Reviewer’s report

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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Reviewer: Claire Thorne

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This is an interesting manuscript describing survival of HIV-infected children enrolled in two HIV programs in Cambodia, between 2003 and 2007. The authors analyzed mortality data from the programme database on all children, investigating mortality both on HAART and prior to HAART initiation, using survival analysis techniques. They document, in this “real-life” setting, very low mortality rates among children on HAART, but a high mortality among children not on HAART (and a high loss to follow-up rate in this group). Their findings highlight that simply looking at on-ART mortality among infected children may give a distorted impression of success of pediatric HIV programmes. The discussion includes a clear discussion of factors that could improve outcomes overall.

Major Compulsory Revisions

1. The context of the “when to start” question regarding paediatric ART could have been flagged up in the background section, and expanded upon in the discussion.

2. Methods Pg 4 - Please could the authors give some more background regarding any PMTCT program in operation in Cambodia / the catchment areas of the HIV programs. In particular, it would be interesting to know what proportion of the infected children in the HIV programs have been followed as a result of identification of HIV in their mothers during pregnancy.

3. Methods Pg 5 – the authors state that CD4 count testing at 1-3 month intervals before starting ART was recommended by the protocol in the early years of the programme, but they don’t state what has been recommended in the more recent years of the programme.

4. Methods Pg 5 – Could the authors indicate why different CD4 thresholds were used in different hospitals for initiation of ART.

5. Methods Pg 6 – How were deaths reported/recorded? Were they verified in any way? How were (contributing) causes of death established?

6. Methods Was this an intention to treat analysis? (did any children stop taking ART, or switch to second line therapy?)

7. Table 1.
In the methods it is stated that early diagnosis of infants <18 months started in 2006. Thirty-two of the 69 HIV-infected children aged <18 months were born before 2006. Presumably, these children were identified as having presumptive HIV infection on the basis of clinical signs/symptoms, with diagnosis confirmed by antibody testing at 18 months? This should be clarified. In the absence of good coverage of early diagnosis among infants born to HIV-infected mothers, infected infants who are symptomatic are more likely to be identified and enter HIV care and treatment programmes. This may partly explain the high mortality in the youngest age group in the program.

8. Table 1: were there any data available on the numbers/ proportions of children who had to switch to second line therapy?

9. Table 2
   It is not clear what the denominators are for the % of total deaths given in each column – please could the authors add these to the table.

10. Results: in referring to Figure 1 in the text on page 8, it would be helpful if the authors could state what proportion of the 248 children not on ART were actually eligible for treatment (and would lead nicely to the next section in which only eligibility of those children with early deaths was investigated, and not that overall). Could the authors add some text to clarify that the 46 children who died whom they refer to were not on ART (could also refer to Fig 1 again).

11. Results: it would be interesting to know some more details regarding the 12 children who died within a month of admission – for example, timing of diagnosis, median age at death.

12. Discussion Pg 10 – could the authors refer back to the cotrimoxazole coverage in the Cambodian setting when discussing possible reasons for the lower mortality rate here vs Zambian example.

13. Discussion Pg 10 – the authors state that “the very low dropout rate… suggested they were better followed”. This should be stated more strongly as the authors have already stated in the methods that, because of limited resources, their follow-up activities were focussed on treated children.

14. Discussion Pg 11 – can the authors suggest possible reasons for the delay in initiating ART after eligibility criteria were met?
   - the authors could give some more background on how children are referred to the programme. Is there a need for training of primary care physicians and paediatricians in hospitals regarding identifying signs indicative of potential HIV infection? How might this be addressed?

15. Discussion Pg 12
   The “conflict” that the authors identify between ensuring ART preparedness of parents/children and the need to initiate treatment quickly is an interesting one, which deserves a little more discussion. For example, has there been any
evaluation of the preparatory ART sessions in terms of their effectiveness with regard to adherence? It seems that there may be a fine risk-benefit balance for this intervention, particularly for severely ill children.

16. Discussion/Results In the methods the authors state that in one clinic there was a strict limit on the numbers of children who could be started on ART due to logistic constraints, but that this was only the case at the “beginning of the program” (although no dates were provided). What proportion of the deaths among children eligible for ART but not receiving it was attributable to this specific situation?

Minor essential revisions
1. Pg 3 “they are do not correct assess overall …”
2. Pg 3 delete “if at all”

Discretionary revisions
1. Discussion Pg 11 – it would be helpful if the authors cited some references relating to TB and paediatric HIV

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests