PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Peer-led HIV care and the UNAIDS 90-90-90 treatment targets in Tigrai, Ethiopia: A cluster randomized trial and economic evaluation of Teach-Test-Link-Trace model (TTLT) trial protocol
AUTHORS	Gesesew, Hailay; Ward, Paul; Karnon, Jonathan; Woodman, Richard; Mwanri, Lillian

VERSION 1 – REVIEW

REVIEWER	Moore, Carolyn The University of Alabama at Birmingham
REVIEW RETURNED	21-Sep-2020

GENERAL COMMENTS	Thank you for the opportunity to review your protocol. Under Outcomes and measurement, it seems your primary outcome under (i) is HIV status at enrolment? Do you mean increase in knowledge of HIV status? Surely at enrolment is baseline? Please clarify. Additionally, if at all possible, I think it would be helpful to have an infographic that clearly shows the structure of the health system with regards to zones, households, kebele's etc Also, please clarify, the line that refers to 'blinding'. I don't believe participants can be blinded in this study. Line 13 on page 18 of 45.

REVIEWER	Kevany, Sebastian University of California San Francisco
REVIEW RETURNED	25-Sep-2020

GENERAL COMMENTS	Looks good....

REVIEWER	Ortblad, Katrina University of Washington , Department of Global Health
REVIEW RETURNED	29-Oct-2020

GENERAL COMMENTS	Manuscript: “Peer-led HIV care and the UNAIDS 90-90-90 treatment targets in Tigrai, Ethiopia: A cluster randomized trial and economic evaluation of Teach-Test-Link-Trace model (TTLT) trial protocol” DECISION: Major revision OVERALL: An interesting study that will generate important evidence on uptake of HIV testing uptake with a number of different testing strategies. However, the motivation for using “peers” and who these peers are/what makes them classified as peers vs. lay counselors is not clear to me. Additionally, the SOC arm having nurses versus peers visit their home seems like it

might bias study results. There is also much emphasis on outcomes among individuals who test HIV-positive, and little emphasis on outcomes (related to HIV prevention) for those who test HIV negative. A number of the outcomes are not clearly defined; it is particularity unclear at what time point the authors plan on measuring these outcomes. The paper is also quite long and these is a lot of redundancy in what is being presented. The authors should consider editing to reduce this redundancy and improve clarity.

MAJOR:
• (Length): Throughout many of the paper section, the level of detail to understand the trial design is unnecessary and somewhat distracting. This paper could be significantly edited down so that just the most important and necessary information is included.
• (Redundancy): There is also a lot of redundancy in this paper (adding to the length), which I have tried to identify when spotted below.
• (Abstract): Is the description of all the different phases necessary for the randomized trial protocol, or should this paper just focus on the randomized trial protocol (phase 2)? (Editor comment?)
• (Peer educators): The majority of peer-led interventions are among key population groups (e.g., FSWs, MSM, IDUs) that are clearly defined, have tight social connectivity, and increased HIV risk. It is not clear to me what the target population of this intervention is. Additionally, it is not clear to me why the peer educators have to be living with HIV. What are the characteristics of these peer educators and what qualifies them as “peers” to the target population? In other studies conducted among the general population, these individual might be classified as “lay counselors”.
• (Standard of care): Why are nurses and not peer educators visiting participants in the SOC arm? This seems like an important variation that could have implications on the study findings.
• (Sample size): While your sample size is powered for your primary outcome, the rest of your outcomes appear to be just among individuals who test HIV-positive – which will be a small fraction of your total sample if HIV prevalence is <2% in your study population. Thus, how much power do you have to measure these secondary outcomes? Please clarify.
• (Linkage to prevention services): While there is much emphasis on linkage to HIV treatment services for those to test HIV positive, there is a missed opportunity to link those who test HIV negative and who are at high HIV risk to prevention services like PrEP. Could you add linkage to PrEP services to your study for those who test HIV negative?

MINOR:
• (Abstract): The introduction should state the problem/motivation for this trial. It currently reads like an abbreviated methods section.
• (Abstract): Not clear to me who the target population is and who the peers are? Are the peers nurses? This should be clear considering that this is a peer educator focused intervention.
• (Page 6, lines 1-2): This is not the first trials to assess the effect of peer-led HIV care interventions, numerous trials have been previously conducted on peer-led HIV care interventions in diverse settings. Maybe the first in this setting?
• (Page 7, Lines 12-13): Is Ethiopia disproportionately affected compared to other SSA countries? How does its HIV incidence, prevalence, mortality rates compare to other SSA countries?

	• (Methods, Data monitoring committee): Consider moving this sub-section from the beginning to the end of the methods section. • (Page 12, Lines 19-20): In addition to the regional HIV prevalence, can you add more details about who is most at risk of HIV infection in this population – e.g., women, children, sex workers, etc. • (Page 13, Line 1): Again, what characteristics of these individuals qualify them as "peer educators", why would you classify them as this when providing services to a diverse general population vs. classifying them as "lay counselors"? • (Page 13, Lines 9-11): These outcomes seem like they are outside the scope of the trial and what it is designed to test. • (Page 14, Line 5): Who are these peer educators? What makes them qualified to be peer educators, how will you recruit them, what is their training? • (Page 14, Lines 5-7): Is this peer educators supported/observed HIV self-testing? What if the participant wants to use the HIV self-test at a later time? • (Page 14, Lines 12-13): What is your motivation for having participants bring back their used test kits? In other HIV self-testing studies, few participants have returned the kits when asked to bring them back, and additionally test results are not valid outside of a window period post-testing. Other studies have suggested that the results on these kits may change over time – resulting in inaccurate readings if read at a later time. • (Page 14, Lines 19-21): Can you elaborate on what the SOC arm is getting? Are they also getting a door-to-door intervention like the other arms? Are nurses not peers delivering this intervention? These are important differences that should be clarified. • (Page 15, Line 12-14): You are measuring your primary outcome at enrollment? Primary outcomes should be measured at a specific time point following the intervention. • (Page 15, Lines 15-17): Can you clarify your definition of linking to HIV care? Is this starting ART? At what time point (post HIV testing) are you measuring this outcome? • (Page 15, Lines 18-20): Measured 6 months post what? Post HIV testing? • (Page 18): Considering separating randomization and blinding into one section, and recruitment and eligibility in another section (with recruitment coming first). • (Page 19, Study procedures): Much information here is redundant with information presented above, consider abbreviating information above. • (Page 23, Acceptability): Much of this information seems redundant with previously presented information. • (Page 30, Data management): Will the quantitative data not be collected electronically? If so, what is the rationale for that decision in 2020? • (Page 31, Lines 6-7): What are these structural, cultural, and individual barriers that are keeping testing low – especially those specific to Ethiopia. Additionally, do you have specific information about 90-90-90 and testing rates in Ethiopia or this region? The whole first paragraph of the discussion could be moved to the introduction (or deleted because already covered there). • (Page 32, Lines 1-2): I believe this third research question is different from that presented above?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Comments to the Author
Thank you for the opportunity to review your protocol. Under Outcomes and measurement, it seems your primary outcome under (i) is HIV status at enrolment? Do you mean increase in knowledge of HIV status? Surely at enrolment is baseline?
Thank you. We have now clarified the primary outcomes, including the outcome related to first UNAIDS-90 in page 7, lines 13-31. For example, the outcome related to knowledge of HIV status is "Change in knowledge of HIV status (UNAIDS 1st 90)- this will be measured through face-to-face interview at enrollment of the trial, followed by HIV testing (diagnosis period) through HIVST and H2H."

Please clarify.
Additionally, if at all possible, I think it would be helpful to have an infographic that clearly shows the structure of the health system with regards to zones, households, kebele's etc
Thank you very much. We have added the Ethiopian organizational structure and Health tier system in page 5, line 27-28.

Also, please clarify, the line that refers to 'blinding'. I don't believe participants can be blinded in this study. Line 13 on page 18 of 45.
Thank you. We have revised this in page 9 of lines 25-26 and page 10 of lines 1-2. We added: "To enhance allocation concealment, the peer educators and household participants will not be told the hypothesis of the research question so that to they are blinded to knowledge of the other interventions being conducted. However, they are unblinded to-the actual treatment they are receiving.

Reviewer: 2

Comments to the Author
Looks good....
Thank you!

Reviewer: 3

Comments to the Author
Manuscript: "Peer-led HIV care and the UNAIDS 90-90-90 treatment targets in Tigrai, Ethiopia: A cluster randomized trial and economic evaluation of Teach-Test-Link-Trace model (TTLT) trial protocol"

DECISION: Major revision

OVERALL: An interesting study that will generate important evidence on uptake of HIV testing uptake with a number of different testing strategies. However, the motivation for using "peers" and who these peers are/what makes them classified as peers vs. lay counselors is not clear to me.
Thank you. In our study, 'peer' refers to those who are HIV positive, on HIV care, and disclose their HIV status publicly. In Ethiopian context, lay counselor involves HIV negative and positive individuals. We have added this in the revised version on page 4, lines 22-23.

Additionally, the SOC arm having nurses versus peers visit their home seems like it might bias study results.
Thanks, we did this deliberately to assess the cost-effectiveness of peer educators versus trained health professionals (i.e. nurses). Furthermore, nurses in Ethiopian health care system perform out of health facility HIV testing routinely to maximize HIV testing coverage and improve detection rate especially in camping periods--- this is a standard of care. We have described this more in page 11 lines 10-14.
There is also much emphasis on outcomes among individuals who test HIV-positive, and little emphasis on outcomes (related to HIV prevention) for those who test HIV negative.
Thank you. We will provide counselling on how to prevent HIV infections to those who are HIV negative. We have added this in page 7, lines 14-15.
A number of the outcomes are not clearly defined; it is particularity unclear at what time point the authors plan on measuring these outcomes.
Thank you. We have added more clarifications, including the point the outcomes are measured, in page 7, lines 13-31; page 8, lines 1-11; and page 12, lines 21-32.
Briefly, (i) outcome 1, UNAIDS first 90, will be measured at diagnosis period; (ii) outcome 2, UNAIDS second 90 will be measured at 0 month after HIV diagnosis; and (iii) outcome 3, UNAIDS third 90, will be measured at 3, 6 and 9 months after starting antiretroviral therapy (ART).
The paper is also quite long and these is a lot of redundancy in what is being presented. The authors should consider editing to reduce this redundancy and improve clarity.
Many thanks, we also feel the paper is a bit long but this is a five years project involving multiple study designs assessing multiple outcomes. However, we have tried to reduce the redundancies and substantially reduce from its previous version.

MAJOR:
• (Length): Throughout many of the paper section, the level of detail to understand the trial design is unnecessary and somewhat distracting. This paper could be significantly edited down so that just the most important and necessary information is included.
Thank you very much. We have edited down substantially.

• (Redundancy): There is also a lot of redundancy in this paper (adding to the length), which I have tried to identify when spotted below.
Thank you again.
We have removed the redundancies.

• (Abstract): Is the description of all the different phases necessary for the randomized trial protocol, or should this paper just focus on the randomized trial protocol (phase 2)? (Editor comment?)
Thank you. The description of all the different phases are necessary as they are linked with the randomized trial. Phase 1 inform the randomized trial (phase 2), and the remaining phases are also extension of phase 2.

• (Peer educators): The majority of peer-led interventions are among key population groups (e.g., FSWs, MSM, IDUs) that are clearly defined, have tight social connectivity, and increased HIV risk. It is not clear to me what the target population of this intervention is. Additionally, it is not clear to me why the peer educators have to be living with HIV. What are the characteristics of these peer educators and what qualifies them as “peers” to the target population? In other studies conducted among the general population, these individual might be classified as “lay counselors”.
Thanks. As we have described above, in the Ethiopian setting, ‘peer educators’ refer to those who are HIV positive, on HIV care, and disclose their HIV status publicly. They receive rigorous training and are assigned in hospitals or health centers working voluntarily. Currently, they provide counselling for non-adherent HIV positive persons given they ‘uderstand’ being HIV positive and its consequences.

Hence, the 'peer educators or per-led HIV care services in this study is contextualized accordingly.' Lay counselor' in the Ethiopian context involves both HIV negative and positive individuals. We have added the definition of peer educators in the revised version on page 4, lines 18-19.

- (Standard of care): Why are nurses and not peer educators visiting participants in the SOC arm? This seems like an important variation that could have implications on the study findings.

Thanks again, we did this deliberately to assess the cost-effectiveness of peer educators versus trained health professionals (nurses). Furthermore, nurses do routinely to maximize HIV testing coverage and improve detection rate in camping periods, which is a standard of care.

- (Sample size): While your sample size is powered for your primary outcome, the rest of your outcomes appear to be just among individuals who test HIV-positive – which will be a small fraction of your total sample if HIV prevalence is <2% in your study population. Thus, how much power do you have to measure these secondary outcomes? Please clarify.

Thank you for picking this point up. We have now added the estimates in page 9, lines 6-9.

- (Linkage to prevention services): While there is much emphasis on linkage to HIV treatment services for those to test HIV positive, there is a missed opportunity to link those who test HIV negative and who are at high HIV risk to prevention services like PrEP. Could you ad linkage to PrEP services to your study for those who test HIV negative?

Thank you and this would have been interesting. However, the PrEP services is just introduced in Ethiopia and we are not sure when the services will be decentralized. Thus, we will only provide a counselling on how to prevent HIV infections to those who are HIV negative, including those who are at high risk. We have added this in the revised document in page 7, lines 14-15.

MINOR:

- (Abstract): The introduction should state the problem/motivation for this trial. It currently reads like an abbreviated methods section.

Thank you but the word count limited us to put the problem. Thus, we described aim of this study.

- (Abstract): Not clear to me who the target population is and who the peers are? Are the peers nurses? This should be clear considering that this is a peer educator focused intervention.

Thanks. We have added the target population in page 2, lines 9-10. We have clarified why nurses are added to this per-led HIV care in the above comments re: "Thanks again, we did this deliberately to assess the cost-effectiveness of peer educators versus trained health professionals (nurses). Furthermore, nurses do routinely to maximize HIV testing coverage and improve detection rate in camping periods, which is a standard of care."

- (Page 6, lines 1-2): This is not the first trials to assess the effect of peer-led HIV care interventions, numerous trials have been previously conducted on peer-led HIV care interventions in diverse settings. Maybe the first in this setting?

Thanks. We have done a literature review and we did not find a randomized trial assessing all the three UNAIDS 90s at a time in a single study using these new testing strategies, although there are studies which assessed either of the UNAIDS targets. Moreover, there is no in Ethiopia. We have added this information in page 5 lines 5-7.

- (Page 7, Lines 12-13): Is Ethiopia disproportionately affected compared to other SSA countries? How does its HIV incidence, prevalence, mortality rates compare to other SSA countries?

Please check this in page 4, lines 5-7. "Ethiopia is one of the sub-Sahara African countries which is disproportionally affected. The most recent data inform that the HIV prevalence in Ethiopia was between 0.1-4.8% in 2017/8."

- (Methods, Data monitoring committee): Consider moving this sub-section from the beginning to the end of the methods section.

Thanks, we have moved to the end of methods section: page 17, lines 19-21 and page 18, lines 1-25.

- (Page 12, Lines 19-20): In addition to the regional HIV prevalence, can you add more details about who is most at risk of HIV infection in this population – e.g., women, children, sex workers, etc.
Thank you. We have added these points in page 6, lines 14-16.

- (Page 13, Line 1): Again, what characteristics of these individuals qualify them as "peer educators", why would you classify them as this when providing services to a diverse general population vs. classifying them as "lay counselors"?
Thanks, we have described in the above concerns of yours.

- (Page 13, Lines 9-11): These outcomes seem like they are outside the scope of the trial and what it is designed to test.
We have described our primary and secondary outcomes in pages 7 and 8, and the outcomes mentioned throughout the protocol are based on these outcomes.

- (Page 14, Line 5): Who are these peer educators? What makes them qualified to be peer educators, how will you recruit them, what is their training?
Thanks, we have addressed these above.

- (Page 14, Lines 5-7): Is this peer educators supported/observed HIV self-testing? What if the participant wants to use the HIV self-test at a later time?
Thanks. Yes, peer educators observe if the participants want but they can also do by themselves. We have described these in page 11 line 31…"Participants will be asked whether they want to be supervised or not during the self-test process."

- (Page 14, Lines 12-13): What is your motivation for having participants bring back their used test kits? In other HIV self-testing studies, few participants have returned the kits when asked to bring them back, and additionally test results are not valid outside of a window period post-testing. Other studies have suggested that the results on these kits may change over time – resulting in inaccurate readings if read at a later time.
Thank you. We want basically: (1) for participants to report their HIV status and we thought that this may motivate them to bring back; (2) to assess the response rate and the technical difficulties (or easiness) and record any challenges; and (3) confirmation of appropriate disposal. We are not interested in confirming the negative results— if the study participant reports 'negative' we will accept; however, if 'positive', the participant will need further confirmatory test, which will be included in the oral HIVST kit package as described in 11 lines 28-32 and page 12 lines 1-11. Hence, the issue of window period is not a matter for this study.

- (Page 14, Lines 19-21): Can you elaborate on what the SOC arm is getting? Are they also getting a door-to-door intervention like the other arms? Are nurses not peers delivering this intervention? These are important differences that should be clarified.
Thanks, yes. We have now described this in page 11, lines 1-3…." In this study group, nurses will visit a household once to counsel participants, distribute condom and refer them to standard HIV testing and care clinics to a nearest (or their preferred) health facility."
- (Page 15, Line 12-14): You are measuring your primary outcome at enrollment? Primary outcomes should be measured at a specific time point following the intervention.
Thanks. For this study, the primary outcome is 'knowing one's HIV status' and which will be known through testing (HIVST and H2H, our interventions) immediately at the time the eligible participants enrolled in the trial. We have clarified this in page 7 lines 17-23.

- (Page 15, Lines 15-17): Can you clarify your definition of linking to HIV care? Is this starting ART? At what time point (post HIV testing) are you measuring this outcome?

Thanks. We have added this in page 8 line 3-4; “Linkage to HIV care refers to enrollment of HIV positive person in to HIV care setting to receiving ART or other HIV care services”.

- (Page 15, Lines 18-20): Measured 6 months post what? Post HIV testing?

Thanks, we have clarified this, which is Post ART initiations.

- (Page 18): Considering separating randomization and blinding into one section, and recruitment and eligibility in another section (with recruitment coming first).

Thanks, we have revised this accordingly as shown in page 9, lines 16 and page 10, line 3.

- (Page 19, Study procedures): Much information here is redundant with information presented above, consider abbreviating information above.

Many thanks. We have shortened this substantially.

- (Page 23, Acceptability): Much of this information seems redundant with previously presented information.

Many thanks. We have shortened some of the redundant points.

- (Page 30, Data management): Will the quantitative data not be collected electronically? If so, what is the rationale for that decision in 2020?

Thanks, but the budget does not allow us to collect data electronically. However, we are applying for additional budget and we will consider this should we receive it.

- (Page 31, Lines 6-7): What are these structural, cultural, and individual barriers that are keeping testing low – especially those specific to Ethiopia. Additionally, do you have specific information about 90-90-90 and testing rates in Ethiopia or this region? The whole first paragraph of the discussion could be moved to the introduction (or deleted because already covered there).

Thank you. Given the paper is originally long, we have put the citations instead of describing each of the structural, cultural, and individual barriers. Furthermore, we have also published papers describing these
barriers (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6982005/ and https://pubmed.ncbi.nlm.nih.gov/32013114/). We believe that adding the arguments about the relatively new HIV testing strategies (to Ethiopia) on improving the entire HIV care program is important for the reader and we decided to leave as is.

- (Page 32, Lines 1-2): I believe this third research question is different from that presented above?

Thank you very much but we believe that this is a per-led HIV study and their involvement is important on the outcomes of HIV care services.

We thank you so very much for the reveiwers valuable time and comments, which the paper is improved substantially.

VERSION 2 – REVIEW

REVIEWER	Moore, Carolyn The University of Alabama at Birmingham
REVIEW RETURNED	03-Jan-2021

GENERAL COMMENTS	Thank you for addressing my earlier comments