Hepatitis C Virus Infections in the Swiss HIV Cohort Study: A Rapidly Evolving Epidemic

Gilles Wandeler,[1,2,a] Thomas Gsponer,[2] Andrea Bregenzer,[3] Huldrych F. Günthard,[4] Olivier Clerc,[5] Alexandra Calmy,[6] Marcel Stöckle,[7] Enos Bernasconi,[8] Hansjakob Furrer,[1] Andri Rauch[1,a]; and the Swiss HIV Cohort Study

[1]Department of Infectious Diseases, Bern University Hospital and University of Bern, [2]Institute of Social and Preventive Medicine, University of Bern, [3]Cantonal Hospital, St Gallen, [4]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, [5]University Hospital Lausanne, [6]University Hospital Geneva; [7]University Hospital Basel, and [8]Regional Hospital, Lugano, Switzerland

Background. Hepatitis C virus (HCV) infection has a growing impact on morbidity and mortality in patients infected with human immunodeficiency virus (HIV). We assessed trends in HCV incidence in the different HIV transmission groups in the Swiss HIV Cohort Study (SHCS).

Methods. HCV infection incidence was assessed from 1998, when routine serial HCV screening was introduced in the SHCS, until 2011. All HCV-seronegative patients with at least 1 follow-up serology were included. Incidence rates (IRs) of HCV infections were compared between men who have sex with men (MSM), injection drug users (IDU), and heterosexuals (HET).

Results. HCV incidence was assessed in 3333 MSM, 123 IDU, and 3078 HET with a negative HCV serology at baseline. Over 23 707 person-years (py) for MSM, 733 py for IDU, and 20 752 py for HET, 101 (3%), 41 (33%), and 25 (1%) of patients seroconverted, respectively. The IR of HCV infections in MSM increased from 0.23 (95% credible interval [CrI], .08–.54) per 100 py in 1998 to 4.09 (95% CrI, 2.57–6.18) in 2011. The IR decreased in IDU and remained <1 per 100 py in HET. In MSM, history of inconsistent condom use (adjusted hazard ratio [HR], 2.09; 95% CI, 1.33–3.29) and past syphilis (adjusted HR, 2.11; 95% confidence interval [CI], 1.39–3.20) predicted HCV seroconversion.

Conclusions. In the SHCS, HCV infection incidence decreased in IDU, remained stable in HET, and increased 18-fold in MSM in the last 13 years. These observations underscore the need for improved HCV surveillance and prevention among HIV-infected MSM.

Hepatitis C virus (HCV) infection is a major cause of morbidity and mortality in patients infected with human immunodeficiency virus (HIV) [1–3]. For many years, HCV infections occurred almost exclusively in injection drug users (IDU) or hemophiliacs. In a previous analysis in the Swiss HIV Cohort Study (SHCS), HCV seroprevalence was 33% overall and 90% among IDU [4]. Recently, there have been several outbreaks of HCV infections among HIV-infected men who have sex with men (MSM), predominantly in large cities in Europe, Australia, and the United States [5–14]. These clusters of HCV infections involved high-risk sexual behaviors within confined social networks. However, the impact of these localized epidemics on the incidence of HCV infections in general HIV-infected populations and the long-term trends in HCV incidence rates among different transmission risk groups are largely unknown. A better understanding of changes in HCV incidence rates and transmission patterns is urgent because of the increasing burden of HCV-related disease in HIV-infected patients [1–3].

The SHCS offers an ideal platform for studying changes in HCV incidence in a general HIV-infected population and in diverse HIV-transmission risk groups, as all HCV-seronegative patients are screened routinely at baseline and during follow-up over the

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[a]G. W. and A. R. contributed equally to this work.

Correspondence: Gilles Wandeler, MD, MSc, Clinic for Infectious Diseases, University Hospital Bern, Inselspital, CH-3010 Bern, Switzerland (gwandeler@ispm.unibe.ch).

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past 13 years. Furthermore, it allows a thorough evaluation of the association of HCV seroconversions with different risk factors, as detailed patient history and clinical data are collected every 6 months.

We assessed changes in the HCV infection incidence in the 3 main HIV transmission groups (IDU, MSM, and heterosexuals [HET]) in the SHCS during the last 13 years, with the expectation that our results would shed light on the magnitude and changes of the HCV epidemic in a general and representative HIV-infected population.

METHODS

Swiss HIV Cohort Study

The SHCS (www.shcs.ch) is a prospective cohort study with ongoing enrollment of HIV-infected adults in Switzerland since 1988. It covers at least 45% of the cumulative number of HIV infections declared to the Swiss public health authorities, 69% of all patients living with AIDS, and 75% of patients receiving antiretroviral therapy (ART) in Switzerland [15]. Representativity has remained stable over the years. Detailed information on demographics, mode of HIV acquisition, risk behavior, clinical events, coinfections, and treatment is collected using a standard protocol at registration and at intervals of 6 months. Local ethical committees of all participating study sites have approved the study and written consent is obtained from all participants.

Inclusion Criteria and Definitions

To compare HCV incidence between risk groups, we categorized patients as IDU, MSM, or HET according to the most probable HIV transmission mode. In order to minimize erroneous classifications, we excluded MSM and HET patients who reported the use of injection drugs at any occasion during follow-up. Since 1998, all SHCS patients have been routinely screened for HCV infection; serology is performed every second year of follow-up, independent of HIV transmission mode. Thus, all HCV-seronegative patients who had at least 1 follow-up HCV antibody measurement after July 1998 were included in the analyses. Positive results by third-generation enzyme-linked immunosorbent assay (ELISA) were confirmed by immunoblotting. Patients with a positive HCV serology at entry and those who seroconverted before 1998 were excluded. Individual follow-up ended at the time of the first positive or last negative HCV serology. A detailed patient flowchart is shown in Figure 1. Previous syphilis was defined as a positive *Treponema pallidum* hemagglutination assay screening test and hepatitis B virus (HBV) exposure as determined by the presence of a positive anti–hepatitis B core antibody test prior to HCV seroconversion, or before the last negative HCV serology in those without HCV seroconversion. In this context, the term "HBV exposure" refers to both resolved and chronic HBV infections.

A subset of HCV seroconverters was found to have a unique positive HCV serology followed by ≥1 negative

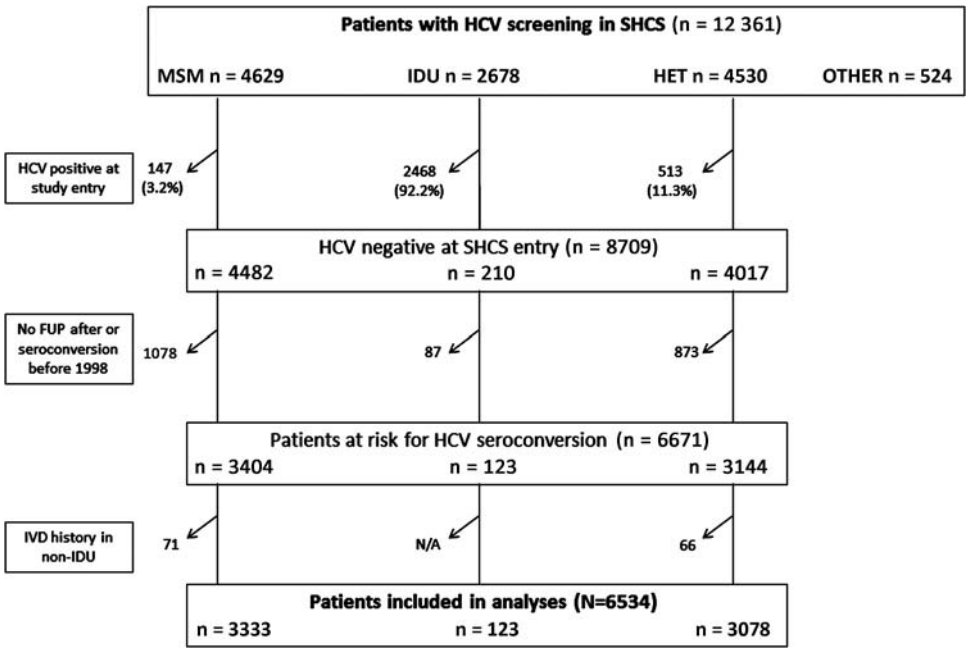

Figure 1. Study flowchart. Abbreviations: FUP, follow-up; HCV, hepatitis C virus; HET, heterosexual; IDU, injection drug user; IVD, intravenous drugs; MSM, men who have sex with men; N/A, not applicable; SHCS, Swiss HIV Cohort Study.

serology. These patients could have cleared HCV antibodies after spontaneous HCV clearance, as described previously [16–18]. Alternatively, false-positive results cannot be excluded despite confirmation by HCV immunoblot. Therefore, the main analyses were repeated after exclusion of these cases.

Statistical Analyses

HCV incidence rates were assessed from introduction of routine HCV screening from July 1998 until November 2011. Patients were considered to be at risk for HCV infection since the date of their first negative HCV serology or since 1 July 1998 if the first measurement preceded this date. Individual follow-up ended at the time of the first positive or last negative HCV serology. Baseline characteristics were compared between the 3 risk groups using analysis of variance and χ^2 tests for continuous and categorical variables, respectively. To calculate the incidence of HCV infections in the different risk groups, events were right-censored so that the date of seroconversion corresponded to the date of the first positive HCV serology. Yearly HCV infection incidence rates (IRs) were obtained using Bayesian Poisson regression models with nonparametric smoothing priors [19]. Incidence rates are reported as number of cases per 100 person-years (py) and shown on a log-scaled graph, by transmission group (ie, MSM, IDU, HET).

In sensitivity analyses, the yearly rates of HCV infection in MSM were compared with the results obtained using 2 alternate censoring approaches: (1) midpoint censoring, in which the date of seroconversion was set to the midpoint between the last negative and first positive HCV serology, and (2) a nonparametric maximum likelihood estimation method for interval-censored data [20]. Interval censoring takes into account that the exact date of seroconversion is not known but lies between the last negative and the first positive serology. However, because of the low number of seroconversions in IDU and HET, this method could only be applied to the MSM risk group.

Demographic characteristics of HCV seroconverters in MSM were compared to those who did not seroconvert during follow-up using χ^2 and Mann-Whitney tests. The difference in incidence of HCV infection between patients of different age groups, condom use patterns, HBV exposure status, and history of past syphilis were also shown in log-scaled graphs. Risk factors for HCV infection in MSM were evaluated using a multivariate Cox regression model. Analyses were adjusted for age category (16–29, 30–39, and ≥40 years), CD4 count category before last HCV serology (<200, 200–499, and ≥500 cells/μL), education level (no, basic, and high-level professional education), region of SHCS follow-up (Zurich or other), ethnicity (Caucasian or other), use of noninjection drugs (yes or no), sexual relationships (stable or occasional partners), condom use (always or inconsistent), past history of syphilis (yes or no), HBV exposure (yes or no), and ART status (yes or no). All statistical analyses were performed using Stata 12 software (Stata Corp, College Station, Texas) and the R package, version 2.14.1 [21] using add-on packages INLA [22] and Icens [23].

RESULTS

Baseline Characteristics

Of 4629 MSM, 2678 IDU, and 4530 HET screened for HCV infection, 147 (3.2%), 2468 (92.2%), and 513 (11.3%), respectively, had a positive HCV serology at baseline (Figure 1). A total of 6534 patients, of whom 3333 were MSM, 123 IDU, and 3078 HET, were included in the HCV incidence analyses. Median age at first HCV screening test was slightly higher in MSM (38 years; interquartile range [IQR], 32–44) and HET (36 years; IQR, 30–44), compared to IDU (33 years; IQR, 28–40), whereas MSM were more likely to have a high-level education than patients in the 2 other groups (Table 1). Almost half of the MSM and IDU, but only 29% of HET, had their regular medical follow-up in Zurich, Switzerland's largest urban center. Finally, HET were much more likely to be non-Caucasians (40.7%), compared with MSM (7.7%) and IDU (8.9%).

HCV Incidence

Over a total follow-up period of 23 707 py for the MSM group, 733 py for the IDU group, and 20 752 py for the HET group, 101 (3.0%), 41 (33.3%), and 25 (0.8%) patients, respectively, experienced an HCV seroconversion during follow-up. Between 1998 and 2011, the IR of HCV infections in MSM increased from 0.23 (95% credible interval [CrI], .08–.54) per 100 py to 4.09 (95% CrI, 2.57–6.18) in 2011, with 51 cases observed in the last 3 years (Figure 2). There was a similar increase in patients followed in Zurich compared with those in the rest of the country (in 2011, IRs were 2.61 [95% CrI, 1.19–5.13] and 4.10 [95% CrI, 2.18–7.16] per 100 py, respectively). Increases in HCV incidence in MSM were similar when right censoring, midpoint censoring, or interval censoring was used to estimate yearly incidence rates (Supplementary Figure 1).

In IDU, the HCV infection IR decreased from 13.89 (95% CrI, 8.20–22.39) per 100 py in 1998 to 2.24 (95% CrI, .55–10.66) in 2011, with only 3 incident cases in the last 3 years. For comparison, the yearly IR of HCV infections in the HET group remained <0.5 per 100 py, with only 2 cases in 2011 (IR, 0.43 per 100 py [95% CrI, .12–1.29]; Figure 2).

Twenty-five (15.0%) HCV seroconverters had a unique positive serology followed by negative tests. Of those, 6 patients had their HCV infection confirmed by HCV RNA testing

Table 1. Baseline Characteristics of Patients Included in Incidence Analyses

Characteristic	MSM	IDU	HET	Total
No. of patients	3333	123	3078	6534
Sex				
Male	3333 (100)	76 (61.8)	1339 (43.5)	4748 (72.7)
Female	0	47 (38.2)	1739 (56.5)	1786 (27.3)
Median age (IQR) at first HCV serology	38 (32–44)	33 (28–40)	36 (30–44)	37 (31–44)
Region of SHCS follow-up				
Outside Zurich	1759 (52.8)	71 (57.7)	2184 (71.0)	4014 (61.4)
Zurich	1574 (47.2)	52 (42.3)	894 (29.0)	2520 (38.6)
Education level				
No prof. education	76 (2.3)	10 (8.9)	348 (11.6)	434 (6.8)
Basic prof. education	1816 (56.1)	90 (80.4)	1979 (65.9)	3885 (61.1)
High-level education	1348 (41.6)	12 (10.7)	676 (22.5)	2036 (32.1)
Ethnicity				
Caucasian	3075 (92.3)	112 (91.1)	1825 (59.3)	5012 (76.7)
Non-Caucasian	258 (7.7)	11 (8.9)	1253 (40.7)	1522 (23.3)

All data are No. (%) unless otherwise specified. Comparison of characteristics between 3 risk groups: $P < .001$ for all variables.

Abbreviations: HCV, hepatitis C virus; HET, heterosexual; IDU, injection drug user; IQR, interquartile range; MSM, men who have sex with men; prof., professional; SHCS, Swiss HIV Cohort Study.

within 1 month of the positive serology. In another 8 patients, HCV RNA testing was negative, which may be reflective of spontaneous HCV clearance and loss of HCV antibodies over time. Eleven patients did not have HCV RNA results available to confirm the HCV infection. After exclusion of these patients, the incidence rates of HCV infection remained similar to the results described above (1998: MSM: IR, 0.11 per 100 py [95% CrI, .03–.35]; IDU: IR, 14.36 [95% CrI, 8.36–23.39];

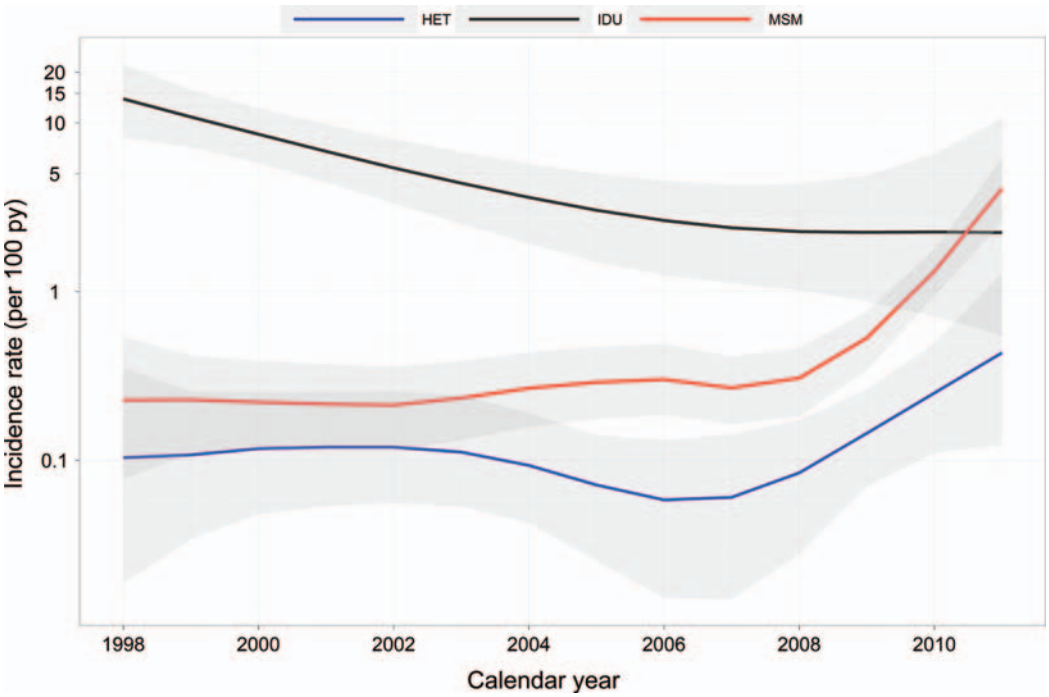

Figure 2. Hepatitis C virus infection incidence rates by transmission group (shaded: 95% credible intervals). Abbreviations: HET, heterosexual; IDU, injection drug user; MSM, men who have sex with men; py, person-year.

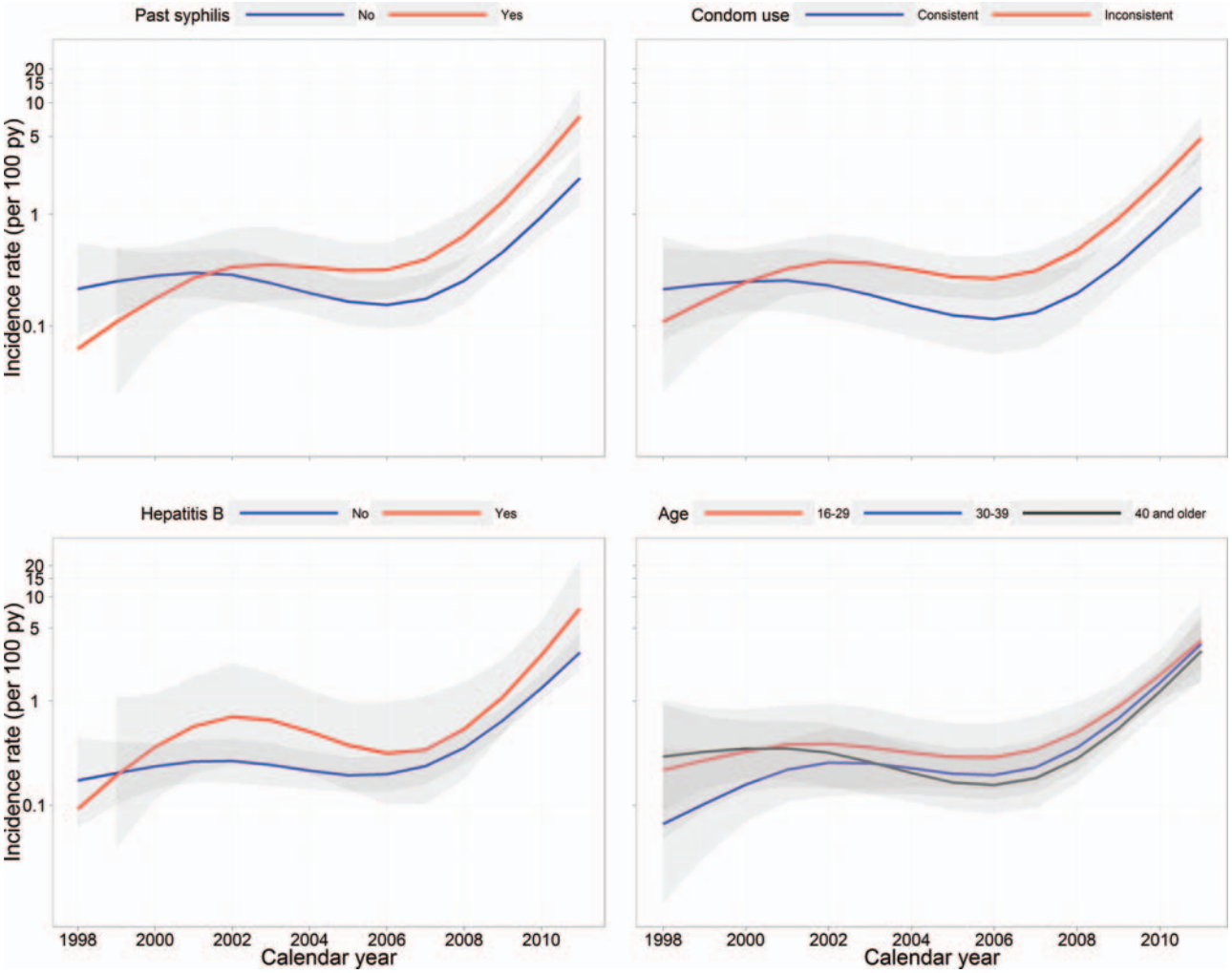

Figure 3. Hepatitis C virus infection incidence by risk factor in men who have sex with men (shaded: 95% credible intervals). Abbreviation: py = person-year.

HET: IR, 0.09 [95% CrI, .02–.35]; 2011: MSM: IR, 3.56 [95% CrI, 2.19–5.53]; IDU: IR, 2.42 [95% CrI, .51–13.36]; HET: IR, 0.47 [95% CrI, .14–1.30]).

Predictors of HCV Infection in MSM

Most demographic and behavioral characteristics were similar in HCV seroconverters compared with patients who did not seroconvert (Supplementary Table 1). Median age was 34.9 years in seroconverters and 37.7 years in nonseroconverters, and the proportion of Caucasians was 93% and 92%, respectively. In both groups, >90% of patients started ART before or during follow-up. However, previous HBV exposure, a past history of syphilis, and inconsistent condom use were more common in HCV seroconverters (Supplementary Table 1). The incidence of HCV infection was higher in patients who reported inconsistent condom use, as well as in those who had a previous episode of syphilis or exposure to HBV compared with the other patients (Figure 3). In adjusted Cox regression analyses, only inconsistent condom use (adjusted hazard ratio [aHR], 2.09 [95% confidence interval {CI}, 1.33–3.29]) and previous diagnosis of syphilis (aHR, 2.11 [95% CI, 1.39–3.20]) were significantly associated with HCV seroconversion (Table 2).

Age, education level, $CD4^+$ T-cell count, ART status, and the other variables included in the multivariate model were not significantly associated with the main outcome. Of note, having occasional sexual partners (aHR, 0.97 [95% CI, .56–1.68]) and being followed up in Zurich (aHR, 1.30 [95% CI, .87–1.97]) did not predict HCV seroconversion.

Of the 63 (62%) HCV infections in MSM with detectable HCV RNA and available genotyping results, the majority were caused by HCV genotype 1 (42 cases [66.7%]), followed by genotypes 4 (12 cases [19.0%]), 3 (8 cases [12.7%]), and 2 (1 case [1.6%]).

Table 2. Predictors of Acquisition of Acute Hepatitis C Virus Infection in Men Who Have Sex With Men (Cox Regression Model)

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Age group, years		.39		.24
16–29	Ref.		Ref.	
30–39	.72 (.43–1.21)		.71 (.42–1.22)	
>39	.71 (.42–1.21)		.60 (.33–1.09)	
CD4 count, cells/μL[a]		.28		.33
<200	Ref.		Ref.	
200–499	1.09 (.39–3.03)		1.22 (.43–3.47)	
>499	.79 (.28–2.18)		.88 (.31–2.54)	
HIV RNA, <50 copies/mL[a]		.04		.08
Undetectable	Ref.		Ref.	
Detectable	1.64 (1.04–2.59)		1.63 (.94–2.83)	
Education level		.91		.71
No prof. education	Ref.		Ref.	
Basic prof. education	1.05 (.26–4.30)		1.24 (.30–5.17)	
High-level education	1.14 (.27–4.70)		1.44 (.34–6.13)	
Region of SHCS follow-up		.28		.20
Outside Zurich	Ref.		Ref.	
Zurich	1.24 (.84–1.84)		1.30 (.87–1.97)	
Ethnicity		.81		.91
Other	Ref.		Ref.	
Caucasian	.91 (.42–1.96)		1.04 (.47–2.31)	
Use of noninjection drugs		.96		.20
No	Ref.		Ref.	
Yes	.99 (.65–1.51)		.74 (.47–1.17)	
Sexual partners[b]		.43		.91
None or only stable	Ref.		Ref.	
Occasional partner(s)	1.23 (.74–2.05)		.97 (.56–1.68)	
Condom use[b]		.001		.002
Always	Ref.		Ref.	
Inconsistently/never	2.03 (1.33–3.10)		2.09 (1.33–3.29)	
Past history of syphilis		<.001		<.001
No	Ref.		Ref.	
Yes	2.20 (1.48–3.27)		2.11 (1.39–3.20)	
HBV exposure		.12		.08
No	Ref.		Ref.	
Yes	1.39 (.92–2.09)		1.48 (.95–2.28)	
ART status[b]		.31		.92
No	Ref.		Ref.	
Yes	.67 (.31–1.45)		1.05 (.43–2.56)	

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; prof., professional; SHCS, Swiss HIV Cohort Study.

[a] Last measurement before last negative HCV serology, or first positive serology in seroconverters.

[b] During follow-up (before last negative test, or first positive test in seroconverters).

DISCUSSION

We assessed trends in HCV infection incidence between 1998 and 2011 in the main HIV transmission groups in the SHCS. In a population of >6500 patients screened every 2 years for HCV infection, we found that the yearly incidence rate had decreased in IDU, remained stable in HET, and dramatically increased in MSM. In the latter subpopulation, 50% of all

HCV infections occurred in the last 3 years. In MSM, a history of inconsistent condom use and a past episode of syphilis were significantly associated with HCV seroconversion.

Since 2005, several local reports have described epidemics of HCV infection among HIV-infected MSM [7–12]. Phylogenetic and sociodemographic analyses have shown that these infections occurred within confined groups of MSM with high-risk sexual behavior in large urban centers [11, 24]. Therefore, incidence estimates in these cohorts were not representative for the general HIV-infected population, in contrast to our study. The systematic, nationwide screening of all HIV-infected patients at risk since 1998 allowed us to accurately estimate the trends in HCV incidence among different risk groups. Since 1998, the incidence of HCV infection among MSM has increased 18-fold, reaching 4.1 cases per 100 py in 2011. This incidence was higher compared with the large majority of previous studies among HIV-infected MSM reporting estimates lower than 1 case per 100 py [5]. However, the most recent HCV incidence in the SHCS was similar to estimates from an international cohort collaboration of HIV seroconverters, where incidence estimates ranged from 2.3 to 5.1 per 100 py in 2007 [25]. In accordance with previous clusters of HCV infections in large cities, the HCV incidence increased markedly among individuals treated in Zurich, the largest urban center in Switzerland which, to some extent, is comparable to other large cities in Europe and the United States. However, our study shows that HCV incidence increased similarly outside the Zurich area, indicating a nationwide increase in HCV infections in HIV-infected MSM.

In line with previous reports [4, 8, 11], unprotected anal sex was an important risk factor for HCV infection in MSM. In the SHCS, inconsistent condom use doubled the risk of HCV infection in MSM. Furthermore, a previous syphilis infection independently increased the risk of an HCV seroconversion approximately 2-fold. Of note, we recently observed a significant increase in syphilis acquisition among MSM in the SHCS, paralleling the current HCV epidemic [26]. The shared route of transmission of the 2 infections is the most likely explanation for this association. Alternatively, it is also conceivable that the mucosal disruption caused by syphilitic ulcers facilitates HCV infections. These findings underscore the importance of the link between high-risk sexual behavior and HCV transmissions. As yearly syphilis screening and baseline HBV serology testing are routine for all MSM in the SHCS, a positive test result should be an important warning sign and lead to intensified counseling on the prevention of sexually transmitted HCV infection in these high-risk patients. Our results support recent guidelines [27] to screen HIV-infected MSM with high-risk sexual behaviors or concomitant ulcerative sexually transmitted diseases for HCV, and to screen for syphilis in MSM with acute hepatitis C. Although the use of noninjection drugs has been associated with HCV infections among HIV-infected MSM [28], we found no association between noninjection drug use and HCV seroconversion in MSM. However, we cannot exclude that our analysis underestimates the effect of noninjection drug use due to underreporting of this behavior. Neither immunological status nor HIV RNA was associated with HCV seroconversion: the large majority (96%) of HCV infections occurred with CD4 T-cell counts >200 cells/μL, and most patients (93%) were undergoing ART.

The incidence of HCV infection in HIV-infected IDU in the SHCS has decreased in recent years, underscoring the considerable success of preventive interventions such as methadone substitution and needle exchange programs in reducing HCV infections in IDU followed in routine HIV care. Furthermore, Switzerland's long-term heroin prescription program likely contributed to the decreasing incidence of HCV seroconversion in this population. Besides a reduction in risk behavior, it is also possible that protective genetic markers have been enriched during the course of the epidemic in uninfected IDU, as has been demonstrated recently [29]. However, the large majority (90%) of IDU were excluded from the incidence analyses because they already had a positive HCV serology at entry, limiting the size of the IDU population available for the incidence calculations. In line with previous studies [30, 31], the incidence of HCV infection in HET has remained very low, and we cannot exclude that the few incident cases were related to undisclosed IDU- and/or MSM-related sexual activity. This is corroborated by recent phylogenetic studies within the SHCS which revealed that approximately 11% HIV *pol* sequences from heterosexuals were linked to transmission clusters of MSM [32].

The major strength of our study is the long-term routine HCV screening at baseline and during follow-up in a representative, nationwide HIV population and in different transmission groups. Routine serological surveillance of HCV infection is paramount to the diagnosis of new infections, as the majority of individuals experiencing such an event remain asymptomatic and transaminase elevations can be transient and unrecognized. Furthermore, we could minimize transmission group misclassification through the availability of detailed longitudinal information on sexual activity and drug abuse. An important limitation of our analysis is that we could not estimate the exact HCV seroconversion dates between 2 serological screening tests. Furthermore, a limited number of patients might have experienced HCV reinfections, which cannot be recognized by serological testing, possibly leading to the underestimation of the true overall incidence of HCV infection. Similarly, the incidence might have been underestimated in patients with late or absent seroconversion, as described by Thomson et al [13]. A further limitation lies in the suboptimal sensitivity and specificity of HCV antibody assays. Although positive ELISA tests were routinely

confirmed by immunoblotting, false-positive results cannot be entirely excluded. Finally, some patients who experienced an HCV seroconversion could have lost their antibodies within a few months after the infection in the setting of spontaneous HCV clearance [16–18]. In the SHCS, 25 seroconverters had a unique positive HCV serology, followed by further negative tests. However, incidence rates remained similar after excluding these patients.

In the SHCS, the large majority of recent HCV infections occurred in MSM. This underscores the need for improved HCV surveillance and prevention among HIV-infected MSM. Accordingly, the intervals of HCV screening were reduced to 1 year in the SHCS. This should allow for earlier identification of patients with new HCV infections in order to optimize counseling with regard to HCV transmission risks, and to improve the response to HCV therapy by initiating treatment during acute infection. The revised screening practice in the SHCS is in line with recent guidelines, which recommend yearly screening for all HIV-infected MSM who engage in any risk behavior [33–35]. Furthermore, a recent study demonstrated that yearly serological HCV screening and biannual liver function testing is cost-effective [36]. Importantly, this analysis demonstrated that the optimal screening strategy strongly depends on HCV incidence. For instance, it suggests that screening every 3 months with liver function tests is cost-effective in settings with HCV incidences >1.25%. Accordingly, our results should provide important information for establishing cost-effective screening programs in HIV-infected patients. However, routine serological screening does not prevent risk behavior, and coordinated efforts between physicians and public health representatives are needed to control the ongoing HCV infection epidemic in HIV-infected MSM. Although most reported HCV transmissions among MSM occurred in HIV-infected patients, it is conceivable that HCV incidence among HIV-negative MSM is underestimated as these individuals are not in regular medical care. Clinicians and patients should be aware of the risk of acute HCV infection in MSM, and intensified prevention and counseling should be performed. Despite the fact that ART is highly efficient in preventing HIV transmission, it does not have any effect on prevention of other sexually transmitted infections. Condom use has declined in recent years in MSM with suppressed HIV load in the SHCS [37], which likely contributes to the increasing incidence of HCV infection in this population. It is crucial that HIV-infected MSM are counseled with regard to the risks of sexual activities that involve traumatic mucosal sex, and that condoms are used consistently during high-risk sexual activity [28]. The example of IDUs demonstrates that it is possible to reduce the incidence of HCV infections through improved screening and preventive interventions.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. G. W., T. G., H. F., and A. R. designed the study, conducted the statistical analyses, and wrote the first draft of the manuscript. All authors contributed to the collection and interpretation of the data, critically revised the paper, and approved its final version.

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References

1. Joshi D, O'Grady J, Dieterich D, Gazzard B, Agarwal K. Increasing burden of liver disease in patients with HIV infection. Lancet **2011**; 377:1198–209.
2. Koziel MJ, Peters MG. Viral hepatitis in HIV infection. N Engl J Med **2007**; 356:1445–54.
3. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med **2006**; 166:1632–41.
4. Rauch A, Rickenbach M, Weber R, et al. Unsafe sex and increased incidence of hepatitis C virus infection among HIV-infected men who have sex with men: the Swiss HIV Cohort Study. Clin Infect Dis **2005**; 41:395–402.
5. Danta M, Rodger AJ. Transmission of HCV in HIV-positive populations. Curr Opin HIV AIDS **2011**; 6:451–8.
6. Vogel M, Boesecke C, Rockstroh JK. Acute hepatitis C infection in HIV-positive patients. Curr Opin Infect Dis **2011**; 24:1–6.
7. Gotz HM, van Doornum G, Niesters HG, den Hollander JG, Thio HBde Zwart O. A cluster of acute hepatitis C virus infection among men who have sex with men—results from contact tracing and public health implications. AIDS **2005**; 19:969–74.
8. Danta M, Brown D, Bhagani S, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. AIDS **2007**; 21:983–91.
9. van de Laar TJ, van der Bij AK, Prins M, et al. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. J Infect Dis **2007**; 196:230–8.

10. Matthews GV, Hellard M, Kaldor J, Lloyd A, Dore GJ. Further evidence of HCV sexual transmission among HIV-positive men who have sex with men: response to Danta et al. AIDS **2007**; 21:2112–3.
11. van de Laar T, Pybus O, Bruisten S, et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. Gastroenterology **2009**; 136:1609–17.
12. Giraudon I, Ruf M, Maguire H, et al. Increase in diagnosed newly acquired hepatitis C in HIV-positive men who have sex with men across London and Brighton, 2002–2006: is this an outbreak? Sex Transm Infect **2008**; 84:111–5.
13. Thomson EC, Nastouli E, Main J, et al. Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV. AIDS **2009**; 23:89–93.
14. Vogel M, Deterding K, Wiegand J, et al. Initial presentation of acute hepatitis C virus (HCV) infection among HIV-negative and HIV-positive individuals—experience from 2 large German networks on the study of acute HCV infection. Clin Infect Dis **2009**; 49:317–9; author reply 319.
15. Cohort profile: the Swiss HIV Cohort Study. Int J Epidemiol **2010**; 39:1179–89.
16. Strasak AM, Kim AY, Lauer GM, et al. Antibody dynamics and spontaneous viral clearance in patients with acute hepatitis C infection in Rio de Janeiro, Brazil. BMC Infect Dis **2011**; 11:15.
17. Thio CL, Nolt KR, Astemborski J, Vlahov D, Nelson KE, Thomas DL. Screening for hepatitis C virus in human immunodeficiency virus-infected individuals. J Clin Microbiol **2000**; 38:575–7.
18. Takaki A, Wiese M, Maertens G, et al. Cellular immune responses persist and humoral responses decrease two decades after recovery from a single-source outbreak of hepatitis C. Nat Med **2000**; 6:578–82.
19. Fong Y, Rue H, Wakefield J. Bayesian inference for generalized linear mixed models. Biostatistics **2010**; 11:397–412.
20. Wellner JA, Zhan Y. A hybrid algorithm for computation of the nonparametric maximum likelihood estimator from censored data. JASA **1997**; 92:945–59.
21. R Development Core Team (**2011**). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN: 3-900051-07-0. Available at: http://www.R-project.org/. Accessed 1 May 2012.
22. Rue H, Martino S, Lindgren F (**2009**). INLA: functions which allow to perform a full Bayesian analysis of structured (geo-)additive models using Integrated Nested Laplace Approximation. R package version 0.0. Available at: http://www.r-inla.org. Accessed 1 May 2012.
23. Gentleman R, Vandal A (**2011**). Icens: NPMLE for censored and truncated data. R package version 1.24.0. Available at: http://CRAN.R-project.org/package=Icens. Accessed on 1 May 2012.
24. Matthews GV, Pham ST, Hellard M, et al. Patterns and characteristics of hepatitis C transmission clusters among HIV-positive and HIV-negative individuals in the Australian trial in acute hepatitis C. Clin Infect Dis **2011**; 52:803–11.
25. van der Helm JJ, Prins M, del Amo J, et al. The hepatitis C epidemic among HIV-positive MSM: incidence estimates from 1990 to 2007. AIDS **2011**; 25:1083–91.
26. Thurnheer MC, Weber R, Toutous-Trellu L, et al. Occurrence, risk factors, diagnosis and treatment of syphilis in the prospective observational Swiss HIV Cohort Study. AIDS **2010**; 24:1907–16.
27. Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep **2010**; 59(RR-12):1–110.
28. Schmidt AJ, Rockstroh JK, Vogel M, et al. Trouble with bleeding: risk factors for acute hepatitis C among HIV-positive gay men from Germany—a case-control study. PLoS One **2011**; 6:e17781.
29. Knapp S, Warshow U, Ho KM, et al. A polymorphism in IL28B distinguishes exposed, uninfected individuals from spontaneous resolvers of HCV infection. Gastroenterology **2011**; 141:320–5, 325. e1–2.
30. Tahan V, Karaca C, Yildirim B, et al. Sexual transmission of HCV between spouses. Am J Gastroenterol **2005**; 100:821–4.
31. Kenfak-Foguena A, Schoni-Affolter F, Burgisser P, et al. Hepatitis E virus seroprevalence and chronic infections in patients with HIV, Switzerland. Emerg Infect Dis **2011**; 17:1074–8.
32. Kouyos RD, von Wyl V, Yerly S, et al. Molecular epidemiology reveals long-term changes in HIV type 1 subtype B transmission in Switzerland. J Infect Dis **2010**; 201:1488–97.
33. Brook G, Main J, Nelson M, et al. British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010. HIV Med **2010**; 11:1–30.
34. Rockstroh JK, Bhagani S, Benhamou Y, et al. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. HIV Med **2008**; 9:82–8.
35. Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference. AIDS **2011**; 25:399–409.
36. Linas BP, Wong AY, Schackman BR, Kim AY, Freedberg KA. Cost-effective screening for acute hepatitis C virus infection in HIV-infected men who have sex with men. Clin Infect Dis **2012**; 55:279–90.
37. Hasse B, Ledergerber B, Hirschel B, et al. Frequency and determinants of unprotected sex among HIV-infected persons: the Swiss HIV Cohort Study. Clin Infect Dis **2010**; 51:1314–22.