Incident Hepatitis C Virus Infections in the Swiss HIV Cohort Study: Changes in Treatment Uptake and Outcomes Between 1991 and 2013

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Background. The hepatitis C virus (HCV) epidemic is evolving rapidly in patients infected with human immunodeficiency virus (HIV). We aimed to describe changes in treatment uptake and outcomes of incident HCV infections before and after 2006, the time-point at which major changes in HCV epidemic became apparent.

Methods. We included all adults with an incident HCV infection before June 2012 in the Swiss HIV Cohort Study, a prospective nationwide representative cohort of individuals infected with HIV. We assessed the following outcomes by time period: the proportion of patients starting an HCV therapy, the proportion of treated patients achieving a sustained virological response (SVR), and the proportion of patients with persistent HCV infection during follow-up.

Results. Of 193 patients with an HCV seroconversion, 106 were diagnosed before and 87 after January 2006. The proportion of men who have sex with men increased from 24% before to 85% after 2006 ($P < .001$). Hepatitis C virus treatment uptake increased from 33% before 2006 to 77% after 2006 ($P < .001$). Treatment was started during early infection in 22% of patients before and 91% after 2006 ($P < .001$). An SVR was achieved in 78% and 29% ($P = .01$) of patients treated during early and chronic HCV infection. The probability of having a detectable viral load 5 years after diagnosis was 0.67 (95% confidence interval [CI], 0.58–0.77) in the group diagnosed before 2006 and 0.24 (95% CI, 0.16–0.35) in the other group ($P < .001$).

Conclusions. In recent years, increased uptake and earlier initiation of HCV therapy among patients with incident infections significantly reduced the proportion of patients with replicating HCV.

Keywords. acute HCV; treatment outcomes; treatment uptake.

We recently observed dramatic changes in the hepatitis C virus (HCV) infection epidemic in the Swiss HIV Cohort Study (SHCS), including an 18-fold incidence increase in men who have sex with men (MSM) [1]. Hepatitis C virus infection is a major cause of morbidity and mortality in patients infected with human immunodeficiency virus (HIV) and, if left untreated, often leads to liver cirrhosis and hepatocellular carcinoma [2]. The long-term trends in treatment uptake and outcomes of incident HCV infections are largely unknown. Because spontaneous clearance of the virus is only seen in a minority of patients [3, 4], most individuals infected with HIV with an acute HCV infection would benefit from early diagnosis and treatment. Sustained virological response (SVR) rates of 60%–80% have been observed in selected groups of patients infected with HIV if antiviral therapy with pegylated interferon (Peg-IFN) and ribavirin (RBV) was initiated within 1 year after

HCV diagnosis [5, 6]. However, no clinical trial comparing the success of early versus deferred HCV therapy in patients infected with HIV have been performed to date, and previous observational studies were limited by small patient numbers or restricted to outbreaks in large urban centers [7–9].

Early diagnosis of HCV infections and uptake of treatment have generally been suboptimal in most HIV clinics [10, 11]. This implies that despite the availability of effective HCV therapy, the overall burden of liver disease due to HCV in patients infected with HIV remains very high and that HIV/HCV-coinfected patients can transmit HCV for many years. Thus, it is now evident that a relevant impact on global HCV transmission and HCV-related mortality will only be achieved if uptake of treatment is massively increased [12, 13]. In recent years, the concept of a cascade or pyramid of care for HIV infection has attracted much attention from public health authorities, in both low- and high-income countries, and helped evaluate and improve the progress of HIV care [14, 15]. The evaluation of HCV care and treatment programs with a similar approach would help identify the most important gaps in HCV management and inform future strategies and policies regarding HCV management.

We studied the natural history and treatment uptake of all incident HCV infections between 1991 and 2012 in a nationwide HIV cohort and compared HCV treatment outcomes between patients who experienced a seroconversion before and after the first description of the surging epidemic among MSM in 2005 [16–18]. We also intended to show the impact of early treatment on the pyramid of HCV care and the proportion of the population with a detectable viral load.

METHODS

Swiss HIV Cohort Study

The SHCS (www.shcs.ch) is a prospective nationwide cohort study with ongoing enrollment of adults infected with HIV in Switzerland since 1988. It covers approximately 50% of the cumulative number of HIV infections declared to the Swiss public health authorities and 75% of patients receiving antiretroviral therapy (ART) in Switzerland [19]. Detailed information on demographics, mode of HIV acquisition, risk behavior, clinical events, coinfections, and treatment is collected using a standard protocol at registration and then at 6-month intervals. All participants are screened for HCV infection at study entry. Since 1998, HCV serology is repeated at least every 24 months in all patients. Local ethical committees of all participating study sites have approved the study, and written consent has been obtained from all participants.

Inclusion Criteria and Definitions

All patients with a documented HCV seroconversion before June 2012 and a follow-up of at least 6 months thereafter

were considered. Patients who had a single positive anti-HCV antibody test but a negative immunoblot, no positive RNA measurement, and negative follow-up anti-HCV antibody tests were classified as false-positives and excluded from the analyses. Natural history and treatment outcomes were defined as follows: spontaneous clearance, single negative HCV viral load after a confirmed incident infection without any HCV treatment; SVR, undetectable HCV RNA 6 months after completion of HCV treatment; persistent infection, detectable HCV RNA at least 1 year after diagnosis of incident HCV infection; reinfection, either an HCV genotype switch after a first infection or a newly detectable HCV viral load after spontaneous clearance or treatment-induced SVR; early infection, within 12 months of HCV diagnosis. The latter definition takes into account previous studies that demonstrated that high SVR are achieved if HCV treatment is started within the first year after seroconversion [6].

Data Collection

In addition to the individual data collected routinely within the framework of the SHCS, we performed medical chart reviews to collect detailed information on HCV diagnosis, natural history, and treatment using standardized case report forms. The reasons (from the provider's perspective) for not starting HCV treatment, as well as symptoms and side-effects leading to an HCV treatment interruption or dosage adaptation, were also retrieved. Furthermore, all additional HCV viral load and transaminase measurements were included. *IL28B* genotypes were determined using TaqMan Genotyping Master Mix (Life Technologies, Carlsbad, CA), as described previously [20].

Statistical Analyses

Baseline demographic and clinical characteristics at time of HCV seroconversion were described using absolute numbers and proportions, or medians and interquartile ranges, and were compared between time periods (before and after January 1, 2006) using the χ^2, Fisher's exact, or Mann–Whitney U test, where appropriate. January 2006 was chosen because by then the first reports on the possible sexual transmission of HCV in MSM in Europe had been published, and the awareness of this epidemiological trend among physicians and public health authorities was increasing in Switzerland [16–18, 21]. Similarly, natural history as well as treatment uptake were compared between time periods. Hepatitis C virus therapy outcomes were compared between patients who received treatment during the first year after seroconversion ("early infection") and the others. Kaplan–Meier analyses were used to compare the probability of HCV suppression over time between patients diagnosed before and after 2006. For the latter analysis, follow-up was censored at first HCV suppression, death, or drop out, whichever happened first. This analysis included only follow-up time after 2002 because HCV viral load measurements were infrequent

before that year. All statistical analyses were performed using Stata 12.0 (Stata Corp, College Station, TX) and R version 3.0.2 with the survival and ggplot2 (http://cran.r-project.org/web/packages/ggplot2/index.html) and survival (http://cran.r-project.org/web/packages/survival/index.html) special packages.

RESULTS

Patient Characteristics

Of 237 patients with a newly positive screening HCV serology, 34 were considered false-positives and 203 were HCV seroconversions. Ten additional patients were excluded due to insufficient information. The baseline demographic and clinical characteristics of the 193 patients included in our analyses are shown in Table 1. One hundred six patients were diagnosed with an incident HCV infection before 2006, and 87 patients were diagnosed after January 2006. Patients with incident infections diagnosed from 2006 onwards were more likely to be

MSM (85% vs 24%, $P < .001$) and to be on ART (94% vs 76%, $P < .001$) compared with individuals diagnosed before 2006. Of 64 HCV infections in people who inject drugs (PWID), only 4 were diagnosed after 2006. Patients with acute HCV infections after 2006 had a higher sexual risk behavior than those diagnosed in earlier years: the proportion with inconsistent condom use (78% vs 33%, $P < .001$), occasional sexual partners (84% vs 26%, $P < .001$), and history of syphilis (45% vs 7%, $P < .001$) was higher after 2006. Hepatitis C virus genotype 1 was more frequent after 2006 (57% vs 49%), whereas the proportion of genotype 3 infections decreased after January 2006 (19% vs 25% before 2006). The proportion of genotype 4 infections remained stable over time, and only 3 patients had a genotype 2 infection.

Natural Course and Treatment Uptake

A spontaneous clearance was observed in 48 cases (32% of those not treated during acute infection) (Figure 1). Treatment uptake changed over time, with a major increase from 2006 onwards (Supplementary Figure 1). Overall, 49 patients (25%) were treated during the early phase of HCV infection, and 96 patients (50%) progressed to chronic HCV infection. Hepatitis C virus treatment uptake increased from 33% before 2006 to 77% after 2006 ($P < .001$). Among those treated, only 22% (6 patients, including 3 MSM) started treatment during early infection before 2006, compared with 91% (43 patients, including 40 MSM) after 2006 ($P < .001$). Among patients without spontaneous clearance, HCV treatment uptake was higher in MSM compared with PWID before (21% vs 0%) and after 2006 (71% vs 50%). Of 96 patients with persistent infection, only 25 (26%) were treated during follow-up. The most frequent reasons for patients diagnosed before 2006 not to be treated were "persistent alcohol or drug abuse" (25%), followed by "patient's refusal" (21%). After 2006, "other psychiatric comorbidities" and "waiting for new direct-acting antivirals (DAAs)" became additional important reason for not starting therapy (20% each). Past noninjecting drug use was not a barrier for early HCV therapy: for patients diagnosed after 2006, it was reported in 56% of patients with early HCV therapy, compared with 44% in those with spontaneous clearance and 47% in patients who were not treated for HCV. Overall, 11 patients experienced an HCV reinfection, including 9 MSM and 2 PWID. Of these, 6 patients (all MSM) had a reinfection after a treatment-induced SVR, and 5 patients had a reinfection after spontaneous clearance. In total, 23 (12%) patients died during follow-up.

Treatment Outcomes

Seventy of 74 treated patients had an available treatment outcome at time of database closure and were included in this analysis. All patients were treated with Peg-IFN and RBV, but DAAs were not used. An SVR was achieved in 78% and 29% ($P = .01$) of patients treated during early and chronic HCV infection,
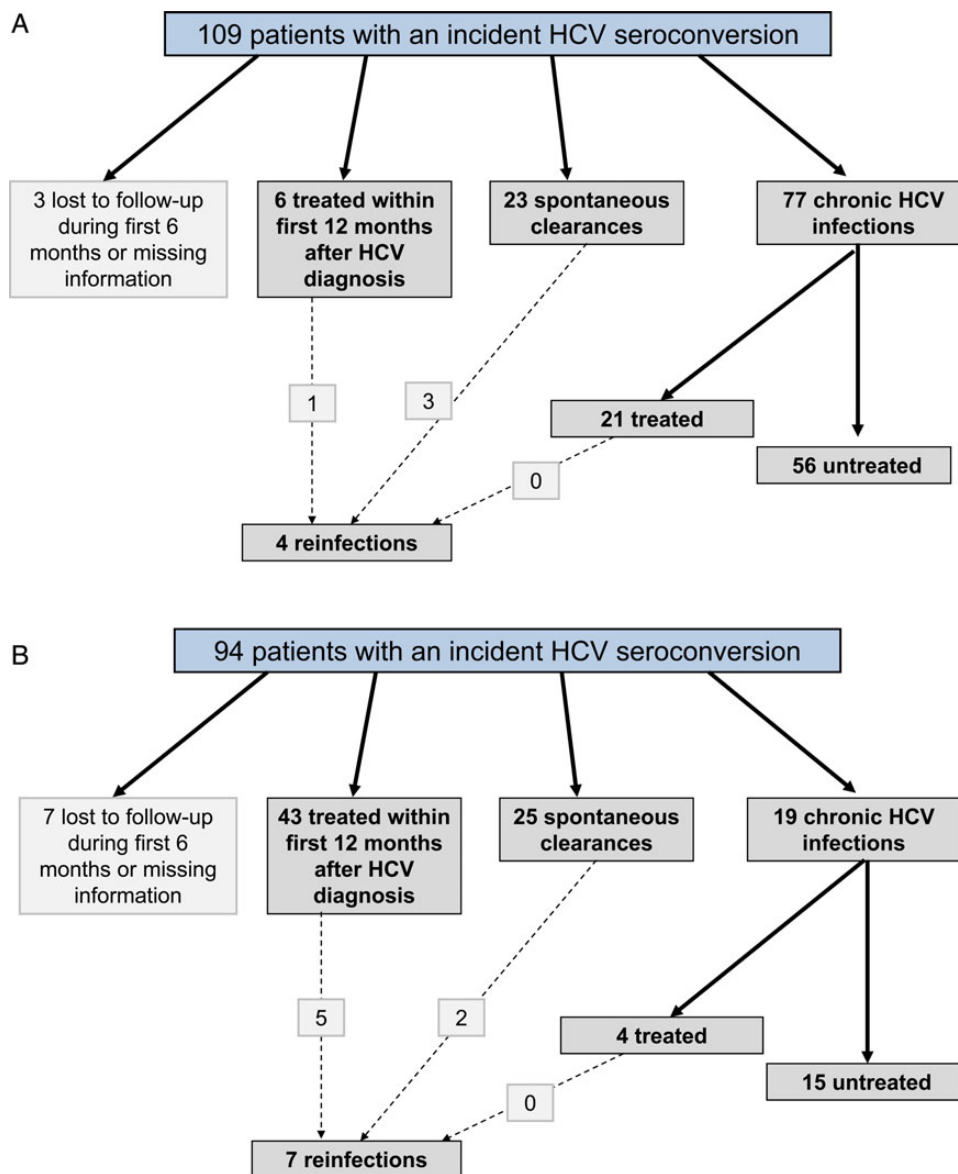
Table 1. Characteristics of Patients With Incident HCV Infection in the Swiss HIV Cohort Study at Time of Diagnosis

Characteristic	Diagnosis Before Jan 2006 (n = 106)	Diagnosis During or After Jan 2006 (n = 87)	P Value
Female sex (%)	29 (27.4)	4 (4.6)	<.001
Median age in years (IQR)	31 (28–39)	34 (30–40)	.03
Median CD4 in cells/µL (IQR)	363 (220–613)	507 (359–675)	.001
On ART (%)	80 (75.5)	82 (94.3)	<.001
Suppressed HIV VL (%)	58 (54.7)	69 (79.3)	<.001
Occasional sexual partners (%)	27 (25.5)	73 (83.9)	<.001
Inconsistent condom use (%)	35 (33.0)	68 (78.2)	<.001
History of syphilis (%)	7 (6.6)	39 (44.8)	<.001
HIV transmission group (%)			<.001
MSM	25 (23.6)	74 (85.1)	
PWID	60 (56.6)	4 (4.6)	
HET	15 (14.2)	7 (8.1)	
Other	6 (5.7)	2 (2.3)	
HCV genotype (n = 136)			.01
1	34 (49.3)	38 (56.7)	
2	2 (2.9)	1 (1.5)	
3	17 (24.6)	13 (19.4)	
4	16 (23.2)	15 (22.4)	

Abbreviations: ART, antiretroviral therapy; HCV, hepatitis C infection; HET, heterosexual; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; PWID, people who inject drugs; VL, viral load.

Figure 1. Natural course of hepatitis C virus (HCV) infection and treatment uptake in HIV-infected patients with incident HCV infection before (A) and after (B) January 2006.

respectively (Figure 2). In patients treated during early HCV infection, SVR was high irrespective of the *IL28B* genotype (19 of 25 [76%] in C/C and 16 of 20 [80%] in non-C/C genotypes), whereas SVR differed between *IL28B* genotypes in those treated during chronic infection (3 of 6 [50%] vs 4 of 16 [25%] in CC and non-CC, respectively). Among patients treated during early infection, there was no significant difference in SVR rates between genotypes: genotype 1, 17 of 26 (65%); genotype 2, 2 of 2 (100%); genotype 3, 8 of 8 (100%); genotype 4, 7 of 8 (88%) (*P* = .14). Of 46 patients treated during the early phase of infection, only 9 (20%) experienced a relapse or a nonresponse, whereas this proportion reached 50% in those treated during the chronic phase of infection.

Pyramid of Care and Population Effect

Before 2006, only 33% of patients without spontaneous clearance of HCV were treated for their HCV infection, and 12% patients achieved a treatment-induced SVR overall (Figure 3). If the 23 patients with a spontaneous clearance were added to this estimation, the overall proportion with a resolved infection in this time period was 31%. In comparison, after 2006, 77% of patients without a spontaneous clearance were treated, and 53% achieved a SVR. Adding the 25 spontaneous clearances during this period resulted in an overall proportion of individuals with a resolved infection reaching 67%. Figure 4A shows the Kaplan–Meier curves of HCV viral load detectability by time period, over a total of 706 person-years of follow-up. The 5-year
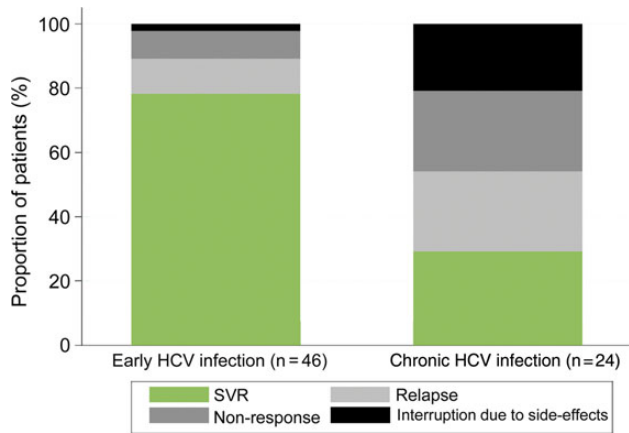
Figure 2. Hepatitis C virus (HCV) treatment outcomes by stage of infection. Abbreviation: SVR, sustained virological response.

probability of having a detectable viral load was 0.67 (95% confidence interval [CI], 0.58–0.77) in the group diagnosed before 2006 and 0.24 (95% CI, 0.16–0.35) in the other group (log rank test; $P < .001$). The overall proportion of patients with a detectable HCV viral load in the cohort decreased over time, from 0.95 (95% CI, 0.84–0.98) in 2002 to 0.70 (95% CI, 0.61–0.77) in 2012 (Figure 4B). The full picture of individual HCV viral loads over time in the whole cohort is shown in Supplementary Figure 2.

DISCUSSION

In this nationwide cohort of patients infected with HIV with an incident HCV infection, overall treatment uptake during early infection was low, but it improved after 2006, the year after the dissemination of the first reports on sexual transmission of HCV in HIV-infected MSM. After 2006, 85% of acute HCV infections were observed in MSM. These patients were much more likely to be treated during early stages of infection compared with patients diagnosed before 2006, who were mainly PWID. In HCV infections treated during the first year after diagnosis, an SVR was reached in 78% of cases, compared with only 29% in those treated during chronic infection. Improved treatment uptake after 2006 led to a continuous decrease in the overall proportion of patients with a detectable HCV viral load.

Trends in the epidemiology of HCV infections among patients infected with HIV are rapidly evolving. This nationwide observational study underlines these changes, because the proportion of MSM in acute HCV infections increased from 24% before 2006 to 85% after 2006. We previously showed that this increase was associated with high-risk sexual behavior, including a history of past syphilis infection [1]. The present study highlights the dramatic change in sociobehavioral trends of the population affected by the HCV epidemic: from mainly PWID before 2006 to MSM with stable HIV infections under ART but poor condom use and frequent occasional partners after January 2006.
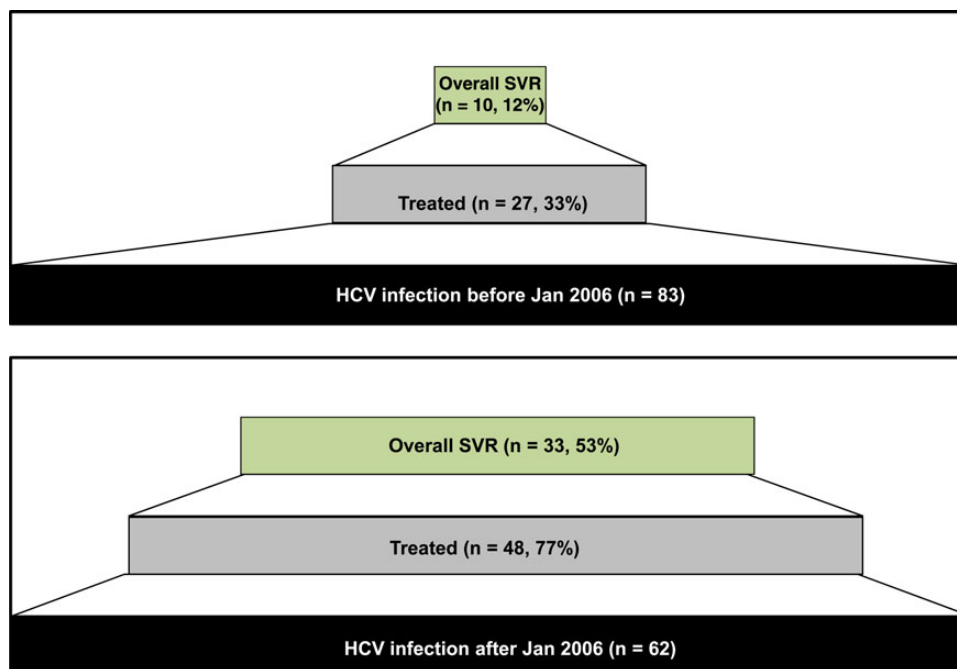
Figure 3. Pyramid of care for incident hepatitis C virus (HCV) infections in the Swiss HIV Cohort Study. (Patients with spontaneous clearance of HCV have been excluded from this analysis.) Abbreviation: SVR, sustained virological response.
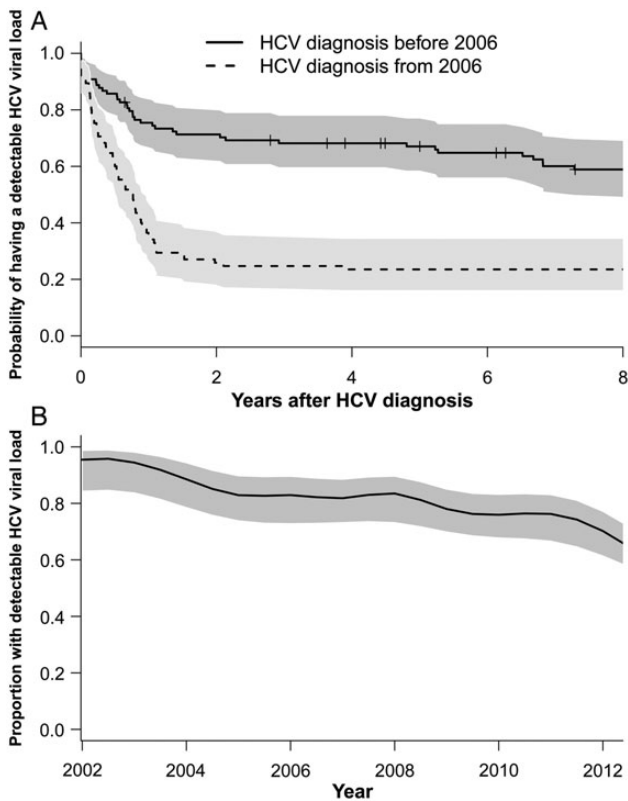
Figure 4. Impact of treatment uptake on cumulative probability of having a detectable hepatitis C virus (HCV) viral load (A) and on the proportion in patients with incident HCV infections (B)

Hepatitis C virus therapy outcomes with Peg-IFN and RBV are improved when treatment is started during the early phase of infection, as shown in large trials of HCV-monoinfected patients [22] and in several observational studies in cohorts of patients infected with HIV [7, 8]. Our results confirm these findings, because 78% of the patients treated within the first year after HCV seroconversion achieved an SVR. This estimate was slightly higher than what was observed in a multi-center European cohort study (62% SVR) [7]. In accordance with the results from a large HIV cohort collaboration [23], *IL28B* genotype did not have an impact on acute HCV treatment outcomes in the SHCS.

Early HCV diagnosis and treatment uptake are 2 of the most important bottlenecks towards the eradication of HCV infection [12, 13, 24]. Treatment uptake for acute and chronic HCV infections has been consistently poor in most settings. In a single center of the SHCS, only 8% of the patients chronically infected started treatment with Peg-IFN and RBV by 2005 [10]. In the present study, we showed that before 2006, only a minority of patients with an acute HCV infection was treated accordingly. However, we observed a dramatic improvement in treatment uptake after 2006: three quarters of acute HCV

infections were treated, including a large majority at an early stage of infection, leading to a 2-fold increase in the overall proportion of patients with a resolved infection in recent years. The reports on the high cure rates that can be achieved if treatment is started during acute infection were the rationale for starting treatment before chronic HCV infection was established [25]. However, there are several additional reasons for this major increase in treatment uptake: the most obvious one is the recent changes in the characteristics of the populations infected with an acute HCV. Treating MSM under stable ART and living in good socioeconomic situations is often seen as being easier to implement compared with the management of PWID in unstable conditions. This is in part reflected by the reasons for failing to initiate HCV therapy in our study; as expected, these reasons changed over time, mainly due to the comorbidities of the risk population. Continuous substance abuse, an important issue in assessing treatment eligibility in PWID, was replaced by other psychiatric comorbidities in the most frequent reason for not starting HCV therapy as an increasing number of noninjecting MSM became infected. This underlines the need for the ongoing optimal appraisal of psychiatric comorbidities in all HIV/HCV-coinfected patients and gives rise to the hope that this barrier will be less important in the context of HCV treatment with new DAAs. However, several reports demonstrated that HCV therapy is feasible despite ongoing substance abuse and, in light of its individual and public health benefits, should not be withheld in patients willing to initiate anti-HCV therapy [26]. Unlike in MSM, none of the PWID in our study had a reinfection after treatment-induced clearance, which supports evidence from other settings [27] and further underscores the benefit of HCV therapy in this population. Another explanation for the increase in HCV treatment uptake may be the improvement of the awareness of physicians regarding the diagnosis and treatment of acute HCV infection since the description of the first HCV epidemics in MSM.

This study is the first one to describe national long-term trends in acute HCV treatment uptake and efficacy among patients infected with HIV. It relies on detailed data from routine monitoring and review of the medical charts of all patients, including information on follow-up virological assessments and reasons for not receiving HCV treatment. However, a substantial number of patients had to be excluded because of possible false-positive HCV serology results, which could not be confirmed by RNA measurements or immunoblot. This might have led to the exclusion of patients with rapid spontaneous HCV clearance and negative HCV follow-up serology and, as a consequence, to an underestimation of the number of acute HCV infections. Reinfections were identified using the SHCS database complemented by review of patient charts including transaminase levels and HCV RNA measurements. However, we cannot exclude that some reinfections were not recognized if transaminase levels had normalized before the next follow-up

visits, which are typically performed every 3 months. In contrast, patients with fluctuating HCV viral loads after infection who ultimately progressed to chronic infection could have been misclassified as reinfected, which could have led to an overestimation of the rate of reinfections. Furthermore, the reason for not receiving any HCV therapy was not found in approximately one third of the patients with a chronic, untreated HCV infection.

In analogy to the reduction of acquired immune deficiency syndrome-related mortality in the context of the rapid scale up of ART, a significant impact on HCV-related mortality will only be achieved with a massive improvement in the diagnosis and treatment uptake of HCV infection. In the HIV field, the continuous assessment of the cascade of care, including HIV diagnosis, ART coverage, and efficacy, has allowed the adaption and improvement of public health policies and strategies. Likewise, it is of primary importance to evaluate the pyramid of care in terms of HCV infection management and compare results across cohorts, settings, and countries. Our study is the first one to describe such a pyramid of care for incident HCV infections in a nationwide cohort of individuals infected with HIV. In future work, the proportion of patients with an undetectable HCV viral load should be used as an important measure of HCV treatment success, in analogy to the proportion of patients with an undetectable HIV viral load in HIV programs.

CONCLUSION

In the context of the increasing burden of liver-related morbidity and mortality in HIV-infected individuals, the improvement of HCV treatment uptake is of high priority. In the SHCS, HCV treatment uptake during the early phase of HCV infection improved over the years, leading to a 2-fold increase in the proportion of patients with a resolved HCV infection in the cohort. Even though most recent infections were diagnosed in MSM with stable HIV infections, there remained important barriers for treatment initiation including the presence of psychiatric comorbidities. The increasing availability of new IFN-free combinations will reduce the impact of these treatment barriers. Nevertheless, it is necessary to continue the efforts in terms of early diagnosis and treatment uptake if HCV-related complications are to be reduced. Eradicating HCV infection dramatically reduces the risk of liver-related death in patients infected with HIV [28] and prevents further HCV transmissions. As we demonstrate here, improvements in treatment uptake and efficacy substantially reduce the burden of replicating hepatitis C among patients with incident HCV infections. Our study demonstrates that frequent screening in clinical routine settings, early diagnoses, and treatment of HCV infections in persons with continued risk of infection are highly efficient interventions to reduce the burden of HCV disease at both the individual and the population level.

Supplementary Material

References

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