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The impact of methadone maintenance therapy on heptatis c incidence among illicit drug users.

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Abstract

Aims—To determine the relationship between methadone maintenance therapy (MMT) and hepatitis C (HCV) seroconversion among illicit drug users.

Design—Generalized Estimating Equation model assuming a binomial distribution and a logit link function was used to examine for a possible protective effect of MMT use on HCV incidence.

Setting—Data from three prospective cohort studies of illicit drug users in Vancouver, Canada between 1996 and 2012.

Participants—1004 HCV antibody negative illicit drug users stratified by exposure to MMT.

Measurements—Baseline and semi-annual HCV antibody testing and standardised interviewer administered questionnaire soliciting self-reported data relating to drug use patterns, risk behaviours, detailed sociodemographic data and status of active participation in an MMT program.

Findings—184 HCV seroconversions were observed for an HCV incidence density of 6.32 [95% confidence interval [CI]: 5.44 – 7.31] per 100 person-years. After adjusting for potential confounders, MMT exposure was protective against HCV seroconversion (Adjusted Odds Ratio [AOR] = 0.47; 95% CI: 0.29 - 0.76). In sub-analyses, a dose-response protective effect of increasing MMT exposure on HCV incidence (AOR = 0.87; 95% CI: 0.78 – 0.97) per increasing 6-month period exposed to MMT was observed.

Conclusion—Participation in methadone maintenance treatment appears to be highly protective against hepatitis C incidence among illicit drug users. There appears to be a dose-response protective effect of increasing methadone exposure on hepatitis C incidence.

Keywords

hepatitis C; HCV; illicit drug use; methadone; opioid; incident infection; seroconversion

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INTRODUCTION

Hepatitis C virus (HCV) infection is a major global public health concern. Currently, more than 170 million people are infected [1-4] and between 3 – 4 million new infections occur annually worldwide [2]. Chronic HCV infection manifests in a variety of ways [5] with the major burden of serious illness resulting from cirrhosis and hepatocellular carcinoma (HCC) [1, 3, 6]. A substantial economic burden is associated with these conditions due to high morbidity and mortality and associated health care costs. Specifically, more than 350,000 people die from HCV-related liver disease every year [2] and HCV infection is the leading cause for liver transplantations worldwide [7].

The risk of HCV infection is increased among persons who use illicit drugs [8, 9]. Furthermore, injection drug users (IDU) are at particularly high risk with a global HCV prevalence of approximately 67 percent [10]. A major risk factor for HCV infection among IDU is through the sharing of injection equipment [11-13]. The reported incidence of HCV among IDU ranges from 10 – 40 cases per 100 person-years [13-15], with most infections occurring within 3 years of injection initiation [16]. To date, few interventions are proven to reduce the risk of HCV transmission among IDU [17]. Specifically, reviews of harm reduction strategies have shown needle exchange programs to likely be modestly effective in preventing HCV infection [18, 19] whereas the evidence for opiate substitution treatment (e.g. methadone maintenance treatment [MMT]), behavioural interventions and syringe disinfection is less convincing [20-22]. Among the reviews of addiction treatments, a recent systematic review and meta-analysis found that various forms of addiction treatment including MMT were not effective at reducing the risk of HCV [17]. The uncertainty regarding the effectiveness of MMT in preventing HCV is problematic given the well described barriers to its availability in many settings, and significant differences in the way methadone programs are delivered [23-25].

In British Columbia, Canada, MMT is widely available and can be prescribed by community physicians and dispensed through a network of community pharmacies [26]. While past studies have shown MMT to be associated with reductions in heroin injecting in this setting [27], analyses have not examined the impact of MMT on HCV incidence. We therefore conducted the present study to examine for a protective effect of MMT exposure on HCV seroconversion within a longstanding sample of illicit drug users.

METHODS

Sample

Data for this analysis was derived from three related prospective cohort studies of illicit drug users in Vancouver, Canada. All cohorts used identical methods for data collection to allow for combined analyses. Specifically, the At Risk Youth Study (ARYS), the Vancouver Injection Drug Users Study (VIDUS) and the AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS), are three open prospective cohorts of people who use illicit drugs. Described in detail previously [28-32], each cohort was populated through snowball sampling and extensive street outreach and participants were eligible for inclusion if they live in the greater Vancouver region at enrolment, report using an illicit drug other than

marijuana in the past 30 days and provide written informed consent. Recruitment for VIDUS and ACCESS (individual studies of HIV-negative and HIV-positive drug users respectively) began in 1996. ARYS, a cohort of drug using street-involved youth between the ages of 14 and 26, began recruitment in 2005.

Measures

MMT exposure—At baseline and every six-month follow-up interview, participants answered a standardised interviewer administered questionnaire and HCV negative participants provided blood samples for HCV. Data related to drug use patterns, risk behaviours, detailed sociodemographic data and self-reported status of active participation in an MMT program is solicited. Participants are given a $20 monetary honorarium after each study visit, provided with basic medical care by nurses and, if appropriate, referred to health care services. The ARYS, VIDUS and ACCESS cohorts have been approved by the University of British Columbia/Providence Health Care research ethics board.

HCV antibody status—All participants who were HCV-negative at baseline and had at least one follow up visit to assess for HCV incidence between May 1996 and December 2012 were eligible for inclusion. HCV seroconversion, defined by an HCV antibody negative test at enrolment followed by a subsequent HCV antibody positive test, was the primary study outcome. Since HCV testing was done every six months, as described previously [33], the date of seroconversion was estimated as the midpoint between the last HCV negative and the first HCV positive antibody test. As described above, methadone use was in reference to the last six months at each semi-annual follow-up visit and was treated as a time-updated covariate in the multivariate analysis. For those with HCV seroconversion, follow up time was calculated from the first HCV antibody negative test until the estimated date of HCV seroconversion after which participants were censored. For those without HCV seroconversion, follow-up time was calculated from the first to the last HCV antibody negative test observed during the study period. Individuals who did not seroconvert were censored at the last contact date, December 31, 2012 or at the death date, whichever came first. HCV incidence density and confidence intervals were calculated by the person-years method.

Covariates—Our primary independent variable of interest was enrolment in MMT (yes vs. no), which was time updated at each six month assessment based on self-report of having filled any methadone prescription in the prior six months. Other hypothesized factors associated with HCV incidence were determined *a priori* and included the following baseline characteristics: age (per year older), gender (male vs. female), ethnicity (Caucasian vs. other) and education defined as high school completion (yes vs. no). Behaviours and exposures that were measured at baseline and repeatedly during each semi-annual follow-up were treated as time-dependent variables and included: unstable housing, defined as living in a single occupancy room in a hotel, a recovery house or treatment, hostel, shelter, jail, or having no fixed address in the last 6 months (yes vs. no), syringe borrowing, defined as injecting with a used syringe in the last 6 months (yes vs. no), and various measures of drug use in the last 6 months, including daily injecting of cocaine, heroin or methamphetamine (all yes vs. no).

Statistical Analyses

Initially, to describe the baseline study sample, we stratified the cohort based on the above variables and into those on or off MMT at baseline. Categorical variables were compared using the Fisher Exact test, and continuous variables were compared using the Wilcoxon Rank Sum test.

The explanatory variables were selected *a priori* based on expert opinion and previous publications [27]. In the primary analysis, we examined the effect of MMT use in the last six months. Then, as a sub-analysis, we assessed for a dose-response effect by defining the independent variable of interest as the number of six-month periods the individual was enrolled in MMT.

We built a confounder model using the Generalized Estimating Equation (GEE) methodology assuming a binomial distribution, a logit link function and an unstructured correlation structure. The advantage of using this methodology is that it produces robust standard errors and it takes into consideration the correlation of responses for each participant [34]. For both the primary and sub-analyses, we sought to adjust for potential confounding due to possible within cohort clustering or other cohort effects. Here, we forced into the multivariate models a variable representing cohort of recruitment to control for heterogeneity across cohorts, a variable representing calendar year of recruitment to control for the cohort effect and a variable representing follow-up time to control for different follow up durations.

Beyond the cohort variables that were forced into the multivariate models, other potential confounders were selected for inclusion in the final models using a conservative backward selection approach proposed by Maldonado and Greenland which considered the magnitude of change in the coefficient of the methadone maintenance variable [29, 35]. Specifically, starting with a fixed model, which considered all available variables, potential confounders were dropped 1 at a time, using the relative change in the coefficient for the variable related to the MMT variable as a criterion, until the maximum change from the full model exceeded 5%.

RESULTS

A total of 3741 participants were recruited between May 1996 and December 2012. Overall, baseline HCV prevalence was 63.1%. At baseline, the prevalence of HCV was 24% among those enrolled in MMT and was 76% among those not enrolled in MMT ($p < 0.01$). Of the 1379 (36.9%) individuals who were HCV antibody negative at baseline, 1004 (72.8%) had at least one follow up visit to assess for HCV incidence and were therefore eligible for the present study. In comparison to the 375 (27.2%) participants who were HCV negative at baseline and were excluded from the analyses of HCV incidence due to inadequate follow up, the 1004 individuals included in these analyses were more likely to be non-white and older (both $p < 0.05$), although they did not differ by gender ($p = 0.248$) and MMT use at baseline ($p = 0.891$).

Table 1 provides baseline characteristics of the study population stratified by baseline MMT use. Only 55 (5.5%) individuals were on MMT at baseline. Within the cohort, the median year of MMT initiation was 2006 (interquartile range [IQR]: 2003 – 2009). Participants on MMT at baseline had characteristics that implied a history of more experienced and entrenched drug use as they were older, had at least a high school education, and were more likely to report daily cocaine injection, heroin injection and methamphetamine injection in the preceding 6 months. There were no statistically significant differences on the basis of gender, ethnicity, housing status or reported syringe borrowing at baseline.

Overall, median follow up was 2.1 years (25^{th} - 75^{th} percentiles 1.1 – 3.6 years). A total of 111 (11%) participants initiated MMT during follow-up. The median number of 6-month intervals where MMT use was reported was 2 (25^{th} - 75^{th} percentiles 1 - 6).

As of December 2012, 184 HCV seroconversions were observed for an incidence density of 6.32 (95% confidence interval [CI]: 5.44 – 7.31) per 100 person-years. Among those on MMT at baseline, 14 HCV seroconversions were observed (incidence density 0.48 per 100 person-years; 95% CI: 0.26 – 0.81 per 100 person-years) and 170 among those not on MMT at baseline (incidence density 5.84 per 100 person-years; 95% CI: 5.00 – 6.79 per 100 person-years). Moreover, cumulative MMT exposure was found to further reduce the risk of HCV seroconversion. Among those with no methadone exposure throughout follow up, the incidence density was 5.46 (95% CI: 4.65 – 6.38) per 100 person years, whereas it was 0.52 (95% CI: 0.29 – 0.85) per 100 person years among those reporting methadone at one follow up, and 0.34 (95% CI: 0.16 – 0.63) per 100 person-years among those reporting methadone at two or more follow up visits.

Table 2 shows the results of the Generalized Estimating Equation regression analysis of factors associated with HCV seroconversion. MMT use had a statistically significant protective effect against HCV seroconversion in the multivariate (Adjusted Odds Ratio [AOR] = 0.47; 95% CI: 0.29 – 0.76) analyses after adjustment for unstable housing, cocaine injection, heroin injection, methamphetamine injection, cohort of recruitment, calendar year of recruitment and follow up time. A similar protective effect of methadone on HCV incidence was observed amongst those participants aged less than 30 years at baseline (AOR = 0.55; 95% CI: 0.31 – 0.99).

In sub-analyses, we found a dose-response protective effect of increasing MMT exposure, measured as the number of 6-month periods individuals were enrolled in MMT on HCV incidence in both the unadjusted (unadjusted odds ratio = 0.89; 95% CI: 0.81 – 0.99) analysis and after adjustment for unstable housing, syringe borrowing, cocaine injection, cohort of recruitment, calendar year of recruitment and follow up time (AOR = 0.87; 95% CI: 0.78 – 0.97).

DISCUSSION

The present study demonstrated a high incidence of HCV seroconversion among drug users in this setting. Furthermore, enrolment in MMT was found to be independently protective after adjustment for a range of sociodemographic and drug use characteristics including

unstable housing, syringe borrowing and daily injection of cocaine, heroin and crystal methamphetamine. Additionally, despite higher risk drug users being attracted into MMT use, the protective effect was maintained with prolonged duration of MMT exposure in a dose dependent fashion.

Although high rates of HCV among drug users have previously been reported [10, 36, 37], the literature investigating the effect of MMT on HCV incidence in this patient population is scarce. While MMT use has been shown to decrease self-reported high-risk behaviours associated with blood-borne infection amongst this population, including frequency of heroin injection, needle or syringe sharing and unsafe sex [4, 38], the evidence that MMT itself reduces HCV incidence has been mixed. As described above, a meta-analysis published in 2011 [17] was able to identify only 8 studies which examined the impact of opioid replacement therapy on HCV incidence with the overall effect not reaching statistical significance. This may be explained by the heterogeneity of the studies included as they were conducted in a variety of settings ranging from a general practitioner's office to an incarcerated male population [39, 40]. Additionally the sample sizes (n = 54 – 468) and number of HCV seroconversions (n = 7 – 39) were small. Lastly these studies were of short duration, with typical follow-up periods of less than 5 years. The limitations of such short follow up periods when assessing intervention impacts on HCV incidence have previously been reported [17]. A more recent analysis, which pooled data from six settings in the United Kingdom, found opioid substitution therapy was associated with a 60% reduction in new HCV infections [41]. These findings, however, were limited as only 40 HCV seroconversions were observed throughout the study period. The present study was conducted among a large community recruited cohort in a setting where access to MMT is less restricted than in the United States since it is provided in office practices and dispensed through community pharmacies [26]. Among a population that experienced 184 HCV seroconversions, we found that MMT use was independently associated with reduced HCV incidence and that greater MMT exposure had a dose-response effect on reducing HCV infections.

Our study has limitations. First, since there are no registries of drug user populations in our setting, the study sample was not a random sample. Second, since this was an observational study, we cannot infer causation and it is possible that unmeasured confounders explain our findings. In particular, although those prescribed MMT generally had a profile that would predict higher risk of HCV, comparison of medication outcomes in non-randomized trials raises concerns regarding unmeasured confounding. However, a randomized trial that investigated the impact of MMT on HCV infection rates would raise feasibility issues due to duration of follow-up required to demonstrate an effect. More importantly, this would raise ethical concerns due to non-provision of MMT given its proven benefits in the treatment of heroin addiction [42, 43]. Use of a needle exchange facility is another potential confounder, however, past analyses have demonstrated selection effects and inaccuracies in measuring this variable in our setting [44]. Third, the variables in our study often relied on self-report and are behaviours of a socially sensitive nature and therefore may be subject to underreporting as a consequence of either recall or social desirability bias [45]. While some drug use behaviours and other variables may be collinear, given that both the univariable and multivariable models produced similar odds ratios (with the same direction and

strength) for each explanatory variable, we are reassured and feel confident multicollinearity did not influence our final results. Finally, in some settings buprenorphine/naloxone is more widely available than MMT and we were unable to assess the impact of this medication due to its infrequent use in this setting [26].

In conclusion, we found a strong protective effect of MMT on HCV incidence among a longstanding cohort of drug users in a Canadian setting. We also found a dose-response protective effect of increasing MMT exposure on HCV incidence. Our results add to the known benefits of MMT on reducing the harms associated with heroin and other drug use [42, 43]. These findings have important implications for healthcare systems and settings which continue to limit the availability of MMT [46, 47].

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Table 1

Baseline characteristics of HCV negative participants, seen between 1996 - 2012, Vancouver, Canada stratified by use of methadone (N = 1004)

Characteristic	No Methadone use n = 949(%)	Methadone Use n = 55(%)	*p* - value
Age			
Median (IQR)	23 (20 - 25)	34 (23 - 43)	<0.001
Gender			
Female	287 (30)	20 (36)	0.367
Male	662 (70)	35 (64)	
Caucasian ethnicity			
Yes	594 (62.6)	39 (70.9)	0.251
No	355 (37.4)	16 (29.1)	
High school education or greater			
Yes	493 (51.9)	19 (34.5)	0.013
No	456 (48.1)	36 (65.5)	
Unstable housing *			
Yes	646 (68.1)	33 (60.0)	0.236
No	303 (31.9)	22 (40.0)	
Syringe borrowing *			
Yes	114 (12.1)	9 (16.4)	0.394
No	834 (87.9)	46 (83.6)	
Cocaine injection *			
Yes	230 (24.2)	24 (43.6)	0.002
No	719 (75.8)	31 (56.4)	
Heroin injection *			
Yes	304 (32.0)	43 (78.2)	<0.001
No	645 (68.0)	12 (21.8)	
Methamphetamine injection *			
Yes	97 (10.2)	11 (20.0)	0.040
No	852 (89.2)	44 (80.0)	

IQR – Interquartile range,

* Denotes activities in the previous 6 months

TABLE 2

Generalized Estimating Equation (GEE) logistic regression analysis of factors associated with HCV seroconversion among participants in Vancouver, Canada 1996 – 2012 (n = 1004)

Characteristic	Odds Ratio (OR)	
	Unadjusted OR (95% CI)	Adjusted OR** (95% CI)
Methadone treatment		
Yes vs. No	0.67 (0.45 – 0.99)	0.47 (0.29 – 0.76)
Age		
Per year older	0.99 (0.98 –1.01)	0.99 (0.97 –1.02)
Gender		
Female vs. Male	1.60 (1.17 –2.17)	1.38 (0.90 –2.10)
Caucasian ethnicity		
Yes vs. No	1.10 (0.81 –1.50)	1.16 (0.78 –1.73)
Unstable Housing		
Yes vs. No	2.03 (1.51 –2.73)	1.83 (1.30 –2.59)
Cocaine Injection *		
Yes vs. No	4.67 (3.55 –6.15)	2.46 (1.65 –3.66)
Heroin Injection *		
Yes vs. No	4.61 (3.42 –6.21)	2.21 (1.44 –3.40)
Methamphetamine Injection *		
Yes vs. No	2.59 (1.83 –3.68)	3.77 (2.41 –5.89)

Abbreviations: OR = odds ratio, CI = confidence interval,

* Denotes activities in the previous 6 months.

** Estimates also adjusted for cohort of recruitment, calendar year of recruitment and follow up time for each participant.