Reviewer's report

Title: Improved Virologic Outcomes over Time for HIV-infected Patients on Antiretroviral Therapy in a Cohort from Rio de Janeiro, 1997-2011

Version: 2 Date: 14 March 2014

Reviewer: Anna Schultze

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Minor Essential Revisions

1. Introduction, Paragraph 2: Use of language “Given the importance of maintaining virologic suppression for assessing response to treatment and decreasing HIV transmissibility” – would reformulate, as this sentence seems to imply that one of the primary reasons for maintaining VL suppression is to allow the response to treatment to be measured. Clearly the main importance of maintaining VL suppression is because this reduces the risk of clinical progression, AIDS and ultimately death.

2. Materials and Methods, Study Population, Paragraph 1: Use of language “dates prescribed” should read “prescription dates”.

3. Materials and Methods, Study Population, Paragraph 2: Spelling mistake “PI-based regimens were defined a PI plus” should read "PI-based regimens were defined as a PI plus”

4. Materials and Methods, Study Population, Paragraph 2: Spelling mistake “Patients initiating on non NNRTI- or PI-based..” should read “Patients initiating on neither NNRTI- or PI-based..”

5. Materials and Methods, Study Population, Paragraph 2: Grammatical clarification “…with a documented date of death or through December 31, 2011” could benefit from reading “…with a documented date of death or was put as December 31, 2011, whichever occurred first”.

6. Materials and Methods, Variables of Interest, Paragraph 2: Justification and/or clarification needed regarding how ART regimen per calendar year was determined. Considering that RNA values were taken at the mid-point of the year, what was the rationale for not just using the ART regimen a patient was on at the time of the relevant RNA measurement? If I understand it correctly, the current definition could lead to instances like this: If a patient had an RNA measurement from June 1st included in the analysis, and was on a PI regimen from April 1st to July 1st, but on an NNRTI regimen from July 1st to December 31st –this patient would be classified as being on an NNRTI regimen for that year (because more months were documented on an NNRTI regimen), but in fact the RNA measurement included in the analysis was taken while the patient was on a
PI regimen. If this is indeed the case, it would be good to know why this approach was taken (rather than just using the drug information at the time of the RNA measurement), and potentially also interesting to know if changing the approach to drug classification would actually change the number of people classified as being on a PI/NNRTI regimen.

7. Materials and Methods, Statistical Methods, Paragraph 2: It is described how missing covariate data is dealt with (imputation) but not how missing outcome data is dealt with (although from Table 2 it becomes clear that these patients were excluded for the years where they had no RNA data). Would make this explicit in the methods.

8. Materials and Methods, Statistical Methods, Paragraph 2: Grammatical mistake. “Sensitivity analysis assuming all missing virologic outcomes as detectable..” should read “A sensitivity analysis assuming that all virologic outcomes were detectable..”.

9. Results, Demographic and Clinical Time Trends, Paragraph 4: Clarification needed. “The median duration of ART interruption was 7 [4-12] months..” – does this refer only to continuous ART interruptions? If not, would perhaps be good to rephrase this to avoid the use of “duration”, as the variable was constructed from potentially non-continuous months of no ART. Eg “The median number of months spent off ART per year was 7”.

10. Results, Demographic and Clinical Time Trends, Paragraph 4: Clarification needed. Demographics of patients with at least one ART interruption were compared to the overall cohort characteristics, but as 74% of the cohort had at least one ART interruption this seems a little bit redundant. Would be more interesting to see how characteristics differed between patients who had at least one ART interruption vs those who had none.

11. Results, Demographic and Clinical Time Trends, Paragraph 4: Clarification needed - “Patients contributed a total of 7,278 viral load outcomes with a median of 1 [0.8, 1] viral load measurement per patient per year”. Not sure I understand the rational of including the median number of measurements for VL per year when by definition a patient could only have 1 measurement per year? Would probably leave this out or just mention the % with missing VL outcomes overall.

12. Results, Factors associated with undetectable viral load, Paragraph 2: Use of language. “the factors most negatively associated with” should read “the factors most strongly negatively associated with”.

13. Results, Factors associated with undetectable viral load, Paragraph 2: Use of language. “There was a decreased odds of achieving undetectable viral load per each year increase in time since HIV diagnosis” should read “The odds of having an undetectable viral load decreased with each year since HIV diagnosis”.

14. Results, Factors associated with undetectable viral load, Paragraph 2: Use of language. “had an increased odds of being undetectable” should read “had an increased risk of being undetectable”.
15. Discussion, Paragraph 2: Use of language “… ART interruptions may be secondary to” could benefit from reading “ART interruptions may be a consequence of”.

16. Discussion, Paragraph 5: Use of language “Those differences in outcomes may be attributable to” could benefit from reading “This may be attributable to”.

17. Discussion, Paragraph 7: Use of language “did not change overall time trends” should read “did not change the overall time trends”.

18. Conclusions, Paragraph 1: Spelling mistake “publicly-run” should read “publicly run”.

19. Conclusions, Paragraph 1: Clarification needed “of an entire community” – the results are probably representative of some communities in Brazil, but not others. Would rephrase.

20. In Table 2, grammatical mistake: “1,00 (reference)” should be “1.00 (reference)” – a full stop instead of a comma.

21. In Table 2, description: “Time-update variables” should read “Time-updated variables”.

22. Table 1. Number of decimal points used in these p-values are different from those used in Table 2 – would suggest to use same number of decimal points.

23. Throughout the manuscript the authors use the phrases “achieving an undetectable VL” and “being undetectable/having an undetectable VL” almost interchangeably. Personally, I would stick to the latter description. Patients only achieve an undetectable VL when they move from detectable to undetectable, whereas in this analysis patients who achieve an undetectable VL in year 1 and then stay undetectable are retained in the analysis until the end of FU. Technically, the paper therefore describes factors associated with having an undetectable VL, rather than factors associated with achieving an undetectable VL.

24. Similar to my point above, the phrase “ART-naïve patients” is used throughout to describe the study population, but as patients were included for several years and allowed to have treatment interruptions, the analysis also included patients who were no longer naïve or had experienced virological failure. So if I have understood it correctly, the descriptions of RNA and CD4 counts over time are not for ART naïve individuals (as indicated in Materials and Methods, Variables of Interest, Paragraph 1), but of individuals who started ART for the first time between 1997 and 2011. To me, it would make more sense to just mention that individuals were included from the first start of ART once in the methods, and then avoid describing the cohort as ART-naïve.

Discretionary Revisions

1. Results, Factors associated with Undetectable Viral Load, Paragraph 1: Use of
language. “The following variables within the Risk Group and Pre-Treatment CD4+ categories had significant negative associations with the outcome only in the unadjusted model respectively:” could benefit from reformulating.

2. Discussion, Paragraph 1: “In particular, the introduction of newer drugs and drug classes in Brazil, such as raltegravir, darunavir, etravirine and enfuvirtide, within the ART guidelines for salvage therapy, and resistance testing to guide regimen changes after treatment failure have undoubtedly played a role in the observed improvements over time” could benefit from reformulating.

3. Table 2: I would not bold the lines where the p-value is less than 0.05 (the negative findings, such as ethnicity not being associated with lower odds of achieving virological suppression, are also of interest).

4. Table 1: I would suggest having an N instead of the # symbol – and repeating the % sign throughout the table is somewhat redundant when it is specified in the heading that it is a percentage.

5. Throughout tables: Would ensure that same number of decimal points are used (ie if 2 decimal points are used, make sure tables say 0.50 rather than 0.5).

6. I would personally prefer to see the actual p-value unless it is very small (p<0.001), rather than p<0.05 or p<0.10 throughout the manuscript.

**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:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests