Author’s response to reviews

Title: Healthy Options: Study protocol and baseline characteristics for a cluster randomized controlled trial of group psychotherapy for perinatal women living with HIV and depression in Tanzania

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Author’s response to reviews:

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Dr. Haochu Li
Dear Dr. Li:

Thank you very much for the opportunity to resubmit our article entitled “Healthy Options: Design, methods, and baseline results of a cluster randomized controlled trial of group psychotherapy for perinatal women living with HIV and depression in Tanzania” to BMC Public Health.

Based on feedback from Reviewer #2, we have decided to resubmit this paper as a ‘protocol’ manuscript. Therefore, the title has changed to “Healthy Options: Study protocol and baseline characteristics for a cluster randomized controlled trial of group psychotherapy for perinatal women living with HIV and depression in Tanzania.” We will address reviewers’ comments in a point-by-point manner below using italicized text. Related changes in the text are indicated by page/line numbers and are highlighted in yellow in the revised manuscript.

Reviewer #1 comments:

Background:
1) Overall: I am wondering about the focus on depression and specifically major depression, when many perinatal women may have other mental health issues (anxiety, PTSD, etc.), or even less severe depression, which could also impede PMTCT and other health behaviors. The authors should justify their focus on major depression, and/or expand their background information to include other mental health issues.

Thank you very much for this comment. The precedence for the focus on major depression relates to earlier work among women accessing HIV-related services in Tanzania, whereby a high level of depressive symptoms comparable with major depression was observed (point prevalence of 43%). Following women longitudinally in the same study, 57% demonstrated symptoms comparable with major depression during the follow-up period. Based on findings from this prospective cohort study, having symptoms comparable with major depression increased the risk of mortality by over 2.5-fold.(1) A more recent study in Tanzania demonstrated that nearly 58% of women accessing antiretroviral treatment (ART) had symptoms comparable with major depression. Although women were receiving ART, major depression increased the risk of mortality by nearly 2-fold.(2) Given the high prevalence of depression among women in Tanzania living with HIV and the increased risk of mortality documented in this context, a trial was designed to attempt to reduce this burden in this high-risk population. This is an excellent point made by the reviewer and future studies that we undertake will broaden this work and consider a trans-diagnostic intervention, that would also address PTSD, anxiety, mild depression, and other co-morbid conditions.

2) Page 6, lines 112-120: The literature review on the approach of using lay health workers for mental health interventions in LMICs seems limited and does not include several more recent studies on this topic conducted in various settings globally.

Thank you for this comment, we have updated the literature review in this section and this is reflected on pages 6-7, lines 123-134.

Methods:
3) Page 8, lines 179-180: It would be good if the authors can justify their use of a cut-off of 9 or above on the PHQ-9 here where it is first mentioned, with relevant references of studies with women in SSA,
Thank you for this point. For the PHQ-9, we had conducted a validation study prior to the trial that examined the validity of the PHQ-9 in the context of primary care in Tanzania.(3) In that study we demonstrated an optimal cut-off score of 9 for the PHQ-9 when comparing the responses with a ‘gold standard’ for major depression (clinical diagnosis by a local psychiatrist or psychiatric nurse using the MINI). To address this issue additional detail on the PHQ-9 in the Tanzanian context is provided on page 9, lines 197-98 and page 11, lines 251-55.

4) Page 8, lines 180-181: Did each of these low resource health facilities have a psychiatric nurse for referrals in case of suicidality? This seems unlikely. How are these situations handled? Also, are referrals for treatment of depression by medications available to women participating in the study who potentially needed depression medications?

Intervention and control sites received training in enhanced standard of mental health care consistent with guidelines in the WHO Mental Health Gap Action Programme (mhGAP) prior to initiation of the trial. Through this training, providers based at study sites would be able to identify the nearest facility that can provide psychiatric care in order to make an active referral for follow-up for mental health assessment and care as needed. This standard referral process would take place in the event of suicidal ideation without immediate indication of a plan to commit suicide. In the case of immediate care (i.e. for a person at acute risk of committing suicide), study participants were escorted to a facility that offered services for further evaluation of suicidality and treatment by mental health professions. When indicated, psychiatric medications were provided, which was also consistent with the mhGAP guidelines. Additional text is provided on page 11, lines 242-45.

5) Page 9, lines 186-187: It is appreciated that the researchers allowed women who just received their HIV-positive diagnosis a few weeks to come to terms with their diagnosis before eligibility screening. But how many women were identified in this way and what % of these were able to be located 2 weeks later to determine eligibility? If there was considerable loss to follow-up here, this could be a source of bias in the sample.

Thank you for this comment. Among the pregnant women that were approached, we delayed the eligibility and baseline data collection by 2 weeks if she had just received her HIV-positive test result. We did not document what percent of the women had just received their HIV-positive diagnosis. However, randomization was done at the time of the eligibility and baseline interview (performed on the same day), so any loss in that 2 week time interval will likely not bias the findings since study enrollment did not occur until the time of eligibility/ baseline assessment.

6) Page 12, line 266: How was the coefficient of variation of 0.05 used in the sample size calculations determined? It seems that the intracluster correlation coefficient (ICC) should have instead been used in these sample size and power calculations for a cluster-randomized trial. It is often best to calculate for a range of ICCs, since actual values are rarely known. See for example, Odeny et al., 2018.

Thank you for this point. In order to account for the degree of clustering either the coefficient of variation (CV; between-cluster variance) or intra-cluster correlation (ICC) can be used and they are equivalent for binary outcomes.(4) You can calculate the ICC from the CV using \( \frac{k}{\pi} \), where k is the CV and \( \pi \) is the probability of the binary outcome. However, the CV is often easier to understand and therefore we decided to present the CV rather than the ICC.(4)
In terms of sample size we used the standard formula for unmatched cRCTs using CV as indicated by Hayes and Moulton (5):

Here \( c \) is number of clusters, \( \pi_1 \) and \( \pi_2 \) and the percentage with outcomes in the two groups and \( k \) is the CV. However, we agree that both ICC and CVs are not often known and may affect power if underestimated. We will determine and report CVs in the main results report.

Results:
8) Page 13, line 283-285: I am confused to how 91% of HIV+ pregnant women screened would have screened positive for symptoms consistent with major depression. This is an extremely high rate, even among HIV-positive women in SSA. Was there some sort of pre-screening that identified women who were likely to suffer from depression for study eligibility screening? If so, this needs to be described in the manuscript. Other studies in similar populations have found rates considerably less than 50%, depending on the depression measure and cut-off used.

Thank you for noting this issue. Women were screened for depression using a measure for depression that was previously validated in Tanzania (PHQ-9). Although the study staff waited until two weeks after the woman received her HIV-positive test result, it is likely that depressive symptoms occurring as a response to this news may have persisted beyond this point, resulting in a higher percentage of women with symptoms consistent with major depression than expected. As a result, this will be revised in the manuscript and this finding will not be reported as a prevalence of major depression in this context. However, since this occurred at intervention and control sites it does not pose a threat to the internal validity of the study. This point is referred to in the limitations section of the discussion (page 19, lines 419-24).

8) Page 13, lines 292-296: Education and marital status are potentially very important factors. How will the researchers account for these imbalances between the randomized study arms? Also, why are marriage rates so low in this sample? It seems unusual for East Africa. Did the questionnaire only consider formal marriages?

To account for any imbalance in sociodemographic factors at baseline, a sensitivity analysis will be performed, controlling for these variables and comparing the results with standard analyses typically conducted for randomized controlled trials (i.e. intent-to-treat analysis without controlling for confounding). This information is included in the methods section of the paper (page 14, lines 307-19).

In this study, being married was reported separately from ‘cohabiting with proposal for marriage’ and ‘cohabiting without proposal for marriage.’ If all three categories are merged, this results in 70.9% in the control group and 74.0% in the intervention group. This type of categorization may have demonstrated lower rates of marriage compared to other studies in the region (see page 16, Table 2).

Discussion:
9) Page 16: lines 343-344: Here the authors should discuss how this high rate of symptoms compatible with MDD compares with other studies of pregnant women living with HIV in SSA, as well as reasons why their rate is much higher than that seen in other studies in similar contexts.

Thank you for this point. We agree with the reviewer’s concern about this issue. In light of what is described above regarding the screening process, we removed this from the conclusion and described the issue in the limitations section of the discussion (page 19, lines 419-24).
10) Page 17, lines 364-365: It seems the issue of depression treatment using psychiatric medications needs to come into the discussion somewhere.

Thank you for this comment. This is now described in the manuscript (page 19, lines 405-6).

11) Page 17, lines 378-380: Some important baseline characteristics (education and marital status) were not balanced in the intervention and control arms. How will the researchers deal with this in the analyses of the trial data?

Thank you for this point. Sensitivity analysis will be performed to control for variables that demonstrate imbalance at baseline. These results will be compared with the standard intent-to-treat analysis for trials that does not control for confounding variables. This is described on page 14, lines 307-19.

Reviewer #2 comments:

1) Overall, the paper seems torn between a report of baseline results and a protocol paper. If a report of baseline results, the authors should describe their research questions/hypotheses in the introduction and report on these results. For example, based on literature, one might wonder if self-efficacy is related to HIV stigma in this population of pregnant women. Then, as a baseline results paper, a detailed description of the analyses would be presented in the methods. Further, if this is a report of baseline results, then the words 'design' and 'methods' should be taken out of the title. The paper seems more appropriate as a protocol paper. If the authors settle on this as a protocol paper, some points below are suggested, including more detail on the follow-up procedures (at what point are the women assessed at follow-up?) and data analysis (mixed effects models?) that will be performed for the primary and secondary outcomes.

Thank you for this feedback. Based on this input, we are revising the manuscript to reflect a protocol paper. We have added greater detail on the follow-up of study participants (page 12, lines 276-81) as well as the data analysis (page 14, lines 307-19).

Title/abstract:

2) If a protocol paper, remove 'baseline results' and change to 'baseline characteristics' in title. The term 'characteristic' is used at the end of the introduction and that term seems more appropriate than 'result.'

Thank you for this comment. The change to ‘baseline characteristics’ was made in the title (page 1, lines 1-2). This change was also made in the abstract (page 3, lines 54 and 60).

Intro:

3) Add background/citation on statement 'lower access to formal education' and risk for depression. Statements that follow are limited to income/employment opportunities.

Thank you for this input. We have added a citations to support this content (page 5, line 97, references 9-11).

4) Add background on secondary constructs (e.g. social support, self-efficacy, hope, stigma, food insecurity, adherence, etc) to provide justification for their inclusion as measures. Are these variables associated with perinatal depression and HIV comorbidity? Background is good in depressive symptoms and IPV.
Thank you for this comment. We have added this background to the introduction of the paper (page 5, lines 102-6).

5) The phrase 'symptoms comparable with MDD' seems unclear, especially in later use in the paper. Is there a reason why the authors did not simply state 'depressive symptoms'?

Thank you for this feedback. For the study, we used the PHQ-9 with a validated cut-off score of ‘9’ based on a comparison with a clinical diagnosis of major depression as determined by a psychiatrist or psychiatric nurse using the MINI, a diagnostic instrument. Therefore, the study is reporting more than ‘depressive symptoms’ on a continuum. On the other hand, since the PHQ-9 is a screening measure, it would be inappropriate to indicate that the women had major depressive disorder. In order to clarify this, we changed ‘symptoms comparable with MDD’ to ‘symptoms consistent with MDD’ throughout the text.

Methods
6) There is mention here of an "original list of facilities" from which included facilities were chosen at random. How many facilities were eligible for inclusion on the initial list?

A list of government-run reproductive and child health (RCH) facilities, supported by a local non-governmental organization (Management and Development for Health, MDH), was constructed and then grouped according to cumulative enrollment of women accessing PMTCT care into small (200-249 women), medium (250-349), and large (350 or greater) sites. District hospitals were excluded, since the study was focused on recruiting from clinic-based sites. After this exclusion, 12 large sites remained for randomization into intervention and control groups. Large sites were selected in order to ensure that an adequate number of women would be available for participation in the study. However, given decreasing incidence of HIV in this setting, the large sites did not yield an adequate number of women for recruitment. In order to address this four additional ‘satellite’ sites were selected and randomly allocated to intervention and control groups. These ‘satellite sites’ were identified through nearby sites close to the initial sites to ensure consistency with the source population of the original 12 sites. Four additional sites were selected since these facilities provided an adequate number of women for enrollment.

7) The intervention appears to take a stepped care approach, with additional CBT offered after delivery. If this is a protocol paper, a diagram of the participants trajectory through the study would be helpful.

Thank you for this comment. We agree that these data are important to include; however, this diagram will be presented in the outcomes paper for the study, consistent with CONSORT guidelines.(6)

8) Good to add to the data collection section with a description of the consent, screening process, and other data collected at screening. Since this is a protocol paper for the entire study, good to describe in detail the other procedures for intervention and follow-up surveys.

Thank you for this input. We have included this content in the data collection section of the manuscript (page 12, lines 276-81).

9) STATA should have a version number and reference.

This information is now provided on page 13, line 287, reference 49.
10) Were the sample size estimations based on previous work? How did you figure 80% of participants screened might enroll, 30% might drop-out, and the effect size?

Based on previous research in Tanzania, we estimated that the effect size would be RR=0.82.(7) In terms of the 80% enrollment rate and 30% anticipated drop-out rate, we included these as standard conservative estimates for sample size calculations to ensure we would have at least 80% power at the end of the study.

11) What are the research questions/hypotheses for the larger study? What type of analysis will be conducted on the primary outcome?

Thank you for this comment. The primary outcome for the study was the burden of depressive symptoms. The research question as it relates to this outcome is indicated as: Does a task-sharing approach (i.e. problem-solving and cognitive behavioral therapy components delivered to groups facilitated by lay community based health care workers; CBHWs) reduce the burden of depression among HIV-positive women accessing PMTCT-plus services. The same research question is relevant for the secondary outcomes as well, including intimate partner violence, social support, self-efficacy, hope, HIV-related stigma, and ART adherence. For primary and secondary outcomes, an intent-to-treat analysis will be performed. See page 14, lines 307-19 for additional details about the analysis.

Results:

12) If 90.7% of the participants screened met inclusion criteria, what percent were excluded based on not meeting inclusion criteria? A flow diagram of inclusion would be helpful here.

Thank you for this input. We have added these statistics to the text, since the diagram will be included in the outcomes paper for the study as indicated above (page 14, lines 326-27). We did not include a flow diagram, since CONSORT guidelines indicate this should be included in the outcomes analysis (see point above following reviewer’s comment #7).

Discussion:

13) At the start of this section, the authors state "The present cluster randomized controlled trial will compare two strategies for the treatment of symptoms…” The methods section outlines a stepped care model, rather than a comparison of PST and CBT. Please clarify.

Thank you for this feedback. The design of the study includes both the PST and the CBT in the intervention group and compares the outcomes with an enhanced standard of care group; therefore, it would not be possible to compare PST versus CBT outcomes (page 10, lines 207-25).

We sincerely hope that our responses appropriately and adequately address all of the reviewers’ comprehensive comments. We greatly appreciate the reviewers’ feedback and it enables us to strengthen the manuscript. Thank you for considering this revised manuscript for possible publication in BMC Public Health.

Sincerely,

Mary C. Smith Fawzi, ScD
Assistant Professor, Harvard Medical School


