Author’s response to reviews

Title: Quantifying cognition at the bedside: A novel approach combining cognitive symptoms and signs in HIV

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Author’s response to reviews:

We thank the reviewers for their helpful comments, and appreciate their overall positive assessment of this manuscript. We have undertaken revisions to address their comments, which we detail point-by-point, below.

1. “Interventions may be more likely to succeed at earlier stages of [cognitive] impairment.” To better motivate the need for early screening and identification, please clarify which interventions, and provide citation

This sentence has been reworded, and references provided.

2. Please clarify the limitations of existing screening tools (currently described simply as "poorly targeted") - are these only valid for a greater degree of impairment?

We have reworded this sentence to clarify that existing screening tools have been shown to be insensitive to mild cognitive impairment in HIV.

3. The authors state that a "systems" approach to neuropsychological testing "may be less appropriate in HIV, where deficits likely arise from diffuse network degradation rather than the focal cortical or hippocampal degeneration seen in many primary neurological disorders." Most neurodegenerative disorders are associated with disruptions in specific networks rather than focal degeneration (Seeley 2009, Neuron). Some degenerative disorders, including vascular dementia, chronic traumatic encephalopathy, and others, can show similar cognitive deficits to those described in HIV (attention, executive
function, processing speed). The authors should clarify what makes HIV cognitive impairment special and why it is appropriate to measure cognitive function as a single construct in this disorder, as opposed to other disorders.

We did not mean to imply that HIV was “special” in this regard. We fully agree with the reviewer that there are many conditions that involve diffuse network degradation. We have reworded this sentence to remove the unintended implication. The question of whether it is appropriate to measure cognition as a single construct is an empirical one that is addressed by this paper. It might also apply in other conditions, but this is beyond the scope of the current work.

4. In referring to their prior work with Rasch models for MOCA items in HIV, the authors state that "these items alone were too easy to precisely measure the two samples we studied." Please clarify what is meant by "too easy" — was there a ceiling effect? What exactly was disappointing about the MOCA results that motivated the present study?

We have reworded this section to clarify that the MoCA showed ceiling effects in the sample we studied.

5. In the results section, the authors state that "three-quarters of this sample met criteria for depression," but in Table 1 only 37% do. Please clarify.

We thank the reviewer for picking this error in the text, we have now corrected it.

6. As the data from computerized items and self-report items are added to the Rasch model, the p-value for global fit gets smaller, approaching the 0.05 threshold at which the Rasch model would be rejected — though internal reliability/PSI improves. For readers less familiar with this statistical approach, authors may want to touch on this aspect of fitting the model. Should readers focus only on the measure of internal reliability?

A comment on this was added in the Discussion.

7. The authors identify the need for a shorter, more economical alternative to full neuropsychological testing in this population and include a battery of computerized tests in their assessment, with which they hope to capture subtler cognitive impairment than can be seen on the MOCA. However, details on which computerized tasks remained in the model and how participants performed, compared with healthy controls, are not included. This will be important to readers' understanding of what the computerized tasks add to the MOCA.

We now list the performance items, including the items from the MoCA and the computerized items that were retained, in the legend for Table 4. We also refer readers to a prior publication where the computerized tasks are described in more detail. The measure is being developed to quantify cognitive ability in people with HIV but free from dementia. The aim of the measure is to have values that can used to mathematically compare persons to themselves overtime, as opposed to classifying someone as “not normal”. Once we have a validated measure for HIV, a
The subsequent step would be to collect information on typical values for different groups of people, including those without HIV and are otherwise “presumed normal”.

8. The single outlier participant is described as having “likely cultural and educational differences” — is he or she an outlier in terms of years of education or other standardized measures that were collected?

This individual was a recent immigrant from a rural area of an African country with little education. We can’t be sure which of these factors explains their outlier status on the assessment. We have now simply provided this information.

9. There is already evidence linking self-reported cognitive complaints with objective assessment of everyday function in this patient population. What does this work add from the clinician's perspective?

We agree that there is a link between self-report cognitive complaints and everyday function but the link with performance on tests known to tap component processes of cognition has rarely been shown. This may be because of lack of awareness, the lack ecological validity of the test, or poor questions. We think this measure is very helpful to clinicians because in the absence of access to formal neuropsychological testing, several simple questions or tests will provide information on cognitive ability which could be used to reassure patients or stimulate further investigation.

10. The implications of a large percentage of participants meeting criteria for depression are very important here, especially as authors describe depression being a major confound for clinicians confronted with patients with mild cognitive complaints, and prior reports have shown that self-reported cognitive symptoms correlate highly with depressive symptoms and not as well with objective task measures (cited in Valcour 2011). Depression in itself could certainly contribute to impaired attention and cognitive slowing. Does subgroup analysis show that the non-depressed patients perform similarly to depressed patients? Does the model hold in both cases?

First, we clarify that only 37% of the sample met the cut-off for depression on the HADS or the BDI. We are able to confirm that those with and without depressive symptoms all fit the same Rasch model: that is, the presence of depressive symptoms did not exclude the person from being accurately measured on the items. At this stage of development, the aim was to create a measure for the target sample; we focused on testing DIF by personal factors that are known to have no measurement bias (age, education). Once there is a true measure, further testing in different subgroups is planned. Future work should be undertaken, in larger samples, to more fully elucidate the relationship between depression and cognition in this population. We now state this limitation more explicitly in the Discussion. We are currently carrying out a much larger-scale study that will, we hope, address this more definitively.