Author's response to reviews

Title: The Cedar Project: High incidence of HCV infections in a longitudinal study of young Aboriginal people who use drugs in two Canadian cities

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Response to reviewers

Please note that our written responses to the reviewers below are in *italics* and any additional wording that has been added to the manuscript has been highlighted in yellow.

Reviewer 1:

Major revisions:

1. Provide descriptive statistics (carried over from review 1). I am happy with the authors’ decision not to report descriptives, providing they refer the reader to the prior publication containing these statistics for the current subsample (n=148). They should also make clear any concerns relating to cell size. Preferentially, these data would be made available in Table 2 so these issues and the scale of the effects under examination can be more readily examined.

As suggested by the reviewer we have provided further baseline descriptive statistics on the sample of 148 participants in the Results section. Because we would like to focus on the longitudinal risks for HCV incidence, we have not included an additional table for these results. The first paragraph of the Results now reads:

In total, 148 participants were eligible for inclusion in the analysis. Among those participants, the median age at baseline was 23 years, 53% were women and 57% were located in Vancouver. In addition, 12% identified as gay/lesbian/bisexual/transgender or two-spirited, 52% reported that they had ever been sexually abused and 68% had ever been taken from their biological parents into the child welfare system.

Minor essential revisions:

1. Abstract: Make reference categories explicit for non-binary terms, e.g. “using injection drugs for <2 years...or for between 2-5 years...compared to >5 years”.

“Very little is understood regarding factors associated with HCV infection” seems to undersell the authors’ earlier analyses of this issue - consider changing infection to incidence. “Rigs” is culture-specific, explain that it refers to injection equipment. Change BC to British Columbia (BC).

We have changed the abstract to reflect the reviewer’s suggestions. Please note that with the additional words the abstract is now 358 words.

2. Methods para 4: Suggest replacing “frequency of injection” with “daily injection” and delete sentence "Frequency of injection was defined as injecting drugs on a daily or less than daily basis". Clarify whether the opioids listed are examples or were all the opioids that were enquired about (i.e. that oxycontin bupe etc were excluded). State whether speedballs were coded as cocaine, opioid, or other.
As suggested we have changed the ‘frequency of injection’ to daily vs. less than daily injection. In addition, we regret that we did not include speedballs in the description of the types of opioid drugs that were included in the opiates category. We have therefore included speedballs within the bracketed description of opioids. Finally, with regards to other opioids such as oxycontin, participants have not been identifying those specific drugs in the questionnaire as a type of opioid that they use.

3. Referencing: clarify whether refs #25 and #28 pertain to Aboriginal women or to female users per se (see conclusions para 3). A reference to your earlier assessment of HCV incidence among IDU (Craib et al 2009) should be inserted in bkgrd para 2 – perhaps explaining what the current paper adds to that paper.

Reference #5 (Shannon et. al) is a study that includes a disproportionate number of young Aboriginal people in Vancouver. We would be happy to add in an additional sentence to explain that the study includes non-Aboriginal people and men at the Editor’s request. For #28, we mistakenly used the wrong reference (Fox et. al) and have corrected the mistake with the correct reference which is now #25 (Spittal et al.).

4. Typos. Abstract: use used, any of follow, change comma to colon in “95% CI, 7.7”. Methods 2nd last para: delete young from “among young participants”. Conclusion Para 1: “the therefore”. Conclusion Para 2: is “participants at high risk for HCV” meant to say “to high risk”? Conclusion Para 3: “hazard risk”. Table 2: “On street for > nights”. Check referencing: ref #33 is incomplete, style seems inconsistent (e.g. use of et al). Change opiates to opioids throughout your paper. Might be worth checking for other typos before publication.

We have corrected the typos and have changed ‘opiates’ to ‘opioids’. In addition we have corrected the incomplete reference and have amended another reference in the Methods section (reference #14).

5. Limitations? Regarding omitted risk factors, the authors clearly explained why non-IDU were not included in these analyses. Adding a comment that “only 5 (out of XX) NIDU seroconverted over the study period” would be informative and support the focus on the IDU sub-sample, but is not essential. More important is the unaddressed issue of poly-drug use. Prior research suggests it is highly prevalent in such samples and is a marker of injecting risk. Uncertainty about its impact on HCV incidence should be acknowledged at least as a limitation. It could also be expanded upon - see suggestion 3 below.

We have added a sentence to the Limitations paragraph in the Conclusions to read:

Because the number of participants who had never used injection drugs and seroconverted to HCV positive over the study period was very low (n=5) we were unable to examine the risks for HCV incidence among those participants.
Furthermore, we have changed the second paragraph of the Conclusion to address the issue of poly-drug use. The changes to the paragraph now read:

This study also demonstrated that participants who reported frequent drug injection and rig sharing over the study period had over twice the risk for HCV infection. Poly-drug use was common in this group. More than half of those who reported daily cocaine injection also reported daily opiate injection (data not shown). It is noteworthy that daily cocaine injection remained associated with HCV infection in the multivariable model while daily opiate injection did not. This is consistent with a previous study in Vancouver that demonstrated acquisition of HIV among injection drug users was directly related to frequent use of injection cocaine as opposed to opiates, particularly as a consequence of ‘cocaine binges’.17

Discretionary revisions:

1. The abstract could be more compelling and better reflect the paper’s contribution. Why do we need to know about the risk factors for HCV incidence? Why should we read the full article? If word count is strict use numerals and abbreviations (editor permitting) or chop some results.

We are hesitant to cut out results from the Abstract but will certainly change it at the discretion of the Editor. Although our word count for the Abstract is higher, we have added the following sentence to the Conclusion section of the Abstract:

This study contributes to the limited body of research addressing HCV infection among Aboriginal people in Canada.

2. Expand treatment comments. The not insubstantial rates of seroconversion amongst youth with longer histories of IDU, and the limits of basic harm reduction efforts give pause for thought on other treatment implications and options (positive impacts of OST, psychosocial treatment for cocaine dependence etc).

We have added the following sentences to the final paragraph of the Conclusion.

Furthermore, current policies and practices guiding addiction treatment delivery may be reinforcing the marginalization of street-involved young Aboriginal people because they fail to address historical and social injustices that influence resilience, particularly racial discrimination32-34. Treatment delivery for optimal adherence among young, HCV positive Aboriginal people who inject drugs must be individually tailored, enriched with ancillary psychosocial supports and provided within a culturally safe setting7,35. These findings may be applicable to at-risk young Indigenous people globally, for example in Australia, where similar patterns of vulnerabilities have been identified36.

3. Poly drug use/making sense of drug-HCV relationships (further to minor revision 5). Daily opioid injection is a strong bivariate risk factor for incidence, and in the authors' earlier work (Craib) was correlated with HCV prevalence. It is unclear how
drug-specific the associations with these different epidemiological parameters really are. Reporting the overlap of opioid with cocaine injection would be useful. 

*Please refer to our response to Minor Revision #5.*

**Reviewer 2:**

Minor Essential Revisions:

1. Please check that the sample size is correct from page 8: "Overall, 605 (300 in Vancouver and 300 in Prince George) young Aboriginal people..." as the math doesn't quite add up.

*We have corrected this typo to now read:*

Overall, 605 (305 in Vancouver and 300 in Prince George) young Aboriginal people were recruited and screened for enrolment in the Cedar Project study.