Author's response to reviews

Title: The Cedar Project: Rapid increase of HCV infection in a longitudinal study 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 Compulsory Revisions

1. Attribution of sero-conversion to explanatory factors. There is no suggestion of causal relationships here which is good, but it would be prudent to go further and explain that HCV and risk data collected at the same time cannot be used to identify the temporal sequence between these phenomena. ‘predictors’ (e.g. results final para) and ‘likely to become’ (Interp.Para 2) can too easily suggest a sequence rather than association. You can then address the harm reduction implications of HCV preceding risk behaviour. See Kim et al 2009 BMCPH.

We appreciate the Reviewer's comments regarding temporality. We have added a sentence to the Limitations section to read:

Additionally, although data were analyzed using time-dependent variables, we cannot make firm conclusions regarding temporal sequences between HCV risk patterns and infection.

As suggested by the reviewer, we have adjusted the language of the final paragraph of the Results section to read:

In the adjusted Cox regression model, independent associations with HCV seroconversion among Cedar Project participants who used injection drugs...

In addition, we have changed the language in the second paragraph of the Interpretation section to read:

This study also demonstrated that participants who reported high frequency cocaine injection and sharing rigs over the study period had over twice the risk for HCV infection.

2. Elaborate on coding decisions: It would be best to reference or explain why variables were dichotomised and how splits were determined. Re time since initiation, methods para 3 actually argues against splitting (given it can result in imprecision and worse). If coding was data-driven the model should be rerun with this variable in original form (e.g. Spittal 2007 IJCH) or at least opt for greater precision amongst recent initiates, e.g. report rates for <1y. given yours and others’ interest here. Essential refs here are Hagan 2008 AJE meta-regression, Royston 2006 Stat Med.
We agree with the Reviewer’s comment regarding further explanation needed for the coding scheme for time since initiation of injection drug use. The decision to dichotomize the variable into three categories, <2 years, 2-5 years and 5+ years was based on the relatively equal distribution of participants within categories. There were 40 participants in the <2 year category, 40 participants in the 2-5 year category and 66 participants in the 5+ years category. The alternative coding scheme we explored for this variable was to use a <1 year category (18 participants), 1-3 year category (33 participants) and 3+ years category (95 participants). We tested this variable in the Cox regression model and found that while the results were very similar to the previous coding scheme, the confidence intervals were very wide, particularly for the <1 year category. We therefore proceeded to use the time since initiation of injection drug use variable with categories <2 years, 2-5 years, and 5+ years. We have adjusted the third paragraph of the Methods section to read:

Because of the known association of the HCV virus with parenteral drug use, HCV incidence rates were estimated by three categories using the variable time since initiation of injection drug use. The variable was coded for relatively equal distribution between participants who had been injecting for <2 years (n=40), those who had been injecting for 2-5 years (n=40) and those who had been injecting over 5 years (n=66).

3. Address omitted risk factors

A strength of this work is that your wide consideration of risk factors. However, this makes the omission of others more perplexing. What about non-injecting, poly-drug and alcohol use, and HIV? These do need to be considered in your text, at least. Including in your model would clarify existing relationships (e.g. Willner 2008 JSAT).

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 made the decision to focus only on the risks among participants who reported injection drug use either at their baseline interview or at some time point between 2003-2009.

In consideration of the Reviewer’s request, we have provided this additional sentence in the 5th paragraph of the Methods section:

The Cedar Project cohort includes 605 participants in total, however this study included only participants who reported injection drug use, were HCV negative at baseline, reported injection drug use and who returned for at least one of eight follow-up interviews up to December 2008 (n=148).

4. Reconsider your model-building strategy: Your criterion (bivariate associations p<.05) is highly selective, it might be informative to relax this (p<.2? see Hosmer&Lemeshow) – especially given your sample size. You are also free to force in predictors of interest to you – doing so with gender would allow you to consider confounding with sex work. Likewise location is important, your project can offer unique insight here, why only speculate about this in the discussion? Consider running a location specific model, exploring interactions. Rig sharing and daily cocaine use, given your comments in interpretation para 2? Finally,
given the small number of terms in the model, observing the impact of adding and removing terms could clarify these relationships and the relative impacts of given risks (would be useful for aspects of sharing, see Craine et al 2009 Epi Infect).

As suggested by the reviewer, and in consideration of our small sample size, we relaxed our variable selection criteria to include variables that were significant at the p≤0.10 level in univariate analysis into the adjusted Cox model. We chose to use backward stepwise modelling because it is preferred to forced method as a parsimonious modelling technique. We have updated Table 2 and the Results section to reflect the new estimates from this model.

As suggested by the reviewer, we also forced gender into the model to compare the hazard ratio for paid sex with the model without gender and found that the variable did not affect the results (HR with gender: 1.66; HR without gender: 1.61). We are therefore confident that gender is not a significant confounder in the model.

Finally, we are hesitant to carry out separate models for each location for this analysis because location was non-significantly associated with HCV incidence (p=0.676) and because the resulting small sample sizes may have lead to unstable estimates of HR in the multivariable models.

5. Focus on stated objective and findings, clarify aspects of discussion: I felt the discussion drifted at times. Again re sex work, this constitutes an undue proportion of the discussion given the weak association with seroconversion. It would not trivialise sex workers’ welfare to devote greater attention to more persuasive correlates.

Our previous studies have demonstrated the highly important association between initiation of injection drug use and sex work involvement among Cedar Project participants (Miller et al., 2011). Considering the high risk for HCV infection early after initiation of injection, we feel that some discussion about the role of sex work is warranted. However, as suggested by the reviewer we have shortened the paragraph that addresses the association between sex work and HCV infection.

Interppara 3 also switches between Aboriginal ‘people’ and ‘women’. Be consistent and if focussing on females, why?

We have clarified the language of this paragraph to be consistent.

Further on in interppara 2, writing briefly about such profound issues is a challenge. Can you expand a little here on ‘complex interplay... must be acknowledged’? How can intergenerational trauma be recognised by service providers and what implications does this have for practice- integrating care-givers in treatment? Aboriginal health workers? Any examples of effective application of your suggestions, or if not, perhaps the Cedar project will go some way to providing? Your thoughts will be valuable to workers in similar settings.
In consideration of the Reviewer’s comments, we have elaborated on some of the qualities that strength-based approach to health care for young Aboriginal people who use drugs, and have cited Michel Tousignant’s important work in this field:

When designing new programming service providers must be mindful of how the past can shape the response to prevention initiatives and nurture flexible, trust-based relationships that seek to build upon young Aboriginal people’s resiliency in the face of intergenerational and lifetime traumas.

Minor Essential Revisions

1. Correct title to reflect content and contribution of paper. Consistent with what you can demonstrate and amongst whom, your title should read to the effect of ‘High incidence of HCV infections among young Aboriginal people who use injection drugs’.

As requested by the Reviewer we have amended the title to:

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

2. Clarity re description of sample. Providing sample n in abstract (e.g. “45/148 participants seroconverted”) helpsimmensely when reviewing abstracts. Results para 1 describes the sample so I’drather see this in the methods. Study results proper begin in results para 2.

We have changed the first line of the Results section in the Abstract to read:

In total, 45 out of 148 participants seroconverted over the study period.

In addition we have moved the paragraph describing the sample (previously the first paragraph of the Results section) to the final paragraph of the Methods section.

3. Add brief detail on follow-up outcomes and attrition.e.g. average number of interviews per participant, time between interviews. Given the time-varying nature of the risk behaviours, shorter intervals would lendgreater confidence to their association with seroconversion (and reduce the likelihood that seroconversion itself has precipitated behavioural change/treatment etc). Add sentence on those lost to follow up (did they evincercrisk factors for seroconversion?)

As suggested by the Reviewer we have added the follow up rate to the last paragraph of the Methods section:

Out of 175 participants, 148 completed at least one follow-up visit, yielding a follow-up rate of 85%.
4. Provide descriptive statistics and p-values. Provide descriptives for all variables per Teutsch et al 2011 BMCPH. Incidencerates if space. P-values throughout the document, not only CIs.

As suggested by the Reviewer we have added p-values to the statistics in Tables 1 and 2. We are unclear as to the value of descriptive statistics in addition to those that are already provided in the text. We have provided citations for previous studies that have described variables from the Cedar Project cohort study in detail.

5. Confirm whether proportional hazard assumption holds for IVs. Confirming this may matters not only to the interested reader but will improve the article’s chances of being included in subsequent reviews that grade methodological quality. If any IVs breached the assumption (crossed KM lines) then explain that (for example) they were included as strata variables. Might be best to run by statistician.

As suggested by the Reviewer, we have provided the following information about the proportional hazards assumption of the adjusted Cox model in the Methods section of the paper:

We also assessed the proportionality assumptions using the log minus log curve for the fixed covariates used in the model and observed no violations of assumptions.

Discretionary Revisions

1. Place the research in broader and international context. The paper has an opportunity to connect with literature outside Canada particularly work with young Indigenous samples – these are scarce and this group is often under-represented. E.g. Van der Poorten 2008 MJA, Maher 2006 Addiction.

As suggested by the Reviewer we have added the following sentence to the final paragraph of the Discussion section of the paper:
Moreover, these findings may be applicable to at-risk young Indigenous people globally, for example in Australia, where similar patterns of vulnerabilities have been identified34.

Reviewer #2

Summary of major concerns:

1. The authors provide a clear description as to where the sub-sample used for the analysis come from. However, they do not provide any information about how this subsample compares to the larger population in which it was drawn. If significant differences are present they should be recorded in the results paragraph and discussed within the limitations section.
The participants of the Cedar Project are part of a hidden population of young Aboriginal people who use drugs in BC. To our knowledge, there are no provincial population statistics that accurately describe the proportion of the number of Aboriginal young people who use drugs in BC. Furthermore, we know of no other dataset from which to draw comparisons. We have, however, made reference to our first paper on HIV infection prevalence (Spittal et al., 2007) which generally describes the population of Aboriginal people living in the Northern Health Authority and Vancouver Coastal Health Authority catchment areas.

2. Reuse of own rig, rig sharing, and difficulty finding new rig are likely highly correlated. More details as to the rationale for leaving all variables in the multivariate model is needed. Additionally, a comment regarding how multicollinearity of independent variables were assessed is needed.

We assessed the multi-collinearity of independent variables in the model building process - removing and addition of the potential collinear variable and observing the changes of adjusted HR estimate and the standard error. For example, as mentioned above, we looked the changes in the HR estimate and the confidence interval for rig sharing by adding potential collinear variables such as “reuse of own rig” and “difficulty finding new rig” separately in the model building process.

Currently we have used stepwise method and reported the variables from the final step that included the significant predictors. The final step model did not include the variables “reuse of own rig” and “difficulty finding new rig” reassuring the significant effect of rig sharing.

3. For variables: frequency of injection of opiates, methamphetamine, and cocaine in the past 6 months the authors collapsed the continuous variable into a binary variable (<daily vs. #daily). However, they do not specify how individuals who do not inject cocaine are categorized. For example, do these variables only include individuals who reported any [opiate, meth, cocaine] injection in the past 6 months? If so, the difference in sample size for these variables should be noted.

As noted above, we have added a sentence to the Methods section of the paper to be clear that only participants who reported injection drug use were included in the analysis. The variable for measuring frequency of injection drug use was kept in its original form as a categorical variable (i.e. we did not collapse a continuous variable into a categorical variable). The frequency of drug use variable had multiple nominal responses. In consideration of sample size, we collapsed those responses into two groups - daily, less than daily which also included participants who did not inject specific drug at each visit. Less than daily has been used as a reference group. Due to low number of participants that did not use specific drug and being a time-dependent covariate, we do not think that there is added benefit to providing a denominator for each variable.

4. Discussion is well written and notes the important contributions of findings. The manuscript could benefit for further expansion of the discussion points within the “sex
work and HCV seroconversion” paragraph (starting on pg. 11). It is agreed that this finding suggest a need to scale up services aimed at reducing drug or sex related harm for young Aboriginal women. But are the authors suggesting that these women are in fact getting HCV through the sexual behaviors encountered during sex work? Traditionally HCV is transmitted through intravenous rather than sexual behaviors. Additional discussion/interpretation of this finding is needed. For example, is it possibly that these women are injecting with clients? Or they are conducting more risky sexual behaviors with clients that are exposing them to HCV?

We have not found any evidence of sexual risk for HCV infection among Cedar participants involved in sex work but prior studies (cited in the paper) have highlighted the importance of intimate partnerships in power and control over injection equipment. In order to be more clear, we have changed these sentences in the paragraph addressing sex work to read:

It is important to highlight that many young Aboriginal women involved in sex work are intimately involved with men who are usually older and who also use injection drugs. Indeed research has demonstrated that for women who rely on their intimate partners for drug acquisition, preparation and injection, the distribution of power and control in intimate relationships often lies with drug injecting men who control the money and the drugs.

Summary of minor changes/suggestions:

1. Page 3: Sentence starting “In British Columbia, it is estimated that over half the population of people living…” It is unclear if “and that incidence for HCV infection is twice as high among Aboriginal people compared to non-Aboriginal people…” refers to HCV among HIV positive or not. Please clarify.

   For better clarity, we have reorganized the sentence to now read:
   
   In British Columbia, it is estimated that incidence for HCV infection is twice as high among Aboriginal people compared to non-Aboriginal people and that over half the population of Aboriginal people living with HIV are HCV co-infected, making the treatment challenges associated with being HCV and HIV co-infected far more complex.

2. Page 5. How long were participants followed within the cohort? Also, what type of diagnostic tests were used to determine HCV and HIV serostatus? At minimum the authors should refer to another paper for this information.

   We have clarified in the Methods section the timeframe of the study:
   
   The main outcome of interest in this study was HCV antibody seroconversion among participants who reported injection drug use between January 2003 and January 2009.

   We have also included the following paragraph to the third paragraph of the Methods section:

   We used algorithms for HCV serologic testing similar to those used in other studies conducted in this region. In brief, AxSYM HCV version 3.0 (Abbott Laboratories, Chicago, Ill.) was used to screen all plasma samples. Negative samples did not undergo further
testing. All positive samples underwent further testing with the recombinant Ortho HCV 3.0 ELISA test system (OrthoClinical Diagnostic Inc., Rochester, NY). Samples that tested positive with both assays were classified as positive. Samples that tested positive by the AxSYM HCV test and negative by the Ortho HCV test were classified as negative.

3. Page 6. During the description of covariates, it is difficult to assess which are time dependent and which are not. Specifically, “history of sexually transmitted infection” is listed under the time depended covariates, but it “history” typically refers to “ever” tested positive. This same issue is present for “ever having been incarcerated”. Additionally, Table 3 could benefit from a clear denotation of which variables are time dependent and which only appear at baseline.

*We have clarified this paragraph to now read:*

Nonfixed (occurred in the past six months) covariates included being in a relationship, having lived on the streets for a period of three nights or more, having been in jail or prison overnight or longer, having been denied shelter because of drug use, having been involved in sex work, having any sexually transmitted infection, having been incarcerated overnight or longer, presence of antibodies to HIV, frequency of injection cocaine, frequency of injection opiates (heroin, morphine, methadone, dilaudid or talwin), frequency of injection methamphetamine, rig sharing, having overdosed, and inconsistent use of condoms during insertive sex (vaginal, anal) with casual, regular or client partners.

*In addition, we have amended Table 2 with clearer variable denotations.*

4. Table 2: consider changing “ever/recently involved in sex work” to “ever/recently traded sex for money, shelter, food, or drugs” as defined in the covariate section of methods. Engaging in sex work means something slightly different.

*If the Editor wishes, we will change the variable name in Table 2 as suggested by the Reviewer.*

5. Possible typo on page 12: Predation.

*This was not a typo, but rather a description of the violence aimed at Aboriginal women that has been predatory in nature. We have changed the sentence to be clearer, and it now reads:*

Recent studies conducted in British Columbia’s lower mainland have demonstrated that impoverished Aboriginal women involved in sex work and concomitant illicit drug use continue to be exposed to alarming levels of drug related harm, infectious disease and violent predation.

*Please note that we have adjusted the sentence explaining our ethical conduct to be updated to reflect the new Tri-council Policy Statement. The first sentence of the second paragraph in the Methods section now reads:*
Since they were established in 2010, we have enthusiastically embraced the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, with particular attention to Section 9, which pertains to research involving Aboriginal participants.

**Additional editorial requirements:**

(1) Abstract needs a background section which includes context info in addition to the aims of the study.

The abstracts of manuscripts submitted to the BMC Public Health should be structured as follows:

- **Background:** This should place the study into the context of the current knowledge in its field and list the purpose of the work; in other words, the authors should summarize why they carried out their research.
- **Methods:** This should summarize how the study was performed and mention the different techniques employed. It should also include details of any statistical tests employed.
- **Results:** This section should describe the main findings of the study.
- **Conclusions:** A brief summary of the content of the manuscript and the potential implications of its results.

*We have changed the Abstract to reflect the requirements of the Journal.*

(2) Please see the attached file to ensure that your manuscript follows the correct structure for this journal and article type.

- Change 'Introduction' to 'Background'.
- Add 'Discussion' section.
- Add ‘Conclusions’ section.

*We have amended the headings of the manuscript to be consistent with the abstract.*

(3) Please include an Authors’ Contributions section after Competing interests. Please check the instructions for authors on the journal website for the correct format to use for Authors’ Contributions.

*We have moved the Contributions section below the Competing Interests section and have amended those section headings as suggested. We have also checked the Contributions requirements and are satisfied that we have provided the correct format.*

(4) Please note that we are unable to display vertical lines or text within tables, no display merged cells: please re-layout your table without these elements.

*We have removed the vertical lines from both Tables 1 and 2.*
(5) The figure file should not include the title (e.g. Figure 1... etc.) or the figure number. The legend and title should be part of the manuscript file, given after the reference list. Every figure must be cited in the text, using Arabic numerals.
- It is important for the final layout of the manuscript that the figures are cropped as closely as possible to minimize white space around the image.

*We have removed the title from the figure file and placed it below the Reference list. The figure is cited in the Results section, as Figure 1. We have also cropped the picture of the Figure to remove as much white space as possible.*