Reviewer’s report

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

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Reviewer: Charles Parry

Reviewer's report:

This manuscript decisively moves forward the debate regarding the nexus between alcohol use and HIV and whether and how alcohol should be included in global burden of disease estimates. After reviewing the evidence the authors make a bold statement that we now have enough evidence to say that alcohol has a causal role in both the incidence of HIV and in the progression of the disease and that that this can be estimated - which is what the authors set out to do with reference to South Africa.

Please see comments below:

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

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

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?

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.

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.

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).

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)".

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.

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.

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.

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