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Low Incidence and Prevalence of Hepatitis C Virus Infection Among Sexually Active Non-Intravenous Drug-Using Adults, San Francisco, 1997–2000

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Background: **The rate of sexual transmission of hepatitis C virus (HCV) is debated.**

Goal: **The goal was to measure the risk of sexual transmission of hepatitis C virus (HCV) in a sexually active population.**

Study Design: **Sexual behaviors and HCV antibody status were measured in persons seeking repeat HIV testing in San Francisco from October 1997 through March 2000.**

Results: **Among 981 repeat testers, the prevalence of HCV antibody was 2.5%. Among men who have sex with men who denied intravenous drug use (n = 746), factors associated with HCV antibody positivity include age greater than 50 years (odds ratio [OR], 8.5; 95% confidence interval [CI], 2.6–27.7), HIV infection (OR, 5.7; 95% CI, 1.6–20.6), and being nonwhite (OR, 3.3; 95% CI, 1.1–10.0). HCV antibody positivity was not associated with sexual risk behaviors. In 576.6 person-years of observation, no new HCV seroconversions occurred (incidence = 0 per 100 person-year; 95% CI, 0–.6), whereas 6 new herpes simplex virus-2 infections (2.8 per 100 person-years) and 10 new HIV infections (1.8 per 100 person-years) occurred.**

Conclusion: **The absence of new HCV infections in this sample supports the hypothesis that the risk of sexual transmission of HCV is low.**

HEPATITIS C VIRUS (HCV) infection is the most common chronic bloodborne viral infection in the United States.[1] An estimated 4 million people, 1.8% of all Americans, have been infected with the virus.[1] Parenteral transmission of HCV is well established as a major risk factor and accounts for high rates of transmission among intravenous drug users and hemophiliacs. However, considerable inconsistencies exist among published studies regarding the role of sexual transmission of HCV.[2,3]

Several seroprevalence studies in heterosexual populations have suggested that transmission of HCV through sexual transmission was an important risk factor for infection.[4–11] Conversely, other studies demonstrated that sexual transmission of HCV infection was rare.[3,12–15] Studies to evaluate the sexual transmission of HCV among men who have sex with men (MSM) have been inconclusive.[16–22] Few studies in MSM[16,23–25] or heterosexual populations[6,14,15] have examined the incidence of HCV infection.

In October 1997, the San Francisco Department of Public Health (SFDPH), in collaboration with The University of California, San Francisco (UCSF) AIDS Health Project, implemented a system to link, anonymously, HIV test results among persons seeking repeat anonymous HIV testing.[26]

The objectives of this study were to estimate the prevalence and incidence of HCV, to estimate the risk of sexual transmission of HCV infection among persons seeking anonymous HIV testing, and to evaluate these HIV testing sites as sites for HCV screening.

Methods

Study Design and Subjects

A retrospective study of persons seeking repeat anonymous HIV testing in San Francisco who had more than 1 test from October 1997 through March 2000 was conducted. Inclusion in the study required at least 2 serologic specimens be retrieved from routinely archived serum from the same person during the study period. Seven persons with missing data were excluded.

Data Collection

As part of the routine UCSF AIDS Health Project protocol, clients were interviewed by staff using the Demographic and Risk Assessment Form (DRAF) developed by the State of California AIDS Office (Sacramento, CA). Data collected during the study period included demographic information, sexual orientation, reason for testing, testing history, gender of sexual partner(s), sexual behavior, use of condoms, lifetime history of intravenous drug use (IDU) among testers and their partners, and other bloodborne exposures. To assess correlates of prevalent infection, the interview data

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TABLE 1. Characteristics of Persons Seeking Repeat Anonymous HIV Testing, San Francisco, 1997–2000

Characteristics	Total (n = 981) No.	Non-Intravenous Drug Use (IDU) MSM (n = 746) No. (%)	All Others* (n = 235) No. (%)
Age (yr, n = 977)†			
18–29	307	198 (27)	109 (46)
30–39	434	348 (47)	86 (37)
40–49	169	142 (19)	27 (11)
50+	67	54 (7)	13 (6)
Race (n = 957)†			
White	741	591 (79)	150 (64)
Nonwhite	216	124 (17)	92 (39)
No. of sex partners in last year (n = 967)†			
<6	494	286 (38)	200 (85)
6–10	195	168 (23)	27 (12)
11–50	253	245 (33)	8 (3)
>50	25	25 (3)	0 (0)
Sexual risk during testing interval			
Sex partner with IDU history			
No	929	718 (96)	211 (90)
Yes	52	28 (4)	24 (10)
Unprotected anal insertive sex			
No	660	443 (59)	217 (92)
Yes	321	303 (41)	18 (8)
Unprotected rectal anal sex			
No	737	517 (69)	220 (94)
Yes	244	229 (31)	15 (6)
Sexually transmitted disease diagnosis			
No	875	655 (88)	220 (94)
Yes	106	91 (12)	15 (6)
Sex work			
No	963	733 (98)	230 (98)
Yes	18	13 (2)	5 (2)
Concomitant viral infection			
HIV positive			
No	928	696 (93)	232 (99)
Yes	53	50 (7)	3 (1)
Herpes simplex virus-2 (n = 970)†			
No	732	538 (72)	194 (83)
Yes	238	197 (26)	41 (17)
Non-intravenous drug use during testing interval			
Amphetamine			
No	922	698 (94)	224 (95)
Yes	59	48 (6)	11 (5)
Cocaine			
No	915	699 (94)	216 (92)
Yes	66	47 (6)	19 (8)
Blood/needle exposures during testing interval			
Tattoo			
No	969	737 (99)	232 (99)
Yes	12	9 (1)	3 (1)
Occupational			
No	957	728 (98)	229 (97)
Yes	24	18 (2)	6 (3)

*Heterosexual men (n = 92), women (n = 135), IDU MSM (n = 8).
†Some numbers and percentages do not add to 100% as a result of missing values.

collected for the year before the second visit were used. The median interval between tests was 9 months (range, 1–28 mo).

Methods

During each anonymous HIV test visit, clients were routinely asked to create a unique testing code (UTC) by using a combination of letters and numbers based on personal information that could easily and consistently be recalled.[27] To identify repeat testers, DRAF data and test results with the same UTC and demographic information were matched. To verify the matching algorithm, a subsample of 45 matched pairs were evaluated by testing their antibody profile with a human antibody fingerprinting method.[28] Of the 45 matched pairs, 43 (96%) had identical antibody profiles, indicating that individuals with matching UTC and similar demographic features between tests had a high probability of being the same tester.

TABLE 2. HCV Antibody Prevalence by Sexual Orientation and Intravenous Drug Use (IDU) in Persons Repeatedly Seeking Anonymous HIV Testing, San Francisco, 1997–2000

	IDU		Non-IDU		Total Sample	
Sexual Orientation	No.	HCV† No. (%)	No.	HCV† No. (%)	Prevalence Ratio (95% confidence interval)	*P* Value
MSM*	8	1 (12.5)	746	15 (2.0)	6.2 (3.7–11.2)	<0.01
Heterosexual men	4	3 (75.0)	88	1 (1.1)	66.0 (11.5–2,636)	<0.01
Women	3	2 (66.7)	132	3 (2.3)	29.3 (9.8–144.1)	<0.01
Overall	15	6 (40.0)	966	19 (2.0)	20.3 (13.0–33.9)	<0.01

*Men who have sex with men.
†HCV antibody-positive.
HCV = hepatitis C virus.

Using the testing algorithm, individual testers were identified as persistently HCV antibody-negative, persistently HCV antibody-positive, or newly seroconverted. For each subject, the most recent serologic specimen was tested for HCV antibody. Prior specimens from HCV antibody-seropositive persons were then also tested for HCV antibody.

Serology

Serum samples were stored at -35°F. Samples were tested in duplicate for HCV antibody using a second-generation enzyme immunoassay (Abbott HCV EIA 2.0; Abbott Laboratories, Abbott Park, IL).[29] The manufacturer reported sensitivity ranged from 95% to 97% and specificity was 99.8%.[30] Repeatedly reactive specimens were retested in duplicate at the Centers for Disease Control and Prevention in Atlanta, Georgia, with an equivalent third-generation enzyme immunoassay (Ortho HCV EIA 3.0; Ortho Diagnostic Systems, Inc., Raritan, NJ). Repeatedly reactive specimens by the third-generation assay underwent supplemental testing (RIBA 3.0; Chiron Corp., Emeryville, CA). Samples positive by supplemental testing were categorized as HCV antibody-positive.

Sera were tested for HIV antibodies using an enzyme immunoassay (Organon Teknika, Durham, NC), and positive specimens were confirmed using immunofluorescent antibody (IFA, Waldheim Neufield, Vienna, Austria). As part of a simultaneous study, sera were tested for herpes simplex virus-2 (HSV-2) antibody with the Focus Technology (Cypress, CA) HSV-2 enzyme-linked immunosorbent assay (ELISA). The test uses recombinant HSV-2 gG2 antigen to identify herpes simplex virus type-specific HSV-2 antibody.

Statistical Analysis

Univariate analyses of associations with HCV antibody status were conducted for demographic variables, sexual behaviors, and drug-related behaviors. The chi-squared and Fisher exact tests of association were used when appropriate. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported for all variables. A *P* value of <0.05 was considered statistically significant.

Multivariate analyses were restricted to non-intravenous drug-using MSM. Independent correlates associated with prevalent HCV antibody positivity were determined using backward stepwise logistic regression SAS 6.12 (SAS Institute, Cary, NC). The confidence intervals for prevalence and incidence estimates were calculated for person-years using a binomial exact distribution (STATA 6.0, College Station, TX).

Results

Study Subjects

Of 981 persons seeking repeat HIV testing during the study period, 754 (77%) were MSM, 135 (1%) were women, and 92 (9%) were heterosexual men. Fifteen (1.5%) reported a history of IDU. Table 1 presents the characteristics of persons seeking repeat anonymous HIV testing.

HCV Seroincidence

There were 576.6 person-years of observation time among the 703 subjects who had blood specimens for both HIV tests. No new HCV antibody seroconversions occurred. The HCV antibody incidence rate was 0 per 100 person-years (95% CI, 0–.6). In this same group, 6 new HSV-2 infections and 10 new HIV infections occurred for an incidence rate of 2.8 per 100 person-years (95% CI, 1.6–4.5) and 1.8 per 100 person-years (95% CI, 1.0–3.0), respectively.

HCV Seroprevalence

The prevalence of HCV antibody in the study population (n = 981) was 2.5% (95% CI, 1.7–3.7): 4.3% in heterosexual men, 3.7% in women, and 2.1% in MSM. Table 2 shows the prevalence of HCV antibody by sexual orientation and IDU. On univariate analysis, those who had a history of IDU were 33.4 (95% CI, 10.8–103.4) times more likely to be HCV antibody-positive compared with those who had no history of IDU. Among heterosexual men and women, those who had a history of IDU were 39 (95% CI, 13.4–115.9) times more likely to be HCV antibody-positive than those who had no history of IDU. However, among MSM, there was a trend for those who had a history of IDU; although not statistically significant, they were more likely to be HCV antibody positive then those who had no history of IDU (OR, 6.9; 95% CI, 0.8–60.1).

The seroprevalence of HCV antibody in those with HSV-2 antibody was 2.0% (95% CI, 0.6–5.1), whereas those without HSV-2 antibodies, the prevalence was 1.3% (95% CI, 0.5–2.7). There was no statistical difference between those infected with HSV-2 and those not infected ($P = 0.5$).

Table 3 shows selected characteristics and prevalence of HCV antibody in MSM without a history of IDU. Persons who were 50 years of age or greater were more likely to be HCV antibody-positive than those who were 18 to 29 years of age (OR, 6.6; 95% CI, 1.2–44.0). Those who were HIV-infected were more likely to be HCV antibody-positive than those who were not HIV-infected (OR, 5.4; 95% CI, 1.2–19.1). Although not statistically significant,

TABLE 3. Characteristics and HCV Antibody Prevalence in Gay Men and Other Men Who Have Sex With Men Seeking Anonymous HIV Testing, Non-Intravenous Drug Users Only, San Francisco, 1997–2000

Characteristic	Total Sample	Anti-HCV No. (%)	Unadjusted Odds Ratio (95% Confidence interval)
Total	746	15 (2.0)	
Age (yr, n = 742)*			
18–29	198	3 (1.5)	Referent
30–39	348	3 (0.9)	0.6 (.07–4.3)
40–49	142	3 (2.1)	1.4 (0.2–11.0)
50+	54	5 (9.3)	6.6 (1.2–44.0)
Race (n = 715)†			
White	591	8 (1.4)	Referent
Nonwhite	124	4 (3.2)	2.4 (0.5–9.2)
No. of sex partners in last year (n = 732)‡			
<6	286	2 (0.7)	Referent
6–10	168	9 (5.4)	8.0 (1.6–77.0)
11–50	245	4 (1.6)	2.4 (0.3–26.2)
>50	25	0 (0.0)	—
Sexual risk during testing interval			
Sex partner with IDU history			
No	718	15 (2.1)	—
Yes	28	0 (0.0)	
Unprotected anal-insertive			
No	443	9 (2.0)	Referent
Yes	303	6 (2.0)	1.0 (0.3–3.1)
Unprotected rectal anal sex			
No	517	10 (1.9)	Referent
Yes	229	5 (2.2)	1.1 (0.3–3.7)
Sexually transmitted disease diagnosis			
No	655	14 (2.1)	Referent
Yes	91	1 (1.1)	0.5 (0.01–3.4)
Sex work			
No	733	15 (2.0)	—
Yes	13	0 (0.0)	
Concomitant viral infection			
HIV-positive			
No	696	11 (1.6)	Referent
Yes	50	4 (8.0)	5.4 (1.2–19.1)
Herpes simplex virus-2 (n = 735)			
No	538	7 (1.3)	Referent
Yes	197	4 (2.0)	1.6 (0.3–6.3)
Non-intravenous drug use during testing interval			
Amphetamine			
No	698	14 (2.0)	Referent
Yes	48	1 (2.1)	1.0 (0.02–7.1)
Cocaine			
No	699	13 (1.9)	Referent
Yes	47	2 (4.3)	2.4 (0.3–10.8)
Blood/needle exposures during testing interval			
Tattoo			
No	737	14 (1.9)	Referent
Yes	9	1 (11.1)	6.5 (0.1–54.0)
Occupational			
No	728	14 (2.0)	Referent
Yes	18	1 (5.6)	3.0 (0.07–22.0)

*Chi-squared test for trend, $P = 0.01$; chi-squared test, age ≤ 50 vs. >50, $P = <0.001$.
†Those with unknown race excluded.
‡Chi-squared test for trend, $P = 0.35$.
HCV = hepatitis C virus.

an elevated odds ratio was noted for nonwhite subjects compared with white subjects. No statistically significant association was found with recent risk behaviors such as sex with an intravenous drug-using partner, unprotected insertive and receptive anal sex, sex work, receiving a tattoo, or occupational exposure to blood. Using the chi-squared test for trend, a statistically significant association was found with increasing age ($P = 0.01$) but not for number of sexual partners ($P = 0.35$).

All the variables listed in Table 2 were entered into the multivariate logistic regression models. Age 50 years or greater (OR, 8.5; 95% CI, 2.6–27.7) and HIV infection (OR, 5.7; 95% CI, 1.6–20.6) remained associated with HCV antibody positivity.

Whereas white race was found to be associated with a lower risk of HCV infection (OR, .3; 95% CI, .1–.9) than with those who were nonwhite. No interaction between race and age was found.

Discussion

This study provides estimates of HCV antibody prevalence and incidence in a population who repeatedly sought HIV counseling and testing in San Francisco. Despite having more than 575 person-years of observation in this sexually active sample and documented new sexually transmitted viral infections like HSV-2 and HIV, no cases of HCV antibody seroconversion were detected. In addition, no correlation was found between HCV antibody prevalence and recent sexual behaviors such as number of sex partners in the past year and unprotected insertive or receptive anal sex. Thus, the data support previous studies that have suggested that HCV is inefficiently spread through sexual contact.[3,12–15,17,19]

Because the overall prevalence of HCV antibody in this population was low (2.5%), it is possible that the incidence was low because the likelihood of exposure to someone infectious with HCV was uncommon. It was assumed that persons seeking anonymous HIV testing had engaged in sexual risk behaviors that placed them at risk for STDs. This was validated in the study by the presence of incident HIV and HSV-2 infections. Studies have shown that the detection of HCV in semen is uncommon, and when measurable, the viral burden is extremely low, approximately 20 to 100 copies of viral RNA per milliliter.[31] Thus, the low infectiousness of semen further supports the conclusion that the actual sexual transmission of HCV could be rare.

There were 19 persons HCV antibody-positive without a history of IDU. The route of transmission among these subjects is unknown. It could be secondary to underreported parenteral exposure or transfusion history, although safety from transfusion transmitted HCV infection has declined in the general population secondary to the safety of the blood supply.[32] Further research should be undertaken to define more accurately individual exposure to blood products or needle use.

In a simultaneous study conducted during the same period in the same MSM study population, an incidence of HSV-2 of 3.1 per 100 person-years was found.[33] In our study, MSM who acquired other STDs in the past year such as HSV-2 were not statistically more likely to acquire HCV ($P = 0.5$). The seroprevalence of HCV antibody in those with HSV-2 antibodies was 2.0%, which was similar to those without HSV-2 antibodies (prevalence = 1.3%).

The high prevalence of HCV antibody among older MSM in this study suggests an age-related cohort effect with the risk of acquiring HCV infection higher in the more distant past than recently. In addition, the prevalence of HCV antibody was higher in those who were HIV-positive. This observation supports previous studies showing an epidemiologic association between HCV and HIV infections, indicating overlapping risk behaviors like drug use or HIV infection preceding HCV exposure.[10,11,16,17,34]

There are limitations to this study. The data used to address the study objectives were collected for the purpose of risk assessment and counseling for HIV testing and not for describing the epidemiology of HCV infection. Thus, some questions such as "history of transfusion before 1985" do not address the change in policy for testing blood and blood products to prevent HCV transmission enacted in the early 1990s. There was also no question asking if participants had sex with an HCV antibody-positive partner. In addition, sex behavior questions only asked about recent behavior when more distant sexual behavior could have been associated with HCV positivity.

Self-selection limits the generalizability of this study. We examined a sample of persons seeking repeat HIV testing at anonymous HIV testing sites that might not be representative of first-time HIV testers and could have different rates of infection and/or sexual risk behaviors. The risk behavior information was self-reported and was not always collected consistently or completely. Furthermore, a large proportion of MSM are not represented, because approximately only 16% of MSM in San Francisco use anonymous testing services.[35,36]

The Centers for Disease Control and Prevention and the California Department of Health Services recommended that counseling and testing for HCV infection should be integrated into all HIV counseling testing sites, especially those associated with substance abuse treatment.[37,38] Because this study does not support sexual transmission of HCV, but demonstrates the high prevalence of HCV antibody in intravenous drug users, we agree that testing for HCV infection should be offered in populations in whom IDU is common. In San Francisco, less than 1% of the estimated 15,000 intravenous drug users use anonymous HIV testing sites.[36] Thus, intravenous drug users might not access these specific testing services, so HCV screening at these facilities would not be useful.

We recommend that HCV screening programs determine which type of facilities intravenous drug users and those with a history of IDU frequent and target testing for HCV infection at these sites. Also, it might be helpful to target people born before 1950, because in our study, these persons were at increased risk for infection. Public health dollars could be better spent by appropriately integrating testing services based on the careful evaluation of risk behaviors and the prevalence of infection with selective screening in a variety of settings, including STD clinics.[39] Studies of prevention programs for HIV and HCV infection should continue to investigate whether multi-infection screening and counseling can further impact risk reduction.[40] Finally, behavioral risk reduction for hepatitis C infection prevention will need to focus on reducing parenteral exposures through needle or intravenous drug use equipment-sharing as the sexual transmission of hepatitis C continues to appear uncommon.

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