Author's response to reviews

Title: Outcome Of Highly Active Antiretroviral Therapy in HIV-infected Indian children.

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Version: 5
Date: 22 October 2014

Author's response to reviews: see over
The Editor,
BMC infectious diseases

Sub: Outcome of highly active antiretroviral therapy in HIV- infected Indian children (MS: 1703235581136216)

Dear Sir,
We would like to thank the reviewers for their valuable suggestions. We have attempted to give a point by point response to the comments as follows:

Reviewer: Linda Aurpibul

Major Compulsory Revisions

1. Inclusion criteria should be listed including age range of enrolled participants. Details in this part should be re-arranged starting from inclusion criteria, treatment regimen, follow-up and monitoring.

RESPONSE: We have added the inclusion criteria and age range in the methods section. Methods’ section has been re-arranged as inclusion criteria, diagnosis, treatment regime and follow-up and monitoring.

2. The term “default” used for children with missing dose is vague and should better be replaced with a more conventional term i.e. non-adherence, or suboptimal adherence.

RESPONSE: We have replaced the term “default” with “non-adherence” in this section as well as rest of the manuscript.

3. Line 129; what were the causes of death?

RESPONSE: The final cause of death was not recorded for these children.

4. Line 129-130; How long did it take from HAART initiation to death or LTFU?

RESPONSE: The median interval between initiation of HAART and death/ LTFU was 24 (12,24) months. This has been added in the text.

5. Line 138; For TB occurred after HAART initiation, were they IRS? The diagnosis was made by sputum AFB, culture, or others? Were they confirmed or probable cases of TB?
RESPONSE: Diagnosis of TB was made on the basis of clinico-radiological criteria as followed in the hospital. We attempted to demonstrate Mycobacterium tuberculosis on smear/culture. However, tuberculosis was confirmed mycobacteriologically in only one child. This information has been added to the text. The cases were not classified as IRIS.

6. Line 148-149; A trend towards more chances of default in case with expired father, what was the comparison group, those with both parents alive or those who lost both?

RESPONSE: The comparison group was children whose father was alive, irrespective of whether mother was alive or not. This has now been mentioned in the text.

7. Line 150-154, how long did it take from HAART initiation to changing regimen?

RESPONSE: The median time of changing of regime from initiation of HAART for indications other than treatment failure was 8 (4, 22) months. This has been added in the text.

8. Line 163: mean time to treatment failure should be presented with SD, or much better to be presented as median (IQR) as I don’t think the data was normally distributed.

RESPONSE: The time to treatment failure has been presented as median (IQR) now.

9. 177-179 and line 185-192, change in CD4, WAZ, HAZ, and ESR should be accompanying with p-value so that the readers could know whether the change was significant or not. To describe a change in CD4, it would be better to separately report children aged < 5 in percentage, and those > 5 in number of cells.

RESPONSE: The respective p-values have been added in the text. For children <5 years of age, CD4 percentages have been reported.

Minor Essential Revisions

1. Title should be written in all upper case letters.

RESPONSE: Title has been modified to upper case letters.

2. Abstract, please consider consistency in term and pattern of data presentation:
   Line 23 and 37: HIV-infected children (some with dash in between, some without),
   Line 28-32 median XX (IQR XX-XX), or whatever pattern used should be reconciled.

RESPONSE: Changes have been made throughout the text so that it is always written as HIV-infected and median XX (IQR: XX, XX).

Line 32 misspelling “cells”

RESPONSE: The spelling has been corrected.
Line 33 ....improvement with time after HAART initiation.

RESPONSE: This phrase has been included.

Line 33 baseline WAZ should be -2.8 (the minus sign is missing)

RESPONSE: The minus sign was inadvertently dropped, it has been now included.

Line 35 The last sentence of results, Treatment failure, death and non-adherence should be re-arranged by their severity (non-adherence, treatment failure, and death). Number (%) should be presented for all three items.

RESPONSE: The sentence has been re-arranged and the percentages added.

3. Table 1: what does “H/O” mean? All abbreviations used in the table should be defined at footnote. If the authors stated that number in n(%) at footnote, they did not have to put “%” at the number within the table again.

RESPONSE: “H/O” meant history of. This has been now spelt clearly. All abbreviations have been defined in the footnote.”%” within table have been removed. The same have also been removed from Table 3.

Reviewer: Dalton Wamalwa

Major Compulsory revisions

1. The results should be presented in a sequential style with appropriate subheadings in order for readers to follow. Suggested subheadings are Baseline characteristics, Response to antiretroviral therapy, Predictors of response to antiretroviral therapy and Adherence and safety.

RESPONSE: The results have been re-organized into appropriate subheadings of baseline characteristics, response to anti-retroviral therapy, predictors of response to anti-retroviral therapy, adherence and adverse events, as suggested.

2. More information should be provided on how adherence to ART was measured and the level of adherence found.

RESPONSE: Adherence to treatment was monitored by interviewing the child/guardian at each visit and by performing a pill count.
We did not routinely perform drug levels to confirm adherence.

3. The results on treatment failure should be separated from toxicity to ART. In the
current version treatment failure is presented along with toxicity-related treatment switches yet the two are entirely different.

RESPONSE: The number of children needing treatment switch for adverse events and for treatment failure has now been mentioned in different paragraphs.

4. Data on viral load should be presented systematically to include the number of children with baseline viral available and more critically the change in viral load following ART. This is important missing information which should be either shown or acknowledged to be a limitation. This is because in many settings there is a significant disparity between clinical and virologic failure and it would be important to see the situation in this Indian study. Viral load response should be presented as proportion of children with suppressed viral load at various points in time as well as mean drop in log 10 viral load.

RESPONSE: We did not have data on baseline viral loads for majority of the children; in the country program, viral load determination is not available. We were able to perform assays in a few children under different research projects. The viral loads at different time points are also too few, hence a systematic approach could not be adopted. We have mentioned this as a limitation. “Also, the viral load studies were not available for all the patients in our study at different time points.”

Minor Essential revisions

1. Indicate whether the mean duration to treatment failure (given as 38.8 months) refers to clinical or immunological failure or both.

RESPONSE: Treatment failure indicates either clinical or immunological or virologic failure. This has been stated in a preceding sentence in the text.

2. Clarify the seeming discrepancy between the high level of failure to thrive (given as 70%) and the anthropometric data shown in table 1 that indicate that 77% of the children did not have severe malnutrition at baseline (based on WAZ scores).

RESPONSE: We regret to state that there has been a mistake in stating these data. 77% of the children did not have severe malnutrition. Weight loss (failure to thrive) was a presenting symptom in 70 (40%) children.

3. Comment on the male: female disparity found in this study

RESPONSE: In our setting the male: female disparity is commonly seen for most disease conditions suggesting a gender bias in health care seeking behaviors of the population (Khera R, Jain S, Lodha R, Ramakrishnan S. Gender bias in child care and child health: global patterns. Arch Dis Child. 2014;99:369-74.). This aspect has been now discussed in discussion section.

4. Statistical review: Predictors of response could be best shown in a separate table with appropriate statistics.
RESPONSE: A separate table (Table 3) has been added to this effect.