Reviewer's report

Title: Neuropsychological Outcomes in Adults Commencing Highly Active Anti-Retroviral Treatment in South Africa: A Prospective Study

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Reviewer: David Clifford, MD

Reviewer's report:

Joska et al present data from neurocognitive assessment of a South African cohort of patients initiating HIV therapy. This adds to the scant data from developing countries in regard to impact of the virus on the brain, and the implications for therapy. The study has been systematically performed, and has substantial power, and thus is of interest. After a year of HIV therapy, there was evidence of neurocognitive improvement in this cohort, but it appears that the baseline cognitive status is the most important feature with greater impairment corresponding to greater improvement on therapy. Several non-viral factors including gender (male not female…), lower educational attainment were significant in unadjusted associations with improvement, with baseline CD4 being the only viral factor even in the unadjusted analysis.

Greater clarity about the analysis by GDS groups is needed. The figures/table show analysis dividing the population by baseline GDS, but the range and variability of the baseline GDS for the groups was not clearly stated.

The authors imply that their findings are suggesting that the Clade C virus is associated with neurocognitive impairment, in contrast to some reports that have raised the question that this subtype may have less propensity to affect the brain. The discussion of this interesting consideration in international studies probably requires greater clarity, while repeating the result section in the discussion is not necessary. Since viral factors are not very strong in predicting change, one might argue that there is less evidence that the impairment is driven by the virus, which would be consistent with the virus in this region being less likely to cause cognitive loss.

Another potential implication might be that in a region with limited resources, triggering start of therapy with a neurocognitive endpoint might select a population most likely to benefit. This would be a testable hypothesis. Thus, screening for neurocognitive disability might drive earlier initiation of therapy (ignoring CD4 guidelines) for the subgroup with more impairment who might see a greater benefit with therapy.

The therapy used might be better described. It sounds as if there may be little variation, and the power to tell anything about CPE may be very limited in this setting. Was the usual therapy a stavudine, 3TC, and nevirapine combination with high CPE?
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests