Author's response to reviews

Title: Viral hepatitis and HIV-associated tuberculosis: Risk factors and TB treatment outcomes in Thailand

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Version: 2 Date: 16 June 2008

Author's response to reviews: see over
16 June 2008

Dear BMC Editors,

Thank you for the prompt and thorough review of our manuscript. Below you will find a point-by-point response to the comments by the reviewers. Where indicated, we have revised our manuscript to reflect these comments.

Sincerely,

Jay Varma
Reviewer's report
Title: Viral hepatitis and HIV-associated tuberculosis: Risk factors and TB treatment outcomes in Thailand
Version: 1 Date: 2 June 2008
Reviewer: Robert Paris
Reviewer's report:
The authors have studied the impact of serologic evidence for viral hepatitis on TB treatment in a Thai population that is HIV co-infected. This study has important implications for the treatment of co-infected persons from low-to-middle income countries.

Major comments:
1. The methods section says that CD4+ T-lymphocyte counts were obtained, but there is no presentation of this data. The effect of CD4 count on the incidence of hepatitis, IRIS, and death would help with the interpretation of the data. It would also be important to exclude an association with hepatotoxicity and CD4 count. This may be difficult since liver profiles were collected at only one time point.
RESPONSE TO REVIEWER: We have added data about CD4 (median and range) to Table 1. We adjusted for CD4 in the analysis of death or death/default; this was noted in the table as “HIV disease severity”, but now has been explicitly noted in the Results with the following sentence: “Factors adjusted for in this analysis included TB disease severity, HIV disease severity (i.e., CD4 count at time of enrollment), co-trimoxazole use, fluconazole use, anti-retroviral use, directly observed therapy use, hospitalization at enrollment, and previous TB treatment.” We did not report the relationship between CD4 and acquired hepatitis or IRIS by viral hepatitis subgroup because of small numbers; for example, only 3 patients that were HBsAg+, 12 patients that were anti-HCV+, and 2 patients with both were diagnosed with liver disease during TB treatment.

2. The statement, "Our study provides reassurance that TB patients with HCV and HIV infection have adverse event rates and treatment outcomes no worse than TB patients with only HIV infection"(page 15, first paragraph, 3rd sentence) should be removed. As pointed out in the subsequent paragraph, the limitations of the study preclude saying this.
RESPONSE TO REVIEWER: Done. We have changed this sentence and the following sentence now to read: “We found that TB patients with HCV and HIV infection had adverse event rates and treatment outcomes no worse than TB patients with only HIV infection. Further research is needed to confirm this finding in other countries and in populations whose HCV infection is better characterized through measurement of HCV viral load, HCV genotype, and pathological evidence of liver disease.”

3. Selection bias is one potential limitation that was not addressed. If available, how many persons were screened for enrollment? This should be mentioned in the discussion of limitations on page 15, second paragraph.
RESPONSE TO REVIEWER: The numbers screened, eligible, and enrolled are already presented in Figure 1. We have added the following sentence to the Discussion: “The population we studied may not be representative of all HIV-infected TB patients in Thailand.”

Minor comments:
1. Laboratory reference ranges (upper limit) for liver enzymes would be helpful to the reader as only small elevations in ALT or AST in someone with chronic active hepatitis may portend TB treatment complications depending upon age.
   RESPONSE TO REVIEWER: The following statement has been added to the Results: “In these laboratories, the upper limit of normal for AST was 35 units/L, ALT 33 units/L, and total bilirubin 1 mg/dL.”

2. Were there standardized criteria to diagnose clinical hepatitis?
   RESPONSE TO REVIEWER: No. As noted in the discussion, this depended on a “clinician diagnos[ing] clinical hepatitis.”
Reviewer's report
Title: Viral hepatitis and HIV-associated tuberculosis: Risk factors and TB treatment outcomes in Thailand
Version: 1 Date: 4 June 2008
Reviewer: Ekaterina Kourbatova

Reviewer's report:
General comments
This paper reports study of seroprevalence and risk factors for having markers of viral hepatitis B and C among patients co-infected with TB and HIV, and assessment of adverse effects during treatment and outcomes of TB treatment in Thailand. The study has clear objectives, methodology is appropriate and well described, the Results are clearly presented and relate to the study objectives, the Discussion covers the main issues raised by the results, and the study limitations are clearly stated.
Taking into consideration that the data and analysis done are pretty solid, the article can serve as evidence for further studies, and all suggestions are minor and could be easily addressed, I recommend this article for publishing.

Specific comments
I. Minor Essential Revisions
Methods
1. On page 6, line 7 stated that patients received anti-TB therapy for <4 weeks before enrollment. Please clarify that this is during current episode of active TB.
RESPONSE TO REVIEWER: Yes, for the current episode of active TB. We have added the phrase “for this episode of TB” to this sentence.

2. Please provide detailed description of factors that were assessed in the study. For example, in Discussion on page 14 there was mentioned that no association was found between high-risk sexual practices (not using a condom, multiple partners) and HBsAg seropositivity, but in Methods, Results or Tables there is no mention of which exactly risk factors were assessed.
RESPONSE TO REVIEWER: In fact, high-risk sex practices and the relationship with HBsAg are listed in Table 2, including “had >4 sex partners in past 6 months” and “men having sex with men.” We did not list all factors in this table, however – only those that were statistically significant in bivariate analysis and included in final multivariate models. We have added sexual risk factors assessed to Table 1.

3. On page 8 under “Statistical analysis” term “saturated model” was used. Although some statisticians use this term for defining full model, the most accepted meaning of term “saturated model” is a model that has as many parameters as there are values of the independent variable. I advise to change this term for “full model”.
RESPONSE TO REVIEWER: Done.

4. Please provide definition of the “adverse event during TB treatment”. Please define adverse event “liver disease” reported in results/tables.
RESPONSE TO REVIEWER: The following sentence has been added to the Methods: “Adverse events were defined as any health-related problem that occurred during study follow-up, that was plausibly related to TB or HIV treatment, and that necessitated a physician evaluation. For adverse events, a definition of “liver disease” was applied to any patient who was diagnosed by a physician as having hepatitis, jaundice, or cirrhosis.”

Results
5. What was the median and range of CD4 counts?
RESPONSE TO REVIEWER: We have added data about CD4 (median and range) to Table 1.

6. Was the difference in median ALT, AST, and bilirubin at the beginning of treatment significant among patients reactive to HBsAg, anti-HCV, and both compared to non-reactive patients?
RESPONSE TO REVIEWER: The medians were not significantly different. We did not report a p-value, because the numbers are so similar and ranges clearly overlap substantially. This comment prompted us to re-analyze the data to examine the proportion of patients with elevated liver function tests in each subgroup. See comment below.

Discussion
7. Part of the second sentence in first paragraph of the Discussion on page 14 “Viral hepatitis markers were not strongly associated with elevated liver enzymes at the beginning of TB treatment…or the development of clinical hepatitis during TB treatment” is not supported by reported in paper study findings.
RESPONSE TO REVIEWER: The finding of clinical hepatitis is indicated in the Results and the Table. The lack of a strong association with viral hepatitis markers is shown in the Results when comparing the median liver-function tests according to all groups. We re-analyzed the data, however, to look at the proportion with elevated liver function enzymes (rather than just the median) and did find an association with HBsAg that was statistically significant. We have revised the sentence in the Discussion and in the Results to reflect this. The sentence in the Results now reads: “Of the 759 with available liver function test results, elevated liver function enzymes were found in 18/70 (26%) patients with HBsAg (p=0.02 compared to non-reactive), 37/236 (16%) patients with HCV (p=0.93 compared to non-reactive), 6/27 (22%) patients with both (p=0.42 compared to non-reactive), and 69/465 (15%) patients that were non-reactive.” We have removed the phrase in the Discussion that says “with elevated liver enzymes at the beginning of TB treatment.” We have modified the same phrase in the Abstract as well.

II. Discretionary Revisions
Introduction
RESPONSE TO REVIEWER: Done.

Methods
9. Please add dates when study was conducted (or move from Results to Methods).
RESPONSE TO REVIEWER: Done.

10. Please state under “Study settings and population” that study population included new and re-treatment cases of tuberculosis.
RESPONSE TO REVIEWER: We have added the following sentence: “Patients with previous history of TB treatment were eligible for the study.”

11. Please state if patients provided written or oral informed consent for participation in the study.
RESPONSE TO REVIEWER: We have modified the sentence in Methods to say: “Patients providing written informed consent were followed from TB treatment initiation to…”

Table 3
12. Please provide denominators for number of patients for whom assessment of immune reconstitution inflammatory syndrome adverse event was applicable.
RESPONSE TO REVIEWER: Done.

Figure 1
13. It is advisable to add percentages after absolute numbers of enrolled patients to enrollment chart.
RESPONSE TO REVIEWER: We have chosen not to do this, because the percentages needed for each reader are not always intuitively obvious. For example, some prefer to see the proportion of enrolled divided by all patients screened, whereas others prefer the proportion of enrolled divided by all patients eligible.
Reviewer's report
Title: Viral hepatitis and HIV-associated tuberculosis: Risk factors and TB treatment outcomes in Thailand
Version: 1 Date: 10 June 2008
Reviewer: Giovanni Rezza
Reviewer's report:
Major criticisms (compulsory):
I am not sure what is the meaning of identifying factors associated to HBsAg. In fact, only a relatively small proportion of those who become HBV infected will remain HBsAg positive. Thus, factors associated with HBsAg positivity may be either considered risk factors for HBV infection (i.e., exposure) or determinant of chronic HBV disease. This should be carefully considered and either modified in the study design (i.e. repeating the analysis taking into account also other HBV markers) or explained in the text.
RESPONSE TO REVIEWER: As noted in the Methods, we only measured HBsAg positivity, not any other markers for HBV infection. Therefore, we have incorporated this comment into the limitations section of the Discussion: “Only a small proportion of those who become HBV infected will remain HBsAg positive; thus, factors associated with HBsAg positivity may be risk factors for HBV infection or determinants of chronic HBV disease.”

Minor points:
In the 'Discussion' section, the authors showed higher rates of death and default among HBsAg+ individuals but this was mainly due to higher default rates and apparently not to higher death rate. Thus, an analysis restricted only to default should be presented. However, the results should better address this issue.
RESPONSE TO REVIEWER: We have chosen not to do this, because the results would not change our interpretation at all. Most readers prefer an analysis of death, because it is a hard (clearly adjudicated) endpoint. By including all unsuccessful outcomes (adding default) in an additional table, we see that unsuccessful outcomes are driven largely by default. Presenting a third table restricted only to the analysis of default would not add to our conclusions, and it would add to the number of tables that a reader needs to interpret. If the editors feel strongly about this, we can, however, add a table only examining risk of default. We have revised Table 4 slightly to make it easier to interpret, removing some of the comparisons that were non-significant and not discussed in the manuscript.