates were yearly.

Added value of this study

In the Netherlands, we report that although the incidence of both primary infection and reinfection with HCV has substantially decreased in MSM with HIV within the first year after unrestricted access to DAA treatment, it remained steady for the following 4 years. HCV incidence was already low in PWID and other groups before unrestricted access. These changes in incidence were not due to changes in age structure, HIV RNA or CD4 levels, or possibly HCV testing frequency. Meanwhile, the high and rapid uptake of DAAs and increased sustained virological response points towards a treatment-as-prevention effect. Of note, two decades worth of prospective data suggest that 2016–19 incidence of primary HCV infection is similar to incidence before 2007.

Implications of all the available evidence

There is a consistent effect of decreasing HCV incidence following high DAA uptake during universal access to DAA. However, infections are still occurring suggesting that other means of preventing HCV infection, possibly including increased HCV testing or reducing behaviours associated with HCV acquisition, are needed.

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In the Netherlands, DAAs were initially made available in 2014 for individuals with HIV and HCV infection under the condition that they had advanced liver fibrosis or cirrhosis. In 2015, these restrictions were removed and rapid uptake of DAAs was observed in individuals with HIV and HCV infection, particularly by MSM.[9] Initial data from a large subset of HIV-treatment centres in the Netherlands have reported that HCV incidence almost halved directly after unrestricted access to DAAs was made available.[10] In other countries without treatment restrictions (including the UK, Switzerland, and Australia) similar findings in individuals with HIV have been reported;[11–13] however, in France, no such decrease has been observed.[14]

The aim of this study was to determine the incidence of both primary HCV infection and in those with previous infection, HCV reinfection over the past two decades using comprehensive data of nearly all individuals with HIV actively followed in care in the Netherlands. Particular attention was focused on key populations and the years before and directly after restrictions on access to DAAs were lifted.

Methods

Study design and participants

HIV care in the Netherlands is provided by 24 treatment centres. As an integral part of HIV care, the HIV Monitoring Foundation is responsible for prospectively collecting demographic, relevant HIV and treatment, and viral hepatitis co-infection data from people with HIV in the Netherlands receiving care in one of the treatment centres.

This data collection is known as the ATHENA cohort,[15] which was initiated in 1998 and captures data from more than 98% of all patients with HIV who are in care in the Netherlands. Data collection is continuous, and the database of the ATHENA cohort is locked and updated twice a year. This Article includes data from Jan 1, 2000, to Dec 31, 2019 (database lock June 2020).

At its inception, the ATHENA cohort was approved by the institutional review boards of all participating centres. Individuals can opt out after being informed by their treating physician of the purpose of data and sample collection. Data are pseudonymised and made available to investigators in a coded form. Coded data might be used for scientific purposes without consent. For our analysis, only existing data have been used and therefore no additional review or consent was required.

Procedures

Included patients were assessed at first visit for age, sex, and HIV transmission route; each patient was then assigned to an HCV key population based on the route of HIV transmission. We considered any MSM who ever injected drugs as part of the MSM key population. CD4 cell count and HIV-1 RNA measurements were obtained during follow-up visits. Date of initiation and discontinuation for each HIV and HCV treatment and data on HCV treatment response were also collected during follow-up.

Physicians were recommended to do HCV testing according to European AIDS Clinical Society (EACS) guidelines. We used ELISA-based assays to test for HCV antibodies and PCR-based assays to test for HCV RNA

For more on the **HIV Monitoring Foundation** see https://www.hiv-monitoring.nl/en

	Jan 1, 2000 (n=4916)	Jan 1, 2005 (n=8763)	Jan 1, 2010 (n=13 308)	Jan 1, 2015 (n=16 858)
Median age, years (IQR)	39 (34–46)	41 (35–48)	44 (37–51)	47 (39–55)
Sex				
Male	4139 (84·2%)	6961 (79·4%)	10 706 (80·5%)	13 808 (81·9%)
Female	777 (15·8%)	1801 (20·6%)*	2597 (19·5%)†	3039 (18·0%)‡
Mode of HIV and HCV transmission				
MSM	3312 (67·4%)	5249 (59·9%)	8183 (61·4%)	10 814 (64·1%)
PWID	47 (1·0%)	90 (1·0%)	139 (1·0%)	132 (0·8%)
Heterosexual or other	1557 (31·6%)	3424 (39·1%)	4986 (37·4%)	5912 (35·1%)
Country or region of origin				
Netherlands	2948 (60·0%)	4846 (55·3%)	7583 (57·0%)	9976 (59·2%)
Rest of Europe	406 (8·3%)	613 (7·0%)	848 (6·4%)	937 (5·6%)
Sub-Saharan Africa	500 (10·2%)	1428 (16·3%)	1993 (15·0%)	2188 (13·0%)
Caribbean or South America	592 (12·0%)	1074 (12·3%)	1640 (12·3%)	2038 (12·1%)
Southeast Asia	148 (3·0%)	289 (3·3%)	451 (3·4%)	605 (3·6%)
Other	322 (6·5%)	513 (5·8%)	793 (6·0%)	1114 (6·6%)
Ever AIDS	1945 (39·6%)	2966 (33·8%)	3770 (28·3%)	4145 (24·6%)
AIDS at diagnosis	708 (14·4%)	1290 (14·7%)	1834 (13·8%)	2223 (13·2%)
Median CD4 cells per µL (IQR)	460 (290–650)	470 (330–655)	530 (390–700)	640 (480–830)
Median CD8 cells per µL (IQR)	1040 (730–1420)	960 (690–1300)	880 (640–1200)	850 (620–1150)
HIV RNA <200 copies per mL	2451 (49·8%)	6032 (68·8%)	10 097 (75·9%)	15 663 (92·9%)
Current HIV treatment				
On combined ART	3170 (64·5%)	5900 (67·3%)	10 007 (75·2%)	15 205 (90·2%)
Not on combined ART	1746 (35·5%)	2863 (32·%)	3301 (24·8%)	1653 (9·8%)
Never initiated combined ART	1320 (27·%)	2863 (32·7%)	2547 (19·1%)	960 (5·7%)
HCV infection risk				
At risk of primary infection	4883 (99·3%)	8621 (98·4%)	12 944 (97·3%)	16 108 (96·6%)
At risk of reinfection	33 (0·2%)	142 (1·6%)	364 (2·7%)	750 (4·4%)

All data are n (%) unless otherwise stated. Median calendar year of inclusion was 2007 (IQR 2001–2012). ART=antiretroviral therapy. HCV=hepatitis C virus. MSM=men who have sex with men. PWID=people who injects drugs. *Information missing for one person. †Information missing for five people. ‡Information missing for 11 people.

Table: **Description of the study population at specific years**

(range of detection thresholds was 15–615 copies per mL). If an HCV test was not done at a given visit, we assumed that the HCV status did not change since the most recent test (ie, last observation carried forward).

Primary HCV infection was evaluated in individuals with no evidence of previous infection, which was defined as never having had a previous positive anti-HCV antibody or HCV RNA test, with testing being a requirement for inclusion in this study. We defined HCV infection as either seroconversion from anti-HCV antibody negative to positive or change from undetectable HCV RNA to detectable HCV RNA. Date of primary HCV infection was defined as the date of first positive anti-HCV antibody or HCV RNA test.

HCV reinfection was evaluated in individuals with treatment-induced sustained virological response or spontaneous clearance of HCV and was defined by detectable HCV RNA at any visit after HCV clearance. Date of HCV reinfection was the date of first positive HCV RNA test after sustained virological response or spontaneous clearance. Sustained virological response was defined as a negative HCV RNA test result at the assessment done closest to 24 weeks (at a maximum of 34 weeks) after the end of treatment with an interferon-based regimen or a negative HCV RNA test result at the assessment done closest to 12 weeks (with a maximum of 34 weeks) after the end of treatment with DAAs. If there was no HCV RNA test result within this timeframe, we used the treatment outcome reported in the patient file. Spontaneous clearance was defined by having a positive test result for HCV antibody or HCV RNA, a subsequent negative HCV RNA test result after 2 weeks or more, and no previous history of HCV treatment. Similar to a previous study,[16] spontaneous clearance was distinguished as either definitive (ie, two consecutive negative HCV RNA test results after a positive HCV antibody or RNA test result) or possible (one negative HCV RNA test result following an earlier positive HCV antibody or RNA test result, or only two HCV RNA negative results within <2 weeks).

Statistical analysis

We evaluated primary HCV infection and HCV reinfection from Jan 1, 2000, to Dec 31, 2019. Primary infection analysis was restricted to individuals with HIV whose first documented anti-HCV antibody result was negative. The observation period began at the individual's first cohort visit after Jan 1, 2000, and continued until incident primary HCV infection, death, loss to follow-up, last visit, or Dec 31, 2019, whichever occurred first. Reinfection analysis was restricted to individuals with HIV and a positive anti-HCV antibody or positive HCV RNA test who had sustained virological response or spontaneous clearance. The individual's observation period began at the first visit less than 6 months after the end of treatment (for sustained virological response) or following spontaneous clearance after Jan 1, 2000, and continued until HCV reinfection, death, loss to follow-up, last visit, or Dec 31, 2019, whichever occurred first. Individuals restarted follow-up after sustained virological response or spontaneous clearance of reinfection until the next censoring event. For both primary infection and re-infection, we included patients who had one visit at the beginning of the observation period and at least one visit during follow-up.

We first examined the yearly testing rate across calendar years within key populations. We then described the numbers of primary HCV infections and HCV reinfection and the proportion of the total infections according to key population group. Given the preponderance of primary

infection and reinfection in MSM, we restricted all further analysis to this group. Incidence of both primary HCV infection and HCV reinfection per 1000 person-years and their 95% CIs were estimated over calendar years using parametric proportional hazards models with a piecewise exponential survival function. We also evaluated incidence rates with respect to age, CD4 cell count, and HIV RNA concentrations (appendix p 2). The proportion initiating treatment less than 12 months and less than 6 months after first anti-HCV antibody positive or HCV RNA-positive test for primary infection and first HCV RNA-positive test for reinfection (ie, treatment uptake) and the proportion of those treated reaching sustained virological response were estimated across calendar years (appendix p 2). 2019 was not included in this analysis because follow-up was too short to confirm sustained virological response for individuals starting treatment in 2018.

Statistical analysis was done using STATA (v15.1) and significance was determined using a p value less than 0·05.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 31070 individuals with HIV-1 ever registered in the ATHENA cohort, 24443 were included in the analysis of primary HCV infection and HCV reinfection (appendix p 3). Most were MSM; the proportion of PWID included in the analysis remained stable at 1% from 2000 to 2015 (table).

23590 individuals were susceptible to primary HCV infection, of whom 8695 (37%) had only one HCV test (4008 [26·7%] of 14992 MSM, 193 [59%] of 328 PWID, and 4494 [54·3%] of 8270 in the heterosexual or other group). The proportion of individuals who had at least one HCV test during the calendar year increased in the MSM group (figure 1A) with stable testing at 31·5–43·1% per year from 2008 to 2019. Testing remained stable in PWID (14·6–21·2%) and the heterosexual or other group (10·4–23·1%) per year over time (figure 1A).

During a median follow-up of 9·8 years (IQR 4·8–15·6), 1269 incident primary infections were observed (incidence 5·2 per 1000 person-years [95% CI 5·0–5·5]), with the highest number reported in 2015 (116 cases; figure 2A). Across calendar years, MSM with HIV constituted 92·7% of all primary HCV infections (incidence 7·7 per 1000 person-years [7·3–8·2]) compared with 0·4% in PWID (incidence 1·7 per 1000 person-years [0·7–4·1]) or 6·9% in the heterosexual or other group (incidence 1·0 per 1000 person-years [0·8–1·2]; figure 2B). Of those with genotyped sequences, 696 (70·4%) infections involved genotype one, 214 (21·6%) involved genotype four, 55 (5·6%) involved genotype two, and 24 (2·4%) involved genotype three.

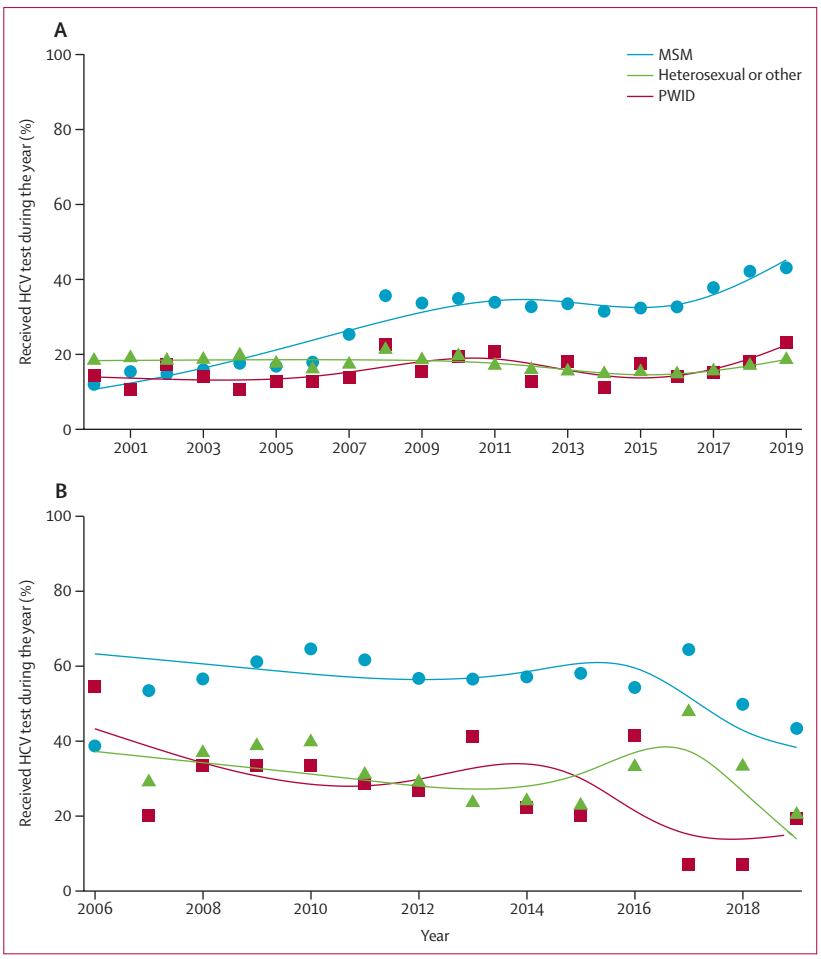

***Figure 1*: Yearly HCV testing across calendar years in individuals with HIV**
(A) Proportion of individuals with HIV who were susceptible to primary HCV infection and who had a yearly HCV test. (B) Proportion of individuals with HIV who were susceptible to HCV reinfection and who had a yearly HCV test. HCV=hepatitis C virus. MSM=men who have sex with men. PWID=people who inject drugs.

A total of 1866 individuals were susceptible to HCV reinfection following sustained virological response during follow-up (appendix p 3). Of the individuals with HIV susceptible to reinfection, the percentage of MSM with an HCV test at least once during the calendar year was 53·4–64·6% between 2006 and 2016 (figure 1B), followed by a decline to 49·8% in 2017 and to 38·2% in 2019. Yearly HCV testing rates averaged 25·1% for PWID and 30·0% for the heterosexual or other group with substantial variation over the years because of the small number of people in these two key populations.

During a median follow-up of 4·0 years (IQR 2·8–8·1), 274 cases of HCV reinfection were reported (incidence 26·9 per 1000 person-years [95% CI 23·9–30·3]); the highest number of reinfections occurred in 2018 (32 cases; figure 2A). HIV-positive MSM constituted 86·9% of HCV reinfections (38·5 per 1000 person-years [95% CI 33·9–43·7]) compared with 1·1% in PWID

See **Online** for appendix

For **Statistical codes** see https://github.com/boyd0094/SHM_HCV_incidence

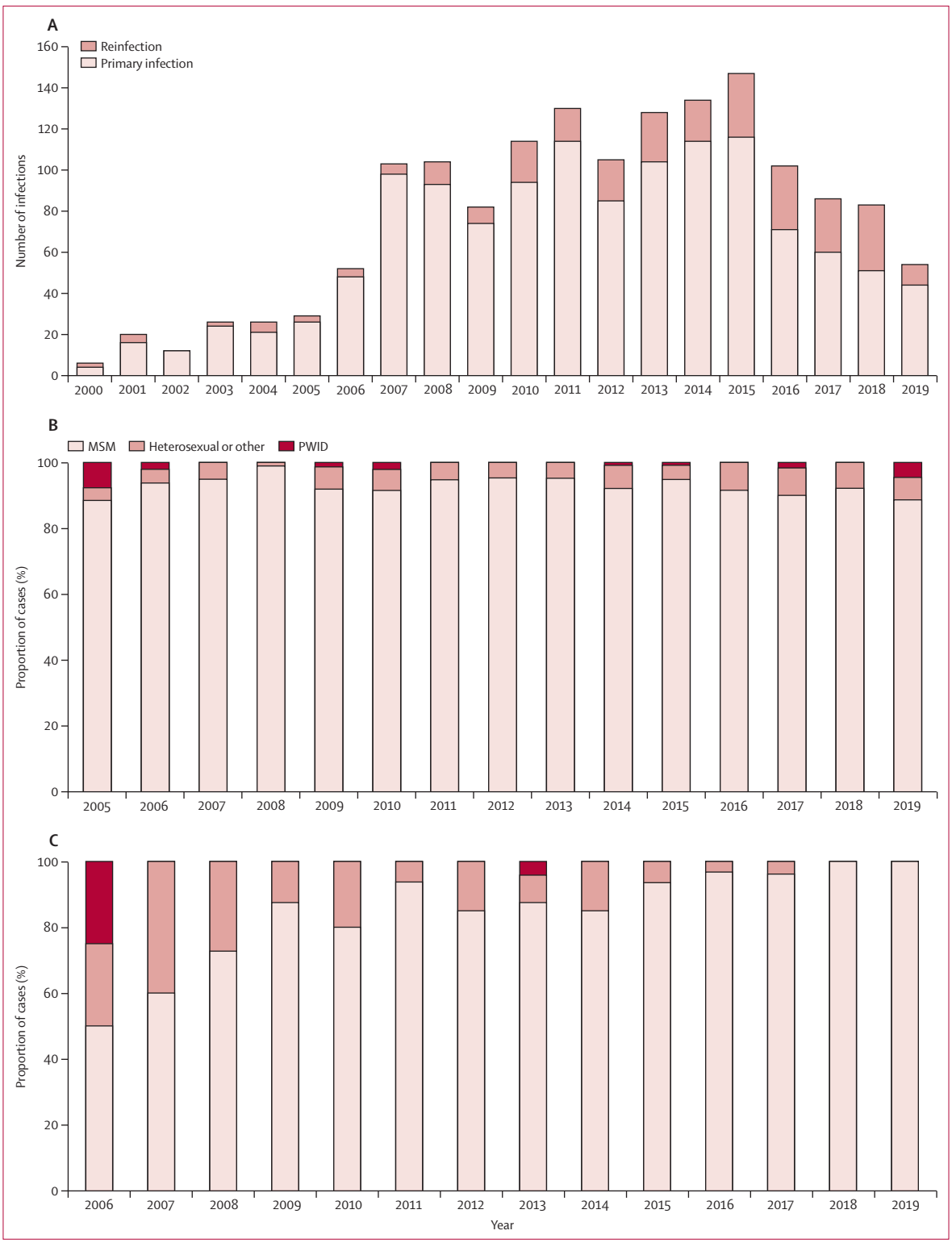

***Figure 2*: HCV primary infection and reinfection in individuals with HIV**

Data are from the ATHENA cohort of HIV-positive individuals in care from 2000 to 2019. (A) Total number of primary infections and reinfections with HCV per calendar year. The proportion of cases in MSM, the heterosexual or other group, and PWID are given across calendar years for HCV primary infection (B) and HCV reinfection (C). HCV=hepatitis C virus. MSM=men who have sex with men. PWID=people who inject drugs.

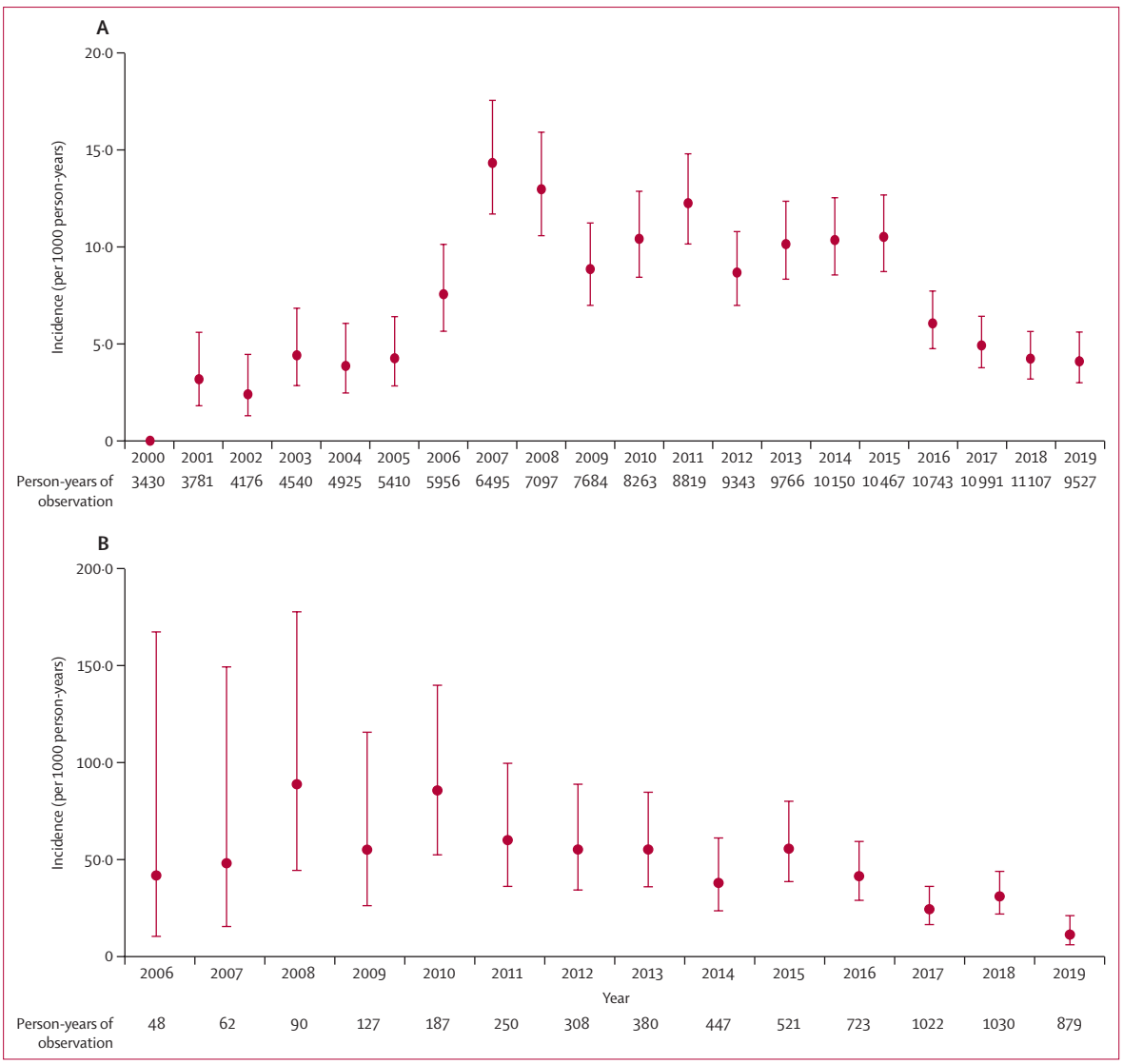

***Figure 3*: Estimated incidence of HCV primary infection and reinfection in MSM with HIV**
The incidence rate per 1000 person-years for HCV primary infection (A) and HCV reinfection (B) in MSM. Error bars are 95% CI. HCV=hepatitis C virus. MSM=men who have sex with men.

(incidence 10·9 per 1000 person-years [3·5–33·8]) and 12·0% in the heterosexual and other group (incidence 8·9 per 1000 person-years [6·3–12·5]; figure 2B).

Most HCV infections occurred in MSM; as such, analysis was focused on this group. During 152 671 person-years, 1176 primary HCV infections occurred in MSM. Incidence of primary HCV infection (figure 3A) substantially increased in 2007 (incidence 14·3 per 1000 person-years [95% CI 11·7–17·5]) and fluctuated between 8·7 and 13·0 per 1000 person-years from 2008 to 2015. A significant decline in incidence occurred in 2016 (6·1 cases per 1000 person-years [4·7–7·7]) compared with 2015 (p=0·0004) with a non-significant decline of between 4·1 and 4·9 per 1000 person-years each year until 2019 (2016 *vs* 2017 p=0·26; 2016 *vs* 2018 p=0·06; and 2016 *vs* 2019 p=0·05).

During 6186 person-years, 238 cases of HCV re-infection occurred in MSM. Of these cases, 134 occurred after previous treatment-induced sustained virological response and 104 after previous spontaneous clearance (64 after probable clearance and 40 after definitive clearance). Incidence of reinfection was lower after DAA-induced sustained virological response (incidence 29·8 per 1000 person-years [95% CI 21·0–42·3]) or interferon-induced or interferon and DAA-induced sustained virological response (incidence 34·2 per 1000 person-years [25·6–45·8]) compared with spontaneous clearance (incidence rate 55·2 per 1000 person-years [44·5–68·4]; incidence rate ratio 0·54 [0·38–0·77] for DAA-induced sustained virological response; incidence rate ratio 0·62 [0·46–0·83] for interferon-induced or interferon and

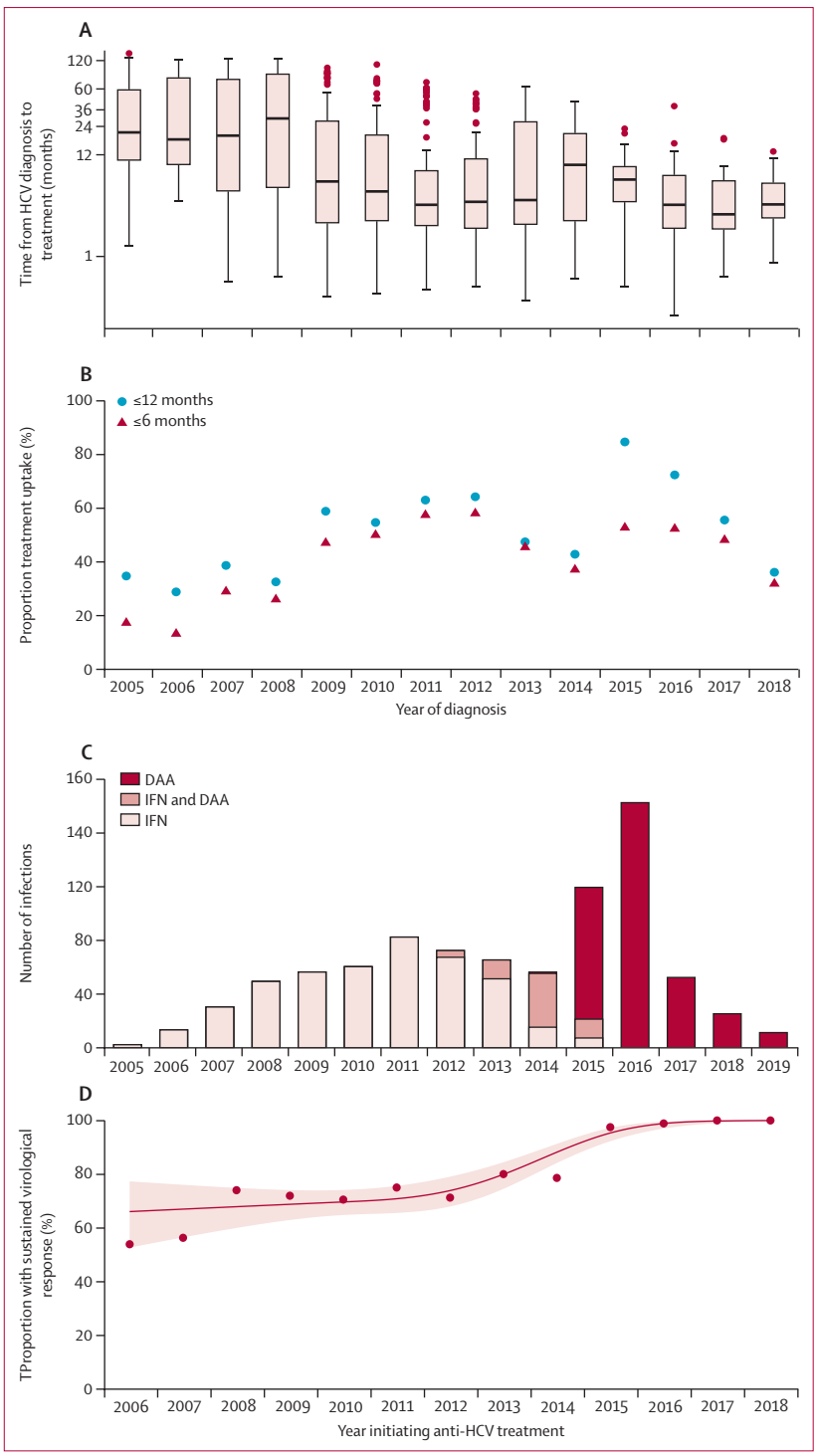

***Figure 4*: Treatment of primary infections per calendar year in in MSM with HIV**
Data include only MSM with HIV and primary HCV infection. (A) Box plots of time from HCV diagnosis to anti-HCV treatment. The Y axis represents time on a log scale. (B) Proportion with treatment initiation within 6 months or 12 months after HCV diagnosis. (C) The number of primary HCV infections treated with IFN only, combined IFN and DAA (boceprevir or telaprevir), or only DAAs. (D) Proportion of treated individuals with sustained virological response. Fitted lines (solid) along with 95% CI (shaded area) are given for proportion with treatment uptake and with sustained virological response. DAA=direct-acting antivirals. HCV=hepatitis C virus. IFN=interferon. MSM=men who have sex with men.

DAA-induced sustained virological response). Of the MSM who had HCV reinfection, 186 had one reinfection, 20 had two reinfections, and four had three reinfections. Incidence of HCV reinfection in MSM (figure 3B) fluctuated between 38·0 and 88·9 per 1000 person-years from 2006 to 2015, reaching 55·6 per 1000 person-years in 2015. However, a decline was observed in 2016 (incidence 41·4 per 1000 person-years) compared with 2015 (p=0·26), which was followed by a decrease to 24·4 per 1000 person-years in 2017 and 11·4 per 1000 person-years in 2019 (2015 *vs* 2017 p=0·003 and 2015 *vs* 2019 p<0·0001).

Mean age at primary HCV diagnosis in MSM was 42 years (SD 9) and did not substantially vary during follow-up (appendix p 4). Incidence of primary HCV infection was highest between the ages of 30 and 50 years. The proportion of MSM with undetectable HIV RNA at primary HCV diagnosis increased from 69·6% in 2005 to 89·7% in 2019 (appendix p 4), yet no discernible variation was observed in incidence with respect to HIV RNA viral load (appendix p 4). Similarly, mean CD4 count at primary HCV diagnosis in MSM increased from 559 cells per µL in 2005 to 677 cells per µL in 2019 (appendix p 4), and there was little variation in incidence with respect to CD4 count (appendix p 4). Similar findings were observed in MSM with HCV reinfection (appendix p 5).

For primary infections in MSM, the median time from HCV diagnosis to the start of treatment decreased from 21 months (IQR 6–86) between 2005 and 2008 to 5 months (3–8) between 2015 and 2018 (figure 4A; p=0·0001). Accordingly, treatment uptake within 6 months of diagnosis increased from 24·1% between 2005 and 2008 to 48·2% between 2015 and 2018 and within 12 months from 34·4% between 2005 and 2008 to 67·8% between 2015 and 2018 (p<0·0001; figure 4B).

All individuals treated for primary HCV infection received pegylated interferon until 2011 (figure 4C). From then, individuals received pegylated interferon or pegylated interferon with DAA until 2016, from which point all individuals received DAAs. Sustained virological response also significantly increased from 74·6% (95% CI 68·2–80·4) between 2005 and 2008 to 98·0% (95·1–99·5) between 2015 and 2018 (p<0·0001; figure 4D). Similar findings were observed in MSM with HCV reinfection (appendix p 6).

Discussion

MSM with HIV had a 61% overall drop in primary HCV incidence and 79% drop in HCV reinfection incidence in 2019 compared with 2015, 4 years after the introduction of universal access to DAAs for all individuals with HCV infection in the Netherlands. These data provide epidemiological evidence that the unrestricted availability of potent antiviral therapy is contributing to reductions in HCV incidence in MSM. However, this reduction falls short of WHO's goal for micro-elimination, and, given the stable or fluctuating incidence between 2016 and 2019, the WHO target might not be met in 2030. On the basis of

a nationwide database of individuals with HIV, we have observed that the HCV epidemic has disproportionally affected MSM with very few cases of primary HCV infection or reinfection in PWID or heterosexuals even before universal access to DAAs. As indicated in modelling studies,[4,8,17] an increase in sustained virological response with highly effective DAAs would decrease the number of people infected with HCV and consequently prevent transmission.

Other circumstances could have explained the decrease in incidence. Treating physicians have increased awareness of the ongoing HCV epidemic in MSM with HIV, which might have resulted in more frequent HCV testing in this group from 2007 onwards. Incidence could have been simply a reflection of identifying all those unaware of their infection. Yearly testing has remained mostly stable since 2008.

Sexual risk behaviour necessary for HCV transmission could have decreased, resulting in decreases of the spread of HCV in MSM. These behaviours are varied and are not routinely measured in ATHENA. The yearly prevalence of more common sexually transmitted infections (eg, chlamydia, gonorrhoea, and infectious syphilis) has either remained unchanged or has slightly increased in MSM with HIV over the past decade,[18] possibly implying that the proportion engaging in anal sex without condoms, which is associated with an increased risk of HCV transmission, has also been steady. Fisting without gloves and sharing sex toys have also been strongly linked to HCV reinfection, the frequency of which has remained static in the Netherlands from 2010 to 2018.[16] Cocaine use, the sharing of snorting straws, and so-called chemsex (occasionally involving shared injecting equipment) are factors associated with HCV infections that are still frequent in MSM with HIV[19] and have been reportedly increasing over the past decade.[20]

Higher sustained virological response rates for patients with HCV infection were reported in the period shortly before any DAA were available when compared with results from clinical trials investigating the use of pegylated-interferon,[2] possibly because of earlier initiation of pegylated-interferon treatment.[21] There were also several studies actively recruiting MSM with HIV and early HCV infection (DAHHS1,[22] DAHHS2,[23] and REACT [NCT02625909]). However, the only large decrease in HCV infection incidence was observed in the DAHHS2 study,[23] and a modelling study has shown that no difference in HCV incidence would be observed with immediate initiation of DAA therapy compared with initiation of DAA therapy at 6 months.[17] Given these aspects discussed, factors other than DAAs do not seem to explain the drop in incidence in 2016.

The incidence of reinfection in MSM continued to slightly decrease from 2016 to 2019, and, although it was still high at 11 per 1000 person-years in 2019, it was much lower than in other European settings.[16,24] From 2010 to 2015, reinfection rates were variable and although the decrease in incidence since 2015 is encouraging, it could be an artifact of the variation normally seen across Europe.[24] Furthermore, individuals at a higher risk of HCV reinfection, particularly MSM, witnessed a substantial decline in yearly HCV testing from 64% in 2016 to 38% in 2019 (figure 1B). This could have been because of preferential HCV RNA testing when alanine aminotransferase concentrations were elevated, the physicians' view that the HCV epidemic is no longer of concern and hence HCV testing for reinfection is no longer a priority, or reduction in numbers of individuals at high risk of reinfection. This observation might also partly explain the decrease in HCV reinfection incidence rates observed in our cohort.

Albeit significantly reduced, the source of onwards transmission of HCV in the DAA era is unclear. HCV transmission in MSM with HIV is known to occur in widespread networks across Europe.[25] However, research from Switzerland suggests a shift towards more domestic transmission of HCV infection.[26] MSM who do not have HIV who use pre-exposure prophylaxis against HIV have also witnessed high incidence of HCV infection.[27] Phylogenetic evidence suggests clustering of these HCV strains with those from MSM with HIV, but specific risk behaviours are known to be inconsistent within clusters.[28] Studies are needed to find out whether MSM who do not have HIV are a relevant source of undiagnosed HCV. Testing for HCV is currently not standard practice at most sexual health centres in the Netherlands. Of the MSM with HIV in care in 2019, only 43% of those susceptible to primary infection and a much lower 38% susceptible to reinfection were tested for HCV, showing that case finding of HCV (re)infections could also be improved in HIV care.

The major question is how to buttress micro-elimination in a population with already high DAA uptake and regular HCV testing. As the modelling studies suggest,[8,17] some improvement could be made in even earlier initiation of DAA treatment and more frequent or better facilitated access to HCV testing, including in individuals with previous spontaneous clearance or treatment-associated sustained virological response who are susceptible to reinfection. In some settings, behavioural interventions aimed at education and reducing activities associated with HCV acquisition are essential for reducing incidence.[29] Improvements in contact tracing and communication with the community should also be considered. Given that HCV infections are more commonly observed in MSM who do not have HIV, particularly those taking pre-exposure prophylaxis,[27] these public health tools will have to focus on the broader MSM population engaging in high risk behaviours.[30]

Several limitations of the study should be addressed. HCV key populations were determined from HIV transmission and could have been misclassified, particularly for those who acquired HIV via heterosexual or other routes. We depended on laboratory data collected during

routine visits to define HCV infections and assess HCV testing frequency. HIV physicians were recommended to follow HCV testing guidelines from the EACS; however, we were unable to ascertain the adherence to these guidelines. Some cases could be missed by not testing unsuspected or asymptomatic HCV infections and only a few cases of definitive spontaneous clearance were not confirmed with two consecutive HCV RNA negative tests at least 4 weeks apart (ie, EACS definition of spontaneous clearance). The period to determine sustained virological response might have been too short and thus some of the HCV reinfections could have been late relapses, particularly during the interferon era. The testing interval after spontaneous clearance could have also been too short to differentiate reinfection from recrudescence. Nevertheless, the median time until first HCV RNA test to detect HCV reinfection after spontaneous seroclearance was 13 months (IQR 4–37), with 85% of these tests being negative, and 33% of re-infections confirmed by genotype switches, both of which would restrict this error.

In conclusion, a decline in primary HCV infection and HCV reinfection was observed in MSM with HIV in the years following unrestricted access to DAAs in the Netherlands, suggesting a treatment as prevention effect. Our results provide evidence that widespread DAA use is reducing the HCV epidemic in this key population. At the same time, the persisting incidence of primary HCV infection and to a lesser extent HCV reinfection in 2016–19 exemplifies the difficulty in HCV micro-elimination. Increased testing and behavioural interventions for those at risk could assist in meeting this public health challenge.

Contributors

CS, ABoy, and PR contributed to study, conceived of, and designed the study. CS and ABoy did the study analysis. BJAR, EML, WFB, KB, MAAC, JdH, JEA, and MvdV collected the data. BJAR, EML, WFB, KB, MAC, JdH, JEA, MvdV, TJWvdL, ABoe, AMN, JS, MP, and ELModC interpreted the data. CS and ABoy wrote the first draft of the Article. All authors critically revised and approved the final version for publication. CS and ABoy have accessed and verified the underlying data.

Declaration of interests

BJAR reports grants from MSD and Gilead, outside the submitted work and is a member of advisory boards for MSD, Gilead, Pfizer, ViiV Healthcare, Jansen-Cilag, and Abbvie. WFB reports reimbursement of costs inclusion patient in industry-sponsored RCT from GSK and non-financial support from Janssen, all outside the submitted work. KB is an advisory board member for ViiV Healthcare, Gilead, MSD, and Janssen; and reports grants form ViiV Healthcare and Gilead. JS reports grants from Gilead Sciences, outside the submitted work. MP reports grants, personal fees, speakers fees and independent scientific support to their institution from Gilead Sciences, Roche, MSD, and Abbvie, all outside the submitted work. JEA reports fees paid to their institution from Gilead, Janssen-Cilag, Abbvie, Bristol-Myers Squibb, and MSD for advisory membership, all outside the submitted work. MvdV reports grants and personal fees from Abbvie, Gilead, Johnson & Johnson, MSD, and ViiV Healthcare, all outside the submitted work. PR reports grants from Gilead, ViiV Healthcare, and Merck & Co; and honoraria and is an advisory board member for Gilead Sciences, ViiV Healthcare, Merck & Co, and Teva Pharmaceutical Industries, all outside the submitted work. All other authors report no competing interests.

Data sharing

HIV physicians can review the data of their own treatment centre and compare these data with the full Dutch ATHENA cohort through an online report builder. Statistical information or data for own research purposes can be requested by submitting a research proposal (https://www.hiv- monitoring.nl/english/research/research- projects/). For correspondence, contact hiv.monitoring@ amc.uva.nl.

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