Author’s response to reviews

Title: High prevalence of HIV, HBsAg and anti-HCV positivity among people who injected drugs: Results of the first bio-behavioral survey using respondent-driven sampling in two urban areas in Mozambique

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Author’s response to reviews:

Dear Dr Sacks-Davis,

We are submitting a revision of the original research manuscript titled, “High prevalence of HIV, HBsAg and anti-HCV positivity among people who injected drugs: Results of the first bio-behavioral survey using respondent-driven sampling in two urban areas in Mozambique” (INFD-D-19-01370). We appreciate the helpful comments from the reviewers and the opportunity to respond to them. Please find below our responses to each comment and the description of the changes to the manuscript.
All contributing authors have reviewed the revision and agree with this updated submission.

Sincerely,
Cynthia Semá Baltazar

Eva Matiko (Reviewer 1): The manuscript is clear and shares important findings on the topic. I noted a few issues that could be resolved through additional proofreading and minor edits. I am also proposing one suggestion for additional comparison.

Line 85-86 (page 4) has a sentence that repeats information in line 84
A: Thanks for catching this. We have revised accordingly.

Line 92 (page 4) citation referenced does not have the information provided (data as of 2017 while the citation was published in 1999)
A: The corrected citation is: The Global State of Harm Reduction 2016

Line 140-141 (page 7) provides a prevalence estimate, please indicate time period for that estimate
A: Included

Line 184 (page 9) please indicate whether this applied for self-reported positive as well
A: No. HIV positivity was assessed by biological testing

Line 194-201 (page 9) is repeated in line 201-208
A: Sentence deleted

Line 280 (page 13) indicates ... (up to three... This should be corrected to state ...(up to five...
A: Corrected
Line 348 (page 19) data cited in text is different from that in table 4 (170 vs 179)
A: Corrected

Line 392 (page 22) statement that "the majority of PWID with HIV were also coinfected with HBV and HCV" is inaccurate from the data presented (data indicates this "majority" is only for HIV-HCV in Maputo). Suggest using a different term such as "many PWID..."
A: Corrected

Line 397 (page 22) Prevalence value from citation is missing
A: Included

Line 416 (page 23) citation referenced provided for data on Tanzania. I recommend consider including a comparison and comment on the differences found between the two cities.
A: We have included a discussion of HIV prevalence estimates and regional characteristics of the epidemic in the country.

Heng Sopheab, MD, MPH, PhD. (Reviewer 2):

In summary, in this paper, the authors used the Mozambique IBBS conducting in March 2014 with a sample size of 492 people who inject drug (PWID) in two urban areas. The survey used Respondent
Dirven Sampling (RDS) to collect behavioral data and blood specimen to test HIV, HBsAg and anti-HCV. The authors reported the high prevalence of HIV, HBsAg and anti-HCV. Also, common HIV determinants in the both urban areas included longer duration use of drug injection (≥ 5 years), use of heroin as their primary drug of choice, other factors associated with HV are study sites specific. Finally, the authors suggested immediate implementation of HIV infection and hepatitis B and C prevention, care and treatment service for PWID; the evidence-based harm reduction intervention, also should be considered where possible.

Reviewing this paper, I have found the paper containing a significant piece of data useful for Mozambique HIV/Drug use program. However, there is a shortage of technical detail and structural issues of manuscript organization. Therefore, they must be further addressed, clarified, revised to improve the manuscript before it could be considered for publication. My comments are the followings:

Introduction
1- Line 84-87: “a systematic review determined…. but estimates in the region vary widely” (Degenhardt et al. 2017). The estimated HIV prevalence in sub-Saharan (56%) is higher than the global average (18%), could you elaborate why was that?
A: We cannot comment on why the regional prevalence is higher than the global. This likely has do with the nature of a generalized HIV epidemic in Sub-Saharan Africa. We suggest the reviewer reach out to the author of the systematic reviewer where the information was extracted.

2- Line 92-93: The authors mentioned that “… fund for harm reduction…. for PWID did not exist prior to this study”. However, on line 332-342, the PWID to some extent, reported access to new sterile needles, peer education, free condom, overdose treatment and HIV testing. Please clarify this inconsistency?
A: There is not an integrated harm reduction policy in Mozambique, although various elements exist within the National HIV and Mental Health Programs, such as free condoms, and HIV counselling, testing and treatment. Sterile needles are available to the general population at pharmacies, for diabetic patients for example, and are not explicitly promoted for safe injection drug use. The purpose of our analysis is to advocate for the importance of Integrated Harm Reduction Policy, specific targeting PWID.

3- Line 98-99: Why the first IBBS among PWID was decided in two urban areas of Mozambique? This should be rationally at least described in specific about the two selected urban areas in terms of population, economic, key populations including PWID size, gov/NGOs programs on HIV prevention, care and treatment, harm reduction? I saw fewer descriptions in the Study Setting (Line 118-122) but it did not give enough picture of the two cities and be helpful for the discussion later.
A: More clarification has been added on city selection.

Methods
4- The authors mentioned that the Formative assessment was conducted in the two cities with the communities prior to the IBBS, aimed at answering operational questions and feasibilities of the potential use of the RDS technique and other relevant questions. However, I did not see any conclusion from the formative assessment. Please at least describe a short paragraph your conclusion about this. Since later in the text, it could help you to answer questions such as why the collected samples did not reach the required sample size in Nampula/Nacala though you mentioned that large number of PWID in the area was informed by NGO (Line 121-123)?
A: A specific paper that describes the results of the formative assessment is currently under review for publication and is beyond the scope of this paper. The focus of our manuscript is to describe the prevalence estimates and associated risk factors.
5- Line 108: RDS was first mentioned in the text. Therefore, explanation on this could be better for readers what are not familiar with this, rather than to mention it very late in line 128-130.
A: An explanation on RDS methodology has been included in the Participant Recruitment and Sample size section. It did not feel appropriate to include it earlier on in the Methodology where we discuss the formative assessment and survey settings.

6- Line 115-125: The Study setting should be focused on the study area description (See my comments on Question #3) rather than mentioned about biological samples taking. I suggest moving line 117-118 (HIV, hepatitis B… anti-HCV) to under the Sample collection and testing (Line 175). Also, moving “Survey sites were private … and a security guard” from line 122-125 to under the Participant recruitment and sample size (Line 127) to avoid confusion and easy to follow.
A: We have edited the sample collection and testing section in line with the feedback. However, we decided to keep the description of the survey site to the Study Setting section because it is consistent the rest of the content in that section.

7- Line 122-123: How many survey sites were allocated in each city? This should be mentioned.
A: There was one survey site per city. We have added this information.

8- Line 130-132: How many seeds in total were recruited in the two cities stratified by at least sex and age group. I don’t see stratified subgroup by education and neighborhood of drug purchase or consumption were necessary since participants could lied you when dealing with sensitive questions and make the subgroup identified complicated for the fieldwork such as screening for eligibilities. Also, how many waves should be determined in advanced. As far as my experience and RDS theories 3-5 waves should be expected to achieve the equilibrium.
A: We have added additional information on seed selection in the methods section. In terms of waves, determining the number of waves in advance is not a feature of RDS. While RDS theory posits that equilibrium can be reached in 5 waves, this is theoretical, not implementation where one must commonly continue to recruit past 5 waves to reach stability.

9- Line 152: Participant eligibility section and its content should be moved to after the Study setting section. Generally, it makes sense to describe the eligible criteria before the participant recruitment or talking about the sampling.
A: Moved

10- Line 156-157: What does it mean “injected drugs without prescription”?  
A: This line refers to illicit drug use. In the Mozambican context, it is important to distinguish between prescription injection (eg. Insulin) from non-prescription injection (eg. Illicit drug use).

11- Line 164: Under this section, why the survey decided to use CAPI? The tool was pretested and well accepted? Please mentioned this briefly; this could affect the sample collection? I guess it may be part of your formative assessment to collect the information on this? Also, I am aware that tools were developed either in Portuguese or English. Is there any local dialect spoken language in the areas? Interviewers and field researchers were trained to collect the IBBS data? This should be mentioned to address partially internal QC process.
A: Corrected and clarified.

12- Line 175: Suggested changing Sample collection and testing to Biological sample collection and testing to be clearer.
A: Changed
13- Line 179-180: “Following national norm…HIV positive results… were not retested…” My question whether they were included and interviewed. However, I guess that they were not part of the QA (line 183-184). How the IBBS team reconciled this; and if the PWID lied that they were tested previously and the HIV was positive (in fact it was negative)? Was it possible?
A: Yes. Anyone who self-reported as HIV positive was included in the behavioural questionnaire. It is of course possible that a person can lie about their HIV status, and there was no way confirm this (generally one way to follow-up is to request the ART card as confirmation of diagnosis). However, per national guidelines we were not authorized to re-test and confirm HIV status. As a result, biological samples were not collected and subsequently not included in the QA analysis. The potential biases associated with self-report were explored in the limitations section.

14- In the sample collection, what amount of blood was collected, 5 ml or 10 ml for HIV, HBsAg and anti-HCV through veino-puncture on top of the DBS collected for QC? This should be mentioned.
A: All blood for point-of-care testing and for DBS were collected using a single finger prick. We have clarified this and also added the type of filter paper. Formative research revealed that participants would be less willing to test and provide blood samples if a venipuncture was required because they wanted to save their veins for shooting up. Also, venous blood draws on PWID can be especially challenging given the difficulty in finding appropriate locations to be able to do so.

15- I strongly suggest having three main paragraphs separately including blood collection process, blood sample testing and external QC process. Throughout the section, these were mixed up and hard to follow.
A: We acknowledge the suggestion. The authors suggest keeping the following structure: HIV test procedures, Hepatitis B and Hepatitis C.
The external QC was only performed for HIV test.

16- Line 193-208: Need to revise since many sentences are repetitive.
A: Thanks for catching this. We have revised accordingly.

17- Line 239: I don’t see any rational for putting incentives and ethical consideration together. I suggest moving “giving incentives to participants to under the Sample collection”.
A: The mention of incentives has been moved to Participant Recruitment and Sample Size section.

Results
18- Crude % in Table 1-4 should be removed since it was not part of your analysis using RDSAT. Also, it just brings confusion.
A: We have retained crude in table 1 to show effect of RDS on key demographics but dropped them from the remaining tables.

19- Line 347: This is the main part of your paper about measuring HIV, HBs. Ag, anti-HCV; therefore inserting a summary table should be needed on the prevalence and 95% CI by two urban cities after line 360.
A: We have added confidence intervals to all these estimates.

20- Line 43-46 in Table 5: it seems there were inconsistent in adjusting covariates in the multivariate model in the two cities. Why was that since you set any p value&lt; 0.2, potential
confounders… in the model? Though Akaike information criterion was used, was there any concerns of under or over adjustment particularly in a smaller sample size (n = 137) in Nampula/Nacala?
A: We agree this may not have been clear. We have changed the wording to reflect that the variables selected for the multivariable model were those p &lt;0.2 in bivariable analysis. For the multivariable model, full and reduced models were developed, and reduction criteria was based on AIC.

Discussion
21- Line 381- 391: The authors reported the high prevalence of HIV comparing to neighboring countries but not elaborate why was that? Brief explanation should be made about this higher prevalence such as cultural, belief, social or structural dimensions that have played a role in this higher prevalence?
A: A discussion of regional estimates has been Included on the first paragraph

22- In Table 3- 4, I have observed many differences of risk sexual behaviors and injecting drug use behaviors between the two cities. It maybe better to highlight few key variables and discuss such as paid sex, access to condom, pee educator, and % previous HIV testing? It could contribute to the harm reduction and HIV prevention formulation policy later.
A: Thanks for the suggestion. We have added more context in the discussion related to this.

23- Line 417-419: The authors discussed the low use and high access to new, unused syringes. Any harm reduction program locally run by at least NGO at these two cities, and any gov. policy on the harm reduction program existed in Mozambique?
A: Mozambique does not have a Comprehensive Harm Reduction Program. However, there was a project implemented by a non-governmental organization in some provinces which worked with a high-risk group, including PWID. The project interventions include voluntary testing and counselling in public health facilities

24- Could the authors elaborate in the study limitation on the low proportion of female PWID? I have been aware that IBBS team tried to stratify seed recruitment by sex and age group at the beginning; how many female PWID seeds recruited at the beginning; were there any program estimate, on what % of female drug users in the cities? This could give a gap estimate between the % female PWID in the samples and the estimated female PWIDS in the two cities.
A: Formative assessment revealed that females would be hard to reach and that they were few and very hidden (often watched over closely by their male counterparts). Community outreach workers, who were also current injection drug users themselves, made great effort in reaching out to known females in their social circles. In terms of seeds, we have added more information in the first paragraph.

25- Line 449-451, the authors mentioned on “… face to face interviewing ... are prone to social and undesirability bias”. Therefore, did the authors had trained the interviewers and pretested tools before the survey to ensure the quality of the data and minimize the bias? (See my previous question # 11). A: Yes. All interviewers were trained. Also, interviewers and annotators had a degree in social science disciplines and research experience with vulnerable social groups and HIV. In addition, all field staff had professional command of the Portuguese language and were fluent in local languages so as to ensure the comprehension of the participants. The teams were supervised centrally by survey researchers and the community liaison coordinator. We have added this information in the text.
Allison McFall, PhD (Reviewer 3): Thank you for the opportunity to review this study. This work aims to determine the seroprevalence of HIV, Hepatitis B and C virus infection among PWID in two cities in Mozambique and to assess other population demographics and risk behaviors. The authors use respondent-driven sampling (RDS) to recruit and enroll PWID. With no prior information on disease burden and risk behaviors among PWID in Mozambique, this paper fills an important gap in knowledge and provides data to guide implementation of prevention/health service needs for the population. Overall, the paper is clearly written with well described methods (though a thorough read thru is needed for small grammatical/spelling mistakes). There are a few minor comments below.

INTRODUCTION

Global HIV prevalence among PWID is stated twice in second paragraph.
A: Thanks for catching this. We have corrected accordingly.

METHODS

If no personal identifying information was collected from participants, how was prior participation in the survey assessed?
A: The same staff worked at a single facility for the duration of the survey. Community outreach workers staffed at the site and coupon managers were trained to be especially familiar with faces of participants. Also, the coupon manager would note specific markings (e.g. tattoos and scars). The interviewers also asked the participants about their previous participation in the survey. We have added this information in the text.

Last several sentences in the Sample collection and testing section are repeated.
A: Good catch. Corrected

Suggest dropping the first sentence in the Data analysis section on data cleaning, seems unnecessary.
A: Deleted

If space allows, could describe what "enhanced data-smoothing" is.
A: Data-Smoothing is a method for eliminating deviations in cross-group recruitments that occur due to chance and has been recommended for RDS data analysis. It involves a demographic adjustment of the recruitment matrix. It also produces narrower confidence intervals. We were asked to add this level of detail by a previous reviewer.

Can the authors clarify what is meant by "Results with denominator of less than 20 are excluded"? Would the sample for the logistic regression model not be all those with an HIV test/self-reported positive?
A: We agree this was not clear. What is meant here is that variables with fewer than 20 respondents were not considered for modeling, so for example questions that were only asked of female PWID. Since we don’t show any separate female PWID analysis we decided to exclude this statement.

Since participants with missing values are dropped from the regression model, the authors should include the extent of missingness (e.g., no more than 5% missing for any one characteristic).
A: Good suggestion. For modelling, we did not consider variables with high missingness in modelling. We have added this information in the methods section.
RESULTS

line 280-1: "(up to three [coupons] per participant)" - thought this was up to 5 coupons?
A: Corrected

line 286-7: Was there no difference in the proportion of active injectors (injected in prior 12 mo) before vs. after the eligibility criteria changed?
A: There was no difference. We believe there was a bottleneck in the network chains and changing the criteria removed the bottleneck and helped reach more active injectors. Analysis of key variables pre- and post-exclusion criteria change found no difference between participant composition. We have added this information to the limitations.

Did the authors look at whether the sexual or injection risk behaviors or HIV/HBV/HCV infection varied by sex (male vs. female)? There were few women but is worth looking to see if large differences exist.
A: Given the sample of females reach, we chose not to explore differences between sexes as no meaningful conclusions could be drawn.

Table 5 - Suggest adding model results for sex.
A: Sexual behaviours were excluded from the modelling because this question was only asked of the sub-population that was sexually active, of which they were few. A separate paper is being written about correlation between drug injection and sexual risk behaviours.

Table 5 - It looks like NO access to clean needles/syringes was associated with lower prevalence of HIV (OR=0.1). This seems counter intuitive. Can the authors describe why they think this is?
This could be related to the fact that people who already know they are at high-risk for having HIV or already know their HIV positive status are already aware of locations where they can get sterile injection equipment in order to reduce HIV transmission to their friends. This is not surprising and not different from findings we have seen in other surveys among FSW where those who have regular access to condoms or who use condoms regularly have higher prevalence of HIV. We have added this discussion in the text. We have added more in the discussion.

Table 5 - Suggest a sensitivity analysis for modelling daily injection in the prior 30 days - dropping those aware of their HIV+ status since this could cause a change in injecting behavior.
A: We agree that this would be an interesting sensitivity analysis, but feel it is beyond the scope of this paper. Separately some authors on this manuscript are working on a different manuscript specifically on HIV+ PWID.

DISCUSSION

Line 397 - Think the HBV prevalence estimate from other studies in Maputo among untreated HIV+ adults is missing.
A: Thanks for catching that. We have included it.

HCV prevalence in Nampula/Nacala seems low for an injecting population (7%), especially when compared to the HIV prevalence. Can the authors comment on why this may be?
A: It could be participants who refused testing were highest risk for HCV given the lack of HCV treatment in the country. This would lead to an underestimation of true prevalence of HCV in this
population. This has been included in the discussion section under the limitations. The finding also helps affirm that sexual transmission may play an important role in the HIV epidemic among PWID in Nampula. We have added this information to the discussion.