Reviewer’s report

Title: Empirical treatment for tuberculosis in HIV: lessons from a cohort study of people living with HIV treated in two referral centers in Recife, Brazil

Version: 2 Date: 3 July 2013

Reviewer: Valeria Saraceni

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Major Complimentary Revisions

Although I found merit in your study, and the topic is quite interesting, I have some comments:

1 – Are those without TB test different from those who tested negative? It would imply a misclassification bias in those who were tested and were negative as TB suspects.

2 – If I understood it correctly from Tables 1 to 3, you’re referring directly to Hazard Ratios, and not comparing the 2 groups, those who started and those who didn’t start TB therapy. Direct comparison of the 2 groups by visualizing if they are comparable always makes it easier for the reader. I’d like to see the proportions of CD4<200, HAART at baseline, etc, and the homogeneity test. Table 5 gives a clue that those who died were sicker than those who didn’t.

3 – Then I’d like to see the KM (Figure 2) depicting both groups (TB Therapy yes and no).

4 – I guess that, once you’ve rejected your null hypothesis, you should look at time from TB therapy initiation and death. Another KM by CD4 category (<200 and >=200) would make it clearer to help explain your findings. I have a general idea that those who died had little time between starting TB therapy and death. As you’ve stated, the median time from cough to decide to initiate TB therapy was 6 months. This is a major point to be further explored.

5 – In Conclusions, you’ve said: “Those with strong indications of advanced HIV diseases were more likely to receive empirical TB treatment (even if they had few indications of having tuberculosis); those receiving treatment in this group had a marked increase in mortality, likely to be a result of their advanced HIV disease, and possibly of other causes for the cough.” So HIV advanced disease is a confounder, and CD4<200 was a strong predictor of death and cough. Therefore, the doctors may have tried TB therapy as salvage therapy. I wonder if this group of patients who had a cough and died was composed of smokers, had PCP, was failing HAART. I guess you have in your cohort data about those questions that would elucidate your points better. A table by CD4 category and risk factors would help to check on that.

6 – HIV patients have a greater chance to have disseminated TB, and no cough.
How many of those patients were checked for disseminated TB? Especially those with lower CD4?

7 – You’ve mentioned “controlling for CD4” and in Table 3 it says as time-dependent. Yet again, on page 8, 4th paragraph, you’ve said “During the follow up, almost all (99.4%) had at least one CD4 cell count measurement and 73% used HAART at entry.” I wonder how many CD4 per patient do you have. And which CD4 was used to categorize the value? The one nearest to starting coughing?

Answering those questions and presenting further results will help the reader get a better view of your findings.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.