Reviewer’s report

Title: Central Nervous System Antiretroviral Efficacy in HIV infection: A Qualitative and Quantitative Review and implications for future research

Version: 1 Date: 16 October 2011

Reviewer: Scott Letendre

Reviewer’s report:

The submitted manuscript is an impressive work of scholarship by highly experienced and accomplished investigators and addresses a very important and timely topic, the importance of antiretroviral distribution into the CNS in people with HIV. While others have summarized previously published studies, none have taken the careful and systematic approach described here. Since the investigators use qualitative assessments to rate the reviewed manuscripts, the exact methods will be debated by reviewers and readers but the authors’ decisions in this regard are reasonable, defensible, and perhaps even overly conservative. Ideally, a manuscript of this importance should be published on an expedited timeline but there are a few issues that should be addressed first.

1. Abstract: Shouldn’t future studies also carefully control for comorbid conditions?

2. Aren’t analyses that meet a pre-defined alpha value (e.g., 0.05) for their primary hypotheses inherently adequately powered? Stated differently, shouldn’t the standard for adequate power be applied only to those projects that did not find a statistically significant effect for their primary hypotheses?

3. Under the section “Study selection and data extraction”, was this truly a Boolean “and” search or were combinations of these keywords used. In other words, would a more apt description of the search approach be the use of the Boolean “or” term (or at least a combination)?

4. An error in Table 1: The correct finding in the Smurzynski et al manuscript is that higher CPE was associated with better NP performance when ART was composed of more than 3 drugs (as opposed to at least 3 drugs as stated in the table).

5. An error in Figure A1: The correct sample size for the Smurzynski et al manuscript is 2,636 (not 3,046)

6. Please clearly state in the Methods that you used 15 quality criteria that fell into 5 categories (Blinded: Design, Outcomes, Subjects, Controls, and Unblinded Outcomes). Also, state that analyses had to meet at least 13 of 15 criteria to qualify (if this is correct). Readers will be able to conclude this once they refer to Table A2 but including this information in the Methods will ease the understanding of the readers and will not require that they refer to the Appendix.

a. Please consider summarizing in the Results how many studies met different
ranges of criteria (e.g., < 5, 5-8, 9-12, 13-15)

7. Some publications included multiple elements. For example, Marra et al included an assessment of CSF viral loads (n = 79) and NP performance (n = 26). DeLuca et al included both cross-sectional and longitudinal analyses with somewhat different findings. Should you group manuscripts with more than one major analysis into separate component assessments?

8. I suggest revising the following sentence to read “clinical trials” (plural) since no single clinical trial suffices to answer all aspects of other important clinical questions and this same standard should be applied for the treatment (and perhaps the prevention) of HAND. “Nonetheless, the most definitive answer to the issue of the potential superior efficacy of neuroHAART remains a randomised controlled clinical trial.” This applies to the sentence in the Conclusions that begins, “Therefore, a large randomised trial is needed…” . This may seem a subtle point but the field has suffered from clinicians placing too many expectations on a single publication even though the likelihood that a single analysis, even a randomized clinical trial, will definitively answer this complex question is small.

9. Regarding the recommendation to use the CPE score as an estimate of antiretroviral effectiveness in the CNS, I would also recommend planning secondary analyses with the version of the CPE that is current at the time enrollment in future clinical trials ends. The CPE will continue to evolve as new drugs are approved and new evidence on the effectiveness of these drugs in the CNS is generated so it is likely that different versions will be available when a clinical trial is designed and when the data are analyzed.

10. A final comment: One must admire the authors objectivity in excluding one of their own analyses for not having a quality score > 80% and two others that had estimated power below 80%.

Level of interest: An exceptional article

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