Author’s response to reviews

Title: HIV-associated tuberculosis: relationship between disease severity and the sensitivity of new sputum-based and urine-based diagnostic assays

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

Many thanks for your e-mail of the 14th August and for forwarding the reviewers’ comments. I am pleased that this article was found to be of interest by BMC Medicine and that you have invited submission of a revised version. Below I have provided a point-by-point response to each of the comments.

Reviewer: Giuseppe Ippolito

Reviewer's report:
The diagnosis of HIV-associated TB, particularly in sub-Saharan Africa, is often challenging. The article is complete and accurate, the design and statistical analysis are well performed, and the authors are really competent in the field. They already published several papers on different diagnostic and prognostic approaches in HIV-TB coinfected patients in South-Africa. The paper gives a contribution to the assessment of relationship between severity of tuberculosis and the sensitivity of diagnostic procedures. The overall judgment is positive, and I recommend to accept it.

Response: Thank you.

I have just few comments that can be considered in the revision of the discussion and in the interpretation of results. Find them listed below:
- the general issue of diagnostics in less developed countries, including deciding on and monitoring treatment, would certainly require a capillary yet simple system of laboratories. Previous experiences made in some countries have proven low sustainability and have almost always heavily relied on international
aid. A robust and locally managed laboratory network for the first line management of HIV- and TB-related problems would be sustainable in the long run. The importance of starting a debate on the issue could be acknowledged; -the new tools for TB are really promising, but data on validity and impact of outcome for patients are still controversial, especially in less developed countries. Recently a study conducted in Johannesburg [Hanrahan CF. PLoS One. 2013 Jun 6;8(6) and the design of a trial to evaluate the new diagnostics in rural South Africa [Lessells RJ. Trials. 2013 Jun 12;14:170] have been published.

**Response:** We completely agree that studies are needed to evaluate the impact of new diagnostic assays and strategies on clinical outcomes of patients and to assess the feasibility and sustainability of these new technologies. This is reflected in the Discussion of the revised paper.

**Reviewer: Patricia Price**

The cohort is actually quite small for a study of this type (n=86 where some lack data from urine samples). There were only 6 deaths.

**Response:** The sample size should be appropriately judged in regard to whether it was sufficient to address the stated hypotheses. Our hypothesis was that the sensitivities of novel sputum-based and urine-based diagnostic approaches are associated with disease severity among patients with HIV-associated TB. The data presented in Figures 2 and 3 clearly demonstrate a consistent relationship between increasing disease severity and increasing diagnostic sensitivity using these assays. Statistically robust associations were seen when assessed using a range of different prognostic indices and using both sputum-based and urine-based assays. The conclusions that we have drawn are very clearly supported by the data as presented.

We acknowledge that the number of deaths was limited. However, despite this, statistically strong associations were observed between vital status and diagnostic sensitivity using urine-based diagnostics (Fig 3).

We have modified the strengths and limitations section of the Discussion section of the revised manuscript accordingly.

**Major Compulsory Revision**

Table 1 has no statistical analysis and is very hard to read. Are ranges or IQR shown? The number of decimal places can be reduced and comparisons with a significant difference should be marked (eg: with an asterisk *). What is the basis of the cut-offs for the categories? Perhaps it would have been better to show correlations (r and p values) for the continuous variables.

**Response:** Table 1 presents the characteristics of the various patient groups when stratified by the prognostic indices. This is essential background descriptive information that underpins the rationale for the data stratification. It is widely agreed that such descriptive Table 1 data should not include statistical analyses as these are not the primary comparisons from which conclusions
are drawn. It was for this reason that P values were not included. Moreover, inclusion would add complexity to the table and make it less readable.
The readability of the Table will be substantially improved when in publication format. We have indicated in column 1 that the figures included in parentheses are either IQRs or percentages. Where this information was missing, these have now been included.
All data are shown to just one decimal place which is an appropriate degree of precision.
Stratification by Hb concentration was done according to the WHO classification of anaemia.
CD4 stratification was done according to clinically relevant groupings.
CRP stratification was done in approximation to quartiles.
Data stratification for symptom severity and vital status is self-evident.
The Methods section of the revised paper has been amended to include this.

Minor essential revisions
The title implies study is compares diagnostic tests with “disease severity” when it actually excludes patients with only extrapulmonary TB. This Ok but it should be clearer.

Response: Although all TB cases were defined by positive sputum cultures, there were actually no patients with a diagnosis of isolated extrapulmonary TB who were excluded from this analysis. However, that may simply reflect that only sputum and urine samples were tested. This has been clarified in the revised discussion.

Figure 1 showing the derivation of the 86 samples is not needed…especially as it is duplicated in the text.

Response: Such a figure is widely regarded as an essential component of studies reporting on the evaluation of diagnostic tests. The figure provides a very clear summary of any exclusions and therefore potential sources of bias. We would therefore much prefer to retain the figure if this acceptable to the editorial team.

Figure 2 is unreadable…axes are off the page. This looks careless…not a good sign.

Response: This composite figure was correctly formatted and uploaded according to the instructions for authors. I suspect that the problem is that the reviewer has not scaled this to A4 size when printing.

Figure 3 distinguishes patients who lived and died…which isn’t really the point. A positive reaction doesn't mean that a patient will die…clearly it important to have a diagnostic that picks that a patient who will die has TB but I am not convinced that this would not be detected on medical grounds. I note that the sputum assays were less discriminating than the urine…presumably this means patients were dying of extra pulmonary TB…perhaps TB meningitis which has its own symptoms and diagnostics. This could be explored if the study was larger.

Response: The simple point being made here is that the assays had high sensitivity for HIV-associated TB (greatly exceeding that of sputum smear microscopy) among those who had the worst prognosis and died. This is of real importance, especially when one considers that numbers of post-mortem studies conducted in sub-Saharan Africa have all reported very high frequencies of
undiagnosed disseminated TB among people dying with HIV/AIDS both before and during the scale-up of antiretroviral treatment (ART). These new diagnostic approaches will now enable a considerable proportion of this disease to be diagnosed ante-mortem. This is clearly important and provides a clear rationale for prospective trials assessing impact on mortality outcomes as stated in the discussion section.

We are grateful for the careful assessment of this manuscript by the reviewers and for the opportunity to respond to these comments. I hope that the paper is a useful contribution to BMC Medicine and is acceptable for publication.

Yours sincerely,

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