Reviewer's report

Title: Response to M. tuberculosis RD1 selected peptides in Ugandan HIV-infected patients with tuberculosis

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Reviewer: Madhukar Pai

Reviewer's report:

Major Compulsory Revisions

1. This is an interesting study of relevance to working in this field. However, as pointed out by the authors, a major limitation is the small sample size. The authors acknowledge that this is pilot work that needs to be confirmed. So, I think the title and the abstract should explicitly state that this is a pilot study.

2. I think the authors overstate the issue of change in responses over time. The authors claim (Page 10) that a successful therapy for TB causes a significant decrease of the sum of ESAT6 and CFP10 peptide responses. However, even after successful therapy, the median SFC count was as high as 100! Surely, if a dichotomous result were to be used, then all patients would be scored ELISPOT positive, even after completion of treatment. So, although treatment may lead to a decline in ELISPOT responses, all patients still had high residual responses at the end of therapy. None probably reverted to negativity. The authors need to address this issue and provide some explanation as to why all treated patients had fairly high responses at the end of therapy. At least 3 studies from India have shown high T cell responses despite therapy (Infection. 2007 Apr;35(2):98-103; J Occup Med Toxicol. 2006 May 23;1:7; and Am J Respir Crit Care Med. 2006 Aug 1;174(3):349-55.). I suspect TB patients in TB endemic countries often have strong baseline T cell responses. So, the responses have to drastically drop for the assays to revert to negativity. Alternatively, there may be other factors that keep the T cells partially stimulated in high burden countries – exposure to NTM, repeat exposures to TB, etc. These issues deserve some discussion.

3. Figures 3A and 3B show correlation between CD4 counts and responses to ESAT6/CFP10. Although the correlation coefficients are statistically significant, I find the plot unimpressive. Visually, it is hard to make out a linear trend, and I suspect the R is significant because of one outlier (the person with a very high CD4 (>500) and SFC of nearly 1000. If this outlier were to be dropped, I am sure the correlation coefficient will not look impressive. I suggest the authors repeat the analyses after excluding the outlier and report these results as well.

4. The authors have done a ROC analysis, but because their controls are from a high endemic area, they have no way of excluding LTBI among the controls. Figure 1 clearly shows that controls are demonstrating responses to ESAT6 and CFP10, and that tells me that at least some were latently infected. In fact, this is
confirmed by the lower specificity reported by the authors. I would recommend adding the ROC plots to the paper, and to discuss the impact of including controls from a high TB endemic country.

Minor Essential Revisions

1. The authors use the word “overtime.” It should be “over time”.

2. In the background, the authors state that IGRAs should be shown to be useful in TB-endemic settings. I agree with this assertion. In fact, FIND, TDR and Stop TB recently published a research agenda on IGRAs and specifically called for more studies in TB endemic countries (Lancet Infect Dis. 2007 Jun;7(6):428-38).

3. Page 5, first line: please substitute the word “circulation” with “transmission.”

4. Page 7: because an in-house ELISPOT was used, it will be helpful to add more text on how exactly the assay was performed. Readers should be able to reproduce the assay, if they so wished.

5. Page 8: Table 1 shows that controls were less immunosuppressed than TB cases. What implications can this have for the comparison between cases and controls?

6. Page 8: The authors found one patient with “anergy.” Why was mitogen not used as the positive control? If it was used, what was the mitogen response for this individual?

7. Figure 1B: p-value not included.

8. Figure 2B: p-value not included. Also, please only include 1, 3 and 6 months on the x-axis.

What next?: Accept after minor essential revisions

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

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.