Author's response to reviews

Title: Reliability and validity of the Center for Epidemiologic Studies-Depression scale in screening for depression among HIV-infected and -uninfected pregnant women attending antenatal services in northern Uganda. A cross-sectional study

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Author's response to reviews: see over
Editor-in-Chief,
BMC Psychiatry

Thank you very much for facilitating the very informative review process for our manuscript “MS: 7173297651311516 Reliability and validity of the Center for Epidemiologic Studies-Depression scale in screening for depression among HIV-infected and -uninfected pregnant women attending antenatal services in northern Uganda.” The comments and suggestions of the two reviewers and the Associate Editor were very helpful. Importantly, we have revised the background section and removed sections deemed partially relevant by the Associate Editor. Also, we provide in Table 1 descriptive comparisons between HIV infected and uninfected pregnant women. We also included measures of specificity together with those of sensitivity and positive predictive values in deciding the appropriate CES-D cutoff score for probable MDD.

In the table below, we address each of the reviewers’ and associate editor’s comments in the order of how they were mentioned. Page and lines refer to the clean copy of the manuscript. The manuscript with tracked changes is provided as an additional attachment and page and line numbers might differ from those in the clean copy.

<table>
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<tr>
<th>Comment/correction</th>
<th>Response/rebuttal</th>
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<tr>
<td><strong>Associate editor’s comments</strong></td>
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<td>The Background section needs to be restructured, especially the paragraphs that start at line 67 and end at line 89. These paragraphs seem only partially relevant. Try to make a clear why depression screening needs to be validated in this very particular group.</td>
<td>As suggested we have edited and removed partially relevant sections of the introduction.</td>
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<td>79: The word ‘thus’ seems out of place, because the preceding does not explain the following.</td>
<td>The word “thus” has been removed.</td>
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<td>The comment of one of the reviewers that the description of the participants should be in the Method section should be taken as a suggestion, but it is not compulsory.</td>
<td>We moved the description of participant recruitment and total numbers to the methods section, and retained the results of the analysis of their characteristics in the results section. We believe this addresses the reviewer’s point.</td>
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<td>Is there any information about the validity of the MINI among the study population? If not, then this is a limitation of this study.</td>
<td>On page 12 lines 16-19, we note this limitation to our study i.e. that the MINI depression (MINI-D) module has been used extensively in Uganda but no one has validated this diagnostic questionnaire.</td>
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<td>Please also state the specificity of the CES-D, even though it is not a primary aim of this study. Looking at the ROC curve, it looks like it’s a bit low at cut-off 15.</td>
<td>On pages 2 (line 11) &amp; 7 (line 20), &amp; Figure 3, the current revision uses sensitivity, specificity, and positive predictive values to arrive at the optimum CES-D cutoff.</td>
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<td>You’re testing a few hypotheses to ascertain some degree of construct validity. These hypotheses need to be well-defined beforehand. What kind of differences did you expect and how large?</td>
<td>We thank the reviewer for this comment. Upon reflection, we request that the focus of this paper remain on validation of the CES-D in the studied population using measures of criterion validity i.e. AUROC, Se, Sp, and PPV. Given the lack of prior estimation studies upon which to base hypothesis...</td>
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testing, the phrase hypothesis generation rather than hypothesis testing is most appropriate. We request the Editor to allow us revise the text referring to hypotheses testing. We submit that this study provides pilot data for hypothesis generation – not testing - on differences in HIV negative and HIV positive women. We are happy to reconsider based on the Editor’s guidance.

Even with our small sample size, and, due to observed differences between HIV –infected and –uninfected pregnant women in this study, in terms of age and marital status (table 1), we were able to adjust for these variables and report adjusted differences in CES-D scores by maternal HIV status.

Concerning the comparison with literature, the CES-D was developed as a self-report measure, while it is (understandably) used as an interview in this study. It cannot be assumed that the interview version of an instrument has the same cut-off point as the self-report version. In think it’s most relevant to compare the cut-off point of the present study with other studies where the CES-D was used as an interview.

This is an important consideration and we appreciate the Associate Editor for bringing this up. We revised our discussion section as shown at page 10 lines 6-9 by comparing our interviewer administered CES-D to previous CES-D measures from Sub-Saharan Africa that employed a similar approach.

The cut-off point of 15 seems rather low in this population. I would expect this population to have some physical symptoms related to HIV or to their pregnancy that would push the cut-off point up (e.g. fatigue that is not caused by depression). Can this be clarified? It partially has to do with the applied methods. The cut-off 15 is based on the sensitivity and the PPV and not on sensitivity and specificity, as most studies do. This should be taken into account when comparing the cut-off point of the present study with those found in other studies.

In the revised analysis that takes into account Se, Sp, and PPV, we find that the optimum cutoff score is between 16 & 17 and because of the associate editor’s and one of the reviewer’s comments, we are selecting the cutoff value of 17 for our pregnant population with about 30% of the sample HIV infected. Taking a cutoff score of 17 allows us to take into account the possibility that HIV infection and pregnancy share similar symptoms as depression (figure 3). Indeed HIV –infected participants scored higher on the CES-D than HIV-uninfected participants. We believe if we had sufficient numbers to test the validity of CES-D among HIV-infected women alone, the optimum cutoff would have been higher than what we recommended for this mixed HIV status population.

247: lever = level

253: od = of

281: ((20), one bracket too many.

These corrections have been revised. Thank you.

Reviewer 1 (Dickson Chibanda) comments

1. Major compulsory revisions:

The study looks at HIV+ and HIV- women, in Table 1, we now provide a descriptive statistics for the entire sample as well as a comparison of HIV+ and HIV- pregnant women on measured variables.
therefore, the table describing characteristics of participants should really be reflecting this. Suggest this table reflects characteristics of participants by HIV status. Table should have column for HIV+, HIV-, and P-values. The variables between these two groups have to be compared for level of significant and comment on differences.

2. Multivariate analysis will be better than bivariate for any comparison of multiple variables.

We appreciate the reviewers comment. However, as outlined above in responding to the Associate Editor's comments, we have revised the focus of the paper to the validation of the CES-D in our studied population using MINI-D module as a “gold standard” by establishing the CES-D's criterion validity (i.e. AUROC, Se, Sp, and PPV) at selected cutoff values. The small sample size for this validation study does not allow us to carry out robust hypotheses testing including multivariable analysis. We agree with the reviewer that multivariate analysis is better, note the small sample size, and report the univariate results, adjust for maternal age and marital status when reporting differences in CES-D scores by maternal HIV status, and list the sample size as a limitation of the study.

Minor
1. Line 122. How was data collected? What is the sampling frame? This should be described in the methods.

2. Line 69 First time Sub saharan Africa is mentioned should be followed by the abbreviation (SSA) which you use throughout the manuscript.

We used consecutive sampling procedure to recruit participants meeting our inclusion criteria and excluded those who didn't meet our criteria. We have further clarified on this procedure in the methods section of this revision. We aimed to recruit a significant number of HIV-infected pregnant women to compare with HIV-uninfected participants on several cross-sectional and longitudinal outcomes including CES-D scores. In the study limitation section, we note that our population may not be representative of the pregnant population in northern Uganda.

SSA has been adopted at first mention and then only referred to SSA thereafter.

## Reviewer 2 (Aurore Boulard) comments

1. Efforts in the structure of the introduction should be done. The introduction is difficult to read. Understand the value of this research is also complicated. Despite the underlying relevance of this research among HIV-infected and -uninfected pregnant women, the authors should better emphasize the relationship between both disorders and the consequences of this comorbidity.

We thank the reviewer for these comments. The introduction has been rewritten to improve the ease of understanding. We have also rewritten the introduction to improve understanding of the importance of this research. We have also used the recommendations of the associate editor to improve the introduction section of this paper including removing sections that we deemed partially relevant. The value of the research is that we don't have an appropriate method for screening for depression in our population and the CES-D, as validated in this
study, could help fill this gap. We note that both depression and HIV disproportionately impact women especially during the prenatal period and limited data from SSA exist on these co-morbidities.

2. Regarding the CES-D, the description of the scale should be more precise. It’s not a scale to diagnose MDD but the presence of depressive symptoms in a normal population. A score that exceeds the threshold is a score of severe depression but you may not diagnose psychiatric disorder (MDD) with this scale We take the reviewer’s point. In rewording and rewriting the manuscript we have been careful to make sure there is no instance where we are referring to using the CES-D to diagnose MDD. For clarity here, and as stated in the paper, we would like to further state that we employ the CES-D in this study as a screening tool and, like others before us, indicate that above a certain threshold CES-D score, then the person affected can be thought of being at sufficiently higher risk of MDD to use the term “probable” MDD. We have checked again through the manuscript and made sure that where we used the CES-D in reference to MDD, we always indicate that the outcome is probable MDD. We use/refer to the psychiatrist administered MINI–D module, but not the CES-D scale, as the tool we used to diagnose MDD.

3. The description of the participants should come in this section (material and method) and not in the results section. This shift makes it difficult to understand the article. Analyses described subsequently are incomprehensible without knowing that the low number of subjects does not allow you to use parametric statistics. Per the associate editors comment your recommendation (see above), we have moved the description of the recruitment and numbers to the Methods section – so the reader knows the number of subjects before the analysis. We then maintain the analysis of participant characteristics in the results section. We also follow reviewer 1 suggestions and present participant characteristics by women’s HIV status.

4. I regret not to have a clearer description of the group of pregnant women with HIV. Do they have a different IFIAS score, a different status from other women? In this revision, we provide a table comparing HIV- to HIV+ participants (Table 1) by measured characteristics/variables at baseline. Thank you.

5. Given the small sample used in this research, I understand the selected statistics. However, I wonder about the results of this research. The recent literature on the topic (CESD and pregnant women) shows that a cutoff score of 16 raises questions especially for pregnant women because pregnancy symptoms can be common with some symptoms of depression. They suggest an increasing in this threshold value. For example, Fall et al (2013) use a cutoff score >= 23 (according to Radloff & Locke, 1986) for a similar population of pregnant women. But your results indicate a score of 15. Could you comment and discuss your results by relying on previous work? Increase the size of your sample allows us to perform parametric statistics and would undoubtedly respond to the question of the cutoff. We appreciate the reviewers comment. We have two major reasons for believing our validation work is appropriate. First, the populations are very different. We note that Radloff & Locke (1986) recommended the use of a self reported CES-D cutoff value of 23 to be indicative of probable cases of depression in the US general population. Fall (2013) adopts this cutoff with pregnant US women in the US. We are not able to use or adopt this cutoff, because, unlike these authors, the CES-D scale used in this study was: (1) administered by interviewers, and not self-reported (see other reviewer comments); (2) used a language different from English (predominantly Acholi or Langi), and (3) tested among non-US women of mixed HIV status. Therefore, we believe our method of administering the CES-D, language adaptation, and context of using
the scale demands that we further validate the scale in our population. Our results, probably due to contextual differences, show that our optimum CES-D cutoff (≥17) indicative of probable MDD is significantly different from what was recommended by Radloff and Locke (1986).

The second reason we believe our study has validity is that a cutoff score of ≥23 on our CES-D is associated with an unacceptably low sensitivity (Se=50%; Figure 4) for detecting probable MDD (Supplemental table 1).

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<th>6. No indication is given on the number of weeks of pregnancy of these women. But the common symptoms are more frequent during the first 3 months of pregnancy. An indication of the mean and standard deviation of this variable is needed. This variable may influence scores of the CESD?</th>
<th>We have corrected this and in table 1, the first variable is gestational week. Interviews were conducted at about 18 weeks of gestation and we cannot comment on any possible influence of gestational age and have added this to the list of potential limitations.</th>
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<td>7. « P10, L234: Our theoretical predictions were that women who are HIV infected, poorer, or more food insecure would score higher on the CES-D scale than their better off counterparts.” I have not seen hypotheses about these points including food insecurity in the introduction. In other words: What are your theoretical predictions?</td>
<td>We thank the reviewer for this question. As noted above, in the interest of being more specific, we have refined the focus of this paper on establishing the criterion validity of the CES-D. Our sample size is small and precludes us from conducting robust multivariate analyses that would be crucial for adequate hypothesis testing. The respective edits in the revised paper have been made to reflect this focus, and we have more appropriately termed our results around HIV to be useful for hypothesis generation rather than hypothesis testing</td>
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<td>1. There is a lack of indications concerning the abbreviations used in the text (eg SSA, p4-L79; WHO, p4-L84, TB, p9-L226) 2. There is no reference to Table 1 in the text, which describes the participants.</td>
<td>We have corrected these errors. Thank you.</td>
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We regret to inform the Editor-in-Chief that one our co-authors, Dr. Thomas Okello Oyok, passed away on 6th of August 2014. Dr. Oyok worked as the study psychiatrist and administered all the MINI-D interviews and contributed to the drafting and submission of the initial draft. We would like to request the Editor to maintain Dr. Oyok as a co-author on this paper. We also included an obituary paragraph in the acknowledgement section of the paper. We would strongly appreciate, in case our paper is accepted, that the Editor publishes the obituary together with this paper.

Thank you very much.

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