Author’s response to reviews

Title: High Rates of Unplanned Interruptions from HIV Care Early After Antiretroviral Therapy Initiation in Nigeria

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Author’s response to reviews: see over
May 26, 2015
BioMed Central Editorial Board
236 Gray's Inn Road
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Re: Manuscript BMC Infectious Disease; MS: 1782613771160053

Dear Dr. Calcagno,

We are pleased to submit the revised manuscript entitled: “High Rates of Unplanned Interruptions from HIV Care Early After Antiretroviral Therapy Initiation in Nigeria” to BMC Infectious Disease for consideration for publication. We appreciate the comments made by the reviewers, and have detailed our response to each comment below. In our response, reviewer comments are in non-italicized text, and our responses are in italicized text. Revised portions of the manuscript are included in bold text. The revised manuscript is attached with all revisions highlighted in bold text.

All authors have contributed significantly to the work, and have seen and approved of this manuscript. Thank you for your consideration of our revised paper.

Sincerely,

Aimaloaij A honkhai MD, MPH for the co-authors
REVIEWER 1

Major compulsory revisions

Comment 1:

Please add a phrase or sentence clarifying why pregnant women were not included in the analysis. In the subsection of the methods called “Study Design”, the authors write “Pregnant women were not included in the cohort”. Does that mean that pregnant women were not receiving HIV care at this clinic? Or does it mean that pregnant women were purposefully excluded from this analysis? If the latter, please include a reason why.

We appreciate this feedback, and have clarified this exclusion in the text. We excluded pregnant women (both those pregnant at baseline and those who became pregnant during the follow-up period). The visit protocol at the ABUTH Clinic for pregnant women differs from that of non-pregnant adults, and we wanted to use a uniform definition of unplanned care interruption (UCI). Additionally, although the ABUTH clinic provides services for prevention of mother-to-child transmission, we anticipated that pregnant patients might transfer care (either through documented or undocumented transfers) to locations more convenient for their peripartum needs. We have revised the text on page 5, lines 120-122, which now reads as follows: “Women who were pregnant at enrollment or became pregnant during the follow-up period were not included in the analysis, as the protocol for clinic follow-up differed between this group and the general adult population.”

Comment 2:

Under the running head, I would recommend addition of the following words in bold: “High Rates of Unplanned HIV Care Interruption”. It is currently written “High Rates of Unplanned Care Interruption.”

The character limit for the running head is 40 (with spaces), and making this change would increase the character count to 45. If the editors permit 45 characters, we agree with making this change.

Comment 3:

a) Within the subsection of the methods called “Study Design”, please clarify whether all patients received adherence counseling, clinical examination, and TB screening at subsequent appointments. If not all patients received these services, are there differences between those with and without UCI? Are data available to be able to answer this question? If not, please include this as a limitation.

We agree that this section should be clarified, as all patients should have received this range of services according to APIN’s clinical protocol. Some (clinical evaluation, TB screening, and CD4/VL testing) are documented in APIN’s electronic medical record while, others (receipt of adherence counseling) are not. Unfortunately, the dataset to which we had access for this analysis only contained information on baseline demographics, encounter (lab, pharmacy, clinic) dates, and CD4/VL data. We have revised the text to clarify this on page 5, lines 122-126, and it now reads: “Upon clinic enrollment, patients received a variety of services according to protocol including clinical evaluation, TB symptom screening, receipt of adherence counseling, and CD4 count as well as viral load testing. Information on receipt of adherence counseling was not available in the electronic medical record.”

We revised the Discussion (page 15, lines 363-366) to include this limitation as follows: “We did not have information about which patients received ongoing adherence counseling, nor did we have full data about patient deaths, and thus could not assess the relationship between unplanned care interruption and these factors.”

b) Within the subsection of the methods called “Study Design”, please clarify the following sentence: “Upon clinic enrollment, patients were expected to receive a variety of services including...” does “expected” imply
that not all patients received all of these services? If that is the case, why? Might services received have an impact on UCI? If it is impossible to discern this, please include it as a limitation.

*We have clarified this in Comment 3a above.*

**Comment 4:**

Within the subsection of the results called “Patterns of Care”, please discuss patients who switched clinics. How much is known about this group, who are sometimes called “silent transfers”? Could it be possible that some of the inactive or patients with UCI actually switched clinics for some time? While the authors mention this group, I am curious to know whether data are available that could describe it further. If not, please consider including this as a limitation.

*We had information available to us on documented clinic transfers, which are likely a minority of all transfers. Since the study was retrospective, we were unable to determine whether patients who had unplanned care interruptions from the ABUTH clinic temporarily transferred care to other clinics. However, we suspect that many of these patients did not temporarily transfer care since 55% of those with UCI who had available viral load upon return to care had measurable HIV viremia (>1000 copies/mL). We have revised the text in the discussion section to include this as a limitation. The text (page 15, line 360) now reads: “Because of the retrospective design, we were not able to assess reasons for UCI, including whether some temporarily transferred care, or to assess outcomes among patients who became inactive from clinic.”*

**Minor essential revisions**

**Comment 5**

In the final paragraph of the methods [background] section, there is a space missing between reference #15 “[15]” and the preceding word, “patients”.

*We have corrected the spacing on page 4, line 99.*

**Comment 6**

Within the results subsection called “Factors Associated with UCI in the First Year on ART”, second paragraph, first sentence: please add a space between “>350” and “cells/µL”. Please also correct the unit from “µL” to “uL”.

*We have corrected the spacing on page 10, line 236, and we have changed “µL” to “uL” throughout the manuscript.*
REVIEWER 2

Minor essential revisions

Comment 1

Background: For citation 21 you should reference UNAIDS 2012 instead of 2004

We have updated Reference 21, (now Reference 20), to the UNAIDS 2013 report on page 5 (lines 102 and 109) and page 15 (line 370).

Comment 2

Background: You are missing a space next to [15] in paragraph 4.

We have corrected the spacing on page 4, line 99.

Comment 3

Discussion: This sentence is not clear “In a systematic review of cohorts in Sub-Saharan Africa, between 31% and 95% of patients not initially ART-eligible are retained in care between completion of clinical staging and becoming ART-eligible”

We have clarified the text (page 12, lines 296-299) as follows: “In a systematic review of cohorts in Sub-Saharan Africa, between 31% and 95% of patients who have not yet met criteria to initiate ART are retained in care between enrolling in care and becoming ART eligible.”

Comment 4

Discussion: This sentence should be revised: “one in ten adolescents/young adults are enrolled in higher and tertiary education [39].”

We have revised the text in the manuscript (page 13, lines 323-324) as follows: “At least 1 in 10 Nigerian youth are enrolled in secondary or tertiary educational programs.”

Major Compulsory Revisions

Comment 5

Abstract: The Abstract conclusion is a summation of the results. What are the implications of these results?

We have expanded upon the conclusions in the Abstract (page 3, lines 71-72) as follows: “Interventions focused on the first year on ART are needed to improve continuity of HIV care.”

Comment 6

Background: In the last paragraph of the background, line 95 you mention 25% of patients have care interruptions. It would be helpful to know if these are patients on ART, especially since you make that point in paragraph 2. In addition it would be helpful to know how care interruption is being defined since you make this distinction in paragraph 2 as well.

We clarified the text in the manuscript to include this information (page 4, lines 97-99) which now reads: “The largest review of interruptions in care and treatment among HIV-infected patients highlights that such interruptions are common, occurring in approximately 25% of patients initiated on ART [15]. This review also describes wide variation in the definition of care interruption ranging from 1 day to 1 year or more without HIV treatment or care [15].”

Comment 7

Methods: You mention in the study design paragraph that pregnant women were not included. What if women...
in the cohort became pregnant during the study? Why was this specific age range included?

We excluded pregnant women (both those pregnant at baseline and those who became pregnant during the follow-up period), because the visit protocol at ABUTH for pregnant women differs from that of non-pregnant adults, and we wanted to use a uniform definition of UCI. Additionally, although the ABUTH clinic provides services for prevention of mother-to-child transmission, we realized that pregnant patients might transfer care (either through documented or undocumented transfers) to locations more convenient for their peri-partum needs. We have revised the text on page 5, lines 120-122, which now reads as follows:

“Women who were pregnant at enrollment or became pregnant during the follow-up period were not included in the analysis, as the protocol for clinic follow-up differed between this group and the general adult population.”

Comment 8

Methods: Newly diagnosed patients are required to come more often and therefore more likely to miss an appointment. This therefore biases your results and should be listed as a limitation.

We appreciate the point raised here. All patients included in the analysis were enrolled in the ABUTH clinic and initiated on ART, and therefore experienced the same higher frequency of visits in the first 2 months on ART. There was, however differential follow-up since we included patients in the analysis who enrolled between January 2009 and December 2011, and were followed through December 2012. In our analysis of predictors of UCI, we restricted follow-up time to the first year on ART to remove biases introduced by differential follow-up time. We have reorganized the text in the method section (page 5, lines 117-120) to clarify the duration of follow up. The text now reads: “We conducted a retrospective cohort study of ART eligible patients ≥ 14 years of age enrolled in the ABUTH clinic, who initiated ART between January 1, 2009 and December 31, 2011. Patients were followed through December 31, 2012 to allow for a minimum of 1-year of observation for all patients.”

Later, in the section on statistical analysis, we have also amended the text (page 7, lines 161-162) to clarify why we used data from the first year on ART for the regression model (built to assess predictors of UCI).

“We focused the analysis on predictors of UCI in the first year on ART since other studies have linked early missed visits to mortality, and to ensure consistent follow-up time for all patients in the analysis [13, 16, 18].”

Comment 9

Methods: The definitions in the outcome measures paragraph are confusing. How would you classify a patient if the time between any two consecutive visits was >90 days and the time between the last visit and the censor date was also >180 days.

We have revised the text in this section of the manuscript to address this comment, and clarify how UCI was defined. The definition of UCI was not dependent on the time between the last visit and censor date, only 1) having >90 days between 2 consecutive visits, and 2) later returning to care (please see table below). In the scenario posed above, this patient would therefore be categorized as having UCI. The text on page 6, lines 142-143 now reads: “Patients were defined as having an unplanned care interruption (UCI) if the time between any two consecutive visits was ever >90 days, but they returned to clinic before the censor date. This definition was not dependent upon the time between the last visit and the censor date.”
### Last seen >180 days before censor date?

<table>
<thead>
<tr>
<th>Ever experienced a gap of &gt;90 days between consecutive visits?</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Unplanned Care</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Interruption</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

**Comment 10**

Methods: Not everyone is on the same visit schedule, are you basing this on calendar year or patient year? If this is calendar year, there is a bias that needs to be accounted for. How were there people on ART for 4 years if the study only went for three years?

*The patients included the analysis enrolled in the ABUTH clinic between January 2009 and December 2011, and were followed through December 2012, thus patients who enrolled early in 2009 had 4 years of potential follow-up. Please see our response to Comment 8 above for additional clarification.*

**Comment 11**

Results: In the first line of paragraph 2, you use the denominator 2,029 to report the number of participants with available cd4 counts? In the regression analysis did you exclude participants who did not have cd4 counts? Why or why not? If you adjusted for CD4 count all of the participants who did not have a CD4 count would have dropped out of the analysis. Therefore, you should clearly state that your n for this analysis was 2,029 participants.

*We appreciate this suggestion, and have added to the Results section to clarify the effect of missing data on the number of patients included in the analysis. We felt it was necessary to include CD4 count in the multivariate analysis because of the strength of the bivariate association, but did not feel that imputation was reasonable given the number of patients with missing values. Line 230-234 in the Results section now reads: “We conducted a multivariate analysis including variables significant in the bivariate analyses. A total of 467 patients (19%) were excluded from the multivariate analysis due to unknown baseline CD4 count (158/632 with and 309/1864 without a care interruption). An additional 33 patients (1%) were excluded due to missing values for other variables in the model.” We have also added a footnote to Table 2 to reflect this. Page 26, line 603 now includes n=2000.*

**Comment 12**

Results: Prior studies have shown that HIV infected youth have much higher attrition rates compared to adults. Given your range of ages, treating age as a continuous variable does not take this factor into account. It would be more meaningful to treat age as a categorical variable and it likely has a collinear relationship with being a student, which is not as well accounted for when treating age as a continuous variable.

*We have conducted additional analyses to explore this issue further. We found that categorizing age into groups that separated adolescents and youth from adults did not change the relationship between age and rate of first UCI in the first year on ART in multivariate analysis. While students did tend to be younger than non-students, we tested the model for collinearity, and found that there was no evidence of this relationship affecting the variance estimates. We have amended the text in the Discussion (page 13, lines 328-330) to clarify this. “In our analysis, age was not a significant predictor of UCI in the first year on ART, even when categorized to compare adolescents to young and older adults.”*
Comment 13

a) Results: It would be useful to know the level of education of the students. If the students were in tertiary education this would impact your results and interpretation of your results.

There were 201 patients who identified as students in the cohort. Among them 72% (n=145) described having tertiary education, and 26% (n=52) described having primary or secondary level education. On the other hand, there were 791 patients with tertiary-level education, only 18% (n=145) of whom were also students. While the majority of students had tertiary level education, the multivariate model, which adjusted for both employment status and level of education, showed that both student status and having less than tertiary level education were independent predictors of UCI.

We revised the text on page 11, lines 262-264 to clarify this: “Students, 72% of whom were university matriculates, had a 2-fold increase in UCI. Additionally patients with less than tertiary education had a 50% increased risk of UCI.”

b) Discussion: “Additionally, students, most of whom were university students, had a 2-fold increase in UCI; patients with less than tertiary education had a 50% increased risk of UCI.” These are not mutually exclusive groups and seem to be a contradiction that should be addressed in the Discussion.

Please see response to Comment 13a above.

Comment 14

Discussion: “Our data showed a trend towards improvement in the risk of UCI over time in the context of local and national efforts to improve retention.” This result is in Table 2 but it is not reported in the results section at all. If you are going to include in the Discussion it should be reported; however the evidence for this conclusion is somewhat weak.

As suggested, these data are now summarized in the Results section on page 10, lines 240-242 of the manuscript. The added text reads as follows: “While not statistically significant, there appeared to be a trend towards reduced risk of UCI among patients who enrolled in care in 2011 compared to those who enrolled in 2009 (IRR 0.08, p=0.061).”

Comment 15

Discussion: Line 285-The literature has shown that there is a discrepancy in stigma for HIV concordant vs discordant marriages. This should be addressed.

We appreciate this suggestion, and have edited this portion of the Discussion to include this point on page 13, lines 315-318. “Other studies have underscored the challenges with trust, communication, discrimination and stigma faced by patients in both sero-concordant and sero-discordant relationships, often making it difficult to look to a marital or sexual partner for consistent adherence support [41-43].”

Discretionary Revisions

Comment 16

Discussion: Line 283- Guidelines are moving toward test and treat regardless of CD4 count. This should be taken into account.

We have revised the text (page 12, lines 304-305) as suggested: “This has important implications for retention efforts as HIV treatment programs operationalize guidelines for ART initiation at higher CD4 thresholds, and some are calling for “test and treat” models regardless of CD4 count [31-34].”