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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 randomised, controlled, cross-over studies in South Africa and Zimbabwe

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ABSTRACT

Introduction Oral pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention method; however, uptake and persistence have been low among southern African women. A dual prevention pill (DPP) that combines PrEP with oral contraception (OC) may increase PrEP use and better meet women's sexual and reproductive health needs. We will gauge the DPP's acceptability in two cross-over clinical trials.

Methods and analysis PC952 (Zimbabwe) and PC953 (South Africa) will compare acceptability, adherence and preference for an over-encapsulated DPP versus PrEP and OCs taken separately. HIV-negative, non-pregnant cisgender females in Johannesburg, South Africa (n=96, 16–40 years) and Harare, Zimbabwe (n=30, 16–24 years) will be randomised 1:1 to the order of regimens—DPP or two separate tablets—each used for three 28-day cycles, followed by a 6-month choice period in South Africa. Monthly clinic visits include HIV and pregnancy testing; safety assessments and risk reduction and adherence counselling. We will assess adherence (monthly) based on tenofovir diphosphate drug levels in dried blood spots and by self-report. We will evaluate acceptability (monthly) and preference (end of cross-over) via computer-assisted self-interviewing and in-depth interviews with a subset of participants. Data collection started in September 2022 and ended in January 2024.

Ethics and dissemination PC952 was approved by the Ministry of Health and Child Care, Medical Research Council, Research Council and Medicines Control Authority of Zimbabwe; the Chitungwiza City Health Ethics Committee; and the Joint Research Ethics Committee

STRENGTHS AND LIMITATIONS OF THESE STUDIES

⇒ The cross-over design enables a direct comparison between the intervention (DPP) and standard of care or control (oral pre-exposure prophylaxis (PrEP) and combined oral contraceptives (COCs) separately) regimens that enables a smaller sample size with women serving as their own controls.

⇒ Participants will be followed monthly, which will enable frequent assessments of PrEP drug levels in blood, however, it will not be feasible to measure contraceptive drug levels in blood due to the short half-life of COCs.

⇒ The two pilot studies enable early assessments of the DPP in two different contexts: South Africa (low COC use/high HIV incidence and prevalence) and Zimbabwe (high COC use/moderate HIV incidence and prevalence) and among adolescent girls and young women and older women.

⇒ The key limitation of the studies is the use of an overencapsulated DPP as a proxy for the ultimate coformulated tablet, which may not accurately capture acceptability, preference and adherence for the ultimate DPP, which will be a smaller tablet versus a capsule.

⇒ Another limitation is the different study designs and sample sizes for the two studies, primarily related to their respective funding mechanisms, which may limit the ability to directly compare results from the two countries.

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for the University of Zimbabwe Faculty of Medicine and Health Sciences and Parirenyatwa Group of Hospitals. PC953 was approved by the South African Health Products Regulatory Authority and the University of the Witwatersrand's Human Research Ethics Committee. The Population Council IRB approved both studies. We will disseminate results in open-access journals, clinical trials registries, and at local and international meetings and conferences.

Trial registration numbers NCT04778514, NCT04778527.

INTRODUCTION

Despite substantial advances in HIV treatment and prevention over the last decade, women and girls in eastern and southern Africa continue to be disproportionally affected by HIV/AIDS, accounting for 63% of all new HIV infections in the region in 2021.[1] In 2021, new HIV infections in South Africa were almost double among women aged 15 and over than among men of the same age (130 000 vs 70 000, respectively).[2] Similarly, in Zimbabwe, nearly twice as many women 15 and older acquired HIV in 2021 compared with their male peers.[1]

Oral pre-exposure prophylaxis (PrEP) is more than 90% effective in reducing HIV transmission.[3] However, many oral PrEP trials and demonstration projects in sub-Saharan Africa have been plagued by low adherence, particularly among adolescent girls and young women (AGYW).[4 5] Stigma and fear of intimate partner violence or relationship dissolution are often cited as reasons for non-use of PrEP.[6–9] Novel strategies to bolster uptake and adherence are needed to increase PrEP use among women and girls at high risk of HIV.

Many women—and AGYW in particular—are more worried about unintended pregnancy than HIV.[10 11] Furthermore, there is a growing body of evidence indicating that many women may be more likely to use an HIV prevention method that also prevents pregnancy.[12–19] Condoms are currently the only multipurpose prevention technologies (MPTs) that prevent both HIV and unintended pregnancy.[20] Male condoms, however, are not under a woman's control; female condoms have had limited uptake due to access and acceptability issues[21 22]; and many women risk gender-based violence by merely suggesting condom use.[23] Several novel MPTs are in the pipeline,[24] including a dual prevention pill (DPP) containing the ingredients in oral PrEP and oral contraception. The first DPP being developed is based on the commonly used 28-day combined oral contraceptive (COC) regimen (150 µg levonorgestrel (LNG), 30 µg ethinyl estradiol (EE)) and a generic equivalent of Truvada (300 mg tenofovir disoproxil fumarate (TDF), 200 mg of emtricitabine (FTC)).[25 26] The DPP is likely to be the fastest route to an approved MPT as it contains two registered products that are safe and effective for their respective indications[27–30] with no evidence of drug–drug interactions.[31–34] 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 among those using a modern method.[37] Data on oral contraceptive use among adolescents in sub-Saharan Africa are limited; however, an analysis from 33 sub-Saharan African countries indicated that COC use ranged from approximately 15%–20% among 15–24 year-olds.[38] Truvada is approved as PrEP in more than 20 countries globally, including South Africa and Zimbabwe, and is recommended by WHO and CDC ((US) Centers for Disease Control and Prevention) for women at risk of HIV using COCs.[29 39]



Figure 1 Overencapsulated dual prevention pill. *The hand shown is of one of the coauthors and is not a patient.*

We hypothesise that the DPP could greatly increase PrEP adherence, while also meeting women's unmet FP needs. Our goal is to generate data to inform DPP introduction through two clinical cross-over studies comparing acceptability of, adherence to and preference for the DPP versus two separate tablets. To that end, and in parallel with the development of the coformulated DPP, we have overencapsulated PrEP (Truvada) and a COC (Zinnia F (150 LNG/30 EE)), into a single capsule (figure 1) for our studies to provide an early indication of DPP acceptability.

METHODS AND ANALYSIS

Trial design

(The Standard Protocol Items for Randomised Trials reporting guidelines is used.) Population Council Protocols 952 and 953 are randomised, controlled, open-label, cross-over studies.

Participant and public involvement

Formative research (December 2020–June 2021) with service providers and potential end users in South Africa and Zimbabwe informed the clinical trial design, materials and recruitment methods. Established community and/or youth advisory groups at each site reviewed the protocols and provided input into the consent forms, behavioural questionnaires and translations. The study teams have also benefited from participation in the DPP consortium, a collaborative group of researchers, donors and civil society advocates established to inform and accelerate DPP development and introduction.[40]

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Study settings

Hillbrow (Johannesburg), South Africa

PC953 is being conducted at the Wits RHI (Wits Reproductive Health and HIV Institute) Research Centre, a large research clinic situated in Hillbrow, Johannesburg. As of 2020, Johannesburg had 756 751 people living with HIV with an overall HIV prevalence of 13%. HIV prevalence was highest among females across all age groups: 28.3% for 25–49 years, 15% for women 50 and above and 9% for 15–24 years.[41] Wits RHI conducts research on HIV, sexual and reproductive health (SRH) and vaccine-preventable diseases.

Chitungwiza (Harare), Zimbabwe

PC952 is being implemented by the University of Zimbabwe Clinical Trials Research Centre (UZ-CTRC) at the Zengeza Clinical Research Site (CRS) in Chitungwiza, Zimbabwe's second-largest city approximately 30 km south of Harare, with a generalised epidemic and HIV prevalence of 3.8% among women aged 15–19 years and 6.4% among women aged 20–24 years.[42] The Zengeza CRS is located within a Chitungwiza City Health Department Municipal Clinic and conducts research on female-controlled HIV/STI (sexually transmitted infection) prevention strategies, including microbicides, oral and injectable PrEP and cervical barriers, and integrated HIV prevention strategies.

Study populations

We are recruiting participants (n=96, 16–40 years, South Africa; n=30, 16–24 years, Zimbabwe) from FP, PrEP and SRH clinics, and the general population. Although the DPP may ultimately appeal to individuals using other contraceptives or with an unmet FP need, we are enrolling participants who are already using COCs and are accustomed to daily pill-taking and the associated side effects of COCs (though they will not be used to the large DPP capsule). In addition, a recent study in Cape Town found that only 52% of 15–19 years (n=50/96) randomly assigned to use COCs (vs 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 3 months.

Inclusion/exclusion criteria

Eligible participants are healthy, HIV-negative, non-pregnant, sexually active, cisgender females at moderate to high risk of HIV infection. Specific eligibility criteria (table 1) for the two protocols are similar, with several differences based on routine national protocols for PrEP provision and age range. Screening by nurses/clinicians includes medical history, physical examination and clinical laboratory tests. HIV risk is assessed by clinicians using local PrEP guidelines and by participants who are offered access to tools, such as BWise,[44] to help them make that determination. Key exclusion criteria and prohibited medications relate to contraindications for COCs or PrEP use. We are also excluding those unable to swallow a large vitamin pill similar in size to the overencapsulated DPP (figure 1).

Study schema

At enrolment, participants are randomised to the sequence of study regimens (figure 2): sequence 1=single DPP capsule once daily for three 28-day cycles (regimen A), followed by two separate tablets (oral PrEP and COC) once daily for three 28-day cycles (regimen B); sequence 2=regimen B followed by regimen A. In South Africa, after the 6-month cross-over period, participants may choose regimen A, B or neither for up to six additional 28-day cycles. Study product regimens are described in detail in table 2.

All participants take PrEP (FTC/TDF 200/300 mg) once daily by mouth throughout the entire study and 21 days of active COCs, followed by 7 days of placebo tablets, regardless of regimen. The selection and timing of doses correspond to the labels for Truvada (Gilead Sciences; Foster City, California, USA) and Zinnia F COCs (Mylan Laboratories, Hyderabad, India). Zinnia F was selected because it is the same formulation as Control L, the COC purchased for public FP programmes in Zimbabwe. During the 'placebo' days of regimen A, participants take one capsule containing Truvada only, whereas the placebo days of regimen B consist of two separate tablets: Truvada and a placebo COC tablet. The DPP capsules were manufactured and packaged by PCI Pharma Services (Rockford, Illinois, USA) from the same batches of Truvada and Zinnia F as the separate pills procured from Gilead and Mylan, respectively.

Study objectives

Objectives and outcomes are similar in both trials (table 3).

Study procedures

Informed consent

Before undergoing screening procedures, a counsellor/designee leads a discussion to review the informed consent form in detail with potential participants in their preferred language (English or isiZulu, South Africa; English or Shona, Zimbabwe). 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. For unemancipated minors (16–17 years), informed consent from the parent/legal guardian is obtained before assent from the minor. Key elements of the informed consent are reviewed on an ongoing basis and willingness to continue study participation is ascertained.

Eligibility screening

After consenting, potential participants are assigned a unique participant identification number (ID) and undergo screening procedures. All screening test results and, if enrolled, study information (data, specimens)

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Table 1 Inclusion and exclusion criteria for South Africa (SA) and Zimbabwe (Zim)

Criteria	SA	Zim
Inclusion criteria		
Age 16–40 years old (inclusive) at screening, verified per site-specific SOPs.	X	
Age 16–24 years old (inclusive) at screening, verified per site-specific SOPs.		X
Able and willing to provide informed consent per site SOPs. (If under the legal age of consent (18 years old) be able to provide informed assent and obtain parental or guardian consent, to be screened for and to enrol in the study.)	X	X
Fluent in spoken Zulu and/or English.	X	
Fluent in spoken Shona and/or English.		X
Able and willing to provide adequate locator information, as defined in site SOPs.	X	X
Able and willing to comply with all study procedures, including being comfortable taking the study products as evident by nurse/clinician-observed swallowing at Screening of a large vitamin capsule that is of similar size to the study products.	X	X
Postmenarche, per participant report at screening.	X	X
Sexually active, defined as having had penile-vaginal sex with a male within the 3 months before screening (per self-report).	X	X
At moderate to high risk of HIV infection based on clinician assessment.	X	X
Considers herself to be at moderate to high risk of HIV acquisition based on self-assessment.	X	X
Has been using COCs for contraception for at least 3 months prior to screening as confirmed by contraceptive card and intends to continue using COCs for at least 12 months.	X	
Currently using COCs for contraception and has been using them for at least 3 months prior to screening.		X
HIV-negative per rapid test at screening and enrolment per site-specific SOP.	X	X
Negative pregnancy test at screening and enrolment.	X	X
Negative for chlamydia, gonorrhoea, trichomoniasis and syphilis at screening; women who test positive at screening may be treated and enrolled.	X	X
Hepatitis B surface antigen negative per blood test at screening.	X	
Hepatitis B surface antigen and hepatitis C negative per blood test at screening.		X
Normal estimated creatinine clearance ≥60 mL/min per blood test at screening.	X	X
Exclusion criteria		
Currently using emtricitabine or tenofovir (TDF) at screening (per self-report).		X
Intends to become pregnant within the next 12 months.	X	X
Intolerance, adverse reaction or laboratory abnormality associated with PrEP use in the past.	X	X
Use of PEP within 3 months of Screening (per self-report).	X	X
Breastfeeding <6 months postpartum (per self-report).	X	X
Less than 6 weeks (≤42 days) post partum and not breast feeding (per self-report).	X	X
For women 35 and older, currently smoke cigarettes (self-report).	X	
History of deep vein thrombosis/pulmonary embolism (self-report) or history of thrombophlebitis or thromboembolic disorders at screening (per self-report or medical records).	X	X
Prolonged immobilisation (self-report).	X	X
Known thrombogenic mutation/complicated valvular disease (per self-report).	X	X
History of cerebrovascular or coronary artery disease reported at screening.		X
Ischaemic heart disease (per self-report).	X	X
Systemic lupus erythematosus with positive or unknown antiphospholipid antibodies (per self-report).	X	X
Migraines with aura.	X	X
For women over 35 years old, migraines without aura (per self-report).	X	
History of undiagnosed abnormal genital bleeding reported at screening.		X
Current breast cancer or within 5 years of past breast cancer (per self-report) or history of carcinoma of the breast or other oestrogen-dependent neoplasia reported at screening.	X	X

Continued

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Table 1 Continued

Criteria	SA	Zim
Diabetes with nephropathy, retinopathy or neuropathy (per self-report).	X	X
Diabetes for >20 years (per self-report).	X	X
Symptomatic gall bladder disease (per self-report).	X	X
Severe cirrhosis (per self-report).	X	X
Liver tumour (per self-report).	X	X
Any other condition the clinician feels would jeopardise the health and well-being of the participant.	X	X

COC, combined oral contraceptive; PrEP, pre-exposure prophylaxis; TDF, tenofovir disoproxil fumarate.

are recorded with IDs and no other identifying information to preserve participant confidentiality. Locator information is collected at screening and reviewed at each study visit to ensure participants are contactable for retention purposes. The screening process typically takes more than one day because several lab tests are outsourced. At screening (visit 0), a nurse/clinician takes a complete medical history, including gynaecological and obstetric history. A clinical exam is performed to assess overall health (including complete blood count (CBC) in Zimbabwe). Urine is tested for pregnancy (human chorionic gonadotrophin (hCG)), and *Neisseria gonorrhoeae/Chlamydia trachomatis* (nucleic acid amplification test (NAAT)). Blood is tested for HIV, syphilis and hepatitis B virus (and Hepatitis C in Zimbabwe), and to measure creatinine clearance. Screening also includes direct observation of participants swallowing a large vitamin capsule, similar in size to the 000 DPP capsule (figure 1).

Enrolment and randomisation

Enrolment (visit 1) is scheduled when participants are starting their next COC pack (±5 days). At enrolment, participants are tested for HIV (rapid antigen blood test) and pregnancy (urine hCG) to confirm eligibility. Those eligible are enrolled and randomised (1:1) to the sequence of regimens, are given a supply of their first study product with detailed dosing instructions and take their first dose directly observed in the clinic. Participants are counselled on management of anticipated side effects and missed pills based on recommendations that incorporate differing guidelines for COCs and oral PrEP.[45] Participants also receive counselling on HIV/STI risk reduction, contraception and protocol compliance—including the importance of attending clinic visits and taking the study products—at every visit.

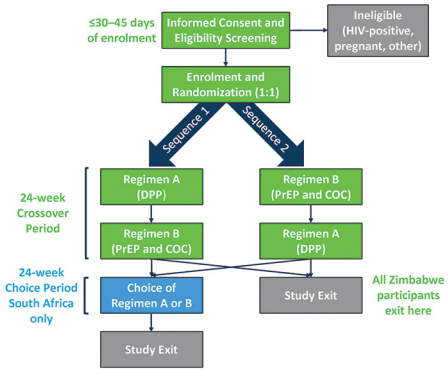


Figure 2 Study schema. COC, combined oral contraceptive; DPP, dual prevention pill; PrEP, pre-exposure prophylaxis.

Follow-up visits

Online supplemental table 1 contains the detailed schedule of visits and procedures. At all visits, blood is collected for dried blood spots (DBS) to assess tenofovir-diphosphate (TFV-DP) levels as a measure of PrEP adherence[46] and for rapid HIV testing. Urine is collected for pregnancy testing. After the first three cycles, participants 'cross-over' to their second regimen at month 3/visit 4 and return unused study product from their first regimen. They then receive their first supply of the second regimen, with detailed instructions, and take their first dose directly observed in the clinic. Participants attend monthly follow-up visits during the second regimen (month 4/visit 5; month 5/visit 6). At month 6/visit 7, all participants exit in Zimbabwe. In South Africa, participants may choose to continue using either regimen for up to another 6 months during a 'choice' period, with similar monthly visits.

Laboratory procedures

Laboratory assessments are listed in online supplemental table 1. Blood specimens for hepatitis, creatinine, HIV confirmation testing (and CBC in Zimbabwe) are processed off-site by BARC (South Africa) and UZ-CTRC (Zimbabwe). DBS specimens are analysed at the University of Cape Town by liquid chromatography-tandem mass spectrometry.[46]

Safety monitoring and adverse event reporting

Clinical assessments at each visit post-enrolment are done to monitor potential adverse events (AEs) and social harms. Individual participants who develop grade 1 or unrelated grade 2 AEs, based on the Division of AIDS Grading system,[47] may continue using their assigned study product(s) per protocol, at the site PI's/designee's discretion. Individuals who develop a related grade 2 AE, or any grade 3 AE, regardless of relatedness, will be evaluated by the site PI/designee and medical monitor for

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Table 2 Study products

Regimen	Description	Dose, route and frequency
A: dual prevention pill (DPP)	Each DPP kit contains 28 capsules divided into 4 pouches, 1 per cycle week. Each pouch contains a blister strip of 7 capsules (plus desiccant). ► 3 pouches contain 21 pink and white capsules which each have 1 Truvada tablet (FTC 200 mg/TDF 300 mg) and one Zinnia F tablet (EE/LNG 30/150 µg). ► 1 pouch contains 7 white capsules containing 1 Truvada tablet.	► Participants will take 1 DPP capsule orally, once daily at approximately the same time each day for 12 weeks (cross-over period), taking the next consecutively numbered capsule from each pouch, in order (week 1, week 2, week 3, week 4). In South Africa, the DPP may be taken for ≤6 additional months (choice period). ► If they miss 1 DPP capsule, participants will be instructed to take it as soon as they remember, up to the time of their next dose, but no more than 2 doses in a 24-hour period. ► Participants will be counselled to use back-up contraception (eg, condoms or abstinence) for 7 days if they miss 2 or more consecutive doses.
B: 2 separate tablets	Bottle of 30* Truvada (FTC/TDF 200/300 mg) tablets (PrEP) Blister card of Zinnia F COCs: 21 white active EE/LNG 30/150 µg pills and 7 brown placebo pills (no hormone)	► Participants will take 1 Zinnia F tablet and 1 Truvada tablet once daily. Tablets may be taken together or separately, but each tablet (Zinnia F, Truvada) should be taken at the same time each day. ► Zinnia F tablets are to be taken in the order indicated on the pack, including the 7 placebo tablets. If a participant misses a COC dose, she will be instructed to take it as soon as she remembers. If a full day has passed, she should take 2 tablets the next day, per the label. Participants will be counselled to use back-up protection for 7 days if they miss ≥2 consecutive doses. ► If a participant misses 1 Truvada dose, she will be counselled to take 1 tablet the next day, per the label, but not to take more than 1 dose in 24 hours. ► Participants will be counselled that the effectiveness of PrEP may be reduced if doses are missed.

*At the end of the 28-day period, participants should have 2 Truvada tablets remaining in the bottle and will be instructed to return those tablets to the study clinic.
EE, ethinyl estradiol; FTC, emtricitabine; LNG, levonorgestrel; PrEP, pre-exposure prophylaxis; TDF, tenofovir disoproxil fumarate.

possible discontinuation from the study. Grade 4 AEs, regardless of relatedness, will be evaluated by the site PI/designee and Population Council Medical Monitor and those participants will be discontinued from the study. No dose modifications will be undertaken nor are there any a priori stopping rules because both study products (PrEP and COCs) are marketed drugs.

Seroconversion or pregnancy

Participants who seroconvert are terminated from the study. At their closing visit, study staff will collect unused pills, conduct resistance and viral load testing, and link the participant to HIV/FP care per local guidelines. Similarly, participants who become pregnant will be terminated and referred to services for pregnant individuals, including PrEP provision, if desired. The sites will make every effort to follow-up on all pregnancy outcomes. The sites may continue counselling participants as they transition to services to preserve their confidentiality after discontinuation.

Creatinine

Creatinine levels are monitored according to PrEP guidelines in each country, approximately quarterly.[48 49] Participants with abnormal creatinine levels may be put on a temporary product hold, pending the PI/designee's decision, until a repeat test can be done. Participants who have two tests outside the normal range will be permanently discontinued to reduce their risk if the DPP or PrEP is contraindicated.

Data and safety monitoring

The Population Council monitor conducted site qualification and initiation visits at both sites before data collection began. Periodic monitoring visits ensure the protocol and good clinical practice are being followed. The monitor reviews source documents to confirm that the data recorded on case report forms (CRFs) is accurate, and reviews relevant documents to verify protocol compliance. A data safety and monitoring board (DSMB) was established, consisting of three experts with clinical expertise in HIV and contraception, epidemiology, biostatistics and clinical trials. The DSMB (charter available on request) will review data after all participants are enrolled (both countries), and after all participants complete the cross-over visit (South Africa). All serious AEs (SAEs) and AEs leading to discontinuation will be reported to the relevant IRBs/ethics committees, drug regulatory authorities, sponsor, DSMB and funders. Unanticipated AEs that are potentially related to the study product(s) will be reported as suspected unexpected serious adverse reactions to the manufacturers (Gilead or Mylan).

Clinical staff are trained to identify, probe for, manage and report AEs and social harms at every visit. Study clinicians review abnormal test results, liaise with local clinic doctors and have the authority to terminate participants based on clinical opinion. On completion of the study, participants are referred to local clinics for PrEP and COC services, if they want to continue the methods. Any breaches in confidentiality, study protocol or AEs attributable to this study will be reported to the relevant IRBs/ethics committees and regulatory authorities.

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Table 3 Objectives and endpoints for PC952 (Zimbabwe) and PC953 (South Africa)

Objective	Endpoint	Type of endpoint (country)
Preference		
To determine preference for taking a single DPP capsule vs 2 separate tablets (PrEP and COC) once daily among women after using each regimen for three 28-day cycles.	Proportion of women who prefer the DPP (regimen A) vs 2 separate tablets (regimen B) after using each regimen for 3 28-day cycles, per self-report on computer-assisted self-interviewing (CASI).	Primary (South Africa and Zimbabwe)
To determine if more women choose regimen A vs regimen B for the choice period.	Proportion of women who choose regimen A vs B for the choice period.	Primary (South Africa)
Adherence		
To compare adherence to the DPP capsule (regimen A) vs 2 separate tablets (regimen B) among women using each regimen daily for 3 28-day menstrual cycles during the cross-over period.	TFV-DP levels in dried blood spots (DBS) by regimen, and overall, at follow-up visits every 4 weeks during cross-over period.	Primary (South Africa)
To compare adherence among women who choose the DPP capsule (regimen A) vs adherence among women who choose 2 separate tablets (regimen B), each taken daily during the choice period.	TFV-DP levels in DBS by regimen, and overall, at follow-up visits every 4 weeks during choice period.	Primary (South Africa)
To assess and compare self-reported adherence to regimen A vs regimen B during the cross-over period, and to the chosen method during the choice period.	Self-assessment of ability to adhere to instructions for product use (DPP capsule, FTC/TDF and COCs as applicable) in CASI interviews at follow-up visits every 4 weeks during the cross-over and choice periods.	Primary (South Africa)
To assess and compare adherence to regimen A vs regimen B during the cross-over period, and to the chosen method during the choice period based on pill count.	Proportion of doses taken versus expected by pill count (DPP capsule, FTC/TDF and COCs as applicable) at follow-up visits every 4 weeks during the cross-over and choice periods.	Primary (South Africa)
To assess and compare daily adherence to PrEP for six 28-day cycles among AGYW when taken in the DPP capsule (regimen A) or as a separate tablet (regimen B) via a biomarker.	TFV-DP drug levels in DBS.	Secondary (Zimbabwe)
To assess and compare self-reported adherence to PrEP for six 28-day cycles among AGYW when taken in the DPP capsule (regimen A) or as a separate tablet (regimen B).	Proportion of PrEP doses taken compared with total no of doses expected per self-report based on a CASI questionnaire.	Secondary (Zimbabwe)
To assess and compare adherence to the DPP (regimen A) vs PrEP as a separate tablet (regimen B) each used for 3 28-day cycles by pill count.	Proportion of DPP and PrEP doses taken compared with total no of doses expected per pill count.	Secondary (Zimbabwe)
To explore if socioecological factors, product characteristics and product use experiences are associated with adherence to PrEP whether taken as part of the DPP capsule or as a separate tablet.	Results of multivariate modelling indicating which, if any, factors are associated with adherence.	Secondary (Zimbabwe)
To explore facilitators and barriers to use, as well as socioecological factors that may be associated with adherence.	Results of multivariate modelling indicating which, if any, factors are associated with adherence.	Secondary (South Africa)
Acceptability		
To assess the acceptability of taking the DPP capsule vs two separate tablets once daily to prevent HIV and unintended pregnancy among women who use each regimen for three 28-day cycles.	Acceptability scores by regimen and overall, per a quantitative acceptability questionnaire via CASI.	Primary (Zimbabwe)
To assess the acceptability of the DPP vs 2 separate tablets taken daily to prevent HIV and unintended pregnancy among women using each regimen for 3 28-day cycles during the cross-over period, and for up to 6 28-day cycles during the choice period.	Scores by regimen and overall, as measured in a quantitative acceptability questionnaire via CASI at the cross-over visit, the start of the choice period and the end of the study.	Secondary (South Africa)
To assess if preuse opinions are associated with actual experiences and preferences after using each regimen.	Proportion of women whose preuse preference matches postuse experience based on a CASI questionnaire at baseline and at the end of the cross-over period.	Secondary (South Africa)
To qualitatively understand barriers and facilitators to product use and adherence.	Results of thematic qualitative data analysis from in-depth interviews with participants at study exit focusing on facilitators and barriers of product use and adherence.	Secondary (South Africa and Zimbabwe)

Continued

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Table 3 Continued

Objective	Endpoint	Type of endpoint (country)
To explore if socioecological factors, product characteristics and product use experiences are associated with acceptability of the DPP and of 2 separate tablets.	Results of multivariate modelling indicating which, if any, factors are associated with acceptability.	Secondary (South Africa and Zimbabwe)
Safety		
To compare the safety of regimen A vs regimen B among women using each regimen for 3 28-day cycles during the cross-over period, and the safety of regimen A vs regimen B among women choosing each regimen during the choice period.	Number of AEs by regimen (including social harms, drug side effects) during the cross-over and choice periods.	Secondary (South Africa)

AE, adverse event; COC, combined oral contraceptive; DPP, dual prevention pill; FTC, emtricitabine; PrEP, pre-exposure prophylaxis; TDF, tenofovir disoproxil fumarate; TFV-DP, tenofovir-diphosphate.

Data collection and management

Clinical CRFs

CRFs were developed by the Population Council and the trial sites to capture demographics, medical history, clinical exam results, laboratory test results, product supply/pill counts, AEs, randomisation and termination data. Data are collected and managed using REDCap (Research Electronic Data Capture) hosted at the Population Council.[50 51] Data are entered into REDCap within 5 days of each participant's visit. Queries are triggered during data entry or by the Population Council data manager during weekly data reviews.

Quantitative behavioural surveys

At each visit, participants complete a behavioural questionnaire via computer-assisted self-interview (CASI) in their choice of English or the local language (isiZulu in South Africa, Shona in Zimbabwe). CASI questionnaires take approximately 30 min to complete and include questions about product acceptability, adherence and overall trial experiences. Participants complete their interviews privately on tablet computers, with study staff nearby to address potential technical challenges.

Qualitative exit interviews

A subset of participants will take part in an in-depth interview (IDI) after exiting the study. In South Africa, we will interview up to 30 participants representing those exiting early (during the cross-over period), those exiting after the cross-over period, and those completing the choice period (half who chose the DPP and half who chose two separate tablets). In Zimbabwe, we will interview all willing participants. IDIs will be conducted by female research assistants using a semistructured guide to explore preference for the DPP or two separate tablets; reasons for continuation/discontinuation; influence of partners, family and support structures; side effects; provider interactions and other factors affecting DPP acceptability and adherence. IDIs will last 40–60 min and will be scheduled at the closing visit or on a separate date, depending on participant availability. IDIs will be conducted in the participant's choice of language; will be audiorecorded and transcribed; and translated into English (if necessary) for analysis.

STATISTICAL CONSIDERATIONS

Sample size and power calculations

South Africa

The sample size calculation was based on comparing adherence between the two regimens. A sample size of 86 has 80% power to detect a difference between the proportion of women who are adherent to each regimen assuming 25% of women are adherent to PrEP alone, 40% are adherent to the DPP, with a correlation between regimens of 50% and no period effect. We estimated 25% of participants would be adherent to the 2-pill regimen based on findings from other PrEP studies among young women in sub-Saharan Africa.[5 52] We increased the sample to 96 in case 10% of participants discontinued early while still having 86 participants complete the cross-over period.

Zimbabwe

The sample size was calculated based on detecting a difference in preference for the DPP versus two separate pills. A sample size of 30 has 94% power to detect a preference for one regimen over the other when the true preference for one regimen is at least 80% based on the exact binomial test (alpha=0.04). If only 27 AGYW complete the study (10% loss to follow-up), we have 84% power to detect a preference for one regimen over the other when the true preference for one regimen is at least 80%, based on the exact binomial test (alpha=0.02).

Randomisation

Randomisation schemes for each study were developed by the Population Council biostatistician using SAS/STAT V.9.4 (SAS Institute Inc., Cary, North Carolina) with a 1:1 allocation using permutated block sizes. In South Africa, randomisation is in blocks of 12, 6 participants per sequence in each of 8 blocks. In Zimbabwe, randomisation is in blocks of 10, 5 participants per sequence in each of three blocks. The randomisation schemes are embedded within the REDCap systems for each study.

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At enrolment, the clinician consults REDCap to assign the treatment sequence for each sequentially enrolled participant.

Data analysis

The 'all participants' population includes all enrolled participants, the 'safety population' includes all participants who have used at least one dose of either regimen, and the 'per-protocol' population includes all participants who complete both regimens. In general, descriptive statistics (frequencies, mean, standard deviation, range) will be used to summarise and characterise data collated on differences in participants assigned to each sequence. Point estimates and corresponding two-sided 95% confidence intervals will be presented for endpoints, where appropriate. Missing data will not be imputed.

Preference

Preference for the DPP will be measured as the proportion of women (per-protocol population) reporting at the end of the cross-over period that they prefer the DPP capsule versus two separate tablets (or vice versa) by testing whether this proportion is greater than 0.5 using a z-test statistic under the exact binomial test in Zimbabwe (n=30) and normal approximation of the binomial distribution in South Africa (n=96). However, if the number of women completing each sequence is unbalanced, the comparison will be done using a random effects mixed model adjusting for effects treatment sequence may have on preference. In South Africa, we will similarly analyse the proportion of women who choose the DPP versus two separate tablets for the choice period.

Adherence

Adherence (overall) will be measured (safety population) by self-report, pill count and TFV-DP levels in DBS measured at each visit and will be compared by regimen. Adherence in DBS will be assessed by comparing the proportion of women with TFV-DP levels consistently greater than the threshold known to provide efficacy, using McNemar's test for paired proportions. Adherence by pill count and self-report will be measured as the proportion of the total number of doses taken versus the total number of expected doses. If all women do not complete the cross-over period, analyses will be conducted with those who completed all six visits (24 weeks). Adherence during the choice period (South Africa) will be analysed similarly.

Acceptability

Acceptability of using the DPP capsule versus two separate pills will be measured in the safety population using a quantitative acceptability questionnaire. The primary outcome of acceptability will be measured based on responses to questions in the following acceptability domains: use attributes, product attributes, side effects and effect on sexual activity. Acceptability scores will be summarised by regimen and time point and compared by regimen at each visit. Scores will be compared using a random effects mixed model to evaluate the effects of regimen and time point.

Safety

Safety data include findings from physical (and pelvic, when indicated) exams, laboratory tests and AEs. AEs will be coded in accordance with the Medical Dictionary for Regulatory Activities.[53] A summary of AEs will be based on treatment-emergent AEs, which include all AEs occurring on or after the first dose. The number and percent of participants for each AE and SAE will be summarised by system organ class and preferred term, overall and by regimen.

Effects of sociocultural and demographic characteristics

Effects of sociocultural and demographic characteristics (eg, age, education, income, employment, relationship status, HIV risk perception, self-efficacy for HIV prevention) on preference, acceptability and adherence will be explored using random effects mixed models. Sociocultural and demographic data will be collected at screening and enrolment.

Qualitative data

Qualitative data will be analysed thematically by researchers at the study sites and the Population Council. We will apply inductive (data driven) and deductive (a priori) codes to the data using software, such as NVivo. Coded data will be synthesised to generate descriptions of behaviours, attitudes and beliefs about the acceptability of the DPP capsule, preference for the DPP or two separate pills, trial experiences and other emergent themes.[54–56]

ETHICS AND DISSEMINATION

Ethics

Both protocols and amendments, informed consent forms and recruitment materials were approved by the Institutional Review Board of the Population Council (New York, New York, USA). The South Africa protocol and amendments (PC 953, V.3.0, 8 June 2022), consent forms, recruitment materials (where relevant) and data collection instruments in English (and isiZulu where relevant) were reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee and South African Health Products Regulatory Authority. The Zimbabwe protocol and amendments (PC952, V.3.0, 17 June 2022), consent forms, recruitment materials (where relevant) and data collection instruments in English (and Shona where relevant) were approved by the Medical Research Council of Zimbabwe, the Medicines Control Authority of Zimbabwe, the Joint Research Ethics Committee of the University of Zimbabwe, the Ministry of Health and Child Care of Zimbabwe, the Chitungwiza City Health Ethics Committee and the Research Council of Zimbabwe. Both studies are being conducted in accordance with the US Code of Federal Regulations, the International Conference for Harmonisation of

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Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice E6 (R2), and local standard operating procedures at each site. Participants are compensated for each visit commensurate with the norms and standards in each country. Both trials are registered on ClinicalTrials.gov (NCT04778527 and NCT04778514). Screening began in August 2022 and data collection ended in January 2024.

DISSEMINATION

The study teams provide periodic updates to their communities and Community Advisory Boards during trial implementation. On completion, results will be presented locally at each site during in-person/virtual meetings with study participants, community advisory boards and other local stakeholders; at national and international conferences; through the DPP consortium; and posted on PrEP Watch. Manuscripts will be submitted to peer-reviewed journals and will be made available via open-access whenever feasible. Data will be uploaded on the ClinicalTrials.gov site, the US Agency for International Development's Data Development Library (South Africa only) and in-country registries, as applicable. Datasets and protocols will be available from the sponsor on request.

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REFERENCES

1 Joint United Nations Programme on HIV/AIDS. UNAIDS DATA 2022. Geneva. 2022. Available: https://www.unaids.org/sites/default/files/media_asset/data-book-2022_en.pdf [Accessed 27 Feb 2023].
2 UNAIDS. Country Factsheets South Africa. 2021. Available: https://www.unaids.org/en/regionscountries/countries/southafrica [Accessed 27 Feb 2023].
3 Eakle R, Venter F, Rees H. Pre-exposure prophylaxis (PrEP) in an era of stalled HIV prevention: can it change the game *Retrovirology* 2018;15:29.
4 Van Damme L, Corneli A, Ahmed K, *et al*. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2012;367:411–22.
5 Marrazzo JM, Ramjee G, Richardson BA, *et al*. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2015;372:509–18.
6 Amico KR, Wallace M, Bekker L-G, *et al*. Experiences with HPTN 067/ADAPT study-provided open-label prep among women in Cape town: Facilitators and barriers within a mutuality framework. *AIDS Behav* 2017;21:1361–75.
7 Calabrese SK, Dovidio JF, Tekeste M, *et al*. HIV pre-exposure prophylaxis stigma as a multidimensional barrier to uptake among women who attend planned parenthood. *J Int AIDS Soc* 2018;79:46–53.
8 Corneli A, Perry B, McKenna K, *et al*. Participants' explanations for Nonadherence in the FEM-prep clinical trial. *J Int AIDS Soc* 2016;71:452–61.
9 Population Council. Adolescent girls and young women's perceptions of oral pre-exposure prophylaxis introduction in Tanzania: findings from implementation science research. DREAMS Tanzania results brief 3. Washington, DC Population Council; 2017.
10 Tenza S, Maboa O, Mampuru L, *et al*. One stone, two birds: perspectives of health care providers (HCP) and women regarding the dual prevention pill (DPP) for pregnancy and HIV prevention in Johannesburg, South Africa, oral presentation at Adherence 2021. Orlando, Florida. 2021.
11 Dandadzi A, Musara P, Mutero P, *et al*. Dual prevention pill (DPP) for HIV and pregnancy prevention: perspectives of Stakeholders in Zimbabwe. oral presentation at Adherence 2021. Orlando, Florida. 2021.
12 Friedland BA, Plagianos M, Savel C, *et al*. Women want choices: opinions from the share.learn.shape global Internet survey about multipurpose prevention technology (MPT) products in development. *AIDS Behav* 2023;27:2190–204.

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13 Hynes JS, Sales JM, Sheth AN, *et al*. Interest in multipurpose prevention technologies to prevent HIV/Stis and unintended pregnancy among young women in the United States. *Contraception* 2018;97:277–84.
14 van der Straten A, Agot K, Ahmed K, *et al*. The tablets, ring, injections as options (TRIO) study: what young African women chose and used for future HIV and pregnancy prevention. *J Int AIDS Soc* 2018;21:e25094.
15 Karim SA, Baxter C, Frohlich J, *et al*. The need for multipurpose prevention Technologies in sub-Saharan Africa. *BJOG* 2014;121:27–34.
16 Vickerman P, Quaife M, Kilbourne-Brook M, *et al*. HIV prevention is not all about HIV–using a discrete choice experiment among women to model how the uptake and effectiveness of HIV prevention products may also rely on pregnancy and STI protection. *BMC Infect Dis* 2020;20:704.
17 Laborde ND, Pleasants E, Reddy K, *et al*. Impact of the Dapivirine vaginal ring on sexual experiences and intimate partnerships of women in an HIV prevention clinical trial: managing ring detection and hot sex. *AIDS Behav* 2018;22:437–46.
18 Beksinska M, Greener R, Smit J, *et al*. A randomized crossover study evaluating the use and acceptability of the SILCS diaphragm compared to vaginal Applicators for vaginal GEL delivery. *AIDS Behav* 2018;22:127–32.
19 IPSOS. Assessing the potential of Mpts in Uganda, Nigeria and South Africa. Report commissioned by the Bill and Melinda gates foundation. 2014. Available: http://www.theimpt.org/resource-results/35-reports/202-assessing-the-potential-of-mpts-in-south-africa-uganda-and-nigeria [Accessed 9 Feb 2021].
20 ESHRI Capri Workshop Group. Simultaneous prevention of unintended pregnancy and STIs: a challenging compromise. *Hum Reprod Update* 2014;20:952–63.
21 Exavery A, Kanté AM, Jackson E, *et al*. Role of condom negotiation on condom use among women of reproductive age in three districts in Tanzania. *BMC Public Health* 2012;12:1097.
22 Moore L, Beksinska M, Rumphs A, *et al*. Knowledge, attitudes, practices and behaviors associated with female condoms in developing countries: A Scoping review. *OAJC* 2015;6:125.
23 Peasant C, Sullivan TP, Weiss NH, *et al*. Beyond the Syndemic: condom negotiation and use among women experiencing partner violence. *AIDS Care* 2017;29:516–23.
24 IMPT for Reproductive Health. MPT product development database. *MPT Prod Dev Database* 2022. Available: https://mpts101.org/ [Accessed 5 Dec 2022].
25 Viatris. Viatris. Available: https://www.viatris.com/en [Accessed 27 Feb 2023].
26 The DPP Consortium. Frequently asked questions about the dual prevention pill. 2021. Available: https://www.prepwatch.org/wp-content/uploads/2021/09/FAQS-about-the-DPP.pdf [Accessed 27 Feb 2023].
27 Dragoman MV, Tepper NK, Fu R, *et al*. A systematic review and Meta-Analysis of venous thrombosis risk among users of combined oral contraception. *Int J Gynaecol Obstet* 2018;141:287–94.
28 Roach REJ, Helmerhorst FM, Lijfering WM, *et al*. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database Syst Rev* 2015;2015:CD011054.
29 Tepper NK, Curtis KM, Cox S, *et al*. Update to US medical eligibility criteria for contraceptive use, 2016: updated recommendations for the use of contraception among women at high risk for HIV infection. *MMWR Morb Mortal Wkly Rep* 2020;69:405–10.
30 Fonner VA, Dalglish SL, Kennedy CE, *et al*. Effectiveness and safety of oral HIV Preexposure prophylaxis for all populations. *AIDS* 2016;30:1973–83.
31 Curtis KM, Hannaford PC, Rodriguez MI, *et al*. Hormonal contraception and HIV acquisition among women: an updated systematic review. *BMJ Sex Reprod Health* 2020;46:8–16.
32 Nanda K, Stuart GS, Robinson J, *et al*. Drug interactions between hormonal contraceptives and Antiretrovirals. *AIDS* 2017;31:917–52.
33 Kearney BP, Mathias A. Lack of effect of tenofovir disoproxil fumarate on pharmacokinetics of hormonal contraceptives. *Pharmacotherapy* 2009;29:924–9.
34 Schöller-Gyüre M, Kakuda TN, Woodfall B, *et al*. Effect of steady-state Etravirine on the pharmacokinetics and pharmacodynamics of ethinylestradiol and Norethindrone. *Contraception* 2009;80:44–52.
35 Chersich MF, Wabiri N, Risher K, *et al*. Contraception coverage and methods used among women in South Africa: a national household survey. *S Afr Med J* 2017;107:307.
36 National Department of Health. *South Africa Demographic and Health Survey 2016: Report, National Department of Health (NDoH), Statistics South Africa (Stats SA), South African Medical Research Council (SAMRC), and ICF*. 2019. Available: https://dhsprogram.com/pubs/pdf/FR337/FR337.pdf [accessed 17 Oct 2023].
37 Family Planning 2020. Zimbabwe: actions for acceleration. 2018. Available: https://www.fp2030.org/zimbabwe/documents/ [Accessed 9 Feb 2021].
38 Radovich E, Dennis ML, Wong KLM, *et al*. Who meets the contraceptive needs of young women in sub-Saharan Africa. *J Adolesc Health* 2018;62:273–80.
39 Centers for Disease Control and Prevention. US public health service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2017 update: a clinical practice guideline. 2018. Available: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf [Accessed 9 Feb 2021].
40 PrEPWatch. Dual prevention pill. Prepwatch- an initiative of AVAC. 2022. Available: https://www.prepwatch.org/products/dual-prevention-pill/ [Accessed 27 Feb 2023].
41 City of Johannesburg. City of Johannesburg profile on the HIV epidemic trends to accelerate progress of HIV response [2018 – 2020]. 2020. Available: https://fasttrackcitiesmap.unaids.org/wp-content/uploads/2021/04/19.-COJ-Report-Profile-.pdf [Accessed 21 Apr 2023].
42 Ministry of Health and Child Care (MoHCC). Zimbabwe population-based HIV impact assessment 2020 (ZIMPHIA 2020)-Final report. Harare MoHCC; 2021. Available: https://phia.icap.columbia.edu/wp-content/uploads/2023/09/010923_ZIMPHIA2020-interactive-versionFinal.pdf [Accessed 27 Feb 2023].
43 Gill K, Happel A-U, Pidwell T, *et al*. An open-label, randomized crossover study to evaluate the acceptability and preference for contraceptive options in female adolescents, 15 to 19 years of age in Cape town, as a proxy for HIV prevention methods (Uchoose). *J Int AIDS Soc* 2020;23:e25626.
44 B-Wise. Is PrEP for me? B-Wise; 2022. Available: https://www.bwisehealth.com/is-prep-for-me/ [Accessed 27 Feb 2023].
45 Segal K, Harris DM, Carmone A, *et al*. Equipping providers to offer novel Mpts: developing counseling messages for the dual prevention pill in clinical studies and beyond. *Front Reprod Health* 2023;5:1155948.
46 Zheng J-H, Guida LA, Rower C, *et al*. Quantitation of tenofovir and Emtricitabine in dried blood spots (DBS) with LC-MS/MS. *J Pharm Biomed Anal* 2014;88:144–51.
47 US Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events. CORRECTED version 2.1. 2017. Available: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf [Accessed 27 Feb 2023].
48 Department of Health, Republic of South Africa, Phila, NDP 2030. South African guidelines for the provision of pre-exposure prophylaxis (PrEP) to persons at substantial risk of HIV infection. 2020. Available: https://www.prepwatch.org/resources/south-african-guidelines-prep-2020/ [Accessed 27 Feb 2023].
49 Zimbabwe Ministry of Health and Child Care. Implementation plan for HIV pre-exposure prophylaxis in Zimbabwe 2018-2020. 2018. Available: https://www.prepwatch.org/wp-content/uploads/2018/07/Implementation_Plan_PrEP_Zim2018.pdf [Accessed 9 Feb 2021].
50 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (Redcap)—A Metadata-driven methodology and Workflow process for providing Translational research Informatics support. *J Biomed Inform* 2009;42:377–81.
51 Harris PA, Taylor R, Minor BL, *et al*. The Redcap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
52 Corneli AL, Deese J, Wang M, *et al*. FEM-prep: adherence patterns and factors associated with adherence to a daily oral study product for pre-exposure prophylaxis. *J Acquir Immune Defic Syndr* 2014;66:324–31.
53 MedDra. Welcome to Meddra | Meddra. Meddra- MED. Dict. Regul. Act. 2023. Available: https://www.meddra.org/ [Accessed 27 Feb 2023].
54 Miles MB, Huberman AM. *Qualitative data analysis: An expanded sourcebook*. Sage, 1994.
55 Hsieh H-F, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res* 2005;15:1277–88.
56 Patton MQ. *Qualitative evaluation and research methods*. SAGE Publications, Inc, 1990.

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