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MAJOR ARTICLE

# Favorable Socioeconomic Status and Recreational Polydrug Use Are Linked With Sexual Hepatitis C Virus Transmission Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men

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***Background.*** Sexual transmission of hepatitis C virus (HCV) among human immunodeficiency virus (HIV)-infected men who have sex with men (MSM) is an emerging issue. Studies addressing the temporal trends and risk factors associated with incident HCV in HIV-infected MSM in the community-based primary care settings in the United States are scarce.

***Methods.*** Using a retrospective cohort study design, HCV incidence, defined as HCV antibody seroconversion, was determined in 1147 HIV-infected men receiving care at Chase Brexton Health Care clinics in Baltimore, Maryland between 2004 and 2014. Multivariate regression analyses were used to identify factors associated with incident HCV.

***Results.*** There were 42 incident HCV infections during 5242 person-years (PY) of follow up (incidence rate [IR], 8.01/1000 PY). Thirty-seven (88%) of the incident infections were in MSM, of whom 31 (84%) reported no injection-drug use (IDU). The annual IRs for MSM were 13.1–15.8/1000 PY between 2004 and 2007, decreased to 2.7–6.2/1000 PY between 2008 and 2011, and increased to 10.4/1000 PY and 13.3/1000 PY in 2013 and 2014, respectively. Injection-drug use was strongly associated with incident HCV among all MSM (IR ratio [IRR], 14.15; $P = .003$); however, among MSM without IDU, entering care between 2010 and 2013 (IRR, 3.32; $P = .01$), being employed (IRR, 3.14; $P = .03$), and having a history of ulcerative sexually transmitted infections (IRR, 3.70; $P = .009$) or of polydrug use (IRR, 5.54; $P = .01$) independently predicted incident HCV.

***Conclusions.*** In this cohort of HIV-infected men, a re-emerging HCV epidemic was observed from 2011 to 2014 among MSM. In addition to IDU, high-risk sexual behaviors, favorable socioeconomic status, and polydrug use fueled this increase in HCV infections.

**Keywords.** HIV; MSM; polydrug use; sexual HCV transmission; socioeconomic status.

Sexual transmission of hepatitis C virus (HCV) across mucosal surfaces occurs among men who have sex with men (MSM), particularly those who are infected with human immunodeficiency virus (HIV) [1–4]. It remains elusive as to how HIV infection increases the risk for HCV acquisition in MSM, although lower CD4 T-cell counts or inadequate HIV suppression have been implicated [5, 6]. Certain behavioral risks and clinical factors might predispose HIV-infected MSM to HCV infection. These include unprotected or traumatic sexual practices, use of recreational noninjection drugs (NIDs), which enhance risk-taking behavior, and past or concurrent anogenital sexually transmitted infections (STIs) [1–4]. The availability and effectiveness of antiretroviral therapy has been shown to increase these risk factors in HIV-infected MSM [7, 8].

Increased incident rates (IRs) of HCV infection in HIV-positive MSM over the last 2 decades have been reported in several European and Asian studies [9–13], although some of the analyses might represent the time trend of new vigilance in diagnosing HCV rather than true incident HCV infection [14]. In the United States, the results from the Multicenter AIDS Cohort Study, a closed, prospective cohort in which the subjects were recruited during designated enrollment periods, found no evidence of increased HCV IRs in HIV-infected MSM over the past 3 decades [5]. Indeed, studies of the temporal trend of HCV IRs in the context of HIV primary care settings are scarce, partly due to the low rate of HCV surveillance screening [15, 16]. Studies of primary care settings provide a

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unique view because there is a constant influx of new patients from the community.

The State of Maryland and metropolitan Baltimore are among the areas with the highest prevalence and incidence of HIV infection in the United States in recent years [17]. Thus, we conducted a retrospective cohort study to investigate HCV incidence in HIV-infected men engaged in primary care at Chase Brexton Health Care (CBHC), a Community Health Center with multiple clinics in metropolitan Baltimore and rural Eastern Shore. Chase Brexton Health Care was founded in Baltimore in the 1970s as a volunteer-run gay men's clinic, and it has become one of the first, longest-serving, and largest clinics in Baltimore and surrounding areas to provide HIV care to MSM and people of various minority and underserved groups. Thus, the HIV-positive patients receiving primary care at CBHC represent a heterogeneous population, encompassing various transmission risk groups [18]. Many of these patients were diagnosed with HIV in recent years, enabling us to analyze HCV incidence in the context of the latest HIV epidemic.

## METHODS

### Study Population

To determine incident HCV infections from January 2004 to September 2014, this study included HIV-infected men who were >17 years old, had ≥1 medical visit to CBHC between 2011 and 2013, were engaged in care for >1 year, and had an initial negative HCV antibody (Ab) test followed by at least 1 subsequent HCV Ab test. Because there were only 2 onsite infectious diseases (ID) specialists at any point during the study period, these patients might have received their HIV care from their primary care providers (PCPs) or been referred to the ID specialists within CBHC. The initial HCV Ab test had to be performed after (1) entering care at CBHC, (2) testing positive for HIV, and (3) 2003 or later. The patients who had no visits during 2011–2013 were excluded because some medical records of these inactive patients could not be accurately retrieved from the Electronic Medical Record (EMR) database (Centricity). Ten patients whose first and last negative HCV tests were <6 months apart were excluded from analyses. The Institutional Review Board of Morgan State University and the Research Committee of CBHC approved the study.

### Study Design and Definition of Incident Hepatitis C Virus

For each patient, follow-up time began on the date of the first HCV Ab negative visit. For those who were diagnosed with HIV after entering care at CBHC, follow up commenced on the day of first negative HCV Ab test after HIV diagnosis. Individual follow-up time was censored on the day of last negative HCV Ab test or the postulated date of incident HCV infection (see below).

Incident HCV was defined as HCV Ab positive at any visit after the first HCV Ab negative visit (ie, HCV seroconversion). Hepatitis C virus Ab tests were not performed at every visit, but alanine aminotransferase (ALT) values were; thus, the date of incident infection was estimated by ALT elevation during the period between the last negative and first positive HCV Ab tests (Supplementary Figure 1). The ALT elevation was defined as a >3-fold increase compared with the baseline level or a value exceeding 40 U/mL [19]. If an ALT elevation was detected and not associated with hepatitis A, hepatitis B, or substance/alcohol abuse, the postulated date of HCV infection was designated as 3 weeks before the date of first ALT elevation. This method is justified because during an acute HCV infection, ALT elevation usually occurs several weeks after the initial infection and appearance of viremia [19, 20]. In the absence of a measured ALT elevation, the midpoint between the last negative and first positive HCV Ab tests was the postulated date of HCV infection.

### Data Collection

Data from 2004 to 2014 were retrospectively collected through a comprehensive medical chart review combined with manual data abstraction from the EMR database. The demographic, clinical, laboratory, and behavioral data of each patient were reviewed and abstracted independently by 2 of the trained medical abstractors, followed by data quality assessment. Data were abstracted from multiple sources in the EMR, including case management interviews, HIV wellness nurse interviews, self-administered questionnaires, laboratory reports, and providers' notes throughout care at CBHC, and all pertinent information/documents were obtained from outside of CBHC, allowing for data validation and minimizing the chance of underreporting.

Time-updated variables, including drug use, smoking, sexual practices, hepatitis B virus (HBV) status, and anogenital STIs, were collected up to the date when the subject was censored. Patients were classified as injection drug use (IDU) and/or MSM if they ever reported those behaviors. For HCV seroconverters (ie, incident cases), all data on ALT, CD4 T-cell counts, HIV ribonucleic acid (RNA), and detailed information on sexual practices were collected up to the date of HCV diagnosis. Anogenital STIs included laboratory-confirmed syphilis, gonorrhea, and chlamydia as well as laboratory-confirmed and/or clinically diagnosed herpes simplex virus and human papillomavirus. Hepatitis B virus exposure was determined by a positive anti-HBV core Ab test. Detailed information on the history and types of anogenital STIs and noninjection drug (NID) use were collected for MSM. The calendar year of HIV diagnosis was self-reported, with or without supporting documents, because most patients were diagnosed with HIV before seeking care at CBHC. For those who were diagnosed with HIV after entry into care at CBHC, the precise date of HIV diagnosis was obtained.

### Statistical Analyses

Bivariate analyses were performed using Pearson $\chi^2$ test for categorical variables and Mann-Whitney *U* test for continuous variables. Mood's median test and Kruskal-Wallis test were used to compare the median numbers of years from HIV diagnosis to HCV acquisition between 2 or among multiple subgroups, respectively. The IR

was calculated by dividing the number of incident HCV infections by the number of person-years (PY) of follow up. For analyzing annual IRs, we excluded men whose postulated incident HCV infection date was determined by the midpoint between the last negative and first positive HCV tests that were >1 year apart (n = 6), considering the increased uncertainty about the date of infection. Due to the smaller number of patients and PY in 2004, the analyses of annual IRs for 2004 and 2005 were combined and the result was designated as the annual IR for 2005. Temporal trends of annual IRs were modeled via Poisson regression and fitted using restricted cubic splines to allow for smoothly varying trends over time [9–11]. A sensitivity analysis was conducted, in which all seroconverters were included.

Univariate Poisson regression analyses were performed to calculate the crude IR ratio (IRR) between subgroups. Survival curves for the probability of remaining HCV-uninfected over the follow up were established using the Kaplan-Meier estimates and compared using the log-rank test. Multivariate analyses were performed using the negative binomial regression model. The variables found to have a *P* value of <.2 in the univariate analysis were included for model construction/selection, adjusting for all demographic variables, sexual behavior, IDU history, smoking history, HBV exposure, and baseline HIV RNA. All statistical analyses were performed using Stata software, version 14 (StataCorp, College Station, TX).

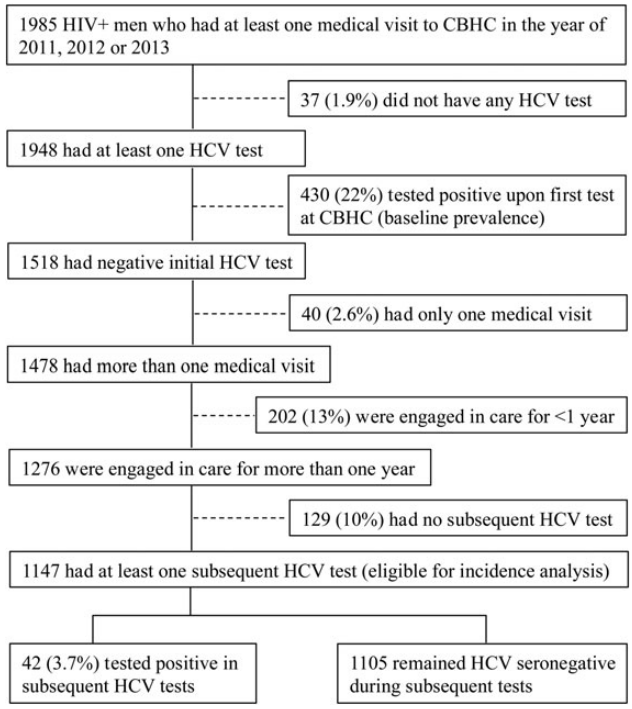


**Figure 1.** Study flowchart of inclusion of human immunodeficiency virus (HIV)-infected men engaged in primary care at Chase-Brexton Health Care (CBHC) for hepatitis C virus (HCV) incidence analyses. The HCV test indicates anti-HCV antibody test after HIV diagnosis.

## RESULTS

There were 1985 HIV-positive men who had at least 1 medical visit to CBHC between 2011 and 2013, 1948 (98%) of whom had at least 1 HCV Ab test (Figure 1). Of those 1948, 430 (22%) had an initial positive test, leaving 1518 men who were at risk for incident HCV. Of those, 242 (16%) were engaged in care for <1 year and were excluded. Of the remaining 1276 men, 1147 (90%) had at least 1 subsequent HCV Ab test, and they differed from the other 129 men who were not rescreened for HCV Ab in several characteristics (Table 1). Of the 1147 men included in incidence analysis, 67% were black, 72% sought care at the clinic in downtown Baltimore, 49% had more than high school education, and 44% were unemployed. Moreover, 81% were MSM, 4% reported IDU, 97% considered sexual transmission as the mode of their HIV acquisition, and 53% were diagnosed with HIV after 2003. At the initial CBHC visit, 22% had undetectable HIV RNA.

The mean follow-up time of the 1147 men was 4.6 years (interquartile range [IQR], 2.2–6.8 years), with 52% of the patients contributing >4 years of person-time for a total of 5242 PY of follow up. During follow up, HCV Ab was tested 2, 3, 4, 5, and ≥6 times for 363 (32%), 326 (28%), 257 (22%), 120 (11%), and 81 (7%) men, respectively. Incident HCV was identified in 42 men yielding an IR of 8.01 cases per 1000 PY (95% confidence interval [CI], 5.92–10.84). The HCV seroconverters were more likely to have reported IDU and attained a higher educational level (Table 1). Among the seroconverters, 16% (6 of 37) of MSM and 80% (4 of 5) of non-MSM reported a history of IDU (*P* = .002).

The postulated date of incident HCV infection could be determined by ALT elevation in 32 (76%) of the seroconverters (Table 2 and Supplementary Figure 1). For the other 10 seroconverters, the date of incident HCV infection was assigned as the midpoint between the last negative and first positive HCV tests (median duration, 2.6 years; IQR, 1.4–4.5). Only 8 (19%) of the seroconverters reported current IDU at the time of HCV infection, including 2 MSM who began IDU after HIV acquisition. The rest reported no parenteral risk for their HCV acquisition. At the time of incident HCV infection, 79% had a CD4 count of >350 cells/mm$^3$, and 83% had an HIV RNA level of <400 copies/mL. The seroconverters who were younger than 30 years had a median time of 2.3 years from HIV diagnosis to HCV acquisition, whereas those older than 30 years had a median time of 10.6 years (*P* = .01). Moreover, the median time to incident HCV infection from HIV diagnosis was 13.0 years in the seroconverters who were diagnosed with HIV before 2004, and it was 2.7 and 1.6 years in those who were diagnosed with HIV between 2004 and 2007 and after 2007, respectively (*P* < .0001).

Annual HCV IRs were determined in all patients, as well as in subgroups restricted to MSM and then to MSM without IDU (Figure 2). Although the IRs during each calendar year differed among these 3 groups, the temporal trends were similar. Thus,

**Table 1. Characteristics of HIV-Infected Men Who Were Engaged in Care at CBHC for >1 Year and Had an Initial Negative HCV Ab Test[a]**

| Characteristic | Receiving >1 HCV Ab Test | | | Receiving Only 1 HCV Ab Test | %HCV Ab Rescreening[b] |
|---|---|---|---|---|---|
| | Total (n = 1147) | HCV Negative (n = 1105) | Seroconverters (n = 42) | (n = 129) | |
| Age[c,*,**], years, median (range) | 38.4 (17–74) | 38.5 (17–74) | 37.0 (19–63) | 41.9 (19–70) | |
| <30 | 335 (29) | 323 (29) | 12 (29) | 24 (19) | 93% |
| 30–39 | 305 (27) | 289 (26) | 16 (38) | 30 (23) | 91% |
| 40–49 | 355 (31) | 343 (31) | 12 (29) | 47 (36) | 88% |
| ≥50 | 152 (13) | 150 (14) | 2 (5) | 28 (22) | 84% |
| Time of entering care at CBHC** | | | | | |
| ≤2005 | 328 (29) | 312 (28) | 16 (38) | 16 (12) | 95% |
| 2006–2009 | 417 (36) | 404 (37) | 13 (31) | 21 (16) | 95% |
| 2010–2013 | 402 (35) | 389 (35) | 13 (31) | 92 (71) | 81% |
| Race/ethnicity | | | | | |
| Black | 765 (67) | 738 (67) | 27 (64) | 93 (72) | 89% |
| White | 324 (28) | 312 (28) | 12 (29) | 29 (23) | 92% |
| Hispanic or other | 58 (5) | 55 (5) | 3 (7) | 7 (5) | 89% |
| Clinic sites** | | | | | |
| Urban Baltimore | 829 (72) | 793 (72) | 36 (86) | 73 (57) | 92% |
| Suburban Baltimore | 182 (16) | 178 (16) | 4 (9) | 22 (17) | 89% |
| Eastern Shore | 136 (12) | 134 (12) | 2 (5) | 34 (26) | 80% |
| Education[c,*] | (31 missing) | | | (10 missing) | |
| High school or less | 568 (51) | 553 (51) | 15 (36) | 67 (56) | 89% |
| More than high school | 548 (49) | 521 (49) | 27 (64) | 52 (44) | 91% |
| Employment[c] | | | | | |
| Employed | 618 (54) | 591 (53) | 27 (64) | 61 (47) | 91% |
| Unemployed | 510 (44) | 496 (45) | 14 (33) | 65 (50) | 89% |
| Retired | 19 (2) | 18 (2) | 1 (2) | 3 (2) | 86% |
| Sexual behavior[d,**] | | | | | |
| HET | 219 (19) | 214 (19) | 5 (12) | 65 (50) | 77% |
| MSM | 928 (81) | 891 (81) | 37 (88) | 64 (50) | 94% |
| IDU history[d,*] | (3 missing) | | | | |
| Ever | 46 (4) | 36 (3) | 10 (24) | 10 (8) | 82% |
| No | 1098 (96) | 1066 (97) | 32 (76) | 119 (92) | 90% |
| Self-reported mode of HIV transmission[c,*,**] | | | | | |
| IDU | 8 (<1) | 7 (<1) | 1 (2) | 0 (0) | 100% |
| IDU + HET | 6 (<1) | 4 (<1) | 2 (5) | 1 (<1) | 86% |
| IDU + MSM | 13 (1) | 9 (1) | 4 (10) | 1 (<1) | 93% |
| HET only | 190 (17) | 188 (17) | 2 (5) | 58 (45) | 77% |
| MSM only | 913 (80) | 880 (80) | 33 (79) | 63 (50) | 94% |
| Other/unknown | 17 (1) | 17 (2) | 0 (0) | 6 (5) | 74% |
| HBV exposure[d] | (7 missing) | | | (3 missing) | |
| Yes | 466 (41) | 444 (40) | 22 (52) | 52 (41) | 90% |
| No | 674 (59) | 654 (60) | 20 (48) | 74 (59) | 90% |
| HBsAg[d] | (2 missing) | | | (2 missing) | |
| Positive | 58 (5) | 55 (5) | 3 (7) | 7 (6) | 89% |
| Negative | 1087 (95) | 1048 (95) | 39 (93) | 120 (94) | 90% |
| HIV diagnosis** | | | | | |
| Before 2004 | 534 (47) | 512 (46) | 22 (52) | 53 (41) | 91% |
| 2004–2006 | 186 (16) | 179 (16) | 7 (17) | 12 (9) | 94% |
| 2007–2009 | 219 (19) | 212 (19) | 7 (17) | 20 (16) | 92% |
| 2010–2013 | 208 (18) | 202 (18) | 6 (14) | 44 (34) | 83% |
| $CD4^+$ cell counts at initial visit[c] | | | | (1 missing) | |
| 0–200 cell/$mm^3$ | 262 (23) | 250 (23) | 12 (29) | 31 (24) | 89% |
| 201–500 cell/$mm^3$ | 505 (44) | 488 (44) | 17 (40) | 53 (41) | 91% |
| >500 cell/$mm^3$ | 380 (33) | 367 (33) | 13 (31) | 44 (34) | 90% |

*Table 1 continued.*

| Characteristic | Receiving >1 HCV Ab Test | | | Receiving Only 1 HCV Ab Test | %HCV Ab Rescreening[b] |
|---|---|---|---|---|---|
| | Total (n = 1147) | HCV Negative (n = 1105) | Seroconverters (n = 42) | (n = 129) | |
| HIV RNA at initial visit[c,**] | | | | (1 missing) | |
| Undetectable[e] | 251 (22) | 246 (22) | 5 (12) | 41 (32) | 86% |
| Detectable | 896 (78) | 859 (78) | 37 (88) | 87 (68) | 91% |

Abbreviations: Ab, antibody; CBHC, Chase Brexton Health Care; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HET, heterosexual; HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men; RNA, ribonucleic acid.

[a] Data are presented as no. (%), except where noted.

[b] %HCV Ab rescreening indicates the proportion of patients receiving at least 1 subsequent HCV Ab test after the initial negative HCV Ab test among all patients engaged in care for >1 year in defined subgroups. It is calculated as follows: (the number of patients receiving >1 test)/[(the number of patients receiving >1 test) + (the number of patients receiving only 1 test)] × 100%.

[c] Baseline status.

[d] Time-updated status or behavioral risks.

[e] The level of HIV RNA was below the limit of detection of the test used at the point.

* Statistically significant differences ($P < .05$) between the groups of HCV seroconverters and HCV-seronegative patients in those who received >1 HCV Ab test.

** Statistically significant differences ($P < .05$) between the groups of patients who received >1 HCV Ab test and those who received only 1 HCV Ab test.

higher HCV IRs were observed between 2004 and 2007, followed by a remarkable reduction from 2008 through 2011, and then an increase from 2012 to 2014. Similar temporal trends were observed among individuals with an IDU history, as well as in the sensitivity analyses that included all seroconverters (Supplementary Figure 2).

In the full cohort, IDU was the strongest risk factor for incident HCV and, among those without IDU, being MSM, having a higher educational attainment, or being employed at entry into the clinic were associated with increased incident HCV (Figure 3 and Supplementary Table 1).

Given that the majority of the HCV seroconverters were MSM, further analyses focused on this group (Table 3 and Figure 3). The univariate analyses and Kaplan-Meier estimates revealed that IDU, noninjection methamphetamine or poppers use, poly-NID use (ie, using multiple types of NIDs), or ulcerative STIs had increased risk for incident HCV. It is noteworthy to mention that there was a significant trend for the association between the number of NID types and HCV incidence. Similar trends were observed for the association of HCV incidence with the number of anogenital STI types or the calendar year of HIV diagnosis, although these were not statistically significant.

In the multivariate analysis adjusting for age, race, clinic sites, and baseline HIV RNA, self-reported IDU (IRR, 14.2), entering care in later years (ie, 2010–2013; IRR, 2.8), history of ulcerative STIs (IRR, 3.0), and history of poly-NID use (IRR, 4.3) increased the risk for incident HCV, whereas former smoking (IRR, 0.25) independently predicted lower risk (Table 3).

Because the majority of the MSM never reported IDU, we determined which factors were independently associated with HCV incidence in the 899 men whose only risk factor for HCV was sex with men (Table 4). In this subanalysis, the results were similar to the full MSM cohort, with entry in later years (IRR, 3.3), history of ulcerative STIs (IRR, 3.7), and history of poly-NID use (IRR, 5.5) as independent risk factors. However, being employed at entry into the clinic (IRR, 3.1) became independently associated with higher HCV incidence and both former smoking (IRR, 0.23) and current smoking (IRR, 0.29) were independently associated with reduced HCV incidence.

## DISCUSSION

To our knowledge, this is the first study to demonstrate that sexual HCV transmission among HIV-infected MSM was associated with polydrug use and favorable socioeconomic status (ie, having employment) in a retrospective community-based cohort. We also demonstrate for the first time the temporal trend of incident HCV among HIV-infected men in a primary care setting in the United States.

Several studies have determined the HCV incidence among HIV-infected men or HIV-infected MSM up to 2011 in the United States, including the Multicenter AIDS Cohort [5], the AIDS Clinical Trial Group Longitudinal Linked Randomized Trials cohort [6], and the Fenway clinic in Boston [21]. The HCV IRs were different among these studies, ranging from 1.9 to 16.3 cases/1000 PY. In the CBHC cohort, the HCV IRs were 8.01 and 8.75 cases/1000 PY in all HIV-infected men and in HIV-infected MSM, respectively, during 2004–2014. Different demographics, study periods, HCV rescreening rates, and proportions of seroconverters using injection-drug might account for the differences. Because the relative risks were not analyzed in the Fenway study, it is unclear whether the HIV-infected patients engaged in care at Fenway clinic and CBHC shared certain risk factors for incident HCV.

Although many case-control studies have linked NID use to high-risk sexual behaviors and HCV acquisition in HIV-positive MSM [22–26], the association between NID use and incident HCV remains inconclusive. A retrospective cohort study showed an association of NID use with incident HCV in HIV-positive MSM [13], whereas 2 large prospective cohort studies failed to

**Table 2. Characteristics of HCV Acquisition in the Seroconverters (N = 42)[a]**

| Characteristics | Incident HCV |
|---|---|
| Age at incident HCV infection, years, mean (SD) | 39.6 (9.7) |
| Number of negative HCV Ab test before seroconversion | |
| 1 | 26/42 (62%) |
| 2 | 3/42 (7%) |
| 3 | 10/42 (24%) |
| ≥4 | 3/42 (7%) |
| Duration between the dates of the last (–) HCV test and the first (+) HCV test, years, median (IQR) | 1.7 (1.0–3.9) |
| <1.5 | 20/42 (48%) |
| 1.5–2.9 | 8/42 (19%) |
| 3–4.9 | 10/42 (24%) |
| >5 | 4/42 (9%) |
| Time of incident HCV infection determined by[b] | |
| Elevated ALT | 32/42 (76%) |
| Midpoint | 10/42 (24%) |
| HCV diagnosis during the acute phase of infection[c,d] | |
| Confirmed | 6/42 (14%) |
| Probable | 7/42 (17%) |
| ALT level (U/L) before seroconversion (n = 38), median (IQR)[b,e] | |
| Baseline | 20 (14–27) |
| Peak | 136 (50–262) |
| Duration between the dates of first ALT elevation and HCV diagnosis (n = 32), months, median (IQR)[b] | 4.9 (0.8–15.7) |
| Initial HCV RNA (n = 26) | |
| ≤400 000 IU/mL | 5/26 (19%) |
| >400 000 IU/mL | 21/26 (81%) |
| Concurrent CD4$^+$ cell counts (cell/mm$^3$)[f] | |
| 0–200 | 3/42 (7%) |
| 201–350 | 6/42 (14%) |
| 351–500 | 12/42 (29%) |
| >500 | 21/42 (50%) |
| Concurrent HIV RNA (copies/mL)[f] | |
| Undetectable | 30/42 (71%) |
| 0–399 | 5/42 (12%) |
| 400–10 000 | 3/42 (7%) |
| >10 000 | 4/42 (10%) |
| Ever receiving HAART[g] | 39/42 (93%) |
| IDU (n = 10) | |
| Current/New | 8/10 (80%) |
| Former | 2/10 (20%) |
| Ever use NID[g] | 33/42 (79%) |
| Concurrent anogenital STIs[h] | 17/42 (40%) |
| Concurrent syphilis[h] | 4/42 (10%) |
| Condom use after HIV[g] (n = 39) | |
| Consistent | 12/39 (31%) |
| Inconsistent/never | 27/39 (69%) |
| Receptive rectal intercourse?[g] (n = 21) | |
| Yes | 17/21 (81%) |
| Unprotected receptive rectal intercourse?[g] (n = 17) | |
| Yes | 12/17 (71%) |
| Number of lifetime sexual intercourse partners[g] (n = 22) | |
| 4–9 | 6/22 (27%) |
| 10–49 | 5/22 (23%) |
| 50–499 | 8/22 (36%) |
| >500 | 3/22 (14%) |
| Self-reported HCV risk behavior | |
| IDU | 2/42 (5%) |
| Sexual/IDU | 6/42 (14%) |
| Sexual | 34/42 (81%) |
| Duration between the dates of HIV diagnosis and incident HCV infection, years, median (IQR) | |
| All patients (n = 42) | 6.1 (2.5–13.0) |
| ≥30 y old (n = 30) | 10.6 (4.7–14.7) |
| <30 y old (n = 12) | 2.3 (1.3–3.5) |
| HIV diagnosis <2004 (n = 22) | 13.0 (10.2–16.8) |
| HIV diagnosis between 2004–2007 (n = 10) | 2.7 (2.1–4.5) |
| HIV diagnosis ≥2008 (n = 10) | 1.6 (1.2–2.7) |

Abbreviations: Ab, antibody; ALT, alanine aminotransferase; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; IQR, interquartile range; NID, noninjection drug; RNA, ribonucleic acid; SD, standard deviation; STIs, sexually transmitted infections.

[a] Data are presented as no. (%) unless otherwise specified. The number of individuals (n) whose data is available for analysis is depicted for each variable, if it is not the total number of 42.

[b] Three patients with chronic hepatitis B virus infection and 1 patient with binge alcoholic consumption were excluded from analyses involving ALT.

[c] An acute HCV infection was confirmed if the seroconverter had 1 of the followings: (1) a positive HCV RNA test before seroconversion; (2) first positive HCV RNA test followed by a negative HCV RNA test within 3 months; or (3) the duration between the last negative and first positive HCV Ab tests was shorter than 4 months.

[d] A seroconverter was considered to have a probable acute HCV infection if the duration between the last negative and first positive HCV Ab tests was shorter than 1 year and an ALT elevation occurred shortly before the day of diagnosis.

[e] The baseline and peak ALT levels were determined for the period between the dates of last negative and first positive HCV Ab tests, and the baseline level was the one closest to the date of last negative test.

[f] Status at or right before the postulated time of incident HCV infection.

[g] Status up to the date of HCV diagnosis.

[h] Status in the previous 6 months before the postulated date of HCV acquisition.

detect such an association [5, 10]. In this study, our results showed that using multiple types of NID, but not "history of NID use" alone or single type of NID use, significantly increased the risk for incident HCV. Thus, "polydrug use" appeared to be a stronger risk factor than history of NID use for predicting incident HCV among HIV-infected MSM. It is possible that the lack of association between NID use and incident HCV found in previous studies was due to the use of history of NID use, but not polydrug use, for analysis [5, 10]. A recent cross-sectional study has shown that polydrug use was strongly associated with high-risk condomless sex and acquisition of STIs in HIV-diagnosed MSM in the United Kingdom [27]. It is interesting to note that polydrug use was more prevalent in those with employment and/or higher educational attainment in this large cohort [27].

In addition to polydrug use, we found that being employed was associated with nonparenteral incident HCV transmission among MSM. It is likely that the patients who were employed had more resources and "means" to attain, afford, and engage in polydrug use, leading to more high-risk sexual activities.

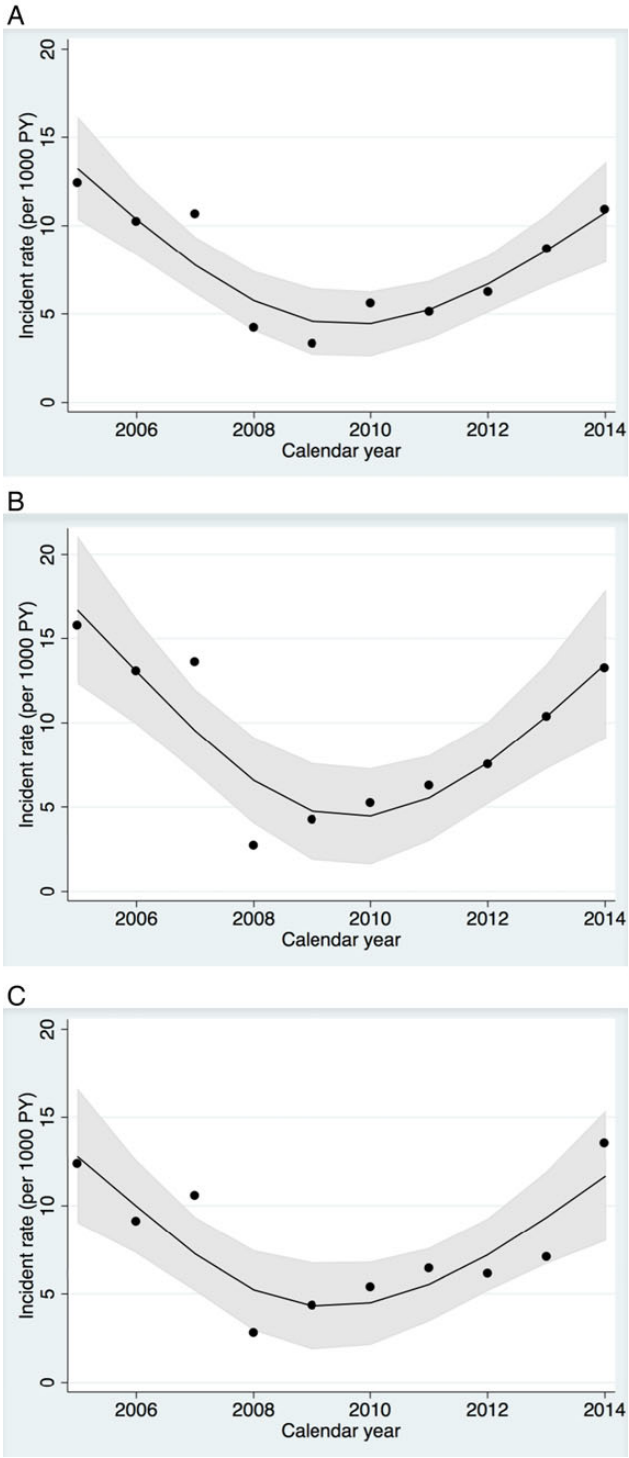


**Figure 2.** Temporal trends for annual incident rates (IRs) of hepatitis C virus (HCV) infection from 2005 through 2014. The seroconverters whose postulated dates of incident HCV infection were determined by serum alanine aminotransferase elevation or whose first positive anti-HCV antibody test date was within 1 year of the last negative test date were included in the analysis (n = 36). The IRs were determined in groups of (A) all patients, (B) all men who have sex with men (MSM), and (C) MSM without a history of injection drug use. Each dot depicts the annual IR, and the solid lines were obtained by using the restricted cubic splines method for fitting and smoothing the modeled incidence trend. The shaded areas represent 95% credible intervals. The 2005 data were derived from combined analyses of 2004 and 2005 because of the smaller number of patients and person-years (PY) in 2004.

Thus, certain negative social or (macro)economic determinant (s) that could restrict access to expensive (poly)drugs (eg, less income or job security) or frequency of sexual activities (eg, lack of opportunity or barriers to it) might influence the chance of sexual HCV transmission [28–31].

The temporal trends revealed a remarkable decline in the annual HCV IRs between the years 2007 and 2008 (>5-fold reduction among MSM), and the annual IRs remained at a lower level through 2011. Thereafter, the IRs increased and, during 2013–2014, recovered to the level seen during 2004–2007. The decline and resurgence of incident HCV was especially remarkable among MSM. It is interesting to note that the temporal trends appeared to coincide with that of the "Great Recession", which began in December 2007 and had negative economic impact in following years. It is remarkable that parallel changes in time trends were seen in the yearly quantity of illegal methamphetamine seizures and the yearly number of methamphetamine clandestine laboratory incidents in the United States during 2004–2014, according to data from the Drug Enforcement Administration (Supplementary Figure 3). Likewise, increasing rates of syphilis and chlamydia were observed among men and MSM since 2010 in Maryland and Metropolitan Baltimore [32]. Taken together, the parallel time trends of (inter)national economic downturn/recovery, national methamphetamine consumption, local incidence of STIs among MSM, and HCV incidence in the CBHC cohort suggest that the factors of high-risk sexual activities, (poly)drug uses, economic circumstances, and transmission of STIs might be linked with one another, at least among HIV-infected MSM. Finally, that the lower HCV IRs were observed among MSM who smoked might reflect the fact that smoking is associated with lower income or educational attainment in US men [33].

Some limitations are noted. First, because the time-updated data on CD4 T-cell counts and HIV RNA levels were not abstracted for HCV-seronegative patients, we were unable to assess the relative risk for these variables. However, the majority of the seroconverters had undetectable HIV and favorable CD4 counts at the time of incident HCV infection, indicating that these patients might have engaged in risk behaviors when HIV did not pose an immediate threat to their health. Indeed, many of them were diagnosed with HIV in recent years and acquired HCV shortly afterwards, suggesting that HIV optimism might have promoted the risk-taking behaviors in these individuals [34–36]. Second, certain behavioral risks such as acupuncture, tattooing, alcohol consumption, intranasal drug use, erectile enhancer use, sexual techniques, HIV "serosorting", and use of online hookup services were not assessed. Third, because only patients with at least 1 visit to CBHC between 2011 and 2013 were included, incident HCV infections in men who did not visit during this period could not be detected. This would have biased our data towards missing infections in the earliest period (2004–2007); thus, this would not change our

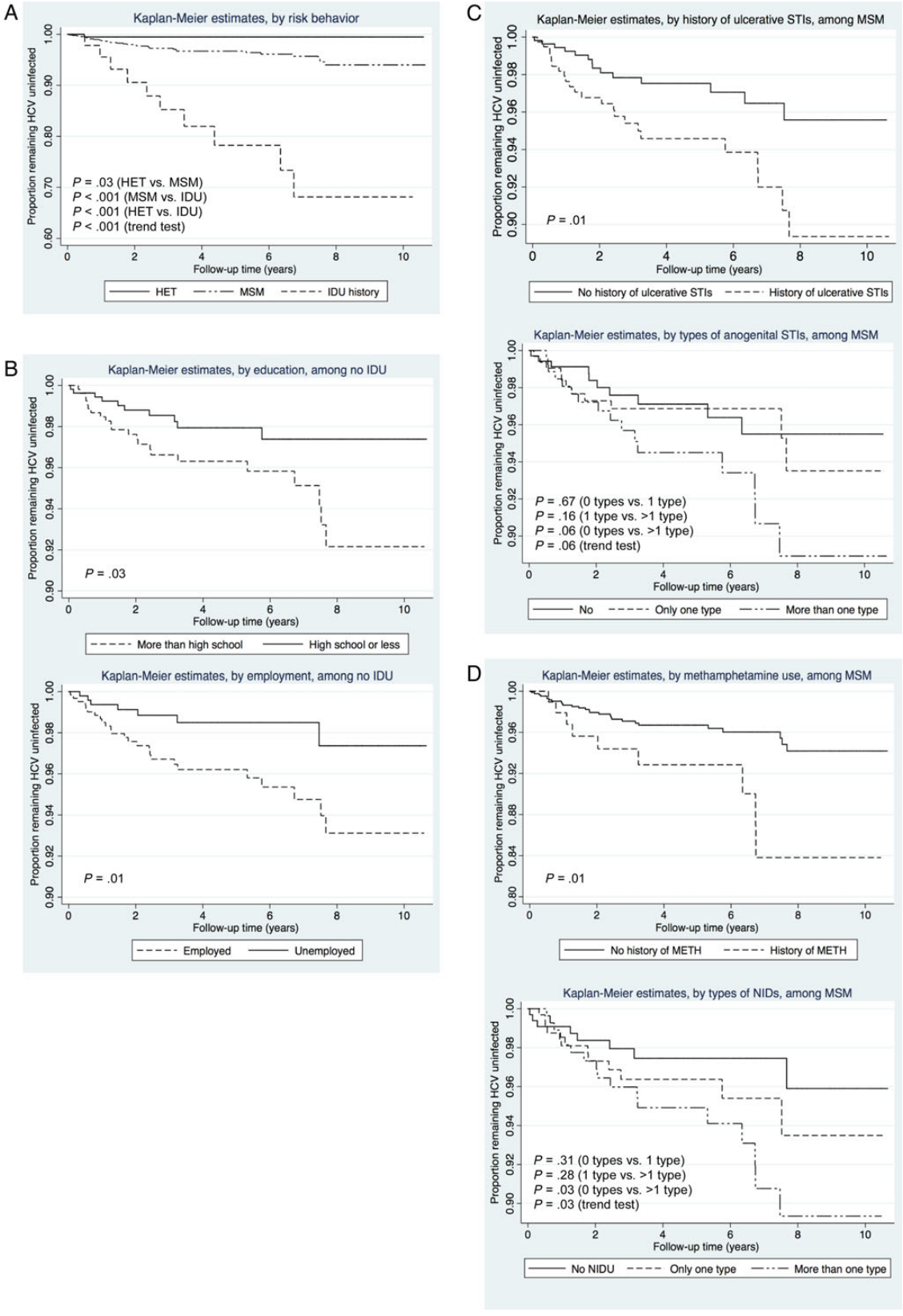


**Figure 3.** Kaplan-Meier estimates of the probability of remaining hepatitis C virus-uninfected over the period of follow-up. The analyses were performed according to (A) risk behaviors among all men, (B) educational attainment or employment status among men with no history of injection drug use (IDU), (C) history of ulcerative anogenital sexually transmitted infections (STIs) or the number of types of anogenital STIs ever acquired among men who have sex with men (MSM), and (D) history of methamphetamine use or the number of types of noninjection drugs (NIDs) ever used among MSM. In A, men with an IDU history were assigned to the IDU group, regardless of their sexual behaviors, whereas those in the MSM or heterosexual (HET) groups did not report an IDU history. Comparisons between 2 groups and trend analyses among multiple groups were performed using the log-rank test.

**Table 3. Univariate and Multivariate Analyses for Risk Factors Associated With Incident Hepatitis C Virus Infection Among All HIV-Infected Men Who Have Sex With Men (N = 928)[a]**

| | | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|---|
| Characteristics | IR/1000 PYs | IRR (95% CI) | *P* Value | Adjusted IRR[b] (95% CI) | *P* Value |
| General characteristics | | | | | |
| Time of entering care at CBHC | | | | | |
| <2010 | 7.29 | Ref | | Ref | |
| 2010–2013 | **16.56** | **2.27 (1.14–4.51)** | **.032** | **2.80 (1.14–6.89)** | **.025** |
| Education (more than high school) | | | | | |
| No | 6.37 | Ref | | Ref | |
| Yes | 11.21 | 1.76 (.89–3.47) | .10 | 1.53 (.65–3.64) | .33 |
| Employment | | | | | |
| No | 6.60 | Ref | | Ref | |
| Yes | 10.15 | 1.54 (.76–3.10) | .23 | 2.32 (.87–6.15) | .09 |
| IDU history | | | | | |
| No | 7.58 | Ref | | Ref | |
| Ever | **48.43** | **6.39 (2.99–13.66)** | **<.001** | **14.15 (2.39–83.65)** | **.003** |
| Smoking | | | | | |
| Never | 11.24 | Ref | | Ref | |
| Former | 4.66 | 0.41 (.16–1.08) | .07 | **0.25 (.07–.92)** | **.037** |
| Current | 9.01 | 0.80 (.40–1.61) | .54 | 0.40 (.14–1.18) | .10 |
| HIV RNA at initial visit | | | | | |
| Undetectable | 3.42 | Ref | | Ref | |
| Detectable | **10.14** | **2.97 (1.02–12.18)** | **.046** | 3.92 (.91–16.87) | .07 |
| HIV diagnosis | | | | | |
| <2004 | 6.91 | Ref | | — | — |
| 2004–2006 | 9.57 | 1.38 (.58–3.33) | .47 | — | — |
| 2007–2009 | 10.26 | 1.49 (.62–3.56) | .38 | — | — |
| 2010–2013 | 16.89 | 2.44 (.99–6.02) | .08 | — | — |
| Anogenital STIs-related characteristics | | | | | |
| History of any anogenital STI | | | | | |
| No | 6.29 | Ref | | — | — |
| Yes | 10.23 | 1.63 (.80–3.33) | .19 | — | — |
| History of syphilis | | | | | |
| No | 6.54 | Ref | | — | — |
| Yes | **13.57** | **2.07 (1.10–3.89)** | **.030** | — | — |
| History of gonorrhea | | | | | |
| No | 9.00 | Ref | | — | — |
| Yes | 7.41 | 0.82 (.32–2.11) | .72 | — | — |
| History of chlamydia | | | | | |
| No | 9.06 | Ref | | — | — |
| Yes | 6.79 | 0.75 (.27–2.11) | .62 | — | — |
| History of HSV | | | | | |
| No | 7.74 | Ref | | — | — |
| Yes | 13.47 | 1.74 (.85–3.56) | .15 | — | — |
| History of HPV | | | | | |
| No | 7.45 | Ref | | — | — |
| Yes | 11.76 | 1.58 (.82–3.03) | .18 | — | — |
| History of ulcerative anogenital STIs (syphilis and/or HSV) | | | | | |
| No | 5.68 | Ref | | Ref | |
| Yes | **13.05** | **2.30 (1.21–4.38)** | **.013** | **2.97 (1.18–7.47)** | **.020** |
| Number of the type of anogenital STI | | | | | |
| 0 | 6.29 | Ref | | — | — |
| 1 | 7.74 | 1.23 (.52–2.89) | .64 | — | — |
| ≥2 | 13.13 | 2.09 (.96–4.52) | .06 | — | — |
| NID-related characteristics | | | | | |
| History of any NID use | | | | | |
| No | 5.32 | Ref | | — | — |
| Yes | 10.64 | 2.00 (.94–4.31) | .07 | — | — |
| Marijuana use | | | | | |
| No | 5.74 | Ref | | — | — |
| Yes | 11.23 | 1.96 (.98–3.90) | .06 | — | — |

*Table 3 continued.*

| Characteristics | IR/1000 PYs | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|---|
| | | IRR (95% CI) | *P* Value | Adjusted IRR[b] (95% CI) | *P* Value |
| Cocaine use | | | | | |
| No | 7.91 | Ref | | — | — |
| Yes | 10.36 | 1.31 (.68–2.52) | .42 | — | — |
| Ecstasy use | | | | | |
| No | 8.95 | Ref | | — | — |
| Yes | 4.79 | 0.53 (.08–3.78) | .60 | — | — |
| Methamphetamine use | | | | | |
| No | 7.45 | Ref | | — | — |
| Yes | **19.04** | **2.56 (1.24–5.27)** | **.024** | — | — |
| Poppers use | | | | | |
| No | 8.31 | Ref | | — | — |
| Yes | **123.77** | **14.9 (5.12–43.39)** | **.009** | — | — |
| Number of the type of NID | | | | | |
| 0 | 5.32 | Ref | | Ref | |
| 1 | 8.68 | 1.63 (.67–3.96) | .29 | 1.37 (.44–4.20) | .59 |
| ≥2 | **12.66** | **2.38 (1.05–5.38)** | **.039** | **4.25 (1.23–14.69)** | **.022** |

Abbreviations: CBHC, Chase Brexton Health Care; CI, confidence interval; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; IDU, injection drug use; IR, incident rate; IRR, incidence rate ratio; NID, noninjection drug; PY, person-years; Ref, reference level; RNA, ribonucleic acid; STI, sexually transmitted infection.

[a] Boldface type indicates $P < .05$.

[b] The variables included in the multivariate regression model were age, race, clinic site, time of entering care at CBHC, education, employment status, IDU history, smoking history, HIV RNA at initial visit, history of ulcerative anogenital STIs, and number of the type of NIDs.

observation of a decrease in infections during the 2007–2010 period. Moreover, some incident HCV might have been missed in MSM because of the high rate of spontaneous viral clearance [37], which could result in accelerated seroreversion [38]. Finally, we did not perform the analysis to discern whether the HCV IRs were different among patients who received cares from ID specialists or nonspecialized PCPs.

**Table 4. Multivariate Analysis for Risk Factors Associated With Incident Hepatitis C Virus Infection Among HIV-Infected Men Who Have Sex With Men Without Injection Drug Use (N = 899)[a]**

| Characteristics | Adjusted IRR[b] (95% CI) | *P* Value |
|---|---|---|
| Time of entering care at CBHC | | |
| <2010 | Ref | |
| 2010–2013 | **3.32 (1.28–8.61)** | **.014** |
| Education (more than high school) | | |
| No | Ref | |
| Yes | 1.56 (.62–3.92) | .35 |
| Employment | | |
| No | Ref | |
| Yes | **3.14 (1.09–9.01)** | **.034** |
| Smoking | | |
| Never | Ref | |
| Former | **0.23 (.06–.93)** | **.038** |
| Current | **0.29 (.09–.96)** | **.043** |
| History of ulcerative anogenital STIs (syphilis and/or HSV) | | |
| No | Ref | |
| Yes | **3.70 (1.39–9.85)** | **.009** |
| Number of the type of NID | | |
| 0 | Ref | |
| 1 | 1.28 (.40–4.12) | .68 |
| ≥2 | **5.54 (1.46–20.96)** | **.012** |

Abbreviations: CBHC, Chase Brexton Health Care; CI, confidence interval; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IRR, incidence rate ratio; NID, noninjection drug; Ref, reference level; RNA, ribonucleic acid; STI, sexually transmitted infection.

[a] Boldface type indicates $P < .05$.

[b] The variables included in the multivariate regression model were age, race, clinic site, time of entering care at CBHC, education, employment status, smoking history, HIV RNA at initial visit, history of ulcerative anogenital STIs, and number of the type of NIDs.

One strength of the present study is the high rate of HCV surveillance screening in the HIV-infected men (>90%), which could minimize potential selection bias. Indeed, one of the major hurdles for studying incident HCV in HIV-infected patients in the primary care settings in the United States is lack of more routine screening for incident HCV. A recent study investigating the rates of HCV surveillance screening in HIV-infected patients in 8 clinics across the United States between 2000 and 2011 showed rescreening rates of 35%–79%, depending on the clinics [15]. The higher rate of HCV surveillance screening at CBHC might be the result of having onsite ID specialists, leading to increased compliance with updated Centers for Disease Control and Prevention screening guidelines.

## CONCLUSIONS

When preventive measures are aimed at removing traditional risk factors for HCV infection in people living with or at risk of HIV infection (eg, lower education, unemployment, IDU, impaired immune status, and inadequate HIV suppression [4–6]), it will inevitably introduce some of the new, unconventional risk factors shown to be associated with the re-emerging HCV epidemic observed in the present study. Thus, HCV awareness education and surveillance screening should be

intensified for all HIV-positive individuals, especially when their socioeconomic conditions and HIV immunologic and virologic parameters are favorable.

## Supplementary Data

Supplementary material is available online at *Open Forum Infectious Diseases* online (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

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***Author contributions.*** Y.-C. C. conceived the study, obtained institutional review board approval, designed the study, established the study cohort, analyzed all the data, and wrote the paper; Y.-C. C. and K. W. coordinated and oversaw the study and performed data quality assessment; K. W., A. L. C., and C. L. T. participated in study design, Y.-C. C., A. B., P. B., J. A. G., and E. N. M. participated in data abstraction; K. W., Y.-H. H., A. B., P. B., J. A. G., A. L. C., and C. L. T. participated in data analyses; Y.-C. C., K. W., Y.-H. H., A. L. C., and C. L. T. interpreted the results; K. W., Y.-H. H., A. B., P. B., A. L. C., and C. L. T. co-wrote and edited the paper.

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