Author’s response to reviews

Title: Does alcohol use have a causal effect on HIV incidence and disease progression? A review of the literature and a modeling strategy for quantifying the effect

Authors:

Jürgen Rehm (jtrehm@gmail.com)
Charlotte Probst (charlotte.probst@camh.ca)
Kevin Shield (kevin.david.shield@gmail.com)
Paul Shuper (paul.shuper@camh.ca)

Version: 1 Date: 20 Oct 2016

Author’s response to reviews:

Dear Ladies and Gentlemen,

Thank you for your reviews and the opportunity to resubmit our article entitled ‘Does alcohol use have a causal effect on HIV incidence and disease progression? A review of the literature and a modelling strategy for quantifying the effect’ to Population Health Metrics.

Please find below a thorough revision of the above mentioned manuscript, where we believe to have responded to all of the comments of the reviewers. We changed the structure of the text as well following the suggestions of the reviewers, separating the empirical results of the example from discussion, which became a new own point. Finally, 23 new references were added. A detailed table containing responses to all reviewer comments is attached in a separate file.

We hope, the revision is now acceptable for Population Health Metrics and look forward to hearing from you.

Sincerely,

Charlotte Probst for the authors
Reviewer comments

Reviewer #2

1. Page 3, line 17 (using computer-generated lines on left hand side): something appears to be missing after "based on".

"Based on" is referring to the cited literature in brackets. We have clarified this link now in the revised version.

2. Page 4, line 8, wasn't alcohol the "main" factor experimentally manipulated? What else was manipulated?

"One of the factors" was removed and the statement was clarified.

Alcohol use was experimentally manipulated in all studies included in the referenced meta-analysis. Other factors such as sexual arousal were manipulated in some studies.

3. Page 4, lines 31-44: what about the pharmacological effect of alcohol on ARVs and medications used to treat side-effects (see papers by Manuela Neumann)? Would that not also have an impact on the efficacy of ARVs in people living with HIV and AIDS who drink heavily?

This point was added in the revised version and underlying literature added.

4. In the manuscript there is a great deal of emphasis on causality, it would be helpful to spell out to readers the criteria by which causality can be determined - e.g. association, temporal relationship, dose response effects, etc.

The underlying criteria for causality have been made explicit now in one paragraph and including references for additional considerations.

5. Page 4, lines 47-59 it would be helpful also to give a formula (in the text or web appendix) or at least a reference for how you got from 0.07 g/dl to 49g of AA for women and 61g for men.

The grams of pure alcohol corresponding to a BAC of 0.07 g/dL were derived from standard tables provided by NIAAA. The latter are now referenced in the manuscript.
6. Page 5, lines 11-37. Are there not other factors that could come into play in terms of whether a person without a condom who has sex with an HIV infected person becomes HIV positive? For example the woman might be using spermicidal gels (see work of Slim and Quarraisha Abdool Karim). The number of sex acts without a condom with an HIV-infected person is also crucial in determining whether the person becomes infected. These should just be mentioned. Re the link between alcohol and disease progression no mention is made of drinking increasing the likelihood of IV reinfection (though this would play into the point made by the authors that he estimates are likely to be under-estimates - with which I agree).

These considerations have been added.

7. Page 5, line 8, it might be useful to add after "high prevalence of HIV/AIDS" …. "and high levels of heavy drinking among males and females who drink (WHO, 2014)".

The sentence was modified accordingly.

8. Page 6 (lines 4-40) and page 7 (lines 16-20). It would be better to put this in a Discussion section (which is missing) and to follow the usual pattern of discussing the findings (with reference to what others have shown - e.g. how does adding the effect of alcohol use on the incidence or HIV effect WHO estimates which currently only include the effect of alcohol on HIV disease progression and what impact do you think it would have on the IHME estimates?), study limitations and future research.

We changed the structure of the article following the recommendations of the reviewer.

9. Page 5, lines 4—40, point out that future research needs to work on quantifying the dose-response relationship so we can move beyond a "step-function" approach, and also that as it becomes clearer how to quantify other aspects of the effect of alcohol on HIV disease progression, that they be added into the estimation.

The point was added in the new Discussion section.

10. Conclusion (p. 7) - the authors may want to make the point that the approach set out in this paper provides a step forward in better estimating the effects of alcohol on HIV and that further refinements and improvements in estimation can be made in future as it becomes
clearer how to measure aspects of the HIV/AIDS nexus that to date cannot be quantified well.

This point was added in the revised manuscript, albeit more clearly in the new Discussion section.

Reviewer #3

This article reads like a perspective piece rather than a research paper. It is not a systematic review, and does not incorporate modeling in any form that resembles standards of the field. Its basic point: If HIV-infected persons with BAC>0.07 continue to have sex at rates unmodified by ART and if intentions for risky sex predict risky sex behavior (a gigantic "if") then the population-attributable fraction of HIV deaths from alcohol is 4.5%. It's a reasonable argument, but the article overstates the rigor of the underlying methods.

We have elaborated both on the conceptual piece and on the modelling strategy in the Web Appendix.

Reviewer #4

1. The manuscript in many places is not clearly written. In many places, I had to read the sentence 2-3 times to try to guess its meaning. For example, line 46. Associations between HIV prevalence, incidence, mortality, ??? There are other places and it is suggested that the authors have the manuscript read by others less familiar with the work (someone outside the burden of disease area) to add clarity.

We carefully revised the manuscript to add more clarity.

2. While a major conclusion of the manuscript is the lower attributable risk, no description of the methodology is provided. The supplemental material provides a formula for PAF that is different from the standard formula, and although a reference is given for the formula, no explanation of this difference is provided. For excess mortality due to adherence, and the combined estimates, we are solely given references.

As alcohol use has not been included as a risk factor for HIV/AIDS in the CRAs in either the GBD or the WHO Global Status Reports with exception to the effects of alcohol use on non-adherence on the latter, we do not see this a the major conclusion.
The point in the original manuscript was that the current modelling results in lower estimates compared to applying the usual AAF formula (e.g., with 40.6% alcohol users in South Africa and a RR of 1.98 (1.59–2.47) as based on meta-analyses) would result in a PAF of about 28%.

We have given this example now as requested but in the discussion as one of many points why the chosen operationalization is conservative.

3. The manuscript states that the attributable fractions are substantially lower than in standard calculations, but the estimates from these are not given so there is no way to compare.

Now included (see answer to point above for details).

4. There is no sensitivity analysis.

We changed this phrase about the possibility for future sensitivity analyses.

5. The discussion of the causal link between alcohol and sexual risk taking does not mention event level studies.

We have added a paragraph on this topic.

6. The authors might want to consider that the cutoff for the biological impact of alcohol use is high. See Justice AC DAD 2016.

We have added Justice et al., 2016. In this sense, whether the cutoff is seen high or low is relative. Our threshold for inclusion of 60g per day surely are above the cutoff found by Justice.

7. The relationship between the PAFs for incidence (shown on page 5) and the burden of disease (shown on page 6) is unclear. If the latter is calculated from the former, it should directly follow.

We have turned around the succession. The relationships are made more explicit in the Web Appendix.

8. There is almost no discussion of the implications of the PAFs.
We have enlarged our discussion. However, we are not clear what exactly the reviewer meant by implications. We did add a number of sentences on health programming and policy implications.