Reviewer's report

Title: Risk and Prognostic Significance of Tuberculosis in patients from The TREAT Asia HIV Observational Database

Version: 1 Date: 29 October 2008

Reviewer: Gavin John G Churchyard

Reviewer's report:

Major compulsory revisions
• The manuscript evaluates the prognostic value of TB on survival, which is dependant in part on the TB treatment outcomes. I suggest that a description of the TB treatment outcomes are included.
• A justification for including factors in the multivariate analysis that are potentially collinear, such as CD4 category, antiretroviral treatment and CDC category, should be provided.
• Even though only 58% of patients had at least one viral load during follow up, I would suggest having a second model that includes viral load as a variable and describing the results in the text

Minor essential revisions
I suggest adding words in () and deleting words in []

Abstract:
• Results – “At baseline 22% (of) patients were diagnosed (with) TB.”
• Conclusion: “Overall prognosis .... appeared to be similar to that following a diagnosis of (non TB) [other] ADI”

Introduction
• I suggest providing more recent statistics of TB and HIV in the Asia-Pacific region
• “Using data from (the) TREAT Asia HIV Observational Database....17 clinical sites in (the) Asia-Pacific region...”

Methods
• “Upon recruitment....(are extracted from) [required if available] in patient case notes.”
• A brief description of the criteria for starting ART and the regimens used should be provided.
• “(The) risk of [prospective] TB [diagnosis] among patients with prospective follow up was assessed using ...”
• “Antiretroviral therapy was included in the model following the intention to [continue] to treat principle”
• A description of the time split analysis and what is meant by “recent CD4 count” should be included in the paragraph describing the statistical analysis.
• The sentence about the sensitivity analysis can be dropped

Results
• Page 7, Paragraph 1. The sentence “TAHOD sites are encouraged....” should be moved to the methods section
• “At entry to TAHOD, 759(/3516) (22% of all patients)....”
• “... the median number of CD4 test(s) in each patient...”
• “412 (of the 830) not on ART at baseline and were started on treatment during follow up.”
• Page 7, paragraph3. Should be moved to the methods section.
• Among 3279 patients..., 135 (developed) [developing] TB, giving a TB (incidence) [diagnosis rate] of 1.98...
• The following sentence does not make sense. “Most of the TB diagnoses were definitive (92 of122, 75% 13 unknown), with 30 (25% presumptive.” There were 135 TB cases diagnosed during follow up. I assume the 122 refers to TB cases that had a definite or presumptive diagnosis and that the 13 patients with an unknown diagnosis did not meet the criteria for definite or presumptive but were started on TB treatment. If so, I suggest referring to this group as “possible” TB. If the diagnosis is truly unknown then they should not be included as TB cases.
• The percentages in the sentence starting “The most frequent cases were pulmonary TB...” do not add up to 100%.
• “Compared to patients who were not receiving ART.....within 90 days after (initiating ART) [treatment initiation]....”"
• “Compared to patients with CDC category A disease only, mortality was (greatest) [poorest]...”
• Be consistent in the use of abbreviations. ADIs rather than ADIS

Discussion
• “Much of the disparity (in the) [of] prevalence of pre-exisiting ADI...”
• “... consistent with data from other [cohorts in countries with] high TB burden (countries) in Asia and Africa.”
• “... by the (non) [none]-directional nature....”
• The sentence starting “” Although no data on rate of multidrug resistance,.....” is unclear.
• Provide a reference for the statement that treatment of latent TB infection in addition to ART may further reduce TB incidence (Golub JE et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. AIDS, 21: 1441-8, 2007)

Tables
• The number of patients not on ART differs in Table 1 (830) and 2 (918).
• Table 2 and 3. I would have expected the number of patients and person years
to decrease with duration of ART, not increase. Surely all patients that had more
than 361 days of treatment should also contribute time at risk to the period 0-90
days. Please explain
• Table 4. I suggest dropping table 4 as it duplicates a lot of the information in
Table 3 and the results of the combined variables are included in the text.

Discretionary Revisions
• Was TB drug resistance data collected? If so, I suggest including
• It would be of interest to also do an as treated analysis and compare TB
incidence among patients that stop ART to those that continue ART although the
effect of stopping ART would be captured by CD4 category as a time dependant
variable
• Provide information on what proportion of patients defaulted treatment or
switched regimens?
• As concluded in this manuscript ART results in incomplete
immune-reconstitution. However, the CD4 category as a time dependant variable
includes time at risk from the pre-ART and post ART periods. It would be of
interest to see if TB risk in each CD4 category differs by whether patients are on
ART or not?

Level of interest: An article of importance in its field

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