Author's response to reviews

Title: HIV-associated neurocognitive disorders in sub-Saharan Africa: a pilot study in Cameroon.

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Author's response to reviews: see over
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Dear Drs Mellins-Cohen and Alam,

We are pleased to provide this re-submission of our manuscript entitled “HIV-associated neurocognitive disorders in sub-Saharan Africa: a pilot study in Cameroon”, for publication in BMC Neurology. Thorough point by point responses to each of the queries raised by the reviewers are outlined below. In the revised manuscript, sections in red represent changes made in response to reviewers’ comments.

RESPONSE TO COMMENTS OF REVIEWER 1 (REVIEWER: DR ANDREA KUBLER)

Comment 1: “HIV-associated neurocognitive disorders in sub-Saharan Africa: a pilot study in Cameroon” Kanmogne et al. This study examined cognitive function in a sample of Cameroonians diagnosed with HIV/AIDS (N=22 in each group) and compared them to an age, gender, education, and depression matched sample of control subjects (N=44). The aim of the study was to investigate whether the pattern of cognitive deficits in sub-saharan patients, who present with high a diversity of HIV strains, would be the same as in most developed countries in which patients are mostly infected with the HIV-1 subtype B. The paper is well and concisely written and has the appropriate amount of figures and tables. Results and limitations of the discussion are adequately addressed.”
Response: Thank you

Comment 2: “I have only minor comments and suggestions: The authors use many abbreviations and provide a list of abbreviations at the end of the manuscript which is helpful. However, all abbreviations should be explained when first used; namely FACS, JMP, CDC.”
Response: We apologize for this oversight, and have now explained all abbreviations when first used in the text. However, for the JMP statistical software, the manufacturer (SAS Institute Inc, website: www.jmp.com) does not provide any explanation for the abbreviation JMP.

Comment 3: “Methods Page 5: The authors state that they adapted the neuropsychological battery. What exactly was done besides the translation?”
Response: We apologize for the confusion. We only translated the tests in the battery and this translation did not change the form or content of the NP tests. We have revised the manuscript accordingly (page 5, lines 14-15).
Response to Comments of Reviewer 2 (Reviewer: Dr Inga Zerr)

Comment 1. “The objectives of this study were to determine whether Western neuropsychological (NP) methods are appropriate for use in Cameroon, and to evaluate cognitive function in a sample of HIV-infected adults. The authors used a battery of 19 NP measures in a cross-sectional study with 44 HIV+ adults and 44 demographically matched HIV- controls, to explore the validity of these NP measures in Cameroon, and evaluated the effect of viral infection on seven cognitive ability domains. Significantly lower performance was seen in the HIV+ sample on tests of executive function, speed of information processing, working memory, and psychomotor speed. HIV+ participants with AIDS performed worse than those with less advanced HIV disease. This study is well-planned and carried out, the results are clearly presented”.

Response. Thank you.

Comment 2. “I have no further comments except to shorten the manuscript by omitting the repeating information”.

Comment 4: “Further it is stated that the back translation of tests were similar to the original. This should be more precise. Who decided that the back translation was similar enough to the original”?

Response: Our study team included bilingual scientists who are both fluent in written and spoken English, and fluent in written and spoken French (GDK, CTK, LAC, AKN), experienced neuropsychologists (RKH, LAC), neurologists (AKJ, RJE, CTK), psychologists and psychometrists (DRF, SE, RD). French translation and back translation of the NP battery was done by the bilingual scientists on the team (French is the primary language of GDK, CTK, and LAC); back translated tests were again double checked in comparison to the original by English-speaking neuropsychologist and psychometrist on the team (RKH, DRF).

Comment 5: “Page 6, last line of first paragraph: after “confounding” something is missing”.

Response: We apologize for this oversight and have corrected the mistake.

Comment 6. “It should be explained in the method section what the different neuropsychological tests are measuring – this is currently in the discussion.”

Response: We have complied with the reviewer’s requests and have explained in the method section what the different neuropsychological tests are measuring (page 6 and page 7, lines 1-4).

Comment 7: “Results. Headlines should indicate the content of the following paragraph not the results (AIDS patients performed worse…; neuropsychological impairment…)”

Response: We have changed the headlines to indicate the paragraph content (page 9, 3rd paragraph and page 10, 3rd paragraph).

Comment 8. “Age and education adjusted values of tests could be reported in Table 1”.

Response: We appreciate the reviewer’s remarks. Our small sample size (44 HIV- controls) was not enough to create demographically adjusted test scores, and we have further discussed this limitation in the manuscript (page 14, 4th paragraph, line 3). However, we do provide a table (Table 4) that indicates the presence of robust age and education effects (similar in size and direction to what is seen in Western countries and in other developing countries). Thus such norms do eventually need to be created when resources become available to accrue larger samples. Nevertheless, our control and HIV+ groups were well matched for age and education (Table 2); therefore, the group differences on NP performance cannot be explained by any demographic confounds.

Comment 9: “The authors state that there was no gender effect, which is true for all but one test (verbal). This should be pointed out. As indicated in Table 4 gender has a significant influence on performance in verbal tests”.

Response: We agree and have pointed out the effect of gender on verbal ability domain (page 10, 2nd paragraph, line 6-7).
**Response.** We have revised the manuscript and omitted the sentences that appeared to be repeating information.

**Comment 3.** “Discussion. The authors may wish to discuss that the difference in performance between non-AIDS and AIDS (Figure 1) seems to be purely quantitative not qualitative, meaning the pattern of deficits stays the same over time, e.g. executive functions scores worse than others in non-AIDS and also in AIDS patients.”

**Response.** We appreciate the reviewer’s remarks and have revised the manuscript to discuss performance pattern in Figure 1 (page 12, 2nd paragraph, lines 5-7).

**RESPONSE TO COMMENTS OF REVIEWER 3 (REVIEWER: DR INGO UTTNER)**

**Comment 1.** “Georgette Kanmogne and coworkers present an interesting study, which is nicely written, methodically well performed and concise in its conclusions”.

**Response:** Thank you.

**Comment 2.** “Nevertheless, I have some doubt, if the cognitive impairment profile reported here is really representative as suggested. So, the authors did investigate primarily urban dwellers who are well trained in academic skills (educational level: 12 y, Table 2), but what is with the rural HIV+ population? Did they have similar neuropsychological deficits as subjects who are more familiar with the “Western” lifestyle?”

**Response:** We agree with the reviewer that this study was conducted in an urban setting and we cannot assume that these findings can be generalized to rural settings. We have mentioned this limitation in the revised manuscript (page 14, 4th paragraph, line 8; page 15, lines 1-2). With the limited resources available, this pilot study could not be performed in multiple settings (rural and urban). However using the same NP battery translated in Mandarin, similar HIV effect sizes were found in rural China, with HIV+ and HIV- groups that had a much lower education levels than exist in the current Cameroonian groups (Heaton et al, 2007 manuscript reference 29).

**Comment 3.** “Moreover, how feasible are the tests used here in terms of culture fairness and ecological validity? Given the fact, they are: How could be dealt with differences due to different educational levels? Although some aspects have been already addressed (p 11 ff), authors should discuss these important issues more in detail”.

**Response:** We agree with the reviewer that “culture-fairness” and "ecological validity" are important points to consider, and this underscores the necessity of obtaining appropriate-relevant normative data for a given population. We assume that cultural differences probably do affect performances on these tests (perhaps similar to education differences). However this does not necessarily affect the validity of the NP tests (e.g., tests validity for measuring disease related CNS dysfunction) as long as the basic abilities assessed (verbal fluency, learning, attention and working memory, cognitive processing speed, etc.) exist and have some relevance in different populations. Indeed, one important goal of the current study was to explore the validity of these tests in this Cameroonian context. Unfortunately assessing the ecological validity of the tests was beyond the scope of the current pilot study, but we agree that this will be an important goal for future research.

**Comment 4.** “Discretionary revisions: Were the significances shown in Table 1 corrected for multiple testing? If not, why?”

**Response.** The significances shown in Table 1 were not corrected for multiple testing because this was an exploratory study with limited sample size; for this reason we focused on effect sizes. We will also like to
point out that our use of 2-tailed significance testing is somewhat conservative since we did have the prior hypothesis of relatively worse performances being associated with HIV infection, which was consistently found.

We thank the reviewers and editor for the thorough and complete critique offered our manuscript and trust that the additional amendments provided permit its acceptance for publication in *BMC Neurology*.

Sincerely,

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