The rising prevalence of prescription opioid injection and its association with hepatitis C incidence among street-drug users.

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ABSTRACT

Aims: The study objectives were to examine trends in prescription opioid (PO) injection and to assess its association with HCV seroconversion among injection drug users (IDUs), accounting for other risk factors.

Design and Setting: A prospective cohort study of IDUs was carried out between 2004 and 2009 in Montreal, Canada.

Participants and Measurements: 246 HCV-negative IDUs were included in this analysis. Semi-annual visits included HCV antibody testing and an interview-administered questionnaire assessing risk behaviours. HCV incidence rate was calculated using the person-time method. Time-updated Cox regression models were conducted to examine predictors of HCV incidence.

Findings: The proportion of IDUs reporting PO injection increased from 21% to 75% between 2004 and 2009 ($p < 0.001$). Of the 246 participants (81.6% male; mean age 34.5 years; mean follow-up time 23 months), 83 seroconverted to HCV (incidence rate: 17.9 per 100 person-years; 95% CI 14.3, 22.1). PO injectors were more likely to become infected if they did not use injection heroin (Adjusted Hazard Ratio (AHR): 2.9 (95% CI: 1.5, 5.5)), whereas the association was not statistically significant for participants who reported using both drugs (AHR: 1.2 (95%CI: 0.6, 2.3). Other independent predictors of HCV incidence were: cocaine injection, recent incarceration, and > 30 injections per month.

Conclusion: PO injection has increased rapidly in recent years, and appears to be an important risk factor for HCV acquisition. Our results suggest that the risks related to PO injection may be conditioned by specific drug practices which differ from those of heroin users.

INTRODUCTION

For nearly 20 years, consumption of opioid analgesics has increased in several parts of the world, with highest frequencies being reported in North-America, Europe and Oceania (1). The growing availability of these analgesics has been accompanied by an increase in prescription opioid (PO) misuse. Not surprisingly, the percentage of patients admitted to detoxification units for abuse of opioids other than heroin in the United States has quintupled from 1% in 1997 to 5% in 2007 (2). In Ontario, Canada, the proportion of new admissions for substance abuse related PO injection increased from 10.6% in 2004-2005 to 17.4% in 2009-2010 (3) .

This upward trend was also observed among North-American street-based drug users. In New York, the prevalence of PO recreational use was observed among 32% of 586 street-based users (4). In Miami, Florida, 12% of 588 drug-involved, street-based sex workers surveyed reported having used PO without a legitimate prescription (5). To our knowledge, only two Canadian studies have examined PO misuse among street-based drug users. A study conducted among regular opiate users between 2001 and 2005 revealed that in five out of seven cities in the country, POs, not heroin, was the major form of illicit opioid drug in use (6). In Montreal, a recent study showed that 40.6% of street-based regular cocaine users were using illicit POs (7).

Studies conducted in diverse settings have also examined the use of POs by injection. In Australia, 46% of injection drug users (IDUs) reported having used morphine in the previous six months, with significant variations across states and up to a prevalence of 85% in the northern territories (8). In a study conducted in rural Kentucky among non-medical PO users, 35.3% reported having injected POs in their lifetime (9). In Quebec, Canada, the prevalence of PO

injection, specifically hydromorphone tablets, increased from 27.4% to 41.8% among street-drug users recruited between 2003 and 2007 through SurvIDU (a provincial epidemiologic surveillance network targeting active injectors recruited mainly through syringe access programs) (10).

The recent increase in the use of illicit POs and the growing evidence of intravenous administration by a significant number of users is worrisome. IDUs are the population most at risk for hepatitis C virus (HCV) transmission in the developed world (11). In countries such as the USA, Canada and Australia, where the highest seroprevalence is among middle-aged people, injection drug use accounts for 68% to 80% of current infections (12-15).

There is little evidence indicating how PO injection might be associated with HCV infection. Among IDUs, syringe sharing is the strongest determinant of HCV seroconversion (16). Sharing is highly correlated with behaviours driven by specific drug use patterns. The intermediate steps required in the process of drug preparation and apportioning (17), that may include communal use or sharing of injection paraphernalia (cookers, filters and water), increase the risk for HCV infection (18-20). According to recent ethnographic work, POs have to be crushed, dissolved and filtered before being injected, yielding opportunities for HCV transmission between injection partners (21).

The present study was conducted in a population of active drug users recruited and followed longitudinally between 2004 and 2009 in Montreal, Canada. The objectives of the study were twofold: i) to examine trends in the types of drugs used at the time of recruitment, with a specific

focus on POs, and ii) to assess the association between PO injection use and HCV seroconversion among IDUs. We specifically tested whether the incidence of HCV would be associated with PO injection, after adjusting for other covariates.

MATERIAL AND METHODS

Study population:

The study population was drawn from the St. Luc Cohort, an open cohort of current IDUs established in Montreal in 1988 to study determinants of Human Immunodeficiency Virus (HIV) transmission (22). To be eligible, participants had to be current IDUs (i.e., as having injected drugs within the previous six month) and be 18 years of age or older.

In November, 2004, the cohort's objectives were expanded and a new cohort was assembled to examine individual and contextual factors associated with HCV and HIV infections among current IDUs.. Eligible HCV-negative IDUs already enrolled in the former cohort were invited to participate in the new HCV incidence studies (n=101). New participants (n=210) were recruited in a manner consistent with previous strategies, and using the same eligibility criteria. A detailed description of the recruitment and follow-up procedures has been previously published (23). The sample population included HCV-negative participants recruited from the former cohort (32%), as well as new participants recruited through street-level strategies such as word-of-mouth (34%) or through community program referrals (34%). All participants signed an informed consent in compliance with institutional review board regulations of the Centre hospitalier de l'Université de Montréal. Cohort visits were scheduled at six-months intervals and consisted of behavioural questionnaires administered by trained interviewers and venous blood samples drawn for HIV

and HCV antibody testing. Participants were asked to return for their serostatus test results two weeks after their visits, at which time post-test counselling and referrals were provided. All participants received a CAD $15.00 stipend at each visit to compensate them for their time.

Of the overall sample (n= 311), 246 participants (79%), HCV-seronegative at enrolment, were followed up at least once between November 2004 and December 2009, and were included in the incidence analysis. All seroconverters had a documented negative HCV antibody test at the time of enrolment and a subsequent positive HCV antibody test during a follow-up visit.

Measures:

The main outcome variable was HCV infection detected by the presence of HCV antibodies. A positive HCV antibody test was determined by *enzyme immunoassay assay (Abbott Laboratories)* and confirmed by RT-PCR (Roche Diagnostic Systems). Specimens with indeterminate results were sent for confirmatory tests by dual EIA and/or RIBA (gold standard). Socio-demographic characteristics (age, gender, education, housing arrangement), drug use patterns, and injection behaviours were examined according to PO injection use and as potential determinants of HCV seroconversion. Higher education was defined as having completed a college degree. Consistent with previous studies, the idiom “unstable housing arrangement” was defined as living on the street, in shelters, or in apartment-hotels rented on a monthly basis (indicating a rapid turnover compared to typical 12-month rent-lease accommodation standards in Montreal) (24). Drug-use patterns and injection behaviours were assessed by questioning participants on the type of drugs used, modes of administration and sharing practices regarding syringes or other injection paraphernalia in the past 6 months. For example, participants were

asked whether they used illicit POs, heroin, cocaine or crack through snorting, smoking or injecting. A list of known commercial and street denominations helped distinguish between the varieties of substances in circulation. The terms “injection paraphernalia” were said to encompass the drug preparation container, water or dilution liquid and filter or cotton.

Statistical Analyses:

Cochran-Armitage trend tests were conducted to compare types of drugs used over the five-year period. Descriptive analyses were used to compare IDU characteristics according to PO injection use. Kaplan–Meier technique was used to estimate the survival function (25). Cox proportional hazards regression was used to estimate crude and adjusted Hazard ratios (HR), and corresponding 95% Confidence Interval (CI) to examine the relations between PO injection use and incidence of HCV. Following the purposeful selection procedure (26), significant variables at the 5% level as well as those that showed a confounding effect on significant covariates (that is, those that changed a significant variable’s coefficient by more than 20%) were retained in the final multivariate models. In addition, age and gender were retained in the final model.

To investigate whether the effects of particular risk factors on the hazard of HCV seroconversion varied according to PO injection use, Cox regression analyses tested two-way interactions with relevant risk factors. In the case of a significant interaction, we estimated separate hazard ratios for the associations between a corresponding factor and HCV incidence in each of the two PO injection groups. Individual exposure measures, except gender and age, were modelled as time-dependent covariates representing their most recent values. A covariate “recruitment scheme” was included in analyses to account for the differential cohort participation duration and the

potential influence of serial HCV counselling and testing on behaviours and transmission between participants recruited from the former cohort membership and those recruited from street-level and community-based strategies.

For all hypothesis testing, $p<0.05$ for the 2-tailed Wald test was used as the criterion for statistical significance. All analyses were conducted using SAS® v 9.2.

RESULTS

Of the 1,042 cohort participants recruited (HIV and/or HCV-negative active IDUs) between November, 2004 and December, 2009, 731 (70%) had HCV antibodies. Of the 311 HCV-negative cohort members eligible for this investigation, 246 (79%) were followed up at least once and were included in the incidence analyses. The majority was male (81.6%), with a mean age of 34.5 years (SD=9.2). The average duration of injection-drug use was 9.9 years (SD 8.4).

Figure 1 shows the trends in IDU proportions for each drug of interest by year of enrolment. Increasing trends were observed for PO and heroin injection use. The proportion of IDUs reporting PO injection use more than tripled between 2005 and 2009, from 21% to 75%. When including only the 210 participants who were recruited from street-level and community-based strategies, PO injection use increased significantly, i.e., from 42.4% in 2004-2005 to 75% in 2009 (p-value for trend test= 0.002), while cocaine injection, heroin injection and crack use remained stable.

Table 1 compares baseline characteristics of the 246 participants included in incidence analyses according to PO injection use. Compared to non-users, PO injection users were younger, more likely to report heroin injection, and to have been recruited from street-level and community-based strategies. They were also more likely to report high-risk injection behaviours (including sharing syringes, frequent injections and injection in public places) and to have recently been incarcerated.

Prior to seroconversion, participants contributed a total of 463 person-years of observation. The mean follow-up time was 23 months (SD 16.7) and the median time between consecutive visits was 5.9 months. A total of 83 individuals (33.7%) seroconverted to HCV, for an incidence rate (IR) of 17.9 per 100 person-years (95% confidence interval (CI): 14.3, 22.1).

Table 2 provides crude associations between socio-demographic and behavioural characteristics and the risk of HCV seroconversion. Injecting POs was associated with a 3.2 fold increased risk of HCV acquisition, whereas the association with heroin injection did not reach statistical significance. Injecting cocaine was associated with an increased risk of HCV seroconversion. In addition, several injection-related practices were associated with an increased risk of HCV infection; for example, the sharing of syringes or other paraphernalia, injection frequency and injection in public places. IDUs reporting unstable housing arrangements or recent incarceration were also more likely to seroconvert to HCV, as were IDUs recruited through street-level and community-based strategies, compared to those recruited among members of the former cohort.

Results from the Cox's multivariable model are presented in Table 3. We found only one marginally statistically significant interaction between PO injection use and heroin injection use. PO injectors were three times more likely to become infected if they did not use IV heroin (HR: 2.88 (95% CI: 1. 52, 5.45)), whereas the association was not statistically significant for participants who reported using both drugs (HR: 1.19 (95% CI: 0.61, 2.30); p value for interaction term: 0.05). Other variables significantly associated with an increased risk of HCV acquisition included IV cocaine use, frequency of injection and recent incarceration. In the multivariate model, the effect of sharing syringes or paraphernalia and of the recruitment scheme were deemed non significant.

DISCUSSION

Our results confirm a significant increase in the prevalence of PO injection among HCV-negative IDUs in Montreal between 2005 and 2009. Younger IDUs, and those recruited outside of the cohort assembled by the end of 2004, were more likely to report PO injection, suggesting the emergence of PO injection among IDUs at an early stage of their injectors' drug-use trajectory.

In Australia and Vancouver, Canada, a reduction of heroin availability was implicated in significant shifts in drug-use patterns and possibly in increased drug-related harms (8, 27-29). In Estonia, a shift in use from heroin to POs was observed following heroin shortages in 2001(30). In our study, we did not find a concomitant reduction in heroin injection that could partially account for the observed PO use increase. Rather, recent ethnographic data has shown that easy access, through independent operators and without the need for personal contacts, as well as low

prices, are likely at the root of this emerging illicit market (21).

Evidence of health risks associated with PO injection is relatively scarce. In Australia, recent morphine injectors were more likely to report morphine dependence (38%), difficulty finding veins into which to inject (36%), as well as scarring and bruising (27%) (8). To our knowledge, our study is the first to examine PO injection in relation to HCV transmission. Of concern, we observed that HCV-negative PO injectors were more likely to report high-risk injection practices associated with HCV seroconversion in previous studies, such as high injection frequency (31, 32), sharing of used syringes (16, 33) and injection in public places (34) when compared to non PO injectors. In multivariate analyses, PO injectors who did not report heroin injection were three times more likely to acquire HCV infection relative to non PO injectors, after controlling for other high-risk behaviours. . Interestingly, PO injectors who were also reporting heroin use were not at higher risk of seroconverting when compared to those who did not report PO injection.

Consistent with previous study findings in Canada and in Australia (27, 31, 32, 35), cocaine injection was an independent risk factor for HCV transmission. Injection cocaine use was not associated with PO use, and did not explain the relation between HCV seroconversion and PO use among non-heroin users. Imprisonment in the past six months was independently associated with higher HCV incidence. It has been demonstrated that having injected while in prison predicts HIV and HCV infections (36). Of the 57 participants who reported a recent imprisonment during the study period, only 3 reported having injected drugs while in prison. One of these individuals did seroconvert to HCV, an event which occurred more than 18 months after

being released. Besides the documented risk associated with injection drug use while in prison, heightened vulnerability may play an important role in increasing high-risk injection behaviours and HCV acquisition after release (37).

Contrary to our primary hypothesis, the sharing of syringes or other injection paraphernalia did not predict HCV transmission, after accounting for other covariates. While several studies have reported associations between HCV seroconversion and syringe sharing, many associations were relatively weak after controlling for other factors; other studies failed to find any association (38-41). Sharing is highly correlated with behaviours driven by specific drug use patterns. This has been mainly documented among cocaine users, whose consumption is often characterized as bursts of high intensity use or 'drug runs', which in turn induce sharing and higher risks of infection (42). Unmeasured drug-use patterns, combined with the possible under-reporting of syringe or paraphernalia sharing while intoxicated, have been offered as an explanation for the preponderance of cocaine as an independent predictor of HIV infection over sharing behaviours (42-44). Possibly, the independent association between PO injection and HCV seroconversion observed in our study proceeds from an analogous paradigm.

Recent ethnographic observations carried out in downtown Montreal have shown that the logistical aspects of the PO preparation process, coupled with indigent social practices, may increase the risk of infection (21). Some PO formats require large amounts of water in order to be dissolved. Given that the largest syringe distributed (1cc) cannot hold the entire dissolved solution, users have to inject themselves more than once. Consequently, the cup and filter may become contaminated as a result of the same syringe being used for repeated injections.

Furthermore, PO preparation for injection produces residue that adheres to the cup and the filter. This residue, known as “wash”, may contain enough opioid substance to produce a minimal effect or to stem withdrawal symptoms; thus it is usually kept for ulterior use. What becomes worrisome is that a potentially contaminated “wash” could be given to another user. “Washes” have an economic value and are one of the goods that are exchanged or given among street-based users. These “washes” play an important role in the moral economy of “gift-giving” among Montreal street-based users (45, 46). Ethnographic observation suggests that “wash” giving and exchanging is not necessarily equated with ancillary paraphernalia sharing, since “washes” are considered independent drugs capable of producing a high or countering withdrawal symptoms, a factor which may have contributed to the under-reporting of injection equipment sharing.

The present study presents a number of limitations: Participants were not randomly selected; hence our sample cannot be considered an adequate representation of the Montreal IDU population as a whole. The sample is over-represented in terms of males and chronic cocaine IDUs, compared to Quebec provincial data on IDUs (47). The study was conducted in a large cosmopolitan North-American city, facing a rising PO injection use epidemic. As such, it may serve as a valid representation of PO injection misuse relevant to IDUs elsewhere.

Even though our follow-up rates were high for a drug-using population, our data may have been influenced by losses to follow-up. Because of the risk of “socially desirable” responses, the study of illicit drug use and related behaviours is problematic; especially as the study progresses and bonds evolve between participants and staff. Although there is some published evidence to suggest that drug users do provide reliable and valid responses, the risk of bias if it exists, is

more likely to go unreported (48). In addition, we did not include the “wash” as a specific item in our definition of injection paraphernalia, allowing only for indirect evidence of its potential role as a driver of HCV transmission among PO users.

As for other cohort studies, a lead-time bias exists wherein potentially important risk-behaviour events, which may have occurred prior to participants joining the cohort, could not be measured or accounted for; hence, residual confounding of our results is a possibility.

This study clearly illustrates the rising prevalence of PO injection use among Montreal IDUs. While many have hypothesized that PO injection use is involved with numerous risky behaviours related to blood-borne pathogen transmission, we have shown for the first time that PO injection actually is an independent predictor of HCV transmission. Aside from well-documented individual risk-behaviours, our results suggest that risks related to PO injections may be conditioned by specific drug practices and contexts prevailing outside of the traditional networks of heroin IDUs. To act on such a complex phenomenon will thus require innovative strategies. Current approaches such as increasing the coverage of syringe through comprehensive exchange and distribution services, and providing drug treatment, may be only part of the solution. These results underscore the need for a better understanding of the processes and contexts associated with PO injection use will lead to new and more comprehensive prevention and intervention strategies.

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Figure 1:

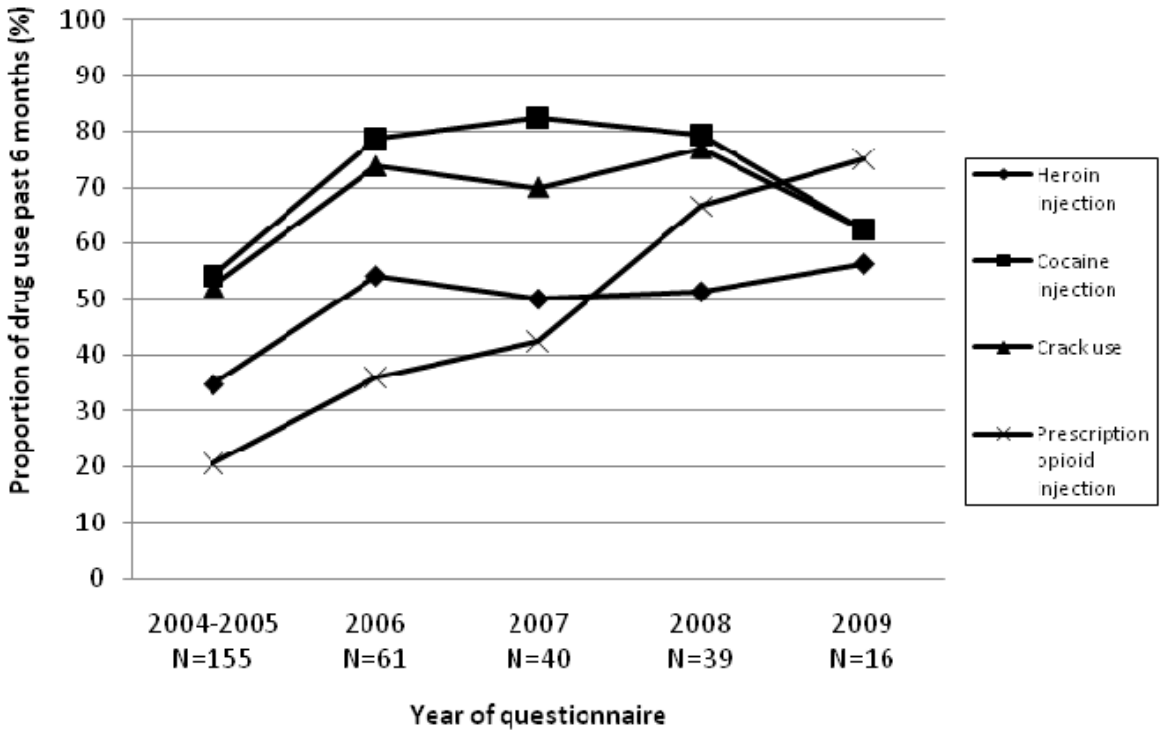
Proportion of drug use past 6 months (%)
100
90
80
70
60
50
40
30
20
10
0
2004-2005
N=155
2006
N=61
2007
N=40
2008
N=39
2009
N=16
Year of questionnaire
Heroin injection
Cocaine injection
Crack use
Prescription opioid injection

FIGURE 1

Legend:

P-values by Cochran-Armitage trend tests: Prescription opioid injection: < 0.001; Cocaine injection = 0.01; Heroin injection = 0.01; Crack use = 0.05.

Table 1 : Baseline Characteristics of 246 HCV initially antibody-negative injection drug users, according to their prescription opioid injection use, recruited between November 2004 and December 2009 in the St. Luc Cohort, Montreal, Quebec, Canada.

Variable	Total n=246 % (SD)	Prescription Opioid injection n=80 % (SD)	No Prescription Opioid injection n=166 % (SD)	P-Value*
Less than 30 YOA	38.6 (3.1)	53.7 (5.6)	31.3 (3.6)	<0.001
Male gender	81.6 (2.5)	81.2 (4.4)	81.8 (3.0)	0.914
College education or higher	13.4 (2.2)	13.7 (3.9)	13.2 (2.6)	0.915
Unstable housing arrangements past 6 months	36.6 (3.1)	42.5 (5.5)	33.7 (3.7)	0.181
> 30 injections past month	52.9 (3.2)	80.0 (4.5)	39.8 (3.8)	<0.001
Heroin injection past 6 months	43.5 (3.2)	57.5 (5.5)	36.7 (3.7)	0.002
Cocaine injection past 6 months	69.1 (3.0)	75.0 (4.8)	66.3 (3.7)	0.165
Crack use past 6 months	65.8 (3.0)	68.7 (5.2)	64.5 (3.7)	0.506
Sharing syringe past 6 months	28.5 (2.9)	42.5 (5.5)	21.7 (3.2)	<0.001
Sharing injection paraphernalia	39.4 (3.1)	47.5 (5.6)	35.5 (3.7)	0.072
Incarcerated past 6 months	23.2 (2.7)	33.7 (5.3)	18.1 (3.0)	0.006

Injecting in public places past 6 months	48.4 (3.2)	72.5 (5.0)	36.7 (3.7)	<0.001
Recruited through street-level and community-based strategies (vs. former cohort)	67.5 (3.0)	93.7 (2.7)	54.8 (3.9)	<0.001

* : P-values by chi-squared test.

Table 2 : Unadjusted estimated relative hazard of hepatitis C virus (HCV) seroconversion according to socio-demographic and behavioural factors for 246 initially HCV-negative injection drug users participating in a prospective cohort in Montreal, Canada, between November 2004 and December 2009.

Variable	N seroconversions	Person-time	Incidence rate	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
Less than 30 YOA						
No	47	281.07	16.72	12.44, 22.03	1	
Yes	36	156.49	23.00	16.38, 31.48	1.32	0.86, 2.05
Female Gender						
No	71	346.45	20.49	16.13, 25.69	1	
Yes	12	89.22	13.45	7.29, 22.86	0.70	0.38, 1.29
College education or higher						
No	77	370.31	20.79	16.53, 25.84	1	
Yes	6	67.25	8.92	3.62, 18.56	0.46	0.20, 1.05

Unstable housing arrangements past 6 months						
No	50	330.97	15.11	11.34, 19.75	1	
Yes	32	105.88	30.22	21.06, 42.11	1.62	1.03, 2.55
> 30 injections past month						
No	22	286.55	7.68	4.95, 11.41	1	
Yes	61	150.58	40.51	31.28, 51.66	4.59	2.80, 7.53
Prescription opioid injection past 6 months						
No	44	358.23	12.28	9.04, 16.33	1	
Yes	39	79.33	49.16	35.49, 66.48	3.20	2.06, 4.99
Heroin injection past 6 months						
No	44	277.95	15.83	11.65, 21.05	1	

Yes	39	159.61	24.43	17.64, 33.04	1.40	0.90, 2.16
Cocaine injection past 6 months						
No	9	168.31	5.35	2.61, 9.81	1	
Yes	74	269.25	27.48	21.74, 34.30	4.63	2.31, 9.27
Crack use past 6 months						
No	36	221.94	16.22	11.55, 22.20	1	
Yes	47	215.61	21.80	16.21, 28.72	1.07	0.69, 1.67
Sharing syringe past 6 months						
No	51	337.00	15.13	11.40, 19.73	1	
Yes	32	100.56	31.82	22.17, 44.34	1.87	1.20, 2.92
Sharing injection paraphernalia past 6 months	47	309.01	15.21	11.31, 20.04	1	
No	36	127.54	28.23	20.09, 38.62	1.55	1.00, 2.42

Yes						
Incarceration past 6 months						
No	53	361.19	14.67	11.11, 19.04	1	
Yes	30	76.36	39.29	27.04, 55.32	2.45	1.57, 3.85
Injection in public places past 6 months						
No	29	272.87	10.63	7.27, 15.05	1	
Yes	54	164.69	32.79	24.89, 42.44	2.67	1.69, 4.23
Recruited through street-level and community-based strategies (vs. former cohort)						
No	16	213.41	7.50	4.44, 11.92	1	
Yes	67	224.15	29.89	23.36, 37.71	3.34	1.92, 5.81

Table 3 : Covariate-adjusted associations between hepatitis C virus (HCV) seroconversion and prescription opioid injection among 246 initially HCV-negative injection drug users participating in a prospective cohort in Montreal, Canada, between November 2004 and December 2009.

Variable	Adjusted Hazard Ratio	95% Confidence Interval
Less than 30 years of age		
No	1	
Yes	0.90	0.52, 1.56
Female gender		
No	1	
Yes	0.90	0.46, 1.74
Interaction between IV illicit prescription opioid use and IV heroin use		
No IV opioid use past 6months	1	
Prescription opioid injection past 6 months		
and heroin injection past 6 months	1.19	0.61, 2.30
Prescription opioid injection past 6 months		
and no heroin injection IV past 6 months	2.88	1.52, 5.45
Cocaine injection past 6 months		
No	1	
Yes	3.00	1.44, 6.24
Sharing syringe past 6 months		

No	1	
Yes	1.29	0.81, 2.07
Incarceration past 6 months		
No	1	
Yes	2.41	1.50, 3.89
Recruited through street-level and community-based strategies (vs. former cohort)		
No	1	
Yes	1.71	0.92, 3.18
>30 injections past month		
No	1	
Yes	2.72	1.58, 4.70