PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessing the acceptability of, adherence to, and preference for a dual prevention pill (DPP) for HIV and pregnancy prevention compared to oral pre-exposure prophylaxis (PrEP) and oral contraception taken separately: protocols for two randomized, controlled, crossover studies in South Africa and Zimbabwe
AUTHORS	Friedland, Barbara; Mgodi, Nyaradzo; Palanee-Phillips, Thesla; Mathur, Sanyukta; Plagianos, Marlena; Bruce, Irene; Lansiaux, Maud; Murombedzi, Caroline; Musara, Petina; Dandadzi, Adlight; Reddy, Krishnaveni; Ndlovu, Nkosiphile; Zulu, Sihle; Shale, Lerato; Zieman, Brady; Haddad, Lisa

VERSION 1 – REVIEW

REVIEWER	Hatzold, Karin Population Services International, HIV and TB
REVIEW RETURNED	02-Sep-2023

GENERAL COMMENTS	Consider including additional references discussing adherence to COCs among adolescents in Southern Africa. The over-encapsulated DPP might be a barrier for study participants. It disadvantages and penitential risks should be included in the ICF. See my comments in the document (The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.)

REVIEWER	Ayieko, James Kenya Medical Research Institute
REVIEW RETURNED	19-Nov-2023

GENERAL COMMENTS	The manuscript is well written clearly describing the two protocols in adequate detail. A dual prevention pill combining PrEP and Oral contraceptives is a novel intervention that addresses reproductive health as well as individual sexual needs of women. The procedures and methods are well described. The cross over design presents excellent strengths in conducting this evaluation with intervention participants serving as their own controls. It is also important to note that the authors have thought through other related aspects such as sexually transmitted diseases and included screening for these. Participant evaluations for safety at baseline and follow up are comprehensive. I have a minor comment on the methods that does not alter my verdict. Sample sizes are well described, loss to follow up have been factored in the samples while preserving power to detect the difference of interest. I would however have anticipated larger

	sample size than 96, especially for the adherence question. Are the authors confident about this difference they have powered their sample to detect? Isn't it too large? I recommend that this article be accepted for publication. Congratulations on a well thought through study and a well written article!

REVIEWER	Duncan, Sarah Newcastle Upon Tyne Hospitals NHS Foundation Trust, Sexual Health
REVIEW RETURNED	20-Nov-2023

GENERAL COMMENTS	Many thanks for the invitation to review this manuscript. This is an important study which has the potential to make a significant contribution to HIV prevention efforts in women. Please find some comments on the manuscript attached (The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.)

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. Consider including additional references discussing adherence to COCs among adolescents in Southern Africa.

Response: We thank the reviewer for this suggestion, however, we have found limited specific data on adherence to COCs among adolescents in Southern Africa. We have updated the manuscript to include this information, but because the South Africa study is enrolling both adult women and adolescents, we thought it best to add general information about COC use among adolescents in southern Africa to the introduction and adherence information in the methods section (see below). For the introduction, we have added the following (p. 4, lines 82-85):

> "Data on oral contraceptive use among adolescents in sub-Saharan Africa is limited, however, an analysis from 33 sub-Saharan African countries indicated that prevalence of COC use ranged from approximately 15% to 20% among 15-24 year olds"

2. The over-encapsulated DPP might be a barrier for study participants. It disadvantages and penitential [potential?] risks should be included in the ICF.

Response: Thank you for this comment. The informed consent form does contain a section on the risks of taking the DPP, which we have now summarized and added to the informed consent section of the manuscript on p. 13, lines 185-186:

> "The same study staff member implements a comprehension assessment to check participants' understanding of key study aspects, including the potential increased risk of HIV or unintended pregnancy if difficulty swallowing the large DPP capsule leads to more missed doses, before they both sign the consent form."

3. P2. Line 7: Oral pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention method; however, uptake and persistence have been low among southern African women. ***Reviewer: Do you mean effective use (vs "persistence)?***

Response: We have seen both "persistence" and "effective use" in the literature and decided to keep "persistence" in the abstract.

4. P5, lines 7-12: In South Africa 25.6% of women report ever having used COCs and 10.5% currently use them [35,36]. In Zimbabwe, COCs are the most common family planning (FP) method, used by 57% of women on contraceptives [37]. ***Reviewer: Need to discuss adherence to COC use among AGYW.***

Response: As noted above, data on adherence to COCs among adolescents in southern Africa is limited. We have added the following text to Page 6, lines 139-143:

> "In addition, a recent study in Cape Town found that only 52% of 15-19 year olds (n=50/96) randomly assigned to use COCs (versus intravaginal rings or injectables) reported being fully adherent over an 8-week period [43], highlighting the importance of enrolling participants who have already been using COCs for at least three months."

5. P7, lines 12-16: we are enrolling participants who are already using COCs in these pilot acceptability studies because they are already accustomed to taking a daily pill with any associated side effects. ***Reviewer noted: but not a pill of this size.***

Response: We thank the reviewer for pointing this out. We have revised the text (page 6, lines 134-136) as follows:

> "Although participants will already be accustomed to daily pill-taking and the associated side effects of COCs, they will not be used to the large size of the DPP capsule."

We have further emphasized that women will need to be able to swallow a large vitamin pill similar in size to the DPP as we acknowledge not everyone will be able to swallow the large DPP capsule.

6. P 7, lines 37-39: …, and inability to swallow a large vitamin pill similar in size to the over-encapsulated DPP (Figure 1). ***Reviewer says: needs to be in ICF of participants advising them about the potential inconvenience to swallow large pill.***

Response: as noted above, the informed consent already includes language about the inconvenience/ potential risk of the large pill. We have now added to the informed consent section of the manuscript on p. 13, lines 185-186:

> "The same study staff member implements a comprehension assessment to check participants' understanding of key study aspects, including the potential increased risk of HIV or unintended pregnancy if difficulty swallowing the large DPP capsule leads to more missed doses, before they both sign the consent form.

7. p. 8, line 42: Hepatitis B surface antigen and Hepatitis C negative per blood test at Screening. ***Reviewer asks: why difference in Hepatitis testing between Zimbabwe versus South Africa? Routine national protocol?***

Response: The reviewer is correct that the slight differences in inclusion/exclusion criteria are related to the different national protocols. We have added this language into the manuscript on Page 6, lines 142-143:

> "Specific eligibility criteria (**Table 1**) for the two protocols are similar, with several differences based on routine national protocols for PrEP provision, as well as age range."

Reviewer 2

1. I have a minor comment on the methods that does not alter my verdict. Sample sizes are well described, loss to follow up have been factored in the samples while preserving power to detect the difference of interest. I would however have anticipated larger sample size than 96, especially for the adherence question. Are the authors confident about this difference they have powered their sample to detect? Isn't it too large?

Response: We selected our sample size as a compromise between the difference in levels of adherence between the two regimens that would be clinically significant and available resources for implementing the trial. We assumed approximately 25% mean adherence in the 2-pill regimen, which was a conservative estimate based on findings from other recent PrEP studies in AGYW in sub-Saharan Africa, several of which we have added to the citations. Several different scenarios were considered, as per the table below; 86 completing the study with 96 being enrolled to account for drop out was selected.

% adherent while using treatment 1	% adherent while using treatment 2	Number to complete to have 80% power
25%	45%	44
25%	40%	86
25%	35%	164
25%	30%	640

We added a sentence to the methods explaining the rationale for the 25% (see page 21, lines 337-339).

Reviewer 3

1. P.3, lines 38-45: The pill regimen is relatively complicated, due to different colours and the need to be able to take the correctly coloured pills for a 4 week cycle without getting the weeks mixed up - although the women are experienced COC users, do they normally use a COC with placebo pills? If not, this may add confusion, and make the acceptability and adherence between the regimens more difficult to extrapolate.

Response:

We thank the reviewer for this question. One of our primary research questions is if it is easier to take the single pill vs. the two pills, which includes confusion about order of taking the pills when they are using the DPP regimen. If participants find it overly complicated, that is something we will learn in the study. We aimed to simplify the instructions as much as possible, and we believe we have packaged the DPP in such a way that women will find it easy to use. As outlined in Table 2, each month's supply of the DPP comes in a box, and within the box there are 4 blister strips – 1 for each week in the month. The DPP capsules come in blister strips that are numbered 1-28 indicating the order that they are to be taken. There are 3 weeks where women will be taking the active COC (pink and white capsules) and 1 week when they will be taking the placebo (white capsule), a regimen they are accustomed to. They will be counseled about how to take the DPP and will be given an information sheet explaining how to take the DPP. There is a photograph of the DPP in the manuscript and we have added some additional text to Table 2 to further clarify how they will take the DPP.

2. Inclusion of COC as opposed to POP limits the population of women who may be eligible to use the DPP if licensed due to a woman's medical and personal characteristics. Similarly, COC is usually acquired via medical prescription whereas POP can be issued in many countries without the need for it to be prescribed. Study populations are relatively small, thus study outcomes are somewhat dependent on avoiding large numbers of participants being excluded or dropping out of the study

Response: The first DPP being developed is based on a 150 LNG/30 EE COC, which is one of the most common types of oral contraceptives available in low and middle-income countries. Because the co-formulated DPP will contain ethanol estradiol and levonorgestrel, we chose the same type of COC for this study. COCs are the most commonly-used method in Zimbabwe and the type of COC that we are using in this study – Zinnia F – is the exact same pill as Control L, the brand that is purchased by UNFPA for use in Zimbabwe. To underscore the rationale for using Zinnia F, we added the following sentence on Page 10, Lines 181- YY:

> "Zinnia F was selected because it is the exact same formulation as Control L, the COC purchased for public family planning programs in Zimbabwe."

3. P 3, lines 47-52: Another limitation is the different study designs and sample sizes for the two studies, primarily related to their respective funding mechanisms, that may limit the ability to directly compare results from the two countries.

Response: the studies were developed in parallel to explore the acceptability of the DPP in two different settings but not to compile the data from the two countries. We chose to present the protocols in the same paper, however, because of the overwhelming similarities in the study designs.

4. P5, lines 7-11: in South Africa 25.6% of women report ever having used COCs and 10.5% currently use them [35,36]. In Zimbabwe, COCs are the most common family planning (FP) method, used by 57% of women on contraceptives [37]. ***Reviewer: What is the most common type of COC used by the general population? Different progesterones can be associated with different side effect profiles, thus it would be helpful to know if the DPP represents the same COC as most women are already using or something different***.

Response: As noted above in the response to #2, women enrolled in the study are using the same type of COC (150 EE/30 LNG) to minimize side effects attributable to COCs during the trial.

5. COCs have prescribing restrictions in terms of patients who cannot use them due to other medical conditions or personal characteristics, whereas POPs are often considered suitable for a more diverse population and can now be bought over the counter without a prescription in many settings - could the authors comment on why the DPP focuses on COC rather than POP combined with PrEP?

Response: As noted above in #2, the first DPP being developed is based on a COC, which is why we chose a 150 LNG/30 EE OC for this study.

6. P5, Figure 1 – Is there any data to describe how women using COC in these settings might be similar or different from the general population? for example education level, income, relationship status or other factors which might reassure the reader that outcomes generated by the study will be applicable more broadly?

Response: We thank the reviewer for this suggestion, however, these studies are not intended to be generalizable but rather specific for women already using oral contraceptives. Secondly, we have found limited specific data on adherence to COCs among adolescents in Southern Africa. Furthermore, because the South Africa study is enrolling adults and adolescents, we thought it might be best to add general information about COC use among adolescents in southern Africa to the introduction and adherence information in the methods section (see below). For the introduction, we have added the following (p. 4, lines 82-85) and cited Radovich et al. Who Meets the Contraceptive Needs of Young Women in Sub-Saharan Africa? 2018;62:273–80. 10.1016/j.jadohealth.2017.09.013:

> "Data on oral contraceptive use among adolescents in sub-Saharan Africa is limited, however, an analysis from 33 sub-Saharan African countries indicated that prevalence of COC use increased between the ages of 15-24 and ranged from approximately 15% to 20% among 15-24 year olds."

7. No comment on body weight. Smokers > 35 are only excluded in SA but not in Zimbabwe - can the authors comment on why this is?

Response: Thank you for your comment. Weight in and of itself is not a contraindication for COC use, however, people with hypertension or other conditions that are contraindicated for COC or PrEP use are excluded. Smokers >35 were only excluded in South Africa because in Zimbabwe all participants are under the age of 35 so it was not necessary to add that exclusion criterion for Zimbabwe. Please note that the detailed inclusion criteria are provided later in the paper (Page 8, line 9).

8. Emergency contraception, If not available, can authors explain the advice women were given re pregnancy testing.

Response: Thank you for this question. Participants are counseled about missed doses as per Table 2 (study products). Participants are tested for pregnancy monthly so there was no additional pregnancy testing recommended. Emergency contraception was not part of the protocol as it is not the standard of care in the study settings.

9. Can the authors define "preference" in the primary end point? How is this measured? Is this self-reported or is this a composite end point? - this is explained later in the paper but it would help the reader if it is described in the table

Response: Thank you for this question. We are measuring preference by self-report based on a question in the self-administered CASI questionnaire at Visit 7 (exit in Zimbabwe and choice visit in South Africa). The specific question is, “Would you prefer to use contraceptive pills and PrEP (two pills daily) or the DPP (one pill daily) for pregnancy and HIV prevention?” We have added additional text to Table 3 (page 12) to clarify that this is a self-reported measure.

10. ? unintended pregnancy as an outcome, surrogate marker of adherence and data is being collected P12

Response: Unintended pregnancy is not an outcome, per se, but we agree with the reviewer that unintended pregnancy during the study would be a surrogate marker of adherence. However, we have not made specific plans *a priori* to do any analyses of adherence based on pregnancy outcomes, which we hope will be rare.

11. Are the study participants given any financial (or other) incentive to take part?

Response: Thank you for this comment, as noted in the ethics section on page 25, participants receive compensation for each visit to cover their time, transportation costs, and inconvenience of the study visits commensurate with the norms and standards in each country. Because the amounts differ by country, we did not include the specific amounts in the paper.

12. Reviewer asks: Do the interviews include participants who are excluded due to HIV seroconversion or pregnancy?

Response: Thank you for this comment. The goal of the interviews is to gain a better understanding of participants’ opinions about the two different regimens. In South Africa, which includes a Choice period, we are interviewing a subset of women who choose each regimen for the Choice period (e.g. those who chose the DPP and those who chose 2 separate pills) and those who choose to exit before the Choice period. In Zimbabwe, which is a smaller study, are interviewing all willing participants after they exit the study. We have not specifically excluded anyone from the exit interviews and each study team can make a determination if participants who terminate early due to pregnancy or seroconversion are open to being interviewed.

13. ? qualitative methods: will the interview be conducted in the participant's language of choice? will it be recorded and transcribed by a native speaker, with the coding done in the original language or in English?

Response: Thank you for your question. As noted on page 21, the interviews will be conducted in the participant's choice of language. All interviews will be audio recorded and transcribed, and translated into English, as relevant. Coding and analysis will be done in English as it will be a collaborative effort between the local teams at each site and Population Council researchers.

14. The sample size calculation is based on identifying a difference between the two regimens where the adherence to PrEP alone is expected to be low, with the adherence to DPP higher. What happens if the adherence to PrEP alone is higher than expected (in the context of a study environment where the participant is also given COC) - does the study still have the power to detect a difference?

Response: The sample size would be able to detect a difference in adherence by regimen, whether it was the DPP or the 2 separate pills that yielded higher adherence.

15. Can the authors define "adherent"ie how well does the TDF-DP level chosen correlate to missed pills? for example, might a participant have taken 80% of the pills and have an "adherent" TDF-DF level? Does the TDF-DP level associated with "adherence" also correlate to having taken enough pills to prevent pregnancy? The adherence required to prevent HIV infection and to prevent pregnancy might differ.

Response: We thank the reviewer for this comment. At the time that we wrote the protocols, there was a lack of conclusive data regarding the level of adherence/number of pills per week needed for PrEP to be effective in women. Therefore, we did not define a specific level as "adherent." In the last several years after we wrote the protocols, there have been several studies estimating number of doses/week and TDF levels in DBS associated with adherence. We are using these data to inform our analysis plan and will describe our adherence measures in detail in the manuscripts that report the results. We also acknowledge that the level of and patterns of adherence required to prevent HIV and pregnancy are different. In this study, we are focusing on adherence to PrEP because our overarching hypothesis is that combining PrEP with a contraceptive will increase PrEP adherence.

16. It would be helpful to understand if the participants would want to continue using the DPP in real life and the underlying reasons for and against.

Response: Thank you for your important question. We agree that it is very important to understand if the study participants would want to use the DPP "in real life." We are asking questions both quantitatively in the CASI interviews and qualitatively regarding interest in DPP use in the future. In the context of the qualitative exit interviews, we will also be showing participants a picture of the co-formulated DPP in development. The questions focus on facilitators and barriers of product use, acceptability and adherence.

17. Who conducts the interviews ? male or female - how might their characteristics influences responses? how are the different languages accounted for? Are the interviews semi-structured? Is the coding done using Nvivo? or by hand? Is this done by a single researcher or by a team? Can the authors say more about the process of coding - will the interviews be analysed for SA and Zimbabwe separately or combined together?

Response: Thank you for your question. Based on space (word count) limitations, we were unable to describe the qualitative research methods in detail, however, we have updated the data collection (page 21, lines 328-342) and analysis (page 24, lines 421-425) sections to include the fact that interviews are being conducted by females, using a semi-structured interview guide, that the interviews are in the participants' choice of language and translated into English for coding and analysis by the teams at the sites and at the Population Council. Currently, the plan is to analyze the data separately given the different study designs (no Choice period in Zimbabwe).

VERSION 2 – REVIEW

REVIEWER	Duncan, Sarah Newcastle Upon Tyne Hospitals NHS Foundation Trust, Sexual Health
REVIEW RETURNED	22-Jan-2024

GENERAL COMMENTS	Thank you for your detail responses to my questions and provision of further clarity regarding methods and rationale for the details of the study design.

VERSION 2 – AUTHOR RESPONSE