Reviewer’s report

Title: Rapid diagnosis of new and relapse tuberculosis by quantification of a circulating antigen in HIV-infected adults in the Greater Houston Metropolitan area

Version: 0 Date: 29 May 2017

Reviewer: Jacqueline Achkar

Reviewer’s report:

In this study, the authors used an immunoaffinity-based parallel reaction monitoring (iPRM) liquid chromatography mass spectrometry (LC-MS) assay that used MS/MS fractionation to confirm the target peptide identity of the M. tuberculosis protein CFP10 in blood/serum for diagnosis of HIV-associated TB. The study uses a novel technique, the study design is sound, and the data are interesting to the field of TB diagnostics. Overall the results show a high sensitivity in culture-confirmed (~90%) as well as culture-negative TB (~67%) with a specificity between 80-90%. I have no major concerns although I am wondering how applicable this MS-based assay would be in TB endemic regions even with the advantage of being able to use blood rather than a specimen from the site of disease. The authors should certainly discuss this in more detail but overall, my comments are mostly minor.

Abstract:

The authors should give condensed information about their assay and antigen in the methods section of the abstract.

The authors should give specific sensitivity and specificity information of their assay relative to gold standard of Mtb culture in the results section; the term "microbial methods" should be more specific.

Intro/Background:

Line 29 - it should be "incidence" not "prevalence" for pulmonary and extrapulmonary TB.

Lines 31 - 39 - another major reason for TB recurrence in HIV-infected individuals is reinfection which in regions of high TB incidence occurs between 30-50%; the authors should include that.

Lines 4-12 - when the authors provide reasons why Mtb antigens are not detected sufficiently in body fluids by other assays they should also mention that the antigen levels might simply be too low.

Methods:
iPRM assay - did the authors have any positive controls in their assay? They should comment on
this.

Results:

The results section can be shorten for information that is shown in tables 1 and 2.

It would be helpful to know what diagnoses were obtained for the non-TB patients.

Lines 46 - 54 - Tuberculin skin test is not a diagnostic method for active TB. Thus listing
sensitivity and specificity for it does not add any valuable information and the section on this
should be taken out.

Lines 11/12 - mycobacterial culture is not an "assay", referring to it as culture is sufficient.

Discussion:

Although I agree with the point the authors are making regarding the need of invasive sampling
for Gene Xpert in cases of extrapulmonary TB, they should review the gene Xpert literature a bit
more thoroughly - much has been published recently on using Xpert for extrapulmonary TB
samples and Xpert in contrast to MS is widely available in TB endemic regions; it would be of
interest to see the comparison of a few more larger studies here.

The authors should discuss where they would see the applicability of their assay as most TB
endemic regions will have little availability of MS technology.

Tables & Figures:

Table 1 - The authors should clarify in the footnote what the p value compares; they should not
compare all groups listed as all TB is comprised of culture-pos and culture-negative TB.

Table 2 - Culture-negative/smear-positive does not make sense - culture is much more sensitive
than smear and typically all smear-positive patients are culture-positive, unless the one patient
listed in table 2 either a contaminated smear or has already received treatment and would thus be
culture-negative. The authors should review the clinical data and address, but either way should
not list this one unusual patient with 100% sensitivity.

Fig. 3 - should include the data for cured TB and non-TB cases and also contain a line to show
where the cut-off value was. The figure legend should include the explanation for "pM" as most
readers will not be familiar with this abbreviation. It would further be of interest to see a p value
for the comparison between culture-pos and culture-neg TB.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?
If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal