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Sex Discrepancies in the Protective Effect of Opioid Agonist Therapy on Incident Hepatitis C Infection

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Background. While opioid agonist therapy (OAT) reduces the risk of hepatitis C virus (HCV) acquisition among people who inject drugs (PWID), protective effects may be attenuated in females. We used pooled data from an international collaboration of prospective cohorts to assess sex disparities in HCV incidence among PWID exposed to OAT.

Methods. Independent predictors of HCV infection were identified using Cox regression models with random effects after accounting for the clustering effect of study sites. Unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) are presented in sex-specific analyses.

Results. Among 701 participants exposed to OAT, HCV incidence was 16.5/100 person-years of observation (PYO) (95% CI, 13.1–20.7) in females and 7.6/100 PYO (95% CI, 6.0–9.5) in males (female:male adjusted HR [aHR], 1.80 [95% CI, 1.37–2.22]; $P < .001$). Factors associated with HCV acquisition among females exposed to OAT included nonwhite race (aHR, 1.79 [95% CI, 1.25–2.56]; $P = .001$), unstable housing (aHR, 4.00 [95% CI, 3.62–4.41]; $P < .001$), daily or more frequent injection (aHR, 1.45 [95% CI, 1.01–2.08]; $P = .042$), and receptive syringe sharing (aHR, 1.43 [95% CI, 1.33–1.53]; $P < .001$).

Conclusions. Female PWID exposed to OAT are twice as likely as their male counterparts to acquire HCV. While there is a need for better understanding of sex differences in immune function and opioid pharmacokinetic and pharmacodynamic parameters, structural and behavioral interventions that target women are required to bolster the efficacy of OAT in preventing HCV transmission.

Keywords. sex; hepatitis C virus; people who inject drugs; opioid agonist therapy; harm reduction.

An estimated 71 million adults worldwide (1%) are living with hepatitis C virus (HCV) [1]. HCV transmission through sexual contact is rare in heterosexual couples (1 per 190 000 sexual contacts) [2] and HCV incidence among human immunodeficiency virus (HIV)–infected men who have sex with men (with presumed sexual acquisition) is also low (0.53% per year) [3], compared to parenterally acquired HCV (ranging from 40% to 100%) [4].

In developed countries, exposure to HCV through injection drug use remains the predominant mode of transmission [5]. There are approximately 16 million people who inject drugs (PWID) worldwide, including an estimated 3.2 million women, with 1 in 2 PWID exposed to HCV [6]. Chronic HCV infection is a major global health burden, associated with severe morbidity, including cirrhosis, hepatocellular cancer, and liver failure, as well as mortality [7].

A recent study reported that female PWID had a 38% higher risk of incident HCV infection, compared to males [8]. The primary risk factor for HCV transmission among PWID is receptive sharing of needles and syringes [6], and several studies indicate females are significantly more likely to engage in receptive syringe sharing (RSS) compared to males [9]. Other risk factors include the sharing of ancillary injecting equipment, such as cookers and cotton filters [10, 11], and drug preparation techniques such as backloading [12]. Some evidence suggests that increased risk of HCV infection among females may also be due to health services not addressing gender-specific needs or services being tailored to males [13]. Although females are at higher risk of acquiring HCV, they are also more likely to spontaneously clear the infection [14].

The advent of direct-acting antiviral treatments for HCV infection has resulted in cure rates of >95% [15]. Despite the efficacy of these treatments, barriers to uptake remain such as the cost of treatment, management of other comorbidities,

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advanced liver disease, inadequate levels of screening and confirmatory testing, practitioner unfamiliarity with HCV treatment regimens, and non–evidence-based guidelines that render people ineligible for treatment due to current drug or alcohol use [16]. Interventions that prevent transmission of HCV are still required, including access to sterile injection equipment and rapid and accurate point-of-care testing and interventions to reduce risk behavior such as frequency of injection, including effective drug treatment [17].

Opioid agonist therapy (OAT) has been shown to reduce the incidence of HCV infection among PWID [18–20]. When provided continuously and at therapeutic doses, OAT reduces opioid cravings, injection frequency, and high-risk injection practices [21]. A systematic review and meta-analysis of 12 studies found that current OAT (defined as the use of prescribed methadone or buprenorphine within the previous 6 months) was associated with a 50% reduction in risk of acquiring HCV, compared to no current OAT [22]. Furthermore, a lifetime history of OAT was associated with a 19% reduction in HCV incidence, compared with no history of OAT [22]. This analysis also suggested that the effectiveness of OAT differed between females and males, with a 59% reduction in the effectiveness of the intervention with every 10% increase in female participants [22].

The current study aimed to assess differences in HCV incidence by sex among PWID exposed to OAT and to identify factors independently associated with any decrease in protective efficacy.

METHODS

Study Design

The International Collaboration of Incident HIV and HCV in Injecting Cohorts (InC3) is a collaborative of 10 prospective cohort studies with pooled behavioral and serological data. InC3 methodology has been described in detail elsewhere [23]. Cohorts included in the collaboration originated from 4 countries and include the Amsterdam Cohort Study (ACS), Australian Trial in Acute Hepatitis C (ATAHC), Baltimore Before and After Acute Study in Hepatitis (BBAASH), Boston Acute HCV Study: Transmission, Immunity, Outcomes Network (BAHSTION), Hepatitis C Incidence and Transmission Study–community (HITS-c, Sydney), Hepatitis C Incidence and Transmission Study–prison (HITS-p, Sydney), Hepatitis C Virus Cohort Study (HCVC, Sydney), St Luc Hepatitis Cohort (HepCo, Montreal), Melbourne Injecting Drug User Cohort Study (SuperMIX, Melbourne), and U-Find-Out Study (UFO, San Francisco). Protocols for each study were approved by local institutional research ethics committees. InC3 was determined to be "exempt" from ethical review by the University of New Mexico institutional review board as all data are de-identified.

Study Population

Of the 10 cohorts included in InC3, 3 were excluded from the analysis as the study design did not allow for HCV incidence to be calculated (ATAHC) or data on injection exposure were not available (BAHSTION and BBAASH). HCV-negative participants from the remaining 7 cohorts were included in the current study where the following criteria were met: (1) a history of injection drug use was recorded; (2) at least 1 follow-up serological cohort visit was recorded; (3) biological sex was recorded as male or female; and (4) exposure to OAT in the previous 12 months was recorded at any cohort visit.

Measures

Serological and molecular markers for HCV infection were collected along with self-reported data on sociodemographic characteristics and drug use history and behaviors at 3-month (SuperMix and UFO) and 6-month (ACS, HCVC, HITS-c, HITS-p, and HepCo) intervals. Exposure to OAT was defined as the prescription of OAT (methadone, buprenorphine, or buprenorphine-naloxone) in the previous 12 months on at least 1 cohort visit. Sociodemographic characteristics included race, sexual identity (heterosexual vs homosexual and bisexual), age at baseline, education, recent unstable housing, employment status (full time, part time, casual, or home duties), and recent alcohol intake. Participants whose race was recorded as Asian, black, Hispanic, Indigenous, white-Asian, white-black, and other were classified as nonwhite, and those who reported completing 12 or more years of education were classified as having completed high school.

Injection risk behaviors included number of years since injection initiation, frequency of injection (less than daily vs daily or more frequent), recent RSS, and drug most frequently injected. Drugs injected were classified as either opioids (heroin, pharmaceutical opioids, OAT, or a mixture of heroin and cocaine) or nonopioids (amphetamine, methamphetamine, cocaine, or "other" drugs). Time since injection initiation was calculated using year of first injection and year of baseline visit and subsequently collapsed into tertiles.

HCV Incident Infection

Among HCV-naive participants, HCV incident infection was determined to have occurred if a positive anti-HCV or HCV RNA test was recorded within 2 years of a negative anti-HCV test, or if there was recorded evidence of seroconversion illness (clinically diagnosed jaundice or alanine aminotransferase level >400 IU/L) along with a history of high-risk injection behaviors or the detection of HCV RNA within 3 months of clinical manifestation of acute HCV. Anti-HCV and HCV RNA assays are described elsewhere and varied between, but not within, cohorts [14].

Time to HCV infection was estimated using a hierarchy of successive serological (anti-HCV), virological (HCV RNA), and clinical (symptoms and liver function tests) data. Among

participants with a documented seroconversion illness, date of infection was determined as 6 weeks prior to the onset of symptoms. Participants who recorded a positive HCV RNA test following a negative anti-HCV test during acute HCV detection had an estimated date of infection of 28 days prior to the positive test. Participants with a positive RNA test following a negative anti-HCV test and with no acute HCV detection were estimated to have seroconverted at the midpoint between the last negative anti-HCV test and first positive anti-HCV test or positive HCV RNA test.

Statistical Analysis

The primary study outcome was HCV incident infection while exposed to OAT. Participants who seroconverted were censored at the first HCV-positive visit date, whereas participants who did not record a positive HCV antibody or RNA test were censored at the last recorded visit where laboratory results were available. Time from entry in each study was used to calculate person-years of observation (PYO). Sex-specific crude HCV incidence rates were determined using Kaplan-Meier methods. Cox proportional hazards regression models with random effects were used to identify the independent predictors of incident HCV infection after accounting for the clustering effect of study sites and adjusting for missing data in each variable. Sociodemographic variables included in bivariate analysis included race, sexual identity, education, recent unstable housing, employment status, and recent alcohol intake, while injection-related variables included years since injecting initiation, drug most frequently injected, injection frequency, and recent RSS. The current study only included variables where <50% of data were missing, with variables relating to recent imprisonment and utilization of needle and syringe programs excluded from the analysis (51% and 54% missing, respectively). Those variables with <50% of missing data were all considered in our analysis. We handled the missing observations based on recommended statistical principles [24, 25]. A separate missing category was created and included in our analysis for variables with >5% missing data, while missing data was included in the reference category for variables with <5% missing data. Sex-specific sensitivity analyses were conducted to fit the final multivariable models using only available data to assess the impact of the missing data on our analyses. Data were analyzed using Stata version 14.2 software (StataCorp, College Station, Texas).

RESULTS

Sample Characteristics

A total of 701 participants from 7 cohorts were eligible for inclusion (Figure 1). As shown in Table 1, the majority were male (64%) and white (75%). The median age was 26 years (interquartile range [IQR], 17–49 years) and the median number of years since injection initiation was 7 (IQR, 1–34 years). Forty percent had completed high school and 29% reported recent unstable housing. One in 5 (22%) participants reported daily or more frequent injection and 18% reported recent RSS. Seven participants tested HIV positive at baseline, 4 of whom were subsequently exposed to HCV.

HCV Incidence by Sex

A total of 3003 observed visits were recorded by the 701 participants exposed to OAT included here. Over 1427 PYO, 148 incident HCV infections were recorded, resulting in HCV incidence (per 100 PYO) of 16.5 (95% confidence interval [CI], 13.1–20.7) and 7.6 (95% CI, 6.0–9.5) among females and males, respectively (Figure 2). The unadjusted female-to-male hazard ratio (HR) was 1.90 (95% CI, 1.37–2.61; $P < .001$), and the adjusted HR (aHR) was 1.80 (95% CI, 1.37–2.22; $P < .001$).

Factors Associated With HCV Incident Infection by Sex

In bivariate analysis, incident HCV infection was significantly higher among females exposed to OAT who were nonwhite (HR, 2.39 [95% CI, 2.25–2.52]; $P < .001$), did not complete high school (HR, 2.05 [95% CI, 1.08–3.90]; $P = .029$), reported recent unstable housing (HR, 5.13 [95% CI, 4.42–5.96]; $P < .001$), had an injection history of between 6 and 10 years (HR, 1.35 [95% CI, 1.06–1.72]; $P = .014$), injected daily or more frequently (HR, 2.65 [95% CI, 1.97–3.57]; $P < .001$) and reported recent RSS (HR, 1.71 [95% CI, 1.47–1.97]; $P < .001$). In multivariable analysis (Table 2), incident HCV infection was significantly higher among females exposed to OAT who were nonwhite (aHR, 1.79 [95% CI, 1.25–2.56]; $P = .001$) and who reported recent unstable housing (aHR, 4.00 [95% CI, 3.62–4.41]; $P < .001$), recent daily or more frequent injection (aHR, 1.45 [95% CI, 1.01–2.08]; $P = .042$), and recent RSS (aHR, 1.43 [95% CI, 1.33–1.53]; $P < .001$).

In bivariate analysis, incident HCV infection was significantly higher among males exposed to OAT who did not complete high school (HR, 1.73 [95% CI, 1.24–2.42]; $P = .001$), reported recent unstable housing (HR, 3.99 [95% CI, 3.25–4.89]; $P < .001$), injected daily or more frequently (HR, 4.02 [95% CI, 2.27–7.09]; $P < .001$), and reported recent RSS (HR, 2.25 [95% CI, 1.22–4.15]; $P = .010$). Males who reported most frequently injecting opioids were significantly less likely to acquire HCV (HR, 0.60 [95% CI, .45–.82]; $P = .001$). In multivariable analysis, incident HCV infection was significantly higher among males exposed to OAT who were nonwhite (aHR, 1.40 [95% CI, 1.06–1.84]; $P = .017$) reported recent unstable housing (aHR, 3.29 [95% CI, 2.03–5.32]; $P < .001$), and injected daily or more frequently (aHR, 3.79 [95% CI, 3.43–4.18]; $P < .001$). Frequent injection of opioids remained independently associated with lower risk of HCV acquisition in males (aHR, 0.60 [95% CI, .48–.75]; $P < .001$).

DISCUSSION

Results indicate that among PWID exposed to OAT, females were almost twice as likely as males to acquire HCV infection.
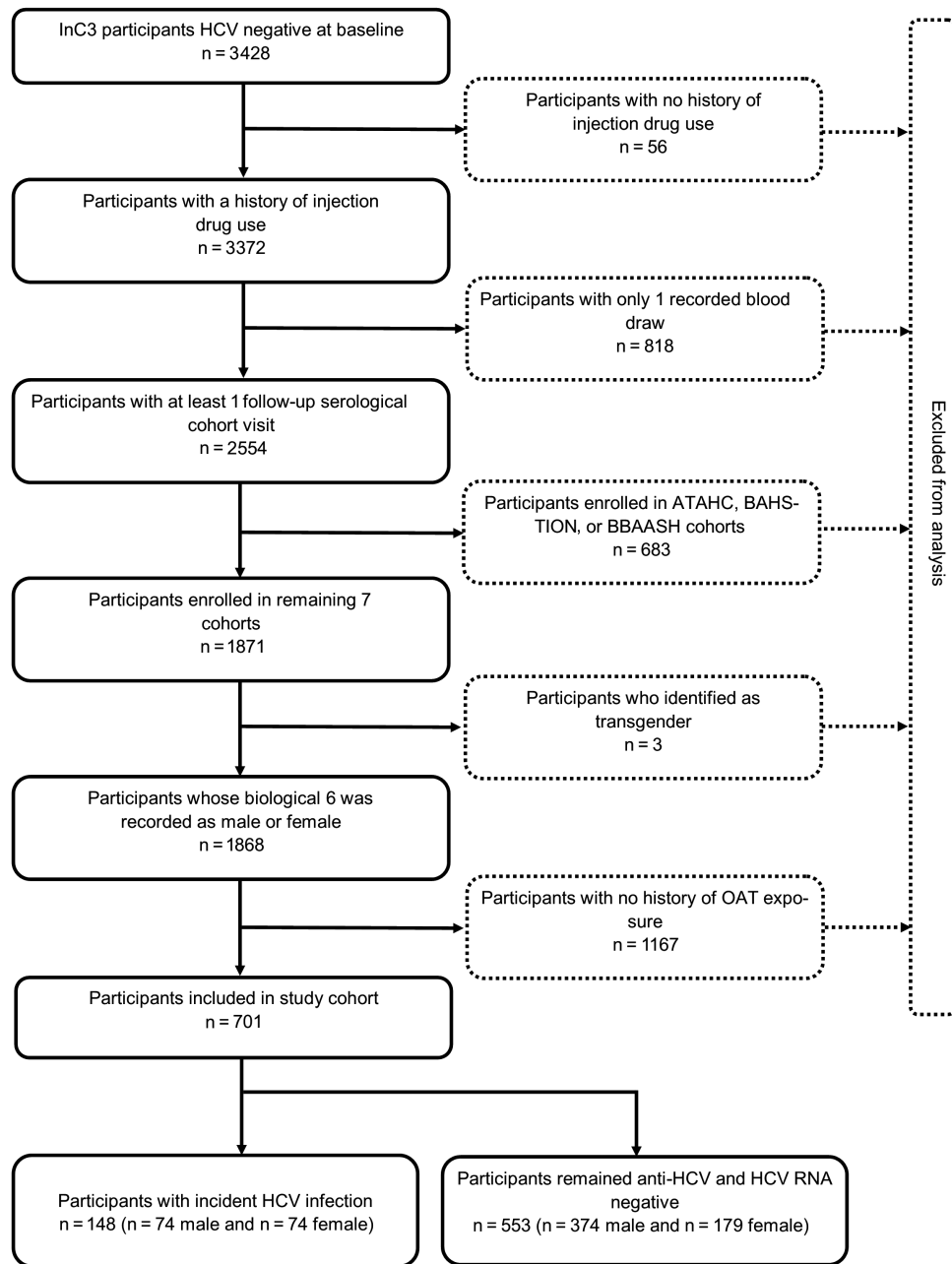
Figure 1. Participant inclusion flowchart. Abbreviations: ATAHC, Australian Trial in Acute Hepatitis C; BAHSTION, Boston Acute HCV Study: Transmission, Immunity, Outcomes Network; BBAASH, Baltimore Before and After Acute Study in Hepatitis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; InC3, International Collaboration of Incident HIV and HCV in Injecting Cohorts, OAT, opioid agonist therapy.

This finding is consistent with the meta-analysis by Platt et al, which observed a 59% reduction in the effectiveness of OAT with every 10% increase in female participants [22]. Previous research has documented sex-based differences in immune function [26]. Compared to males, females produce more vigorous cellular and humoral immune reactions and although females are more resistant to infections, they also experience higher prevalence of several autoimmune diseases [27], with increased severity and number of immune and inflammatory responses compared to males [26]. Sex differences in immunity have been linked to influences on the function of immune cells caused by the binding of sex steroids to specific receptors expressed in lymphoid tissue cells, macrophages, dendritic cells, and lymphocytes [26]. Some evidence also suggests sex-based differences in human brain μ- and κ-opioid receptor binding potential as measured by positron emission tomography [28, 29]. These studies merely suggest differences in the opioid pathways in the central nervous system that could lead to differential effects for opioid effects, including those relevant for reward, withdrawal, and addiction. This is merely to suggest that the effects of OAT on withdrawal and addiction may not be the same among females compared to males [29]. Fluctuations in

Table 1. Baseline Characteristics of Study Participants, Overall and by Sex (N = 701)

Variable	Total Sample (N = 701)	Male (n = 448)	Female (n = 253)
Race			
Asian	46 (7)	32 (7)	14 (6)
Black	2 (<1)	2 (<1)	0 (0)
Hispanic	6 (1)	5 (1)	1 (<1)
Indigenous	41 (6)	15 (3)	26 (10)
White	525 (75)	338 (75)	187 (74)
Other	40 (6)	26 (6)	14 (5)
Missing	41 (6)	30 (7)	11 (5)
Sexual identity			
Heterosexual	416 (59)	282 (63)	134 (53)
Homosexual or bisexual	56 (8)	18 (4)	38 (15)
Missing	229 (33)	148 (33)	81 (32)
Age, y, median (IQR)	26 (17–49)	27 (18–48)	25 (17–45)
Education			
Completed high school	283 (40)	183 (41)	100 (40)
Did not complete high school	262 (37)	158 (35)	104 (41)
Missing	156 (22)	107 (24)	49 (19)
Unstable housing[a]			
No	256 (37)	168 (38)	88 (35)
Yes	202 (29)	138 (31)	64 (25)
Missing	243 (35)	142 (32)	101 (40)
Unemployed[a]			
No	180 (26)	126 (28)	54 (21)
Yes	182 (26)	113 (25)	69 (27)
Missing	339 (48)	209 (47)	130 (51)
Alcohol intake[a]			
No	145 (21)	93 (21)	52 (21)
Yes	257 (37)	178 (40)	79 (31)
Missing	299 (43)	177 (40)	122 (48)
Years since injecting initiation, median (IQR)	7 (1–34)	8 (1–34)	7 (1–27)
Drug most frequently injected[a]			
Nonopioids	61 (9)	38 (9)	23 (9)
Opioids	331 (47)	224 (50)	107 (42)
Missing	309 (44)	186 (42)	123 (49)
Injection frequency[a]			
Less than daily	405 (58)	271 (60)	134 (53)
Daily	154 (22)	104 (23)	50 (20)
Missing	142 (20)	73 (16)	69 (27)
Receptive syringe sharing[a]			
No	339 (48)	230 (51)	109 (43)
Yes	127 (18)	85 (19)	42 (17)
Missing	235 (34)	133 (30)	102 (40)
HIV status			
Negative	491 (70)	308 (69)	183 (72)
Positive	7 (1)	7 (2)	0 (0)
Unknown	1 (<1)	1 (<1)	0 (0)
Missing	202 (29)	132 (29)	70 (28)
Participating sites			
ACS (Amsterdam)	126 (18)	87 (19)	39 (15)
HCVC (Sydney)	133 (19)	86 (19)	47 (19)
HITS-c (Sydney)	67 (10)	49 (11)	18 (7)
HITS-p (Sydney)	140 (20)	71 (16)	69 (27)
HepCo (Montreal)	81 (12)	56 (13)	25 (10)
SuperMIX Study (Melbourne)	79 (11)	54 (12)	25 (10)
UFO Study (San Francisco)	75 (11)	45 (10)	30 (12)

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: ACS, Amsterdam Cohort Study; HCVC, Hepatitis C Virus Cohort Study; HepCo, St Luc Hepatitis Cohort; HITS-c, Hepatitis C Incidence and Transmission–community study; HITS-p, Hepatitis C Incidence and Transmission–prison study; HIV, human immunodeficiency virus; IQR, interquartile range; SuperMIX Study, Networks 2 and Melbourne Injecting Drug User Cohort Study; UFO, U-Find-Out Study.

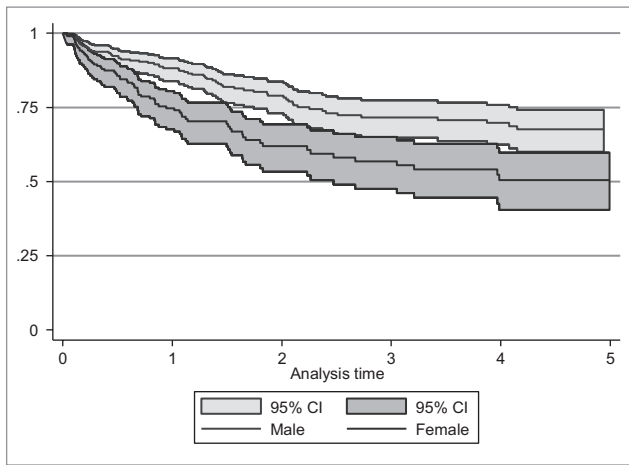[a]In the previous 3 or 6 months depending on cohort interview intervals.

Figure 2. Kaplan-Meier survival estimates of hepatitis C virus incidence by sex among participants exposed to opioid agonist therapy. Abbreviation: CI, confidence interval.

female hormone levels (eg, during pregnancy) may also influence opioid binding and dosing requirements [30]. It is possible that sex differences observed in the current study could, in part, be related to differences in pharmacokinetics and drug metabolism of OAT among females compared to males. While methadone metabolism is clearly altered in pregnancy, there is an absence of literature to fully establish whether differences might also exist among nonpregnant women compared to men [31].

Among females in the current study, nonwhite race, recent unstable housing, daily or more frequent injection, and RSS were associated with an increased risk of incident HCV infection. Nonwhite females exposed to OAT were almost twice as likely as white females to acquire HCV infection. The attenuated protective effect of OAT observed in nonwhite females is consistent with previous work by our group, which found that HCV incidence among nonwhite females was twice that of white females [8]. The association between nonwhite race and the attenuated protective effect of OAT against incident HCV is significant, as race not only plays a role in the transmission of HCV [12], but is associated with an increased risk of disease progression. In a US study of 464 people living with chronic HCV, African American and Asian females were, respectively, 2.2 and 4.6 times more likely to develop hepatocellular cancer than white females [32]. Moreover, compared to white patients, African American and Hispanic patients in real-world settings are significantly less likely to achieve a sustained virological response when treated with HCV direct-acting antiviral therapies [33]. Further work is required to explore the relationship between race and incident HCV infection, including the attenuated protective efficacy of OAT, as well as HCV-related disease progression and treatment outcomes.

Recent unstable housing was significantly associated with incident HCV infection in both females and males. Females who acquired HCV were 4 times more likely to report unstable housing

in the previous 6 months, compared with females who did not. Housing instability has been independently associated with both HIV [34, 35] and HCV acquisition [36, 37], and unstably housed PWID are more likely to engage in injection risk behavior [35], such as RSS [37]. Stable housing is associated with better health status [34, 36], including more frequent and timely utilization of health and social services [38]. Further work is needed to evaluate novel interventions to address housing instability among PWID, and to better integrate HCV prevention, testing, and linkage to care and treatment services into such services.

When taken continuously and at therapeutic doses, OAT is protective against incident HIV and HCV infection due to reduced frequency of injection and high-risk injecting practices [21, 22]. However, our results indicate that females exposed to OAT who acquired HCV were 1.5 times more likely to report daily or more frequent injection compared to females who did not. Similarly, males who acquired HCV were 2.1 times more likely to inject daily or more frequently compared to males who did not acquire HCV. These findings suggest that dosage and retention in OAT (not measured in the current study) may have a significant impact on the epidemiology of HCV transmission through their influence on injection frequency. Future research should examine this in order to fully assess sex differences in HCV acquisition among PWID.

Finally, among females exposed to OAT, those who reported recent RSS were 1.4 times more likely to have acquired HCV compared to those who did not. Parenteral transmission of HCV, through the sharing of needles and syringes, is the predominant route of exposure for HCV and HIV among PWID [5]. Several studies have concluded that female PWID have elevated rates of RSS compared to male PWID [9, 39]. Gender inequalities likely play a role, as females who experience intimate partner violence are more likely to engage in RSS [39], and females who experience violence are often reluctant to access health services [13]. Harm reduction services need to be sensitive to the specific needs of females, and how gender neutrality may inadvertently disadvantage female PWID [12, 13].

Our study has several limitations. Data were retrospectively merged from 7 cohort studies, and there were inconsistencies in data collected and biological measures. Variability between sites was addressed through use of a random-effects model for clustered data. Nonetheless, there was heterogeneity with regard to data availability for some variables of possible interest; for example, recent imprisonment, sexual relationships with other PWID, and utilization of needle syringe programs were excluded due to >50% missing data. However, we conducted sex-specific sensitivity analyses and results demonstrated complete alignment with the multivariable model for males and near-complete alignment for females (Supplementary Tables 1 and 2). Because detailed data on OAT were not available in the InC3 dataset, potentially unmeasured confounders such as duration, type, and dose of OAT, as well as sexual risk behavior, mental health,

Table 2. Factors Associated With Hepatitis C Virus Acquisition Among People Who Inject Drugs Exposed to Opioid Agonist Therapy, by Sex

| | Females | | | | | | Males | | | | | |
| | Unadjusted | | | Adjusted[a] | | | Unadjusted | | | Adjusted[a] | | |
Variable	HR	(95% CI)	P Value	HR	(95% CI)	P Value	HR	(95% CI)	P Value	HR	(95% CI)	P Value
Race												
White (reference)	…	1	…	…	1	…	…	1	…	…	1	…
Nonwhite	2.39	(2.25–2.52)	< .001	1.79	(1.25–2.56)	.001	1.20	(.98–1.46)	.077	1.40	(1.06–1.84)	.017
Sexual identity												
Heterosexual (reference)	…	1	…	…	…	…	…	1	…	…	…	…
Homosexual or bisexual	0.98	(.68–1.42)	.925	…	…	…	1.06	(.09–12.66)	.966	…	…	…
Education												
Completed high school (reference)	…	1	…	…	…	…	…	1	…	…	…	…
Did not complete high school	2.05	(1.08–3.90)	.029	…	…	…	1.73	(1.24–2.42)	.001	…	…	…
Unstable housing[b]												
No (reference)	…	1	…	…	1	…	…	1	…	…	1	…
Yes	5.13	(4.42–5.96)	< .001	4.00	(3.62–4.41)	< .001	3.99	(3.25–4.89)	< .001	3.29	(2.03–5.32)	< .001
Unemployed[b]												
No (reference)	…	1	…	…	…	…	…	1	…	…	…	…
Yes	0.82	(.61–1.11)	.194	…	…	…	1.26	(.69–2.28)	.452	…	…	…
Alcohol intake[b]												
No (reference)	…	1	…	…	…	…	…	1	…	…	…	…
Yes	0.68	(.12–3.92)	.668	…	…	…	0.66	(.33–1.31)	.232	…	…	…
Years since injecting initiation at baseline (quartiles)												
>10 (reference)	…	1	…	…	…	…	…	1	…	…	…	…
6–10	1.35	(1.06–1.72)	.014	…	…	…	1.18	(.90–1.56)	.233	…	…	…
<6	1.40	(.74–2.64)	.301	…	…	…	0.96	(.57–1.62)	.867	…	…	…
Drug most frequently injected[b]												
Nonopioids (reference)	…	1	…	…	…	…	…	1	…	…	1	…
Opioids	1.33	(.70–2.53)	.379	…	…	…	0.60	(.45–.82)	.001	0.60	(.48–.75)	< .001
Injection frequency[b]												
Less than daily (reference)	…	1	…	…	1	…	…	1	…	…	1	…
Daily or more frequent injection	2.65	(1.97–3.57)	< .001	1.45	(1.01–2.08)	.042	4.02	(2.27–7.09)	< .001	3.79	(3.43–4.18)	< .001
Receptive syringe sharing[b]												
No (reference)	…	1	…	…	1	…	…	1	…	…	…	…
Yes	1.71	(1.47–1.97)	< .001	1.43	(1.33–1.53)	< .001	2.25	(1.22–4.15)	.010	…	…	…

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Adjusted for missing data.

[b]In the previous 3 or 6 months depending on cohort interview intervals.

intimate partner violence, and pregnancy and/or breastfeeding among female participants, may have influenced our results.

CONCLUSIONS

Our study has shown that despite exposure to OAT, female PWID were twice as likely to acquire HCV than were their male counterparts. Our findings are consistent with those of Platt et al where a disparity in the protective effect of OAT was reported based on biological sex [22]. Factors independently associated with the attenuated effect of OAT in females included biosocial (nonwhite race), structural (unstable housing), and behavioral (frequent injecting and RSS) factors. Structural and behavioral interventions that target women, such as access to affordable housing and increasing safe injection self-efficacy to reduce RSS [40], are needed to bolster the efficacy of OAT in females

to prevent HCV transmission. Additionally, further research regarding the dose and duration of OAT is required to better understand sex-related differences in immune function and opioid pharmacokinetic and pharmacodynamic parameters, as well as the impact of factors such as mental health, homelessness, injecting networks, and pregnancy and breastfeeding, on incident HCV infection among PWID exposed to OAT.

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