Project Brief: Dual Prevention Pill (DPP) for HIV and Pregnancy Prevention

Full Title of Study/Programme	**Dual Prevention Pill (DPP) for HIV and Pregnancy Prevention**
Technical Focus Area/Key Words	HIV and Pregnancy Prevention, multipurpose prevention technology (MPT), oral PrEP, COC
Rationale	In South Africa (SA), women (including adolescent girls and young women [AGYW]) experience high rates of incident HIV infection. The 2017 South African National household-based HIV Prevalence, Incidence, Behaviour and Communication Survey reported decreased national HIV incidence, including among women aged 15-49 years (estimate 0.93 per 100 woman-years from 2.28 in 2015). However, two years later, the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial of contraception and HIV-1 risk demonstrated an alarming quadrupling of incidence rates across women (ages 15-35 years) in SA, with an HIV incidence of 5.03 per 100 woman-years of follow-up among women aged 18-20. Thus, despite significant improvements in access to antiretroviral therapy (ART) to treat and prevent HIV and a decline in HIV incidence in the general population in SA, women of reproductive age -remain vulnerable to HIV. Additionally, AGYW are considered a priority population as an estimated 13% annual increase in new infections leading to 3.5 million new infections by 2030 is projected in the absence of improved delivery of effective HIV prevention and care. The women who are most likely to acquire infection are typically from socio-economically deprived communities with high background HIV-prevalence rates, with limited or no schooling, who engage in high-risk behaviors, and/or have a history of sexually transmitted infections (STIs)/reproductive tract infections (RTI) and unintended pregnancies. Combining oral PrEP with a COC is likely to be the fastest route to an approved cMPT, that protects against unintended pregnancy and HIV, because it combines two licensed, marketed drugs. The Population Council is developing a DPP regimen based on a 28-day contraceptive regimen – a COC pill containing 150 mcg of LNG and 30 mcg of ethinyl estradiol [EE]) co-formulated with Truvada® (300 mg of tenofovir disoproxil fumarate [TDF], 200 mg of emtricitabine (FTC)] for HIV PrEP. Once produced the DPP will protect against pregnancy and HIV (but not other STIs). COCs are widely available and are used by 11% of current modern contraceptive users in SA. We hypothesize that the DPP, which will combine PrEP and a COC in a single tablet, could greatly increase PrEP uptake and adherence.
Primary Objectives	**Component 1:**

	• To understand women's interest in using a DPP and gather input regarding informational materials needed for DPP introduction • To assess DPP acceptability among providers and explore their training needs and recommendations for appropriate service-delivery settings; and • To inform the implementation plan for the planned randomized clinical crossover study in Component 2. **Component 2:** **Adherence** • To compare adherence to the DPP (Regimen A) versus 2 separate pills (Regimen B) among women using each regimen daily for three 28-day menstrual cycles during the CROSSOVER period among women aged 16-40 in Johannesburg, SA • To compare adherence among women who choose the DPP (Regimen A) versus adherence among women who choose 2 separate pills (Regimen B), each taken daily during the CHOICE period. • To assess and compare self-reported **adherence** to Regimen A versus Regimen B among women during the CROSSOVER period, and to the chosen method during the CHOICE period. **Preference** To determine if more women choose Regimen A versus Regimen B for the CHOICE period.
Secondary Objectives	Component 1 - Not applicable Component 2: **Safety** • To assess and compare the **safety** of Regimen A versus Regimen B among women using each regimen for three 28-day cycles during the CROSSOVER period, and the safety of Regimen A versus Regimen B among women choosing each regimen during the CHOICE period. **Acceptability** • To assess the **acceptability** of Regimen A versus Regimen B for prevention of HIV and unintended pregnancy among 16-40-year-old women who use each regimen for three 28-day cycles during the CROSSOVER period. • To assess if **pre-use opinions** are associated with actual experiences and preferences after using each regimen
Tertiary Objectives	Component 1 - Not applicable Component 2:

	Adherence To assess and compare adherence to Regimen A versus Regimen B during the CROSSOVER period, and during the CHOICE period.
Primary Endpoints/Outcomes	Component 1 - Not applicable Component 2: **Adherence** • Level of TDF in dried blood spots (DBS) by regimen and overall at monthly visits during the CROSSOVER period. • Level of TDF in DBS by regimen and overall at monthly visits during the CHOICE period. • Self-reported adherence in ACASI interviews and by pill count at monthly visits during the CROSSOVER and CHOICE periods. **Preference** Proportion of women who choose to use Regimen A (DPP) versus Regimen B (2 separate pills) for the CHOICE period.
Secondary Endpoints/Outcomes	Component 1 - Not applicable Component 2: **Safety** • Number of adverse events overall and by regimen (including social harms, drug side effects, pregnancy and HIV seroconversion) **Acceptability** • Scores by regimen and overall, as measured using a self-administered (CASI) quantitative acceptability measurement tool at the CROSSOVER visit, the start of the CHOICE period, and the end of the study. • Proportion of women whose pre-use preference matches post-use experience based on a self-administered (CASI) questionnaire at baseline and at the end of the CROSSOVER period. • Evaluation of factors associated with acceptability and adherence based on ACASI interviews, and in-depth exit
Tertiary Endpoints/Outcomes	Component 1 - Not applicable Component 2: **Adherence** Positive or negative results on urine test assessing presence of TDF at monthly visits during the CROSSOVER period, and during the CHOICE period.
Study Design	**Component 1:** Qualitative study with in-depth interviews and focus group discussions

	Component 2: The design is a randomized, open-label, parallel group, 2-way crossover study among 96 women to compare the adherence, acceptability, and preference of a single over-encapsulated pill (dual prevention pill [DPP]) containing a pre-exposure prophylaxis (PrEP) pill (FTC/TDF) and a combined oral contraceptive pill (COC) versus 2 separate tablets. At enrollment, participants will be randomly assigned to the sequence of regimens – DPP or 2 separate tablets and will use each regimen for three consecutive 28-day cycles (corresponding to the 28-day COC regimen). At the end of the crossover period, women will choose which regimen they wish to use for up to six additional months.
Study arms	**Component 1**: Not applicable **Component 2:** FTC/TDF Tablet as oral PrEP and EE/LNG Tablet as COC
Study population	**Component 1:** • Women who currently use COC and those who do not use COC, stratified by age (16-17, 18-24 and 25-40 years) • Cadres of Health Care Providers (clinicians, nurses, and lay counselors) from 2 types of service delivery settings (family planning/general health clinics and HIV counseling and testing centers/PrEP delivery sites) **Component 2:** • Healthy, sexually active, HIV-seronegative, non-pregnant women aged 16-40 years old (inclusive) who are using COCs as their contraceptive method and are at risk of HIV.
Study sample size	**Component 1:** • ≤ 96 participants for focus group discussions • 20 participants for IDIs **Component 2:** • 96 participants
Follow up/duration	**Component 1:** Single/once off visit **Component 2:** Approximately 1 year, including screening
Study/Programme sites	Hillbrow, Johannesburg
Study/Programme duration	In development
Intervention	**Component 1:** Not applicable **Component 2:** FTC/TDF Tablet as oral PrEP and EE/LNG Tablet as COC
Operations	The study team, in coordination with the funders will define key metrics
Investigators	**Wits RHI** Dr. Thesla Palanee-Phillips, Co-Principal Investigator

	Krishnaveni Reddy, Co- Principal Investigator Dr Yuthika Naidoo, Co- Principal Investigator **Population Council** Barbara Friedland, Principal Investigator Dr Sanyukta Mathur, Co- Principal Investigator
Other Partners & Collaborators	Population Council Mylan Laboratories Limited PCI Pharma Services Center for Biomedical Research
Sponsors/Donors	United States Agency For International Development (USAID)
Linked Sub Studies and post grad projects	Not applicable
Publications/key presentations to date	Estimating the market size for a dual prevention pill: adding contraception to pre-exposure prophylaxis (PrEP) to increase uptake published in BMJ Sex Reprod Health on 31 July 2020
Progress Update as at 11 Nov 20	Ethics approval in place for formative research protocol, informed consent forms and interview guides. Ethics submission for crossover protocol done on O4 November 2020 and SAHPRA submission on 06 November 2020
Frequency of donor narrative report	To be decided
Overall Study/Project Contact	Dr. Thesla Palanee-Phillips (tpalanee@wrhi.ac.za)
Briefing owner and date	Lebogang Maila, 23 October 2020