BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-004988
Article Type:	Research
Date Submitted by the Author:	02-Feb-2014
Complete List of Authors:	Tracy, Daniel; Albert Einstein College of Medicine, Hahn, Judith; UCSF, Medicine Fuller Lewis, Crystal; Columbia University, Mailman School of Public Health Evans, Jennifer; UCSF, Epidemiology & Biostatistics Briceno, Alya; UCSF, Epidemiology & Biostatistics Morris, Meghan; UCSF, Epidemiology & Biostatistics Lum, Paula; UCSF, Positive Health Program Page, Kimberly; University of California San Francisco, Epidemiology & Biostatistics
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Addiction, Epidemiology, Infectious diseases, Public health
Keywords:	Substance misuse < PSYCHIATRY, PUBLIC HEALTH, Epidemiology < INFECTIOUS DISEASES

Title

Higher risk of incident hepatitis C virus among young females who inject drugs compared to young males in association with sexual relationships: a prospective analysis from the UFO Study Cohort

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Word count: Abstract: 157; Text 3000; Tables: 4.

Abstract

BACKGROUND**:** Female injection drug users may report differences in injection behaviors that put them at greater risk for 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 analyzed. Cox proportional hazards was used to model female sex as a predictor of new HCV infection. GEE was used to model female sex as a predictor of HCV-associated risk behavior prospectively.

RESULTS: Females were significantly more likely than males to become infected with HCV during study follow-up (HR 1.4, $p<0.05$), and were also more likely than males to report high risk injecting behaviors, especially in the context of sexual and injecting relationships. Such behaviors appeared to mediate the relationship between sex and HCV infection.

CONCLUSIONS: Young females' riskier injection practices leads to their higher rates of HCV infection. Further study on the impact on intimate partnership on females' risk behavior is warranted.

Key Words: young injection drug users, females; hepatitis C virus; relationship risks

Article summary

Article Focus

- Hepatitis C virus (HCV) is the most common of all chronic blood-borne infections in the United States and injection drug use is a leading transmission risk with rapid rates of infection occurring soon after injection initiation.
- Young women who inject drugs may especially vulnerable to HCV infection and some, but not all assessments have suggested differences in high-risk injection practices and incidence of HCV.
- This study was undertaken to more fully assess sex-related differences in risk for and HCV infection rates in a well-characterized cohort of young injectors.

Strengths and Limitations

- Few if any studies have examined how HCV incidence is impacted by sex-related differences in risk behavior.
- Data are analyzed from a large well characterized prospective cohort of young adult injectors at high risk for HCV infection, in San Francisco, California.
- HCV incidence and risk measures are well-defined and measured systematically.
- Women represent only one-third of the sample, which may impact power and generalizability.
- The UFO Study samples a large number of young injectors in San Francisco, but it is unknown how representative it is of the young IDU population in San Francisco or elsewhere.

Key Messages

- Young female injectors have specific risk factors that put them at higher risk of HCV infection compared to men, especially in association with social and sexual partnerships.
- Risk behavior differences between female and male injectors should be addressed in prevention programs targeting young injectors.

Author Contributions: All authors contributed to this manuscript. DT, JAH, and KP compiled the first draft of the manuscript, and authors CFL, JE, AB, MDM, and PJL reviewed and provided further scientific and editorial input. The primary statistical analysis was conducted by DT; JE provided supplemental data review, and JAH and KP reviewed all data analyses. All authors contributed to and have approved the final manuscript. KP, JAH, JE, AB, MDM, PJL, and KP designed and conducted the UFO Study from which data for this study were obtained. All authors provided expertise on the research presented in this manuscript including the methods, analysis, and final manuscript.

Data Sharing: no additional data available.

Background

Hepatitis C virus (HCV) is the most common of all chronic blood-borne infections in the United States(1) and injection drug use 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% and 25% (5, 6), and prevalence ranges from 39% to 60% (6-8). Recent reports of HCV outbreaks among young adult injectors by the U.S. 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 cohorts the 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 amongst female IDU (17-20). There is some evidence that females engage in riskier injection practices (21); more consistent is the finding that females 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 if 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 (SVR) to therapy as well 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 behavior by females would not necessarily translate into higher rates of HCV infection, and that associations between direct risk factors and incident HCV might be stronger for males than females. Even if not true, there remains the possibility that factors known to be sex-specific in their associations with injecting behavior, such as being in a heterosexual partnership 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-behavior and HCV incidence with the following questions in mind: (1) are there differences between young female and male IDU in terms of their risk-behaviors and characteristics?; (2) do these differences correspond to differences in sex-specific rates of HCV incidence?; and, 3) are there risk-factors associated with incident HCV infection that differ between males and females?

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 IDU (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 NJ), and qualitative HCV RNA testing (Procleix® HIV-1/HCV assay, Gen-Probe Inc., San Diego).

In this analysis, we included data from male and female participants enrolled in the UFO Study from January 2000 through 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, 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 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 if their partner was also an IDU. All behaviors 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. All study procedures were reviewed and approved by the UCSF Institutional Review Board.

We assessed baseline differences in risk characteristics between males and females using the chi-square test for categorical variables and the Wilcoxon test for continuous variables. To determine if 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, analyzed separately. We assessed associations between individual exposure variables, including sex, and new HCV infection by modeling 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 examine potential mediation by the behavioral variables that were associated with both sex and incident HCV infection, we entered each variable 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 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

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 both HCV-antibody and 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 males and 140 females) returned for at least one follow-up visit. Participants with follow-up compared to 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), and pooling money with more than one other IDU to buy drugs (61% vs. 69%, p<0.05), and 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 males (vs. non-participant males 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) and 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 females (vs. non-participant females 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).

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 enrollment and reported younger age of initiation of injecting (median 17 vs. 19 years, p<0.01) (Table 1). At baseline interviews, females reported greater injection risk, compared to males (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). Females 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). Females were less likely to report injecting speed (53% vs. 63%, p<0.05). During study follow-up, females more frequently reported risky injection practices, including: borrowing used syringes (OR: 1.8, 95%CI: 1.3, 2.6), reuse of a cooker previously used by another injector (OR: 1.5, 95%CI: 1.03, 2.3), and doing a rinse (OR: 1.9, 95%CI: 1.3, 2.7) (Table 2). Females were also more likely to report injecting every day (OR: 1.5, 95%CI: 1.1, 2.2), injecting heroin (OR: 2.1, 95%CI: 1.4, 3.1), pooling money with others to buy drugs (OR: 2.1, 95%CI: 1.5, 3.0), and having a steady IDU sex partner (OR: 3.8, 95%CI: 2.7, 5.3). Females were significantly less likely than males to report injecting alone (OR: 0.31, 95%CI: 0.2, 0.5).

Over a period of 11+ years of data collection, 1497 unique risk intervals were captured, during which these 417 subjects were followed for a total of 650 person-years (PY) of follow up. During the period, 129 new HCV infections, 78 in males and 51 in females, were identified resulting in an incidence rate of 19.8/100 PY (95% CI: 19.1, 20.6). The HCV incidence rate was significantly higher in females than in males (25.4/100 PY; 95% CI: 24.0, 26.8) vs. (17.3/100 PY; 95% CI: 16.4, 18.3); hazard ratio (HR) 1.4 (95% CI: 1.03, 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, 3.1), injecting heroin (HR: 2.7; 95%CI: 1.8, 4.1), injecting cocaine (HR: 2.3; 95%CI: 1.7, 3.3), use of a syringe previously used by another injector (HR: 2.6; 95%CI: 1.9, 3.7), use of a cooker previously used by another injector (HR: 2.4; 95%CI: 1.7, 3.4), doing a rinse (HR: 2.7; 95%CI: 1.9, 3.7), injecting alone (HR: 2.0; 95%CI: 1.3, 2.9), and having a steady IDU sex partner (HR: 2.23, 95%CI: 1.58, 3.14). There

were no significant interactions between any of the risk variables and sex in predicting new HCV infection.

We examined risk behaviors and other factors as mediators of the 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 hazard ratio 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

Females in our sample reported more frequent risk behavior at baseline and throughout their study participation, and had a significantly higher unadjusted incidence of HCV than males. When adjusted for risk factors that were more frequently reported by females, the hazard ratio 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 behavior. Our results did not support the hypothesis that females 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, 29) but are in contrast with others (7, 15, 16). These inconsistencies may be associated various factors including: small sample size (7), the inclusion of older IDU who have lower risk profiles overall compared to their younger counterparts (15, 30-32), or both (16). All 417 IDU included in this analysis were under 30 years of age at the time of their enrollment into the study. In early analyses of 195 UFO participants, we found a hazard ratio 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 females in the UFO cohort were more likely than males to report engaging in risk behavior both prior to their enrollment as well as throughout the course of their study participation deserves attention. Female sex was significantly associated with several important risk factors including injecting heroin, reuse of a cooker, doing a rinse, pooling with others to buy drugs, and

having a steady IDU sex partner. There are several potential interpretations of this finding: one possibility is that aspects inherent to heterosexual partnership between IDU influence the likelihood of engaging in risk behavior differently for males and females; in other words, female IDUs' higher overall rates of risk behavior may be consequent to complexities of their sexual and injecting relationships with male IDU partners. In this study as well as in others (22, 25), 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 (33-35). Some have suggested that 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 be in a position that makes it more difficult for them to practice safe injecting within the context of such a partnership (36).

Given the previous literature about differences in injecting behavior by sex along with our initial idea that females may be biologically less susceptible to HCV infection, we hypothesized 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 females than males in stratified analysis, statistical significance was not reached for any interactions. As an example, females had higher odds compared to males of having a steady IDU/sex partner and a non-significantly higher hazard of HCV in association with this characteristic (HR: 2.55 vs. 1.88, p for interaction with sex <0.26). The complexities that intimate relationships introduce to HCV risk deserve more attention, however, and may be

difficult to disentangle completely with quantitative data. In our sample, females were also more likely than males to report borrowing used syringes from only one other IDU. Although it is unclear whether or not borrowing behavior occurred within the context of an intimate relationship, the HRs for HCV for borrowing from one IDU and from more than one IDU (vs. no borrowing) were 3.31 ($p<0.01$) and 1.78 ($p\leq0.20$) for females, respectively, while the HRs for males were 2.22 ($p<0.01$) and 2.93 ($p<0.01$). One might expect a dose-response relationship between the number of partners from which one borrowed used syringes and the hazard of new HCV infection, but the results for females suggest the need for sex-specific models that acknowledge intimate partnerships as high-risk contexts for young female IDUs.

Our analysis has some of limitations. There were fewer women in the cohort than males, 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 exists 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%)(37). There were some differences in risk characteristics between the participants included in our analysis versus those who refused enrollment 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 modeling technique by which each subject'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 behaviors over three month intervals, however there were cases in which the duration of time between a participant's interviews

exceeded three 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 behaviors, which if non-differential would have caused bias toward the null. Risk behavior 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 behaviors 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 behaviors and concomitant high rates of HCV infection, females 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 behavior, as well as new prevention approaches that specifically target young women and encourage safe injecting behavior, especially in the context of overlapping sexual and injecting relationships.

Table 1: Baseline characteristics of females and males participating in the UFO Study with at least 1 follow-up visit (N=424)

	Females (n=140)	Males (n=277)	P
Age	21.6 (3.4)	23.5 (3.3)	<0.01
Non-white race	38 (27.3%)	68 (24.6%)	0.57
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
# 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%)	
# 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 IDU sex partner	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

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

Outcome	OR (95% CI)	p
Injected every day	1.53 (1.06, 2.22)	0.02
Injected heroin	2.10 (1.40, 3.13)	<0.01
Injected speed	0.86 (0.61, 1.22)	0.40
Injected cocaine	1.15 (0.78, 1.70)	0.47
Reused a syringe	1.02 (0.72, 1.44)	0.92
Reused a cooker	2.02 (1.46, 2.80)	<0.01
Used a syringe previously used by another injector	1.82 (1.27, 2.60)	0.01
Used a cooker previously used by another injector	1.55 (1.03, 2.33)	0.03
Did a rinse	1.88 (1.31, 2.69)	<0.01
Borrowed from 1 person only	2.08 (1.41, 3.07)	<0.01
Borrowed from >1 person	1.08 (0.62, 1.90)	0.78
Injected alone	0.99 (0.70, 1.40)	0.96
Always injected alone	0.31 (0.19, 0.53)	<0.01
Poole with others to buy drugs	2.14 (1.51, 3.02)	<0.01
Always pooled to buy drugs	2.42 (1.61, 3.63)	<0.01
Pooled with 1 person only	1.48 (1.06, 2.07)	0.02
Pooled with >1 person	1.66 (1.19, 2.31)	<0.01
Had a steady sex partner	3.50 (2.45, 4.98)	<0.01
Had a steady IDU sex partner	3.76 (2.66, 5.33)	<0.01

Table 3: Predictors of incident HCV infection stratified by sex

	All Participants		Females (n = 140)		Males (n = 277)		p for interaction with sex
	Hazard Ratio	p	Hazard Ratio	p	Hazard Ratio	p	
Female	1.43 (1.03 – 2.00)	0.03					
Age	0.92 (0.88, 0.96)	<0.01	0.93 (0.86, 1.01)	0.07	0.93 (0.88, 0.98)	0.01	0.87
Non-white race	0.91 (0.61, 1.34)	0.62	1.19 (0.64, 2.23)	0.59	0.77 (0.47, 1.27)	0.31	0.37
Age of first injection	0.96 (0.93, 1.00)	0.048	0.96 (0.90, 1.03)	0.29	0.97 (0.92, 1.02)	0.17	0.82
Years injecting	1.00 (0.96, 1.05)	0.84	1.02 (0.95, 1.09)	0.69	1.01 (0.96, 1.07)	0.67	0.93
Injected every day	2.58 (1.84, 3.62)	<0.01	2.06 (1.17, 3.66)	0.01	2.86 (1.87, 4.38)	<0.01	0.53
Injected heroin	2.71 (1.79, 4.11)	<0.01	2.34 (1.14, 4.83)	0.02	2.87 (1.73, 4.75)	<0.01	0.73
Injected speed	1.48 (1.05, 2.08)	0.03	1.12 (0.65, 1.92)	0.68	1.80 (1.13, 2.84)	0.01	0.36
Injected cocaine	2.32 (1.65, 3.26)	<0.01	2.27 (1.34, 3.83)	<0.01	2.49 (1.59, 3.91)	<0.01	0.91
Reused a syringe	1.68 (1.11, 2.54)	0.01	1.65 (0.85, 3.19)	0.14	1.71 (1.1, 2.91)	0.05	0.83
Reused a cooker	2.38 (1.70, 3.33)	<0.01	1.96 (1.13, 3.43)	0.02	2.47 (1.61, 3.79)	<0.01	0.69
Used a syringe previously used by another injector	2.64 (1.88, 3.70)	<0.01	2.71 (1.56, 4.71)	<0.01	2.47 (1.61, 3.79)	<0.01	0.65
Used a cooker previously used by another injector	2.38 (1.67, 3.40)	<0.01	2.16 (1.31, 3.59)	<0.01	2.26 (1.37, 3.72)	<0.01	0.92
Did a rinse	2.66 (1.92, 3.70)	<0.01	1.93 (1.13, 3.28)	0.02	3.22 (2.16, 4.81)	<0.01	0.19
# of Borrowing Partners							
1 (vs. 0)	2.74 (1.84, 4.09)	<0.01	3.31 (1.88, 5.82)	<0.01	2.22 (1.26, 3.91)	<0.01	0.35
>1 (vs. 0)	2.54 (1.59, 4.06)	<0.01	1.78 (0.73, 4.35)	0.2	2.93 (1.74, 4.95)	<0.01	
Frequency of Injecting alone							
Sometimes (vs. never)	2.20 (1.48, 3.26)	<0.01	1.84 (1.03, 3.29)	0.04	2.54 (1.48, 4.36)	<0.01	0.99
Always (vs. never)	0.96 (0.50, 1.83)	0.9	1.12 (0.34, 3.70)	0.85	1.11 (0.50, 2.45)	0.79	
Frequency of Pooling							
Sometimes (vs. never)	2.53 (1.70, 3.76)	<0.01	1.61 (0.78, 3.33)	0.2	2.93 (1.83, 4.68)	<0.01	0.28
Aways (vs. never)	2.33 (1.40, 3.87)	<0.01	2.29 (1.04, 5.02)	0.04	1.56 (0.68, 3.61)	0.3	
# of Pooling Partners							
1 (vs. 0)	2.62 (1.66, 4.14)	<0.01	1.94 (0.88, 4.27)	0.1	2.91 (1.65, 5.12)	<0.01	0.97
>1 (vs. 0)	2.50 (1.65, 3.78)	<0.01	1.84 (0.87, 3.87)	0.11	2.61 (1.58, 4.34)	<0.01	
Had a steady sex partner	1.73 (1.22, 2.46)	<0.01	1.73 (0.88, 3.39)	0.11	1.52 (0.96, 2.38)	0.07	0.43
Had a steady IDU sex partner	2.23 (1.58, 3.14)	<0.01	2.55 (1.32, 4.94)	<0.01	1.88 (1.20, 2.95)	<0.01	0.26

Table 4: Hazard ratios for incident HCV for females vs. males, adjusted by risk behavior, one at a time

	Hazard Ratio Females vs Males (95% CI)	p
Unadjusted	1.43 (1.03 – 2.00)	0.03
Age of first injection	1.33 (0.95, 1.86)	0.10
Years injecting	1.45 (1.04, 2.02)	0.03
Injected every day*¥	1.36 (0.98, 1.89)	0.06
Injected heroin*¥	1.28 (0.91, 1.80)	0.16
Injected speed	1.48 (1.06, 2.06)	0.02
Injected cocaine	1.42 (1.02, 1.97)	0.04
Reused a syringe	1.43 (1.02, 1.99)	0.04
Reused a cooker*¥	1.30 (0.93, 1.82)	0.12
Used a syringe previously used by another injector	1.30 (0.94, 1.81)	0.12
Used a cooker previously used by another injector	1.35 (0.97, 1.89)	0.08
Did a rinse*¥	1.29 (0.93, 1.80)	0.13
# Borrowing Partners	1.29 (0.93, 1.80)	0.13
Frequency of Injecting alone	1.43 (1.03, 1.99)	0.03
Frequency of Pooling	1.29 (0.92, 1.81)	0.14
# Pooling Partners	1.28 (0.89, 1.77)	0.19
Had a steady sex partner*¥	1.27 (0.90, 1.79)	0.18
Had a steady IDU sex partner*¥	1.16 (0.83, 1.64)	0.38

** Significantly associated with female sex at baseline*

¥ Significantly associated with female sex during foll

Acknowledgements

Acknowledgments: The authors would like to acknowledge the helpful contributions from colleagues: Drs. Michael P. Busch and Leslie Tobler at Blood Systems Research Institute for ongoing laboratory expertise; Dr. Stephen Shiboski for statistical consultation; and all of the UFO Study staff and volunteers for research assistance and support. We thank the San Francisco Department of Public Health for their ongoing commitment to the health of the young people who participate; their contributions, including preventive vaccines and primary care for participants is invaluable. We thank our community partners at the Housing and Urban Health Clinic, Homeless Youth Alliance, San Francisco Needle Exchange and San Francisco AIDS Foundation. Last but not least, we especially acknowledge the participation of all the UFO Study participants without whom this research and the knowledge we gain to help prevent HCV would not be possible.

Funding: The authors received support from the National Institutes of Health - National Institute on Drug Abuse Award Number R01DA016017 and National Institute on Alcohol and Alcoholism K24AA022586 (JAH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse or the National Institutes of Health. We also acknowledge support from the UCSF CTSI (NIH UL1 RR024131) and the UCSF Liver Center (NIH P30 DK026743).

Contributorship Statement: All authors contributed to this manuscript. DT, JAH, and KP compiled the first draft of the manuscript, and authors CFL, JE, AB, MDM, and PJL reviewed and provided further scientific and editorial input. The primary statistical analysis was conducted

by DT; JE provided supplemental data review, and JAH and KP reviewed all data analyses. All authors contributed to and have approved the final manuscript. KP, JAH, JE, AB, MDM, PJL, and KP designed and conducted the UFO Study from which data for this study were obtained. All authors provided expertise on the research presented in this manuscript including the methods, analysis, and final manuscript. None of the authors have any conflicts of interest to disclose. This manuscript is not under submission or consideration elsewhere.

Conflicts: The authors declare that they have no commercial or other association that might pose a conflict of interest with this research.

Data Sharing Statement: No additional data

References

1. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144(10):705-14.
2. Hagan H, Pouget ER, Des Jarlais DC, Lelutiu-Weinberger C. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. Am J Epidemiol 2008;168(10):1099-109.
3. Hahn JA, Page-Shafer K, Lum PJ, Bourgois P, Stein E, Evans JL, et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis 2002;186(11):1558-64.
4. Hahn JA, Page-Shafer K, Lum PJ, Ochoa K, Moss AR. Hepatitis C virus infection and needle exchange use among young injection drug users in San Francisco. Hepatology 2001;34(1):180-7.
5. Mehta SH, Astemborski J, Kirk GD, Strathdee SA, Nelson KE, Vlahov D, et al. Changes in blood-borne infection risk among injection drug users. J Infect Dis 2011;203(5):587-94.
6. Page K, Hahn JA, Evans J, Shiboski S, Lum P, Delwart E, et al. Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. J Infect Dis 2009;200(8):1216-26.
7. Miller CL, Johnston C, Spittal PM, Li K, Laliberte N, Montaner JS, et al. Opportunities for prevention: hepatitis C prevalence and incidence in a cohort of young injection drug users. Hepatology 2002;36(3):737-42.
8. Miller CL, Wood E, Spittal PM, Li K, Frankish JC, Braitstein P, et al. The future face of coinfection: prevalence and incidence of HIV and hepatitis C virus coinfection among young injection drug users. J Acquir Immune Defic Syndr 2004;36(2):743-9.
9. Use of enhanced surveillance for hepatitis C virus infection to detect a cluster among young injection-drug users--New York, November 2004-April 2007. Mmwr. Morbidity and Mortality Weekly Report 2008;57(19):517-21.
10. Notes from the field: risk factors for hepatitis C virus infections among young adults--Massachusetts, 2010. Mmwr. Morbidity and Mortality Weekly Report 2011;60(42):1457-8.
11. Hepatitis C virus infection among adolescents and young adults:Massachusetts, 2002-2009. Mmwr. Morbidity and Mortality Weekly Report 2011;60(17):537-41.
12. Notes from the field : hepatitis C virus infections among young adults--rural Wisconsin, 2010. Mmwr. Morbidity and Mortality Weekly Report 2012;61(19):358.
13. Christian WJ, Hopenhayn C, Christian A, McIntosh D, Koch A. Viral hepatitis and injection drug use in Appalachian Kentucky: a survey of rural health department clients. Public Health Rep 2010;125(1):121-8.
14. Holmberg S. The emerging epidemic of hepatitis C among young non-urban injection drug users. 2013.
15. Micallef JM, Macdonald V, Jauncey M, Amin J, Rawlinson W, van Beek I, et al. High incidence of hepatitis C virus reinfection within a cohort of injecting drug users. J Viral Hepat 2007;14(6):413-8.
16. Craine N, Hickman M, Parry JV, Smith J, Walker AM, Russell D, et al. Incidence of hepatitis C in drug injectors: the role of homelessness, opiate substitution treatment, equipment sharing, and community size. Epidemiol Infect 2009;137(9):1255-65.

17. Patrick DM, Tyndall MW, Cornelisse PG, Li K, Sherlock CH, Rekart ML, et al. Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection. CMAJ 2001;165(7):889-95.
18. van den Berg CH, Smit C, Bakker M, Geskus RB, Berkhout B, Jurriaans S, et al. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. Eur J Epidemiol 2007;22(3):183-93.
19. Hagan H, Thiede H, Des Jarlais DC. Hepatitis C virus infection among injection drug users: survival analysis of time to seroconversion. Epidemiology 2004;15(5):543-9.
20. Maher L, Jalaludin B, Chant KG, Jayasuriya R, Sladden T, Kaldor JM, et al. Incidence and risk factors for hepatitis C seroconversion in injecting drug users in Australia. Addiction 2006;101(10):1499-508.
21. Montgomery SB, Hyde J, De Rosa CJ, Rohrbach LA, Ennett S, Harvey SM, et al. Gender differences in HIV risk behaviors among young injectors and their social network members. Am J Drug Alcohol Abuse 2002;28(3):453-75.
22. Gollub EL, Rey D, Obadia Y, Moatti JP. Gender differences in risk behaviors among HIV+ persons with an IDU history. The link between partner characteristics and women's higher drug-sex risks. The Manif 2000 Study Group. Sex Transm Dis 1998;25(9):483-8.
23. Miller M, Neaigus A. Networks, resources and risk among women who use drugs. Soc Sci Med 2001;52(6):967-78.
24. Strathdee SA, Galai N, Safaiean M, Celentano DD, Vlahov D, Johnson L, et al. Sex differences in risk factors for hiv seroconversion among injection drug users: a 10-year perspective. Arch Intern Med 2001;161(10):1281-8.
25. Spittal PM, Craib KJ, Wood E, Laliberte N, Li K, Tyndall MW, et al. Risk factors for elevated HIV incidence rates among female injection drug users in Vancouver. CMAJ 2002;166(7):894-9.
26. Evans JL, Hahn JA, Page-Shafer K, Lum PJ, Stein ES, Davidson PJ, et al. Gender differences in sexual and injection risk behavior among active young injection drug users in San Francisco (the UFO Study). J Urban Health 2003;80(1):137-46.
27. Bakr I, Rekacewicz C, El Hosseiny M, Ismail S, El Daly M, El-Kafrawy S, et al. Higher clearance of hepatitis C virus infection in females compared with males. Gut 2006;55(8):1183-7.
28. Di Martino V, Lebray P, Myers RP, Pannier E, Paradis V, Charlotte F, et al. Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure. Hepatology 2004;40(6):1426-33.
29. Vanichseni S, Kitayaporn D, Mastro TD, Mock PA, Raktham S, Des Jarlais DC, et al. Continued high HIV-1 incidence in a vaccine trial preparatory cohort of injection drug users in Bangkok, Thailand. AIDS 2001;15(3):397-405.
30. Kral AH, Lorvick J, Edlin BR. Sex- and drug-related risk among populations of younger and older injection drug users in adjacent neighborhoods in San Francisco. Journal of Acquired Immune Deficiency Syndromes 2000;24(2):162-7.
31. Broz D, Ouellet LJ. Racial and ethnic changes in heroin injection in the United States: implications for the HIV/AIDS epidemic. Drug Alcohol Depend 2008;94(1-3):221-33.
32. Fennema JS, Van Ameijden EJ, Van Den Hoek A, Coutinho RA. Young and recent-onset injecting drug users are at higher risk for HIV. Addiction 1997;92(11):1457-65.
33. Seear K, Gray R, Fraser S, Treloar C, Bryant J, Brener L. Rethinking safety and fidelity: The role of love and intimacy in hepatitis C transmission and prevention. Health Sociology Review 2012;21(3):272-286.

34. Rhodes T, Treloar C. The social production of hepatitis C risk among injecting drug users: a qualitative synthesis. Addiction 2008;103(10):1593-603.
35. Jackson L, Parker J, Dykeman M, Gahagan J, Karabanow J. The power ofrelationships: implications for safer and unsafe practices among injection drugusers. Drugs Educ. Prev. Policy 2010;17:189-204.
36. Fraser S, Treloar C, Bryant J, Rhodes T. Hepatitis C prevention educaqtion needs to be grounded in social relationships. Drugs: education, prevention, and policy 2013.
37. Kral AH, Malekinejad M, Vaudrey J, Martinez AN, Lorvick J, McFarland W, et al. Comparing respondent-driven sampling and targeted sampling methods of recruiting injection drug users in San Francisco. J Urban Health 2010;87(5):839-50.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

Tracy et al.,

	Item No	Item, Section and PAGE NUMBER
Title and abstract	1	(*a*) Study's design with a commonly used terms – PAGE 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – PAGE 3
Introduction		
Background/rationale	2	Scientific background and rationale for the investigation being reported – PAGE 5-6
Objectives	3	State specific objectives, including any prespecified hypotheses- PAGE 6
Methods		
Study design	4	Present key elements of study design early in the paper- PAGE 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection- PAGE 7-
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up- PAGE 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, - PAGE 7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – PAGE 7-8
Bias	9	Describe any efforts to address potential sources of bias –comparisons were made between those in follow up and those lost
Study size	10	Explain how the study size was arrived at – PAGE 7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why- PAGE 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding- PAGE 8
		(*b*) Describe any methods used to examine subgroups and interactions- PAGE 8
		(*c*) Explain how missing data were addressed- Page 8-9
		(*d*) If applicable, explain how loss to follow-up was addressed: only participants with follow up were included, but comparisons made to assess differences between groups.
		(*e*) Describe any sensitivity analyses None
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed- PAGE 8-9
		(b) Give reasons for non-participation at each stage: none
		(c) Consider use of a flow diagram NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders- PAGE 8-9; and TABLE 1
		(b) Indicate number of participants with missing data for each variable of interest NA
		(c) Summarise follow-up time (eg, average and total amount) PAGE 10

Outcome data	15*	Report numbers of outcome events or summary measures over time – PAGE 10, TABLES 2-3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. TABLES 2-4
		(*b*) Report category boundaries when continuous variables were categorized NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses –PAGE 11; Table 4
Discussion		
Key results	18	Summarise key results with reference to study objectives – PAGE 12-
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – PAGE 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence PAGE 13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results PAGE 14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based PAGE 20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Higher risk of incident hepatitis C virus among young females who inject drugs compared to young males in association with sexual relationships: a prospective analysis from the UFO Study Cohort

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-004988.R1
Article Type:	Research
Date Submitted by the Author:	22-Apr-2014
Complete List of Authors:	Tracy, Daniel; Columbia University, Mailman School of Public Health, Hahn, Judith; UCSF, Medicine Fuller Lewis, Crystal; Columbia University, Mailman School of Public Health Evans, Jennifer; UCSF, Epidemiology & Biostatistics Briceno, Alya; UCSF, Epidemiology & Biostatistics Morris, Meghan; UCSF, Epidemiology & Biostatistics Lum, Paula; UCSF, Positive Health Program Page, Kimberly; University of California San Francisco, Epidemiology & Biostatistics
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Addiction, Epidemiology, Infectious diseases, Public health
Keywords:	Substance misuse < PSYCHIATRY, PUBLIC HEALTH, Epidemiology < INFECTIOUS DISEASES

Title

Higher risk of incident hepatitis C virus among young females who inject drugs compared to young males in association with sexual relationships: a prospective analysis from the UFO Study Cohort

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Word count: Abstract: 160; Text 3160; Tables: 4.

Abstract

BACKGROUND**:** Female injection drug users may report differences in injection behaviors that put them at greater risk for 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 analyzed. Cox proportional hazards was used to model female sex as a predictor of new HCV infection. GEE was used to model female sex as a predictor of HCV-associated risk behavior prospectively.

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

CONCLUSIONS: Young females' riskier injection practices leads to their higher rates of HCV infection. Further study on the impact on intimate partnership on females' risk behavior is warranted.

Key Words: young injection drug users, females; hepatitis C virus; relationship risks

Article summary

Article Focus

- Hepatitis C virus (HCV) is the most common of all chronic blood-borne infections in the United States and injection drug use is a leading transmission risk with rapid rates of infection occurring soon after injection initiation.
- Young women who inject drugs may especially vulnerable to HCV infection and some, but not all assessments have suggested differences in high-risk injection practices and incidence of HCV.
- This study was undertaken to more fully assess sex-related differences in risk for and HCV infection rates in a well-characterized cohort of young injectors.

Strengths and Limitations

- Few if any studies have examined how HCV incidence is impacted by sex-related differences in risk behavior.
- Data are analyzed from a large well characterized prospective cohort of young adult injectors at high risk for HCV infection, in San Francisco, California.
- HCV incidence and risk measures are well-defined and measured systematically.
- Women represent only one-third of the sample, which may impact power and generalizability.
- The UFO Study samples a large number of young injectors in San Francisco, but it is unknown how representative it is of the young IDU population in San Francisco or elsewhere.

Key Messages

- Young female injectors have specific risk factors that put them at higher risk of HCV infection compared to men, especially in association with social and sexual partnerships.
- Risk behavior differences between female and male injectors should be addressed in prevention programs targeting young injectors.

Background

Hepatitis C virus (HCV) is the most common of all chronic blood-borne infections in the United States(1) and injection drug use 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% and 25% (5, 6), and prevalence ranges from 39% to 60% (6-8). Recent reports of HCV outbreaks among young adult injectors by the U.S. 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 cohorts the 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 amongst female IDU (17-20). There is some evidence that females engage in riskier injection practices (21); more consistent is the finding that females 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 if 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 (SVR) to therapy as well 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 behavior by females would not necessarily translate into higher rates of HCV infection, and that associations between direct risk factors and incident HCV might be stronger for males than females. Even if not true, there remains the possibility that factors known to be sex-specific in their associations with injecting behavior, such as being in a heterosexual partnership 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-behavior and HCV incidence with the following questions in mind: (1) are there differences between young female and male IDU in terms of their risk-behaviors 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 IDU (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 NJ), and qualitative HCV RNA testing (Procleix® HIV-1/HCV assay, Gen-Probe Inc., San Diego).

In this analysis, we included data from male and female participants enrolled in the UFO Study from January 2000 through 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 (i.e. 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 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 if their partner was also an IDU. All behaviors 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 males and females using the chi-square test for categorical variables and the Wilcoxon test for continuous variables. To determine if 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, analyzed separately. We assessed associations between individual exposure variables, including sex, and new HCV infection by modeling 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 if sex differences in behavior were indirectly associated with sex differences in incident HCV infection, we entered any behavioral variable associated both 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 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

The protocol and all study procedures were reviewed and approved by the 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 both HCV-antibody and 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 males and 140 females) returned for at least one follow-up visit. Participants with follow-up compared to 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), and pooling money with more than one other IDU to buy drugs (61% vs. 69%, p<0.05), and 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 males (vs. non-participant males 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) and 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 females (vs. non-participant females 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). Amongst all participants self-reported HIV prevalence was 2%; those reporting HIV positive status were more likely to be followed than HIV negative or unknown (3% vs. 1%, p<0.05). Participating males (vs. non-participant males 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 weren't significant differences in self-reported HIV prevalence between participating females (vs. non-participant females 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 enrollment and reported younger age of initiation of injecting (median 17 vs. 19 years, p<0.01) (Table 1). At baseline interviews, females reported greater injection risk, compared to males (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). Females 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). Females were less likely to report injecting speed (53% vs. 63%, p<0.05). Baseline self-reported HIV prevalence was not significantly different between females and males (1.5% vs 3.4, p 0.29). During study follow-up, females more frequently reported risky injection practices, including: borrowing used syringes (OR: 1.8, 95%CI: 1.3, 2.6), reuse of a cooker previously used by another injector (OR: 1.5, 95%CI: 1.03, 2.3), and doing a rinse (OR: 1.9, 95%CI: 1.3, 2.7) (Table 2). Females were also more likely to report injecting every day (OR: 1.5, 95%CI: 1.1, 2.2), injecting heroin (OR: 2.1, 95%CI: 1.4, 3.1), pooling money with others to buy drugs (OR: 2.1, 95%CI: 1.5, 3.0), and having a steady IDU sex partner (OR: 3.8, 95%CI: 2.7, 5.3). Females were significantly less likely than males to report injecting alone (OR: 0.31, 95%CI: 0.2, 0.5).

Over a period of 11+ years of data collection, 1497 unique risk intervals were captured, during which these 417 subjects were followed for a total of 650 person-years (PY) of follow up.

During the period, 129 new HCV infections, 78 in males and 51 in females, were identified resulting in an incidence rate of 19.8/100 PY (95% CI: 19.1, 20.6). The HCV incidence rate was significantly higher in females than in males (25.4/100 PY; 95% CI: 24.0, 26.8) vs. (17.3/100 PY; 95% CI: 16.4, 18.3); hazard ratio (HR) 1.4 (95% CI: 1.03, 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, 3.1), injecting heroin (HR: 2.7; 95%CI: 1.8, 4.1), injecting cocaine (HR: 2.3; 95%CI: 1.7, 3.3), use of a syringe previously used by another injector (HR: 2.6; 95%CI: 1.9, 3.7), use of a cooker previously used by another injector (HR: 2.4; 95%CI: 1.7, 3.4), doing a rinse (HR: 2.7; 95%CI: 1.9, 3.7), injecting alone (HR: 2.0; 95%CI: 1.3, 2.9), and having a steady IDU sex partner (HR: 2.23, 95%CI: 1.58, 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 behaviors 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 hazard ratio 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 in San Francisco, 19% is comparable to that seen in other locales. For instance in the DUIT study conducted in five U.S. 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. Females in our sample reported more frequent risk behavior at baseline and throughout their study participation, and had a significantly higher unadjusted incidence of HCV than males. When adjusted for risk factors that were more frequently reported by females, the hazard ratio 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 behavior. Our results did not support the hypothesis that females 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 various factors including: small sample size (7), the inclusion of older IDU who have lower risk profiles overall compared to 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 enrollment into the study. In early analyses of 195 UFO participants, we found a hazard ratio 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 females in the UFO cohort were more likely than males to report engaging in high risk behavior both prior to their enrollment 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 behavior among females is with respect to the complexities inherent in their relationships with male IDU. In our sample, females were also more likely than males to report borrowing used syringes from only *one* other IDU. Although it is unclear whether or not borrowing behavior 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 males there was no difference in risk by number of people they borrowed from (Table 3) . The absence of a 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 females, suggest the need for sex-specific models that acknowledge pontential 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 behavior by sex along with our initial idea that females may be biologically less susceptible to HCV infection, we hypothesized 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 females than males in stratified analysis, statistical significance was not reached for any interactions. As an example, females had higher odds compared to males 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, males reported higher odds of several risk factors than females (for instance 'doing'a rinse), that were also not associated with increased HCV risk.

Our analysis has some of limitations. There were fewer women in the cohort than males, 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 exists 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 enrollment 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 modeling technique by which each subject'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 behaviors over three month intervals, however there were cases in which the duration of time between a participant's interviews exceeded three 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 behaviors, which if non-differential would have caused bias toward the null. Risk behavior 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 behaviors 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 behaviors and concomitant high rates of HCV infection, females 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 behavior, as well as new prevention approaches that specifically target young women and encourage safe injecting behavior, especially in the context of overlapping sexual and injecting relationships.

Table 1: Baseline characteristics of females and males participating in the UFO Study with at least 1 follow-up visit (N=424)

	Females (n=140)	Males (n=277)	P
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
# 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%)	
# 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

[¥]Subjects were asked to report the total number of people from whom they borrowed a previously used needle to inject. [£]Subjects were asked to report the total number of people with whom they pooled money in order to purchase drugs.

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

Outcome	OR (95% CI)	p
Injected every day	1.53 (1.06, 2.22)	0.02
Injected heroin	2.10 (1.40, 3.13)	<0.01
Injected speed	0.86 (0.61, 1.22)	0.40
Injected cocaine	1.15 (0.78, 1.70)	0.47
Reused a syringe	1.02 (0.72, 1.44)	0.92
Reused a cooker	2.02 (1.46, 2.80)	<0.01
Used a syringe previously used by another injector	1.82 (1.27, 2.60)	0.01
Used a cooker previously used by another injector	1.55 (1.03, 2.33)	0.03
Did a rinse	1.88 (1.31, 2.69)	<0.01
Borrowed needles from only one other person	2.08 (1.41, 3.07)	<0.01
Borrowed needles from >1 person	1.08 (0.62, 1.90)	0.78
Injected alone	0.99 (0.70, 1.40)	0.96
Always injected alone	0.31 (0.19, 0.53)	<0.01
Pooled with others to buy drugs	2.14 (1.51, 3.02)	<0.01
Always pooled to buy drugs	2.42 (1.61, 3.63)	<0.01
Pooled with only one other person	1.48 (1.06, 2.07)	0.02
Pooled with >1 person	1.66 (1.19, 2.31)	<0.01
Had a steady sex partner	3.50 (2.45, 4.98)	<0.01
Had a steady sex partner who was also an IDU	3.76 (2.66, 5.33)	<0.01

Table 3: Predictors of incident HCV infection stratified by sex*

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

* Although interactions between primary predictor variables and female sex were also modeled, none reached significance at p<0.20

Table 4: Hazard ratios for incident HCV for females vs. males, adjusted by risk behavior, one at a time

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

** Significantly associated with female sex at baseline*

¥ Significantly associated with female sex during follow-u

Acknowledgements

Acknowledgments: The authors would like to acknowledge the helpful contributions from colleagues: Drs. Michael P. Busch and Leslie Tobler at Blood Systems Research Institute for ongoing laboratory expertise; Dr. Stephen Shiboski for statistical consultation; and all of the UFO Study staff and volunteers for research assistance and support. We thank the San Francisco Department of Public Health for their ongoing commitment to the health of the young people who participate; their contributions, including preventive vaccines and primary care for participants is invaluable. We thank our community partners at the Housing and Urban Health Clinic, Homeless Youth Alliance, San Francisco Needle Exchange and San Francisco AIDS Foundation. Last but not least, we especially acknowledge the participation of all the UFO Study participants without whom this research and the knowledge we gain to help prevent HCV would not be possible.

Funding: The authors received support from the National Institutes of Health - National Institute on Drug Abuse Award Number R01DA016017 and National Institute on Alcohol and Alcoholism K24AA022586 (JAH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse or the National Institutes of Health. We also acknowledge support from the UCSF CTSI (NIH UL1 RR024131) and the UCSF Liver Center (NIH P30 DK026743).

Contributorship Statement: All authors contributed to this manuscript. DT, JAH, and KP compiled the first draft of the manuscript, and authors CFL, JE, AB, MDM, and PJL reviewed and provided further scientific and editorial input. The primary statistical analysis was conducted

by DT; JE provided supplemental data review, and JAH and KP reviewed all data analyses. All authors contributed to and have approved the final manuscript. KP, JAH, JE, AB, MDM, PJL, and KP designed and conducted the UFO Study from which data for this study were obtained. All authors provided expertise on the research presented in this manuscript including the methods, analysis, and final manuscript. None of the authors have any conflicts of interest to disclose. This manuscript is not under submission or consideration elsewhere.

Conflicts: The authors declare that they have no commercial or other association that might pose a conflict of interest with this research.

Data Sharing Statement: No additional data available.

References

1. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144(10):705-14.
2. Hagan H, Pouget ER, Des Jarlais DC, et al. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. Am J Epidemiol 2008;168(10):1099-109.
3. Hahn JA, Page-Shafer K, Lum PJ, et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis 2002;186(11):1558-64.
4. Hahn JA, Page-Shafer K, Lum PJ, et al. Hepatitis C virus infection and needle exchange use among young injection drug users in San Francisco. Hepatology 2001;34(1):180-7.
5. Mehta SH, Astemborski J, Kirk GD, et al. Changes in blood-borne infection risk among injection drug users. J Infect Dis 2011;203(5):587-94.
6. Page K, Hahn JA, Evans J, et al. Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. J Infect Dis 2009;200(8):1216-26.
7. Miller CL, Johnston C, Spittal PM, et al. Opportunities for prevention: hepatitis C prevalence and incidence in a cohort of young injection drug users. Hepatology 2002;36(3):737-42.
8. Miller CL, Wood E, Spittal PM, et al. The future face of coinfection: prevalence and incidence of HIV and hepatitis C virus coinfection among young injection drug users. J Acquir Immune Defic Syndr 2004;36(2):743-9.
9. Use of enhanced surveillance for hepatitis C virus infection to detect a cluster among young injection-drug users--New York, November 2004-April 2007. Mmwr. Morbidity and Mortality Weekly Report 2008;57(19):517-21.
10. Notes from the field: risk factors for hepatitis C virus infections among young adults--Massachusetts, 2010. Mmwr. Morbidity and Mortality Weekly Report 2011;60(42):1457-8.
11. Hepatitis C virus infection among adolescents and young adults:Massachusetts, 2002-2009. Mmwr. Morbidity and Mortality Weekly Report 2011;60(17):537-41.
12. Notes from the field : hepatitis C virus infections among young adults--rural Wisconsin, 2010. Mmwr. Morbidity and Mortality Weekly Report 2012;61(19):358.
13. Christian WJ, Hopenhayn C, Christian A, et al. Viral hepatitis and injection drug use in Appalachian Kentucky: a survey of rural health department clients. Public Health Rep 2010;125(1):121-8.
14. Holmberg S. The emerging epidemic of hepatitis C among young non-urban injection drug users. 2013.
15. Micallef JM, Macdonald V, Jauncey M, et al. High incidence of hepatitis C virus reinfection within a cohort of injecting drug users. J Viral Hepat 2007;14(6):413-8.
16. Craine N, Hickman M, Parry JV, et al. Incidence of hepatitis C in drug injectors: the role of homelessness, opiate substitution treatment, equipment sharing, and community size. Epidemiol Infect 2009;137(9):1255-65.
17. Patrick DM, Tyndall MW, Cornelisse PG, et al. Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection. CMAJ 2001;165(7):889-95.
18. van den Berg CH, Smit C, Bakker M, et al. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. Eur J Epidemiol 2007;22(3):183-93.

19. Hagan H, Thiede H, Des Jarlais DC. Hepatitis C virus infection among injection drug users: survival analysis of time to seroconversion. Epidemiology 2004;15(5):543-9.
20. Maher L, Jalaludin B, Chant KG, et al. Incidence and risk factors for hepatitis C seroconversion in injecting drug users in Australia. Addiction 2006;101(10):1499-508.
21. Montgomery SB, Hyde J, De Rosa CJ, et al. Gender differences in HIV risk behaviors among young injectors and their social network members. Am J Drug Alcohol Abuse 2002;28(3):453-75.
22. Gollub EL, Rey D, Obadia Y, et al. Gender differences in risk behaviors among HIV+ persons with an IDU history. The link between partner characteristics and women's higher drug-sex risks. The Manif 2000 Study Group. Sex Transm Dis 1998;25(9):483-8.
23. Miller M, Neaigus A. Networks, resources and risk among women who use drugs. Soc Sci Med 2001;52(6):967-78.
24. Strathdee SA, Galai N, Safaiean M, et al. Sex differences in risk factors for HIV seroconversion among injection drug users: a 10-year perspective. Arch Intern Med 2001;161(10):1281-8.
25. Spittal PM, Craib KJ, Wood E, et al. Risk factors for elevated HIV incidence rates among female injection drug users in Vancouver. CMAJ 2002;166(7):894-9.
26. Evans JL, Hahn JA, Page-Shafer K, et al. Gender differences in sexual and injection risk behavior among active young injection drug users in San Francisco (the UFO Study). J Urban Health 2003;80(1):137-46.
27. Bakr I, Rekacewicz C, El Hosseiny M, et al. Higher clearance of hepatitis C virus infection in females compared with males. Gut 2006;55(8):1183-7.
28. Di Martino V, Lebray P, Myers RP, et al. Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure. Hepatology 2004;40(6):1426-33.
29. Garfein RS, Golub ET, Greenberg AE, et al. A peer-education intervention to reduce injection risk behaviors for HIV and hepatitis C virus infection in young injection drug users. AIDS 2007;21(14):1923-32.
30. Vanichseni S, Kitayaporn D, Mastro TD, et al. Continued high HIV-1 incidence in a vaccine trial preparatory cohort of injection drug users in Bangkok, Thailand. AIDS 2001;15(3):397-405.
31. Kral AH, Lorvick J, Edlin BR. Sex- and drug-related risk among populations of younger and older injection drug users in adjacent neighborhoods in San Francisco. Journal of Acquired Immune Deficiency Syndromes 2000;24(2):162-7.
32. Broz D, Ouellet LJ. Racial and ethnic changes in heroin injection in the United States: implications for the HIV/AIDS epidemic. Drug Alcohol Depend 2008;94(1-3):221-33.
33. Fennema JS, Van Ameijden EJ, Van Den Hoek A, et al. Young and recent-onset injecting drug users are at higher risk for HIV. Addiction 1997;92(11):1457-65.
34. Seear K, Gray R, Fraser S, et al. Rethinking safety and fidelity: The role of love and intimacy in hepatitis C transmission and prevention. Health Sociology Review 2012;21(3):272-286.
35. Rhodes T, Treloar C. The social production of hepatitis C risk among injecting drug users: a qualitative synthesis. Addiction 2008;103(10):1593-603.
36. Jackson L, Parker J, Dykeman M, et al. The power ofrelationships: implications for safer and unsafe practices among injection drugusers. Drugs Educ. Prev. Policy 2010;17:189-204.
37. Fraser S, Treloar C, Bryant J, et al.. Hepatitis C prevention educaqtion needs to be grounded in social relationships. Drugs: education, prevention, and policy 2013.

38. Kral AH, Malekinejad M, Vaudrey J, et al. Comparing respondent-driven sampling and targeted sampling methods of recruiting injection drug users in San Francisco. J Urban Health 2010;87(5):839-50.

Title

Higher risk of incident hepatitis C virus among young females who inject drugs compared to young males in association with sexual relationships: a prospective analysis from the UFO Study Cohort

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Word count: Abstract: 157; Text 3000; Tables: 4.

Abstract

BACKGROUND**:** Female injection drug users may report differences in injection behaviors that put them at greater risk for 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 analyzed. Cox proportional hazards was used to model female sex as a predictor of new HCV infection. GEE was used to model female sex as a predictor of HCV-associated risk behavior prospectively.

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

CONCLUSIONS: Young females' riskier injection practices leads to their higher rates of HCV infection. Further study on the impact on intimate partnership on females' risk behavior is warranted.

Key Words: young injection drug users, females; hepatitis C virus; relationship risks

Article summary

Article Focus

- Hepatitis C virus (HCV) is the most common of all chronic blood-borne infections in the United States and injection drug use is a leading transmission risk with rapid rates of infection occurring soon after injection initiation.
- Young women who inject drugs may especially vulnerable to HCV infection and some, but not all assessments have suggested differences in high-risk injection practices and incidence of HCV.
- This study was undertaken to more fully assess sex-related differences in risk for and HCV infection rates in a well-characterized cohort of young injectors.

Strengths and Limitations

- Few if any studies have examined how HCV incidence is impacted by sex-related differences in risk behavior.
- Data are analyzed from a large well characterized prospective cohort of young adult injectors at high risk for HCV infection, in San Francisco, California.
- HCV incidence and risk measures are well-defined and measured systematically.
- Women represent only one-third of the sample, which may impact power and generalizability.
- The UFO Study samples a large number of young injectors in San Francisco, but it is unknown how representative it is of the young IDU population in San Francisco or elsewhere.

Key Messages

- Young female injectors have specific risk factors that put them at higher risk of HCV infection compared to men, especially in association with social and sexual partnerships.
- Risk behavior differences between female and male injectors should be addressed in prevention programs targeting young injectors.

Author Contributions: All authors contributed to this manuscript. DT, JAH, and KP compiled the first draft of the manuscript, and authors CFL, JE, AB, MDM, and PJL reviewed and provided further scientific and editorial input. The primary statistical analysis was conducted by DT; JE provided supplemental data review, and JAH and KP reviewed all data analyses. All authors contributed to and have approved the final manuscript. KP, JAH, JE, AB, MDM, PJL, and KP designed and conducted the UFO Study from which data for this study were obtained. All authors provided expertise on the research presented in this manuscript including the methods, analysis, and final manuscript.

Data Sharing: no additional data available.

Background

Hepatitis C virus (HCV) is the most common of all chronic blood-borne infections in the United States(1) and injection drug use 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% and 25% (5, 6), and prevalence ranges from 39% to 60% (6-8). Recent reports of HCV outbreaks among young adult injectors by the U.S. 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 cohorts the 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 amongst female IDU (17-20). There is some evidence that females engage in riskier injection practices (21); more consistent is the finding that females 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 if 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 (SVR) to therapy as well 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 behavior by females would not necessarily translate into higher rates of HCV infection, and that associations between direct risk factors and incident HCV might be stronger for males than females. Even if not true, there remains the possibility that factors known to be sex-specific in their associations with injecting behavior, such as being in a heterosexual partnership 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-behavior and HCV incidence with the following questions in mind: (1) are there differences between young female and male IDU in terms of their risk-behaviors and characteristics?; (2) do these differences correspond to differences in sex-specific rates of HCV incidence? ~~; and, 3) are there risk-factors associated with incident HCV infection that differ between males and females?~~

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 IDU (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 NJ), and qualitative HCV RNA testing (Procleix® HIV-1/HCV assay, Gen-Probe Inc., San Diego).

In this analysis, we included data from male and female participants enrolled in the UFO Study from January 2000 through 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 (i.e. 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 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 if their partner was also an IDU. All behaviors 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. ~~All study procedures were reviewed and approved by the UCSF Institutional Review Board.~~

We assessed baseline differences in risk characteristics between males and females using the chi-square test for categorical variables and the Wilcoxon test for continuous variables. To determine if 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, analyzed separately. We assessed associations between individual exposure variables, including sex, and new HCV infection by modeling 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 ~~examine potential mediation by these~~see if sex differences in behavior were indirectly associated with sex differences in incident HCV infection, we entered any behavioral variable associated both with sex and with incident HCV (in ~~un~~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 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

The protocol and all study procedures were reviewed and approved by the 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 both HCV-antibody and 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 males and 140 females) returned for at least one follow-up visit. Participants with follow-up compared to 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%, $p<0.05$), and pooling money with more than one other IDU to buy drugs (61% vs. 69%, $p<0.05$), and 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 males (vs. non-participant males 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%, $p<0.05$) and 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 females (vs. non-participant females 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%, $p<0.05$). Amongst all participants self-reported HIV prevalence was 2%; those reporting HIV positive status were more likely to be followed than HIV negative or unknown (3% vs. 1%, $p<0.05$). Participating males (vs. non-participant males 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 weren't significant differences in self-reported HIV prevalence between participating females (vs. non-participant females 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 enrollment and reported younger age of initiation of injecting (median 17 vs. 19 years, p<0.01) (Table 1). At baseline interviews, females reported greater injection risk, compared to males (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). Females 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). Females were less likely to report injecting speed (53% vs. 63%, p<0.05). Baseline self-reported HIV prevalence was not significantly different between females and males (1.5% vs 3.4, p 0.29). During study follow-up, females more frequently reported risky injection practices, including: borrowing used syringes (OR: 1.8, 95%CI: 1.3, 2.6), reuse of a cooker previously used by another injector (OR: 1.5, 95%CI: 1.03, 2.3), and doing a rinse (OR: 1.9, 95%CI: 1.3, 2.7) (Table 2). Females were also more likely to report injecting every day (OR: 1.5, 95%CI: 1.1, 2.2), injecting heroin (OR: 2.1, 95%CI: 1.4, 3.1), pooling money with others to buy drugs (OR: 2.1, 95%CI: 1.5, 3.0), and having a steady IDU sex partner (OR: 3.8, 95%CI: 2.7, 5.3). Females were significantly less likely than males to report injecting alone (OR: 0.31, 95%CI: 0.2, 0.5).

Over a period of 11+ years of data collection, 1497 unique risk intervals were captured, during which these 417 subjects were followed for a total of 650 person-years (PY) of follow up. During the period, 129 new HCV infections, 78 in males and 51 in females, were identified resulting in an incidence rate of 19.8/100 PY (95% CI: 19.1, 20.6). The HCV incidence rate was significantly higher in females than in males (25.4/100 PY; 95% CI: 24.0, 26.8) vs. (17.3/100 PY; 95% CI: 16.4, 18.3); hazard ratio (HR) 1.4 (95% CI: 1.03, 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, 3.1), injecting heroin (HR: 2.7; 95%CI: 1.8, 4.1), injecting cocaine (HR: 2.3; 95%CI: 1.7, 3.3), use of a syringe previously used by another injector (HR: 2.6; 95%CI: 1.9, 3.7), use of a cooker previously used by another injector (HR: 2.4; 95%CI: 1.7, 3.4), doing a rinse (HR: 2.7; 95%CI: 1.9, 3.7), injecting alone (HR: 2.0; 95%CI: 1.3, 2.9), and having a steady IDU sex partner (HR: 2.23, 95%CI: 1.58, 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 behaviors 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 hazard ratio 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 in San Francisco, 19% is comparable to that seen in other locales. For instance in the DUIT study conducted in five U.S. 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. Females in our sample reported more frequent risk behavior at baseline and throughout their study participation, and had a significantly higher unadjusted incidence of HCV than males. When adjusted for risk factors that were more frequently reported by females, the hazard ratio 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 behavior. Our results did not support the hypothesis that females 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 various factors including: small sample size (7), the inclusion of older IDU who have lower risk profiles overall compared to 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 enrollment into the study. In early analyses of 195 UFO participants, we found a hazard ratio 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~~. Overall HCV incidence was similar (/100 PY) to that found in the DUIT study (33).~~

That females in the UFO cohort were more likely than males to report engaging in high risk behavior both prior to their enrollment as well as throughout the course of their study participation deserves attention. ~~Female sex was significantly associated with several important risk factors including injecting H~~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 behavior among females is with respect to the complexities inherent in their relationships with male IDU. ~~.~~ In our sample, females were also more likely than males to report borrowing used syringes from only *one* other IDU. Although it is unclear whether or not borrowing behavior occurred within the context of an intimate relationship, the excess risk ~~HR~~ associated with ~~s for HCV for~~ borrowing from one IDU was higher (HR=3.31) than ~~and~~ from more than one IDU (HR=1.78) (vs. no borrowing) Among males there was no difference in risk by number of people they borrowed from (Table 3) ~~were 3.31 (p<0.01) and 1.78 (p≤0.20) for females, respectively, while the HRs for males were 2.22 (p<0.01) and 2.93 (p<0.01).~~ The absence of a ~~One might expect~~ 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 females, ~~for females~~ suggest the need for sex-specific models that acknowledge pontential ~~intimate~~ partnership associated risks~~s as high risk contexts for young female IDUs.~~ ~~There are several potential interpretations of this finding: one possibility is that aspects inherent to heterosexual partnership between IDU influence the likelihood of engaging in risk behavior differently for males and~~

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~~females; in other words, female IDUs' higher overall rates of risk behavior may be consequent to complexities of their sexual and injecting relationships with male IDU partners~~.Supporting this, is our finding ~~In this study~~ 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). ~~Some have suggested that F~~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 behavior by sex along with our initial idea that females may be biologically less susceptible to HCV infection, we hypothesized 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 females than males in stratified analysis, statistical significance was not reached for any interactions. As an example, females had higher odds compared to males of having a steady IDU/sex partner, of having only one borrowing partner, and of pooling drugs, but none of these exposures conferred a ~~and a non~~ significantly higher hazard of HCV ~~in association with this characteristic (HR: 2.55 vs. 1.88, p for interaction with sex <0.26~~). Conversely, males reported

higher odds of several risk factors than females (for instance 'doing'a rinse), that were also not associated with increased HCV risk.

~~The complexities that intimate relationships introduce to HCV risk deserve more attention, however, and may be difficult to disentangle completely with quantitative data. In our sample, females were also more likely than males to report borrowing used syringes from only one other IDU. Although it is unclear whether or not borrowing behavior occurred within the context of an intimate relationship, the HRs for HCV for borrowing from one IDU and from more than one IDU (vs. no borrowing) were 3.31 ($p<0.01$) and 1.78 ($p\leq0.20$) for females, respectively, while the HRs for males were 2.22 ($p<0.01$) and 2.93 ($p<0.01$). One might expect a dose-response relationship between the number of partners from which one borrowed used syringes and the hazard of new HCV infection, but the results for females suggest the need for sex-specific models that acknowledge intimate partnerships as high-risk contexts for young female IDUs.~~

Our analysis has some of limitations. There were fewer women in the cohort than males, 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 exists 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 enrollment 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 modeling technique by

which each subject'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 behaviors over three month intervals, however there were cases in which the duration of time between a participant's interviews exceeded three 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 behaviors, which if non-differential would have caused bias toward the null. Risk behavior 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 behaviors 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 behaviors and concomitant high rates of HCV infection, females 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 behavior, as well as new prevention approaches that specifically target young women and encourage safe injecting behavior, especially in the context of overlapping sexual and injecting relationships.

Table 1: Baseline characteristics of females and males participating in the UFO Study with at least 1 follow-up visit (N=424)

	Females (n=140)	Males (n=277)	P
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
# 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%)	
# 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

[¥] Subjects were asked to report the total number of people from whom they borrowed a previously used needle to inject. [£] Subjects were asked to report the total number of people with whom they pooled money in order to purchase drugs.

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

Outcome	OR (95% CI)	p
Injected every day	1.53 (1.06, 2.22)	0.02
Injected heroin	2.10 (1.40, 3.13)	<0.01
Injected speed	0.86 (0.61, 1.22)	0.40
Injected cocaine	1.15 (0.78, 1.70)	0.47
Reused a syringe	1.02 (0.72, 1.44)	0.92
Reused a cooker	2.02 (1.46, 2.80)	<0.01
Used a syringe previously used by another injector	1.82 (1.27, 2.60)	0.01
Used a cooker previously used by another injector	1.55 (1.03, 2.33)	0.03
Did a rinse	1.88 (1.31, 2.69)	<0.01
Borrowed needles from only one other person	2.08 (1.41, 3.07)	<0.01
Borrowed needles from >1 person	1.08 (0.62, 1.90)	0.78
Injected alone	0.99 (0.70, 1.40)	0.96
Always injected alone	0.31 (0.19, 0.53)	<0.01
Pooled with others to buy drugs	2.14 (1.51, 3.02)	<0.01
Always pooled to buy drugs	2.42 (1.61, 3.63)	<0.01
Pooled with only one other person	1.48 (1.06, 2.07)	0.02
Pooled with >1 person	1.66 (1.19, 2.31)	<0.01
Had a steady sex partner	3.50 (2.45, 4.98)	<0.01
Had a steady sex partner who was also an IDU	3.76 (2.66, 5.33)	<0.01

Table 3: Predictors of incident HCV infection stratified by sex

	Including Covariates Significantly Associated with HCV for Males or Females		Including Covariates Significantly Associated with HCV for Females		Including Covariates Significantly Associated with HCV for Males	
	Females (n = 140)	Males (n = 277)	Females (n = 140)		Males (n = 277)	
	Hazard Ratio	p	Hazard Ratio	p	Hazard Ratio	p	Hazard Ratio	p
Injected every day								
Injected heroin								
Injected speed								
Injected cocaine								
Reused a syringe								
Reused a cooker								
Used a syringe previously used by another injector								
Used a cooker previously used by another injector								
Did a rinse								
# of Borrowing Partners								
1 (vs. 0)								
>1 (vs. 0)								
Frequency of Injecting alone								

~~Sometimes (vs. never)~~
~~Always (vs. never)~~

~~Frequency of Pooling~~
~~Sometimes (vs. never)~~
~~Aways (vs. never)~~

~~# of Pooling Partners~~
~~1 (vs. 0)~~
~~>1 (vs. 0)~~

~~Had a steady sex partner who was also an IDU~~

Table 3: Predictors of incident HCV infection stratified by sex*

	All Participants		Females (n = 140)		Males (n = 277)	
	Hazard Ratio	p	Hazard Ratio	p	Hazard Ratio	p
Female	1.43 (1.03 – 2.00)	0.03				
Age	0.92 (0.88, 0.96)	<0.01	0.93 (0.86, 1.01)	0.07	0.93 (0.88, 0.98)	0.01
Non-white race	0.91 (0.61, 1.34)	0.62	1.19 (0.64, 2.23)	0.59	0.77 (0.47, 1.27)	0.31
Age of first injection	0.96 (0.93, 1.00)	0.048	0.96 (0.90, 1.03)	0.29	0.97 (0.92, 1.02)	0.17
Years injecting	1.00 (0.96, 1.05)	0.84	1.02 (0.95, 1.09)	0.69	1.01 (0.96, 1.07)	0.67
Injected every day	2.58 (1.84, 3.62)	<0.01	2.06 (1.17, 3.66)	0.01	2.86 (1.87, 4.38)	<0.01
Injected heroin	2.71 (1.79, 4.11)	<0.01	2.34 (1.14, 4.83)	0.02	2.87 (1.73, 4.75)	<0.01
Injected speed	1.48 (1.05, 2.08)	0.03	1.12 (0.65, 1.92)	0.68	1.80 (1.13, 2.84)	0.01
Injected cocaine	2.32 (1.65, 3.26)	<0.01	2.27 (1.34, 3.83)	<0.01	2.49 (1.59, 3.91)	<0.01
Reused a syringe	1.68 (1.11, 2.54)	0.01	1.65 (0.85, 3.19)	0.14	1.71 (1.1, 2.91)	0.05
Reused a cooker	2.38 (1.70, 3.33)	<0.01	1.96 (1.13, 3.43)	0.02	2.47 (1.61, 3.79)	<0.01
Used a syringe previously used by another injector	2.64 (1.88, 3.70)	<0.01	2.71 (1.56, 4.71)	<0.01	2.47 (1.61, 3.79)	<0.01
Used a cooker previously used by another injector	2.38 (1.67, 3.40)	<0.01	2.16 (1.31, 3.59)	<0.01	2.26 (1.37, 3.72)	<0.01
Did a rinse	2.66 (1.92, 3.70)	<0.01	1.93 (1.13, 3.28)	0.02	3.22 (2.16, 4.81)	<0.01

# of Borrowing Partners						
1 (vs. 0)	2.74 (1.84, 4.09)	<0.01	3.31 (1.88, 5.82)	<0.01	2.22 (1.26, 3.91)	<0.01
>1 (vs. 0)	2.54 (1.59, 4.06)	<0.01	1.78 (0.73, 4.35)	0.2	2.93 (1.74, 4.95)	<0.01
Frequency of Injecting alone						
Sometimes (vs. never)	2.20 (1.48, 3.26)	<0.01	1.84 (1.03, 3.29)	0.04	2.54 (1.48, 4.36)	<0.01
Always (vs. never)	0.96 (0.50, 1.83)	0.9	1.12 (0.34, 3.70)	0.85	1.11 (0.50, 2.45)	0.79
Frequency of Pooling						
Sometimes (vs. never)	2.53 (1.70, 3.76)	<0.01	1.61 (0.78, 3.33)	0.2	2.93 (1.83, 4.68)	<0.01
Aways (vs. never)	2.33 (1.40, 3.87)	<0.01	2.29 (1.04, 5.02)	0.04	1.56 (0.68, 3.61)	0.3
# of Pooling Partners						
1 (vs. 0)	2.62 (1.66, 4.14)	<0.01	1.94 (0.88, 4.27)	0.1	2.91 (1.65, 5.12)	<0.01
>1 (vs. 0)	2.50 (1.65, 3.78)	<0.01	1.84 (0.87, 3.87)	0.11	2.61 (1.58, 4.34)	<0.01
Had a steady sex partner	1.73 (1.22, 2.46)	<0.01	1.73 (0.88, 3.39)	0.11	1.52 (0.96, 2.38)	0.07
Had a steady sex partner who was also an IDU	2.23 (1.58, 3.14)	<0.01	2.55 (1.32, 4.94)	<0.01	1.88 (1.20, 2.95)	<0.01

* Although interactions between primary predictor variables and female sex were also modeled, none reached significance at p<0.20

Table 4: Hazard ratios for incident HCV for females vs. males, adjusted by risk behavior, one at a time

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

** Significantly associated with female sex at baseline*

¥ Significantly associated with female sex during follow-u

Acknowledgements

Acknowledgments: The authors would like to acknowledge the helpful contributions from colleagues: Drs. Michael P. Busch and Leslie Tobler at Blood Systems Research Institute for ongoing laboratory expertise; Dr. Stephen Shiboski for statistical consultation; and all of the UFO Study staff and volunteers for research assistance and support. We thank the San Francisco Department of Public Health for their ongoing commitment to the health of the young people who participate; their contributions, including preventive vaccines and primary care for participants is invaluable. We thank our community partners at the Housing and Urban Health Clinic, Homeless Youth Alliance, San Francisco Needle Exchange and San Francisco AIDS Foundation. Last but not least, we especially acknowledge the participation of all the UFO Study participants without whom this research and the knowledge we gain to help prevent HCV would not be possible.

Funding: The authors received support from the National Institutes of Health - National Institute on Drug Abuse Award Number R01DA016017 and National Institute on Alcohol and Alcoholism K24AA022586 (JAH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse or the National Institutes of Health. We also acknowledge support from the UCSF CTSI (NIH UL1 RR024131) and the UCSF Liver Center (NIH P30 DK026743).

Contributorship Statement: All authors contributed to this manuscript. DT, JAH, and KP compiled the first draft of the manuscript, and authors CFL, JE, AB, MDM, and PJL reviewed and provided further scientific and editorial input. The primary statistical analysis was conducted

by DT; JE provided supplemental data review, and JAH and KP reviewed all data analyses. All authors contributed to and have approved the final manuscript. KP, JAH, JE, AB, MDM, PJL, and KP designed and conducted the UFO Study from which data for this study were obtained. All authors provided expertise on the research presented in this manuscript including the methods, analysis, and final manuscript. None of the authors have any conflicts of interest to disclose. This manuscript is not under submission or consideration elsewhere.

Conflicts: The authors declare that they have no commercial or other association that might pose a conflict of interest with this research.

Data Sharing Statement: No additional data

References

1. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144(10):705-14.
2. Hagan H, Pouget ER, Des Jarlais DC, Lelutiu-Weinberger C. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. Am J Epidemiol 2008;168(10):1099-109.
3. Hahn JA, Page-Shafer K, Lum PJ, Bourgois P, Stein E, Evans JL, et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis 2002;186(11):1558-64.
4. Hahn JA, Page-Shafer K, Lum PJ, Ochoa K, Moss AR. Hepatitis C virus infection and needle exchange use among young injection drug users in San Francisco. Hepatology 2001;34(1):180-7.
5. Mehta SH, Astemborski J, Kirk GD, Strathdee SA, Nelson KE, Vlahov D, et al. Changes in blood-borne infection risk among injection drug users. J Infect Dis 2011;203(5):587-94.
6. Page K, Hahn JA, Evans J, Shiboski S, Lum P, Delwart E, et al. Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. J Infect Dis 2009;200(8):1216-26.
7. Miller CL, Johnston C, Spittal PM, Li K, Laliberte N, Montaner JS, et al. Opportunities for prevention: hepatitis C prevalence and incidence in a cohort of young injection drug users. Hepatology 2002;36(3):737-42.
8. Miller CL, Wood E, Spittal PM, Li K, Frankish JC, Braitstein P, et al. The future face of coinfection: prevalence and incidence of HIV and hepatitis C virus coinfection among young injection drug users. J Acquir Immune Defic Syndr 2004;36(2):743-9.
9. Use of enhanced surveillance for hepatitis C virus infection to detect a cluster among young injection-drug users--New York, November 2004-April 2007. Mmwr. Morbidity and Mortality Weekly Report 2008;57(19):517-21.
10. Notes from the field: risk factors for hepatitis C virus infections among young adults--Massachusetts, 2010. Mmwr. Morbidity and Mortality Weekly Report 2011;60(42):1457-8.
11. Hepatitis C virus infection among adolescents and young adults:Massachusetts, 2002-2009. Mmwr. Morbidity and Mortality Weekly Report 2011;60(17):537-41.
12. Notes from the field : hepatitis C virus infections among young adults--rural Wisconsin, 2010. Mmwr. Morbidity and Mortality Weekly Report 2012;61(19):358.
13. Christian WJ, Hopenhayn C, Christian A, McIntosh D, Koch A. Viral hepatitis and injection drug use in Appalachian Kentucky: a survey of rural health department clients. Public Health Rep 2010;125(1):121-8.
14. Holmberg S. The emerging epidemic of hepatitis C among young non-urban injection drug users. 2013.
15. Micallef JM, Macdonald V, Jauncey M, Amin J, Rawlinson W, van Beek I, et al. High incidence of hepatitis C virus reinfection within a cohort of injecting drug users. J Viral Hepat 2007;14(6):413-8.
16. Craine N, Hickman M, Parry JV, Smith J, Walker AM, Russell D, et al. Incidence of hepatitis C in drug injectors: the role of homelessness, opiate substitution treatment, equipment sharing, and community size. Epidemiol Infect 2009;137(9):1255-65.

17. Patrick DM, Tyndall MW, Cornelisse PG, Li K, Sherlock CH, Rekart ML, et al. Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection. CMAJ 2001;165(7):889-95.
18. van den Berg CH, Smit C, Bakker M, Geskus RB, Berkhout B, Jurriaans S, et al. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. Eur J Epidemiol 2007;22(3):183-93.
19. Hagan H, Thiede H, Des Jarlais DC. Hepatitis C virus infection among injection drug users: survival analysis of time to seroconversion. Epidemiology 2004;15(5):543-9.
20. Maher L, Jalaludin B, Chant KG, Jayasuriya R, Sladden T, Kaldor JM, et al. Incidence and risk factors for hepatitis C seroconversion in injecting drug users in Australia. Addiction 2006;101(10):1499-508.
21. Montgomery SB, Hyde J, De Rosa CJ, Rohrbach LA, Ennett S, Harvey SM, et al. Gender differences in HIV risk behaviors among young injectors and their social network members. Am J Drug Alcohol Abuse 2002;28(3):453-75.
22. Gollub EL, Rey D, Obadia Y, Moatti JP. Gender differences in risk behaviors among HIV+ persons with an IDU history. The link between partner characteristics and women's higher drug-sex risks. The Manif 2000 Study Group. Sex Transm Dis 1998;25(9):483-8.
23. Miller M, Neaigus A. Networks, resources and risk among women who use drugs. Soc Sci Med 2001;52(6):967-78.
24. Strathdee SA, Galai N, Safaiean M, Celentano DD, Vlahov D, Johnson L, et al. Sex differences in risk factors for HIV seroconversion among injection drug users: a 10-year perspective. Arch Intern Med 2001;161(10):1281-8.
25. Spittal PM, Craib KJ, Wood E, Laliberte N, Li K, Tyndall MW, et al. Risk factors for elevated HIV incidence rates among female injection drug users in Vancouver. CMAJ 2002;166(7):894-9.
26. Evans JL, Hahn JA, Page-Shafer K, Lum PJ, Stein ES, Davidson PJ, et al. Gender differences in sexual and injection risk behavior among active young injection drug users in San Francisco (the UFO Study). J Urban Health 2003;80(1):137-46.
27. Bakr I, Rekacewicz C, El Hosseiny M, Ismail S, El Daly M, El-Kafrawy S, et al. Higher clearance of hepatitis C virus infection in females compared with males. Gut 2006;55(8):1183-7.
28. Di Martino V, Lebray P, Myers RP, Pannier E, Paradis V, Charlotte F, et al. Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure. Hepatology 2004;40(6):1426-33.
29. Garfein RS, Golub ET, Greenberg AE, Hagan H, Hanson DL, Hudson SM, et al. A peer-education intervention to reduce injection risk behaviors for HIV and hepatitis C virus infection in young injection drug users. AIDS 2007;21(14):1923-32.
30. Vanichseni S, Kitayaporn D, Mastro TD, Mock PA, Raktham S, Des Jarlais DC, et al. Continued high HIV-1 incidence in a vaccine trial preparatory cohort of injection drug users in Bangkok, Thailand. AIDS 2001;15(3):397-405.
31. Kral AH, Lorvick J, Edlin BR. Sex- and drug-related risk among populations of younger and older injection drug users in adjacent neighborhoods in San Francisco. Journal of Acquired Immune Deficiency Syndromes 2000;24(2):162-7.
32. Broz D, Ouellet LJ. Racial and ethnic changes in heroin injection in the United States: implications for the HIV/AIDS epidemic. Drug Alcohol Depend 2008;94(1-3):221-33.
33. Fennema JS, Van Ameijden EJ, Van Den Hoek A, Coutinho RA. Young and recent-onset injecting drug users are at higher risk for HIV. Addiction 1997;92(11):1457-65.

34. Seear K, Gray R, Fraser S, Treloar C, Bryant J, Brener L. Rethinking safety and fidelity: The role of love and intimacy in hepatitis C transmission and prevention. Health Sociology Review 2012;21(3):272-286.
35. Rhodes T, Treloar C. The social production of hepatitis C risk among injecting drug users: a qualitative synthesis. Addiction 2008;103(10):1593-603.
36. Jackson L, Parker J, Dykeman M, Gahagan J, Karabanow J. The power ofrelationships: implications for safer and unsafe practices among injection drugusers. Drugs Educ. Prev. Policy 2010;17:189-204.
37. Fraser S, Treloar C, Bryant J, Rhodes T. Hepatitis C prevention educaqtion needs to be grounded in social relationships. Drugs: education, prevention, and policy 2013.
38. Kral AH, Malekinejad M, Vaudrey J, Martinez AN, Lorvick J, McFarland W, et al. Comparing respondent-driven sampling and targeted sampling methods of recruiting injection drug users in San Francisco. J Urban Health 2010;87(5):839-50.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

Tracy et al.,

	Item No	Item, Section and PAGE NUMBER
Title and abstract	1	(*a*) Study's design with a commonly used terms – PAGE 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – PAGE 3
Introduction		
Background/rationale	2	Scientific background and rationale for the investigation being reported – PAGE 5-6
Objectives	3	State specific objectives, including any prespecified hypotheses- PAGE 6
Methods		
Study design	4	Present key elements of study design early in the paper- PAGE 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection- PAGE 7-
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up- PAGE 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, - PAGE 7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – PAGE 7-8
Bias	9	Describe any efforts to address potential sources of bias –comparisons were made between those in follow up and those lost
Study size	10	Explain how the study size was arrived at – PAGE 7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why- PAGE 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding- PAGE 8
		(*b*) Describe any methods used to examine subgroups and interactions- PAGE 8
		(*c*) Explain how missing data were addressed- Page 8-9
		(*d*) If applicable, explain how loss to follow-up was addressed: only participants with follow up were included, but comparisons made to assess differences between groups.
		(*e*) Describe any sensitivity analyses None
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed- PAGE 8-9
		(b) Give reasons for non-participation at each stage: none
		(c) Consider use of a flow diagram NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders- PAGE 8-9; and TABLE 1
		(b) Indicate number of participants with missing data for each variable of interest NA
		(c) Summarise follow-up time (eg, average and total amount) PAGE 10

Outcome data	15*	Report numbers of outcome events or summary measures over time – PAGE 10, TABLES 2-3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. TABLES 2-4
		(*b*) Report category boundaries when continuous variables were categorized NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses –PAGE 11; Table 4
Discussion		
Key results	18	Summarise key results with reference to study objectives – PAGE 12-
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – PAGE 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence PAGE 13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results PAGE 14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based PAGE 20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.