Author’s response to reviews

Title: “Effects of antiretroviral therapy among HIV positive adults on HIV infections among young women: a systematic review protocol”.

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Responses to Reviewers Comments – Project ID: SYSR-D-18-00421

Please find below a point-by-point response to the issues raised by the reviewer and the editorial requests. The changes made to the manuscript are highlighted in track changes in the revised version.

Original Title: Effects of antiretroviral therapy in HIV positive adults on new HIV infections among young women: a systematic review protocol
Editorial comments:

1. Since the authors planned to conduct a meta-analysis if studies are eligible for, authors should include the term “meta-analysis” in the title and throughout the text when necessary. For example: “Effects of antiretroviral therapy among HIV positive adults on HIV infections among young women: a systematic review and meta-analysis protocol”

We appreciate the editors’ view regarding the protocol title. However, meta-analysis is contingent on the data we find. Meta-analysis being one of many methods we can use to synthesis data, it does not define this work. We have therefore kept the title unchanged: “Effects of antiretroviral therapy in HIV positive adults on new HIV infections among young women: a systematic review protocol”.

2. It is not clear why authors focused in Southern (and Eastern) parts of Africa in the first, second, and third paragraph of the background since this is a global review.

We thank the editor for this comment and understand the importance of reporting on global statistics in our manuscript. We single out Eastern and Southern Africa to highlight the HIV/AIDS burden relative to the global statistics. Our approach in summary: in the first paragraph we highlight the high level global statistics on HIV/AIDS pandemic and go on in paragraph 3 to emphasize the burden in East and Southern Africa regions which are the most affected. In paragraph 4 we zoom into the population of interest: young women. Throughout the background introduction we do highlight the global statistics paying attention to the specific reported statistics in the region of high burden. We then end the background introduction by highlight that the work that will precede this review will only focus on a specific country i.e. eSwatini - formerly known as Swaziland.
3. The importance of the 4th paragraph of the Background section is not clear for me since the review will not focus on key populations.

We agree with the editors’ comment and have rephrased paragraph 5 to highlight and acknowledge that the HIV/AIDS pandemic is also a well-known problem for the key population. However, this will not be the key focus of our current work.

4. In the second paragraph, you talk about the HPTN 052 trial that reported a decrease of 96% of HIV transmission. It would be interesting to have a balanced information on this field since there is also a RCT conducted in South Africa that reported a non-significant effect of “test and treat” strategy on the incidence of HIV in adult populations


We thank the editor for this comment and we agree with the need to have balanced information. We have now included a brief to include the ANRS 12249 trial in paragraph 2, reading: “On the other hand, the ANRS 12249 trial showed no decrease in the HIV incidence as a result of universal test and treat and suggest that if the conditions necessary (linkage in care, ART coverage, ART adherence, retention on treatment) are not met, the benefits of universal test and treat are unlikely to be realized. The ANRS 12249 trial however provided strong evidence on individual benefits and recommended the roll out of universal test and treat without any restriction.”

5. It is not clear in the Background section why the authors have chosen to focus on young females rather than considering both females and males.

We have motivated the burden of HIV to be more predominant in the females as opposed to their male counterparts, see paragraph 4. We have also indicated the age-disparate relationships that seem to be cushioning the spread of the virus among the female population, paragraph 4: line 122-124.
6. Types of participants. Write more for this paragraph. It should be clear that authors will include studies that included HIV infected adults with antiretroviral treatment. AND that the outcome will measure the incidence of HIV infection in young females.

In line 163-164, we have indicated the types of participants: We will identify studies that include young women aged 15-24 years who are not infected with HIV. The studies should also include HIV infected adults who are on antiretroviral treatment. Furthermore, we have in line 171 indicated the Primary outcome to be measured.

7. Secondary outcomes: for all these outcomes, clarify whether the population considered = young females 15-24 years.

We thank the editor for this comment, we have added the following clarifying paragraph from line 177-179: “The information collected here will be for young women aged 15-24 years. This information will help in synthesizing the information of the conditions necessary to realize the results reported in the primary outcome.”

8. Data synthesis. Please write on

- Publication bias.
- Software and package for meta-analysis.
- Prediction interval (https://bmjopen.bmj.com/content/6/7/e010247)

We acknowledge the reviewer comments and have included in line 245-246 an address on how publication bias will be assessed i.e. “Funnel-plots and Egger’s test will be used to determine publication bias.” and in line 253 indicated the platform where all the analysis will be done, i.e. “All analysis will be performed using R software”. We further rephrased line 249 to read “If the I² statistic is high (75% to 100% - as suggested by Higgins et al.) indicating high heterogeneity, a random effects model will be used and we will report prediction interval (PI) as opposed to CI for better appreciation of uncertainty around effect estimate”
Reviewer #1

9. Could not understand line 93 "Since the 1980's, HIV/AIDS disease burden has not been even across different regions, countries and populations." Please rephrase

We have rephrased this sentence in paragraph 1, line 93 to read: “HIV/AIDS disease burden varies considerably across countries, regions and population.”

10. Could authors better explain exclusion criteria? For example, cannot understand why the rejection of the pediatric population if authors wish to include adolescents aging 15+. Please see guidelines elsewhere (example http://pediatrics.aappublications.org/content/81/5/736.long). Also, why not in younger?

We appreciate the view of the reviewer and grateful for the guideline provided. Our concern however is to focus on the sexually transmission and more precise measure HIV incidence in the younger population aged 15-24 years were we hypothesis that HIV infection is mediated by age-desperate relationships. We have rephrased the exclusion criteria in line 193-194 to read: “We will exclude studies that focus on: paediatric population (defined as infancy, between birth and 2 years; childhood, 2-12 years and early adolescence, 11-14 years)”.


We appreciate the reviewers point raised in this comment. However, the dynamics of sexual transmission via assault are expected to be different from other forms of cross-generational and transactional sex transmissions. In our current review, our working framework does not cater for rape dynamics we will therefore not be considering HIV transmission through assault.
12. I applaud you for your efforts for taking on a systematic review for this topic. However, I think this protocol has several methodological issues that need to be addressed. From what I read in this protocol, you are trying to look at population-level incidence of new HIV among young women in an ART intervention setting. As this protocol is currently written, I am not sure if this systematic review will yield meaningful results. I provided several areas I wish for you to revisit as a research team

We thank the reviewers for the positive comments. Below we address the areas that have been identified by this reviewer that needs revisiting.

13. "We will conduct a comprehensive search of MEDLINE (PubMed)". This needs more clarity, are you searching both Medline (the US National Library of Medicine) and PubMed, or just Medline? Although Medline and PubMed are quite similar (PubMed contains what is in Medline) they do have differences, please read here: [https://www.nlm.nih.gov/bsd/difference.html](https://www.nlm.nih.gov/bsd/difference.html). I highlight this difference because searching pubmed.gov yields different results than searching nlm.nih.gov.

We thank the reviewer for highlighting this, we however note that the differences as highlighted in [https://www.nlm.nih.gov/bsd/difference.html](https://www.nlm.nih.gov/bsd/difference.html) between PubMed and Medline will not affect our search results since everything in MEDLINE is in PubMed.
14. Thank you for providing the PRISMA-P checklist in the supplement. I would like to see the checklist filled out with the details of this proposed study, and not just refer to lines in the manuscript where the information can be found. Checklists are helpful for making sure you report the items, but the items reported in this protocol need more description.

We thank the reviewers for the positive comments. Precisely, the PRISMA-P checklist does not provide a way to detail description of the item being reported however provision is made to provide line numbers as referenced in the protocol where the detailed description is located/provided. We have revised the PRISMA-P checklist to reflect the revised protocol changes.

15. As it is written, the types of participants, types of interventions, and types of outcomes are a bit confusing. The stated objective of this systematic review are broad (to summarize the effects of ART in HIV positive adults on new HIV infection among young women aged 15 to 24 years) and the inclusion criteria are narrow (exclusion criteria: children, PREP, mother-to-child, MSM, TG, FSWs, and IDUs). You are looking at ART interventions for HIV positive adults 18 years or older and your outcome is new incidence of HIV in young women 15-24 years. Do you expect intervention studies to report on the incidence of HIV in young women 15-24 years? Are these young women only in South Africa, or only in places where ART interventions are taking place? I suggest you revise the research objectives to describe PICOT - population, intervention, control, outcome, and time frame.

We appreciate the reviewer’s comments and have provided more clarity on the type of participants in line 163-164, type of intervention in line 167 and type of outcomes in line 171. Furthermore, we do expect that for those studies identified to meet the inclusion criteria these will report on incidence of HIV in young women 15-24 years or alternatively, the reported HIV incidence should be adjusted for age. More importantly, the reported statistics on young women would be from places where ART intervention are taking place not just South Africa.
16. You describe how the risk of bias will be handled for randomized and non-randomized studies. How do you plan to handle conference abstracts and grey literature sources? I would like to see more detail regarding how the grey literature will be assessed and included in the synthesis of results. Grey literature is not peer-reviewed research and should not be lumped together with peer-reviewed literature. I suggest using the AACODS Checklist to appraise the grey literature.

We agree and appreciate the reviewer suggestion. We have now modified the included in line 206-208 the following sentence “We will search for grey literature to identify any relevant unpublished literature and the identified literature will be appraised through the Authority, Accuracy, Coverage, Objectivity, Date and Significance (AACODS) checklist”

17. "If the studies are relatively homogeneous in terms of methodology and outcomes, meta-analyses of the data will be performed". You need to decide beforehand whether you are conducting a systematic review, a meta-analysis, or a systematic review and meta-analysis. Systematic reviews and meta-analyses are conducted for different reasons. Systematic reviews are used to provide a complete and exhaustive summary of the research question. A meta-analysis refers to statistical methods of combining evidence in order to assess the utility of an intervention or the validity of a hypothesis. Conducting a systematic review and meta-analysis can provide a robust answer to the research question. How will the meta-analysis help achieve the study objectives? What research question is the meta-analysis answering? Do you anticipate having enough results to perform a meta-analysis? Are you going to include grey literature in the meta-analysis?

We thank the reviewer for raising these questions and we do agree with the definitions as outlined by the reviewer. However, the decision to conduct a meta-analysis in a systematic review is contingent on the availability of sufficiently homogenous and poolable data. We cannot be absolutely certain a meta-analysis will be conducted at the protocol stage. In this work, meta-analysis is planned, but not guaranteed. In the event that we do conduct a meta-analysis we will add that to the title of the full report, but not the protocol as it might be misleading to readers.
18. "The extraction form will be used to extract relevant data from the eligible studies such as: bibliometric information, participants' demographics, study location, reported outcomes and measures of effect related to the risk of HIV infection among young women in the study, and other outcomes." Will the extraction form be used to provide a narrative synthesis of the results or will you provide a study summary table?

Yes, the extraction form will provide information that will be used for the narrative synthesis of the results. Contents of the extraction form with all the extracted information will also be submitted together with the final manuscript as an appendix to the final manuscript.

19. When writing up a protocol for a systematic review or meta-analysis, it is important to look at examples of protocols that have been published in the journal you are submitting to. Please look at the following: Systematic review and meta-analysis protocol from Sicotte et al (2014): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5372295/ and Systematic review protocol from Bigna et al (2017): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3922999/

We thank the reviewer for these suggestions and we have used these examples to improve our protocol.