Reviewer’s report

Title: The complex relationship between human immunodeficiency virus infection and death in adults being treated for tuberculosis in Cape Town, South Africa

Version: 1
Date: 26 December 2014

Reviewer: Jacquie Firth

Reviewer’s report:

Major Compulsory revisions:

• Are the discussion and conclusions well balanced and adequately supported by the data?

Unfortunately, it is difficult to say that the conclusions are adequately supported by the data – the author seems to be conflating an elevated risk ratio of mortality associated with HIV at a certain age or with a differing impact of HIV in different age groups. The statement “health systems need to focus attention on young patients with HIV, especially women, as they are at very high risk of death on treatment” implies that older persons are less likely to die from TB when in actuality, it just the gap in mortality rates between those dying who did and did not have HIV that is relatively smaller. In table 1, the authors clearly show that relative mortality rates for older persons are 21.1% (HIV+) vs 15.8% (HIV-) as compared to the rates among younger persons which were 4.4% (HIV+) vs. 0.9% (HIV-).

This is logical as younger HIV-uninfected patients with TB are generally unlikely to die as they are easier to diagnose and tend to do well on treatment. Older HIV-uninfected patients with TB would be expected to have a higher mortality than younger patients (due to TB or other factors – clearly shown by the authors own RR of 9.16 for cases >65 years compared to 15-24yo) - thus the risk ratio between the HIV infected and uninfected in the older age group would be smaller, not because HIV has "less of an impact" in older people, but because the mortality rates in the comparison group (HIV uninfected) are higher at baseline. Also, it should be noted that many of the >65yo patients who died had an unknown HIV status (8.6% vs 3.7% in the 15-24yo).

Rather than suggesting that health systems focus more on younger patients rather than older ones, it would be more logical (and defensible) to emphasize that improved HIV prevention efforts could prevent deaths among young TB patients, as most young TB patients will not die during treatment except those who also have HIV. Also, one could use this data to point out the increase risk of death associated with HIV in patients with TB can be mitigated by ensuring that all patients with TB are tested for HIV and started on HIV treatment as soon as possible (ideally 2 weeks after starting TB treatment unless they have TB meningitis).

Additionally, the authors state that "it is satisfying to see a falling mortality rate
during the four year study period” – however the data covers only a 3.5 year period because data in 2012 only go until June, therefore this year cannot be justifiably compared with the others. Furthermore, even if p values are provided to show that the decreased mortality is actually significant from 2009 to 2011, a drop in mortality from 5.5% to 4.5% could just be a fluctuation, and the mortality rate in 2012 could conceivably go back up if the full data for the year were available. Thus, I don’t think it’s reasonable to be very “satisfied” with this finding, although it is fair to present the data with the statistical analysis and hope that the trend continues downward.

Minor Essential Revisions:
• Are limitations of the work clearly stated?
  o The limitations of the work are stated relatively clearly, although the authors do not address the question of how their findings might have been changed if they were able to know the mortality rate among the patients who defaulted or were lost to followup (neither the methods section nor Figure 1 show any patients being excluded for defaulting but the conclusions state that they were excluded). They authors also might have discussed the potential change in findings if they were able to know the HIV status of the patients whose status was unknown. Sensitivity analyses might have been helpful to address both of these questions, as both could have a significant impact on the findings presented and consequently the conclusions.

• Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
  o Yes, although the references section needs a little attention (esp refs 2, 3, 13, 17, 26 – missing full page refs)

• Do the title and abstract accurately convey what has been found?
  o The title implies a level of “complexity” that I think is overstated in the conclusions (see major revisions above), and the abstract reflects this as well.

Other Comments:
• Is the question posed by the authors well defined?
  o Yes, the question is well-defined.

• Are the methods appropriate and well described?
  o Yes, the methods are well-described, however, the authors do not describe how they classified patients who defaulted or were lost to followup (included as alive?) and how many patients were excluded for lack of data.

• Are the data sound?
  o The data appear to be sound (I did not repeat the analyses, but they reflect similar findings from other studies).

• Do the figures appear to be genuine, i.e. without evidence of manipulation?
  o The figures appear to be genuine, again reflecting what one would generally
expect from this data

• Does the manuscript adhere to the relevant standards for reporting and data deposition?
  o I am unclear on what is meant by “data deposition”, but the presentation of the data appears to conform to usual standards.
• Is the writing acceptable?
  o The writing could use some grammatical editing for clarity but is overall acceptable.

**Level of interest:** An article whose findings are important to those with closely related research interests

**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