BMJ Open

Prescription Opioid Injection and Risk of Hepatitis C in Relation to Traditional Drugs of Abuse in a Prospective Cohort of Street Youth

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005419
Article Type:	Research
Date Submitted by the Author:	07-Apr-2014
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Primary Subject Heading:	Addiction
Secondary Subject Heading:	HIV/AIDS, Infectious diseases, Public health
Keywords:	Hepatobiliary disease < GASTROENTEROLOGY, Epidemiology < INFECTIOUS DISEASES, INFECTIOUS DISEASES, Hepatology < INTERNAL MEDICINE, Child & adolescent psychiatry < PSYCHIATRY, Substance misuse < PSYCHIATRY

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PRESCRIPTION OPIOID INJECTION AND RISK OF HEPATITIS C IN RELATION TO TRADITIONAL DRUGS OF ABUSE IN A PROSPECTIVE COHORT OF STREET YOUTH

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Abstract Word Count: 296
Word Count (excluding abstract): 2,997
Figures: 2
Tables: 2
Submitted: Monday, April 7, 2014
Running Head: Hepatitis C and prescription opioid use
MeSH Terms: hepatitis C; analgesics, opioid; heroin; drug abuse; adolescent

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ABSTRACT

Objective: Despite dramatic increases in misuse of prescription opioids, the extent to which their intravenous injection places drug users at risk of acquiring hepatitis C virus (HCV) remains unclear. We sought to compare risk of HCV acquisition from injection of prescription opioid to that from other street drugs among high-risk street youth.

Design: Prospective cohort study.

Setting: Vancouver, British Columbia, Canada, from September 2005 to November 2011.

Participants: The At-Risk Youth Study (ARYS) is a prospective cohort of actively drug-using adolescents and young adults aged 14-26 years. Participants were recruited through extensive street-based outreach and snowball sampling.

Primary Outcome Measure: HCV antibody seroconversion, measured every 6 months during study follow-up. Risk for seroconversion from injection of prescription opioids was compared to injection of other street drugs of abuse, including heroin, cocaine or crystal methamphetamine, using Cox proportional hazards regression, controlling for age, gender and active syringe sharing.

Results: Baseline HCV seropositivity was 10.6%. Among 512 HCV-seronegative youth contributing 860.2 person-years of total follow-up, 56 (10.9%) seroconverted, resulting in an incidence density of 6.5 per 100 person-years. In bivariate analyses, prescription opioid injection (hazard ratio [HR], 3.48; 95% CI, 1.57-7.70) predicted HCV seroconversion. However, in multivariate modeling, only injection of heroin (adjusted HR, 4.56; 95% CI, 2.39-8.70),

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cocaine (adjusted HR, 1.88; 95% CI, 1.00-3.54), and crystal methamphetamine (adjusted HR, 2.91; 95% CI, 1.57-5.38) remained independently associated with HCV seroconversion, whereas injection of prescription opioids did not (adjusted HR, 0.94; 95% CI, 0.40-2.21).

Conclusions: Although misuse of prescription opioids is on the rise, traditional street drugs still appeared to pose the greatest threat of HCV transmission in this setting. Nonetheless, the high prevalence and incidence of HCV seropositivity among Canadian street youth underscores the need for evidence-based drug prevention, treatment, and harm reduction interventions targeting this vulnerable population.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength of this prospective cohort study is that it followed street youth, a marginalized and difficult-to-reach population with a high prevalence of injection drug use and blood-borne infection, including human immunodeficiency virus (HIV) and hepatitis C virus (HCV)

- An additional strength is that it is among the first studies to examine the association between injection of prescription opioids (including, for example, oxycodone and morphine) and acquisition of HCV; it has previously not been known how the risk for acquiring HCV from injecting prescription opioids compares to that from injection more traditionally studied street drugs, such as heroin, cocaine and crystal methamphetamine

- Findings demonstrate elevated risk for HCV seroconversion in relation to heroin, cocaine and crystal methamphetamine injection, but not prescription opioid injection following covariate adjustment; however, the relatively small number of youth injecting prescription opioids may have limited detection of marginal risk differences

- Since youth in the study were recruited by snowball sampling, results are not obtained from a truly random sample, but characteristics of the cohort are comparable to those from studies of street youth conducted elsewhere

- This study demonstrates novel findings that should prompt further study of risk for blood-borne infection among drug-injecting youth populations

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INTRODUCTION

Hepatitis C virus (HCV) infection is a leading cause of morbidity and mortality worldwide.[1-3] While the incidence of HCV may be decreasing in some age groups, infection rates appear to be increasing among adolescents and young adults.[4] Street youth – that is, youth who spend all or part of their time working or living on the street[5,6] – represent a marginalized and stigmatized population at elevated risk for HCV acquisition owing to a high prevalence of injection drug use.[3,7,8]

The emergence of elevated rates of HCV among street youth coincides with important changes in patterns of youth substance use. In recent years, misuse of prescription opioids such as morphine, oxycodone and hydrocodone has emerged as a public health emergency.[9] Although injection of illicit drugs is known to place users at high risk of blood-borne infection,[10,11] the abundance of studies to date have focused on traditional street drugs, such as heroin and cocaine, rather than prescription opioids.[12]

This constitutes a serious gap in our understanding of HCV epidemiology given that, in many jurisdictions, overdose mortality attributed to prescription opioid use has surpassed that attributed to the use of heroin and cocaine combined.[13] The prevalence of non-medical prescription opioid use is increasing in the general adolescent population,[14] with approximately 8-10% of high school students in the United States reporting past-year use.[15] Many prescription opioid formulations are readily injected,[16,17] but despite their widespread availability, there is a paucity of epidemiologic data examining this practice or its risk for disease transmission.[18]

At this time, it remains unclear whether heroin injectors and prescription opioid injectors represent overlapping or distinct subpopulations of injection drug users.[19] There is evidence that some users follow a trajectory from initially using prescription opioids to ultimately using heroin, since in some settings, heroin is less expensive and more potent and available.[16] On

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the other hand, there may be a sizeable subgroup of users who inject prescription opioids to the exclusion of heroin and other drugs.[20] Regardless, there is reason to believe that certain injection practices associated with heroin as compared with prescription opioids may place users at differential risk for infectious disease transmission.[17,20]

Understanding how injection of prescription opioids may place users at risk for acquiring HCV is imperative, given that injection drug users represent the population at greatest risk for HCV infection in North America,[21,22] and that mortality from HCV has increased to the extent that it recently surpassed that from human immunodeficiency virus (HIV) in the United States.[2] We conducted the present study of HCV acquisition among a prospective cohort of street youth in Vancouver, Canada. Our study objective was to compare differences in risk for HCV seroconversion from injection of prescription opioids to that from injection of traditional street drugs.

METHODS

The At-Risk Youth Study (ARYS) is a cohort of street-involved youth in Vancouver, Canada.[23] Inclusion criteria for enrollment included age 14 to 26 years and use of an illicit drug other than marijuana during the month prior to enrollment. Recruitment relied on extensive daytime and nighttime street-based outreach and snowball sampling. After, full study details were disclosed and informed consent was obtained. At baseline and every six months thereafter, participants completed an interview and underwent HCV antibody testing. Participants were remunerated $20 CAN per visit. ARYS was approved by the University of British Columbia/Providence Health Care Research Ethics Board.

We compared HCV prevalence at recruitment and subsequent HCV incidence among youth according to recent (*i.e.,* during the preceding six months) injection of prescription opioid

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and recent injection of heroin, cocaine and crystal methamphetamine. Prescription opioids were broadly defined to include morphine, oxycodone, hydromorphone, meperidine, fentanyl or methadone. We also examined patterns of non-injection use of prescription opioids in the sample. All ARYS participants were included in the baseline HCV prevalence analyses. Participants who were HCV antibody negative at baseline and returned for ≥1 follow-up visit were included in the incidence analyses.

We also examined an additional array of covariates including: gender, age (as a continuous variable), Aboriginal ancestry, high school education (having completed or currently enrolled in high school), self-reported gay/lesbian/bisexual orientation, recent homelessness, recent incarceration, recent sharing of injection syringes, recent inconsistent condom use (vaginal or anal penetrative sex without condom use 100% of the time), and recent sex work (having traded sex for money, drugs, shelter or gifts). In the baseline prevalence analysis, all participants were compared according to HCV serostatus through chi-square (for categorical variables) and Wilcoxin rank sum tests (for continuous variables). Similar statistics were also calculated to compare drug-related behaviors between Aboriginal and non-Aboriginal youth.[24]

We then conducted the incidence analysis with the outcome of time to HCV seroconversion, limiting the sample to those who were HCV antibody negative at baseline and returned for ≥1 follow-up visit. Youth with prior history of injection were first compared in univariate analyses.[25] We subsequently used Kaplan-Meier methods to plot the cumulative incidence of HCV seroconversion as a function of time. All follow-up data were included, even if a participant had missed an intervening follow-up appointment.

We also used Cox proportional hazards regression to determine unadjusted and adjusted hazard ratios (HR) for HCV seroconversion for the range of drug use-related variables and other covariates listed above. An interaction term between heroin and prescription opioid

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injection was also tested. Time of seroconversion was estimated as the midpoint of the date of last known seronegativity and of that of first seropositivity.[26-28] Independent variables were time-updated in regression models if they referred to non-fixed characteristics or behaviors in the preceding six months. In the event of differential follow-up duration among participants recruited earlier in the study period compared to later in the study period, we examined the prevalence of prescription opioid injection and heroin in the first two years of study and that of the last two years of study to determine whether these behaviors were becoming more common with time.[14]

We sought to directly compare the risk for HCV seroconversion from injection of heroin and other traditional drugs of abuse to that of injection of prescription opioids,[17,20] and created three multivariable models to do so. The first model included recent heroin injection but not recent prescription opioid injection; the second, recent prescription opioid injection but not recent heroin injection; and the third, both recent heroin injection and recent prescription opioid injection. To adjust for potential confounders, age and gender were included in multivariable models as well as covariates significant at $p<0.05$ in the initial bivariate Cox regression analyses of time to HCV seroconversion.

Analyses were conducted with SAS version 9.1 (SAS Institute, Inc, Cary, North Carolina). All p values were two-sided and tests were considered significant at $p<0.05$. Adjustments were not made for multiple comparisons given that this was a single-outcome, observational study.

RESULTS

From September 2005 to November 2011, 940 youth were recruited into the ARYS cohort and completed baseline HCV antibody testing. One-hundred youth (10.6%) were HCV-

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seropositive at study enrollment. **Table 1** shows baseline characteristics and recent (*i.e.,* in the six months preceding study enrollment) drug-related and sexual risk behaviors according to HCV serostatus. Aboriginal youth comprised 224 (23.8%) of the sample. Aboriginal and non-Aboriginal youth did not differ with regard to recent non-injection prescription opioid use, recent injection of prescription opioids, heroin, cocaine, or crystal methamphetamine, or recent syringe sharing ($p>0.05$ for all). As shown, baseline HCV seropositivity was associated with older age, recent homelessness, recent incarceration, recent injection of prescription opioids, heroin, cocaine, and crystal methamphetamine, recent syringe sharing, and recent sex work. Recent injection of prescription opioids and of heroin were correlated ($p<0.05$).

Of the 840 youth who were HCV antibody negative at baseline, 512 (60.9%) had at least one follow-up visit and provided blood samples for HCV antibody testing. Among these 512 youth, 151 (29.5%) were female and 135 (67.2%) identified as Aboriginal. The mean age was 21.7 (standard deviation, 2.6) years. Compared with the 328 (29.1%) participants who were HCV antibody negative at baseline and did not provide follow-up data, the 512 participants included in subsequent incidence analyses tended to be older ($p<0.05$), but did not differ at baseline in terms of gender, Aboriginal ancestry, recent incarceration, recent sex work, recent injection of prescription opioids, heroin, cocaine or crystal methamphetamine, or recent syringe sharing.

At study enrollment, 166 (32.4%) of the 512 youth included in the incidence analysis reported prior drug injection. Compared to those who had not previously injected, those who had injected were more likely to be older ($p<0.05$), but otherwise did not differ by gender, Aboriginal ancestry, recent incarceration, or recent sex work. Of the 166 youth who had previously injected, 56 (33.7%) reported recently having injected two or more drugs among prescription opioids, heroin, cocaine and crystal methamphetamine, and 11 (6.6%) reported having injected three or more of these drugs.

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During the follow-up period (median follow-up, 18.5 months; median number of follow-up visits after baseline visit, 2 visits; total follow-up, 860.2 person-years), there were 56 (10.9%) HCV seroconversions, resulting in an incidence density of 6.5 per 100 person-years. As might be expected, median follow-up was longer in the earlier years of study enrollment (22.0 months in the first two years of enrollment *vs*. 17.0 months in the final two years; $p<0.001$). The median number of missed visits during follow-up was 1 visit. Individuals lost to follow up were censored at the time of their last visit.

Figure 1a shows the Kaplan-Meier cumulative incidence of HCV seroconversion according to heroin injection in the entire sample and **Figure 1b** shows the cumulative incidence according to heroin injection with the sample restricted to drug-injecting youth only. In both cases, heroin injectors had a markedly elevated risk of HCV seroconversion in comparison to others in the sample, including prescription opioid injectors (full data available from the corresponding author). Crude incidence density of HCV seroconversion among heroin-injecting youth was 20.8 per 100 person-years and among prescription opioid-injecting youth was 21.4 per 100 person-years. Mean number of visits prior to seroconversion did not differ between heroin and prescription opioid injectors ($p>0.05$). Over the study period, the prevalence of prescription opioid injection remained unchanged (4.2% in the first two years of enrollment *vs.* 4.4% in the last two years; $p=0.880$) as did that of heroin injection (13.5% *vs.* 11.8%; $p=0.489$). At baseline, recent heroin injectors and recent prescription opioid injectors did not differ in terms of age (mean, 21.8 *vs.* 22.3 years, respectively; $p=0.524$), gender (65.5% *vs.* 72.2% male; $p=0.202$), ethnicity (20.7% Aboriginal *vs*. 16.7% other; $p=0.256$), age of initiation of injection drug use (mean, 17.7 *vs.* 18.7 years; $p=0.271$) or in total number of years of injecting (mean, 4.1 *vs.* 3.6 years; $p=0.567$).

Table 2 displays the results of the unadjusted and adjusted Cox proportional hazard regression analyses of the time to detected HCV seroconversion according to demographic

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characteristics and risk behaviors. As shown, HCV seroconversion was significantly associated with female gender, prescription opioid injection, heroin injection, cocaine injection, crystal methamphetamine injection, and syringe sharing in unadjusted analyses. Age was not associated with HCV seroconversion. Additional variables not listed in the table that were not significantly associated with HCV seroconversion included Aboriginal ancestry (unadjusted hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.49-1.59; p=0.662), recent incarceration (HR, 1.25; 95% CI, 0.67-2.32; p=0.482), recent inconsistent condom use (unadjusted HR, 0.90; 95% CI, 0.52-1.55; p=0.703), and recent sex work (unadjusted HR, 0.91; 95% CI, 0.28-2.90; p=0.869). Additionally, the interaction term between heroin and prescription opioid injection was not significant.

The three multivariable models examining the relative effects of prescription opioid injection and heroin injection all were adjusted for gender and age, as well for variables significant at p<0.05 in unadjusted Cox regression analyses (cocaine injection, crystal methamphetamine injection, and syringe sharing). In the model including all covariates except prescription opioid injection, heroin injection remained significantly associated with HCV seroconversion (Model 1), whereas prescription opioid injection did not retain significance in the model including all covariates except heroin (Model 2). When both heroin injection and prescription opioid injection were included a combined model, heroin injection, but not prescription opioid injection, retained statistical significance (Model 3).

DISCUSSION

In this longitudinal study, we observed a high prevalence of HCV seropositivity among adolescents and young adults on the street, with more than one in ten youth infected with HCV at baseline, as well as high incidence HCV acquisition during follow-up. We observed that

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injection of heroin, cocaine and crystal methamphetamine were all strongly associated with risk HCV seroconversion following adjustment for potential confounders. Injection of prescription opioids, by contrast, was not independently associated with HCV seroconversion in adjusted models, although it was associated with HCV seropositivity at baseline and with HCV seroconversion in unadjusted analyses. Taken together, these findings highlight street youth as a population that should remain a critical focus for evidence-based drug preventive and treatment services to prevent a worsening HCV epidemic.

Although misuse of prescription opioids is on the rise in North America,[15] and although they are readily injected,[16,17] we did not observe excess risk for HCV seroconversion from injection of prescription opioids among Vancouver street youth after controlling for other factors. There are several plausible explanations for the null finding in this setting. First, we acknowledge that despite a large sample of drug-using youth, the proportion of participants in the cohort who engaged in prescription opioid injection was relatively small and may have somewhat limited detection of marginal risk differences. Prescription opioid injection was significantly associated with HCV seroconversion in univariate incidence analyses, suggesting increased risk from this behavior. However, in the setting of polysubstance use, which was common in this setting, the contribution of prescription opioid injection to risk for HCV seroconversion appears to be relatively less important than that of traditional drugs of abuse including heroin, cocaine and crystal methamphetamine. We recommend that future studies actively recruit prescription opioid-injecting youth in order to improve estimates of risk for HCV.

Second, as has been described elsewhere, populations of drug users often show great heterogeneity, with subpopulations exhibiting widely varying risk for blood-borne disease.[19] In Vancouver, youth who inject prescription opioids, regardless of whether they also inject other drugs, may represent a distinct subpopulation from other higher risk youth who inject heroin, cocaine or crystal methamphetamine but not prescription opioids, as has been observed in

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other settings.[20] It is possible prescription opioid-injecting youth may not be as entrenched in the local drug scene,[29] and as a result, may not associate as frequently with HCV-seropositive drug users. Similarly, youth who inject prescription opioids may have received different preventive messaging regarding safe injection practices, or have better access to harm reduction services. Better understanding the risk environment for prescription opioid users will prove important for preventing transmission of HCV in this high-risk population.

Although prescription opioid injection was not independently associated with risk for HCV seroconversion, more traditional risk factors, including injection of heroin, cocaine, and crystal methamphetamine were strongly and independently associated with HCV acquisition in this setting. These findings are consistent with those from previous youth studies.[8,30-32] It is well established that HCV is spread when drug users share injection paraphernalia.[33,34] Interestingly, although syringe sharing was associated with HCV seroconversion in the ARYS sample, it did not fully explain the risk for HCV associated with injection of heroin, cocaine and crystal methamphetamine in final multivariable models. A possible explanation may be that youth underreported syringe sharing, which might be perceived as a stigmatized behavior. The result of such socially desirable reporting could be the incomplete effect sizes observed in our statistical models.[35,36] Regardless, attempts to prevent the spread of HCV among at-risk youth will require careful attention to factors that interfere with safe injection practices, including peer dynamics and chaotic injection environments.[37,38]

The excess risk for HCV among street youth necessitates evidence-based strategies to prevent drug use and mitigate injection-related harm. Although maintenance therapy with methadone or buprenorphine is efficacious among adolescents and young adults,[39,40] challenges remain in making these services accessible to street youth, who are a marginalized and difficult-to-reach population.[41,42] Other effective harm reduction services such as needle exchange and supervised safe injection facilities are often developed for adult drug users and

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may not effectively target younger drug users.[3] Barriers to preventive and treatment modalities for young drug users are well documented, and include excessively long waiting lists, difficulty complying with program rules, program fees that exceed young people's ability to pay, and locations that are inconvenient for youth.[41] Existing drug treatment and harm reduction services should be extended in a way that is sensitive to the unique circumstances of youth.

There are limitations to this study. First, as outlined above, we acknowledge a relatively small proportion of the sample who injected prescription opioids, which may have affected the precision of our estimates. Second, we employed snowball sampling in order to recruit heavily drug-involved youth, who are frequently homeless and represent a population 'hidden' from traditional population-based sampling. Although snowball sampling does not produce a truly random sample,[23] it is noteworthy that the characteristics of the ARYS cohort are similar to those of other at-risk youth in western Canada.[43,44] Third, our study relied on self-report, which, as outlined above, may have resulted in social desirability bias for questions probing sensitive details. Finally, for polysubstance-using youth in sample, we cannot rule out that the risk for HCV our models attributed to heroin may have been better attributed to risky behaviors associated with injection of other drugs. However, we sought to explore the independent effects of other drugs in our modeling by controlling for injection of the most common of other substances of abuse.

In summary, we found the risk for HCV acquisition among street youth in this setting was alarmingly high, and that intravenous drug injection remains a primary risk factor. Interestingly, although prescription opioid misuse is on the rise in North America, in our sample, risk of HCV acquisition from injection of prescription opioids did not exceed that of traditional street drugs, including heroin, cocaine and crystal methamphetamine. Regardless, these results highlight an urgent need for evidence-based strategies, including educational programming, addiction treatment and harm reduction services, to prevent disease transmission among street youth.

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Role of Funding Source
This work was supported by the US National Institutes of Health [grant number R01DA028532]; the Canadian Institutes of Health Research [grant number MOP–102742]; the Canada Research Chairs [Tier 1 Canada Research Chair in Inner City Medicine, E. W.]; Maternal Child Health Bureau of the Health Services Research Administration [Leadership Education in Adolescent Health, grant number T71 MC00009, S. E. H.]; and National Institute of Drug Abuse, United States National Institutes of Health [Avant-Garde award, grant number DP1DA026182, J. S. M.].

Conflict of Interest Statement
J. S. M. has received educational grants from, served as an ad hoc advisor to or spoken at various events sponsored by Abbott Laboratories, Agouron Pharmaceuticals Inc., Boehringer Ingelheim Pharmaceuticals Inc., Borean Pharma AS, Bristol–Myers Squibb, DuPont Pharma, Gilead Sciences, GlaxoSmithKline, Hoffmann–La Roche, Immune Response Corporation, Incyte, Janssen–Ortho Inc., Kucera Pharmaceutical Company, Merck Frosst Laboratories, Pfizer Canada Inc., Sanofi Pasteur, Shire Biochem Inc., Tibotec Pharmaceuticals Ltd. and Trimeris Inc.

Acknowledgements
The authors thank the study participants for their contribution to the research, as well as current and past researchers and staff. We would specifically like to thank Deborah Graham, Peter Vann, Caitlin Johnston, Steve Kain, and Calvin Lai for their research and administrative assistance. We also appreciate support from Dr. Bob Vinci and the Boston Combined Residency Program, as well as Dr. Jean Emans and the Division of Adolescent / Young Adult Medicine at Boston Children's Hospital. The corresponding author affirms that all who contributed significantly to the work are acknowledged here. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Contributors
Drs. Hadland, DeBeck, Kerr and Wood designed the study. Drs. Hadland, DeBeck and Wood wrote the protocol. Dr. Hadland conducted the literature review and wrote the first draft of the manuscript. Dr. Feng undertook statistical analyses with additional input from Dr. Hadland. All authors contributed to and have approved the final manuscript.

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TABLE 1. Baseline characteristics of 940 street youth, according to hepatitis C virus (HCV) serostatus at study enrollment: At-Risk Youth Study (ARYS), Vancouver, British Columbia, 2005-2011.

Characteristic	Total (%) (*n* = 940)	HCV-Seropositive		Odds Ratio (95% CI)	*p* Value
		Yes (%) (*n* = 100)	No (%) (*n* = 840)		
Sociodemographic factors					
Male gender	654 (69.6)	63 (63.0)	591 (70.4)	0.72 (0.47 – 1.11)	0.131
Mean age (SD)[a]	21.7 (2.7)	23.4 (2.5)	21.5 (2.7)	1.34 (1.23 – 1.47)	< 0.001
Aboriginal ancestry	224 (23.8)	30 (30.0)	194 (23.1)	1.43 (0.90 – 2.25)	0.126
High school education[b]	415 (64.8)	35 (35.0)	380 (45.2)	0.65 (0.42 – 1.00)	0.051
Gay/lesbian/bisexual	151 (16.1)	22 (22.0)	129 (15.4)	0.64 (0.39 – 1.07)	0.087
Recent homelessness[c]	348 (37.0)	54 (54.0)	294 (35.0)	2.18 (1.44 – 3.31)	< 0.001
Recent incarceration[c]	176 (18.7)	26 (26.0)	150 (17.9)	1.62 (1.00 – 2.61)	0.048
Substance use-related behaviors					
Mean years injecting (SD)[d]	4.3 (3.2)	4.0 (3.3)	4.6 (3.2)	0.94 (0.82 – 1.07)	0.350
Non-injection prescription opioid use[c]	90 (9.6)	12 (12.0)	78 (9.3)	1.33 (0.70 – 2.54)	0.383
Prescription opioid injection[c]	64 (6.8)	28 (28.0)	36 (4.3)	8.69 (5.01 – 15.1)	< 0.001
Heroin injection[c]	191 (20.3)	66 (66.0)	125 (14.9)	11.1 (7.04 – 17.5)	< 0.001
Cocaine injection[c]	93 (9.9)	31 (31.0)	62 (7.4)	5.54 (3.43 – 9.26)	< 0.001
Crystal methamphetamine injection[c]	154 (16.4)	50 (50.0)	104 (12.4)	7.08 (4.55 – 11.0)	< 0.001
Syringe sharing[c]	56 (6.0)	18 (18.0)	38 (4.5)	4.63 (2.53 – 8.48)	< 0.001
Sexual risk behaviors					
Inconsistent condom use[c]	433 (46.1)	40 (40.0)	393 (46.8)	0.76 (0.50 – 1.16)	0.198
Sex work[c]	65 (6.9)	14 (14.0)	51 (6.1)	2.52 (1.34 – 4.74)	0.003

a. Odds ratio calculated per year older

b. Prior completion of or current enrollment in high school

c. During the six months preceding study enrollment

d. Includes only actively injecting youth

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TABLE 2. Unadjusted and adjusted Cox proportional hazard analysis of time to hepatitis C infection among 512 drug-using youth: At-Risk Youth Study (ARYS), Vancouver, British Columbia, 2005-2011.

		Adjusted HR (95% CI)		
Characteristic	**Unadjusted HR (95% CI)**	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**
Male gender	0.48 (0.28 – 0.81)	0.50 (0.28 – 0.90)	0.42 (0.24 – 0.75)	0.50 (0.28 – 0.90)
Age (per year older)	0.96 (0.87 – 1.06)	1.10 (0.91 – 1.10)	1.00 (0.91 – 1.11)	1.00 (0.91 – 1.10)
Prescription opioid injection	3.48 (1.57 – 7.70)	–	2.02 (0.89 – 4.61)	0.94 (0.40 – 2.21)
Heroin injection	9.89 (5.72 – 17.1)	4.49 (2.42 – 8.33)	–	4.56 (2.39 – 8.70)
Cocaine injection	5.69 (3.18 – 10.2)	1.87 (1.00 – 3.47)	2.20 (1.14 – 4.23)	1.88 (1.00 – 3.54)
Crystal methamphetamine injection	7.39 (4.36 – 12.5)	2.94 (1.62 – 5.34)	5.11 (2.79 – 9.34)	2.91 (1.57 – 5.38)
Syringe sharing	7.69 (3.93 – 15.0)	2.47 (1.20 – 5.09)	2.57 (1.24 – 5.32)	2.47 (1.20 – 5.10)

a. Model 1 includes all covariates listed except prescription opioid injection

b. Model 2 includes all covariates listed except heroin injection

c. Model 3 includes all covariates listed

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FIGURE 1a. Cumulative incidence of hepatitis C infection among 512 drug-using youth, by injection heroin use: At-Risk Youth Study (ARYS), Vancouver, Canada, 2005-2010.

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FIGURE 1b. Cumulative incidence of hepatitis C infection among drug-injecting youth by heroin use: At-Risk Youth Study (ARYS), Vancouver, Canada, 2005-2010.

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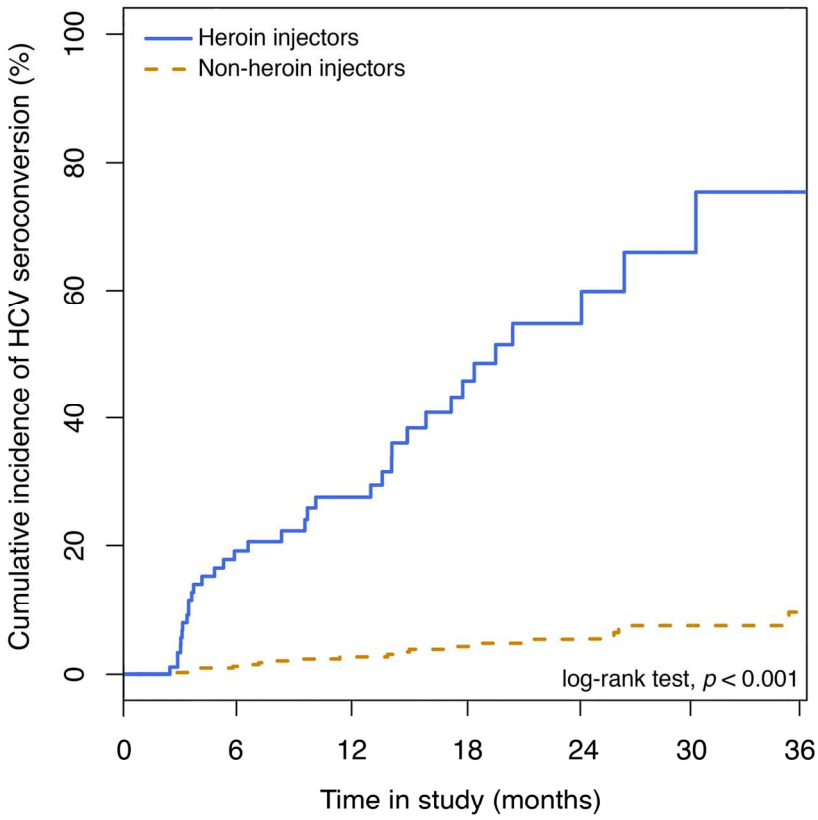

Figure 1a
76x76mm (600 x 600 DPI)

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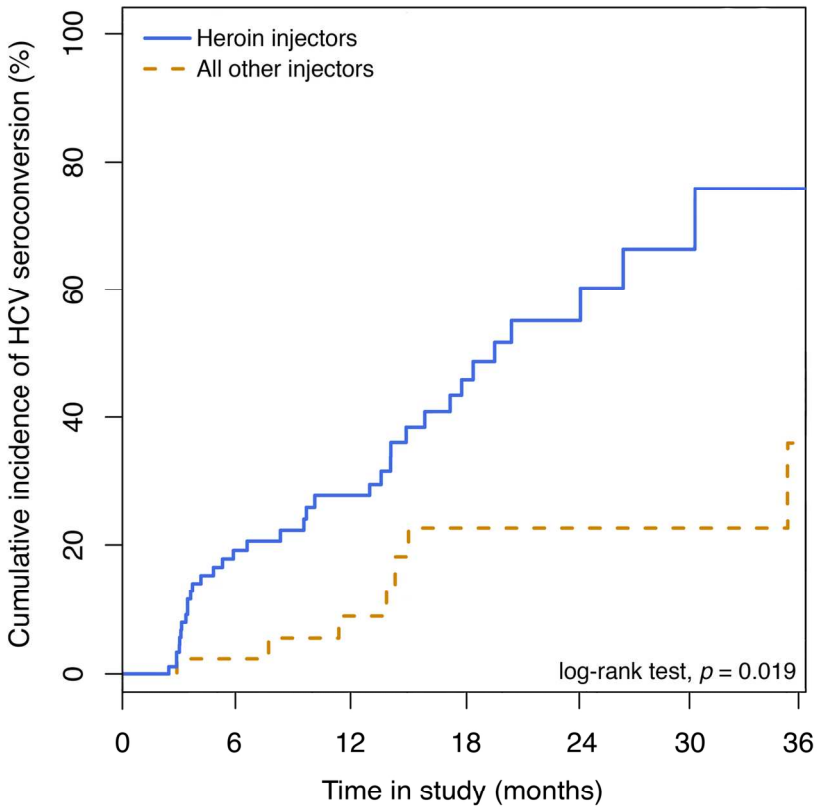

Figure 1b
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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1 **x**	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 **x**	Explain the scientific background and rationale for the investigation being reported
Objectives	3 **x**	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 **x**	Present key elements of study design early in the paper
Setting	5 **x**	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 **x**	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7 **x**	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* **x**	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
Bias	9 **x**	Describe any efforts to address potential sources of bias
Study size	10 **x**	Explain how the study size was arrived at
Quantitative variables	11 **x**	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 **x**	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

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Results		
Participants	13* x	(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
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* x	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* x	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 x	(*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
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 x	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 x	Summarise key results with reference to study objectives
Limitations	19 x	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 x	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 x	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 x	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

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

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Prescription Opioid Injection and Risk of Hepatitis C in Relation to Traditional Drugs of Abuse in a Prospective Cohort of Street Youth

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005419.R1
Article Type:	Research
Date Submitted by the Author:	17-Jun-2014
Complete List of Authors:	Hadland, Scott; Boston Children's Hospital, Division of Adolescent / Young Adult Medicine Debeck, Kora; BC Centre for Excellence in HIV/AIDS, Kerr, Thomas; BC Centre for Excellence in HIV/AIDS, Feng, Cindy; BC Centre for Excellence in HIV/AIDS, Montaner, Julio; BC Centre for Excellence in HIV/AIDS, Wood, Evan; BC Centre for Excellence in HIV/AIDS,
Primary Subject Heading:	Addiction
Secondary Subject Heading:	HIV/AIDS, Infectious diseases, Public health
Keywords:	Hepatobiliary disease < GASTROENTEROLOGY, Epidemiology < INFECTIOUS DISEASES, INFECTIOUS DISEASES, Hepatology < INTERNAL MEDICINE, Child & adolescent psychiatry < PSYCHIATRY, Substance misuse < PSYCHIATRY

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PRESCRIPTION OPIOID INJECTION AND RISK OF HEPATITIS C IN RELATION TO TRADITIONAL DRUGS OF ABUSE IN A PROSPECTIVE COHORT OF STREET YOUTH

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Abstract Word Count: 296
Word Count (excluding abstract): 2,997
Figures: 2
Tables: 2
Submitted: Monday, April 7, 2014
Resubmitted: Monday, June 30, 2014
Running Head: Hepatitis C and prescription opioid use
MeSH Terms: hepatitis C; analgesics, opioid; heroin; drug abuse; adolescent

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ABSTRACT

Objective: Despite dramatic increases in misuse of prescription opioids, the extent to which their intravenous injection places drug users at risk of acquiring hepatitis C virus (HCV) remains unclear. We sought to compare risk of HCV acquisition from injection of prescription opioids to that from other street drugs among high-risk street youth.

Design: Prospective cohort study.

Setting: Vancouver, British Columbia, Canada, from September 2005 to November 2011.

Participants: The At-Risk Youth Study (ARYS) is a prospective cohort of actively drug-using adolescents and young adults aged 14-26 years. Participants were recruited through extensive street-based outreach and snowball sampling.

Primary Outcome Measure: HCV antibody seroconversion, measured every 6 months during study follow-up. Risk for seroconversion from injection of prescription opioids was compared to injection of other street drugs of abuse, including heroin, cocaine or crystal methamphetamine, using Cox proportional hazards regression controlling for age, gender and active syringe sharing.

Results: Baseline HCV seropositivity was 10.6%. Among 512 HCV-seronegative youth contributing 860.2 person-years of total follow-up, 56 (10.9%) seroconverted, resulting in an incidence density of 6.5 per 100 person-years. In bivariate analyses, prescription opioid injection (hazard ratio [HR], 3.48; 95% CI, 1.57-7.70) predicted HCV seroconversion. However, in multivariate modeling, only injection of heroin (adjusted HR, 4.56; 95% CI, 2.39-8.70),

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cocaine (adjusted HR, 1.88; 95% CI, 1.00-3.54), and crystal methamphetamine (adjusted HR, 2.91; 95% CI, 1.57-5.38) remained independently associated with HCV seroconversion, whereas injection of prescription opioids did not (adjusted HR, 0.94; 95% CI, 0.40-2.21).

Conclusions: Although misuse of prescription opioids is on the rise, traditional street drugs still appeared to pose the greatest threat of HCV transmission in this setting. Nonetheless, the high prevalence and incidence of HCV seropositivity among Canadian street youth underscores the need for evidence-based drug prevention, treatment, and harm reduction interventions targeting this vulnerable population.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength of this prospective cohort study is that it followed street youth, a marginalized and difficult-to-reach population with a high prevalence of injection drug use and blood-borne infection, including human immunodeficiency virus (HIV) and hepatitis C virus (HCV)

- An additional strength is that it is among the first studies to examine the association between injection of prescription opioids (including, for example, oxycodone and morphine) and acquisition of HCV; it is not well understood how the risk for acquiring HCV from injecting prescription opioids compares to that from injection of more traditionally studied street drugs, such as heroin, cocaine and crystal methamphetamine

- The study's findings demonstrate elevated risk for HCV seroconversion in relation to heroin, cocaine and crystal methamphetamine injection, but not prescription opioid injection after adjustment for covariates; however, the relatively small number of youth injecting prescription opioids may have limited detection of marginal risk differences

- Since youth in the study were recruited by snowball sampling, results are not obtained from a truly random sample, but characteristics of the cohort are comparable to those from studies of street youth conducted elsewhere

- This study demonstrates novel findings that should prompt further study of risk for blood-borne infection among drug-injecting youth populations

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INTRODUCTION

Hepatitis C virus (HCV) infection is a leading cause of morbidity and mortality worldwide.[1-3] While the incidence of HCV may be decreasing in some age groups, infection rates appear to be increasing among adolescents and young adults.[4] Street youth – that is, youth who spend all or part of their time working or living on the street[5,6] – represent a marginalized and stigmatized population at elevated risk for HCV acquisition owing to a high prevalence of injection drug use.[3,7,8]

The emergence of elevated rates of HCV among street youth coincides with important changes in patterns of youth substance use. In recent years, misuse of prescription opioids such as morphine, oxycodone and hydrocodone has emerged as a public health emergency.[9] Although injection of illicit drugs is known to place users at high risk of blood-borne infection,[10,11] the abundance of studies to date have focused on traditional street drugs, such as heroin and cocaine, rather than prescription opioids.[12]

This constitutes a serious gap in our understanding of HCV epidemiology given that, in many jurisdictions, overdose mortality attributed to prescription opioid use has surpassed that attributed to the use of heroin and cocaine combined.[13] The prevalence of non-medical prescription opioid use is increasing in the general adolescent population,[14] with approximately 8-10% of high school students in the United States reporting past-year use.[15] Many prescription opioid formulations are readily injected,[16,17] but despite their widespread availability, there is a paucity of epidemiologic data examining this practice or its risk for disease transmission.[18]

At this time, it remains unclear whether heroin injectors and prescription opioid injectors represent overlapping or distinct subpopulations of injection drug users.[19] There is evidence that some users follow a trajectory from initially using prescription opioids to ultimately using heroin, since in some settings, heroin is less expensive and more potent and available.[16] On

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the other hand, there may be a sizeable subgroup of users who inject prescription opioids to the exclusion of heroin and other drugs.[20] Regardless, there is reason to believe that certain injection practices associated with heroin as compared with prescription opioids may place users at differential risk for infectious disease transmission.[17,20]

Understanding how injection of prescription opioids may place users at risk for acquiring HCV is imperative, given that injection drug users represent the population at greatest risk for HCV infection in North America,[21,22] and that mortality from HCV has increased to the extent that it recently surpassed that from human immunodeficiency virus (HIV) in the United States.[2] We conducted the present study of HCV acquisition in Vancouver, Canada, among a prospective cohort of street youth, a population including a high proportion of Aboriginal youth who may be at elevated risk for blood-borne infection.[23] Our study objective was to examine the contribution of injection of prescription opioids and that of traditional street drugs of abuse to the risk for HCV seroconversion.

METHODS

The At-Risk Youth Study (ARYS) is a cohort of street-involved youth in Vancouver, Canada.[24] Inclusion criteria for enrollment included age 14 to 26 years and use of an illicit drug other than marijuana during the month prior to enrollment. Recruitment relied on extensive daytime and nighttime street-based outreach and snowball sampling, and was systematically conducted in parks, streets and alleyways of Vancouver where street youth are known to congregate. Although no inclusion criterion explicitly required a minimum amount of time on the street to qualify for the study, in practice, the street-based recruitment resulted in a sample of youth who spent substantial time on the street, a large proportion of whom were homeless.[25] Full study details were disclosed to participants and informed consent was obtained. At

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baseline and every six months thereafter, participants completed an interview and underwent HCV antibody testing. Participants were remunerated $20 CAN per visit. Additionally, a $5 CAN incentive was provided to youth three months after their baseline interview to return to the study site to update their contact information in an attempt to improve study follow-up. ARYS was approved by the University of British Columbia/Providence Health Care Research Ethics Board.

We compared HCV prevalence at recruitment and subsequent HCV incidence among youth according to recent (*i.e.,* during the preceding six months) injection of prescription opioid and recent injection of heroin, cocaine and crystal methamphetamine. Prescription opioids were broadly defined to include morphine, oxycodone, hydromorphone, meperidine, fentanyl or methadone. The exact question used was, "In the last 6 months, when you were using, which of the following drugs did you inject and how often?", with possible answers including, "Less than once per month / One to three times per month / About once per week / Two or three times per week / At least daily". Using this question, each of the prescription opioids listed above was individually and sequentially probed. We also examined patterns of non-injection use of prescription opioids in the sample. All ARYS participants were included in the baseline HCV prevalence analyses. Participants who were HCV antibody negative at baseline and returned for ≥1 follow-up visit were included in the incidence analyses.

We also examined an additional array of covariates including: gender, age (as a continuous variable), Aboriginal ancestry, high school education (having completed or currently enrolled in high school), self-reported gay/lesbian/bisexual orientation, recent homelessness, recent incarceration, recent sharing of injection syringes, recent inconsistent condom use (vaginal or anal penetrative sex without condom use 100% of the time), and recent sex work (having traded sex for money, drugs, shelter or gifts). In the baseline prevalence analysis, all participants were compared according to HCV serostatus through chi-square (for categorical

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variables) and Wilcoxin rank sum tests (for continuous variables). Similar statistics were also calculated to compare drug-related behaviors between Aboriginal and non-Aboriginal youth.[23]

We then conducted the incidence analysis with the outcome of time to HCV seroconversion, limiting the sample to those who were HCV antibody negative at baseline and returned for ≥1 follow-up visit. Youth with prior history of injection were first compared in univariate analyses.[26] We subsequently used Kaplan-Meier methods to plot the cumulative incidence of HCV seroconversion as a function of time. All follow-up data were included, even if a participant had missed an intervening follow-up appointment.

We also used Cox proportional hazards regression to determine unadjusted and adjusted hazard ratios (HR) for HCV seroconversion for the range of drug use-related variables and other covariates listed above. An interaction term between heroin and prescription opioid injection was also tested. Time of seroconversion was estimated as the midpoint of the date of last known seronegativity and of that of first seropositivity.[27-29] Independent variables were time-updated in regression models if they referred to non-fixed characteristics or behaviors in the preceding six months. In the event of differential follow-up duration among participants recruited earlier in the study period compared to later in the study period, we examined the prevalence of prescription opioid injection and heroin in the first two years of study and that of the last two years of study to determine whether these behaviors were becoming more common with time.[14] We also examined prevalence of cocaine and crystal methamphetamine over the course of the study.

We sought to directly compare the risk for HCV seroconversion from injection of heroin and other traditional drugs of abuse to that of injection of prescription opioids,[17,20] and created three multivariable models to do so. The first model included recent heroin injection but not recent prescription opioid injection; the second, recent prescription opioid injection but not

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recent heroin injection; and the third, both recent heroin injection and recent prescription opioid injection. To adjust for potential confounders, age and gender were included in multivariable models as well as covariates significant at $p<0.05$ in the initial bivariate Cox regression analyses of time to HCV seroconversion. Finally, as a sub-analysis, we restricted the sample to drug-injecting youth and examined bivariate associations between injection of prescription opioids, heroin, cocaine and crystal methamphetamine, and HCV seroconversion. We also repeated the third multivariate model using this subsample.

Analyses were conducted with SAS version 9.1 (SAS Institute, Inc, Cary, North Carolina). All *p* values were two-sided and tests were considered significant at $p<0.05$. Adjustments were not made for multiple comparisons given that this was a single-outcome, observational study.

RESULTS

From September 2005 to November 2011, 940 youth were recruited into the ARYS cohort and completed baseline HCV antibody testing. One-hundred youth (10.6%) were HCV-seropositive at study enrollment. **Table 1** shows baseline characteristics and recent (*i.e.,* in the six months preceding study enrollment) drug-related and sexual risk behaviors according to HCV serostatus. The cohort spent a median of 12 hours on the street per day (IQR: 6–24 h). Aboriginal youth comprised 224 (23.8%) of the sample. Aboriginal and non-Aboriginal youth did not differ with regard to recent non-injection prescription opioid use, recent injection of prescription opioids, heroin, cocaine, or crystal methamphetamine, or recent syringe sharing ($p>0.05$ for all). As shown, baseline HCV seropositivity was associated with older age, recent homelessness, recent incarceration, recent injection of prescription opioids, heroin, cocaine, and crystal methamphetamine, recent syringe sharing, and recent sex work. Recent injection

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of prescription opioids and of heroin were correlated (p<0.05).

Of the 840 youth who were HCV antibody negative at baseline, 512 (60.9%) had at least one follow-up visit and provided blood samples for HCV antibody testing. Among these 512 youth, 151 (29.5%) were female and 135 (67.2%) identified as Aboriginal. The mean age was 21.7 (standard deviation, 2.6) years. Compared with the 328 (29.1%) participants who were HCV antibody negative at baseline and did not provide follow-up data, the 512 participants included in subsequent incidence analyses tended to be older (p<0.05), but did not differ at baseline in terms of gender, Aboriginal ancestry, recent incarceration, recent sex work, recent injection of prescription opioids, heroin, cocaine or crystal methamphetamine, or recent syringe sharing.

At study enrollment, 166 (32.4%) of the 512 youth included in the incidence analysis reported prior drug injection. Compared to those who had not previously injected, those who had injected were more likely to be older (p<0.05), but otherwise did not differ by gender, Aboriginal ancestry, recent incarceration, or recent sex work. Of the 166 youth who had previously injected, 56 (33.7%) reported recently having injected two or more drugs among prescription opioids, heroin, cocaine and crystal methamphetamine, and 11 (6.6%) reported having injected three or more of these drugs.

During the follow-up period (median follow-up, 18.5 months; median number of follow-up visits after baseline visit, 2 visits; total follow-up, 860.2 person-years), there were 56 (10.9%) HCV seroconversions, resulting in an incidence density of 6.5 per 100 person-years. As might be expected, median follow-up was longer in the earlier years of study enrollment (22.0 months in the first two years of enrollment *vs*. 17.0 months in the final two years; p<0.001). The median number of missed visits during follow-up was 1 visit. Individuals lost to follow up were censored at the time of their last visit.

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Over the study period, the prevalence of prescription opioid injection remained relatively unchanged (4.2% of the entire sample in the first two years of enrollment *vs.* 4.4% in the last two years) as did that of heroin injection (13.5% *vs.* 11.8%). Similarly, there was very little change in the prevalence of cocaine injection (12.2% of the entire sample in the first two years of enrollment *vs.* 10.0% in the last two years) and crystal methamphetamine injection (18.0% *vs.* 16.8%). At baseline, recent heroin injectors and recent prescription opioid injectors did not differ in terms of age (mean, 21.8 *vs.* 22.3 years, respectively; p=0.524), gender (65.5% *vs.* 72.2% male; p=0.202), ethnicity (20.7% Aboriginal *vs.* 16.7% other; p=0.256), age of initiation of injection drug use (mean, 17.7 *vs.* 18.7 years; p=0.271) or in total number of years of injecting (mean, 4.1 *vs.* 3.6 years; p=0.567).

Figure 1a shows the Kaplan-Meier cumulative incidence of HCV seroconversion according to heroin injection in the entire sample and **Figure 1b** shows the cumulative incidence according to heroin injection with the sample restricted to drug-injecting youth only. In both cases, heroin injectors had a markedly elevated risk of HCV seroconversion in comparison to others in the sample, including prescription opioid injectors (full data available from the corresponding author). Crude incidence density of HCV seroconversion among heroin-injecting youth was 20.8 per 100 person-years and among prescription opioid-injecting youth was 21.4 per 100 person-years. Mean number of visits prior to seroconversion did not differ between heroin and prescription opioid injectors (p>0.05).

Table 2 displays the results of the unadjusted and adjusted Cox proportional hazard regression analyses of the time to detected HCV seroconversion according to demographic characteristics and risk behaviors. As shown, HCV seroconversion was significantly associated with female gender, prescription opioid injection, heroin injection, cocaine injection, crystal methamphetamine injection, and syringe sharing in unadjusted analyses. Age was not associated with HCV seroconversion. Additional variables not listed in the table that were not

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significantly associated with HCV seroconversion included Aboriginal ancestry (unadjusted hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.49-1.59; *p*=0.662), recent incarceration (HR, 1.25; 95% CI, 0.67-2.32; *p*=0.482), recent inconsistent condom use (unadjusted HR, 0.90; 95% CI, 0.52-1.55; *p*=0.703), and recent sex work (unadjusted HR, 0.91; 95% CI, 0.28-2.90; *p*=0.869). Additionally, the interaction term between heroin and prescription opioid injection was not significant. [xxx]

The three multivariable models examining the relative effects of prescription opioid injection and heroin injection all were adjusted for gender and age, as well for variables significant at *p*<0.05 in unadjusted Cox regression analyses (cocaine injection, crystal methamphetamine injection, and syringe sharing). In the model including all covariates except prescription opioid injection, heroin injection remained significantly associated with HCV seroconversion (Model 1), whereas prescription opioid injection did not retain significance in the model including all covariates except heroin (Model 2). When both heroin injection and prescription opioid injection were included a combined model, heroin injection, but not prescription opioid injection, retained statistical significance (Model 3).

When the sample was restricted to only drug-injecting youth (*n*=166), prescription opioid injection was not associated with HCV seroconversion in bivariate analyses (unadjusted HR, 1.27; 95% CI, 0.57-2.84; *p*=0.555). Heroin injection was associated with HCV seroconversion in this subsample (unadjusted HR, 2.93; 95% CI, 1.77-6.13; *p*<0.001), as was cocaine injection (unadjusted HR, 2.02; 95% CI, 1.11-3.68; *p*=0.021), but not crystal methamphetamine injection (unadjusted HR, 4.52; 95% CI, 0.61-33.3; *p*=0.136). Syringe sharing was also associated with HCV seroconversion (unadjusted HR, 2.93; 95% CI, 1.48-5.79; *p*=0.002). When Model 3 was rerun using this subsample, variables remaining significantly associated with HCV seroconversion included heroin injection (adjusted HR, 2.79; 95% CI, 1.46-5.34; *p*=0.002) and syringe sharing (adjusted HR 2.47; 95% CI, 1.22-4.98; *p*=0.012), but not prescription opioid

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injection (adjusted HR, 0.60; 95% CI, 0.25-1.47; *p*=0.268), cocaine injection (adjusted HR, 1.83; 95% CI, 0.98-3.40; *p*=0.057), or crystal methamphetamine injection (adjusted HR, 4.13; 95% CI, 0.47-36.0; *p*=0.199).

DISCUSSION

In this longitudinal study, we observed a high prevalence of HCV seropositivity among adolescents and young adults on the street, with more than one in ten youth infected with HCV at baseline, as well as high incidence HCV acquisition during follow-up. We observed that injection of heroin, cocaine and crystal methamphetamine were all strongly associated with risk HCV seroconversion following adjustment for potential confounders. Injection of prescription opioids, by contrast, was not independently associated with HCV seroconversion in adjusted models, although it was associated with HCV seropositivity at baseline and with HCV seroconversion in unadjusted analyses. Taken together, these findings highlight street youth as a population that should remain a critical focus for evidence-based drug preventive and treatment services to prevent a worsening HCV epidemic.

Although misuse of prescription opioids is on the rise in North America,[15] and although they are readily injected,[16,17] we did not observe excess risk for HCV seroconversion from injection of prescription opioids among Vancouver street youth after controlling for other factors. There are several plausible explanations for the null finding in this setting. First, we acknowledge that despite a large sample of drug-using youth, the proportion of participants in the cohort who engaged in prescription opioid injection was relatively small and may have somewhat limited detection of marginal risk differences. Prescription opioid injection was significantly associated with HCV seroconversion in univariate incidence analyses, suggesting increased risk from this behavior. However, in the setting of polysubstance use, which was

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common in this setting, the contribution of prescription opioid injection to risk for HCV seroconversion appears to be relatively less important than that of traditional drugs of abuse including heroin, cocaine and crystal methamphetamine. Indeed, because injection of prescription opioids and of heroin were correlated in our sample, our results are consistent with other reports that many heroin injectors also inject prescription opioids when they cannot easily locate heroin or cannot afford it.[17] We recommend that future studies actively recruit prescription opioid-injecting youth in order to improve estimates of risk for HCV.

Second, as has been described elsewhere, populations of drug users often show great heterogeneity, with subpopulations exhibiting widely varying risk for blood-borne disease.[19] In Vancouver, youth who inject prescription opioids, regardless of whether they also inject other drugs, may represent a distinct subpopulation from other higher risk youth who inject heroin, cocaine or crystal methamphetamine but not prescription opioids, as has been observed in other settings.[20] It is possible prescription opioid-injecting youth may not be as entrenched in the local drug scene,[30] and as a result, may not associate as frequently with HCV-seropositive drug users. Similarly, youth who inject prescription opioids may have received different preventive messaging regarding safe injection practices, or have better access to harm reduction services. Better understanding the risk environment for prescription opioid users will prove important for preventing transmission of HCV in this high-risk population.

Although prescription opioid injection was not independently associated with risk for HCV seroconversion, more traditional risk factors, including injection of heroin, cocaine, and crystal methamphetamine were strongly and independently associated with HCV acquisition in this setting. These findings are consistent with those from previous youth studies.[8,31-33] It is well established that HCV is spread when drug users share injection paraphernalia.[34,35] Interestingly, although syringe sharing was associated with HCV seroconversion in the ARYS sample, it did not fully explain the risk for HCV associated with injection of heroin, cocaine and

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crystal methamphetamine in final multivariable models. A possible explanation may be that youth underreported syringe sharing, which might be perceived as a stigmatized behavior. The result of such socially desirable reporting could be the incomplete effect sizes observed in our statistical models.[36,37] Regardless, attempts to prevent the spread of HCV among at-risk youth will require careful attention to factors that interfere with safe injection practices, including peer dynamics and chaotic injection environments.[38,39]

The excess risk for HCV among street youth necessitates evidence-based strategies to prevent drug use and mitigate injection-related harm. Although maintenance therapy with methadone or buprenorphine is efficacious among adolescents and young adults,[40,41] challenges remain in making these services accessible to street youth, who are a marginalized and difficult-to-reach population.[42,43] Other effective harm reduction services such as needle exchange and supervised safe injection facilities are often developed for adult drug users and may not effectively target younger drug users.[3] Barriers to preventive and treatment modalities for young drug users are well documented, and include excessively long waiting lists, difficulty complying with program rules, program fees that exceed young people's ability to pay, and locations that are inconvenient for youth.[42] Existing drug treatment and harm reduction services should be extended in a way that is sensitive to the unique circumstances of youth.

There are limitations to this study. First, as outlined above, we acknowledge a relatively small proportion of the sample who injected prescription opioids, which may have affected the precision of our estimates. Second, we employed snowball sampling in order to recruit heavily drug-involved youth, who are frequently homeless and represent a population 'hidden' from traditional population-based sampling. Although snowball sampling does not produce a truly random sample,[24] it is noteworthy that the characteristics of the ARYS cohort are similar to those of other at-risk youth in western Canada.[44,45] A final point regarding representativeness is the refusal rate among youth who are approached for enrolment into the study. Unfortunately,

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as youth often self-refer and street-based outreach often requires a very low threshold approach commonly involving repeated contact, rates of refusal can only be estimated. Study staff estimate that 30% of youth first approached for participation ultimately agree to be assessed for eligibility. Third, our study relied on self-report, which, as outlined above, may have resulted in social desirability bias for questions probing sensitive details. Finally, for polysubstance-using youth in sample, we cannot rule out that the risk for HCV our models attributed to heroin may have been better attributed to risky behaviors associated with injection of other drugs. However, we sought to explore the independent effects of other drugs in our modeling by controlling for injection of the most common of other substances of abuse.

In summary, we found the risk for HCV acquisition among street youth in this setting was alarmingly high, and that intravenous drug injection remains a primary risk factor. Interestingly, although prescription opioid misuse is on the rise in North America, in our sample, risk of HCV acquisition from injection of prescription opioids did not exceed that of traditional street drugs, including heroin, cocaine and crystal methamphetamine. Nonetheless, prescription opioid injection should be the focus of further study to explore this emerging and poorly understood practice. Given the high prevalence and incidence of HCV seropositivity among street youth, there is an urgent need for evidence-based strategies, including educational programming, addiction treatment and harm reduction services, to prevent disease transmission in this vulnerable population.

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Acknowledgements
The authors thank the study participants for their contribution to the research, as well as current and past researchers and staff. We would specifically like to thank Deborah Graham, Peter Vann, Caitlin Johnston, Steve Kain, and Calvin Lai for their research and administrative assistance. We also appreciate support from Dr. Bob Vinci and the Boston Combined Residency Program, as well as Dr. Jean Emans and the Division of Adolescent / Young Adult Medicine at Boston Children's Hospital. The corresponding author affirms that all who contributed significantly to the work are acknowledged here. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Role of Funding Source
This work was supported by the US National Institutes of Health [grant number R01DA028532]; the Canadian Institutes of Health Research [grant number MOP–102742]; the Canada Research Chairs [Tier 1 Canada Research Chair in Inner City Medicine, E. W.]; Maternal Child Health Bureau of the Health Services Research Administration [Leadership Education in Adolescent Health, grant number T71 MC00009, S. E. H.]; and National Institute of Drug Abuse, United States National Institutes of Health [Avant-Garde award, grant number DP1DA026182, J. S. M.].

Conflict of Interest Statement
J. S. M. has received educational grants from, served as an ad hoc advisor to or spoken at various events sponsored by Abbott Laboratories, Agouron Pharmaceuticals Inc., Boehringer Ingelheim Pharmaceuticals Inc., Borean Pharma AS, Bristol–Myers Squibb, DuPont Pharma, Gilead Sciences, GlaxoSmithKline, Hoffmann–La Roche, Immune Response Corporation, Incyte, Janssen–Ortho Inc., Kucera Pharmaceutical Company, Merck Frosst Laboratories, Pfizer Canada Inc., Sanofi Pasteur, Shire Biochem Inc., Tibotec Pharmaceuticals Ltd. and Trimeris Inc.

Contributors
Drs. Hadland, DeBeck, Kerr and Wood designed the study. Drs. Hadland, DeBeck and Wood wrote the protocol. Dr. Hadland conducted the literature review and wrote the first draft of the manuscript. Dr. Feng undertook statistical analyses with additional input from Dr. Hadland. All authors contributed to and have approved the final manuscript.

Data Sharing Statement

Statistical code and data maintained by the corresponding author at the British Columbia Centre for Excellence in HIV/AIDS. The Centre provides a permanent home for the data set. Data is available by emailing the Corresponding Author at uhri-ew@cfenet.ubc.ca.

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TABLE 1. Baseline characteristics of 940 street youth, according to hepatitis C virus (HCV) serostatus at study enrollment: At-Risk Youth Study (ARYS), Vancouver, British Columbia, 2005-2011.

Characteristic	Total (%) (*n* = 940)	HCV-Seropositive		Odds Ratio (95% CI)	*p* Value
		Yes (%) (*n* = 100)	No (%) (*n* = 840)		
Sociodemographic factors					
Male gender	654 (69.6)	63 (63.0)	591 (70.4)	0.72 (0.47 – 1.11)	0.131
Mean age (SD)[a]	21.7 (2.7)	23.4 (2.5)	21.5 (2.7)	1.34 (1.23 – 1.47)	< 0.001
Aboriginal ancestry	224 (23.8)	30 (30.0)	194 (23.1)	1.43 (0.90 – 2.25)	0.126
High school education[b]	415 (64.8)	35 (35.0)	380 (45.2)	0.65 (0.42 – 1.00)	0.051
Gay/lesbian/bisexual	151 (16.1)	22 (22.0)	129 (15.4)	0.64 (0.39 – 1.07)	0.087
Recent homelessness[c]	348 (37.0)	54 (54.0)	294 (35.0)	2.18 (1.44 – 3.31)	< 0.001
Recent incarceration[c]	176 (18.7)	26 (26.0)	150 (17.9)	1.62 (1.00 – 2.61)	0.048
Substance use-related behaviors					
Mean years injecting (SD)[d]	4.3 (3.2)	4.0 (3.3)	4.6 (3.2)	0.94 (0.82 – 1.07)	0.350
Non-injection prescription opioid use[c]	90 (9.6)	12 (12.0)	78 (9.3)	1.33 (0.70 – 2.54)	0.383
Prescription opioid injection[c]	64 (6.8)	28 (28.0)	36 (4.3)	8.69 (5.01 – 15.1)	< 0.001
Heroin injection[c]	191 (20.3)	66 (66.0)	125 (14.9)	11.1 (7.04 – 17.5)	< 0.001
Cocaine injection[c]	93 (9.9)	31 (31.0)	62 (7.4)	5.54 (3.43 – 9.26)	< 0.001
Crystal methamphetamine injection[c]	154 (16.4)	50 (50.0)	104 (12.4)	7.08 (4.55 – 11.0)	< 0.001
Syringe sharing[c]	56 (6.0)	18 (18.0)	38 (4.5)	4.63 (2.53 – 8.48)	< 0.001
Sexual risk behaviors					
Inconsistent condom use[c]	433 (46.1)	40 (40.0)	393 (46.8)	0.76 (0.50 – 1.16)	0.198
Sex work[c]	65 (6.9)	14 (14.0)	51 (6.1)	2.52 (1.34 – 4.74)	0.003

a. Odds ratio calculated per year older

b. Prior completion of or current enrollment in high school

c. During the six months preceding study enrollment

d. Includes only actively injecting youth

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TABLE 2. Unadjusted and adjusted Cox proportional hazard analysis of time to hepatitis C infection among 512 drug-using youth: At-Risk Youth Study (ARYS), Vancouver, British Columbia, 2005-2011.

		Adjusted HR (95% CI)		
Characteristic	**Unadjusted HR (95% CI)**	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**
Male gender	0.48 (0.28 – 0.81)	0.50 (0.28 – 0.90)	0.42 (0.24 – 0.75)	0.50 (0.28 – 0.90)
Age (per year older)	0.96 (0.87 – 1.06)	1.10 (0.91 – 1.10)	1.00 (0.91 – 1.11)	1.00 (0.91 – 1.10)
Prescription opioid injection	3.48 (1.57 – 7.70)	–	2.02 (0.89 – 4.61)	0.94 (0.40 – 2.21)
Heroin injection	9.89 (5.72 – 17.1)	4.49 (2.42 – 8.33)	–	4.56 (2.39 – 8.70)
Cocaine injection	5.69 (3.18 – 10.2)	1.87 (1.00 – 3.47)	2.20 (1.14 – 4.23)	1.88 (1.00 – 3.54)
Crystal methamphetamine injection	7.39 (4.36 – 12.5)	2.94 (1.62 – 5.34)	5.11 (2.79 – 9.34)	2.91 (1.57 – 5.38)
Syringe sharing	7.69 (3.93 – 15.0)	2.47 (1.20 – 5.09)	2.57 (1.24 – 5.32)	2.47 (1.20 – 5.10)

a. Model 1 includes all covariates listed except prescription opioid injection

b. Model 2 includes all covariates listed except heroin injection

c. Model 3 includes all covariates listed

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FIGURE LEGENDS

FIGURE 1a. Cumulative incidence of hepatitis C infection among 512 drug-using youth, by injection heroin use: At-Risk Youth Study (ARYS), Vancouver, Canada, 2005-2010.

FIGURE 1b. Cumulative incidence of hepatitis C infection among drug-injecting youth by heroin use: At-Risk Youth Study (ARYS), Vancouver, Canada, 2005-2010.

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PRESCRIPTION OPIOID INJECTION AND RISK OF HEPATITIS C IN RELATION TO TRADITIONAL DRUGS OF ABUSE IN A PROSPECTIVE COHORT OF STREET YOUTH

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Abstract Word Count: 296
Word Count (excluding abstract): 2,997
Figures: 2
Tables: 2
Submitted: Monday, April 7, 2014
Resubmitted: Monday, June 16, 2014
Running Head: Hepatitis C and prescription opioid use
MeSH Terms: hepatitis C; analgesics, opioid; heroin; drug abuse; adolescent

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ABSTRACT

Objective: Despite dramatic increases in misuse of prescription opioids, the extent to which their intravenous injection places drug users at risk of acquiring hepatitis C virus (HCV) remains unclear. We sought to compare risk of HCV acquisition from injection of prescription opioids to that from other street drugs among high-risk street youth.

Design: Prospective cohort study.

Setting: Vancouver, British Columbia, Canada, from September 2005 to November 2011.

Participants: The At-Risk Youth Study (ARYS) is a prospective cohort of actively drug-using adolescents and young adults aged 14-26 years. Participants were recruited through extensive street-based outreach and snowball sampling.

Primary Outcome Measure: HCV antibody seroconversion, measured every 6 months during study follow-up. Risk for seroconversion from injection of prescription opioids was compared to injection of other street drugs of abuse, including heroin, cocaine or crystal methamphetamine, using Cox proportional hazards regression controlling for age, gender and active syringe sharing.

Results: Baseline HCV seropositivity was 10.6%. Among 512 HCV-seronegative youth contributing 860.2 person-years of total follow-up, 56 (10.9%) seroconverted, resulting in an incidence density of 6.5 per 100 person-years. In bivariate analyses, prescription opioid injection (hazard ratio [HR], 3.48; 95% CI, 1.57-7.70) predicted HCV seroconversion. However, in multivariate modeling, only injection of heroin (adjusted HR, 4.56; 95% CI, 2.39-8.70),

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cocaine (adjusted HR, 1.88; 95% CI, 1.00-3.54), and crystal methamphetamine (adjusted HR, 2.91; 95% CI, 1.57-5.38) remained independently associated with HCV seroconversion, whereas injection of prescription opioids did not (adjusted HR, 0.94; 95% CI, 0.40-2.21).

Conclusions: Although misuse of prescription opioids is on the rise, traditional street drugs still appeared to pose the greatest threat of HCV transmission in this setting. Nonetheless, the high prevalence and incidence of HCV seropositivity among Canadian street youth underscores the need for evidence-based drug prevention, treatment, and harm reduction interventions targeting this vulnerable population.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength of this prospective cohort study is that it followed street youth, a marginalized and difficult-to-reach population with a high prevalence of injection drug use and blood-borne infection, including human immunodeficiency virus (HIV) and hepatitis C virus (HCV)

- An additional strength is that it is among the first studies to examine the association between injection of prescription opioids (including, for example, oxycodone and morphine) and acquisition of HCV; it is not well understood how the risk for acquiring HCV from injecting prescription opioids compares to that from injection of more traditionally studied street drugs, such as heroin, cocaine and crystal methamphetamine

- The study's findings demonstrate elevated risk for HCV seroconversion in relation to heroin, cocaine and crystal methamphetamine injection, but not prescription opioid injection after adjustment for covariates; however, the relatively small number of youth injecting prescription opioids may have limited detection of marginal risk differences

- Since youth in the study were recruited by snowball sampling, results are not obtained from a truly random sample, but characteristics of the cohort are comparable to those from studies of street youth conducted elsewhere

- This study demonstrates novel findings that should prompt further study of risk for blood-borne infection among drug-injecting youth populations

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INTRODUCTION

Hepatitis C virus (HCV) infection is a leading cause of morbidity and mortality worldwide.[1-3] While the incidence of HCV may be decreasing in some age groups, infection rates appear to be increasing among adolescents and young adults.[4] Street youth – that is, youth who spend all or part of their time working or living on the street[5,6] – represent a marginalized and stigmatized population at elevated risk for HCV acquisition owing to a high prevalence of injection drug use.[3,7,8]

The emergence of elevated rates of HCV among street youth coincides with important changes in patterns of youth substance use. In recent years, misuse of prescription opioids such as morphine, oxycodone and hydrocodone has emerged as a public health emergency.[9] Although injection of illicit drugs is known to place users at high risk of blood-borne infection,[10,11] the abundance of studies to date have focused on traditional street drugs, such as heroin and cocaine, rather than prescription opioids.[12]

This constitutes a serious gap in our understanding of HCV epidemiology given that, in many jurisdictions, overdose mortality attributed to prescription opioid use has surpassed that attributed to the use of heroin and cocaine combined.[13] The prevalence of non-medical prescription opioid use is increasing in the general adolescent population,[14] with approximately 8-10% of high school students in the United States reporting past-year use.[15] Many prescription opioid formulations are readily injected,[16,17] but despite their widespread availability, there is a paucity of epidemiologic data examining this practice or its risk for disease transmission.[18]

At this time, it remains unclear whether heroin injectors and prescription opioid injectors represent overlapping or distinct subpopulations of injection drug users.[19] There is evidence that some users follow a trajectory from initially using prescription opioids to ultimately using heroin, since in some settings, heroin is less expensive and more potent and available.[16] On

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the other hand, there may be a sizeable subgroup of users who inject prescription opioids to the exclusion of heroin and other drugs.[20] Regardless, there is reason to believe that certain injection practices associated with heroin as compared with prescription opioids may place users at differential risk for infectious disease transmission.[17,20]

Understanding how injection of prescription opioids may place users at risk for acquiring HCV is imperative, given that injection drug users represent the population at greatest risk for HCV infection in North America,[21,22] and that mortality from HCV has increased to the extent that it recently surpassed that from human immunodeficiency virus (HIV) in the United States.[2] We conducted the present study of HCV acquisition in Vancouver, Canada, among a prospective cohort of street youth, a population including a high proportion of Aboriginal youth who may be at elevated risk for blood-borne infection.[23] Our study objective was to examine the contribution of injection of prescription opioids and that of traditional street drugs of abuse to the risk for HCV seroconversion.

METHODS

The At-Risk Youth Study (ARYS) is a cohort of street-involved youth in Vancouver, Canada.[24] Inclusion criteria for enrollment included age 14 to 26 years and use of an illicit drug other than marijuana during the month prior to enrollment. Recruitment relied on extensive daytime and nighttime street-based outreach and snowball sampling, and was systematically conducted in parks, streets and alleyways of Vancouver where street youth are known to congregate. Although no inclusion criterion explicitly required a minimum amount of time on the street to qualify for the study, in practice, the street-based recruitment resulted in a sample of youth who spent substantial time on the street, a large proportion of whom were homeless.[25] Full study details were disclosed to participants and informed consent was obtained. At

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baseline and every six months thereafter, participants completed an interview and underwent HCV antibody testing. Participants were remunerated $20 CAN per visit. Additionally, a $5 CAN incentive was provided to youth three months after their baseline interview to return to the study site to update their contact information in an attempt to improve study follow-up. ARYS was approved by the University of British Columbia/Providence Health Care Research Ethics Board.

We compared HCV prevalence at recruitment and subsequent HCV incidence among youth according to recent (*i.e.,* during the preceding six months) injection of prescription opioid and recent injection of heroin, cocaine and crystal methamphetamine. Prescription opioids were broadly defined to include morphine, oxycodone, hydromorphone, meperidine, fentanyl or methadone. The exact question used was, "In the last 6 months, when you were using, which of the following drugs did you inject and how often?", with possible answers including, "Less than once per month / One to three times per month / About once per week / Two or three times per week / At least daily". Using this question, each of the prescription opioids listed above was individually and sequentially probed. We also examined patterns of non-injection use of prescription opioids in the sample. All ARYS participants were included in the baseline HCV prevalence analyses. Participants who were HCV antibody negative at baseline and returned for ≥1 follow-up visit were included in the incidence analyses.

We also examined an additional array of covariates including: gender, age (as a continuous variable), Aboriginal ancestry, high school education (having completed or currently enrolled in high school), self-reported gay/lesbian/bisexual orientation, recent homelessness, recent incarceration, recent sharing of injection syringes, recent inconsistent condom use (vaginal or anal penetrative sex without condom use 100% of the time), and recent sex work (having traded sex for money, drugs, shelter or gifts). In the baseline prevalence analysis, all participants were compared according to HCV serostatus through chi-square (for categorical

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variables) and Wilcoxin rank sum tests (for continuous variables). Similar statistics were also calculated to compare drug-related behaviors between Aboriginal and non-Aboriginal youth.[23]

We then conducted the incidence analysis with the outcome of time to HCV seroconversion, limiting the sample to those who were HCV antibody negative at baseline and returned for ≥1 follow-up visit. Youth with prior history of injection were first compared in univariate analyses.[26] We subsequently used Kaplan-Meier methods to plot the cumulative incidence of HCV seroconversion as a function of time. All follow-up data were included, even if a participant had missed an intervening follow-up appointment.

We also used Cox proportional hazards regression to determine unadjusted and adjusted hazard ratios (HR) for HCV seroconversion for the range of drug use-related variables and other covariates listed above. An interaction term between heroin and prescription opioid injection was also tested. Time of seroconversion was estimated as the midpoint of the date of last known seronegativity and of that of first seropositivity.[27-29] Independent variables were time-updated in regression models if they referred to non-fixed characteristics or behaviors in the preceding six months. In the event of differential follow-up duration among participants recruited earlier in the study period compared to later in the study period, we examined the prevalence of prescription opioid injection and heroin in the first two years of study and that of the last two years of study to determine whether these behaviors were becoming more common with time.[14] We also examined prevalence of cocaine and crystal methamphetamine over the course of the study.

We sought to directly compare the risk for HCV seroconversion from injection of heroin and other traditional drugs of abuse to that of injection of prescription opioids,[17,20] and created three multivariable models to do so. The first model included recent heroin injection but not recent prescription opioid injection; the second, recent prescription opioid injection but not

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recent heroin injection; and the third, both recent heroin injection and recent prescription opioid injection. To adjust for potential confounders, age and gender were included in multivariable models as well as covariates significant at $p<0.05$ in the initial bivariate Cox regression analyses of time to HCV seroconversion. Finally, as a sub-analysis, we restricted the sample to drug-injecting youth and examined bivariate associations between injection of prescription opioids, heroin, cocaine and crystal methamphetamine, and HCV seroconversion. We also repeated the third multivariate model using this subsample.

Analyses were conducted with SAS version 9.1 (SAS Institute, Inc, Cary, North Carolina). All *p* values were two-sided and tests were considered significant at $p<0.05$. Adjustments were not made for multiple comparisons given that this was a single-outcome, observational study.

RESULTS

From September 2005 to November 2011, 940 youth were recruited into the ARYS cohort and completed baseline HCV antibody testing. One-hundred youth (10.6%) were HCV-seropositive at study enrollment. **Table 1** shows baseline characteristics and recent (*i.e.,* in the six months preceding study enrollment) drug-related and sexual risk behaviors according to HCV serostatus. The cohort spent a median of 12 hours on the street per day (IQR: 6–24 h). Aboriginal youth comprised 224 (23.8%) of the sample. Aboriginal and non-Aboriginal youth did not differ with regard to recent non-injection prescription opioid use, recent injection of prescription opioids, heroin, cocaine, or crystal methamphetamine, or recent syringe sharing ($p>0.05$ for all). As shown, baseline HCV seropositivity was associated with older age, recent homelessness, recent incarceration, recent injection of prescription opioids, heroin, cocaine, and crystal methamphetamine, recent syringe sharing, and recent sex work. Recent injection

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of prescription opioids and of heroin were correlated (p<0.05).

Of the 840 youth who were HCV antibody negative at baseline, 512 (60.9%) had at least one follow-up visit and provided blood samples for HCV antibody testing. Among these 512 youth, 151 (29.5%) were female and 135 (67.2%) identified as Aboriginal. The mean age was 21.7 (standard deviation, 2.6) years. Compared with the 328 (29.1%) participants who were HCV antibody negative at baseline and did not provide follow-up data, the 512 participants included in subsequent incidence analyses tended to be older (p<0.05), but did not differ at baseline in terms of gender, Aboriginal ancestry, recent incarceration, recent sex work, recent injection of prescription opioids, heroin, cocaine or crystal methamphetamine, or recent syringe sharing.

At study enrollment, 166 (32.4%) of the 512 youth included in the incidence analysis reported prior drug injection. Compared to those who had not previously injected, those who had injected were more likely to be older (p<0.05), but otherwise did not differ by gender, Aboriginal ancestry, recent incarceration, or recent sex work. Of the 166 youth who had previously injected, 56 (33.7%) reported recently having injected two or more drugs among prescription opioids, heroin, cocaine and crystal methamphetamine, and 11 (6.6%) reported having injected three or more of these drugs.

During the follow-up period (median follow-up, 18.5 months; median number of follow-up visits after baseline visit, 2 visits; total follow-up, 860.2 person-years), there were 56 (10.9%) HCV seroconversions, resulting in an incidence density of 6.5 per 100 person-years. As might be expected, median follow-up was longer in the earlier years of study enrollment (22.0 months in the first two years of enrollment *vs*. 17.0 months in the final two years; p<0.001). The median number of missed visits during follow-up was 1 visit. Individuals lost to follow up were censored at the time of their last visit.

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Over the study period, the prevalence of prescription opioid injection remained relatively unchanged (4.2% of the entire sample in the first two years of enrollment *vs.* 4.4% in the last two years) as did that of heroin injection (13.5% *vs.* 11.8%). Similarly, there was very little change in the prevalence of cocaine injection (12.2% of the entire sample in the first two years of enrollment *vs.* 10.0% in the last two years) and crystal methamphetamine injection (18.0% *vs.* 16.8%). At baseline, recent heroin injectors and recent prescription opioid injectors did not differ in terms of age (mean, 21.8 *vs.* 22.3 years, respectively; p=0.524), gender (65.5% *vs.* 72.2% male; p=0.202), ethnicity (20.7% Aboriginal *vs.* 16.7% other; p=0.256), age of initiation of injection drug use (mean, 17.7 *vs.* 18.7 years; p=0.271) or in total number of years of injecting (mean, 4.1 *vs.* 3.6 years; p=0.567).

Figure 1a shows the Kaplan-Meier cumulative incidence of HCV seroconversion according to heroin injection in the entire sample and **Figure 1b** shows the cumulative incidence according to heroin injection with the sample restricted to drug-injecting youth only. In both cases, heroin injectors had a markedly elevated risk of HCV seroconversion in comparison to others in the sample, including prescription opioid injectors (full data available from the corresponding author). Crude incidence density of HCV seroconversion among heroin-injecting youth was 20.8 per 100 person-years and among prescription opioid-injecting youth was 21.4 per 100 person-years. Mean number of visits prior to seroconversion did not differ between heroin and prescription opioid injectors (p>0.05).

Table 2 displays the results of the unadjusted and adjusted Cox proportional hazard regression analyses of the time to detected HCV seroconversion according to demographic characteristics and risk behaviors. As shown, HCV seroconversion was significantly associated with female gender, prescription opioid injection, heroin injection, cocaine injection, crystal methamphetamine injection, and syringe sharing in unadjusted analyses. Age was not associated with HCV seroconversion. Additional variables not listed in the table that were not

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significantly associated with HCV seroconversion included Aboriginal ancestry (unadjusted hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.49-1.59; *p*=0.662), recent incarceration (HR, 1.25; 95% CI, 0.67-2.32; *p*=0.482), recent inconsistent condom use (unadjusted HR, 0.90; 95% CI, 0.52-1.55; *p*=0.703), and recent sex work (unadjusted HR, 0.91; 95% CI, 0.28-2.90; *p*=0.869). Additionally, the interaction term between heroin and prescription opioid injection was not significant. [xxx]

The three multivariable models examining the relative effects of prescription opioid injection and heroin injection all were adjusted for gender and age, as well for variables significant at *p*<0.05 in unadjusted Cox regression analyses (cocaine injection, crystal methamphetamine injection, and syringe sharing). In the model including all covariates except prescription opioid injection, heroin injection remained significantly associated with HCV seroconversion (Model 1), whereas prescription opioid injection did not retain significance in the model including all covariates except heroin (Model 2). When both heroin injection and prescription opioid injection were included a combined model, heroin injection, but not prescription opioid injection, retained statistical significance (Model 3).

When the sample was restricted to only drug-injecting youth (*n*=166), prescription opioid injection was not associated with HCV seroconversion in bivariate analyses (unadjusted HR, 1.27; 95% CI, 0.57-2.84; *p*=0.555). Heroin injection was associated with HCV seroconversion in this subsample (unadjusted HR, 2.93; 95% CI, 1.77-6.13; *p*<0.001), as was cocaine injection (unadjusted HR, 2.02; 95% CI, 1.11-3.68; *p*=0.021), but not crystal methamphetamine injection (unadjusted HR, 4.52; 95% CI, 0.61-33.3; *p*=0.136). Syringe sharing was also associated with HCV seroconversion (unadjusted HR, 2.93; 95% CI, 1.48-5.79; *p*=0.002). When Model 3 was rerun using this subsample, variables remaining significantly associated with HCV seroconversion included heroin injection (adjusted HR, 2.79; 95% CI, 1.46-5.34; *p*=0.002) and syringe sharing (adjusted HR 2.47; 95% CI, 1.22-4.98; *p*=0.012), but not prescription opioid

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injection (adjusted HR, 0.60; 95% CI, 0.25-1.47; *p*=0.268), cocaine injection (adjusted HR, 1.83; 95% CI, 0.98-3.40; *p*=0.057), or crystal methamphetamine injection (adjusted HR, 4.13; 95% CI, 0.47-36.0; *p*=0.199).

DISCUSSION

In this longitudinal study, we observed a high prevalence of HCV seropositivity among adolescents and young adults on the street, with more than one in ten youth infected with HCV at baseline, as well as high incidence HCV acquisition during follow-up. We observed that injection of heroin, cocaine and crystal methamphetamine were all strongly associated with risk HCV seroconversion following adjustment for potential confounders. Injection of prescription opioids, by contrast, was not independently associated with HCV seroconversion in adjusted models, although it was associated with HCV seropositivity at baseline and with HCV seroconversion in unadjusted analyses. Taken together, these findings highlight street youth as a population that should remain a critical focus for evidence-based drug preventive and treatment services to prevent a worsening HCV epidemic.

Although misuse of prescription opioids is on the rise in North America,[15] and although they are readily injected,[16,17] we did not observe excess risk for HCV seroconversion from injection of prescription opioids among Vancouver street youth after controlling for other factors. There are several plausible explanations for the null finding in this setting. First, we acknowledge that despite a large sample of drug-using youth, the proportion of participants in the cohort who engaged in prescription opioid injection was relatively small and may have somewhat limited detection of marginal risk differences. Prescription opioid injection was significantly associated with HCV seroconversion in univariate incidence analyses, suggesting increased risk from this behavior. However, in the setting of polysubstance use, which was

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common in this setting, the contribution of prescription opioid injection to risk for HCV seroconversion appears to be relatively less important than that of traditional drugs of abuse including heroin, cocaine and crystal methamphetamine. Indeed, because injection of prescription opioids and of heroin were correlated in our sample, our results are consistent with other reports that many heroin injectors also inject prescription opioids when they cannot easily locate heroin or cannot afford it.[17] We recommend that future studies actively recruit prescription opioid-injecting youth in order to improve estimates of risk for HCV.

Second, as has been described elsewhere, populations of drug users often show great heterogeneity, with subpopulations exhibiting widely varying risk for blood-borne disease.[19] In Vancouver, youth who inject prescription opioids, regardless of whether they also inject other drugs, may represent a distinct subpopulation from other higher risk youth who inject heroin, cocaine or crystal methamphetamine but not prescription opioids, as has been observed in other settings.[20] It is possible prescription opioid-injecting youth may not be as entrenched in the local drug scene,[30] and as a result, may not associate as frequently with HCV-seropositive drug users. Similarly, youth who inject prescription opioids may have received different preventive messaging regarding safe injection practices, or have better access to harm reduction services. Better understanding the risk environment for prescription opioid users will prove important for preventing transmission of HCV in this high-risk population.

Although prescription opioid injection was not independently associated with risk for HCV seroconversion, more traditional risk factors, including injection of heroin, cocaine, and crystal methamphetamine were strongly and independently associated with HCV acquisition in this setting. These findings are consistent with those from previous youth studies.[8,31-33] It is well established that HCV is spread when drug users share injection paraphernalia.[34,35] Interestingly, although syringe sharing was associated with HCV seroconversion in the ARYS sample, it did not fully explain the risk for HCV associated with injection of heroin, cocaine and

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crystal methamphetamine in final multivariable models. A possible explanation may be that youth underreported syringe sharing, which might be perceived as a stigmatized behavior. The result of such socially desirable reporting could be the incomplete effect sizes observed in our statistical models.[36,37] Regardless, attempts to prevent the spread of HCV among at-risk youth will require careful attention to factors that interfere with safe injection practices, including peer dynamics and chaotic injection environments.[38,39]

The excess risk for HCV among street youth necessitates evidence-based strategies to prevent drug use and mitigate injection-related harm. Although maintenance therapy with methadone or buprenorphine is efficacious among adolescents and young adults,[40,41] challenges remain in making these services accessible to street youth, who are a marginalized and difficult-to-reach population.[42,43] Other effective harm reduction services such as needle exchange and supervised safe injection facilities are often developed for adult drug users and may not effectively target younger drug users.[3] Barriers to preventive and treatment modalities for young drug users are well documented, and include excessively long waiting lists, difficulty complying with program rules, program fees that exceed young people's ability to pay, and locations that are inconvenient for youth.[42] Existing drug treatment and harm reduction services should be extended in a way that is sensitive to the unique circumstances of youth.

There are limitations to this study. First, as outlined above, we acknowledge a relatively small proportion of the sample who injected prescription opioids, which may have affected the precision of our estimates. Second, we employed snowball sampling in order to recruit heavily drug-involved youth, who are frequently homeless and represent a population 'hidden' from traditional population-based sampling. Although snowball sampling does not produce a truly random sample,[24] it is noteworthy that the characteristics of the ARYS cohort are similar to those of other at-risk youth in western Canada.[44,45] A final point regarding representativeness is the refusal rate among youth who are approached for enrolment into the study. Unfortunately,

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as youth often self-refer and street-based outreach often requires a very low threshold approach commonly involving repeated contact, rates of refusal can only be estimated. Study staff estimate that 30% of youth first approached for participation ultimately agree to be assessed for eligibility. Third, our study relied on self-report, which, as outlined above, may have resulted in social desirability bias for questions probing sensitive details. Finally, for polysubstance-using youth in sample, we cannot rule out that the risk for HCV our models attributed to heroin may have been better attributed to risky behaviors associated with injection of other drugs. However, we sought to explore the independent effects of other drugs in our modeling by controlling for injection of the most common of other substances of abuse.

In summary, we found the risk for HCV acquisition among street youth in this setting was alarmingly high, and that intravenous drug injection remains a primary risk factor. Interestingly, although prescription opioid misuse is on the rise in North America, in our sample, risk of HCV acquisition from injection of prescription opioids did not exceed that of traditional street drugs, including heroin, cocaine and crystal methamphetamine. Nonetheless, prescription opioid injection should be the focus of further study to explore this emerging and poorly understood practice. Given the high prevalence and incidence of HCV seropositivity among street youth, there is an urgent need for evidence-based strategies, including educational programming, addiction treatment and harm reduction services, to prevent disease transmission in this vulnerable population.

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Role of Funding Source
This work was supported by the US National Institutes of Health [grant number R01DA028532]; the Canadian Institutes of Health Research [grant number MOP–102742]; the Canada Research Chairs [Tier 1 Canada Research Chair in Inner City Medicine, E. W.]; Maternal Child Health Bureau of the Health Services Research Administration [Leadership Education in Adolescent Health, grant number T71 MC00009, S. E. H.]; and National Institute of Drug Abuse, United States National Institutes of Health [Avant-Garde award, grant number DP1DA026182, J. S. M.].

Conflict of Interest Statement
J. S. M. has received educational grants from, served as an ad hoc advisor to or spoken at various events sponsored by Abbott Laboratories, Agouron Pharmaceuticals Inc., Boehringer Ingelheim Pharmaceuticals Inc., Borean Pharma AS, Bristol–Myers Squibb, DuPont Pharma, Gilead Sciences, GlaxoSmithKline, Hoffmann–La Roche, Immune Response Corporation, Incyte, Janssen–Ortho Inc., Kucera Pharmaceutical Company, Merck Frosst Laboratories, Pfizer Canada Inc., Sanofi Pasteur, Shire Biochem Inc., Tibotec Pharmaceuticals Ltd. and Trimeris Inc.

Acknowledgements
The authors thank the study participants for their contribution to the research, as well as current and past researchers and staff. We would specifically like to thank Deborah Graham, Peter Vann, Caitlin Johnston, Steve Kain, and Calvin Lai for their research and administrative assistance. We also appreciate support from Dr. Bob Vinci and the Boston Combined Residency Program, as well as Dr. Jean Emans and the Division of Adolescent / Young Adult Medicine at Boston Children's Hospital. The corresponding author affirms that all who contributed significantly to the work are acknowledged here. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Contributors
Drs. Hadland, DeBeck, Kerr and Wood designed the study. Drs. Hadland, DeBeck and Wood wrote the protocol. Dr. Hadland conducted the literature review and wrote the first draft of the manuscript. Dr. Feng undertook statistical analyses with additional input from Dr. Hadland. All authors contributed to and have approved the final manuscript.

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TABLE 1. Baseline characteristics of 940 street youth, according to hepatitis C virus (HCV) serostatus at study enrollment: At-Risk Youth Study (ARYS), Vancouver, British Columbia, 2005-2011.

Characteristic	Total (%) (*n* = 940)	HCV-Seropositive		Odds Ratio (95% CI)	*p* Value
		Yes (%) (*n* = 100)	No (%) (*n* = 840)		
Sociodemographic factors					
Male gender	654 (69.6)	63 (63.0)	591 (70.4)	0.72 (0.47 – 1.11)	0.131
Mean age (SD)[a]	21.7 (2.7)	23.4 (2.5)	21.5 (2.7)	1.34 (1.23 – 1.47)	< 0.001
Aboriginal ancestry	224 (23.8)	30 (30.0)	194 (23.1)	1.43 (0.90 – 2.25)	0.126
High school education[b]	415 (64.8)	35 (35.0)	380 (45.2)	0.65 (0.42 – 1.00)	0.051
Gay/lesbian/bisexual	151 (16.1)	22 (22.0)	129 (15.4)	0.64 (0.39 – 1.07)	0.087
Recent homelessness[c]	348 (37.0)	54 (54.0)	294 (35.0)	2.18 (1.44 – 3.31)	< 0.001
Recent incarceration[c]	176 (18.7)	26 (26.0)	150 (17.9)	1.62 (1.00 – 2.61)	0.048
Substance use-related behaviors					
Mean years injecting (SD)[d]	4.3 (3.2)	4.0 (3.3)	4.6 (3.2)	0.94 (0.82 – 1.07)	0.350
Non-injection prescription opioid use[c]	90 (9.6)	12 (12.0)	78 (9.3)	1.33 (0.70 – 2.54)	0.383
Prescription opioid injection[c]	64 (6.8)	28 (28.0)	36 (4.3)	8.69 (5.01 – 15.1)	< 0.001
Heroin injection[c]	191 (20.3)	66 (66.0)	125 (14.9)	11.1 (7.04 – 17.5)	< 0.001
Cocaine injection[c]	93 (9.9)	31 (31.0)	62 (7.4)	5.54 (3.43 – 9.26)	< 0.001
Crystal methamphetamine injection[c]	154 (16.4)	50 (50.0)	104 (12.4)	7.08 (4.55 – 11.0)	< 0.001
Syringe sharing[c]	56 (6.0)	18 (18.0)	38 (4.5)	4.63 (2.53 – 8.48)	< 0.001
Sexual risk behaviors					
Inconsistent condom use[c]	433 (46.1)	40 (40.0)	393 (46.8)	0.76 (0.50 – 1.16)	0.198
Sex work[c]	65 (6.9)	14 (14.0)	51 (6.1)	2.52 (1.34 – 4.74)	0.003

a. Odds ratio calculated per year older

b. Prior completion of or current enrollment in high school

c. During the six months preceding study enrollment

d. Includes only actively injecting youth

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TABLE 2. Unadjusted and adjusted Cox proportional hazard analysis of time to hepatitis C infection among 512 drug-using youth: At-Risk Youth Study (ARYS), Vancouver, British Columbia, 2005-2011.

		Adjusted HR (95% CI)		
Characteristic	**Unadjusted HR (95% CI)**	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**
Male gender	0.48 (0.28 – 0.81)	0.50 (0.28 – 0.90)	0.42 (0.24 – 0.75)	0.50 (0.28 – 0.90)
Age (per year older)	0.96 (0.87 – 1.06)	1.10 (0.91 – 1.10)	1.00 (0.91 – 1.11)	1.00 (0.91 – 1.10)
Prescription opioid injection	3.48 (1.57 – 7.70)	–	2.02 (0.89 – 4.61)	0.94 (0.40 – 2.21)
Heroin injection	9.89 (5.72 – 17.1)	4.49 (2.42 – 8.33)	–	4.56 (2.39 – 8.70)
Cocaine injection	5.69 (3.18 – 10.2)	1.87 (1.00 – 3.47)	2.20 (1.14 – 4.23)	1.88 (1.00 – 3.54)
Crystal methamphetamine injection	7.39 (4.36 – 12.5)	2.94 (1.62 – 5.34)	5.11 (2.79 – 9.34)	2.91 (1.57 – 5.38)
Syringe sharing	7.69 (3.93 – 15.0)	2.47 (1.20 – 5.09)	2.57 (1.24 – 5.32)	2.47 (1.20 – 5.10)

a. Model 1 includes all covariates listed except prescription opioid injection

b. Model 2 includes all covariates listed except heroin injection

c. Model 3 includes all covariates listed

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FIGURE 1a. Cumulative incidence of hepatitis C infection among 512 drug-using youth, by injection heroin use: At-Risk Youth Study (ARYS), Vancouver, Canada, 2005-2010.

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FIGURE 1b. Cumulative incidence of hepatitis C infection among drug-injecting youth by heroin use: At-Risk Youth Study (ARYS), Vancouver, Canada, 2005-2010.

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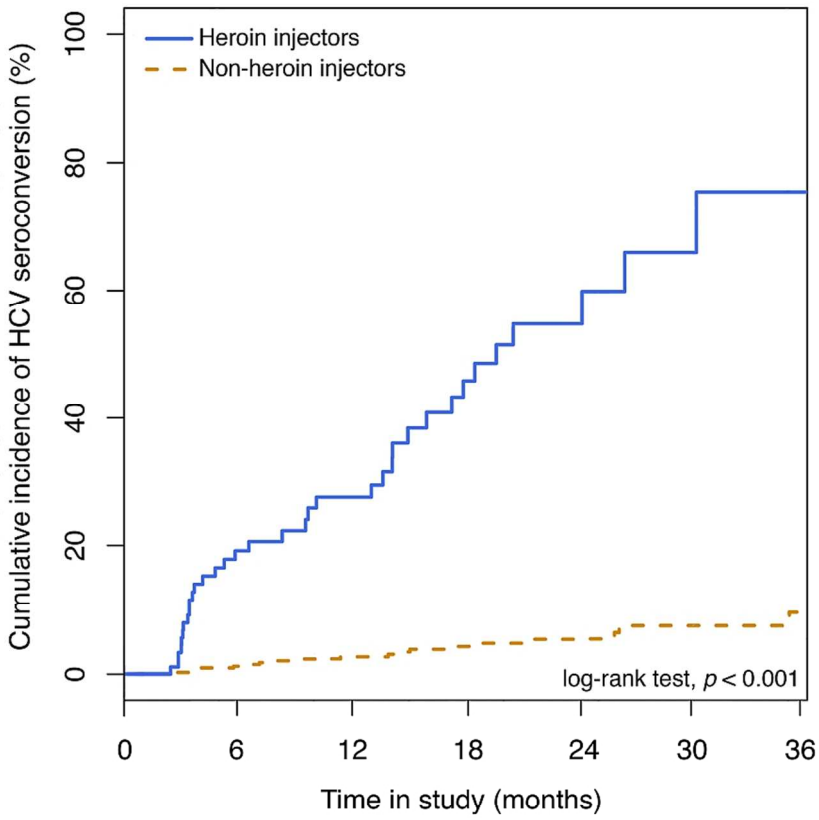

Figure 1a
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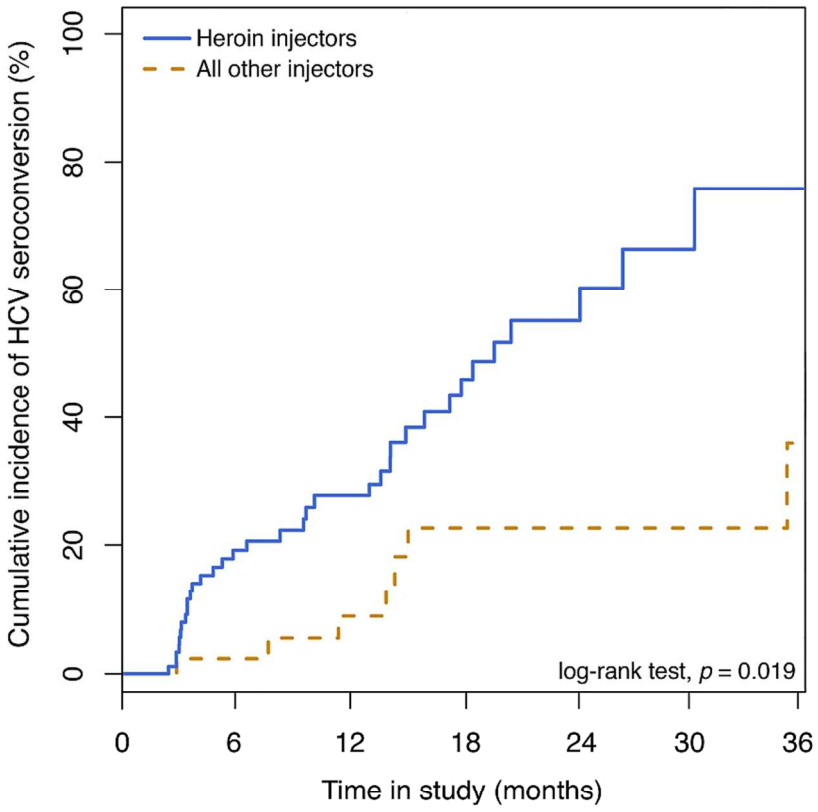

Figure 1b
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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1 **x**	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 **x**	Explain the scientific background and rationale for the investigation being reported
Objectives	3 **x**	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 **x**	Present key elements of study design early in the paper
Setting	5 **x**	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 **x**	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7 **x**	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* **x**	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
Bias	9 **x**	Describe any efforts to address potential sources of bias
Study size	10 **x**	Explain how the study size was arrived at
Quantitative variables	11 **x**	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 **x**	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

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Results		
Participants	13* x	(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
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* x	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* x	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 x	(*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
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 x	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 x	Summarise key results with reference to study objectives
Limitations	19 x	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 x	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 x	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 x	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

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

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