Author's response to reviews

Title: Excellent outcomes among HIV+ children on ART, but unacceptably high pre-ART mortality and losses to follow-up: a cohort study from Cambodia

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

Thank you very much indeed for your letter dated April 20 and the very useful comments/suggestions of the reviewers.

We have now revised the paper in line with the reviewers comments.

Please find the following for your kind consideration:

1) A “point by point” response to the comments of the reviewers specific responses (XXX R1.doc)

2) A new revised version of the manuscript marked R1.

While hoping that these changes would meet with your favourable consideration, we meanwhile remain completely open to further suggestions and comments.

May I meanwhile hold myself at your entire disposition for any further information you might require.

Yours Sincerely,

Marie-Eve Raguenaud
Author for correspondence
Cover letter: reply to reviewers' comments

MS: 2000759564248192
Title: Excellent outcomes among HIV+ children on ART, but unacceptably high pre-ART mortality and losses to follow-up: a cohort study from Cambodia

Date: May 22, 2009

Editorial points:

1) As this was a retrospective study using routine programme data and the package of care offered is part of the standard in Cambodia, we did not obtain informed consent from individual patients. The study protocol was however approved by two ethics review boards. We have clarified this at the end of the Methods.

2) A Conclusion was added at the end of the Discussion.

Reply to review #1 (Margaret May):

Major compulsory revisions:

2) P7 Methods:
We would like to clarify a point on the way the KM analysis was performed. We retrospectively divided the cohort of children into 2 groups: children never started on ART (n=454) and those ever started on ART (n=714) during the study period. We then performed a KM analysis for each patient group with the outcome death (Fig 2a) and death + LTFU (Fig 2b). Data was only censored on LFU and not on 'start of treatment'. There are thus no competing events (death and treatment) and the predicted probabilities of the 2 endpoints should not add up to more than 1. However, we realize that this figure could be misleading and thus have modified the KM curves to only show survival on treatment. In order to visually describe the differences in outcomes between the 2 patient groups, we added a bar chart (Figure 4).
We thank the reviewer for this useful statistical advice.

3) P7 Results:
Baseline refers to first contact (time of registration in the program). We have clarified this in the text and also in the title of Table 1.

4) Table 2 (and figure 2)
Following the reviewer’s comments, we checked that all deaths occurring after start of ART were indeed included regardless of time on treatment. But we noticed that very early and early deaths 'on ART' were counted for the time period starting at day of registration and not at day of ART start. Thus there
are actually more deaths on ART than calculated previously. We are grateful to the reviewer for this remark as it allowed us to correct Table 2. The early death rate and the early death rate are now similar.

Minor essential revisions:

5) P9:
Among patients not started on ART, we looked at geographical origin, sex, and age:

- There are 73/100 (73.0%) cases lost to follow-up (LTFU) who lived outside province; 161/354 (45.5%) cases not LTFU who lived outside province (OR 3.2; 95%CI: 1.96-5.36); P<0.001).
- There are 46/100 (46.0%) cases LTFU who are girls and 174/354 (49.1%) not LTFU who are girls (OR 0.88; 95%CI: 0.56-1.38; P=0.58).
- There are 53/100 (53.0%) cases LFU aged < 60 months and 173/354 (48.9%) not LTFU aged <60 months (OR: 1.2; 95%CI: 0.75-1.84; P=0.466).

This suggests that longer travelling distances made access to care more difficult to the point that children stopped coming back for consultation. We have mentioned this interesting finding in the Discussion section, paragraph 2.

6) P10 line 8 typo corrected.

7) Figure 1
Extra information on ART eligibility criteria was added in the left branch.

Discretionary revisions:

8) P5
The new criteria to start ART after 2006 (WHO) were added in the text.

9) P11
We have cited the reference used by the clinicians of the program [12].

Reply to review #2 (Claire Thorne):

Major compulsory revisions:

1) We thank the reviewer for this remark. In the Discussion, paragraph 9, point #3, we discuss on immunological criteria for ART, we include presumptive diagnosis, and we cite the latest recommendations for ART initiation in infants regardless CD4.

2) Methods Pg 4:
In 2007 the national AIDS program of Cambodia estimated that 33% of HIV+ pregnant women were receiving ARV for preventing mother to child transmission. In both study locations a PMTCT program was in place albeit with limited coverage. 21% of children enrolled in the HIV program in Takeo
entered care through the PMTCT program (no data available for Siem Reap location).
We have inserted this comment in the Methods section, paragraph 2, p.4.

3) Methods Pg 5:
CD4 count was measured every 6 months and this information was added as per your recommendation, Methods paragraph 3.

4) Methods Pg 5:
In the early years of the program, the protocols and guidelines were still not standardized. Moreover, the 2 clinics were substantially different (one located in a public hospital and the other in a charity-owned private hospital). Differences were reduced over the years as protocols were standardized.

5) Methods Pg 6:
Deaths were recorded in patients' charts and encoded in the electronic software. As mentioned in 'Data management and statistical analysis' section at bottom of page 6, the most attributable cause of death was the last diagnosis recorded in the patient file. All diagnoses were made by HIV-specialized hospital doctors.

6) Methods:
Yes, this was an 'intention to treat' analysis and therefore included children who switched to second line therapy. We have clarified this in the Methods section, Study population, paragraph 1.

7) Table 1:
Indeed, before 2006, presumptive HIV infection diagnosis was used for children <18 months and diagnosis was confirmed by antibody testing at 18 months. This was clarified in the Methods section, paragraph 2. For 2 children with presumptive AIDS who died before the age of 18 months we were not able to confirm the diagnosis.
We also agree with the reviewer that symptomatic children were more likely to be identified, which could partly explain the high mortality in the youngest age group in the program. We added a clarification on this in the Discussion paragraph 5.

8) Table 1:
By the end of the study period, April 2008, a total of 32 children were switched to second line therapy. We added this information as a note in Table 1.

9) Table 2:
We have slightly modified the table and preferred to include the proportions in the text to avoid confusion.

10) Results:
We added the proportion of the 248 children not on ART who were eligible for treatment in the text on page 8 (last sentence of sub-part of Results: Enrolment, follow-up and main outcomes) and have also added this information in Figure 1.
We also clarified in the test (in the sub-part: ART eligibility and early deaths) that the children with early deaths were not on ART, and referred to Fig 1 again.

11) Results:
We have added more details regarding the children who died within one month of admission (Results section, ART eligibility and early death, last sentence).

12) Discussion Pg 10:
We have referred to the fact that cotrimoxazole prophylaxis was widely implemented in the study setting (Discussion, paragraph 3).

13) Discussion Pg 10:
We have added a statement to emphasize the link between limited resources and follow-up activities. (paragraph 4)

14) Discussion Pg 11:
We have added a paragraph on possible reasons for delay in ART initiation in our program (Discussion, paragraph 7). We agree with the reviewer on the general need for training of primary care physicians and paediatricians in hospitals. In our setting there was actually an abundant offer of various trainings performed by various actors, and we were reluctant to advocate for more.

15) Discussion Pg 12:
The preparatory ART sessions were never assessed in terms of effectiveness, there is thus no strong argument for delaying ART initiation in severely ill children. In our experience, ART was delayed in some cases because of planned preparatory sessions. However, we believe that counselling and treatment literacy are an integral part of ART and should be offered as much as possible. To avoid compromising treatment literacy we propose that preparatory sessions start before ART eligibility.

16) Discussion/Results:
Nearly half of the early deaths among children not started on ART occurred in the first two years of the program (2003/2004). However we are reluctant to hypothesize that this was due to the quota in place as there were other factors that might have contributed to this (lack of clinical experience, conservative criteria for ART initiation, limited access to CD4 measurement, etc).

Minor essential revisions:

1) Pg 3
 correction made ("correctly assess")

2) Pg 3 "if at all" was deleted

Discretionary revisions:
1) Discussion Pg 11
One reference on clinical management of TB/HIV co-infection in children was added and mentioned in the discussion p.11 [ref 12].

**Reply to review #3 (Stephane Blanche):**

- As recommended by the reviewer, we have suggested possible reasons in our setting for delaying ART initiation after eligibility criteria were met (Discussion, paragraph 7).

- The main objective of this study was to evaluate the overall mortality of children enrolled in the HIV program. Over the last five years we have been monitoring our program mainly by looking at children on ART and "under pressure" to prove the efficiency of ART in a resource-limited setting. We all neglected to look at the overall cohort with the "intention to treat" concept. We thought it was high time we started documenting the overall performance of the HIV programs and advocating for their appropriate monitoring. We perfectly agree with the reviewer that an analysis of parameters associated with non-treatment is deemed necessary. However, we think that this would be best done in a separate study, including multivariate analysis of factors associated with non-treatment, as suggested by reviewer. We intend to do so in the future. We added a sentence suggesting this as future research at the end of the Discussion, in the paragraph on study limitations, in light of the reviewer's comment.