Reviewer’s report

Title: Factors associated with first-line antiretroviral treatment failure in adult HIV-positive patients: a case-control study from Ethiopia

Version: 0 Date: 11 Feb 2019

Reviewer: Iñigo Sagastagoitia

Reviewer's report:

General:
In general well written and easy to understand. There are some limitations which may invalidate some conclusions. Before submission revision should be done and several minor limitations included. Discussion should answer an important query.

Major:
Background:
-No major querys

Methods:
-Study design is adequate a priori for a case-control study but results show on the multivariate analysis that the highest risk for treatment failure is TB coinfection and this could be biased as only 9 out of 182 patients in the control group were under treatment for TB. Out of 3238 possible controls this should be revised as conclusions could differ if more controls were coinfected by TB. TB coinfection is under-represented in the control cohort.
-Drug resistance data is not available. This is a major query for an obvious reason and could bias conclusions.
-Questionnaire was cross checked for consistency, piloted and modified but not validated.

Results:
Persistent diarrhea was associated with ART failure in the univariate analysis but not in the multivariate. The number of patients with persistent diarrhea is not available in Table 1. The main factors that have been previously proved to be associated with virological failure are treatment discontinuation, poor absorption, drug interactions and drug resistance. Poor absorption was not determined. This could have been defined by the combination of persistent diarrhea and wheat as main diet (which accelerates bowel transit), as they are both registered.

Discussion:
-You state that the major limitation is you could not differentiate whether TB coinfection was a risk factor or manifestation of treatment failure but your results show on the multivariate analysis that the risk of treatment failure is higher in the setting of TB coinfection than in those who discontinue treatment and that should be a major issue to be mentioned in the discussion as ART is the Key to success no matter what viral load nor CD4+ count.
Minor:
Background:
Switching to second line therapy does not necessarily mean a less effective therapy, as a WHO first line could include AZT and EFV plus a third drug and a second line for that patient in case of failure would include Tenofovir and a PI which is a better therapy in terms of genetic barrier and toxicity.

Results:
AZT based regimen was associated with treatment failure in the univariate analysis but not in the multivariate (close to statistical significance p-value 0.07). Actually in Ethiopia one of the recommended ART first line regimens is AZT+3TC+NVP as it has been associated with low treatment failure. Table 1 does not include the difference between groups in AZT exposure. Is it well represented?

WHO stage 4 was associated with treatment failure in the univariate analysis but not in the multivariate. Table 1 does not include this data.

Discussion:
TB coinfection indicates AIDS; as in your study it has been associated with treatment failure in high and low income cohorts. ART must be tailored in such setting in order to avoid drug interactions (we assume this was done), so this possibly has not been determinant as safe regimes have been published in the different guidelines. Treatment adequacy could be revised.

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.

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