Author’s response to reviews

Title: Adolescent coordinated transition (ACT) to improve health outcomes among young people living with HIV in Nigeria: study protocol for a randomized controlled trial

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Response to Reviewers

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Trials Manuscript TRLS-D-17-00497:

Adolescent Coordinated Transition (ACT) to Improve Health Outcomes among Young People Living with HIV in Nigeria: Protocol for a Cluster Randomized Controlled Trial

Dear Trials Editor and Reviewers, thank you for the helpful feedback on our manuscript. Please see below our point-by-point responses.
Reviewer reports:

Reviewer #1: This manuscript describes the protocol for a cluster randomized study designed to evaluate the effectiveness of Adolescent Coordinated Transition on retention rate, viral suppression and psychosocial wellbeing in adolescent children aged 13-17 years compared to usual care.

The manuscript is very well written. I have few suggestions/comments to the authors:

1. The study design incorporates an hybrid design that looks at both effectiveness of the intervention and implementation. The manuscript talks in detail about the effectiveness part. But it will be helpful to the readers if you could elaborate on the implementation. It is important to understand the feasibility of this intervention in the real world scenario.

Response: Thank you for this feedback; it is identical to Reviewer 2’s comment #8 below. We have attended to both comments, using RE-AIM to guide our narrative response in the manuscript in (Lines 186-192, p.8-9 and Lines 314-324, p.15).

2. The study administers 5 different questionnaires (4 psychosocial + 1 TRAQ) for the study participants. More information on why these tools are administered and what different information are collected using these tools will help the readers understand the need for so many tools.

Response: More detailed descriptions of the different types of information collected using each of the 4 psychosocial tools has been added. (Lines 337-353, p.16)
3. The information on the role of DSMB may be minimized to important key points for this manuscript.

Response: Thank you for this suggestion. We have minimized the information regarding role of the DSMB to only important key points (Lines 413-437, p. 19-20)

Reviewer #2: This study addresses an important public health problem, the transition of adolescents from pediatric to adult HIV care. Overall, this protocol is generally well written. My main concern is that the sample size does not seem plausible. Comments are as follows:

1. Study Objectives and Hypotheses-The primary outcome should probably be stated here up front rather than just saying one is evaluating the effectiveness of the intervention. Also, would have your primary outcome only as your #1 hypothesis and everything else in your #2 hypothesis.

Response: We have revised the Study Objectives and Hypotheses are suggested by stating our primary outcome in the first sentence and having only our primary outcome as hypothesis #1. Thank you for these suggestions. (Lines 157-161, p. 7)

2. Randomization-could use more details on actual randomization methods (see CONSORT extension to CRCT section on randomization).

Response: We have completely rewritten the section on randomization and added specific citations related to both methods and the CONSORT extension to cluster randomised trials document (Lines 214-228, p. 10).
3. Study Population—not sure why you would include individuals who might not transition during the study period, e.g. persons age 13.

Response: Regardless of study arm, our target age at the point of transfer to adult care is designed to align with that of the study site, which for some sites is 15 years, and others, 18 years. To allow for the 12 month pre-transfer intervention period, we would be targeting 14 and 17 year olds. However, much like it occurs in real-time per usual care, the age at transfer (and therefore recruitment) allows for some limited flexibility around the target ages. We will therefore be recruiting 13-14 and 16-17 yr ALHIV towards a target transfer age of 15 and 18 yrs, respectively. This ensures that all transferring ALHIV are at minimum, just entering the developmental period of middle adolescence. (Lines 234-235, p. 10-11)

4. Intervention Description—not exactly clear whether the OSG will continue after 12 month transition, same for case management team.

Response: The OSG will be extended until the end of study follow-up, not only to assess its effectiveness during the 12 month transition period, but potential impact beyond that; up to 24 months post-transfer. (Lines 254-258, p. 12).

5. Data Collection—Is viral load routinely done in Nigeria? Will results be returned to participants and their providers?

Response: Viral Load testing and application to clinical management was previously inconsistently done across the country, however, following the introduction of UNAIDS’ 90-90-90 initiative in 2014, viral load collection targeting achievement of the third 90-the viral suppression target is being massively scaled up, including set-up and strengthening of new and pre-existing molecular laboratories, respectively. The most recent (2016) national treatment guidelines require at least one viral load test annually for stable patients once they have attained 6 months on treatment. All of the study sites are already activated to collect VL samples for onsite or referral lab processing. Results of all viral load tests collected during the study will be
returned to providers who will inform their patients and apply the results to their participants’ care. (Line 309-312 p. 14)

6. Primary outcome-the composite outcome for retention is a bit worrisome and seems overly complicated. Why not just pick one, relatively standard outcome for retention?

Response: Our goal is to measure retention in care at 12 and 24 months, so we will be evaluating each of the outcomes separately; in addition, drawing from experience from our study team’s prior studies, we are confident that these data collections will not be overly complicated.

7. Sample Size Calculations-I suspect that the sample size calculations are optimistic and that it would be preferable to enroll a significantly larger number of participants. Was matching accounted for in the calculations? What are the expected intervention and control arm rates for the primary outcome? Drawing inferences from only 216 participants, of whom only 108 will receive the intervention, across all of Nigeria, when there are 200,000 ALHIV in Nigeria will be challenging, and I suspect many will be skeptical of generalizability. I would refer you to Hayes and Moulton’s textbook on CRCTs and the chapter on samples size/power.

Response: We appreciate your comments and acknowledge that sample-size calculation are, in fact, always optimistic, as they require numerous assumptions that may or may not be met in the field. We also acknowledge your suggestion of the excellent text by Hayes & Moulton, as it is a very valuable resource for CRCTs. Our calculations were based on several assumptions, and we attempted to follow the CONSORT guidelines in this case (e.g., how sample size was determined, methods of calculation, number and distribution of clusters, and intraclass correlation); additionally, we built into our estimates several potential loss estimates (i.e., transfers, patients moving away, deaths, and withdrawals), all of which were taken from either first-hand knowledge of the investigators, or from the literature from Nigeria or other similar African location.

The driving factor behind the base calculation is the 20% effect size difference between CGs and IGs and the intraclass correlation, both of which demonstrably impact sample-size calculations,
and we feel we have made appropriate assumptions in this case. Matching was included in the calculation inasmuch as it is related to the number of sites, as was the assumption of equal cluster sizes between and within CG and IG. To address the question of rates for the primary outcome, this drives the total number of participants that are available for the study and who ultimately will be approached for inclusion into the appropriate clusters. This number may be much greater than the estimated sample size for analyses, as it is anticipated that the recruitment goals may need to be greater in order to obtain the total necessary, consented participants. Additionally, recruitment is very tightly defined across 13-14 and 17-18 year olds only and is 1 per cluster/healthcare facility and not per individual, and meaning we are limited to finding an average of 18 13-14 or 17-18 year old ALHIVs, per each facility. Nigeria’s 200,000 are spread across tens of thousands of healthcare facilities. We have just 12 of them and in our experience, it takes a very large facility to be able to have 18 active, enrolled 13-14 or 17-18 year olds in care.

8. "Hybrid" design-while the authors indicate they are using a hybrid design, there is not much in the protocol on what implementation indicators they will be tracking, e.g. are OSG’s formed as desired, OSG attendance, etc. Might want to consider a framework such as RE-AIM to guide this inquiry.

Response: Thank you for this feedback; it is identical to Reviewer 1’s first comment. We have attended to both comments, using RE-AIM to guide our narrative response in the manuscript in (Lines 186-192, p.8-9 and Lines 314-324, p.15).

9. Discussion-a section on study limitations would be helpful.

Response: A limitations section has been added to the discussion. (Lines 520-536, p. 24)