Reviewer's report

Title: Virologic versus immunologic monitoring and the rate of accumulated genotypic resistance to first-line antiretroviral drugs in Uganda

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Reviewer: Maurizio Zazzi

Reviewer's report:

1. [minor essential revision] Abstract. The sentence “Samples from VLM clients at 12, 24 and 36 months and IM clients with VL>2000 copies/ml (36-40 months) underwent genotypic drug resistance testing.” is unclear because it is stated that IM clients did not undergo viral load monitoring. Probably the sentence should read “Samples from VLM clients at 12, 24 and 36 months and IM clients at 36-40 months with VL>2000 copies/ml underwent genotypic drug resistance testing.”

2. [major compulsory revision] Page 5. The VLM group is presented as a nested cohort within the routine care clinic, i.e. nested within the IM group. Inclusion in the VLM group does not appear to be randomized and could be subject to biases. In particular, regular attendance at clinic visit and willingness to be followed for at least two years are indicated as inclusion criteria. This can be associated with better adherence to treatment with respect to the IM group and have an impact on the results and interpretation of the study. Are there any available indicators that this is not the case?

3. [major compulsory revision] Page 5-6. It is unclear whether follow-up included only those patients not changing their first-line regimen, please clarify here rather than giving this information later in the last paragraph of the Results section. The rate of treatment change or discontinuation must be clearly reported since it is a relevant information possibly impacting the performance of virological vs. immunological monitoring.

4. [major compulsory revision] Page 6. The authors compared HIV genotypes obtained at the first occurrence of VL >2000 copies/ml in the VLM group with those obtained at 36-40 months in the IM group. I understand the limitations imposed by the study setting however this design does not appear to be correct. Development of drug resistance is analyzed at very different time points in the two groups and hence any comparison can be misleading. For example, some mutations in the VLM group appear to be more prevalent at earlier time points (e.g. TAMs and M184V).

5. [minor essential revision] Page 6. Since there are only two groups, why not to use the Mann–Whitney U-test instead of the Kruskal-Wallis test?


7. [minor essential revision] Page 8. “Very few VLM clients developed any resistance to the nucleoside reverse transcriptase inhibitors (NRTIs).” I suggest
to rephrase because M184V is indeed an NRTI mutation.

8. [major compulsory revision] Page 10. The authors make the reasonable hypothesis that the lower prevalence of drug resistance mutations detected at treatment failure in the VLM group may have resulted from “frequent VL monitoring and ability to detect and allow caregivers to discuss adherence and possibly switch to second-line regimens”. However, only 26 patients were switched to a new regimen during the 36-month study period which makes the above argument weak. The implications may be relevant because if more effective counseling and improved adherence is the explanation one may wonder that implementing better counseling could achieve the same results as employing virological monitoring. The authors should comment on this possibility.

Level of interest: An article of importance in its field

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