Author’s response to reviews

Title: A cross-sectional, population-based study measuring comorbidity among people living with HIV in Ontario

Authors:

Claire E Kendall (ckendall@uottawa.ca)
Jenna Wong (Jenna.wong@gmail.com)
Monica Taljaard (mtaljaard@ohri.ca)
Richard H Glazier (rick.glazier@ices.on.ca)
William Hogg (whogg@uottawa.ca)
Jaime Younger (jyounger@ohri.ca)
Douglas G Manuel (Dmanuel@ohri.ca)

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Author’s response to reviews: see over
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Re: MS 1435626954979540 - A cross-sectional, population-based study measuring comorbidity among people living with HIV in Ontario

Dear Dr. Calleja and BioMed Central Public Health Editorial Team,

Thank you for the opportunity to revise our manuscript based on peer review and editorial comments. Below please find an enumerated response letter addressing all of the points raised in our revisions request. We have bolded the specific questions/comments and italicized our responses, indicating where changes have been made in the marked up revision document. We have also uploaded a document with all of these changes accepted. We hope that with these revisions the manuscript will suitable for publication and look forward to your feedback.

Best regards,

Claire E. Kendall
Associate Professor
C.T. Lamont Primary Health Care Research Centre, Bruyère Research Institute, 43 Bruyère St, RM 337Y, Ottawa, Ontario, K1N 5C8;
Department of Family Medicine, University of Ottawa, 43 Bruyère St., Floor 3JB, Ottawa, Ontario, K1N 5C8
ckendall@uottawa.ca
Telephone: 613-562-6262 ext. 1449
Fax: 613-562-6099
Reviewer 1:

1. This is a well written paper on an important topic – the prevalence of co-morbid conditions among HIV infected individuals receiving HIV treatment. As discussed in the introduction, people with HIV are living longer and, if appropriately treated, are much less likely to succumb to classical HIV-related conditions. Consequently, non-HIV related conditions may be becoming a more important group of conditions which can affect the health of people living with HIV. The study makes efficient use of several large administrative databases available in Ontario to examine the burden of these diseases in HIV infected individuals receiving treatment and compare them to controls from the general population without HIV. My only major concern is that the time window in which these the billing codes were examined to assign participants to the disease or non-disease categories and if this differed between the two cohorts.

Thank you for the thoughtful review of and kind words about our paper. We hope we address the reviewer's concern specifically in response 5, below.

2. Abstract:
Concisely relates the contents of the study.

Introduction:
Concise statement of the problem under study

Thank you for these comments.

Methods

3. The inclusion criteria for the HIV cohort are clearly stated. It is not clear to me how participants were determined to be living on April 1, 2009.

We were able to determine whether individuals had died prior to April 1, 2009, as their linked records in the health administrative databases held at the Institute for Clinical Evaluative Sciences include the Registered Person’s Database (RPDB), which captures demographic information (age, sex, postal code, mortality data) demographic information, including age, sex, postal code and mortality data. This is now specified in the following line under Study Population on page 6: “We identified eligible individuals from the Registered Persons Database (RPDB), an electronic registry of all Ontarians eligible for health coverage that captures patient demographic information, including age, sex, postal code and mortality data.”

4. By not matching the controls on any factors (including age and sex) it becomes possible to see how these factors differ between the two cohorts.
Thank you.

5. The chronic diseases under investigation are well described. However, it is unclear to me whether the prevalence estimates include any physician billing claim from 1992 to 2009 or whether a specific time period closer to 2009 was chosen. If the period in which the HIV infected cohort could have had an eligible physician claim was longer, might this offer a partial explanation for the greater burden of co-morbidities in this group?

Thanks for allowing us to clarify this point. Both cohorts (HIV and general population) had chronic diseases ascertained in identical ways, which we have clarified on page 6 in the statement “All variables for patients in the HIV and Ontario cohorts were captured using identical methods”. The look back window for ascertainment varies by chronic disease based on the databases required for the disease algorithm. For example, algorithms requiring Ontario Health Insurance Plan data date back to 1991, those requiring the National Ambulatory Care Reporting System to 2003. The look back for individuals in both cohorts dates from the index date of April 1, 2009 to the first available date for these databases. Due to space constraints, we have not delineated the details of each chronic condition ascertainment, but have referenced their source publications on the first full paragraph on page 7.

6. The statistical analyses are well described.

Thank you for the positive remark.

Results

7. I would like to see more descriptive information (with numbers and p values) written in the 1st paragraph, rather than just having the reader refer to the text.

We have included the numbers and p values in the first paragraph of the results section on page 9, as requested.

8. Is it possible to report on what proportion of the HIV infected cohort had died by 2009 and also what the duration of follow-up for these individuals was?

Thank you for this comment. We appreciate that follow up of individuals with HIV could be different from those in the general population. However, the purpose of our paper was to describe the prevalence of comorbidities in a cross-section of the population, namely those alive on April 1, 2009. The percentage of people who died before this date and their "duration of follow-up" wouldn’t affect these prevalence estimates. We hope this clarifies this reviewer’s concerns.
9. Tables 2 and 3 could be merged.

Both reviewers made this comment. Table 2 presents the non-age/sex-standardized data alone for the actual comorbidity prevalence estimates, and Table 3 presents the age/sex standardized prevalence estimates and prevalence ratios comparing people with HIV to the general population. As they provide different estimates, we feel that combining them would be confusing for readers. However, if the reviewer feels strongly, we could delete Table 2 to avoid the confusion of presenting both data within one table.

Discussion

10. With regards to the statement “Both men and women with HIV acquired an increasing number of chronic conditions as they aged”. Is this not also true of HIV uninfected individuals?

This is true. We have clarified this within the sentence in question on page 11: “In addition, as is seen in the general population, our study confirms the accumulation of multiple chronic conditions with age for both men and women with HIV.”

11. The authors do discuss how differences in mortality rates between the HIV infected and uninfected populations, can affect estimates of prevalence for comorbid conditions. However, it would be helpful to discuss this in specific reference to the issues raised above – i.e. observation time periods.

We appreciate the reviewer’s feedback on this aspect of our study. However, we have a cohort of individuals diagnosed with HIV who are alive at a cross-section in time. We used historical data to comprehensively identify their comorbidities. Then we took a random sample of the general population who are also alive at that same cross-section in time, and determined their prevalence of comorbidities in an identical way. As such, the comparison is simply the descriptive prevalence of comorbidities among HIV persons versus general population. We hope this explains the methods more clearly.

12. If people infected with HIV are from more marginalized populations are more likely to seek care at CHCs wouldn’t we expect that a much larger proportion of HIV-infected individuals access their care through CHCs?

The reviewer is right to point out that we might be missing some patients with HIV who are cared for in CHCs. However, as described on page 13 "Community health centres are estimated to provide primary care for about 1% of the Ontario population [42], thus our findings are unlikely to be substantially affected by missing these individuals." We hope the reviewer accepts this as a limitation of our administrative data.

13. Some discussion of the possible reasons for these differences between HIV
infected and uninfected people would be appreciated. Does the literature suggest that these are independent associations with HIV, or do they represent an overabundance of traditional risk factors (smoking, poor diet, sedentary behaviour...) among populations who are also at high risk for HIV infection.

The reviewer is correct in stating that comorbidity in HIV represents a complex interplay of factors. We have tried to make this statement more clearly in this sentence on page 12: “It is likely that the prevalence of individual comorbidities is a result of the complex interplay of aging, behavioral risk factors such as smoking, known to be higher among those with HIV, genetic risk factors, HIV severity, and ART history[8, 33–36].” The references cited speak to this issue in more depth.

Reviewer 2

14. This is a useful paper that contributes some new knowledge about co-morbidities among people living with HIV in Ontario population. However, the paper is hard to read – at times I wondered whether there were two writers struggling with varying concepts and unable to agree on a simple narrative.

We thank the reviewer for their constructive comments and hope our responses below have improved the readability of the manuscript.

General comments

15. I could find no operational definition of chronic disease and the concept of ‘disease burden’ caused me no end of problems.

In fact, I think the paper would be vastly improved if ‘prevalence’ rather than ‘burden’ was used throughout. This is shown in the first sentence of the Discussion (Our study quantifies the substantial comorbidity burden among people living with HIV...) I would suggest (Our study quantifies the substantial prevalence of comorbidity among people living with HIV...) The paragraphs that follow then flow more logically.
The burden of disease appears to be defined in terms of prevalence/number of conditions ‘...disease count was used to measure morbidity burden.’ Is this sufficient? Having read the paper a few times, I’m still left with a feeling that it lacks something to convey exactly what ‘morbidity burden’ is. The study measures types and numbers of chronic conditions but the nature of the burden is not described – is it severe, very severe, mild or moderate burden? There is no indication of how diseases are quantified apart from a count of numbers but isn’t this just recording the prevalence? The opening section states that ‘the specific objectives ... are to describe the burden of co- morbidities for people living with HIV and to compare this burden to an age and sex adjusted general population.’ Here again, replacing the word ‘burden’ with ‘prevalence’ tells me what precisely the paper is about. (I don’t think it is really measuring ‘burden’).
From data linkage combining RDDB and OHIP, the quantum of physician visits over 12 or 24 months might have been able to put more meaning on disease burden or severity but I accept this may be outside your remit in undertaking this study. I feel this paper could be improved if the Introduction/Background was re-written and clarified (as in parts of the Abstract, for example).

We appreciate that this reviewer took issue with the term “burden” to describe comorbidity and multimorbidity. However, “burden” is used frequently to measure chronic disease in the health system specifically using similar data to this study (see reference 6) as well as in specifically for individuals with HIV (Samaras, K. The Burden of Diabetes and Hyperlipidemia in Treated HIV Infection. Curr HIV/AIDS Rep (2012) 9:206–217). Furthermore, reference 28 is a systematic review looking at different measures of morbidity burden and includes comorbidity count as a valid measure for determining the relationship between multimorbidity and health care utilization and between multimorbidity and quality of life.

However, we have taken a careful review of the manuscript and have changed wording to reflect prevalence rather than burden throughout, including the two sentences specified by the reviewer. We have been careful to use “comorbidity” to represent one specific condition and “multimorbidity” to represent more than one condition in the same individual above and beyond their index HIV. These can be found in the marked up version of the manuscript.

Results
16. The Results are presented in ‘cut and paste’ type blocks with a paragraph each for Tables and the Figures. The narrative slips at times between co-morbidity and multimorbidity. It might be useful for readers not familiar with the topic if it was clearly stated that HIV is the index case when describing co-morbidities. In fact, it might be smarter to stick with the term ‘comorbidities’ throughout (as the title suggests!) and not add the complication of multimorbidity at all. The first sentence of the second paragraph of the Results is especially difficult to read... (Table 2 presents the burden of individual comorbidities and measures of multimorbidity among individuals in the HIV cohort).

Multimorbidity is defined in various ways, but most commonly as the presence of more than one complex condition in the same individual. It is an increasingly important concept in the medical literature as we seek to understand how to care for patients not only with specific diseases, but in the reality that patients often have multiple conditions that make disease focused care challenging (see reference 45). On page 7, we have clarified that the term multimorbidity in this paper pertains to conditions above and beyond HIV as the index condition (“In patients in the HIV cohort, this multimorbidity is in addition to HIV as their index condition”). As per point 15, we have been careful to streamline the terminology used by removing the term “morbidity” and using “comorbidity” when referring to one specific condition and “multimorbidity” when referring to two or more conditions.

17. Tables 2 and 3 could be incorporated into a single table. The slight difference in the %
prevalence of the HIV cohort for age-sex standardization could be explained if Tables collapsed into one.

*Kindly refer to our response to point 9, above.*

18. Similarly, Figures 2(a) and 2 (b) could form a single graphic.

*We have combined the figures as suggested and revised the captions accordingly.*

19. The finding that multimorbidity was (comorbidities were...) higher among HIV women as compared to HIV men and when compared to Ontario women across all age groups is interesting new knowledge. It would be useful to have alluded to the topic in the Introduction, provide the results and proceed to integrate both into the Discussion. It suddenly appears in the results...

*Thank you to the reviewer for pointing this out. This was an unexpected finding. In fact, most referenced studies aiming to understand comorbidity in clinical cohorts of people with HIV do not compare the differences between men and women, and many of these studies describe their populations as underrepresenting women with HIV in general. Only Salter et al (reference 34) commented on a greater prevalence of multimorbidity among female than male HIV positive drug users. It would seem forced to introduce this in the background, but have ensured our intent is presented in the methods (statistical analysis, page 8), results (page 10), and discussion section (pages 11 and 12) more clearly.*

**Discussion**

20. The first paragraph of the Discussion is very repetitive and needs rewriting/editing/shortening. (See above)

*We have substantially revised this paragraph as suggested.*

21. The second paragraph does not link logically with the Introduction/Background and there is little attempt to integrate the new knowledge from the results into the discussion.

*Thanks to the reviewer for suggesting ways to tighten the flow of the manuscript. We have made changes to the introduction and discussion sections so that they flow more clearly and consistently from a) the changing landscape of HIV as a chronic condition, b) the need to measure the prevalence of specific comorbidities, c) the increasing role of multimorbidity among people with HIV, and d) the potential change in approach to care that may be required given these findings.*

22. In addition, the discussion about specific conditions (diabetes, COPD, etc.) appears out of place and perhaps also needed to be mentioned in the ‘Statement of the problem’ in
the Introduction/Background. This would improve the paper, make it less jarring and improve the flow of the narrative.

*We have added the following sentence and a reference to the background on page 4: “While the literature regarding what factors contribute to the prevalence of specific conditions is evolving, it is clear that multimorbidity, the presence of several of these conditions, is increasingly the norm for people with HIV[9].”*

23. The sentence ‘as the focus of our study was to describe comorbidity burden in the context of health services delivery needs...’ is a bit forced and somewhat out of place. No mention of this focus in the Introduction...

*The reviewer is right – this sounds forced – and as such we’ve simply deleted it to keep the limitations more clear.*

Abstract

24. *Methods:* I would suggest omitting the word ‘burden’ from the second last sentence.

*We have changed burden to prevalence in this sentence.*

25. In addition, separating mental health morbidity from physical health morbidity adds little to the paper.

*We respectfully disagree with the reviewer on this point. The prevalence of mental health conditions is incredibly high in people with HIV, a reality with a significant impact on their ability to access and sustain care and therapy. In fact, the adverse role of mental health conditions on the care and treatment of other conditions, like diabetes, is increasingly understood. We believe it’s important to leave mental health as a separate entity and feel doing so doesn’t hamper the readability of the paper. We hope the reviewer and editor agree.*

26. **Conclusion:** Including co-morbidity and multimorbidity and then adding ‘burden’ complicates what should be a relative straight-forward narrative here. It makes much more sense without the word ‘burden’.

*We have made the suggested changes to these sentences.*
28. Overall
Overall, interesting paper with new information and should be published.
I would suggest some serious editing of the document, reduce the length (repetitive in places) and improve the flow/style of the writing.
I would seek to integrate Introduction, Results and Discussion in a more seamless fashion.
Improve the consistency of the terms used – co-morbidity and multimorbidity – it might be better to concentrate on co-morbidity only, using HIV as the index case. I would have mental illness as a morbidity like the other nine chronic conditions.
I would omit the term ‘burden’ and use prevalence instead.

We thank the reviewer for his/her suggestions and hope the detailed changes improve the readability of the manuscript.

Additional Editorial Request:

29.) Please include your figure legends separately at the end of your manuscript file rather than as part of your figures files as described in our guidelines: (http://www.biomedcentral.com/bmcpublichealth/authors/instructions/researcharticle#preparing-figures).

We have included only the captions in the article and have uploaded the figures as a separate file.