A Pilot Randomized Controlled Trial to Assess a Model of Decentralised STI-Self Testing and Risk Self-Assessment Among Adolescent Girls and Young Women in South Africa to Trigger PrEP Re-start

Short name:
PALESA: PrEP restart for **A**do**le**scent girls and young women using **S**TI **S**elf Testing and **A**ssessment of risk

Version 1.1

13 October 2022

Funding Agency

US National Institute of Mental Health

Grant Number: 1R34MH126743 - 01

Key Collaborating Organizations:

Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Faculty of Health Sciences, Johannesburg, South Africa

Division of Infectious Diseases, Department of Medicine, University of Alabama, Birmingham, Alabama, USA

Division of Global Health and Infectious Disease Epidemiology, Department of Epidemiology & Biostatistics, University of California, San Francisco

PALESA: PrEP restart for Adolescent girls and young women using STI Self Testing and Assessment of risk

Table of Contents

List of Abbreviations

AG	Adolescent Girls
AGYW	Adolescent Girls and Young Women
ART	Antiretroviral therapy
CAB	Community Advisory Board
CLO	Community Liaison Officer
COVID	Coronavirus disease
CRF	Case Report Form
CT	*Chlamydia trachomatis*
DBS	Dried Blood Spot
GCP	Good Clinical Practice
GDOH	Gauteng Provincial Depart of Health
ECHO	Evidence for Contraceptive Options and HIV Outcomes
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
HBM	Health Belief Model
HIV	Human Immunodeficiency Virus
HCP	Healthcare Provider
HREC	Human Research Ethics Committee
HSP	Human Subjects Protection
IA	Informed Assent
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference Harmonization
IDI	In-Depth Interview
IPV	Intimate Partner Violence
IRBs	Institutional Review Boards
NDoH	National Department of Health
NG	*Neisseria gonorrhea*
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
PI	Principal Investigator
POC	Point-Of-Care
PPE	Personal Protective Equipment
PrEP	Pre-Exposure Prophylaxis
PTID	Participant Identifier
RC	Research Centre
RCT	Randomized Controlled Trial
SA	South Africa
SA NDoH	South African National Department of Health
SH	Social Harms
SOP	Standard Operating Procedure
SRH	Sexual and Reproductive Health
STI	Sexually Transmitted Infection
UAB	University of Alabama, Birmingham
UCSF	University of California, San Francisco
WHO	World Health Organization
Wits RHI	Wits Reproductive Health and HIV Institute

PALESA: PrEP restart for Adolescent girls and young women using STI Self Testing and Assessment of risk

Investigators Signature Page

Version 1.1; 13 October 2022

Funded by:
US National Institute of Mental Health

Wits Reproductive Health and HIV Institute (Wits RHI) Research Centre Clinical Research Site; Johannesburg, South Africa

The signature below constitutes the approval of this protocol and any attachments and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to all applicable legal and regulatory requirements and regulations as well as International Conference Harmonization (ICH) and South African Good Clinical Practice (GCP) guidelines.

We, as the Principal Investigator/Co-Principal Investigator/s, agree to conduct this study in full accordance with the provisions of this protocol. Publication of the results of this study will be governed by Wits RHI, University of Alabama, Birmingham (UAB) and University of California, San Francisco (UCSF) policies.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contributionto the study.

Principal Investigator:

Signature	Name: Thesla Palanee-Phillips
	Title: Director of Clinical Trials, MMedSci, PhD, MSc
	Date:

Co-Principal Investigator/s:

Signature	Name: Krishnaveni Reddy
	Title: Technical Head: Clinical Trials, MMedSci
	Date:

Signature	Name: Renee Heffron
	Title: Associate Professor
	Date:

Key Roles and Contact Details

PRINCIPAL INVESTIGATORS		
Name: Organization: Address:	Thesla Palanee-Phillips, MMedSci, PhD, MSc Wits Reproductive Health and HIV Institute No 7 Esselen Street, Hillbrow, Johannesburg, South Africa, 2000	Tel: +27 113585471 Mobile: +27 837833574 Fax: +27 865541093 E-mail: tpalanee@wrhi.ac.za
Name: Organization: Address:	Krishnaveni Reddy, MMedSci, Wits Reproductive Health and HIV Institute No 7 Esselen Street, Hillbrow, Johannesburg, South Africa, 2000	Tel: +27 113585470 Mobile: +27 836446667 E-mail: kreddy@wrhi.ac.za
Name: Organization: Address:	Renee Heffron, MPH, PhD University of Alabama Birmingham Department of Medicine BDB 420 1720 2nd Ave South Birmingham, AL 35233 United States	Tel: +1 205 934 7821 E-mail: rheffron@uabmc.edu
CO-INVESTIGATORS		
Name: Organization: Address:	Jennifer Velloza, PhD, MPH Division of Global Health and Infectious Disease Epidemiology, Department of Epidemiology & Biostatistics, University of California, San Francisco (UCSF) 550 16th Street, Second Floor San Francisco, CA 94158	Tel: (415) 476-2300 E-mail: Jennifer.Velloza@ucsf.edu
Name: Organization: Address:	Siyanda Tenza, B. Soc.Sci Wits Reproductive Health and HIV Institute No 7 Esselen Street, Hillbrow, Johannesburg, South Africa, 2000	Tel: +27 113585424 Mobile: +27 647537439 E-mail: stenza@wrhi.ac.za

PALESA: PrEP restart for Adolescent girls and young women using STI Self Testing and Assessment of risk

Summary

The PALESA study aims to determine the feasibility of conducting a randomized controlled trial (RCT) to determine the impact of decentralized sexually transmitted infection (STI) point of care (POC) self-testing and risk self-assessment interventions to trigger pre-exposure prophylaxis (PrEP) re-start among adolescent girls and young women (AGYW) in South Africa at potential ongoing risk of re- acquiring STIs and HIV**.**

This overall study comprises two components that include a formative research study enrolling ~60 participants for qualitative in-depth interviews (IDIs) and a prospective cohort study (Pilot randomized controlled trial - RCT) enrolling 50 AGYW with both clinical, diagnostic laboratory and nested qualitative methodologies. These components will be implemented under two distinct protocols:

- **Formative:** To qualitatively explore, using IDIs with the below stated populations, the barriers to and facilitators of PrEP uptake and experiences with PrEP discontinuation, how AGYW self-assess their risk for HIV/STIs, perspectives on re-starting PrEP, and willingness to use at-home STI testing and behavioural risk assessments to trigger re-engagement in PrEP use.
  - ~ 20 Sexually active AGYW (aged 18-20 years) who were previously using PrEP and have discontinued use within the past 2 years (when they were 16-18 years old). Both oral Truvada and the Dapivirine vaginal ring-based PrEP options apply
  - ~ 20 Parents/legal guardians of AGYW who used PrEP (including oral PrEP and the Dapivirine vaginal ring) when they were between the ages of 16 to 24 years (Inclusive of current and past use) will be recruited from past trials and the general community.
  - ~ 20 Healthcare providers (HCP) from local adolescent clinics and PrEP clinics that serve 16-18 years old AGYW.

  This formative research study is currently in implementation and is being conducted through a protocol that was reviewed and approved by the Wits HREC (HREC Ref. No. 211017). Findings from this study will inform aspects of the RCT.

- **Pilot RCT:** To establish the feasibility of conducting a randomized controlled trial among AGYW in South Africa to determine the impact of decentralized or at-home STI testing [(for *Neisseria gonorrhea* (NG), *Chlamydia trachomatis* (CT) and *Trichomonas vaginalis* (TV)] on restarting PrEP relative to a self-administered behavioural risk assessment.
  Nested qualitative interviews: To assess AGYW experiences of at-home STI testing, behavioural risk assessment, and re-starting PrEP while participating in the pilot trial through exit interviews.

This protocol describes the research procedures required for the RCT component

Full Title:	A Pilot Randomized Controlled Trial to Assess a Model of Decentralised STI-Self Testing and Risk Self-Assessment Among Adolescent Girls and Young Women in South Africa to Trigger PrEP Re-start
Short Title:	**P**rEP restart for **A**do**le**scent girls using **S**elf STI Testing and **A**ssessment of risk (PALESA)
Funders:	US National Institute of Mental Health
Design:	Pilot RCT with nested qualitative component (In-Depth Interviews at study exit))
Population & Sample Size:	Approximately 50 AGYW aged 16-20, non-pregnant, HIV negative who discontinued PrEP use within the past 6 months
Study Site:	Wits Reproductive Health and HIV Institute (Wits RHI) Research Centre Clinical Research Site (RC CRS)

Objectives	**Objective 1:** To determine the feasibility and acceptability of conducting a RCT among South African AGYW to determine the impact of STI self-testing coupled with a self-administered behavioural risk assessment on restarting PrEP relative to a self-administered behavioural risk assessment only **Objective 2:** To assess AGYW acceptability of and experiences with use at-home STI testing, self-administered behavioural risk assessment, and re-starting PrEP while participating in the pilot RCT
Primary Outcomes	**Objective 1:** Feasibility of study implementation including attainment of operational metrics as per below o Recruitment target achieved o High retention rate maintained (≥ 90%) o Participants are able to assess their risk of acquiring HIV by self-testing for STIs and/or completing a self-administered behavioural risk assessment o Frequency of oral PrEP restarting o PrEP continuation 1 month after re-start o High frequency of all research procedures are completed **Objective 2:** Data collected on experiences of at-home STI testing, self-administered behavioural risk assessment, and re-starting PrEP while participating in the pilot trial

1. Introduction

In South Africa (SA), adolescent girls and young women (AGYW) experience high rates of incident HIV infection in settings with high background HIV prevalence. The Evidence for Contraceptive Options and HIV Outcomes (ECHO) clinical trial (1) and HVTN 702 (2) studies demonstrated an alarming HIV incidence rate of 5.03 per 100 woman years (95% CI 4.1-6.12) among females ages 18-20 years (3) , 3.3 between ages 18-35 years (2), and as high as 6.8 among females ages 18-35 years at the ECHO site with highest incidence in South Africa (**Table 1**). In the ECHO trial, of 12,750 women screened, 1,540 (12%) were ineligible due to an HIV-positive serostatus, indicating that many women in the trial communities were already living with HIV by the time they reach early adulthood (1). Thus, despite significant improvements in access to antiretroviral therapy (ART) to both treat and prevent HIV, the introduction of pre-exposure prophylaxis (PrEP), and a decline in HIV incidence in the general population, AGYW in SA remain highly vulnerable to HIV. Young women most likely to acquire infection are typically from socio-economically deprived communities with high background HIV-prevalence rates, have limited schooling, engage in high-risk behaviours, and/or have a history of sexually transmitted infections (STI) (4). In addition, new partnerships and partnership concurrency are features of sexual behaviour often linked to newly acquired HIV infections (**Table 2**)(3) .

Table 1. HIV incidence among South African women in the ECHO trial (3)

Age range (years)	HIV incidence/100 woman years)
18-20 (n=1493),	5.03 (95% CI 4.1-6.12)
21-30 (n= 3470)	4.72 (95% CI 4.13-5.36)
31-35 (n= 535)	1.67 (95% CI 0.86-2.91)

Table 2. STI and behavioural factors associated with incident HIV infection, ECHO Trial 2015-2018 (3)

	HR (95% CI)	p-value
Age ≤24	1.31 (0.99-1.72)	0.055
Positive for *N. gonorrhea* at any visit	1.42 (1.11-1.81)	0.005
Positive for HSV-2 at baseline	1.49 (1.18-1.90)	0.001
Fewer than nine coital acts reported at baseline	1.16 (0.91-1.48)	0.222
New or multiple partners	1.6 (1.16-2.21)	0.004
Does not live with partner	1.39 (0.92-2.10)	0.118

There is clear evidence that curable bacterial STIs increase the risk of HIV transmission (5, 6) and the syndemic nature of concomitant HIV and STI infections through condomless receptive vaginal sex with male partners exacerbates individual prognoses and burdens of disease (7). Sub-Saharan Africa and South Africa itself have high prevalence rates of *Chlamydia Trachomatis* (CT), *Neisseria Gonorrhea* (NG) and *Trichomonas vaginalis* (TV) among women and men aged between 15 and 49 (8). A meta-analysis published in 2018 of over 37 000 women across 18 HIV prevention studies(9) estimated relatively high STI prevalences among women aged 15–24 years in clinic/community-based populations in South Africa **(Table 3)**. Additionally, the ECHO trial that enrolled 7829 women in Eswatini, Kenya, South Africa and Zambia found 18% of all participants had CT and 5% had NG at entry into the study (baseline) and despite quarterly visit attendance and clinical management of any reported signs and symptoms of possible STIs, 15% had incident CT at the final study visit and 5% had incident NG. Among participants restricted to just the South African sites, baseline and final visit CT prevalence ranged from 20%-28% and 12-20% respectively while NG baseline and final visit CT prevalence ranged from 4-9% indicating STI persistence or high rates of reinfection in this population. Women aged 24 and younger were more likely to have CT or NG compared with women aged 25 and older at both baseline and the final visit(10). Most recently, the MTN-034/REACH study demonstrated alarmingly high STI prevalence and incidence among younger AGYW (aged 16-21 years) in South Africa, Uganda and Zimbabwe. STI incidence per 100 person-years was 49.1 (95% CI 39.3-58.8) for CT, 21.3 (95% CI 14.8-27.9) for NG and 18.8 (95% CI 12.4-25.1) for TV. Incidence for these STIs was higher among AGYW who were diagnosed with that STI at baseline, despite receiving treatment, compared to those who were STI-negative as baseline (Under embargo) again speaking to possible persistence off or re-infection with STIs. These STIs can have devastating effects on sexual, reproductive, and general health causing acute urogenital conditions such as cervicitis, urethritis, vaginitis and genital ulceration, and some of the etiological agents also infect the rectum and pharynx

Table 3: Estimated STI prevalence ranges among women aged 15–24 years in clinic/community-based populations in South Africa (7)

	Estimated Prevalence Range in Individual Studies	Summary Estimate
CT	8.0% to 20.6%	15.1% [95% CI: 12.7%, 17.8%];I2 = 82.3%
NG	1.4% to 8.9%	4.6% [95% CI: 3.3%, 6.4%];I2 = 82.8%
TV	3.1% to 20%	7.9% [95% CI: 5.9%, 10.5%];I2 = 88%

through receptive anal and oral sex. CT and NG can cause serious short- and long-term complications, including pelvic inflammatory disease, ectopic pregnancy, infertility, chronic pelvic pain and arthritis, and they can be transmitted during pregnancy or delivery to the foetus/new-born. TV has additionally been associated with adverse pregnancy outcome, preterm birth or premature labor, low birth weight, premature rupture of membranes, greater risk of tubal infertility, and increased risk of cervical cancer (11). Significant social harms (negative consequences that manifest in social, psychological, or physical ways (12, 13)) including experiences with stigma, stereotyping, vulnerability, shame and intimate partner violence (IPV), are also frequently cited as downstream effects of STI diagnoses (14). As such effective identification, diagnosis and timely management of STIs remains among the most important global health challenges within both developing countries and developed countries (15).

PrEP has potential to impact population-level HIV incidence. Clinical trials and demonstration projects of oral PrEP that enrolled a high proportion of young African women have shown that PrEP adherence and persistence in PrEP programs are common challenges for AGYW <25 years old (16) and younger adolescent girls (AGYW, ages ≤18 years). The HPTN 082/HERS study demonstrated oral PrEP uptake of 99% in Cape Town and 88% in Johannesburg, South Africa among young women aged 16-25 years, with 83.6% of participants having detectable levels of tenofovir that declined significantly after month 3 and was associated with change to quarterly visit follow-up (17). In the recently completed POWER study, ~96% of women in South Africa initiated oral PrEP yet only 25% of these women were engaged with the study 1 month later. Among those who discontinued oral PrEP, 26% eventually re-started oral PrEP and nearly one-quarter of these women went on to use oral PrEP for at least 6 months (personal communication, Connie Celum, Study PI). Thus, although oral PrEP initiation may be high, drop out and discontinuation of oral PrEP use are frequent. PrEP use may however be non-continuous and still effective, since HIV risk fluctuates(18). In oral PrEP demonstration projects, we are seeing women re-start oral PrEP(19, 20), potentially when their perceived risk for HIV returns however it remains to be better understood how to trigger them to stop and re-start oral PrEP based on their oscillating levels of potential risk of HIV exposure.

In addition to daily oral PrEP, the dapivirine vaginal ring (referred to hereafter as the “ring”) will soon be another HIV prevention option in South Africa for adult women at substantial risk of HIV infection (21).The ring is made out of a silicone matrix containing the antiretroviral-dapivirine that slowly releases into the vagina over a one-month period and must be in place for at least 24 hours to help protect a woman against HIV (22). The ring was tested by the Microbicide Trials Network (MTN) and International Partnership for Microbicides (IPM) in two phase III trials (MTN-020/ASPIRE study and IPM-027/Ring Study) (23, 24) and two corresponding open label extension studies (MTN-025/HOPE study and IPM-032/DREAM study) (25, 26) over a six year period. The two clinical trials demonstrated the ring to be well tolerated and to reduce HIV risk by approximately 37% (ASPIRE) and 31% (Ring Study) respectively, with modelling from open-label extension trials suggesting up to 63% risk reduction with increased use (25, 27, 28). The monthly use nature of the ring allows for higher adherence potentially leading to higher HIV protection in the real world. At the time of this review the ring was approved by the national medicines regulatory authorities in Zimbabwe (29) and South Africa (30). Similarly, to oral PrEP, the ring needs to be used per its dosing schedule when women are at risk to HIV and as such has been included in this research. Hereafter the term PrEP will refer to both oral PrEP and ring.

These oral and vaginal PrEP options prevent HIV only and not STIs and until a multipurpose technology (MPT) product that prevents both becomes available, methods for early identification and management of STIs so they do not increase risk of HIV are urgently needed. Empowering young people to predict and raise self-awareness of their own periods of risk associated with condomless sex is crucial**.** Adolescence is the period between childhood and adulthood encompassed by changes in physical, psychological, and social development (31). These changes make this period a time of exploration, vulnerability and adjustment (32) characterized at times by sub-optimal decision making and actions that are associated with an increased incidence of unintentional injuries, violence, substance abuse, unintended pregnancy, and STIs (33). Additionally, in the South African context, there is exposure to harmful social norms which make it increasingly difficult to negotiate condom use, partnership dynamics and boundaries. Through this transition to adulthood, adolescents develop levels of maturity associated with growing personal autonomy and are most likely the best advocates and custodians of their sexual health if they have the tools and the support

they need to make safer choices (34). In high HIV incidence settings, adolescents may be empowered to make informed decisions to consider using PrEP in ways that match their patterns of possible exposure to HIV. This should include guidance on knowing how to practically assess their perceived versus actual sexual health risk, when to seek out clinical care and when to consider using HIV prevention options, including condoms and PrEP. Creating awareness of sexual health through STI testing is one way of assessing risk for HIV and other STIs as they are transmitted sexually through the same route. Furthermore, data from trials with AGYW indicate access to STI testing was considered a benefit and a popular reason for wanting to join studies (35). Therefore, using STIs detection as a marker for HIV risk may be suitable to trigger PrEP resumption.

The concept of self-testing has been a trail blazer in the HIV testing world as it alleviates stigma associated to testing and offers the convenience of discrete testing external to a public facility or less private setting. HIV self-testing kits give people autonomy to decide when and where to test in private and on their own terms (36, 37). Uptake, and by proxy, acceptability, of HIV self-testing among adolescents has been shown to be high in initiatives in East and southern Africa and has been described as having potential to revolutionize HIV testing among young people (38).Self-testing options for common manageable STIs, such as NG, CT and TV would appear the next logical innovation needed to facilitate discrete and independent assessment of risk and timely management of STIs, especially for possible asymptomatic infections following high risk exposures.

Although HIV self-testing kits are increasing in popularity, self-testing options for NG, CT and TV are not yet available. There is however potential for AGYW to use commercially available NG, CT and TV rapid test kits to self-test for STI, based on recent studies showing high rates of acceptability and feasibility of self-collected swabs for STI testing (39-41). This would support the World Health Organization's (WHO) global health sector strategy on STIs, which emphasises the need for identifying accessible interventions to ensure that people use the quality health services they need without suffering financial hardship or stigmatisation (42). Self-testing as an approach for STI testing for AGYW could also contribute to the achievement of the United Nations Sustainable Development Goals, including universal health coverage and integrated services for sexual and reproductive health, which requires achieving early diagnosis of STIs and linkage to effective treatment (43). Importantly, for AGYW, STI self-testing in a private setting meets the needs of their cognitive and social development space and allows the opportunity for self-care for health promotion as recommended by WHO.(44)

This protocol seeks to leverage the known acceptability of HIV self-test kits to test the impact of STI self-testing on PrEP re-start among AGYW. This pilot trial provides an opportunity to test a strategy that is de-medicalized and decentralized and compare outcomes between AGYW randomized to use a phone-based behavioural questionnaire coupled with the self-test kits to assess their risk of HIV acquisition relative to a phone-based behavioural questionnaire only that is more consistent with the standard of care (SOC). The approach is grounded in the Health Belief Model, particularly the "cues to action" theory, and the well-documented importance of promoting autonomy during AGYW sexual development. We have selected the narrow age range of 16–18-year-old AGYW to facilitate focus on those who are not yet considered as "adults," and who lack complete autonomy and face unique challenges accessing services without perceptions of being discriminated against or judged for being sexually active. Data have shown that AGYW are among the most at risk for HIV in South Africa, that persistence on PrEP through intermittent periods of heightened risk is critical, and that better understanding of how to trigger awareness of these risk periods are crucial. Recognizing that discontinuation is common and may often be very appropriate given partnership dynamics and potential for HIV exposure, a focus on mechanisms to trigger PrEP re-start addresses the main constraint with PrEP use that AGYW face. The data from this pilot RCT will have potential to inform a full-scale RCT and inform policy on PrEP re-start among AGYW using self-identified STIs as a marker of heightened risk.

2. Study Aims

To determine the feasibility of conducting a randomized trial among South African AGYW to determine the impact of at-home STI testing on restarting PrEP relative to a self-administered behavioural risk assessment

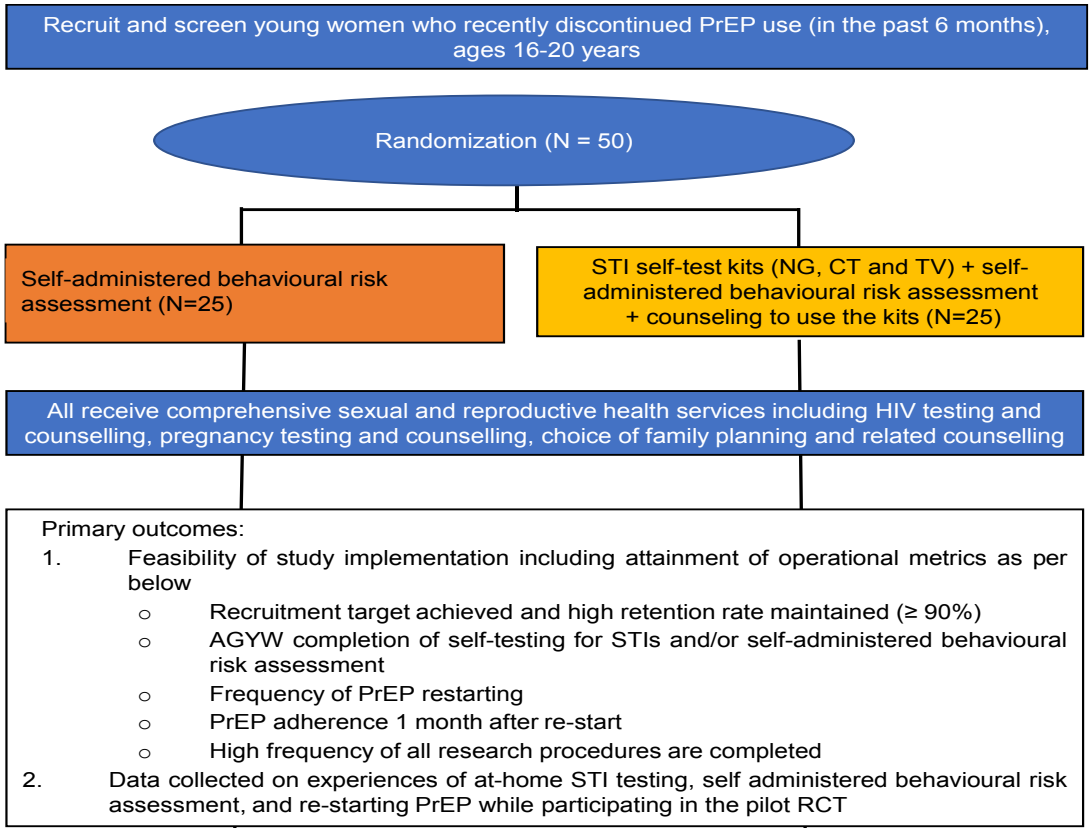
To assess AGYW acceptability and experiences of at-home STI testing, behavioural assessment, and re-starting PrEP while participating in the pilot trial

3. Study design and Population

3.1: Identification of Study Design

This is a pilot randomized trial among 50 AGYW (aged 16-20 years), who discontinued PrEP use within the past 6 months, assigned in a 1:1 ratio to receive: 1) STI self-test kits (NG, CT and TV) with in-person instruction at enrolment and telephone/video-based instructions for home use coupled with self-administered behavioural risk assessment or 2) self-administered behavioural risk assessment only (standard of care) **(Figure 1)**.

Figure 1. Study design schema



3.2: Sites

Participants will be enrolled at the Wits Reproductive Health and HIV Institute (Wits RHI) Research Centre Clinical Research Site in Johannesburg, South Africa.

3.3: Time to complete Accrual

Time to complete accrual will be approximately 6 months

3.4: Expected Duration of Participation

Each enrolled AGYW will be followed for approximately 6 months

3.5: Description of Study Population

- Approximately 50 non-pregnant, HIV negative, cis-gender AGYW aged 16-20 years, who have discontinued PrEP use within the last 6 months. The target population is restricted to AGYW who previously used PrEP as part of a concerted effort to focus this protocol on methods to cue young people to re-start PrEP.
- Up to 30 AGYW participating in the pilot RCT will be selected for qualitative IDIs. We will employ a mix of random and purposive selection of any interesting cases. If saturation is reached before the maximum number of IDIs are completed, conduct of IDIs will be concluded.

3.6: Eligibility criteria

Eligibility criteria are limited to those needed to identify AGYW who recently discontinued PrEP use and would be willing to consider re-starting PrEP during study follow up (6 months)

Inclusion Criteria

For the full cohort, all participants must:

- Be cis-gender adolescent females (16-20 years of age)
- Be literate
- Currently sexually active
- Be willing to participate in in-person and virtual study visits
- Not be pregnant or planning to be pregnant for the next 6 months
- Be HIV-negative but not ready to initiate PrEP at the screening and enrolment visit
- Have used PrEP with subsequent discontinuation within the last 6 months
- Have no contraindications to oral PrEP per self-report
- Have no indication of possible acute HIV infection, according to South African PrEP guidelines
- Have their own personal smart phone
- Willing to provide written informed consent/assent to participate in this study

For the subset invited to qualitative interviews, all participants must be:

- Willing to participate in an IDI at/before their month 6 visit (study exit visit)

Exclusion Criteria

Potential AGYW participants who meet any of the following criteria will be excluded from the study:

- At Screening and Enrollment, parent/guardian (for those participants <18 years) is unwilling to provide written informed consent
- At Screening and Enrollment, is already participating in another research study involving drugs, medical devices, or vaccines for STI prevention or treatment.
- Is not willing to comply with study procedures
- As determined by the PIs/designee, any current or historical physical health, mental health or social issue or condition that the site investigator or designee determines should exclude participation.
- Has any other condition that, in the opinion of the PIs/designee, would preclude informed consent, make study participation unsafe, or otherwise interfere with achieving the study objectives.

3.7: Recruitment

Once approvals for this protocol are secured from the Wits Human Research Ethics Committee (Wits HREC) and the University of Alabama Birmingham Institutional Review Board, the Wits RHI team regulatory compliance officer and site principal investigator (PI) will seek permission from the Gauteng Provincial Department of Health (GDOH) and the Johannesburg Health District Committee for the Wits RHI study team to recruit AG at public sector facilities.

The Wits RHI research team has well-established relationships and regular engagement with the staff/healthcare providers (HCP) from these local clinics and will reach out to these contacts by email, face to face meetings, telephone or virtual/MS Teams/Zoom calls to inform them about the study and to seek their assistance with recruiting the AGYW population required for this protocol. We will draft a list of talking points for them to guide their referrals for this purpose. These initiation meetings will set the stage for recruitment of AGYW.

Both active and passive recruitment methods will be employed. IRB-approved recruitment and educational materials will be used during recruitment sessions to educate AGYW about the risks and benefits associated with oral PrEP and STI self-testing. Active recruitment will include the Wits RHI community liaison officer (CLO) working with the community team to visit and recruit from local adolescent clinics and PrEP clinics that serve AGYW (with clinic permission) as well as other community areas. Passive recruitment will include sharing of study informational fliers with staff/HCP (including counseling staff from PrEP programs) at local adolescent clinics and PrEP clinics that

serve AGYW. HCP will be asked to identify AGYW (aged 16-20 years) who initiated PrEP and discontinued PrEP use within the last 6 months using their clinic records and invite them to reach out to the research clinic to learn about the study and be assessed for eligibility, should they want to explore participating. Additionally, the study community team will contact AGYW who participated in recent PrEP demonstration projects and trials at Wits RHI who provided permission to contact them post study exit and offer them the opportunity to be screened for eligibility. They may also engage in active street recruitment for this purpose and word of mouth referral if needed. Peer-to-peer recruitment is an additional strategy that may be utilized. The CRS community team may also host parent information sessions as part of recruitment activities.

Potential participants will be provided with study information and pre-screened to assess eligibility for the study. Clarifying questions will be addressed and potential participants will be given an agreeable date and time to visit the study clinic for an in-person screening visit. Locator contact information such as cellular phone numbers will be collected from the participants for this purpose and to remind them a day before their visit to present at the study site. Participants will also be advised that written informed consent/assent will be required from them as part of the study procedures and a copy of the informed consent forms (ICF) may be shared with them to review prior to the screening date. If ≥16 and <18 years old, they will also be advised that they will be required to bring along their parent/guardian to their screening visit to give written permission (consent) for them to be in the study. Study staff will also guide potential participants on public transport options from their home to the study site where required.

As the team proceeds with recruitment, strategies that are highest yielding in terms of accrual will be identified and focus will be shifted to rely on those to maximize efficiency in enrolment.

3.8: Co-enrolment Guidelines

As indicated in Section 3.6, participants should not take part in other research studies involving drugs, medical devices, or vaccines for HIV or STI prevention or treatment after the Screening and Enrolment Visit and while taking part in this study. The study site will be responsible for defining procedures for management and prevention of co-enrollment prior to initiation. Participants may take part in ancillary studies approved by the PALESA Protocol Team.

3.9: Retention

Once a participant is enrolled into the study, the study team will make every effort to retain the participant in follow-up. We will leverage the experience and commonly used effective strategies of the Wits RHI community team to ensure high retention rates among participants in the proposed study. These strategies may include:

- Exclusion of participants who indicate a high likelihood of travel outside of the study area, who appear to lack understanding of the research objectives or commitment to the research process, or who may experience personal challenges with compliance with study visits
- Collection and verification of adequate participant locator information (including residential address, contact numbers and multiple alternate contacts if we are unable to make direct contact with the participant
- Regular update and verification of locator information at every study visit along with reminders to contact the study team should details change between visits
- Regular telephonic reminders to participants to remind them of their visits (both virtual and in-person) in the days leading up to the scheduled visit
- Phone calls to participants who do not attend a scheduled visit the day after the scheduled visit and as needed until the visit is attended and telephonic verbal or instant message (IM) reminders to participants when self-administered procedures (e.g., self-administered behavioural risk survey) are not completed on the targeted day
- Provision of funds to support long distance transport (e.g., bus tickets) or additional reimbursement (with local IRB approval) for participants who relocate out of Johannesburg and are willing to return for in-person follow-up visits
- Conduct of off-site visits (with participants permission and consent) for those who chronically miss visits due to work, school or personal commitments at a venue of their choice should they be willing to accommodate these

- Home visits when needed and with participant's consent
- Partner support events where AGYW will be invited to bring their partners to learn more about the study
- Invitation to the study site to complete remote follow-up assessments should AGYW lose their phones or be unable to connect to a smart phone or computer remotely. Alternatively, a tablet will be taken to the participant at her convenience to complete at her home to reduce burden of returning to site.

4: Research Procedures, Data Capture Instruments and Data Collection Methods

Consented participants will be assigned in a 1:1 ratio to receive: 1) STI rapid test kits (NG, CT and TV) with in-person instruction at enrolment and telephone/video-based instructions for self-administration use coupled with self-administered behavioural risk assessment or 2) self-administered behavioural risk assessment only (standard of care) (**Figure 1**). All participants will receive comprehensive sexual and reproductive health (SRH) services during their study visits including choice of family planning method initiation and support, behavioural HIV/STI risk reduction counselling, STI management and partner STI management via partner notification slips. Precautions to minimize the transmission of SARS-CoV-2 (COVID-19) including sanitizing, social distancing and use of face masks will be implemented throughout the duration of the study.

4.1: Pre-screening

AGYW interested in participating in PALESA will be pre-screened at the site or during recruitment outreach activities using a recruitment checklist approved by all relevant ethics committees. Additionally, due to the high HIV-1 burden in this community, they will also be invited to have an HIV test at the site. This will entail the implementation of a Wits HREC approved in-house HIV Counselling and Testing (HCT) model expanded to include rapid pregnancy testing and education on requirements of the study. Minors with potentially consenting parents or guardians may also be informed about the study during the pre-screening process. If eligible and interested at that stage, potential participants will be scheduled for a screening visit at the study site. Those that test positive for HIV-1 will be counseled immediately and then referred to local ART clinics for care and immediate initiation of treatment. Likewise, those that test positive for pregnancy will be counseled and then referred to local antenatal clinics for further care.

4.1: Study Visit Schedule

We will follow all participants monthly for 6 months through a combination of remote and in-person visits **(Table 4).**

4.2: Screening and Enrollment visit(s)

Screening and enrolment for this study will ideally be conducted over the course of one visit. The visit may be split if the participant cannot stay for the full visit or if there are logistical issues at the study site that prevent visit completion on the same day. The visit should be completed within 1 to 28 days (Ideally within 7 days to avoid repetition of pregnancy and HIV testing). There is no limit to the number of times a participant may screen for this study.

For AGYW interested in participation, study counselors or designees will conduct an informed consent process to obtain consent/assent prior to initiation of study procedures. Written informed consent will be obtained from all adult AGYW (≥18 years) and parental/legal guardians and written assent will be obtained for minor AGYW (<18 years), as per US, international, and local regulations. Minor AGYW will not be enrolled if parental or legal guardian consent cannot be obtained or if the parent/legal guardian is unwilling to provide consent.

Table 4. Proposed study schedule and procedures

	Screening and Enrollment (In clinic)	Routine virtual visit (months 1,2,4,5))	STI Treatment Visit (following positive self-test result) (In clinic)	Routine clinic visit (quarterly-Month 3), as needed) (In clinic)	PrEP re-start visit (as-needed) (In clinic)	Exit (month 6) (In clinic)
For all AGYW						
Informed Consent	X					
Locator (and locator review at follow up visits)	X	X	X	X	X	X
Assign unique PTID	X					
Demographics	X					
HIV testing & counselling	X		X	X	X	X
HIV and STI risk reduction counselling	X	X	X	X	X	X
Urine pregnancy testing	X		X	X	X	X
Sexual behavior assessment (Baseline)	X					
Sexual behavior assessment (Follow-up)		X		X		X
Social experiences and impact	X			X		X
Contraceptive counselling & provision	X			X		X
Syndromic STI assessment & management	X			X	X	
Laboratory STI testing (NG, CT and TV)	X					X
Pelvic exam	X					X
STI treatment (NG, CT and/or TV)	X		X			X
Eligibility Determination and randomization	X					
PrEP counselling	X	[X]	[X]	[X]	X	[X]
PrEP provision	[X]	[X]	[X]	[X]	X	[X]
Provision of a personal PIN passcode for the self-administered behavioural risk questionnaire	X					
Self-administered behavioural risk questionnaire	X	X		X	[X]	X
Partner referral for STI management	[X]	[X]	[X]	[X]	[X]	[X]
Qualitative data collection (For up to 30 AGYW participating in the pilot RCT)						X
Scheduling of next visit	X	X	X	X	X	
For AG who re-start PrEP						
Creatinine & Hepatitis B testing					X	
PrEP adherence counselling					X	
PrEP provision					X	
DBS and plasma collection and storage						X
Referral to public PrEP program						X
For AG randomized to at-home STI testing arm						
AGYW to self-collect a genital swab to be stored and tested retrospectively if she has a positive STI test during her at-home testing	X			X		
Instruction for self-testing and provision of kits	X			X		
NG, CT and TV self-testing		X				
[X] Procedure conducted as needed.						

Following consenting, the following procedures will be performed as part of the Screening process:

- Collection and verification of adequate participant locator information
- Interviewer administered questionnaires will be conducted to collect data on participant demographics
- Laboratory testing for pregnancy and HIV with rapid point of care tests
- HIV and risk reduction counselling. If they are at risk of HIV, they will be referred for PrEP access.
- Syndromic STI assessment
- Laboratory STI testing and management
- Contraceptive counselling and provision
- Eligibility determination and randomization

Eligibility status will be determined and recorded using an eligibility checklist as well as a screening log. For participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility is determined.

Participants who meet eligibility criteria will have the following procedures:

- They will receive additional information about study participation
- They will be counselled about the risks and benefits of oral PrEP.
- They will be offered enrollment and randomization
- AGYW who accept enrollment will be allocated or select a personal PIN passcode that they will use to verify their identity when completing the online behavioural risk assessments. Access to the online platform may change depending on the platform requirements.
- They will complete self-administered behavioural risk assessment.
- AGYW who are randomized to self-testing arm
  - will be requested to self-collect a genital swab to be stored and tested retrospectively if she has a positive STI test during her self-testing
  - receive instruction for STI self-testing
  - receive kits for STI self-testing

4.2.1: Randomization

AGYW will be randomly assigned in a 1:1 ratio to receive STI test kits (NG, CT and TV) for home use coupled with self-administered behavioural risk assessment or self-administered behavioural risk assessment only (standard of care). Randomization will be based off a schema designed by the study data manager and revealed by opening a sealed Randomization Envelope with the participant's assignment.

4.2.2: Instruction for at-home STI self-testing

AGYW randomized to the at-home STI testing arm will be provided with in-person instruction at enrollment and flyers (in English and isiZulu) with printed step-by-step instructions for kit use. Information will include details on how to store the kits, criteria for adequate specimen collection and preparation, how to run the test, and how to interpret the test results. Video-based instructions with accompanying text subtitles and audio options may also be provided for home use. They will be counselled to use the kits when in a private space (such as at home) and with sufficient alone time to read the kit results within the recommended times free of disturbance. They will also be advised that telephonic/video-based check-ins are available for support as needed and to walk them through the process of testing and interpreting the results. They will also be given a phone number for support 24/7 on test kit use and result interpretation. Women will also be given verbal instructions (with accompanying written reminders) to contact the study site if they have any difficulties when conducting the test, who to contact if they are unclear on interpretation of the kit, if they experience any anxiety related to testing or testing outcomes, guidance on it being a single use kit so should not be shared or used repeatedly and about what to do in the case of a positive test for any of the infections.

4.2.3: Provision of STI kits for Self-testing

Self-testing options for common manageable STIs, such as NG, CT and TV are not yet available. The site is currently validating the use of commercially available STI POC NG, CT and TV rapid kits for self-testing among a subset of participants in the ARISE study (HREC Ref No. 210614). See **Table 5** for listing of potential rapid test kits to be used if they are successfully validated with good sensitivity and specificity. Should the validation outcomes yield characteristics lower than ideal, troubleshooting and repetition will be pursued. Alternative rapid test kits may also be considered to yield the most reliable kit options for use in the study. One validated kit per bacterial STI will be selected for use in PALESA (one kit for NG, one kit for CT and one kit for TV). If the validations of all kits for a particular STI are unsuccessful or have lower than optimal sensitivity and specificity, self-testing for that particular STI will be omitted from PALESA and only the optimally validated kits will be used.

Table 5: List of potential POC rapid test kits being validated currently

Test
Rapid Labs Gonorrhoea
ACRO Biotech Gonorrhoea
NADAL Chlamydia Test

AGYW will be provided with 2 of each validated rapid POC rapid test kits selected for PALESA at their enrolment (Month 0) and quarterly (Month 3) visits to use at their monthly routine virtual visits (months 1,2,4 & 5). If AGYW require further kits, reasoning behind the additional kit request will be assessed and where feasible they may return to the clinic to collect these or request for them to be dropped off with them at a location of their choice discretely by study staff. The site will assess whether the AGYW is using the kit according to test specifications and for herself and not her friends or family and will offer to bring her to site to test under clinical/laboratory staff guidance should the reason for the additional kits request be due to the participant having difficulty. AGYW will also be offered STI testing options for partners as needed through referrals or at the clinical research site.

4.2.4: Instruction for self-assessment of behavioural risk

At their enrolment visit, AGYW will be taught to self-administer a brief questionnaire about their sexual behaviour and partnership status that will be housed on an online portal and accessible via a shared link on their cellular phones. AGYW will be provided with a link to their individual internet-based survey and they can complete this on their personal phone. During follow-up, this survey will be completed on the participant's phone and so the training at baseline will ensure that she knows how to access and complete this survey and how to respond to each question. The survey will also assess AGYW experience with IPV, social harms (SH) and her past experiences with PrEP use and disclosure as well as comfort with communication of partner STI management needs.

4.2.5: HIV prevention and risk reduction counseling

Participant-centered approaches will be used when assessing participant risk for HIV/STI infection at enrollment and follow up. HIV prevention and risk reduction counseling will be provided in accordance with local counseling standards. All available methods of HIV prevention will be discussed including PrEP, correct use of condoms, engaging in lower risk sexual activities, understanding what STI symptoms and acute HIV infection symptoms include and knowing their own and their partners HIV/STI status. Participants will also be counselled on increased HIV acquisition risk related to unmanaged STIs as well as change to partners with unknown HIV/STI status. The counselor will ask open-ended questions in a nonjudgmental manner, actively listen to participant responses, probe as needed for further information, and guide the participant in identifying her risk factors and barriers to engaging in risk reduction practices, as well as strategies and action plans to try to address reported risk factors and barriers to use.

4.2.6: Contraceptive counseling and provision.

A range of locally available contraceptives options will be offered to all AGYW to reduce risk of unintended pregnancies as per the current South African National Department of Health (SA NDoH) guidelines.

4.2.7: STI assessment and treatment.

At enrollment, AGYW will undergo laboratory STI testing for NG, CT and TV using Cepheid GeneXpert platform and management of genital infections, in line with SA NDoH guidelines. They will also be offered partner notification cards to ensure their partner/s are able to access care.In addition, a clinical staff member will assist all AGYW to self-collect a genital swab that will be stored and tested retrospectively if she has a positive STI test during her at-home testing. AGYW will also be educated on how to assess a normal vaginal discharge and its potential causes (e.g., ovulation during a menstrual cycle).

4.3: Scheduling for remote virtual check-ins and in- person clinic visits.

At the conclusion of the enrolment visit, AGYW will be given a schedule for upcoming virtual check-ins with study staff and an appointment for a 3-month (quarterly) clinic visit. AGYW will be encouraged to call, send a *please-call-me* request, WhatsApp or text to study staff as soon as she would like to re-start PrEP. This re-start can happen at any time and does not need to align with or coincide with a planned study visit. The study team will accommodate her needs.

4.3.1 Follow-up

Monthly follow-up for 6 months will be conducted with all participants. Quarterly follow-up (Month 3) and study exit (Month 6) will occur in clinic and non-quarterly visits (Months 1, 2, 4, 5) will be conducted virtually. Per **Table 4,** procedures for virtual and in-person follow-up will include:

- **Use of commercially available STI rapid test kits for self-testing.** AGYW randomized to the STI self-testing arm will receive reminders monthly to use their kits/devices and record their results on a paper or web-based data collection tool. Should the web-based data system allow, we will request participants to upload photos of the test kits/devices so the test results and date of testing can be observed. All participants who test positive for CT, NG and/or TV will be provided with treatment at the study site and will be instructed to abstain from condomless sex for seven days following treatment. In addition, participants will receive counseling and referral for their partners using a patient-centered approach (45).
- **Self administered behavioural risk assessment.** All AGYW will complete a behavioural risk assessment monthly using a unique individual link that is texted to them on their phones. AGYW will first enter their personal PIN number to ensure that they are the true person enrolled in the study and then proceed with questions.
- **Messages to accompany results from STI and behavioural risk assessments.** Counseling messages developed based on findings from the PALESA formative research regarding perceived susceptibility and severity of HIV, motivation for PrEP use, perceived benefits and barriers to PrEP use, and cues to action around PrEP use will be delivered to participants when they have a positive STI test result and/or indicate sexual behaviour that aligns with HIV risk (new partners, increase in sexual frequency, STI symptoms). These messages will be delivered electronically at first and then in a follow-up phone call from a study counselor.
- **Virtual check-ins:** At a minimum frequency of monthly, and then as needed, telephonic or video-based support will be conducted to keep AGYW in both arms engaged in the study. These calls will include discussion of experiences with the self-administered behavioural risk assessment tool and STI self-testing using the provided test kits (for participants in that arm), any symptoms of STI, as well as assessment of any IPV/SH experienced. This may be in the form of text messaging, telephone calls, or video calls based on participant's cell-phone capability and her ability to talk freely and privately. Permission to conduct these sessions as well as the preferred method of contact will be collected at screening and revisited at every study contact should personal circumstances or preferences change. Counselling sessions will be conducted by clinical/counselling staff trained and experienced in working with AGYW as well as HIV prevention, PrEP, STI, and SRH needs. Participants who experience SH and IPV will be offered one on one counselling with a trained counselor or designee and provided with referral to appropriate services.
- **PrEP provision and refills.** When a participant would like to re-start PrEP, she will be asked to come to the study clinic to facilitate an in-person conversation with study counselors. Based on SA NDoH guidelines, routine kidney function testing (creatine with calculation of creatinine clearance and Hepatitis B), HIV testing and PrEP counseling (46) will be performed and she will be provided with daily oral PrEP medication. Counselling will be accompanied by provision of SA NDoH PrEP education materials to reinforce information provided during in-person counselling sessions. PrEP will be dispensed in quantities of 1-3 bottles depending on the time since PrEP initiation in accordance with NDoH guidance. Refills will be available at the study clinic or through local delivery service facilitated by study staff. Should participants report accessing PrEP outside of the study, the date of the refill will be verified with any medical record the AGYW is willing to share and captured in study records.
- **Adherence support to facilitate success with oral PrEP.** For AGYW who have re-started PrEP, regardless of study arm, their monthly virtual telephonic/video follow-up counseling will provide opportunities to talk about their PrEP use and implement adherence counseling. In addition, reminder messages will be provided, and participant concerns will be triaged for follow-up phone calls with study staff.
- **Additionally, at Month 3 of follow-up,** contraceptive counseling and provision, risk reduction counselling, swabs for retrospective STI testing, and syndromic STI assessment and treatment will be conducted. HIV and pregnancy testing and relevant counselling may be provided as applicable (See Table 4).

4.4: Study Exit

After 6 months in study follow up, all AGYW will be scheduled for a clinic-based visit to close out their study participation and up to 20 AGYW will be selected to collect qualitative data about their experience with the study. Proposed visit procedures **(Table 4)** will include

- Laboratory testing for pregnancy and HIV with rapid point of care tests
- HIV and risk reduction counselling
- Laboratory STI testing and management
- Contraceptive counselling and provision
- Self-administered behavioural risk questionnaire
- **DBS collection for PrEP adherence assessment.** AGYW who have initiated PrEP during the course of the study will have a dried blood spot (DBS) collected to measure tenofovir diphosphate (TFV-DP) level as an objective assessment of adherence to PrEP during the prior 30 days. TFV-DP drug level testing will be conducted by the University of Cape Town's (UCT) Clinical Pharmacokinetic Laboratory (Division of Clinical Pharmacology).
- **Referral to public PrEP program**: Referrals at the end of study will be provided to AGYW through written referral and if required through "warm referrals" where study staff will accompany her to the PrEP facility to ensure supported entry. Wits RHI has an established referral network in place for uninterrupted PrEP access for AGYW once they exit the research studies we implement.
- **Qualitative data collection**: Questions for the in-depth interview at exit will be conceptually grounded in the **Consolidated Framework for Implementation Research** (CFIR), a meta-theoretical framework designed to identify implementation determinants by guiding data collection, analysis, and evidence interpretation(47). Comprised of 5 domains and 39 constructs, the CFIR is a flexible framework well suited to describe heterogeneity in implementation across settings, as well as the relative effect of key constructs in influencing implementation outcomes such as intervention fidelity. Interviews will use a topic guide structured per the CFIR to ensure that multiple constructs of study implementation are discussed including experiences with the interventions, people who influenced participation, and ways that AGYW suggest refining the intervention to best reach their peers. Interviews will be conducted by trained and experienced Wits RHI social scientists with Qualitative interviewing skills using a standardized semi-structured interview guide with questions and probes developed by the study team in English and the predominant local language, isiZulu. The interviews are expected to last ~60-minutes and will be audio recorded Summary debriefing reports, describing the main information gathered and any key findings will be completed, within 24 hours of the interview. These will undergo internal quality control prior to circulation to the study team for rapid internal dissemination and communication of the preliminary findings and emergent themes, and to adjust study guides with additional probes and questions if indicated. Audio recordings will be saved to a secure online platform accessible to key staff on password-protected computers in the project offices and destroyed at the end of the project or per South Africa's GCP guidance taking precedence. The recorded interviews will be translated into English (if required) and transcribed. Once complete transcripts will undergo relevant quality control procedures (checked for content, clarity, detail, and grammar) and then be submitted to the study team.

4.5: Interim Visits

Interim visits and telephone contacts may be performed at any time during the study, for the following or other reasons:

- For administrative reasons, e.g., a participant may have questions for study staff, or may need to re-schedule a follow-up visits or to perform missed procedures.
- For interim counseling and/or testing in response to STI symptoms.
- For interim HIV counseling and testing in response to participant report of symptoms consistent with acute infection or presumed exposure to HIV.
- To provide participants STI results, partner notification slips or referral for treatment.

- To provide participants with the results of confirmatory HIV test results.
- For other reasons at participant request, e.g., to report a social harm, incident IPV or per study needs.

Interim contacts and visits will occur when more than one visit takes place within an allowable visit window or takes place between specified visits windows. All interim contacts and visits will be documented in participants' study records and on CRFs, if applicable.

4.6: HIV seroconversion

HIV rapid testing and counselling will be conducted according to the study algorithm at screening and subsequent on-site visits, as well as when clinically indicated. Dual rapid tests will be conducted in parallel. All discordant or potential seroconversions will be confirmed using HIV enzyme-linked immunosorbent assay (ELISA) and viral load testing. At the seroconversion visit, PrEP will be discontinued, and participants will be referred and linked to adolescent friendly HIV care and treatment. In addition, for research purposes and on availability of additional funding beyond the present protocol, DBS and plasma will be archived for determining tenofovir levels in the blood at the time of seroconversion and for future assessment of antiviral resistance. AGYW with confirmed HIV seroconversion will be exited from the study and referred to local clinics providing ART medications based on the current universal test and treat guidelines. They will also receive counselling regarding disclosure of HIV status to partners and HIV testing referrals for partners (as needed). Written SOPs for referral for HIV care and treatment are in place at the study site and include referral to facilities that can offer psychological and social services and medical care, including ART, to people infected with HIV-1. Study staff will actively follow-up on referrals to HIV care and support services, to determine whether the participant sought the care to which she was referred, the outcome of the referral, and whether additional referrals are needed. All follow-up actions, outcomes, counselling, and plans for next steps are documented in participant study records

4.7: Pregnancy

Should a participant become pregnant during the study, she will not be withdrawn from the study. She will be counselled on HIV transmission risk during pregnancy, safety of PrEP use during pregnancy, and supported to make an informed decision about whether to continue PrEP during pregnancy, as per SA DOH guidelines (which recommends PrEP use during pregnancy when there is ongoing HIV risk). She will be referred for antenatal care according to the local standard of care and receive STI treatment in line with her pregnancy status (per SA guidelines) should she test positive for STIs

4.8: Laboratory Evaluations

- Endocervical/vaginal specimens for point of care testing
  - *C. trachomatis*
  - *N. gonorrhoeae*
  - *T. vaginalis*
- Blood
  - HIV-1 rapid testing
  - HIV-1 confirmatory testing*
  - Hepatitis B**
  - Creatinine**
  - DBS and Plasma storage
- Urine
  - Beta-HCG for pregnancy

**If indicated. **At PrEP re-start*

Once all required study analyses of collected specimens are complete, any remaining sample may be discarded.

4.9: Specimen Management

The study site will adhere to the standards of good clinical laboratory practice in accordance with *DAIDS Laboratory Policy*, https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf and site SOPs for proper collection, processing, labeling, transport, and storage of specimens to standardize procedures. Specimen collection, testing, and storage at the site laboratories will be documented. In

cases where laboratory results are not available due to administrative or laboratory error or sample quality/adequacy, sites are permitted to re-collect specimens.

4.10: Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the U.S. Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH). Biohazard waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

5: Safety Assessments

5.1: Safety Monitoring and Reporting

The study site investigators at Wits RHI are the first layer of safety monitoring and are responsible for the initial evaluation and reporting of safety information at the participant level and for alerting the other investigators if unexpected concerns arise. The full study team will participate in weekly calls to review study progress, including any concerns related to participant safety. Events that require reporting will be reported to IRBs/ECs according to their individual requirements.

5.2: Social Harms Monitoring

Although the study site will make every effort to protect participant privacy and confidentiality, it is possible that involvement in the study could become known to others and that social harms – non-medical adverse consequences – may result. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities as a result of their study participation. On a monthly basis, the study team will generate data reports of the frequency of social harms and will distribute them to the study PIs and other members of the study team for review and discussion on the regularly scheduled calls. Social harms that are judged by the PI/designee to be serious or unexpected will be reported to the study PIs and responsible site IRBs/ECs according to their individual requirements beginning at the time of enrollment (i.e., after a participant signs the informed consent and eligibility is confirmed) until Study exit. If a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. The study site will provide care and counseling in accordance with standardized guidance provided in site specific SOPs. While maintaining participant confidentiality, the study site may engage their community advisory boards (CABs) in exploring the social context surrounding instances of social harm.

5.3: Regulatory Requirements

Study PIs/designees will submit information in accordance with local regulatory agencies' or other local authorities' requirements. Study PIs/designees also will submit information and any other relevant safety information to their IRBs/ECs in accordance with IRB/EC requirements

6: Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The Wits RHI PI also may terminate participants from the study to protect their safety, and/or if they are unwilling or unable to comply with required study procedures. Participants may also be terminated if the study funder or Wits RHI EC terminates the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records.

7: Data Management and Analysis

Study CRFs will be developed collaboratively by study team members from UAB, UCSF and Wits RHI. A secure web-based application will be used to collect data from participants. Data will be entered directly into the web-based application by study staff. Data from laboratory analyses will be sent to the study data manager, stored securely on computers at the UAB, and merged with clinical data needed for statistical analyses. Automated legal range checks will be programmed to reduce

data entry errors and internal quality control reports will be run on a monthly basis and shared with the Wits RHI data staff for reconciliation and confirmation. Recruitment, retention, procedures completion, entry of results from at-home STI testing and completion of behavioural assessments will be tracked via operational reports run by the data manager and shared with the investigative team on a regular basis.

Wits RHI will maintain source data/documents in accordance with local IRB/EC and each engaged institution's requirements. Study PIs/designee will maintain, and store securely, complete, accurate and current study records throughout the study. Study records must be maintained on site for the entire period of study implementation. Thereafter, instructions for record storage will be provided by all engaged institutions and records will be maintained to account for the longest time period required. All Wits RHI study staff are trained in Good Clinical Practice (GCP) and Human Subjects Protection (HSP) and sign confidentiality agreements upon joining the organization to ensure compliance with rules of confidentiality of all participant specific information.

Study data will be in the form of questionnaire responses, laboratory testing logs, laboratory result reports, individual IDI debriefing reports, and transcripts. The study team will use a case report forms (CRF) to collect relevant participant characteristics including age, education, age at sexual debut, current regular sex partner, lifetime number of sex partners and personal perception of risk of HIV acquisition to describe the participants in this study. A laboratory CRF will be used to document AGYW's HIV, pregnancy and STI test results. Additionally, other non CRF source documents will be used to capture the participants study visit in her study binder. Additional qualitative data will be in the form of summary debriefing reports, audio recordings and transcripts. Summary debriefing reports, describing the main information gathered and any key findings, will be completed within 24 hours of the interview. These will undergo internal quality control prior to circulation to the study team for rapid internal dissemination and communication of the preliminary findings and emergent themes, and to adjust study guides with additional probes and questions if indicated. Audio recordings will be saved to a secure online platform accessible to key staff on password-protected computers in the project offices and destroyed at the end of the project or per South Africa's GCP guidance taking precedence. The recorded interviews will be translated into English (if required) and transcribed. Once complete transcripts will undergo relevant quality control procedures (checked for content, clarity, detail, and grammar) and then be submitted to the study team.

All study participants will receive a unique study identification number (PTID) that will be recorded on all study forms and interview transcripts as well as audio recordings. PTIDs will be maintained by the site PI or designee, and only a Participant Identifier Log will provide a link between participant name and PTID. This log will be stored in a secure location in the PI's (or designees') offices, separate from participant data to ensure confidentiality is maintained consistently. Paper based participant data will all be anonymized using these coded PTIDs and stored in a locked file cabinet located in the Wits RHI RC CRS Data Centre. Hard-copies of informed consent forms (including AGYW consent (≥18≤20 years), AGYW assent (≥16<18 years) and parent/legal guardian consent) and contact/locator information sheets containing personal identifying information such as name, age, phone number and residential contact information, will likewise be stored in a secure, limited-access location within the Data Centre and separate from all participant data bearing PTID.

All information will be stored securely under double lock at the Wits RHI Data Centre with restricted access to key personnel only. UAB and UCSF staff will not have access to any personal identifiers or link logs. Only de-identified data, such as transcripts from IDIs and data collected via CRF, will be shared with these investigators. CRF data will be entered directly into a password-protected web-based application.

Electronic versions of qualitative debriefing reports and transcripts will be uploaded using a secure file transfer platform that can be accessed by UAB, UCSF and Wits RHI project staff. Transcripts will be coded using qualitative software (e.g. Dedoose or NVivo) by a team of research associates at Wits RHI and UCSF. The codebook will be initially developed based on the transcripts, CFIR constructs, and key findings from interview debrief reports. We will iteratively refine the codebook during the analysis phase. Coders will meet weekly to discuss code applications and resolve discrepancies. Thematic network analysis will be used to group our findings into larger thematic categories and describe AGYW experiences of STI self-testing, self-administered behavioural risk

assessment, and re-starting PrEP while participating in the pilot trial. Specifically, we will conduct a four-step analysis process, whereby we will: 1. Apply codes to the clean transcripts; 2. Write analytic and narrative memos to identify key themes across codes and participants; 3. Use diagrammatic techniques to group findings by basic, organizing, or global themes (thematic network analysis) and to determine relationships between themes; and 4. Extract representative quotations to elucidate themes.

8: Internal Quality Assurance and Monitoring

Site quality assurance staff will do the following:

- Review informed consent forms (ICFs), procedures, and documentation.
- Assess compliance with the study protocol, GCP Guidelines, and applicable regulatory requirements (US and non-US), including Code of Federal Regulations (CFR) Title 45 Part 46 and Title 21 Parts 50, 56, and 312.
- Perform source document verification to ensure the accuracy and completeness of study data.
- Verify proper collection and maintenance of biological specimens.
- Assess implementation and documentation of internal site quality management procedures.
- Verify that current license/certification is available on site for study staff listed on the Delegation of Responsibilities Log/Form.

The Wits RHI PI/designee will allow inspection of all study-related documentation by authorized representatives of the NIMH, site IRBs/ECs, and other local, US, and international regulatory entities or study partners as requested. A site visit log will be maintained at the study site to document all visits.

9: Human Subjects Considerations

9.1: Institutional Review Boards/Ethics Committees

The study team will make every effort to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process, as per the site's Informed Consent Process SOP. Before beginning the study, the study PIs will have obtained IRB/EC approval. The study PIs will permit audits by NIMH, site IRBs/ECs, and other local, US, and international regulatory entities if they are requested.

9.2: Informed Consent Process

In obtaining and documenting informed consent, the study PIs and their designees will comply with applicable local, US and other international regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. All informed consent and assent forms and study information will be provided in English and isiZulu, the languages most commonly spoken by the target populations in the Wits RHI catchment area. All translated materials will be backtranslated into English by a second, blinded staff member or an outsourced provider and any discrepancies reconciled through group consensus. Original English documents, isiZulu translations and English backtranslations will be reviewed and submitted to Wits HREC for approval prior to data collection. For individuals who choose to review the consent form in isiZulu, they will be paired with a study staff member who speaks isiZulu to answer any questions about the study or material in the consent or assent form. In addition to ICFs, the study team will work with study staff and community representatives to develop appropriate materials about the study.

Written informed consent will be obtained from all adult AGYW (≥18years) and parental/legal guardians and written assent will be obtained for minor AGYW (<18 years), as per US, international, and local regulations. Minor AGYW will not be enrolled if parental or legal guardian consent cannot be obtained. Participants who are unable to read or write will not be allowed to participate due to the need for literacy with regard to understanding and following instructions for self-testing. Parents/legal guardians who are unable to read or write will be permitted to provide permission for AGYW to participate. In this circumstance, the consent form will be read to the parent/legal guardian, and a witness must be present to observe the consent process. The parent/legal guardian will be required to provide a thumb print on the consent forms and a witness will need to provide a signature as well.

Briefly, potential participants will meet with a designated staff member in a private space to

complete the informed consent (IC) or assent (IA) procedures. All necessary COVID-19 risk mitigation strategies will be implemented as required. The IC/IA process will be conducted in the preferred language of the participant so that they may fully understand what they are consenting to. The designee will assess the individual's literacy before reading the consent/assent form aloud and explaining the study, including inclusion and exclusion criteria, risks and benefits, procedures and expected time commitment. This will include the intention to audio record, transcribe, and translate (if applicable) the IDI discussions and the rights of participants to refuse to answer any questions or terminate participation at any time during the process. An informed consent/assent comprehension assessment checklist will then be administered by the research staff to ensure that the participant understands the core purpose of the research and the associated risks and benefits prior to providing consent to participate. Participants will not be enrolled if they are not able to respond adequately to these questions and hence do not "pass" the comprehension checklist. Similar procedures apply to the consent of parents/legal guardians. These procedures will be detailed in a site specific standard operating procedure (SOP).

A signed copy of the informed consent/assent forms will be offered to each participant and parents/legal guardians; however, they may choose not to take the consent forms home with them if they fear loss of confidentiality related to their/their child's research participation. The signed consent/assent form will become part of the participant's record and will be filed separately from other documents with study identifiers in secure lockable cabinet accessible to authorized personnel only. All participants and parents/legal guardians will be informed that all records are confidential.

The team has had training and has procedures in place to protect the rights and safety of all study participants which include making sure the consent/assent form has been written in a non-coercive, easy to understand language. Participants are also given adequate opportunity to decline participation without consequence or ill feelings from study staff.

9.3: Description of Risks and Benefits and Steps to Minimize Risks

Following the provision of written informed consent/assent, participants will be asked a series of questions to collect data on participant demographics and sexual behaviour. They will be told that they can choose not to answer any question if it makes them feel uncomfortable. These procedures will involve minimal risk as they will occur on a one-on-one basis and responses will be stored on a secure database. Interviewers are trained to conduct questionnaires in a non-judgemental manner and to maintain confidentiality.

Participants may feel uncomfortable or worried learning about HIV/STI risk or disclose current or recent IPV during the study. Should this occur, study staff are trained to provide suitable counselling and have an extensive list of resources that can be provided to the participant to link them to applicable psycho-social counselling support, shelters, legal support and services.

When conducting STI self-testing in their homes, participants may inadvertently disclose their use of the test kits to others in the home and this could lead to SH or IPV. For these reasons, discrete videos and remotely accessed study material will be used to reduce the chance that participants experience stigma, discrimination, harm or violence due to visibility of study materials by peers, friends, partners or others. At study screening and enrolment and all participant visits (virtual or in-person), participants will be counselled to self-test in what they assess to be a private safe space and to consult with study staff if they have any fears or concerns about self-testing. Should any SH that is related to study participation be reported, the study team will leverage the lessons learned from previous HIV prevention and PrEP trials to systematically collect data on SH experienced by AGYW participating in the study sensitively and provide appropriate virtual and in person counselling, support and referrals as per participants needs. Where possible and desired by the participant, "warm" referrals will be provided, where a staff member will accompany the individual to the referral facility to ensure that she is introduced to the correct referral personnel and receives the necessary support to feel safe to seek out care. Aside from referrals, study staff will ensure the participant is advised on strategies to better understand the triggers of the SH or IPV, to role play possible risky scenarios to be better prepared and to consider safety planning to ensure rapid extraction of herself from a volatile situation in the future, if there is a recurrence.

There may be security risk concerns related to AGYW taking STI test kits home. For the pilot study, parental/guardian consent for the inclusion of 16- and 17-year old sexually active AGYW will be sought in order to test the feasibility of conducting the trial in a population less at-risk for inadvertent disclosure to parents and mitigate risk of unplanned disclosure in the family home. Aside from the consenting parent/guardians' awareness as a safety measure to support the young women, the STI kits will be packaged discretely, and the AGYW counselled on strategies to safely store these kits.

Risk of sharing kits with peers will also be discussed explicitly in the context that STI management will be informed by the outcomes of the test results and the treatment uptake will be observed at the study site for that participant and that those who are not in the study will not be eligible for care within the study.

In-depth interviews (IDI) also involve minimal risk to participants because they are providing their opinions in the context of a one-on-one discussion with a study staff member. As such a breach of confidentiality is unlikely. During the IDI, interviewers will elicit AGYW experiences of STI self-testing, their thoughts on the self-administered behavioural risk assessment, and experiences re-starting PrEP while participating in the pilot trial. All participants will be advised that it is entirely up to them if they choose to participate in the IDIs and that refusal to participate will have no impact on their care at their recruitment site/local clinics. They will also be told that they can choose not to answer any question if it makes them feel uncomfortable.

All participants will be informed that only study numbers or PTIDS will be used during the study and that all study materials/documents will be kept confidential and stored in locked/secure locations (hardcopy and electronic). Additionally, they will be told that joining the study is voluntary and that they can leave at anytime, that they can choose not to answer any question if it makes them feel uncomfortable and that their participation or lack thereof, will not affect any services they normally receive/access at the recruitment site. Participants will also be given the name and contact information for the site PIs if they have any questions about the study.

In addition to the strategies described above for protecting against/minimizing risks relevant for all those participating in any part of the study, the Wits RHI HIV Prevention and Youth community advisory boards (CABs) will be involved in the planning and implementation of the study. The CABs will be important for developing strategies for recruiting and retaining participants.

There are no direct benefits to the study participants apart from access to applicable referrals if needed. The data from this pilot RCT will have potential to inform policy on PrEP re-start among AGYW using self-identified STIs as a marker of heightened risk.

9.4: Confidentiality

All computers and laptops are configured for secure operations (password required for login, short time to goingto sleep with no activity, and password required to activate computers after it goes to sleep). The study team will use a REDCap database that is stored on a secure server to collect data. Access to the REDCap database will be limited to study staff and will be password protected. Participants will be allocated PTIDs and there will be no link between participants name and PTID other than the study link log which will be stored securely at the study site. All participant data (audio recordings, debriefing reports, and transcripts) will be stored on a secure platform and will not be stored on individual computers or laptops. No participant's name will be revealed by the study staff to anyone outside thei. Analysis will not include any names or personal identifiers. The participants will not be addressed by their real name during the interview to preserve confidentiality. Once analysis has been completed, recordings will be destroyed as per local ethics guidelines.

Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- Representatives of the US Federal Government, the US Office for Human Research Protections, National Institutes of Mental Health (NIMH) and/or contractors of the NIMH, and other local, US, and international regulatory entities
- Study staff
- IRBs/ECs

9.5: Distress during Study Visits

It is possible that participants will disclose sensitive events that may lead to discomfort and/or distress during their in clinic or virtual study visits.

The site study team is well trained in distress identification and management. A generic Wits RHI Research Centre distress management protocol is used by the study team across all studies and will help guide training and implementation of this study. The distress management document includes detailed information about how staff should respond to such cases, such as:

- Before starting any study visit procedure, study staff will indicate that the session may be interrupted or concluded at any time should the participant wish to have a break, if the participant is distressed,or does not want to go on completing the visit for any reason.
- Study staff will explain that sometimes talking about personal experiences in a research project may mean that a participant would like to talk further about some of the issues raised, either with a lay counsellor or with someone else afterwards. Hard-copy or digital resource cards and referral letters will be provided to participants for referral options.
- If a participant should become distressed, study staff will inform the participant that the study visit will be paused and offer the option to continue at a later time or date when she is more comfortable.
- For participants whose distress is not alleviated through these initial strategies, study staff will offer a meeting time with a trained counsellor at the clinic and the study PI will be consulted for additional support.

10: Participant Reimbursement

Participants will be reimbursed ZAR 400 (~22 USD) on completion of their in-person clinic study visits and ZAR 150 (~10USD) for their virtual visits, in accordance with local ethical and regulatory requirements and guidelines. The reimbursement amount compensates participants for costs related to their time, inconvenience and expenses related to travel to and from the study site, and provides a contribution towards data top-up costs, when necessary (if visits are conducted virtually). The site uses an electronic reimbursement system that allows money to be sent to anyone with a valid South African cellphone number. This will be used for in-person and virtual visit reimbursement. Additionally, cash can be made available on site as a backup reimbursement arrangement.

11: Results dissemination

Results of this study will be shared first with Wits HREC, study staff at Wits RHI, UAB and UCSF, and then study participants, CAB members, and other key stakeholders. Results will additionally be disseminated to the local and research community and the public at large through conference presentations and publication in peer-reviewed journals. All publications will be submitted to PubMed Central, in accordance with NIMH Public Access Policy.

12: References

1. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. Lancet. 2019;394(10195):303-13.
2. Gray GE, Bekker LG, Laher F, Malahleha M, Allen M, Moodie Z, et al. Vaccine Efficacy of ALVAC-HIV and Bivalent Subtype C gp120-MF59 in Adults. The New England journal of medicine. 2021;384(12):1089-100.
3. Palanee-Phillips T, Rees HV, Heller KB, Ahmed K, Batting J, Beesham I, et al. High HIV incidence among young women in South Africa: Data from a large prospective study. PloS one. 2022;17(6):e0269317.
4. Dellar R, Karim QA. Understanding and responding to HIV risk in young South African women: Clinical perspectives. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2015;105(11):952.
5. Cameron DW, Simonsen JN, D'Costa LJ, Ronald AR, Maitha GM, Gakinya MN, et al. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. Lancet. 1989;2(8660):403-7.
6. Laga M, Manoka A, Kivuvu M, Malele B, Tuliza M, Nzila N, et al. Non-ulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: results from a cohort study. Aids. 1993;7(1):95-102.
7. Mayer KH, de Vries HJ. HIV and sexually transmitted infections: reconciling estranged bedfellows in the U = U and PrEP era. Journal of the International AIDS Society. 2019;22(S6):e25357.
8. Kufa-Chakezha T. Preventing Sexually Transmitted Infections: Why South Africa Isn't Winning Online: National Institute for Communicable Diseases; 2019 [Available from: https://www.nicd.ac.za/preventing-sexually-transmitted-infections-why-south-africa-isnt-winning/#:~:text=STI%20prevention%20in%20the%20past&text=HIV%20prevention%20concentrated%20on%20reducing,benefit%20in%20preventing%20other%20STIs.
9. Torrone EA, Morrison CS, Chen PL, Kwok C, Francis SC, Hayes RJ, et al. Prevalence of sexually transmitted infections and bacterial vaginosis among women in sub-Saharan Africa: An individual participant data meta-analysis of 18 HIV prevention studies. PLoS medicine. 2018;15(2):e1002511.
10. Deese J, Philip N, Lind M, Ahmed K, Batting J, Beksinska M, et al. Sexually transmitted infections among women randomised to depot medroxyprogesterone acetate, a copper intrauterine device or a levonorgestrel implant. Sexually transmitted infections. 2020:sextrans-2020-054590.
11. Harp DF, Chowdhury I. Trichomoniasis: evaluation to execution. European journal of obstetrics, gynecology, and reproductive biology. 2011;157(1):3-9.
12. Milford C, Barsdorf N, Kafaar Z. What should South African HIV vaccine trials do about social harms? AIDS care. 2007;19(9):1110-7.
13. Montgomery ET, Roberts ST, Nel A, Malherbe M, Torjesen K, Bunge K, et al. Social Harms in Female-initiated HIV Prevention Method Research : State of the Evidence. Aids. 2019.
14. Rowley J, Vander Hoorn S, Korenromp E, Low N, Unemo M, Abu-Raddad LJ, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. Bulletin of the World Health Organization. 2019;97(8):548-62p.
15. Albanghali MA, Othman BA. A Cross-Sectional Study on the Knowledge of Sexually Transmitted Diseases among Young Adults Living in Albaha, Saudi Arabia. International journal of environmental research and public health. 2020;17(6):1872.
16. Dunbar MS, Kripke K, Haberer J, Castor D, Dalal S, Mukoma W, et al. Understanding and measuring uptake and coverage of oral pre-exposure prophylaxis delivery among adolescent girls and young women in sub-Saharan Africa. Sexual health. 2018;15(6):513-21.
17. Connie Celum NM, Linda-Gail Bekker, Sybil Hosek, Deborah, Donnell PA, Bonnie Dye, Subash Pathak, Yaw Agyei, Jessica Fogel,, Mark Marzinke KM, Sheetal Kassim, Shorai Mukaka,, Heather Noble AA, Sinead Delany-Moretlwe, Team obotHS, editors. PrEP use in young African women in HPTN 082: Effect of drug level feedback. 10th IAS Conference on HIV Science; 2019 21-24 July 2019; Mexico City, Mexico.
18. Reed JB, Shrestha P, Were D, Chakare T, Mutegi J, Wakhutu B, et al. HIV PrEP is more than ART-lite: Longitudinal study of real-world PrEP services data identifies missing measures

meaningful to HIV prevention programming. Journal of the International AIDS Society. 2021;24(10):e25827.
19. Cairns G. Many people in African PrEP programmes stop and restart PrEP Online: AIDSMap; 2020 [Available from: https://www.aidsmap.com/news/jul-2020/many-people-african-prep-programmes-stop-and-restart-prep.
20. Rousseau E, Katz AWK, O'Rourke S, Bekker LG, Delany-Moretlwe S, Bukusi E, et al. Adolescent girls and young women's PrEP-user journey during an implementation science study in South Africa and Kenya. PloS one. 2021;16(10):e0258542.
21. WHO recommends the dapivirine vaginal ring as a new choice for HIV prevention for women at substantial risk of HIV infection Online: World Health Organization; 2021 [Available from: https://www.who.int/news/item/26-01-2021-who-recommends-the-dapivirine-vaginal-ring-as-a-new-choice-for-hiv-prevention-for-women-at-substantial-risk-of-hiv-infection#:~:text=WHO%20today%20recommended%20that%20the,the%20risk%20of%20HIV%20infection.
22. International Partnership for Microbicides. The Monthly Dapivirine Ring: Frequently Asked Questions 2020 [Available from: https://www.ipmglobal.org/sites/default/files/media_block_files/ring_public_qa_dec_2020.pdf.
23. Baeten JM, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V, et al. Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women. The New England journal of medicine. 2016;375(22):2121-32.
24. Nel A, van Niekerk N, Kapiga S, Bekker L-G, Gama C, Gill K, et al. Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women. New England Journal of Medicine. 2016;375(22):2133-43.
25. International Partnership for Microbicides. Final Results of Open-label Study of IPM's Dapivirine Vaginal Ring Show Increased Use and Suggest Lower Infection Rates Compared to Earlier Phase III Study 2019 [updated 11-14 June 2019. Available from: https://www.ipmglobal.org/content/final-results-open-label-study-ipm%E2%80%99s-dapivirine-vaginal-ring-show-increased-use-and-suggest.
26. Baeten JM, Palanee-Phillips T, Mgodi NM, Mayo AJ, Szydlo DW, Ramjee G, et al. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. The lancet HIV. 2021;8(2):e87-e95.
27. Brown ER, Hendrix CW, van der Straten A, Kiweewa FM, Mgodi NM, Palanee-Philips T, et al. Greater dapivirine release from the dapivirine vaginal ring is correlated with lower risk of HIV-1 acquisition: a secondary analysis from a randomized, placebo-controlled trial. Journal of the International AIDS Society. 2020;23(11):e25634.
28. International Partnership for Microbicides. Dapivirine Ring [Available from: https://www.ipmglobal.org/our-work/our-products/dapivirine-ring#Results%20presentations.
29. Gwarisa M. Dapivirine Vaginal Ring approved for use in Zimbabwe: Health Times; 2021 [Available from: https://healthtimes.co.zw/2021/07/14/breaking-dapivirine-vaginal-ring-approved-for-use-in-zimbabwe/.
30. South Africa Approves Dapivirine Vaginal Ring for Use by Women Online: International Partnership for Microbicides; 2022 [Available from: https://www.ipmglobal.org/content/south-africa-approves-dapivirine-vaginal-ring-use-women#:~:text=(March%2011%2C%202022)%E2%80%94,to%20reduce%20their%20HIV%20risk.
31. Ernst M, Pine DS, Hardin M. Triadic model of the neurobiology of motivated behavior in adolescence. Psychological medicine. 2006;36(3):299-312.
32. Steinberg L. Cognitive and affective development in adolescence. Trends Cogn Sci. 2005;9(2):69-74.
33. Casey BJ, Jones RM, Hare TA. The adolescent brain. Annals of the New York Academy of Sciences. 2008;1124:111-26.
34. Archary M, Pettifor AE, Toska E. Adolescents and young people at the centre: global perspectives and approaches to transform HIV testing, treatment and care. Journal of the International AIDS Society. 2020;23(S5):e25581.
35. van der Straten A, Stadler J, Luecke E, Laborde N, Hartmann M, Montgomery ET. Perspectives on use of oral and vaginal antiretrovirals for HIV prevention: the VOICE-C qualitative study in Johannesburg, South Africa. Journal of the International AIDS Society. 2014;17(3 Suppl 2):19146.
36. Makusha T, Knight L, Taegtmeyer M, Tulloch O, Davids A, Lim J, et al. HIV self-testing

could "revolutionize testing in South Africa, but it has got to be done properly": perceptions of key stakeholders. PloS one. 2015;10(3):e0122783.
37. Holmes LE, Kaufman MR, Casella A, Mudavanhu M, Mutunga L, Polzer T, et al. Qualitative characterizations of relationships among South African adolescent girls and young women and male partners: implications for engagement across HIV self-testing and pre-exposure prophylaxis prevention cascades. Journal of the International AIDS Society. 2020;23 Suppl 3(Suppl 3):e25521-e.
38. Bekker LG, Hughes J, Amico R, Roux S, Hendrix C, Anderson PL, et al. HPTN 067/ADAPT background and methods and Cape Town results. IAS 2015: 8th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 19-22; Vancouver, Canada2015. p. Abstract #MOSY0103.
39. Gaydos CA. Let's Take A "Selfie": Self-Collected Samples for Sexually Transmitted Infections. Sex Transm Dis. 2018;45(4):278-9.
40. Gaydos CA, Barnes M, Holden J, Silver B, Smith R, Hardick J, et al. Acceptability and feasibility of recruiting women to collect a self-administered vaginal swab at a pharmacy clinic for sexually transmissible infection screening. Sexual health. 2020.
41. Kharsany AB, McKinnon LR, Lewis L, Cawood C, Khanyile D, Maseko DV, et al. Population Prevalence of sexually transmitted infections in a high HIV burden district in KwaZulu-Natal, South Africa: Implications for HIV epidemic control. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2020.
42. Baeten JM, Heffron R, Kidoguchi L, Mugo NR, Katabira E, Bukusi EA, et al. Integrated Delivery of Antiretroviral Treatment and Pre-exposure Prophylaxis to HIV-1-Serodiscordant Couples: A Prospective Implementation Study in Kenya and Uganda. PLoS Med. 2016;13(8):e1002099.
43. Dias S, Gama A, Tavares AM, Reigado V, Simões D, Carreiras E, et al. Are Opportunities Being Missed? Burden of HIV, STI and TB, and Unawareness of HIV among African Migrants. International journal of environmental research and public health. 2019;16(15).
44. WHO guideline on self-care interventions for health and well-being, Online: World Health Organization; 2022 [updated 27 June 2022. Available from: https://www.who.int/publications/i/item/9789240052192.
45. Alam N, Streatfield PK, Shahidullah M, Mitra D, Vermund SH, Kristensen S. Effect of single session counselling on partner referral for sexually transmitted infections management in Bangladesh. Sex Transm Infect. 2011;87(1):46-51.
46. PrEP Implementation Pack: South Africa 2016-1017 2016 [Available from: https://www.prepwatch.org/wp-content/uploads/2017/07/SA_ImplementationPack.pdf.
47. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci. 2009;4:50.