Author’s response to reviews

Title: Factors Associated with Vaccination Completion and Retention among HIV Negative Female Sex Workers Enrolled in a Simulated Vaccine Efficacy Trial in Kampala, Uganda

Authors:

Yunia Mayanja (yunia.mayanja@mrcuganda.org)
Andrew Abaasa (andrew.abaasa@mrcuganda.org)
Gertrude Namale (gertrude.namale@mrcuganda.org)
Gershim Asiki (gershim@gmail.com)
Matthew Price (MPrice@iavi.org)
Anatoli Kamali (AKamali@iavi.org)

Version: 1 Date: 12 Jul 2019

Author’s response to reviews:

Dear Editor,

We are delighted that BMC Infectious Diseases considered our manuscript for review. We have given careful consideration to all the comments from the reviewers and editor, and have addressed them all.

The following is a point by point explanation of how we have addressed the concerns and revised our manuscript. The line number(s) on the revised manuscript with track changes are specified to show the text representing each response.

Editor Comments:
Please pay particular attention to revisions required (or detailed response if not addressed) to Reviewer #2 suggestions for the title and methods. Also, please ensure all typos and grammar are checked and corrected.

Suggestions from Reviewer #2 have been considered and addressed, all typos and grammatical errors have been checked and corrected.

Reviewer reports:

Fiona Guerra (Reviewer 1):
1. Page 4, lines 97-100: Consider being more clear that this was done using a hepatitis B vaccine, and possibly why ENGERIX-B was selected as the vaccine to simulate an HIV vaccine. Is it similar to
HIV vaccines in trial in terms of number of injections or frequency or follow up?
Response: We have clarified that Hepatitis B vaccine was used to simulate an HIV vaccine in lines 121-122. Reasons for selecting hepatitis B vaccine have been included under the study design (lines 131-136). Though HIV vaccine trials will vary in terms of dose administration and visit follow up, we felt the three-dose regimen mimicked what might be a “typical” HIV vaccine trial.

2. Page 4, lines 110-112: Helpful to know if these visits (at months 3, 9, 12) also involved medication or testing or counselling as this might impact completion of these scheduled visits. For example, a participant might be more likely to attend a scheduled visit if it involved receiving a vaccine than if it involves only counselling. There could be value to expanding on the strategies to stay in contact with FSWs.
Response: We have added additional details to describe the procedures done at the other visits at months 3, 9 and 12 have been described in lines 147-150.

3. Page 6, line 154: I think the word "up" is missing from this sentence. Should it read "picking up volunteers..." or do you actually mean picking/selecting volunteers who needed help to access this clinic. Unclear.
Response: The sentence has been corrected in line 204.

4. Page 7, lines 176-184: In the first line you mention "the vaccine regimen". It might be helpful to clarify if this means the 3-doses at the scheduled times, or if it includes all 9 visits. If the additional visits are going to be critical to an HIV vaccine efficacy study, then you should consider reporting this as a secondary outcome.
Response: In this context, we are referring specifically to the vaccine regimen (i.e., the three visits where vaccine is administered, lines 232-233). We have made the study outcomes clearer in lines 229-235.

5. Page 10, lines 229-230: The language "attended up to the 12-month study visit" is unclear. It is unclear if this measurement is just attending the 12-month study visit, or having attended the visits "up to" and including the 12-month study visit. The problem is "attended up to".
Response: We have removed the phrase “attended up to” and clarified that the 212 women are those that attended the 12-month visit out the 239 who completed all vaccinations (line 298).

6. Page 12, lines 277-279: Is "community stakeholders" referring to the pimps and middlemen mentioned in the previous sentence? It could be clearer by providing examples of community stakeholders.
Response: In lines 376-379, we have included more information on stakeholders in sex worker communities and given examples.

7. Page 12, lines 283-287: It is interesting that there was no association between STIs and vaccination completion, but there is only one reference here. Is there only one study on this? Or is the reporting consistent and you are only providing one reference? Are there any studies that do show an association? I am asking more out of interest and also if there are other studies that show an association, then this needs to be rephrased because it is misleading.
Response: We agree with the reviewer that our reference to the one study that shows no association is misleading. In lines 385-387, we have included studies that found an association between STIs and Hepatitis B vaccination completion.

8. Page 13, lines 309-310/Results: The end of the results section is a good opportunity or segue to
report on a secondary outcome e.g. results for attendance at the other 6 scheduled visits that were not for vaccine doses.
Response: We acknowledge that retention at other study visits is a good secondary outcome to report. The paper is also interested in those that completed all doses of vaccination and yet at some of the earlier visits before month 6, volunteers had not completed all 3 vaccination doses. We have maintained the results to focus on vaccination completion and retention at month 12 for those who completed the 3 doses of vaccine.

9. Please review the entire manuscript for minor typos/spacing/capitalization etc.
Response: We have reviewed the manuscript for grammatical errors

Monika Doshi (Reviewer 2):
General Comments:
1. The authors tackle an important and timely issue. Suggest modifying title to more tightly fit the crux of the investigation (i.e., factors associated with retention and vaccination completion...).
Response: The title has been modified (line 1)

2. General flow and connections between paragraphs need to be strengthened further. Suggest linking paragraphs more tightly throughout the manuscript.
Response: We have reviewed the manuscript and strengthened links between paragraphs. Your comments and the comments from reviewer #1 have also very much helped to make this a more concise, clear paper.

3. Given that the scientific inquiry is timely and important, the authors may consider strengthening the manuscript by highlighting the Ugandan context in relation to FSWs and sex work. That is, the literature review can be strengthened with additional examples from the African context generally and the Ugandan context more specifically.
Response: We thank the reviewer for this comment. The manuscript has been revised to include the Ugandan context in relation to sex work and several more relevant references have been added in lines 108-113

4. Correct for typos
Response: The manuscript has been revised and typos corrected

5. The acronym list does not include all the acronyms from the body of the text. For example, the following (among others) are missing: AVD, MRC, UVRI. Suggest updating.
Response: We have updated all abbreviations in the acronym list lines 54, 55 and 63. The acronym AVD is for abnormal vaginal discharge. We already have VDS (Vaginal discharge syndrome) in the manuscript and acronym list and will maintain vaginal discharge syndrome in line 252. AVD has been replaced with VDS in Tables 1 and 2.

6. Consider revision of formatting, especially section headers, of the manuscript to conform to an existing template.
Response: In lines 127-278, we have revised section headers as advised

Specific Comments:

Introduction
Clarifications are required for the following:

1. Lines 65-69: How does HVTN702 relate to RV144? The mention of these together seems a bit disjointed -- recommend making the needed connections.  
Response: The text has been modified to show the links between vaccine trials from RV144 to HVTN702 (lines 71-76).

2. Lines 71-77: What are the other interventions being referred to here?  
Response: The other HIV prevention interventions which would be tested for efficacy and for which populations are being prepared have been listed in lines 84-85.

3. Lines 77 & 80: How is "good retention" defined? It would be helpful to specify this.  
Response: In lines 91 and 95, we have given specific figures reported by the studies.

4. Lines 83-84: What is meant by preparedness education? And what types of studies specifically?  
Response: We have made the statement clearer in line 98-102 and referred to preparedness studies rather than preparedness education and mentioned awareness and acceptability studies as examples.

5. Line 87: The current literature specifies terminology such as MARPs (most-at-risk populations) or key populations. Consider using one of these and providing reasons for why FSWs are more at risk. If the choice is to stay with characterizing FSWs as having high HIV incidence then consider providing related statistics.  
Response: We have used the term key populations and only refer to FSWs as an example of key populations. References that show high incidence and prevalence of HIV are included. This is in lines 104 and 107.

6. Line 90: Consider providing characteristics of FSWs in Uganda as opposed to India. The mobility of FSWs varies by context as well as by sex work type in India (e.g., street-based, brothel-based, home-based, etc.). It will be more important to characterize the context in Uganda.  
Response: In lines 108-117, we have revised the manuscript and focused on the Ugandan context of sex work, and added the relevant references.

7. Line 92: Consider elaborating on the criminalization and discrimination of FSWs specifically in the context of Uganda. It will be important to ground the introduction more specifically to the Ugandan context. This is largely missing from the manuscript.  
Response: This is a very good point, and the criminalization of sex work is a significant hurdle for these women to get both health care and to participate in clinical research. We have given more details on criminalization of FSWs in lines 108-113.

8. Line 99: It is unclear what is meant by site operational tools.  
Response: In line 124-125, we have given examples of the site operational tools (e.g., SOPs and QA systems) that were strengthened by implementing the SiVET study.

Methods

1. The clinic visit schedule is unclear. Consider using a table or some sort of a graphic to facilitate understanding.  
Response: The visit schedule has been inserted in a tabular form to give a better understanding of the
2a. For more clarity and to improve flow, consider combining the sections on "Study setting and source population" and "Sampling and eligibility criteria".
Response: The sections on study setting, source population and sampling have been combined to clarify the flow of participants from the main GHWP cohort to the SiVET study sample. This is in lines 154-173. After eligibility criteria, we have included withdrawal criteria in line 174-180.

2b. Line 123: Mention of ART causes confusion since the study is focused on HIV negative FSWs. Consider revising.
Response: We would like to mention that the main GHWP clinic enrolls FSWs irrespective of HIV status as stated in line 158. Given that this section describes the study source population, we have given an overview of main cohort procedures done for all women including the HIV positive. In addition, 7 enrolled women acquired HIV infection during follow up in SiVET. Specifics for HIV positives such as ART have been removed and we have maintained use of the phrase “care and treatment” in lines 162-163, 177. We hope this makes this section clearer.

3. What about determining/calculating sample size? There is no mention of this.
Response: We have included sample size calculation in lines 167-169.

4. Line 134: It is unclear what is meant by baseline safety assessments.
Response: The baseline assessments were done to assess for any clinical events before vaccination. We have corrected the statement in line 140-141.

5. Line 154: Was transportation provided? This is unclear. If so, how did the honorarium differ between those who received transportation and those who did not?
Response: A vehicle was only used to pick up volunteers who failed to make it for study visits as most responded to the phone call reminders. The statement has been made clear and the amount given to facilitate coming for study visits has been included (lines 203-206).

6. Line 155: What was the amount of the honorarium? This should be included.
Response: This has been included in line 206.

7. The laboratory methods section may not be required. Consider removing/deleting.
Response: The laboratory methods section has been shortened. Since we censored those who became pregnant and HIV infected, we have only included information on how these two conditions were diagnosed (lines 214-223).

8. Primary study outcomes: This section needs to be more clear. It is unclear, for example, how a volunteer would be categorized (retained or not retained) if they completed 2 of the 3 vaccination visits and the 12 months. That is, the primary study outcomes can be more clear here -- they become more clear as one reads on but that’s a bit too late.
Response: We have made the study outcomes clearer in lines 229-235.

9. Consider elaborating further on independent variables including whether any preexisting instruments/measures were used. How were the independent variables chosen/informed by literature? Why those and not others, for example?
Response: The choice of independent variables (behavioural characteristics, clinical characteristics)
was informed by literature review of multi-dose vaccine studies that have assessed vaccination completion and/or retention (lines 242-244).

We collected data using pre-designed interviewer administered questionnaires as indicated in line 228.

At analysis stage, independent variables to adjust for were chosen based on log likelihood ratio tests and details have been included in lines 274-278.

10. Line 205: Unclear what is meant by total expected.
Response: In lines 266-267, we have clarified that the total number expected for month 12 (denominator) was all those who had received 3 vaccination doses and had not been censored between month 6 (3rd Vaccination) and month 12 (last study visit).

11. Lines 207-211: More details need to be provided regarding the statistical analysis for both the bivariate and the multivariate analysis. What models were tested and how?
Response: We have included details of the statistical analysis and the models tested in lines 274-278.

12. Overall this section needs to strengthened. Currently, there is information here that is not essential (e.g., laboratory methods) while pertinent information is missing (e.g., sample size calculation).
Response: We have considered all reviewer comments and addressed them in order to improve the methods section.

Results

1. Line 217: Unclear what 'citing frequent blood draws' means. This can be made more clear.
Response: The statement has been made clear in lines 284-285.

2. Line 219: Consider providing the age range of the sample instead of IQR.
Response: We have added age range (18-56) in line 285.

3. Line 221: How has the volunteer not reporting exchanging sex for money, gifts, etc been categorized? As a FSW? How is the current study defining FSWs?
Response: We are defining FSWs as women who exchange sex for money, gifts or other favors. This variable was asking for sex in exchange for money, gifts or favors in the past 3 months so the one volunteer who answered no was still FSW but had not exchanged sex for money in the past 3 months. Line 250-251 gives the definition next to the variable.

In addition, lines 108-111 mention that FSWs in Uganda have different social structures, and some do not rely entirely on sex work for their livelihood.

4. Table #1: Consider breaking down the age group "35+" further as this will give a better descriptive sense of the study population.
Response: We recognize why the reader might be interested in seeing these data, however we had initially categorized age as indicated below, and, we noted that retention rates were similar in the age categories 18-24 and 25-34; thus we combined those two strata. Furthermore the category 35+ had only 62 participants, creating more categories within this created sparse data. Therefore we would like to
maintain age categories as (18-34, 35+).

<table>
<thead>
<tr>
<th>Age (years) Category</th>
<th>Total</th>
<th>Completed All Vaccinations</th>
<th>Completed All Vaccinations and Month 12 visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>85</td>
<td>(29.3)</td>
<td>67 (78.8)</td>
</tr>
<tr>
<td>25-34</td>
<td>143</td>
<td>(49.3)</td>
<td>114 (79.7)</td>
</tr>
<tr>
<td>≥35</td>
<td>62</td>
<td>(21.4)</td>
<td>58 (93.6)</td>
</tr>
</tbody>
</table>

5. Line 232: Addresses 18 volunteers. What about the remaining? Consider combining with the sentence that follows to facilitate flow and ease of understanding.
Response: The statement has been modified to make the flow better (lines 300-302)

Response: We have added the variables adjusted for in the multivariable model at the footnote of Table 2 in line 315 i.e. age, genital ulcer disease in the past 3 months and condom use with a new partner(s).

7. Table #2: Consider inserting into the body of the manuscript as opposed to the Appendix/end of manuscript.
Response: We agree, this has been done to conform to journal requirements (lines 314-315).

8. Consider reporting other findings, including those that are insignificant as this is the "Results" section.
Response: In lines 311-312, we have mentioned variables that we did not find significant even though other studies have reported them to be associated with retention or vaccination completion.

Discussion

1. Line 244: How can the retention rate of this study be explained further? It is on the lower end of the ranges reported by other studies. What does this mean or imply for the way forward?
Response: We have explained the lower retention with the Ugandan context of FSWs in perspective in lines 336-343.

2. Lines 253-257: The current study's retention strategies don't seem to support or counter the named barriers to retention. So, this begs the question, what did the study do differently?
Response: The study set out to assess vaccination completion and retention of FSWs in a simulated vaccine trial with frequent study visits and blood draws (given structural barriers concerning legality of their work in our setting). Since they are potential participants in future trials and this was among the first SiVET studies being done among FSWs in SSA, we used existing strategies to get a baseline.

The retention strategies (though not completely novel) have been discussed as having been important for the team to attain the retention of 78% in a setting where sex work is not supported by the social structures (lines 340-346).

3. Overall: The discussion section highlights were the study's findings converge with past findings. However, it is unclear what new knowledge or current gaps in extant literature have been filled by this study. The authors should consider being more pointed and direct about how their study advances scholarship. It may also be important to contextualize to the Ugandan context and also provide related discussions and explanations.
Response: Lines 336-346 have been re-written to highlight sex work in the Ugandan context and how it may affect vaccination completion and retention of FSWs in trials.

Limitations

1. Consider elaborating on this section. For example, how does context and study design shape limitations, including generalizability?
Response: We have expanded on the study limitations in lines 415-420.

2. The authors have also included study strengths in this section. Consider revising the header to "Limitations & Strengths".
Response: We have done this in line 414.

Conclusions & Recommendations

1. This section needs more information. Consider summarizing key study findings, their implications and related implications in more depth.
Response: In lines 427-436, we have included more information and summarized key findings.

We thank the editor and reviewers for these comments and feel that the manuscript has been greatly improved. We hope it will receive favorable consideration for publication in BMC Infectious Diseases.

Thank you for the consideration of our manuscript

Sincerely,

Corresponding Author
On behalf of all authors