BRIEF REPORT

Impact of Direct-Acting Antivirals on the Burden of HCV Infection Among Persons Who Inject Drugs and Men Who Have Sex With Men in the Swiss HIV Cohort Study

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In the Swiss HIV Cohort Study, the number of people who inject drugs with replicating hepatitis C virus (HCV) infection decreased substantially after the introduction of direct-acting antivirals (DAAs). Among men who have sex with men, the increase in DAA uptake and efficacy was counterbalanced by frequent incident HCV infections.

Keywords. DAA; HCV; viral replication; PWID; MSM.

Hepatitis C virus (HCV) infection is a major cause of liver cancer and mortality among HIV-infected patients [1]. Achieving a sustained virological response (SVR) substantially reduces HCV-related mortality and morbidity and prevents further HCV transmission [2]. After the approval of interferon-free second-generation direct-acting antivirals (DAAs) in Switzerland, we observed a 4-fold increase in treatment uptake and a 2-fold increase in treatment efficacy, with an SVR rate above 90% across all HCV genotypes [3]. Previous modeling studies indicated that a major increase in DAA treatment uptake has the potential to curb the HCV epidemic [4, 5]. But depending on risk behavior and background prevalence, this may not be sufficient to reduce HCV incidence and prevalence among all people living with HIV (PLWH) [5]. In populations with increasing risk behavior, the impact of treatment upscale can be counterbalanced by frequent incident infections. Such is the case among HIV-infected men who have sex with men (MSM), for whom a substantial decrease in the number of people with replicating HCV infection may not occur despite treatment upscale [4].

Understanding the trends in the number of PLWH with replicating HCV infection in key populations is paramount to achieving the World Health Organization elimination targets by 2030 (www.who.int/hepatitis/publications/global-hepatitis-report2017/en). The aim of this study was to describe and compare DAA upscale and its impact on the number of replicating HCV infections among people who inject drugs (PWID) and MSM. The Swiss HIV Cohort Study (SHCS) provides an optimal framework to address these trends in routine clinical practice in a nationwide representative population.

METHODS

All MSM and PWID enrolled in the SHCS (www.shcs.ch) with follow-up between June 2005 and June 2016 were included. Detailed clinical and laboratory data were recorded at study entry and every 6 months thereafter. HCV infection assessments included yearly serology followed by HCV RNA determination in seropositive individuals, as well as a detailed treatment history, as described previously [3].

We estimated the absolute number of prevalent and incident (primary and re-infections) HCV infections over time among PWID and MSM separately. For incident infections, we also calculated incidence as events per 100 patient-years of individual follow-up time:

Prevalent HCV Infection

Positive HCV serology with detectable HCV viral load (VL) at registration in the SHCS.

Incident Primary HCV Infection

New positive HCV serology with a previous negative HCV serology.

Incident HCV Re-infection

Detectable HCV VL measurement after a patient had achieved spontaneous clearance or SVR (see definition below). Patients

were considered at risk of re-infection following HCV clearance and until the last available HCV RNA measurement.

Temporal trends in distribution of patients across the following 3 categories were assessed at weekly intervals as follows: The number of patients with *replicating HCV infection* was estimated as the sum of patients with prevalent and incident HCV infections at every time point. *Spontaneous clearance* was defined as 2 consecutive undetectable HCV VLs within 6 months after a positive HCV VL measurement without a history of HCV treatment, or a positive HCV serology at enrollment in the SHCS and undetectable HCV VL in the first available measurement. *Sustained virological response* was defined as undetectable HCV VL for at least 6 months after successful antiviral therapy of a replicating HCV infection with either interferon-based or DAA-based therapy.

We estimated the incidence of HCV treatment for the study period stratified by type of treatment (DAA-based therapy vs treatment with pegylated interferon/ribavirin) and HIV transmission group (PWID vs MSM). All calculations were performed using R.

RESULTS

Five thousand two hundred sixty-seven MSM and 1805 PWID were followed by the SHCS over the study period, resulting in 38 693 and 14 748 person-years of follow-up for MSM and PWID, respectively (Supplementary Figure 1). Of those, 1455 PWID and 314 MSM had a positive HCV serology and at least 1 RNA measurement during follow-up. Median follow-up (IQR) was 11.1 (5.0–11.4) years for PWID and 5.4 (2.5–9.9) years for MSM. Sixteen MSM and 330 PWID died during the study period. The incidence of interferon-based therapy initiation was higher in MSM (11.1/100 person-years [py]) than in PWID (4.1/100 py) and dropped to almost 0 in 2015 in both groups (Figure 1A). DAAs were approved in Switzerland in April 2014. At the time, treatment was restricted to patients with advanced fibrosis or cirrhosis (Metavir ≥F3) or defined extrahepatic manifestation of chronic HCV infection. In August 2015, the threshold was reduced to Metavir F2. At the start of the DAA era, 19% of PWID and 17% of MSM had an advanced liver fibrosis or cirrhosis and thus fulfilled the fibrosis requirements for reimbursement. The incidence of DAA treatments increased rapidly
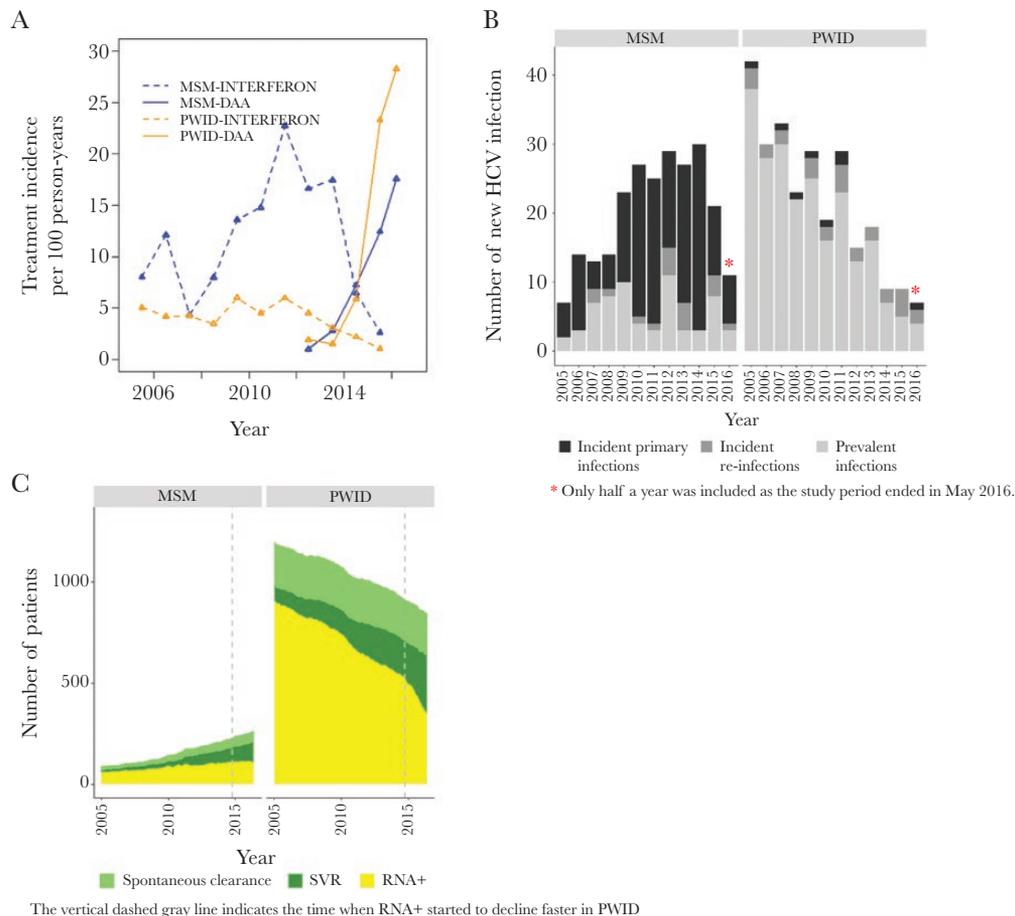

Figure 1. A, Direct-acting antiretroviral (DAA)– and interferon-based treatment uptake (incidence). B, Number and distribution of new hepatitis C virus (HCV) infections. C, Distribution of people who inject drugs (PWID) and men who have sex with men (MSM) among spontaneous clearers, treatment-induced clearance (sustained virological response [SVR]), and replicating infection (RNA+).

from 2012 on and reached 28.3 and 17.6/100 py for PWID and MSM, respectively, in 2016.

The number of incident primary HCV infections during the study period was much higher among MSM than PWID (incident primary infections: 159 in MSM vs 8 in PWID) (Figure 1B). In MSM, the incidence of primary infections increased from 0.2/100 (95% CI: 0.1–0.5) to 0.9/100 (95% CI: 0.4–1.9) py. In PWID, there was only 1 case of primary infection since 2012. The incidence of reinfection increased in MSM (from 0/100 [95% CI: 0–242.3] to 9.5/100 [95% CI: 0.2–53.1]), whereas it decreased 3-fold in PWID (from 13/100 [95% CI: 2.7–38.0] to 4.7/100 [95% CI: 0.6–16.8]). The total numbers of reinfections were 17 and 28 among MSM and PWID, respectively.

Figure 1C shows the distribution of HCV-infected patients among the 3 categories (spontaneous clearance, SVR, and replicating HCV infection) over the study period. Although the number of patients with replicating HCV infection consistently declined in PWID (from 889 to 351), it increased in MSM (from 62 to 110). From October 2014 onwards, we noticed a faster decline in the number of patients with replicating HCV infection in PWID (indicated with the dashed grey line in Figure 1C). Between October 2015 and the end of the study period (May 31, 2016), the number of PWID with replicating HCV infection decreased at an approximate rate of 129 patients per year (from 525 to 314). In contrast, the number of MSM with replicating HCV remained stable over the same period.

DISCUSSION

The trends in the number of patients with replicating HCV infection differed substantially between PWID and MSM in this nationwide representative cohort study. Among PWID, the introduction of DAAs boosted the already ongoing decline in the burden of HCV infection. In MSM, the increase in treatment uptake and efficacy after introduction of DAAs was counterbalanced by high numbers of primary and re-infections. Accordingly, the introduction of DAAs did not result in a decline in the number of MSM with replicating HCV infection.

In PWID, the number of new HCV infections steadily declined over time. We previously reported a decrease in HCV incidence in this population [6]. This can be mainly attributed to the success of opioid and needle exchange programs. In line with previous studies [7], we also observed a 3-fold decline in re-infections, resulting in a decreased rate (4.7/100 [95% CI: 0.6–16.8] py) at the end of the study period, as well as very few primary infections (1 since 2012). The low rate of incident HCV and HIV infections and treatment upscale in recent years contributed to a substantial decline in the number of patients with replicating infection. The rapid upscale of treatment among PWID might have a population-level prevention benefit by reducing the reservoir of HCV viremic persons. Our study lines up with previous modeling work suggesting that treatment upscale among PWID combined with harm reduction programs would substantially reduce the number of patients with replicating HCV infection [8].

HCV has continued to spread among HIV-infected MSM in recent years, although the total number of patients with replication infection remains significantly lower than among PWID [9]. In the SHCS, HCV incidence increased substantially in MSM whereas it declined in PWID [6]. The increase has been linked to changes in sexual risk behavior and recreational drug use. During the study period, we observed a high number of primary HCV infections, and the incidence of HCV re-infections increased and reached 9.5/100 (95% CI: 0.4–1.9) py at the end of the study period. Ingiliz et al. found a re-infection incidence of 7.3/100 (95% CI: 6.2–8.6) among HIV-positive MSM, with 25% being re-infected at 3 years [10]. Our previous modeling studies indicated that treatment upscale would reduce HCV infection incidence and prevalence if risk behavior stabilized or decreased [5]. The current study demonstrates that the number of patients with replication HCV infection did not decrease despite an increase in treatment-induced HCV cure after the introduction of DAAs.

Until recently, reimbursement for DAAs was restricted to those with significant fibrosis in Switzerland and many other countries. At the start of the DAA era, less than 20% of individuals fulfilled the fibrosis reimbursement criteria, with no significant differences between MSM and PWID. This limitation substantially prolongs the time individuals spend with replicating HCV infection. This may have led to further HCV transmissions among HIV-infected MSM with high-risk behavior and might have contributed to the lack of decline in the number of replicating HCV infections observed in this study. The Swiss HCVree trial (ClinicalTrials.gov: NCT02785666) investigates the impact of an intensive HCV RNA–based screening, treatment irrespective of fibrosis stage, and behavioral intervention on HCV prevalence and incidence in MSM participating in the SHCS [11]. The experience from the Netherlands indicates that a massive treatment scale-up could indeed reduce HCV incidence in this population [12]. Future analyses will reveal to what extent intensified treatment and risk reduction decrease the burden of HCV infection among MSM.

Our study was strengthened by the availability of long-term data on HCV replication and treatment in a large, nationwide representative cohort study. We were able to assess long-term trends in the number of patients with replicating HCV infection in a clinical routine situation. Our study has limitations. Re-infections were assessed in clinical routine following international guidelines, but not according to a standardized protocol for repeated HCV RNA screening. Therefore, the rate of re-infections could have been underestimated. In addition, the number of patients who died or left the cohort was higher among PWID than MSM, which makes it difficult to compare both groups with regard to the number of patients with replicating HCV infection.

In conclusion, the increase in treatment uptake and efficacy observed after the approval of DAAs boosted the decline of replicating HCV infections among PWID in the SHCS. However, among MSM, the potential beneficial impact of new treatments was counterbalanced by the high rate of incident HCV infections and by postponing treatment because of reimbursement limitations.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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