Author’s response to reviews

Title: Secular trends in pediatric antiretroviral treatment programs in rural and urban Zambia: a retrospective cohort study

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The Editor

*BMC Pediatrics*

Dear Editor,

We are pleased to submit a revised manuscript titled “Secular trends in pediatric antiretroviral treatment programs in rural and urban Zambia: a retrospective cohort study” for publication in *BMC Pediatrics*. Our responses to the comments and suggestions of the reviewers follow:

**Reviewer #1:**

**General:**

This is an important reflection on the programmatic aspects of pediatric ART in Africa. It also adds to evidence that outcome in rural clinics with access to ART may be as good as urban clinics particularly where enrollment depends on health systems. The authors highlight some interesting points and unexpected findings with regards enrolment and outcomes in different settings.

**Major Compulsory Revisions**

1) Statistical Methods

   a. Re WAZ scores. Children up to 15 where enrolled, however WHO only provides Z-scores till age of 10 and recommends BMI after 10. How did the authors address this? Other than excluding them from analysis for WAZ. These children are a significant number of the total especially in the urban clinic.

   We acknowledge that this is a limitation and an issue that we struggled with. There were several issues that lead us to use WAZ scores and exclude children > 10 years. First, height was only consistently measured in the clinics at the initial evaluation visit; therefore we could not use BMI or any other anthropometric measure relying on height in the assessment of treatment outcomes. Second, even at the initial evaluation visit, height was very poorly measured and we were not sufficiently confident in the data to report BMI. For consistency and comparison with other studies, we reported only WAZ scores.
b. Re CD4 response: Using the CD4 percent in children > 5 is not appropriate in addition achieving this level of improvement at 6 months given the severity of disease and the age of the children may not be the best measure. It may be more useful to reflect improvement as a % change in CD4 in children < 5 and change in absolute count in those older than 5. Using CD4 Z scores may also be an alternative way to address this.

We thank the reviewer for her comment and have carefully considered the best measure to present. We decided to continue to use CD4% for all age groups for the following reasons:

1. While CD4 counts are used for children > 5 years of age, the WHO recommendations also report a threshold CD4% for this group.
2. Much of the literature reports results with CD4% aggregated over all age groups, and we would like to report results that enable comparison with other study populations.
3. Sample sizes were small for the immunologic parameters in the rural sites, and were even smaller when stratified by age (some cells had no children).
4. CD4% is the value that is actually measured in the laboratory tests, while CD4 count is calculated based on TLC and CD4%. We felt much more confident in the accuracy of the CD4% data.

We agree that presenting the proportion of children achieving a CD4%>25% may not be the most appropriate and depends on the baseline levels, although this level can be viewed as the lower end of the normal range of CD4%. We changed the immunologic outcome to the median CD4% and the median change in CD4% from ART initiation at 6 months, which are measures that are consistently reported in the literature and are more readily interpretable than a percent change or a CD4 z-score.

2) State the when PCR access for infants where established for the sites.

DNA-based diagnostic testing methods were available in Lusaka in 2007, however they were not widely used by public-sector health centers until 2008. These testing methods only became available in Macha and Mukinge in February 2008. This is stated in the Methods section under ‘Clinic Procedures’ (2nd paragraph).

3) Please indicate number of infants initiated on ART that was stopped at 18 months if the data is available.

These data are not available in the electronic medical records database.

4) Indicate if possible if deaths occurred between enrolment and initiation of therapy for eligible and ineligible children if the data is available.

We added a section on outcomes for eligible and ineligible children (see Table 3).

Minor Essential Revisions
1) Indicate if possible if deaths occurred between enrolment and initiation of therapy for eligible and ineligible children.

See #4 above.

2) Can the authors provide further possible explanations for the low enrolment of infants into urban clinics? Given rapid progression with early clinical disease the “lack” of infants in the program is both interesting and worrying.

We agree that the low enrollment of infants in the urban clinic is worrying and unexpected, and was one of the main conclusions from this study. We had many discussions with our co-authors to determine why enrollment was so low in the urban clinics. We concluded that this difference was likely due to the passive system of referrals and the high attrition from programs in the urban clinics. Linkage between programs was much stronger in the rural areas and follow-up of infants was more aggressively performed. We have elaborated on this explanation in the discussion section. Without more data from the clinics, we do not wish to further speculate on reasons for the low enrollment of infants.

3) The reduction in TB self report in urban children is also interesting given that there was not a significant reduction is age (as in rural clinic). I think explaining this for rural clinics may be easier as age of infected children lowered and children may have been uninfected.

We agree that the decreasing trend for TB is expected in the rural areas given the decreasing age of the children and is not as easily interpreted in the urban area. As these data are self-reported and the reliability is uncertain given that the data are provided by caregivers who may not be the child’s primary caregiver or parents, we have chosen not focus on this particular indicator.

4) Can clinical improvement be reflected change in WAZ?

We used nutritional status (WAZ scores) as a measure of clinical status as it was measured consistently over time in all of the clinics. Staging of disease according to WHO guidelines was only reliably done at the initial evaluation visit and therefore could not be used to assess disease status during follow-up. WAZ scores have been found to be predictive of progression and mortality among HIV-infected children (Obimbo EM PIDJ 2004; Walker AS JAIDS 2006), and improvements in WAZ scores are expected after HAART initiation (Sutcliffe CG Lancet ID 2008; Davies M-A African J AIDS Research 2009). WAZ scores are also consistently used throughout the literature as a measure of clinical status, and we were therefore able to make comparisons across studies and populations.

5) In the introduction reference 9 may be used inappropriate
We removed reference 9 from the introduction.

Discretionary Revisions

1) The challenges to rural clinics are similar to those in urban settings. If space allows it may be valuable to unpack the issues little better when describing the setting ie reflect staff patient ratios, income, community stability and numbers in parental care.

   We added a sentence on staffing, which was similar in the three clinics, to the ‘Clinic Procedures’. Information on income and numbers in parental care were not available in the database, as this information was not collected and entered consistently for children.

2) Also some information on seroprevalence rates at antenatal clinic and numbers of exposed infants per year at each site will be interesting as this will reflect the success in linkages as well.

   While this information would be very useful and relevant, it was not available from the HIV clinic databases. The different wards within the hospitals have separate filing and reporting systems.

3) Can the distance from the clinic for urban children be assessed? Some urban children also need to travel significant distances to clinics.

   Distance was not captured on the forms used in the urban clinic as it was in the rural clinics, but participants did provide township of residence. We added the proportion residing within Matero township during each year of program implementation in Table 1.

4) Please state if there are differences between the Zambian or WHO guidelines since most readers will not know the Zambian guidelines. Alternatively state the treatment criteria for infected children.

   As the Zambian national treatment guidelines are based on the WHO treatment guidelines, we deleted ‘Zambian national guidelines’ from the text to avoid confusion. We elected not to state the treatment criteria due to space limitations, as the study period covers both the 2003 and 2006 guidelines.

5) Figure 1 - Add into the legend if cumulative / number at the bars/lines, this will make it easier for the reader.

   We added to the legend to clarify which bars/lines indicate monthly and cumulative enrollment.

6) Though virological outcomes for African children are similar to high income countries I think the authors should include a comment about the lack of outcomes available for infants. The current published literature mostly has data for older children. Also there is little information on
children that initiated on ART on a presumptive diagnosis of HIV. There may also be some differences in some clinical outcomes for all children ie growth.

*We added this comment to the discussion section.*

**Reviewer #2:**

**General**

This is an interesting and well written paper on an important topic. Analysis of secular trends in paediatric HIV service and ART scale up are critical to monitor and understand how to improve service delivery.

**Major Compulsory Revisions**

1. In the last sentence of the first paragraph under the heading “Statistical Methods”: a 90 day window used to consider measurements as being at ART initiation may be too long. For CD4% and CD4 count, it would be better to use a relatively short window after ART initiation as CD4 levels can increase rapidly after ART start. Measurements beyond 2 weeks to 1 month after ART start probably do not reflect measurements at ART initiation.

   *The 90 day window in this paragraph refers to the initial evaluation visit rather than ART initiation. As children who transferred into the clinic on ART were excluded, the measurements at the initial evaluation visit were prior to ART initiation. The vast majority of children had measures at initial evaluation or within one month, which would also be prior to ART initiation given the 1-2 month delay between eligibility and initiation of treatment.*

   *For characteristics at ART initiation in Table 3, a 90 day window prior to ART initiation was used for CD4%. This was clarified in the second paragraph under ‘Statistics Methods’.*

2. It would be nice to also see a figure of the number of children initiated on ART over time and the proportion of eligible children that were actually initiated. In this respect, were all eligible children initiated, and if not, what were the reasons for this? It seemed that in the urban clinics in year 4 and year 2, more children were initiated than were eligible, while in the rural clinics this was the case in year 4. Perhaps the additional children were identified as eligible in the previous year but initiated the following year?

   *We added a figure of the number of children initiated on ART over time (Figure 2).*

   *There are two reasons for the discrepancy between the number eligible and the number initiated on ART in a given year. First, eligibility was only defined at the initial evaluation visit; therefore children could have become eligible later in the year (of
program implementation) and started ART. Second, there is a lag of ~1-2 months between eligibility and initiation, therefore, as the reviewer suggested, some children may have become eligible in one year and started ART in the next.

We added a section on outcomes for eligible and ineligible children (see Table 3). Reasons for not initiating ART were not available as ‘eligibility’ was defined by the authors retrospectively.

3. The authors comment that there is a decrease in the proportion of deaths over time in the urban areas. While a detailed analysis of mortality risk factors is clearly not the focus of this analysis, the authors should mention as a limitation that they have not examined predictors of mortality so cannot comment on whether the change in mortality is programme-related or related to differences in the profile of children initiating treatment. For example, the authors state in the discussion that “it is unknown whether the observed decrease in the urban clinic was due to better survival or differential ascertainment of deaths in the clinics.” The authors could expand on this to talk about not having looked at whether the change in survival (if this is real) is explained by differences in baseline characteristics alone, or whether there is an independent secular trend.

We expanded this section of the discussion.

4. The number of children in whom CD4 and WAZ measurements are available at 6 months is very small and not consistently the same proportion of those initiating ART across the different years. It would be helpful to know the percentage completeness for each measure (i.e. proportion of those in care at 6 months in whom a measure is available) and also for the authors to comment in the discussion on the possible factors that may determine which children have measurements available and which do not – e.g. are younger or sicker children more likely to have their CD4 and weight measured at the 6 month visit?

We added a measure of completeness to Table 3 for both CD4 and WAZ in the rural and urban population. We added a comment to the discussion regarding this limitation of the data, as well as a discussion of the factors associated with completeness of data.

5. Can the authors comment on follow-up of children not eligible for ART? In the Methods section, it states that children not on ART return for clinical and laboratory evaluation every 3 months. A key issue in many programmes is loss to follow-up of children not yet eligible for and initiated on treatment and the ability to keep these children in care so that treatment is initiated in a timely way when needed. Outcomes of these children would therefore be a useful indicator of programme performance, if the data is available.

We agree that this is an important issue. We added a section on outcomes for eligible and ineligible children (see Table 3).

6. In the Discussion, comparisons are made between the urban and rural programmes. For example: “Mortality was consistently higher in the rural clinics…” The Results section does not
include a formal statistical comparison of the urban and rural programmes, but rather looks at secular trends within the urban and rural programmes separately. The authors should therefore be more guarded in the discussion about comparisons between the urban and rural programme. For example: “Mortality appeared to be higher at rural clinics…”

We tempered our language in the discussion when comparing the urban and rural clinics.

**Minor Essential Revisions**

Nil

**Discretionary Revisions**

1. In paragraph 1 under results, the authors should state in the text that the decrease in age at urban clinics over time is a trend, as the table shows this not to be significant.

   We changed the first sentence to indicate that this trend was non-significant.

2. Figure 1 could be simplified by rather showing the number enrolled per quarter or half-year, than the number per month, unless there is a particular seasonal variation that the authors wish to comment on.

   We agree that reporting numbers quarterly or biannually would simplify the graph and acknowledge that there is no seasonal variation illustrated in the figure. However, if we were to simplify the graph, we would not be able include calendar time. We believe that calendar time is an important element to the study and have decided to keep the original format of the graph.

**Editorial requests:**

1. Include a section on competing interests.

   We included a section on ‘Competing Interests’.

2. Include a section on the authors’ contributions.

   We included a section on ‘Authors’ contributions’.

3. Clarify the status of the related paper.

   The related manuscript was accepted for publication in PIDJ and will be published this fall (it is currently on PubMed). We updated the references accordingly (ref # 24).

Thank you for your consideration of our revised manuscript.
Sincerely,

Catherine Sutcliffe, PhD, ScM