Author’s response to reviews

Title: The Association between a Detectable HIV Viral Load and Non-Communicable Diseases Comorbidity in HIV positive adults on antiretroviral therapy in Western Cape, South Africa

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Dr Cecilia Devoto
Editor of BMC Infectious Diseases

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The Association between a Detectable HIV Viral Load and Non-Communicable Diseases Comorbidity in HIV positive adults on antiretroviral therapy in Western Cape, South Africa

Dear Dr Devoto,

Thank you for the editorial boards comments; we welcome the opportunity to revise and resubmit the paper. We have sought to address their helpful suggestions. We note your inclusion of the previous reviewer’s comments, we have included our response to these which we submitted, with a revised manuscript by email, on 23rd August 2018 and have added to this in
greater detail. We describe how we have responded to specific comments below. We note that this topic remains an area with limited published research from low and middle-income settings; highlighting the importance of this work and the potential contribution of this paper to this knowledge base.

Throughout this letter we indicate our responses in italics and areas of revision with red text. Line numbers refer to the interim submission by email to Dr Devoto in August.

We look forward to further comments from your reviewers and editorial staff.

Yours sincerely,

Tolu Oni

Editor Comments (on behalf of AE Medstrand):

1.

General Comment: The study reports no association between detectable HIV viral load and comorbidities but found association with being female, younger age, having low CD4 counts and smoking.

Two previous studies, references 4 and 6 of the present manuscript found association between viral load and comorbidities. However, these studies used different definitions of viral failure. A clinical significant definition of viremia may be set higher, than the threshold used in the current
study. Recent data indicate that low level viremia in the range 50-1000 cp/ml may be clinically important (See Hermans Lancet Infect Dis 2018; 18: 188- and Poveda and Crespo; PMID: 29628513). How would different thresholds of viral failure associate with comorbidities of the present study?

RESPONSE

We have insufficient power to analyse by viral load sub-category. We have now addressed this in our results section by including the percentage of participants with a VL>1000; and in our discussion as potentially contributing factor for our differing results and included the two references highlighted by the reviewer. We have inserted this text from line 278.

“Notably these studies had different definitions for viraemia. Two recent papers noted an association between low level viremia (>50-1000 copies/ml) and increased risk of virological failure. (19, 20) While eight percent of our sample had a viral load of greater than 1000 copies/ml, due to insufficient statistical power, we did not sub-categorise viral load, and this may have contributed to our differing results.”

We have also included this descriptive result into the results section as follows:

“Nineteen percent of the study population had a detectable HIV viral load (>40 copies/ml), and 8% had viral load >1000 copies/ml.”

ABSTRACT

CONCLUSION

2.

Comment: The statement (starting on line 45) “The lack of systematic screening of non-communicable disease in largely vertical HIV clinics contributes to under diagnosis of NCDs in the HIV-infected population” is odd and is not a finding of the study?
To my understanding, the authors observed a higher number of participants with hypertension than reported in hospital folders or self-reported but this must not necessarily mean that there is a general under diagnosis of NCDs among HIV infected individuals? This section needs to be rephrased to better align with the findings. The conclusion after discussion lines 359 – is a more appropriate synopsis.

RESPONSE

The line of text highlighted above was deleted from the manuscript before it was resubmitted to the journal on 23/08/18. The abstract conclusion in the most recently submitted version of the paper reads:

“The lack of association between viral load and NCDs in this setting is consistent with previous investigation in South Africa but differs from studies in high-income countries. Lower NCD prevalence in clinic records than self-report and a higher level of hypertension on the day than self-reported or recorded in clinic folders suggest under-diagnosis of NCDs in this population. This potential under-detection of NCDs may differ from a high-income setting and have contributed to our finding of a null association. Our findings also highlight the importance of the integration of HIV and primary care systems to facilitate routine monitoring for non-communicable diseases in HIV-infected patients.”

MAIN TEXT

METHODOLOGY

3.

Comment: Classifications of indicators of comorbidity, starting on line 144. Why is indicator iii an interesting group? How was indicator iii scored? Was the report in the clinical folder preferred above the self-reported?

RESPONSE
We have revised the text to provide further clarification, from ‘…and iv) comorbidity indicator (iii) plus measured hypertension (diastolic ≥90mmHg or a systolic ≥140mmHg in line with SAGE, NIDS and SANHANES-1 studies (14, 15)) on the day of interview.’ to ‘and iv) a composite indicator consisting of comorbidity indicator (iii) (comorbidity reported in clinic folder OR self-report during interview) plus measured hypertension on the day of interview (diastolic ≥90mmHg or a systolic ≥140mmHg in line with SAGE, NIDS and SANHANES-1 studies (14, 15))’.

In our discussion, we explain the difference between comorbidity iii) and iv) may be due to incomplete clinic records. We retained this indicator to highlight the missed diagnoses of hypertension, potentially due to vertical and siloed healthcare system that did not routinely screen for common NCDs in the HIV clinic.

RESULTS

4. Comment: Tables are referred as to Table one, not Table 1 etc throughout the Results section

RESPONSE

This has been resolved.

5. Comment: As discussed above, viremia was defined as detectable at 40 copies/ml. Why? Is this clinically significant or just because the VL assay has this limit? I would suggest the author to do a number of sub analyses with different levels of VL.

RESPONSE

This was chosen as the VL assay in Ubuntu clinic, Khayelitsha had this limit at the time of data collection. We have insufficient power to analyse using viral load sub-categories and have now included this in response to the editor’s first comment above.
6.

Comment: Lines 240-242. It is hard to compare with previous studies since a different levels of viremia were used in the studies.

RESPONSE

This limitation has been addressed, see new text inserted from line 278.

DISCUSSION

7.

Comment: In general very long and a bit tiresome to read (in particular lines 249-290). It could be shortened while keeping the essence.

RESPONSE

Redundant sentences have been deleted and re-phrased to shorten this section whilst maintaining clarity.

8.

Comment: Line 325: growing NCF epidemic; more correct to use “growing NCD prevalence”?

RESPONSE

This has been resolved.
Reviewer Comments (initially responded to through resubmission by email to Dr Devoto on August 23, 2018)

ABSTRACT

1. Conclusion

Author: The lack of systematic screening of non-communicable disease in largely vertical HIV clinics contributes to under diagnosis of NCDs in the HIV-infected population.

Comment: This conclusion is not supported by the results presented in the abstract. The authors observed higher prevalence of hypertension as compared to patient self-report or noted in the clinic folder. Site characteristics should be presented in the methods rather than in the discussion - i.e., that the clinics were part of a vertical health system.

RESPONSE:

We have addressed both these comments and edited the background, methods, results, and conclusion of the abstract to address the reviewer’s comments.

2. Author: The discrepancy between this study and past findings may be due to this, and highlights the importance of the integration of HIV and primary care systems to facilitate routine monitoring for non-communicable diseases and their risk factors in HIV-infected patients.

Comment: It is unclear what discrepancy the authors are referring to - they present a (null) association between NCDs and detectable HIV, correlates of detectable HIV and relation of self-reported and measured hypertension.

RESPONSE:
We have addressed both these comments and edited the background, methods, results, and conclusion of the abstract to address the reviewer’s comments.

We would also like to note that we have removed reference to the vertical health system in the abstract. The methodology section of our manuscript describes in detail the vertical nature of the healthcare system in SA, highlighting the lack of integration between the primary healthcare and HIV clinic and the implications for patient clinical care this may have.

INTRODUCTION

3.

Line 78-80

Author: The rising prevalence of non-communicable diseases (NCDs) in SSA, combined with high levels of chronic infectious diseases is resulting in a different pattern of multimorbidity than is seen in high-income countries. (3)

Reviewer Comment: I am unclear what chronic infectious diseases the authors are referring to.

RESPONSE:

The text above has been amended from ‘….combined with high levels of chronic infectious diseases…’ to ‘combined with high levels of chronic infectious diseases such as HIV…’.

4.

Line 81-83

Author: Low-income groups in South Africa (SA) have seen a dramatic increase in prevalence of NCDs and have the highest burden of infectious disease resulting in concurrent epidemics.(7)
Reviewer Comment: Again, the authors should specify which infectious diseases they are referring to.

RESPONSE:

The text above has been amended from ‘….have the highest burden of infectious disease resulting …’ to ‘have the highest burden of HIV, a chronic infectious disease resulting ….’

5.
Line 87 - 90

Author: In the Western Cape province, primary care clinics are organised into disease-specific clubs, with a focus on four diseases (based on prevalence and importance): diabetes, hypertension, asthma/chronic obstructive pulmonary disease, and epilepsy.

Reviewer Comment: The authors should clarify what is meant by importance. Is this mortality rate? Disability-adjusted life years (DALYs)? Something else?

RESPONSE:

We have clarified what is meant by importance and revised the text from ‘…. (based on prevalence and importance)…..’ to ‘… (based on prevalence and importance as determined by contribution to disability adjusted life years, and the need for specialist expertise input in the primary care setting).

6.
Line 92 - 94

Author: Yet, despite the increasing co-morbidity with HIV, and the potential for co-morbidity to impact outcomes, there is little known about the association between HIV and these diseases.

Reviewer Comment: It is unclear what prior data the authors are referring to here.
Yet, despite the increasing co-morbidity of NCDs with HIV in SA and an increasing body of research in high-income countries on the association between a detectable HIV load and NCDs, there is little known about the association between HIV and these diseases in low and middle-income settings.

RESPONSE:

We have revised the text ‘…co-morbidity with HIV, and the potential for co-morbidity to impact outcomes ..’ to ‘…co-morbidity of NCDs with HIV in SA and an increasing body of research in high-income countries on the association between a detectable HIV load and NCDs…’ and added to the end of the sentence ‘in low and middle-income settings’.

7.
Line 94 - 96

Author: The objective of this study was therefore to examine the association between common NCDs (hypertension, diabetes, epilepsy or chronic respiratory disease (CRD) and a current detectable HIV viral load.

Reviewer Comment: The authors should be precise with their terminology. In the text above these NCDs were foci of clinical care because of "prevalence and importance".

RESPONSE:

We have revised the text from ‘…between common NCDs…’ to ‘…between prevalent NCDs of importance…’

METHODOLOGY

8.
Line 116 – 117
Author: Once those eligible has participated, the next available ten folders were screened, this system was continued until the sample size was reached.

Reviewer Comment: Grammatical error.

RESPONSE:
‘has’ has been changed to ‘had’

9.
Line 123 - 124
Author: These NCDs were selected as a priority due to their high prevalence in this population.

Reviewer Comment: Again, the authors should be precise. It appears from the text above that these conditions were prioritized by the government health system based on "prevalence and importance".

RESPONSE:
We have revised the text from ‘…high prevalence ..’ to ‘high prevalence and importance…’.

10.
Line 128 - 129
Author: The diagnosis of these NCDs is in line with guidelines set out by the South African government for primary care.(12)

Reviewer Comment: Since these NCDs are the primary phenotypes of interest in the paper, the authors should describe specifically how they are diagnosed in their setting.

RESPONSE:
After ‘The diagnosis of these NCDs is in line with guidelines set out by the South African government for primary care,(12)’ we have added “Specifically hypertension was diagnosed based on two elevated (>140/90) blood pressure readings, diabetes diagnosed on the basis of a random blood glucose measurement >11 and fasting blood glucose > 7, CRD was a clinical diagnosis based on symptoms and risk factors as set out in the primary care guidelines (12), and epilepsy is diagnosed by a physician with specialist expertise based on the presence of two seizures with no other clear cause.”

11.

Line 150 - 154

Author: Four indicators of comorbidity (hypertension, diabetes, CRD and/or epilepsy) were created: i) comorbidity reported in clinic folder; ii) self-reported comorbidity on interview; iii) comorbidity reported in clinic folder OR on interview, and iv) comorbidity indicator (iii) plus measured hypertension (diastolic ≥90mmHg or a systolic ≥140mmHg in line with SAGE, NIDS and SANHANES-1 studies (14, 15)) on the day of interview.

Reviewer Comment: It is unclear what " iv) comorbidity indicator" refers to.

RESPONSE:

We have revised the text to provide further clarification, from ‘…and iv) comorbidity indicator (iii) plus measured hypertension (diastolic ≥90mmHg or a systolic ≥140mmHg in line with SAGE, NIDS and SANHANES-1 studies (14, 15)) on the day of interview.’ to ‘and iv) a composite indicator consisting of comorbidity indicator (iii) plus measured hypertension on the day of interview (diastolic ≥90mmHg or a systolic ≥140mmHg in line with SAGE, NIDS and SANHANES-1 studies (14, 15))’.

12.

Line 165 - 168

Author: In the multivariable model exploring the association between a detectable viral load and comorbidity, indicator iv) was used as the measure of comorbidity as it incorporated those with undiagnosed hypertension and so was the most comprehensive measure of comorbidity.
Reviewer Comment: I find this text confusing.

RESPONSE:

We have revised the text from ‘…indicator iv) was used as the measure of comorbidity as it incorporated those with undiagnosed hypertension and so was the most comprehensive measure of comorbidity.’ to ‘… indicator iv) was used as the measure of overall comorbidity as it incorporated those who were measured as hypertensive on the day of recruitment into the study, comorbidity recorded in clinic folders and self-reported comorbidity.’