Reviewer's report

Title: Estimating past hepatitis C infection risk from reported risk factor histories: implications for imputing age of infection and modeling fibrosis progression

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Reviewer: maria prins

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General

This is an interesting study addressing the problems surrounding the use of age of first infection as a proxy for moment of infection in HCV progression studies. In general the paper is well-written but several parts might be difficult to follow for clinicians/basic scientist. The discussion is quite long and would benefit from shortening and focusing on the main objective of the present study. Furthermore, the conclusion should include a take-home message relevant and understandable for clinicians/basic scientist.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Abstract: Conclusion
Using reported age of first infection as time of infection is likely to produce a spuriously strong association between younger age with slower disease progression. This is somewhat misleading because this is only true when participants enter a progression study several years/decades after their start of injection drug use. If everyone would have been included in progression studies shortly after starting injection this is not likely to be a major problem. Therefore the authors should add to the conclusion the situation in which the situation described is valid

2. Methods
The authors collected data on whether drug users typically injected every day. However, the assumption for UHS that subjects current injecting frequency was typical for their entire IDU history is very unlikely to be reliable. Do the authors have data/literature references to demonstrate that this assumption is unreliable? Furthermore how was the WIHS information used: was the mean/median frequency over the total period since start injecting calculated or the median frequency of the periods in which they injected?

3. Results
Descriptive summaries. If I am right only WIHS participants with 8 years of follow-up were included in the present analysis. This is likely to introduce survivor bias. Moreover, was HCV status at that visit used or at the first visit. These details should be given in this section.

4. Table 1.
Add information on frequency of injecting.

5. Table 2. The increasing prevalence of HCV with increasing duration of IDU might be biased due to informative censoring. E.g. those with the highest risk are more likely to be infected earlier after their start of IDU and to die soon after starting IDU, resulting in an underestimation of the true prevalence at later durations following start of IDU in cross-sectional studies.
It is commonly assumed that around 50% become infected in the first year, which is in line with the data presented taken into account the underestimation mentioned above.
This paragraph should be changed taken into account these comments.

6. Table 5.
Change male into male sex.

7. Figure 2 illustrates... The authors should add some text to help the reader to interpret this figure e.g: the figure suggests that those infected at the age of 30 or less are ...., whereas those infected at .....etc.
8. Discussion
Earlier in this paper (see point 5) the authors mention that the common assumption is that most infections occur in the first year of infection, whereas here they suggest that the common assumption is that infection occurred at the reported age of first IDU, which might not be the same. I think the authors aim to say that in progression studies among IDU it is common to use the reported age of first IDU as the time of infection.

9. 4th paragraph end.
The end of this paragraph is about bias in prevalent cohort studies and has not that much to do with estimating past HCV infection risk from the reported start of injection. This paragraph can be shortened and one could refer to other studies that have been published on this topic.

10. limitations
It has been described that the risk of HCV chronicity rates vary by age with lower rates among younger individuals. If true, how could one accounted for this difference in the models. The authors should discuss this.

11. HIV co-infection.
In general injection drug users first acquire HCV and subsequently HIV because HCV is transmitted more efficiently than HIV by blood-blood contact. Therefore, the paragraph of greater susceptibility to HCV when HIV infection is present might be deleted.

12. A very desirable design would be following individuals from HCV seroconversion until progression of fibrosis and not the sub-optimal design suggested by the authors, although the latter might be more realistic.

13. Conclusion In particular, the use is likely to produce…… associated with younger age of infection. The authors should add: in fibrosis studies where individuals are included several years/decades after start of IDU use.

14 Table 3. Does time from start IDU until study entry influence the HCV infection risk?

What next?: Accept after minor essential revisions
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests