Reviewer's report

Title: Risk factors for treatment delay in pulmonary tuberculosis in HIV-infected individuals: a nested case-control study

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Reviewer: Anete Trajman

Reviewer's report:

The study raises a relevant question and the methods are adequate. A few suggestions are made below with the purpose of improving data analysis and clarifying the lessons to be learned.

Major issues

1. The definition of delay used in this analysis may be tricky. If the median time to diagnosis is very high, than many very long periods can be classified as not delayed", whilst if the median is very low, e.g. in a very good health service, many timely diagnosed cases would be classified as delayed. Although there is not a well-established ideal timing for diagnosing TB, since all patients in this cohort were already medically followed in these referral units, 41 days seem a very long period to be classified as “non-delayed”. I would suggest the authors to use different arbitrary cut-off values, starting from 7 or 10 days (eventually including 41 days) and analyze possible different associated factors. This could show different factors for different delays. They could start comparing the mean (or median) time to diagnosis to have a first idea on the magnitude of the differences between time according to the analyzed variables. Not all analyses need to be shown but should be mentioned. This would also show if their findings are consistent.

2. Exclusion criteria are only made clear in Figure 1. They should be described in the method section. Change of diagnosis and death without diagnosis seem reasonable exclusion criteria. It is, however, not clear why transfer out and default (thus treatment outcomes) were also considered exclusion criteria. I would recommend to include these patients in the analysis.

3. Some (most) of the relevant “risk” factors are actually associated factors, since they are not present “before” the diagnosis. Sputum smear results and symptoms are the best examples. The authors should thus consider calculating hazard ratios.

4. What is the frequency of the “regular” visits in theses referral centers? Depending on the frequency of these routine visits, patients’ delay could also have been addressed. Does the patient seek for medical help, i.e., an extra visit when they have unusual symptoms, such as cough or fever? If authors have access to these data, they should include in their analysis as separate periods (patients’ and health system delay).

5. When was CD4 measured and treatment for TB started? “At the time of
“diagnosis” means up to how long before? Or is it after TB diagnosis (which clearly not be a “risk” factor)? CD4 counts are deeply influenced by TB. This is an important issue to be dressed.

6. The discussion needs major revision. It should not be a simple comparison of each finding with the literature’s findings. Besides HIV infection, how can the differences in the health system organization influence the difference in the results of this and other articles, in other cities and countries? It is quite understandable that negative sputum smears delay diagnosis, but how do the authors explain that the presence of constitutional symptoms delay the diagnosis? Above all, what are lessons learned? What to the authors suggest in order to improve (reduce) the timing of diagnosis, based on Cain’s relevant findings? What to the authors suggest regarding drug users?

Minor issues

1. Title: It would be more appropriate to use the term associated – instead of risk-factors in a case control study.

2. Background:
   • First paragraph: incidence rate of 17/100,000
   • Please replace dots by commas to indicate thousands (100,000 instead of 100.000)
   • Third paragraph: “Several studies have addressed the problem of delayed diagnosis and treatment for TB in HIV-infected individuals”. Did the authors really mean in HIV-infected individuals? There appears to be a contradiction with the following sentence. Please clarify.

3. Methods:
   • Please explain and why the periods of observation were different in units.
   • How was CD4 categorized (should be in the definition of terms)? Age? Although it is clear from the tables, it should be described in the methods section.
   • Classification of alcohol use seems confusing. What about those who drink more than 4 days a week? Or those who drink 3 drinks 3 times a week? What was considered a “drink”?
   • What did the authors considered unemployed? How were retired, people with informal jobs, students classified?
   • Is weakness the same as asthenia? Please use the same term in text and table.

4. Tables:
   • Tables 3 and 4 show adjusted OR, not OR. I would suggest to show aHR. I would also suggest to change the reference variables to the more logical “protective” factor, such as having symptoms, having typical Rx, etc. This will ease the understanding of the measure of association.
   • Missing data (number and percentage) should be displayed, the totals are not always the same.

5. Discussion:
• More recent papers on factors associated to TB diagnosis delay in Brazil should be added to the discussion.

• Please do not repeat the methods in the discussion. The first paragraph is unnecessary, as is the explanation of the referral centers on the 5th paragraph.

6. The manuscript needs language review.

Level of interest: An article of importance in its field

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

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests