Author's response to reviews

Title: Depression symptoms and cognitive function among HIV-positive individuals in Uganda.

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Author's response to reviews: see over
Dear Scientific Editor,
BMC series journals

Re: Response to reviewers’ comments on MS: 1908145036298464- Depression symptoms and cognitive impairment among HIV positive individuals in Uganda.

We appreciate all the comments that were made by the reviewers to our manuscript submitted to BMC Psychiatry. We hereby respond to the comments that were made, however I will first respond to the concern you raised about the consent of the study participants.

All study participants gave informed consent. Individuals who could read and write signed their names after reading through the consent form. For individuals who were unable to read, the consent form was read to them by the research assistants. Signing of the form was done with the use of a thumb print. In addition there was an observer to the consenting process who also signed the form.

We have included the statement about consent on page 3 under the section on ethical considerations. I now address the points of concern that were raised by each of the reviewers.

Reviewer 1:
Comment 2. Further clarification in this report of the cohort inclusion criteria is needed.

Response: The following were the inclusion criteria: CD4 lymphocyte count <200, clinic attendance of ≥ 2 in the past 6 months, residence within a 20-km radius of Kampala for the previous 6 to 12 months and unlikely to move out of this area. The exclusion criteria included age less than 18 years, an active or known past CNS opportunistic infection, fever of >37.5 °C, a history of a chronic neurologic disorder, active psychotic disorder, alcoholism, physical deficit (e.g., amputation), a Karnofsky Performance Scale <50 or a severe medical illness that would interfere with the ability to perform study evaluations. Able to speak Luganda or English. All the above criteria applied for the HIV negative group with a confirmation by ELISA of an HIV negative test and there was no need for this group to have had any prior visits to the AIC. We have included the cohort inclusion criteria on page 3.
Reviewer: Succinct description of the population from which the 102 individuals were recruited would assist the reader, enabling more generalizability of findings (e.g. is this an inpatient, or outpatient, specialized referral service or general HIV treatment service and what proportion of all patients does this cohort represent.

Response: The IDI clinic from where the HIV positive participants were selected; is a specialized outpatient HIV clinic that provides quality care, including antiretroviral therapy (free of charge). The clinic also serves as a national referral centre, providing specialist consultations for patients who are not responding well to treatment at other health facilities. The clinic serves over 10,000 HIV/AIDS clients; 5,600 receive life-saving antiretroviral therapy. See page 4. Individuals with cognitive impairment represent 1/3 of all clinic attendees as evidenced by a previous research (Sacktor et al 2005).

Comment 3. The tool used to measure depressive symptoms is Center for Epidemiologic Studies Depression Scale CES-D, essentially a well validated screening tool which requires followed up with a clinical interview to establish the diagnosis of depression (DSM-IV). The authors should include any confirmatory data. Otherwise “depressive symptoms” would be better terminology than depression throughout the report.

Response: No confirmatory diagnosis was made on the participants. We therefore agree with the reviewer and have changed depression to depression symptoms whenever appropriate in the text.

Reviewer: Similarly the cognitive impairment is measured using a screening tool International HIV Dementia Scale (IHDS) defining abnormal as < 10. Reference to a lack of association with the clinically validated MSK score should be clarified both in terms of explanation of the “MSK” (i.e. Memorial Sloan-Kettering score) and consideration of inclusion of summary results as in reference 18 to the full neurocognitive assessment used to allocate a dementia categorization according to MSK.

Response: The Memorial Sloan Kettering Scale (MSK) has been the most commonly used scale in describing the presence of HIV dementia for the past 20 years. It is scored on a scale of 0-4 (ref Price and Brew 1988). The summary results for the study group showed that there was a greater trend for improvement on the neuropsychological battery tests among the HIV positive subjects but the only significant change was in Color Trails 2 test \( p = _0.02 \) after adjusting for differences in sex. See page 7.
Comment 4: The results of the longitudinal analysis (table 1) should identify denominators from which the prevalence is calculated so as to clarify the loss to follow up of 9 individuals (8.8%) by month 6.

Response: The denominators were as follows.

<table>
<thead>
<tr>
<th>HIV Positive</th>
<th>HIV Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>102</td>
</tr>
<tr>
<td>3 months</td>
<td>95</td>
</tr>
<tr>
<td>6 months</td>
<td>93</td>
</tr>
</tbody>
</table>

These have been fitted into table 1.

Reviewer: Method of dealing with the individuals lost to follow up in analysis of associations should be stated.

Individuals missing at follow up contribute 0 observations for the outcome of interest at specific time points.

Reviewer: Do the authors have any data on risk factors for depressive symptoms (e.g. FH, alcohol use, baseline immune function or plasma HIV RNA). Is there any confirmatory data on those screened with depressive symptoms in this group?

Response: We excluded any patients with alcohol related problems who scored 2/4 on the cage questionnaire. We also excluded any individuals with severe psychiatric illness that was clinically overt. This is stated on page 4. Baseline, mean (SD), HIV RNA was 239720 (267034) and for those with a CESD ≤ 16 it was 241636 (240054) and the difference was not significant between the two groups (p = 0.970). This information has been fitted in the text see page 6.

Reviewer: Would a time to event analysis (time to recovery of depression, time to normalization of cognitive screen) clarify the outcome of those treated with HAART with and without depressive symptoms at baseline?

The data was collected at six-month intervals. Information of recovery of depressive symptoms is not detailed enough to allow for a time to event analysis.

Reviewer: The meaning of the statement “There were 81 HIV positive individuals with CD4 cell count <= 200 at baseline. Among these, there was no association between increasing CD4 count and decreasing CES-D score over the study period (p=.168)” is not clear. How this fits with published inclusion criteria and whether this is a valid examination in the absence of data about HIV RNA
suppression or CD4 changes in the entire cohort population (Is there any correlation between markers of treatment response and depression symptoms?) Are the numbers large enough to have the power to exclude a type II error?

Response: We wish to clarify that, at the baseline, there was a total of 102 HIV patients. When the group was followed up at 3 months (N= 95) and at 6 months (N=93) there was improvement in the mean CD4 count from 129 at baseline to 268 at 3 months (p < 0.001) and to 272 at 6 months (p < 0.01). (Ref Sacktor et al 2009)

There is evidence that depression prevalence increases with a decreasing CD4 count. In this study we would then have expected that the rise in CD4 would lead to a significant decrease in the CES-D score but this did not happen (p = .168). It is also argued that when individuals are very ill before the start of HAART they may have symptoms that could be classified as depressive but once they improve physically then these symptoms are expected to resolve. However in this study we show that even when the CD4 count improved there is remnant depressive symptomatology even after the initiation of HAART.

Reviewer: Could the authors distinguish between the somatic and affective symptoms in the CESD and did both correlate with HIV status and did improve to the same extent with HAART

Response: We did not perform that analysis as we felt it would fit more in a validation study of the CESD.

Reviewer: Were any patients treated with antidepressants or other treatments?

Response: Patients with persisting high score were referred to the psychiatric clinic for further management. This is has been shown on page 4.

There was are minor discrepancies between reports of this cohort with reference 18 which should be clarified e.g Karnofsky 98 V 91 and dementia case in controls.

Response: We have corrected this error the true Karnofsky score was 98 in the HIV negative group. The second correction is not clear “dementia case in controls” However there no cases of dementia in the control group though there individual who performed poorly on some of the cognitive tests as shown in table 1.

Reviewer: One decimal point in age, other demographics seem sufficient.

Response: We have correct the age to one decimal point in table 1
Comment 5: Are the discussions and conclusions well balanced and adequately supported by the data?
Yes excepting in the relation to the lack of association between treatment outcome and improved depression scores. This could be clarified by including HIV RNA data or further clarification of actual clinical and immune measures.

Response: There was improvement in the CD4 counts of the HIV positive group from CD4 129 to 272 by the 6 months review. We have included a statement to that effect on page 8.

Comment 8: Do the title and abstract accurately convey what has been found?
Perhaps consider changing
Depression symptoms and cognitive function among HIV-positive individuals in Uganda
To
Depression symptoms and cognitive function amongst high risk HIV-positive individuals treated with HAART in Uganda

Response: We appreciate the suggestion however if we say these were “high risk HIV-positive” it changes the meaning of the group of patients that were studied. We did not study high risk populations like sex workers or injection drug users specifically.
And if we add “treated with HAART” it may imply that these were patients that were recruited when they were already taking HARRT yet we recruited them before they initiated HAART

We have included in the abstract that the HIV patients were being initiated on HAART, in the methods section we have also added “HARRT” to the keywords.

9. Is the writing acceptable?
Yes. A few typographical errors page 4 HIV dementi)a

Response: The errors have been corrected.

1 Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
1.1 Further clarification in this report of the cohort inclusion criteria is needed to identify the fact that those selected are HIV infected attendees at substantial risk for dementia.
Response: Done as explained above
1.2 Succinct description of the population from which the 102 individuals were recruited would assist the reader.

Response: As explained above

1.3 “Depressive symptoms” would be better terminology than depression throughout the report

Response: As explained above

1.4 Consideration of inclusion of summary results of dementia categorization according to MSK (based on full neurocognitive battery used as in reference 18) to the IHDS screening tool results in order to further strengthen analysis of association with depressive symptoms

Response: Done as above

1.5 Further interesting information included if available. Do the authors have any data on risk factors for depressive symptoms (eg FH, alcohol use, prior AIDS opportunistic infections (esp CNS), baseline immune function or plasma HIV RNA). Is there any confirmatory clinical data on those screened with depressive symptoms in this group (DSM IV defined depression)? Were any individual treated for depression?

Response: Done as above

1.6 Could the authors distinguish between the somatic and affective symptoms in the CES-D and did both correlate with HIV+ status and did both improve to the same extent with HAART?

Response: We believe this would give very good information however we did not attempt this in our study as it was not initially designed to assess the depressive symptoms against a gold standard measurement.

1.7 The method of dealing with those individuals lost to follow-up in analysis of associations should be stated.

Response: Individuals missing at follow up contributed 0 observations for the outcome of interest.

1.8 The meaning of the statement “There were 81 HIV-positive individuals with CD4 cell count <=200 at baseline. Among these, there was no association between increasing CD4 cell count and decreasing CES-D score over the study period (p=.168)” is not clear. How does this fit with published inclusion criteria and is this a supportable statement in the absence of data about HIV RNA suppression or CD4 changes in the entire cohort population (Is there any
correlation between markers of treatment response and depression symptoms?) Are the numbers large enough to have the power to exclude a type 11 error?
Response: As above

2 Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
2.1 explanation of the “MSK” (i.e. Memorial Sloan-Kettering)
Response: As above

2.2 The results of the longitudinal analysis (table 1) should identify denominators from which the prevalence is calculated so as to clarify the loss to follow-up of 9 individuals (8.8%) by month 6.
Response: As above

Reviewer 2
Introduction
The last sentence in the introduction is unnecessary and should be removed or moved to another place. It is really out of context where it is.

Response: We have deleted the sentence

Methods
What exclusion/inclusion criterion were used in this study? This information is particularly important with regards to the HIV negative controls.

Response: Exclusion criteria for the HIV negative group were as follows:
If they were younger than 18 years of age, had an active or known past CNS opportunistic infection, a fever ≥37.5 °C, a history of a chronic neurologic disorder, active psychiatric disorder, alcoholism, physical deficit (e.g., amputation), severe functional impairment (Karnofsky score less than 50) or severe medical illness that would interfere with the ability to perform the study evaluations. Non Luganda or English speakers. We have included selection criteria on page 3.

The description of the tools used to assess depression and cognition are poorly reference and require additional explanation. For example, are there studies that describe the validity and reliability of these measures in the population of study?

Response: Validation of the IHDS and the neurocognitive battery has already been done in the Ugandan population. The sensitivity and specificity being 88% and 57% respectively. We have included a reference to the instrument on page 5.
The CES-D has been used in Uganda (Kaharuza et al 2006 and other African countries (Myer et al 2008.)

Were the tools administered in native languages?
Response: Yes the tools were translated and administered in the local language and in English for those individuals that did not speak the commonly spoken language. Please see page 3.

It also needs to be made clear if the statement in the methods regarding the CESD (In a general population, approximately 20% of individuals would be expected to score in this range.) is valid in Uganda. There is literature out there suggesting that the socially acceptable cultural expression of depression can vary widely from culture to culture. So, a well validated instrument in one culture may not yield the same results.

Response: Whereas the CESD has not been validated in Uganda, it has previously been used as stated as well as other countries whose setting is similar to Uganda. We therefore believe that the scores generated by the instrument in our study population are valid.

You mention “a battery of 8 neuropsychological test” administered. Is this in addition to the IHDS or are these tests used to derive the IHDS score? If they are not used to derive the score, I would not mention them otherwise you should provide some explanation as to what tests the are and how they were used in your study.

Response: The battery of neuropsychological test is used to derive the cognitive MSK scores of the individuals. The IHDS only acts as a screening tool. The battery includes
1. World Health Organization (WHO)–University of California-Los Angeles (UCLA) Auditory Verbal Learning Test (AVLT)
2. Timed Gait
3. Finger Tapping
4. Grooved Pegboard tests
5. Symbol Digit Modalities test
6. Color Trails test
7. Digit Span Forward and Backward
8. Verbal fluency.
Please see page 6.

Since the cut-off scores factor heavily into your analyses, some discuss of the validity of this instruments in this population is critical.
Response: The IHDS as mentioned above has been validated in the Ugandan HIV population. Sacktor et al 2005. We elaborate this in the discussion. The CESD has not and this is discussed.

Can you provide some rationale for the use of logistic regression when determining the differences in prevalence measures? Are you certain these data meet the assumptions for regression of this type to be valid?

Response: We were interested in modeling the likelihood of a participant to screen positive for depression using the CES-D as a function of other characteristics, such as HIV sero-status. Given that the outcome was binary, logistic regression was a reasonable analytic tool. Further, logistic regression makes no assumption about the distribution of the independent variables (in this case, HIV sero-status).

How exactly were your confidence intervals for prevalence calculated? Where did you get your prevalence error estimates for this calculation?

Response: Confidence intervals for prevalence were calculated using the binomial distribution. The prevalence error was estimated using the formula to estimate the standard error of a proportion.

When discussing the proposed statistics on page six, it is unclear if the last statement is a summary finding in your data are you are making some sort of expectation statement.

Response: The last statement sets the threshold for statistical significance set for this analysis.

Results
You don’t need the first sentence of the results. Already established in the methods.
Age may be comparable, but it is still different statistically speaking and the HIV positive patients have almost twice the degree of variability. Karnofsky Performance Scale scores are reported in the results but not discussed in the methods.

Response: The score was used in generating the MSK score. We have included a sentence that indicates the impotence of the Karnofsky scores on page 5.
MSK scores are compared to depression in the results but MSK is not mentioned in the methods nor is it clear what statistic is used in this comparison.

Response: We have mentioned the MSK in the methods as stated above. In order to make a comparison of between the MSK and the CES-D, we used a Chi square and Fisher’s exact test. See page 6.

In the longitudinal follow-up it is unclear what statistic is used to determine the decrease in prevalence. Is this the repeated measures logistic regression?

Response: Yes repeated measures logistic regression was used to determine the decrease in prevalence and this is mentioned on page 7.

Not sure what is meant by the statement in the results on page 7 that says “However, the symptoms did not completely resolve.” This statement is repeated again in the discussion (page 8) and I am not sure what is exactly meant there as well.

Response: Despite the generally held view that depressive symptoms should occur in an individual when they are HIV positive and not surprising that these symptoms should disappear when they start on ART, we did find that not all patients have a drop in the CES-D to less than the cut off point and that is what we meant by that statement. We have reworded the statement see page 9.

The only reference given for the CES-D is the early normative paper. There are studies suggesting that the CES-D performs different across different ethnic groups. Can the authors please provide some sort of rationale that supports the use of the CES-D in Uganda?

Response: Whereas we agree that there is a possibility of the CESD to perform different in different cultures, there is literature that shows it has been able to measure depressive symptomatology. We are cautious not to label our study patients as depressed since even with the CESD one has to carry out a confirmatory diagnostic test in order to come to a definitive diagnosis of depression. We have included other in addition to the original list.
I think the discussion could be greatly improved by including a broader review of the literature. A brief literature search of the subject tends to bring up more references than described in the discussion.

Response: We have added literature.

Reviewer 3

1. My main concern is about the selection of patients. In the methods section, authors say they selected patients at risk for cognitive impairment i.e. who had CD4 < 200 or poor performance on a screening test for HIV dementia. Due to this latter criteria, patients are not representative of all patients initiated on antiretroviral therapy because they are selected on neuropsychological symptoms. The prevalence of depressive symptoms and cognitive impairment is thus probably largely overestimated in this study.

Response: We selected our study population from a clinic pool that sees between 200-300 patients per day. We then went ahead to screen for those that may be at risk of cognitive impairment. Our findings of depression symptoms for this group is the emphasis of the paper. We have clarified this in the abstract and the first paragraph of the discussion.

2- I have another concern is about the validity of the questionnaires used for this study. English is not the maternal language of Ugandans. Therefore, the validity of these questionnaires, whether or not translated, must have been specifically studied in this particular population before their use in clinical studies. Indeed their reproducibility is questionable when one sees the huge variations of both scores in the control population (table 1).

Response: The IHDS and the rest of the cognitive instruments has been validated in the setting. The CESD has been used in many other settings within the Uganda population and among other HIV populations as well as other African settings. The variations seen between the HIV positive and the HIV negative are a reflection of the difference HIV infection has on the affect, in this case-depression and on cognition as the study phenomena.

3- Authors state that neuropsychological symptoms persist in patients treated with antiretroviral drugs but at 6 months, the prevalence of depression is similar in HIV-infected patients and controls (30% and 24% respectively, p= 0.21) and the prevalence of cognitive impairment is even lower in HIV-infected patients compared to controls (if the prevalence in controls is true…). Authors should check if results in controls are truly those shown in table 1 and if yes, they should check the validity of the conduction of the study among controls. If results are
true and valid, they should rewrite the last paragraph of the results section and mitigate their discussion (page 9) about the persistence of depressive symptoms in HAART-treated patients.

Response: Yes, the results are as shown in Table 1. The low cognitive impairment in the HIV positive group in comparison with the HIV negatives is a result of the loss to follow up. We have included the samples size at each of the follow up clinic visits in the table for clarification. The last paragraph has also been re-written and the discussion mitigated.

Those are the reposes to the comments made. We look forward to hearing from you.

Sincerely
Noeline Nakasujja
Corresponding author.