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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Author's response to reviews: see over
Reviewer's report
Title: Cognitive and psychosocial development of HIV pediatric patients receiving highly active anti-retroviral therapy: a case-control study
Version: 2 Date: 30 September 2010
Reviewer: Diane Melvin

Reviewer's report:
I think the authors have addressed my main original queries. Just a couple of points (discretionary revisions)
1. Re Ethnicity - were all the non greek children born in Greece as early experiences, nutrition, health and psychosocial factors as well as HIV can affect later developmental progress. Was there any difference on IQ scores for those born in Greece compared to those not? Might be helpful just to mention this.

   **Thank you for this indeed important comment. Please find that no significant difference was found in the ordinal values of the general intelligence quotient scores when comparing Greek to non-Greek study participants (Wilcoxon rank sum test p-value=0.487).**

2. Discussion (Malee ref) There is an emerging literature base that the relationship between disclosure of the diagnosis and emotional adjustment is very complex and needs to be considered a process over time. Would be suggesting that the kinds of difficulties you are reporting re over activity and increased emotional vulnerability need to be identified early so interventions or support can be provided independently of 'naming' of the diagnosis.

   **Thank you for this comment. The majority of research indicates the vital importance of children’s underlying cognitive and emotional status prior to disclosure in order to better comprehend and cope with effects inherent at the time of disclosure (1-5). We recognise that the relationship between disclosure and consequent emotional adjustments is a complex process over time. However, we uphold that addressing pre-existing emotional and behavioural difficulties may aid pediatric patients with HIV in their consequent adjustment following the critical time of disclosure of their HIV diagnosis.**

3. Perhaps there is a lack of considering the developmental stage in reporting on the SDQ results? were all those who scored high on hyperactivity scale at younger age and those high on emotional or social difficulties scales at older age.

*Thank you for this comment. Please find that of all component and total SDQ scores, only scores on the hyperactivity scale were found to occur more frequently among young (<7 years old) children (Wilcoxon rank-sum test p-value=0.030). No significant differences were found with respect to either emotional difficulties and/or social difficulties scales between age groups. However, please note that age-specific SDQ questionnaires were distributed to study participants.*

4. Abstract. Perhaps mention limitations - small study sample size / large age range here as well as in discussion

*Thank you for this comment. Please find limitations added to both the Abstract (conclusions, lines 4-6) and discussion (paragraph 10, lines 5-7).*

**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.
Reviewer's report
Title: Cognitive and psychosocial development of HIV pediatric patients receiving highly active anti-retroviral therapy: a case-control study
Version: 2 Date: 1 October 2010
Reviewer: Bruce Brew

Reviewer's report:
Unfortunately I am still concerned at the criteria for the diagnosis of HIV neuroimaging abnormalities. Page 8 Under the section Case Groups it is stated "The diagnosis of neuroimaging abnormalities was based on brain imaging findings indicative of HIV related neuroimaging abnormalities". This is not the basis of the diagnosis. It must be primarily clinical/neuropsychological. The imaging abnormalities may or may not be present in im[aired patients. From the revised manuscript it still appears that the primary criterion is the imaging. The primary criterion must be clinical/neuropsychological.

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 interests.

Thank you for this indeed important comment. Please note that all five patients presented with neuroimaging abnormalities suggestive of HIV encephalopathy e.g. symmetrical multiple hyperintense signals localized bilaterally in the subcortical area. Three out of five patients also fulfilled the clinical criteria of the diagnosis. The other 2 patients had no other underlying condition that could be causatively associated with those neuroimaging findings. We agree that imaging abnormalities should not be the primary criterion for diagnosis of HIV encephalopathy therefore we replaced the term “HIV encephalopathy” with the phrase “HIV-patients with neuroimaging abnormalities” in relevant parts of the text, as suggested.
Reviewer's report
Title: Cognitive and psychosocial development of HIV pediatric patients receiving highly active anti-retroviral therapy: a case-control study
Version: 2 Date: 20 September 2010
Reviewer: Miriam Chernoff
Reviewer's report:
General comments:
The authors have responded to my previous comments and I thank them. There remain a few comments, which I believe will be needed prior to publication.
Discretionary:
1. Abstract. I believe the p-value associated with the Hyperactivity score comparison between HIV patients without neuroimaging abnormalities and the Control group should be 0.009 (from Table 4). This would correspond to the value reported for Emotional symptoms, that is, the p-value for the Wilcoxon rank-sum test.
   Thank you for correcting us on this point. Please find that the p-value now presented in the abstract regarding the hyperactivity score comparison between HIV patients without neuroimaging abnormalities and the control group corresponds to that of the Wilcoxon rank-sum test (p-value 0.009).

2. Methods, “Case Groups” and Table 2. I earlier requested reporting CD4% in addition to CD4 counts. Either they should describe the CD4% values separately from counts or delete them from Table 2, which, as it stands, is very confusing. Typically, these values are reported as the number and percent of participants with CD4% from 0-14%, 15-24%, 25% or more, as these relate to levels of immune suppression in children.
   In order to avoid any confusion to the journal's readers, please find that we have retained in Table 2 only CD4 counts.

3. Methods, Statistical analysis and Results.
In two sets of instances, the authors use the Fisher’s exact test when they should preferentially use another test.
For example, in comparing Mother’s profession (Table 1) and Father’s profession (Table 1), they should be using the generalized Exact test. There should be just one p-value associated with each comparison of the different educational levels between HIV-infected and control groups (manual, employee, academic). Theoretically, if they find a statistically significant difference, they could explore the specific contrasts in more detail with the separate Fisher’s Exact tests. But I believe the reader will be confused by their current presentation.
In the comparison of CDC Stage, Viral load and CD4 Count, CD4% (all in Table 2), they should use the Wilcoxon rank-sum test and not the Fisher’s exact test, since these values are ordinal/ordered.
For more information, see SAS online documentation (for the PROCEDURE, “FREQ”; look under “Details” > “Statistical computations” > “Chi square tests and statistics”):
“Fisher’s exact test was extended to general RxC tables by Freeman and Halton (1951), and this test is also known as the Freeman-Halton test. For RxC tables, the two-sided p-value is defined the same as it is for 2xC tables. The set contains all tables with less than or equal to the probability of the observed table.
A small p-value supports the alternative hypothesis of association between the row and column variables. For R × C tables, Fisher's exact test is inherently two-sided. … For R × C tables, PROC FREQ computes Fisher's exact test using the network algorithm of Mehta and Patel (1983), which provides a faster and more efficient solution than direct enumeration. See the section "Exact Statistics" for more details.”

Thank you for your kind recommendations for the statistical analyses. Please find that changes have been made according to your recommendations so that mother’s profession and father’s profession in each of the case groups are assessed with the likelihood ratio exact test (Table 1). Following your recommendation, we have excluded the Fisher’s exact test p-values since the overall exact test p-values were non-significant for both aforementioned variables in both case groups. In addition, please find that the Wilcoxon rank-sum test p-values are presented in Table 2 for the comparison between groups of the following variables: disease stage, viral load, and CD4 cell count.

4. Results. 1st paragraph; It would seem to make more sense to express age in terms of years for this study population, rather than in terms of months. This also relates to Table 2.

Thank you for this comment. Please find that all ages are now expressed in terms of years in both the Results section (1st paragraph), and Table 2.

5. Results. Tables 3 and 4 would be improved by including the counts and %s for the “Normal” levels of each of the tests.

Following your recommendation, please find that the counts and percentages for the “normal” levels of each of the tests have been added to both Tables 3 and 4.

Minor issues not for publication
1. Abstract, Methods. Included the word, “with” in the following sentence: “CNS imaging and clinical findings were used to identify patients with HIV-related neuroimaging abnormalities”.

Thank you for noting this. Please find that the word “with” has been added in the Abstract (methods, line 5).

2. Methods, Statistical analysis. Normally, a significance cut-off is expressed as “less than” (i.e., “<”) rather than less than or equal.

Thank you for this correction. Please find that the Methods, Statistical analyses section (paragraph 1, line 6) is corrected as follows: “A p-value (p) of <0.05….”.

3. In some instances, the authors refer to “HIV children” and in others to “HIV-infected children.” I think the term “children with HIV” would be preferable to “HIV children”. Perhaps the journal editors can help here.

Thank you for noting this. In order to avoid confusion, please find that the terms “HIV children” and “HIV-infected children.” has been changed to “children with HIV in the whole text.

4. Table 1. “Private education” is not referenced in the manuscript text. I find the entry confusing. The authors should either elaborate in the text or delete.

In order to avoid confusion, please find that the term “private education” has been changed to “attendance in private school” in Table 1.

5. Discussion, paragraph 7, 1st sentence. I think it should read “In contrast,
HIV-infected children with neuroimaging abnormalities had an elevated frequency of … “.
Again, the journal editor can help here.

Thank you for your comment. Please find that the Discussion section, paragraph 7, line 1 has been changed as follows: “…In contrast, children with HIV who presented with neuroimaging abnormalities had an elevated frequency of Abnormal Peer Problems…”.

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.
Reviewer's report
Title: Cognitive and psychosocial development of HIV pediatric patients receiving highly active anti-retroviral therapy: a case-control study
Version: 2 Date: 16 November 2010
Reviewer: Shally Awasthi

Reviewer's report:
I have gone through the attachments. I agree with Brew that HIV neuroimaging abnormalities is a clinical/neurological diagnosis. The authors have only used neuro-imaging to categorise patients. However they have been consistent in categorising patients. Therefore, it is suggested the authors may consider replacing the word "neuroimaging abnormalities" with "HIV-patients with neuroimaging abnormalities". Since there is not must litterature on Pediatric HIV I favour publication of the work.

Thank you for noting this. We agree that imaging abnormalities should not be the primary criterion for diagnosis of HIV encephalopathy. In order to avoid confusion, please find that the term “Encephalopathy” has been changed to “Neuroimaging abnormalities’ in the whole text.