Author’s response to reviews

Title: Chronic kidney disease and HIV in the era of antiretroviral treatment: findings from a 10-year cohort study in a West African setting

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Version: 2 Date: 25 Mar 2019

Author’s response to reviews:

Response to reviewers – Mars, 19th, 2019

We are grateful to the academic editor and reviewers for the interest they showed towards our work and their useful remarks for improvement. Following is a detailed account of what revisions were made.

Technical Comments:

Editor Comments:
1) Please note that we require all manuscripts to have a full and complete Declarations section, our submission guidelines outlines how to complete this (https://bmcnephrol.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article#declarations).

2) All figure titles/legends should be placed at the end of the main manuscript, after the References.

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Reviewer reports:

Ikechi Okpechi (Reviewer 1): This is an interesting manuscript from Burkina Faso by Kabore et al. In this paper titled "Chronic kidney disease and HIV in the era of antiretroviral treatment: findings from a 10-year cohort study in a West African setting", the authors aim is to "determine the frequency of CKD and changes in kidney function during antiretroviral treatment (ART) in a large cohort of HIV-patients followed in Burkina Faso". They present data on 3138 HIV positive patients starting ART in Burkina Faso and describe baseline renal function as well as changes (loss / gain) of GFR over a 10-year period from the time of treatment initiation. They identified some factors associated with CKD.

My main concern about this paper is regarding the prevalence of CKD reported. At baseline the prevalence of CKD was found to be (0.5%). However, even though there were fluctuations in GFR in all the groups, it did not appear that the prevalence of CKD changed over the 10-year period, this even after reporting factors associated with CKD progression. If they have to discuss disease progression, at least they should give an indication of CKD prevalence at end of follow-up (at 10-years). I think this is where their paper is confusing: you can't seem to determine if the study methodology is designed to follow up patients from the time of starting ARTs or if it is just a snap-shot study to determine at one time the prevalence of CKD. The authors should fix this. Otherwise, it is a good paper.

Response :

We would like to thank the reviewer for his thoughtful comments. Our study was not intended to measure changes in CKD prevalence over 10 years, but rather to focus on changes in the average eGFR measure and CKD incidence over this period. It is a follow-up study of patients from the time of starting ARTs that was designed to assess:

- how the kidney function of patients evolves under ARTs to identify the factors influencing this evolution,
the incidence of CKD on ARTs and the associated risk factors.

This is an open cohort study and we determined CKD prevalence at baseline to establish the baseline health status of our population with respect to kidney disease.

A measure of the annual CKD prevalence would not have allowed us to achieve our objectives because a series of snap-shot studies do not take into account the follow-up duration of each patient.

Frank Post (Reviewer 2): Kabore and colleagues report the burden of CKD in a cohort of West African patients, with a prevalence of 3% at baseline and a low incidence of 1.9/1000 PYFU. In line with previous studies from Africa and the USA (Reid et al, CID 2008; 46: 1271-81 and AIDS 2008; 22: 481-7), they noted eGFR decline during follow up on ART in those with eGFR >90, and improvements in renal function among those with CKD and mildly impaired eGFR. They report associations between eGFR decline and known risk factors such as immunodeficiency, TDF/PI exposure and hypertension.

The authors may wish to contextualise their findings with data from the UK CHIC cohort, which reported a prevalence of CKD of 3% among patients in the UK who were born in West-Africa (JID 2018; 218: 1767-1172). By contrast, the incidence of CKD during follow up in this cohort (mostly on ART) was substantially higher (7.9/1000 PYFU), and no association with TDF exposure was observed.

Response :

We would like to thank the reviewer for bringing this paper to our knowledge. This contribution has been integrated into the manuscript (lines 259 to 261 and line 279).

HIVAN is a major cause of ESKD in West Africa, and it would be useful to understand to what extent early mortality (ESKD with early mortality) may have precluded enrollment into the cohort, and ESKD during follow up may have remained undiagnosed. This might have been a major source of survival bias and an over-representation of low risk individuals in the present analyses. The exclusion of patients who did not start ART and those that left the cohort early (with no renal follow up data) may have further skewed the results towards a group of "relative well patients who started ART". These biases may explain the low CKD incidence rate, should be mentioned as major limitations of the study, and the conclusion should probably reflect this.

Response :

We thank the reviewer for this contribution. We acknowledged this limitation in the ‘limitations of study’ and ‘conclusion’, and have now put even more emphasis on it (lines 305 to 311 and 320 to 322).
Comments:

The statistical methods deserve further detail: were mixed effects models used to create eGFR slopes or were absolute changes analysed? What were the models adjusted for? Were viral load data included in the models?

Response:

We apologize for the confusion in our methods. We used a mixed-effect linear model for evaluating the changes of eGFR over time. The coefficients presented in Table 3 correspond to the differences in slope between the reference category and the other modalities for each variable. A positive coefficient indicates a more favorable evolution whereas a negative coefficient indicates a less favorable evolution. We added these details in the manuscript (lines 113 to 114 and 214 to 216). The models were only adjusted for variables indicated in Table 3. There were not adjusted for viral load because we did not have measures at baseline nor regular measurements of it.

I prefer the term "greater eGFR decline" over "faster eGFR loss"

Response:

We have edited the manuscript accordingly.

In Table 3, it would be helpful to include the number of patients included in the analyses (reminding the reader that the number of participants with eGFR <60 at baseline was small)

Response:

Thanks for the suggestion. We have added this information to Table 3.

I would remove or rephrase line 245/246 "this could be explained by a catch up effect linked to restoration of kidney function induced by ART" - I am not sure what the authors are trying to describe.

Response:

Thanks for pointing this. As suggested, the sentence has been removed.

The authors may wish to acknowledge that PI's have an effect of tubular secretion of creatinine and this may in part explain the greater reductions in eGFR observed with this class of drugs.

Response:

We do not found evidence for a direct effect of PIs on the tubular secretion of creatinine. The action of PIs, the most described, would result from an increase in plasma and intracellular concentrations of TDF (Infect Dis Ther 2015 ; 4:15–50 ). Pruvost et al. reported an increase in

In the manuscript, we have replaced the expression "cumulative effect" with "potentiating effect" which seems more appropriate.

The conclusions refers to a CKD prevalence of 0.5% which is confusing - with infrequent measurement of creatinine, attrition and exclusions, this is more likely to reflect the prevalence of CKD in the cohort. I am also not sure that the authors' data support kidney function monitoring in those on TDF + PI; after the initial (benign) effects on creatinine clearance, renal function was fairly stable during more prolonged follow up.

Response :

We completely agree with the reviewer on his comment on CKD prevalence. Our study design probably underestimate CKD prevalence. We have emphasized this more clearly in our conclusion (line 320 to 322). The conclusion has been modified to further qualify the renal toxicity of treatments containing both TDF and PI (line 330 to 331).