Author's response to reviews

Title: Integration of antenatal syphilis screening in an urban HIV clinic: A feasibility study

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Author's response to reviews: see over
We appreciate the detailed comments of the reviewers and editorial and scientific suggestions that have improved the manuscript considerably. Our responses in standard type follow the specific comments of the reviewers in italics.

Reviewer 1
Major comments:
1. The WHO has called for the dual elimination of HIV and syphilis through a harmonized/integrated approach. This important to highlight in this manuscript as this study provides evidence for the success of integration. Include as a reference the WHO dual elimination strategy: available here: http://www.who.int/reproductivehealth/publications/rtis/9789241505888/en/

Thank you for suggesting this. We have added this reference.

2. This is a feasibility study, however the authors do not fully discuss whether this was a feasible intervention.

We have added this to the conclusion in the abstract and have restated this in the second sentence of the discussion.

3. The discussion touches on recommendations for use of treponemal rapid tests. Please clarify the distinction between rapid treponemal tests and RPR (non-treponemal), which was used in this study. Also – since this study was about the use of a non-treponemal test for screening, please add more information and evidence for why you recommend the use of a treponemal test. You could touch on the ease of use of the rapid treponemal tests etc.

We have clarified this in the second paragraph of the discussion. At the time that our study was planned, non-treponemal testing was the standard testing methodology. Unfortunately, POC treponemal antibody tests are still not routinely provided by the Ministry of Health despite continued advocacy by our group and others.

4. Please report the percentage of RPR confirmed TPPA+ confirmed and the distribution of RPR titers.

We have added the treponemal antibody confirmed cases. For economic reasons, we were unable to perform RPR titers. We have added several sentences into the discussion about this as well.

Minor comments:
1. Line 32: Rapid plasma reagin is misspelled in the abstract Corrected.
2. Line 52: remove “It is estimated that” and leave the sentence as “In sub-Saharan Africa there are approximately…” Corrected.
3. Line 60: The authors state that 23% of women were screened, but should specify what they were screened for. Corrected.
4. Line 62: The first sentence of the second paragraph is confusing, please clarify. Additionally, the word “offer” should only be used once in this sentence. Corrected.
5. Line 77: Please remove the phrase “we wondered if” and replace it with something like “We aimed to…” Corrected.
6. Line 97: you state you used RPR, a non-treponemal test to define a syphilis positive case. The next sentence you mention a treponemal test. What was this used for? Please clarify how the treponemal test was used. Also, please state the name and manufacturer of the treponemal test. Corrected. We have clarified the test that was used. For the purposes of the study, we had a surprising number of false positives which also endorses the use of a treponemal test initially. Of course, over time, women who have repeated pregnancies will need to have RPR tested as well. New POC tests with both treponemal and non-treponemal tests in a single test strip are now under investigation.
7. Line 103: Was RPR the only test that was used to identify women that required treatment? Was the test result confirmed with another test? Was patient history also used to determine
treatment requirements? No, in this study, all RPR positive women were treated given the economic constraints of this descriptive demonstration study.

8. Line 104: Were participants treated with 1 IM of benzathine penicillin? Please state if it was 1 injection or more. We have clarified this in the methods. This is Uganda national guidelines and there is data from Watson-Jones and colleagues from Tanzania supporting reasonable efficacy.

9. Line 118: Please include the version number of STATA. Corrected.

10. Line 125: The sentence says “606 pregnant, HIV-infected were approached…” Please include ‘women’ or ‘participants’ so that the sentence is something such as: “606 HIV-infected pregnant women were approached…” This sentence has been modified.

11. Line 149: In the results the authors say that only age was significantly different between those with and without a positive RPR. In the table it looks like RPR-positive participants tended to be younger. Please state this in the results. We have stated this as suggested.

12. Line 151-152: This sentence is confusing, please clarify. We have modified this sentence.

13. Line 151-154: Please include both the N and the percentage for clarification. Corrected.

14. Line 166-168: This sentence is confusing and should be clarified. Please also discuss the reporting bias further. Why is there a reporting bias? Which direction would this bias the results? We have eliminated this sentence as it is not germane to the main conclusions of the paper. We relied on patient recall for adverse birth outcomes in previous pregnancies. We were simply alluding to recall bias; women often do not consider or know if they had a low birthweight baby, for example.

15. Line 169-170: This sentence doesn’t relate to anything else in the discussion. Either remove it or discuss it further. It has been removed.

16. Line 176: The authors stated that “Data from Chico et al. suggests that screening for multiple STIs may also be warranted…”. This comes from a review paper so please replace the word “data” with something more suggestive of a review paper. Amended.

17. Line 178: This might be a good place to discuss the advent of new rapid point of care tests that can detect multiple infections with one test device using one fingerprick of blood. There are currently 5 manufacturers of dual HIV/syphilis point-of-care tests. Here is an example: http://ofid.oxfordjournals.org/content/1/1/ofu015.full We have added this reference.

18. Line 188: Here you mention that one quarter of partners of infected women from your study come in for testing. However, in the results you state that its 10/29, this is more than one quarter. Please clarify. Corrected.

19. Line 199: what challenges are you referring to? Challenges related to RPR testing. We have clarified this.

20. Line 204-205: “We need to seize the opportunity of this roll out, and the training of healthcare workers during this period to integrate syphilis screening into PMTCT B and B plus programs.” This is a very important point and should be expanded upon. This should be a main conclusion. Thank you. We agree that this is the main conclusion.

21. Line 207: “Vertical care”. If you integrate these HIV programs would they no longer be called “vertical care”? Please remove “vertical care” from this sentence. Corrected.

22. Reference 4: This reference is incomplete Corrected.

23. Reference 10: This reference is incomplete Corrected.

24. Table 1: Please add a footnote that states what tests were used to generate p-values. Or remove the p-values from the table. We have stated this in the methods.

25. Table 1: Please add more detail to the title of the table. We are unsure how to address this comment. Suggestions are welcome.
Reviewer 2

Thank-you for the opportunity to review this very good paper which looks at an important issue of operational research. I do agree with the authors' conclusions regarding integrating syphilis testing into HIV antenatal clinics. I have some minor issues and some discretionary comments.

**Discretionary revisions:**
1. Is it worthwhile mentioning that there is now no Yaws in Uganda? This would help to reinforce the fact that positive treponemal serology is almost certainly due to syphilis.
2. Which treponemal antibody test (besides the RPR) was performed? Are results available? It is possible that some of the low-level positive RPR results are due to biological false-positives. **We have included this data in both the results and the discussion.**
3. What was the mean RPR result? Given that the authors state that the women with a positive RPR result had no side-effects from treatment with benzathine penicillin, I am assuming that no Jarisch-Herxheimer reactions occurred. If so, it is likely the positive RPR results represented latent syphilis or past treated (perhaps inadvertently) syphilis. If this is so, then the risk of congenital/neonatal syphilis would be significantly lowered if the women were not treated for their RPR reactivity. **Given the low number and proportion of women who had positive RPRs confirmed by treponemal antibody testing, the main conclusions of the paper are that opt-out syphilis testing is feasible. The study was too small to detect a difference in adverse outcomes.**
4. Can the authors confirm that even for latent syphilis or syphilis of uncertain duration, the recommended treatment in Uganda is only one dose of benzathine penicillin? In many other countries a course of 3 injections, one week apart, is the usual treatment. **Yes, we have confirmed this and stated it in the paper as well. Furthermore, data from Watson-Jones and colleagues from Tanzania has shown that a single dose is efficacious in treating pregnant mothers.**
5. With regards to the male partners of these women not attending the authors' clinic, is it possible they may have sought treatment elsewhere, or is that very unlikely? **It is possible that the men were treated elsewhere and that the pregnant mother was unaware of this. Data from other studies confirms low uptake in men, however (see discussion, p9)**

**Minor revision:**
1. Under Prevalence and factors associated with a positive RPR..(paragraph 2, line 2) - "did" should be "were" **We have revised this poorly constructed sentence.**
2. Under Discussion - (paragraph 3) - the sentence commencing "Low partner notification in Mozambican..." does not make sense to me. **We have also revised this poorly constructed sentence.**
Reviewer 3

Major Compulsory revisions
1. What about women with a history of past treated syphilis? If they were RPR reactive but serofast were they excluded? Were there any women who fitted this criteria? If so how did you manage them in the study? None of the participants in the study had previously been treated for syphilis. Although syphilis screening has been in the Ugandan guidelines resources to perform the tested including test kits have not been provided. This was a new program and we found no women who had previously been screened.
2. Uptake of partner notification was low as you note but what would your recommendations for improvement be? Thanks for this comment. We have included a sentence in the discussion (p10) to address this comment.
3. How many eligible women presented to the clinic during the study period? Six hundred and six were approached but was this all eligible for the study? We have clarified in the methods that these were consecutive women enrolled in the antenatal clinic at the IDI. This was all of the eligible women during the study period.
4. How did you arrive at the study period? Was this based on a study power calculation and estimated time to recruit the numbers? Was a power calculation done? Please describe how you arrived at the study number and/or study time period. This was a descriptive study of a demonstration project. The study period was determined by the funding period.

Minor Essential revisions
1. Please write all numbers out in full if they begin a sentence. Corrected.
2. Please ensure all proportions reported on in the text have number and percentage. Corrected.
3. Line 35. The title Results should be bolded and on a different line. Corrected.
4. Line 36 - replace existing with "..... with a median CD4 of 372..." Corrected.
5. Line 125 - replace existing with "...606 pregnant HIV infected women ..." Corrected.
6. Line 129. Did the women present for syphilis testing or presented and enrolled in the study? I would suggest the later. If so this sentence should be changed. Corrected.
7. Line 103 - ".....return to the clinic ..." Corrected.
8. Line 141 - I would insert the term woman or study participants into this sentence to make it clearer. Corrected.
9. Line 153 - replace with "only 2.8% of the patients with a negative RPR..." Corrected.
10. Line 172 - suggest record to make it clearer. eg. Data from Zambia showed that combined research and service delivery programs had positive influence on syphilis testing (OR 2.5.....)
Corrected.
11. Line 151. Suggest reword to make clearer. "Of the 484 women who had been pregnant (24 (x%) RPR positive this pregnancy and 457 (x%) RPR negative). there were no adverse birth events in those with a positive test. We have revised this poorly worded sentence.
13. Line 189. "...than has previously been reported" Corrected.