Reviewer’s report

Title: Interferon-γ release assay as a sensitive diagnostic tool of latent tuberculosis infection in patients with HIV: a cross-sectional study

Version: 0 Date: 01 Jun 2018

Reviewer: Walter N. Dehority

Reviewer's report:

Overall, this is an interesting study addressing an important issue in the management of patients with LTBI. The authors are to be commended on undertaking this project. A few specific comments are included below:

Introduction:

Well written, and represents a good discussion of the issues.

Methods:

How is active TB defined in contacts (page 5, line 120)? Did they require culture-confirmation? PCR/DNA amplification? Chest X-ray only?

Page 5, line 125: What is meant by ’…contact with the bacillus…”? Is this meant to refer to smear positive individuals, those with culture positive disease, those with suspected active TB without microbiologic confirmation? I would try to clarify this point.

Lines 127-129, page 6: It is stated that ’…those who had no contact with smear positive individuals who also had a positive TST…” were considered low risk. But if they were in contact with a smear positive individual with a non-reactive TST, this individual may have had a reactive IGRA test, or never have undergone IGRA testing and had floridly active TB but according to this definition, would their contacts would be considered low-risk just because the TST was not reactive? Were symptoms (or the lack thereof) part of this classification, or chest X-rays? It also states that those without treatment for LTBI in the last two years were considered low-risk. What if they had received treatment for LTBI? Did this change their classification? Some data suggests that IGRA's may exhibit sustained positivity in adults with prior TB infection. Hence, with prior LTBI (and hence possible prior LTBI treatment), a reactive IGRA may represent reactivity from an old LTBI, not from a recent exposure. I would clarify this section.
What is the background data on TB in this population (Sao Paulo)? Information such as the incidence rate/prevalence may help readers determine whether the data from this study would be applicable to their patient population

Is Mycobacterium bovis endemic in this region? The effect of this organism on IGRA and TST testing is interesting, and if it is endemic, would probably warrant a brief discussion of how or if it would have affected your results

Were CXR's done on LTBI patients? Were they asymptomatic, or was this known? How was it ensured that they likely had LTBI as opposed to active TB? This would be important and central to the study.

There should be a definition of LTBI in the methods section. The first time this is mentioned is on page 10 in the results section, by my read (lines 213 and 221).

At least one positive test (either IGRA or TST) was required for classification of LTBI. This may represent a form of detection bias, however, as a positive result for either test was required for entry, and then the performances of each test were assessed. If, for example, IGRA positivity was one possible criteria for enrollment, and then one assessed the sensitivity and specificity of the IGRA test (upon a sample which required IGRA positivity for enrollment), it may be difficult to determine the true accuracy of this test. If one enrolled, alternatively, a group of individuals whose risk of LTBI was independent of the test being assessed (e.g. epidemiological risk factors only), this may provide a less biased estimation of the utility of the assay. Would address this issue in the text and/or results section. This is very tricky, admittedly, given the lack of a gold standard for this disease.

Skin color is listed in Table 1. I would re-write this as ethnic or racial classifications. The categorization as 'black' or 'brown' may be offensive to some, and doesn't carry any clear medical significance of which I am aware.

The categorization of HIV control (viral load, CD4 counts) is important; the addition of this strengthens the manuscript

Discussion

Good discussion of the limitations of the study. Also a nice discussion of the limitations and advantages of IGRA and TST testing on page 14.
Might need a brief mention of resource-limited countries where IGRA testing may not feasible, and reliance upon the TST may still be necessary.

References

Reference 8 is the 2013 'WHO Global Tuberculosis Report', accessed in 2014. However, there is a 2017 WHO 'Global Tuberculosis Report'. As this reference is 4 years out of date, would consider replacing it (and any referenced data) with more current information.

Reference 19: the ‘F’ in Feb should be capitalized.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

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.

No

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

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