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Declining Hepatitis C Virus (HCV) Incidence in Dutch Human Immunodeficiency Virus-Positive Men Who Have Sex With Men After Unrestricted Access to HCV Therapy

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(See the Major Article by Boerekamps et al on pages 1352–9 and the Editorial Commentary by Rockstroh on pages 1366–7.)

Background. Direct-acting antivirals (DAAa) cure hepatitis C virus (HCV) infections in 95% of infected patients. Modeling studies predict that universal HCV treatment will lead to a decrease in the incidence of new infections but real-life data are lacking. The incidence of HCV among Dutch human immunodeficiency virus (HIV)–positive men who have sex with men (MSM) has been high for >10 years. In 2015 DAAs became available to all Dutch HCV patients and resulted in a rapid treatment uptake in HIV-positive MSM. We assessed whether this uptake was followed by a decrease in the incidence of HCV infections.

Methods. Two prospective studies of treatment for acute HCV infection enrolled patients in 17 Dutch HIV centers, having 76% of the total HIV-positive MSM population in care in the Netherlands. Patients were recruited in 2014 and 2016, the years before and after unrestricted DAA availability. We compared the HCV incidence in both years.

Results. The incidence of acute HCV infection decreased from 93 infections during 8290 person-years of follow-up (PYFU) in 2014 (11.2/1000 PYFU; 95% confidence interval [CI], 9.1–13.7) to 49 during 8961 PYFU in 2016 (5.5/1000 PYFU; 4.1–7.2). The incidence rate ratio of 2016 compared with 2014 was 0.49 (95% CI, .35–.69). Simultaneously, a significant increase in the percentage positive syphilis (+2.2%) and gonorrhea (+2.8%) tests in HIV-positive MSM was observed at sexual health clinics across the Netherlands and contradicts a decrease in risk behavior as an alternative explanation.

Conclusions. Unrestricted DAA availability in the Netherlands was followed by a 51% decrease in acute HCV infections among HIV-positive MSM.

Keywords. Incidence; hepatitis C; acute Hepatitis C; direct acting antiviral therapy; men having sex with men.

A high incidence of acute hepatitis C virus (HCV) infections in human immunodeficiency virus (HIV)–positive men who have sex with men (MSM) has been observed in many European countries, as well as in Australia and the United States [1–3]. Indeed, during anal intercourse and additional high-risk behavior with increased likelihood of blood-blood contact, HCV can be readily transmitted from man to man [4]. This contrasts with the very low incidence of transmission during heterosexual contacts [5]. Several recent studies described an *incidence* of acute HCV infection in Dutch HIV-positive MSM of 1.1% or 11/1000 person-years of follow-up (PYFU) [6–8]. This is an extremely high incidence in a country where the overall HCV *prevalence* is estimated at 0.2% [9]. Van Santen et al [10] described a comparably high incidence of acute HCV infection among HIV-positive MSM in several other European countries.

As of July 2014, interferon-free HCV therapy with direct-acting antivirals (DAAs) became reimbursed for all Dutch inhabitants with chronic HCV-induced severe liver fibrosis or cirrhosis. At that time, the very high costs of these drugs were the reason DAA therapy did not became available to all patients infected

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with HCV. Eventually, the restriction to patients with severe liver disease was lifted on 1 November 2015. As a result, the Netherlands was one of the first European countries in which DAA therapy became available to all chronically HCV-infected patients without any restrictions.

We recently showed that the unrestricted DAA availability was followed by a very rapid HCV treatment uptake among HIV-positive MSM with chronic HCV. Indeed, 76% of the Dutch HIV-positive MSM ever infected with HCV were already shown to have their HCV infection cured as of January 2017 [11].

Mathematical modeling studies have predicted that by decreasing the pool of infectious persons in the population, the immediate treatment with DAAs of all HCV-infected HIV-positive MSM would lead to a progressive decline in the incidence of acute HCV infections [12–14]. However, this assumed decline in incidence has yet to be confirmed with real-life observational data. Therefore, the aim of this study was to investigate whether the countrywide rollout of DAAs was followed by a decline in the number of acute HCV infections among HIV-positive MSM within the Netherlands.

PATIENTS AND METHODS

According to Dutch HIV treatment guidelines, HCV infections in HIV-positive MSM attending the HIV outpatient clinic are diagnosed by means of HCV antibody testing (followed by HCV RNA testing when antibody test results are positive) at entry into HIV care. Thereafter, HCV immunoglobulin G testing is performed once a year, and HCV RNA testing is also done if a new alanine aminotransferase (ALT) elevation is observed. Liver enzyme level are measured during the biannual HIV viral load monitoring.

An acute HCV infection was defined as a positive HCV RNA test, preceded by a negative HCV test in the previous 12 months. Because HIV centers in the Netherlands store leftover plasma from each outpatient visit, retesting of superfluous plasma from the preceding outpatient visit was possible in the majority of the patients to confirm that the patient had been HCV negative in the previous year. However, if stored plasma was not available, a new HCV diagnosis was also considered to be an acute HCV infection if a normal ALT measurement within the last 12 months preceded the first positive HCV RNA test and a documented negative HCV test was available from any time in the past and no other possible explanation for the ALT elevation was found [15].

An acute HCV reinfection was defined as a positive HCV RNA test after a previously documented sustained virological response 12 weeks or more after the end of HCV therapy. For patients treated in the Dutch Acute HCV in HIV Studies (DAHHS), in case HCV RNA became detectable again within 12 weeks after the end of therapy, HCV RNA was also genotyped and sequenced to differentiate relapse from reinfection.

Currently there is no systematic registry in place for acute HCV infections in the Netherlands. We therefore used the data from 2 prospective studies as a proxy. The DAHHS group is a network of 17 hospitals that performs multicenter clinical trials on the treatment of acute HCV infection [16, 17]. None of the currently available DAAs have been registered for the treatment of an acute HCV infection. Therefore and to evaluate the effectiveness of DAAs for the treatment of acute HCV infection, the DAHHS1 and DAHHS2 studies were designed. Both are prospective studies that evaluated (DAHHS1 in 2014) or are evaluating (DAHHS2 in 2016 and ongoing) different DAA-based options for the treatment of acute HCV infection. Because these studies enroll patients prospectively, they enabled us to register all acute HCV infections diagnosed in the DAHHS centers and compare the incidence of acute HCV infections among HIV-positive MSM in the year before (2014) and in the first year after (2016) interferon-free DAAs became available for the treatment of chronic HCV infection in the Netherlands.

Patient characteristics were collected by the treating physician and transferred to the study coordinator after pseudonymization. All patients consented to have their data used for research purposes in the context of the HIV AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort [18]. Data on the number of HIV-positive MSM and on the HCV prevalence among HIV-positive MSM in care across all HIV centers in the Netherlands were provided by Stichting HIV Monitoring (HIV Monitoring Foundation), responsible for data collection of the patients in the ATHENA cohort. The ATHENA cohort consists of 98% of the patients in care for a diagnosed HIV infection in the Netherlands [18].

The incidence of acute HCV infection in the year 2014, the last year before DAAs became available, and 2016, the first year after unrestricted DAA availability, was calculated by dividing the number of acute HCV infection cases by the PYFU of all HIV-positive MSM in that year in the 17 study centers. To compare the acute HCV incidence in 2016 with 2014, we calculated the incidence rate ratio (IRR) with 95% confidence intervals (CIs).

Because HCV infections are transmitted sexually among MSM, national data on the incidence of the sexually transmitted diseases (STDs) syphilis and gonorrhea in MSM were used as a surrogate marker for the evaluation of possible trends in sexual risk behavior. These data are provided by the STD/HIV Surveillance Unit of the National Institute for Public Health and Environment, which collects, integrates and interprets data from multiple surveillance sources in the Netherlands, including data from registration by sentinel STD clinics and HIV treatment centers [19, 20].

RESULTS

In 2014, a total of 93 acute HCV infections were diagnosed in the 17 study centers during 8290 PYFU (incidence, 11.2/1000 PYFU; 95% CI, 9.1–13.7). In contrast, 49 acute HCV infections were diagnosed during 8961 PYFU in 2016 (incidence of 5.5/1000 PYFU; 4.1–7.2). Thus, the IRR for 2016 compared with 2014 was 0.49 (95% CI, .35–.69). During the first 4 months of 2017, the incidence was 5.6 per 1000 PYFU (17/3047 PYFU) and comparable to the overall incidence in 2016.

In 2014, the majority of acute HCV infections were caused by HCV genotype 1 (72 of 93; 77%). The proportion of genotype 1 in acute HCV infection decreased in 2016 (27 of 49; 55%) (Figure 1). Consequently, the IRR for genotype 1 infections comparing 2016 with 2014 was 0.35 (95% CI, .22–.54). Looking at the smaller group of genotype 4 infections only, the decline was less pronounced and not statistically significant (IRR, 0.77; 95% CI, .54–1.09). A change in the distribution of the nation of origin of the patients with acute HCV infection of genotype 1 or 4 could not explain the difference in decline in the incidence of genotype 1 and 4. Indeed, 23 of 93 patients with an acute HCV infection diagnosed in 2014 were born outside the Netherlands, comparable to the proportion in 2016 (8 of 49; $P = .29$). Figure 2 illustrates the incidence of acute HCV infection for every 4 months of the calendar year and per genotype in 2014, 2016, and the first 4 months of 2017.

The absolute number of acute HCV infections decreased both in patients with a first acute HCV infection and in patients who had an acute HCV reinfection after a previously cured HCV infection, whereas the proportion of reinfections remained constant between 2014 and 2016 (23% [21 of 93] and 24% [12 of 49], respectively) ($P = .8$) (Table 1).

In the years that preceded the introduction of DAAs, the proportion of HIV-positive MSM in the Netherlands who were HCV RNA positive (and thus a potential source for new infections) was stable, at 4.2 % in 2013 (396 of 9513) and 4.1% in 2015 (450 of 11 070). The unrestricted access to DAAs caused a prompt and substantial decrease of this infectious pool to 1.5% (176 of 11 749) by the end of 2016 (data provided by Stichting HIV Monitoring; Figure 1). Comparing 2016 with 2014, there was a substantial increase in the percentage of positive syphilis (from 6.6% [281 of 4240] to 8.4% [435 of 5185], respectively; $P = .001$) and gonorrhea (from 16.4% [697 of 4239] to 19.2% [1005 of 5228]; $P < .001$) tests among HIV-positive MSM attending sentinel STD clinics in the Netherlands [19, 20].

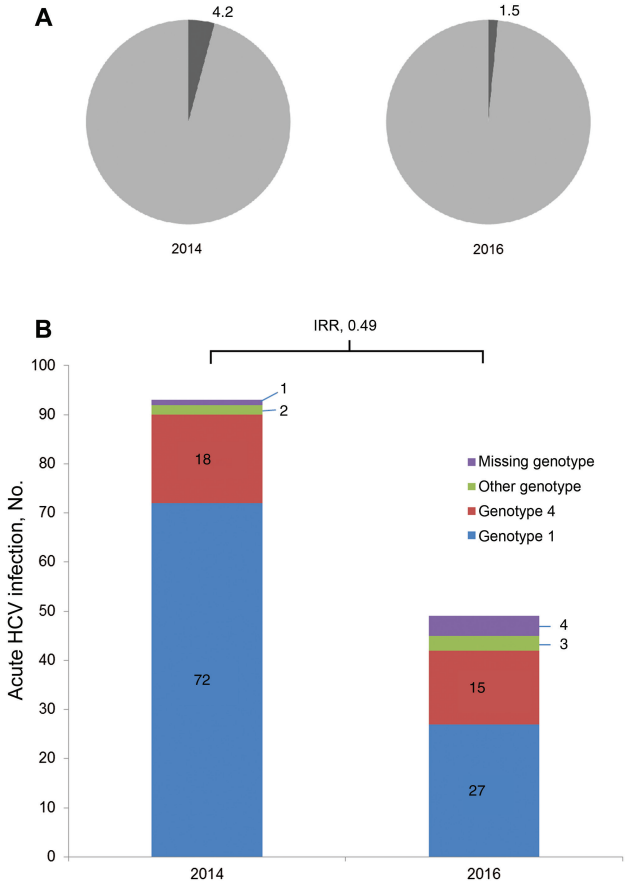

Figure 1. Hepatitis C virus (HCV) infections in human immunodeficiency virus (HIV)–positive men who have sex with men (MSM) in care in the Netherlands. *A,* Percentage of HIV-positive MSM in care in the Netherlands who remained HCV RNA positive in 2014 and 2016. *B,* Number of acute HCV infections in 2014 and 2016. IRR, incidence rate ratio.

DISCUSSION

We observed a 51% decrease in acute HCV infections in 2016 compared with 2014. As far as we know, ours is the first study using real-life data to lend support to what recent modeling studies have predicted: universal HCV therapy for all HIV-positive MSM chronically infected with HCV will decrease the number of acute HCV infections in this population [12–14].

The decline in acute HCV infections was more pronounced for HCV genotype 1 (65% decrease) than for genotype 4 (23%). Treatment of acute HCV infection in the context of the DAHHS1 study (only HCV genotype 1 infections could be treated in this study) may possibly explain the more substantial decrease we observed in genotype 1 infections compared with genotype 4 infections. Indeed, as many as 79% of the 72 patients with an acute HCV genotype 1 infection diagnosed in the 17 study centers in 2014 were treated in the DAHHS1 study, and 86% of them had their infection cured and therefore no longer a source of new genotype 1 infections [15, 16]. However, the chronic HCV treatment uptake among Dutch HIV-positive patients in general did not differ between genotype 1 and 4, and neither was there a difference in uptake in relation to their country of origin, so a disparity in HCV treatment uptake based on country of origin or genotype cannot explain the smaller decrease in the incidence of acute HCV infection of genotype 4 compared with genotype 1. It is well known that outbreaks of acute HCV infection occur frequently and this may have been the case for genotype 4. Indeed, as illustrated in Figure 2, 80% of the genotype 4 infections in 2016 were diagnosed in the first 4 months of 2016.

The incidence of HCV reinfection among HIV-positive MSM with a previously cured HCV infection has historically been very high [21]. Therefore, this subgroup of patients may be at the core of the HCV epidemic. In this regard, it is reassuring that we observed a decrease in the number of HCV reinfections as well (from 21 to 12), despite a substantial increase in the population at risk for reinfection. Indeed, as a result of the HCV treatment

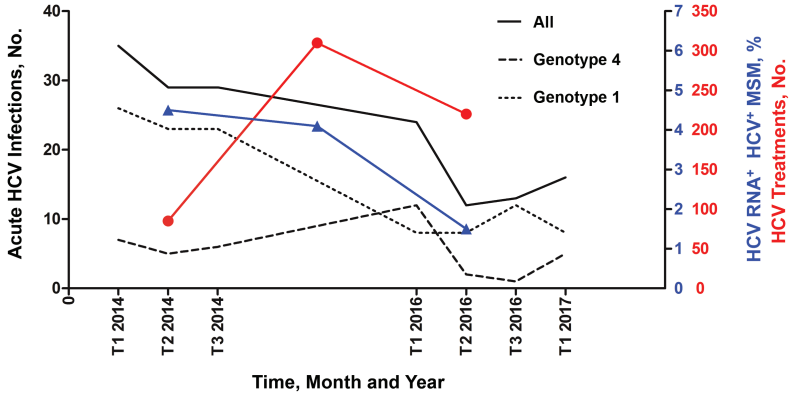

Figure 2. *Left axis,* Acute hepatitis C virus (HCV) infections per 4 months and per genotype. *Right axis,* Percentage of HCV RNA–positive human immunodeficiency virus (HIV)–positive men who have sex with men (MSM) (*blue*) and number of HCV treatments (*red*) in the Netherlands per year (data for both obtained from Stichting HIV Monitoring; personal communication). T1: Jan–Apr; T2: May–Aug; T3: Sept–Dec.

uptake and the consequent decline of HCV RNA positive patients from 4.2% in 2013 to 1.5% at the end of 2016, the number of patients whose HCV infection has been cured and who are therefore at risk for reinfection has increased substantially.

In contrast to the decline in acute HCV infections, the number of MSM with syphilis or gonorrhea diagnosed at STD clinics across the Netherlands increased substantially in 2016. Therefore, it is very unlikely that the decline in acute HCV infections we observed is the result of reduced sexual risk behavior. In 2015, Vanhommerig et al found [4] that in HIV-positive MSM, receptive unprotected anal intercourse, sharing sex toys, unprotected fisting and a recent diagnosis of ulcerative STDs were all independent risk factors for the acquisition of acute HCV infection. Moreover, intravenous drug use (IVDU) before or during sex (also called slamming or "slamsex") was another significant risk factor. However, only 11% (9 of 82) of the patients with an acute HCV infection included in their study reported IVDU as a risk factor. Therefore, we consider it unlikely that a decrease in IVDU among HIV-positive MSM in 2016 compared with 2014 can explain our observations. Second, a recent study into Q80K phylogeny in Dutch HCV genotype 1a–infected patients showed no intermingling of HIV-positive MSM and people who inject drugs (PWID) [22]. Although injection drug use (whether intravenous or subcutaneous) during sex does occur in a small number of HIV-positive MSM [4] and sexual networks seem to be highly dynamic [23], it is unlikely that HCV strains from Dutch PWID fuel the HCV epidemic in Dutch HIV-positive MSM [22].

Table 1. Baseline Characteristics of Patients With Acute Hepatitis C Virus Infection Diagnosed in 2014 or 2016

	Patients With Acute HCV Infection		
Characteristic	2014 (n = 93)	2016 (n = 49)	*P* Value
Age, mean (SD), y	42 (9)	46 (9)	.06
Receiving cART, No. (%)	84 (90)	43 (94)	.53
CD4 cell count, median (IQR), cells/μL	610 (430–810)	620 (465–763)	.86
Reinfection, No. (%)	21 (23)	12 (25)	.75
HCV genotype, No. (%)			
Genotype 1	72 (77)	27 (55)	.02
Genotype 2	2 (2)	1 (2)	
Genotype 3	0	2 (4)	
Genotype 4	18 (19)	15 (31)	
Missing	1 (1)	4 (8)	
HCV genotype 1 subtype, No. (%)			
Subtype a	68 (73)	27 (55)	.57
Subtype b	4 (4)	0	

Abbreviations: cART, combination antiretroviral therapy; HCV, hepatitis C virus; IQR, interquartile range; SD, standard deviation.

The strength of our study is the prospective data collection on the incidence of acute HCV in 17 HIV centers. These 17 centers are representative of the whole of the Netherlands, because they are located in all major Dutch cities and provide HIV therapy to >75% of all HIV-positive MSM in care in the Netherlands.

Our study has several limitations. First, an observational study cannot prove that the DAA uptake is the cause of the decline in the incidence of acute HCV infection. A substantial change in risk behavior may have led to a similar decrease. We did not measure IVDU in our cohort; however, as stated above, IVDU does not seem to be an important risk behavior in Dutch HIV-positive MSM, although this may change over time. Second, from modeling studies in PWID it is known that treatment scale-up can have a bigger impact on a stable versus an increasing HCV epidemic [24]. In contrast to the stable HCV incidence in HIV-positive MSM in the Netherlands, other parts of Europe still see a rising incidence of HCV infections [10], so treatment scale-up may not have the same effect on those epidemics. Therefore, our data should be extrapoloated to other settings with caution.

Third, the proportion of chronically HCV-infected patients, who are very unlikely to have a new acute HCV superinfection diagnosed (because they are already HCV RNA positive) was not subtracted from the total PYFU of HIV-positive MSM in the

incidence calculations. However, excluding them from the IRR calculation would further lower the IRR from 0.49 to 0.47. Fourth, by the end of 2015 a certain number of MSM were living with HIV but were unaware of their HIV infection and therefore not in care. As such, our conclusions cannot be extrapolated to this HIV-infected MSM population. However, in the Netherlands this fraction has been estimated to be small, about 10% [25]. Finally, acute HCV infections often occur in localized outbreaks, and temporary fluctuations in the incidence can be expected; longer-term data are therefore needed to confirm that the decrease we have observed is not the result of an extreme fluctuation by chance.

Although the 51% decrease of acute HCV infections we describe is encouraging, it is very unlikely that DAA therapy for all HCV/HIV-coinfected patients as a single intervention will lead to elimination of HCV among Dutch HIV-positive MSM [12, 13]. This prediction is also suggested by the apparent lack of a further decline in incidence during the first 4 months of 2017. Other interventions are thus needed. First, the incidence of acute HCV infections in HIV-positive MSM is high in major cities of all countries neighboring the Netherlands [26, 27]. Owing to the continuous restrictions of DAAs to patients with severe liver disease in some of these countries, the DAA treatment uptake there has been limited. Therefore, cross-border HCV transmissions will continue to occur as long as comparable treatment uptake does not occur in neighboring countries [28].

Second, although in the Netherlands the prevalence of HCV infection in HIV-negative MSM attending STD clinics [7] and the number of reported cases of acute HCV infection in HIV-negative MSM has been low [29], the prevalence is probably substantially higher in a certain subset of MSM. Exemplary for this are the very recent observations in an HIV preexposure prophylaxis (PrEP) implementation project in Amsterdam. On entering the PrEP program 15 patients (4%) had detectable HCV RNA [30]. Risk compensation and an increase in the incidence of STD during PrEP use may also occur and could lead to an increase in HCV transmission among PrEP recipients [31]. We therefore think that the prevalence of HCV must be monitored among HIV-negative MSM engaging in unprotected anal intercourse, and in particular MSM receiving PrEP.

Third, several studies have observed an extremely high acute HCV reinfection rate in patients with a previously cured HCV infection [26, 32, 33]. Therefore, a specific focus on HIV-positive MSM with a history of an HCV infection is needed. This may consist of very frequent HCV testing (eg, every 3 months) with the aim of diagnosing and treating HCV reinfections as early as possible [34]. Last but not least, counseling on sexual risk behavior is important, along with, when appropriate, referral to specialized clinics for problematic recreational drug use in the context of "chemsex" or slamsex [13], because not only IVDU but also orally administrated drugs seem to be associated with HCV transmission among HIV-positive MSM [4].

In conclusion, a 51% decrease in acute HCV infections was observed among HIV-positive MSM in 2016 compared with 2014. An HCV "treatment as prevention" effect caused by the rapid DAA treatment uptake among HIV-positive MSM with chronic HCV is the most plausible explanation for this decline.

Notes

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