

Sustained drug use changes following hepatitis C screening and counseling among recently infected persons who inject drugs: a longitudinal study.

Bruneau, J^{1,2}, Zang, G¹, Abrahamowicz, M³, Jutras-Aswad, D^{1,4}, Daniel, M⁵, Roy, E^{6,7}.

1 Research Center, Centre hospitalier de l'Université de Montréal (CRCHUM), Montréal, Québec, Canada.

2 Department of Family Medicine, Faculty of Medicine, Université de Montréal, Montréal, Québec, Canada.

3 Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Québec, Canada;

4 Department of Psychiatry, Faculty of Medicine, Université de Montréal, Montréal, Québec, Canada.

5 School of Population Health, University of South Australia, Adelaide, South Australia, Australia

6 Addiction Research and Study Program, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Longueuil, Québec, Canada.

7 Montreal Public Health Department, Agence de la santé et des services sociaux de Montréal, Montréal, Québec, Canada.

Contact Information (Corresponding Author) :

Julie Bruneau, MD, MSc

Centre de recherche, Centre hospitalier de l'Université de Montréal (CRCHUM)

Pavillon Edouard Asselin

264 René-Lévesque est, Montréal, QC H2X 1P1, Canada

Tél : +1 (514) 890-8000 Ext. 35713 · Fax : +1 (514) 412-7280

E-mail : julie.bruneau@umontreal.ca

Contact Information (Alternate Corresponding Author) :

Élise Roy, MD, MSc

Addiction Research and Study Program, Faculty of Medicine and Health Sciences

Université de Sherbrooke

150, Place Charles-Le Moyne, bureau 200, Longueuil, QC J4K 0A8, Canada

Tel : +1 (450) 463-1835 Ext. 61823, Fax : +1 (450) 463-6594

E-mail : Elise.Roy@usherbrooke.ca

Running head : Behavior changes after HCV status notification.

40-word summary of the article's main points :

Substance use and injection behaviors were longitudinally assessed following HCV status notification among persons who inject drugs. Among those who acquired HCV but not those who remained seronegative, a linear decrease was observed in injection use of heroin and cocaine.

Keywords: Hepatitis C, Injection drug use, Screening, Behavior

Word count : 3000

ABSTRACT

Background: Notification of hepatitis C (HCV) positive status is known to have short-term impacts on subsequent alcohol, drug use and injection behaviors among persons who inject drugs (PWID). Whether post-screening behavioral changes extend over time for PWIDs, and whether screening test notification has behavioral impacts among HCV-negative PWIDs, remain to be established. This study sought to longitudinally assess substance use and injection behaviors after HCV status notification among HCV seroconverters and HCV-negative PWIDs.

Methods: Initially HCV-seronegative PWIDs (n=208) were followed prospectively between 2004 and 2011 in Montreal, Canada. Semi-annual screening visits included blood sampling and an interview-administered questionnaire assessing substance use and injection behaviors. Multivariable general estimating equations (GEE) analyses were conducted to assess substance use and behavior changes over time, and compare changes between HCV seroconverters and HCV-seronegative subjects while adjusting for baseline characteristics.

Results: Of the 208 participants (83% male; mean age 34.7 years, mean follow-up time 39 months), 69 (33.2%) seroconverted to HCV. A linear decrease in syringe sharing behavior was observed over time after HCV+ and HCV- status notification, whereas a 10% decrease for each additional 3-month follow-up was observed for injection cocaine and heroin use among HCV seroconverters, but not among HCV-seronegative PWIDs ($p<0.05$). No significant changes were observed in alcohol use.

Conclusions: Our results indicate that notification of HCV-positive status is associated with reduced injection drug use among seroconverters. Amongst PWIDs

deemed seronegative after screening, there is no sustained trend for change in risk behavior.

Illicit injection drug use is the most important cause of new hepatitis C infection worldwide [1]. In Canada, 83% of the estimated 8,000 yearly new HCV infections occur among persons who inject drugs (PWID) [2]. It is largely acknowledged that an integrated harm-reduction strategy involving early access and broad coverage to a combination of interventions is required to control HCV transmission [3, 4]. These approaches and assumptions are largely based on data generated through HIV research, and endorsed by the World Health Organization, the United Nations AIDS and the United Nations Office on Drugs and Crime [5]. Specific evidence of their effectiveness for HCV prevention is, however, considered weak [6]. It has also been suggested that HCV testing programs that combine screening and counseling can decrease HCV transmission by reducing risk behaviors among uninfected PWIDs as well as chronically HCV-infected injectors [4]. Yet, HCV screening programs were found only moderately cost effective, although an associated decrease in needle-sharing by 5% annually substantially improved their cost-effectiveness [7].

Hence, it is unclear whether HCV status awareness, after testing, and counseling can influence behaviors and reduce risk of transmission. Moreover, whether any behavior change extends over time remains to be established. Most studies on HCV screening and awareness relied on cross-sectional study designs, and yielded diverse results. Lower alcohol use [8] and injection risk behaviors [9, 10] were observed among PWIDs aware of their HCV positive status in some studies, but not in others [11, 12]. Only three studies have prospectively examined changes in behaviors after HCV status notification among PWIDs. In Baltimore, reductions in syringe sharing at 3 to 6 months after HCV notification were observed for less than a fifth of participants, all HCV-positive at

recruitment [13]. In Melbourne, Australia, an increased use of new syringes was observed after HCV peer-delivered testing and counseling among both HCV-positive and negative PWIDs [14]. Finally, in a cohort of young PWIDs in San Francisco, recent HCV infection post-screening notification and counseling was followed by an initial decrease in alcohol and non-injection drug use, but no statistically significant change in injection drug use, and these changes were not sustained at 6 and 12-month follow-up [15]. None of these three studies has specifically compared the effect of HCV status notification between HCV-positive and HCV-negative PWIDs.

This study, conducted in a population of HCV-seronegative active injection drug users recruited and followed longitudinally between 2004 and 2011 in Montreal, Canada, aimed to i) longitudinally assess substance use and injection behaviors following HCV status notification, and ii) to compare changes overtime between PWIDs who received a positive result and those who stayed negative. Hence, this study has the potential to provide valuable information on the effect of counseling given the serostatus notification.

Methods

Population:

The study population was drawn from the St. Luc Cohort, an open cohort of PWIDs established in Montreal in 1988 to study determinants of HIV transmission. In late 2004 the study focus was expanded to include determinants of HCV, and HEPCO, an embedded cohort of HCV-negative PWIDs, was constituted. To be eligible for recruitment into HEPCO, participants are required to be current PWIDs (i.e., as having injected drugs within the previous six months), negative for HCV antibodies, and be 18 years of age or older.

A detailed description of the recruitment and follow-up procedures has been previously published [16]. HEPCO includes HCV and HIV-negative participants already followed in the St. Luc cohort (30%), as well as new participants recruited through street-level strategies such as word-of-mouth (36%) or through community program referrals (34%). Participants who stopped injection for more than 24 months are no longer followed. All participants signed an informed consent in compliance with institutional review board regulations of the Centre Hospitalier de l'Université de Montréal (CHUM). Cohort visits were scheduled at six-month intervals and consisted of behavioral questionnaires administered by trained interviewers as well as 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 counseling and referrals were provided. Syringes and condoms were provided upon request, and Hepatitis B immunization was offered through the CHUM clinic next door. All participants received a CAD \$15.00 stipend at each visit. Seroconverting participants were systematically referred for medical follow-up and treatment assessment to the CHUM Addiction Medicine program, which offers multidisciplinary services for patients with drug-related problems, including hepatitis C treatment.

For the total number of individuals included in HEPCO (n= 345), 208 participants (60%) who had undergone at least three visits between November 2004 and March 2011 were included in this investigation. All seroconverters had a documented negative HCV antibody test at the time of enrolment, a subsequent positive HCV antibody test during a follow-up visit, and at least one other follow-up visit. We found no differences in baseline characteristics between the 208 participants who completed at least three visits

and, thus, were included in the main analyses, and the remaining 137 cohort members (data not shown).

Measures:

Several outcome variables were examined to assess potential changes associated with notification of HCV status. Drug use and injection behavior outcomes were chosen because of their positive association with HCV acquisition previously observed in our population [16]. Measures included cocaine, heroin and illicit prescription opioid (mainly hydromorphone, hydrocodone and fentanyl) injection, as well as syringe sharing defined as the use of a syringe already used by someone else. In addition, alcohol use was chosen for its clinical relevance in relation to liver disease. All outcomes were measured by questions pertaining to use within the past 6 months, expressed as dichotomous variables (yes/no).

HCV infection was detected by the presence of HCV antibodies. A positive HCV antibody test was determined by enzyme immunoassay assay (EIA - Abbott Laboratories) and confirmed by reverse transcription polymerase chain reaction (RT-PCR-Roche Diagnostic Systems). Indeterminate results were sent for confirmation by dual EIA and/or recombinant immunoblot assay.

To deal with the potential decrease in risk behaviors over time among cohort participants exposed to serial counseling [17, 18], we redefined the ‘baseline’ visit, at which the characteristics of the participants were compared in this investigation. For seroconverters, the visit immediately preceding the seroconversion visit was selected as the ‘baseline’. For each PWID who remained seronegative, consecutive numbers were first assigned to each follow-up visit since recruitment. One of these numbers was then

randomly selected to represent 'baseline'. As shown in Figure 1, that selection for baseline visits enabled the resulting distribution to be frequency-matched between the seroconverter and the seronegative groups.

Statistical analyses:

Descriptive statistics used to summarize the participants' baseline characteristics included means, standard deviations (SD), medians and interquartile ranges (IQR) for continuous variables, and frequency distributions for categorical variables. To compare the baseline characteristics according to HCV serostatus, we used the chi-square test for categorical variables. For continuous variables, we used the independent groups t-test for normally distributed variables or the non-parametric Wilcoxon test if the normality assumption was violated.

Main analyses were performed separately for each outcome. Analyses focused on changes over time in the frequency of the corresponding binary outcome across all post-baseline visits ('baseline' as described in the 'Measures' section above). A multivariable generalized estimating equations (GEE) extension of logistic regression, with autoregressive order 1 covariance structure, was used to account for the correlation of consecutive outcome measures for the same subject [19]. First, separate GEE models were estimated for the HCV-seroconverters and HCV-seronegative subjects. These subgroup-specific models estimated the effect of a continuous variable indicating time-since-baseline, while adjusting for age and gender, as well as for the baseline value of the binary indicator of the behavior being assessed. The effect of time was estimated through the adjusted odds ratio (OR), with 95% confidence interval (CI), and its statistical significance was assessed with a model-based Wald test at a 2-tailed $\alpha=0.05$. Next, to

compare changes over time between HCV-seroconverter and HCV-seronegative subjects, a multivariable GEE model was estimated using data on all participants. This model included, in addition to the time variable, (i) baseline covariates and the baseline value of the behavior being assessed, (ii) a binary indicator of the seroconversion group, and (iii) a two-way interaction between the time and the seroconversion group indicator. The test of the interaction was then used to assess if the rates of change in the respective behavior did differ significantly between the two groups.

Preliminary analyses assessed whether the changes in specific behaviors over time were consistent with the linearity assumption. We first employed the flexible Generalized Additive Model (GAM) extension of logistic regression, with spline smoothing [20, 21] to estimate potentially non-linear changes in each behavior and each group. If the visually inspection of the GAM plots suggested possible non-linearity of changes, the corresponding GEE model was expanded to include interactions with quadratic and cubic functions of time. Because, for all outcomes, the non-linear interactions were definitely non-significant (all p-values > 0.15), the final analyses were limited to linear changes over time.

Significance level of 0.05 was used for all statistical tests. All statistical analyses were performed using SAS[®] 9.2.

Results

The majority of participants were male (83.1%), with a mean and median age of 34.1 (SD 9.6) and 31.8 (IQR: 26.6-41.2) years. The mean and median duration of injection-drug use was 10.0 (SD 8.6) and 8.2 (IQR: 3.6-13.2) years. Of the 208 participants analyzed, 69 individuals (33.2%) seroconverted to HCV, an incidence rate

(IR) of 14.4 per 100 person-years (95% confidence interval (CI): 11.3, 18.1). Participants contributed a total of 528 person-years of observation to this investigation. The mean and median follow-up time was 30.4 (SD 17.3) and 27.9 (IQR: 15.7-45.1) months. The median time between consecutive visits was 5.9 months. At the end of 2011, rates of attrition and discontinuation of follow-up (> 24 months without injection) were 10.1% and 4.3% among HCV seroconverters and 13.6% and 11.5% among HCV negative participants respectively.

Table 1 compares the baseline characteristics of the 208 participants according to their HCV status. Compared to participants who remained HCV-negative, those who seroconverted to HCV were significantly more likely to report injecting cocaine (87.0% vs. 63.3%), opioids (50.7% vs. 22.3%), and to report sharing of syringes (39.1% vs. 23.7).

Table 2 presents the results of analyses of changes in drug use behaviors, estimated through the GEE models. The two columns report the adjusted odds ratios (OR's), for each additional 3 months of follow-up, separately for subjects who have been informed about their HCV positive or negative serostatus. Figure 2 displays the proportion of participants reporting each outcome at 6-month interval, for participants who seroconverted and those who stayed seronegative separately. For most behaviors, there is no evidence of systematic changes overtime in the HCV seronegative group, graphically and as estimated by OR's close to 1.0 and the 95% CI's that include 1.0. In contrast, for HCV seroconverters, all analyses indicated a decrease in the frequency of the corresponding behavior, and most of these decreases were statistically significant. For example, among participants who seroconverted to HCV, the odds of subsequent

injections of cocaine (OR=0.90, 95% CI: 0.85-0.94) or heroin (OR= 0.90, 0.83-0.97) decreased by 10% with each additional 3 months of follow-up. The pattern of these changes in the HCV seroconverters was consistent with the linearity assumption, which suggests the trend to gradual reduction of these behaviors applied across the follow-up period. No such changes were observed among PWIDs who stayed seronegative. Consistent with these results, statistically significant ($p<0.05$) interactions (last column of Table 2) indicate that participants who were informed that they had contracted HCV were more likely to report having stopped cocaine and heroin injections. Both groups reported statistically significant decreases over time in the odds of sharing syringes, and these changes were greatest among those who seroconverted to HCV. Finally, the changes in alcohol use were smaller than for other behaviors and did not vary according to HCV seroconversion status.

Discussion

Our results indicate that HCV-seronegative PWIDs living in Montreal are polydrug users at high-risk of HCV infection. Altogether, close to a third of participants in our study reported having shared a syringe in the past 6 months. Not surprisingly, PWIDs who seroconverted were more likely to report syringe sharing, compared to participants who remained seronegative. They were also more likely to report opioid injection, a factor independently associated with seroconversion in our setting [16]. The main finding of this study is that notification of HCV test results and counseling is related to reductions in subsequent drug use behavior for PWIDs learning that they recently contracted an HCV infection, but not for those who are uninfected. This is the first time, to our knowledge, that changes in risk behaviors after HCV notification have been shown

to vary according to serostatus. As time-since-notification increased, seroconverters underwent a linear decrease in cocaine and heroin injection whereas no such decrease was observed among PWIDs who remained seronegative. Short-term behavioral changes following individual awareness of HCV screening status have been reported among HCV-positive individuals [9, 10]. Evidence that changes persist over time has not previously been ascertained. For example, in a cohort of young injectors aged between 15 and 24 years old, post-screening changes in drug use behavior were less consistent and were not sustained [8]. Age differences might be implicated, the mean age for our cohort being 34 years old. Young PWIDs have been shown not to be concerned by an HCV infection diagnosis when they go through intense periods of drug consumption and street involvement [22].

Reductions in drug use behaviors are likely to reflect a response to being informed about the recent seroconversion. The notion of “teachable moment” has been used in the disease prevention literature, to describe health events thought to motivate individuals to spontaneously adopt risk-reduction health behaviors [23]. Notification of abnormal test results has been shown to prompt lifestyle changes among patients with a variety of conditions, including cancer, HIV, and cardiovascular diseases [24-26]. For PWIDs who became seropositive in this study, the notification of a newly acquired diagnosis may be a cue prompting motivation for change to improve their own health or to reduce the risk of infecting others. In a study examining patient’s priorities relative to HCV counseling in a clinical setting, the combined risk of viral transmission to family members and others represented the principal volunteered concern among newly diagnosed and follow-up patients alike [27]. It is also possible that changes in behaviors

are partially explained by increased intervention. In our study, participants recently infected were offered, in addition to counseling and support, a personalized reference to a multidisciplinary team for assessment and the possibility of being treated. Unfortunately, we did not have information on treatment uptake among our participants. Regular follow-up in a multidisciplinary setting and the perspective of getting cured might have triggered persistent changes in some of the participants [28].

Aside from a differential impact of the notification and of consequent interventions, the difference in the magnitude of changes observed between the two groups could be attributed to the possibility that PWIDs staying HCV-seronegative had modified their behavior prior to enrolment in this study. It was recently demonstrated that many long-term PWIDs engage in planning strategies to avoid risk behaviors [29]. In addition, as shown in Figure 2, a higher proportion of participants stopped being followed because they have stopped injecting for more than 2 years compared to the seroconverter group.

Typically, alcohol use is not a predominant item in prevention messages for PWIDs. The observation that changes in alcohol use was relatively modest in both groups should raise concerns, given the recent recommendations by the United States Center for Disease Control in August 2012. One of the reasons invoked for this public health measure, aside from HCV detection and treatment, was to increase awareness on alcohol-related harm for those already infected with the virus [30]. At least for PWIDs, this does not seem to translate in significant changes over time. Pairing alcohol abuse interventions with HCV screening may be needed to truly have an impact on alcohol use behaviors.

Our study presents strength and limitations. The sample population provides a unique opportunity to study the impact of HCV status notification among active injectors likely to have engaged in recent risky behaviors and potentially amenable to change. Participants were not randomly selected, and our study excluded HIV-infected individuals, hence our sample cannot be considered an adequate representation of the Montreal PWID population as a whole. Even though follow-up was fairly high for a drug-using population, and that no difference was found between participants retained and those lost at inception, our data may have been influenced by losses to follow-up. Long-term changes should be interpreted with caution given the smaller number of subjects followed in later years of follow-up. 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 [31]. In addition, we did not have information on HCV treatment uptake after HCV notification, and mental health status, variables that could have influenced behavior changes.

Altogether, our results suggest that it is mainly the notification of the HCV positive status that induces the decrease in risk among PWIDs while there is no sustained trend for change in risk among those who continue to be seronegative. A new research agenda should aim at identifying what « works », e.g. whether it is the impact of the result itself (new infection), the impact of intensified counseling, and support the reference for care, or a combination of all these actions. Also, specific and possibly sustained intervention should be developed, studied and eventually implemented for those screened negative for HCV. The identification of health events, meaningful for

PWIDs at the time of HCV status notification, whether testing positive or negative, could enhance the impact of counseling and willingness to initiate changes.

In the meantime, our study underscore the need for regular and individualized HCV screening and counseling for all PWIDs with linkage to HCV treatment and opiate substitution therapy when appropriate.

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CONFLICTS OF INTEREST

Julie Bruneau, no conflict; Geng Zang, no conflict; Michal Abrahamowicz, no conflict; Didier Jutras-Aswad, no conflict; Mark Daniel, no conflict; .Élise Roy, no conflict.

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Table 1: Participant characteristics at study baseline, according to serostatus communicated at the disclosure visit.

Variable	All participants n=208 (%)	HCV seroconverters n=69 (%)	HCV negative n=139 (%)	p-value
Male gender	173 (83.1)	60 (87.0)	113 (81.2)	0.294
Less than 30 years of age	72 (34.6)	29 (42.0)	43 (30.9)	0.113
College education or higher	31 (14.9)	8 (11.6)	23 (16.6)	0.345
Total income \geq \$6000 CDN	103 (49.3)	36 (52.2)	67 (47.8)	0.555
Alcohol use past 6 months	151 (72.6)	45 (65.2)	106 (76.3)	0.092
IV heroin use past 6 months	84 (40.4)	33 (47.8)	51 (36.7)	0.123
IV opioid use past 6 months	66 (31.7)	35 (50.7)	31 (22.3)	<0.0001
IV cocaine use past 6 months	148 (71.2)	60 (87.0)	88 (63.3)	0.0004
Crack use past 6 months	111 (53.4)	40 (58.0)	71 (51.1)	0.348
Cannabis use past 6 months	146 (70.2)	51 (73.9)	95 (68.4)	0.408

Sharing syringes past 6 months	60 (28.9)	27 (39.1)	33 (23.7)	0.021
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Table 2: Changes of drug use behaviors overtime , by 3-month increment, stratified according to post-screening disclosure of HCV status.

Behaviors of interest	HCV seroconverters N = 69	HCV negative N = 139	
	Adjusted Odds Ratio ^a and 95% confidence interval of change, by 3-month increment		p-value for interaction ^b
Alcohol use past 6 months	0.94 (0.89, 1.00)*	0.97 (0.92, 1.03)	0.441
Cocaine injection past 6 months	0.90 (0.85, 0.94)**	0.97 (0.93, 1.02)	0.019
Heroin injection past 6 months	0.90 (0.83, 0.97)**	1.00 (0.94, 1.06)	0.046
Opioid injection past 6 months	0.93 (0.87, 1.00)*	1.00 (0.94, 1.07)	0.132
Sharing syringes past 6 months	0.85 (0.77, 0.94)**	0.92 (0.85, 0.99)*	0.220

** if $p < 0.01$; * if $0.01 < p \leq 0.05$

^a Adjusted for baseline value of each of the outcome of interest, age and gender, respectively

^b 2-sided p-value for the test of the interaction between the time and the group indicator, in the GEE model; $p < 0.05$ indicates that the rate of changes in a given behavior over time

differs significantly between the two groups

Figure 1

Title:

Distribution of visits selected to serve as baseline for participants who seroconverted to HCV and participants who stayed HCV-seronegative.

Legend:

The baseline visits used for this study were frequency matched by the number of visits since recruitment between the seroconverter and the seronegative groups.

Figure 2

Title:

Proportion of participants reporting each outcome at 6-month intervals, stratified by the serostatus notification.