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

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Summary : In the Swiss HIV Cohort Study, a nationwide cohort with systematic Hepatitis C Virus (HCV) infection screening since 1998, HCV incidence decreased in injection drug users, remained low in heterosexuals and dramatically increased in men who have sex with men.

ABSTRACT

Background. Hepatitis C Virus (HCV) infection has a growing impact on morbidity and mortality in HIV-infected patients. We assessed trends in HCV incidence in the different HIV transmission groups in the Swiss HIV Cohort Study (SHCS) in order to optimize surveillance and prevention.

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 one follow-up serology were included. Incidence rates (IR) of HCV infections were compared between men who have sex with men (MSM), injection drug users (IDU) and heterosexuals (HET). Predictors of HCV seroconversion in MSM were estimated.

Results. Of 4,629 MSM, 2,678 IDU and 4,530 HET screened for HCV infection, 3,333 (72%), 123 (5%) and 3,078 (68%) had a negative HCV serology at baseline and available serological follow-up. 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%) seroconverted, respectively. The IR of HCV infections in MSM increased from 0.23 (95% CI: 0.08-0.54) per 100py in 1998 to 4.09 (2.57-6.18) in 2011. The IR decreased in IDU and remained below 1 per 100 py in HET. In MSM, history of inconsistent condom use (aHR: 2.09, 1.33-3.29) and past syphilis (2.11, 1.39-3.20) predicted HCV seroconversions.

Conclusions. In the SHCS, HCV 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 HIV-infected patients [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 individuals reporting 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 USA [5-14]. These clusters of HCV infections involved high-risk sexual practices 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 in 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 since 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 is collected every six months.

We assessed changes in the HCV infection incidence in the three 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 Swiss HIV Cohort Study (SHCS, www.shcs.ch) is a prospective cohort study with ongoing enrolment 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 in Switzerland [15]. Representativity remained stable over the years. Detailed information on demographics, mode of HIV acquisition, risk behavior, clinical events, co-infections, and treatment is collected using a standard protocol at registration and then at intervals of 6 months. 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

To compare HCV incidence between risk groups, we categorised 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, independently of HIV transmission mode. Thus, all HCV-seronegative patients who had at least one follow-up HCV antibody measurement after July 1998 were included in the analyses. Positive results by third-generation ELISA are confirmed by immunoblot. 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 flow chart is shown in

Figure 1. Previous syphilis was defined as a positive *Treponema-pallidum*-hemagglutination-assay (TPHA) screening test and hepatitis B virus (HBV) exposure by the presence of a positive anti-HBc 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 one or several negative serologies. These patients could have cleared HCV antibodies after spontaneous HCV clearance, as described before [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 01.07.1998 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 three risk groups using analysis of variance (ANOVA) and chi-squared 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 (IR) were obtained using Bayesian Poisson regression models with non-parametric smoothing priors [19]. IR are reported as number of cases per 100 person-years (py) and shown on a log scaled graph, by transmission group (MSM, IDU, HET).

In sensitivity analyses, the yearly rates of HCV infection in MSM were compared to the results obtained using two alternate censoring approaches: (1) Mid-point censoring, in which the date of seroconversion was set to the mid-point between the last negative and first positive HCV serology, and (2) a non-parametric 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, due to 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 Chi-square and Mann-Whitney tests. The difference in incidence of HCV infections between patients of different age groups, condom use patterns, hepatitis B 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 multivariable 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 non-IDU 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 antiretroviral therapy (ART) status (yes or no). All statistical analyses were performed using Stata 12 (Stata Corp, College Station, USA) and R-2.14.1 [21] using add-on packages INLA [22] and Icens [23].

RESULTS

Baseline characteristics

Of 4,629 MSM, 2,678 IDU and 4,530 HET screened for HCV infection, 147 (3.2%), 2,468 (92.2%) and 513 (11.3%) had a positive HCV serology at baseline (Figure 1). 6,534 patients, of which 3,333 MSM, 123 IDU and 3,078 HET, were included in the HCV incidence analyses. Median age at first HCV screening test was slightly higher in MSM (38 years, inter-quartile range (IQR) 32-44) and HET (36, 30-44), compared to IDU (33, 28-40), whereas MSM were more likely to have a high-level education than patients in the two 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 to MSM (7.7) and IDU (8.9).

HCV incidence

Over a total follow-up time of 23,707 person-years (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 experienced an HCV seroconversion during follow-up, respectively. Between 1998 and 2011, the IR of HCV infections in MSM increased from 0.23 (95% CI: 0.08-0.54) per 100 py to 4.09 (2.57-6.18) in 2011in 2011, with 51 cases observed in the last 3 years (Figure 2). There was a similar increase in patients followed in Zurich compared to the rest of the country (IR in 2011 were 2.61 (1.19-5.13) and 4.10 (2.18-7.16) per 100 py, respectively). Increases in HCV-incidence in MSM were similar when right-censoring, midpoint-censoring or interval-censoring were used to estimate yearly incidence rates (Web-Figure 1).

In IDU, HCV infection IR decreased from 13.89 (95% CI: 8.20-22.39) per 100 py in 1998 to 2.24 (0.55-10.66) 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 below 0.5 per 100 py, with only 2 cases in 2011 (IR 0.43 per 100py, 95% CI: 0.12-1.29; Figure 2). Twenty-five (15.0%) HCV-seroconverters had a unique positive serology followed by negative tests. Of those, six patients had their HCV infection confirmed by HCV RNA testing within one month of the positive serology. In another eight 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 an HCV RNA 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: 0.11 per 100 py, 95% CI 0.03-0.35; IDU: 14.36, 8.36-23.39; HET: 0.09, 0.02-0.35. 2011: MSM: 3.56, 2.19-5.53; IDU: 2.42, 0.51-13.36; HET: 0.47, 0.14-1.30).

Predictors of HCV infections in MSM

Most demographic and behavioural characteristics were similar in HCV-seroconverters compared to patients who did not seroconvert (Web-Table 1). Median age was 34.9 years in seroconverters and 37.7 years in non-seroconverters, and the proportion of Caucasians was 93% and 92%, respectively. In both groups, over 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 (Web-Table 1). The incidence of HCV infections 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 to the other patients (Figure 3). In adjusted Cox regression analyses, only inconsistent condom use (adjusted Hazard Ratio (aHR): 2.09, 95% CI 1.33-3.29) and

previous diagnosis of syphilis (2.11, 1.39-3.20) were significantly associated with HCV seroconversions (Table 2).

Age, education level, $CD4^+$ T cell counts, ART status and the other variables included in the multivariable model were not significantly associated with the main outcome. Of note, having occasional sexual partners (aHR 0.97, 0.56-1.68) and being followed-up in Zurich (aHR 1.30, 0.87-1.97) did not predict HCV seroconversions.

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, 19.0%), 3 (8, 12.7%) and 2 (1, 1.6%).

DISCUSSION

We assessed trends in HCV incidence between 1998 and 2011 in the main HIV transmission groups in the SHCS. In a population of over 6,500 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 sub-population, 50% of all HCV infections occurred in the last three 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 described epidemics of HCV infections among HIV-infected MSM [7-12]. Phylogenetic and socio-demographic 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 increased 18-fold, reaching 4.1 cases per 100 py in 2011. This incidence was higher compared to the large majority of previous studies among HIV-infected MSM reporting estimates lower than one 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 5.1/100 py in 2007 [25]. In accordance to 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 US. However, our study shows that HCV-incidence increased similarly outside of 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 infections 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 twofold. 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 two 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-infections 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 hepatitis C, and to screen for syphilis in MSM with acute hepatitis C. Although the use of non-injection drugs has been associated with HCV infections among HIV-infected MSM [28], we found no association between non-injection drug use and HCV seroconversions in MSM. However, we cannot exclude that our analysis underestimates the effect of non-injection 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 at CD4-T cell counts above 200/µl and most cases (93%) were on ART.

The incidence of HCV infections 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 IDUs followed in routine HIV care. Furthermore, Switzerland's long-term heroin prescription program likely contributed to the decreasing incidence of HCV seroconversions 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 IDUs, 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 resides in the fact that we could not estimate the exact HCV seroconversion dates between two 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 infections. Similarly, the incidence might have been underestimated through patients with late or absent seroconversion, as described by Thomson et al. [13]. A further limitation lies in the sub-optimal sensitivity and specificity of HCV antibody assays. Although positive ELISA tests were routinely confirmed by immunoblot, 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 will be reduced to 1 year in the SHCS. This should allow identifying patients with new HCV-infections earlier in order to optimize counselling 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 still engage in any risk behavior [33-35]. Furthermore, a recent study demonstrated that yearly serological HCV screening and 6-monthly 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 3-monthly screening with liver function tests is cost-effective in settings with HCV-incidences above 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 behaviour, 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 counselling should be performed. Despite the fact that antiretroviral treatment is highly efficient in preventing HIV-transmission it does not have any effect on prevention of other sexually transmitted diseases. Condom use declined in recent years in MSM with suppressed HIV viral load in the SHCS [37], which likely contributes to the increasing incidence of HCV-infections in this population. It is crucial that HIV-infected MSM are counselled with regard to the risks of sexual activities that involve traumatic mucosal sex, and that condoms are used consistently in sexual risk situations [28]. The example of IDUs demonstrates that it is possible to reduce the incidence of HCV-infections through improved screening and preventive interventions.

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Author contribution. GW, TG, HF and AR designed the study, conducted the statistical analyses and wrote the first draft of the manuscript. All authors contributed to the interpretation of the data, critically revised the paper and approved its final version.

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Table 1: Baseline characteristics of patients included in incidence analyses

	MSM	IDU	HET	Total
Number of patients	3,333	123	3,078	6,534
Sex				
Male (%)	3,333 (100)	76 (61.8)	1,339 (43.5)	4,748 (72.7)
Female (%)	0	47 (38.2)	1,739 (56.5)	1,786 (27.3)
Median age at first HCV serology (IQR)	38 (32-44)	33 (28-40)	36 (30-44)	37 (31-44)
Region of SHCS follow-up				
Outside ZH (%)	1,759 (52.8)	71 (57.7)	2,184 (71.0)	4,014 (61.4)
ZH (%)	1,574 (47.2)	52 (42.3)	894 (29.0)	2,520 (38.6)
Education level				
No prof. education (%)	76 (2.3)	10 (8.9)	348 (11.6)	434 (6.8)
Basic prof. education (%)	1,816 (56.1)	90 (80.4)	1,979 (65.9)	3,885 (61.1)
High level education (%)	1,348 (41.6)	12 (10.7)	676 (22.5)	2,036 (32.1)
Ethnicity				
Caucasian	3,075 (92.3)	112 (91.1)	1,825 (59.3)	5,012 (76.7)
Non-Caucasian	258 (7.7)	11 (8.9)	1,253 (40.7)	1,522 (23.3)

MSM: Men who have sex with men; IDU: injection drug use; HET: Heterosexual
Comparison of characteristics between 3 risk groups: $p<0.001$ for all variables

Table 2: Predictors of acquiring acute HCV infection in MSM (from Cox regression model)

	Univariable analysis		Multivariable analysis	
	HR (95%CI)	p-value	aHR (95%CI)	p-value
Age category (years)		0.39		0.24
16-29	Ref.		Ref.	
30-39	0.72 (0.43-1.21)		0.71 (0.42-1.22)	
>39	0.71 (0.42-1.21)		0.60 (0.33-1.09)	
CD4 category (cells/ µl)*		0.28		0.33
<200	Ref.		Ref.	
200-499	1.09 (0.39-3.03)		1.22 (0.43-3.47)	
>499	0.79 (0.28-2.18)		0.88 (0.31-2.54)	
HIV viral load (<50 cp/ml)*		0.04		0.08
Undetectable	Ref.		Ref.	
Detectable	1.64 (1.04-2.59)		1.63 (0.94-2.83)	
Education level		0.91		0.71
No prof. education	Ref.		Ref.	
Basic prof. education	1.05 (0.26-4.30)		1.24 (0.30-5.17)	
High level education	1.14 (0.27-4.70)		1.44 (0.34-6.13)	
Region of SHCS follow-up		0.28		0.20
Outside ZH	Ref.		Ref.	
ZH	1.24 (0.84-1.84)		1.30 (0.87-1.97)	
Ethnicity		0.81		0.91
Other	Ref.		Ref.	
Caucasian	0.91 (0.42-1.96)		1.04 (0.47-2.31)	
Use of non-IDU drugs		0.96		0.20
No	Ref.		Ref.	
Yes	0.99 (0.65-1.51)		0.74 (0.47-1.17)	
Sexual partners**		0.43		0.91
None or only stable	Ref.		Ref.	
Occasional partner(s)	1.23 (0.74-2.05)		0.97 (0.56-1.68)	
Condom use**		0.001		0.002
always	Ref.		Ref.	
Inconsistently/never	2.03 (1.33-3.10)		2.09 (1.33-3.29)	
Past history of syphilis		<0.001		<0.001
No	Ref.		Ref.	
Yes	2.20 (1.48-3.27)		2.11 (1.39-3.20)	
HBV exposure		0.12		0.08
No	Ref.		Ref.	
Yes	1.39 (0.92-2.09)		1.48 (0.95-2.28)	
ART status**		0.31		0.92
No	Ref.		Ref.	
Yes	0.67 (0.31-1.45)		1.05 (0.43-2.56)	

HR: hazard ratio, aHR: adjusted hazard ratio

*last measurement before last negative HCV serology, or first positive serology in seroconverters

**during follow-up (before last negative test, or first positive test in seroconverters)

Figure legends

Figure 1: Patients flow chart

HCV: Hepatitis C Virus; SHCS: Swiss HIV Cohort Study; MSM: Men who have sex with men; IDU: Injection drug users; HET: heterosexuals; FUP: Follow-up

Figure 2: Hepatitis C yearly incidence rates by transmission group (shaded: 95% credible intervals)

HET: Heterosexuals; IDU: Injection drug users; MSM: Men who have sex with men

Figure 3: HCV incidence by risk factor in MSM

Figure 1: Patients flow chart

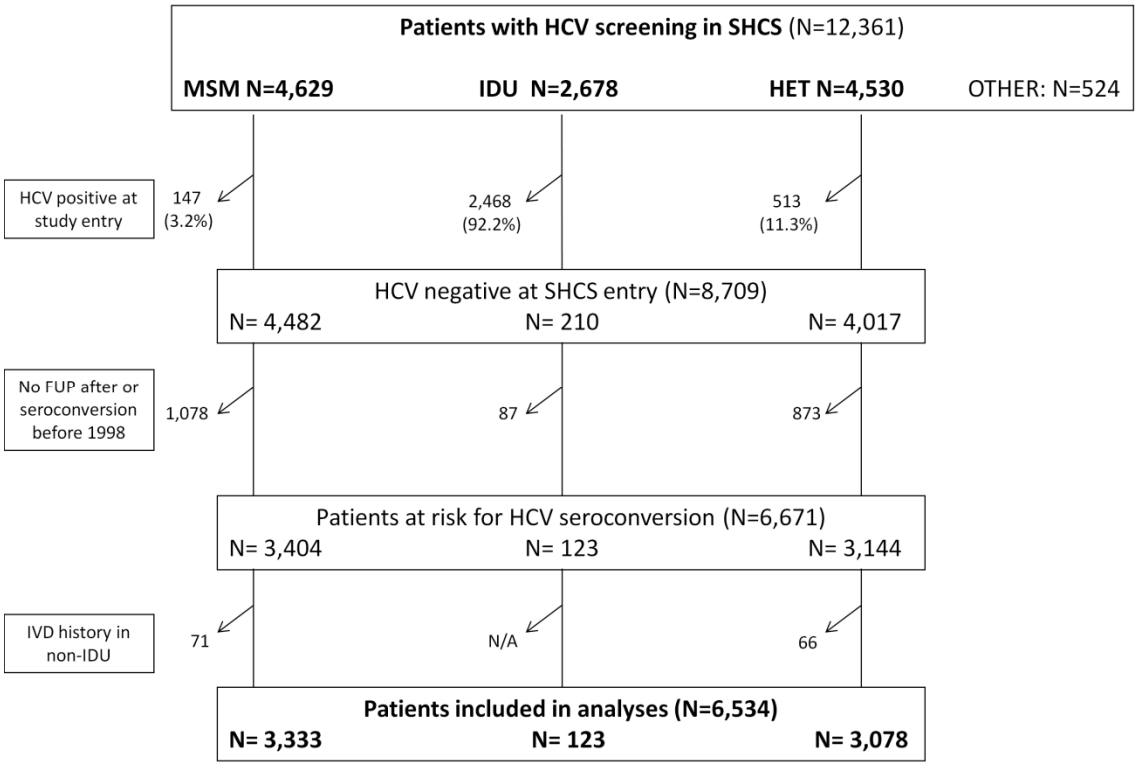

Figure 2: Hepatitis C yearly incidence rates by transmission group (shaded: 95% credible intervals)

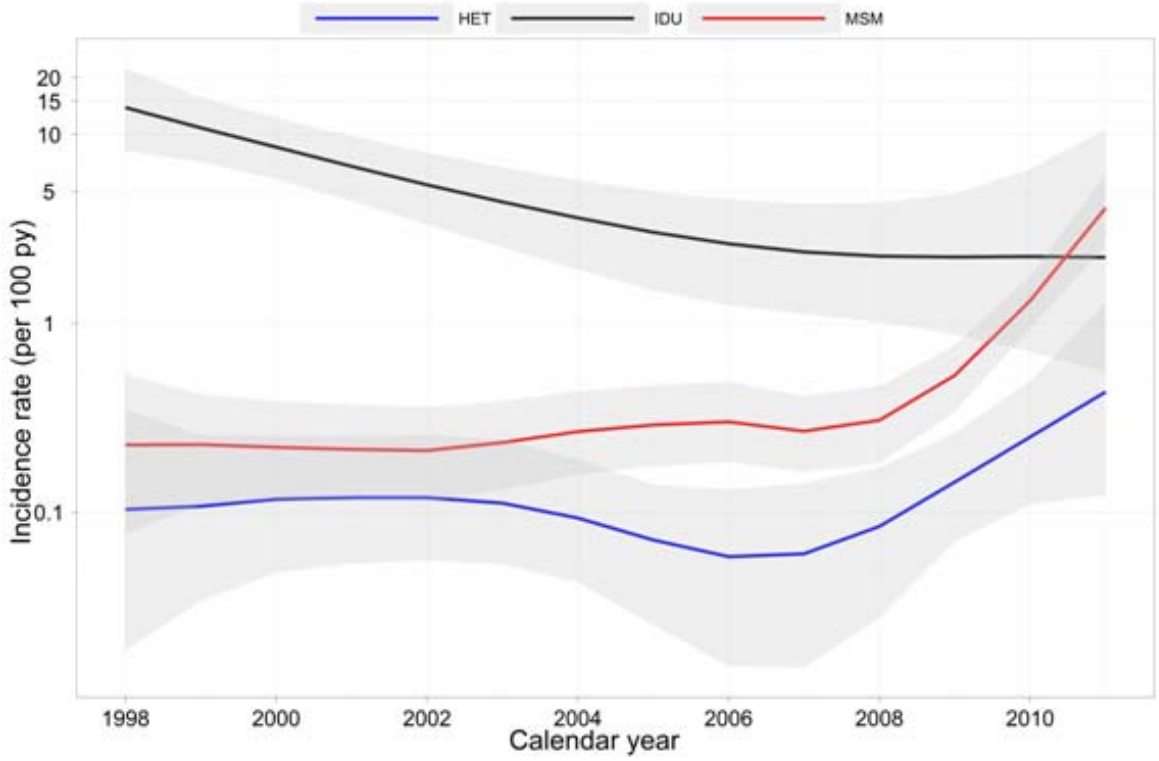

Figure 3: HCV incidence by risk factor in MSM