Author's response to reviews

Title: Highly active antiretroviral therapy and hospital readmission: Comparison of a matched cohort

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Author's response to reviews: see over
Dear Dr. Phillips:

RE: Highly active antiretroviral therapy and hospital readmission: Comparison of a matched cohort

Thank you for your recent correspondence inviting us to revise and resubmit the above manuscript. In the current version of the paper, we have responded to each of the reviewers’ comments and the appropriate changes to the manuscript have been made. We provide a point-by-point response to the comments of the editor and both referees below.

Responses to Comments from the Editor

1. Please can you clarify if you obtained ethical approval for the study?

No changes requested. Ethical approval for this study had been obtained from the Providence Health Care Research Ethics Board; acknowledgement of this approval has been included in the manuscript, page 6, paragraph 1. We thank the reviewer for raising this issue.

Responses to Comments of Referee 1: Ellie Shoenbaum

General Comments

1. HAART is so effective in reducing the frequency of opportunistic infections associated with HIV, it is not surprising that it reduces readmissions.

No changes requested. The authors recognize this result has been found elsewhere, however results found in other observational studies may be subject to selection bias. We believe our analytical approach of propensity score matching reduces the possibility of this form of bias, thus providing a meaningful contribution to the literature on the effectiveness of HAART, as well as serve as a good application of a highly useful analytic technique.

2. The index hospitalizations to an HIV service were largely due to OIs. This is unusual for a person on HAART and suggests that the persons in the study were just recently started on HAART, which could have exacerbated an underlying infection (e.g., CMV or
The other possibility is a lack of adherence which the study could not readily assess.

**Done.** The manuscript sent for review did not include information on the reasons for index admission. Table 2 lists all of the AIDS-defining illnesses of patients in each cohort at index admission (i.e., OIs previously experienced) pre- and post-propensity score match. The objective was to show that patient populations were similar following the propensity score matching exercise. We recognize this may have appeared misleading to the reader, and have thus added a sentence clarifying this distinction in the results section, page 9, paragraph 2.

3. One also wonders if the persons not on HAART at baseline began taking it during follow-up. This would have been relevant information to report and factor in the analysis.

**Done.** Given the nature of the data available to us, we were not able to observe changes in medication usage over the follow-up period. We believe, however, that the estimates we have produced are conservative ones, given the possibility of patients switching from both ‘on HAART’ to ‘not on HAART’ and ‘not on HAART’ to ‘on HAART’. Our reasoning is as follows: Assuming HAART does, in fact reduce hospital admissions,

- Let $R_1$ be the one year readmission rate of all patients remaining ‘on HAART’
- Let $r_1$ be the one year readmission rate of patients beginning ‘on HAART’, but some proportion transitioning to ‘not on HAART’ over the course of the year
- Let $R_2$ be the one year readmission rate of all patients ‘not on HAART’
- Let $r_2$ be the one year readmission rate of patients starting ‘not on HAART’, but some proportion transitioning to ‘on HAART’ over the course of the year
- Assume: 1) $R_1 < R_2$
  2) $r_1 > R_1$
  3) $r_2 < R_2$

If the proportion transitioning in the follow-up period is, in fact, non-negative, our results state that $r_1/r_2 < 1$, implying that $r_1 < r_2$. If this is true, then $r_1/r_2 > R_1/R_2$, thus proving that we have, in fact, produced a conservative estimate. We have included an abbreviated version of the above in the discussion section, page 11, paragraph 2.

4. The analysis period (1997-2002) is broad and covers a time when uptake of HAART likely increased dramatically. Re-hospitalization patterns may have changed over time, just as the kind of person not on HAART in 2002 vs. 1997 likely differed.

**No change requested.** The above argument implies that the comparison may not have been valid given that 1) uptake of HAART was different throughout the period of analysis, 2) Re-hospitalization patterns may have changed over the period of analysis, and 3) patient characteristics within the given cohorts may have changed over the period of analysis. In regards to 1), because we are not concerned with changes in uptake over time and focus instead on a static comparison of chose on and not on HAART, this fact
does not affect our results. With regards to point 2), the contingency table presented below indicates that the distributions the two groups of patients by year of admission are nearly identical. Finally, distributions of patient characteristics were made to mirror one another through the propensity scoring procedure, thus eliminating the possibility of argument 3) compromising the validity of our results.

**Treatment arm by year of index admission**

<table>
<thead>
<tr>
<th></th>
<th>1997</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HAART</td>
<td>82 (25)</td>
<td>66 (20)</td>
<td>59 (18)</td>
<td>46 (14)</td>
<td>43 (13)</td>
<td>35 (11)</td>
<td>331</td>
</tr>
<tr>
<td>HAART</td>
<td>83 (25)</td>
<td>67 (20)</td>
<td>52 (16)</td>
<td>48 (15)</td>
<td>49 (15)</td>
<td>32 (10)</td>
<td>331</td>
</tr>
</tbody>
</table>

5. The use of propensity scores to match was appropriate but limited the analysis to HAART without much explanatory potential. This diminished interest.

No change requested. Given that many of the determinants of success of HAART and of access to HAART have already been identified, we chose a different analytical approach, which we believe to be of value in that it produced results verifying the effectiveness of HAART in an observational setting, controlling for selection bias, which is an important consideration in any naturalistic study.

6. The analysis was designed to rule out IDU-related admissions. However, there is substantial overlap in IDU and HIV morbidity, particularly related to bacterial infections (e.g. sepsis and bacterial pneumonia). How were these handled?

No change requested. One of the authors (AP – AIDS physician and researcher) reviewed all most responsible diagnoses found within the database and identified all IDU-related diagnoses, which are shown below. A very low proportion of total readmissions were considered IDU-related based on the list. We avoided such overlap by separating out only admissions that were clearly only related to Intravenous drug use, and were neither directly nor indirectly related to their HIV/AIDS illness.
ICD-9 Code  | Diagnoses related to IDU
--- | ---
292.0  | DRUG WITHDRAWAL SYNDROME
292.11 | DRUG-INDUCED ORGANIC DELUSIONAL SYNDROME
292.84 | DRUG-INDUCED ORGANIC AFFECTIVE SYNDROME
303.90 | UNSPECIFIED ALCOHOL DEPENDENCE, UNSPECIFIED USE
304.01 | OPIOID TYPE DEPENDENCE, CONTINUOUS USE
305.00 | ALCOHOL ABUSE UNSPECIFIED USE
305.50 | OPIOID ABUSE UNSPECIFIED USE
305.60 | COCAINE ABUSE UNSPECIFIED USE
305.90 | MIXED/UNSPECIFIED DRUG ABUSE UNSPECIFIED USE
38.11  | STAPHYLOCOCCAL AUREUS SEPTICEMIA
38.9   | UNSPECIFIED SEPTICEMIA
41.9   | UNSPECIFIED BACTERIAL INFECTION IN CONDITIONS C
421.0  | ACUTE/SUBACUTE BACTERIAL ENDOCARDITIS;
482.41 | PNEUMONIA DUE TO STAPHYLOCOCCUS AUREUS
590.80 | PYELONEPHRITIS, UNSPECIFIED;
682.0  | CELLULITIS AND ABSCESS OF FACE
682.1  | CELLULITIS AND ABSCESS OF NECK
682.3  | CELLULITIS AND ABSCESS OF UPPER ARM AND FOREARM
682.4  | CELLULITIS AND ABSCESS OF HAND, EXCEPT FINGER A
682.6  | CELLULITIS AND ABSCESS OF LEG, EXCEPT FOOT;
682.7  | CELLULITIS AND ABSCESS OF FOOT, EXCEPT TOE
686.9  | UNSPECIFIED LOCAL INFECTION OF SKIN AND SUBCUTA
707.1  | ULCER OF LOWER LIMBS, EXCEPT DECUBITUS ULCE
707.8  | CHRONIC ULCER OF SPECIFIED SITE
711.01 | PYOGENIC ARTHRITIS, SHOULDER REGION
711.05 | PYOGENIC ARTHRITIS, PELVIC REGION/THIGH
711.06 | PYOGENIC ARTHRITIS, LOWER LEG
711.07 | PYOGENIC ARTHRITIS, ANKLE/FOOT
730.15 | CHRONIC OSTEOMYELITIS, PELVIC REGION/THIGH
730.17 | CHRONIC OSTEOMYELITIS, ANKLE/FOOT;
730.21 | OSTEOMYELITIS, SHOULDER REGION
730.25 | OSTEOMYELITIS, PELVIC REGION/THIGH;
730.27 | OSTEOMYELITIS, ANKLE/FOOT
730.28 | OSTEOMYELITIS, SPECIFIED SITE;
790.7  | BACTEREMIA
965.01 | POISONING BY HEROIN;
965.02 | POISONING BY METHADONE
977.9  | POISONING BY UNSPECIFIED DRUG OR MEDICINAL SUBS
7. Most of the readmissions were non-IDU related but the investigators did not report the nature of these non-IDU diagnoses, except to say that they were non-IDU but included AIDS and other admissions not associated with IDU. This suggests that other medical/surgical/psychiatric admissions occurred but were not addressed in the analysis.

**Done.** We presented three multivariate analyses, including ALL hospital readmission, non-IDU related readmission, and AIDS-related readmission, thus capturing all admissions of each cohort within the study period. Other types of hospital admissions, which may have been indirectly related to their HIV/AIDS status, were included in the overall analysis. We recognize that our justification for presenting each of the separate analyses made not have been clear; we have therefore included an additional sentence in the methods section (page 7, paragraph 1) clarifying our intentions.

8. The cost/benefit analysis of HAART was very limited. There was no stratification by diagnosis, age or gender, etc. There was no discussion of length of stay, frequency of admission, time to admissions within the year or their relation to baseline diagnosis.

**Done.** The comparison of costs between cohorts was added as a supporting result, to underline the economic implications of this cohort of patients’ inability to access HAART. The comment above outlines many good suggestions, but fall outside the intended scope of the article. Nonetheless, the length of stay among those readmitted was reported in the results section, page 10, paragraph 2, as was the individual readmission frequency, which proved to be not statistically significantly different among those admitted within either cohort. Furthermore, time to admission was assessed using a multivariate Cox Proportional Hazards Model, indicating that, following propensity score match and controlling for discharge against medical advice, those not on HAART were readmitted to hospital statistically significantly sooner (Hazard Ratio: 0.79; p-value: 0.0360). This result is noted in the discussion section, page 11, paragraph 2.

9. Finally, the lack of CD4 count from a study using medical records is surprising and unfortunate.

**No change requested.** This is an inherent limitation in our analysis, as CD4 count data was not available to us for this study, as we have noted in our limitations, we believe the causal relationship between CD4 count and HAART initiation is unclear, as a low CD4 count (high plasma viral load) may be the result of using HAART, while a high CD4 count (low plasma viral load) may the reason for the use of HAART. Furthermore, we believe the high level of correlation between CD4 count and HAART use combine to make CD4 count an inappropriate variable to include into an analysis with exposure
defined as HAART use, and hospital resource use as the outcome measure. We therefore believe our propensity score match created patient groups that were comparable on the appropriate patient characteristics.

10. The finding that persons leaving AMA were more likely to be readmitted made sense but this finding in isolation is less compelling.

No change requested. As noted in the methods section (page 8, paragraph 3), leaving hospital AMA was not an appropriate variable to include in the propensity score match as it is related to hospital readmission, however not related to HAART use. The variable was thus included separately in the multivariate logistic regressions.

Minor Comments

1. Sum n and % in columns in table 2.

Not Done. See response to comment #2 and clarification in manuscript (page 9, paragraph 2).

2. Page 11 last paragraph, ART is used. IS this HAART?

Done. Among patients on HAART, over 70% of the patients were on 3 or more antiretrovirals, and 94% were on 2 or more drug combination. We thank you for pointing out this typographical error, which has been corrected (page 11, paragraph 4).

Responses to Comments of Referee 2: Reto Neusch

Major Compulsory Revisions

1. How many patients were on ART at index admission?

No changes requested. In the overall sample, 358 (31%) of 1150 patients were on antiretroviral therapy (the majority on 3 or more-drug regimens) at the time of index admission. This figure can be found in the results section, page 9, paragraph 1. The figures listed table 1, column 1 represent patients remaining following exclusion of deaths at index admission; 342 (32%) of 1084 were on HAART.

2. It is surprising that the number of patients readmitted for AIDS was not different between the two groups. Why is this? Were there any readmissions due to immune reconstitution?

Done. We note that this figure was only not statistically significantly different in univariate analysis. After controlling for AMA, those on HAART had lower odds of readmission for AIDS. Furthermore, univariate analysis showed that those not on HAART who had no prior indication of AIDS had more AIDS hospitalizations.
3. Also the high rate of 42% patients on ART being readmitted is intriguing. Can you provide information on CD4 counts and viral load on HAART vs. not on HAART?

**Done.** Among patients for whom data was available, Mean (Log 10) plasma viral loads of patients on HAART were 2.79 (n=279) and 4.68 (n=236) for those not on HAART, suggesting that individuals observed in our analysis in both cohorts were sicker than a general HIV population. CD4 count data was not available to us (see response to reviewer 1, comment 9; the same argument applies to the use of plasma viral load). We also note that a relatively high proportion of our population were engaged in illicit drug use, which account for both direct and indirect hospitalizations.

4. Time between admission and readmission on HAART vs. not on HAART?

**Done.** See response to comment 8, reviewer 1 and addition to manuscript, page 11, paragraph 2.

5. Further information on hospitalization characteristics like length of stay, ICU admission.

**Done.** Further information on details of hospitalizations has been included in the results section, page 10, paragraph 2. Among those readmitted to hospital, we reported median length of hospital stay (page 10, paragraph 2), indicating that length of stay was significantly different among patients readmitted to hospital in the two cohorts. Hospital stay in the Intensive Care Unit was quite low in either cohort and not statistically significantly different in follow-up (results reported below), as the majority of patients were admitted through the emergency department and were subsequently transferred to a general or specialized AIDS care unit.

### ICU stay during index admission by treatment arm

<table>
<thead>
<tr>
<th>N (%)</th>
<th>No ICU</th>
<th>ICU</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HAART</td>
<td>318 (96)</td>
<td>13 (4)</td>
<td>331</td>
</tr>
<tr>
<td>HAART</td>
<td>327 (99)</td>
<td>4 (1)</td>
<td>331</td>
</tr>
</tbody>
</table>

### ICU stay during re-admission by treatment arm

<table>
<thead>
<tr>
<th>N (%)</th>
<th>No ICU</th>
<th>ICU</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HAART</td>
<td>178 (98)</td>
<td>3 (2)</td>
<td>181</td>
</tr>
<tr>
<td>HAART</td>
<td>148 (99)</td>
<td>1 (1)</td>
<td>149</td>
</tr>
</tbody>
</table>

**Minor Essential Revisions**

1. **Were there any differences in AIDS defining illness at index admission and readmission?**

**No changes requested.** Table 2 (page 15) compares AIDS-defining illnesses at index admission, and shows that percentages of patients with each of the forms of AIDS were
not statistically significantly different, aside from Cytomegalovirus (CMV), which was more prevalent among those on HAART. Following index admission, those on HAART had lower odds of AIDS readmission (OR = 0.66, 95% C.I. = (0.46, 0.96)). These results can be found in table 4, page 17.

**Discretionary Revisions**

1. *Tables: please explain abbreviations used with a footnote. Table 1 and 2 could be merged.*

**Done.** Abbreviations are included at the bottoms of tables 1 and 2 (page 14, 15). In regards to the second recommendation, we have chosen not to merge the tables due to the fact that table 1 displays variables that comprised the propensity score match, while table 2 lists the numbers of AIDS-defining illnesses experienced in each of the cohorts, which were not included in the propensity score match.

Finally, we believe we have significantly improved the paper in making the changes suggested by the reviewers, and we thank them for their useful comments. We hope that you find our responses satisfactory and agree to publish our manuscript.

Best Regards,

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