Author’s response to reviews

Title: Five-year trends in treatment changes in an adult cohort of HIV/AIDS patients in Ghana: A retrospective cohort study

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RESPONSE TO COMMENTS FROM REVIEWERS

Fred Stephen Sarfo (Reviewer 1):

1. Author should consider a different phraseology for "HAART initiators"? They could consider "subjects initiated on HAART".

Response

This has been done.

2. Table 1: AZT/ETC/NVP: Please consider changing ETC to 3TC

Response

The comment has been addressed.

3. Table 1: Please provide p-values for comparisons of WHO stage, Age groups, gender, and initial treatment for the years under consideration
Response

This information has been provided.

4. It is not clear from the manuscript whether adjusted Hazards ratios were calculated to identify independent predictors of treatment change. Authors should please provide adjusted analysis

Response

This has been done. Table 2 now provides for both crude and adjusted hazard ratios.

5. Loss to follow up rate is important as are reasons for therapy changes but are not available

Response

The data we used did not capture loss to follow up distinctly and so it was difficult to separate abscondees (and unknown deaths) from those who were discharged to their original treatment sites. A statement to that effect has been made as limitation to this study.

6. It is not clear to this reviewer why authors didn't just break down ART into an NRTI backbone of D4T+3TC, TDF+3TC/FTC, AZT+3TC and then the NNRTI into NVP and EFV to conduct their analysis. Are all their HAART combinations provided as fixed dose combinations? If not so, they should consider re-doing the analysis to show rates of change of D4T-, AZT-, and TDF-changes as well as EFV-, NVP-based changes. This may highlight their central message of declining D4T use in their cohort and provide clinically relevant information for clinicians and policy makers.

Response

Throughout the results we have described just what you are asking us to do, that is to analyse the HAART as NRTI combinations as d4T, ZVD and TDF backbones. HAART is always a triple therapy and must be captured as such. Furthermore, the Kaplan-Meier (K-M) curve in Figure 3 is a compilation of the NRTI backbone combinations. A second K-M curve of NNRTI has been
added as Figure 3B to further address your comment. With a sample size of almost 4000 we felt it was large enough, and would be good to show all the major HAART combinations, hence the disaggregated HAART regimens on Table 1. This gave a clear picture of the major subgroups on HAART at the treatment centre. From such disaggregated information one can always calculate the proportion on a d4T, ZVD, or TDF backbones. If we should aggregate this it would be impossible to have this information. Again, it must be mentioned here that each major treatment option is unique in itself.

7. Consider improving the quality of figures

Response

This has been done.

Seth Inzaule (Reviewer 2):

Major comments

1. It is not clear whether the objective of this study was to assess the determinants for treatment modifications as indicated in the background and cover letter. Indeed this could have been a key finding of public health significance as understanding the reasons for this changes would give direction for public health response. At the moment the paper seems to have mainly shown the trends of response to the WHO guidelines for treatment change from stavudine-based regimens. If this is the main focus as is also seen in the discussion then perhaps the authors would revise the article in this direction as it appears that they were limited to assess both the reasons and the determinants for treatment modifications. I would also suggest that the authors also report the exact switches that were made. This would also help distinguish between treatment modifications due to the guideline change, other toxicities in the drug combinations, TB-coinfections or other drug-to-drug interactions as well as switches due to treatment failure.
Response

Table 2 has provided for both crude and adjusted hazard ratios to address this comment. Further information has been given in the discussion to address these comments.

2. In addition it would be good for the authors to also revise their analysis to reflect the adoption of the guideline changes. In the current analysis, the time on treatment and the Kaplan-Meir analysis are discussed as being random events while in reality they were triggered by a change in the guidelines. If this is not taken into consideration it confounds the interpretation of the analysis.

Response

The way we conducted this research it would be difficult to adjust for a policy intervention like the one we have now. It would have been easier if we had done an interrupted time series analysis. We have addressed your concern and discussed it thoroughly, which in our view prevents leading to wrong interpretation.

3. The authors note that disease severity was associated with increased treatment change. This possibly suggests that such patients were either at risk of side effects or drug contraindications due to opportunistic infections. In general this highlights the need for information on the exact reasons for treatment modifications, which the authors should discuss further as a key limitation of their study. This could also give a framework to discuss the need for incorporating pharmacovigilance into routine data collection as advised by WHO.

Minor suggestions.

Response

This has been resolved. Please see last sentence under discussion.
1. It would be good for the authors to cite in the references the source and the date accessed for the guidelines in references 15-17 & 23 and the policy brief (reference 4)

Response

The author had personal copies of the documents 15-17 & 23. They were not sourced from the internet. The policy brief and other similar citations have been updated according to your suggestion.

2. It is not clear whether the rates given in the 2nd last paragraph in introduction reflects the incidence rate or mother-to-child HIV transmission rates.

Response

Yes, this concerns mother-to-child HIV transmission rates. The anomaly has been corrected.

3. The word 'median prevalence' in the same paragraph in introduction is also confusing. Its better for the authors to just give the prevalence as the term median may denote a different concept and ideally prevalence denotes mean.

Response

This has been corrected.

4. It would also be good for the authors to give the absolute numbers in addition to the percentages in the results sections

Response

This has been inserted.
5. The statements in study outcome and data analysis pertaining the type of treatment change for patients on d4T appears contradictory. In the section of study outcome it appears that this was determined by laboratory tests but in the latter it appears that all patients were switched to TDF.

Response

You are right. This has been addressed.

6. The statement on death rates comparisons of the different regimens in the discussions need to be qualified by a statistical test as the percentages for deaths among patients on AZT vs d4T appears to be similar

Response

This has been done

7. The explanation given for low death rates in the study in particular referring to the type of patients seen at the referral center is confusing. Ideally it would be expected that more deaths are seen at the referral center because it received more complicated (sicker) cases. Perhaps they need to reword this to reflect the quality of services offered at the referral site.

Response

We explained this in the discussion. We gave different scenarios as possible causes for this occurrence in the discussion session.