Author’s response to reviews

Title: Physician experience and rates of plasma HIV-1 RNA suppression among illicit drug users: An observational study

Authors:

Sassan Sangsari (sassan.sangsari@gmail.com)
M-J Milloy (mjmilloy@cfenet.ubc.ca)
Amir Ibrahim (amir.ibrahim@mail.mcgill.ca)
Thomas Kerr (uhri-tk@cfenet.ubc.ca)
Ruth Zhang (rzhang@cfenet.ubc.ca)
Julio Montaner (jmontaner@cfenet.ubc.ca)
Evan Wood (uhri-ew@cfenet.ubc.ca)

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Author’s response to reviews: see over
Dear Roselle:

Thank you for your correspondence of November 1, 2011. As requested, we have revised the manuscript in light of the peer-reviewer comments. We have addressed all suggested changes to the revised paper.

A revised manuscript has been uploaded and we have listed below the changes we have made. We hope you find our revisions acceptable. We would be happy to hear from you if you have further comments or suggestions.

Thank you for your assistance with the manuscript.

Best personal regards.

Sincerely,

Evan Wood, MD, PhD, ABIM, FRCPC
Director, Urban Health Research Initiative
BC Centre for Excellence in HIV/AIDS
**Peer Reviewer Comments (Enrico Girardi)**

1. As suggested by the reviewer, we have added text describing how patients were referred to the different physicians. The relevant text (page 5) reads:

   In British Columbia, antiretroviral prescribing physicians could be located anywhere in the province and not at only one institution.

2. We agree that the manuscript is improved by describing the location where different physicians worked. The relevant text which has been added to the manuscript (page 5) reads:

   Patients selected antiretroviral-prescribing primary care or specialist physicians in a non-random manner through self-selection or referral from other physicians.

3. We agree that the paper is improved by adding a brief discussion of the previous literature on physician experience and outcomes from ARV. The relevant added text in the Discussion (page 8) reads:

   Prior to the advent of combination antiretroviral therapy, a US study found that higher physician experience was associated with longer patient survival [13]. Similar results have also been reported in the era of combination antiretroviral therapy [14].

**Peer Reviewer Comments (Alessandro Cozzi-Lepri)**

1. We agree with the reviewer that it would be ideal if real time data were available from our cohort. Unfortunately, because of delays secondary to data entry and being limited to periodic linkages with laboratory data, the current data set only includes data up until 2008. As a result much of the data were collected at a time when the lower limit of detection for the viral load assay was 500 copies/mL. We feel, however, that this is not a major limitation and have added the following text to the second to last paragraph (page 9) to address this suggestion:

   Finally, our analyses only includes follow-up information until 2008 and data collected when the lower limit of detection was 500 copies/mL. Future studies should continue to assess whether physician experience is associated with outcomes from HIV treatment, especially as modern HAART regimens are increasingly simple to take.
2. As suggested, we have consistently used the definition of viral suppression as being \(500\) copies/mL throughout the manuscript. Please see revised paper.

3. We agree with the Reviewer that there are a range of reasons for failure to achieve virological suppression, including drug toxicities. During the period of our study, the therapeutic guidelines recommended altering ART regimens rather than discontinuation when toxicities occur. A limitation of our province-wide data set is also that toxicities have not been routinely recorded in a standardized way. This precludes a sub-analysis of toxicity assessment between those with more or less experienced physicians. To address this suggestion, the following text has been added to the Discussion (page 10):

   In addition, while this study demonstrated an association between physician experience and higher rates of plasma HIV RNA suppression, we were not able to explore explanations for this association. It is likely that physicians with greater HIV-related experience were able to more skilfully address drug toxicities and other concerns that may limit patient adherence.

4. We agree with the reviewer that the manuscript is improved if we provide justification for using Greenland’s \(a \text{ priori}\) model building protocol. Thus, the following text has been added to the Methods (page 6):

   This strategy aims to produce a parsimonious set of covariates to better estimate the adjusted relationship between a primary explanatory variable and an outcome of interest. It has previously been used, for example, to assess the independent relationship between incarceration patterns and non-adherence to ART among injection drug users [12].

   To further address the reviewer’s suggestion, we also provide the results of the multivariate analysis adjusted for methadone use, DTES residence and daily cocaine use. The relevant text in the Results (page 8) reads:

   When we fit a multivariate model including the three main associations shown in Table 1, we found that physician experience was associated with higher rates of plasma HIV-1 RNA viral load suppression (AHR = \(1.23\) per 100 patients enrolled, 95% CI: \(1.07 – 1.40\), p-value = \(0.003\)) after adjustment for Downtown Eastside residence, methadone maintenance therapy and daily cocaine injection.
5. As suggested by the Reviewer, we explored the results of our analyses when physician experience was defined as a categorical variable using tertiles. The relevant text of the Results (page 8) reads:

In a sub-analysis, we explored the impact of physician experience on time to viral load suppression when physician experience was defined as a categorical variable using tertiles. In the first tertile, physicians had treated less than 22 patients previously and the median time to plasma HIV-1 RNA < 500 copies/mL was 9.5 months (95% CI: 4.4 – 14.5). In the middle tertile, physicians had treated 22 – 81 patients previously and the median time to suppression was 6.2 months (95% CI: 3.0 – 13.4). In the most experienced tertile, physicians had treated greater than 81 patients previously and the median time to plasma HIV-1 RNA suppression < 500 copies/mL was 3.0 months (95% CI: 2.3 – 4.7).

We would be willing to include a Kaplan-Meier plot should the editors feel this is necessary but we believe the above results present a clear description of the impact of physician experience when this variable is categorized as the reviewer suggests.

6. We agree with the Reviewer that the manuscript is improved by explaining why some variables were time updated while others were fixed at baseline. The relevant text of the Methods (page 5) now reads:

Physician experience was fixed as a baseline characteristic at the time the patient initiated ART as we believe that this was the best way to estimate physician experience. We recognized certain behaviours (e.g. drug use activity) could confound this association so these measures were treated as time-updated variables based on each participant’s semi-annual follow up visit.

7. We agree with the Reviewer that the manuscript is improved if we justified how we adjusted for which antiretrovirals were included in each patient’s regimen. To address this suggestion, the following text has been added to the Methods (page 6):

Patients were prescribed antiretroviral therapy consistent with therapeutic guidelines which, beginning in 1996 for all patients, recommended triple combination therapy. While the drugs used over the study period changed markedly over time, consistent with previous analyses, we adjusted for whether protease inhibitors were used in the initial regimen or not as a strategy to adjust for confounding that could occur as a result of regimen type. Given the large number of nucleosides used in the
backbone of the ART regimen during the study period, we elected to not adjust for this in the analysis.

8. As suggested by the Reviewer, the number of patients included in the study and the number that achieved plasma HIV RNA levels < 500 copies/mL is now included in the Abstract and Results (please see revised manuscript).

9. As suggested, “per year increase” has been changed to “per more recent year”.

10. As suggested, we have clarified that older age refers to patients not treating physicians.

11. As suggested, we have corrected the erroneous reference to Figure 1 in the test to Table 2 (page 8).

12. As suggested, we have moved the text regarding the limitations of our adherence measure to the Discuss (page 9).

13. As suggested, we have updated Table 2 to state that the HR refer to the time to plasma HIV RNA suppression < 500 copies per mL (page 15).