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MAJOR ARTICLE

Incidence of Hepatitis C Virus Infection in the Human Immunodeficiency Virus Outpatient Study Cohort, 2000–2013

Taraz Samandari,[1] Ellen Tedaldi,[2] Carl Armon,[3] Rachel Hart,[3] Joan S. Chmiel,[4] John T. Brooks,[1] and Kate Buchacz,[1] and the HIV Outpatient Study Investigators

[1]Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; [2] Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania; [3]Cerner Corporation, Kansas City, Missouri; and [4]Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Background. There are few recent studies of incident hepatitis C virus (HCV) infection among human immunodeficiency virus (HIV)-infected patients in the United States.

Methods. We studied HIV Outpatient Study (HOPS) participants seen in 9 HIV-specialty clinics who had ≥1 clinical encounter during 2000–2013 and ≥2 HCV-related tests, the first of which was a negative HCV antibody test (Ab). Hepatitis C virus incident cases were identified by first positive HCV Ab, viral load, or genotype. We assessed rates of incident HCV overall, by calendar intervals, and by demographic and HIV risk strata, and we explored risk factors for incident HCV using Cox proportional hazards models.

Results. The 1941 eligible patients (median age 40 years, 23% female, 61% men who had sex with men [MSM], and 3% persons who injected drugs [PWID]) experienced 102 (5.3%) incident HCV infections for an overall incidence of 1.07 (95% confidence interval [CI], 0.87–1.30) per 100 person-years (py). Hepatitis C virus incidence decreased from 1.83 in 2000–2003 to 0.88 in 2011–2013 ($P = .024$), with decreases observed ($P < .05$) among PWID and heterosexuals, but not among MSM. Overall, MSM comprised 59% of incident cases, and PWID were at most risk for incident HCV infection (adjusted hazard ratio [aHR] for PWID = 4.62 and 95% CI = 2.11–10.13; for MSM, aHR = 1.48 and 95% CI = 0.86–2.55 compared with heterosexuals).

Conclusions. Among HIV-infected patients in care during 2000–2013, incidence of HCV infection exceeded 1 case per 100 py. Our findings support recommendations for annual HCV screenings for HIV-infected persons, including persons with only MSM risk, to enable HCV diagnosis and treatment for coinfected individuals.

Keywords. hepatitis C; HIV/HCV coinfection; HIV cohort; incidence; risk factors.

In the United States, an estimated 20%–30% of human immunodeficiency virus (HIV)-infected persons are coinfected with hepatitis C virus (HCV) [1–4]. Although HIV antiretroviral (ARV) therapy decreases death rates due to liver disease [5], liver-related mortality has become a leading non-acquired immunodeficiency disease cause of death in this population [6, 7]. Overall risk of mortality is increased in HIV/HCV-coinfected patients compared with HIV-monoinfected patients [8]. The course of HCV disease is more aggressive in persons living with HIV infection (PLWH), resulting in a greater likelihood of fibrosis [9, 10]. Liver decompensation is increased [11], and the incidence of hepatocellular carcinoma is higher in HIV/HCV-coinfected patients compared with HCV-monoinfected counterparts [12].

Before the availability of directly acting antivirals [DAAs], HCV treatment uptake among HIV-infected persons was lower than among HCV-monoinfected persons because of perceived lower efficacy in the context of HIV infection and the high incidence of adverse effects associated with pegylated interferon and ribavirin [13]. Dramatic successes reported from several studies of HCV treatment of HIV-coinfected patients in recent years [14–17] have led the World Health Organization to declare that HIV/HCV-coinfected patients are no longer a "special population" because interferon-free regimens are equally effective in HIV-infected and uninfected persons [18]. Given these treatment opportunities, the Infectious Disease Society of America and the US Centers for Disease Control and Prevention ([CDC] Atlanta, GA) recommend annual testing for persons who inject drugs (PWID) and for HIV-seropositive men who have unprotected sex with other men (MSM) [19–22]. However, a recent large HIV cohort analysis found that, although almost all HIV-infected

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Correspondence: T. Samandari, MD, PhD, Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, 1800 Clifton Road NE, MS E-45, Atlanta, GA 30329 (tts0@cdc.gov).

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patients are tested at baseline, just over half of HIV-infected patients are being screened regularly at subsequent visits [23].

Although numerous epidemiologic studies have found that male-to-male sexual activity is a risk factor for HCV acquisition [24–27], recent data from large and robust studies of incident HCV infection in US HIV-infected populations are limited [28–31]. Recent outbreaks [32–34] have highlighted the need for better prevention and diagnosis of new HCV infections in HIV-infected persons, particularly MSM, in addition to the traditional risk group of PWID. Given that 59% of US-diagnosed PLWH have male-male sexual transmission risk [35], monitoring trends in HCV infection in this population is of public health importance. The objective of this analysis was to examine incidence of HCV and risk factors for HCV infection over time in a well characterized, multisite US-based cohort of HIV-infected persons in care.

METHODS

The HIV Outpatient Study

The HIV Outpatient Study (HOPS) is an ongoing, longitudinal, open cohort study that has prospectively followed HIV-infected adults receiving care at specialty HIV clinics since 1993. Patient data, including demographic and social characteristics, symptoms, diagnoses, prescribed medications (including dose and duration), and laboratory values, including ARV resistance mutations reported on commercial genotypic tests, were abstracted from medical records and entered by trained staff into a single Cerner database. Data quality assurance measures included supervisory reviews of randomly selected charts and centralized checks of data files to resolve discrepancies before analyses. The HOPS protocol has been reviewed and approved annually by the institutional review boards of the CDC and each local site. The study protocol conforms to the guidelines of the US Department of Health and Human Services for the protection of human participants in research, and all participants have provided written, informed consent.

Study Design, Population, Independent Variables, and Outcomes of Interest

We analyzed data from HOPS patients attending 9 university-based, public, and private clinics in 6 cities (Chicago, IL; Denver, CO; Stony Brook, NY; Philadelphia, PA; Tampa, FL; and Washington, DC) after January 1, 2000. We selected patients who had a HOPS clinical encounter anytime between January 2000 and December 2013 and at least 2 HCV-related test results. The first test in that time frame had to be a negative HCV antibody test (in the absence of proximal HCV ribonucleic acid [RNA]-positive results) and was considered to be the beginning of follow-up (baseline date) for HCV incidence analyses. The end of follow-up was (1) the last HCV-negative antibody test during 2000–2013 or (2) for those with evidence of incident HCV: the midpoint date between the last negative HCV antibody test and the earliest positive HCV antibody, viral load, or genotype test. Patients who had an HCV antibody positive result and a negative HCV RNA test within 90 days, and had no accompanying HCV diagnosis, were not counted as cases. Two physicians (T.S. and E.T.) reviewed the available HCV laboratory, treatment, and diagnosis data to adjudicate incident HCV cases. We classified patients by HIV transmission risk group; MSM who also reported injection drug use (IDU) were categorized into the PWID group to better isolate the potential risk of HCV acquisition associated with male-to-male sexual activity versus heterosexual activity. Payer source was defined as private, public, or none/other/unknown. The present analyses were based on the HOPS dataset updated as of September 30, 2015.

Statistical Analyses

We calculated the rates of incident HCV infection per 100 person-years (py), using the mid-point method to estimate the date of infection [36] during 4 calendar periods: 2000–2003, 2004–2007, 2008–2010, and overall, with further stratification by patient demographic factors. Temporal trends in HCV incidence were assessed using the Mantel-Haenszel χ^2 test for trend. We compared characteristics of patients who were included in our analysis with those of patients who were excluded (due to having no or only 1 recorded HCV antibody test) using Yates-corrected χ^2 tests for categorical variables and Kruskal-Wallis test of medians for continuous variables. Characteristics of patients who did versus did not acquire HCV infection were compared using the same methods. We used univariate and multivariable Cox proportional hazards regression models to assess correlates of incident HCV infection, including the following variables measured at the start of follow-up: age, sex, race/ethnicity, HIV transmission risk factor, insurance status, receiving care at a public clinic, presence of an acquired immune deficiency syndrome (AIDS) diagnosis, years since receiving diagnosis of HIV infection, and HOPS site city. Factors with univariate associations at $P < .10$ level were considered in the multivariable analysis. We constructed final models by a backward stepwise selection process, excluding variables one at a time by descending order of their P values. Confidence intervals (CIs) for HCV incidence rates and tests of trends over time were obtained using the Byar approximation to the Poisson distribution using OpenEpi.com. All other analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Statistical significance was defined as $P < .05$.

RESULTS

Study Population and Incident Hepatitis C Virus Cases

There were 8795 HOPS participants enrolled at active HOPS sites as of September 30, 2015, 6539 of whom had a clinical encounter during 2000–2013 and at least 2 HOPS visits

(Figure 1). We identified 5798 patients with no evidence of prevalent HCV infection at baseline (excluded n = 741). We further excluded 2283 patients having no negative HCV-antibody test in the record, 1547 who did not have a second HCV test, and 27 with inconclusive HCV results to determine study outcome (including concurrent HCV RNA positive and HCV antibody test at start of observation and no prior laboratory results, or a single isolated HCV antibody positive result with subsequent antibody negative results). Thus, our analytic cohort comprised 1941 patients with either a second negative HCV antibody test result, a positive HCV antibody result, a detectable HCV viral load, or a positive genotype test during follow up. Among these 1941 patients (9555.6 py of observation), 102 (5.3%) had an incident HCV infection during follow up, which was confirmed for 74 (73%) patients with HCV viral load or HCV genotype result. Among the remaining incident cases with a positive HCV antibody test only (n = 28), 14 (50%) had a concurrent hepatitis C diagnosis in the medical record.

Comparison of Included and Excluded Patients

Of 5798 patients (Figure 1), we excluded 2283 (39%) patients who did not have any documented negative HCV antibody test (range across sites: 9%–78%) and a further 1547 (27%) patients who only had 1 HCV test (range across HOPS sites: 16%–60%) in the study period, for a total of 66% of patients excluded. Some of the variability in the percentages excluded across HOPS sites could be attributed to differences in HOPS sites' longevity (2 sites joined during 2000–2013) and the resulting average length of their patients' follow up. When assessing patient characteristics at their first HOPS visit after January 1, 2000, compared with the 1941 patients included in the analyses, the 3857 patients whom we excluded were significantly older (median, 40 vs 38 years; $P < .001$), less likely to be female (20% vs 23%; $P = .01$), more likely to have had IDU as an HIV risk factor (6.1% vs 2.7%; $P < .001$) and to be diagnosed with HIV before 1996 (46% vs 37%; $P < .001$), but did not differ significantly by

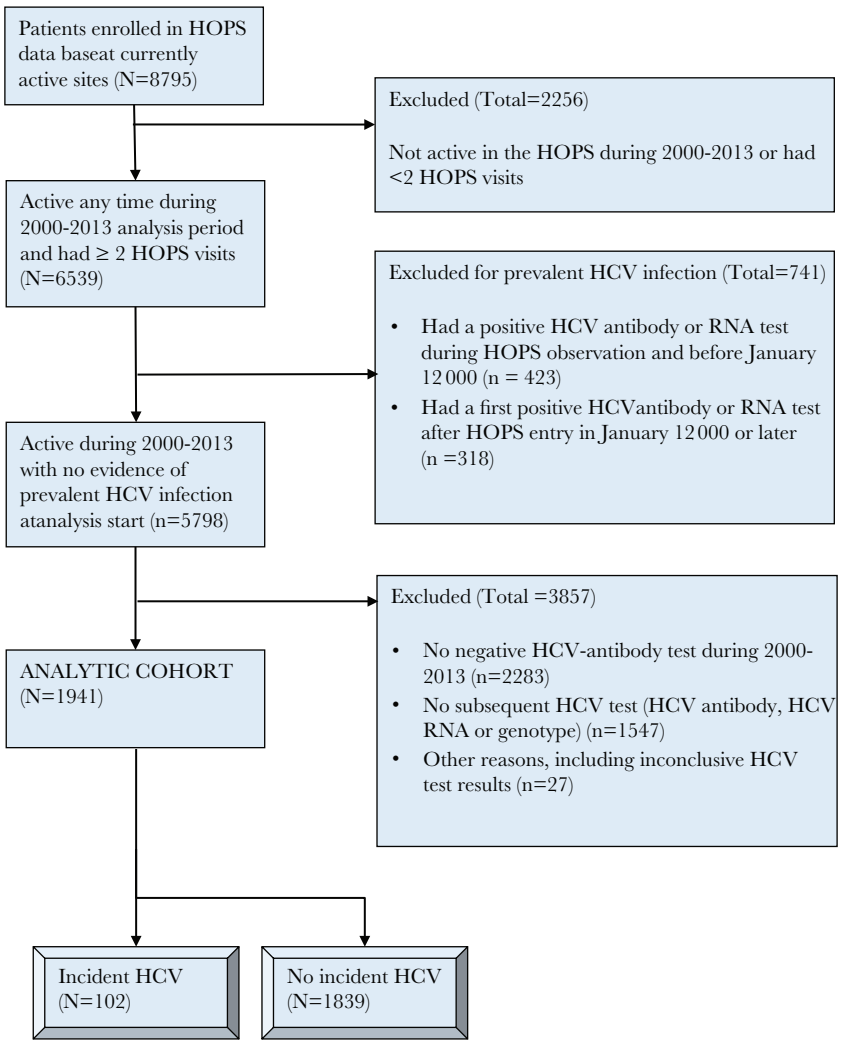

Figure 1. Patient summary flowchart. HCV, hepatitis C virus; HOPS, HIV Outpatient Study; RNA, ribonucleic acid.

race/ethnicity (52% vs 50% non-Hispanic white); excluded patients had fewer years of subsequent observation (median, 3.6 vs 9.6 years; $P < .001$).

Correlates of Incident Hepatitis C Virus Infection and Temporal Trends

Of the 1941 patients studied (median age, 40 years), 77% were male, 50% were of non-Hispanic white race/ethnicity, 61% were

Table 1. Characteristics of Patients Who Did and Did Not Have Incident HCV Infection, HIV Outpatient Study, 2000–2013 (N = 1941)[a]

	Total		Incident HCV		No HCV Infection		
Total in Analytic Cohort	N = 1941		N = 102 (5.3%)		N = 1839 (94.7%)		
Baseline Predictor Variables	N or Median	% or IQR	N or Median	% or IQR	N or Median	% or IQR	*P* Value[b]
Age, years, median (IQR)	40	34–47	40	35–46	40	34–47	.46
Median years follow-up in this study (IQR)	7.8	4.8–11.3	9.8	6.8–12.7	7.7	4.7–11.1	<.001
Sex, n (%)							.51
Female	442	22.8	20	19.6	422	22.9	
Male	1499	77.2	82	80.4	1417	77.1	
Race/ethnicity							.18
White, non-Hispanic	978	50.4	48	47.1	930	50.6	
Black, non-Hispanic	668	34.4	42	41.2	626	34.0	
Hispanic	230	11.8	7	6.9	223	12.1	
Other/unknown	65	3.3	5	4.9	60	3.3	
HIV Risk							.016
IDU	52	2.7	9	8.8	43	2.3	
MSM[b]	1184	61.0	60	58.8	1124	61.1	
Heterosexual	584	30.1	27	26.5	557	30.3	
Other/unknown	121	6.2	6	5.9	115	6.3	
Year of HIV diagnosis, n (%)							.004
<1996	710	36.6	40	39.2	670	36.4	
1996–2004	809	41.7	52	51.0	757	41.2	
2005–2013	422	21.7	10	9.8	412	22.4	
AIDS at baseline, n (%)							.37
No	930	47.9	44	43.1	886	48.2	
Yes	1011	52.1	58	56.9	953	51.8	
Insurance							.12
Private	1042	53.7	49	48.0	993	54.0	
Public	653	33.6	33	32.4	620	33.7	
None/other/unknown	246	12.7	20	19.6	226	12.3	
Seen at public clinic, n (%)							.07
No	1222	63.0	55	53.9	1167	63.5	
Yes	719	37.0	47	46.1	672	36.5	
Median CD4 cell count, cells/mm^3 (IQR) (n = 1915)	404	231–617	366	234–569	408	231–619	.35
ARV experience							.12
Experienced	1304	67.2	77	75.5	1227	66.7	
Naïve	584	30.1	24	23.5	560	30.5	
Unknown	53	2.7	1	1.0	52	2.8	
Year of first negative HCV antibody test, n (%)							<.001
2000–2003	793	40.9	63	61.8	730	39.7	
2004–2007	650	33.5	24	23.5	626	34.0	
2008–2010	373	19.2	13	12.7	360	19.6	
2011–2013	125	6.4	2	2.0	123	6.7	
Years between first and next HCV test (IQR)	1.7	1.0–3.6	1.8	1.0–4.2	1.7	1.0–3.6	.57
HOPS site city							.002
Denver	712	36.7	21	20.6	691	37.6	
Chicago	545	28.1	42	41.2	503	27.4	
Philadelphia	359	18.5	21	20.6	338	18.4	
Other[c]	325	16.7	18	17.6	307	16.7	

Abbreviations: AIDS, acquired immunodeficiency disease; ARV, antiretroviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HOPS, HIV Outpatient Study; IDU, injection drug use; IQR, interquartile range; MSM, men who have sex with men.

[a]"Baseline" refers to date of first HCV-negative antibody test during 2000–2013. Statistical tests used were as follows: Yates-corrected χ^2 test for categorical variables, a Kruskal-Wallis test of medians for continuous variables.

[b]Persons with dual MSM/IDU HIV risk were placed in the IDU category.

[c]"Other" = Washington, DC, Stonybrook, NY, and Tampa, FL, which were combined due to small numbers.

Table 2. HCV Incidence and Person-Years of Observation by Calendar Period, the HIV Outpatient Study, 2000–2013 (N = 1941)

	2000–2013	2000–2003	2004–2007	2008–2010	2011–2013
	N	n	n	n	n
HCV incident infections	102	27	31	28	16
Persons at risk	1941	791	1325	1421	1078
Person-years observation	9555.6	1478.3	3305.2	2946.3	1825.9
Mean years (10th–90th percentile) from last negative to first positive test	2.30 (0.49–5.01)	2.53 (0.49–5.20)	2.85 (0.88–5.98)	1.99 (0.50–4.31)	1.41 (0.39–3.20)
Median years (IQR) from last negative to first positive test	1.64 (0.89–3.17)	2.33 (0.90–3.64)	1.82 (1.19–3.33)	1.15 (0.87–2.77)	1.02 (0.76–1.92)
Overall HCV incidence rate per 100 py (95% CI)	1.07 (0.87–1.30)	1.83 (1.20–2.66)	0.94 (0.64–1.33)	0.95 (0.63–1.37)	0.88 (0.50–1.42)

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; py, person-years.

MSM, 54% were privately insured, 63% were seen at a private clinic, 52% had a prior AIDS diagnosis, and 67% were ARV-experienced at baseline, increasing to 97% by the end of observation (Table 1). The 102 patients with incident HCV infection (median age, 40 years) were also predominantly male (80%), 47% were non-Hispanic white, and 59% were MSM. Compared with patients who remained HCV negative, the 102 patients with incident HCV infection were under observation in this study for a longer period of time (median, 9.8 vs 7.7 years), were more likely to have had IDU HIV risk (8.8% vs 2.3%), received their HIV diagnosis earlier, and had a greater number of years since receiving their baseline negative HCV antibody test (all $P < .05$) (Table 1).

In unadjusted analyses, there were differences (based on non-overlapping 95% CIs) in overall HCV incidence rates (2000–2013) by race/ethnicity, HIV risk, insurance type, and clinic type (see Tables 2 and 3, first numeric column). Overall, rates were highest among non-Hispanic blacks (1.3 cases per 100 py) and persons of other race/ethnicity (1.8 per 100 py) and lowest among Hispanic participants (0.6 cases per 100 py). Rates were highest among persons with IDU HIV risk (3.4 per 100 py), and they were higher among publicly insured versus privately insured patients and higher among those seen in public clinic versus private clinics. Hepatitis C virus incidence rates decreased during the observation period in the overall population, and they also decreased among females, black non-Hispanics, persons with IDU or heterosexual HIV risk, those with HIV diagnosis before 1996, or with an AIDS diagnosis at/before baseline, those with public insurance or seen at a public clinic, and those with first negative HCV antibody test during 2000–2003 (Table 3, Figure 2).

In multivariable Cox proportional hazards analysis over the entire period of 2000–2013, risk factors for incident HCV infection were having IDU HIV risk (adjusted hazard ratio [aHR] = 4.62 and 95% CI = 2.11–10.13, vs heterosexual risk) and being followed in sites other than Denver, CO sites: Chicago (aHR, 3.16; 95% CI, 1.74–5.74), Philadelphia (aHR, 3.30; 95% CI, 1.41–7.75), or the combined group of Washington, DC, Stony Brook, NY, and Tampa, FL sites (aHR, 2.38; 95% CI, 1.19–4.73) (Table 4). In an analysis restricted to the more recent timeframe of 2008–2013, male gender and having no/other/unknown insurance (compared with private insurance) were each associated with incident HCV infection, but not MSM or IDU risk (Table 4).

DISCUSSION

The incidence of "acute" HCV infection is estimated to be 0.7 cases per 100 000 in the US population [37]. Cases of HCV infection in the US general population have been increasing, with a 2.5-fold increase in acute HCV cases from 2000 to 2013 due primarily to IDU [38]. In our US cohort of HIV-infected persons, the overall HCV incidence was approximately 1% per year, consistent with higher frequency of substance use and other behavioral and social factors that predispose to acquisition of viral hepatitis among HIV-infected persons. We found that across all study years, HOPS participants at highest risk for new HCV infections were PWID or participants who lacked either public or private insurance. In the contemporary period (2008–2013), HCV incidence was elevated among males and persons with unknown/missing information on health insurance. In addition, although the highest incidence rate over the study period was observed among PWID, these persons constituted only 2.7% of our analytic cohort. Most cases of HCV infection in our study occurred among MSM (59%), who also represent the majority (60%) of patients in our cohort and of PLWH in the United States in general. It is worth noting that MSM were the only HIV risk group for which we did not observe a decrease in HCV incidence over the study period.

A review and meta-analysis of global data showed increases in HCV infections among HIV-infected MSM since 1995 that were associated with traumatic sex and methamphetamine use during sex; the observed rate among HIV-infected MSM in 2012 was 1.3 per 100 py [31]. In our study, the overall annual HCV incidence rate for MSM was 1.0%, and it was somewhat elevated in the most recent period, at 1.3% in the 2011–2013. Although information about IDU behavior among HOPS participants

Table 3. HCV Incidence Rates per 100 Person-Years (95% CI) by Baseline Characteristic and Period of Observation, the HIV Outpatient Study, 2000–2013 (N = 1941)[a]

Baseline Patient Characteristics	2000–2013 n = 1941	2000–2003 n = 791	2004–2007, n = 1325	2008–2010 n = 1421	2011–2013, n = 1078	Mantel-Haenszel *P* Value
Overall	1.07 (0.87–1.30)	1.83 (1.20–2.66)	0.94 (0.64–1.33)	0.95 (0.63–1.37)	0.88 (0.50–1.42)	.024
Age, years						
<40	0.99 (0.73–1.32)	1.26 (0.60–2.32)	0.99 (0.56–1.60)	0.90 (0.48–1.55)	0.90 (0.39–1.77)	.41
40–50	1.14 (0.80–1.56)	2.63 (1.40–4.50)	0.76 (0.35–1.44)	0.87 (0.40–1.65)	1.11 (0.45–2.30)	.07
>50	1.16 (0.68–1.86)	2.10 (0.56–5.36)	1.21 (0.44–2.64)	1.27 (0.47–2.77)	0.32 (0.00–1.81)	.08
Sex						
Female	0.90 (0.55–1.39)	2.39 (1.03–4.71)	1.14 (0.52–2.17)	0.29 (0.03–1.05)	0.24 (0.00–1.34)	<.001
Male	1.12 (0.89–1.39)	1.66 (1.00–2.60)	0.87 (0.55–1.32)	1.15 (0.75–1.69)	1.06 (0.59–1.75)	.39
Race/Ethnicity						
White, non-Hispanic	0.96 (0.71–1.28)	1.42 (0.74–2.49)	0.79 (0.43–1.32)	0.87 (0.46–1.48)	1.05 (0.48–1.99)	.51
Black, non-Hispanic	1.34 (0.97–1.82)	2.74 (1.41–4.78)	1.46 (0.82–2.41)	1.11 (0.56–1.99)	0.59 (0.16–1.52)	.003
Hispanic	0.60 (0.24–1.24)	0.61 (0.01–3.37)	0.24 (0.00–1.35)	0.83 (0.17–2.43)	0.87 (0.10–3.15)	.54
Other/unknown	1.78 (0.57–4.16)	6.17 (0.69–22.30)	1.15 (0.02–6.42)	1.01 (0.01–5.61)	1.60 (0.02–8.92)	.17
HIV Risk						
IDU	3.44 (1.57–6.52)	12.00 (4.38–26.11)	2.14 (0.24–7.73)	1.31 (0.02–7.28)	(n/a)	.002
MSM	1.04 (0.80–1.34)	1.33 (0.69–2.32)	0.87 (0.51–1.39)	0.96 (0.56–1.54)	1.26 (0.69–2.12)	.97
Heterosexual	0.92 (0.61–1.34)	1.77 (0.76–3.49)	0.87 (0.40–1.65)	0.90 (0.39–1.78)	0.36 (0.04–1.30)	.034
Other/unknown	0.97 (0.35–2.11)	1.37 (0.02–7.64)	1.39 (0.28–4.07)	0.94 (0.11–3.40)	(n/a)	.17
Year of HIV Diagnosis						
<1996	0.99 (0.71–1.35)	1.92 (1.10–3.12)	0.74 (0.37–1.32)	0.83 (0.38–1.57)	0.64 (0.17–1.64)	.020
1996–2004	1.20 (0.90–1.58)	1.70 (0.85–3.05)	1.17 (0.70–1.83)	1.13 (0.63–1.87)	0.97 (0.39–1.99)	.23
2005–2013	0.83 (0.40–1.53)	n/a	0.52 (0.01–2.89)	0.75 (0.20–1.92)	1.05 (0.34–2.45)	.61
AIDS at Baseline						
No	1.00 (0.73–1.34)	1.56 (0.75–2.86)	0.80 (0.41–1.40)	0.86 (0.44–1.50)	1.16 (0.56–2.14)	.26
Yes	1.12 (0.85–1.45)	2.03 (1.18–3.26)	1.05 (0.63–1.64)	1.03 (0.59–1.68)	0.62 (0.23–1.35)	.010
Insurance						
Private	0.93 (0.69–1.23)	1.51 (0.81–2.59)	0.86 (0.49–1.40)	0.87 (0.48–1.46)	0.65 (0.24–1.41)	.08
Public	1.03 (0.71–1.44)	1.98 (0.95–3.63)	1.08 (0.56–1.88)	0.83 (0.36–1.63)	0.48 (0.10–1.41)	.013
None/other/unknown	1.83 (1.12–2.82)	3.53 (0.95–9.04)	0.89 (0.18–2.61)	1.61 (0.59–3.51)	2.54 (1.02–5.24)	.87
Seen at public clinic						
No	0.94 (0.71–1.23)	1.40 (0.72–2.44)	0.91 (0.54–1.43)	0.81 (0.45–1.33)	0.88 (0.42–1.62)	.25
Yes	1.26 (0.93–1.68)	2.42 (1.36–4.00)	0.99 (0.52–1.69)	1.19 (0.63–2.04)	0.87 (0.32–1.88)	.039
Year of First Negative HCV Antibody Test						
2000–2003	1.15 (0.88–1.47)	1.83 (1.20–2.66)	0.99 (0.62–1.50)	0.66 (0.29–1.31)	1.01 (0.37–2.20)	.017
2004–2007	0.83 (0.53–1.23)	n/a	0.83 (0.38–1.58)	0.89 (0.44–1.59)	0.68 (0.18–1.74)	.69
2008–2010	1.31 (0.69–2.23)	n/a	n/a	1.78 (0.81–3.37)	0.82 (0.22–2.10)	n/a
2011–2013	1.27 (0.14–4.60)	n/a	n/a	n/a	1.27 (0.14–4.60)	n/a
HOPS Site City						
Denver	0.57 (0.35–0.87)	0.53 (0.11–1.55)	0.40 (0.13–0.93)	0.60 (0.24–1.24)	0.84 (0.31–1.82)	.37
Chicago	1.72 (1.24–2.32)	2.66 (1.22–5.06)	2.04 (1.19–3.26)	1.29 (0.62–2.38)	1.21 (0.44–2.62)	.054
Philadelphia	1.16 (0.72–1.78)	3.47 (1.58–6.58)	0.49 (0.01–1.42)	1.12 (0.41–2.43)	0.77 (0.16–2.26)	.031
Other[b]	1.12 (0.66–1.77)	1.92 (0.70–4.17)	1.00 (0.36–2.17)	1.06 (0.34–2.48)	0.45 (0.01–2.50)	.12

Abbreviations: AIDS, acquired immunodeficiency disease; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HOPS, HIV Outpatient Study; IDU, injection drug use; MSM, men who have sex with men; n/a, not applicable; py, person-years.

[a]"Baseline" refers to date of first HCV negative antibody test during 2000–2013. OpenEpi.com was used to obtain rate of CIs (using Byar approximation to the Poisson), and Mantel-Haenszel χ^2 trend was used for *P* values.

[b]"Other" = Washington, DC, Stonybrook, NY, and Tampa, FL, which were combined due to small numbers.

was not asked systematically after initial assessment of HIV risk at enrollment, approximately 4% of MSM reported IDU sometime during our study follow-up; after excluding these men, the incidence was 0.95 per 100 py overall, and 1.1 per 100 py for 2011–2013, suggesting that male-to-male sexual activity by itself remains an important route of HCV acquisition.

In this analysis of nearly 5800 patients who were active in the HOPS and at risk for HCV infection (median observation of 5.5 years during 2000–2013), approximately two thirds had no or only 1 HCV test documented in the medical record and thus had to be excluded from the analyses. Although screening for hepatitis C infection has been a long-standing performance

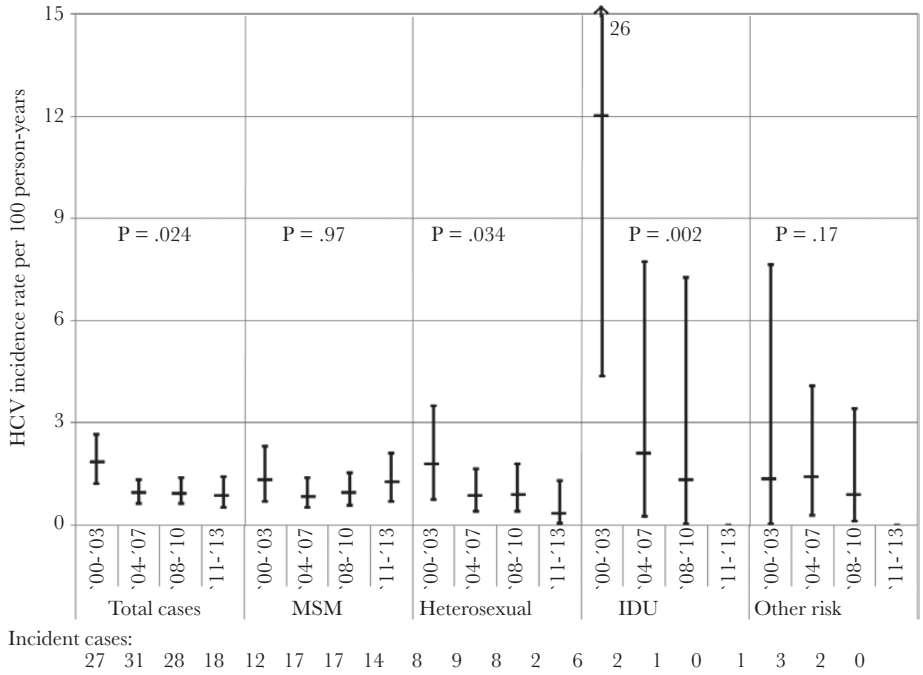

Figure 2. Hepatitis C virus (HCV) incidence rates per 100 person-years with 95% confidence intervals, overall, by calendar period and by human immunodeficiency virus (HIV) risk group, HIV Outpatient Study, 2000–2013 (N = 1914). *P* values were obtained using Mantel-Haenszel χ^2 test for trend over time. HIV risk factors include IDU, injection drug use; MSM, a man who has sex with men.

measure in the national standards for HIV/AIDS care [39], efforts both to screen all patients at initiation of HIV care and to rescreen at-risk patients during care (as recommended in clinical guidelines [https://aidsinfo.nih.gov/guidelines/]) have not been fully optimized [2, 4, 23]. The most recent CDC screening recommendations for hepatitis C for the general US population have focused on persons born between 1945 and 1965 regardless of risk factors, relevant to our cohort which had a median age of 40 years at the start of observation [40]. Given the preponderance of HCV infections among MSM in our cohort, the recent recommendations for annual HCV screening of MSM with HIV infection appear most appropriate [22]. The impetus to screen for HCV should only increase given the availability of highly effective DAAs for treatment of hepatitis C and grave consequences of chronic HCV infection in PLWH [19].

The strengths of our study include a prospective multisite cohort design, including 9 well established, community-based, private, public, and academic clinics and a demographically diverse study population. There are certain limitations to our study. The HOPS is a prospective, medical chart-abstraction cohort of patients in routine HIV clinical care for whom HCV screening was not performed at regular intervals but was performed instead at the discretion of providers and, not surprisingly, varied across the participating HOPS clinics. Only 61% of approximately 5800 HOPS patients at risk of HCV had at least 1 HCV test documented during the observation, and one third of that total had repeat HCV testing; therefore, HCV incidence estimates that we found may not apply to the entire HOPS population. Of incident HCV cases in our study, approximately 73% had a confirmation with HCV viral load or genotype results, and a minority had corroborating evidence of HCV infection based upon charted hepatitis C diagnosis. We assumed that HCV infection occurred at the mid-point of time between the last HCV-negative and first HCV-positive test; however, some HCV infection events may have occurred closer to the time of the positive test, that test having been prompted by clinical suspicion of recent HCV infection (eg, asymptomatic transaminitis on routine follow-up laboratory tests). Finally, although the HOPS cohort broadly resembles all PLWH in the United States [35], it remains a convenience sample, and the differences in HCV incidence by HOPS site may stem from varying participant characteristics and HCV testing patterns.

CONCLUSIONS

In conclusion, in the HOPS cohort of PLWH in care in the United States, we observed a rate of approximately 1% per year of new HCV infections between 2000 and 2013. A consistent trend of incident HCV among HIV-infected MSM supports previous observations in well resourced countries that MSM contribute increasingly to new HCV cases among

Table 4. Results From Cox Proportional Hazards Analysis of Selected Factors and Their Association With Incident HCV Infection, 2000–2013 (N = 1941; Incident HCV Cases = 102) and 2008–2013 (N = 1546; Incident HCV Cases = 44)[a]

	2000–2013				2008–2013			
	Univariate Analysis		Multivariable Analysis		Univariate Analysis		Multivariable Analysis	
Patient Characteristics at Baseline	HR (95% CI)	*P* Value	aHR (95% CI)	*P* Value	HR (95% CI)	*P* Value	aHR (95% CI)	*P* Value
Age, years								
<40	Referent				Referent			
40–50	1.16 (0.76–1.78)	.50			1.13 (0.59–2.17)	.71		
>50	1.17 (0.67–2.04)	.58			1.19 (0.50–2.79)	.70		
Sex								
Female	Referent				Referent		Referent	
Male	1.22 (0.75–1.99)	.43			4.06 (1.26–13.11)	.019	5.01 (1.19–16.86)	.009
Race/Ethnicity								
White, non-Hispanic	Referent				Referent			
Black, non-Hispanic	1.38 (0.91–2.08)	.13			1.09 (0.57–2.11)	.79		
Hispanic	0.64 (0.29–1.41)	.26			0.99 (0.37–2.61)	.98		
Other/unknown	1.86 (0.74–4.68)	.19			1.75 (0.41–7.44)	.45		
HIV Risk								
IDU	3.73 (1.75–7.94)	<.001	4.62 (2.11–10.13)	<.001	1.05 (0.13–8.23)	.96		
MSM	1.12 (0.71–1.77)	.62	1.48 (0.86–2.55)	.16	1.56 (0.76–3.18)	.22		
Heterosexual	Referent		Referent		Referent			
Other/unknown	1.06 (0.44–2.56)	.91	1.14 (0.46–2.83)	.78	0.91 (0.20–4.15)	.90		
Insurance								
Private	Referent		Referent		Referent		Referent	
Public	1.11 (0.72–1.73)	.64	0.87 (0.53–1.44)	.59	0.91 (0.44–1.91)	.81	0.94 (0.41–2.17)	.88
None/other/unknown	1.82 (1.08–3.07)	.024	1.24 (0.70–2.18)	.47	2.93 (1.46–5.89)	.003	2.54 (1.14–5.64)	.022
Seen at Public Clinic								
No	Referent				Referent			
Yes	1.34 (0.91–1.98)	.14			1.18 (0.65–2.14)	.59		
Year of First Negative HCV Antibody Test								
2000–2003	Referent							
2004–2007	0.66 (0.41–1.07)	.09						
2008–2010	0.97 (0.52–1.80)	.91						
2011–2013	0.93 (0.22–3.91)	.92						
HOPS Site City								
Denver	Referent		Referent		Referent		Referent	
Chicago	2.93 (1.73–4.96)	<.001	3.16 (1.74–5.74)	<.001	2.13 (1.02–4.44)	.044	1.66 (0.72–3.84)	.24
Philadelphia	2.03 (1.11–3.71)	.022	3.30 (1.41–7.75)	.006	1.43 (0.61–3.34)	.41	2.35 (0.89–6.20)	.08
Other[b]	2.01 (1.07–3.78)	.030	2.38 (1.19–4.73)	.014	1.23 (0.47–3.23)	.68	1.46 (0.53–4.04)	.47

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HOPS, HIV Outpatient Study; HR, hazard ratio; IDU, injection drug use; MSM, men who have sex with men.

[a]"Baseline" refers to date of first HCV-negative antibody test during 2000–2013. Backward selection for multivariable analysis yielded only HIV risk factor and HOPS site cities as included variables during 2000–2013.

[b]"Other" = Washington, DC, Stonybrook, NY, and Tampa, FL, which were combined due to small numbers.

HIV-infected persons. Our results emphasize the importance of regular HCV testing and interventions to prevent HCV infection in this risk group. Clinicians caring for PLWH should follow the current guideline to test annually for HCV infection, particularly among MSM and PWID, and offer DAA treatments to those found to be infected with HCV. Persons who injected drugs and MSM who receive HIV care should be counseled on risk reduction related to injection and needle-sharing practices and sexual practices. Future research should follow HCV incidence trends among HIV-infected persons, including MSM, monitor the proportion of all coinfected persons cured of HCV and reinfected with HCV after cure, and assess the impact of HCV prevention interventions in this population.

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APPENDIX

The HIV Outpatient Study Investigators include the following persons and sites: Kate Buchacz, Marcus D. Durham, John T. Brooks Division of HIV/AIDS Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention (CDC), Atlanta, GA; Harlen Hays, Rachel Hart, Thilakavathy Subramanian, Carl Armon, Bonnie Dean, Stacey Purinton, Dana Franklin, Cheryl Akridge, Nabil Rayeed, Cerner Corporation, Kansas City, MO; Frank J. Palella, Joan S. Chmiel, Saira Jahangir, Conor Daniel Flaherty, Genevieve Looby, Feinberg School of Medicine, Northwestern University, Chicago, IL; John Hammer, Kenneth S. Greenberg, Barbara Widick, Rosa Franklin, Rose Medical Center, Denver,

CO; Bienvenido G. Yangco, Kalliope Chagaris, Infectious Disease Research Institute, Tampa, FL; Douglas J. Ward, Troy Thomas, Cheryl Stewart, Dupont Circle Physicians Group, Washington, DC; Jack Fuhrer, Linda Ording-Bauer, Rita Kelly, Jane Esteves, State University of New York, Stony Brook, NY; Ellen M. Tedaldi, Ramona A. Christian, Faye Ruley, Dania Beadle, Princess Davenport, Temple University School of Medicine, Philadelphia, PA; Richard M. Novak, Andrea Wendrow, University of Illinois at Chicago, Chicago, IL; Benjamin Young, Mia Scott, Barbara Widick, APEX Family Medicine, Denver, CO.