Hepatitis C Virus seroconversion among persons who inject drugs in relation to primary care physician visiting: The potential role of primary healthcare in a combined approach to Hepatitis C prevention

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ABSTRACT:

Background: Meaningful reductions in Hepatitis C Virus (HCV) transmission rates among persons who inject drugs (PWID) require a comprehensive prevention approach, including access to harm reduction measures and to healthcare-related interventions, such as HCV screening, testing and antiviral treatment. Little is known, however, about the role of visiting a primary care physician (PCP) in relation to HCV infection risk among PWID, when integrated within a combined prevention approach. This study assessed the association between PCP visiting and HCV seroconversion among PWID attending needle exchange programs (NEP).

Methods: A prospective cohort study, HEPCO, was conducted among active PWID in Montréal (2004-2013). Interviews scheduled at three- or six-month intervals included completion of an interviewer-administered questionnaire, and collection of blood samples for HCV antibody testing. HCV-seronegative participants who reported NEP attendance at baseline and had at least one follow-up visit were eligible for this study. HCV incidence was calculated using the person-time method. Time-varying Cox regression modeling was conducted to evaluate the relationship between self-reported recent PCP visiting and HCV incidence.

Results: At baseline assessment, of 226 participants (80.5% male; median age: 30.6 years), 37.2% reported having recently visited a PCP. During 449.6 person-years of follow-up, 79 participants seroconverted to HCV [incidence rate: 17.6 per 100 person-years, 95% confidence interval (CI): 14.0-21.8]. Covariate-adjusted analyses indicated that visiting a PCP was associated with a lower risk of HCV infection [Adjusted Hazard Ratio: 0.54, 95% CI: 0.31-0.93].

Other independent predictors of HCV infection included unstable housing, cocaine injection and prescription opioid injection.

Conclusion: Among PWID attending NEP, visiting a PCP was associated with a lower risk of HCV infection. Yet, only a minority of participants reported PCP visiting. Efforts to intensify engagement with PCP among PWID could potentially contribute to lower HCV transmission when integrated within a combined approach to prevention.

Background

Injection drug use is the primary driving force behind the spread of Hepatitis C Virus (HCV), particularly in developed countries (Hajarizadeh, Grebely, & Dore, 2013). Although gradual declines in HCV transmission among persons who inject drugs (PWID) have been reported in some settings in recent years, including Vancouver, Canada (Grebely, et al., 2014) and Australia (Iversen, Wand, Topp, Kaldor, & Maher, 2013), the incidence of HCV remains high [20-25 per 100 person-years (p-y)] in many parts of the world (Leclerc, et al., 2014; Page, Morris, Hahn, Maher, & Prins, 2013; Wiessing, et al., 2014). In the SurvUDI network, an epidemiologic surveillance network of blood-borne infections among PWID in Eastern Canada, the incidence of HCV was estimated at 23.2 per 100 p-y in 2010, a rate that remained relatively stable since 1998 (Leclerc, et al., 2014).

In the absence of a vaccine conferring protection against HCV infection, prevention efforts require a strong foundation of harm reduction interventions (Centers for Disease Control and Prevention, 2012). Broad access to needle exchange programs (NEP) is considered, by and large, a cornerstone measure to an effective HCV prevention response. Sterile syringe provision has been shown to play an important role in altering high-risk injection practices, thereby potentially reducing the risk of HCV infection (MacArthur, et al., 2014). Access to substance use treatment is also considered key in harm reduction. For opiate users, receipt of opiate substitution treatment (OST) has been demonstrated to have positive impacts on risky injection behaviours (MacArthur, et al., 2014) and more recently, on HCV seroconversion (Nolan, et al., 2014; Tsui, Evans, Lum, Hahn, & Page, 2014), though limited evidence exists in support of other addiction treatment interventions (e.g., outpatient drug-free programs) (Hagan, Pouget, & Des Jarlais, 2011). In parallel, timely HCV screening, counseling and testing constitute essential actions for

prevention (Centers for Disease Control and Prevention, 2012), as they have the potential to impact HCV acquisition and transmission rates by reducing high-risk drug use practices (Aspinall, et al., 2014; Bruneau, et al., 2014). Altogether, it is now largely acknowledged that substantial reductions in HCV incidence require a comprehensive approach to prevention, involving multiple combined strategies (Page, et al., 2013).

The emphasis on timely HCV screening and testing among high-risk persons has included calls for a greater role for primary care physicians (PCP) in HCV prevention and care. Clinical reviews (Huffman & Mounsey, 2014; Wong & Lee, 2006) and professional guidelines (Public Health Agency of Canada & The College of Family Physicians of Canada, 2009; The Royal College of General Practitioners, 2007) on HCV screening, testing, treatment and management intended for PCP have served to gradually raise awareness. However, little evidence exists to support whether contact with PCP, as part of a combined prevention approach, relates to any difference in the incidence of HCV among PWID.

Previous research has suggested a role for PCP in improving access to HCV assessment and harm reduction interventions. Among PWID, contact with PCP has been associated with better knowledge surrounding HCV (Treloar, et al., 2011), higher levels of screening and testing (Barocas, et al., 2014), and greater interest in treatment initiation for those infected (Strathdee, et al., 2005). PCP are also increasingly involved in providing substance use treatment, notably OST (Luce & Strike, 2011; Strang, et al., 2005), and contact with primary health care services has been linked to lower levels of drug and alcohol use and improved addiction severity among drug-using populations (Friedmann, Zhang, Hendrickson, Stein, & Gerstein, 2003; Saitz, Larson, Horton, Winter, & Samet, 2004).

Beyond their role in HCV-specific interventions, PCP, with their focus on mainstream health care, can play a broader role in HCV prevention, complementing efforts provided through harm reduction strategies. PCP have a well-established role in chronic disease prevention (U.S. Preventive Services Task Force, 2014). For Human Immunodeficiency Virus (HIV), they have been recognized as having been at the forefront of prevention efforts in Australia, and attributes such as whole-person approach to care and continuum of care have been identified as key to their contribution (Newman, et al., 2012).

The overall aim of this study was to examine the role of visiting a PCP in relation to HCV infection among PWID, within a combined prevention approach involving contact with NEP. Hence, we investigated the association between PCP visiting and HCV seroconversion in a sample of HCV-negative PWID attending NEP in Montréal, Canada.

Methods

Study design and participants

Participants were selected from the Hepatitis Cohort (HEPCO), a cohort of PWID established in November 2004 in Montréal, to examine individual and contextual factors associated with HCV transmission. Eligibility criteria for recruitment into HEPCO included self-reported use of injection drugs in the six-month period prior to the interview, being 18 years of age or older, living in the Greater Montréal region and providing informed consent in compliance with institutional review board regulations of the Centre Hospitalier de l'Université de Montréal. For the purposes of this study, participants were eligible if they reported attending a NEP through community-based programs, clinics or pharmacies, at least once in the previous six-month period preceding their first assessment. Montréal has a liberal syringe distribution

policy, including no limits on the number of syringes and injection kits (cotton, cup, sterile water and alcohol pad) that can be obtained. NEP also provide risk reduction counselling and references for diverse services, as needed (Leclerc, et al., 2014).

Cohort recruitment and follow-up procedures have been described in detail previously (Bruneau, Roy, Arruda, Zang, & Jutras-Aswad, 2012). Briefly, participants were recruited through street-level strategies such as word-of-mouth or community program referrals. Follow-up visits were scheduled at six-month intervals for the period of November 2004 to March 2011, and three-month intervals thereafter. At baseline and at each follow-up visit, participants completed a behavioural questionnaire administered by a trained interviewer in a private, face-to-face setting. The questionnaire elicited information on socio-demographic characteristics, drug use patterns and related behaviours, and healthcare services utilization. Venous blood samples were drawn for HCV antibody testing at each visit. Participants were asked to return two weeks after the interview to obtain their test results, at which point post-test counseling and medical referrals were provided as necessary. A CAD 15.00$ honorary was offered to all study participants upon completion of the questionnaire.

Between November 2004 and December 2013, 459 HCV-seronegative participants were recruited into HEPCO, of which 283 (61.7%) reported NEP attendance within the six months prior to baseline assessment. Of these, 226 participants (79.9%) had at least one follow-up visit and were therefore included in the present analyses.

Measures

The outcome of interest was incident HCV infection, determined by the detection of HCV antibodies at a follow-up visit among previously HCV-antibody negative participants. Blood specimens yielding positive results for HCV antibodies using enzyme immunoassay (EIA,

Abbott Laboratories) were confirmed by reverse-transcription polymerase chain reaction (RT-PCR, Roche Diagnostic Systems). Indeterminate results were subsequently confirmed by dual EIA and/or recombinant immunoblot assay (RIBA). The date of HCV seroconversion was considered to be the midpoint between the dates of the participants' visits corresponding to the last negative and the first positive HCV test.

The primary exposure variable was a dichotomous measure assessing whether or not participants had visited a PCP working in a clinic or in a local community service center at least once in the past six months prior to baseline assessment and between follow-up visits (past six months until March 2011, and past three months thereafter). Thorough information on the number of visits that were made to PCP was not collected. In Montréal, visits to PCP are free of charge, as they are entirely covered by the provincial healthcare insurance.

Potential confounders included variables previously identified as significant correlates of HCV seroconversion among PWID populations, with a prominent focus on those that are most important in the Montréal setting where HEPCO participants live (Bruneau, et al., 2012). Socio-demographic characteristics included age, gender, education and past six-month housing arrangements. As previously (Bruneau, et al., 2012), unstable housing 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 Montréal). Drug use patterns and injection practices included past-month cocaine, heroin and prescription opioid injection, expressed as dichotomous variables (at least once versus none) and syringe sharing, defined as the borrowing of a used syringe at least once in the previous six months. A dichotomous variable assessing whether or not participants received methadone maintenance therapy in the previous six months was also examined.

Statistical analyses

Descriptive statistics were used to characterize the study sample at baseline assessment, and included medians and corresponding interquartile ranges (IQR) for continuous variables, and frequency distributions for categorical variables. To compare the characteristics of participants who did and did not visit a PCP at baseline, χ^2 tests were conducted for categorical variables. For continuous variables, nonparametric Mann-Whitney U-tests were used, given their non-normal distribution.

HCV incidence was estimated using the person-time method, and 95% confidence intervals (CI) were calculated using the Poisson distribution. Kaplan-Meier survival curves estimated for participants who did and did not report PCP visiting at baseline assessment were compared using the log-rank test. For all participants, study follow-up ended at their time of HCV seroconversion or at their last visit, which ever came first.

To examine the association between PCP visiting and HCV seroconversion, univariate and multivariate Cox proportional hazards regression analyses were conducted (Cox, 1972). In a first step, univariate Cox models were used to calculate crude hazard ratios (HR) and corresponding 95% CI for the association between visiting a PCP, candidate confounder variables, and HCV seroconversion. Subsequently, a multivariate Cox regression model was constructed to assess the independent association between PCP visiting and HCV seroconversion, whereby all variables with a p-value≤ 0.1 in univariate analyses were considered for inclusion in the multivariate analysis. Using a backward selection approach, all variables with a p-value< 0.05 were retained in the final multivariate model. Age and gender were retained in the final model, as important *a priori* covariates of HCV infection risk.

Except for age, gender and education, all variables were modeled as time-dependent covariates. Thus, at any time during follow-up, the values from the visit preceding the date of HCV seroconversion or the last completed questionnaire were used. For all statistical tests, the significance level was set at 0.05. All statistical analyses were conducted using SAS 9.3 software (SAS Institute, Cary, NC).

Results

Two hundred and twenty-six PWID who reported NEP attendance at baseline and had at least one follow-up visit were eligible for the present analyses. At baseline assessment, the median age of participants was 30.6 years (IQR: 25.7 – 39.4), the majority (80.5%) male, and 20.4% reported having completed college education. Unstable housing arrangements were reported by 48.2%. Eighty-four participants (37.2%) had visited a PCP in the six-month period preceding the baseline assessment. With the exception of being slightly younger (median age: 27.3 versus 30.6, p=0.01) and more likely to inject heroin (57.9% versus 42.9%, p=0.04), participants with no follow-up assessments were not statistically significantly different from those included in the analyses with regards to socio-demographic characteristics, drug use and sharing practices or PCP visiting.

Table 1 presents the baseline characteristics of participating PWID, stratified according to whether or not they had visited a PCP. Compared with PWID who did not visit a PCP, those who did so were significantly less likely to be male (71.4% versus 85.9%) and more likely to have completed college education (28.6% versus 15.5%). With regards to drug use patterns, they were less likely to report cocaine injection (54.8% versus 73.9%).

Table 1: Descriptive characteristics at study enrollment of 226 initially HCV-seronegative persons who inject drugs attending needle exchange programs in the six months prior, stratified by whether or not participants reported past six-month primary care physician visiting

Category	Total participants N=226 n (%)	Visited a PCP N=84 n (%)	Did not visit a PCP N=142 n (%)	*p*-value [a]
Age				
Median (IQR)	30.6 (25.7 - 39.4)	31.8 (26.7 - 41.0)	30.4 (25.3 - 38.4)	0.21
Gender				
Male	182 (80.5)	60 (71.4)	122 (85.9%)	0.008
Female	44 (19.5%)	24 (28.6%)	20 (14.1%)	
Completed college education				
Yes	46 (20.4%)	24 (28.6%)	22 (15.5%)	0.018
No	180 (79.6%)	60 (71.4%)	120 (84.5)	
Unstable housing past six months				
Yes	109 (48.2)	36 (42.9%)	73 (51.4%)	0.214
No	117 (51.8%)	48 (57.1%)	69 (48.6%)	
Cocaine injection past month				
Yes	151 (66.8%)	46 (54.8%)	105 (73.9%)	0.003
No	75 (33.2%)	38 (45.2%)	37 (26.1%)	
Heroin injection past month				
Yes	97 (42.9%)	46 (54.8%)	83 (58.5%)	0.588
No	129 (57.1%)	38 (45.2%)	59 (41.5%)	
Prescription opioid injection past month				
Yes	99 (43.8%)	41 (48.8%)	58 (40.8%)	0.244
No	127 (56.2%)	43 (51.2%)	84 (59.2%)	
Syringe sharing past six months				
Yes	64 (28.3%)	26 (31.0%)	38 (26.8%)	0.499
No	162 (71.7%)	58 (69.0%)	104 (73.2%)	
Methadone maintenance treatment past six months				

Yes	43 (19.0%)	17 (20.2%)	26 (18.3%)	0.722
No	183 (81.0%)	67 (79.8%)	116 (81.7%)	

Abbreviations: PCP, primary care physician; IQR, interquartile range

[a] *p*-value derived from the χ^2 test for categorical variables and the Mann-Whitney U-test for continuous variables

Prior to seroconversion, 226 participants contributed a total of 449.6 person-years of observation, with a median follow-up time of 12.4 months. A total of 79 participating PWID (35.0%) seroconverted to HCV during the study period, for an incidence rate of 17.6 per 100 p-y (95% CI: 14.0 – 21.8). Among participants who did and did not report visiting a PCP prior to baseline assessment, HCV incidence was estimated at 12.3 per 100 p-y (95% CI: 7.9 – 18.5), and 20.8 per 100 p-y (95% CI: 15.9 – 26.7), respectively. As shown in Figure 1, compared to participants who did not report visiting a PCP prior to baseline, those who did so were significantly more likely to remain HCV-seronegative at follow-up (p=0.03, log-rank test).

Figure 1: Kaplan-Meier survival curve for Hepatitis C Virus seroconversion among 226 initially HCV-seronegative persons who inject drug reporting past six-month needle exchange program attendance at baseline assessment, stratified by whether or not participants reported having visited a primary care physician

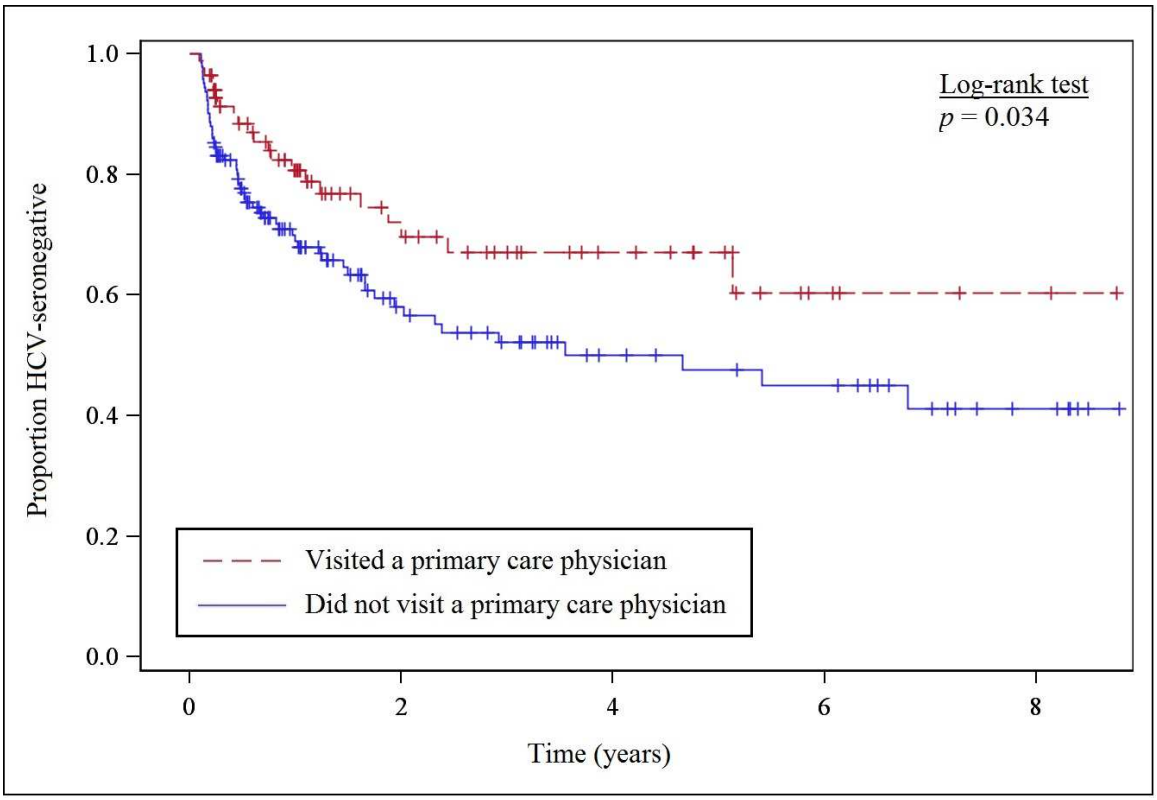

Table 2 presents unadjusted and adjusted HR for the associations between visiting a PCP, socio-demographic and behavioural characteristics, and the risk of HCV seroconversion. In univariate Cox regression analyses, visiting a PCP was associated with a 0.52 lower risk of HCV seroconversion. In addition, unstable housing, cocaine injection, prescription opioid injection and syringe sharing were associated with a greater risk of HCV infection. In the multivariate Cox

regression analyses, visiting a PCP remained independently associated with a lower risk of HCV seroconversion (HR: 0.54, 95% CI: 0.31 - 0.93). Other variables that remained independently associated with incident HCV infection included unstable housing (HR: 2.08, 95% CI: 1.26 – 3.43), cocaine injection (HR: 2.96, 95% CI: 1.66 – 5.27) and prescription opioid injection (HR: 2.31, 95% CI: 1.41 – 3.78).

Table 2: Univariate and covariate-adjusted associations with HCV seroconversion among 226 initially HCV-seronegative persons who inject drugs reporting needle exchange program attendance at baseline assessment, by Cox proportional hazards regression analyses

Variable	Unadjusted HR	95% CI	Adjusted HR	95% CI
Visited a PCP past six months	0.52	0.31 - 0.89	0.54	0.31 - 0.93
Age (per 5-year older)	0.94	0.83 - 1.06	0.96	0.84 - 1.10
Male gender	0.9	0.51 - 1.58	0.55	0.30 - 1.02
Completed college education	0.62	0.33 - 1.18		
Unstable housing past six months	2.61	1.65 - 4.13	2.08	1.26 - 3.43
Cocaine injection past month	3.36	1.90 - 5.93	2.96	1.66 - 5.27
Heroin injection past month	1.47	0.94 - 2.29		
Prescription opioid injection past month	2.81	1.78 - 4.42	2.31	1.41 - 3.78
Syringe sharing past six months	1.81	1.14 - 2.87		
Methadone maintenance treatment past six months	0.91	0.55 - 1.53		

Abbreviations: PCP, primary care physician; HR, hazard ratio; CI, confidence interval

Discussion

Our results indicate markedly lower HCV seroconversion rates among NEP-attending PWID in Montréal who visited a PCP compared to those who did not report doing so. Further, in multivariate analyses adjusting for known confounders, visiting a PCP remained independently associated with a nearly 50% lower risk of HCV infection. To our knowledge, this is the first time that the impact of PCP visiting in relation to HCV seroconversion has been examined. This finding aligns with, and supports a growing emphasis on the role of PCP in HCV prevention.

The observed lower risk of incident HCV infection among PWID attending NEP who visited a PCP could reflect a response to a multi-faceted prevention approach. Typically, in addition to providing sterile injection equipment, contact with NEP offers an opportunity for ongoing education and risk behaviour counseling. Visits to PCP are likely to reinforce and add to HCV prevention efforts offered through harm reduction programs like NEP. It is possible that our finding is attributed to increased evaluation with regards to HCV, as previous studies have illustrated that PWID who have been in contact with a PCP were more knowledgeable about HCV (Treloar, et al., 2011) and more likely to have received HCV screening and testing (Barocas, et al., 2014). Primary health care settings foster continuity of care and the development of familiarity and trust between PWID and their PCP (Hopwood & Treloar, 2013). These factors have been shown to encourage PWID's engagement in the HCV assessment process, as they feel more comfortable seeking and receiving information regarding HCV (Swan, et al., 2010). For PWID who have visited their PCP, timely HCV screening and counseling may have had a positive impact on the adoption of risky injection practices (Aitken, Kerger, & Crofts, 2002; Bruneau, et al., 2014).

The observed lower risk of HCV acquisition among participants reporting PCP visiting may also be partly attributed to increased assessment and intervention with regards to drug and alcohol problems, and greater access to mainstream healthcare. PCP are increasingly involved in providing treatment for substance use (Strang, et al., 2005), and contact with primary health care services has been shown to be associated with improved addiction-related outcomes (Friedmann, et al., 2003; Saitz, et al., 2004). Although our finding does not appear to be mediated by exposure to OST, it is noteworthy that a high proportion of participants were mainly cocaine-users, and therefore, not eligible for this type of therapy. Access to substance use treatment other than OST may have played a role (Hagan, et al., 2011), although our data did not permit detailed assessment of this possibility. More broadly, it is possible that access to timely assessment and management of co-morbidities through ongoing care may have encouraged some PWID to modify their perception of themselves, leading them to identify with ordinary patients rather than with "simply drug users" (Jauffret-Roustide, et al., 2012). This change in perception may have added, in turn, an important motivational element to their concern with their general health, possibly prompting them to engage in safer injection practices (Jauffret-Roustide, et al., 2012).

Although our finding illustrates that contacts with PCP in combination with access to NEP can potentially play an important role in reducing HCV transmission rates among PWID, only slightly more than a third (37.2%) of NEP attendees reported having visited a PCP. This low proportion suggests an inadequate level of communication between harm reduction programs and primary healthcare, despite recommendations regarding the importance of coordinating care services for PWID (Centers for Disease Control and Prevention, 2012). In Montréal, NEP do not typically have PCP directly affiliated to their service. In addition, the late operating-hour system prevailing among NEP may result in fewer opportunities to establish

direct linkage with primary healthcare services, which typically function during daytime hours. One strategy to overcome this division of services and foster timely engagement in primary care among PWID would be to integrate PCP within NEP (Islam, Topp, Day, Dawson, & Conigrave, 2012). Similarly, outreach workers such as street nurses may also contribute to enhancing linkage with primary healthcare services in this population (Artenie, et al., 2015).

Consistent with previous studies (Grebely, et al., 2014; Kim, et al., 2009), unstable housing was associated with an elevated risk of HCV seroconversion among PWID. Greater exposure to risky injection practices among PWID who are unstably-housed, such as injecting in public spaces, has been put forward as a possible explanation for this finding (Kim, et al., 2009). Cocaine and prescription opioid injection were also found to be associated with an elevated risk of HCV acquisition in our study. The link between cocaine injection and HCV transmission risk is well documented (Bruneau, et al., 2012; Grebely, et al., 2014), this finding attributed mainly to the greater likelihood of exposure to contaminated blood as a result of high injection frequency during "binge days" (up to 30 times per day) (Bux, Lamb, & Iguchi, 1995). More recently, our group showed that injection of prescription opioids is an independent risk factor for HCV transmission among PWID (Bruneau, et al., 2012). The repeated number of injections required to administer a single dose of prescribed opioids coupled with specific social practices prevailing among PWID injecting prescription opioids, such as sharing of potentially contaminated drug residues, have been proposed as possible explanations for the greater risk of HCV transmission in this sub-group (Roy, Arruda, & Bourgois, 2011). Syringe sharing did not remain significantly associated with HCV acquisition when adjusted for other covariates. This suggests that HCV exposure through cocaine and prescription opioid drug injection patterns may outweigh the risk of HCV acquisition through syringe sharing in our study.

Our study is subject to a number of limitations. Similar to most studies involving illicit drug-using populations, participants were not randomly recruited into the study, thereby limiting the generalisability of our findings. Yet, the socio-demographic and drug use characteristics of the HEPCO participants are, by and large, reflective of the PWID population in Québec (Public Health Agency of Canada, 2006). Although follow-up was high for a drug-using population, and few differences were found between participants retained in the study and those lost since their first visit, there is still a possibility that our findings are influenced by losses to follow-up. Further, since data for this study were collected through self-report, social desirability bias might arise as a result of eliciting information on socially sensitive behaviour. However, self-reported data collected from drug-using populations appear to be generally reliable and valid (Darke, 1998). As with all cohort studies, residual confounding of our results due to unmeasured factors associated with HCV-seroconversion is a possibility. For instance, it may be that participants who visited a PCP were more likely to engage in harm reduction and HCV prevention programs relative to participants who did not indicate PCP visiting. Yet, it is noteworthy that, at baseline assessment, we did not find any difference between participants who did and did not report PCP visiting with regards to receipt of OST. Lastly, as this study relied on secondarily collected data, the absence of information detailing the number of visits made to PCP precluded assessment of a potential dose-response relationship between PCP visiting and risk of HCV-seroconversion.

In summary, our results indicate, for the first time, that contact with PCP as part of a combined HCV prevention approach involving attendance at NEP, is associated with a lower risk of HCV acquisition among PWID. Future research is needed to examine which interventions, as delivered by PCP, are responsible for the observed lesser extent of HCV seroconversion. Furthermore, while our findings are encouraging, the extent of communication and interaction

between NEP and PCP seems insufficient, suggesting that steps be taken to enhance dialogue between harm reduction and primary healthcare services.

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CONFLICTS OF INTEREST:

The authors have no conflicts of interest to disclose.

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