MAJOR ARTICLE

Sustained Drug Use Changes After Hepatitis C Screening and Counseling Among Recently Infected Persons Who Inject Drugs: A Longitudinal Study

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

Methods. Initially HCV-seronegative PWID (n = 208) were followed prospectively between 2004 and 2011 in Montreal, Canada. Semiannual screening visits included blood sampling and an interview-administered questionnaire assessing substance use and injection behaviors. Multivariable generalized estimating equation analyses were conducted to assess substance use and behavior changes over time and compare changes between HCV seroconverters and HCV-seronegative participants 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 status notification, whereas a 10% decrease for each additional 3 months of follow-up was observed for injection cocaine and heroin use among HCV seroconverters but not among HCV-seronegative PWID ($P < .05$). 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. Among PWID deemed seronegative after screening, there is no sustained trend for change in risk behavior.

Keywords. hepatitis C; injection drug use; screening; behavior change.

Illicit injection drug use is the most important cause of new hepatitis C virus (HCV) infection worldwide [1]. In Canada, 83% of the estimated 8000 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 human immunodeficiency virus (HIV) research, and endorsed by the World Health Organization, the UNAIDS (Joint United Nations Programme on HIV/AIDS), and the United Nations Office on

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Drugs and Crime [5]. Specific evidence of their effectiveness for HCV prevention is considered weak, however [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 PWID as well as chronically HCV-infected injectors [4]. Even so, 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 posttest HCV status awareness 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 have relied on cross-sectional study designs and yielded diverse results. Lower alcohol use [8] and injection risk behaviors [9, 10] were observed among PWID aware of their HCV positive status in some studies but not in others [11, 12]. Only 3 studies have prospectively examined changes in behaviors after HCV status notification among PWID. In Baltimore, reductions in syringe sharing at 3–6 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 HCV-negative PWID [14]. Finally, in a cohort of young PWID in San Francisco, recent HCV infection postscreening notification and counseling was followed by an initial decrease in alcohol and noninjection 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 3 studies has specifically compared the effect of HCV status notification between HCV-positive and HCV-negative PWID.

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 (1) to longitudinally assess substance use and injection behaviors after HCV status notification and (2) to compare changes overtime between PWID who received a positive result and those whose results remained negative. Hence, this study has the potential to provide valuable information on the effect of counseling given serostatus notification.

METHODS

Population

The study population was drawn from the St Luc Cohort, an open cohort of PWID 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 the Hepatitis Cohort (HEPCO), an embedded cohort of HCV-negative PWID, was constituted. To be eligible for recruitment into HEPCO, participants are required to be current PWID (ie, to have injected drugs within the previous 6 months), negative for HCV antibodies, and ≥18 years of age.

A detailed description of the recruitment and follow-up procedures has been published elsewhere [16]. HEPCO includes HCV- and HIV-negative participants already followed up 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 >24 months are no longer followed up. 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 6-month intervals and consisted of behavioral questionnaires administered by trained interviewers as well as venous blood samples obtained for HIV and HCV antibody testing. Participants were asked to return for their serostatus test results 2 weeks after their visits, when posttest counseling and referrals were provided. Syringes and condoms were provided on request, and hepatitis B immunization was offered through the CHUM clinic next door. All participants received a CaD$15 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.

Of the 345 individuals included in HEPCO, 208 participants (60%) who had undergone ≥3 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 enrollment, a subsequent positive HCV antibody test during a follow-up visit, and ≥1 other follow-up visit. We found no differences in baseline characteristics between the 208 participants who completed ≥3 visits and were thus 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 (with yes or no responses).

HCV infection was detected by the presence of HCV antibodies. A positive HCV antibody test result was determined

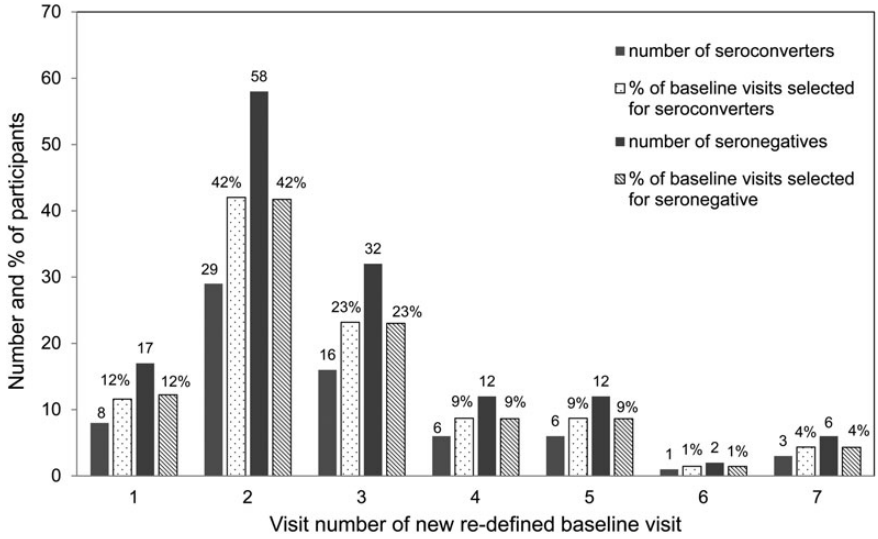

Figure 1. Distribution of visits selected to serve as baseline for participants who seroconverted to hepatitis C virus (HCV) and those who stayed HCV seronegative. The baseline visits used for this study were frequency matched by the number of visits since recruitment between the seroconverter and the seronegative groups.

by enzyme immunoassay assay (Abbott Laboratories) and confirmed by reverse-transcription polymerase chain reaction (Roche Diagnostic Systems). Indeterminate results were sent for confirmation by dual enzyme immunoassay assay 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 the 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 (SDs), medians, and interquartile ranges (IQRs) for continuous variables and frequency distributions for categorical variables. To compare the baseline characteristics according to HCV serostatus, we used the χ^2 test for categorical variables. For continuous variables, we used the independent-groups t test for normally distributed variables or the nonparametric 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 postbaseline visits (with baselines defined as already described). A multivariable generalized estimating equation (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 participant [19]. First, separate GEE models were estimated for the HCV seroconverters and HCV-seronegative participants. These subgroup-specific models estimated the effect of a continuous variable indicating time since baseline, while adjusting for age and sex, 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 (2-tailed $\alpha = .05$). Next, to compare changes over time between HCV seroconverters and HCV-seronegative participants, a multivariable GEE model was estimated, using data from all participants. In addition to the time variable this model included (1) baseline covariates and the baseline value of the behavior being assessed, (2) a binary indicator of the seroconversion group, and (3) a 2-way interaction between the time and the seroconversion group indicator. The test of the interaction was then used to assess whether the rates of change in the respective behavior differed significantly between the 2 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 GAM changes in each behavior and each group. If the visually inspection of the GAM plots

suggested possible nonlinearity of changes, the corresponding GEE model was expanded to include interactions with quadratic and cubic functions of time. Because the nonlinear interactions were definitely nonsignificant for all outcomes (all $P > .15$), the final analyses were limited to linear changes over time. A significance level of .05 was used for all statistical tests. All statistical analyses were performed using SAS 9.2 software (SAS Institute).

RESULTS

The majority of participants were male (83.1%), with mean and median ages of 34.1 (SD, 9.6) and 31.8 (IQR, 26.6–41.2) years. The mean and median durations of injection drug use were 10.0 (SD, 8.6) and 8.2 (IQR, 3.6–13.2) years. Of the 208 participants analyzed, 69 (33.2%) seroconverted to HCV, an incidence rate of 14.4 per 100 person-years (95% CI, 11.3–18.1). Participants contributed a total of 528 person-years of observation to this investigation. The mean and median follow-up times were 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 with participants who remained HCV negative, those who seroconverted to HCV were significantly more likely to report injecting cocaine (87.0% vs 63.3%) and 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 2 columns show the adjusted ORs, for each additional 3 months of follow-up, separately for participants 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, separately for participants who seroconverted and those who stayed seronegative. For most behaviors, there is no evidence of systematic changes overtime in the HCV seronegative group, graphically and as estimated by ORs close to 1.0 and the 95% CIs 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, .85–.94) or heroin (OR, 0.90; 95% CI, .83–.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 that the trend to gradual reduction of these behaviors applied across the follow-up period. No such changes were observed among PWID who stayed seronegative. Consistent with these results, statistically significant ($P < .05$) interactions (last column of Table 2) indicate that participants who were informed that they had contracted HCV were more likely

Table 1. Participant Characteristics at Study Baseline, According to Serostatus Communicated at the Notification Visit

Variable	No. (%)			
	All Participants, (n = 208)	HCV Seroconverters, (n = 69)	HCV Negative (n = 139)	*P* Value
Male sex	173 (83.2)	60 (87.0)	113 (81.2)	.29
Age <30 y	72 (34.6)	29 (42.0)	43 (30.9)	.11
College education or higher	31 (14.9)	8 (11.6)	23 (16.6)	.34
Total income ≥CaD$6000	103 (49.5)	36 (52.2)	67 (48.2)	.55
Behavior in past 6 mo				
Alcohol use	151 (72.6)	45 (65.2)	106 (76.3)	.09
Heroin injection	84 (40.4)	33 (47.8)	51 (36.7)	.12
Opioid injection	66 (31.7)	35 (50.7)	31 (22.3)	<.001
Cocaine injection	148 (71.2)	60 (87.0)	88 (63.3)	<.001
Crack use	111 (53.4)	40 (58.0)	71 (51.1)	.35
Cannabis use	146 (70.2)	51 (73.9)	95 (68.4)	.41
Sharing syringes	60 (28.9)	27 (39.1)	33 (23.7)	.02

Abbreviation: HCV, hepatitis C virus.

Table 2. Changes in Drug Use Behaviors Over Time by 3-Month Increments, Stratified According to Postscreening Notification of HCV Status

Behavior of Interest in Past 6 mo	Adjusted OR[a] (95% CI) for Change by 3-mo Increments		
	HCV Seroconverters (n = 69)	HCV Negative (n = 139)	*P* Value for Interaction[b]
Alcohol use	0.94 (.89–1.00)[c]	0.97 (.92–1.03)	.44
Cocaine injection	0.90 (.85–.94)[d]	0.97 (.93–1.02)	.02
Heroin injection	0.90 (.83–.97)[d]	1.00 (.94–1.06)	.046
Opioid injection	0.93 (.87–1.00)[c]	1.00 (.94–1.07)	.13
Sharing syringes	0.85 (.77–.94)[d]	0.92 (.85–.99)[c]	.22

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; OR, odds ratio.

[a] Adjusted for baseline value of each outcome of interest, age, and sex.

[b] Two-sided *P* value for the test of the interaction between the time and the group indicator in the generalized estimating equation model; $P < .05$ indicates that the rate of changes in a given behavior over time differs significantly between the 2 groups

[c] If $.01 < P \leq .05$.

[d] If $P < .01$.

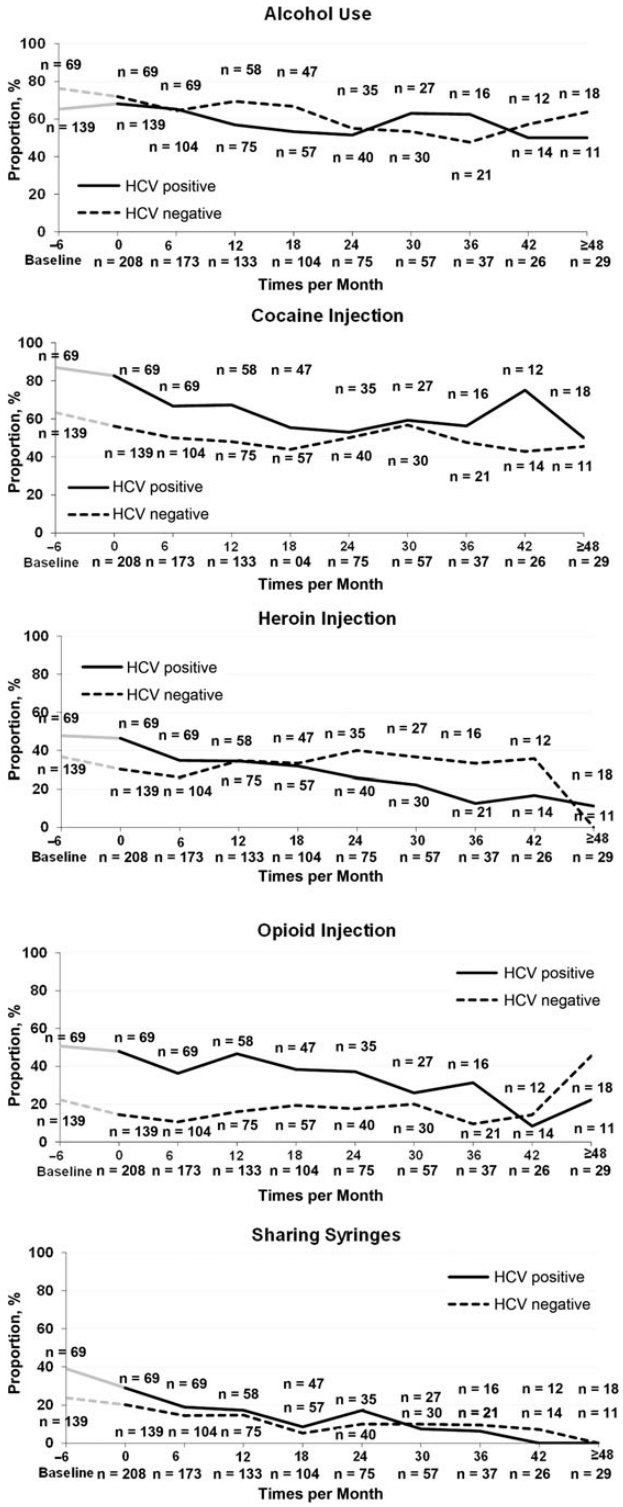

Figure 2. Proportion of participants reporting each outcome at 6-month intervals, stratified by serostatus notification. Abbreviation: HCV, hepatitis C virus.

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 PWID 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 within the past 6 months. Not surprisingly, PWID who seroconverted were more likely to report syringe sharing than those 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 PWID learning that they recently contracted an HCV infection but not for those who are uninfected. To our knowledge, this is the first time 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 PWID who remained seronegative. Short-term behavioral changes after 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 15–24 years old, postscreening 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 PWID 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 infection, and cardiovascular diseases [24–26]. For PWID 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 reduce the risk of infecting others. In a study examining patients' 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 patients with new diagnoses and follow-up patients

alike [27]. It is also possible that changes in behaviors are partially explained by increased intervention. In our study, in addition to counseling and support, participants recently infected were offered 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 may 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 2 groups could be attributed to the possibility that PWID staying HCV seronegative had modified his or her behavior before enrollment in this study. It was recently demonstrated that many long-term PWID engage in planning strategies to avoid risk behaviors [29]. In addition, as shown in Figure 2, a higher proportion of participants than seroconverters stopped being followed up because they have stopped injecting for >2 years.

Typically, alcohol use is not a predominant item in prevention messages for PWID. 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 reason 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 PWID, this does not seem to translate in significant changes over time. Alcohol abuse interventions may need to be paired with HCV screening to truly have an effect on alcohol use behaviors.

Our study has strengths 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 HIV-infected individuals were excluded; 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 no difference was found between participants retained and those lost since first visit, our data may have been influenced by losses to follow-up. Long-term changes should be interpreted with caution given the smaller number of participants followed up in later years. 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 may have influenced behavior changes.

Altogether, our results suggest that it is mainly the notification of HCV-positive status that induces the decrease in risk among PWID, whereas 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, that is, whether it is the impact of the result itself (new infection), the intensified counseling, the reference for care, or a combination of all these actions. Furthermore, specific and possibly sustained intervention should be developed, studied, and eventually implemented for those with negative screening results for HCV. The identification of health events, meaningful for PWID at the time of HCV status notification, whether results are positive or negative, could enhance the impact of counseling and the willingness to initiate changes. In the meantime, our study underscore the need for regular and individualized HCV screening and counseling for all PWID, with linkage to HCV treatment and opiate substitution therapy when appropriate.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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