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 authors

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Reviewer: Jeffrey Kopp

Reviewer’s report: The authors have done an excellent job of responding to the questions raised.

Response: We thank the reviewer for his positive comments.

Comment 1: One issue that remains is that for the reader, it is unclear what the definition of renal disease was in each study. The authors define the primary outcome as CKD defined as eGFR<60 for 3 months. However, the text used various terms with uncertain definitions. Thus, to cite a few examples: P8: GFR <60 P10: renal failure, all-cause nephropathy, CKD, renal failure, CKD, renal impairment P11: CRF, CKD, CKD #60 Figure 2, graphs. renal disease. The reader must presume that CRF and CKD and renal impairment mean something other than CKD<60, otherwise this more precise term would have been used.

I suggest as a solution the following terminology:
   a) when the study used eGFR<60 ml/min/1.73m2, then refer to this as CKD stage 3 [this is used by some authors, but might a first glance appear to exclude CKD 4 or 5] or CKD#60,
   b) when the study has not been clear on the definition, use CKD-undefined,
   3) for end-stage kidney disease, say ESKD.
   4) AKI

I would avoid terms like renal failure, renal impairment, and all-cause nephropathy. If a table or figure includes data from multiple studies have used diverse definitions for kidney disease, that this should be communicated in some fashion – perhaps CKD, various definitions or alternatively AKI and CKD, various definitions.

Response: We would like to thank the reviewer for providing suggestions to clarify the definition of renal disease. We have now clarified the definitions and used the reviewer’s suggested classification. This is now included in the ‘Outcome measures’ section and these terms are now used throughout the text and consistently in all analyses.

Comment 2: A minor point, on P11: “Renal replacement therapy, defined as end-stage renal disease.” In fact it is the reverse: ESKD defined as receiving RRT.

Response: As indicated, we have now reversed the terms on page 11.

Comment 3: The legend to Figure 2E remains unclear. I would add a sentence stating that each point/bar presents data from a single study, illustrating the RR/95% CI of CKD<60 for the low CD4 group (CD4 value shown on the abscissa) compared to the high CD4 group (presented in table 3).

Response: We have now added this suggested sentence to ‘Figure 2e’ for greater clarity.
Reviewer: Meredith Shiels

Though the authors state in their response to my previous comments that the end points were all defined the same way, I am still concerned by the different names for the endpoints listed on pages 9 and 10. On these two pages alone, the author mentions the following endpoints: HIVAN, all-cause nephropathy, acute renal failure, chronic kidney disease, tubular dysfunction and renal impairment. If these endpoints are defined the same way in each study, but just have different names, then this should be mentioned up front and consistent terminology should be used throughout the results. However, if these endpoints are defined differently in each study, then these endpoints should not be combined in a pooled analysis. Either way, the text remains confusing and must be addressed.

Response: We agree with the reviewer that heterogeneous terms described on pages 9 and 10 used by individual study may cause confusion. This was also raised by Reviewer 1. We have now clarified this, according to the suggested classifications of another reviewer. The rational of inclusion of each individual study’s results is provided at the beginning of the review in the ‘Outcome measures’ section; this section also contains our definitions for renal disease.

Response to Editor’s Comment:
We have now formatted the manuscript and figures according to the points raised to conform to the journal's requirements.