Author's response to reviews

Title: Weight and height Z-scores improve after initiating ART among HIV-infected children in rural Zambia: a cohort study

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Author's response to reviews: see over
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The Editor

BMC Infectious Diseases

Dear Editor,

We are pleased to submit a revised manuscript titled “Weight and height Z-scores improve after initiating ART among HIV-infected children in rural Zambia: a cohort study” for publication in BMC Infectious Diseases. Our responses to the reviewer’s comments follow:

Reviewer: Luisa Galli

Reviewer's report:

1. Major compulsory revisions

Methods: The authors stated that children were evaluated every 3 months and blood specimens were obtained, but they not specify which type of blood evaluation was performed. Were CD4+ T-cell% evaluated at 3 months check? If yes, why changes in WAZ and HAZ were not compared with changes in CD4+ %, as a marker of ART success?
This is a very important issue: if children have not a strong and durable immunereconstitution (due to lack of compliance or ART resistance mutations, which cannot be monitored in resource-poor settings) they will not have a full recovery of growth. If CD4+ %/counts are not available after ART initiation, the authors have to report this lacking and they could discuss this limit in the discussion.

CD4 T-cell counts and % were measured as part of the study at each visit (every 3 months). This information has been added to the methods section (pg. 7).

The children in the study had a good immunologic response to ART and we now report the median CD4 T-cell percentage at 6, 12 and 24 months after ART initiation in the first section of the Results (pg. 8). This outcome is reported in more detail in a separate paper that is under review. The purpose of this analysis was to describe growth trajectories after ART initiation and identify factors at ART initiation that may impact those trajectories, and help to explain inconsistencies in the literature. We have clarified this objective in the Introduction section. We feel that exploring the relationship between different treatment outcomes, while interesting and important, is beyond the scope of this analysis.
Moreover, ART regimens available in 2007-09 and described in the methods were probably suboptimal. As a matter of fact, WHO 2010 guidelines (which were cited as ref 5, but were not clearly followed during this study) suggest ART including protease inhibitors in selected conditions. Therefore, in the study population, HIV infection might have been poorly controlled and authors cannot exclude that lack of sustained improvement in growth may be due to suboptimal ART.

This study was conducted from 2007-2009. During this time the 2006 and 2008 WHO treatment guidelines were in effect and were being followed in the clinic. The regimens used in this study are the same as those recommended by WHO. In 2010, WHO did revise their guidelines to recommend the use of protease inhibitors in the event of prior exposure to nevirapine for prevention of mother-to-child transmission (PMTCT). While these guidelines were not in effect at the time of this study, very few children had prior exposure to nevirapine, and so received the appropriate regimen. Information regarding PMTCT has been added to Table 1 and the Results section (pg. 7).

2. Minor essential revisions: change ref 5 to WHO guidelines followed during the study period. Ref 8 lack year of publication.

In the methods section we have changed the reference to refer now to the 2006 and 2008 WHO guidelines that were in effect during this study. Ref 8 has been revised.

Reviewer: Raffaele Badolato

Reviewer's report:
Sutcliff et al. describe the effect of antiretroviral therapy on growth of HIV-infected with severe malnutrition. The study demonstrates a significant effect of the therapy on both height and weight which is more evident in younger children and in females. However, the study fails to address the contribution of diet and the role of immunodeficiency in the growth after starting ART. These points should be at least discussed in more detail.

We explored the role of immunodeficiency at ART initiation in growth after starting ART. As shown in Table 2 and described in the Results section for HAZ (pg. 8), and now for WAZ, severe immunodeficiency was marginally associated with lower WAZ/HAZ throughout treatment. Interactions between severe immunodeficiency and growth trajectories were also explored, as stated in the Methods section (pg. 7), although none were found.

We did not collect any information on diet in this study. This limitation has been acknowledged at the end of the Discussion section (pg. 11).

Reviewer: vania giacomet

Reviewer's report:
Minor essential revisions: authors should better define whether nutritional assessments were performed and the antiretroviral drugs used.

_The nutritional assessments that were performed included measurement of weight and height to determine weight-for-age and height-for-age z-scores every 3 months. This information is provided in the Methods section, under Study Procedures (pg. 6). Other nutritional assessments, such as arm or head circumference, were not performed in this study._

_The antiretroviral drugs available are described in the Methods section (pg. 5). The distribution of initial drug regimens for this study population has been added to the Results section (pg. 8)._  

**Reviewer:** Elena Chiappini

**Reviewer's report:**

Minor discretionary revisions

I would suggest, if it is possible, to describe other possible factors that may at least partly influenced the study results, including comorbidities (i.e. tuberculosis,…).

_Unfortunately, reliable data on specific comorbidities were not available in this study and so could not be included in this study. This has been added to the limitations in the Discussion section._