Author's response to reviews

Title: Predictors of Treatment Failure and Time to Detection and Switching in HIV-infected Ethiopian Children Receiving First Line Antiretroviral Therapy

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Author's response to reviews: see over
Point-by-Point Response:

Thank you for your essential comments. They are addressed as follows (comments of both reviewers). The comments are first put in italics and then the responses follow;

1. *The word “delay” could discourage readers from further reading. Rewritten would make it more understandable and interesting i.e. “Predictors of Treatment Failure and Time to Detection and Switching in HIV-infected Ethiopian Children Receiving First Line Antiretroviral Therapy”*

   Done! (Title page)

2. *There were 167 cases with treatment failure (80 clinical and 87 immunologic failure), while there were 18 with both types of failure, were they included in 167? Should it be easier to understand saying how many had only clinical, how many had only immunologic, and how many had both of them?*

   Done! (Page 1, Abstract, Results subtopic). Yes, they were included in the 167; in the current version of the MS they are presented separately.

3. *In the results part, the authors claimed that there were 167 cases with treatment failure which meant they were readily been diagnosed as having treatment failure. Why they said that 143 cases were not detected? Actually there were 24 children who have been switched to second line ART, while other 124 have already been detected as having treatment failure but not yet switched to the second line regimen. The authors should make it clearer.*

   Done! (Page 1, Abstract, Results subtopic; and page 7, results part, last paragraph). The 143 cases of ART failure were diagnosed by the authors based on the medical records (using clinical and laboratory data). Only the 24 cases of ART failure were detected by the ART team at the respective centers.

4. *References for z-score calculation should be provided.*

   Done! (Page 5, Statistical Analysis, First Paragraph, Line 1-2)

5. *Why the authors use cut-off at -3SD? (While -2SD is approximately 3rd percentile which is commonly used as a cut-off for delayed physical growth)?*

   Done! Basically, the 3rd percentile was used for all the anthropometric variables; the -3SD was meant to represent the 3rd centile. In the current version, all –3SDs read as 3rd centile. It was more like a typographical mistake!

6. *What is the mean time of detection of treatment failure? Was it extracted from medical record? Whether it was from the date of ART initiation to the date when VL > 100, or having clinical sign/symptoms, or date when the word “failure” was noted should be clarified (and also the mean time to switch regimen is needed to be clarified)?*
Done! (Page 5, Under Data/Measures, 3rd paragraph, Line 1-4) . Yes, it was extracted from medical records!

7. **Chronic diarrhea which was found to be a strong predictor for treatment failure did not include in the Table 3.**

Done! (Page 16, Table 3, last raw)

8. The authors should provide some explanation for why the five predictors led to treatment failure in Ethiopian context i.e. associated with inevitable suboptimal adherence, poor family environment, or concomitant illnesses/medication used etc.

Done! (Page 8, Under Discussion part, paragraph 3)

9. All 4 figures added no additional information to what we have learned from Table 3. They can be removed without effect on the completeness of results.

Done!

10. Reading only abstract, the number of hospitals included was questionable. It should be stated as “at four major hospitals”

Done! (Page 2, Under Abstract Part, Methods sub topic, line 2)

11. What is AHR stand for? Abbreviations are needed to be defined at the first use.

Done! (Page 2, Abstract, Results, Line 6)

12. Did 95CI mean 95% confidence interval?

Done! (Page 2, Abstract, Results, Line 6)

13. Descriptive statistic should be presented in number (percentage), median (range or interquartile range), or mean (standard deviation).

Done! (Page 5, Under Statistical Analysis, Line 2-3)

14. Why did the analysis not start with univariate and follow by multivariate analysis, what is the bi-variate?

We actually started the analysis with a univariate analysis (descriptive statistics), and did the association between each variable and the outcome (ART failure) one at a time (Bivariate analysis). Then, variables with P-values <0.2 were entered in a multivariable Cox regression model. So, the word “bivariate” in this cohort is to indicate the testing of association between one variable at a time and the outcome (ART failure)! The word “univariate” was left for the descriptive presentation of a single variable!

15. As more than half of children were > 5 years of age, the mean age should be better reported in years than months.

Done! (Page 6, under Results part, Paragraph 1, Line 3-4)
16. CD4 count should have unit (cells/mm3).

Done!

17. Only horizontal lines are needed for tables!

Done! (All Tables)

18. There should be no abbreviation in table’s legends; all abbreviations used should be defined in footnote.

Done! (All Tables)

19. Number of decimal should be consistent everywhere in the table (either 1 or 2 decimals).

Done!

20. Number of cases in each hospital could be described in text if there was no difference in outcome or baseline demographic information between hospitals.

Done! (Page 6, Results part, First paragraph)

21. The number “n=1186 was not needed to be presented for every character, as there was only parental status which the number was 1155, they might better add the number of “unknown” instead.

Done! (Table 1)

22. The fact that only 36 cases received TB treatment could better be described in text than presented in the table.

Done! (Page 7, under Results part, Paragraph 4, line 4)

23. WHO clinical staging should be “stage 1 or 2” and “stage 3 or 4” (not “and”)

Done! (Table 3)

24. Level of adherence (good, fair, poor) should be defined.

Done! (Page 5, Under Data/Measures, Paragraph 3, Line 3-4) . Because the number of children with a reported adherence of poor is few, we combined fair and poor adherence reports and used the definition by national guideline as: optimal and sub-optimal. It didn’t affect the results because the number of cases for poor adherence was small.

25. English language editing (grammar and spelling) is needed, and many typo errors are presented.

Corrected!

26. IRIS is mentioned in the manuscript but not clearly defined. Give a clear definition of what constituted IRIS in this cohort.
27. Table 1 should include the following key parameters: anthropometric data (categories of weight-for-age, weight-for-height and height-for-age z scores) and CD4 count/percentage including the proportion with severe immune deficiency categories.

Done! (Page 12-13, Table 1)

28. Regimen change due to toxicity: Provide details on which drugs contributed to the most toxicity and the types of toxicities experienced.

Done! (Page 7, Under Results part, Paragraph 5, Line 3-8)

29. In the discussion factor in the known limitations of self-reported adherence which tends to overestimate actual adherence as a possible explanation why adherence is found not to predict failure.

Done! (Page 9, Under Discussion part, Paragraph 6, Line 2-3)

30. Include the lack of viral load data as a limitation into the discussion section.

Done! (Page 9, Under Discussion part, Paragraph 7, Last line)

31. In the background section specify whether the Ethiopian study that found clinical failure of 6.2% was an adult or pediatric study.

Done! (Page 4, Under Introduction part, Paragraph 6, Line 2)

32. In the Methods Section: References should be inserted at the end of sentences and not in mid-sentence as is done in this section.

Done! (Page 4, Under Methodology, Settings subtopic, paragraph 1, Last line)

33. Rather than stating that children are followed at regularly-defined intervals provide the actual schedule e.g. monthly for one year then 3-monthly thereafter.

Done! (Page 4, Under Methodology part, Sample subtopic, Line 3-4)

34. Data Measures: (Under Growth failure): clarify whether this refers to weight for age below the 3rd percentile (important because other measures exists including weight for height and height for age).

Done! (Page 5, Under Data/Measures, Paragraph 2, Line 4-5)

35. Provide the median (or mean) CD4 count and percentage for the entire cohort. These are important measures that make it possible to describe the increase in CD4% over time.

Done! (Page 6, Under Results Part, Paragraph 3, Line 5-6 and 10-13)
36. Use of the term Incidence: Incidence of opportunistic infections: If the term incidence is used it should describe events per person time e.g. 41 episodes per 100 person years etc. Otherwise leave out the word incidence and use simple proportions.

Done! (Page 7, Under Results Part, Paragraph 4, Line 1-2)

37. Clinical failure not clinical failures; Evidence not evidences.: Change Isoniazide to isoniazid.

Corrected!

Thank You,

Authors,