PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

| TITLE (PROVISIONAL) | Point-of-care viral load testing among adolescents and youth living with HIV in Haiti: A protocol for a randomized trial to evaluate implementation and effect |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Reif, Lindsey; Belizaire, Marie Elmase; Seo, Grace; Rouzier, Vanessa; Severe, Patrice; Joseph, Joseph Marie; Joseph, Bernadette; Apollon, Sandra; Abrams, Elaine; Arpadi, Stephen; Elul, Batya; Pape, Jean William; McNairy, Margaret; Fitzgerald, DW; Kuhn, Louise |

VERSION 1 – REVIEW

| REVIEWER             | Dr Jienchi Dorward |
|----------------------|-------------------|
|                      | University of Oxford (United Kingdom) and CAPRISA (South Africa) |
| REVIEW RETURNED      | 20-Dec-2019 |

| GENERAL COMMENTS | Thank you for the opportunity to review this protocol for a study of point of care HIV viral load testing to monitor ART amongst adolescents and young people in Haiti. This study is important as HIV treatment outcomes are particularly poor amongst adolescents, meaning point-of-care viral load testing may be particularly beneficial in this group. The study appears well designed however there are some inconsistencies between the manuscript, protocol and clinicaltrials.gov entry that need clarification, particularly regarding the study schedule and main outcomes. Also, the primary objective of the study is to assess POC VL implementation, while the secondary aims are to assess effectiveness regarding VL suppression and self-reported adherence. The small sample size means the study is powered to detect a 25% difference in VL suppression, which the authors acknowledge is optimistic. Therefore, it seems that the study is mainly assessing implementation of POC VL testing, rather than effectiveness. The aims and objectives throughout the manuscript need to be better defined and clarified to consistently reflect this. Lastly, much of the recent literature on point of care viral load testing is not included in the background/discussion. |

| ABSTRACT | Methods and analysis: ‘designed to evaluate the effectiveness of POC VL testing….’ Suggests effectiveness at changing a clinical outcome e.g. viral load suppression or levels of adherence, but primary outcome is focussed more on implementation? Suggest rephrasing. |
STRENGTHS AND LIMITATIONS
The first two points describe the study, rather than stating its strengths. The study population of adolescents and young people is a particular strength as there are no other studies looking at this specific group that I am aware of.

INTRODUCTION
References generally quite old, would be good to cite some more recent work looking at the challenges of VL testing and lots of recent work on POC VL testing is also missing. Some suggestions (full disclosure, including some which I am author on):

1 Ehrenkranz PD, Baptiste SL, Bygrave H, et al. The missed potential of CD4 and viral load testing to improve clinical outcomes for people living with HIV in lower-resource settings. PLOS Med 2019;16:e1002820.
doi:10.1371/journal.pmed.1002820
2 Drain PK, Dorward J, Violette L, et al. Point-of-care viral load testing improves HIV viral suppression and retention in care. In: Conference on Retroviruses and Opportunistic Infections. Seattle, Washington: 2019.
3 Nicholas S, Poulet E, Wolters L, et al. Point-of-care viral load monitoring: outcomes from a decentralized programme in Malawi. J Int AIDS Soc 2019;22:1–9. doi:10.1002/jia2.25387
4 Ndlouv Z, Fajardo E, Mbofana E, et al. Multidisease testing for HIV and TB using the GeneXpert platform: A feasibility study in rural Zimbabwe. PLoS One 2018;13:e0193577.
doi:10.1371/journal.pone.0193577
5 Sacks JA, Fong Y, Gonzalez MP, et al. Performance of Cepheid Xpert HIV-1 viral load plasma assay to accurately detect treatment failure. AIDS 2019;33:1881–9.
doi:10.1097/QAD.0000000000002303
6 Drain PK, Dorward J, Bender A, et al. Point-of-Care HIV Viral Load Testing: an Essential Tool for a Sustainable Global HIV/AIDS Response. Clin Microbiol Rev 2019;32:e00097-18.
doi:10.1128/CMR.00097-18
7 Simeon K, Sharma M, Dorward J, et al. Comparative cost analysis of point-of-care versus laboratory-based testing to initiate and monitor HIV treatment in South Africa. PLoS One 2019;14:e0223669.
doi:10.1371/journal.pone.0223669
8 Girdwood SJ, Nichols BE, Moyo C, et al. Optimizing viral load testing access for the last mile: Geospatial cost model for point of care instrument placement. PLoS One 2019;14:e0221586.
doi:10.1371/journal.pone.0221586
9 Bianchi F, Cohn J, Sacks E, et al. Evaluation of a routine point-of-care intervention for early infant diagnosis of HIV: an observational study in eight African countries. Lancet HIV 2019;:1–
9. doi:10.1016/S2352-3018(19)30033-5

Page 6 Line 31: Reference 7 describes the DART trial results which focussed on CD4 count testing, not viral load monitoring.

Page 7 Line 3: The introduction does not clearly outline that a high viral load may be due to HIV drug resistance in the presence of perfect adherence. This is an important point and should be discussed.

Page 7 line 50-54: As well as the potential benefits of POC VL testing, the authors should also mention the potential down
sides of POC VL testing including the need for assay maintenance,
quality assurance, cartridge supply and safe disposal, which could limit the feasibility of POC VL testing.

Page 8 Line 8: ‘…including regimen changes’ As mentioned above, regimen changes need to be discussed in the context of HIV drug resistance.

Page 8 Line 24: ‘impact’ is not entirely clear and not consistent with the abstract which states ‘designed to evaluate the effectiveness of POC VL testing’. Throughout the manuscript, the aims need to be clear and consistent – is this primarily a trial assessing implementation or clinical effectiveness?

Page 8 Line 33: Please briefly describe the patient population at this clinic, and the type of clinic, as this is important for understanding generalisability of implementation findings. Is this a research clinic? Are there on site laboratories of any type (protocol suggests there are)?

Page 8 line 50: linked to above, is the study powered to demonstrate an improvement? If not, it would be better to state something along the lines of ‘the study aims to provide estimates of ART adherence and VL suppression outcomes with POC VL and Laboratory VL testing’

METHODS

Page 9 Line 51: What type of healthcare worker is performing the POC VL testing? Also, the protocol states the Xpert is in an on-site laboratory – this needs to be specified in the manuscript

Page 10 Line 6: To my knowledge the Xpert HIV-1 VL (as opposed to the Xpert HIV Qual assay) is only WHO prequalified for plasma testing, not DBS.

Page 10 Line 6: Please ensure that the full assay name is correctly used through the document to make the above distinction clear.

Page 10 Line 6: Please reference the WHO Prequal document.

Page 10 Line 12: Two systematic reviews of the Xpert HIV 1 VL have now been published which should be cited here (e.g. Sacks et al 2019 in references I provided above)

Page 10 Line 16: What happens if there are errors with the POC assay or the patient arrives in the afternoon within an hour of clinic closure? The protocol states patients will be asked to attend before 11am, and called a week before their appt to remind them. This important detail should be mentioned in the manuscript, and whether this is study specific or routine practice, and whether it is the same for both arms.

Page 10 Line 16: Also, it is stated here that a study nurse will provide the POC VL results with adherence counselling to the participants. In the lab VL arm, who will be providing the results? Will this also be a study team member or a routine clinic staff member, and will it be a nurse or physician? In the protocol, there seem to be some physician appointments and some nurse appointments, and maybe more physician appointments in the POC arm than the SOC arm? Please clarify.
Page 12 Line 10: The protocol only has 2 secondary outcomes (self reported adherence is not mentioned in the protocol). The manuscript and protocol should be consistent. The main primary outcome on clinicaltrials.gov is different from the manuscript and protocol.

Page 13 Line 20: If someone has just had a VL result in the past few months, would they still be eligible?

Page 13 Line 20: The protocol and manuscript eligibility/exclusion criteria are not consistent (e.g permanent resident in Port au Prince, requires same day VL test)

Page 14 Line 3: It would help the reader to know what is done with this repeat VL test – regimen switch, more adherence counselling?

Page 14 Line 14: Will steps be taken to to ensure that VL knowledge questionnaires are administered only if the patient received a VL result? If not, then the questionnaire could prompt someone to be given the result, thereby artificially shortening time to results?

Page 15 Line 6: It is not clear why an assumption of 70% getting VLs <6 weeks in the standard of care arm is used when the observed prevalence in the clinic is 50%? A statistician should review the sample size calculations

Page 16 Line 16: I would advise against setting a cut off for a ‘statistically significant’ p – value. P values of 0.049 and 0.051 are essentially the same and so an arbitrary cut off does not help with interpretation.

DISCUSSION

Page 17 Line 10-40: The potential limitations of POC testing are well described, but from the methods described it is unclear how the study will identify the potential impact of these issues. If POC testing is not successful, how will the authors determine whether electricity supply versus patients not waiting for results versus cartridge supply was the problem?

Page 18 Line 14-16: Regarding feeling ‘caught or shamed’ – the authors may like to reference this useful paper

Bernays S, Paparini S, Seeley J, et al. “Not Taking it Will Just be Like a Sin”: Young People Living with HIV and the Stigmatization of Less-Than-Perfect Adherence to Antiretroviral Therapy. Med Anthropol 2017;36:485–99. doi:10.1080/01459740.2017.1306856

Page 18 Line 35-36: The concepts of linkage to care and clinical decision making have not really been outlined before, so it seems odd to mention them in this last sentence. Furthermore, given the small sample size it could be optimistic to suggest that this trial will provide evidence regarding clinical outcomes.

ETHICS AND DISSEMINATION

Page 18 Line 45: Please clarify whether enrolment is complete and if so on which date.
TABLES AND FIGURES

Table 2: The timings of various interventions do not seem to agree with the text. Are VLs not done on the day of enrolment (Month 0)? The Table has them at Month 1. The timing of VL tests in relation to enrolment needs to be made very clear in the text and Table 2. In the clinicaltrials.gov entry, the timing of VLs are stated as:

‘Participants in the standard-of-care arm will receive a standard
laboratory-based viral load test at baseline, 3, and 6 months.’

In Table 2 why is follow up in SOC arm up to Month 7?

For patients with VL > 1000 in SOC arm, shouldn’t the repeat VL be one month later than the POC arm, as they would need 3 months of adherence counselling after receiving the result of the first high VL test?

Table 2 has no Xpert VL test at Month 6, whereas the protocol ‘Schematic Study Design’ does. Please clarify.

Figure 1a and 1b: This figure is very simplified and does not provide any insight into the context of the study site – the text provides more detail (ie Excel spreadsheet of results being emailed, manual entry into EMR).

Figure 2: Same questions re timing of VL test as in Table 2

REVIEWER Obinna Ekwunife
Nnamdi Azikiwe University, Awka, Nigeria
REVIEW RETURNED 07-Jan-2020

GENERAL COMMENTS

This is a well-designed and well-written protocol. I have made the following observations which the authors could consider to improve the protocol:
1. Since the adolescents in the intervention arm visit the same hospital as the control arm, there could be possible contamination. How will this be mitigated? Perhaps the authors need to discuss this possible limitation
2. The authors did not discuss the mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
3. It will be great if the authors can include plans to promote participant retention and complete follow-up
4. The authors should include plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).
5. The authors should state plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

REVIEWER Christopher Hoffmann
Johns Hopkins, USA
REVIEW RETURNED 18-Feb-2020

GENERAL COMMENTS Thank you for the opportunity to review “Point-of-care viral load testing among adolescents and youth in Haiti”. Research on how
best to apply advances in routine testing is critical to maximize potential benefits. This is a protocol for a pilot RCT to assess whether use of POC viral load testing (using GeneXpert) increases the proportion of participants receiving viral load results within 6 weeks of testing. Increasing appropriate use of VL testing is important and the ongoing study will contribute. I am enthusiastic about the study. Unfortunately, the manuscript has substantial flaws that I describe below. I suggest a careful rewriting with attention to content and composition.

I have the following comments on this protocol manuscript for areas that could use improvement and/or increased clarity.

1. The abstract states that the primary outcome “will describe the implementation of POC VL testing”. Exactly what is being compared needs to be stated. Later it appears to be proportion receiving results within 6 weeks. This is not really the “implementation”.
2. Background. More references are needed. For example, there is a statement that adequate adherence needed for VL suppression is 80-90%. This depends on the regimen. The references are general reviews of adherence. Please include references related to current regimens used by adolescents in Haiti.
3. The strengths and limitations state a RCT … to evaluate … adherence and viral suppression. These are listed as secondary outcomes and should not be stated in the strengths / limitations box.
4. The authors shift between describing the primary outcome and the secondary outcomes. In the methods the primary outcome is briefly mentioned in a paragraph followed by three paragraphs of the secondary outcomes, this seems out of balance. In the sample size and analysis sections primary and secondary outcomes are described together. These should be separated. In addition, sample sizes are generally powered to a primary outcome rather than secondary outcomes.
5. The primary outcome in the manuscript is “proportion with VL test results in 6 weeks”. In the study protocol and the clinicaltrials.gov protocol it is “to describe the steps within the HIV care cascade involved with VL testing, comparing standard laboratory-based testing to POC testing”. This discrepancy should be addressed. This should include what steps are being referred to and exactly how these steps will be measured and at what level they will be compared.
6. An analysis plan is needed for the “steps” primary outcome.
7. A description of the theory of change is needed in the methods. This can be provided for both the primary outcome and secondary outcomes. Along with the theory of change, there should be a model as to current barriers and how this technology overcomes those barriers. This should specifically address the reason why POC VL is likely to lead to a greater number of VL results getting back to the patient within 6 weeks. If it is a charting issue, will POC VL solve this problem or would another approach be superior.
8. It is suggested, but not directly stated, that participants in the POC VL arm may get results on the day of appointment. I assume that testing for VL will be performed toward the end of a clinical encounter. Then the blood needs to be spun and then run on a Xpert machine (possibly batched) taking 2.5-3.5 hours for a result. Does the study team think that the patients will wait around for the result? If so, how will the patient know to be re-integrated into the patient flow once the result is back? How would this happen in routine practice (outside of the RCT).
9. There is insufficient description of the clinical pathway for when a VL testing decision is made, who obtains a specimen, who takes it to a processing / Xpert area, etc.

10. The protocol mentions that process steps measured are "generating a valid VL test result", "returning the VL test results to the participant", and "providing counseling..." but how these will be measured is not described.

11. Given a goal of "implementation" outcomes, including test completion, sample failures, fidelity, acceptability, would be useful to include (and possibly are included but not described in this manuscript).

12. On page 12 a “viral load knowledge questionnaire” is introduced. This doesn’t fit into any of the listed primary or secondary outcomes nor the overall goal to increase the proportion of patients receiving results within 6 weeks. It either needs to support the underlying theory and should be a secondary outcomes or should be removed.

13. It is unclear why 60% was selected for a binary outcome for the VL questionnaire. This needs to be justified through instrument validation if it is being selected a priori. If these validation studies have been completed they need to be cited.

14. The power / sample size descriptions are vague. Specifics on the calculation approach is needed (beyond stating a power and alpha).

15. The analysis section discussing propensity scoring but also states that for the primary outcome participants will be compared. It is unclear what the analysis is and how it will be performed. Since it is randomized it is unclear why propensity scores would be used for the primary analysis. Nor are the planned characteristics for propensity matching described (should be included).

16. Subgroup analyses are referred to. Given the small sample size this seems inappropriate.

17. The discussion describes same day return of results; however, nowhere is this mentioned as a metric or an outcome. (Nor as I have stated above is it clear how this will occur given the time it takes from getting a sample to having the results).

18. The discussion describes important health system considerations for a new technology. This is relevant, but none of the aspects described in the discussion are measured as part of the protocol.

19. A limitation is the relative uniqueness of the study clinic. Whether a success with POC VL can fit a more routine context will not be a finding and is a limitation. Given a feasibility is mentioned in places (such as the discussion) as a key finding, this is a major limitation.

20. Study timelines should be included. The study started in May 2018. I would expect it would be complete by now given the modest sample size and short term follow-up. Please clarify. (IE the primary completion date is listed as November 2019 in clinicaltrials.gov)

21. The funders should be included in the body of the manuscript.

22. The clinicaltrials.gov registration should be in the body of the manuscript.
The paper is well written. The study was designed as an un-blinded randomized clinical trial to evaluate the effectiveness of point-of-care (POC) VL testing compared with standard laboratory-based (SOC) VL testing among adolescents and youths ages 10-24 years living with HIV who have been on ART for ≥ 6 months. Total 150 adolescents and youths are randomized into POC and standard of care (SOC) arm with a ratio of 1:1. The primary objective is to describe and compare the HIV testing between POC and SOC. One primary outcome is the proportion of participants who received their HIV test results within 6 weeks of HIV testing. The secondary objective is to evaluate the effect of POC HIV testing on ART adherence, VL suppression at 6 months from enrollment, and correlation between ART adherence and VL suppression.

Sample size and power calculations
1. Authors assume 80% follow-up in both arms. If 150 (75 per arm) are enrolled, it would be 120 participants who will be at 6 months based on 80% follow-up assumption. Why was a sample size of 124 used in the power calculations?
2. In POC arm, would all participants receive their HIV testing results in the same day?

Analysis and statistical methods
3. The authors have planned an analysis using propensity score weighting to account any differences between participants in two arms if equivalence is not achieved by randomization. Would the authors provide a strong justification for use the propensity score weight method for this randomized clinical trial?
4. Why use R 2.14.2 not later version for all analyses?

RESPONSE TO REVIEWER

Reviewer: 1

ABSTRACT
Methods and analysis:

1. ‘designed to evaluate the effectiveness of POC VL testing….’ Suggests effectiveness at changing a clinical outcome e.g. viral load suppression or levels of adherence, but primary outcome is focused more on implementation? Suggest rephrasing.

Response: We have revised to clarify that the trial evaluates both the implementation and effectiveness of POC VL testing. (Page 2, Line 11)

STRENGTHS AND LIMITATIONS
2. The first two points describe the study, rather than stating its strengths. The study population of adolescents and young people is a particular strength as there are no other studies looking at this specific group that I am aware of.

Response: We have revised these to clarify the strengths include the particular study population. (Page 4, Line 3-5).

INTRODUCTION
3. References generally quite old, would be good to cite some more recent work looking at the challenges of VL testing and lots of recent work on POC VL testing is also missing. Some suggestions (full disclosure, including some which I am author on):

1) Ehrenkranz PD, Baptiste SL, Bygrave H, et al. The missed potential of CD4 and viral load testing to improve clinical outcomes for people living with HIV in lower-resource settings. PLOS Med 2019;16:e1002820. doi:10.1371/journal.pmed.1002820

2) Drain PK, Dorward J, Violette L, et al. Point-of-care viral load testing improves HIV viral suppression and retention in care. In: Conference on Retroviruses and Opportunistic Infections. Seattle, Washington: 2019.

3) Nicholas S, Poulet E, Wolters L, et al. Point-of-care viral load monitoring: outcomes from a decentralized programme in Malawi. J Int AIDS Soc 2019;22:1–9. doi:10.1002/jia2.25387

4) Ndlovu Z, Fajardo E, Mbofana E, et al. Multidisease testing for HIV and TB using the GeneXpert platform: A feasibility study in rural Zimbabwe. PLoS One 2019;13:e0193577. doi:10.1371/journal.pone.0193577

5) Sacks JA, Fong Y, Gonzalez MP, et al. Performance of Cepheid Xpert HIV-1 viral load plasma assay to accurately detect treatment failure. AIDS 2019;33:1881–9. doi:10.1097/QAD.0000000000002303

6) Drain PK, Dorward J, Bender A, et al. Point-of-Care HIV Viral Load Testing: an Essential Tool for a Sustainable Global HIV/AIDS Response. Clin Microbiol Rev 2019;32:e00097-18. doi:10.1128/CMR.00097-18

7) Simeon K, Sharma M, Dorward J, et al. Comparative cost analysis of point-of-care versus laboratory-based testing to initiate and monitor HIV treatment in South Africa. PLoS One 2019;14:e0223669. doi:10.1371/journal.pone.0223669

8) Girdwood SJ, Nichols BE, Moyo C, et al. Optimizing viral load testing access for the last mile: Geospatial cost model for point of care instrument placement. PLoS One 2019;14:e0221586. doi:10.1371/journal.pone.0221586

9) Bianchi F, Cohn J, Sacks E, et al. Evaluation of a routine point-of-care intervention for early infant diagnosis of HIV: an observational study in eight African countries. Lancet HIV 2019;6:1–9. doi:10.1016/S2352-3018(19)30033-5

Response: Thank you for these reference suggestions. We have updated our references with several of those you have listed. (Ehrenkranz et al. 2019 added to Page 5, Line 24 (ref 16); Nicholas et al. 2019 added to Page 6, Line 10 (ref 22); Ndlovu et al. 2019 and Drain et al. 2019 added to Page 6, Line 16 (ref 24 and ref 25)

4. Page 6 Line 31: Reference 7 describes the DART trial results which focused on CD4 count testing, not viral load monitoring.

Response: We have corrected this reference with the WHO guidance reference. (Page 5, Line 14 (ref 7))

5. Page 7 Line 3: The introduction does not clearly outline that a high viral load may be due to HIV drug resistance in the presence of perfect adherence. This is an important point and should be discussed.

Response: We have added this important point about the potential for drug resistance, not poor adherence, resulting in a high viral load. (Page 5, Line 22)

6. Page 7 line 50-54: As well as the potential benefits of POC VL testing, the authors should also mention the potential downsides of POC VL testing including the need for assay maintenance, quality assurance, cartridge supply and safe disposal, which could limit the feasibility of POC VL testing.
Response: We have added these potential limitations regarding the feasibility of implementing POC VL testing. (Page 7, Line 12)

7. Page 8 Line 8: ‘…including regimen changes’ As mentioned above, regimen changes need to be discussed in the context of HIV drug resistance.

Response: We have added a discussion on the potential for drug resistance. (Page 5, Line 22)

8. Page 8 line 24: ‘impact’ is not entirely clear and not consistent with the abstract which states ‘designed to evaluate the effectiveness of POC VL testing’. Throughout the manuscript, the aims need to be clear and consistent – is this primarily a trial assessing implementation or clinical effectiveness?

Response: We have clarified that the trial’s primary objective is to assess implementation of POC VL testing and the secondary objective is to assess the effect on health outcomes. We have added clarity to several sections of the manuscript (Page 2, Line 18; Page 7, Line 19; Page 12, Line 2). These objectives and measured outcomes are also included in revised Table 1.

9. Page 8 Line 33: Please briefly describe the patient population at this clinic, and the type of clinic, as this is important for understanding generalisability of implementation findings. Is this a research clinic? Are there on site laboratories of any type (protocol suggests there are)?

Response: We have added a section to the Methods section to describe the Study Site including patient population and on site laboratory. (Page 8, Line 23)

10. Page 8 line 50: linked to above, is the study powered to demonstrate an improvement? If not, it would be better to state something along the lines of ‘the study aims to provide estimates of ART adherence and VL suppression outcomes with POC VL and Laboratory VL testing’

Response: The study is powered for both the primary outcome (proportion of participants who receive a VL test result within 6 weeks) and a secondary outcome (proportion of participants who achieve or sustain a VL <1000 copies/ml at month 6). We have included the power analysis for the primary and secondary outcomes (implementation and effect) in the Methods section. (Page 15, Line 13; Page 16, Line 1)

METHODS

11. Page 9 Line 51: What type of healthcare worker is performing the POC VL testing? Also, the protocol states the Xpert is in an on-site laboratory – this needs to be specified in the manuscript

Response: We have added detail about the onsite laboratory (Page 9, Line 7) and clarified that a laboratory technician performs the POC VL testing. (Page 9, Line 13)

12. Page 10 Line 6: To my knowledge the Xpert HIV-1 VL (as opposed to the Xpert HIV Qual assay) is only WHO prequalified for plasma testing, not DBS.

Response: We have edited this to indicate the Xpert HIV-1 VL test is WHO prequalified only for plasma testing. (Page 9, Line 19)

13. Page 10 Line 6: Please ensure that the full assay name is correctly used through the document to make the above distinction clear.
Response: We have now made sure to use the full name (GeneXpert HIV-1 VL system) throughout the manuscript.

14. Page 10 Line 6: Please reference the WHO Prequal document.

Response: We have added this reference document. (Page 9, Line 19 (ref 31))

15. Page 10 Line 12: Two systematic reviews of the Xpert HIV-1 VL have now been published which should be cited here (e.g. Sacks et al 2019 in references I provided above)

Response: We have added these two systematic reviews. Thank you for suggesting these. (Page 9, Line 18 (ref 25 and ref 30))

16. Page 10 Line 16: What happens if there are errors with the POC assay or the patient arrives in the afternoon within an hour of clinic closure? The protocol states patients will be asked to attend before 11am, and called a week before their appt to remind them. This important detail should be mentioned in the manuscript, and whether this is study specific or routine practice, and whether it is the same for both arms.

Response: If there are test errors or the patient arrives too late for the test to be processed the same day, the participant is called back when the result is ready. Participants in both arms receive reminder phone calls for visits and on this call, the POC arm is reminded to arrive before 11am for a visit when a VL test is scheduled. We have added this detail to the manuscript. (Page 10, Line 1)

17. Page 10 Line 16: Also, it is stated here that a study nurse will provide the POC VL results with adherence counselling to the participants. In the lab VL arm, who will be providing the results? Will this also be a study team member or a routine clinic staff member, and will it be a nurse or physician? In the protocol, there seem to be some physician appointments and some nurse appointments, and maybe more physician appointments in the POC arm than the SOC arm? Please clarify.

Response: The same study nurse provides the VL results with adherence counseling to participants in both arms arm to keep the adherence counseling uniform. All participants meet with the physician for a clinical check-up monthly, per standard care. They meet with the study nurse for any research-related activities (e.g. adherence counseling, questionnaires). We have indicated this in Table 2.

18. Page 12 Line 10: The protocol only has 2 secondary outcomes (self reported adherence is not mentioned in the protocol). The manuscript and protocol should be consistent. The main primary outcome on clinicaltrials.gov is different from the manuscript and protocol.

Response: We have revised the manuscript so that it clearly aligns with the protocol. Self-reported adherence is no longer listed as an outcome in the manuscript. (Page 11, Line 15 and Page 12, Line 2)

19. Page 13 line 20: If someone has just had a VL result in the past few months, would they still be eligible?

Response: We conducted recruitment so that enrollment would occur approximately 6 months from a participants’ last VL test. We have clarified this in the manuscript. (Page 14, Line 1)

20. Page 13 Line 20: The protocol and manuscript eligibility/exclusion criteria are not consistent (e.g permanent resident in Port au Prince, requires same day VL test)
Response: We have revised this so that the protocol and manuscript agree. (Page 14, Lines 4, 5 and 8)

21. Page 14 line 3: It would help the reader to know what is done with this repeat VL test – regimen switch, more adherence counselling?

Response: We have added that adherence counseling is also conducted at the repeat VL test which adheres to the recommended guidelines. (Page 14, Line 19)

22. Page 14 line 14: Will steps be taken to ensure that VL knowledge questionnaires are administered only if the patient received a VL result? If not, then the questionnaire could prompt someone to be given the result, thereby artificially shortening time to results?

Response: Yes, this is a good point. We have trained all study staff on the order of the questionnaires and the VL knowledge questionnaires are administered one month after the participant receives the VL result with adherence counseling (and only after the VL result is given).

23. Page 15 Line 6: It is not clear why an assumption of 70% getting VLs <6 weeks in the standard of care arm is used when the observed prevalence in the clinic is 50%? A statistician should review the sample size calculations

Response: We elected to use a conservative estimate of the proportion of participants who would receive their VL test result. The estimated observations in the clinic (50% receiving the test result within 6 weeks) was conducted in 2016 when routine VL testing first became part of the Haitian national guidelines. We made the assumption that standard times for processing tests and returning results could gradually improve over time and so elected to use an estimate of 70%.

24. Page 16 Line 16: I would advise against setting a cut off for a ‘statistically significant’ p-value. P values of 0.049 and 0.051 are essentially the same and so an arbitrary cut off does not help with interpretation.

Response: We have removed this cut off in the manuscript. (Page 17, Line 12)

DISCUSSION

25. Page 17 Line 10-40: The potential limitations of POC testing are well described, but from the methods described it is unclear how the study will identify the potential impact of these issues. If POC testing is not successful, how will the authors determine whether electricity supply versus patients not waiting for results versus cartridge supply was the problem?

Response: We will describe the reason for each instance in which a POC VL test result is not returned the same day and/or not returned within 6 weeks of sample collection. (Page 11, Line 19) This will allow us to determine which factors contribute to POC testing being unsuccessful if that is the case.

26. Page 18 Line 14-16: Regarding feeling ‘caught or shamed’ – the authors may like to reference this useful paper

Bernays S, Paparini S, Seeley J, et al. “Not Taking it Will Just be Like a Sin”: Young People Living with HIV and the Stigmatization of Less-Than-Perfect Adherence to Antiretroviral Therapy. Med Anthropol 2017;36:485–99. doi:10.1080/01459740.2017.1306856
Response: Thank you for this suggestion. We have included this reference. (Page 19, Line 9 (ref 52))

27. Page 18 Line 35-36: The concepts of linkage to care and clinical decision making have not really been outlined before, so it seems odd to mention them in this last sentence. Furthermore, given the small sample size it could be optimistic to suggest that this trial will provide evidence regarding clinical outcomes.

Response: We have revised this sentence to clarify that POC VL testing could lead to faster clinical decision-making. (Page 19, Line 18) We agree that a small sample size is a limitation and have included this in the Discussion. (Page 18, Line 22)

ETHICS AND DISSEMINATION

28. Page 18 Line 45: Please clarify whether enrolment is complete and if so on which date.

Response: Enrollment ended in August 2019. We have added this to the manuscript. (Page 19, Line 24)

TABLES AND FIGURES

29. Table 2: The timings of various interventions do not seem to agree with the text. Are VLs not done on the day of enrolment (Month 0)? The Table has them at Month 1. The timing of VL tests in relation to enrolment needs to be made very clear in the text and Table 2. In the clinicaltrials.gov entry, the timing of VLs are stated as: ‘Participants in the standard-of-care arm will receive a standard laboratory-based viral load test at baseline, 3, and 6 months.’

Response: The enrollment visit (Month 0) includes consent/assent, randomization, and baseline questionnaires. VL tests are done at Month 1. We have clarified this throughout the manuscript and in Table 2.

30. In Table 2 why is follow up in SOC arm up to Month 7?

Response: The SOC arm receives their VL test result one month after sample collection, the Month 7 visit is when they would receive the Month 6 VL test result. We have clarified this in the manuscript. (Page 11, Line 12)

31. For patients with VL > 1000 in SOC arm, shouldn’t the repeat VL be one month later than the POC arm, as they would need 3 months of adherence counselling after receiving the result of the first high VL test?

Response: Standard care for all participants at the clinic includes a repeat VL test for participants with a VL >1000 copies/µl 3 months from the testing date, so we have scheduled the visits accordingly. Since both arms receive the VL test at month 1, participants in either arm would receive a repeat VL test 3 months later, at month 4.

32. Table 2 has no Xpert VL test at Month 6, whereas the protocol ‘Schematic Study Design’ does. Please clarify.

Response: Thank you for catching this omission. We have added the Xpert VL test for the POC arm at Month 6 in Table 2.
33. Figure 1a and 1b: This figure is very simplified and does not provide any insight into the context of the study site – the text provides more detail (i.e., Excel spreadsheet of results being emailed, manual entry into EMR).

Response: We have added detail to Figure 1a and 1b to include details about health system requirements for laboratory VL testing compared to POC VL testing.

34. Figure 2: Same questions re timing of VL test as in Table 2

Response: We have clarified in Table 2 the timing of the VL tests for both arms.

Reviewer: 2

1. Since the adolescents in the intervention arm visit the same hospital as the control arm, there could be possible contamination. How will this be mitigated? Perhaps the authors need to discuss this possible limitation.

Response: This is a key concern. We have carefully designed all study materials so that the study activities specific to each arm are implemented to participants strictly according to their randomization arm. We feel it would be highly unlikely that a participant would be provided a service that did not align with that assigned for their study arm.

2. The authors did not discuss the mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.

Response: Allocation to study arm is conducted through a computer-generated randomization program called “Study Manager” which is used for all trials at GHESKIO including trials in the GHESKIO NIAID Clinical Trials Unit. We have included this in the manuscript. (Page 14, Line 16)

3. It will be great if the authors can include plans to promote participant retention and complete follow-up.

Response: Participants in both arms receive a reminder phone call one week before a visit. We have included this in the manuscript. (Page 11, Line 1)

4. The authors should include plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values).

Response: We conduct regular data quality control and assurance checking for ranges and impossible values. We have added this to the manuscript. (Page 15, Line 8)

5. The authors should state plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct.

Response: Standard data collection, assessment, and reporting for any adverse events or other unintended effects of the trial intervention is conducted. We have added this to the manuscript. (Page 15, Line 9)

Reviewer: 3
1. The abstract states that the primary outcome “will describe the implementation of POC VL testing”. Exactly what is being compared needs to be stated. Later it appears to be proportion receiving results within 6 weeks. This is not really the “implementation”.

Response: We have clarified that the primary objective is to describe the implementation of POC VL testing which will describe the proportion of participants who achieve each process step of VL testing. The primary outcome will compare the proportion of participants in each arm who receive VL test results within 6 weeks. We have clarified this in the abstract (Page 2, Line 18) and the manuscript. (Page 11, Line 19)

2. Background. More references are needed. For example, there is a statement that adequate adherence needed for VL suppression is 80-90%. This depends on the regimen. The references are general reviews of adherence. Please include references related to current regimens used by adolescents in Haiti.

Response: We have added several references to the Background. (Ehrenkranz et al. 2019 added to Page 5, Line 24 (ref 16); Nicholas et al. 2019 added to Page 6, Line 10 (ref 22); Ndlovu et al. 2019 and Drain et al. 2019 added to Introduction, Page 6, Line 16 (ref 24 and ref 25)). We have also added a recent reference on the level of adherence and HIV RNA suppression for regimens used in Haiti. (Page 5, Line 18 (ref 11))

3. The strengths and limitations state a RCT … to evaluate … adherence and viral suppression. These are listed as secondary outcomes and should not be stated in the strengths / limitations box.

Response: We have revised the strengths and limitations section. (Page 4, Line 3)

4. The authors shift between describing the primary outcome and the secondary outcomes. In the methods the primary outcome is briefly mentioned in a paragraph followed by three paragraphs of the secondary outcomes, this seems out of balance. In the sample size and analysis sections primary and secondary outcomes are described together. These should be separated. In addition, sample sizes are generally powered to a primary outcome rather than secondary outcomes.

Response: We have revised the manuscript so that the primary outcome is discussed first followed by the secondary outcome in both the methods section and the sample size section. (Page 15, Line 13; Page 16, Line 1) We have also revised to balance the discussion on the primary and secondary outcomes.

5. The primary outcome in the manuscript is “proportion with VL test results in 6 weeks”. In the study protocol and the clinicaltrials.gov protocol it is “to describe the steps within the HIV care cascade involved with VL testing, comparing standard laboratory-based testing to POC testing”. This discrepancy should be addressed. This should include what steps are being referred to and exactly how these steps will be measured and at what level they will be compared.

Response: We have clarified this discrepancy. The primary objective is to describe the implementation of POC VL testing so we will describe the process steps in POC VL testing including generating a valid VL test result, returning the VL test results to the participant and providing adherence counseling informed by the VL result. We will describe the proportion of these steps achieved, the timing between steps and reasons for any delays or failures comparing arms. (Page 11, Line 19) The primary outcome is the proportion of participant who receive the VL test result within 6 weeks of the month 1 VL test. This is clarified in the manuscript. (Page 11, Line 21)

6. An analysis plan is needed for the “steps” primary outcome.
Response: We will do a simple description of the steps involved in VL testing and the proportion who achieved each step by arm so these are not included in the analysis section. We will also describe the reasons for failure to achieve each step to assess the implementation of POC VL testing. (Page 11, Line 15) We have clarified in the Methods section that the primary outcome will compare the proportion of participants in each arm who receive the VL test result <6 weeks from the month 1 VL test. (Page 11, Line 21)

7. A description of the theory of change is needed in the methods. This can be provided for both the primary outcome and secondary outcomes. Along with the theory of change, there should be a model as to current barriers and how this technology overcomes those barriers. This should specifically address the reason why POC VL is likely to lead to a greater number of VL results getting back to the patient within 6 weeks. If it is a charting issue, will POC VL solve this problem or would another approach be superior.

Response: We took a pragmatic health service implementation model approach and indicate the health systems-related barriers associated with POC VL testing compared to standard laboratory-based VL testing in Figure 1. We have revised Figure 1 to include specific barriers associated with the implementation of each testing method.

8. It is suggested, but not directly stated, that participants in the POC VL arm may get results on the day of appointment. I assume that testing for VL will be performed toward the end of a clinical encounter. Then the blood needs to be spun and then run on a Xpert machine (possibly batched) taking 2.5-3.5 hours for a result. Does the study team think that the patients will wait around for the result? If so, how will the patient know to be re-integrated into the patient flow once the result is back? How would this happen in routine practice (outside of the RCT).

Response: Participants in both arms go directly to phlebotomy to provide a blood sample on visits when a VL test is indicated. Then they return to the clinic to wait for their clinical check-up and to receive the result from the study nurse. Part of the study’s objective is to determine if the wait time effects the feasibility of providing results the same day. This process would be the same in routine practice – the participant would provide the blood sample before the clinical encounter so that the time waiting for the result overlaps with the time waiting for the clinical encounter to minimize the amount of extra time spent in the clinic.

9. There is insufficient description of the clinical pathway for when a VL testing decision is made, who obtains a specimen, who takes it to a processing / Xpert area, etc.

Response: We have added detail that the onsite phlebotomy clinic takes the sample and it is processed by a laboratory technician on site. (Page 9, Line 12)

10. The protocol mentions that process steps measured are “generating a valid VL test result”, “returning the VL test results to the participant”, and “providing counseling…” but how these will be measured is not described.

Response: We will describe the proportion of participants for which each of these steps is achieved. We have added this to the manuscript. (Page 11, Line 19)

11. Given a goal of “implementation” outcomes, including test completion, sample failures, fidelity, acceptability, would be useful to include (and possibly are included but not described in this manuscript).
Response: We will be describing the proportion of valid test results generated and reasons for failures. (Page 11, Line 19). We also include a participant acceptability questionnaire for participants in the POC arm. (Table 2)

12. On page 12 a “viral load knowledge questionnaire” is introduced. This doesn’t fit into any of the listed primary or secondary outcomes nor the overall goal to increase the proportion of patients receiving results within 6 weeks. It either needs to support the underlying theory and should be a secondary outcomes or should be removed.

Response: We have clarified that the secondary outcome of comprehension of the correlation of ART adherence and VL is measured by the viral load knowledge questionnaire. (Page 12, Line 23)

13. It is unclear why 60% was selected for a binary outcome for the VL questionnaire. This needs to be justified through instrument validation if it is being selected a priori. If these validation studies have been completed they need to be cited.

Response: The VL knowledge questionnaire has not been previously validated. The questionnaire was adapted from studies which assessed general HIV/AIDS knowledge (Jones et al. 2013; Tique et al 2017; Ownby et al 2013). We adapted questions to relate to VL and ART adherence. We have chosen 60% (> 3/5 questions correct) a priori and will also be conducting sensitivity analyses to determine the appropriate cut-off for number of questions answered correctly.

14. The power / sample size descriptions are vague. Specifics on the calculation approach is needed (beyond stating a power and alpha).

Response: We have revised the sample size and power calculations section with additional details about our methods and assumptions for our sample size calculation. (Page 15, Line 16)

15. The analysis section discussing propensity scoring but also states that for the primary outcome participants will be compared. It is unclear what the analysis is and how it will be performed. Since it is randomized it is unclear why propensity scores would be used for the primary analysis. Nor are the planned characteristics for propensity matching described (should be included).

Response: We have revised the manuscript and removed plans to conduct a propensity score analysis since enrollment indicates we will achieve equivalence in the randomized groups. (Page 17, Line 5)

16. Subgroup analyses are referred to. Given the small sample size this seems inappropriate.

Response: We agree that the small sample size will limit our ability to conduct subgroup analyses. Any subgroup analyses will be simply descriptive. The small sample size is listed as a limitation to this study. (Page 18, Line 22)

17. The discussion describes same day return of results; however, nowhere is this mentioned as a metric or an outcome. (Nor as I have stated above is it clear how this will occur given the time it takes from getting a sample to having the results).

Response: We have added detail to the methods section about the protocol for returning results if it is not available the same day. (Page 10, Line 1)

18. The discussion describes important health system considerations for a new technology. This is relevant, but none of the aspects described in the discussion are measured as part of the protocol.
Response: We will describe the reason for each instance in which a POC VL test result is not returned the same day and/or not returned within 6 weeks of sample collection. (Page 11, Line 19) This will allow us to determine which factors (health system-related or patient-related) contribute to POC testing being unsuccessful if that is the case.

19. A limitation is the relative uniqueness of the study clinic. Whether a success with POC VL can fit a more routine context will not be a finding and is a limitation. Given a feasibility is mentioned in places (such as the discussion) as a key finding, this is a major limitation.

Response: We have included as a limitation that findings may not be generalizable (Page 4, Line 13 and Page 18, Line 23)

20. Study timelines should be included. The study started in May 2018. I would expect it would be complete by now given the modest sample size and short term follow-up. Please clarify. (IE the primary completion date is listed as November 2019 in clinicaltrials.gov)

Response: We have completed enrollment (August 2019). We have included these details in the manuscript. (Page 19, Line 23)

21. The funders should be included in the body of the manuscript.

Response: Two NIH research training grants (NIH/NIAID 5 K24 AI098627 and NIH/FIC 5 D43 TW010062 provided funds for the training of study staff. However, the conduct of research for this study was not externally funded and as such we have not included funders in the body of the manuscript.

22. The clinicaltrials.gov registration should be in the body of the manuscript.

Response: We have added the clinicaltrials.gov registration to the introduction of the manuscript (Page 7, Line 18)

Reviewer: 4

Sample size and power calculations
1. Authors assume 80% follow-up in both arms. If 150 (75 per arm) are enrolled, it would be 120 participants who will be at 6 months based on 80% follow-up assumption. Why was a sample size of 124 used in the power calculations?

Response: We assume that we will achieve 85% follow-up, which we have corrected in the manuscript. This would require total enrollment of 146 participants. To be conservative, we plan to enroll 150 participants. (Page 16, Line 16)

2. In POC arm, would all participants receive their HIV testing results in the same day?

Response: The hypothesis is that all participants could receive the test result the same day. We have included information regarding the protocol if a result is not returned the same day. (Page 10, Line 1)

Analysis and statistical methods
3. The authors have planned an analysis using propensity score weighting to account any differences between participants in two arms if equivalence is not achieved by randomization. Would the authors provide a strong justification for use the propensity score weight method for this randomized clinical trial?

Response: We have revised the manuscript and removed plans to conduct a propensity score analysis since enrollment indicates we will achieve equivalence in the randomized groups. (Page 17, Line 5)

4. Why use R 2.14.2 not later version for all analyses?

Response: We have updated this to indicate we will be using the most recent version of R 3.6.3. (Page 17, Line 13)

VERSION 2 – REVIEW

REVIEWER
Jienchi Dorward
1. Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK.
2. Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, South Africa.

REVIEW RETURNED
20-Apr-2020

GENERAL COMMENTS
Thank you for your response and for addressing the majority of comments. The only remaining issues that I have identified are below:

Original reviewer comment Page 10 Line 16: What happens if there are errors with the POC assay or the patient arrives in the afternoon within an hour of clinic closure? The protocol states patients will be asked to attend before 11am, and called a week before their appointment to remind them. This important detail should be mentioned in the manuscript, and whether this is study specific or routine practice, and whether it is the same for both arms.

Author Response: If there are test errors or the patient arrives too late for the test to be processed the same day, the participant is called back when the result is ready. Participants in both arms receive reminder phone calls for visits and on this call, the POC arm is reminded to arrive before 11am for a visit when a VL test is scheduled. We have added this detail to the manuscript. (Page 10, Line 1)

Reviewer response: So, are patients in the SOC arm also called as soon as their results are ready? If not, then this is a slightly unfair comparison, as the intervention is more than just POC testing, it also involves calling patients as soon as their results are ready. This should be clarified and discussed.

Original reviewer comment Page 12 Line 10: The protocol only has 2 secondary outcomes (self reported adherence is not mentioned in the protocol). The manuscript and protocol should be consistent. The main primary outcome on clinicaltrials.gov is different from the manuscript and protocol.
Reviewer(s)' Comments to Author:

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Author Response (New): Since the POC tests are processed individually and onsite, if a test result is not available the same day, the onsite laboratory staff relays the result to the clinician the next day. In the SOC arm, the tests are batched and results uploaded to the EMR. There is no mechanism to alert the clinician when the result is available – they retrieve the result from the EMR during the participant's next visit. We agree, part of the intervention involves accessibility of the result sooner and calling the participant back earlier than the next visit. We have added clarification related to this added benefit of the POC test compared to the standard laboratory test (Page 9, Line 21 and Page 10, Line 14)

Original reviewer comment Page 12 Line 10: The protocol only has 2 secondary outcomes (self reported adherence is not mentioned in the protocol). The manuscript and protocol should be consistent. The main primary outcome on clinicaltrials.gov is different from the manuscript and protocol.

Author Response: We have revised this so that the protocol and manuscript agree. (Page 14, Lines 4, 5 and 8)

Reviewer response: The outcomes in the clinicaltrials.gov entry are still not consistent with the protocol and manuscript

Author Response (New): We have clarified that self-reported adherence is not a primary or secondary outcome, but this data is collected, as described in the protocol and manuscript (Page 12, Line2 6-9). The primary objective on clinicaltrials.gov, the protocol, and the manuscript align (Page 11, Lines 7-13).
