Author’s response to reviews

Title: Abacavir versus Zidovudine-Based Regimens for treatment of HIV-Infected Children in resource limited settings: A Retrospective Cohort Study

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Author’s response to reviews:

Dear Dr Eric McGrath,

We thank you and the reviewers for their constructive and generous comments on the manuscript. We found the reviewers critique of our initial submission to be very helpful. In responding to their comments, we believe our manuscript is greatly strengthened. Our point-by point responses to the critique are outlined below.

Reply to the reviewer comments
Ronald Thomas (Reviewer 1)

1. Page 6. An a priori power and sample size calculation was not performed, although authors have adequately described their eligibility criteria and total samples sizes in each group described. In the absence of a hypothesized effect size (s) could the authors indicate that the sample size employed in the study was adequate to performing the stated regression techniques?

Even though we have calculated the initial sample size, the number of patients on Abacavir (ABC) based regimen was very limited. So, we included all of them and we randomly selected 92 patients from Zidovudine (AZT) group to keep the ABC to AZT ratio of 1:1.05. For more detail look at the patient enrolment section (page 6).

2. Page 7 and 8. Authors should be commended for the selection and reporting of the correct statistical techniques and why they were chosen. AS a suggestion, authors should include more detail to what a propensity score matching technique provides and why it was necessary to conduct in this study. Most of the readership would probably wonder what propensity score matching is? The propensity score is the probability (from 0 to 1) of a case being in a particular group based on a given set of covariates. Generally, calculated using logistic regression with group (Treatment /Control) as dependent and covariates as independent variables. The propensity score is a balancing score: The
differences between groups on the covariates condensed down into a single score so if two groups are balanced on the propensity score they are then balanced on all the covariates.

We have added some details in the revised manuscript about a propensity risk score matching and why we used it (Methods section, Statistical analysis, page 8).

3. Page 11. Table 1. Baseline CD4+ mean and SD for ABC group is listed as 166.31 + 76.233. The sign should be ± and the SD should be rounded to 2 decimals place (76.22). Functional status A/D for AZT group should be reported as 0 (0.0%) for consistency.
This is corrected in the revised manuscript.

4. Page 13. Figure 2. Can the authors report the days on the horizontal scale in increments of perhaps 50 instead of 500? Although the log rank test indicates insignificant (p=0.38) it is apparent that the largest gap between the lines of the two groups appears somewhere in the middle of 500 and 1000 days. It would make it easier for the readership to determine that it appears to lie around 750 days.

Dear Dr Ronald Thomas, the authors acknowledge your suggestion because of the fact you have provided. However, the very basic reason behind running this analysis is to rule out if there was any significant difference in baseline survival experience in patients allocated among the two regimens. Yet, the statistics failed to reveal this difference (p=0.38). Although it was possible to report the days on the horizontal scale in increments of 50, 100 or more neither it adds any meaning nor it affects the central message of this analytical results, given there was no difference among the regimens. What is crucial for the readers here is the interpretation of the median survival time which lies below 500 days. Moreover, the nature of the curve stated by the reviewer (.....the largest gap between the lines of the two groups appears somewhere in the middle of 500 and 1000 days.....) was the one which ultimately affected by variations in sample size or the intended number of observations among the two regimens.
Remember that, based on this result and the existing facts what remained unaffected is the statement of "no difference among the regimens." These are the facts that readers need. Therefore, the authors prefer this curve to remain as it is since it has no impact on the readership.

5. Table 2. Page 14. Percentages should be included with the raw numbers provided for each variable under OIS. The variable "Age: Media IQR is missing a letter "n". Should read "Median". The p-value for CD4 count, baseline viral load, baseline nutritional status, and TB treatment all read as 0.00. A more appropriate convention would be to replace it with ≤0.01.
We have included the percentages with the raw numbers and replaced 0.00. to ≤0.001 in the revised manuscript.

6. Page 13. Authors have listed three main predictors of OIs and described the results nicely in Table 2. These results describe the predictors for the entire sample size (i.e. both groups combined). Given that comparisons on variables had been made between groups (ABC and AZT) up to this point in Table 1 could authors simply include the group variable as a dichotomous predictor in the regression models? Maybe it would flow better if Tables 2 and 3 were reversed in the results section where the treatment types are the focus (with propensity score matching evaluated) and the regression output for the entire sample (Table 2) is described lastly.

As per your suggestion, we have reversed table 2 and 3. Accordingly, the regression table is described lastly.
Chokechai Rongkavilit, M.D. (Reviewer 2)

1. The author included all subjects (87) who took abacavir but decided to include only some subjects (92 of 212) who took AZT into the analysis. What is the rationale for that. Do those included truly represent those who were excluded in terms of clinical and demographic characteristics?
   Yes, they truly represent because the 92 patients (out of 203) from Zidovudine (AZT) group are randomly selected by computer generated numbers (Look Figure: 1).

2. Co-morbidity data were collected as stated in Study Population and Variables. However, I do not see them in Table 1. Any difference in co-morbidity between 2 groups?
   This is corrected in the revised manuscript.

3. Regarding Opportunistic infections (OI), how do authors define/diagnose bacterial pneumonia clinically, radiographically and microbiologically?
   The diagnosis of bacterial pneumonia was made based on microbiological findings.

4. Are there other OI encountered in the study populations besides bacterial pneumonia? If so, they should be included in findings.
   Yes, there are also other OIs and we have mentioned them in the revised manuscript under table: 2 (page 12).

5. What was the difference in adverse drug reactions between the 2 groups?
   The rate of adverse drug reaction is not measured in this study.

6. The author suggests that patients with anti-TB treatment were 3 times at higher risk of having OIs. Authors should include other studies that demonstrate similar findings. I think this is an important observation.
   The plausible justification for higher risk of OIs among patients treated with anti-tubercular drugs is provided in the manuscript with evidences from other literatures. This is the first observation which needs further investigation.
   For Editor Comments
   Line 12, page 5 – consider revision of “exploited” to “evaluated.”
   This is corrected in the revised manuscript
   Page 6 – “Sample size determination” – a true sample size determination was not presented or noted. Please change the sub-heading or revise to show the number of subjects that were calculated to be required to show significance. If this is a pilot, or experimental, then simply state.
   As per your suggestion, the sub-heading is changed from Sample size determination to Patient recruitment (page 2).
   Page 7 – Sampling technique. This section is also not clear for the reader. Please give more details or expand on your sampling technique.
   This is also corrected in the revised manuscript
   Lines 22 – 29: Please rewrite. This sentence is not clear as written.
   It’s revised.
   Line 14, page 10: problems (needs an s)
Line 19/20, page 10: groups, respectively (typically requires comma)
Line 13, page 12: delete “were” before died.
Line 52, page 13: “anti-tuberculars” needs to be anti-tubercular drugs or medication throughout.
Line 10-12, page 14 need to more fully expand “…they didn’t pass the cell adequacy test.”
Table 2: Need to spell out in full CHR and AHR in footnote
Line 31, page 15 – delete “was” as in “…score matching analysis failed…”
All of the above comments are addressed in the revised manuscript.