Reviewer's report

Title: Relationship between combination antiretroviral therapy regimens and diabetes mellitus-related comorbidities among HIV patients in Gaborone Botswana

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Reviewer: Emmanuel Adewuyi

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Relationship between combination antiretroviral therapy regimens and diabetes mellitus-related comorbidities among HIV patients in Gaborone Botswana

General comment

This study aims to investigate the association between combined antiretroviral regimens, diabetes mellitus/other metabolic disorders. It is an important study which has the capacity to contribute to the available evidence on antiretroviral-metabolic disorders comorbidities. The study was well designed, written and easy to understand. However, I have some concerns which may help to improve the quality of this paper.

Background section needs to include more information.

- A sentence or two need to be written about combined antiretroviral therapy. For example, what are combined antiretroviral regimes, what are first, second and third line regimens, do authors need to mention/talk about HAARTS?

- A little more information is required on diabetes-related comorbidities. What are they? Is there a better term to describe them?

- Some information is needed on how diabetes-related comorbidities contribute to decreased life expectancy among HIV patients on antiretroviral therapy. For instance, comorbidities are associated with increased treatment costs, complicated management plan, etc., which may result in poor prognosis. Any biological mechanism underpinning this?
- Can authors provide a bit information on the epidemiology of HIV in Botswana?

- Please, check to ensure punctuation are correctly used throughout the manuscript. For example, page 5 line16 - 17, page 14 line14 - 15.

**Methods**

- Can the authors separate study design and data collection into sub-sections for clarity?

- Also, can the authors provide a sub-section describing the variables included in this study and justify the selection of the variables? For example, the variables may have been selected following the example of previous studies or using a conceptual framework.

- Page 7 line 43 - 44, why did the authors use the cut-off point of $p \leq 0.9$, any reference to support the use?

- Why was age categorized as < 35 and $\geq$35 years? Any reference to support this categorization? This is partly why there is a need for a section to describe the variables examined in this study so they can be adequately and appropriately described.

- What system of BMI was used in this study (WHO international?), and what are the values for "underweight", "normal", "overweight" and "obese"?

**Results**

- "Age as a continuous variable did not enter the multivariate model as it did not achieve a $p < 0.05$" (page 13 lines 2 - 5). What do the authors mean by this sentence as it was already stated that the cut-off point of $p \leq 0.9$ was used in selecting variables for modelling?

- Authors reported results for Kapler Mier (log-rank test) but did not mention or appropriately describe this in methods.
Discussion

- Patients on second and third line regimens were found in this study to have less risk of developing diabetes-related comorbidities compared to their counterparts on first line regimen. Protease inhibitors are parts of second line and previous studies have mainly implicated them in causing metabolic-related comorbidities. Hence, the findings in the present study appear not to agree with some of the popular opinions in the literature. Authors need to explain their findings well, compare same with previous studies and explain what may contribute to the findings.

- Any insight into the mechanism(s)/pathway(s) underlying the association found between antiretroviral regimens and diabetes-related comorbidities reported in this study? For instance, not all patients developed diabetes-related comorbidities, could genetic/other factors play a role in the association?

- Page 15 lines 13 - 30, the discussion in this paragraph is not clear. "Tenofovir or AZT can be used as the first-line regimen. It is important to discuss (in the background section) what first, second and third line regimens are. Then, authors need to make this paragraph clear.

- Some important findings in this study were not discussed:

  i. adherence to regimen increased the risk of developing diabetes-related comorbidities. This needs to be discussed and compared with findings in previous studies

  ii. finding in respect of CD4 count should equally be discussed

  iii. overweight increased the risk of diabetes-related comorbidities while underweight decreased it, any explanation?

- Page 14 line 44 - 45, change "outstanding" to something else, e.g "important", "notable".

Conclusion

- Based on the data analyzed in this study, can a causal relationship be established? This will need to dictate the conclusion. I will expect to see this stated in the study limitation section and reflected in the conclusion drawn in this study.
Tables
- Table 1 and 3 legends, change "Hazard R" to "HR" for consistency as done in Table 2
- Can we have variables adjusted for in the multivariable analysis listed under Table 3
- Page 12 line 42 - 43, "cART (cART line2/3)" not found in Table 3. Instead, "cART line 2 +1" was written. Authors need to clarify this.
- How do the "unadjusted" results on Table 3 differ from those in Table 2? If not different, why the repetition?

Abbreviations
- Let this be in alphabetical orders
- Please, define terms in full on first appearance in-text, for example, "HIV" page 4 line 1 - 3, "ICD - 10" page 5, line43 - 45. Please, correct throughout the manuscript.

References
- Authors made important statements without referencing, for example, "All these regimens have been to some extent, in different settings, associated with the development of DRCs after some time of exposure" page 4 line 45 - 50. Another example, "While WHO states that treatment programs using Tenofovir or AZT are promising, they may not be the ultimate solution to alleviate the situation since both drugs are known to be expensive and yet to some extent associated with DRCs." Page 15 lines 15 - 23. Please, correct throughout the manuscript.
- Please, check reference number 5, 6 and 12 with respect to their use in page 4 lines 50 - 55. It appears 5 and 6 were not quoted in context. For example, in reference 5, protease inhibitors (indinavir) was the drug implicated and not all the drugs given that the patient had been on nevirapine and combivir® (lamivudine + zidovudine) without dysmetabolic syndrom. Similarly, in reference 6, efavirenz and protease inhibitors were implicated. Please double check and clarify.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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