Author's response to reviews

Title: Predictors of Mortality Among HIV Infected Children on Anti-Retroviral Therapy in Mekelle Hospital, Northern Ethiopia, A retrospective Cohort Study

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Author's response to reviews: see over
Complying to reviewers’ annotations

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<th>Reviewer 1: Tesma Fasil</th>
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<td>♦ Due to the small number of deaths observed in this sample, as reflected from the estimated confidence intervals and pointed out by the authors, the estimates from this sample data might not be reliable and making some strong conclusions and recommendations is not valid.</td>
<td><em>It has been addressed as a weakness of the study.</em></td>
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| • quality of HIV-infected patients in the industrialized world – Not clear what quality means. | ♦ So, this study aims to investigate the predictors of mortality of children on ART therefore, the objective of this study was to identify predictors of mortality among children on HAART. | **Rephrased as**
| ♦ So, this study aims to investigate the predictors of mortality of children on ART therefore, the objective of this study was to identify predictors of mortality among children on HAART. | **Rephrased as**
| ♦ Addressed as recommended. | **Rephrased as follow**
| The mortality of this cohort was 4.8% deaths | The mortality of this cohort was 4.8% deaths |
| ♦ In the final Cox proportional hazard model fitted, age less than 18 months, CD4 percentage <10, - age less than 18 months; whose age at what time – at baseline or at death or what? ...were found to be independently predictors of mortality for children on ART – better to rephrase it as significantly and independently associated with survival of children | ♦ In the final Cox proportional hazard model fitted, age less than 18 months, CD4 percentage <10 at baseline, WHO clinical stage (III&IV), chronic diarrhea and hemoglobin < 8 g/dl all at baseline were significantly and independently associated with survival of children on ART |
| ♦ The high early mortality in the present study would support the value of an earlier treatment start before development of signs of immunodeficiency syndrome despite the method of HIV diagnosis | ♦ The high early mortality in the present study would support the value of an earlier treatment start before development of signs of immunodeficiency syndrome despite the method of HIV diagnosis |

| **Key words** | 
| Children and HIV, Children and ART, ART and HIV better to make it children, HIV, HAART, Survival, Ethiopia |

1
3rd paragraph line: Sub Saharan Africa, Ethiopia – change it as Sub Saharan Africa including Ethiopia and the last sentence should be connected with the previous

Therefore, the available evidence in the country regarding the determinants of survival among children less than 15 years old based on the baseline characteristics is very limited

Rephrased as suggested

The authors are very confident about the reliability of information but modified as follow:

Therefore, the available evidence in the country regarding the determinants of survival among children less than 15 years old is very limited.

### Methods

- Data was collected from Dec 2011 to Feb 2012 – What does this period means is this the amount of time required for investigators to transfer the data from records to the forms used or what?

  Random sample of 432 patients records who started treatment between June 1, 2006 and May 31, 2011 were accessed in this study. – What is the justification for selecting a random sample from this small population (510 started ART)?

- Four experienced ART nurses who were trained on comprehensive HIV care and involved in patient follow ups collected the data and data collection was supervised by trained supervisors – What was the relevance of employing nurse to transferring data from records to forms as this may not increase data quality rather will introduce professional bias as these individuals are part of the ART care and support system in the hospital.

  The data were entered and cleaned by trained data clerks and the investigators before analysis – what methods of data cleaning procedure were used?

- Variables with $p \leq 0.05$ in bivariate analysis and clinically important variables were taken to multivariate analysis – why a $p \leq 0.05$ was used

This is the amount of time required for the investigators to transfer the data from records to the forms used.

78 out of the 510 records of children on ART was transferred in with no baseline information. It is rephrased as follow

- A total of 432 records of children on ART that started treatment between June 1, 2006 and May 31, 2011 were retrieved

Source of information about baseline characteristics of children on ART is not a single form and easy for unfamiliar individuals. Because there are four or more separate forms filled by different peoples. For this reason, use of trained or individuals who are familiar with the forms could increase the data quality, reliability and they are not from the same institution where the study takes place. So, it is with justification that we prefer to use these individuals as data collectors.

We didn’t have any specific name for the technique of data cleaning done by data clerk and ourselves but we try to clean for inconsistencies in the data.

Sorry, $P \leq 0.05$ was misspelt to refer to $P < 0.05$.

Rephrased as follow

Variables that are considered to be important
rather than \( p < 0.05 \)?

§ What does clinical important variables mean and how were these variables selected?

○ If there is no pre-treatment laboratory test, however, results obtained within one month of ART initiation were considered as baseline values – What is the justification for considering within one month after ART as a proxy for pre-treatment CD4 count? What did you do if no pre-treatment or within one month measurement for CD4 values obtained?

✈ What measures did you take in cases where data were incomplete, inconsistent and inaccurate?

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### Results

The ages of the cohort at ART initiation were relatively late with median age of 53 months with IQR (24-96) months – why is 53 months said to be late? What is the country’s policy to start treatment?

✈ Better to use consistent denominator across the rates – either person-months or person-years. Some of the factors in the bivariate model like presence of diarrhoea at baseline has no clear meaning when we look at a median follow-up time of 36 months

§ What is age less 18 years – what was the starting and end date for calculating this value?

- In figure 1, what does analysis time means? and Inconsistent use of decimal digits

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### Discussion

♦ In general there is observed some re-catching of detail results here which is not appropriate. What was the formula to calculate incidence density is that not Number of new cases during a given period over Total person-time of observation? Otherwise you need to give us the formula for the calculated 0.93 per 1000 person-year value.

♦ Which data justifies the following “Mortality was higher in the first 12 months after ART initiation and this was associated with the advanced clinical stage III & IV, hemoglobin level of <8g/dl and age <=18 months”. No data is shown, the information in table 2 is independent effects

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### Modified as follow

♦ The findings of this study indicate that from the registered cohort, there were 20 deaths in 1186.25 person-years of retrospective follow up, providing an incidence density 16.86 deaths per person-years. About 23(5.53%) patients were lost to follow up.

♦ This show results of the multivariate analysis. Because the style we used to organize the discussion was:

Introducing our readers about what to tell, interpreting the results by comparing with other studies, admitting our weakness and finally conclude.

It is to mean compared and it is rephrased as
Page 6, last paragraph – the statement “when results of this study was weighted against a 4 years clinical cohort study in South Africa” is not clear, what does weighed against mean?

“compared”

References


Page 7: Statement related to reference 25 and 26 better stated as studies conducted in Addis Ababa, Ethiopia rather than two studies conducted in Addis Ababa, Ethiopia one at Zewditu memorial hospital, and another study at All African Leprosy and Rehabilitation Centre (ALERT hospital)

The sensitivity analysis was performed including the composite endpoint of lost to follow-up and death. What is this sensitivity analysis? No result for the analysis is indicated.

This study has limitations from in adequate sample size …”. Knowing this limitation why did you continue the study?

Occurrence of 20 deaths is not a conclusion and check the value of the incidence density again.

Results of the sensitivity analysis
The proportion of the lost to follow-up included as being dead were 10.34% (3.02 per 1000 child-months) almost doubled the mortality rate. Age less than 18 months, hemoglobin level, CD4 < 10%, were significantly associated with the event.

This limitation was learnt after data collection and analysis.

References
Check the references example 2, 4, 16, 22, Corrected

Discretionary revisions
Editorial revisions are required throughout the document

Reviewer 2: Johan Nikolai N Bruun

Reviewer’s concerns Answers/modification/rephrases

Major Compulsory Revisions

1. Methods
The descriptions of the methods used are incomplete. 432 records were reviewed and data from 416 was in complete. 432 records were reviewed and data from 416 was complete. The

78 out of 519 children were transferred in. For this reason, they were excluded from the study because it is impossible to get the baseline data.
authors state that the study participants were a random sample from 519 children starting on ART. Why were the last 78 not included in the review? It is not stated whether some children were excluded from the program.

- As the study site was a referral hospital there may be a selection bias due to criteria for referral. The diagnostic criteria for HIV-infection are not given.

Was the diagnosis based on antibody test and if so after how long time? Was PCR used for early diagnosis of HIV infection?

2. Results

- Hemoglobin values are missing among the baseline characteristics given in table 1

  - The bivariate analysis of contributing factors associated with mortality is only shown for factors shown to be significant. Were other factors included in preliminary analysis? The results of such analyses should be given or added to table 2, and the p-values of the statistical comparisons may also be added to the table.

  - Other studies have found weight for age, female gender and prophylaxis with cotrimoxazole to be significant. These factors should be included and analyzed if available.

  - WHO has for at least most of the study period recommended routine cotrimoxazole prophylaxis for children borne to HIV infected mothers. Was this done?

- Hemoglobin included in table 1

  - Yes, there were other factors in the multivariate analysis and they are included in to table 2 with their respective HR and P-value

  - Gender is included but data on cotrimoxazole prophylaxis was not collected

  - Yes , cotrimoxazole is given six weeks after birth routinely

3. Discussion

The main weakness of the study is the composition of the material with almost half of the children being 5 years or more at inclusion. As the mortality of HIV infected children is higher in lower age groups this creates a selection bias and many younger patients with poor prognosis were probably not included as they died early or were not referred to the program

Comments incorporated
### Minor revisions

5. Most of the results given in table 2 are repeated in the text. It is probably better only to outline the main results in the text and refer to the table for details

- Repetition avoided by highlighting the most important things by text referring the rest to the table

### Discretionary revisions

7. A reasonable conclusion I think would be recommendation of a close follow up of all children of HIV positive mothers in order to make the diagnosis and start treatment at an earlier time and to secure implementation of cotrimoxazole prophylaxis to all HIV positives and possibly also to children who’s HIV status has not been clarified. Level of interest: An article whose findings are important to those with closely related research interests

- We didn’t collect information on cotrimoxazole prophylaxis because we think that whether they receive the prophylaxis or not they already have the infection and they are receiving treatment but We didn’t mean that it doesn’t have any impact on survival of children on ART. So, it would be inapplicable and not based on our results to recommend about Contrimoxazole prophylaxis. More over, we didn’t have data showing close follow up of mothers children on ART but we made a strong recommendation to start ART as early as possible to improve survival of children as witnessed in our result.