Reviewer’s report

Title: Association of Knowledge on ART Line of Treatment, Scarcity of Treatment Options and Adherence

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Reviewer: Miguel Lanaspa

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Full title: Association of Knowledge on ART Line of Treatment, Scarcity of Treatment Options and Adherence

Dear Authors,

The manuscript presents interesting results about knowledge and adherence to antiretroviral treatment as an important factor that could be object of measures aiming to improve adherence. The translation of the results into policy is very straightforward and is one of the main values of this manuscript. However, there are some concerns that I will list as follows:

1. The introduction clearly states what is known (adherence is associated with virological suppression, adherence is needed for the success of therapeutic and preventative measures based on ART, adherence is not always optimal). It is however a little unclear about what is not known, or at least the statement "It is not understood whether patients who are fully informed…" is too general to be true. There have been publications showing that knowledge is associated with adherence (some of them even cited in this manuscript). I would suggest to clearly specifying the added value from this study compared to others already published studies: is it the information about limited availability of ART lines? Is it the epidemiological / geographical context? Is it the study design?

2. Related to the previous point, the second paragraph of the introduction is a bit confusing and some ideas are repeated. Clearly explaining the added value of this study may help making this second paragraph more useful.

3. The Methods section is quite clear. I would only try to be more specific in terms of definitions, and in justifying some the decisions regarding the definitions. In particular:
a. Is the good adherence (fewer than 2 missed days per month) / poor adherence definition stated in page 7, line 10-15, a standardized definition in ART adherence or an institutional / national one?

b. Is the percentage adherence calculated over the last 24 months a standard definition or a study-decided definition? This is an important issue of the manuscript, because recoding the variable cumulative adherence the way it is described (months with good adherence/24 months) may not be directly related to the everyday adherence. A patient forgetting/missing only 2 doses every month would have a cumulative adherence much lower than someone who does not take any single pill one month out of two and is very compliant on the next month. In brief, I am not sure this way of recoding the variable is associated to poor virological outcome.

c. If this recoded variable is widely used, please state so and clarify the nomenclature (percentage adherence vs cumulative adherence?).

d. The cut-off for optimal and sub-optimal cumulative adherence is defined at 95%. Is this an extrapolation of the 95% adherence required to be virally suppressed stated in the first paragraph of the introduction?

e. At the end of the methods section under statistical analysis, the authors mention reasons to perform a sensitivity analysis with different cut-offs for cumulative adherence. I am very confused with this part of the manuscript. Is the statement "Due to the lack of variation in plasma viral load when adherence is between 90% and 100%..." based on data from this study or in general? If it is a general finding, then the cut-off of 95% does not make sense and a more meaningful cut-off should be chosen. If it is a finding from the patients of the present study, then it would not be reasonable to change a cut-off that is commonly accepted and based on outcomes from larger studies. The third possibility is that the cumulative adherence as recoded in this manuscript is not associated with the viral load because the definition is flawed, or the methodology to record this variable is not accurate.

The second part of the justification for the sensitivity analysis ("recent finding that showed for drugs with longer half-lives such as NNRTI the preferred adherence of \( \geq \) 95% is not necessary to achieve viral suppression") contradicts the introduction.

I would suggest choosing a definition for adherence that is widely accepted and that makes biological sense (cut-off associated with different viral or clinical outcomes) and keep it throughout the manuscript.

f. The definition of knowledge is unclear as well. If I understood correctly, the variable "knowledge" is defined as "Yes=1" if the patient knows the line he is on (first or second line) AND if he knows the available lines are limited, and it is defined as "No=0" if he doesn't know neither of those data. What does "knowing the options are limited" imply?
That getting the second line is difficult? That there is nothing available if the second line doesn't work? That the resources are generally limited? It strikes me that apparently there are no patients able to answer to only one of the two components of the "knowledge" variable.

4. The results section is a little bit repetitive with similar results from the descriptive, bivariable and adjusted analysis, which are also on tables 1 and 2. General data for the descriptive to have a sense of the study sample, and results from the adjusted analysis should suffice. In general, adding comments of point estimates that change substantially from the crude to the adjusted analysis is very useful to identify confounders and to explore possible effect modifiers. Here, the crude and adjusted estimates are almost the same for all the variables, suggesting that the variables included in the model were not confounders of the main association (knowledge-adherence), or that their confounding effect is compensated by the confounding effect of other variables. In any case, the crude (or more worryingly, the adjusted) analysis does not add anything relevant.

I would delete the sensitivity analysis at the end of the results section and in table 3. I feel that the justification for conducting it is not sound enough, and the interpretability and interpretation of the results is absent. If there is really an association between knowledge and adherence, why is it that this association is lost when using 90% as cut-off, but not when using 85 or 95%? One would expect that different cut-offs would have different misclassification rates that could explain lack of apparent association, but in this case it is not clear why should misclassification be more frequent using the middle value as cut-off.

5. Discussion: I disagree in general with the interpretation of the results. Most of the confidence intervals include 1, which should be considered as not statistically significant according to the methods section. In other words, differences found could just happen by chance. Moreover, the point estimates show an association that cannot be defined as "being much more likely", or as "an important indicator". The point estimates show that patients with knowledge were 10% more likely to be adherent than the rest, which could represent an important result (basis for education as adherence improvement) but it is not a huge difference.

I agree that selection bias could not be ruled out, but not because this is a secondary data analysis, but because selection of participants has not clearly been defined. What does "convenience sample" mean in this study?

Finally, even the cross-sectional design does not allow providing direction of associations, some of them are biological sound and should be taken into account. For example, "Plasma viral load continued to be associated with good adherence to ART" in page 10, line 15, should be stated the other way around.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
No

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Are the conclusions drawn adequately supported by the data shown?
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