Reviewer's report

**Title:** Predictors of Serological Failure After Treatment in HIV-infected Patients with Early Syphilis In the Emerging Era of Universal Antiretroviral Therapy Use

**Version:** 2

**Date:** 27 October 2013

**Reviewer:** Michael Horberg

**Reviewer's report:**

Below are MAJOR COMPULSORY REVISIONS:

Overall: This paper discusses important issues in HIV and syphilis care. However, certain issues with the paper limit its utility and ability to be published as written. The first issue is the power. By the authors own admission, some of the outcomes discussed were underpowered so their lack of findings may be an issue of power only. As such (for example, the finding of 1 injection vs. 3) should NOT be included in the abstract or the conclusions and little mention given. This leads to the question of power for the other outcomes. As such, the data analysis section in the methods section should include the power analysis for all of the outcomes listed.

Second issue is the definition of early syphilis. Most clinicians would not include secondary syphilis as early syphilis, unless the time course is clear. The authors need to define early in the paper (and likely in the abstract) how they defined “early syphilis” and their justification for this definition.

Third, it’s unclear to me why the authors excluded patients who were treated, had successful therapy (by their definition) and then had a rise in RPR titers. I think most could consider these treatment failures and not necessarily re-infection. These need to be re-classified and not excluded either. In fact, a sensitivity analysis of the excluded patients and their effect on results would be most beneficial, given the power issues discussed above.

Fourth, I am concerned about the conclusions drawn about patients with initial titers of #1:16. By definition, many could not have a four-fold decrease in titer easily over time. Some studies have handled this group separately or made the definition that these need to go to negative for meeting treatment success criteria.

Thus, I think the authors need to make major revisions to their manuscript if to be considered for publication in this journal.

Other specific comments:

Abstract:

Background: Why “useful to know”? This is stated as a fact and the need for this should be made more explicit.

Methods: Define early syphilis here (and in introduction).

Results: (and may relate to rest of paper): previous h/o syphilis” is listed as a
reason for failure. So these were reinfection or recurrence of previous infection, which likely would behave differently. These patients need further description (like were they all RPR undetectable prior to inclusion in cohort, etc.)

Conclusions and Results: Should NOT include any results for which the study was underpowered.

Introduction (other than above):

Lines 100-101: Distributor shortage is from 2003. This is old. Either delete or find more recent reference to such an occurrence.

Methods:

Line 129: These patients, as mentioned above, could be recrudescence and not new infection.

Line 142: How was age cutoff of 34 chosen? This seems very arbitrary.

Lines 154-156: Discussed above.

Discussion:

Lines 201-202 and generally: There are many references in the literature, but not included here, that also discuss comparisons to HIV- population and have larger sample size than this study. They should be considered and thus claim in line 201-202 should be amended.

Line 261: Being retrospective is not necessarily a limitation. Being underpowered is.

Line 267-268: Give at least one example of an unmeasured confounder that would make this statement valid.

Line 271-272: Delete.

Answers to Specific BMC Questions:

1. Is the question posed by the authors well defined?
   Yes.

2. Are the methods appropriate and well described?
   Described well—yes. Appropriate—please see above.

3. Are the data sound?
   Please see above.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Please see above.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   Please see above.

6. Are limitations of the work clearly stated?
   I think these need revision as described above.
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes

8. Do the title and abstract accurately convey what has been found?
Abstract needs revision as described above.

9. Is the writing acceptable?
Yes.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interests.