Author’s response to reviews

Title: Improved antiretroviral treatment outcome in a rural African setting is associated with cART initiation at higher CD4 cell counts and better general health condition

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Author's response to reviews: see over
Dear Editor, dear Reviewers

Thank you very much for your very valuable review of our manuscript and for giving us the possibility to resubmit our manuscript. We have thoroughly revised the manuscript according your suggestions, included additional data and updated references. Please find our point-by-point reply below.

Yours sincerely
Prof. Dr. Manuel Battegay

Point-by-point response to MS 7027625444532504: Improved antiretroviral treatment outcome assisted by an adherence supporter in a rural African setting is associated with cART initiation at higher CD4 cell counts and better general health condition. Mossdorf E et al.

Reviewers' comments:

Reviewer 1: Dr. Nathan Ford

1. The data presented in the article (both background data on HIV/AIDS and outcome data from the programme) need to be more carefully framed within an updated review of the literature.

   We followed your advice and have adjusted our citation list with publications of more recent origin using the meSH terms „hiv-1 AND antiretroviral treatment AND outcome AND adult AND africa“.

2. ABSTRACT
   Background: Suggest rethinking the lead in: data on ART in SSA are not as scarce as they once were.

   Corrected according your suggestion.

3. BACKGROUND
   “as of December 2007, an estimated 3 million people were receiving cART,” This needs updating. Similarly, the proceeding para on HIV in Tanzania includes data only up to 2007 and this may need revising.

   As suggested, we modified the introduction on the basis of the UNAIDS Report on the Gobal AIDS Epidemic 2010.

4. METHODS
   “We also considered all patients lost to follow-up as failures, since in a recent survey 81% of patients lost to follow-up were found to have died [28].” It is reasonable to combine RIP and LTF to look at programme attrition, but not to simply assume such a high rate based on an unpublished study. Systematic review on the topic (see Brinkoff et al, Plos One) has found this figure varies considerably. Suggest nuancing how this is presented.

   We rephrased the section according your suggestion and included Brinkhof and al. in our literature list.
5. RESULTS
Response to cART: “The median CD4 cell count increase was 61 cells/µl (IQR 0-167)”
It doesn’t make sense to me that an IQR can start at 0

There was indeed a mistake. The corrected CD4 cell count increase at 6 months was 61 cells/µl (IQR 10-167).

6. “Risk factors of poor survival at 12 months after starting cART”
How were model predictors chosen? This needs to be explained for all the multivariate models.

We built the final multivariate models using a forward stepwise approach, adding each factor significant at the level of 0.1 and other factors defined in the literature as prognostic in the model one by one. We specified this approach in the statistics section.

7. “Treatment modification”
It is not quite right to say that 23.2% of patients switched due to drug-drug interactions; rather I would imagine that it is the potential concern for interaction with TB treatment that drove the switch.

We specified the reasons of changing antiretroviral therapy as follows: “… followed by the concern of potential drug-drug interactions related to antituberculous therapy (23%)…”

8. DISCUSSION
“Only a minority of individuals changed their cART”
I would suggest that the fact that 14.7% had changed regimens after a median of 133 days is quite substantial compared to other cohorts (eg Boulle et al, Antiv Therapy 2007).

As suggested, we corrected the term “minority” to “1 out of 7 patients” and added Boulle et al. to our citation list. Boulle et al. found a rate of treatment change of 39% (8% due to nevirapine, 2% due to efavirenz, 8% due to zidovudine and 21% due to stavudine) over a period of 3 years whereas changes for the first 3 substances took place early in the course of cART and for the latter substance due to cumulative toxicity later in the course of cART. Due to these facts and the different observation period we believe that comparison of the two studies will be prone to misinterpretation.

9. “Study population and treatment response”
Another similarity with other cohorts that is worth commenting on is the gender distribution.

We discussed age and sex distribution under the passage “Study population and treatment response” but added also new references.

Treatment change and toxicity”
Again, these rates are high compared to rates published elsewhere, including the cited studies (refs 8, 14, 34, 40, and 43).

  Cotzee et al. mentioned in 15.1% (95% CI, 10.7-21.1%) of all patients a switch of regimen for any cause (toxicity, side effect, TB treatment pregnancy and treatment failure during a follow-up time of 24 months. As most changes took place soon after starting cART (median time to switch 42 days; IQR 28-56 days) and therefore well under the one year’s observation period of our study we assumed that our rate of 14.7% is to a certain range comparable.
  Switch in 9% of all individuals due to toxicity. There were no other reasons given and the time to switch is not known as well as median time of observation in the study.
  Changes to initial regimen in 21.9% over an observation period of 24 months.
  Switch rate of 6.9% for anemia, 1.3% for cutaneous hypersensitivity, 1.1% for hepatotoxicity and 2.1% for lipodystrophy (summing up to 11.4%). Other reasons such as TB treatment or switch due to cART failure were not mentioned.
  Switch rate of 8% in 12 months.

  Due to the different modelling and different observation periods comparison of the switch rates was impossible. We agree to indicate only the range of switch rates.

“...regimen containing efavirenz and zidovudine combined with lamivudine was associated with a 2-fold higher risk of treatment modification within the first year of cART”

Would the authors not consider pregnancy as a reason for switching away from EFV?

**Only one woman changed her initial antiretroviral regimen due to pregnancy. It is possible that information on pregnancy was not consistently collected during the study.**

10. “interestingly, active tuberculosis was not a risk factor for poor survival in our cohort”

   Could this also be a survival bias – i.e. TB accounting for a substantial proportion of the deaths?

   We agree that tuberculosis may have accounted for a substantial proportion of deaths, leading to a survival bias. We mentioned this problem in the limitations section.

   In our study, a considerable proportion of patients died or was lost to follow-up adding up to 21.7% during the first year of cART. This is similar to other studies [8, 14, 22, 33, 35, 38-39, 41, 46]. Only one cross-sectional survey from Mozambique, Malawi and Tanzania [47] showed a higher retention rate of 91.3%”

   This is not the case. According to the recent systematic review by Fox et al (TMIH 2010) median 1-year attrition across studies 22.6%, and ranged from 7%–45%; some programmes reported 3 year attrition as low as 13%.

   **We corrected the passage accordingly and added Fox et al. as reference.**

   “Finally, our cohort is one of the largest rural HIV-cohorts in sub-Saharan Africa [13, 22-26] showing a 1-year survival on cART similar to studies performed in urban settings”

   See above.

11. TABLES

   Table 1

   Why wasn’t marital status considered in further analyses?
As we only had data on marital status in 880 out of 1463 individuals enrolled we decided to resign from further analysis.

12. Table 2 (and Methods)
   How was proportionality assessed?

   We performed a cox regression to assess risk factors of poor survival and loss to follow up during the first year of antiretroviral treatment. We described in the statistics section how we built the multivariate model.

Reviewer 2: Dr. Harriet Mayanja

Reviewer’s report:

1. Is the question posed by the authors well defined?
   The authors aimed at assessing response to cART in a rural treatment center and risk factors for loss or death. This part was well addressed by the study. The authors also mentioned the assistance of an adherence supporter. However although this aspect seemed to be the most exciting part of the title, it is not the major feature of the study. In fact the study does not look at the impact of this adherence supporter on outcome as I initially expected from the title. It seems all patients had a supporter, so this is not a key factor to assess in the results or conclusion and so should not be included in the title.

   We changed the title according your comment to “Improved antiretroviral treatment outcome in a rural African setting is associated with cART initiation at higher CD4 cell counts and better general health condition”. The impact of the adherence supporters vs. none was not assessed as all individuals were assisted by one of them and data on adherence was inconsistently captured.

MAJOR

2. Are the methods appropriate and well described?
   The methods section is well described in detail and generally well written. The authors pointed out, that first line stavudine based regimen was stopped in December 2006. However overall they do not indicate how many patients were started on stavudine based regimen. Since this has now been revised, it makes the study of less relevance today.

   75% of all patients were started on nevirapine/lamivudine/stavudine, 8.1% on nevirapine/lamivudine/zidovudine, 13.3% on efavirenz/lamivudine/zidovudine, 1.8% on efavirenz/lamivudine/stavudine, and 1.8% on other drug combinations.

3. Also as neuropathy was one of the commonest side effects, it would have been useful knowing how this related to stavudine. The same is true of anemia. What drugs was it related to? Was it mainly AZT, a drug which was not part of the first line regimen, or other drug?

   Among patients with treatment change due to toxicity, the use of stavudine was clearly associated with an increased risk of polyneuropathy (OR 28.7, 95% CI 3.85-214.34, p=0.001), whereas all 26 patients who changed their treatment because of anemia had been initiated on a zidovudine-containing regimen. We added these informations to the results section.

4. Data on numbers on different 1st and 2nd line cART regimens could have been shown and related to adverse effects.

   We added information on first line regimens and their relation to specific side effects under the chapter “Results”: Unfortunately, we are not able to provide sufficient information concerning 2nd
line regimens, as among 215 patients who changed their first treatment only 5 patients changed to a second-line antiretroviral regimen.

MINOR
5. Are the data sound?

Data was collected prospectively using standardized record forms completed at each follow-up visit. The limitation of missing data for certain variables, not allowing to build a multivariate model with all investigated factors, was mentioned in the discussion under the limitations section.

On the other hand, our study reflects the public health setting approach of WHO’s initiative in a rural area of Sub-Saharan Africa. Cohort data from Africa are often derived from urban settings with less infrastructural and distance-related constraints in health care. Additionally, these settings and data sets are often embedded in academic centres and disproportionally supported by foreign funds not available to most of the health care facilities delivering care and treatment to the vast majority of the population. Sound data from rural cohorts helps to improve and support continuous reach- and roll-out of HIV care and treatment to rural areas where about 70% of all Africans live. Therefore, it is relevant for further roll-out to have data supporting the fact that remote rural settings can perform as well as urban settings. We may refer to the first paragraph of Dr. Andrew Kambugu’s review (3rd reviewer).

5. This is a descriptive study. Table 1 does not really show any new information. There is a lot of missing data in this table. Thus although the study has a big sample size, this is weakened by the large amount of missing data.

Please see paragraph above.

6. Also authors should indicate if this was baseline data, which I assume it is, classified by 12 month outcome.

We corrected the heading of Table 1 according your proposal.

MAJOR
7. Table 2 show poor outcome with low baseline CD4 and BMI.
This information has been shown in a number of studies before. Figure 1 information is already indicated in table 2, so it looks like repetition. This is a MINOR revision.

We added Figure 1 in order to clarify our evidence shown in Table 2. Additionally, Figure 1 shows that most deaths and cases of lost to follow-up occurred in the first 3 months after starting cART, which is not mentioned in Table 2.

8. Are limitations of the work clearly stated?
The authors note the limitations of missing data and large loss to follow-up. However most countries have moved away from stavudine based regimens, making the paper of less significance today.

We fully agree that nowadays tenofovir is promoted throughout Sub-Saharan Africa. Though in opposition to WHO’s new guidelines, stavudine will unfortunately remain due to its low costs and wide availability. We added your concern to the limitations section of our study.

9. Also most of the findings have already been reported in other papers, and the paper does not really add much new information to the subject of cART. Also adherence is unknown in this study despite the adherence supporter. This is mentioned in discussion under “Risk factors for poor survival. However it is a limitation of the study and should be pointed out.
We fully agree with your comment and mentioned the lack of adherence data in the limitations section.

10. Do the title and abstract accurately convey what has been found? 
No. the title makes a reader believe that impact of a treatment adherence supporter is the main focus of the paper.

We corrected the misleading title.

Reviewer 3: Dr. Andrew Kambugu

Reviewer’s report:

1. This study fills a critical data gap in the area of cART outcomes in rural settings within resource-limited settings. The initial roll-out as the authors pointed out was centered in urban settings, usually within academic centres.
The objectives of the present study were clearly stated in the background (to assess the clinical and immunological response to cART in a rural cART cohort as well as the risk factors of death or loss to follow-up in this population).
The authors though do not give a rationale for the emphasis on the immunological response in the study aims. Assessing the clinical response, with respect to the incidence of opportunistic infections in this population is also relevant especially since some rural settings may not have the capacity to do CD4 counts measurements. Yet capturing of clinical events may be possible in these settings.

Unfortunately, we did not collect detailed data on clinical events such as opportunistic infections or hospitalizations during the study, as this data is often prone to misclassification and information bias. However, we collected data on the daily activity of the patients (working, not working, or bedridden) as response to cART. This information has already been integrated in our first version in the results section. After review, we added the presumed cause of death in the results section.

2. The methods employed to meet the study aims are appropriate. The one limitation is that adherence data, which is a key determinant of outcomes of cART programmes, is lacking. However, the authors acknowledge this limitation.
Additionally, whereas the authors stated that patients had one-month or 3-month refill visits depending on the CD4 counts, the details of this are important to include in the methods sections for purposes of comparing this study to other studies.

As suggested, we added information on decision for monthly, respectively three-monthly, follow-up under the methods section.
For better understanding, we added definitions of loss to follow-up under the last paragraph of the subchapter “Data collection and definitions”.

3. Moreover for completeness, the authors should mention the level of compliance to the recommended scheduling by CD4 category to assist the reviewer in assessing the manuscript.

The CD4 scheduling was followed by all our clinicians as it was an internal guideline and accordingly SOP existed for that procedure. We didn’t capture data on compliance with internal SOPs. Therefore we can’t give you exact numbers on compliance. Due to weekly education sessions and team rounds we believe that compliance with internal guidelines must have been high.

4. I am in agreement with the authors’ view that patients should present earlier for cART initiation based on their findings. I am of the view however that at best earlier initiation is associated rather than results in better survival.
We agree with your emphasis on “association”.

5. The study title highlights the role of the adherence supporter yet, since no adherence measurements were done, the impact of such a supporter are difficult to assess. So I would remove the component of the adherence supporter out of the title.

*We corrected the title and emphasized on the comparable immunological outcome results between rural and urban cohorts.*

6. Finally, I noted in the background that the authors were quoting studies form 2007, yet there are now more recent studies that the authors should review and include in the background.

*We thoroughly reviewed the literature using the meSH terms „hiv-1 AND antiretroviral treatment AND outcome AND adult AND africa“ and completed our citation list with articles of more recent origin.*