MAJOR ARTICLE

Incident Hepatitis C Virus Infection in Men Who Have Sex With Men: A Prospective Cohort Analysis, 1984–2011

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Background. Prospective characterization of hepatitis C virus (HCV) transmission in both human immunodeficiency virus (HIV)–infected and –uninfected men who have sex with men (MSM) over the entire HIV epidemic has not been comprehensively conducted.

Methods. To determine the trends in and risk factors associated with incident HCV in MSM since 1984, 5310 HCV antibody (anti-HCV)–negative MSM in the Multicenter AIDS Cohort Study were prospectively followed during 1984–2011 for anti-HCV seroconversion.

Results. During 55 343 person-years (PYs) of follow-up, there were 115 incident HCV infections (incidence rate, 2.08/1000 PYs) scattered throughout the study period. In a multivariable analysis with time-varying covariates, older age (incidence rate ratio [IRR], 1.40/10 years, $P < .001$), enrollment in the later (2001–2003) recruitment period (IRR, 3.80, $P = .001$), HIV infection (IRR, 5.98, $P < .001$), drinking >13 alcoholic drinks per week (IRR, 1.68, $P < .001$), hepatitis B surface antigen positivity (IRR, 1.68, $P < .001$), syphilis (IRR, 2.95, $P < .001$), and unprotected receptive anal intercourse with >1 male partner (IRR, 3.37, $P < .001$) were independently associated with incident HCV. Among HIV-infected subjects, every 100 cell/mm^3 increase in CD4 count was associated with a 7% ($P = .002$) decrease in the HCV incidence rate up to a CD4 count of 500 cells/mm^3, whereas there was no association with highly active antiretroviral therapy.

Conclusions. The spread of HCV among both HIV-infected and -uninfected MSM in the United States has been ongoing since the beginning of the HIV epidemic. In HIV-infected men with <500 CD4$^+$ T cells, the HCV incidence rate was inversely proportional to CD4 T-cell count.

Keywords. incident HCV; sexual transmission; MSM.

Hepatitis C virus (HCV) is most efficiently transmitted through percutaneous routes; however, outbreaks of sexual HCV transmission among men who have sex with men (MSM) have recently been reported [1–3]. These outbreaks have been primarily in MSM infected with human immunodeficiency virus (HIV) and suggest that transmission rates may be increasing in this group, an idea supported by some but not all studies [1, 4, 5]. In the largest dataset from the Swiss Cohort Study, the HCV incidence rate (IR) among HIV-infected MSM increased from 0.23 to 4.09 per 100 person-years (PYs) between 1998 and 2011 [4]. However, data are limited on HCV transmission in MSM prior to the antiretroviral era. The Amsterdam

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Cohort Study ascertained incident HCV starting in 1984, but there was no indication whether any infections occurred prior to antiretroviral therapy [6].

Most studies of prevalent HCV in MSM have focused on HIV-infected subjects, but the few that have included HIV-uninfected MSM suggest that the HCV prevalence is lower in this group. In a Dutch study, the HCV prevalence among sexually transmitted disease clinic attendees was 0.4% and 17.8% in HIV-negative and -positive MSM, respectively [7]. In an Australian study, the HCV prevalence in HIV-uninfected MSM was 1.1% compared to 9.4% in the HIV-infected men [8].

A few studies have examined incident, as opposed to prevalent, HCV IRs. In one clinic population followed from 2000 to 2006, the observed HCV IRs were 1.5 and 11.8 per 1000 PYs in HIV-uninfected and -infected men, respectively; however, two-thirds of the population was never tested for HCV [9]. In another study, the HCV IR increased from 0.07 to 0.18 per 100 PYs between 1984 and 2003 [6], but no incident infections occurred in HIV-uninfected subjects. Identified risk factors for HCV acquisition in MSM include high-risk sexual behaviors such as unprotected anal intercourse and fisting, concomitant use of illicit drugs, and prior syphilis [2, 4, 7, 10].

Determining the long-term dynamics and risk factors of HCV transmission in HIV-infected and -uninfected MSM requires a large cohort of both HIV-negative and -positive MSM, followed since the beginning of the HIV epidemic, and in whom HCV infection status is uniformly and repeatedly assessed. The Multicenter AIDS Cohort Study (MACS) is such a cohort that was established in 1984 and enrolled MSM with or at risk for HIV infection. Thus, we prospectively tested HCV antibody in the MACS using stored specimens.

METHODS

Study Subjects

The MACS enrolled 6972 HIV-infected and -uninfected MSM from 4 metropolitan areas in the United States (Baltimore, Maryland/Washington, District of Columbia; Chicago, Illinois; Pittsburgh, Pennsylvania; and Los Angeles, California) during 3 recruitment periods: 1984–1985, 1987–1990, and 2001–2003. The details of the MACS have been described elsewhere [11–13]. At study entry, HIV antibody was tested and, if negative, was repeated semiannually. Participants provided informed consent, and the institutional review boards at each site approved the study.

The inclusion criteria for this study were (1) negative HCV antibody (anti-HCV) within 2 years of enrollment and (2) anti-HCV testing at ≥1 follow-up visit through 30 September 2011. Incident HCV was defined as anti-HCV seroconversion, as determined by 1 of 2 testing protocols. For men recruited before 2001, the last available specimen was tested for anti-HCV. If the result was negative, the participant was classified as HCV negative throughout the subject's follow-up. If the result was positive, the participant was classified as having an incident infection, and we recursively tested a specimen obtained at the midpoint between the last negative and first positive anti-HCV results until no specimens remained to be tested within the seroconversion interval. For men enrolled in the 2001–2003 recruitment, anti-HCV was tested prospectively every 2 years. If a result was positive, the participant was classified as having an incident infection, and recursive testing was done as above. The date of incident infection was defined as the midpoint between the last negative and first positive anti-HCV visit.

To be classified as an incident HCV infection for this study, a subject needed an anti-HCV–positive test at ≥2 follow-up visits. Thus, 8 subjects who were anti-HCV positive only at their last study visit were censored as HCV negative at their last anti-HCV–negative visit. Supplemental analyses were performed to evaluate the sensitivity of the results to censoring these 8 men as HCV-negative. An additional 14 subjects who had a HCV seroconversion interval ≥4 years were censored as HCV negative 2 years following their last anti-HCV–negative visit because of the increased uncertainty about the date of their incident infections and their risk factor status immediately prior to infection.

Laboratory Testing

All testing was performed on serum or plasma specimens frozen at −70°C. HIV status was determined using enzyme immunosorbent assay (EIA) and confirmed with Western blot [11]. Anti-HCV testing was performed with a third-generation EIA in accordance with the manufacturer's instructions (ADVIA Centura HCV assay).

Statistical Analysis

We characterized the study population using standard descriptive statistics and compared subjects who entered the MACS during different recruitment periods using the Pearson χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables.

Follow-up time was accrued from the baseline visit until either incident infection or the last anti-HCV–negative visit. HCV IRs were calculated as the number of incident HCV infections divided by the number of observed PYs of follow-up and compared using Poisson regression. The multivariable analysis included factors selected a priori (ie, center, race, smoking history, education, recent syphilis, and employment status) in addition to factors found to be significant in univariable analyses ($P \leq .05$). We used robust variance estimation [14] to account for within-center correlations. All factors that varied over time were included in the regression analysis using time-varying covariates by partitioning follow-up time at each

Table 1. Baseline Characteristics of Hepatitis C Virus Antibody–Negative Men Who Have Sex With Men Stratified by Recruitment Period Into the Multicenter AIDS Cohort Study

Recruitment Period	1980s/1990s (n = 4384)	2001–2003 (n = 926)	All (N = 5310)
Center			
Baltimore	1154 (26)	224 (24)	1378 (26)
Chicago	941 (21)	208 (22)	1149 (22)
Pittsburgh	988 (23)	227 (25)	1215 (23)
Los Angeles	1301 (30)	267 (29)	1568 (30)
Education[a]			
<12th grade	67 (2)	105 (11)	172 (3)
12th grade	446 (10)	186 (20)	632 (12)
>12th grade	3819 (87)	606 (65)	4425 (83)
Missing	52 (1)	29 (3)	81 (2)
Employment status[a]			
Unemployed	511 (12)	364 (39)	875 (17)
Employed	3838 (87)	524 (57)	4363 (82)
Retired	26 (<1)	12 (1)	38 (<1)
Missing	9 (<1)	26 (3)	35 (<1)
Age, y, median (IQR)[a]	32 (28–37)	37 (31–42)	33 (28–39)
Black[a]	348 (8)	389 (42)	737 (14)
Consume >13 alcohol drinks/wk	732 (18.1)	102 (11.3)	834 (16.8)
Ever smoker	2475 (56.9)	625 (69.2)	3100 (59.0)
HIV positive[a]	1557 (36)	484 (52)	2041 (38)
Ever AIDS among HIV positive[a]	0 (0)	8 (1)	8 (<1)
Ever IDU	199 (5)	48 (5)	247 (5)
History of URAI with multiple partners[a]	1786 (41)	94 (11)	1880 (36)
HBsAg positive[a]	244 (6)	36 (4)	280 (5)
History of blood transfusion[a]	98 (2)	51 (6)	149 (3)

Data are presented as No. (%) unless otherwise specified.

Abbreviations: HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; IDU, injection drug user; IQR, interquartile range; URAI, unprotected receptive anal intercourse.

[a] P value < .05 (χ^2 test or Kruskal-Wallis test for comparison between 1980s and 2001–2003 recruits).

MACS study visit. For example, men who acquired HIV during follow-up were classified as HIV-negative prior to HIV seroconversion and as HIV-positive thereafter. Preliminary analyses of the relationship between CD4 count and HCV incidence suggested that an elevated risk for incident HCV existed among men with low CD4 counts and that this elevated risk was attenuated at CD4 levels >500 cells/mm^3. To account for this observation in the multivariable analysis, we modeled CD4 count using a piecewise linear function to estimate different CD4 effects above and below 500 cells/mm^3. All analyses were performed using SAS version 9.22 (SAS Institute, Cary, NC) or StatXact version 9.0 (Cytel Inc, Cambridge, MA). Statistical significance was inferred when the 2-sided P value was < .05.

RESULTS

Among the 6972 men enrolled in the MACS, 6955 were tested for anti-HCV at study entry, of whom 538 (7.7%) had positive results. Of the 6417 anti-HCV–negative men, 1107 did not complete any MACS study visits >2 years after their baseline anti-HCV test was performed and, thus, were not eligible for follow-up anti-HCV testing. The remaining 5310 anti-HCV–negative men were included in this study. Most of these men were recruited in the 1980s or early 1990s (n = 4384), with the remainder recruited between 2001 and 2003. The men were equally distributed over the 4 MACS sites (Table 1). Unprotected receptive anal intercourse (URAI) with multiple partners was reported by 36% of subjects, 3% had a prior blood transfusion, 5% reported a history of injection drug use, and 5% were positive for hepatitis B surface antigen (HBsAg). Participants recruited between 2001 and 2003 differed from those recruited in the 1980/1990s in several characteristics (Table 1).

Through September 2011, the cohort was followed for a median of 7.1 years (interquartile range, 5.1–16.2 years) and accrued 55 343 PYs of follow-up during which 115 incident HCV infections were observed (IR, 2.08/1000 PYs; 95% confidence interval [CI], 1.73–2.49/1000 PYs). Notably, the HCV IR was nearly 8.5-fold higher among HIV-infected compared to HIV-uninfected men (4.22 and 0.50 per 1000 PYs, respectively, $P < .001$). Several interesting findings were revealed when we stratified follow-up time by recruitment cohort and examined changes in HCV incidence over time. First, incident HCV infections have occurred in both HIV-infected and -uninfected MSM since 1984 and have been consistently higher in HIV-infected MSM regardless of recruitment period (Table 2). Second, among the HIV-positive men, the IR during the 4 years after recruitment was similar among men recruited in the 1980s/1990s and men recruited in the 2000s (5.62 and 6.74 per 1000 PYs, respectively, $P = .66$). Third, the IR among HIV-positive men recruited in the 1980s/1990s declined over time, which was not observed in the other groups. Fourth, the IRs increased from 2000–2004 to 2005–2011 in all groups except for in HIV-positive men recruited after 2000, although these changes are not statistically significant.

In univariable analyses, neither age nor race was associated with HCV incidence (Table 3). However, drinking >13 alcoholic drinks per week, smoking, being HIV infected, being recruited in the 2001–2003 period, being a former or recent injection drug user (IDU), having HBsAg, being recently infected with syphilis (defined as a new diagnosis within the prior 6 months), and having a prior blood transfusion were all associated with

Table 2. Incident Hepatitis C Virus Infection Stratified by Recruitment Period and Calendar-Year Intervals

	1980s and 1990s Recruits				2000–2003 Recruits			
Participants	Incident Infections (no.)	PYs	IR/1000 PYs	95% CI	Incident Infections, No.	PYs	IR/1000 PYs	95% CI
HIV-negative men								
1984–1989	8	12 354	0.65	.28–1.28	NA	NA	NA	NA
1990–1994	0	6913	0	0–.53	NA	NA	NA	NA
1995–1999	0	3064	0	0–1.20	NA	NA	NA	NA
2000–2004	1	3112	0.32	.01–1.79	1	835	1.20	.03–6.67
2005–2011	2	3787	0.53	.06–1.91	4	1715	2.33	.64–5.97
HIV-positive men								
1984–1989	41	7299	5.62	4.03–7.62	NA	NA	NA	NA
1990–1994	18	4779	3.77	2.23–5.95	NA	NA	NA	NA
1995–1999	11	3185	3.45	1.72–6.18	NA	NA	NA	NA
2000–2004	5	2648	1.89	.61–4.41	7	1038	6.74	2.71–10.89
2005–2011	6	2334	2.57	.94–5.60	11	2133	5.16	2.57–9.23

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IR, incidence rate; NA, not applicable; PYs, person-years.

incident HCV (Table 3). Of note, among non-IDUs, men who used other recreational drugs had higher HCV IRs (2.07/1000 PYs) than those who did not use recreational drugs (0.94/1000 PYs, $P = .002$).

The only sexual behavior that was significantly associated with an increased HCV incidence was having URAI during the prior 6 months with multiple partners either as both the insertive and receptive partner (IR, 6.31/1000 PYs, $P < .001$) or as the receptive partner only (IR, 9.67/1000 PYs, $P < .001$) when compared to men with ≤1 male sex partner (IR, 1.30/1000 PYs) (Table 4). In contrast, men who had multiple anal sex partners but only reported unprotected anal sex with ≤1 partner or who had unprotected anal sex only as the insertive partner were not at a significantly increased risk for incident HCV infection (IR, 1.83/1000 PYs [$P = .25$] and 2.53/1000 PYs [$P = .09$], respectively). We also examined whether there was a trend toward increasing incidence as the number of URAI partners increased and found that men with ≥3 URAI partners during the prior 6 months were more likely than those with 2 URAI partners to become HCV infected (IR, 9.03 and 5.34 per 1000 PYs), although these IRs were not significantly different ($P = .14$).

Among the HIV-infected men, the HCV IRs were higher as $CD4^+$ T-cell counts decreased (IR, 3.69/1000 PYs, 4.10/1000 PYs, and 4.98/1000 PYs for $CD4^+$ T-cell counts >500 cells/mm^3, 350–500 cells/mm^3, and <350 cells/mm^3, respectively, $P = .04$ for trend). To determine if this CD4 association was due to differences in risk factor distribution, we compared HCV risk factors among men with CD4 counts above and below 500 cells/mm^3. Interestingly, there was no difference in alcohol, smoking, or recent syphilis infection, but men with a CD4 count of >500 cells/mm^3 were more likely to have used injection drugs (60% vs 54%, $P = .02$), to be recruited in the 2001–2003 period (35% vs 13%, $P < .0001$), to be black (22% vs 14%, $P < .0001$), and to have >1 URAI partner (15% vs 6.7%, $P < .0001$). Among the HIV-infected men, highly active antiretroviral therapy (HAART) use was not associated with an increased risk of acquiring HCV (IR, 3.61/1000 PYs vs 4.42/1000 PYs for those who did and did not ever receive HAART, respectively; $P = .36$).

In the multivariable analysis adjusting for race, smoking history, education, employment status, and history of blood transfusion, the characteristics independently associated with increased risk for incident HCV in the full cohort were older age, being enrolled in the 2001–2003 cohort, HIV infection, being HBsAg positive, history of injection drug use, drinking >13 alcoholic drinks/week, having URAI with multiple male partners in the prior 6 months, and syphilis in the prior 6 months (Table 5). In 2 separate sensitivity analyses where we (1) fit the same multivariable models using follow-up time accrued only during the HAART era (1998–2011) and (2) fit the same multivariable models including the 8 participants who were censored due to being anti-HCV positive only at the last visit, the results were qualitatively similar (data not shown).

The multivariable results were similar among the subgroup of 2377 HIV-infected men (Table 5). In this subanalysis, HCV incidence decreased significantly as CD4 T-cell count increased from 0 to 500 cells/mm^3 (incidence rate ratio [IRR], 0.93; 95% CI, .88–.97/100 cells). In contrast, no association was observed between CD4 count and HCV incidence when CD4 count was >500 cells/mm^3 (IRR, .99; 95% CI, .92–1.07/100 cells). After adjusting for CD4 count and the other risk factors listed in

Table 3. Univariable Analysis for Risk Factors Associated With Incident Hepatitis C Virus Infection

Risk Factor	IR/1000 PYs	IRR, 95% CI	*P* Value
Race			
Nonblack	2.01	1	
Black	2.68	1.34 (.79–2.27)	.28
Age, y			
<30	2.39	1	
30–39	2.21	0.92 (.50–1.69)	.80
40–49	2.07	0.87 (.47–1.60)	.65
≥50	1.73	0.72 (.37–1.42)	.35
Alcoholic drinks/wk			
None	1.94	1	
1–3	1.72	0.88 (.49–1.60)	.69
4–13	1.85	0.95 (.52–1.74)	.87
>13	**4.84**	**16.22 (8.85–29.72)**	**.005**
Smoker			
Never	1.73	1	
Former	1.56	0.90 (.55–1.46)	.66
Current	**3.19**	**1.84 (1.19–2.86)**	**.007**
HIV			
Uninfected	0.50	1	
Infected	**4.22**	**8.40 (4.96–14.25)**	**<.001**
Recruitment period			
1980s/1990s	1.85	1	
2001–2003	**4.02**	**2.17 (1.37–3.42)**	**<.001**
Ever IDU			
Never	1.59	1	
Former	**6.88**	**4.33 (2.68–7.00)**	**<.001**
Current	**25.76**	**16.22 (8.85–29.72)**	**<.001**
HBsAg			
Negative	1.98	1	
Positive	**4.39**	**2.21 (1.19–4.12)**	**.01**
Syphilis			
No	2.00	1	
Yes	**16.94**	**8.45 (3.45–20.70)**	**<.001**
History of blood transfusion			
Never	1.99	1	
Ever	**6.62**	**3.33 (1.62–6.83)**	**.001**

Boldface type indicates $P < .05$.

Abbreviations: HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; IDU, injection drug user; IR, incidence rate; IRR, incidence risk ratio.

Table 5, there was no difference between men with and without HAART experience (IRR, 1.02; 95% CI, .49–2.15). To determine which factors were independently associated with HCV incidence in men whose only risk factor for HCV was sex with men, we limited the analysis to the 4376 men who never reported injection drug use or blood transfusion. In this subanalysis, the results were also similar to the full cohort except that being enrolled in the 2001–2003 cohort, calendar year, >13 alcohol drinks/week, or syphilis during the prior 6 months were no longer associated with HCV incidence (Table 5).

DISCUSSION

Our data demonstrate that HCV acquisition has been ongoing in the MSM population in the United States since early in the HIV epidemic. Although HCV infections occurred in both HIV-infected and -uninfected MSM, the rates in the HIV-infected MSMs are significantly higher. Furthermore, among HIV-infected MSM, this is the first study to report a significantly higher HCV IR in men with lower CD4 T-cell counts.

Recently, reports of HCV outbreaks in HIV-positive MSM [15] have led to speculation that the HCV epidemic is emerging in this population. Our study does not support this because incident HCV infections have occurred in the 4 US sites represented in the MACS since the mid-1980s. In fact, the IR in the men recruited in the 1980s/1990s compared to those recruited since 2000 was similar during the first 4 years after recruitment. Other studies may have missed this important observation by not adequately examining HCV incidence during the 1980s and 1990s [6, 16].

Our study also demonstrates a generally higher HCV incidence between 2005 and 2011 compared to 2000–2004, which is consistent with recent reports of increasing HCV infections among MSM [4]. One large study examined incident HCV in MSM from 8 European countries and Canada, and found the IR increasing from 1990–2000 [17]. Our study does not clearly indicate a similar increase since 1990, which could be due to the fact that the MACS participants enrolled prior to 1990 comprise a closed cohort. Alternatively, it is difficult to determine the validity of the trend in the European/Canadian study because up to 66% of subjects were not tested for HCV; thus, their results could be affected by selection bias.

It is notable that the HCV IR among men enrolled during the 2001–2003 recruitment period was significantly higher than that among men enrolled during the 1980s and 1990s even after adjusting for other factors including history of injection drug use. This observation could be due to effective and simple HAART leading to decreased apprehension about contracting HIV and more risky sexual behaviors. Another plausible explanation is that the HCV prevalence was higher in the general MSM population, which is also likely due to antiretroviral effectiveness, so the probability of having unprotected sex with an HCV-infected partner is higher.

It is intriguing that HIV infection led to a 6- to 8-fold higher incidence of HCV after adjusting for behavioral confounders. Together with our data demonstrating the progressively increasing risk for HCV infection with CD4 counts <500 cells/mm^3, this suggests that the HIV association is not simply due to unaccounted behavioral risk factors, because it is unlikely that those factors would be more common in men with lower

Table 4. Hepatitis C Virus Incidence by Number of Partners and Type of Sexual Exposure

Sexual Behavior in Prior 6 mo	Incident Infections, No.	PYs	Incidence Rate/1000 PYs	IRR (95% CI)	*P* Value
≤1 male sex partner	31	23 853	1.30	1	
Multiple male sex partners, but ≤1 anal sex partner	19	13 686	1.39	1.07 (.60–1.89)	.82
Multiple anal sex partners, but unprotected anal sex with ≤1 partner	17	9265	1.83	1.41 (.78–2.55)	.25
Unprotected insertive anal sex with multiple partners	8	3160	2.53	1.95 (.90–4.24)	.09
Unprotected insertive and receptive anal sex with multiple partners	20	3171	6.31	4.85 (2.77–8.51)	<.001
Unprotected receptive anal sex with multiple partners	20	2068	9.67	7.44 (4.24–13.06)	<.001

Abbreviations: CI, confidence interval; IRR, incidence risk ratio; PYs, person-years.

Table 5. Multivariable Analysis for Incident Hepatitis C Virus Infection in All Subjects, in HIV-Infected Subjects, and in Subjects Without History of Injection Drug Use or Blood Transfusion

	All (n = 4954)[a]		HIV-Infected (n = 2377)[a,b]		Non-IDU/-Blood Transfusion (n = 4376)[a]	
Risk Factor	IRR[c] (95% CI)	*P* Value	IRR[c] (95% CI)	*P* Value	IRR[d]	*P* Value
Age, per 10 y	**1.40 (1.22–1.61)**	**<.001**	**1.44 (1.37–1.52)**	**<.001**	**1.35 (1.04–1.74)**	**.02**
Calendar year, per y	**0.94 (.90–.98)**	**.007**	**0.94 (.90–0.98)**	**.002**	0.97 (.94–1.01)	.11
Enrolled 2001–2003 vs 1980s/1990s	**3.80 (1.67–8.64)**	**.001**	**3.37 (1.55–7.33)**	**.002**	2.14 (.83–5.55)	.12
HIV infected vs uninfected	**5.98 (4.85–7.39)**	**<.001**	Not applicable		**7.56 (5.56–10.44)**	**<.001**
CD4 count in HIV+ men, per 100 cells/mm^3; range 0–500[e]	Not tested		**0.93 (.88–.97)**	**.002**	Not tested	
CD4 count in HIV+ men, per 100 cells/mm^3; range >500[e]			0.99 (.92–1.07)	.81		
HAART experienced vs HAART-naive	Not tested		1.02 (.49–2.15)	.95	Not tested	
HBsAg positive	**1.68 (1.29–2.19)**	**<.001**	**1.85 (1.51–2.25)**	**<.001**	**2.14 (1.53–2.99)**	**<.001**
IDU and RDU						
Never IDU/Not RDU	1		1		1	
Never IDU/current RDU	1.37 (.89–2.12)	.15	1.36 (.85–2.18)	.20	1.37 (.79–2.37)	.26
Ever IDU	**4.72 (2.11–10.53)**	**<.001**	**4.17 (1.84–9.49)**	**<.001**	Not applicable	
Mean alcoholic drinks/wk: >13 vs <0	**1.68 (1.25–2.25)**	**<.001**	**1.75 (1.12–2.74)**	**.01**	1.67 (.93–3.01)	.09
Sexual exposure in prior 6 mo						
≤1 male sex partner	1		1		1	
Multiple male sex partners, but URAI with ≤1 partner	1.36 (.76–2.46)	.30	1.40 (.71–2.75)	.33	1.45 (.59–3.53)	.41
URAI with multiple partners	**3.37 (1.69–6.74)**	**<.001**	**3.12 (1.58–6.17)**	**.001**	**4.02 (1.60–10.13)**	**.003**
Syphilis during prior 6 mo	**2.95 (1.74–5.03)**	**<.001**	**2.75 (1.76–4.29)**	**<.001**	1.90 (.72–5.00)	.19

All multiple regression models included center as a stratification variable, and we accounted for within center correlation using generalized estimating equations. Boldface type indicates $P < .05$.

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; IDU, injection drug user; IRR, incidence risk ratio; RDU, noninjection recreational drug user; URAI, unprotected receptive anal intercourse.

[a] All individuals with complete data on all risk factors included in the table.

[b] All HIV seroconverter and seroprevalent individuals at risk for HCV infection.

[c] Adjusted for center, race, smoking history, education, employment status, and history of blood transfusion.

[d] Adjusted for center, race, smoking history, education, employment status.

[e] CD4 cell count was modeled as a piecewise-linear function with a node at 500. The IRRs reported in this table correspond to the respective changes in the incidence rate per 100 cells in the ranges of 0–500 cells/mm^3 and >500 cells/mm^3.

CD4 T-cell counts. In fact, we found that men with a CD4 count of <500 cells/mm^3 had fewer known HCV risk factors. However, it seems plausible that HIV-related immunosuppression could reduce the infection threshold needed for a productive systemic infection that leads to anti-HCV production as cellular mediated immunity may clear HCV without anti-HCV production [18]. A study of women also found that HIV infection increased the risk for HCV infection, and there was also a trend toward an increased risk with CD4 count <200 cells/mm^3 [19]. In studies of IDUs, neither HIV nor CD4 count has been associated with risk of HCV infection [20, 21], which is not surprising as IDUs often acquire HCV prior to HIV.

This study identified URAI with multiple partners as the sexual behavior carrying the greatest risk for of HCV transmission. In contrast, being the insertive partner did not significantly increase the risk of incident HCV. This finding is supported by the case-control study from New York City MSM HCV outbreak [2]. Other studies have shown that traumatic sexual behaviors are associated with HCV transmission among MSM [22, 23]; however, we did not record these practices throughout follow-up and therefore could not determine if they increased HCV transmission.

It is not readily apparent why increasing age would be associated with incident HCV, but it is not due to an increase in the number of URAI partners, as older men had fewer URAI partners. It is possible that after the introduction of HAART, MSM engaged in more unprotected sex or that older men have a lower infection threshold. This finding supports continuous education of HCV infection risk in MSM of all ages.

The major strength of our study is the prospective testing on a large cohort of MSM since 1984, which eliminates a selection bias for study inclusion, and provides nearly 3 decades of data. In addition, our semiannual data and serological testing strategy allowed determination of the seroconversion date within a 6-month window and for covariates to be updated semiannually. The findings may not be generalizable to women who acquire HCV through sex. It is also possible that we underestimated the risk of incident infection as we did not ascertain reinfection, superinfection, or seronegative HCV; however, we expect these to be infrequent given the low frequency of primary incident HCV.

In summary, this study demonstrates that the HCV epidemic in both HIV-infected and -uninfected MSM has been ongoing for decades. We also demonstrate that HIV infection, especially among men with lower CD4 T-cell counts; older age; and being the receptive partner with multiple unprotected sex partners increase the risk for HCV infection in MSM. Further work is needed to understand how immunosuppression from HIV infection increases the risk for sexual HCV acquisition in MSM. These findings underscore the need for active prevention, counseling, and diagnosis of HCV in all MSM.

Notes

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