Reviewer's report

Title: Cognitive and psychosocial development of HIV pediatric patients receiving highly active anti-retroviral therapy: a case-control study

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Reviewer: Miriam Chernoff

Reviewer's report:

General comments:
This article is important and the research has been well-thought out. The research objectives are clearly defined, to assess whether severity of HIV disease is associated with emotional and cognitive function. The authors compare each case subgroup to the full set of controls, and are interested in conditional independence, or whether the odds ratios for each comparison of interest is equal to or different from 1.0. I have some comments on the methods (see below); the data appear to be reliable and the discussion and conclusions are born out by the data and limitations are acknowledged. There are a few places where the writing could be tightened up, but overall it is very good. I have a few general comments relating to discussion items that would improve the manuscript also.

Major Compulsory Revisions
1. Background; 4th paragraph; it would be important to indicate the context of the study, e.g., children with HIV in Greece.
2. Methods, Case Groups; (a) Note criteria for determination of encephalopathy. (b) How long did children with HIV receive HAART; at what age was HAART initiated? (c) Please report CD4% values as CD4 counts vary widely in the pediatric population.
3. Methods, Control group; Specify how gender, age, parental education and profession were matched for. E.g., by actual year or grouped age? By categorized level of education?
4. Statistical Analysis section:
The authors state they are using Mantel-Haenszel (MH) methods to test the null hypothesis for the different associations between cases and controls for perinatal risk and demographic variables. But, in the tables, they report Fisher’s exact tests. Also, I’m not sure the assumptions of this MH chi-square test hold, as to use it, each variable should be on an ordinal scale. The Fisher’s exact tests are fine but the statistical section needs to be clarified.

In this manuscript, the question of interest is whether each case subgroup differs from the control group on measures of emotional and cognitive function. Also, the authors are interested in whether or not the cases with encephalopathy differ from those without, in the comparison with controls. Yet, if these associations
differed, then the Cochran-Mantel-Haenszel (CMH) test for a common OR=1 might not be appropriate. (They would also have to test for homogeneity of odds ratios across the sub tables.).

The authors say they use the CMH test to compare cases to controls for the SDQ component scores. But this test usually is based on a set of stratified tables (sub tables). Even if the authors are using it to compare the entire control group to each of the case subgroups (each comparison could be considered a sub table), the CMH would test for the null hypothesis of a common odds ratio (OR) of 1 (conditional independence). Yet, in Table 3, the authors report separate p-values for the comparison of each subgroup to the controls for each level of the outcome measures. Thus, it is unclear if the authors are actually using the CMH or, in fact, are doing separate Fisher Exact tests or using the MH statistic noted above. This has to be clarified. If the authors are using the MH statistic noted above, because of the ordinal nature of the SDC scores (normal, borderline, abnormal), there should just be one p-value associated with each comparison (not one for each borderline and abnormal levels).

5. Discussion, 1st paragraph. This background information on prevalence of HIV in Greece, especially among pregnant women, is very interesting and needs to be expanded just a little. 53 can’t be a ‘prevalence’ as it is just a number. What is the mother-to-child transmission rate estimated to be in Greece? Do you know how many pregnant women with HIV there are living? Do you have ideas on why the rates are low for HIV-infection and transmission in Greece?

6. Discussion, 2nd paragraph. It is important to know when the cases in this study initiated HAART therapy. The high incidence of encephalopathy suggests they initiated HAART at older ages, which will contribute to impairment findings.

7. Discussion 3rd paragraph; Could the high incidence of hypoxia explain any of the findings? How might that be related to pregnancies relating to HIV?

8. Discussion, 5th paragraph; Again, timing of initiation of HAART would affect these outcomes.

9. Discussion, 6th paragraph; But you did note in results and elsewhere in discussion that HIV-infected children without encephalopathy had impairment somewhat in emotional score as well as hyperactivity. Here you do not note that.

10. Discussion, 2nd to last paragraph; Do you know that test assessments were done prior to disclosure of HIV status or is this just a supposition?

Minor Essential Revisions

1. Methods, Assessment of cognitive development; “Lectical” is a confusing term to me. Do you mean “Verbal”? It appears throughout the manuscript.

2. There are references to results not tabulated, for example in Results, children without encephalopathy, there is a reference to family composition being in Table 1 but it is not. (1st paragraph)

Minor issues not for publication

1. Background, 3rd paragraph “It is upheld” # “It is thought....”
2. Study population, 1st paragraph; “one patient deceased during …” # “One patient died during…”


4. Discussion 6th paragraph “… skills were deterred.” # “skills were affected”.

Discretionary Revisions

1. The authors might want to mention the cognitive outcomes in the abstract, as well as the emotional/social outcomes.

2. Regarding the statistical methods chosen, if the authors are not analyzing the stratified tables (see above), then it might be more straightforward, assuming a focus on odds ratios estimates and tests of significance, to provide estimates of odds ratios and 95% confidence intervals, reporting the Wald chi-square significance tests for the beta estimates. Or the authors could report Fisher’s exact tests along with the tables as they are, if the focus remains on testing for associations. Another option would be to use the ordered chi-square test (essentially a Wilcoxon rank sum test based on scored outcomes, e.g., normal=1, borderline=2, abnormal=3) for each SDQ component score and comparison (case vs. control).

3. Results, 4th paragraph, 8th paragraph – Cognitive outcomes are referred to as indicating moderate or severe mental retardation. But these classes are not presented in the tables or defined. Presumably they relate to scores on the WISC of < 85 or < 70. These should be clarified in the text and/or a table with categorized outcomes in addition to the mean scores would be very helpful to the reader.

4. Results, 5th paragraph, 9th paragraph – It would be helpful to tabulate the total SDQ scores as well as the components in Table 3.

5. The results section would be strengthened by reporting odds ratios given the choice of Cochran-Mantel-Haenszel (CMH) methods.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.