Author's response to reviews

Title: Relative risk of renal disease among people living with HIV: a systematic review and meta-analysis

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Author's response to reviews: see over
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Dear Editor,

RE: Relative risk of renal disease among people living with HIV: a systematic review and meta-analysis

Thank you for your response to our paper, the review and the opportunity to resubmit our manuscript for publication in Biomed Central. We would like to thank the reviewers for their comments as they have helped to strengthen the paper.

All comments have been addressed in detail and responses to reviewer comments are below. In this submission we provide a manuscript indicating where changes have been made since the previous submission (as ‘track changes’), and also a clean version of the manuscript. We hope that you now find this paper acceptable for publication.

Sincerely,

Associate Professor David P. Wilson, on behalf of all co-authors
Reviewer 1: Fenicia Vescio

Comment: The author carry out a systematic review and a series of meta-analyses to calculate the pooled relative risk of renal disease for people living with HIV. The statistical analysis is appropriate to the objective of the study and is clearly explained in the methods section. Results are well presented and credible.

Response: We thank the reviewer for her positive comments.

Reviewer 2: Jeffrey Kopp

General comments: This is a well-done and apparently comprehensive analysis that provides useful information not previously presented. The methods used are standard and appear to be appropriately employed. Most of the figures are clear. The conclusions are judicious.

Response: We thank the reviewer for his positive comments. We have addressed the concern as listed by the reviewer as follows:

Comment 1: African descent individuals are at increased risk for HIV-associated kidney disease but this important issue is not addressed in the present manuscript. Perhaps geographic variation (P12) that is noted is a proxy for this. The authors are urged to see whether enough study provide data on race to address this point.

Response: We agree with the Reviewer that race is an important factor associated with risk of HIV-associated kidney disease. We have now elicited data on race/ethnicity from all selected studies and included this information in Table 1. However, there were not enough studies which reported the same race/ethnicity in a consistent way and therefore sub-analyses by race could not be conducted. We note that extracted estimates had already been adjusted in the original studies' analyses. But we were able to re-perform the meta-regression analysis, including race/ethnicity as a covariate and found that race/ethnicity was not found to be significant and did not contribute to our existing results in the manuscript as reported previously. We have now added some text to the discussion on race/ethnicity as it pertains to HIV-associated kidney disease.

Comment 2: In the sections on increased kidney disease risk with age, the author should explicitly state that the reference group was age-matched HIV-negative subjects.

Response: We have now explicitly stated this in the manuscript.

Comment 3(part 1): Limitations should add that abstracts not provide final, peer-reviewed, data and that the GFR equations have not been validated in HIV populations.
**Response:** We have now added a statement about limitations regarding abstract selection and GFR equations in the Discussion section.

**Comment 3(part 2):** On page 13, the discussion of ART should be qualified not noting that in non-randomized studies, subjects who are given and take ART may differ in important respects from those who are not treated, limiting definitive conclusions.

**Response:** We have now discussed this point in the Discussion section. We thank the Reviewer for noting this point.

**Comment 3(part 3):** The issue of hepatitis C co-infection, the subject of a meta-analysis (Wyatt, AIDS 2008) is not addressed.

**Response:** We agree that hepatitis C co-infection is an important issue. We have now discussed this in the manuscript and cited the paper by Wyatt.

**Minor essential revisions**

**Comment:** The abstract should state that the unit of analysis was study and not subject, as subject level data was not obtained.

**Response:** This has now been clarified in the abstract.

**Comment:** P6: Egger is not referenced.

**Response:** It is now referenced on page 7.

**Comment:** P7 and P11: eGFR is given as 1.73 ml/min – is unclear if they authors mean ml/min/1.73m2 or if studies differ on their units.

**Response:** It is now clarified on pages 8 & 13 as follows:

“men with abnormal proteinuria, having GFR<60 ml/min/1.73 m⁷, to be 5.1 (95%CI: 2.9-8.9)”

“Potential explanatory covariates considered were study design, study period, duration of follow-up, diseases, study location, study size, race/ethnicity and estimated glomerular filtration rate (eGFR) type. We found that geographic location, type of disease and eGFR methods were significantly associated with the relative risk of renal disease.”

**Comment:** P12: When HIVAN is mentioned, it is unclear if this is a biopsy diagnosis or clinical diagnosis.

**Response:** It is now clarified on page 14. We are referring to a biopsy diagnosis.
**Comment:** Figure 2E is not well-explained in the legend; some CD4 count levels have 2-5 mean/SD bars. If these are distinct studies, perhaps that should be shown.

**Response:** For each study, CD4 groupings were reported; mid-values of the range of reported CD4 categories were chosen for illustration in this figure. The legend has been changed in an attempt to improve clarity. It now reads as:

"Figure 2e: Relative risk of renal disease in PLHIV according to CD4 count. Mid-values of the range of reported CD4 categories are plotted; Comparator groups are listed in Table 3."

**Comment:** Discretionary revisions

The publication bias plot might be presented as Supplemental data.

**Response:** We have now presented all the ‘Funnel plots’ in relation to the publication bias as Supplemental data.

**Comment:** Table 2: Adding the city or cohort name would help orient the reader.

**Response:** Cities, where reported, are now included in Table 2.

**Reviewer 3: Meredith Shiels**

**Reviewer’s report:** This manuscript is a meta-analysis examining the relative risks of renal disease among people with HIV, and by antiretroviral therapy use, tenofovir use and age. Overall, I found the paper somewhat difficult to follow. The authors' definition of the outcome of interest seemed to be defined differently for each study, and not enough information was included for each individual study in the tables.

**Response:** We thank the reviewer for her constructive feedback. We have addressed the concern as listed by the reviewer as follows:

**Major revisions:**

**Overall comment:** Please add a table with all of the pertinent information for each study included in the study. Please include the name of the cohort or a description of the participants, how the study defined their outcome of interest, age range, HIV risk group, adjustment variable, etc. The version of table 1 given to me is missing the majority of the studies, and does not have complete information.

**Response:** We have now modified Table 1 to include additional information, namely description of cohort, age, sex, race/ethnicity and city/state.
**Comment:** Methods:

**Comment 1:** Outcome measures: You state that the primary outcome was “the incidence of CKD defined as estimated eGFR<60 mL/min/1.73 m^2 for greater than or equal to 3 months irrespective of kidney damage.”

a. Your outcome should be defined as the disease endpoint, not the incidence of the disease endpoint.

**Response:** We have clarified this statement accordingly. We do indeed only include the disease end point in our analyses.

b. Did every study report eGFR<60 for at least 3 months?

**Response:** Yes, we strictly applied this criterion in our selection of studies for inclusion in the analysis. Relevant data are provided in Table 1. Differences between studies in terms of methodological aspects of GFR such as MDRD, CG and serum creatinine are also included in Table 1. The strict criterion of at least 3 months, and exclusion of studies only reporting acute disease, resulted in fewer studies overall.

c. You state that each study included in the analysis used this definition, but then proceed to describe each study’s outcome differently (e.g., kidney disease, chronic kidney disease, HIV-associated nephropathy, all-cause nephropathy, acute renal failure, tubular dysfunction, renal impairment). This is extremely confusing, and it concerns me that you might be combining different outcomes. If each study does use the same eGFR cutpoint, it would be helpful to state up front that the studies name their endpoints differently, but they are all defined the same way and you will be referring to all endpoints as X (i.e., chronic kidney disease).

**Response:** We have mentioned multiple outcomes such as kidney disease, chronic kidney disease, HIV-associated nephropathy (HIVAN), all-cause nephropathy, acute renal failure, tubular dysfunction and renal impairment. Also, we have mentioned the pathological abnormalities or markers of kidney damage but strictly applied the criterion of eligibility based on a reported measure of GFR<60 mL/min/1.73 m^2 for at least 3 months. More specifically, although different stages of chronic kidney disease as defined by the National Kidney Foundation are reported, we ensure consistently through use of this strict criterion of GFR<60 mL/min/1.73 m^2. We agree that it could be easier if we simply state the marker of GFR without mentioning classification of diseases. We have simplified our end point and clarified in the text.

**Comment:** Results:

1. Meta-regression and subgroup outcomes
a. I would suggest breaking this paragraph up and presenting results with the overall meta-analysis results.

Response: We have now broken the combined paragraph, by “Meta-regression analysis” and “Subgroup analyses”

b. Your meta-regression method is very confusing to me. Doesn’t meta-regression estimate the association between study characteristics and the overall RR? You stated that you “identified risk factors on renal function” and that “geographic location and eGFR were significantly associated with the degree of renal disease.” These factors should be estimated in relation to the RR and not with the presence of renal disease alone.

Response: We agree with the reviewer and have now revised this paragraph for greater clarity.

c. Twice you report that you performed “subgroup analysis using these two variables,” and then you provide one estimate. Is this estimate from one of the subgroups? I think you mean that you adjusted for potential confounders and produced an adjusted RR from the meta-regression model. Is that correct? This should be clarified.

Response: We conducted three sub-group analyses. The first one was derived from using two variables. The second one was from using type of disease (HIVAN). The third one was from using type of disease (CKD). We have clarified this paragraph in sub-group analyses section and we report relative risks and heterogeneity indicators for all three sub-group analyses.

Comment: Minor revisions:

Abstract

1. Methods: What was the earliest date of publication included in your study?

Response: The earliest date of publication included in our study was year 2002. We have indicated this in the abstract.

2. Methods: You state that eligible studies were observational cohort studies here, but later you state that you also included case-control and cohort studies.

Response: We have stated our eligible studies were observational. We have included all types of observational studies (cohort, case-control and cross-sectional). We have now corrected this in the manuscript.

Comment: Introduction:
1. Please add references to the first paragraph.

Response: We have now added references in the Introduction section.

Comment: Methods:

Comment 2. The description of your search strategy does not include CROI abstracts, though this component is included in the abstract and your results. I think that the use of abstracts from a conference should not be encouraged in a meta-analysis. Conference abstracts have not been edited based on peer review, and results often change before manuscript submission. Further, abstracts often do not present the level of detail needed in a meta-analysis.

Response: We have now included our full search strategy, including conference abstracts. However, such studies were only included where sufficient and complete data were available (7/23).

Comment 3. Selection of studies: Did you exclude papers that present results from the same study? For example, if two studies reported results from MACS, did you exclude one of them?

Response: We used the updated study if two publications reported from the same study occurrences. However, if the outcome measure is different even from the same study, we did not exclude them. For example, we have taken two studies from MACS (Reisler et al & Jacobson et al). The underlying reason is that they measured two different outcomes: Jacobson investigated proteinuria using ratio of protein and creatinine among HAART users; Reisler identified CKD using MDRD methods among HAART and Tenofovir users.

Comment 4: Renal outcomes: You mention the differences in how eGFR was estimated. How do these methods compare? Do they produce similar results? Did the prevalence of CKD differ by studies based on their methods use?

Response: We collated studies that reported different methods for estimating glomerular filtration rate to identify renal outcomes. These include Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) formula of estimating eGFR based on age, sex & race; and the Cockcroft Gault (CG) equation which is based on age, sex & weight. Though these methods produce similar results, there are some differences. Consequently, reported prevalence of CKD may slightly differ across studies. We note that eGFR was one of the covariates that caused heterogeneity in the relative risk of renal disease while we conducted meta-regression and we have mentioned this point in meta-regression section.
Comment 5: Quality assessment: Please add the maximum score of the Downs and Black checklist.

Response: We have added the maximum score, of 27, from the Downs and Black checklist. The greatest score from the included studies was 26.

Comment: Results

Comment 2(a): It is unclear how each study defined ART use. This could be added in the description or to a table.

Response: We have clarified the definition of ART in the “Effect of antiretroviral treatment” section. This description is now noted, namely, that only one out of five studies clearly defined ART use.

Comment 2(b): Did you look at duration of any ART?

Response: Yes, we looked at the duration of ART. However, we were unable to conduct an analysis based on duration of any ART. We have discussed this point as a limitation. We would like to thank the reviewer for raising this point.

Comment: Discussion

Comment 1: First paragraph: You state that the “relative risk of renal disease for PLHIV was found to be 3.87 times more than that of HIV-uninfected people.” This is not correct terminology, you should either say the risk is 3.87 times more or the relative risk was 3.87.

Response: We have clarified this statement.

Comment 2: Please add further information to the discussion about the mechanism for CKD in people with HIV infection and the mechanism by which ART reduces risk and tenofovir increases risk.

Response: We have provided further information to the Discussion section regarding the mechanism for CKD among people living with HIV and its prevention with ART regimen.