Author's response to reviews

Title: Utility of clinical parameters to identify HIV infection in infants below ten weeks of age in South Africa: a prospective cohort study

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Author's response to reviews: see over
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To the Editor,

Thank you for reviewing our manuscript entitled “Utility of clinical parameters to identify HIV infection in infants below ten weeks of age in South Africa”. The responses to the reviewers’ comments are listed below:

**Reviewer 1 responses:**

General: the study identifies clinical parameters to identify HIV infection in infants below ten weeks of age. The finding helps in producing efficient clinical algorithm to be used in program setups. However the result of the study should be interpreted cautiously: it was conducted in areas where the prevalence of BF is very low, the clinicians were aware of the HIV status of the infants and severely ill children were excluded. These limit significantly the application of the algorithm in setups in developing countries. The validation of the study in different setups should be highlighted boldly.

**We have further stressed these points**

**Specific comments**

- Abbreviations should be spelled out in first appearance eg PMTCT. 
  *PMTCT has been changed to Vertical transmission programs and all abbreviations have been checked*
- The conclusion should include the term in similar setup rather than saying resource-constrained settings.
  *“resource constrained” has been changed to “similar”*
- The assertion made should consider the HIV prevalence, the selection criteria of participants (severely ill were excluded) the prevalence of breast feeding is very low (12%).
  *This has been clarified in the conclusion*
- The fourth page should start with title introduction.
  *Corrected*
- The introduction should include review of previous works and should include methodological shortcoming of the previous studies. How the current study overcome the limitations in the previous studies. The added value of the current study compared to previous similar works should be explicitly indicated.
  *We have moved some of the discussion about the prior papers into the introduction and addressed these points.*

**Reviewer 2:**

To develop a clinical definition for HIV infection in children has been regularly tried for more than two decades and it regularly failed. To do it for infants less than 10 weeks is really challenging and to my knowledge, as authors stated, it has never been done. New recommendations of WHO are to treat HIV infected infants as soon their HIV status is known. But
in many places early diagnosis is not available or they are many delays before the diagnosis of infection comes back to pediatrician allowing treating the child with HAART. A clinical algorithm giving a high probability to be infected or not and helping to decide to treat or not is important to have.

Discretionary Revisions
I have no specific comments except that
- Authors should stress in the discussion that specificity is not so important. It is better to treat by excess infants and to change after the final result has been done rather not to treat and have the risk that the child could die of HIV infection.

This has been addressed.

In the text, formula feeding should not be noted as a co-morbidity. Formula feeding IS NOT a co-morbidity but a rational nutritional choice for HIV exposed children that is done in all continents except Africa, because of poverty.

Formula feeding has been listed separately to the comorbidities.

Reviewer 3:
Major compulsory comments
Jaspan and collaborators developed a clinical algorithm to identify HIV infection in young infants (< 10 weeks of age) enrolled in two clinical trials (CHER trial with baseline CD4 ≥ 25%; and additionally an observational cohort with CD4 <25%) conducted in South Africa. It's a very important topic in resource-constrained settings where the early diagnosis of pediatric infection, by using molecular (HIV DNA or RNA) tools, is difficult to implement. The paper is well written, the study well designed, and the results are well expressed. The discussion is informative, including limitations. I have two main comments about this work:

1/ First, the authors indicated that their findings need validation in other settings, due to lack of severe clinical disease amongst children with CD4 ≥ 25% enrolled in the CHER trial. I agree with this point. However, in the present study, 62 HIV-1-infected infants showed CD4<25%. So, my question is: Do the authors investigate clinical spectrum specifically observed in this sub-population more immunocompromised? What about the frequency of clinical signs among these 62 children, compared to those enrolled in the CHER trial? Finally, when stratifying by CD4 (≥ 25% vs. <25%), what about the performance of the algorithms (better amongst children with CD4 <25%??)?
We have included an additional table, Table 2, to address this point and also added additional text in the manuscript.

2/ Second, in methods, the authors explained that they performed quantitative HIV-1 RNA measurements among all HIV-1-infected children (initially identified with qualitative Roche Amplicor HIV-1 DNA assay). My question is: Do the authors assess relationship between the identified symptoms of acute HIV infection and infant viral load measurements? It could be a good plus to know that and report it in the paper.
We analyzed the relationship between screening findings and viral load and found very little association. We have included this in the text of the results.

Minor essential revisions
- Results
P.8: According to Table 1, a history of gastroenteritis was not significantly associated (p=0.17) with acute HIV infection in children.
This has been corrected.
- Bibliography
The authors claimed that this is the first study investigating clinical symptoms/diagnostic algorithms in the VTP era. To my opinion, it’s not completely true. For instance, Rouet et al. described acute retroviral syndrome in children infected through breast-feeding in the DITRAME trial (Ivory Coast). Richardson and colleagues performed a similar work among Kenyan infants (including infection diagnosed at <2 months of age). Probably, the references need to be slightly updated.

Thank you for bringing these papers to our attention. These manuscripts and a corresponding discussion have been added to the paper.
Sincerely,

Mark F Cotton, MBChB, PhD