Author's response to reviews

Title: Virologic Suppression and Mortality of patients who migrate for HIV care in the province of British Columbia, Canada, from 2003 to 2012: a retrospective cohort study

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RE: Treatment outcomes of patients who migrate for HIV care in the province of British Columbia, Canada, from 2003 to 2012: a retrospective cohort study

Dear Editor,

Thanks for the comments. As requested, we have revised the manuscript in light of your comments. A revised version of the manuscript is enclosed. Each response is numbered according to each reviewer’s comment, and it is addressed how the changes were implemented in the new version of the manuscript. The changes are highlighted in yellow in the manuscript.

Please note that we have made a mistake in the spelling of one of the author’s name: It should be Nicola Goldberg and not Nichola Goldberg.

We hope you will find these revisions acceptable. If there is any other information you require, please do not hesitate to contact us. Thank you again for your consideration.

Yours sincerely,

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RESPONSE TO REVIEWERS

Reviewer #1:

Major compulsory revisions

1. The way the results were calculated should be explained. They do not match with table 2 (i.e. they “observed that in HAs 1, 4 and 5 between 10% and 17% of PLWH migrated to HA3 and for HA2 this proportion increased to 65%”. Those percentages are between 5% and 10% from HAs 1, 4 and 5 and 20% from HA 2 according to their table. They found that “in HA 3, 94% of its PLWH residents remained in the same HA for their care”. According to the table, 2,027 from 2,648 residents in HA 3 (76.5%) received care in this HA). Moreover, the results presented in table 2 (second table, line 482), In Migrants, Out Migrants, do not match with the results in the table 2 (first table, line 481). We think these results are inversed. Consequently, the migration rates should be recalculated. Then all results should be verified to avoid the mistakes in the interpretation. Discussion should be reworked from the correct results.

Response: We are deeply sorry for the mistake. The numbers in the text have been revised. We checked Table 2 and the calculations are correct.

In the Methods we have clarified that the in-migrants are the ones who leave the HA that they resided to receive care in another HA. The out-migrants are the ones arriving from different HAs to receive care in the HA that is not their residence. Thus, for example, 184 individuals resided at HA 1. Out of these, 145 received care in HA 1, 39 (i.e. 184-145) left HA 1 to receive care elsewhere and 52 (i.e. 197-145) arrived at HA 1 to receive care.

<table>
<thead>
<tr>
<th>Health Authority where PLWH received care</th>
<th>Health Authority where PLWH resided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Authority</td>
<td>In-</td>
</tr>
<tr>
<td>where PLWH received care</td>
<td>Migrants</td>
</tr>
<tr>
<td>1</td>
<td>145</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>184</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health Authority</th>
<th>Population at risk</th>
<th>In-Migrants</th>
<th>Out-Migrants</th>
<th>In-migration rate</th>
<th>Out-migration rate</th>
<th>Net-migration rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>184</td>
<td>39</td>
<td>52</td>
<td>212.0</td>
<td>282.6</td>
<td>-70.7</td>
</tr>
<tr>
<td>2</td>
<td>314</td>
<td>83</td>
<td>502</td>
<td>264.3</td>
<td>1,598.7</td>
<td>-1334.4</td>
</tr>
<tr>
<td>3</td>
<td>2,648</td>
<td>621</td>
<td>127</td>
<td>234.5</td>
<td>48.0</td>
<td>186.6</td>
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<tr>
<td>4</td>
<td>356</td>
<td>57</td>
<td>84</td>
<td>160.1</td>
<td>236.0</td>
<td>-75.8</td>
</tr>
</tbody>
</table>
Table 2 shows the distribution of PLWH according to their residence and to where they received care during the study period. We observed that in HAs 1, 4, and 5, between 4% and 10% of PLWH migrated to HA 3 (i.e. the largest urban center) to receive care, and for HA 2 this proportion increased to 21%. In HA 3, 77% of its PLWH residents remained in the same HA for their care. Consequently, we obtained a negative net-migration rate of -70.0, -75.8, and -248.2 per 1000 PLWH on cART for the HAs 1, 4 and 5, respectively, indicating that PLWH were leaving these HAs at a higher rate than staying in them (Table 2). HA 3 had a net-migration rate of 186.6 per 1000 PLWH on cART showing that this HA is absorbing most PLWH migrating for care across BC. Interestingly, HA 2 had the highest negative net-migration rate (-1334.4), with most of its PLWH residents leaving to receive care in HA 3.

Our results demonstrate that there is a substantial heterogeneity in the number of PLWH seeking medical care outside the HA where they resided; between 4% and 21% of PLWH in each HA migrated to HA 3, which hosts the province’s largest HIV care center.

Minor essential revisions

The objective posed by the authors is well defined. However, the term “effect” should be replaced by “association” because it’s not possible to determine the casual relationship between migration and virologic suppression and mortality. The same revision should be done at the background (abstract and end of background). In the title the term treatment outcomes” should be replaced by “virologic suppression and mortality” because the association between mortality and treatment is not clear. In the abstract “health outcome” could replace the term “treatment outcomes”.

Response: Thanks for the suggestion. We have revised the text accordingly. The changes are highlighted in yellow.
Reviewer #2:

This paper attempts to quantify the extent to which PLWH are migrating to seek HIV care within BC and its effect on virologic suppression, longevity, and mortality. The authors define ‘migration for care’ as ‘the movement from the HA where the PLWH resided to the HA that he/she received care’. The authors conclude that moving to a larger center was significantly associated with lower all cause mortality rates and slightly higher life expectancies.

General Issues to Note:

1. The findings presented in this paper are based on two important assumptions – 1) patients living with HIV move to a larger center in order to receive better care for their HIV disease (presumably because there are more physicians available in the larger (i.e. HA3) centers), and 2) patients who move to the larger centers experience lower levels of mortality and longer life expectancies presumably due to better HIV care. The first assumption is stated numerous times throughout the paper but never supported by data that patients did indeed move for health reasons only.

Response: We checked the document and the comment that the reviewer made can only be found in the Discussion when we mentioned in lines 263-280 that there are a number of possible explanations for our findings. We did not say that any of those reasons were in fact the cause of better/worse outcomes. We indeed said that “further studies will be needed to fully understand the reasons for this type of migration in BC”.

2. The authors discuss ‘migration indicators’ (in Methods) based primarily on the notion that if there is a difference in the address of where the patient resides and where they received HIV care then the patient must have migrated to get that HIV care. The authors do not indicate how they actually know that patients moved from one HA to another specifically for HIV care.

Response: In our database, we longitudinally track several addresses for patients including their residence, the place in which they go to a physician, the place they go for laboratory testing and the place they pick up their prescriptions. Thus, we are in a good place to track these individuals over time. In this study, in lines 111-117 we defined the addresses we used to access migration in this study.

3. There are numerous reasons – many not related to health – that patients move as pointed out by Gill and Krentz (AIDS Patient Care and STDs 2015 29(7)). The authors do not state how many of the patients who moved actually moved because of their health – all? 75% 50% 25%? The underlying premise of the paper that patients migrate to seek care is thus weak and is totally unsupported in this paper.

Response: Thank you for the suggestion for the article and we have added it to our paper. It should be mentioned that we have stated in lines 166-168 that “We then defined migration for care as the movement from the HA where the PLWH resided to the HA that he/she received care. Note that this movement (within short and long distances) is temporary and may be for voluntary or involuntary reasons”. Thus, we did not say in our definition that these patients changed address, nor we have said that they moved for health reasons. We only said that they sought care outside/inside their HA of residence. As stated in item 2 Reviewer #2, we do know where these individuals seek HIV care in the entire province.
4. Many people migrate from smaller centers to larger centers in BC and elsewhere for economic, personal, or other reasons. How did the authors determine that these HIV infected patients all move seeking better HIV care over the 10 years? Did they control for other factors? This is a serious flaw and major weakness that undermines all interpretation and analysis of the data.

Response: The factors that we have available to us have been controlled for in the analyses. As per lines 279-280, we stated that further studies are necessary to understand the reasons for this type of migration in BC. Additionally, for the use of the term “better care”, please see item 1 Reviewer #2.

2. The second outcome measure used (viral suppression appears not to be impacted) is all cause mortality. The underlying assumption in this paper is that those patients who moved to larger centres had less chance of dying because they migrated. Once again, the supportive evidence is weak at best. How many deaths are due to HIV related conditions versus non HIV related conditions? How many from trauma vs. illness for example? Crude all cause mortality rates are often higher in rural areas regardless of HIV status. The authors imply mortality is decreased because of the migration (and supposedly better care) but other factors (some factors are discussed in the limitations but not all) can and do contribute to decreasing mortality other than HIV care as the paper seems to indicate. The authors may want to consider using only HIV related deaths or other HIV related health outcome markers.

Response: As we have acknowledged, there are lots to be done to understand the results we got in this paper. However, please note that we did not state that there is a causal relationship between migration and less mortality because individuals moved to HA 3. We only observed an association. As for the causes of mortality, the data depends on how the coroner fills out the death certificate. In our data he/she mostly writes ICD10 B24 (i.e. Unspecified human immunodeficiency virus [HIV] disease). It is important to mention that larger care centres in BC offer many non-medical services for PLWH, such as housing, addictions and psychological support, as well as, support groups and peer networks. For an example of these resources please see http://www.vch.ca/your-health/health-topics/hiv-aids/.

3. The authors also use a bit of ‘sleight of hand’ to estimate the number of deaths in the patients deemed LTFU. While the statistical approach may be valid, one wonders why the authors couldn’t simply find LTFU patients who had died in BC in the BC Vital Statistics Agency database. If they had died after leaving HIV care, they should be listed in this database; an attempt should be made to investigate this database before estimated the number of LTFU patients who may or may not have died.

Response: The patients that we have LTFU assigned are indeed LTFU. If a person was LTFU and then died in BC we know when/where they died and they no longer are classified as LTFU. If a person died in another province/country, we do not have data to ascertain whether he/she died outside BC, and therefore, they are coded as LTFU. We also said in lines 310-313 that “Although we adjusted our data by means of a highly predictive statistical model, we continue to conduct ongoing linkages with the BC Vital Statistics Agency to ascertain the health status of these individuals in our database”. At last, for privacy reasons we cannot obtain Canada-wide vital statistics data since it would require us to send data outside our servers.

4. Abstract – The first sentence of the results presents data on physician availability across all HAs, however, this is not discussed in the methods section. This needs to be addressed in the methods section.
Response: We have added the following sentence “We also calculated per-capita rates (per 100 PLWH ever on cART) for each HA by dividing the number of PLWH by the number of physicians attending this population.”

5. Abstract - In the conclusion section it is stated that the ‘life expectancy of PLWHs is increasing over time, and the continued migration of these individuals can potentially overburden the resources of receiving HAs, however, this is not the focus of the paper and nowhere in the paper does it address (with actual data) potential burdens to the receiving HAs. It is misleading to include this statement in the conclusions section.

Response: We have shortened the conclusions to only say “Conclusions: A thorough understanding of the reason(s) for these significant migration rates across BC will be critical to inform resource allocation and optimize the impact of HIV treatment.”

6. Background – Line 68 – ‘...HIV care has increasingly shifted to decentralized community-based medical practices’ needs references.

Response: We have added two references.

7. Methods – Lines 101-102 – How do the authors deal with patients who move or migrate out of BC? It needs to be clearly addressed here. (Note – the clinical and demographic profiles of people who formally move are different from those who are LTFU as recent studies have shown).

Response: We have added the following text:

Eligible PLWH were cART naïve, ≥20 years old, enrolled between January 1, 2003 and December 31, 2012 and followed: (1) until December 31, 2013 (if alive); (2) until the last contact date if they were lost to follow-up or if they moved out of BC; or (3) until the date of death.

8. Methods - Line 123 – The authors need to quantify what is meant by ‘experienced clinical staff’. How is that defined? Do they include nurses for example?

Response: We have deleted the word experienced. It now reads It is also noteworthy that HA 3 has the highest number of clinical staff, prescribing physicians, comprehensive HIV supportive services and it hosts the BC-CFÉ.

9. Methods - Line 131 – What is meant by ...on a ‘continuous basis’?

Response: We receive patient data every day through the Drug Treatment Program (http://www.cfenet.ubc.ca/drug-treatment-program). We have changed the word continuous to daily.

Deaths occurring amongst PLWH during the follow-up period were identified on a daily basis from physician reports and through monthly record linkages carried out with the BC Vital Statistics Agency.

10. Methods - Lines 148-159 – Can this analysis be reconciled with the BC Vital Statistics Agency data on deaths within the province?
Response: We have answered this question in item 3 of Reviewer #2.

11. Methods - Lines 162-164 – Physician availability/accessibility was not previously discussed as a potential driver of migration nor are there any previous references alluding to this point. This issue needs to be addressed first before it can be included here in the discussion. How or why is physician availability directly related to seeking care among HIV patients? Where is the previous evidence for this point?

Response: To address this concern, we removed the word accessibility. However, since we reported the per capita physician rate (lines 163-165) left the word availability in the discussion.

12. Results - Lines 202 and 203 – the statement ‘...PLWH migrated to HA3 to receive care, …’ is not supported by data. These people may have migrated to HA3 but there is no evidence provided that they categorically migrated to receive care. As stated earlier, there may be many non health related reasons why they move. Receiving care in the new HA may be just a side effect of the movement.

Response: Please see item 3 of Reviewer #2. Migration in this study does not mean that they changed their residence address. It says that they only seek HIV care outside the region of their residence.

13. Results - Lines 212-214 – How many patients moved (rather than LTFU) out of the province during this time period?

Response: Overall, in this data, 157 (4.3%) individuals moved out of BC. Of the 666 LTFU, 24% moved out BC. We added the following sentence:

A total of 666 (18%) PLWH were lost to follow-up, and of these, 157 (24%) were LTFU because they moved out of BC.

14. Results - Lines 227-228 – It is interesting that in HAs 1, 2, 3, and 4 had similar life expectancies regardless of where PLWH live or sought care (and no differences in viral suppression rates) as presented here yet the premise of the paper is that key differences are seen based on migration patterns. Mortality rates may be different but the underlying cause of mortality is not explored in detail.

Response: Yes, indeed was it an interesting observation that life expectancies were robust to where patients lived and sought care, and mortality rates had a bit more variation (4-5 years). The issue regarding the causes of death has been addressed in item 2 of Reviewer #2.

15. Results - Lines 233-242 – This discussion on the STOP HIV/AIDS initiative seems irrelevant to migration patterns unless it can be documented that patients moved to HAs specifically for this program. This documentation is not provided in this paper.

Response: We addressed this item by:

Removing the sentence “led by the BC-CfE” from lines 138-141. However, we left the “STOP HIV/AIDS” to justify why we broke down the periods as 2003-2007 and 2008-2012. Additionally, in lines 239-240 we decided to mentioned “STOP HIV/AIDS” twice to describe the results. In the Discussion, we changed
Finally, during the study period, we demonstrated that mortality rates decreased significantly in HAs 2, 3 and 5.

16. Discussion - Line 245 – This statement – ‘our results demonstrate that there is a substantial number of PLWH seeking medical care ...’ is not accurate because it has not been shown that patients are moving specifically for medical care; patients may be migrating but it still is not shown that they are moving for health reasons.

Response: As per the previous items, we believe that we have clarified this issue.

17. Discussion - Lines 248-249 - The authors speculated that physician availability was a driver for migration patterns but once again this is not supported by actual data.

Response: We changed the sentence to read Although we investigated whether out-migration rates in these regions were due to physician availability, we observed that physicians working outside HA 3 were caring for fewer PLWH as many of their patients were seeking care in HA 3.

18. Discussion - Line 250 – The statement that physicians working outside HA3 were caring for fewer PLWH than previously believed is not supported. ‘Previously believed’ by whom?

Response: Please see item 17 Reviewer #2.

4. Discussion - Lines 256-257 – How do the authors account for significant decreases in mortality rates in HA2 where the stop HIV/AIDS was not initiated?

Response: It is an important observation, and we need further investigation to understand this result.

5. Discussion - Line 259 – The statement ‘We hypothesized that receiving community-based HIV care would be associated with better outcomes, ...’ is not accurate. It is alluded to in the introduction but is not stated as a hypothesis.

Response: We modified the Introduction to include the hypothesis.

We hypothesized that receiving community-based HIV care is associated with better health outcomes.

6. Discussion - Lines 272-274 – The third point is self promoting and self gratifying (especially as the authors are all working in HA3) and is not supported by any evidence and should be removed. This type of statement should never appear in an academic paper.

Response: We are sorry that we have offended the reviewer. It was never our intention. We have removed this sentence from the paper.

7. Discussion - Lines 289-290 – The statement that continual migration of these individuals can potentially overburden resources, while potentially accurate, is not supported by any evidence in this study. This would be okay in the discussion section but it also appears in the Abstract giving it more importance than the data used to support it (which there is none).
**Response:** We have removed this sentence from the abstract. Please see item 5 Reviewer #2.