

Original Investigation

Association of Opioid Agonist Therapy With Lower Incidence of Hepatitis C Virus Infection in Young Adult Injection Drug Users

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IMPORTANCE Injection drug use is the primary mode of transmission for hepatitis C virus (HCV) infection. Prior studies suggest opioid agonist therapy may reduce the incidence of HCV infection among injection drug users; however, little is known about the effects of this therapy in younger users.

OBJECTIVE To evaluate whether opioid agonist therapy was associated with a lower incidence of HCV infection in a cohort of young adult injection drug users.

DESIGN, SETTING, AND PARTICIPANTS Observational cohort study conducted from January 3, 2000, through August 21, 2013, with quarterly interviews and blood sampling. We recruited young adult (younger than 30 years) injection drug users who were negative for anti-HCV antibody and/or HCV RNA.

EXPOSURES Substance use treatment within the past 3 months, including non-opioid agonist forms of treatment, opioid agonist (methadone hydrochloride or buprenorphine hydrochloride) detoxification or maintenance therapy, or no treatment.

MAIN OUTCOMES AND MEASURES Incident HCV infection documented with a new positive result for HCV RNA and/or HCV antibodies. Cumulative incidence rates (95% CI) of HCV infection were calculated assuming a Poisson distribution. Cox proportional hazards regression models were fit adjusting for age, sex, race, years of injection drug use, homelessness, and incarceration.

RESULTS Baseline characteristics of the sample (n = 552) included median age of 23 (interquartile range, 20-26) years; 31.9% female; 73.1% white; 39.7% who did not graduate from high school; and 69.2% who were homeless. During the observation period of 680 person-years, 171 incident cases of HCV infection occurred (incidence rate, 25.1 [95% CI, 21.6-29.2] per 100 person-years). The rate ratio was significantly lower for participants who reported recent maintenance opioid agonist therapy (0.31 [95% CI, 0.14-0.65]; $P = .001$) but not for those who reported recent non-opioid agonist forms of treatment (0.63 [95% CI, 0.37-1.08]; $P = .09$) or opioid agonist detoxification (1.45 [95% CI, 0.80-2.69]; $P = .23$). After adjustment for other covariates, maintenance opioid agonist therapy was associated with lower relative hazards for acquiring HCV infection over time (adjusted hazard ratio, 0.39 [95% CI, 0.18-0.87]; $P = .02$).

CONCLUSIONS AND RELEVANCE In this cohort of young adult injection drug users, recent maintenance opioid agonist therapy was associated with a lower incidence of HCV infection. Maintenance treatment with methadone or buprenorphine for opioid use disorders may be an important strategy to prevent the spread of HCV infection among young injection drug users.

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Injection drug use is the primary mode of transmission for hepatitis C virus (HCV) infection^{1,2} and accounts for at least half of all documented new infections, a figure that is likely a significant underestimate.^{1,3,4} Hepatitis C virus infection is endemic among persons who inject drugs, with most estimates of prevalence ranging from 60% to 90%.⁵ Although newer medications for HCV offer the potential for cure with fewer adverse effects, treatment will come at great financial cost. Furthermore, major barriers to HCV treatment for injection drug users exist and will not be easily overcome.⁶ Therefore, a critical need for interventions that can prevent new HCV infections in this group remains. Providing maintenance opioid agonist therapy with methadone hydrochloride or buprenorphine hydrochloride for opioid use disorders is one strategy for reducing injection drug use and the spread of HCV. Maintenance opioid agonist therapy may facilitate injection cessation and thus reduce the risk for HCV acquisition⁷; however, treatment adherence can fluctuate among users, and not all treatment programs require complete abstinence. Two studies, a meta-analysis⁸ and a pooled analysis study,⁹ reported reduced HCV incidence in association with opioid agonist therapy, with reductions ranging from 40% to 60%. However, many of the studies in both analyses^{8,9} were conducted in populations of older adults and prisoners; also, most predated the use of buprenorphine.

Little is known about the effects of opioid agonist therapy in preventing HCV infection in younger injection drug users and those treated in the era of buprenorphine. Younger users are an important population to target because they are at the core of the HCV epidemic.¹⁰⁻¹⁵ Incidence rates are high among new users, among whom one-quarter are estimated will become infected after 2 years of injection drug use.¹⁶ Despite the fact that younger users are a group at high risk for complications, such as HCV and human immunodeficiency virus (HIV) infection, studies suggest that access to treatment for substance use disorders, especially maintenance methadone therapy, in young persons is limited.¹⁷ However, from 2002 to 2007, total numbers of buprenorphine prescriptions increased from approximately 50 000 to 5.7 million, and young adults aged 21 to 30 years constituted the age group most frequently receiving prescriptions.¹⁸ People seeking opioid agonist therapy for opioid use disorders may prefer treatment with buprenorphine rather than methadone¹⁹ because the former can be prescribed by nonspecialist physicians in office-based settings, dispensed by wide networks of community pharmacies, and self-administered without daily observed dosing by treatment program staff. However, with less supervision, patients receiving buprenorphine also have opportunities to interrupt their treatment to engage in illicit opioid use. For these reasons, studies that include young injection drug users, especially those treated with buprenorphine, are needed to determine the current effectiveness of maintenance opioid agonist therapy in reducing new HCV infections in real-world settings.

The purpose of this study was to assess whether opioid agonist therapy was associated with a lower incidence of HCV infection in an observational cohort of young adult injection drug users in San Francisco. Participants in this prospective

cohort underwent systematic testing for HCV infection and reported information about substance use treatment every 3 months, which provided a unique opportunity to study the relationship between opioid agonist therapy and the incidence of HCV infection. We hypothesized that self-reported treatment with maintenance opioid agonist therapy (methadone or buprenorphine) would be associated with a lower incidence of HCV infection.

Methods

Study Sample and Design

This study analysis used observational data from the UFO Study, a prospective study of young adult injection drug users in San Francisco designed to assess factors associated with incident HCV infection. Details of the study design and methods have been published previously.^{7,14} In brief, participants were eligible if they were younger than 30 years, reported injection drug use in the prior month, spoke English as their primary language, and, if recruited in 2003 or later, did not plan to travel outside of San Francisco within the next 3 months because high rates of travel complicating follow-up were noted in the early period of recruitment.⁷ The UFO Study recruited, screened, and enrolled eligible injection drug users (negative for HCV antibody [anti-HCV] and/or HCV RNA at baseline screening) for participation in prospective follow-up during 3 separate waves beginning in January 3, 2000, February 5, 2003, and May 5, 2010, through August 14, 2013. Intermittent pauses in enrollment occurred in 2002, 2005, and 2009 owing to funding lapses. Participants were remunerated for all study visits, including for screening (\$10) and follow-up (\$20-\$25).

All participants provided written informed consent. The study protocol was reviewed and approved by the Committee on Human Research Institutional Review Board at UCSF.

In all waves, HCV testing and behavioral questionnaires were administered quarterly among participants seronegative for HCV. The behavioral questionnaire, administered at quarterly intervals during follow-up, queried participants regarding demographic factors, risk exposures (eg, types of drugs used, frequency of injection, and sharing of injection equipment), and preventive behaviors (eg, use of syringe exchange programs and condoms). Although some questions were modified slightly during the different waves, the focus was on quantitative assessment of exposures associated with injection drug use and HCV and HIV infections throughout all study waves.

The study conducted active outreach with participants using contact information that was updated at each follow-up visit, including telephone, e-mail, social, and familial contacts as well as street-based neighborhood searches where participants indicated they usually stayed. Since 2007, the study followed participants (including collection of serologic and exposure information) who were incarcerated in the San Francisco City jail if their stay was longer than 30 days. Follow-up consisted of monthly check-ins and quarterly study visits that included structured interviews and blood testing conducted at a community-based clinical research site located in the Tenderloin area of San Francisco for the past 9 years (sites

were located in other neighborhoods, including the Mission, Polk, and Haight-Ashbury districts before 2005). The study provided all participants with HIV and HCV prevention counseling, access to sterile injection equipment, and referrals as needed or requested for medical care, substance use treatment, and HCV care if new infections were detected. For this study, the sample was restricted to participants who were negative for anti-HCV antibody and/or HCV RNA at enrollment and who had 2 or more study follow-up visits.

Study Outcomes

The primary outcome was incident HCV infection. Incident HCV infection was defined as (1) a new test result positive for HCV RNA and/or anti-HCV after a previously documented test result negative for anti-HCV or (2) a positive HCV RNA test result concomitant with a negative anti-HCV test result, which was considered an incident acute HCV infection. Quarterly HCV testing included anti-HCV testing by enzyme immunoassay (HCV EIA 2.0 [Abbott Laboratories] or EIA-3 [Ortho Clinical Diagnostics]) and HCV RIBA 3.0 Test System [Novartis Vaccines & Diagnostics]) and HCV RNA testing using a transcription-mediated amplification technique (dHCV transcription-mediated amplification assay component of the Procleix HIV-1/HCV assay [Gen-Probe Inc]) to detect early HCV infection.^{14,20}

Study Predictors

The primary predictor of interest was receipt of treatment for an opioid use disorder based on participant self-report from quarterly interviews. We categorized recent treatment responses into no treatment, non-opioid agonist forms of treatment, opioid agonist detoxification, and maintenance opioid agonist therapy. Non-opioid agonist forms of treatment could include any non-medication-assisted treatment, such as 12-step groups, counseling, and alternative treatment (eg, acupuncture). Recent opioid agonist therapy included treatment with buprenorphine or methadone anytime within the past year at the baseline screening interview, within the past 3 months at quarterly interviews for participants in waves 1 and 3, and within the past week for participants in wave 2 (shortened because the study added questions examining very recent behaviors associated with drug treatment program attendance). Participants who reported receiving multiple categories of treatment were classified hierarchically: if maintenance therapy and detoxification were reported, we classified the participants as receiving maintenance therapy. If detoxification and non-opioid agonist forms of treatment were reported, we classified the participants as receiving detoxification. For waves 1 and 3 of the study, participants were asked specifically about use of opioid agonist therapy for detoxification vs maintenance treatment. For wave 2, open-ended responses describing the type of substance use treatment were grouped into non-opioid agonist therapy, maintenance opioid agonist therapy, and opioid agonist detoxification; participants in wave 2 who responded that they were treated with opioid agonist therapy but did not specify further were labeled as receiving maintenance therapy. For this reason (and for the differing time frame for the question during wave 2),

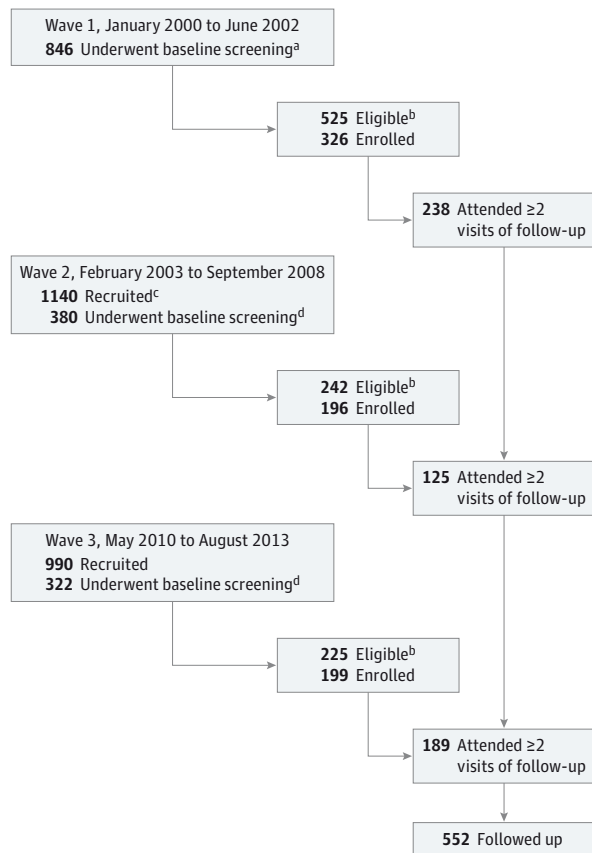
we conducted additional exploratory analyses restricting data from waves 1 and 3 only. We adjusted for the following covariates (which were selected a priori) in multivariate models: age at baseline, sex, nonwhite race, baseline number of years of injection drug use, homelessness, and incarceration within the previous 3 months.

Statistical Analysis

Baseline characteristics of the sample were assessed using simple tabulations and calculation of measures of central tendency (means and medians) and statistical dispersion (SD and interquartile range [IQR]). Cumulative incidence rates of HCV infection by treatment status (no treatment, non-opioid agonist forms of treatment, opioid agonist detoxification, and maintenance opioid agonist therapy) were calculated using person-years of observation, and 95% CIs for the rates were calculated assuming a Poisson distribution. Treatment reported at the time of the last blood test result negative for HCV was used for participants who did not undergo seroconversion; treatment reported at the time of the first blood test result positive for HCV was used for participants who underwent seroconversion. Occurrence dates of infection were imputed as the midpoint of the interval between the dates of the last observed HCV-negative test result and the first HCV RNA-positive test result or the first anti-HCV-positive test result (with or without concurrent HCV RNA detection). For 88 of 171 incident infections, HCV RNA was detected in the acute window before antibody seroconversion. For these cases, the date of infection was 30 days before the first positive transcription-mediated amplification test result. This date is used because the period in which HCV RNA but not anti-HCV is detectable is, on average, 60 days.^{20,21}

Survival time was the time from study enrollment to date of HCV infection. Participants entered into the analysis at the baseline visit and remained until the date of HCV infection or were censored at August 21, 2013, or the last interview date. Censoring at the last visit could occur for various reasons, including loss to or unavailability for follow-up and death. Cox proportional hazards regression models were fit to evaluate the association between treatment category and incident HCV infection, adjusting for potential confounders (age, sex, nonwhite race, number of years of injection drug use, homelessness, and incarceration). Treatment, homelessness, and incarceration were treated as time-varying covariates in the Cox models. We performed multiple imputation with chained equations to impute the values of predictors for visits when only laboratory testing data and not behavioral data were collected. Imputed values were obtained for a total of 11 observations, including 4 regular quarterly interviews and 7 interim visits. Additional exploratory analyses adjusted for the number of days of injection drug use in the past month to assess whether frequency of injection might be a potential mediator of relationships between opioid agonist therapy and HCV incidence and for use of needle-syringe exchange programs in the past month. Adjusted hazard ratios (AHRs) and 95% CIs are reported. Spearman correlations were used to evaluate potential collinearity between independent variables and covariates. All analyses were conducted using 2-sided tests and a sig-

Figure. UFO Study Cohort Participation



Wave 1 eligibility criteria for baseline screening included being younger than 30 years and active injection drug use in the prior month.

^a No records were kept of the number of participants recruited for wave 1.

^b Eligibility criterion for this analysis included seronegative for hepatitis C virus at baseline screening.

^c The number of participants recruited is an estimate based on records kept starting in 2006.

^d Additional eligibility criterion included no plans to travel in next 3 months.

nificance level of .05. Cox models were checked for violation of the proportional hazards assumption by assessing scaled Schoenfeld residuals²² and log-minus-log survival plots for patterns of nonproportionality. Sensitivity analyses were conducted restricting analysis to data from waves 1 and 3 because the questionnaire format differed slightly in wave 2. All analyses were conducted with commercially available software (STATA, version 11.2; StataCorp).

Results

From January 3, 2000, through August 21, 2013, a total of 1548 participants underwent screening, 992 (64.1%) met eligibility criteria, 721 (72.7%) were enrolled, and 552 (76.6%) were followed up (≥ 2 visits) (Figure). Participants who were enrolled and followed up compared with participants who were lost to or unavailable for follow-up did not differ in terms of sex, race/

ethnicity, years of education, or years of injection drug use. Compared with enrolled participants who were lost to follow-up, enrolled participants who were followed up were older (median age, 23 vs 22 years; $P = .003$), more likely to use injection drugs every day in the past month (33.3% vs 20.2%; $P = .001$), more likely to use noninjection methamphetamine (64.5% vs 53.0%; $P = .007$), more likely to have been in substance use treatment (17.6% vs 10.4%; $P = .02$), more likely to have received mental health counseling in the past 3 months (25.5% vs 15.8%; $P = .009$), and less likely to have been incarcerated in the past 3 months (27.1% vs 38.4%; $P = .006$). Characteristics of the sample ($n = 552$) at study enrollment are shown in Table 1. The median age was 23 (IQR, 20-26) years, 73.1% of participants were white, 68.1% were men, 39.7% reported they did not graduate from high school, and 69.2% were homeless or unstably housed in the past 3 months. The median duration of injection drug use was 3.6 (IQR, 1.5-6.6) years, 33.3% of participants were daily users, and most (59.8%) reported heroin as the drug they had used most often in the past month. Most participants (82.4%) reported no substance use treatment in the prior year, and 4.2% reported recent maintenance opioid agonist treatment in the prior year.

The study observation period totaled 680 person-years, during which 171 incident cases of HCV infection occurred for an estimated incidence rate of 25.1 (95% CI, 21.6-29.2) per 100 person-years. Participants completed a median of 3 behavioral interviews (IQR, 2-5), and the median interval between interviews was 93 (IQR, 56-131) days. Participants who reported maintenance opioid agonist therapy in the past 3 months had a lower incidence of HCV infection compared with those who reported no treatment in the past 3 months (Table 2). The rate ratio was significantly lower for participants who reported recent maintenance opioid agonist therapy (0.31 [95% CI, 0.14-0.65]; $P = .001$) but not for those who reported non-opioid agonist forms of treatment (0.63 [95% CI, 0.37-1.08]; $P = .09$) or opioid agonist detoxification (1.45 [95% CI, 0.80-2.69]; $P = .23$) compared with no treatment. Cox proportional hazards regression models adjusted for age, sex, race/ethnicity, years of injection drug use, recent incarceration, and homelessness demonstrated that maintenance opioid agonist therapy was independently associated with significantly lower relative hazards for becoming infected with HCV over time (AHR, 0.39 [95% CI, 0.18-0.87]; $P = .02$) (Table 3). A model fit to examine mediation with adjustment for frequency of injection drug use (number of days of use in the past month) showed that the association became attenuated (AHR, 0.59 [95% CI, 0.27-1.26]). On the other hand, adjustment for use of needle-syringe exchange program had no substantive influence on the maintenance opioid agonist therapy effect (AHR, 0.39 [95% CI, 0.18-0.85]).

In the sensitivity analyses restricted to waves 1 and 3 (for which participants were directly queried about detoxification vs maintenance therapy so that no responses of “unspecified” remained), the results did not differ substantively. Again, the incidence of HCV infection was lower among participants who reported recent maintenance opioid agonist therapy compared with those receiving no treatment (rate ratio, 0.37 [95% CI, 0.14-1.02]; $P = .05$), but incidence of HCV infection was not

Table 1. Selected Demographic and Behavioral Characteristics at Study Enrollment Among 552 Young Adult Injection Drug Users Followed Up in the UFO Cohort Study, San Francisco, California, 2000-2013

Characteristic	No. (%) of Participants ^a
Study wave	
1 (2000-2002)	238 (43.1)
2 (2003-2009)	125 (22.6)
3 (2010-2013)	189 (34.2)
Age, y	
15 to 18	16 (2.9)
19 to 24	340 (61.6)
25 to <30	196 (35.5)
Sex	
Male	376 (68.1)
Female	176 (31.9)
Educational level (n = 549)	
Less than high school	218 (39.7)
High school or more	331 (60.3)
Race (n = 550)	
White	402 (73.1)
Nonwhite	148 (26.9)
Homeless in past 3 mo	
No	170 (30.8)
Yes	382 (69.2)
Sexual behavior	
Female ^b	176 (31.9)
Heterosexual male	214 (38.8)
MSM	162 (29.3)
Seropositive for HIV (n = 475)	
No	454 (95.6)
Yes	21 (4.4)
Age of first drug injection, y (n = 551)	
<18	227 (41.2)
18-19	115 (20.9)
≥20	209 (37.9)
Duration of injection drug use, y (n = 551)	
<3	170 (30.9)
3-5	187 (33.9)
≥6	194 (35.2)
Daily injection drug use in past month	
No	368 (66.7)
Yes	184 (33.3)
Drug injected most days in past month	
Speed/methamphetamine	183 (33.2)
Heroin/heroin mix	330 (59.8)
Other	39 (7.1)
Injection drug use alone in past 3 mo (n = 551)	
No	248 (45.0)
Yes	303 (55.0)
Recent needle-syringe exchange use ^c	
No	124 (22.5)
Yes	428 (77.5)

(continued)

Table 1. Selected Demographic and Behavioral Characteristics at Study Enrollment Among 552 Young Adult Injection Drug Users Followed Up in the UFO Cohort Study, San Francisco, California, 2000-2013 (continued)

Characteristic	No. (%) of Participants ^a
Ever overdosed (n = 548)	
No	362 (66.1)
Yes	186 (33.9)
Overdose in past 3 mo (n = 551)	
No	481 (87.3)
Yes	70 (12.7)
Incarcerated, past 3 mo (n = 549)	
No	400 (72.9)
Yes	149 (27.1)
Recent drug treatment (n = 551) ^d	
None	454 (82.4)
Non-OA therapy	46 (8.3)
OA detoxification	28 (5.1)
Maintenance OA therapy ^e	23 (4.2)

Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; OA, opioid agonist.

^a Percentages have been rounded and may not total 100.

^b Female includes women who had sex with men and women who had sex with women.

^c For participants in wave 1, time frame is past 30 days; for participants in waves 2 and 3, past 3 months.

^d For participants in wave 1, time frame is past year at baseline and past 3 months at follow-up; for participants in wave 2, past week; and for participants in wave 3, past 3 months.

^e Includes OA therapy unspecified for wave 2 only.

lower for those participants who reported recent opioid agonist detoxification (rate ratio, 1.77 [95% CI, 0.95-3.32]; $P = .07$).

Discussion

In this study of young adult injection drug users, we found that maintenance opioid agonist therapy (methadone or buprenorphine) for opioid use disorders was associated with more than a 60% reduction in the incidence of HCV infection over time compared with no treatment. These results are in concordance with prior studies conducted in other populations. A meta-analysis by Hagan et al,⁸ which included 8 studies published from 1996 to 2009, reported a pooled relative risk of 0.60 (95% CI, 0.35-1.03) for incident HCV infection associated with opioid agonist therapy. A pooled analysis of 6 UK studies by Turner et al⁹ also reported that receipt of opioid agonist therapy was significantly associated with lower relative odds for seroconversion (adjusted odds ratio, 0.41 [95% CI, 0.21-0.82]). Our additional analyses adjusting for injection drug use in the past month suggest that maintenance opioid agonist therapy reduces the incidence of HCV infection in part by decreasing the frequency of injection, which will also lower the risk for acquiring HIV and other blood-borne pathogens.²³ Our additional finding of a higher incidence of HCV infection among patients who reported recent opioid agonist detoxification

Table 2. Incident HCV Infection and Type of Drug Treatment Programs Attended in 552 Young Adult Injection Drug Users Followed Up in the UFO Cohort Study, San Francisco, California, 2000-2013

Baseline Characteristic	Incident HCV, No. of Participants	Person-years of Observation	Incidence per 100 Person-years (95% CI) ^a	RR (95% CI)	P Value
Overall	171	680	25.1 (21.6-29.2)	NA	NA
Drug treatment in past 3 mo ^b					
None	138	488	28.2 (23.9-33.4)	1 [Reference]	
Non-OA therapy	15	84	17.9 (10.8-29.6)	0.63 (0.37-1.08)	.09
OA detoxification	11	27	41.1 (22.8-74.2)	1.45 (0.80-2.69)	.23
Maintenance OA therapy ^c	7	81	8.6 (4.1-18.1)	0.31 (0.14-0.65)	.001

Abbreviations: HCV, hepatitis C virus; NA, not applicable; OA, opioid agonist; RR, rate ratio.

^a Incidence was calculated using behavior or characteristic at the last period that patient was seronegative for HCV (uninfected during follow-up) or the first HCV-seropositive risk period (incident infections).

^b For participants in wave 1, time frame is past year at baseline and past 3 months at follow-up; for participants in wave 2, past week; and for participants in wave 3, past 3 months.

^c Includes OA therapy unspecified for wave 2 only.

compared with those who reported no treatment is novel. Studies have demonstrated high relapse rates when buprenorphine and methadone therapy are discontinued,^{24,25} suggesting that detoxification is a less effective treatment strategy than maintenance treatment. Studies also have demonstrated an increased risk for opioid overdose when patients relapse after premature detoxification or periods of abstinence (eg, incarceration),^{26,27} and they may also engage in injecting behaviors that put them at higher risk for HCV acquisition in this period.

This study is, to our knowledge, the first to examine the effects of opioid agonist therapy on HCV infection to be conducted in young adults who are injection drug users; as such, it extends the literature by demonstrating the potential benefits of maintenance opioid agonist therapy in reducing the incidence of HCV infections in this age group. Young injection drug users are a major driving force in the epidemic of HCV infection in the United States and Canada and therefore are an important target for prevention.¹⁵ Buprenorphine is an efficacious treatment for youth with opioid use disorders.^{25,28} Despite this outcome, young adults who inject drugs often encounter significant barriers to receiving opioid agonist therapy for the treatment of opioid use disorders,¹⁷ which is reflected in the general low rates of self-reported use of methadone and buprenorphine in this study. Young adults are typically characterized as having short addiction histories for which maintenance opioid agonist therapy is considered excessive because federal regulations concerning patient admission criteria to methadone maintenance treatment (42 CFR §8.12[e]) stipulate that a person be addicted at least 1 year before admission for treatment and that a person younger than 18 years have 2 documented unsuccessful attempts at short-term detoxification or drug-free treatment within a 12-month period.²⁹ Rules differ from state to state regarding whether an adolescent may obtain substance use disorder treatment without parental consent; in California, however, nonemancipated minors seeking methadone treatment must obtain parental consent and preapproval for treatment from the Department of Alcohol and Drug Programs Narcotic Treatment Program Licensing Branch.³⁰ Although only 16 participants (2.9%) were minors at the time of the study, almost half (41.2%) of all participants re-

Table 3. Multivariate Cox Proportional Hazards Regression Model of Independent Predictors of Incident HCV Infection in 552 Young Adult Injection Drug Users Followed Up in the UFO Cohort Study, San Francisco, California, 2000-2013

Characteristic	AHR (95% CI) ^a	P Value
Drug treatment in past 3 mo ^b		
None	1 [Reference]	NA
Non-OA therapy	0.71 (0.41-1.20)	.20
OA detoxification	1.39 (0.73-2.67)	.32
Maintenance OA therapy ^c	0.39 (0.18-0.87)	.02
Age, y	0.99 (0.94-1.04)	.66
Duration of injection drug use, y	1.03 (0.98-1.07)	.24
Sex		
Male	0.72 (0.52-1.00)	
Female	1 [Reference]	.05
Race/ethnicity		
White	1 [Reference]	
Nonwhite	1.17 (0.82-1.67)	.37
Homeless in past 3 mo		
No	1 [Reference]	
Yes	1.22 (0.86-1.74)	.26
Incarcerated in past 3 mo		
No	1 [Reference]	
Yes	1.58 (1.12-2.23)	<.01

Abbreviations: AHR, adjusted hazard ratio; HCV, hepatitis C virus; NA, not applicable; OA, opioid agonist.

^a For time-dependent covariates, hazard ratios were calculated using time-dependent Cox proportional hazards regression.

^b For participants in wave 1, time frame is past year at baseline and past 3 months at follow-up; for participants in wave 2, past week; and for participants in wave 3, past 3 months.

^c Includes OA therapy unspecified for wave 2 only.

ported that they started injecting drugs before 18 years of age and may have benefited from early initiation of opioid agonist therapy. In addition to these unique barriers for young injection drug users, known barriers to opioid agonist therapy exist for all patients with opioid use disorders, including insufficient providers, treatment facilities, and insurance coverage for medications. Also, motivation to seek treatment may

be lower among young adult users, who typically have fewer comorbidities related to their substance use disorders.

Given that studies have shown frequent HCV seroconversion within the first few years of initiating injection drug use¹⁶ and given evidence from the present study that maintenance opioid agonist therapy is associated with decreased HCV incidence among young adult injection drug users, opioid treatment guidelines and regulations that defer opioid agonist therapy for young adults with opioid use disorders may warrant reconsideration. Furthermore, in keeping with the concern that the risk for opioid overdose increases after cessation of opioid agonist therapy,^{27,31,32} these study results support the view of many addiction experts that maintenance opioid agonist therapy, rather than detoxification, is a safer and more effective strategy for preventing serious medical complications of opioid addiction in young adult users.³³

This study has some limitations. Only a modest number of participants reported receiving opioid agonist therapy, particularly buprenorphine; therefore, we could not analyze the effects of buprenorphine and methadone separately. In an additional limitation, opioid agonist therapy was defined by self-report and not confirmed by treatment episode data. Some participants might report misinformation about treatment status (social desirability bias). Also, no specific duration of treatment was used to differentiate detoxification vs maintenance therapy, and therefore some overlap may have existed. We assume these types of misclassification would bias to the null, in which case our results would be an underestimate of

the true effect. An additional limitation is that the questionnaires for 1 wave of data collection only provided open-ended responses on substance use treatment; therefore, some participants were missing data on whether recent opioid agonist therapy was for detoxification or maintenance. Furthermore, a difference existed in the time frame of the questions asked regarding opioid agonist therapy between waves 1 and 3 and wave 2, which only captured very recent (past week) attendance. This difference should in theory bias our results to the null, which strengthens our findings. Also, sensitivity analyses were performed excluding data from wave 2, and results were not changed substantively. A major strength of the study is the repeated and accurate ascertainment of the outcome measure of incident HCV infection. This study is the only one of which we are aware that performed systematic testing, including HCV viremia, at regular intervals to measure the true incidence of HCV.

Conclusions

Among a cohort of young adult injection drug users, we found that report of recent maintenance treatment with opioid agonist therapy was associated with a lower incidence of HCV infection. Our results suggest that treatment for opioid use disorders with maintenance opioid agonist therapy can reduce transmission of HCV in young adult injection drug users and should be offered as an important component of comprehensive strategies for prevention of primary HCV infection.

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