PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Reducing time to differentiated service delivery for newly-diagnosed people living with HIV in Kigali, Rwanda: study protocol for a pilot, unblinded, randomized controlled study.
AUTHORS	Ross, Jonathan; Murenzi, Gad; Hill, Sarah; remera, eric; Ingabire, Charles; Umwiza, Francine; Munyaneza, Athanase; Muhoza, Benjamin; Habimana, Dominique Savio; Mugwaneza, Placidie; Zhang, Chenshu; Yotebieng, Marcel; Anastos, Kathryn

VERSION 1 – REVIEW

REVIEWER	Amstutz, Alain Schweizerisches Tropen- und Public Health-Institut, Clinical Research Unit
REVIEW RETURNED	12-Jan-2021

GENERAL COMMENTS	Thank you for the opportunity to review this study protocol of a 3-arm open-label pilot RCT in Rwanda assessing earlier and easier entry into differentiated service delivery for people new in HIV care. This pilot trial is important as in many countries in sub-Sahara Africa entry into DSD models is challenging due to extensive lab-based evaluation. Although the upcoming WHO guidelines will probably simplify the criteria for stable patients and thus provide faster entry into DSD models, this trial provides important insight, especially for Rwanda. Overall, I don't have many comments and want to thank the authors for this concise and well written study protocol. It's just a pity that this is a pilot trial and much more than descriptive stats out of 3-arm ITT trial with 90 participants is probably not to get. Title & Abstract: - Please mention that it is a pilot trial. The term comes very late and "exploratory" may be misleading. - Be careful with some of the wording, - e.g. "Abstract" line 8 "test the effect of..." -> If the study is planned as a pilot with that kind of sample size calculation and analysis, you would rather phrase it as "explore the effect of ..." - e-g. "Strengths and limitations of this study" line 35: "A three-armed study will be able to simultaneously assess the impact of" -> this statement is in my view overoptimistic with a pilot trial Methods & Analysis: Trial Design: - Again, please mention that this is a pilot trial Eligibility: - Inclusion criteria 15 years and older: What is the age of consent to research in Rwanda? Can participants aged 15-18y consent for themselves, i.e. is there a waiver from ethics in Rwanda? Or will

	they need a caregiver over 18y to co-sign? Please elaborate here or in paragraph "Informed Consent". Also, what about illiterate participants? - It is not clear to me if defaulters (i.e. diagnoses within last 6 months, on ART for a while - maybe somewhere else - then in care at study clinic) are included or not. This is a growing group of interest. - What happens if someone falls pregnant during study? Will they be taken out of the study or only out of the DSD model? - What about those with other chronic diseases such as Diabetes or art. Hypertension? - What about breastfeeding women - are they eligible? - Are all ART regimens included? PI-based ART might not suppress within 3 months, whereas DTG-based ART (and most of NRTI-based ART) will. Please explain (maybe in study setting?) what the current first-line ART in Rwanda is. Of course, most will be on first-line ART, but defaulters might come into study on a PI-based regimen? PI-based regimens may be problematic if they end up in the 3- & 5-month VL after enrolment. Interventions: - Line 125: "In this arm, participants will have their viral loads measured at 5 months after enrollment in HIV care": - I guess this should be "5 months after enrolment in the trial"? The term "after enrollment in HIV care" comes up many times, please clarify. - Otherwise, I guess the Rwanda HIV guidelines suggest rather a first VL 6months after starting ART? - Line 143: - How do the researchers deal with patients' preferences regarding refill intervals? Will a participant be able to change DSD model, e.g. if assigned to usual care but he/she wants spaced interval like his/her neighbour? How will such a participant be treated in analysis? - May clinicians schedule differently than the study schedule, i.e. due to side-effects of ART, OIs, IRIS, etc.? I am sure they do, please mention and again explain if these cases stay in the study and analysed as ITT or if something else is done with them in terms of analysis. Outcomes: - The primary endpoint of the study is slightly different (200 c/mL) to what's written in clinicaltrials.gov (1000 c/mL), please explain and clarify. - Is the VL measurement based on a venous blood collection or DBS? On which machine will it be analysed and what^'s the lower detection limit of the machine? - Again, is it 12 months "after enrollment in HIV care" or "after enrollment into study"? - Line 167: - "ART adherence will be collected by participant self-report" -> Explain in detail what measure is used - Line 168: - "12-months after ART initiation" -> again, another different time-point. I advise to use the same time point consistently throughout , i.e. "12 months after enrollment into study". - General question re timepoint of outcome assessment: Will there be any window of assessment, i.e. for 12months e.g. 11-14 months?

	Table 1: - There is an error in Arm 1 and 2: The dots of VL measurement do not correspond to the titles of these arms Analytic approach: - line 256: "For the preliminary efficacy outcome of viral suppression, we will first compare proportions of patients achieving viral suppression and attending all appointment/pharmacy visits using chi-square tests." - This does not sound like an ITT approach. This sounds more like a per-protocol analysis, i.e. only with those following the protocol perfectly. - (as mentioned above): Mention how you treat those that change treatment arms, appointment schedule - Mention how you treat those with missing VL at 12 months but otherwise in care (lab problem, blood draw problem etc)

REVIEWER	Grimsrud, Anna International AIDS Society
REVIEW RETURNED	29-Jan-2021

GENERAL COMMENTS	Dear BMJ Open, Thank you for the opportunity to review “Reducing time to differentiated service delivery for newly-diagnosed people living with HIV in Kigali, Rwanda: study protocol for an exploratory, unblinded randomized control study.”. This manuscript describes in the protocol of a pilot study where there are three study arms – each differing in eligibility for a differentiated service delivery (DSD) model for HIV treatment Below are a summary of my main points of feedback split between major and minor. MAJOR • The outlined study as a small sample size aiming to recruit just 90 participants with approximately 30 in each study arm. Given the small size, I understand that the study is not powered for hypothesis testing but rather assessing the acceptability, feasibility and preliminary efficacy. However, I have recommended a statistician assess the proposed analyses as the methods seek to use generalized estimated equations (GEE) to estimate risk differences and risk ratios in assessment the efficiency outcome of viral suppression. I am unsure if the study has a sufficient number of participants for GEE to be used. • There is a small, but growing body of evidence that highlights that many people living with HIV are disengaging from care at various stages in the HIV care cascade, and then re-engaging in care. As this study seeks to enrol “newly-diagnosed” people living with HIV, please can the authors describe in more detail how they will ensure that people are in fact “newly-diagnosed” and not antiretroviral therapy (ART)-experienced and re-engaging in care. • Please describe why randomization is being done at the level of the individual, instead of at the facility level. Given that the study is assessing feasibility, it will be much more challenging for facilities to have three different models of service delivery versus one if the randomized was clustered at the facility level. • There a number of publications related to DSD for HIV treatment that may be relevant for inclusion in the reference list. First, this study is designed to look at the impact of both time from ART initiation and the number of suppressed viral load measurements before eligibility to DSD for HIV treatment. I would recommend the authors discuss how this has changed in the five years since the WHO recommended “differentiated care” in their 2016 guidelines, and how many countries have changed their eligibility criteria in response to COVID-19 expanding eligibility and reducing time on ART before eligibility. o See this policy dashboard - https://differentiatedservicedelivery.org/Portals/0/adam/Content/jcdklT8RzEqirRdlckAjbQ/File/1-Time%20to%20DSD%20Eligibility%20D5.pdf

	o See the PEPFAR Technical guidelines for HIV programs during COVID (updated regularly, available at the bottom of this page) - https://www.state.gov/pepfar/coronavirus/ o Some recent DSD publications that you may want to consider including are: https://journals.lww.com/aidsonline/Fulltext/2021/02020/Community_based_delivery_of_HIV_treatment_in.14.aspx https://differentiatedservicedelivery.org/Resources/DSD_PublishedEvidence • https://onlinelibrary.wiley.com/doi/10.1002/jia2.25640 https://pubmed.ncbi.nlm.nih.gov/32665460/ - where patients were eligible after 6months on ART https://pubmed.ncbi.nlm.nih.gov/32097252/ - where patients were eligible after 6 months on ART Minor • Please revise Table 1 to look less like an internal study document, and more of a publication table. A suggestion is to reduce what's being presented and instead focus on the timing post-allocation of clinical appointments, ART pick-ups and viral load measurements (and maybe also research visits) (rows) by study arm (columns). • Throughout, please revise "PLWH" to "PLHIV" to reflect more up-to-date language. • Please include details as to the building blocks (or the who/what/where/when) of the DSD for HIV treatment model that clients become eligible for and compare this to the standard of care. (columns of the model and SoC with row of who - the provider, where - the location of services, when – frequency of the visits, what – details of the package of care. • Please describe the first-line regimen provided in the study and comment on the anticipated time to viral suppression of this regimen and how this may or may not impact the timing of first viral load.

REVIEWER	Hertzmark, Ellen Harvard Univ, global health and population
REVIEW RETURNED	15-Feb-2021

GENERAL COMMENTS	Review of BMJOPEN-2020-047443 This is a description of a study protocol for a pilot study aimed at possibly changing the timing of determination of "stability" for purposes of visit spacing in people living with HIV. The trial is well-designed. The description needs a bit more specification (below). Specific comments: Page line comment (word) (word) 5 84-88 The authors do not explain here or in the methods how they plan to deal with early deaths or defaulters (in particular those who do not have VL measurement at 12 months). 6 123 add time of randomization (i.e. "At initiation of ART participants will be randomized…." What I wrote may be wrong. "randomized within a month of ART initiation" might be better. Will anyone be randomized on the day of ART initiation? 137 can they give a bit more information on the level of flexibility? 7 152-155 What defines "appointment attendance?" Is there a window after the scheduled date? Does routine care include a program to encourage those who do not show up to return to the clinic?

	The standard of “all visits” will be much harder for those in the 12 month program. Can they make up some other standard that will be more comparable? 167 My experience with participant self-report on adherence is that virtually everyone claims good adherence, regardless of whether they even had enough medications to cover the interval since their last visit. This is a standard data item, but I wouldn’t put too much trust in it. If people are randomized on their date of ART initiation, their medication adherence is not assessable. 10-11 166-179 these are tertiary outcomes. 11 194 It sounds as if the participants will have to come to the clinic 2 extra times for the nonmedical assessments (presumably the QOL, stigma, health-related expenditures). Will the participants be reimbursed for these extra visits? 12 Table 1 In arm 1, presumably the “one suppressed VL” will be the 5-month measurement. It doesn’t make sense otherwise. This should be clarified. In arm 2, I gather that there is no possibility for a patient who was nonsuppressed at 3 months but suppressed at 5 months to have another interim (e.g. 7 or 8 months) VL measurement, which, if suppressed, would allow the patient to have longer intervals for medication pick-up. This is a trial of strategies, so a branching strategy would be acceptable. What does “HIV care” under “Baseline variables” mean? In a “Treat All” world, presumably people start ART when they test positive and have no prior HIV treatment history. 13 218 I know that this study is very small, but is there any reason to think that gender might be a relevant variable here? 225 “generated using SAS” Can the authors be more specific? (consort item) 14 238 “results reported to participants” at the next visit? Is the reporting to staff any more than putting the results into the medical record? 15 291 Are they using a study-specific ID or the health system ID? 17 325 18? Their study only goes to 12 months.

VERSION 1 – AUTHOR RESPONSE

Reviewer: #1

6. Please mention that it is a pilot trial. The term comes very late and "exploratory" may be misleading.

We agree with the reviewer that “pilot study” is more specific and informative than “exploratory study.” We have added the term “pilot” to the title and abstract, and removed “exploratory” from the title and throughout the manuscript.

7. Be careful with some of the wording, e.g. "Abstract" line 8 "test the effect of..." -> If the study is planned as a pilot with that kind of sample size calculation and analysis, you would rather phrase it as "explore the effect of ..."; E-g. "Strengths and limitations of this study" line 35: "A three-armed study will be able to simultaneously assess the impact of" -> this statement is in my view overoptimistic with a pilot trial.

We thank the reviewer for these comments. We have changed the text as suggested in the Abstract (page 2, paragraph 1), Strengths and Limitations (page 3, bullet point 2) and Introduction (page 5, paragraph 3).

8. Inclusion criteria 15 years and older: What is the age of consent to research in Rwanda? Can participants aged 15-18y consent for themselves, i.e. is there a waiver from ethics in Rwanda? Or will they need a caregiver over 18y to co-sign? Please elaborate here or in paragraph "Informed Consent". Also, what about illiterate participants?
We have included adolescents aged 15 and older this study as they receive care in adult HIV programs and are a key population of interest in Rwanda and globally. We clarify that participants aged 15-18 years are not able to provide informed consent, and if enrolled would provide assent while consent would be obtained from a parent or guardian. We have further clarified that research staff will read the informed consent document aloud to all participants; those unable to write will be allowed to sign consent with an "X" (Page 10, paragraph 2).

9. It is not clear to me if defaulters (i.e. diagnoses within last 6 months, on ART for a while - maybe somewhere else - then in care at study clinic) are included or not. This is a growing group of interest.
Thank you for this comment. Our eligibility criteria were designed to include only newly-diagnosed people living with HIV (PLHIV), but with sufficient flexibility to allow recruitment of individuals who may not have been immediately linked to care. Based on these criteria, it is possible that defaulters will be recruited to the study. If present in substantial numbers, this group will be examined separately in exploratory analyses; we comment on this in the text (page 12, paragraph 4). We note that to date, we have completed 60% of the baseline enrollment for the study; all participants were diagnosed within the prior 30 days and had not been in HIV care elsewhere.

10. What happens if someone falls pregnant during study? Will they be taken out of the study or only out of the DSD model?
11. What about those with other chronic diseases such as Diabetes or Hypertension?
12. What about breastfeeding women - are they eligible?
We have based the study eligibility on current Rwandan HIV guidelines with respect to eligibility for differentiated care. These guidelines specify that individuals in the "unstable" category include newly diagnosed PLWH (<12 months on ART), women who are pregnant or lactating, patients with concurrent mental health disorders, and PLWH who are not virally suppressed. Other chronic diseases do not place patients in the "unstable" category and will not exclude participants from the study. Women who become pregnant during the study will continue in the study but will not be allowed to advance to DSD; they will be analyzed by intention to treat in the primary analysis. We have edited the text to clarify that lactating women will not be included (page 7, paragraph 1) and that women who become pregnant will no longer be eligible for DSD (page 7, paragraph 3).

13. Are all ART regimens included? PI-based ART might not suppress within 3 months, whereas DTG-based ART (and most of NRTI-based ART) will. Please explain (maybe in study setting?) what the current first-line ART in Rwanda is. Of course, most will be on first-line ART, but defaulters might come into study on a PI-based regimen? PI-based regimens may be problematic if they end up in the 3- & 5-month VL after enrolment.
Since all participants will be newly-diagnosed, we expect that all will be on first-line ART. In Rwanda, first-line ART is one of two dolutegravir-based regimens: TDF-3TC-DTG or ABC-3TC-DTG. To date, all participants enrolled in the study are on first-line ART. We have added text in the methods describing this (page 6, paragraph 2, and page 7, paragraph 2).

14. Line 125: "In this arm, participants will have their viral loads measured at 5 months after enrollment in HIV care" - I guess this should be "5 months after enrolment in the trial""? The term "after enrollment in HIV care" comes up many times, please clarify. Otherwise, I guess the Rwanda HIV guidelines suggest rather a first VL 6months after starting ART?
We thank the reviewer for noticing these inconsistencies. The anchoring point for viral load measurements as well as research is ART initiation and not enrollment in HIV care, and we have corrected the text to reflect this (page 7, paragraph 2; page 8, paragraph 2; page 9, paragraph

5). Thus viral loads will be measured at 3 months (for Arm 2), 5 months (for all Arms) and 12-months (for all Arms) after ART initiation. Current Rwandan HIV guidelines suggest that the initial viral load is performed at 6 months after ART initiation. However, in order to permit entry into the DSD model at 6 months, we will perform viral load testing at 5 months to allow sufficient time to obtain results and communicate them to health center staff.

15. Line 143: - How do the researchers deal with patients' preferences regarding refill intervals? Will a participant be able to change DSD model, e.g. if assigned to usual care but he/she wants spaced interval like his/her neighbour? How will such a participant be treated in analysis?
16. May clinicians schedule differently than the study schedule, i.e. due to side-effects of ART, OIs, IRIS, etc.? I am sure they do, please mention and again explain if these cases stay in the study and analysed as ITT or if something else is done with them in terms of analysis.
Health care providers at health centers will schedule patients based on study arm and are the ultimate arbiters of advancement to a DSD schedule. As noted in the text, clinicians may determine that patients should not be advanced to DSD models; if patients request more frequent appointments, health care providers may choose to accommodate them. Participants in the usual care arm will not be eligible for advancement to DSD until the study ends. Patients whose ultimate appointment schedule differs from their assigned study arm will remain in the study and be analyzed as intention-to-treat. We have made changes accordingly in the text to clarify these points (page 7, paragraph 3, and page 12, paragraph 3).

17. The primary endpoint of the study is slightly different (200 c/mL) to what's written in clinicaltrials.gov (1000 c/mL), please explain and clarify.
Rwandan guidelines recently changed the threshold for viral suppression from 1000 to 200 copies/ml. We therefore consider viral suppression based on the national guideline of 200 copies/ml. We have updated the entry in clinicaltrials.gov and noted this in the text (page 8, paragraph 2).

18. Is the VL measurement based on a venous blood collection or DBS? On which machine will it be analyzed and what's the lower detection limit of the machine?
We note in the text that viral load measurements will be venous and will be performed using the Abbott Allinity m instrument, with a lower limit of detection of 20 copies/ml (page 11, paragraph 3).

19. Again, is it 12 months "after enrollment in HIV care" or "after enrollment into study"?
As noted above (Critique #9), we have corrected the text to “after ART initiation” (page 7, paragraph 2; page 8, paragraph 2; page 9, paragraph 5).

20. Line 167: - "ART adherence will be collected by participant self-report" -> Explain in detail what measure is used
We have amended the text to indicate that we will use 7- and 30-day self-reported ART adherence measures (page 8, paragraph 5).

21. Line 168: - "12-months after ART initiation" -> again, another different time-point. I advise to use the same time point consistently throughout , i.e. "12 months after enrollment into study."
We thank the reviewer for the careful editing. As noted above (Critique #9), we have corrected the text to “after ART initiation” (page 7, paragraph 2; page 8, paragraph 2; page 9, paragraph 5).

22. General question re timepoint of outcome assessment: Will there be any window of assessment, i.e. for 12months e.g. 11-14 months?
The final viral load will be measured as part of a research visit scheduled at 12 months after ART initiation. We note in the text that participants who do not appear for scheduled research visits will have these rescheduled within 14 days (page 10, paragraph 1).

23. There is an error in Arm 1 and 2: The dots of VL measurement do not correspond to the titles of these arms.
We thank the reviewer for noticing this error, which we have corrected in the (updated) Table (now Table 2).

24. Line 256: "For the preliminary efficacy outcome of viral suppression, we will first compare proportions of patients achieving viral suppression and attending all appointment/pharmacy visits using chi-square tests." This does not sound like an ITT approach. This sounds more like a per-protocol analysis, i.e. only with those following the protocol perfectly. (As mentioned above): Mention how you treat those that change treatment arms, appointment schedule. Mention how you treat those with missing VL at 12 months but otherwise in care (lab problem, blood draw problem etc).
We thank the reviewer for this comment. We have modified the text to indicate that the primary analysis will be intention to treat for the outcomes of viral suppression and appointment adherence (page 12, paragraph 3), and that those missing outcome data will be considered failures. We have also added text to indicate that in a secondary, per-protocol analysis we will use both multiple imputation and censoring for participants missing endpoint data. Comparing these approaches will guide interpretation of the overall results as well as the impact ofhe missing data (page 12, paragraph 4).

Reviewer: #2
25. The outlined study as a small sample size aiming to recruit just 90 participants with approximately 30 in each study arm. Given the small size, I understand that the study is not powered for hypothesis testing but rather assessing the acceptability, feasibility and preliminary efficacy. However, I have recommended a statistician assess the proposed analyses as the methods seek to use generalized estimated equations (GEE) to estimate risk differences and risk ratios in assessment the efficiency outcome of viral suppression. I am unsure if the study has a sufficient number of participants for GEE to be used.
Thank you for this comment. In consultation with author CZ who is a biostatistician, we have modified the approach, and will use logistic regression to compare viral suppression across arms (page 12, paragraph 3).

26. There is a small, but growing body of evidence that highlights that many people living with HIV are disengaging from care at various stages in the HIV care cascade, and then re-engaging in care. As this study seeks to enrol “newly-diagnosed” people living with HIV, please can the authors describe in more detail how they will ensure that people are in fact “newly-diagnosed” and not antiretroviral therapy (ART)-experienced and re-engaging in care.
As noted above (Critique #4), we aim to include only newly-diagnosed people living with HIV (PLHIV), but with sufficient flexibility to allow recruitment of individuals who may not have been immediately linked to care, and it is possible that defaulters will be recruited to the study. We expect that any defaulters would be equally distributed across groups; if present in substantial numbers, we will examine them separately in a sub-analysis (page 12, paragraph 4). As noted above, we have completed 60% of the baseline enrollment for the study; all participants were diagnosed within the prior 30 days and had not been in HIV care elsewhere.

27. Please describe why randomization is being done at the level of the individual, instead of at the facility level. Given that the study is assessing feasibility, it will be much more challenging for facilities to have three different models of service delivery versus one if the randomized was clustered at the facility level.
We appreciate the reviewer's comment. We felt that randomization at the level of the individual would be feasible given the small scope of the study and would provide an opportunity to collect comparative data on acceptability of these models from key stakeholders at health centers. Individual

randomization also allows for equitable opportunity for early entry into the DSD model among participants across the study sites.

28. There a number of publications related to DSD for HIV treatment that may be relevant for inclusion in the reference list. First, this study is designed to look at the impact of both time from ART initiation and the number of suppressed viral load measurements before eligibility to DSD for HIV treatment. I would recommend the authors discuss how this has changed in the five years since the WHO recommended "differentiated care" in their 2016 guidelines, and how many countries have changed their eligibility criteria in response to COVID-19 expanding eligibility and reducing time on ART before eligibility.
We thank the reviewer for these suggestions. We have incorporated many of the suggested references into the manuscript introduction, highlighting global implementation of DSD models, heterogeneity in the definitions of clinical stability, and adaptations in response to the Covid-19 pandemic (page 4, paragraph 2).

29. Please revise Table 1 to look less like an internal study document, and more of a publication table. A suggestion is to reduce what's being presented and instead focus on the timing post-allocation of clinical appointments, ART pick-ups and viral load measurements (and maybe also research visits) (rows) by study arm (columns).
We appreciate this suggestion. We have simplified Table 1 (now Table 2) so that it describes the schedule of clinical visits for each arm as well as research visits, and does not include many of the prior details regarding timing of allocation and specific measures being collected. However, we have opted to retain the prior format of study arms in rows and months in columns, which we feel provides a clearer and more nuanced understanding of the differences in timing between study arms.

30. Throughout, please revise "PLWH" to "PLHIV" to reflect more up-to-date language. We have changed this term throughout the manuscript.

31. Please include details as to the building blocks (or the who/what/where/when) of the DSD for HIV treatment model that clients become eligible for and compare this to the standard of care. (columns of the model and SoC with row of who - the provider, where - the location of services, when – frequency of the visits, what – details of the package of care.
Thank you for this suggestion. We have added a table (new Table 1) that compares routine treatment and DSD with respect to the treatment models.

32. Please describe the first-line regimen provided in the study and comment on the anticipated time to viral suppression of this regimen and how this may or may not impact the timing of first viral load.
As noted above (Critique #13), all participants will be newly-diagnosed and we expect that all will be on first-line ART. In Rwanda, first-line ART is a DTG-based regimen and all participants are expected to be on either TDF-3TC-DTG or ABC-3TC-DTG. To date, all participants enrolled in the study are on one of these two regimens. We have added text in the methods to describe this (page 6, paragraph 2, and page 7, paragraph 2).

REVIEWER #3
33. The authors do not explain here or in the methods how they plan to deal with early deaths or defaulters (in particular those who do not have VL measurement at 12 months). As noted above (Critique #24), we will perform an intention to treat analysis as the primary analysis for the outcomes of viral suppression and appointment adherence. All participants with missing outcomes either as a result of loss to care, death, or any other reason will be classified as not suppressed. We have updated the text to describe that we will analyze results using both intention to treat and per

protocol analyses. Comparing these approaches will guide interpretation of the overall results (Page 12, paragraphs 3 and 4).

34. Add time of randomization (i.e. “At initiation of ART participants will be randomized….” What I wrote may be wrong. “randomized within a month of ART initiation” might be better. Will anyone be randomized on the day of ART initiation?
No participants will be randomized on the day of ART initiation. We have added the text “randomized within 1 month of ART initiation,” as suggested (page 7, paragraph 2).

35. Can they give a bit more information on the level of flexibility?
As noted above (Critique #16), we have added text to the methods to describe scenarios in which participants may not remain in the appointment schedule to which they were randomized (page 7, paragraph 3, and page 12, paragraph 3).

36. What defines “appointment attendance?” Is there a window after the scheduled date? Does routine care include a program to encourage those who do not show up to return to the clinic?
We thank the reviewer for this comment. We have now described in the text that patients at study health centers who do not attend a scheduled appointment are called the next day to reschedule; if this initial effort is unsuccessful, appointments are considered missed, however, outreach efforts continue to be made (page 8, paragraph 2).

37. The standard of “all visits” will be much harder for those in the 12 month program. Can they make up some other standard that will be more comparable?
While the standard of all visits will be harder to meet for those in the usual care arm, stakeholders expressed preference for this outcome in pre-trial preparations. We note in the text that we are also measuring appointment attendance as the overall proportion of scheduled visits attended, which would not be more challenging to meet for those scheduled for additional appointments (page 8, paragraph 2).

38. My experience with participant self-report on adherence is that virtually everyone claims good adherence, regardless of whether they even had enough medications to cover the interval since their last visit. This is a standard data item, but I wouldn’t put too much trust in it. If people are randomized on their date of ART initiation, their medication adherence is not assessable.
We thank the reviewer for noting this. We agree that self-report may not fully reflect true medication adherence, yet we note that it correlates with more stringent measurements and can predict clinical outcomes. Given the limitations of this pilot study, we were not able to assess medication adherence more robustly. As noted above (Critique #34), no patients will be randomized on the day of ART initiation.

39. These are tertiary outcomes.
Thank you for noting this, we have labeled them as such in the manuscript (page 8, paragraph 5).

40. It sounds as if the participants will have to come to the clinic 2 extra times for the nonmedical assessments (presumably the QOL, stigma, health-related expenditures). Will the participants be reimbursed for these extra visits?
Participants will be reimbursed for all research-related visits, including additional visits for viral load measurements. We have added text to clarify this point (page 9, paragraph 5).

41. Table 1 In arm 1, presumably the “one suppressed VL” will be the 5-month measurement. It doesn’t make sense otherwise. This should be clarified.
In arm 2, I gather that there is no possibility for a patient who was nonsuppressed at 3 months but suppressed at 5 months to have another interim (e.g. 7 or 8 months) VL measurement, which, if

suppressed, would allow the patient to have longer intervals for medication pick-up. This is a trial of strategies, so a branching strategy would be acceptable.
We appreciate these suggestions. We have corrected the Table to accurately reflect that participants in Arm 1 will only have a single viral load measured prior to entry into DSD. The reviewer is correct that this pilot study cannot support a subsequent, interim viral load that would allow entry into DSD prior to the 12-month viral load.

42. What does “HIV care” under “Baseline variables” mean? In a “Treat All” world, presumably people start ART when they test positive and have no prior HIV treatment history.
We thank the reviewer for pointing this out. We agree, as noted above (Critique #4), that participants are not expected to have a prior HIV treatment history. We have removed this term from the Table.

43. I know that this study is very small, but is there any reason to think that gender might be a relevant variable here?
We appreciate this comment from the reviewer. There are gender differences within the HIV epidemic in Rwanda, including in prevalence (higher among women) and outcomes (worse among men), and it is possible that gender will impact outcomes. While we did not stratify randomization by gender, if groups are imbalanced by gender we will perform adjusted analyses. We will also separately examine outcomes among men and women. We have commented on these aspects of the analysis (page 12, paragraphs 3 and 4).

44. “generated using SAS” Can the authors be more specific? (consort item)
We have clarified in the text that we used the Proc Plan function in SAS to generate the allocation sequence (page 11, paragraph 2).

45. “results reported to participants” at the next visit? Is the reporting to staff any more than putting the results into the medical record?
We have clarified that results from laboratory testing will be provided to clinical staff at health centers, who will input them into the medical record and report them to patients, consistent with routine clinical practices (Page 11, paragraph 3).

46. Are they using a study-specific ID or the health system ID?
We have clarified that we are using study specific IDs (page 12, paragraph 2).

47. 18? Their study only goes to 12 months.
We thank the reviewer for noticing this inconsistency, which we have corrected to 12. (page 14, paragraph 4).
Thank you for your continued interest and for considering this manuscript for publication in BMJ Open. We very much appreciate the reviewers’ thoughtful critiques and feel that their comments have significantly improved this manuscript and the study. We look forward to hearing back from you.

VERSION 2 – REVIEW

REVIEWER	Amstutz, Alain Schweizerisches Tropen- und Public Health-Institut, Clinical Research Unit
REVIEW RETURNED	21-Mar-2021

GENERAL COMMENTS	My questions and comments have been adequately addressed. Change "control" to "controlled" or "clinical" in the title.

REVIEWER	Hertzmark, Ellen Harvard Univ, global health and population
REVIEW RETURNED	19-Mar-2021

GENERAL COMMENTS	Review of BMJOPEN-2020-047443 R1 This version is much improved and requires only a few clarifications before publication. The one major issue left for me is the question of how much discretion clinicians will have to override the experimental assignment. It would be good to require documentation of each override, including reasons and initiator (clinician or patient). To some extent, overrides are a measure of non-acceptability. As noted by one of the other reviewers, it is hard to know who is truly “newly diagnosed.” The authors should either explain how they know this, or note that this is hard to know, but that they expect whatever problems this produces to be nondifferential (regarding the arms). The word “change(s)” is used. Are they talking about some change withing groups over time or do they mean differences between groups? Specific comments: Line comment (italics show suggested insertions) 32 Note that this is a pilot exploring clinical outcomes. 49 the HIV pandemic 84 must visit the clinic 188 “regular HIV care”—by which time presumably most will be eligible for differentiated care anyway. 191 Missing primary outcome (VL at 12 months) because of death or non-attendance are different. While we don’t expect many deaths, there may be a few, and these are small numbers. 197 all scheduled clinical visits—potentially 3 in arms 1 and 2, and 4 in arm 3. Note should also be taken of whether people pick up their ART as required (presumably with a bit of wiggle room in the schedule). 213 I reiterate my general skepticism of self-reported adherence data. There is probably nothing to be done about it, but possible problems need to be acknowledged. 333 Obviously, some numbers will be very small. 397 and people have a much higher probability of being not suppressed at the 3 month visit. 411 “testing”—language left from the original submission.

VERSION 2 – AUTHOR RESPONSE

REVIEWER #1

1. Change "control" to "controlled" or "clinical" in the title.

We thank the reviewer for this correction and have made the suggested change (Title).

REVIEWER #3

2. The one major issue left for me is the question of how much discretion clinicians will have to override the experimental assignment. It would be good to require documentation of each override, including reasons and initiator (clinician or patient). To some extent, overrides are a measure of non-acceptability.

We have clarified that clinicians have ultimate say in whether a patient can advance to the DSD schedule. We very much appreciate the suggestion to consider overrides in measuring the acceptability of the models of care being examined in the study. We have added text the to the manuscript indicating that all overrides will be documented and will be included in the acceptability analysis (Page 7, Paragraph 3).

3. As noted by one of the other reviewers, it is hard to know who is truly "newly diagnosed." The authors should either explain how they know this, or note that this is hard to know, but that they expect whatever problems this produces to be nondifferential (regarding the arms).

We agree with the reviewer that it is difficult to definitively determine whether participants are truly newly-diagnosed and treatment-naïve. We now note in the limitations that while early defaulters may potentially be enrolled, we expect that they would be equally distributed between study arms given the randomized nature of the study, and thus have a nondifferential impact on study outcomes (Page 15, paragraph 2).

4. The word "change(s)" is used. Are they talking about some change within groups over time or do they mean differences between groups?

We have clarified in the text that for these tertiary outcomes, we will measure both change within groups over time as well as differences between groups (Page 9, Paragraph 2).

5. Specific comments:

a. 32 Note that this is a pilot exploring clinical outcomes.

We have added this text, as suggested (Page 3, first bullet point).

b. 49 the HIV pandemic

We have added this text, as suggested (Page 4, Paragraph 1).

c. 84 must visit the clinic

We have added this text, as suggested (Page 5, Paragraph 1).

d. 188 "regular HIV care"—by which time presumably most will be eligible for differentiated care anyway.

We have added text to note that participants in the usual care arm will be eligible for the DSD schedule if virally suppressed (Page 8, Paragraph 1).

e. 191 Missing primary outcome (VL at 12 months) because of death or non-attendance are different. While we don't expect many deaths, there may be a few, and these are small numbers.

The reviewer is right to point out the differences between death and non-attendance in terms of missing outcomes, which we plan to consider in sensitivity analyses. We previously noted that we will conduct analyses comparing a dataset with imputed values and a dataset that drops missing values. Although we anticipate a small number of deaths, we have added text to describe that we will document reasons for missing outcome and use this information to inform these sensitivity analyses. (Page 13, Paragraph 1).

f. 197 all scheduled clinical visits—potentially 3 in arms 1 and 2, and 4 in arm 3.

g. Note should also be taken of whether people pick up their ART as required (presumably with a bit of wiggle room in the schedule).

We note in the text that appointment adherence will be measured as the proportion of participants who attend all scheduled clinical and pharmacy visits over the first 12 months after ART initiation (11 in arms 1 and 2, 16 in arm 3) (Page 8, Paragraph 2).

h. 213 I reiterate my general skepticism of self-reported adherence data. There is probably nothing to be done about it, but possible problems need to be acknowledged.

We agree with the reviewer that self-report is an imperfect measurement of adherence, and comment on this in the study Limitations (page 15, Paragraph 2).

i. 333 Obviously, some numbers will be very small.

We agree that some subgroups may be small and have noted this in the text (Page 13, Paragraph 1).

j. 397 and people have a much higher probability of being not suppressed at the 3 month visit.

We agree with the reviewer that suppression at 3 months is less likely than at 5 months after ART initiation and have commented on this in the Limitations (Page 15, Paragraph 2).

k. 411 "testing"—language left from the original submission.

We thank the reviewer for noticing this error and have made corresponding changes ("examining" instead of "testing") (Page 11, Paragraph 4; Page 15, Paragraph 3; Page 16; Paragraph 3).

Thank you for your continued interest and for considering this manuscript for publication in BMJ Open. We very much appreciate the reviewers' additional critiques. We look forward to hearing back from you.