Author's response to reviews

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

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Version: 2 Date: 16 September 2010

Author's response to reviews: see over
Dear Members of the Editorial Board of *BMC Pediatrics*,

Thank you for considering the manuscript entitled “Cognitive and psychosocial development of HIV pediatric patients receiving highly active anti-retroviral therapy: a case-control study” for publication. Please find below the point-by-point response to the reviewers’ comments. In order to facilitate the review process we have included all proposed changes with track changes within the revised manuscript, as well as comments annotating the response to each reviewer’s query and/or suggested change.

On behalf of all my co-authors, I sincerely hope that we have addressed all reviewers’ comments adequately and hope that you deem our revised submitted work worthy of publication in your journal.

Sincerely,

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**Reviewer's report (1)**

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

**Version:** 1  **Date:** 6 August 2010

**Reviewer:** Diane Melvin

**Reviewer's report:**

1. There is a paucity of psychological outcome data for European children with HIV, as the authors suggest, and this attempts to redress this. However the report produces more questions than answers. For example were the controls appropriately matched to the case group?

   Controls were frequency matched for actual age +/− 1 year, gender, and parental education and profession, as specified in the Methods section (Control Group, paragraph 1). Please note that in Greece duration of parental education consists a more reliable index of socioeconomic status than parental income [1].


There was no mention of ethnicity in matching the groups or whether the children had similar care situations (particularly important for the psychological adjustment scale)

   Thank you for your comment. While ethnicity was not used as a variable for selecting the study population, please note that ethnicity has been now specified in Table 1. We would like to note that this variable was not selected for matching the groups examined since several studies have indicated that ethnicity is not significantly associated with psychosocial development in children, including peer relationships, self-esteem, and problem behavior [1-3].


Also the control group’s IQ scores were significantly below the test mean norms and lower than the children with HIV without encephalopathy - and there was no mention of why this might be. May suggest these tests were unreliable measures.

*Please note that specifications have been added in the Methods section (Assessment of Cognitive Development, paragraph 1). The assessment tools used have been standardized and are widely used for research purposes to measure IQ [1-2]. The low mean IQ scores of the control group was an unexpected and interesting finding. The difference between the IQ scores of the control group and the HIV without encephalopathy group could be attributed to the fact that the support system offered to children with HIV included supplementary individual educational support, which may have consequently had a beneficial effect upon patient IQ scores [3]. In addition, the wide range of IQ scores observed may also be attributed to cross cultural differences between population groups [2, 4-5].*

Also for the HIV group there was no mention of how long the children had been on HAART.
Thank you for noting this. Please refer to the age at HAART initiation and months of HAART therapy added in Table 2.

2. The small number of children with HIV (especially those with encephalopathy) make the significance of the findings difficult to generalise to other cohorts.
Thank you for this comment. We recognize the limitations of the study findings due to the limited population size and have added relative response in the limitations of the study (Discussion section, paragraph 10). Also the very wide age range adds to the difficulties in reliability e.g. known that developmental scores at 3 years are measuring different things to those on cognitive tasks carried out in adolescence.
Thank you for this note. While we do agree with this, we attempted to minimize such possible effects by utilizing both cognitive development scales and psychosocial adjustment tools specific for each age group measured (Methods, Assessment of Cognitive Development, paragraph 1, and Assessment of Psychosocial Adjustment, paragraph 1).

3. On SDQ scores it may have been more useful to give mean scores on the different subscales as well as numbers in abnormal and borderline groups as this would have been a more real comparison between the groups. It is rather ambitious to say that those with encephalopathy have higher conduct problems as it was only one child. What about the influence of age of children on score of SDQ?
Please find both the mean scores as well as frequencies of abnormal and borderline groups in the revised Table 4. As noted in our response to your comment number 2, we utilized age-specific SDQ scales in order to account for the potential effect of age upon children’s psychosocial development.

4. What about relationship between each of the case's developmental/cognitive scores and score on SDQ - that would have been an interesting comparison to do rather than just using group comparisons and may have backed up your suggestion that there is a relationship between emotional/activity spheres and children with HIV.
Thank you very much for this comment. We do agree that the interaction between developmental/cognitive scores and SDQ outcome would have been interesting to evaluate. However, due to the limited study sample size included in the present study such analyses could not be undertaken. We do hope, though, that a longitudinal study currently underway at our center may take such effects into account for future analyses.
5. The data confirms what has been found from other studies about improving outcomes for children with HIV and in order to add to the knowledge the authors need to provide more justification about why they choose to look at certain background data and the choice of tests and controls. Also to have addressed the issues of small numbers and wide age range in limitations.

*Please note that clarifications have been made for the perinatal risk factors for cognitive development in the Methods section (Measurements, Assessment of Cognitive Development). Also, the limitations of the study regarding both the limited sample size and range of ages have been now referred to in the Discussion section (paragraph 10).*

6. English is good and the presentation is clear.

**Level of interest:** An article whose findings are important to those with closely related research interests

**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 I have no competing interests

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**Reviewer's report (2)**

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

**Version:** 1  **Date:** 23 August 2010  
**Reviewer:** Bruce Brew

**Reviewer's report:**

The major issue with this study is the definition of HIV encephalopathy by imaging. The latter is not a radiological but rather a clinical diagnosis.  
Thank you for this comment. Please refer to the imaging and clinical indications specified in the Methods section (Case group, paragraph 1).

Furthermore, the results need to be placed in a clinical context - are the abnormal findings in relation to behavior likely to significantly affect the patients' lives, adherence to medications etc.

*Please find relative additions made to the Discussion section (paragraph 9).*

Additionally, the discussion is too long and in the main repeats the results rather than analyzes them.

*Thank you for this proposal. Please note that we have tried to reduce the length of both the results and discussion sections, while retaining all necessary information regarding the study findings.*

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing
Reviewer's report (3)

Title: Cognitive and psychosocial development of HIV pediatric patients receiving highly active anti-retroviral therapy: a case-control study
Version: 1 Date: 25 August 2010
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.
   Please refer to specification of population examined in both the Abstract (Methods, p.3) and Background (paragraph 2) sections.

2. Methods, Case Groups;
   (a) Note criteria for determination of encephalopathy.
   Please note that both imaging and clinical findings utilized for the diagnosis of encephalopathy have been specified in the Methods (Case groups, paragraph 1).

   (b) How long did children with HIV receive HAART; at what age was HAART initiated?
   Please find both the age at HAART initiation and months of HAART treatment in Table 2.

   (c) Please report CD4% values as CD4 counts vary widely in the pediatric population.
   Thank you for this comment. Please find both CD4% and CD4 counts in Table 2.

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?
   Please find specifications with regard to both age matching and education in the Methods section (Control group, paragraph 1), as well as comparisons of these variables in Table 1.

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.

Please find clarifications made in Methods section (Statistical analyses).

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).

We greatly appreciate your comments. Following your proposition in “minor issues, comment #2”, please note that we have compared all ordinal variables (i.e. SDQ component and total score categories) with the Wilcoxon rank sum test and have presented the respective exact p-values in Table 4.

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?

Thank you for your comment. Please find further information provided you’re your request in the Discussion section, paragraphs 1-2.

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.

Thank you for noting this. Both the age of HAART initiation and months on HAART are presented in Table 2. The study findings indicate that a confounding effect due to the aforementioned factors may have not been introduced as these did not differ significantly between case groups.

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?
Thank you for noting this finding. Hypoxia constitutes a known perinatal risk factor for adverse cognitive development (Discussion, paragraph 3). However, due to the limited sample size of the present study, multivariate regression analyses could not be applied in order to assess the effects of hypoxia upon either the cognitive development and/or psychosocial profile of study participants.

8. Discussion, 5th paragraph; Again, timing of initiation of HAART would affect these outcomes. Please refer to response to comment 6.

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. Thank you for noting this. Please find correction made in paragraph 6.

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? All test assessments were undertaken prior to disclosure of HIV status.

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. Thank you for observing this point of potential confusion. Please find the term corrected 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) Please find corrections made in the Results section in both paragraphs 2 and 6.

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”.
   For comments 1-4, please find all recommended changes made in the manuscript.

Discretionary Revisions
1. The authors might want to mention the cognitive outcomes in the abstract, as well as the emotional/social outcomes. Thank you for your recommendation. Please find the comparisons of cognitive outcomes presented in the revised Abstract.

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).

We greatly appreciate your recommendations. Please find the response to this in our response to your comment no. 4.

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.

Thank you for this comment. Please note that changes have been made to specify scoring of cognitive development both in the Methods section (Assessment of Cognitive Development, paragraph 1) and Table 3.

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

Thank you for this recommendation. Please find this additional data added in Table 4 (former Table 3).

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

While we certainly agree with your comment, due to the limited study sample size the CMH could not be undertaken. However, following your suggestions, we hope that you find the analyses and results section sufficient for relaying to journal readers adequately the study findings.

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.