Dear Editor,

Re: BMJ-2019-049143

Working title: Unmasking the vulnerabilities of children exposed to HIV and/or antiretroviral drugs
Revised title: Unmasking the vulnerabilities of HIV affected children

Authors: Vundli Ramokolo, Ameena E. Goga, Amy L. Slogrove, Kathleen M. Powis

Thank you so much for the feedback. Please find attached the revised manuscript with changes highlighted in yellow. We thank you for the opportunity to revise the manuscript. We are grateful to the reviewers and editors for their insightful comments and suggestions as they have strengthened the manuscript. A point-by-point response to each of their concerns is below. The reviewer comments are in bold text.

Yours sincerely,
Vundli Ramokolo

EDITORS' COMMENTS TO AUTHOR:

Comment 1: Regarding terminology (raised on other articles in the collection). Across the collection, we are recommending to use "VT" rather than PMTCT, and would guide the authors to do this. This would entail defining VT early on, and here the authors can state the equivalence with MTCT.

Response: Thank you for this suggestion. We have added the words "vertical transmission" in lines 20,86, 161 and 222.

Comment 2: Around the time of preparation of this piece, we noted some recent articles on HEU that may be relevant for the authors to consider (one is a commentary written by two of the present authors). I am not saying the authors definitely need to cite these, but it's just to give you the chance to make sure all data are as up to date as possible:

https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(19)30007-0

/https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(19)30023-9/

https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(18)30361-8/

Response: Thank you for the recommendation. We have considered the articles and included reference to the LeRoux et al manuscript.

Comment 3: On the editors' first read of the paper, we felt that the article does not quite present the clear argument or analytical thread that we hope for in an Analysis piece, however the topic is very important and there would be great value in having an article with this focus within the Collection in BMJ. We found (as also noted by a reviewer) the definitions presented are very useful, and there is an argument made regarding the value of monitoring, and outstanding dilemmas regarding this. However, the argument for monitoring is not made as clearly as it could be, since it's not clear to the reader how this might resolve the issue that many questions around mechanisms of risk for HEU children are unresolved - and that presumably routine data will be of poorer quality than research (trials/cohort)

data, so may not be geared up to answer these (one of the reviewers highlights this too). So more clarity is needed to understand the purpose of monitoring data, what value this will bring distinct from specifically-designed research studies, etc. A clearer narrative thread is needed.

Response: Thank you for the feedback. We have made substantial changes throughout the manuscript to make the main arguments clearer. Regarding the value of monitoring, we argue that data from both research studies and routine monitoring systems are needed. While well designed research studies can identify targeted outcomes, monitoring programs identify population trends, and therefore are more adequately powered then all but the largest of cohort studies. Furthermore, health and educational systems are already monitoring key metrics such as survival, growth, and academic achievement. Monitoring and reporting of these metrics by a child's HIV and/or ARV exposure status will not only allow for reporting of outcomes but will identify vulnerable children most in need of interventions. Conversely, while studies may identify "at risk" HIV affected children enrolled in their study, a study does not have the population reach of a national monitoring system.

Comment 4: The authors might consider hiving off the "definitions" part into a box, for example which presents the various acronyms and definitions, and this would save space for more room in the text to develop the various arguments.

Response: Thank you for the suggestion. We added a Table with definitions for sub-groups of HIV affected children (please see Table 1). All acronyms are not spelt out in full in the manuscript for easy readability.

Comment 5: The editors are happy to discuss options for taking the piece forward anytime the authors would like in order to develop it further along the lines of what we aim for in the Analysis section - perhaps when the authors have had a look over the reviewer comments and considered how to proceed.

Response: Thank you for the meeting on the 30th of April.

REVIEWERS' COMMENTS:

Reviewer: 1

Comments:

This is a well-written article which clearly outlines the issues regarding health and development of HEU children and how we should both investigate and manage these. I have a couple of small comments which need to be addressed and a few ideas for the authors to consider.

Comment 1. p5, line 53 to p 6, line 5: The authors mention the disadvantage of the large Zimbabwean study in that it was conducted when ARVs were hardly available so it can provide no data relevant to today's ARV-exposed cohorts. However, it also be mentioned that it provides an important, and now vanishingly rare, study of the effects of HIV exposure alone, without the complication of varying ARV regimens.

Response: We agree with the reviewer that the data from the Zimbabwe study, and other similar studies conducted prior to the availability of ARV drugs, provides important information about the effect of HIV exposure alone and have amended the text accordingly (please lines 133-139).

Comment 2. In their discussion towards the end on the Way Forward, the authors discuss the practical and ethical issues of routine monitoring of HEU children. However, I think the way forward needs to start by getting more good quality research data in order to determine which groups, including HUA and EHE, have any excess risks at all, what these are, and what cost-effective interventions are available to mitigate risks. If there is no problem or no solution, then implementing a surveillance programme is not a priority.

Response: We agree with the reviewer that effective surveillance is dependent on the availability of good quality data. We have amended the manuscript accordingly. Please see lines 179-181

Comment 3. The 2nd and 3rd key messages are quite similar and could be combined.

Response: Thank you. We have amended the key messages.

Comment 4. Page 4. line 55: It is not clear what is meant by 'efficiency' of ARVs.

Response: The term “efficiency of ARVs” refers to the efficiency of ARV drugs in managing the maternal HIV disease through viral load reduction and an improvement in the CD4 count

Comment 5. Page 10: Reference #9 seems to have got messed up.

Response: Thank you, we have made the correction on the reference.

Reviewer 2

Comment1:

This is an analysis paper regarding the importance of understanding and monitoring of children born to mothers infected with HIV. This is an incredibly important topic, and the authors’ have extensive international expertise and leadership in this area. This is a strong paper that brings up some critical points to consider regarding the vulnerabilities of this population. Having a clear message about this topic helps stakeholders and clinicians understand the current state of HEU children and is tremendously valuable. I strongly recommend that this paper be published, however, in order to maximize its impact and clarity, I have a few suggestions to consider.

Of note, I commend the authors for highlighting the HUA and EHE groups. I don’t think I’ve seen them as clearly defined as they are here. This paper can be an origin point, of sorts, for the use of these terms to describe their respective populations.

Response: Thank you for the feedback

Comment 2: Introduction- It would be valuable to clearly indicate what specific areas appear to be affected within the research on morbidity and mortality of HEUs. The paper generally speaks of health and development early on, and only later notes its association with worse language, growth, and immunity. Being clear/specific early on regarding the evidence would be of great benefit to those less

familiar with this topic and can strengthen the case for why more comprehensive monitoring should take place.

Response: Thank you for the comment. We added more evidence on health disparities of HIV exposed uninfected children in the introduction (please see lines 92-95). The tight limit on the word count and number of references prevented us from expanding more on these health outcomes.

Comment 3: Page 4, "Definition of Exposure Status"- Line 35- the authors listed, "indirect/environmental HIV exposure through an HIV-affected household," which is a valid exposure that many clinicians may not consider (making it even more important to highlight). However, there isn't a lot a clarity about what this means. In the following sentences discussing the heterogeneity of the HEU group, it is unclear if Lines 44-47 are referring to the indirect/environmental HIV exposure through an HIV-affected household or just the general heterogeneity. Additionally, it is unclear how this exposure is the same/different/related to the EHE population, which is mentioned at the end of this section (page 5, lines 33-47). This section would be much stronger if this specific area is made clearer.

Response: The term "indirect/environmental HIV exposure through an HIV-affected household" captures the negative socio-economical and health consequences of living in an environment that is affected by HIV or HIV-related chronic illness. This is the same group of children referred to as the environmentally HIV exposed population referred to in line 143. We have made some changes to the text (lines 137-139) and added a Table of definitions (please see Table 1) for clarity.

Comment 4: I was enthusiastic when reading the ideas laid forward by the authors regarding routine monitoring and how data platforms could help collect information about this population and brings up the need for unique identifiers that can follow a child to adulthood. This would be incredibly valuable and a way to benefit children in ways beyond HIV exposure as well. However, I was a little confused when the discussion switched to disclosure of status. I completely agree that the child should be aware of his/her HIV or exposure status. However, the authors also highlighted that long-term monitoring needs to consider disclosure to those who monitor outcomes or provide interventions. Who are "those" groups? (Page 7, Line 37-39)

Response: Thank you for the comment. We made changes to text for clarity (please see lines 206-226)-193)

Comment 5: Page 7, Lines 39-42- the author's note that documented HIV status for healthcare purposes would disclose a mother's status, and that presents an ethical dilemma. I'm not sure if I follow this. Are the author's talking about medical records? And if so, are they concerned that the data documented within these records are not secure or that people are not willing to share their status or be tested within the healthcare system, making this issue ethically challenging? I may be naïve in this area, but I didn't realize that any of those points might be issues. However, if disclosure is a challenge within healthcare, it would be important to expand on why this is the case.

Response: In this section of the manuscript we are referring to the broader and long-term (beyond the breastfeeding period) disclosure of the child's HIV exposure status, and therefore the mother's HIV infection status, to pediatric health care providers, school teachers and other key professionals who are integral to the child's development. This disclosure is broader than the PMTCT programme and therefore presents an ethical dilemma as benefits may not outweigh or balance out potential harms such as stigma or trauma. Please lines please see lines 206-226.

Comment 6: During Page 7 lines 46-51, who are the authors referring to when they're discussing disclosure of a breastfeeding mothers' status? Health care settings, studies, surveillance, or interventions all may request information regarding HIV exposure or infection status. I wasn't under the impression that many individuals refuse to provide this information if it were otherwise kept confidential, perhaps I'm wrong. Further clarification (see above) would be appreciated.

Response: Many people living with HIV continue to experience stigma and discrimination, even in high HIV burden settings. Therefore, they often refrain from disclosing their HIV status to healthcare providers who are not providing their primary HIV care In lines 214 to 215 of the manuscript we are referring to the disclosure of the mother's status to health care providers and other personnel that monitor child outcomes.

Comment 7: Page 7, lines 53-54, Which article within the International Convention on the Rights of the Child are the authors referring to with their statement that specific health care providers need access to

their HIV and or ARV exposure status throughout their lives? Could providers just directly ask their patients about it, like other exposures that can negatively affect one's long-term health (ACEs, tobacco or alcohol consumption, etc)? Or if more specific data regarding in utero exposure is needed, could there just be a push for individual patient identifiers that are linked to a parent from birth to resolve this issue?

Response: We are referring to article 24 of the International Convention on the Rights of the Child. Yes, the providers can ask the patients about their perinatal HIV and/or ARV exposure. The completeness, accuracy and usefulness of the self-reported exposure status will depend on whether these patients have been disclosed to about their exposure status. The issue is that many parents have been told that if their child in HIV uninfected, they are fine. Therefore, parents see no need to inform their children about their HIV exposure status. One way of circumventing the weaknesses of the self-reported HIV exposure status is to link the mother and child health records, as per your suggestion. However, this approach may raise ethical issues relating to the privacy of the mothers and/or child health information. Please see lines 214-226 in the manuscript.

Comment 8: Again, overall, I think this is a fantastic paper that discusses an important topic, and I'm grateful the authors put this together. It will be valuable to the scientific community and I recommend it for publication, with consideration of the suggested revisions.

Response: Thank you so much for the insightful feedback.

Comment 9: Please check the citation style within the text.

Response: The references have been checked and converted to Vancouver referencing style.

Comment 10: Page 6, line 15- Please consider revising the phase: "well thought through long-term prospective cohort study designs." Having 7 adjectives before "designs" is difficult to follow, even within such an important statement.

Response: Thank you for the comment. We have revised the text. Please see lines 29-31; 154-156.

Comment 11: Page 6, line 29- ART was used instead of ARV for the first time- likely unintentional.

Response: We have amended the text.

Reviewer 3:

Comment 1:

This is a timely and important topic. The number of HEU children is rapidly rising and is becoming one of the largest HIV affected populations. The authors present a nice and balanced discussion of the need to invest in the long-term follow up of these children. Interesting discussion is also presented for HIV unexposed but ARV exposed children born to mothers using PrEP during pregnancy, and HIV and ARV unexposed children living in households affected by HIV. The paper presents the need for defining exposures, encourages prospective cohort studies of HEUs and routine follow up of HEU with a trigger based approach, and discusses the issue of maternal HIV disclosure and HIV stigma in having the HIV/ARV exposure status linked to a child's health record.

Response: Thank you so much for the feedback.

I have a few minor comments:

Comment 2: In the second Key Message which start with "This" – I am not sure what "This" refers to. I suggest editing to increase clarity.

Response: Thank you for the comment. We have revised the key messages. Please see lines 18- 36.

Comment 3: In the Standfirst it is stated "…that short and long-term monitoring of HIV and/or antiretroviral (ARV) exposure in children is critical to identifying ways of improving individual clinical care…". This statement is not quite clear as it is not HIV and ARV exposure that is monitored in the children but rather the health of the HEU children. I suggest editing the statement.

Response: Thank you do much for the comment. We have amended the Standfirst. Please see lines 39-44.

Comment 4: In the Definition of exposure status: I recommend revising the first sentence to increase clarity. The first half of the sentence seems to refer to a general definition of exposures, while in the second half of the sentence the authors mention ARV drug regimens. Splitting into two sentences would be helpful. Plus, I am not sure what "variation in how exposures are constructed" means.

Response: Thank you so much for the suggestions. We have amended the description of the exposure groups (please see lines 111-143 and Table 1)

Comment 5: In the same section, second paragraph the authors mention that high levels of maternal HIV viremia and systemic inflammation could result in immune dysfunction. This is true, but not the only adverse outcomes. Inflammation has been linked to other developmental issues including higher risk of autism spectrum disorder.

Response: Thank you for the comment. We agree that maternal HIV viremia can increase the risk of outcomes such as autism spectrum disorder. The work count limit of the manuscript prevented us from expanding more on the different adverse outcomes that are associated with maternal viremia.

Comment 6: There is a period missing in the sentence ending with reference 9

Response: Noted, thank you. We have checked and amended the punctuation in the manuscript.

Reviewer 4:

Comment 1:

In this manuscript, the authors explain clearly the multiple ways HIV in the parents or caregivers may affect the health of exposed children, and the importance of understanding association between these exposures and health outcomes. This necessitates a new way to monitor these children, as compared to what is currently done, with two major challenges which are (1) the resources given by low and middle

income countries to this problem, which may not be considered everywhere as a priority, and (2) the problem of HEU status “disclosure”.

Response: Thank you for the feedback

Comment 2: P5 lines 23-24 : the authors underline that conceiving while on ARV is expanding because of PreP access, however, this is confusing to me.
The vast majority of women conceiving while on ART are HIV-infected women, women on PreP are a small number, that will probably increase in years to come. Please clarify by adding
- in the HEU paragraph (for example p4, after lines 55) that because of Option B+ a very large number of HIV-infected women will conceive while on ARV;
- and distinctly say later that a new population of children (the HUA) for now a very small number, but maybe in the near future a more important population, may be exposed to ARV at conception.

Response: Thank you so much for the comment and suggestion. We have considered your suggestions and amended the text accordingly. Please see lines 130-135.

Comment 3: Paragraph “routine monitoring of children”. One of the major obstacles to long-term follow-up of HEU children, is that most of them are not aware of the HIV status of their parents, and therefore do not know their own “HEU” status.
This is developed in length later by the authors in the paragraph “the way forward” but should be explained earlier in the text, as it is the major limitation to information collection on these children, even in high income countries.

Response: Thank you for the suggestion. We have included the text on disclosure earlier in the manuscript (please see lines 214-222)

Comment 4: P7, lines 26: the unique identifiers, in order to tackle this problem of “HEU disclosure” would need to link the mother to the child also.

Response: Thank you for the comment. We have amended the text accordingly (please see line 197)