AIDS PATIENT CARE and STDs
Volume 23, Number 11, 2009

DOI: 10.1089/apc.2009.0111

Factors Associated with Prevalent Hepatitis C Infection Among HIV-Infected Women with No Reported History of Injection Drug Use: The Women's Interagency HIV Study (WIHS)

Toni Frederick, Ph.D.,[1] Pamela Burian, P.A.-C.,[2] Norah Terrault, M.D.,[4] Mardge Cohen, M.D.,[5] Michael Augenbraun, M.D.,[6] Mary Young, M.D.,[7] Eric Seaberg, Ph.D.,[8] Jessica Justman, M.D.,[9] Alexandra M. Levine, M.D.,[2] Wendy J. Mack, Ph.D.,[3] and Andrea Kovacs, M.D.[1]

Abstract

Although the primary mode of hepatitis C virus (HCV) transmission is exposure to blood products or injection drug use (IDU), studies have found varying independent risk factors for HCV infection among persons with no history of IDU or exposure to blood products. For HIV-infected women, sexual transmission may be another potential source of HCV infection. HIV-infected and HIV-negative women at risk for HIV enrolled in the Women's Interagency HIV Study (WIHS) during October 1994 to November 1995 and again between October 2001 and November 2002 were studied. Clinical and demographic factors associated with HCV seroprevalence were assessed in multivariate logistic regression models controlling for history of blood transfusion and IDU. Among 3636 women with HCV results, 31.5% were HCV antibody positive (HCV+) including 13.5% with no reported history of IDU or blood transfusions. Multivariate logistic regression analyses stratified on IDU showed that among women with no history of IDU, sex with an IDU male was independently associated with HCV positivity (odds ratio [OR] = 2.8, 95% confidence [CI] = 2.1, 3.8, $p < 0.0001$) after controlling for blood transfusion, age, HIV infection, unemployment, birth in the United States, history of hepatitis B infection, and current smoking status. Further stratification on HIV status showed that the association was significant only for the HIV+ (OR = 1.9, 95% CI = 1.3, 2.7, $p = 0.0007$) compared to the HIV− women (OR = 1.1, 95% CI = 0.4, 2.7) although these odds ratios were not significantly different ($p = 0.25$). For HIV-positive women with no reported history of IDU, sex with an IDU male was independently associated with HCV suggesting that sexual transmission may be an important mode of HCV transmission for these high-risk women.

Introduction

In the United States, an estimated 4.1 million people (1.6% of the population) are infected with hepatitis C virus (HCV).[1] Although the predominant modes of HCV transmission are through exposure to blood or blood products and injection drug use (IDU), there are studies suggesting that sexual transmission can occur in 5%–20%[2,3] of those who are HCV infected and deny any history of blood transfusion or IDU. Various independent risk factors for nonparenteral HCV transmission among those denying a history of IDU include snorting cocaine, crack use, low socioeconomic status, herpes simplex virus (HSV)-2 infection, frequent alcohol use, tattooing/body piercing, gonorrhea, HIV infection, as well as high-risk sexual activity.[4–10] However, it has been difficult to assess HCV infection transmission via nonparenteral routes,

[1]Maternal-Child and Adolescent Center for Infectious Diseases and Virology, [2]Department of Medicine, Division of Hematology, [3]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California.
[4]Division of Gastroenterology, University of California at San Francisco, San Francisco, California.
[5]Cook County Medical Center, Chicago, Illinois.
[6]State University at Downstate Medical Center, Brooklyn, New York.
[7]Georgetown University School of Medicine, Washington, D.C.
[8]Johns Hopkins School of Public Health, Baltimore, Maryland.
[9]Bronx-Lebanon Hospital Center, Bronx, New York.

especially sexual transmission, because of shared risk factors among individuals at risk for HCV infection.

The importance of sexual transmission in HCV transmission is controversial. Studies of monogamous sex partners of patients with HCV viremia and chronic liver disease show infrequent transmission.[11] While there are documented cases of acute HCV infection among non-drug–using men who have sex with men (MSM),[12–18] the ongoing Omega Cohort Study estimated that HCV sexual transmission among MSM is rare.[19] However, evidence for sexual transmission of HCV has been shown in several types of studies including prevalence studies in attendees of sexually transmitted disease (STD) clinics, investigation of cases identified from surveillance reports, and cross-sectional and longitudinal partner studies.[1,9,20–22] Many of these studies have been limited by small size, lack of uninfected controls, and difficulty excluding other routes of transmission. While the role of sexual transmission has been examined in a growing number of diverse populations including urban populations, veterans, individuals attending STD clinics, and homosexual men, none have evaluated a large sample of HIV-infected and HIV-negative women with similar risk histories.

We examined factors associated with HCV antibody positivity among a large sample of HIV-infected (HIV+) and HIV-uninfected (HIV−) women with similar risk who were evaluated for HCV infection. The development of a more complete profile of factors contributing to HCV transmission may assist in further clinical and preventive efforts for both HIV-infected and -uninfected women at high risk for HIV infection.

Materials and Methods

Study population

The Women's Interagency HIV Study (WIHS) is a multicenter, prospective study of the natural history of HIV-1 infection and associated diseases in women. A detailed description of the study population has been published. [23] Women were recruited from six national sites (Los Angeles, San Francisco, Chicago, two sites from New York City, and Washington, D.C.) from HIV clinics, street outreach, referral from other studies, and word of mouth. A total of 3766 women were enrolled. Seventy percent (2623) were enrolled between October 1994 and November 1995 and an additional 1143 were enrolled between October 2001 and November 2002. Women were interviewed and clinical and laboratory evaluations performed at baseline and then prospectively every 6 months.

Data collection

Women were interviewed at baseline using standardized questionnaires that included questions regarding demographics, reported history of IDU, non-IDU, history of blood transfusion, sexual behaviors, alcohol practices, and medical history including self-reported history of sexually transmitted diseases. IDU in the past 6 months was asked at baseline and at each 6-month follow-up visit.

Participants were screened at baseline for presence of HIV at local clinical laboratories using contemporaneous commercial enzyme immunoassay (EIA) kits. HCV antibody testing was performed using Abbott EIA 2.0 and 3.0 assays (Abbott Laboratories, Abbott Park, IL). For 96% of the HCV-positive women in this study, HCV RNA levels at baseline were measured in a single laboratory (A.K., USC) using polymerase chain reaction (Roche Diagnostics, Branchburg, NJ). [24] Women with undetectable HCV RNA were retested by HCV 3.0 EIA (Ortho Diagnostics, Rochester, NY) and all results with S/CO less than 3.9 were confirmed by RIBA 3.0 (Chiron, Emeryville, CA). Overall, 96% of the HCV+ women in our study were confirmed positive. A hepatitis B profile that included hepatitis B surface antigen (HBsAg), anticore, and antisurface antibody was also measured at baseline. History of ever having hepatitis B infection was defined as the presence of HBsAg or core antibody.

Statistical analysis

Sociodemographic, behavioral, and health status variables were examined for their association with HCV antibody status at baseline for the total population and stratified on reported history of IDU using χ^2 analyses. Among those with no IDU, variables associated with HCV status at $p < 0.10$ in unadjusted analyses were evaluated in a multivariate logistic regression model. Variables with $p < 0.05$ were retained in the reduced model. Each variable dropped from the multivariate model was brought back into the reduced model to test for significance. All of the variables in the final reduced model were evaluated for their interaction with HIV status (at $p < 0.05$ level) to test if associations differed in HIV+ and HIV− women. The final reduced model was run separately for HIV+ and HIV− women. The data were also analyzed using HCV viremia as the outcome variable with the nonviremic women removed; these analyses yielded similar associations with the variables of interest. Associations are expressed as prevalence odds ratios (OR) and 95% confidence intervals (CI). SAS statistical software (version 9; SAS Institute, Cary, NC) was used to conduct these analyses.

Results

Study subjects

Among the 3766 women enrolled in WIHS, 3648 (97%) had a baseline HCV antibody result, confirmed HIV antibody status, and baseline IDU data. During the follow-up period (median 4 years), 12 women with no reported history of IDU at the baseline visit reported IDU at a follow-up visit. These 12 women did not differ from the total population by HIV status, age or HCV status. However, to minimize possible misclassification of the non-IDU group, these 12 women were excluded so that a total of 3636 women were included in these analyses. Demographic and clinical characteristics of the study population are shown in Table 1. Most women were HIV-infected (74%), less than 36 years of age (51%), and nonwhite (85%). Almost a third reported a history of IDU at baseline.

Prevalence of HCV+

The prevalence of HCV antibody positive (HCV+) status for the overall population was 31.5% ($n = 1145$) including 154 (13.5%) with no reported history of IDU or blood transfusions. The prevalence was highest among the women with both IDU and a blood transfusion (90.8%) and lowest among women with no IDU or blood transfusions (6.5%) with percentages in

Table 1. Baseline Characteristics of Study Participants

Characteristic	*No. (%) of study participants (n = 3636)*	
Age (in years)		
≤35	1840	(50.6)
>35	1796	(49.4)
HIV status		
HIV negative	933	(25.7)
HIV positive	2703	(74.3)
Unemployed		
Yes	2655	(73.0)
No	974	(26.8)
Missing	7	(0.2)
Annual income		
≤$12,000	2109	(58.0)
>$12,000	1413	(38.9)
Missing	114	(3.1)
Race/ethnicity		
White	541	(14.9)
Black	2104	(57.9)
Hispanic	869	(23.9)
Others	122	(3.4)
Country of birth		
United States	2964	(81.5)
Others	668	(18.4)
Missing	4	(0.1)
Education		
High school or more	2256	(62.0)
Less than high school	1365	(37.6)
Missing	15	(0.4)
Traded sex for drugs or money		
Never	2409	(66.0)
Ever	1226	(33.6)
Missing	13	(0.4)
Alcohol use		
Abstainer	1622	(44.5)
Light (<3 drinks per week)	1079	(29.7)
Moderate (3–13 drinks per week)	566	(15.6)
Heavy (14 or more drinks per week)	292	(8.0)
Missing	81	(2.2)
Current smoking		
No	1720	(47.3)
Yes	1903	(52.4)
Missing	12	(0.3)
History of blood transfusion		
No	3295	(90.7)
Yes	341	(9.4)
History of injection drug use		
No	2522	(69.4)
Yes	1114	(30.6)

between for those with only IDU (85%) or only blood transfusion (20%).

Factors associated with prevalent HCV+ status: unadjusted models

Table 2 summarizes, in unadjusted models, factors associated with HCV+ status for the total population and stratified by IDU. Among both IDU and non-IDU women, history of blood transfusion, being HIV+, older age, unemployment, smoking, gonorrhea, syphilis, and history of hepatitis B were significantly positively associated with HCV+ status. In women who reported IDU, lower education, exchanging sex for drugs or money, and black and Hispanic race/ethnicity (compared to white) were significantly positively associated with HCV+. In women without reported IDU, additional factors significantly associated with HCV+ status were birth in the United States and sex with an IDU male.

Factors associated with HCV+ in non-IDU women: adjusted models

Among women with no IDU, multivariate logistic regression analyses were performed (total group and stratified by HIV status) using those variables associated with prevalent HCV infection in the non-IDU strata with $p < 0.10$ (Table 2). For the total group, factors that remained independently ($p < 0.05$) associated with HCV infection were HIV infection, age greater than 35 years, hepatitis B infection, birth in the United States, unemployment, blood transfusion, current smoking, and sex with an IDU male (OR = 1.8, CI = 1.3, 2.5; Table 3). Variables that were not significant in multivariate modeling were annual income, education, crack, cocaine and heroin use, gonorrhea and syphilis. Each of these variables was brought back into the model one at a time, but none were statistically significant.

In logistic regression analyses stratified on HIV status, all independent variables that were significantly associated with HCV in the total group were also significant in multivariate modeling for the HIV+ women. CD4 lymphocyte count ≤200 cells/mm^3 compared to >200 cells/mm^3 was included in this model and was marginally significant (OR = 1.4, CI = 1.0, 2.1). While the ORs for association were in the same direction and of similar magnitude in HIV− and HIV+ women, statistical significance was reached in HIV− women only for age greater than 35 years and hepatitis B infection. None of the tests for interaction between HIV status and the variables in the final reduced model showed statistically significant differences in the ORs between the HIV+ and HIV− strata. The association of HCV status and sex with an IDU male was of greater magnitude in the HIV+ women (OR = 1.9, 95% CI = 1.3, 2.7, $p = 0.0007$) compared to HIV− women (OR = 1.1, 95% CI = 0.4, 2.7) although these associations were not significantly different ($p = 0.25$).

Discussion

In this large sample of HIV-infected and high-risk HIV-uninfected women, we found that among women who self-reported no history of IDU, sex with an IDU male was independently associated with prevalent HCV infection after controlling for receipt of blood transfusion, older age, unemployment, smoking, birth in the United States, and hepatitis B infection. This effect was statistically significant only for the HIV-infected although no statistically significant interaction was noted. While this study is cross-sectional, it is possible that HIV infection may play a role in increasing the likelihood of HCV sexual transmission because of a compromised immune system in the setting of continued high-risk sexual behaviors.

In this study group, the prevalence of HCV infection among women with no reported history of IDU or receipt of blood transfusion was 6.5% (3.6% for the HIV− and 7.7% for the HIV+). Because of the large proportion of HIV-infected

Table 2. Hepatitis C Antibody Positive (hcv+) by Baseline Characteristics for Total Population and by Reported History of Baseline Injection Drug use

	All participants n = *3636*					*With a history of IDU* n = *1114*					*With no history of IDU* n = *2522*				
		HCV+					*HCV+*					*HCV+*			
Characteristic	*Total*	*No.*	*(%)*	*Odds ratio (95% CI)*	p *value*	*Total*	*No.*	*(%)*	*Odds ratio (95% CI)*	p *value*	*Total*	*No.*	*(%)*	*Odds ratio (95% CI)*	p *value*
HIV status															
Negative	933	188	(20)	1.0		225	160	(71)	1.0		708	28	(4)	1.0	
Positive	2703	957	(35)	2.2 (1.8, 2.6)	<0.0001	889	798	(90)	3.6 (2.5, 5.1)	<0.0001	1814	159	(9)	2.3 (1.5, 3.5)	<0.0001
Age (years)															
≤35	1840	280	(15)	1.0		288	212	(74)	1.0		1552	68	(4)	1.0	
>35	1796	865	(48)	5.2 (4.4, 6.1)	<0.0001	826	746	(90)	3.3 (2.4, 4.7)	<0.0001	970	119	(12)	3.1 (2.2, 4.2)	<0.0001
Unemployed															
No	974	143	(15)	1.0		151	111	(74)	1.0		823	32	(4)	1.0	
Yes	2655	995	(37)	3.5 (2.9, 4.2)	<0.0001	956	840	(88)	2.6 (1.7, 3.9)	<0.0001	1699	155	(9)	2.5 (1.7, 3.7)	<0.0001
Missing	7														
Annual income															
>$12,000	1413	310	(22)	1.0		296	249	(84)	1.0		1117	61	(5)	1.0	
≤$12,000	2109	798	(38)	2.2 (1.9, 2.5)	<0.0001	778	676	(87)	1.3 (0.9, 1.8)	0.24	1331	122	(9)	1.7 (1.3, 2.4)	0.0005
Missing	114														
Race															
White	541	201	(37)	1.0		233	182	(78)	1.0		308	19	(6)	1.0	
Black	2104	685	(33)	0.8 (0.7,1.0)	0.04	620	556	(90)	2.4 (1.6, 3.6)	<0.0001	1484	129	(9)	1.4 (0.9, 2.4)	0.15
Hispanic	869	234	(27)	0.6 (0.5,0.8)	<0.0001	231	199	(86)	1.7 (1.1, 2.8)	0.03	638	35	(5)	0.9 (0.5, 1.6)	0.67
Other	122	25	(20)	0.4 (0.3,0.7)	0.0006	30	21	(70)	0.7 (0.3, 1.5)	0.32	92	4	(4)	0.7 (0.2, 2.1)	0.51
Country of birth															
Outside United States	668	39	(6)	1.0		25	19	(76)	1.0		643	20	(3)	1.0	
United States	2964	1104	(37)	9.6 (6.9,13.3)	<0.0001	1087	937	(86)	2.0 (0.8, 5.0)	0.14	1877	167	(9)	3.0 (1.9, 4.9)	<0.0001
Missing	4														
Education															
High school or more	2256	641	(28)	1.0		641	531	(83)	1.0		1615	110	(7)	1.0	
<High school	1365	504	(37)	1.5 (1.3,1.7)	<0.0001	473	427	(90)	1.9 (1.3, 2.8)	0.0004	892	77	(9)	1.3 (1.0, 1.8)	0.10
Missing	15														
History of blood transfusion															
No	3295	954	(29)	1.0		940	800	(85)	1.0		2355	154	(7)	1.0	
Yes	341	191	(56)	3.1 (2.5, 3.9)	<0.0001	174	158	(91)	1.7 (1.0, 3.0)	0.05	167	33	(20)	3.5 (2.3, 5.3)	<0.0001
Traded sex for drugs or money															
No	2402	498	(21)	1.0		432	358	(83)	1.0		1970	140	(7)	1.0	
Yes	1221	644	(53)	4.3 (3.7, 5.0)	<0.0001	679	597	(88)	1.5 (1.1, 2.1)	0.02	542	47	(9)	1.2 (0.9, 1.8)	0.22
Hepatitis B positive															
No	2315	342	(15)	1.0		316	227	(72)	1.0		1999	115	(6)	1.0	
Yes	1321	803	(61)	8.9 (7.6, 10.5)	<0.0001	798	731	(92)	4.3 (3.0, 6.1)	<.0001	523	72	(14)	2.6 (1.9, 3.6)	<0.0001
Alcohol use (drinks/week)															
Abstainer	1618	522	(32)	1.0		521	448	(86)	1.0		1097	74	(7)	1.0	
Light (<3)	1079	237	(22)	0.6 (0.5, 0.7)	<0.0001	214	181	(85)	0.9 (0.6, 1.4)	0.62	865	56	(6)	1.0 (0.7, 1.4)	0.81
Moderate (3–13)	566	199	(35)	1.1 (0.9, 1.4)	0.21	193	164	(85)	0.9 (0.6, 1.5)	0.73	373	35	(9)	1.4 (0.9, 2.2)	0.09
Heavy (>13)	292	155	(53)	2.4 (1.8, 3.1)	<0.0001	159	141	(89)	1.3 (0.7, 2.2)	0.38	134	15	(11)	1.6 (1.0, 3.0)	0.11
Missing	81														

Current smoker															
No	1720	271	(16)	1.0		242	193	(80)	1.0		1478	78	(5)	1.0	
Yes	1904	872	(46)	4.5 (3.9, 5.3)	<0.0001	870	763	(88)	1.8 (1.2, 2.6)	0.002	1034	109	(11)	2.1 (1.6, 2.9)	<0.0001
Missing	12														
Marijuana/hash use															
No	2735	839	(31)	1.0		789	695	(88)	1.0		1946	144	(7)	1.0	
Yes	886	302	(34)	1.2 (1.0, 1.4)	0.06	320	259	(81)	0.6 (0.4, 0.8)	0.002	566	43	(8)	1.0 (0.7, 1.5)	0.87
Missing	15														
Crack use															
No	3030	797	(26)	1.0		764	641	(84)	1.0		2266	156	(7)	1.0	
Yes	594	346	(58)	3.9 (3.3, 4.7)	<0.0001	348	315	(91)	1.9 (1.2, 2.9)	0.003	246	31	(13)	2.0 (1.3, 2.9)	0.001
Missing	12														
Cocaine use															
No	3188	869	(27)	1.0		835	704	(84)	1.0		2353	165	(7)	1.0	
Yes	436	274	(63)	4.5 (3.7, 5.6)	<0.0001	277	252	(91)	2.0 (1.3, 3.1)	0.006	159	22	(14)	2.1 (1.3, 3.4)	0.002
Missing	12														
Heroin use															
No	3250	841	(26)	1.0		780	660	(85)	1.0		2470	181	(7)	1.0	
Yes	374	302	(81)	12 (9.2, 15.7)	<0.0001	332	296	(89)	1.5 (1.0, 2.2)	0.05	42	6	(14)	2.1 (0.9, 5.1)	0.09
Missing	12														
Lifetime male sex partners															
0–4	827	159	(19)	1.0		130	114	(88)	1.0		697	45	(6)	1.0	
5–10	1073	301	(28)	1.6 (1.3, 2.0)	<0.0001	276	231	(84)	0.7 (0.4, 1.3)	0.29	797	70	(9)	1.4 (1.0, 2.1)	0.09
11–35	788	229	(29)	1.7 (1.4, 2.2)	<0.0001	236	196	(84)	0.7 (0.4, 1.4)	0.36	555	33	(6)	0.9 (0.6, 1.5)	0.71
36+	889	419	(47)	3.7 (3.0, 4.7)	<0.0001	441	384	(87)	0.9 (0.5, 1.7)	0.85	448	35	(8)	1.2 (0.8, 1.9)	0.38
Missing	59														
Ever had gonorrhea															
No	2563	651	(25)	1.0		631	527	(84)	1.0		1932	124	(6)	1.0	
Yes	1044	481	(46)	2.5 (2.2, 2.9)	<0.0001	470	418	(89)	1.7 (1.1, 2.3)	0.01	574	63	(11)	1.8 (1.3, 2.5)	0.0003
Missing	29														
Ever had syphilis															
No	2985	840	(28)	1.0		823	692	(84)	1.0		2162	148	(7)	1.0	
Yes	623	291	(47)	2.2 (1.9, 2.7)	<0.0001	277	252	(91)	1.9 (1.2, 3.0)	0.005	346	39	(12)	1.7 (1.2, 2.5)	0.004
Missing	28														
Ever had sex with HIV+ male															
No	2248	665	(30)	1.0		640	557	(87)	1.0		1608	108	(7)	1.0	
Yes	1179	392	(33)	1.2 (1.0, 1.4)	0.03	385	323	(84)	0.8 (0.5, 1.1)	0.16	794	69	(9)	1.3 (1.0, 1.8)	0.08
Missing	209														
Ever had sex with IDU male															
No	2074	299	(14)	1.0		242	203	(84)	1.0		1832	96	(5)	1.0	
Yes	1481	826	(56)	7.5 (6.4, 8.8)	<0.0001	857	742	(87)	1.2 (0.8, 1.8)	0.29	624	84	(14)	2.8 (2.1, 3.8)	<0.0001
Missing	81														

IDU, injection drug use.

Table 3. Variables Associated with Hepatitis C Antibody Positive in Reduced Multivariate Logistic Regression Models for Women with No Reported Injection Drug Use by HIV Status

	All participants n = *2522*		*HIV+* n = *1814*						*HIV−* n = *708*					
	Adjusted[a]		*HCV+*		*Unadjusted*		*Adjusted*		*HCV+*		*Unadjusted*		*Adjusted*	
Variable	*odds ratio (95% CI)*	p *value*	*No.*	*%*	*odds ratio (95% CI)*	p *value*	*odds ratio (95% CI)*	p *value*	*No.*	*%*	*odds ratio (95% CI)*	p *value*	*odds ratio (95% CI)*	p *value*
HIV status														
Negative	1.0													
Positive	1.9 (1.2, 2.9)	0.005				NA						NA		
Age (years)														
≤35	1.0		57	5.3	1.0				11	2.3	1.0		1.0	
>35	2.3 (1.7, 3.2)	<0.0001	102	13.8	2.8 (2.0, 4.0)	<0.0001	2.2 (1.6, 3.2)	<0.0001	17	7.5	3.4 (1.6, 7.5)	0.001	2.5 (1.1, 5.6)	0.03
History of blood transfusion														
No	1.0		129	7.7	1.0				25	3.6	1.0		1.0	
Yes	2.1 (1.4, 2.7)	0.001	30	20.7	3.1 (2.0, 4.8)	<0.0001	2.1 (1.2, 3.3)	0.003	3	13.6	4.2 (1.2, 15.0)	0.02	2.7 (0.7, 11.1)	0.25
Country of birth														
Outside United States	1.0		17	3.5	1.0				3	1.9	1.0		1.0	
United States	2.0 (1.2, 3.3)	0.008	142	10.7	3.3 (2.0, 5.5)	<0.0001	2.0 (1.1, 3.5)	0.02	25	4.5	2.4 (0.7, 8.2)	0.14	1.6 (0.5, 5.8)	0.45
Hepatitis B positive														
No	1.0		97	7.0	1.0				18	2.9	1.0		1.0	
Yes	2.0 (1.4, 2.7)	<0.0001	62	14.4	2.2 (1.6, 3.1)	<0.0001	1.9 (1.3, 2.7)	0.009	10	11	4.1 (1.8, 9.2)	0.0002	2.9 (1.3, 6.9)	0.01
Employed														
Yes	1.0		25	4.6	1.0				7	2.5	1.0		1.0	
No	1.9 (1.3, 2.9)	0.002	134	10.6	2.5 (1.6, 3.8)	<0.0001	1.7 (1.0, 2.7)	0.0045	21	4.9	2.0 (0.8, 4.7)	0.12	1.4 (0.6, 3.5)	0.45
Sex with IDU male														
No	1.0		76	6.0	1.0				20	3.5	1.0		1.0	
Yes	1.8 (1.3, 2.5)	0.0006	76	15.3	2.8 (2.0, 4.0)	<0.0001	1.9 (1.3, 2.7)	0.0007	8	6.3	1.8 (0.8, 4.3)	0.001	1.1 (0.4, 2.7)	0.84
Current smoking														
No	1.0		70	6.3	1.0				8	2.2	1.0		1.0	
Yes	1.5 (1.0, 2.1)	0.03	89	12.9	2.2 (1.6, 3.1)	<0.0001	1.6 (1.1, 2.2)	0.02	20	5.8	2.7 (1.2, 6.3)	0.01	1.6 (0.6, 4.0)	0.33
CD4 cells/mm^3														
>200			101	7.5	1.0									
≤200	NA		55	12.6	1.8 (1.2, 2.5)	0.001	1.4 (1.0, 2.1)	0.07			NA			

[a]Variables included in the model that were not significant were annual income, education, crack, cocaine, and heroin use, gonorrhea and syphilis.
NA, not applicable.

women in our study with high-risk behaviors for both HIV and HCV infection, this prevalence is higher than has been reported for other high risk groups such as patients at two large STD clinics in Canada (3.4%), a sample of sexually active, nontransfused, inner-city women with no evidence of IDU (1.6%), and among women residing in low-income neighborhoods of northern California (2.5%).[1,8,25]

In the United States, it is estimated that IDU accounts for approximately 60% of HCV transmissions, blood transfusion for less than 5%, sexual exposures approximately 10%–20%, other exposures 10%, with 10% due to unidentified sources of infection.[2] In our cohort of HCV positive women, 86.5% reported exposure through parenteral routes leaving 13.5% potentially due to other exposures, including sexual transmission.

Consistent with other studies, we showed that risk-taking behaviors including history of drug use (including crack, cocaine, and heroin), smoking, drinking, and high-risk sex (trading sex for drugs or money, sex with an HIV-positive male, more lifetime sexual partners and STDs) were associated with a higher prevalence of HCV infection.[7,10,25–28] A recent study of risk factors associated with acute HCV infection found that 11 of 13 cases with unknown mode of transmission reported high-risk sexual behavior.[29] While it has been demonstrated among married couples with one HCV-infected member that HCV sexual transmission is not efficient,[30] molecular epidemiologic studies have nonetheless shown that HCV RNA can be detected in the semen of HCV viremic men, and men coinfected with HIV are more likely to have HCV RNA detected in the semen than men with only HCV infection.[15,31–33] Only further studies using experimental infection in a cell culture system or an animal model would prove that HCV RNA positivity in semen reflects the presence of infectious virus.

Further study of the sexual practices of women with HIV and at risk for HIV may shed light on potential mechanisms of sexual transmission of HCV. Like HIV, STDs may increase the risk of HCV transmission through ulcerative lesions, providing a portal of entry for HCV. Anal sex, intercourse during menstruation, and sex with physical trauma may also provide avenues for enhanced sexual transmission of HCV through exposure to blood. Among HIV-infected MSM, it has been suggested that high-risk sexual practices including anal fisting and sex in the presence of ulcerative coinfections are associated with HCV acquisition and may have fueled recent HCV outbreaks in this subgroup of MSM.[34,35] These same mechanisms may be important for HCV transmission among HIV-infected women engaging in high-risk sexual practices.[36]

Our study supports earlier findings of Hershow[37] et al. in 1998 who evaluated a subgroup of the WIHS cohort ($n = 296$) and found as we did that while IDU was the strongest predictor of HCV infection, sexual risk factors were also independently associated. Our analyses expand on their work by examining the entire WIHS group. While Hershow found only a marginally significant effect of HIV status, we found a statistically significant effect of HIV status for both those with and without IDU.

Because IDU was defined by self-report, it is possible that some women classified as non-IDU chose not to report their own IDU. We attempted to minimize this possible misclassification by excluding 12 women who reported no baseline IDU but later reported IDU at a subsequent WIHS visit. Analysis of the WIHS longitudinal data through 2004 showed overall consistency in reporting of IDU over time. Only 0.5% (12/2522) of the non-IDU women at baseline reported IDU during a follow-up visit compared to 39% of those with IDU at baseline. Of these 12 women, four reported IDU within 1 year of the baseline visit, two within 2 years, and the remaining six reported IDU 5 or more years after the baseline visit. While these 12 women did not differ from the total population by HIV status, age or HCV status, they were removed from the analysis because of the potential for misclassification of their baseline IDU status. Prior studies have also shown that self-reported information from WIHS participants correlates with appropriate biologic markers.[38]

While IDU women are known to partner with IDU men, studies of sexual behaviors of IDU men have found that they commonly choose non-IDU women as their sex partners.[39,40] Neaigus et al. have recently shown that HIV-infected injecting and non-injecting male drug users were more likely to have lower risk sexual partners (HIV- and non-IDU) than high-risk partners, creating a potential bridge for STDs diseases from a high-prevalence to a low-prevalence population.[41]

Consistent with other studies we found that HCV was associated with older age, birth in the United States, level of education, poverty, hepatitis B infection, and being HIV-infected.[1,10,25–27] Being unemployed has not previously been reported as a factor associated with HCV, although low socioeconomic status and poverty have been described as risk factors.[8,18,25,28] It is possible that being unemployed may be related to poor health and greater risk-taking behaviors and thus a greater susceptibility to acquiring HCV through both parenteral and nonparenteral means. Further work is needed to determine the specific types of sexual activity that might predispose to HCV transmission.

Limitations of this study include the potential for underreporting STDs, risk behaviors and recall bias, particularly regarding IDU, STDs, and sexual behaviors. Our study did not address specific sexual habits that may increase HCV transmission risk as well as other possible risk factors for transmission, including sharing of razors or toothbrushes, receipt of tattoos, or body piercings. Data regarding cohabitation where these issues could have been explored were not collected in WIHS. Similarly, data were not collected regarding the sharing of straws or other devices to snort drugs, which have been hypothesized as potential mechanisms for HCV transmission through hyperemic and traumatized nasal mucosa. Importantly, this was a cross-sectional analysis of prevalent HCV infection and thus, no conclusions can be made about the risk factors for acquiring HCV infection over time. In IDU populations, the time since first injection is frequently used to judge length of HCV infection because HCV transmission risk is high due to very high blood HCV levels. However, similar assumptions cannot be made with sexual transmission as the risk following sexual exposure is much lower than following blood exposure, most probably since genital HCV levels are very low or undetectable.[42,43] Finally, another limitation of the study is the possible underestimation of HCV among the HIV-positive women because of the higher rate of false-negative HCV antibody tests in this population, particularly those with IDU and CD4 cell counts <200 cells/mm^3.[44,45]

While in the United States HCV infection due to blood transfusions is diminishing due to blood screening, HCV is

still a major public health concern. Use of injection and non-injection drugs is still a major problem and is associated with trading sex for drugs or money and engaging in risky sexual behaviors. Concerns about the higher HCV prevalence and increasing HIV rates in Hispanics, who are the fastest growing ethnic minority group in the United States, should alert public health officials to the importance of the potential for sexual transmission of HCV.[46] Similarly, in the United States, HCV prevalence rates are highest for non-Hispanic black men between 40–49 years of age raising concern about the potential transmission of HCV to their sexual partners who might engage in high-risk sexual behaviors.[1]

In conclusion, our study demonstrates an overall HCV prevalence of 6.5% among HIV-infected and high-risk HIV-negative women without a history of IDU or receipt of blood transfusions. In multivariate analyses, older age, birth in the United States, unemployment, hepatitis B, HIV coinfection, and sex with an IDU were associated with HCV infection. Further study of other factors that may increase HCV transmission may provide important information regarding the mechanisms of HCV transmission and how to prevent such transmissions among HIV-infected women with multiple risk factors.

Acknowledgments

This study was supported by grant RO1 AI052065 (A.K.) from the National Institute of Allergy and Infectious Diseases. Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS) Collaborative Study Group with centers (Principal Investigators) at New York City/Bronx Consortium (Kathryn Anastos); Brooklyn, NY (Howard Minkoff); Washington, D.C. Metropolitan Consortium (Mary Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt); Los Angeles County/Southern California Consortium (Alexandra Levine); Chicago Consortium (Mardge Cohen); Data Coordinating Center (Stephen Gange). The WIHS is funded by the National Institute of Allergy and Infectious Diseases with supplemental funding from the National Cancer Institute, and the National Institute on Drug Abuse (UO1-AI-35004, UO1-AI-31834, UO1-AI-34994, UO1-AI-34989, UO1-AI-34993, and UO1-AI-42590). Funding is also provided by the National Institute of Child Health and Human Development (grant UO1-HD-23632) and the National Center for Research Resources (grants MO1-RR-00071, MO1-RR-00079, MO1-RR-00083). Funding is also provided by the National Institute of Child Health and Human Development (grant UO1-HD-23632) and the National Center for Research Resources (grants MO1-RR-00071, MO1-RR-00079, MO1-RR-00083).

Author Disclosure Statement

No competing financial interests exist.

References

1. Armstrong L, Wasley A, Simard E, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144:705–714.
2. Alter M. Hepatitis C virus infection in the United States. J Hepatol 1999;31:88–91.
3. Pradat P, Trepo C. HCV: Epidemiology, modes of transmission and prevention of spread. Baillieres Best Pract Res Clin Gastroenterol 2000;14:201–210.
4. Rooney G, Gilson RJ. Sexual transmission of hepatitis C virus infection. Sex Transm Infect 1998;74:399–404.
5. Smikle M, Dowe G, Hylton-Kong T, et al. Hepatitis B and C viruses and sexually transmitted disease patients in Jamaica. Sex Transm Infect 2001;77:295–296.
6. Thomas D, Cannon R, Shapiro C, et al. Hepatitis C, hepatitis B, and human immunodeficiency virus infections among non-intravenous drug-using patients attending clinics for sexually transmitted diseases. J Infect Dis 1994;169:990–995.
7. Feldman J, Minkoff H, Landesman S, et al. Heterosexual transmission of Hepatitis C, Hepatitis B, and HIV-1 in a sample of inner city women. Sex Transm Dis 2000;27:338–342.
8. Romanowski B, Preiksaitis J, Campbell P, et al. Hepatitis C seroprevalence and risk behaviors in patients attending sexually transmitted disease clinics. Sex Transm Dis 2003; 30:33–38.
9. Terrault NA. Sexual activity as a risk factor for hepatitis C. Hepatology 2002;36:S99–S105.
10. Weisbord J, Tarepka J, Zhang G, et al. Prevalence of and risk factors for hepatitis C virus infection among STD clinic clientele in Miami, Florida. Sex Transm Infect 2003;79:58.
11. Neumayr G, Propst A, Schwaighofer H, et al. Sexual transmission of Hepatitis C. Hepatitis C Information Central. 2007. www.hepatitis-central.com/mt/archives/2007/04/heterosexual_mo.html (Last accessed February 16, 2009).
12. Ruys TA, den Hollander JG, Beld MG, et al. Sexual transmission of hepatitis C in homosexual men. Ned Tijdschr Geneeskd 2004;148:2309–2312.
13. Danta M, Brown D, Bhagani S, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviors. AIDS 2007; 21:983–991.
14. van de Laar T, Pybus O, Bruisten S, et al. Evidence of a large, international network of HCV transmission HIV-positive men who have sex with men. Gastroenterology 2009;136: 1609–1617.
15. Briat A, Dulioust E, Galimand J, et al. Hepatitis C virus in the semen of men co-infected with HIV-1: Prevalence and origin. AIDS 2005;19:1827–1835.
16. Serpaggi J, Chaix ML, Batisse D, et al. Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-1–infected men and inefficacy of early antiviral therapy. AIDS 2006;20:233–240.
17. Gilleece YC, Browne RE, Asboe D, et al. Transmission of hepatitis C virus among HIV-positive homosexual men and response to a 24-week course of pegylated interferon and ribavirin. J Acquir Immune Defic Syndr 2005;40:41–46.
18. Browne R, Asboe D, Gilleece Y, et al. Increased numbers of acute hepatitis C infections in HIV positive homosexual men: Is sexual transmission feeding the increase? Sex Transm Infect 2004;80:326–327.
19. Alary M, Joly J, Vincelette J, et al. Lack of evidence of sexual transmission of Hepatitis C virus in a prospective cohort study of men who have sex with men. Am J Public Health 2005;95:502–505.
20. Salleras L, Bruguera M, Vidal J, et al. Importance of sexual transmission of hepatitis C virus in seropositive pregnant women: A case-control study. J Med Virol 1997;52:164–67.
21. Marx MA, Murugavel KG, Tarwater PM, et al. Association of hepatitis C virus infection with sexual exposure in southern India. Clin Infect Dis 2003;37:514–520.

22. Thomas DL, Zenilman JM, Alter HJ, et al. Sexual transmission of hepatitis C virus among patients attending sexually transmitted diseases clinics in Baltimore—An analysis of 309 sex partnerships. J Infect Dis 1995;171:768–775.
23. Barkan SE, Melnick SL, Preston-Martin S, et al. The Women's Interagency HIV Study. Epidemiology 1998;9:117–25.
24. Operskalski EA, Mack WJ, Strickler HD et al. Factors associated with hepatitis C viremia in a large cohort of HIV-infected and -uninfected women. J Clin Virol 2008;41: 255–263.
25. Page-Shafer KA, Cahoon-Young B, Klausner JD, et al. Hepatitis C virus infection in young, low-income women: The role of sexually transmitted infection as a potential cofactor for HCV infection. Am J Public Health 2002;92:670–676.
26. Spengler U, Rockstroh J. Hepatitis C in the patient with human immunodeficiency virus infection. J Hepatol 1998; 29:1023–1030.
27. Mendes-Correa MC, Barone AA, Gianini RJ. Risk factors associated with hepatitis C among patients co-infected with human immunodeficiency virus: A case-control study. Am J Trop Med Hyg 2005;72:762–767.
28. Dehovitz JA, Kelly P, Feldman J, et al. Sexually transmitted diseases, sexual behavior, and cocaine use in inner-city women. Am J Epidemiol 1994;140:1125–1134.
29. Wang CC, Krantz E, Klarquist J, et al. Acute hepatitis C in a contemporary US cohort: Modes of acquisition and factors influencing viral clearance. J Infect Dis 2007;296:1474–1482.
30. Wejstal R. Sexual transmission of hepatitis C virus. J Hepatol 1999;31:92–95.
31. Luruez-Ville M, Kunstmann JM, De Almeida M, et al. Detection of hepatitis C virus in the semen of infected men. Lancet 2000;356:42–43.
32. Pasquier C, Bujan L, Duakin M, et al. Intermittent detection of hepatitis C virus (HCV) in semen from men with human immunodeficiency virus type 1 (HIV-1) and HCV. J Med Virol 2003;69:344–349.
33. Nyamathi A, Robbins WA, Fahey JL, et al. Presence and predictors of hepatitis C virus RNA in the semen of homeless men. Biol Res Nurs 2002;4:22–30.
34. Van de Laar TJ, Van der Bij AK, Prins M, et al. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. J Infect Dis 2007;196:230–238.
35. Cohen DE, Russell CJ, Golub SA, et al. Prevalence of Hepatitis C virus infection among men who have sex with men at a Boston community health center and its association with markers of high-risk behavor. AIDS Patient Care STDs 2006;20:557–564.
36. Halfon P, Riflet H, Renou C, et al. Molecular evidence of male-to-female sexual transmission of hepatitis C virus after vaginal and anal intercourse. J Clin Microbiol 2001;39:204–1206.
37. Hershow RC, Kalish LA, Sha B, et al. Hepatitis C virus infection in Chicago women with or at risk for HIV infection: Evidence for sexual transmission. Sex Transm Dis 1998;25: 527–532.
38. Hessol NA, Schwarcz S, Ameli N, et al. Accuracy of self-reports of acquired immunodeficiency syndrome and acquired immunodeficiency syndrome-related conditions in women. Am J Epidemiol 2001;153:1128–1133.
39. Booth R, Koester S, Brewster J, et al. Intravenous drug users and AIDS: risk behaviors. Am J Drug Alcohol Abuse 1991;17:337.
40. Kim MY, Marmor M, Dubin N, Wolfe H. HIV risk-related sexual behaviors among heterosexuals in New York City: Associations with race, sex, and intravenous drug use. AIDS 1993;7:409–414.
41. Neaigus A, Miller M, Friedman SR, et al. Sexual transmission risk among noninjecting heroin users infected with human immunodeficiency virus or hepatitis C virus. J Infect Dis 2001;184:359–63.
42. Nowicki MJ, Laskus T, Nikolopoulou G, et al. Presence of hepatitis C virus (HCV) RNA in the genital tracts of HCV/HIV-1-coinfected women. J Infect Dis 2005;192:1557–1565.
43. Briant L, Wade CM, Puel J, et al. Analysis of envelope sequence variants suggests multiple mechanisms of mother-to-child transmission of human immunodeficiency virus type 1. J Virol 1995;69:3778–3788.
44. Chamie G, Bonacini M, Bangsber D, et al. Factors associated with seronegative chronic hepatitis C virus infection in HIV infection. Clin Infect Dis 2007;44:577–583.
45. Luetkemeyer A, Hare CB, Stansel J, et al. Clinical presentation and course of acute hepatitis C infection in HIV-infected patients. J Acquir Immune Defic Syndr 2006;41:31–36.
46. Cheung R. Chronic Hepatitis C in the Hispanic population. HCV Advocate 2007. www.hcvadvocate.org/hcsp/articles/hispanics.html. (Last accessed February 26, 2009).

Address correspondence to:
Toni Frederick, Ph.D.
Health Research Association Building
1640 Marengo St., Suite 300
Los Angeles, CA 90033

E-mail: tfrederi@usc.edu