Author's response to reviews

Title: Reviewing progress: 7 year trends in characteristics of adults and children enrolled at HIV care and treatment clinics in the United Republic of Tanzania.

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Author's response to reviews: see over
To the Editors,

Please find uploaded our revised manuscript entitled ‘Reviewing progress: 7 year trends in characteristics of adults and children enrolled at HIV care and treatment clinics in the United Republic of Tanzania.’ for consideration for publication in BMC Public Health.

The authors appreciate the feedback and comments from the reviewers. These have been duly considered and addressed as outlined in this cover letter for the Editors consideration.

Thank you.
The Authors.

Reviewer 1: Simbarashe Takuva

A. Major Compulsory Revisions

Introduction – none

Methods

These are more of clarifications.

1. A total of 127 CTCs located in the North-West of Tanzania, the East coastal regions and Zanzibar are analyzed. Perhaps it would be useful to include a sentence that states the prevalence of or the burden of HIV in each of these districts. Is it the same, is it different? This will give a greater understand in understanding the effectiveness of the ART roll-out including coverage over this period.

Response: We have added 2007-2008 HIV prevalence figures to the first paragraph of the methods section in lines 5-7. In 2007-2008, HIV prevalence among adults aged 15-49 years in these regions was estimated at 5.3% in Pwani, 3.4% in Kagera, 0.9% in Kigoma and 0.6% in Zanzibar. Describing the overall effectiveness of ART-rollout and coverage was beyond the scope of this paper. However, we estimate that our HIV-positive study population represents 43% of the estimated HIV-positive adult population in three regions of mainland Tanzania (further details under response 2 of results comments on page 2 below).

2. Under Data Analysis, You do mention that treatment decisions were based on 2006 WHO guidelines. In deciding the time categories to analyse data i.e. 2005-2007 vs. 2009-2009 vs. 2010-2011; was this based on some criteria i.e. changes in Tanzania guidelines or CD4 eligibility criteria. It is important for this to be clear upfront for if the criteria were different then – the analysis, discussion and implications may be different. If this was based on convenience – make it known.

Response: These time categories were estimated to represent particular phases of the ART program in Tanzania: the early start-up phase in 2005-2007 where ART services were introduced starting at major hospitals; the rapid scale-up and decentralization phase in 2008-2009 where ART was rolled out to a large number of clinics including lower level health facilities; and a maturation phase 2010-2011 where fewer clinics were newly implementing ART services and the focus for existing clinics was ensuring sustainability and enhancing service...
provision through support services. This has been clarified the Methods section, data analysis sub-section, lines 10-16.

3. Again state if eligibility criteria for ART initiation changed or remained the same for the analysis periods - 2005-2007 vs. 2009-2009 vs. 2010-2011.

**Response:** During the study observation period 2003 and 2006 WHO guidelines were used for ART initiation. This has been clarified and appropriate references added to the Methods section, routinely collected patient-level data sub-section, lines 4-5. The analysis was not aimed at identifying changes in practice according to guideline changes.

**RESULTS**
1. A total of 62,801 patients were enrolled at the 44 clinics. Were there patients excluded due to missing data. Please confirm this, and if they are worth analyzing to understand any extent and direction of potential bias that may be introduced.

**Response:** We agree that when using routinely collected data, missing data is an important consideration. Only 7 patients had missing data on age and because they couldn’t be classified as adults or children, they were excluded from the analysis as stated under Methods section, data analysis sub-section, line 4-5. For the rest of the variables, data missing on each variable of interest is reflected in Tables 1 and 2.

2. Missing data issue becomes clearer further down the results section. The authors need to reassure the readers that this missingness was likely random i.e. CD4 count at ART initiation could not be ascertained in at least 20% of patients.

**Response:** Most of the variables in this analysis had minimal missing data, with the exception of the CD4+ cell count variable. We discuss the issue of missing CD4+ cell counts in paragraphs 3 and 4 of the discussion section and explore reasons for it. According to Tanzania and WHO guidelines used during the study period, patients with clinically advanced HIV disease (WHO stage III or IV) could initiate ART without a CD4+ cell count. In our study population, 84% of adults without CD4+ cell count documentation at ART initiation were classified as WHO stage III or IV, suggesting that patients missing CD4+ cell counts were more likely to have advanced disease than patients receiving CD4+ cell counts. Consequently, the median CD4+ cell count at ART initiation observed in our study is likely an overestimate of population CD4 count at ART initiation if the less sick patients preferentially had CD4+ cell count done. This has been clarified in paragraph 4 of the Discussion section, lines 5-10.

Therefore we hypothesize that CD4+ cell count missingness was not random but rather, that in the context of limited resources, CD4+ cell counts were prioritized for patients with lower WHO stage, who comprised about half the study population.

3. Figure 1 data could be (discretionary) improved by presenting proportions rather than absolute numbers. Proportions of those enrolling for ART, the denominator being numbers projected to be in need of ART. This may illustrate improving coverage more reliably.
Response: Our study population is a specific subset of all clinics offering HIV services in 4 regions in Tanzania. Specifically, our study population is restricted to (1) clinics supported by ICAP-Columbia University (2) in 4 regions in Tanzania (3) which maintained electronic patient-level databases and provided de-identified data for analysis. Consequently, we are not comfortable comparing our numbers on ART to regional or national estimates of the population estimated in need of ART in any quantitative fashion.

Estimating the HIV+ population in need of ART by age, gender and pregnancy status was not possible due to limitations in data sources. However, we use National AIDS Control Program estimates of the HIV+ positive population in these regions to estimate that our HIV-positive study population represents 43% of the estimated HIV-positive adult population in three regions in mainland Tanzania (paragraph 1 of the Discussion section, lines 10-12), but we cannot estimate the proportion in need of ART covered in our sample. Consequently, presenting proportional estimates of ART coverage in Figure 1 is beyond the scope of our analysis.

**DISCUSSION**

The discussion and conclusions are well balanced and supported by the findings. However;

1. The authors clearly need to acknowledge the limitation of potential selection bias that might have been introduced by missing data. Possibly as suggested CD4 measurement may have been omitted in very ill patients (i.e. most patients without CD4 were stage III or IV) – in addition I would like to speculate that these clinical records could have been updated well after initiation (i.e. patient data captured retrospectively rather than real time) hence missing data for the sickest who might have had higher mortality and loss to follow up. Hence CD4 trends need be interpreted with caution.

Response: The analysis included the entire population at participating sites (no sample selection), a strength that was noted in the first sentence of the last paragraph of the Discussion section. The databases included all retrospective data as noted in the last sentence routinely collected patient-level data sub-section in the Methods section. We therefore believe that later entry of CD4+ data is an unlikely reason for missing CD4 data but do agree that all routinely collected data ought to be interpreted with caution according to the limitations we outline. This sentence has been added to paragraph 5 of the Discussion section, lines 9-10: ‘Our CD4+ trend data should however be cautiously interpreted due to the significant proportion of missing data’.

**B. MINOR ESSENTIAL REVISIONS**

Introduction
Methods
1. Write out ICAP in full then use abbreviations thereafter.

Response: ICAP is the name of our organization, there is no full version.

2. The first sentence under site data: {Anema, #84; Saito, #132}. Are those references? If so, please use the correct format.

Response: These were improperly formatted reference citations which have been updated in the revised version.

3. Under Data Analysis: It is noted “The CTC2 data” …..Please be clear that
CTC2 means Patient Record Forms. It will not be clear what the authors will be referring to, to a reader without access to TZ protocols. 

**Response:** ‘CTC2’ has been changed to ‘patient record’ data in this sentence.

4. Ethical approval: by Columbia IRB, please write in full - Columbia University IRB?

**Response:** This has been updated as advised.

Discussion

1. Please fix the referencing throughout i.e. Ahonkhai, #129

**Response:** All the improperly formatted references have been fixed in this updated version.

C. DISCRETIONARY REVISIONS/ADDITIONS

Discussion

The authors state….“the proportion of children in the study population did not increase significantly over time…..”. The suggestion of strengthening scale up of EID is great. However, is there not a possibility that the success of PMTCT programme effectiveness (not measured here but can be inferred from increased / expanded enrollment) might be cancelling out any increases in increased paeds uptake (and bear in mind after age 14 years we lose them into the adult group?)

**Response:** The age utilized in this analysis is age at enrolment, which remains constant over time, and would not be affected by transition into adulthood. The proportion of patients who were children at enrolment was constant in our observation period although we observed increasing absolute numbers (up to 2009) in Figure 1.

We agree with the reviewer: it is possible that better PMTCT services resulted in fewer HIV-infected children thereby decreasing the pool of children to be enrolled at HIV clinics. The potential increase in the proportion of enrolled children expected from improved case-finding of pregnant women and children through scale-up of PMTCT services, early infant diagnosis programs and other pediatric focused initiatives could be cancelled out by more successful PMTCT programs, resulting in the stagnant proportion of enrolled children over time we observed.

This is captured in the last sentence of paragraph 7 of the Discussion section.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests
**REVIEWER 2: JENNIFER FURIN**

**A. MINOR ESSENTIAL REVISIONS**

Do the authors have any data on the average time from enrollment in the program to initiation on ART. This might explain some of the CD4 count discrepancies, if the time from enrollment to initiation was short. It would also be interesting to note how this variable may have changed over time.

*Response: The average time between enrolment and ART initiation was beyond the scope of the current paper and is being investigated in a new analysis. We agree that this is an important consideration and plan to have these data ready for presentation soon.*

In the discussion section, it would be interesting to look at how Tanzania compares with other countries in the region who have had a similar maturation over time.

*Response: As noted in the discussion of the study limitations, our data represent 44/127 of all ICAP-supported clinics in Tanzania and 4 of the 30 regions of Tanzania. As such, we do not interpret the data as representing the entire country. However, we do make comparisons with several other countries that have published similar analyses including 2 Mozambique analyses and a multi-country analysis involving 9 sub-Saharan African countries (Lahuerta et al, 2012)*

Are there any data on the number of patients entering into second-line regimens?

*Response: This analysis was limited to 1st line (initial) ART regimens only. Examining for changes to 2nd line ART was beyond the scope of our objectives.*

This information is not essential and is beyond the scope of the paper, but if the authors have it, they might consider adding it into the paper.

Level of interest: An exceptional article  
Quality of written English: Acceptable  
Statistical review: No, the manuscript does not need to be seen by a statistician  
Declaration of competing interests:  
I have no competing interests to declare.