Author's response to reviews

Title: Clinical presentation and outcome of tuberculosis in human immunodeficiency virus infected children on anti-retroviral therapy

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Author's response to reviews:

Dear Editor

Regarding manuscripts: 1579315858154712 and 1466455215472859
1) Clinical presentation and diagnosis of tuberculosis in HIV-infected children on anti-retroviral therapy
2) Treatment and outcome of tuberculosis in HIV-infected children on anti-retroviral therapy

Combined into a single manuscript as requested

New title
Clinical presentation and outcome of tuberculosis in HIV-infected children on anti-retroviral therapy

Thank you for your provisional acceptance of this manuscript. I have addressed all the comments made. Thank you for the constructive input, which enabled us to improve the manuscript considerably.

Reply to editor's comments
C1) The two manuscripts to be combined into one
R1) This has been done.

C2) Add Acknowledgements, Competing Interests and Author contribution sections
R2) This has been done.

Reply to comments made by reviewer 1 (Philippe Msellati)
C1) Mistake in abstract ‡ should be 12% and not 112%
R1) Thank you for pointing this out – it has been corrected.

C2) Were the 18 children for whom the outcome was not established all lost to FU?
R1) Yes, they were all lost to FU - this is specified in the text.

Outcome could not be established in 18 (13%) episodes, where children were lost to follow up.

Reply to comments made by reviewer 2 (Virat Sirisanthana)

C1) The definition of ‘clinically suspected’ is very non-specific. Exclude this category from the analysis.
R1) We retained this category as we believe it is important to demonstrate the complete clinical picture. In reality TB culture facilities are rarely available in resource-limited settings and children with culture positive disease may represent a select sub-population. However, we included the ratio of culture confirmed disease among the pre- and post-HAART groups to demonstrate that there was no diagnostic bias and that the main conclusions hold true for the culture confirmed subgroup as well.

Page 8, paragraph 3
Table 4 reflects the presenting features; CXR data and/or culture results were available in 107 (89.1%) cases, the remainder was classified as ‘clinically suspected TB’. Bacteriologically confirmed TB was diagnosed pre-HAART in 40/116 (35%) and post-HAART in 6/21(29%) cases; the number of bacteriologically confirmed TB cases per 100 patient years were 18.3 pre-HAART and 1.8 post-HAART.

Page 12, paragraph 2
Most TB episodes were diagnosed in the 9 months prior to HAART initiation, during which time a diagnosis of TB is actively excluded. The number of TB diagnoses made pre-HAART was five times greater than post-HAART, which is even greater than the three fold reduction reported by Martinson et al.28 When calculating the number of TB cases per 100 patient years there was an eight fold reduction in TB episodes (53.3 versus 6.4), comparing the 9 months pre-HAART period to the post-HAART period. This was not a manifestation of overzealous diagnosis in the pre-HAART period, as the striking observation was even more pronounced when only bacteriologically confirmed cases were taken into account (18.3 versus 1.8).

C2) Combine the two manuscripts into one.
R2) This has been done.

C3) Indicate in the discussion that weight loss or failure to thrive is a non-specific symptom.
R3) Thank you for the observation, we did include this in the discussion.
Weight loss or failure to thrive was the most frequent presenting symptom, but this may be caused by advanced HIV disease itself or by other HIV-related opportunistic infections. In addition accurate symptom definition, which is essential for optimal specificity,38 is impossible with retrospective analysis of routine clinical data.

C4) Provide definition of IRIS-related phenomena in methodology section.
R4) This has been done.

IRIS was defined as new mycobacterial disease and/or worsening of pre-HAART symptoms/signs diagnosed within the first 6 months after HAART initiation, in a child that demonstrated good immunological recovery and viral suppression.

C5) Remove ¿clinically suspected TB¿ case definition.
R5) See reply to comment 1.

C6) Re-assess the frequency of IRIS among culture confirmed cases and re-evaluate the statement that TB IRIS is not prominent.
R6) Thank you for this suggestion, we did look at this and it is included in the discussion.

The incidence of TB IRIS (7.4%) is slightly higher that that reported by Puthanakit et al,30 and was higher among those with bacteriologically confirmed TB (4/46; 8.7%), compared to those without bacteriologically confirmed TB (6/88; 6.8%).

C7) Typo in abstract ¿ should not be 112%
R7) Thank you for pointing this out ¿ it has been corrected.

C8) Provide definition of IRIS-related phenomena in methodology section.
R8) This has been done ¿ see reply to comment 4

C9) Table 1 ¿ sign # in wrong place
R9) This has been corrected ¿ thank you for drawing our attention to this.

Thank you for these valuable comments. I hope we have adequately addressed the concerns and suggestions made. Please inform me if any additional information or clarification is required.

Regards
Ben Marais