MAJOR ARTICLE

Individual and Couple-Level Risk Factors for Hepatitis C Infection among Heterosexual Drug Users: A Multilevel Dyadic Analysis

James M. McMahon,[1] Enrique R. Pouget,[1,2] and Stephanie Tortu[3]

[1]National Development and Research Institutes, New York, New York; [2]Yale University, School of Epidemiology and Public Health, New Haven, Connecticut; [3]Louisiana State University, School of Public Health, New Orleans

(See the editorial commentary by Hahn, on pages 1556–9.)

Background. Hepatitis C virus (HCV) is the most common bloodborne pathogen in the United States and is a leading cause of liver-related morbidity and mortality. Although it is known that HCV is most commonly transmitted among injection drug users, the role of sexual transmission in the spread of HCV remains controversial because of inconsistent findings across studies involving heterosexual couples.

Methods. A novel multilevel modeling technique designed to overcome the limitations of previous research was performed to assess multiple risk factors for HCV while partitioning the source of risk at the individual and couple level. The analysis was performed on risk exposure and HCV screening data obtained from 265 drug-using couples in East Harlem, New York City.

Results. In multivariable analysis, significant individual risk factors for HCV included a history of injection drug use, tattooing, and older age. At the couple level, HCV infection tended to cluster within couples, and this interdependence was accounted for by couples' drug-injection behavior. Individual and couple-level sexual behavior was not associated with HCV infection.

Conclusions. Our results are consistent with prior research indicating that sexual contact plays little role in HCV transmission. Rather, couples' injection behavior appears to account for the clustering of HCV within heterosexual dyads.

Hepatitis C virus (HCV) is a major cause of morbidity and mortality worldwide, with an estimated global prevalence of 170 million chronic infections. Chronic active hepatitis C is a mildly symptomatic and slowly progressive illness that can lead to chronic liver disease (CLD), including cirrhosis and the development of hepatocellular carcinoma, within 2–3 decades of infection [1, 2]. In the United States, ~1.8% of the population is infected [3, 4], making HCV the most common chronic bloodborne pathogen in the nation. The majority of HCV cases, however, occur among injection drug users (IDUs) and those who received blood products before 1992. This pattern of endemicity reflects the known etiology of the virus—it is primarily transmitted parenterally through contact with infected blood. Approximately 60% of the 25,000 new HCV infections that occur annually in the United States can be attributed to the sharing of contaminated syringes and other drug paraphernalia among IDUs [3]. Acquisition of HCV from blood transfusions, once a major source of infection, has become rare since reliable donor screening for viral hepatitis C was introduced in the early 1990s [5]. Other known parenteral routes of HCV transmission include percutaneous exposure from tattooing and body piercing and occupational needlesticks [6, 7].

Although the majority of HCV cases can be explained by established routes of parenteral transmission, ~10%–15% of HCV-infected individuals report no obvious source of exposure [8–10]. This has led to the hypoth-

Received 15 July 2006; accepted 18 December 2006; electronically published 16 April 2007.

Potential conflicts of interest: none reported.

Presented in part: XVth International AIDS Conference, Bangkok, Thailand, 11–16 July 2004 (abstract TuOrD1220); New Methods for the Analysis of Dyadic Processes, Amherst, MA, 13–15 October 2006 (poster 21).

Financial support: National Institutes of Health, National Institute on Drug Abuse (grants R01DA12805 to S.T. and R01DA15410 to J.M.M.).

Reprints or correspondence: Dr. James M. McMahon, National Development and Research Institutes, 71 W. 23rd St., 8th Fl., New York, NY 10010 (mcmahon@ndri.org).

The Journal of Infectious Diseases 2007; 195:1572–81

0022-1899/2007/19511-0005$15.00
DOI: 10.1086/516785

esis that other parenteral or nonparenteral risk factors, such as sexual contact or the sharing of household items, might play a role in HCV transmission [11, 12]. Because of the close intimate contact between long-term sex partners, studies examining these alternative routes of HCV transmission have typically focused on heterosexual couples [13]. In a meta-analysis of intrafamilial HCV transmission, Ackerman et al. [14] reported that the pooled prevalence of HCV among heterosexual partners of patients with HCV-related CLD was ~15%, compared with only 1% in the sex partners of HCV-negative control subjects. In these prevalence studies, HCV genotype and sequence homology between concordant couples was ~70%, indicating a high rate of interspousal transmission. However, several recent longitudinal studies have found little or no evidence of interspousal transmission of HCV. A recent example was provided by Vandelli et al. [15], who monitored a cohort of 895 anti-HCV–negative subjects whose monogamous heterosexual partners were chronically infected with HCV (index cases). Subjects who reported any parenteral or sexual risk exposure other than sex with the index case were excluded from the analysis. During 7760 person-years of follow-up, no confirmed HCV seroconversions were observed between heterosexual partners. Similar prospective studies have reported either no or low interspousal transmission of HCV [16–20].

Stroffolini et al. [21] suggested that the high prevalence of HCV observed among spouses of index cases might be due to common risk factors other than sexual transmission. Although most couple-based studies have attempted the exclusion of subjects with alternative risk factors, different recruitment strategies may lead to sampling bias, which might account for the inconsistent findings [22]. For example, studies consisting of convenience samples (such as those from blood donors) have been shown to underreport history of drug injection [23] and may therefore yield a higher HCV prevalence among the sex partners of index cases, compared with other types of samples. None of these studies, however, have provided evidence regarding multiple risks for HCV at the individual as well as the couple level. This is an important consideration, especially in high-prevalence communities, where members of heterosexual couples may engage in drug- and sex-related risk behaviors within and outside their primary relationships. In the present study, we applied multilevel dyadic modeling techniques to data collected from drug-using heterosexual couples in a high-prevalence community in New York City to assess multiple risk factors for HCV infection at both the individual and the couple level.

MATERIALS AND METHODS

Study Design

Data for the study were obtained from participants enrolled in the Couples-at-Risk project (S.T., principal investigator), a cross-sectional retrospective study of the social context of HIV and hepatitis B and C risk. The main study sample consisted of 353 drug-using heterosexual couples recruited by outreach workers from the streets of East Harlem, New York City, between February 2001 and July 2003. Couples were recruited through the female partner, using targeted sampling [24] and participant referrals.

Women's eligibility criteria included: (1) age ⩾18 years; (2) use of injected or noninjected crack, cocaine, or heroin during the preceding 30 days; (3) current primary heterosexual partner (defined as husband, common-law husband, or steady boyfriend of at least 1 year); and (4) vaginal or anal sex with the primary partner at least once during the preceding 30 days. Male partners had to be at least 18 years old. A total of 742 women were screened for eligibility, 392 (53%) were deemed eligible, and 353 women enrolled in the study with their primary partner. The majority of ineligible women either did not have a primary male partner or did not use drugs during the preceding 30 days. All study participants provided written, informed consent. Guidelines for the protection of human subjects in clinical research were followed as required by US Department of Health and Human Services, and all research protocols were approved by an institutional review board. Female and male partners were simultaneously administered structured questionnaires in separate offices by sex-matched interviewers using a combination of computer-assisted personal interview and audio computer-assisted self-interview (ACASI) techniques. All participants were offered counseling and testing for HIV and hepatitis B and C. Pre- and posttest counseling was conducted using standard protocols as outlined by the National Institute on Drug Abuse. A more-detailed description of the sample, research design, and data collection methods is shown in McMahon et al. [25]. Of the 353 couples enrolled in the study, 265 voluntarily provided blood samples for HCV antibody screening and were included in the present analysis.

Measures

Outcome measure: HCV antibody screening. Anti-HCV screening was conducted by Abbott Laboratories using the HCV EIA 3.0 (signal:cutoff [s:co] ratio >3.8) and VITROS (s:co ratio >8) anti-HCV screening assays. These assays have near 100% sensitivity and specificity between 95% and 99% [26, 27].

Risk factors. Three types of risk factors were distinguished in the present analysis: (1) specific risk behaviors that can lead directly to HCV transmission, (2) biological moderators/cofactors, and (3) psychosocial moderators/cofactors. The primary known or suspected risk behaviors for HCV include: sharing of syringes and other injection equipment, receiving blood or blood products before 1992, tattooing and body piercing, unprotected vaginal or anal sex, occupational needlesticks, sharing of household items such as razors, and sharing non-

injection drug-use implements. Biological cofactors are conditions that moderate the risk of HCV infection in the context of a given risk behavior. One obvious biological moderator is the HCV status of an individual's sex or drug partner. In addition, coinfection with HIV may act as a biological cofactor that facilitates HCV transmission [12, 28]. Genital lesions symptomatic of certain sexually transmitted diseases (STDs) may also increase the risk for HCV through sexual contact [29]. There is little evidence to suggest that age or racial differences play a biological role in moderating HCV risk. However, age, sex, and ethnicity can moderate HCV risk through various psychosocial cofactors. For instance, cultural norms governing sex roles dictate that women inject drugs after their male partners, thereby increasing women's risk of exposure to contaminated needles and paraphernalia [30, 31]. Racial/ethnic minority status has been linked to a lack of socioeconomic opportunities, which may further increase the likelihood of involvement in multiple risk behaviors [32]. Incarceration is another psychosocial cofactor that may increase the likelihood of involvement in certain risk behaviors, such as unsafe drug-injection practices, unhygienic tattooing and body piercing, and unprotected anal sex [33]. Age can also be viewed as a social moderator of HCV risk—younger individuals tend to engage in higher risk behaviors more frequently than older individuals.

In the present study, we collected data on HCV risk behaviors and biological and psychosocial cofactors from both male and female partners of drug-using heterosexual couples (tables 1 and 2). In table 2, individual (actor)–level risk factors represent sources or moderators of HCV infection that are not specific to a given partner (e.g., ever received a tattoo or lifetime number of sex partners); individual (partner)–level risk factors specify conditions that can moderate HCV infection within the primary partnership (e.g., occurrence of partner STDs); and couple-level risk factors represent sources or moderators of HCV infection that are specific to the primary partnership (e.g., unprotected sex or drug injection within the couple).

Statistical Methods

Conventional methods of inferential data analyses, such as analysis of variance and general linear regression, assume that observations obtained from each subject are independent. Because the data examined here are hierarchically structured as individuals nested within couples (dyads), this assumption is violated and may lead to an underestimation of SEs (i.e., increased type I errors). To overcome this problem, we performed a multilevel modeling analysis developed for use with dyadic data [34–37] using SAS (version 8.02; SAS Institute). Multilevel analysis combines the effects of variables at different levels (in this case, individual- and couple-level effects) while accounting for the interdependence among observations within dyads. A detailed description of the assumptions and limitations of this approach can be found in Newsom [38] and McMahon et al. [37].

To model individual- and couple-level risk factors associated with anti-HCV positivity, the data were restructured in accordance with the actor-partner interdependence model (APIM) proposed by Kashy and Kenny [35], Kenny [39], and Kenny and Cook [40]. In the multilevel APIM framework, each dyad member is considered to be an actor as well as a partner in the dyad. Each individual actor outcome—anti-HCV status in the present study—can be influenced by individual actor effects (level 1), partner effects (level 1), and dyad-level effects (level 2), as well as by interactions within and across levels. This conceptual and analytical framework thus provides a model for assessing disease risk from both within and outside the partnership while accounting for dyadic interdependence.

Before the specification of multivariable or conditional multilevel models, the first step in the analysis was to determine whether there was significant within-dyad interdependence to warrant the use of a multilevel approach. For binomial hierarchical models, the standard test for interdependence—the intraclass correlation coefficient (ICC)—is invalid [41]. In its place, we used the Pearson-type pairwise intraclass correlation coefficient (PICC), which has been shown to provide reliable ICC estimates for binary outcomes using data with reasonably large numbers of clusters, each of small size [42].

Next, bivariate multilevel logistic regression models were estimated to examine the effects of individual (actor or partner) and couple-level risk factors on actor anti-HCV status (table 2). For actor- and couple-level variables, all 3 types of risk factors (risk behaviors, biological cofactors, and psychosocial cofactors) were examined, whereas only cofactors were included in models for partner effects. Because actor anti-HCV status is the dependent variable, only actor- and couple-level risk behaviors can lead directly to actor HCV infection, whereas partner effects are limited to moderating an actor's risk of infection. For instance, a partner receiving a tattoo (risk behavior) will not directly lead to the actor becoming infected. However, a sex partner's history of STDs (biological cofactor) can potentially moderate an actor's risk for infection through sexual contact. A series of theory-derived hierarchical interaction models were also estimated. These included second-order interactions involving theoretically plausible combinations of actor-, partner-, and couple-level risk behaviors and moderators (table 3).

Because of the large number of significance tests, we applied the Holm-Šidák correction for multiple comparison procedures [43, 44]. Like the Bonferroni adjustment, this method corrects *P* values to guard against family-wise error but has the added benefit of protecting against overcorrection due to correlated hypotheses [44].

Parameter estimates and SEs in all multilevel logistic regression models were adjusted to account for misclassification

Table 1. Sample characteristics ($N = 530$).

Characteristic	Women	Men	Dyads ($n = 265$)
Age, mean ± SD, years[a]	39.1 ± 7.3	40.3 ± 7.8	
Race/ethnicity			
Hispanic	48.3	48.3	
Black, non-Hispanic	34.3	38.5	
White/other	17.4	13.2	
Mixed race/ethnicity			19.1
High school education	44.9	60.4	
Past or current IDU	61.5	65.3	
Employment status			
Employed full time	1.1	12.1	
Underemployed (<30 h/week)	4.5	9.8	
Unemployed	58.5	53.2	
Unable to work (disabled)	25.7	22.6	
Out of the work force	10.2	2.3	
Marital status (self-report)			
Single			4.9
Legally married			20.0
Common-law married			70.4
Divorced, separated, or widowed			4.7
Residence pattern			
Permanent residence/housing	52.1	47.2	
Transient (living temporarily with friend, family, or hotel)	31.7	35.9	
Homeless (living in street, car, or shelter)	16.2	17.0	
Ever convicted of a criminal offense	85.3	94.0	
Drug use history			
Ever injected drugs	61.5	65.3	
Ever smoked crack	88.7	82.3	
Ever snorted cocaine	95.9	96.2	
Ever snorted heroin	87.6	87.2	
Ever smoked marijuana	97.4	98.1	
Ever consumed alcohol	96.6	96.2	
Ever smoked cigarettes	97.7	97.0	
Current drug use (used in past 30 days)			
Injected drugs	36.2	37.0	
Smoked crack	56.6	47.9	
Snorted cocaine	24.0	25.8	
Snorted heroin	50.8	42.4	
Smoked marijuana	37.9	43.8	
Consumed alcohol	57.2	58.0	
Smoked cigarettes	96.2	92.1	
Currently in drug treatment	70.9	55.9	
Had unprotected vaginal sex with primary partner in the past 30 days			83.8
Had unprotected anal sex with primary partner in the past 30 days			22.1
Exchanged sex for drugs or money in the past 30 days	15.9	6.4	
HCV status			
Anti-HCV positive	50.6	54.7	
Concordant negative			29.8
Concordant positive			35.1
Male positive/female negative			19.6
Female positive/male negative			15.5
HIV status			
Positive ($n = 258$)	19.9	21.0	
Concordant negative			67.1
Concordant positive			8.5
Male positive/female negative			12.8
Female positive/male negative			11.6

NOTE. Data are % of subjects, unless otherwise indicated. HCV, hepatitis C virus; IDU, injection drug use.

[a] Median age difference between men and women, 4 years.

Table 2. Bivariate multilevel logistic regression estimates of risk factors for actor anti–hepatitis C virus (HCV) positivity.

Risk behaviors and cofactors	Subjects, %	OR (95% CI)	*P*	Adjusted *P*[a]
Actor-level (level 1)				
Risk behaviors				
Ever injected illegal drugs	63.4	400.61 (37.49–4285.53)	<.0001	**.006**
Received blood transfusion before 1992	5.9	1.68 (0.56–5.01)	.353	1.000
Ever received a tattoo	40.2	3.00 (1.72–5.22)	<.0001	**.006**
Lifetime no. of heterosexual sex partners	55.6[b]	0.93 (0.71–1.20)	.568	1.000
Lifetime no. of heterosexual IDU sex partners	4.7[b]	2.21 (1.65–2.96)	<.0001	**.006**
Ever had heterosexual anal sex	66.0	1.01 (0.58–1.78)	.967	.999
Ever traded sex for drugs or money	55.3	0.80 (0.48–1.35)	.409	1.000
Injected with nonprimary partner last 30 days	1.7	2.24 (0.31–16.36)	.425	1.000
Ever sniffed illegal drugs	98.5	2.86 (0.27–30.26)	.379	1.000
Years sniffing illegal drugs	19.2[b]	1.86 (1.35–2.57)	.0002	**.011**
Cofactors/moderators				
HIV positive	20.5	2.80 (1.34–5.91)	.006	.277
Ever had an STD	40.9	1.29 (0.75–2.22)	.359	1.000
Ever had a lesion-producing STD	20.4	1.15 (0.60–2.23)	.658	1.000
Sex (female, 1; male, 0)	50.0	0.77 (0.49–1.21)	.257	1.000
Age, years	39.7[b]	1.99 (1.45–2.72)	<.0001	**.006**
Education (high school or more, 1; less, 0)	52.6	0.74 (0.43–1.28)	.283	1.000
Race/ethnicity				
Black, non-Hispanic	36.4	0.15 (0.06–0.40)	<.0001	**.006**
Hispanic, nonblack	48.3	0.65 (0.29–1.49)	.313	1.000
White/other	15.3	Reference		
Lifetime incarceration of ⩾1 year	60.4	1.59 (0.94–2.68)	.085	.982
Partner-level cofactors (level 1)				
Anti-HCV positive		3.30 (2.26–4.81)	<.0001	**.006**
HIV positive		0.75 (0.37–1.55)	.451	1.000
Ever had an STD		0.70 (0.41–1.21)	.204	1.000
Ever had a lesion-producing STD		0.86 (0.44–1.65)	.645	1.000
Age, years		1.25 (0.95–1.64)	.114	.993
Education (high school or more, 1; less, 0)		1.97 (1.14–3.42)	.016	.561
Race/ethnicity				
Black, non-Hispanic		0.37 (0.16–0.84)	.018	.597
Hispanic, nonblack		0.48 (0.22–1.06)	.068	.963
White/other		Reference		
Couple-level (level 2)				
Injected drugs together in the past 30 days[c]	18.1	12.63 (4.99–31.94)	<.0001	**.006**
No. of unprotected vaginal sex acts in the past 30 days	13.4[b]	0.82 (0.61–1.13)	.230	1.000
Had anal sex in the past 30 days[c]	11.7	0.72 (0.30–1.73)	.462	1.000
Relationship duration, years	7.3[b]	0.99 (0.73–1.35)	.968	.968
Cohabitation[c]	81.9	0.89 (0.35–2.25)	.798	1.000
Age difference between men and women, years	5.6[b]	0.81 (0.60–1.11)	.188	1.000

NOTE. CI, confidence interval; IDU, injection drug use; OR, odds ratio; STD sexually transmitted disease.

[a] Holm-Šidák adjusted *P* value. Significant results are in bold type.

[b] Mean.

[c] For couples, agree yes, 1; disagree, 0.5; agree no, 0.

of anti-HCV assay results based on the correction algorithm of Neuhaus [45]. When dichotomous outcomes are subject to misclassification error, such as with HCV antibody tests, multilevel modeling yields coefficients that are biased toward the null and SEs that are too small. The Neuhaus algorithm was used to correct for these biases on the basis of known sensitivity and specificity values of the anti-HCV assays.

A hierarchical backward stepwise elimination technique was

Table 3. Multilevel logistic regression estimation of theory-derived interaction effects on actor anti–hepatitis C virus (HCV) positivity.

Interaction terms	AOR (95% CI)	*P*	Adjusted *P*[a]
Actor ever injected illegal drugs, moderated by			
Actor HIV positive	1.38 (0.10–18.56)	.809	1.000
Actor female	1.28 (0.18–8.99)	.801	1.000
Actor completed high school	2.80 (0.29–27.03)	.371	1.000
Actor black, non-Hispanic	9.43 (1.66–53.51)	.012	.466
Actor Hispanic, nonblack	0.06 (0.01–0.32)	.001	**.054**
Actor lifetime incarceration of ⩾1 year	0.41 (0.12–1.34)	.140	.997
Actor received blood transfusion before 1992, moderated by age	0.41 (0.11–1.47)	.169	.999
Actor ever received a tattoo, moderated by			
Actor HIV positive	1.76 (0.40–7.06)	.452	1.000
Actor female	0.56 (0.20–1.61)	.282	1.000
Actor lifetime incarceration of ⩾1 year	2.38 (0.76–7.46)	.134	.997
Actor lifetime no. of heterosexual partners, moderated by			
Actor HIV positive	0.92 (0.46–1.84)	.822	1.000
Actor ever had an STD	0.75 (0.43–1.32)	.313	1.000
Actor ever had a lesion-producing STD	1.02 (0.54–1.93)	.942	1.000
Actor female	1.59 (0.94–2.70)	.085	.980
Actor lifetime no. of heterosexual IDU sex partners, moderated by			
Actor HIV positive	0.91 (0.44–1.87)	.803	1.000
Actor ever had an STD	1.27 (0.73–2.21)	.340	1.000
Actor ever had a lesion-producing STD	2.11 (1.02–4.36)	.043	.879
Actor female	1.64 (0.95–2.85)	.073	.969
Actor ever had heterosexual anal sex, moderated by			
Actor HIV positive	4.63 (1.06–20.19)	.041	.871
Actor ever had an STD	2.51 (0.01–7.79)	.112	.993
Actor ever had a lesion-producing STD	1.40 (0.33–5.91)	.649	1.000
Actor female	0.79 (0.27–1.08)	.655	1.000
Actor ever traded sex for drugs or money, moderated by			
Actor HIV positive	0.53 (0.13–2.16)	.374	1.000
Actor ever had an STD	0.66 (0.22–1.93)	.442	1.000
Actor ever had a lesion-producing STD	0.96 (0.25–3.76)	.953	1.000
Actor female	2.40 (0.86–6.73)	.095	.986
Actor no. of years sniffed illegal drugs, moderated by			
Actor HIV positive	0.73 (0.33–1.58)	.418	1.000
Actor female	0.98 (0.48–1.41)	.476	1.000
Actor age	1.13 (0.86–1.49)	.385	1.000
Anti-HCV–positive partner, interaction with			
Actor female	1.13 (0.52–2.44)	.754	1.000
Couple injected drugs together in the past 30 days	18.49 (4.76–71.81)	<.0001	**.006**
Couple no. of unprotected vaginal sex acts in the past 30 days	0.93 (0.23–1.36)	.711	1.000
Couple had anal sex in the past 30 days	0.23 (0.08–0.66)	.010	.413

NOTE. AOR, adjusted odds ratio; CI, confidence interval; IDU, injection drug use; STD sexually transmitted disease.

[a] Holm-Šidák adjusted *P* value. Significant results are in bold type.

used to specify the final model. This method begins with the saturated or full model and proceeds by eliminating nonsignificant terms while retaining significant main effects and effects contained in significant interaction terms [46, 47].

RESULTS

Sample description. The median age of the sample was 40 years for women and 41 years for men; 48% were Hispanic,

Table 4. Multilevel logistic regression estimation of individual- and couple-level risk factors for actor anti–hepatitis C virus (HCV) positivity.

Effects	Full model			Final model		
	β	SE	AOR (95% CI)	β	SE	AOR (95% CI)
Fixed effects						
Intercept	−2.82[a]	0.67	0.06 (0.02–0.22)	−2.12[a]	0.26	0.12 (0.07–0.20)
Individual-level risk factors						
Actor age	0.80[a]	0.20	2.22 (1.51–3.27)	0.66[a]	0.14	1.94 (1.47–2.56)
Actor ever injected illegal drugs	3.16[a]	0.60	23.54 (7.29–75.98)	2.50[a]	0.29	12.19 (6.90–21.54)
Actor ever received a tattoo	0.54	0.29	1.71 (0.98–3.00)	0.63[b]	0.26	1.89 (1.12–3.16)
Actor lifetime no. of IDU sex partners	0.18	0.15	1.20 (0.90–1.60)			
Actor lifetime years sniffing illegal drugs	−0.04	0.16	0.96 (0.70–1.31)			
Actor race/ethnicity						
Black, non-Hispanic	−0.23	0.47	0.79 (0.32–1.98)			
Hispanic, nonblack	1.19	0.70	3.29 (0.83–13.04)			
White/other (reference)						
Partner anti-HCV positive	0.35	0.36	1.42 (0.70–2.88)	0.36	0.28	1.43 (0.82–2.49)
Individual-level interaction: actor ever injected × actor Hispanic, nonblack	−1.15	0.65	0.32 (0.09–1.14)			
Couple-level risk factor: couple injected together in the past 30 days	−1.03	0.64	0.36 (0.10–1.24)	−1.05	0.60	0.35 (0.11–1.14)
Cross-level interaction: couple injected together × partner anti-HCV positive	2.81[a]	0.79	16.50 (3.47–79.21)	2.71[a]	0.74	14.97 (3.49–64.26)
Random effect (level 2 variance component), σ_u	4.53^{-10}			2.19^{-10}		

NOTE. AOR, adjusted odds ratio; CI, confidence interval; IDU, injection drug use.

[a] $P \leq .001$.

[b] $P \leq .05$.

nonblack (mostly Puerto Rican); 36% were black, non-Hispanic; and 16% were white/other. Anti-HCV prevalence was 50.6% for women and 54.7% for men; for past or present IDUs, HCV prevalence was 74.1%, compared with 15.5% for non-IDUs. The median duration of the sexual relationship for couples was 7.7 years. A complete list of individual- and couple-level sample descriptors is presented in table 1.

Multilevel risk assessment. The first step in the analysis was to determine whether significant within-dyad interdependence existed in the data to justify the use of a multilevel approach. The Pearson-type PICC for paired binary responses was used to provide a measure of within-dyad interdependence. Pairwise correlation between male and female anti-HCV status produced a coefficient of 0.30, with an asymptotic SE of 0.06 and 95% confidence limits of 0.18 and 0.41. On the basis of this result, we rejected the null hypothesis of no interdependence on anti-HCV status between members within couples.

After adjustment for family-wise error, bivariate multilevel logistic regression analysis revealed 8 significant risk factors for actor anti-HCV positivity. These included 4 actor-level risk behaviors (ever injected illegal drugs, ever received a tattoo, lifetime number of IDU sex partners, and years sniffing illegal drugs), 2 actor-level cofactors (older age and black, non-Hispanic race/ethnicity), 1 partner-level cofactor (anti-HCV positivity), and 1 couple-level risk behavior (couple injected drugs together during the preceding 30 days). Analysis of theory-derived interaction terms identified 2 additional significant interactions: actor's history of drug injection moderated by Hispanic, nonblack race/ethnicity and couple's recent drug injection, moderated by partner's HCV status.

These main effects and interaction terms were entered into a full model (table 4). Model terms were then eliminated using stepwise backward elimination. The final multivariable model identified 4 significant risk factors for actor anti-HCV positivity: (1) actor older age, (2) actor ever injected illegal drugs, (3) actor ever received a tattoo, and (4) couple's recent drug injection, moderated by partner's anti-HCV positive status. Several variables did not retain significance in the full model and were excluded in the final model: lifetime number of IDU sex partners; years sniffing illegal drugs; black, non-Hispanic race/ethnicity; and the interaction between a history of injection and Hispanic race/ethnicity.

DISCUSSION

The individual-level risk factors for HCV identified in the present study largely replicate findings from previous research. History of drug injection is consistently the strongest predictor of

HCV across studies. Sharing syringes and other drug-injection equipment is an efficient method of transmitting HCV and other bloodborne pathogens. Recent studies have reported an increased risk associated with tattooing, both in commercial and noncommercial settings [6]. Older age is also commonly associated with HCV positivity. This is due, in part, to a cohort effect involving a peak in HCV incidence in the United States in the early to mid-1990s [48]. In contrast to some previous studies, we found no evidence that sexual risk behaviors were associated with HCV infection. The observed bivariate association between lifetime number of IDU sex partners and HCV positivity is likely a spurious effect resulting from common correlations with drug injection history and age.

Even more notable is the absence of any significant sex-related risk factors at the couple level. The results of the PICC test showed that an actor's anti-HCV status is significantly related to his or her partner's anti-HCV status. This clustering of HCV within heterosexual couples has been observed in previous studies and is most often interpreted as evidence of sexual transmission of HCV. However, such clustering may be due to individual risk factors shared by dyad members, to sexual or nonsexual viral transmission between partners, or to both [21]. The multilevel modeling technique used in the present study permitted the assessment of couple-level risk factors—such as unprotected vaginal or anal sex, cohabitation, and drug injection practices by the couple—while controlling for risk factors at the individual level. No significant associations were found between actor anti-HCV status and measures of sexual risk. The only couple-level predictor of actor HCV infection was couples' recent drug injection moderated by partner's HCV status.

That couples' drug-injection behavior alone can account for the observed clustering of HCV in heterosexual couples is indicated by 2 observations. First, couples' drug injection moderated by partner HCV status was the only significant couple-level predictor in the final model. Second, when this interaction term was excluded, the level-2 variance component remained high ($\sigma = 5.30$), which indicated the presence of unexplained variance in actor anti-HCV status associated with couple-level risk; but when the interaction term and main effects were included in the final model, the level-2 random effect was essentially reduced to nil ($\sigma = 2.19^{-10}$), indicating that nearly all of the variance in actor HCV status is accounted for.

In contrast to previous studies [13, 14], we found no differences in HCV risk factors associated with sex. Drug-using men and women in heterosexual partnerships in East Harlem appear to be exposed to the same individual and couple-level risk factors for HCV. Sex-related differences in HCV risk may be population specific.

The present study had several limitations. The cross-sectional study design did not permit causal inferences to be made regarding HCV transmission, and the timing of HCV seroconversion among the infected participants in relation to risk exposure was unknown. Furthermore, it was not feasible to conduct phylogenetic analysis to confirm interspousal HCV transmission among concordant positive couples. Risk-exposure data were based on self-reports that may have been subject to response bias. However, the close rapport of the interviewers with clients and the use of ACASI interviewing techniques may have minimized such bias [49]. Some of our risk-factor measures were also subject to validity concerns. For example, the study instrument did not include measures of sharing noninjection drug-use implements at the individual or couple level. The potential for residual confounding by noninjection drug use thus remains. In addition, some of the couple-level risk measures involved recent behavior that served as a proxy for risk exposures that may have occurred during the entire relationship. Future research will benefit from the development of risk-behavior measures validated for use in multilevel research. Street recruitment of drug users rarely provides a random sample. The extent to which our findings are generalizable to the entire population of drug-using couples in East Harlem or to other similar populations is unknown. Moreover, analyses were conducted on a subsample of subjects who provided blood for HCV screening. The primary reasons for exclusion were (1) inability to draw blood because of vascular occlusions, dermal lesions, or dehydration; and (2) fear of needles. Most of the former were injectors who were more likely to be HCV positive, whereas most of the latter were noninjectors who were less likely to be HCV positive. This selection process may have biased the sample in unanticipated ways.

The study also has several important strengths. It is unique in that it evaluates multiple risk factors for HCV at both the individual and couple level. HCV incidence studies involving long-term heterosexual couples have shown that sexual transmission is rare, but they do not explain the clustering of HCV within sexual dyads observed in many population prevalence studies. These prevalence studies have often assumed that such clustering is due to sexual transmission without considering the alternative risk factors that may be common to both men and women or to nonsexual interspousal transmission of HCV.

Our results indicate that HCV infection is not associated with sexual risk behavior among members of long-term heterosexual couples. This finding must be qualified by the fact that the sample consisted entirely of drug users—a population with very different characteristics and levels of risk than other populations. Although this finding supports a recommendation of optional condom use for HCV-serodiscordant couples, it should be emphasized that populations characterized by high HCV prevalence also tend to have high prevalence for HIV and hepatitis B virus (HBV), both of which are sexually transmitted. Heterosexual couples may be particularly vulnerable to these

sexually transmitted infections [50]. The high prevalence of HIV and HBV observed in our sample of heterosexual couples, who had been together for an average of nearly 8 years, is consistent with this interpretation. Although disease-prevention programs aimed at decreasing unsafe injection practices in high-risk communities have met with some success in recent years, our findings indicate a need to expand HCV prevention efforts to address the injection practices of primary heterosexual couples.

Acknowledgments

Dr. John Neuhaus (Department of Epidemiology and Biostatistics, University of California, San Francisco) kindly provided SAS code for adjusting multilevel model estimates to account for outcome misclassification. We also thank the dedicated staff of the Couples-at-Risk project: Sherelle Bonaparte, Jeanne Campbell, Rahul Hamid, Robert Quiles, William Rodriguez, and Leilani Torres. Jeanine Botta provided technical and editorial assistance in preparation of the manuscript.

References

1. Ebeling F. Epidemiology of the hepatitis C virus. Vox Sang **1998**; 74(Suppl 2):143–6.
2. Alter MJ, Margolis H, Krawczynski Judson FN, et al. The natural history of community acquired hepatitis C in the United States. The Sentinel Counties Chronic Non-A, Non-B Hepatitis Study Team. N Engl J Med **1992**; 327:1899–905.
3. Centers for Disease Control and Prevention (CDC). Hepatitis surveillance report. Atlanta, GA: CDC, **2002**.
4. McQuillan GM, Alter MJ, Moyer LA, Lambert SB, Margolis HS. A population-based serologic study of hepatitis C virus infection in the United States. In: Rizzetto M, Purcell RH, Gerin JL, Verne G, eds. Viral hepatitis and liver disease. Turin, Italy: Edizioni Minerva Medica, **1997**: 267–70.
5. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. N Engl J Med **1996**; 334:1685–90.
6. Haley RW, Fischer RP. Commercial tattooing as a potentially important source of hepatitis C infection: clinical epidemiology of 626 consecutive patients unaware of their hepatitis C serologic status. Medicine **2001**;80: 134–51.
7. Murphy EL, Bryzman SM, Glynn SA, et al. Risk factors for hepatitis C virus infection in United States blood donors. Hepatology **2000**; 31: 756–62.
8. Flamm SL, Parker RA, Chopra S. Risk factors associated with chronic hepatitis C virus infection: limited frequency of an unidentified source of transmission. Am J Gastroenterol **1998**; 93:597–600.
9. Tortu S, Neaigus A, McMahon J, Hagen D. Hepatitis C among noninjecting drug users: a report. Subst Use Misuse **2001**; 36:523–34.
10. Rosenblum A, Nuttbrock L, McQuistion HL, Magura S, Joseph H. Hepatitis C and substance use in a sample of homeless people in New York City. J Addict Dis **2001**; 20:15–25.
11. Caldwell SH, Dickson RC, Driscoll C, Sue M. Sexual, vertical and household transmission of hepatitis C. Va Med Q **1995**; 122:270–4.
12. Terrault NA. Sexual activity as a risk factor for hepatitis C. Hepatology **2002**; 36:S99–105.
13. 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**; 171:768–75.
14. Ackerman Z, Ackerman E, Paltiel O. Intrafamilial transmission of hepatitis C virus: a systematic review. J Viral Hepat **2000**; 7:93–103.
15. Vandelli C, Renzo F, Romano L, et al. Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study. Am J Gastroenterol **2004**; 99:855–9.
16. Piazza M, Sagliocca L, Tosone G, et al. Sexual transmission of the hepatitis C virus and efficacy of prophylaxis with intramuscular immune serum globulin: a randomized controlled trial. Arch Intern Med **1997**; 157:1537–44.
17. Wyld R, Robertson JR, Brettle RP, Mellor J, Prescott L, Simmonds P. Absence of hepatitis C virus transmission but frequent transmission of HIV-1 from sexual contact with doubly-infected individuals. J Infect **1997**; 35:163–6.
18. Kao JH, Liu CJ, Chen PJ, Chen W, Lai MY, Chen DS. Low incidence of hepatitis C virus transmission between spouses: a prospective study. J Gastroenterol Hepatol **2000**; 15:391–5.
19. Sciacca, C, Pellicano R, Berrutti M, et al. Sexual transmission of hepatitis C virus: the Turin study. Panminerva Med **2001**; 43:229–31.
20. Marincovich B, Castilla J, del Romero J, et al. Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples. Sex Transm Infect **2003**; 79:160–2.
21. Stroffolini T, Lorenzoni U, Menniti-Ippolito F, Infantolino D, Chiaramonte M. Hepatitis C virus infection in spouses: sexual transmission or common exposure to the same risk factors? Am J Gastroenterol **2001**; 96:3138–41.
22. Wejstal R. Sexual transmission of hepatitis C virus. J Hepatol **1999**; 31(Suppl 1):92–5.
23. Conry-Cantilena C, VanRaden M, Gibble J, et al. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. N Engl J Med **1996**; 334:1691–6.
24. Watters J, Biernacki P. Targeted sampling: options for the study of hidden populations. Social Problems **1989**; 6:416–30.
25. McMahon JM, Tortu S, Torres L, Pouget ER, Hamid R. Recruitment of heterosexual couples in public health research: a study protocol. BMC Med Res Methodol **2003**; 3:1–12.
26. Alter MK, Kuhners WL, Finelli L, Centers for Disease Control and Prevention. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. MMWR Recomm Rep **2003**; 52(RR-3): 1–13, 15; quiz CE1–14.
27. Zachary P, Ullmann M, Djeddi S, et al. Evaluation of three commercially available hepatitis C virus antibody detection assays under the conditions of a clinical virology laboratory. J Clin Virol **2005**; 34:207–10.
28. Soto B, Rodrigo L, Garcia-Bengoechea M, et al. Heterosexual transmission of hepatitis C virus and the possible role of coexistent human immunodeficiency infection in the index case—a multicentre study of 423 pairings. J Intern Med **1994**; 236:515–9.
29. Marx M, Murugavel KG, Tarwater PM, et al. Association of hepatitis C virus infection with sexual exposure in Southern India. Clin Infect Dis **2003**; 37:514–20.
30. Lum PJ, Sears C, Guydish J. Injection risk behavior among women syringe exchangers in San Francisco. Subst Use Misuse **2005**; 40:1681–96.
31. Dwyer R, Richardson D, Ross MW, Wodak A, Miller ME, Gold J. A comparison of HIV risk between women and men who inject drugs. AIDS Educ Prev **1994**; 6:379–89.
32. House J. Understanding social factors and inequalities in health: 20th century progress and 21st century prospects. J Health Soc Behav **2001**; 43:125–42.
33. Samuel MC, Doherty PM, Bulterys M, Jenison SA. Association between heroin use, needle sharing and tattoos received in prison with hepatitis B and C positivity among street-recruited injecting drug users in New Mexico, USA. Epidemiol Infect **2001**; 127:475–84.
34. Raudenbush SW, Brennan RT, Barnett RC. A multivariate hierarchical model for studying psychological change within married couples. J Family Psychol **1995**; 9:161–74.
35. Kashy DA, Kenny DA. The analysis of data from dyads and groups. In: Reis HT, Judd CM, eds. Handbook of research methods in social and personality psychology. New York: Cambridge University Press, **2000**:451–77.
36. Campbell L, Kashy DA. Estimating actor, partner, and interaction ef-

fects for dyadic data using PROC MIXED and HLM: a user-friendly guide. Pers Relat **2002**; 9:327–42.
37. McMahon JM, Pouget ER, Tortu S. A guide for multilevel modeling of dyadic data with binary outcomes using SAS PROC NLMIXED. Comput Stat Data Anal **2006**; 50:3663–80.
38. Newsom JT. A multilevel structural equation model for dyadic data. Struct Equation Model **2002**; 9:431–47.
39. Kenny DA. Models of non-independence in dyadic research. J Social Pers Relat **1996**; 13:279–94.
40. Kenny DA, Cook W. Partner effects in relationship research: conceptual issues, analytic difficulties, and illustrations. Pers Relat **1999**; 6:433–48.
41. Snijders TAB, Bosker RJ. Multilevel analysis: an introduction to basic and advanced multilevel modeling. London: Sage Publications, **1999**.
42. Donner A, Koval JJ. The estimation of intraclass correlation in the analysis of family data. Biometrics **1980**; 36:19–25.
43. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat **1979**; 6:65–70.
44. Ludbrook J. Multiple comparison procedures updated. Clin Exp Pharmacol Physiol **1998**; 25:1032–7.
45. Neuhaus JM. Analysis of clustered and longitudinal binary data subject to response misclassification. Biometrics **2002**; 58:675–83.
46. Abdellafit M, Anderson RJ, Reda DJ. Automating the building of 2nd and 3rd order interactions and the construction of hierarchical logistic regression models (paper 194-27). In: Proceedings of the 27th Annual SAS Users Group International Conference (Orlando). Cary, NC: SAS, **2002**.
47. Vittinghoff E, Glidden DV, Shiboski SC, McCulloch CE. Regression methods in biostatistics. New York: Springer, **2005**.
48. Wasley A, Alter MJ. Epidemiology of hepatitis C: geographic differences and temporal trends. Semin Liver Dis **2000**; 20:1–16.
49. Newman JC, Des Jarlais DC, Turner CF, Gribble J, Cooley P, Paone D. The differential effects of face-to-face and computer interview modes. Am J Public Health **2002**; 92:294–7.
50. O'Leary A. Women at risk for HIV from a primary partner: balancing risk and intimacy. Ann Rev Sex Res **2000**; 11:191–234.