Reviewer’s report

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

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Reviewer: Ronald Thomas

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Abacavir versus Zidovudine-Based Regimens for treatment of HIV-Infected Children in resource limited settings: A Retrospective Cohort Study
Review: 01/22/2020

Authors state that Abacavir (ABC) and Zidovudine(AZT) based regimens are the preferred first line nucleoside reverse transcriptase (NRTIs) backbones being widely utilized for managing HIV infection in children. However, informations is lacking regarding the clinical outcomes and associated risk factors in Ethiopia. Authors compared the proportion of mortality and the rate of occurrence of Opportunistic Infections (OIs) between ABC versus AZT based regimens in a cohort of HIV-infected children. The study was retrospective and cohort in nature. A total of 179 records were reviewed by including data from October 2014 to April 2017. Data were collected on socio-demographic, clinical characteristics of patients and drug related variables. Data were analyzed using STATA13.1. Kaplan-Meier and Cox regression were used to compare survival experience and identify independent predictors. Propensity score matching analysis was conducted to elucidate the average treatment effects of each regimen over OIs. The results indicated that the incidence of opportunistic infections attributed to ABC group was higher (8.77/100,000 person years) that that found for the AZT group (6.9/100,000). The incidence rate ratio (IRR) for OIs was not significant (IRR=0.87, 95% CI [0.49-1.53] (p=0.304). Baseline CD4 count (AHR= 0.99; 95% CI [0.98-0.99]), Severe acute malnutrition (AHR=15.92; 95% CI [5.34-47.50]), and exposure to tuberculosis treatment (AHR=2.93; 95% CI [1.39-6.17]) were found to be the three best dependent predictors for the development of OIs in this sample of the population. Authors conclude that ABC and AZT based ART regimens seem to have comparable survival benefit among HIV-infected children in Ethiopia. Therefore, both regimens might be used as an alternative in resource limited settings.

Overall comments:

Well written manuscript. One of the common errors in reporting and interpreting medical research is the failure to distinguish between clinical and statistical significance. The authors have done a very solid job of reporting their data in terms of both statistical significance from well conducted/appropriate procedures but interpreting them clinically. Statistical conclusions require adequate amounts of data (sample size and power limitations were noted by the authors) to be valid whereby medical decisions must often be made with insufficient data. Statistical answers are probabilistic (p-values) and medical treatment requires committed decisions. The authors should be commended for reporting the confidence intervals of important predictor variables in their model. Reporting of confidence intervals keep the focus on medicine and not strictly on chance. In short, the authors have provided an original contribution to the field.
Specific comments:

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?

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.

3) Page 9. Excellent Flow Chart. Should always be included in a manuscript.

4) 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.

5) 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.

6) 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.

7) 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.

8) Excellent discussion and conclusion sections.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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