Author's response to reviews

Title: Women experience a better long-term immune recovery and a better survival on HAART in Lao People's Democratic Republic

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

Following the review of our manuscript received on October 2, 2012, I am pleased to submit a revised version of the manuscript. In addition, I provide below specific answers to the two reviewers.

Answers to specific reviewer comments

Reviewer 1

Reviewer’s report:
This article is of interest to those studying HIV treatment outcomes in SE Sia, and provides some of the first data on outcomes among patients receiving ART in Lao. The major findings of this study - that those with lower baseline CD4 count have less impressive CD4 reconstitution (lower CD4 trajectories), and overall poorer outcomes are worth reporting in brief, but have also been well established in multiple countries from SE Asia and sub-Saharan Africa.

The methods used to analyze CD4 trajectories are reported in a complex manner, which seem to complicate the otherwise straightforward findings of the analysis. (Though a statistician should comment on the details of the statistical methods).

The fact that women have a lower mortality in comparison to men after the first 9 months, despite controlling for baseline CD4 count is interesting. Reasons for this difference are proposed in the manuscript-- and mostly relate to adherence, measured as a proxy by clinical appointment keeping. The clinical and public health implications of this should be more clearly discussed.

We have modified the conclusion section to include that our study provides additional evidence for differences between men and women on HAART and, in particular, a difficulty for men to maintain a long-term compliance to treatment. Moreover, this study recommends that clinicians and healthcare providers have to pay special attention to men during treatment.

Would suggest that the manuscript be simplified and shortened as a brief report.
Reviewer 2

Major compulsory revisions

Women experience a better long term immune recovery and a better survival on HAART in Lao People’s Democratic Republic

1. Is the question posed by the authors well defined? 
   The question is well defined; however the justification for conducting this analysis is not very strong as several analyses of data from programs have been conducted and published. The authors state that there are few publications on HAART patients in Lao PDR but this is not sufficient justification as several readers of the paper are likely to have interests beyond Lao. The justification should appeal to readers in Lao and beyond.

   Several studies have been conducted and published on cohorts of HIV-infected patients who received antiretroviral therapy in Thailand and Cambodia. These studies report on programme evaluations and outcomes of patients receiving HAART (mortality, CD4 reconstitution…). Regarding Lao PDR, as stated in the manuscript, very few studies and publication are available. The HIV epidemiology in Laos is not very well documented but the few publications and MoH reports show that it differs from the bordering/surrounding countries with a later epidemic and different modes of transmission, mostly heterosexual and driven by migrants, and much less related to sex workers, IV drug use, MSM. Our study, made on the first patients receiving HAART in Lao PDR, contributes to the knowledge of this local epidemic and extend the evaluation of HAART access programmes and the description of patients’ outcomes in the Southeast Asian region which is important for further research in that region.

   We have modified the fourth paragraph of the background section to focus more on that point and to introduce several references on programme evaluations in Thailand and Cambodia.

2. Are the methods appropriate and well described? 
   The study is retrospective and uses routinely collected data from the HIV clinic. The methods have been clearly described.

3. Are the data sound? 
   The abstract reports mortality at 4 months after initiation of HAART. It is not clear why mortality at one or two years or even more is not reported especially that data on follow up is available for up to 60 months of follow up.

   It is true that, in the abstract, we have focused only on the mortality at 4 months mainly because of the high mortality rates at that time point compared to the mortality generally observed in other cohorts. We agree that mortality at 1 year is also important as it is frequently used as an indicator in other studies. Thus, we have added the estimation of mortality at 1 year in the abstract.
There is a significant amount of mortality (n=127) before the initiation of ART. All these patients were not included in the analysis and hence it is likely the mortality overall has been underestimated. These are likely to have been severely ill patients who might have died even with initiation of ART. What is the impact of their exclusion from the analysis on this data?

As you stated, 127 patients died before receiving HAART in the programme and we are aware of this represents an important proportion of the patients included in the programme. However for the present work, as mentioned in the title of our manuscript, we have decided to focus only on the cohort of patients who received HAART.

We agree that mortality before HAART is an important topic, but this was not the objective of our study. It is also impossible to study rigorously the impact of these deaths as we are not working on the overall mortality in the programme, but only in the cohort of patients who received HAART.

Moreover, we are preparing another paper which focuses on follow-up and outcomes of HIV-infected patients during the period before HAART and we intend to publish the pre-HAART mortality estimates.

Some patients were transferred out to Vientiane and censored in the analysis. Are there reasons as to why some patients were transferred? Is it possible there might be a pattern in the transfer of patients e.g. more sick patients being transferred out?

This is a good point that needs clarifications. As you mentioned, 98/913 patients were transferred to the capital Vientiane during the follow-up. There is no medical reason for this transfer. In fact, at the beginning of the programme in April 2003, the only place where patients could receive HAART was at Savannakhet Provincial Hospital. Patients who lived around Vientiane had to move to Savannakhet to get their treatment and to be followed by the clinicians.

In October 2006, Médecins sans Frontières opened a second treatment centre in capital Vientiane. Therefore, these patients go back to their home. Their transfer is thus independent of the severity of the disease.

Unfortunately, as stated in the manuscript, no information on patients transferred to Vientiane could be retrieved.

We have modified the paragraph “Follow-up of the patients” in the methods section to clarify this issue.

Table 1 has data for 913 patients but the records indicated 1000 patient were alive. What is the fate of the 87 patients who were not initiated on ART? Were these patients too sick to start therapy? (another factor that may contribute to underestimate of overall mortality). The authors should clarify this.

These 87 patients were not initiated on ART because they did not meet the criteria for receiving HAART at the closing date of the database (30 June 2009). As mentioned in the manuscript, at the time of the study, patients started on HAART if they met in one of the following criteria: (1) CD4 cell count < 200 cells/μL irrespective of WHO clinical stage; (2) WHO clinical stage 4 irrespective of CD4 cell count.

We have added this in the first paragraph of the results section.
The results for CD4 count gain show there were 335 patients at 12 months but 336 at 18 months. It is not clear how the numbers increased.

This is due to the fact that CD4 counts are missing for some patients at each time point (6, 12, 18… 60 months). It is thus possible that a patient has a missing CD4 count at 12 months, but has a measure of CD4 at 18 months.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
To a large extent, the manuscript adheres to the standards of reporting. However, Figure 1 needs a better illustration of the lines for clarity. The 4 subgroups cannot be easily distinguished using the current line marks. Figure 2 (a to d) is redundant as the results have already been presented as HR in table 3.

We have modified the pattern of the lines for the 4 subgroups to easily distinguish them.
We agree that Figure 2 is redundant with the text presented in the results section and the HR of the Cox model presented in Table 3. But, we believe that clinicians are more comfortable with graphs of Kaplan-Meier estimates of mortality. Therefore, we let the editors to decide if it is relevant to keep Figure 2 (a to d) or if we should remove it.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
The conclusions on men vulnerability regarding access to HAART is not supported by the data.
Thank you for this comment.
We agree that the term “vulnerability” is too strong and is not appropriate for the conclusion. In addition, we agree that we did not study directly the “access to HAART” but instead, we looked at differences between men and women, once on HAART, with respect to CD4 gain, adherence and mortality. Potential differences in access to treatment between men and women will be explored during our study on the pre-HAART period mentioned in point 3.
We propose to reformulate the last sentence of the conclusion as follow. “This study provides additional evidence for differences between men and women, once on HAART and, in particular, a difficulty for men to maintain a long-term compliance to treatment.”

6. Are limitations of the work clearly stated?
The authors have stated their limitations. However they have not described the impact of the early mortality (even before ART initiation) on these data. The exclusion of these early deaths from the analysis is a major limitation to this study and leads to gross underestimation of the mortality in the study. The authors should discuss this as a limitation.
As said in the point 3 of the review, our study does not focus on the period before receiving HAART, but only on the cohort of patients who receive HAART. We believe that this should not be a limitation of the study as we study only the mortality of patients on HAART, and not the overall mortality of the programme.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
The authors have cited relevant publications in the field and some from south east Asia. The authors should also cite a recent publication that shows the same findings: Cornell M, Schomaker M, Garone DB, Giddy J, Hoffmann CJ, et al. (2012) Gender Differences in Survival among Adult Patients Starting Antiretroviral Therapy in South Africa: A Multicentre Cohort Study. PLoS Med 9(9): e1001304. doi:10.1371/journal.pmed.1001304

This is a very interesting paper published after the time of our submission. We have now added it as a reference in our manuscript as reference number 63.

8. Do the title and abstract accurately convey what has been found?
The title and abstract reflect the findings correctly. However, the abstract does not include sufficient data on mortality, only mentions mortality at 4 months. Also, the comparison of CD4 trajectories for men and women did not state whether this difference was statistically significant. One would also expect to see the HR for mortality comparing men and women in the abstract.

As said in point 3 of the review, we have modified the abstract to incorporate mortality at one year. Trajectories of CD4 counts are estimated separately for men and women thus it is not possible to assess the significance of the difference but it was not the objective of this specific analysis. To study differences between men and women regarding CD4 evolution, we have performed a linear mixed model presented in table 2 which indicates a significant difference between men and women in CD4 evolution over time (gender slope deviation term, p < 0.001).

We have added the estimation of the mortality HR for gender in the abstract.

9. Is the writing acceptable?
Overall, the paper is well written and the writing is to acceptable standards.

Sincerely yours,

Mathieu Bastard

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