**Author’s response to reviews**

**Title:** Nature and Prevalence of Adverse drug reaction of Antiretroviral Medications in Halibet National Referral Hospital: a retrospective study.

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**Version:** 1  **Date:** 16 Dec 2018

**Author’s response to reviews:**

Response to reviewers’ inquiries

Dear Editor,

First we would very much like to appreciate our reviewers for lending their precious time to review our manuscript and give us their indispensable comments that will surely make our paper better. Moreover, we would like to apologize for our late response as it couldn’t be helped.

The questions of the reviewers are in bold while the response of the authors are in ordinary font below each question..

Reviewer 1.
In response to Narumol Jarernsiripornkul’s comments, the following changes have been made.

1) Abstract section

Methods
* The study period is unclear. Please clarify the month in 2005.
  Dear Mr. Jarernsiripornkul, thank you for your apt comment. In Page 2, line 17 – The study collected data of patients that were treated with ART between September 2005 and December 2016 and the necessary changes have been made in the manuscript. However, we would like to kindly point out that
this was not the time that the study took to be conducted, as this was a retrospective study and it took three months.

* Statistical tests should be mentioned.

Thank you Sir for this comment. And in response to your remark we have added specific statistical analysis conducted in Page 2, line 21-22. However if you feel like what we have added is still insufficient or needs more improvement, please do not hesitate to tell us as we are happy to comply.

Results
* Please specify the common suspected drugs in relation to the common ADRs presented.

Dear Sir, drugs that were associated with the commonly occurring ADRs have been added, kindly check this in Page 2, line 29.

Conclusion
We absolutely agree. Thank you. On Page 2, from line 40 onwards, impact of findings on patient health has been addressed.

2. Background
* Please clarify more detail about the magnitude of problems regarding the international level.

Dear Mr. Jarernsiripornkul, thank you for this comment. However, according to WHO HIV and HIV related problem is no longer an international problem but a problem that is confined to certain developing countries, especially sub-Saharan countries, of which Eritrea is one. As such, we believe that this problem which pertains mostly to developing countries has been adequately addressed in the background section especially in the first paragraph, the references mentioned can attest to this. But if you still think this is inadequate, please let us know.

3. Methods
* I was wondering whether the study design was longitudinal study since it was only performed in 3 month-period. Was there any repeated data collection over time during the study period in 2005-2016? Thank you for this comment. We understand that if this wasn’t clear to you, it will not be clear to the readers, therefore we have added that this was a historically longitudinal study in page 4, line 9. However for clarification purposes, the data was collected within three months, we went back in time to collect data of patients who took the ARV medications (the exposure) till the development of disease (the adverse drug reaction), this time ranged months to years (as they were patients who enrolled to the ARV clinic between September 2005 - December 2016), and it is due to this reason that it was a longitudinal study which was retrospective

No data that was collected was repeated, each card that was selected was unique. When selecting, every fifth card was selected from a group of alphabetically ordered cards to ensure randomness. This information has been added on page 4, line 32-33. We hope this clarifies things but again if you’re not satisfied with this please let us know.

*Please clarify more detail about the selection of study samples. How to recruit 309 study samples from the total of 1242 patients? Was there any sampling method used?
Dear Sir, sampling or selecting the cards was done using the formula that is stated in page 5, line 12-30. This formula was used to determine how many samples would be enough to represent the whole population of patients’ cards in the hospital. As is stated, the population size was initially 1242, and using the formula 293 patients were enough to represent that population but we increased the number slightly and studied 309 patients to decrease the margin of error. We hope this satisfies your question. Please let us know if there is more that we can mention to make it clearer.

*How to identify the suspected drug from the combined drugs which are commonly prescribed in patients with HIV.

It was certainly challenging to identify the offending drug among the combination of drugs that are given during an ART therapy. Moreover, this was a retrospective study and that made it more challenging to accurately identify the offending drug. However, the Naranjo-probability scale was used to determine the drug-ADR relationship and to pin out which drug was causing which reaction. For example: If a patient who was taking Zidovudine/Lamivudine+Nevirapine experienced hepatobiliary disorders and had Nevirapine withdrawn because it was suspected to be the offending drug and switched to the drug combination Zidovudine+Lamivudine+Efavirenz, after which the hepatobiliary disorders stopped. In this case the reaction is said to have been associated with Nevirapine using the Naranjo probability scale. Hence, this was how we identified the suspected drugs from the combined drugs. In cases in which all the drugs are capable of causing an ADR, gastrointestinal symptoms for example, we pinned the ADR to the whole drug combination as opposed to a single drug.

Page 4, line 13, September has been added to the year 2005 as per the reviewer’s request.

*Statistical tests should be mentioned in data analysis.

Dear Sir, We believe that all the statistical analysis used have been mentioned in page 6, line 52-59 in the data processing and data analysis section but if you are looking for anything specific, we would appreciate if you can mention it.

4. Results
*Page 7: percentages of male and female should be shown in the results. To make it clear, the common suspected drugs with the specific ADRs should be presented either in table or text.

Dear Sir, in response to your comment, the percentages of male and female; that is background demography has been mentioned. Moreover, the commonly suspected drugs and their specific ADRS have been mentioned in page 8, from line 45 onwards in a table. However the male and female percentages along with the numbers that developed ADRs has been added in page 4, line 48.

* The findings should be presented in order according to the objectives of study.

Dear Sir, we believe that we’ve presented the results in order of objectives, that is, prevalence, nature of the ADRs, seriousness and significant risk factors (main objectives of the study). However, we would very much appreciate any specific order that would be to your satisfaction.
*No causality assessment data classified by Naranjo's algorithm is found. All ADR categories should be shown as number and percentage.

Dear Sir, the causality assessment was stated on page 9, line 34-35, additionally there is a figure that elucidates this assessment. However the sentence has been edited for clarification. If you still feel that we haven’t explained it adequately, please be so kind so as to inform us.

*Further detail of all evaluated factors need to address in the results. Presentation in table would be beneficial.

Thank you Sir for this helpful comment. We have added a table that gives a detailed information of the ADR prevalence based on the background characteristics of the patients as well as significance test(p-value) for those factors that were suspected to be risk factors for ADR.

*Page 9, line 45-46: Specific treatment and symptomatic management are not clear since some of ADRs require both management.
You are absolutely right. And some of the ADRs were managed by both specific treatment and symptomatic treatment. This information has been added to page 9, line 45.

*Please specify or add percentages of patients or ADRs at the heading of Tables and axis of Figures.
We appreciate this comment. Percentages of patients have been mentioned both in tables and figures. However, incase we’ve misunderstood you, can you please clarify which table or figure you mean.

5. Discussion
* Please discuss more detail about the seriousness of ADRs in particular the lipodystrophy. I am uncertain how to assess the seriousness for some types of symptomatic ADRs.
Dear Sir, how seriousness was assessed for the ADRs can be found on page 6, line 26-43. And all ADRs that were lipodystrophy were deemed serious as lipodystrophy is permanent and may lead to other medical complications.

* Further discussion about the common suspected drugs and their related ADRs found in the current study is needed.
We believe that the suspected drugs with their respective ADRs have been discussed sufficiently but kindly if you could be more specific, we would appreciate it as we also want this manuscript to be its best.

* Page 10, line 56-60: It is not clear. Please clarify this sentence.
Dear Sir, it has been slightly edited for clarification. This statement is trying to explain the reason why low CD4 count can be associated with ADR occurrence in the form of IRIS (immune reconstitution inflammatory syndrome). But if it is still unclear, we would appreciate if you could suggest any way that we can make it clearer.
Reviewer 2
1) The authors have mentioned that patients aged 60 years and above were excluded from the study because they may have comorbidities. But one should noted that patients with age below 60 can also have comorbidities.
Dear reviewer, thank you for this comment. And you are right to think so as it possible for the younger patients to also have co-morbidities. However, we felt that those who are older than 60 years of age have more co-morbidities than the younger ones but we understand that was a bias on our side and we have mentioned it in our limitations.

2) It is unclear which statistical tests are used.
Dear reviewer, we are sorry to not have been able to clarify better but we have mentioned the statistical tests used on page 6, line 52-59. However, we would very much welcome any specific information that you are looking for that we can provide incase we’ve misunderstood your comment.

3) It was better to mention in the results section that when the first ADR was happened.
Thank you for this comment dear reviewer. Time to onset of the reactions from the start of medications has been mentioned in page 8, line 28-35. The first occurrence for each ADR varied based both on the drug and the ADR itself. Nonetheless, we would welcome any further suggestions on this matter.

4) The authors said that 70 patients have comorbidities but they did not reported which diseases coexisted. For example, which percent of patients had hepatitis B or C simultaneously?
Dear reviewer, although this is a fair question, we are afraid our questionnaire only addressed availability of the co-morbidities and not the types of co-morbidities that were present. Hence, we have now added this as one of our limitations, this can be found on page 11, in line 21-22.

5) In the method section it is mentioned that the study was a three month retrospective study. But in the results section the authors have said the occurrence of ADR such as Lipodystrophy is delayed and appears 2-3 years after ART onset. So, it seems that the patient groups were not homogeneous and the authors should explain this point clearly.
Dear reviewer, you are absolutely right. However, this was a historically longitudinal retrospective study in which data was collected by going back in time, that is data of patients that were enrolled to the HIV clinic between September 2005 and December 2016. This collection of data took three months. Therefore, whatever results we have presented, in this instance; lipodystrophy, were collected from the data of the above time frame and thus would be possible for the ADR to develop over 2-3 years. However, please notify us in what ways we can further clarify if it is still lacking.

6) There is some typos. For example protein inhibitor, Zidoudine.
Dear reviewer, thank you for your keen observation. We have corrected the typo that you mentioned and would appreciate if you could point out any more errors that we may have made on our part.