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Higher risk of incident hepatitis C virus among young women who inject drugs compared with young men in association with sexual relationships: a prospective analysis from the UFO Study cohort

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ABSTRACT

Background: Female injection drug users (IDUs) may report differences in injection behaviours that put them at greater risk for hepatitis C virus (HCV). Few studies have examined these in association with HCV incidence.

Methods: Longitudinal data from a cohort of 417 HCV-uninfected IDU aged 30 or younger were analysed. Cox proportional hazards was used to model female sex as a predictor of new HCV infection. General estimating equation (GEE) analysis was used to model female sex as a predictor of HCV-associated risk behaviour prospectively.

Results: Women were significantly more likely than men to become infected with HCV during study follow-up (HR 1.4, p<0.05), and were also more likely than men to report high-risk injecting behaviours, especially in the context of sexual and injecting relationships. Sex differences in injecting behaviours appeared to explain the relationship between sex and HCV infection.

Conclusions: Young women's riskier injection practices lead to their higher rates of HCV infection. Further study on the impact of intimate partnership on women's risk behaviour is warranted.

Strengths and limitations of this study

- Few if any studies have examined how hepatitis C virus (HCV) incidence is impacted by sex-related differences in risk behaviour.
- Data are analysed from a large well-characterised prospective cohort of young adult injectors at high risk for HCV infection, in San Francisco, California, USA.
- HCV incidence and risk measures are well defined and measured systematically.
- Women represent only one-third of the sample, which may impact power and generalisability.
- The UFO Study samples a large number of young injectors in San Francisco, but it is unknown how representative it is of the young injection drug user population in San Francisco or elsewhere.

BACKGROUND

Hepatitis C virus (HCV) is the most common of all chronic blood-borne infections in the USA,[1] and injection drug use (IDU) is a leading transmission risk. HCV infection is rapidly acquired after initiation of injecting and incidence rates are highest among newer injectors, a quarter of whom are infected within 2 years of initiating.[2–4] In studies of young adult IDU conducted over the past 10 years, HCV incidence has been documented ranging from 8% to 25%,[5 6] and prevalence ranges from 39% to 60%.[6–8] Recent reports of HCV outbreaks among young adult injectors by the US Centers for Disease Control and Prevention (CDC)[9–13] as well as new investigations in rural and suburban areas of Wisconsin, Indiana, Virginia, Pennsylvania, Florida and the American Indian Community in the Northern Plains[14] are raising serious concerns that the HCV epidemic is expanding among young people.

Young women who inject drugs may be especially vulnerable to HCV infection; however, assessments of sex differences in HCV incidence in a number of IDU cohort results have been mixed. Several studies have examined sex differences in HCV incidence in IDU, and while some found no significant differences in incidence by sex,[7 15 16] others have found higher HCV incidence among

female IDU.[17–20] There is some evidence that women engage in riskier injection practices[21]; more consistent is the finding that women are more likely to report factors indirectly associated with HCV infection, including having a regular IDU sex partner[22–24] and needing help injecting.[25] While it is presumable that any gender differences in HCV risk would correspond with different rates of HCV incidence for male and female IDU, no empiric evidence exists to date. In our own work, we had previously found sex differences in injecting risk[26] but no statistically significant difference in HCV incidence,[3] which led us to wonder whether women were biologically less susceptible than men to HCV infection. Several studies have shown that women are more likely than men to spontaneously clear HCV after initial infection[6 15 27] and that younger premenopausal women may have better chances of achieving sustained viral response to therapy as well as lower rates of disease progression,[28] suggesting that host factors specific to the female sex could affect susceptibility to HCV. If such were true, one would expect that riskier behaviour by women would not necessarily translate into higher rates of HCV infection, and that associations between direct risk factors and incident HCV might be stronger for men than women. Even if not true, there remains the possibility that factors known to be sex-specific in their associations with injecting behaviour, such as being in a heterosexual partnership with another IDU,[26] are also sex-specific in their associations with new HCV infection.

In the context of a long-term prospective observational cohort study of young adult IDU (the UFO Study), we investigated sex differences in risk behaviour and HCV incidence with the following questions in mind[1]: are there differences between young female and male IDU in terms of their risk behaviours and characteristics?[2]; do these differences correspond to differences in sex-specific rates of HCV incidence?

METHODS

The UFO Study is an ongoing prospective study of incident and acute HCV infection and its early natural history conducted in San Francisco, California. Detailed descriptions of the study methods for the UFO Study cohort have been previously published.[3 6] In brief, young adult (<30 years of age) active IDUs (injected in the past 30 days) who are HCV negative by antibody test (anti-HCV) or viremia (HCV RNA) are recruited, enrolled and followed quarterly at a community-based research site. Structured interviewer administered questionnaires are used to assess risk exposures, and participants are tested for HCV infection at follow-up visits using anti-HCV (EIA-3; Ortho Clinical Diagnostics, Raritan, New Jersey, USA) and qualitative HCV RNA testing (Procleix HIV-1/HCV assay, Gen-Probe Inc, San Diego, California, USA).

In this analysis, we included data from male and female participants enrolled in the UFO Study from January 2000 to October 2012 and who returned for at least one follow-up visit. Demographic and drug-use variables including: age of first injection, frequency of injecting, drugs injected, reuse of a syringe, reuse of a cooker (ie, a spoon or other small-sized container used for preparing drug for injection), use of a syringe previously used by another injector, use of a cooker previously used by another injector, injecting the drug residue from a cooker or cotton previously used by another injector during drug preparation ('doing a rinse'), pooling money with others to buy drugs and having a steady sex partner were obtained from interview data. Participants who reported having a steady sex partner were asked whether their partner was also an IDU. All behaviours were reported for the prior 3 months except for frequency of injection, which was reported for the prior month. Incident HCV infection was defined as the new detection of HCV (either by RNA or anti-HCV testing) in a participant whose previous tests were negative.

We assessed baseline differences in risk characteristics between men and women using the χ^2 test for categorical variables and the Wilcoxon test for continuous variables. To determine whether sex was associated with risk exposures during follow-up, we employed GEE-based logistic regression to model female sex as the sole predictor of each factor, analysed separately. We assessed associations between individual exposure variables, including sex, and new HCV infection by modelling each variable as a predictor of new infection using Cox proportional hazards, both overall and stratified by sex. To examine differences between sexes in stratified models, we included an interaction term between each predictor variable and sex in a non-stratified model and used likelihood ratio tests to determine statistical significance. To see whether sex differences in behaviour were indirectly associated with sex differences in incident HCV infection, we entered any behavioural variable associated with sex and with incident HCV (in bivariate analysis) individually into a Cox model that contained female sex as its primary predictor and compared the effect estimate for female sex when it was the only variable in the model. For all Cox models, we used the robust sandwich estimator of covariance to account for repeated observations. For GEE models, we specified an exchangeable correlation matrix. All analyses were conducted using SAS V.9.2 (SAS Institute Inc, Cary, North Carolina, USA).

The protocol and all study procedures were reviewed and approved by the University of California San Francisco (UCSF) Institutional Review Board. Written informed consent was obtained from each participant prior to engaging in any research activities.

RESULTS

Between January 2000 and October 2012, 1464 male and female young adult IDU were recruited into the UFO study, administered a baseline interview and tested

for HCV. Those who tested negative for HCV antibody as well as HCV RNA (58.6%) were eligible to participate in the UFO cohort (n=858); of these, 614 agreed to participate in the study and 417 (277 men and 140 women) returned for at least one follow-up visit. Participants with follow-up compared with non-participants/participants without (w/o) follow-up, respectively, tended to be slightly older (median 22 vs 21 years, p<0.01), less likely to report reuse of a cooker (59% vs 68%, p<0.01), use of a cooker previously used by another injector (32% vs 40%, p<0.05), pooling money with more than one other IDU to buy drugs (61% vs 69%, p<0.05), were more likely to report injecting alone (72% vs 65%, p<0.05), pooling money with only one other IDU to buy drugs (20% vs 15%, p<0.05) and having a steady IDU sex partner (41% vs 35%, p<0.05). Differences were consistent by sex, except that participating men (vs non-participant men and male participants w/o follow-up) were less likely to report reuse of a cooker (53% vs 66%, p<0.01), pooling money with more than one other IDU to buy drugs (58% vs 67%, p<0.05), were more likely to report injecting every day over the past 30 days (29% vs 20%, p<0.05) and have a steady sex partner (44% vs 35%, p<0.05). Participating women (vs non-participant women and female participants w/o follow-up) were more likely to report injecting every day over the past 30 days (38% vs 22%, p<0.01) and less likely to report use of a cooker previously used by another injector (37% vs 52%, p<0.05). Among all participants, self-reported HIV prevalence was 2%; those reporting HIV

Table 1 Baseline characteristics of women and men participating in the UFO Study with at least one follow-up visit (N=424)

	Females (n=140)	Males (n=277)	p Value
Age	21.6 (3.4)	23.5 (3.3)	<0.01
Non-white race	38 (27.3%)	68 (24.6%)	0.57
HIV positive by self-report	2 (1.54%)	9 (3.41%)	0.29
Age of first injection	17.9 (3.5)	19.1 (3.9)	<0.01
Years injecting, median (IQR)	3 (1–5)	4 (1–7)	0.02
Ever used another's syringe	83 (66.9%)	139 (58.7%)	0.12
Ever lent a used syringe	92 (74.2%)	149 (62.6%)	0.03
Ever reused a cooker	111 (80.4%)	194 (70.8%)	0.04
Past 3 months			
Injected heroin	116 (82.9%)	193 (69.9%)	<0.01
Injected speed	73 (52.5%)	175 (63.2%)	0.04
Injected cocaine	39 (27.9%)	82 (29.6%)	0.71
Reused a rig	117 (83.6%)	221 (80.4%)	0.43
Reused a cooker	98 (70.0%)	146 (52.7%)	<0.01
Used a syringe previously used by another injector	59 (42.5%)	85 (30.8%)	0.02
Used a cooker previously used by another injector	52 (37.4%)	80 (29.5%)	0.11
Did a rinse	60 (42.9%)	86 (31.2%)	0.02
Number of borrowing partners*			
0	80 (57.6%)	191 (69.5%)	<0.01
1	38 (27.3%)	39 (14.2%)	
>1	21 (15.1%)	45 (16.4%)	
Frequency of injecting alone			
Never	42 (30.0%)	75 (27.2%)	0.53
Sometimes	89 (63.57%)	175 (63.4%)	
Always	9 (6.43%)	26 (9.42%)	
Frequency of pooling			
Never	15 (10.7%)	61 (22.1%)	<0.01
Sometimes	83 (59.3%)	166 (60.1%)	
Always	42 (30.0%)	49 (17.8%)	
Number of pooling partners†			
0	15 (10.7%)	64 (23.2%)	<0.01
1	31 (22.1%)	52 (18.8%)	
>1	94 (67.1%)	160 (58.0%)	
Had a steady sex partner	90 (64.8%)	120 (43.5%)	<0.01
Had a steady sex partner who was also an IDU	81 (58.3%)	90 (32.6%)	<0.01
Past month			
Days injected, median (IQR)	23 (10–30)	18 (7–30)	0.02
Injected every day	30 (21.7%)	60 (19.8%)	0.04

*Participants were asked to report the total number of people from whom they borrowed a previously used needle to inject.
†Participants were asked to report the total number of people with whom they pooled money in order to purchase drugs.
IDU, injection drug user.

positive status were more likely to be followed than HIV negative or unknown (3% vs 1%, p<0.05). Participating men (vs non-participant men and male participants w/o follow-up) were more likely to report being HIV positive at borderline significance (3.4% vs 1.1%, p=0.07); however, there were no significant differences in self-reported HIV prevalence between participating women (vs non-participant women and female participants w/o follow-up).

Female participants with follow-up were younger than male participants with follow-up (median 21 vs 23 years, p<0.01) at the time of enrolment and reported younger age of initiation of injecting (median 17 vs 19 years, p<0.01; table 1). At baseline interviews, women reported greater injection risk, compared with men (respectively), including: greater frequency of injecting (median 23 vs 18 days of past month, p<0.05), primarily injecting heroin (83% vs 70%, p<0.01), use of a syringe previously used by another injector (43% vs 31%, p<0.05), reuse of a cooker (70% vs 53%, p<0.01) and doing a rinse (43% vs 31%, p<0.05). Women were also more likely to report pooling money to buy drugs (89% vs 78%, p<0.01) and having steady IDU sex partner (58% vs 33%, p<0.01). Women were less likely to report injecting speed (53% vs 63%, p<0.05). Baseline self-reported HIV prevalence was not significantly different between women and men (1.5% vs 3.4%, p=0.29). During study follow-up, women more frequently reported risky injection practices, including: borrowing used syringes (OR=1.8, 95% CI: 1.3 to 2.6), reuse of a cooker previously used by another injector (OR=1.5, 95% CI: 1.03 to 2.3) and doing a rinse (OR 1.9, 95% CI 1.3 to 2.7) (table 2). Women were also more likely to report injecting every day (OR=1.5, 95% CI: 1.1 to 2.2), injecting heroin (OR=2.1, 95% CI: 1.4 to 3.1), pooling money with others to buy drugs (OR=2.1, 95% CI: 1.5 to 3.0) and having a steady IDU sex partner (OR=3.8, 95% CI: 2.7 to 5.3). Women were significantly less likely than men to report injecting alone (OR=0.31, 95% CI: 0.2 to 0.5).

Table 2 Odds of risk behaviour during follow-up as predicted by female sex

Outcomel	OR (95% CI)	p Value
Injected every day	1.53 (1.06 to 2.22)	0.02
Injected heroin	2.10 (1.40 to 3.13)	<0.01
Injected speed	0.86 (0.61 to 1.22)	0.40
Reused a syringe	1.02 (0.72 to 1.44)	0.92
Reused a cooker	2.02 (1.46 to 2.80)	<0.01
Used a syringe previously used by another injector	1.82 (1.27 to 2.60)	0.01
Used a cooker previously used by another injector	1.55 (1.03 to 2.33)	0.03
Did a rinse	1.88 (1.31 to 2.69)	<0.01
Borrowed needles from only one other person	2.08 (1.41 to 3.07)	<0.01
Borrowed needles from >1 person	1.08 (0.62 to 1.90)	0.78
Injected alone	0.99 (0.70 to 1.40)	0.96
Always injected alone	0.31 (0.19 to 0.53)	<0.01
Pooled with others to buy drugs	2.14 (1.51 to 3.02)	<0.01
Always pooled to buy drugs	2.42 (1.61 to 3.63)	<0.01
Pooled with only one other person	1.48 (1.06 to 2.07)	0.02
Pooled with >1 person	1.66 (1.19 to 2.31)	<0.01
Had a steady sex partner	3.50 (2.45 to 4.98)	<0.01
Had a steady sex partner who was also an IDU	3.76 (2.66 to 5.33)	<0.01

IDU, injection drug user.

Over a period of 11+ years of data collection, 1497 unique risk intervals were captured, during which these 417 participants were followed for a total of 650 person-years (PY) of follow-up. During the period, 129 new HCV infections, 78 in men and 51 in women, were identified resulting in an incidence rate of 19.8/100 PY (95% CI: 19.1 to 20.6). The HCV incidence rate was significantly higher in women than in men ((25.4/100 PY; 95% CI: 24.0 to 26.8) vs (17.3/100 PY; 95% CI: 16.4 to 18.3); HR=1.4 (95% CI: 1.03 to 2.0; table 3)). Variables significantly associated with incident HCV infection among the total study sample in unadjusted analysis were: injecting every day (HR=2.6, 95% CI: 1.8 to 3.1), injecting heroin (HR=2.7; 95% CI: 1.8 to 4.1), injecting cocaine (HR=2.3; 95% CI: 1.7 to 3.3), use of a syringe previously used by another injector (HR=2.6; 95% CI: 1.9 to 3.7), use of a cooker previously used by another injector (HR=2.4; 95% CI: 1.7 to 3.4), doing a rinse (HR=2.7; 95% CI: 1.9 to 3.7), injecting alone (HR=2.0; 95% CI: 1.3 to 2.9) and having a steady IDU sex partner (HR=2.23, 95% CI: 1.58 to 3.14). There were no significant interactions between any of the risk variables and sex in predicting new HCV infection.

We examined the indirect effects of risk behaviours and other factors on association between sex and HCV incidence, and found that in many cases the effect size and the statistical significance of the sex/HCV associations were diminished; variables which reduced the HR by greater than 10% were age, years injecting, injecting heroin, number of pooling partners, having a steady sex partner and having a steady IDU sex partner (table 4).

DISCUSSION

HCV incidence among young adult IDU remains extremely high and efforts to reduce this will require multiple targeted approaches. The overall incidence in this group is in San Francisco, 19% is comparable to that seen in other locales. For instance, in the DUIT study conducted in five US cities (Baltimore, Chicago, Los Angeles, New York and Chicago) had a similar incidence of (18.1/100 PY).[29] One way to target prevention could be sex-specific. Women in our sample reported more frequent risk behaviour at baseline and throughout their study participation, and had a significantly higher unadjusted incidence of HCV than men. When

Table 3 Predictors of incident HCV infection stratified by sex*

	All participants		Females (n=140)		Males (n=277)	
	HR	p Value	HR	p Value	HR	p Value
Female	1.43 (1.03 to 2.00)	0.03				
Age	0.92 (0.88 to 0.96)	<0.01	0.93 (0.86 to 1.01)	0.07	0.93 (0.88 to 0.98)	0.01
Non-white race	0.91 (0.61 to 1.34)	0.62	1.19 (0.64 to 2.23)	0.59	0.77 (0.47 to 1.27)	0.31
Age of first injection	0.96 (0.93 to 1.00)	0.048	0.96 (0.90 to 1.03)	0.29	0.97 (0.92 to 1.02)	0.17
Years injecting	1.00 (0.96 to 1.05)	0.84	1.02 (0.95 to 1.09)	0.69	1.01 (0.96 to 1.07)	0.67
Injected every day	2.58 (1.84 to 3.62)	<0.01	2.06 (1.17 to 3.66)	0.01	2.86 (1.87 to 4.38)	<0.01
Injected heroin	2.71 (1.79 to 4.11)	<0.01	2.34 (1.14 to 4.83)	0.02	2.87 (1.73 to 4.75)	<0.01
Injected speed	1.48 (1.05 to 2.08)	0.03	1.12 (0.65 to 1.92)	0.68	1.80 (1.13 to 2.84)	0.01
Injected cocaine	2.32 (1.65 to 3.26)	<0.01	2.27 (1.34 to 3.83)	<0.01	2.49 (1.59 to 3.91)	<0.01
Reused a syringe	1.68 (1.11 to 2.54)	0.01	1.65 (0.85 to 3.19)	0.14	1.71 (1.1 to 2.91)	0.05
Reused a cooker	2.38 (1.70 to 3.33)	<0.01	1.96 (1.13 to 3.43)	0.02	2.47 (1.61 to 3.79)	<0.01
Used a syringe previously used by another injector	2.64 (1.88 to 3.70)	<0.01	2.71 (1.56 to 4.71)	<0.01	2.47 (1.61 to 3.79)	<0.01
Used a cooker previously used by another injector	2.38 (1.67 to 3.40)	<0.01	2.16 (1.31 to 3.59)	<0.01	2.26 (1.37 to 3.72)	<0.01
Did a rinse	2.66 (1.92 to 3.70)	<0.01	1.93 (1.13 to 3.28)	0.02	3.22 (2.16 to 4.81)	<0.01
Number of borrowing partners						
1 (vs 0)	2.74 (1.84 to 4.09)	<0.01	3.31 (1.88 to 5.82)	<0.01	2.22 (1.26 to 3.91)	<0.01
>1 (vs 0)	2.54 (1.59 to 4.06)	<0.01	1.78 (0.73 to 4.35)	0.2	2.93 (1.74 to 4.95)	<0.01
Frequency of Injecting alone						
Sometimes (vs never)	2.20 (1.48 to 3.26)	<0.01	1.84 (1.03 to 3.29)	0.04	2.54 (1.48 to 4.36)	<0.01
Always (vs never)	0.96 (0.50 to 1.83)	0.9	1.12 (0.34 to 3.70)	0.85	1.11 (0.50 to 2.45)	0.79
Frequency of pooling						
Sometimes (vs never)	2.53 (1.70 to 3.76)	<0.01	1.61 (0.78 to 3.33)	0.2	2.93 (1.83 to 4.68)	<0.01
Always (vs never)	2.33 (1.40 to 3.87)	<0.01	2.29 (1.04 to 5.02)	0.04	1.56 (0.68 to 3.61)	0.3
Number of pooling partners						
1 (vs 0)	2.62 (1.66 to 4.14)	<0.01	1.94 (0.88 to 4.27)	0.1	2.91 (1.65 to 5.12)	<0.01
>1 (vs 0)	2.50 (1.65 to 3.78)	<0.01	1.84 (0.87 to 3.87)	0.11	2.61 (1.58 to 4.34)	<0.01
Had a steady sex partner	1.73 (1.22 to 2.46)	<0.01	1.73 (0.88 to 3.39)	0.11	1.52 (0.96 to 2.38)	0.07
Had a steady sex partner who was also an IDU	2.23 (1.58 to 3.14)	<0.01	2.55 (1.32 to 4.94)	<0.01	1.88 (1.20 to 2.95)	<0.01

*Although interactions between primary predictor variables and female sex were also modelled, none reached significance at p<0.20.
HCV, hepatitis C virus; IDU, injection drug user.

adjusted for risk factors that were more frequently reported by women, the HR for female sex for HCV infection decreased in magnitude and in statistical significance, leading us to conclude that female participants' higher HCV incidence rate was principally associated with their increased risk behaviour. Our results did not support the hypothesis that women are biologically less susceptible to new HCV infection.

These findings are consistent with several previous studies documenting higher incidence of blood-borne infections in female versus male IDU[17–20 25 30] but are in contrast with others.[7 15 16] These inconsistencies may be associated with various factors including: small sample size,[7] the inclusion of older IDU who have lower risk profiles overall compared with their younger counterparts[15 31–33] or both.[16] All 417 IDU included in this analysis were under 30 years of age at the time of their enrolment into the study. In early analyses of 195 UFO participants, we found a HR for sex similar to that found here (1.5) but that was not statistically significant,[3] confirming that sample size has important bearing on the detection of significant sex differences in HCV incidence in this population.

That women in the UFO cohort were more likely than men to report engaging in high-risk behaviour prior to their enrolment as well as throughout the course of their study participation deserves attention. Heroin injection, reuse of a cooker, doing a rinse, pooling with others to buy drugs and having a steady IDU sex partner were more common among women. One potential explanation proposed for differential risk behaviour among women is with respect to the complexities inherent in their relationships with male IDU. In our sample, women were also more likely than men to report borrowing used syringes from only one other IDU. Although it is unclear whether or not borrowing behaviour occurred within the context of an intimate relationship, the excess risk associated with borrowing from one IDU was higher (HR=3.31) than from more than one IDU (HR=1.78; vs no borrowing). Among men, there

Table 4 HRs for incident HCV for women versus men, adjusted by risk behaviour, one at a time

	HR Females vs males (95% CI)	p Value
Unadjusted	1.43 (1.03 to 2.00)	0.03
Age of first injection	1.33 (0.95to 1.86)	0.10
Years injecting	1.45 (1.04 to 2.02)	0.03
Injected every day*†	1.36 (0.98 to 1.89)	0.06
Injected heroin*†	1.28 (0.91 to 1.80)	0.16
Injected speed	1.48 (1.06 to 2.06)	0.02
Injected cocaine	1.42 (1.02 to 1.97)	0.04
Reused a syringe	1.43 (1.02 to 1.99)	0.04
Reused a cooker*†	1.30 (0.93 to 1.82)	0.12
Used a syringe previously used by another injector	1.30 (0.94 to 1.81)	0.12
Used a cooker previously used by another injector	1.35 (0.97 to 1.89)	0.08
Did a rinse*†	1.29 (0.93 to 1.80)	0.13
Number of borrowing partners	1.29 (0.93 to 1.80)	0.13
Frequency of injecting alone	1.43 (1.03 to 1.99)	0.03
Frequency of pooling	1.29 (0.92 to 1.81)	0.14
Number of pooling partners	1.28 (0.89 to 1.77)	0.19
Had a steady sex partner*†	1.27 (0.90 to 1.79)	0.18
Had a steady sex partner who was also an IDU*†	1.16 (0.83 to 1.64)	0.38

*Significantly associated with female sex at baseline.
†Significantly associated with female sex during follow-up.
HCV, hepatitis C virus; IDU, injection drug user.

was no difference in risk by number of people they borrowed from (table 3). The absence of a dose–response relationship between the number of partners from which one borrowed used syringes and the hazard of new HCV infection is somewhat counterintuitive, but the results—at least for women—suggest the need for sex-specific models that acknowledge potential partnership associated risks. Supporting this is our finding as well as in others[22 25] that female IDU were more likely to report being in a sexual partnership with another IDU. Several qualitative studies have reported that sexual relationships between IDU are frequently based on commitment, trust and sharing; intimacy factors that may be incompatible with HCV risk avoidance.[34–36] Female IDU, who are sometimes dependent on male IDU partners for resources such as drugs and injecting equipment and for physical safety and support, may therefore be in a position that makes it more difficult for them to practice safe injecting within the context of such a partnership.[37] The complexities that intimate relationships introduce to HCV risk deserve more attention, however, and may be difficult to disentangle completely with quantitative data.

Given the previous literature about differences in injecting behaviour by sex along with our initial idea that women may be biologically less susceptible to HCV infection, we hypothesised that some risk factors might be more or less strongly associated with HCV infection by sex. We tested this two ways: (1) stratifying by sex and (2) by adding interaction terms to our regression models. While some factors did appear to be more strongly associated with HCV infection in women than men in stratified analysis, statistical significance was not reached for any interactions. As an example, women had higher odds compared with men of having a steady IDU/sex partner, of having only one borrowing partner and of pooling drugs, but none of these exposures conferred a significantly higher hazard of HCV. Conversely, men reported higher odds of several risk factors than women (for instance 'doing a rinse'), which were also not associated with increased HCV risk.

Our analysis has some limitations. There were fewer women in the cohort than men, which could have impacted power to detect interactions. It is unknown how representative our sample is of the entire young IDU population in San Francisco, as little data exist in this regard. However, in a recent analysis of data from two other studies of IDU conducted in San Francisco, including one that used respondent-driven sampling methods, women similarly represented a minority of the sample (25%).[38] There were some differences in risk characteristics between the participants included in our analysis versus those who refused enrolment or were lost to follow-up after their baseline visit, but we think it unlikely that these differences introduced systematic bias into our findings pertaining to sex differences. We used a modelling technique by which each participant's overall study experience was subdivided into individual risk periods delineated by the dates of his or her baseline and follow-up interviews. Follow-up questionnaires administered during structured interviews assessed risk behaviours over 3-month intervals; however, there were cases in which the duration of time between a participant's interviews exceeded 3 months (median duration between interviews was 3.3 months (IQR 3.03, 4.90)). For intervals longer than 3 months, there may have been misclassification of the risk behaviours, which if non-differential would have caused bias towards the null. Risk behaviour was assessed by self-report and is vulnerable to reporting bias, including due to social desirability, which would also result in underestimated risk estimates. However, given that differences in self-reported risk behaviours appeared to explain the association between sex and HCV, the validity of the self-report is supported. The strengths of this research include well-defined and systematically collected measures of risk and infection collected prospectively and over a large sample.

The results of this study contribute significantly to the research and public health knowledge regarding differences in risk and HCV acquisition between young male and female IDU. While young IDU of both sexes have high rates of unsafe injecting behaviours and concomitant high rates of HCV infection, women reported consistently higher levels of risk in a variety of measures. Our

findings call for further research on the reasons for such differences, including special focus on the impact of being in an intimate heterosexual partnership on injecting risk behaviour, as well as new prevention approaches that specifically target young women and encourage safe injecting behaviour, especially in the context of overlapping sexual and injecting relationships.

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