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MAJOR ARTICLE

Hepatitis C Virus Reinfection Among Men Who Have Sex With Men With HIV in New York City

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Background. Hepatitis C virus (HCV) reinfection rates are substantially higher than primary infection rates among men who have sex with men (MSM) with human immunodeficiency virus (HIV) in European cohorts. The behaviors mediating this high rate of transmission among MSM are poorly characterized.

Methods. We performed a prospective cohort study in New York City (NYC) of MSM with HIV who cleared HCV to determine the incidence of and risk factors for HCV reinfection. We assessed the risk behaviors for primary HCV in NYC: receipt of semen in the rectum, and sexualized methamphetamine use, along with route of use. Multivariable analysis was performed with Andersen-Gill extension of the Cox proportional hazards model.

Results. From 2000 through 2018, among 304 MSM with HIV who cleared HCV, 42 reinfections occurred over 898 person-years, for an incidence rate of 4.7 per 100 person-years. Assessing 1245 postclearance visits, only receipt of semen into the rectum was associated with reinfection (hazard ratio, 9.7 [95% confidence interval: 3.3–28.3], $P < .001$); methamphetamine use was not.

Conclusions. The high HCV reinfection rate over almost 2 decades demonstrates that sexual transmission of HCV is not inefficient or unusual and that direct-acting antiviral treatment is not sufficient for HCV elimination among MSM in NYC. The contrasts between both the rates of and risk factors for primary and HCV reinfection suggest that HCV prevalence is highly heterogenous among sexual networks and that sexualized methamphetamine use, rather than mediating transmission, is instead a surrogate marker for the highest HCV prevalence networks. As neither condoms nor treatment have been successful strategies for HCV prevention in NYC, novel interventions are needed to stem this sexually transmitted HCV epidemic.

Keywords. transmission; ejaculation of semen into rectum; sexualized drug use; condomless receptive anal intercourse (CRAI); sexual networks.

Hepatitis C virus (HCV) has long been considered to be parenterally and not sexually transmitted, and men who have sex with men (MSM) were not considered to be at risk for HCV infection. But in 2004–2005, HCV outbreaks were reported among MSM with HIV in Western Europe [1–4], and within the next decade, substantial HCV transmission among MSM was shown to have occurred in populous cities on 4 continents in both hemispheres. The studies of risk factors for primary HCV infection suggested sexual transmission as the most common mode, but some suggesting "traumatic" sex as the necessary element; some also found an association with the use of drugs, typically for the purposes of/in conjunction with sex (sexualized drug use) (summarized in [5]). These primary infection rates among MSM with human immunodeficiency virus (HIV) were much lower than among people who inject drugs, in the range of 0.5 per 100 person-years (PY), consistent with the perception that sexual transmission of HCV, if it occurred at all, would be much less efficient than parenteral transmission (summarized in [6]).

Subsequently, however, it was found that reinfection rates among MSM with HIV were an order of magnitude or more higher than primary infection rates, ranging from 2.5 to 15.2 per 100 PY [7–19], higher even than reinfection rates among people who inject drugs [20], calling into question these previous perceptions. Studies of risk factors for reinfection are much sparser, however, and only one group, the MOSAIC investigators in the Netherlands, has published risk factors assessments for both primary and HCV reinfection among MSM with HIV to enable direct comparison. Interestingly, the results of their 2 studies were discordant: primary infection was associated with both sexual and drug-related behaviors [21], while

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reinfection was associated only with sexual behaviors, not with drug-use behaviors [22]. To address these multiple apparently incompatible observations, we therefore followed up our previous risk factor study of primary HCV and performed a prospective cohort study to determine both the incidence of and the risk factors for HCV reinfection among MSM with HIV in New York City (NYC).

METHODS

We established the New York Acute Hepatitis C Surveillance Network to study HCV infection among MSM, as described elsewhere [23–25]. Briefly, MSM with recently acquired or chronic HCV infections were referred for enrollment and HCV care to a practice within the Mount Sinai Medical Center, through a network of providers of HIV healthcare in the NYC area. We obtained written informed consent with approval of the Institutional Review Board of the Icahn School of Medicine at Mount Sinai (Mount Sinai School of Medicine at the time of enrollment of some of the participants), in accordance with the Helsinki Declaration of 1975, as revised in 2000.

We treated early HCV infections as described elsewhere [26–28] and chronic HCV infections using the standard of care at the time of treatment. We defined HCV clearance as (1) having an undetectable HCV viral load (VL) ≥12 weeks after the end of treatment, for those who were treated; or (2) having ≥2 not-detected HCV VL measurements ≥12 weeks apart, for those who had spontaneous clearance (SC). For participants whose infection cleared, monitoring visits were planned every 3 months for the 6 months after clearance, and then every 6 months. Treatment and monitoring visits included laboratory testing for alanine aminotransferase and HCV VL, and review of previous or interval testing from the primary HIV provider. Beginning in 2006, we queried participants about the 2 behavioral risk factors for primary HCV infection in NYC: (1) receipt of semen ejaculated into the rectum with condomless receptive anal intercourse (CRAI) and (2) methamphetamine use during sex [24]. We defined methamphetamine use during sex using the medical phraseology "sexualized methamphetamine use" [5] rather than the colloquial term used by MSM in NYC, "party and play," or the term originating in England, "chemsex." We further queried those who reported sexualized methamphetamine use about the route of use and specifically whether their use was by injection. All study visits were performed by one of the investigators. Laboratory data were also routinely obtained from the primary HIV providers.

For this study, we followed MSM with HIV who had clearance of their primary HCV infection on or after 1 January 2000 to assess for HCV reinfection through 31 December 2018, or until their second reinfection. We defined reinfection as new HCV viremia after clearance of the previous infection. The date of onset of reinfection was the date of the first-noted HCV viremia, or first-noted alanine aminotransferase elevation in those who were subsequently determined to be viremic, whichever was earlier, as described elsewhere [26, 27]. Observation for reinfection began on (1) the date of completion of therapy, for those who were treated, or (2) the date of the first nondetected HCV VL, for those with SC [9].

We collected the following data to consider as risk factors for reinfection: Date of birth, race, ethnicity, health insurance type (public or private), HCV genotype, interferon (IFN) λ3 (formerly *IL28B*) haplotype, calendar year of clearance of primary HCV, mode of clearance of primary HCV (ie, treatment, including type, or SC), timing of HCV clearance, CD4 cell count, and HIV VL suppression (defined as <50 copies/mL). Race and ethnicity were defined using National Institutes of Health reporting criteria. We defined 2 categories of timing of clearance, whether by curative treatment or SC: (1) early, started within 1 year of onset of HCV infection; or (2) late, started >1 year after onset of HCV infection. IFN-based regimens included those that contained a direct-acting antiviral (DAA) (eg, telaprevir or sofosbuvir plus IFN plus ribavirin). All-oral DAA regimens excluded those administered with IFN but included the regimen sofosbuvir plus ribavirin.

Statistical Analysis

We determined the incidence rate of first reinfection, second reinfection, and overall reinfection in the full cohort. Kaplan–Meier survival curves were drawn to assess the cumulative probability of reinfection based on demographic and HCV characteristics, as well as comparing the cumulative probability of first and second reinfections. For those with a first reinfection, observation time was censored from the date of onset of the reinfection through the date of start of observation for second reinfection, as defined above. We determined the risk factors for reinfection, including the 2 behavioral risk factors, in the subset of participants who had in-person follow-up at Mount Sinai after HCV clearance (the "behavioral risk factor subcohort").

For the risk factor analysis, the behaviors of receipt of semen in the rectum and sexualized methamphetamine use that were reported at a visit were assumed to have begun on the day after their last visit, and to have continued until the day after the visit in which the behavior was reported. If visits were >1 year apart, we assumed the behavior to have begun 365 days before the current visit. For visits in which no behavioral data were recorded, we used the behavioral data from the previous visit, as long as the previous visit occurred <90 days prior. Univariable and multivariable analyses were performed using the Andersen-Gill time-to-recurrent-events extension of the Cox method to account for the repeated events that occurred in the cohort [29]. To obtain the parsimonious final model of

variables associated with reinfection, we analyzed all variables with a *P* value <.20 in univariable analysis, using multivariable analyses with manual and computer assisted forward, backward, and stepwise analysis. Analyses were performed using SAS software, version 9.4.

RESULTS

We observed 304 MSM with HIV with clearance of a primary HCV infection for reinfection (Figure 1*A*). The median age at the time of clearance (interquartile range [IQR]) was 45 (36–51) years (Table 1). Fifty-five participants (18%) identified as Black and 65 (21%) as Hispanic. Healthcare coverage was publicly funded for 160 (53%) and privately funded for 140 (47%). The HCV genotype was mostly 1a (n = 237 [80%]); genotype 4 infections were rare. Clearance of primary infection was by treatment in 273 (90%) and by SC in 31 (10%). Among the 273 participants whose primary infections were cleared by treatment, 107 (39%) were cleared with an IFN-based regimen, and 166 (61%) with a DAA regimen. Participants with reinfection differed significantly from those without reinfection in year of clearance ($P < .001$), era of clearance ($P < .001$), mode of clearance ($P = .002$), and timing of clearance ($P = .02$) (Table 1).

The 304 participants were observed for 898 PY; 36 (12%) had a first reinfection, and 6 of the 36 had a second reinfection, for a total of 42 reinfections. The overall reinfection rate was 4.7 (95% confidence interval [CI]: 3.4–6.3) per 100 PY. The rate of first reinfection was 4.3 (95% CI: 3.0–5.9) per 100 PY, and the rate of second reinfection was 9.7 (3.9–20.1) per 100 PY ($P = .09$). The median time (IQR) to first reinfection was 1.9 (1.2–3.5) years, and the median time to second reinfection was 1.1 (0.6–2.5) years ($P = .22$; Wilcoxon rank sum test [*t* approximation]). The time to first reinfection ranged from 0.4 to 11.4 years.

Risk Factors for Reinfection

We collected behavioral risk factor data after clearance of primary and first reinfection from 226 (74%) participants at a total of 1245 visits (median, 4 [IQR, 3–6; range, 1–40]) over 696 PY (Figure 1*B*). There were no differences in demographic, HIV, or HCV characteristics (Supplementary Table 1) or cumulative rates of reinfection (Supplementary Figures 1 and 2) between the behavioral risk factor subcohort and the full cohort.

In univariable then multivariable analyses, reinfection was not associated with any demographic, HIV, or HCV characteristic; mode of HCV clearance or IFN-λ3 polymorphism; or calendar year of HCV clearance, either as a continuous variable or

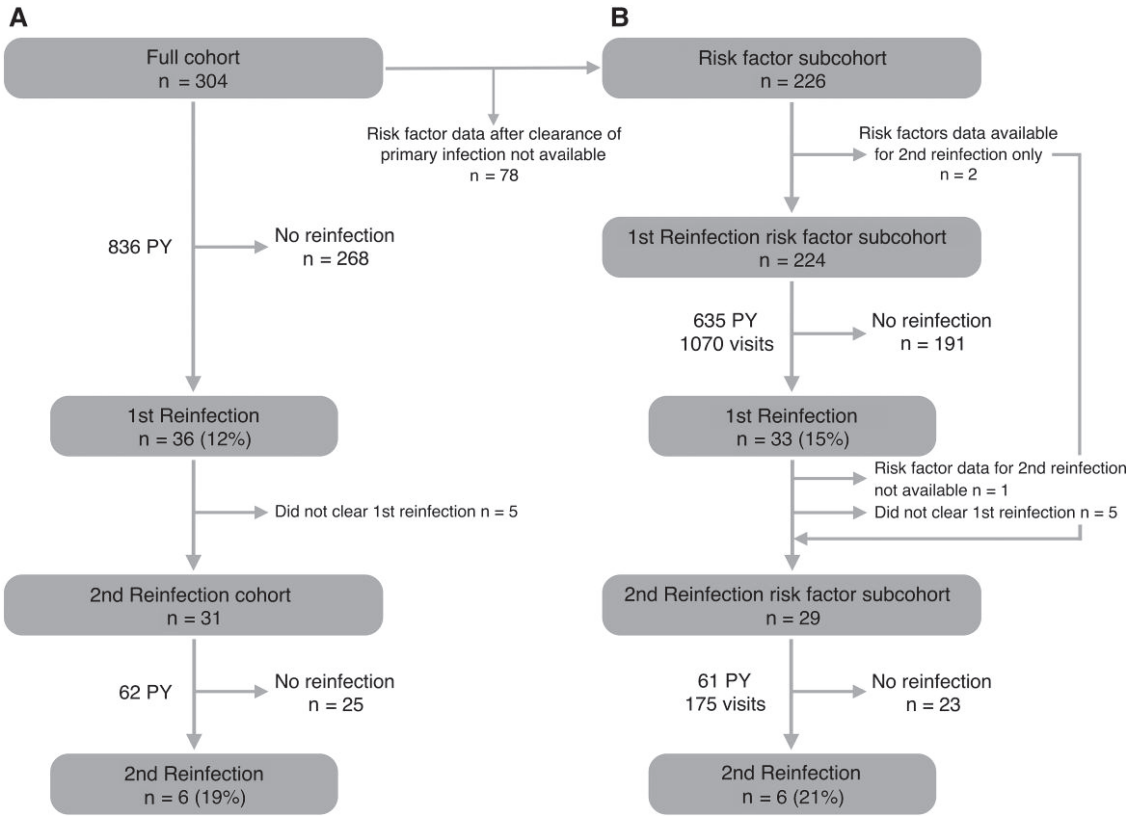

Figure 1. Study flow diagram. *A*, Full cohort. *B*, Behavioral risk factor subcohort. Abbreviation: PY, person-years.

Table 1. Demographic, Primary Hepatitis C Virus (HCV), and Human Immunodeficiency Virus (HIV) Characteristics of Men Who Have Sex With Men (MSM) With HIV Who Had Clearance of Primary HCV Infection

Characteristic	MSM, No. (%)[a]			*P* value[b]
	Total Cohort (n = 304)	HCV Reinfection (n = 36)	No HCV Reinfection (n = 268)	
Demographics				
Age, median (IQR), y	45 (36–51)	43 (38–50)	46 (36–51)	.41
Race				
Black	55 (18)	6 (17)	49 (18)	.85
Asian	2 (1)	0	2 (1)	
White	247 (81)	30 (83)	217 (81)	
Ethnicity				
Hispanic	65 (21)	11 (31)	54 (20)	.15
Non-Hispanic	239 (79)	25 (69)	213 (79)	
Health insurance (n = 300)				
Public	160 (53)	19 (56)	141 (53)	.47
Private	140 (47)	13 (44)	127 (47)	
Primary HCV characteristics				
Genotype (n = 296)				
1a	237 (80)	27 (84)	210 (80)	.14
1b	28 (9)	4 (13)	24 (9)	
2[c]	1 (0.3)	1 (3)	0	
2b	17 (6)	0	17 (6)	
2d	1 (0.3)	0	1 (0.4)	
2f	1 (0.4)	0	1 (0.4)	
3a	4 (1.4)	0	4 (2)	
4[c]	3 (1)	0	3 (1)	
4d	4 (1)	0	4 (2)	
Year of clearance, median (IQR)	2014 (2012–2015)	2012 (2010–2014)	2015 (2012–2015)	<.001[d]
Era of clearance				
2000–2014 (IFN)	156 (51)	30 (83)	126 (47)	<.001
2015–2018 (DAA)	148 (49)	6 (17)	142 (53)	
Mode of clearance				
IFN-based regimen	107 (35)	19 (53)	88 (33)	.002
DAA	166 (55)	10 (28)	156 (58)	
Spontaneous	31 (10)	7 (19)	24 (9)	
Timing of clearance (n = 303)				
Early[e]	180 (59)	28 (78)	152 (57)	.02
Late[f]	123 (41)	8 (22)	115 (43)	
IFN-λ3 (n = 264)[g]				
CC	116 (44)	15(44)	101 (44)	>.99
CT + TT	148 (57)	20 (56)	128 (56)	
HIV characteristics				
Duration of HIV infection				
0–9 y	127 (42)	18 (50)	109 (41)	.56
10–19 y	107 (35)	13 (36)	94 (35)	
20–29 y	56 (18)	4 (11)	52 (19)	
30–39 y	13 (4)	1 (3)	12 (4)	
CD4 cell count, median (IQR), cells/μL (n = 252)	586 (445–756)	598 (505–758)	584 (438–753)	.43[d]
HIV VL suppressed (n = 255)[h]				
Yes	197 (77)	24 (80)	173 (77)	.70
No	58 (23)	6 (20)	52 (23)	

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; IQR, interquartile range; MSM, men who have sex with men; VL, viral load.

[a]Data represent no. (%) of MSM unless otherwise specified.

[b]*P* values based on χ^2 test unless otherwise noted.

[c]Subtype not determined.

[d]*P* value based on Wilcoxon rank sum analysis.

[e]Treatment initiated <1 year after clinical onset of HCV infection and spontaneous clearance.

[f]Treatment initiated >1 year after clinical onset of HCV infection.

[g]Single-nucleotide polymorphism rs12979860 (CC, CT, and TT haplotypes).

[h]Suppression defined as VL <50 copies/mL.

as a dichotomous variable by IFN or DAA treatment era (Supplementary Table 2). Early clearance of HCV was associated with reinfection (hazard ratio [HR], 2.4 [95% CI: 1.0–5.5]; $P = .04$) when assessed in the full cohort, that is, without considering behavioral risk factors, but it was not significantly associated with reinfection when behaviors were accounted for in the risk factor subcohort (Table 2).

The variables that were further evaluated in the multivariable analysis were race, ethnicity, HCV genotype, receiving semen in the rectum, sexualized methamphetamine use overall, and sexualized methamphetamine use by the injection route (Table 2). In the final proportional hazards model for recurrent events, with reinfection as the outcome, only receiving semen in the rectum was associated with HCV reinfection (HR, 9.7 [95% CI: 3.3–28.3]; $P < .001$); no other variable met the level for entry into the model (Table 2).

DISCUSSION

In this prospective cohort study of HCV reinfection among MSM with HIV in NYC, the incidence rate of reinfection was high, 4.7 per 100 PY. In addition, receiving semen in the rectum during CRAI was strongly associated (HR, 9.7) with this high reinfection rate, not only demonstrating that transmission of HCV was sexual but also suggesting that this sexual transmission was neither inefficient nor unusual among these MSM with HIV.

In addition, these findings provide new insights into the epidemiology of HCV transmission among MSM with HIV. In our group's previous study of risk factors for primary infection among MSM with HIV in NYC, the only significant associations were receiving semen in the rectum with CRAI and sexualized noninjection methamphetamine use [24]. In contrast, in the current study, we found that while receiving semen in the rectum was strongly associated with reinfection, sexualized methamphetamine use was not. Strikingly, these apparently discordant findings in NYC mirrored those of the only other group to perform paired studies of risk factors for primary infection and reinfection, the MOSAIC investigators in the Netherlands [21, 22]. They found that primary infection was associated with both sexual and drug-use behaviors, but while reinfection was associated with sexual behaviors, including CRAI, it was not associated with drug use behaviors.

We propose that the best explanation for this strong correlation in findings between our groups is that there is significant heterogeneity in the prevalence of HCV among sexual networks of MSM and that sexualized methamphetamine use is a surrogate for this heterogeneity, specifically of the high-prevalence networks (summarized in [30]). That is, MSM who participate in sexualized methamphetamine use are part of sexual networks in which the HCV prevalence is high enough to result in significant onward HCV transmission, and, conversely, that those who do not participate in sexualized methamphetamine use are part of sexual networks in which the HCV prevalence is low enough to result in few, if any, onward transmissions, independent of the drug use itself. In simplest terms, it is semen that transmits most HCV infection among MSM with HIV, and those who participate in sexualized methamphetamine use are just more likely to receive HCV-containing semen in their rectums.

A number of other important issues are highlighted by our results. We found no decline in the reinfection rate in NYC over the first 4 years after Food and Drug Administration approval of truly effective DAA regimens. Some locales outside the United States, in contrast, have shown at least early declines in HCV incidence and prevalence among MSM with HIV after removal of restrictions to access to DAA (summarized in [31, 32]). We do not have unrestricted access to DAAs in the United States, however. Instead, prescribing of DAA treatments continues to face multiple non–evidence-based restrictions by insurance companies, both public and private [33–35]. These restrictions resulted in significant delays in treatment initiation that likely resulted in preventable onward transmissions [6, 36, 37]. However, treatment as the sole mode of elimination of an infectious disease, particularly one that is sexually transmitted, would be unprecedented, and one that multiple modeling studies predicted to be insufficient [38–40]. Our data suggest that preventing semen ejaculation into the rectum would prevent most HCV infections, but MSM with HIV have not accepted condom use as a means to prevent HCV infection [41]. Finally, even with unrestricted access, DAA treatment cannot reach those who do not attend care. MSM with HIV in the United States whose HCV remained untreated have been less engaged in HIV care and more likely to engage in sexualized drug use and CRAI [42], perpetuating high-prevalence sexual networks.

Our study has a number of limitations. We performed it at a single institution in a single city in a very large country. However, the cohort represented the practices of >50 physicians and other providers of care to people with HIV who live in all 5 boroughs of NYC, in which fully 7% of MSM with HIV in the United States reside [43]. Our cohort had a somewhat lower proportion identifying as Black and Hispanic than the total population of MSM with HIV who had primary HCV, as documented by the NYC Department of Health [44], but our cohort was still more broadly diverse than other reinfection cohorts, and we had sufficient representation to include race and ethnicity in all relevant analyses. An international study published in 2023 reported that sexualized drug use by the injection route was associated with reinfection [45], but it was a univariable analysis only; our univariable analysis also suggested this association with methamphetamine use, but our multivariable model showed this was not the case.

We did not reassess all the possible behavioral risk factors that we assessed in our group's previous study of primary

Table 2. Univariable and Multivariable Recurrent Events Models of All Hepatitis C Virus Reinfections in Men Who Have Sex With Men with HIV: Risk Factor Subcohort (n = 226)

Characteristic	Univariable Analysis[a] HR (95% CI)	*P* Value	Multivariable Analysis[b] HR (95% CI)	*P* Value
Demographics				
Age	1.0 (1.0–1.0)	.43	…	…
Race				
Black	0.8 (.3–1.8)	.56	…	…
Asian	0 (0–0)	<.001	…	…
White	1.0	…	…	…
Ethnicity				
Hispanic	1.6 (.8–3.4)	.19	…	…
Non-Hispanic	1.0		…	
Health insurance				
Public	1.2 (.6–2.5)	.59	…	…
Private	1.0		…	
HCV characteristics				
HCV genotype				
1a	1.0	…	…	…
1b	1.8 (.6–5.4)	.30	…	…
2[c]	0.4 (.1–2.5)	.32	…	…
3a	0 (0–0)	<.001	…	…
4[c]	0 (0–0)	<.001	…	…
Year of clearance, median (IQR)	1.0 (.9–1.1)	.82	…	…
Era of clearance				
2000–2014 (IFN)	1.7 (.7–4.3)	.28	…	…
2015–2018 (DAA)	1.0		…	
Mode of clearance				
IFN-based regimen	1.0	…	…	…
DAA	0.9 (.4–2.0)	.72	…	…
Spontaneous	0.9 (.4–2.4)	.85	…	…
Timing of clearance (primary or first reinfection)				
Early[d]	1.7 (.7–3.8)	.23	…	…
Late[e]	1.0		…	
IFN-λ3[f]				
CC	1.1 (.6–2.2)	.72	…	…
CT + TT	1.0		…	
HIV characteristics				
Duration of HIV infection				
0–9 y	1.0	…	…	…
10–19 y	0.9 (.4–1.8)	.68	…	…
20–29 y	0.9 (.3–2.4)	.79	…	…
30–39 y	1.3 (.2–6.7)	.77	…	…
CD4 cell count (cells/μL)	1.0 (1.0–1.0)	.27	…	…
HIV VL suppressed[g]				
Yes	1.6 (.6–4.1)	.33	…	…
No	1.0		…	
Behavioral risk factors				
Receiving semen into the rectum				
Yes	9.7 (3.3–28.3)	<.001	9.7 (3.3–28.3)	<.001
No	1.0		1.0	
Sexualized methamphetamine use				
Overall				
Yes	4.2 (2.0–8.9)	<.001	…	…
No	1.0		…	
By injection				
Yes	6.4 (3.0–12.8)	<.001	…	…
No	1.0		…	

Abbreviations: CI, confidence interval; DAA, direct-acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IFN, interferon; IQR, interquartile range; MSM, men who have sex with men.

[a]Analyzed using the Andersen-Gill time-to-recurrent-events method, with time to HCV reinfection as the outcome and each characteristic as the only covariate.

[b]Analyzed using the Andersen-Gill time-to-recurrent-events method, with time to HCV reinfection as the outcome.

[c]Subtypes of genotype merged.

[d]Treatment initiated <1 year after clinical onset of HCV infection and spontaneous clearance.

[e]Treatment initiated >1 year after clinical onset of HCV infection.

[f]Single-nucleotide polymorphism rs12979860 (CC, CT, and TT haplotypes).

[g]Suppression defined as VL <50 copies/mL.

HCV [24], including not reassessing for drug use that was not associated with sex, such as heroin use, instead reasoning against repeating questions about risk factors that were not associated with primary HCV in NYC. While it is possible that we missed an association with a behavior that was not significantly associated with primary HCV in our previous study, we note that the MOSAIC study, which did use their full questionnaire for both studies, also found that fewer behaviors, rather than more, were associated with HCV reinfection compared with primary HCV, including no association between HCV reinfection and drug use [22].

In summary, we prospectively assessed the incidence of and risk factors for HCV reinfection in our large cohort of MSM with HIV in NYC over a period spanning almost 2 decades and both the IFN and DAA treatment eras. We found the HCV reinfection rate to be an order of magnitude higher than the primary infection rate, similar to the findings from other cohorts in other countries. Risk factor behaviors collected from >1200 visits indicated that receipt of semen into the rectum with CRAI was strongly associated with reinfection, while in contrast with our study of primary HCV, sexualized noninjection methamphetamine use was not associated with reinfection, and neither was use by the injection route.

Based on the discordance between both the infection rates and the associations with sexualized methamphetamine use comparing primary infection and reinfection in NYC, which are parallel to the results from the Netherlands, we hypothesize

that MSM who participate in sexualized methamphetamine use are part of sexual networks with high HCV prevalence, rather than that the drug use behaviors themselves cause the high reinfection rate. Although most reinfections occurred within the first 2 years after HCV clearance, reinfections continued to occur for >11 years after clearance. Therefore, long-term surveillance for reinfection is warranted for all sexually active MSM with HIV after clearance of HCV infection. The high reinfection rate did not decline in the first 4 years after the Food and Drug Administration approval of multiple DAA regimens, suggesting that, at least without unrestricted access, treatment alone will be insufficient to effect elimination of HCV among MSM. Furthermore, condom use, the most effective currently available intervention to prevent semen ejaculation into the rectum, has not been successful as an HCV prevention strategy. Our results therefore suggest the need for novel interventions to prevent sexual transmission of HCV among MSM.

Supplementary Data

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

Notes

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