

**Protocol**

**CAPRISA 084**

**A demonstration project of daily, oral tenofovir disoproxil fumarate + emtricitabine pre-exposure prophylaxis (PrEP) as part of sexual reproductive health services for young women at high risk of acquiring HIV in KwaZulu-Natal: Informing policy and practice for PrEP scale-up**

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## ABBREVIATIONS AND ACRONYMS

ANC	Antenatal Care
ART	Antiretroviral treatment
ARV	Antiretroviral
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CECRS	CAPRISA eThekweni Clinic Research Site
CP	Community Programme
CVCRS	CAPRISA Vulindlela Clinic Research Site
DBS	Dry blood spots
DMPA	Depot-medroxyprogesterone acetate
DREAMS	<b>D</b> etermined, <b>R</b> esilient, <b>E</b> mpowered, <b>A</b> IDS-free, <b>M</b> entored, and <b>S</b> afe women
HIV	Human Immunodeficiency Virus
IEC	Information, Education and Communication
KOH	Potassium Hydroxide
MCC	Medicines Control Council
PA	Poor Adherers
PAS	Peer Adherence Supporters
PCZCDC	Prince Cyril Zulu Communicable Disease Clinic
PHC	Primary Health Care
PrEP	Pre-Exposure Prophylaxis
SRH	Sexual Reproductive Health
SOP	Standard Operating Procedures
STI	Sexually Transmitted Infection
HCT	HIV counseling and testing
UID	User Identifier
USAID	United States Agency for International Development
VMMC	Voluntary Medical Male Circumcision
WHO	World Health Organisation

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## 1. BACKGROUND AND RATIONALE FOR PROJECT

### 1.1 The Human Immunodeficiency Syndrome Virus (HIV) Epidemic in South Africa

South Africa, is home to about 1% of the world's population but contributes a disproportionate 18% of the global burden of HIV infection with about 1,000 new infections a day<sup>[1]</sup>. The province of KwaZulu-Natal, South Africa is at the epicentre of the pandemic with 4 of its 11 districts having an HIV prevalence among pregnant women of greater than 40% and the remaining seven districts having a HIV prevalence between 30%-40%<sup>[2]</sup>. In one of the heaviest HIV burden districts in rural KwaZulu-Natal, by age 16, one in ten women utilizing antenatal services are already infected with HIV and this increases to one in three by age 20 and one in two by age 24 (Table 1)<sup>[3]</sup>. The incidence rates in this community are extremely high; in the placebo arm of the CAPRISA 004 trial that evaluated the safety and effectiveness of 1% tenofovir gel in urban and rural women in KwaZulu-Natal, HIV incidence was 9.1% per 100 women years of follow-up despite monthly HIV risk reduction counselling and HIV testing<sup>[4]</sup>. High HIV incidence rates have also been observed in post-partum women in peri-urban communities in KwaZulu-Natal.

**Table 1:** HIV prevalence in ANC clients utilising ANC services in rural KwaZulu-Natal

Overall HIV prevalence in rural Vulindlela (2001-2013)	
Age Group (Years)	HIV Prevalence (N=4818)
≤16	11.5%
17-18	21.3%
19-20	30.4%
21-22	39.4%
23-24	49.5%
>25	51.9%

School based surveys in this community in rural KwaZulu-Natal demonstrate that HIV infection in young men <20 years is rare and remains under 2%. In contrast, HIV infection rises rapidly from age 14 in adolescent girls and young women and by age 20 HIV prevalence is 20% (Table 2). This age-sex difference in HIV infection between adolescent girls and young women compared to their male peers is common across Africa and is a key driver of new HIV infections in the region and highlights the impetus for women initiated HIV prevention technologies, particularly for women unable to negotiate mutually faithful monogamous relationships; consistent and correct male or female condom use; partner HIV testing and disclosure of results or partners uptake of voluntary medical male circumcision (VMMC).

**Table 2:** HIV prevalence in Grade 9 & 10 high school learners in rural KwaZulu-Natal (2010)

Age Group (years)	HIV Prevalence (2010) % (95% Confidence Interval)	
	Male (n=1252)	Female (n= 1423)
≤15	<b>1.0</b> (0.0 - 2.2)	<b>2.6</b> (1.2 - 4.0)
16-17	<b>1.1</b> (0.2 - 2.0)	<b>6.1</b> (2.6 - 9.6)
18-19	<b>1.5</b> (0 - 3.7)	<b>13.6</b> (9.0 - 18.1)
≥20	<b>1.8</b> (0 - 3.9)	<b>24.7</b> (6.3 - 43.1)

### 1.2 Factors influencing HIV risk in women

The high HIV incidence rates observed among adolescent girls and young women in sub-Saharan Africa suggest that other factors beyond behaviour may be contributing to the heightened vulnerability in this group. Women are biologically more vulnerable to HIV and are, on average, twice as likely as men to become infected after a single sexual encounter<sup>[5]</sup>.

Although the biological mechanisms that make women more vulnerable than men in acquiring HIV are not fully understood, the large exposed mucosal surface of the vagina may facilitate HIV acquisition. Further, the high levels of activation of the immune cells in the female genital tract and the increased expression of HIV co-receptors in cervical cells compared to foreskin cells may also explain why women have a higher per-act risk of HIV acquisition than men<sup>[6, 7]</sup>. Genital trauma experienced as a result of forced or unwanted sexual intercourse can facilitate HIV transmission<sup>[8]</sup>.

Inflammation of the female genital tract may also be an important risk factor facilitating HIV acquisition. Analysis of female genital tract samples from a recent microbicide trial that assessed tenofovir gel for HIV prevention showed that genital inflammation, defined by combinations of elevated pro-inflammatory cytokines, was associated with a 3-fold increased risk of HIV acquisition<sup>[9]</sup>. The cause of this inflammation is still unclear, and a better understanding of the immunological basis of correlates of HIV transmission in young women could yield useful clues to future HIV prevention technologies and strategies.

Sexual debut also marks the initial exposure to a number of sexually transmitted pathogens, including viruses such as herpes simplex type-2 virus and human papillomavirus, which have been associated with a 2- to 3-fold increased risk of HIV transmission<sup>[10, 11]</sup>. The use of injectable hormonal contraception, particularly depot-medroxyprogesterone acetate (DMPA), has also recently emerged as a potential mediator of HIV risk. There remains uncertainty about the association between DMPA use and HIV risk in young women, DMPA remains the most common choice of contraceptive in sub-Saharan Africa. A meta-analysis that included 18 studies has suggested that DMPA is associated with a moderate increased risk of HIV acquisition<sup>[12]</sup>.

The World Health Organisation (WHO) recommends that while we wait for definitive evidence of the association between DMPA and HIV risk from an ongoing randomized controlled trial, women at high risk of HIV using this method should be strongly advised to also use condoms (male or female). The United States Agency for International Development (USAID) has developed a strategic communication framework to guide country-level activities to communicate the risks and benefits of hormonal contraception among women at risk of, or living with, HIV in an easy-to-understand and comprehensive format<sup>[13]</sup>.

### **1.3 ARV based pre-exposure prophylaxis (PrEP) – a new prevention tool**

Since 2010, the outcomes of several trials have demonstrated the prevention benefit of the prophylactic use of antiretroviral (ARV) drugs that has generated new hope in preventing sexually acquired HIV infection. These PrEP clinical trials using tenofovir alone, or in combination with emtricitabine (Truvada<sup>®</sup>), have demonstrated safety and efficacy in preventing HIV acquisition among men who have sex with men, transgender women, injecting drug users, sero-discordant couples, and heterosexual men and women<sup>[14-19]</sup>. Importantly, no major safety concerns have been identified. A key and consistent message from these trials is that PrEP needs to be used in order for it to work and that efficacy is dependent on adherence. While the PrEP data from men is consistent across all trials with a protective benefit ranging from 44%-96% using both daily and intermittent dosing strategies<sup>[14-19]</sup>, the data in women in trials that have evaluated oral and topical PrEP in southern Africa have yielded mixed results<sup>[4, 20-22]</sup>.

Microbiome analysis of vaginal specimens from a sample of CAPRISA 004 participants with genital inflammation and controls demonstrated that the presence of *Prevotella bivia* was 19 times more likely to be associated with genital inflammation and 13 times more likely to be associated with HIV infection. Proteomics analysis of vaginal specimens from participants in the CAPRISA 004 trial suggests that a vaginal environment with a pH between 4.5-5.5 that supports a Lactobacillus dominant genital tract is associated with lower rates of HIV acquisition and enhanced efficacy of tenofovir gel compared to those with vaginal dysbiosis characterized by a high pH and dominance of *Gardenerella vaginalis*, *Trichomonas* and *Prevotella bivia*. Even as these findings are further investigated they highlight the importance of monitoring vaginal health during PrEP use.



In September 2015 the WHO ARV Guidelines included the provision of tenofovir-containing PrEP to be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches<sup>[23]</sup>. In November 2015, the South African Medicines Control Council (MCC) licensed the daily use of Truvada® as PrEP for those at risk for HIV infection<sup>[24]</sup>. The South African Ministry of Health has held several consultative meetings on inclusion of PrEP as part of combination prevention and is currently providing PrEP to sex workers. It has taken a more cautious approach on provision to PrEP to other populations and has indicated that their decision will be based on the outcome of demonstration projects.

Given the high HIV incidence rates in adolescent girls and young women, this proposed demonstration project is being undertaken to advance understanding of programmatic scale-up of PrEP as part of combination prevention and particularly for young women. Daily tenofovir disoproxil fumarate + emtricitabine is the only woman initiated HIV prevention option available to young women at high risk of acquiring HIV infection but unable to practice the traditional ABC (Abstinence, behaviour change, condoms and medical male circumcision) approach. We cannot afford to exclude young women from access to oral PrEP if we are to realize the goals of an AIDS -free generation.

Questions such as who will need or want oral PrEP? who will consistently adhere?, and what support needs to be in place to facilitate adoption of PrEP? need to be addressed now as part of demonstration projects. For those who choose to use PrEP - what proportion are adherent and what are the factors influencing adherence? and for those who are non-adherent what are the barriers to adherence? This data could be used to generate predictors of adherent PrEP clients and would enable providers to assess the appropriateness of PrEP as a prevention option for young women. There are several options to support adherence in volunteers experiencing challenges such as the use of trained adherence counsellors, the use of peer support programmes using adherent PrEP acceptors, and the monitoring of adherence using pharmacokinetic analysis in combination with adherence counselling.

There are a range of novel agents and formulations in development however these data will not be available before the next 5-7 years. In the meantime we need to address the current HIV prevention needs of women with what is available and optimise their provision for women who are willing to use these interventions.

#### **1.4 The CAPRISA PrEP Demonstration Project**

In the past 8 years, CAPRISA has garnered extensive implementation science experience in introducing new HIV prevention and treatment interventions into the public sector in KwaZulu-Natal that include, amongst others, integration of HIV and TB services<sup>[25]</sup>; task shifting for ARV treatment provision<sup>[26, 27]</sup>; targeting, demand creation and provision of high throughput VMMC to young men in school<sup>[27]</sup>; provision of mobile sexual reproductive health (SRH) services to adolescent girls and young women in and out of schools; integration of tenofovir gel provision into family planning services<sup>[28]</sup> and HIV prevention in breastfeeding mothers<sup>[29]</sup>. These experiences have underscored the importance of:

- partnerships with the community and health care providers at public sector health facilities;
- regular community and public awareness raising of new interventions and dispelling of myths and rumours;
- active demand creation for the new intervention;
- working with early and instant adopters of the new intervention for onward diffusion of the intervention and peer supporters to those having challenges adopting new interventions;
- facilitating access to the intervention;
- starting health care provider training early in the process so that the processes are validated they are internalising what is evolving;
- having an opportunity to input into what is emerging for future programmatic scale-up and identifying health system delivery and scope of practice challenges;

- taking the diversity of user needs,
- facilitators and challenges to uptake and adoption of new interventions.

This demonstration project for oral PrEP provision draws on these lessons and builds on foundations that have been laid in the communities we will be working in. Importantly, PrEP is not a stand-alone intervention but rather integrated into existing HIV prevention options and SRH services. PrEP provision for over 18 year old persons will include adherence support in the context of clear, positive messaging and integration with delivery of other services that meet their HIV prevention and SRH needs and will include: HIV testing, fertility control services that include family planning, emergency contraception, screening and treatment of sexually transmitted infections (STI), pre-natal care, post-exposure prophylaxis, social support and referrals if there is intimate partner violence. This demonstration project will address how best to innovate, implement and integrate oral PrEP within a combination HIV prevention package. In addition to increasing public awareness, demand creation and support as well as various innovative adherence strategies will be developed to facilitate uptake and PrEP effectiveness in the demonstration project. This PrEP demonstration project will identify in two high HIV burden districts in KwaZulu-Natal: who is likely to use PrEP; how PrEP will be used (understanding pill taking practices); barriers to consistent adherence; how PrEP will change current behavioural practices for HIV prevention (risk compensation); and what support and training is required for service providers.

Stigma and discrimination, perceived or real, is extensive and has been a barrier to our ability to deliver programmes to scale and reach key populations. In order to minimise labelling of PrEP as a young women intervention and re-enforcing HIV as a women's only issue, information and services will be provided to both men and women who are eligible and at risk of acquiring HIV infection and willing to use oral PrEP for HIV prevention. Indeed, the inclusion of men in the introduction of PrEP through public awareness raising and demand creation, will be pivotal to acceptability and uptake of a comprehensive prevention package as younger women in these settings typically infected by older men and HIV acquisition in men occurs about 5-7 years later compared to adolescent girls and young women. At this point PrEP will not be provided to women under 18 years of age but we will share information and include them in SRH service provision and access to other interventions available in the DREAMS (**D**etermined, **R**esilient, **E**mpowered, **A**IDS-free, **M**entored, and **S**afe women) package including more preparatory activities that will be undertaken for PrEP introduction and support them to remain HIV-free, free of other STIs, prevent unplanned pregnancies and to complete high school. Based on demand for PrEP in young people under 18 years of age, the MCC will be approached to discuss access to PrEP for <18 year old boys and girls.

The success of PrEP to meet the needs of adolescent girls and young women will also require technically skilled and competent providers. In parallel with implementing PrEP as part of SRH services at the CAPRISA urban, peri-urban and rural Research Clinics, we will start training and capacity building of staff at the primary health care (PHC) clinics in the sub-districts where the CAPRISA clinics are based. This will ensure a smooth transition from the demonstration project to public sector PHC facilities at the end of the project. Our experiences with clients and providers in the rural CAPRISA clinic and PHC facilities will be manualized and validated for use an urban and peri-urban setting.

## **2. PROJECT GOALS AND ANTICIPATED OUTCOMES**

### **2.1 Project Goal**

To assess the feasibility, acceptability, uptake and patterns of use of daily, **tenofovir** disoproxil fumarate + emtricitabine provided as part of SRH services to young women and men at risk of acquiring HIV in urban and rural KwaZulu-Natal.

### **2.2 Anticipated outcomes**

- A new integrated approach for preventing unplanned pregnancies, STI prevention, enhanced vaginal health and HIV prevention;

- Approach for establishing public awareness, demand for, acceptability, adherence and support of oral daily PrEP for men and women;
- Identify patterns of PrEP use in volunteers to inform programmatic scale-up;
- Monitor safety of PrEP provision;
- Identify predictors of adherence and non-adherence;
- Assess the effectiveness of peer adherence support for non-adherers of PrEP;
- Monitor trends in sexual behaviour with the introduction of PrEP as part of a combination HIV prevention package;
- Determine contraceptive use and pregnancy rates among female PrEP clients;
- Develop a critical mass of trained health care workers skilled to provide PrEP in these settings within a context of combination HIV prevention and integrated into SRH services.

### **3 APPROACH**

#### **3.1 Project Site and Population**

This project will be conducted at the urban, peri-urban and rural CAPRISA Clinics in KwaZulu-Natal, South Africa. The high HIV prevalence and incidence rate in eThekweni, Vulindlela and Umlazi settings in KwaZulu-Natal, South Africa highlights the importance of HIV prevention technologies for young women in this setting.

We anticipate that we will be providing oral PrEP to a total of 2,000 women and men with about 1,200 young people in Vulindlela in year one; 500 young people in the urban CAPRISA clinic and about 300 young post-partum women in peri-urban KwaZulu-Natal within the first 12 months of PrEP initiation. This protocol is primarily written for female clients but will be open for access by men in this community.

The demonstration project will be implemented at the following CAPRISA clinics in partnership with the adjoining public sector health facility:

- Rural: CAPRISA Vulindlela Clinical Research Site, KwaZulu-Natal, South Africa
- Urban: CAPRISA eThekweni Clinical Research Site, Durban, South Africa (STI Clients)
- Peri-Urban: CAPRISA Umlazi Clinical Research Site, Umlazi, Durban South Africa (Peri- and post-partum cohort)

##### **3.1.1 CAPRISA Vulindlela and sub-district Primary Health Clinics (rural)**

The CAPRISA Vulindlela Clinic Research Site (CVCRS) is situated in the sub-district of Vulindlela, a rural community, with approximately 90,000 residents in the KwaZulu-Natal midlands, about 150km north-west of Durban. Public sector PHC services are provided through seven clinics in the sub-district. These nurse-managed services provide antenatal care (ANC), family planning, childhood immunizations, STI treatment, minor ailment care, tuberculosis treatment and HIV voluntary counseling and testing (HCT). The CVC adjoins the Mafakathini PHC clinic, which has an average of 500 clients per month seeking family planning, ANC and post-partum services.

##### **3.1.2 CAPRISA eThekweni (Urban), PCZCDC (Urban)**

The CAPRISA eThekweni Clinic Research Site (CECRS), adjoins the Prince Cyril Zulu Communicable Disease Centre (PCZCDC), a designated dedicated PHC clinic of the Durban City Health Department primarily for the diagnosis and treatment of STIs and tuberculosis. The PCZCDC and CEC are conveniently situated in the Warwick triangle in the metropolitan region of Durban which is a public transportation hub. Annually, approximately 40,000 cases of STIs are treated at this clinic, about 36,000 of which are new cases. Given the high prevalence of HIV infection in South Africa and the strong association between STIs and HIV acquisition, these PCZCDC clients are at high risk of acquiring and transmitting HIV through sex.

### **3.1.3 CAPRISA Umlazi Research Clinic and Primary Health clinics (Peri-Urban)**

The CAPRISA Umlazi Research Clinic is a well-established research facility that has been conducting HIV prevention research with a particular focus on prevention of mother-to-child transmission for the past 9 years. Umlazi, the largest township in KwaZulu-Natal, has a population of about 400,000, with 40 secondary schools, one district hospital, the Prince Mshiyeni Memorial Hospital, and 17 provincial clinics and 3 municipal clinics in the Umlazi district. More than 40% of prenatal clinic attendees in Umlazi are HIV positive.

A multi-pronged approach will be used to identify potential PrEP clients with a particular emphasis on most at risk cohorts. Previous CAPRISA 008 participants of public sector antenatal, post-natal, STI and family planning fixed and mobile services; participants of research of investigational new products underway at the CAPRISA research clinic; and clients who walk into the CAPRISA clinics requesting PrEP. General information about PrEP will be provided to these groups.

### **3.2 Procedures**

An overview of visit flow and sequence of procedures and follow-up of PrEP volunteers over 18 years of age is provided in Figure 1.

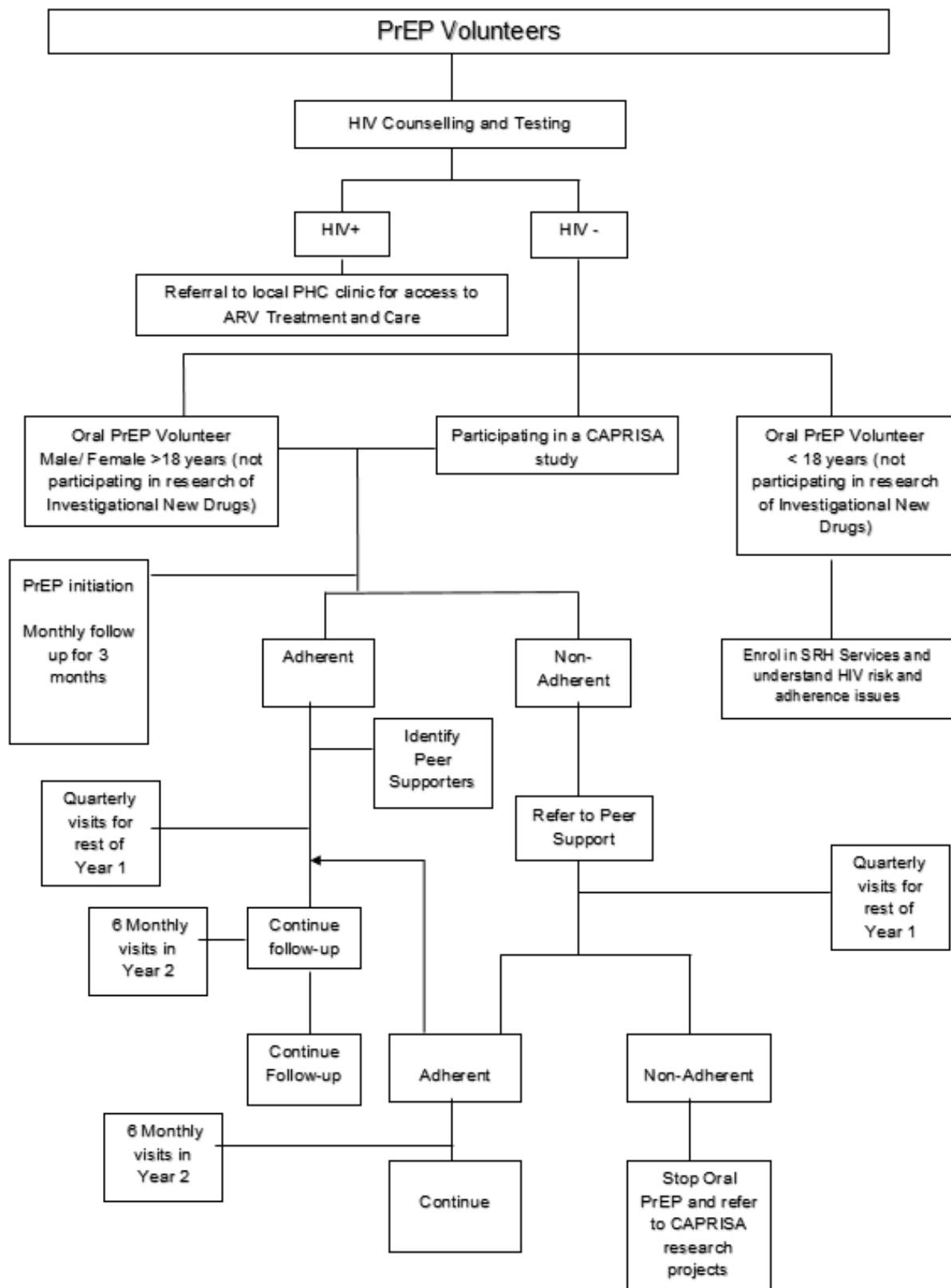
Follow-up will be monthly in the first three months post-PrEP initiation and for adherers (as measured by monthly drug levels) will switch to quarterly visits. After the initial 3 month period, those clients facing adherence challenges and who were classified as being Poor Adherers (PA) based on pharmacokinetic results, but who are keen to continue using PrEP and willing to receive peer adherence support, will be assigned to a peer adherence support group.

Following a three month period of exposure to the peer adherence support strategy with monthly drug level monitoring those who are adherent will be switched to a quarterly visit schedule. Clients who continue to demonstrate poor adherence, will be discontinued from oral PrEP and offered referral into other HIV prevention research studies underway at the respective CAPRISA research facility. Annual creatinine clearance assays will be undertaken.

Volunteers under the age of 18 years will be provided information on PrEP, to understand motivation to use PrEP and anticipated adherence challenges. They will have access to comprehensive SRH services. The key focus will be prevention of HIV infection, STI, unplanned pregnancies and keeping them in school.

Initially, oral PrEP will be provided to volunteers using both CAPRISA's mobile and fixed SRH services. As staff training and capacity is built at the public sector PHC clinics the PrEP service will start to transition to the PHC clinics. Volunteers testing positive will be referred to the PHC clinic where treatment can be accessed at no cost.

Those who are not interested in PrEP but are interested in other research for HIV prevention will be referred to studies underway at CAPRISA and, if they meet the respective study eligibility criteria, will be enrolled. Participants from research underway at CAPRISA and wanting to use PrEP simultaneously will be able to access PrEP through this demonstration project following the procedures outlined above.



**Figure 1:** Overview of Project Procedures and Follow up

### 3.3 Inclusion criteria

Volunteers must meet all of the following criteria at enrollment in order to be eligible to access daily, oral tenofovir disoproxil fumarate + emtricitabine as PrEP:

- Be 18 years and older
- Able and willing to provide first person informed consent for screening, cognitive ability to understand interventions and follow up procedures relating to PrEP use and specimen storage
- HIV negative
- Normal creatinine clearance levels (>60ml/min)

### 3.4 Exclusion criteria

- HIV positive status
- Any medical condition or other factors contra-indicated for PrEP use
- Any mental health condition which would preclude comprehension of informed consent and adherence to PrEP

### 3.5 General information sessions on PrEP

Volunteers will receive information about PrEP in the context of comprehensive HIV prevention and SRH service information. Available written material available from the Department of Health on PrEP will be used and includes information on oral PrEP, how it works, benefits of use and potential side effects (refer to appendix II).

### 3.6 HIV Counselling and testing linked to SRH services

HIV testing will be provided in the context of pre- and post-test counselling at screening and designated follow-up visits. Male and female condoms, access to contraceptives, screening and treatment of STIs will be accessible at all visits and as needed.

### 3.7 Diagnosis of vaginal dysbiosis

In addition to the reported history, the following will be done:

3.7.1 Microscopic examination will be done for the clinical diagnosis of vaginal dysbiosis also known as Bacterial Vaginosis (BV). A single vulvo vaginal swab will be collected and this swab will be used for:

- vaginal pH testing
- making a BV slide for Bacterial Vaginosis screen and recording of Nugent score
- performing a wet mount to establish the presence of Clue cells, Trichomonas vaginalis, yeast,
- rapid Trichomonas test using the OSOM Rapid Trichomonas test kit

Demonstration of clue cells on a saline smear is the most specific diagnostic criterion. A pH greater than 4.5 is an indication of BV in up to 90% of patients, whilst a positive whiff test is an indicator in up to 70% of patients. Nugent's criteria will be used to quantify or grade bacteria via Gram staining of vaginal cells. These criteria evaluate the following 3 types of bacteria and assign scores to each as shown:

- Lactobacillus (score, 0-4)
- Bacteroides/Gardnerella (score, 0-4)
- Mobiluncus (score, 0-2)
- Total scores are calculated and interpreted as follows:
- 0-3: Normal
- 4-6: Intermediate bacterial count
- 7-10: BV

## The Nugent scoring criteria used to evaluate Gram stain

Lactobacilli Morphotypes	<i>Gardnerella / Bacteroides</i> Morphotypes	<i>Mobiluncus</i> Morphotypes (Curved Gram Variable rods)
<ul style="list-style-type: none"> <li>Score 0 for &gt;30</li> <li>Score 1 for 15-30</li> <li>Score 2 for 14</li> <li>Score 3 for &lt;1&gt;</li> <li>Score 4 for 0</li> </ul>	<ul style="list-style-type: none"> <li>Score 0 for 0</li> <li>Score 1 for &lt;1&gt;</li> <li>Score 2 for 1-4</li> <li>Score 3 for 5-30</li> <li>Score 4 for &gt;30</li> </ul>	<ul style="list-style-type: none"> <li>Score 0 for 0</li> <li>Score 1 for &lt;5</li> <li>Score 2 for 5+</li> </ul>

3.7.2 A second vulvo-vaginal swab will be collected, for storage and later evaluation of vaginal microbiome. This will be done by using pyrosequencing analysis of PCR-amplified 16S V4 rDNA.

### 3.8 PrEP initiation and follow-up

Volunteers who are HIV negative, have normal creatinine clearance levels (>60ml/min), will be initiated on daily oral combination of tenofovir disoproxil fumarate + emtricitabine. Clients will be provided with a 30 day supply of PrEP and requested to return to the facility for monitoring of side-effects and adherence support if indicated. However, in the first 14 days, a bidirectional system will be used where the client will have an option to call the clinic for adherence support or have the site staff call them to discuss any challenges. After the Month 1 visit, two additional monthly visits will be scheduled.

HIV status, STI screening will be completed and family planning needs assessed. Adherence will be assessed using pill counts and blood draws for drug levels. Thereafter, follow-up contact visits will occur quarterly for adherent clients and only pill counts will be used to measure adherence. HIV status, STI screening will be completed and fertility control needs assessed at these quarterly visits. Creatinine clearance will be monitored in the first quarter of PrEP use and thereafter annually.

### 3.9 Peer adherence support

Those experiencing adherence challenges will be linked to a peer adherence support programme and if adherence does not improve within three months they will be referred to other research underway at CAPRISA evaluating less user dependent HIV prevention technologies.

### 3.10 Expanding PrEP initiation to other sites

In the first 3-6 months, oral PrEP access will be limited to men and women over 18 years old. Following this period, based on demand and barring any safety concerns, permission to expand PrEP to young women under 18 years of age will be sought from the South African Medical Control Council.

### 3.11 Treatment and Care

PrEP clients who become infected or pregnant will be referred to the local PHC clinics for ongoing care. HIV-infected clients will be offered the option to join the CAPRISA 002 study of recently infected individuals.

### 3.12 Laboratory Procedures

Validation of laboratory procedures and systems for shipping specimens and receipt of laboratory results will be undertaken as per the CAPRISA Laboratory standard operating procedures (SOPs). These systems will be reviewed regularly to ensure streamlined, high quality and efficient services.

## **4 OVERVIEW OF VISITS, PROCEDURES AND DATA COLLECTION**

A detailed schedule of procedures is presented in Appendix II. Study staff will be trained to conduct study procedures in a customized manner to meet user needs. SOPs will be used to guide the relevant standardized aspects of the project such as laboratory assays.

### **4.1 Screening visit**

Volunteers will receive information about the CAPRISA PrEP Demonstration Project using the Department of Health oral PrEP materials. Screening will be completed in a stepwise manner. The first step includes the provision of introductory PrEP information and obtaining written informed consent for screening procedures. HIV testing including pre- and post-test counselling will be done and only HIV negative clients will continue with the screening process. A screening assessment will be administered by the counselor to determine volunteer's eligibility for PrEP. Two rapid HIV tests will be utilized to determine HIV status. Blood will be drawn for creatinine clearance levels to be determined. Locator data will be recorded in a locator log and a follow up second visit date will be allocated. For potential volunteers who do not meet the project eligibility criteria, the screening process will be discontinued when ineligibility is determined.

The following procedures will be completed:

#### ***Administrative, behavioural, and regulatory procedures***

- Informed consent for screening
- Collection of the following:
  - Demographic information
  - Locator information
- Eligibility assessment
- HIV pre- / post-test counselling and HIV risk reduction counselling
- Provision of HIV prevention methods (i.e.: condoms), and fertility control options
- Schedule next visit

#### ***Clinical procedures***

- Medical history
- Blood draw / phlebotomy
- Provision of test results

#### ***Laboratory procedures***

- HIV rapid testing
- Urine pregnancy testing (if indicated)
- Vaginal pH screen
- Creatinine level testing, Hepatitis B surface antigen (HBsAg), Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST)

### **4.2 Enrolment visit (day/month 0)**

By this visit, the following would have been created for the potential PrEP user:

- Study file that includes a locator log, source documents, vitals chart
- Copy of consent for screening procedures
- HIV test results and creatinine clearance level results

All potential PrEP clients will be seen by a nurse for a complete medical history and clinical assessment. As part of STI screening, five vaginal swabs will be collected by the nurse one for wet prep, KOH and pH; one for Gram staining; one for Trichomonas culture; one for DNA extraction (microbiome) and one for storage. Two genital swabs will be collected from men, one for STI testing and one for storage. PrEP will be initiated if deemed appropriate. If necessary the site clinician will be consulted about PrEP initiation.



A follow-up visit will be scheduled, according to the appointment schedule outlined below. A multidisciplinary team approach will be undertaken involving the nurse, counselor, pharmacist, administrator, and other linked services. If a potential PrEP user is found to have any medical problems that require further investigation and/or treatment they will be directed first to the site clinician and thereafter to the closest referral hospital with a referral letter.

#### ***Administrative, behavioural, and regulatory procedures***

- Review eligibility
- HIV risk perception and behavioural assessment
- Update locator information
- Schedule next visit

#### ***Clinical procedures***

- Medical history
- Pelvic exam and genital specimen collection
- Blood draw/ phlebotomy
- Provision of test results

#### ***Pharmacy procedures***

- Provision of oral PrEP

#### ***Laboratory procedures***

- HIV rapid testing
- Urine pregnancy testing (if indicated)
- Vaginal pH screen
- STI testing

### **4.3 Follow-up visits (monthly and quarterly)**

On completion of the scheduled procedures and following review of screening bloods and any abnormalities addressed, the clinical staff will assess the clients PrEP adherence through self-reports, pill counts and bloods. PrEP clients who experience toxicity, intolerance, or other contra-indications will be exited from the project.

PrEP clients will receive information to recognize side effects and to seek medical advice promptly. If the adverse event can be managed on site, the appropriate treatment will be implemented and user treated on an out-patient basis.

Clients who have adherence challenges will be enrolled in the peer adherence support programme, and those with persistent adherence challenges but would still like to participate in other HIV prevention studies of alternate formulations and/or dosing options will be referred to other studies underway at the CAPRISA research site.

Monthly follow-up visits are scheduled on a 28-day schedule for the first three months, with a 14-day visit window on either side. Thereafter visits will be scheduled on an 84-day schedule (every three months), with a 28-day visit window on either side. For clients who do not complete scheduled visits within the allowable window, the visit will be considered “missed” and relevant CRFs will be completed to document the missed visit.

To minimise monotherapy in those with breakthrough infection, clients will be provided with information on acute infection signs and symptoms and will be requested to come back to the CAPRISA Clinic

HIV-uninfected clients who become infected during follow-up will be referred to the long-term CAPRISA Acute Infection cohort study, which have provisions for care, antiretroviral therapy (ART) and support for those infected with HIV. These services are provided at no cost to the user. For those who do not wish to enrol in the CAPRISA Acute Infection Study post-seroconversion, they will be referred to their preferred AIDS care provider which could

include government or non-governmental AIDS care services for ongoing clinical management and care.

Clients who become pregnant during follow-up may be maintained in this study, however follow-up procedures may be modified with the principal change being the discontinuation of pelvic examinations and genital specimen collection after 24 weeks of pregnancy.

#### ***Administrative, behavioural, and regulatory procedures***

- Update locator information
- HIV pre- / post-test counselling and HIV/STI risk reduction counselling
- Provision of HIV prevention methods (e.g. condoms);
- Diagnostic screening and treat STIs (quarterly) and syndromic treatment (monthly)
- Fertility control (if indicated)
- Assessment of PrEP adherence (questionnaire)
- Collect HIV risk perception and behavioural data
- Schedule next visit

#### ***Clinical procedures***

- Medical history
- Blood draw (monthly for first 3 months and quarterly thereafter)
- Assessment of PrEP side effects
- Pelvic examination (month 3 only and quarterly thereafter)
- Provision of test results
- Prescription for PrEP

#### ***Laboratory procedures***

- HIV rapid testing
- Urine pregnancy testing if indicated
- Tenofovir drug level testing (DBS)
- STI testing and treatment if indicated
- Vaginal pH screen
- Creatinine level testing, HBsAg, ALT and AST (first quarter, thereafter annually)

#### ***Pharmacy procedures***

- Provision of oral PrEP
- Provision of additional medication if indicated

### **4.4 Exit Visit**

#### ***Administrative, behavioural, and regulatory procedures***

- Update locator information
- HIV pre- / post-test counselling and HIV/STI risk reduction counselling
- Provision of HIV prevention methods (e.g. condoms),
- Fertility control (if indicated)
- HIV risk perception and behavioural assessment
- Assessment of PrEP adherence (questionnaire)

#### ***Clinical procedures***

- Medical history
- STI screening
- Assessment of PrEP side effects
- Pelvic examination and genital specimen collection
- Provision of test results

### **Laboratory procedures**

- HIV rapid testing
- Urine pregnancy testing if indicated
- Tenofovir drug level testing (DBS)
- Vaginal pH screen
- STI testing

### **4.5 Interim/Unscheduled contacts and visits**

Interim visits may be performed at any time during follow-up for a number of reasons, which include, but may not be limited to, the following:

- For administrative reasons, e.g., a user may have questions for staff or may need to re-schedule a follow-up visit.
- For interim STI counselling and or treatment in response to STI symptoms.
- For interim HIV counselling and testing in response to presumed exposure to HIV or seroconversion symptoms.
- Contraception counselling and/or provision
- To provide clients with the results of confirmatory HIV or other test results
- For other reasons – at the request of project staff or the user

## **5 STAFFING**

A multidisciplinary disciplinary team will be established at each site. Final clinical staff numbers will be dependent on PrEP uptake and demand at each site.

<b>DESIGNATION</b>	<b>Numbers</b>	<b>ROLE</b>
Site Project Manager	1	Overall oversight and Management of Team and Implementation of Project
Project assistant	1	Assist the Site Manager with day to day implementation of project; regulatory oversight
Clinician	2	Overall care of all PrEP clients
Nurses	3	Monitoring & f/up of all patients Adherence support Clinical assessments
Pharmacist	1	Drug procurement, dispensing and accountability
Pharmacist assistant	1	Support pharmacist
Data Manager	1	Capture & management of data
Admin Assistant	1	General secretarial and admin duties
Counselors	2	Pre- & post-test counseling Information
Peer Volunteers	Up to 6	Adherence support

## **6 PHARMACY**

The CAPRISA protocol pharmacist/designate will take overall responsibility for the acquisition and distribution of oral PrEP (tenofovir disoproxil fumarate + emtricitabine) to the project sites. A site based pharmacist at each of the three CAPRISA research sites will be responsible for temperature controlled, secure storage, dispensing and accountability of oral PrEP.

### **6.1 Drug Procurement**

Procurement will be either via a donation programme and/or if purchased the lowest priced generic drugs will be procured.

### **6.2 Drug Storage & Feasibility**

Each research site has a registered pharmacy where PrEP will be dispensed. The CAPRISA eThekweni pharmacy source the bulk PrEP for all sites. Procurement records

(invoices) will be maintained by the protocol pharmacist for all drug purchases and/or donations. Electronic dispensing records (iDART) will be maintained each time stock is dispensed at the site pharmacies. All procurement, storage, transport and dispensing procedures will be in accordance with South African Pharmacy Council stipulated Good Pharmacy Practice guidelines, as amended from time to time.

### **6.3 Dispensing Procedure**

The Site Pharmacist receives an original prescription from the project clinician. This prescription is then reviewed for clinical accuracy and the following information:

- Client's name and UID.
- allergies known or suspected
- date
- name and quantity of the medicine to be dispensed, as well as instruction for use
- signature of the authorized prescriber.

The Site Pharmacist or designee identifies the bulk pack of medicine in the appropriate designated storage space by its international non-proprietary name, dosage form and strength. Quantity dispensed will be sufficient for a 30 day supply per month (issued as 30 tablets at enrollment for month 0) for the first 3 months, thereafter 3 months' supply (90 tablets) will be provided.

Each site will be supplied with 7 day pill boxes to be provided to the PrEP users when the drugs are dispensed.

## **7 SUPPORTING PREP USE THROUGH PEER ADHERENCE SUPPORT**

Structured adherence assessments will be undertaken at scheduled follow up visits using a combination of pill counts, self-reports and drugs levels.

### **7.1 Adherence support**

Non-adherers will be assigned to peer adherence support programme. The adherence support programme will require an understanding of the key motivators for adoption, barriers and challenges to adherence, ways to routinize pill taking behaviour, and how to promote consistent adherence to oral PrEP. Community advocacy and peer adherence support will be utilised as an innovative way to promote product uptake and sustainable adherence.

Using a combination of self-report adherence data and objective markers such as pill counts and drug levels we will be able to identify adherent and non-adherent PrEP users. Non-adherent PrEP users will receive counselling and support using motivational interviewing to try and understand their challenges to adherence – this could include weekly SMS reminders or a phone call or participation in group activities, and referral to participate in a peer adherence support programme (CAP-PAS).

After three months of project staff provision of adherence support, those still experiencing challenges will be given the option to explore other prevention options or receive support from a peer adherence programme supporter (PAPS). Adherent PrEP users will be identified using the same indicators as the non-adherers and provided the option to be trained as peer adherence programme supporters.

Those who agree to be PAPS must remain high adherers and have characteristics that are supportive and facilitative. They will receive customised structured training that builds on factors that have enabled them to be good adherers and address skills that they may require to support them to be effective PAPS. Peer Ambassadors will receive interactive training to provide adherence support and counselling initially over two days. The peer ambassadors will be given a reimbursement of R150 per month for peer support. Based on what the study staff learn in the first three months of the implementation of the demonstration project and on an ongoing basis from the peer adherence programme supporters this will be refined in an iterative manner.

The PAPS will where and if possible, be matched with non-adherers who are facing barriers that they have been able to overcome. Non-adherers will be provided with three months of peer adherence support. If they are unable to be adherent they will be referred to other options and terminated from further participation in this PrEP demonstration project.

## 7.2 Peer Adherence Support Enrolment

Peer adherence supports will consist of a demographically chosen group of individuals that are representative of the cohort and who will be matched to the poor adherers, either demographically or through similarity in risk profile, to the target population.

Clients who are non-adherent, will be counselled and offered peer adherence support.

The counselling support will be based on motivational interviewing and cover HIV and other sexual reproductive health needs. Motivational interviewing is based on an approach which focuses on identifying user barriers to PrEP use and finding self-initiated solutions to these barriers. Motivational interviewing is user-centred and aims to facilitate solutions that the user finds self-motivating and therefore more likely to be implemented. The key steps include:

- Introducing the discussion on PrEP use
- Assessing the user's PrEP use behaviours
- Assess importance of PrEP and confidence to use it
- Identify barriers in the importance/confidence of PrEP use and identify barriers
- Discuss strategies for addressing identified barriers
- Summarise potential strategies and ask the participant to select a realistic strategy
- Negotiate an action plan with the user and discuss how it will be implemented so that it can be reviewed when they meet again
- Document the action plan or next target so that it can be discussed and reviewed at the next visit.

A set of guidelines for the selection of effective peer adherence supporters (PAS) will be elaborated in the standard operating procedures (SOP) manual. Individuals who meet the following (minimum) criteria will be offered the opportunity to be trained as PAS to support and mentor non-adherent PrEP clients. Clients who:

- are consistently adherent to PrEP on assessment of drug levels
- willing to commit to providing adherence support
- have psychological variables like trustworthiness, confidentiality and supportiveness
- are able to maintain high levels of adherence to retain their designation

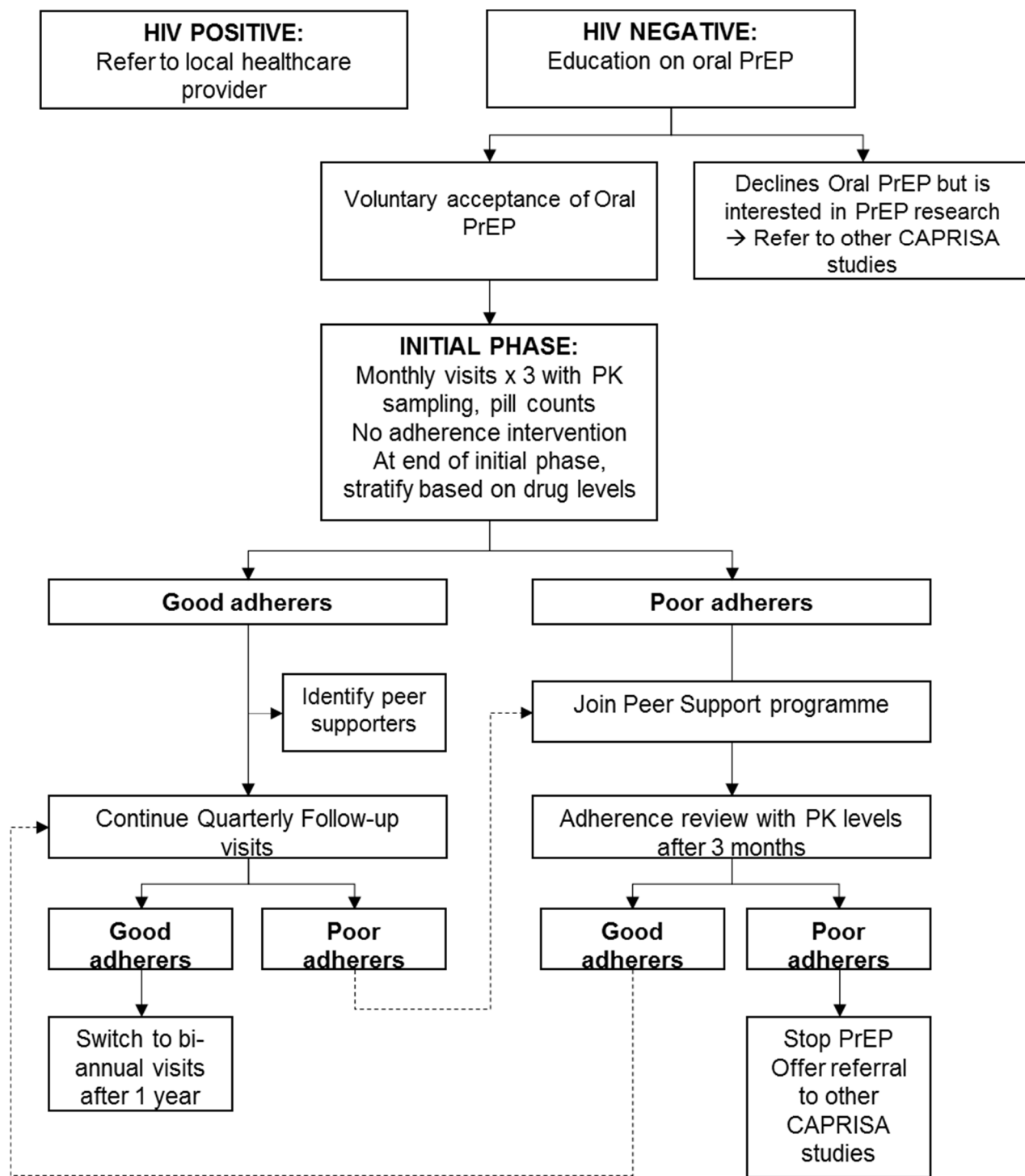
Clients who transition from non-adherent to adherent may become eligible to apply to become PAS (Figure 2).

At the end of a three month period following the participation in the peer adherence support programme, if a user is still experiencing adherence challenges they will be advised to explore other prevention options including other research underway at CAPRISA. The research studies underway at the CAPRISA sites pending meeting of eligibility criteria include:

- **HPTN 081:** A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection (BFC434/15)
- **CAPRISA 082:** Prospective Study of HIV Risk Factors and Prevention Choices in Young Women in KwaZulu-Natal, South Africa (BE458/15)
- **Other behavioural studies, including** CAPRISA Cognitive Project (BE304/16) and Partners Protocol (HSS/0945/015).

These studies are all approved through registered UKZN ethics committees, and recruitment is specified for each protocol. Clients will be made aware that this is optional and that they may not necessarily be eligible for the studies, but that if they would like to participate we

will link them to the study recruitment teams and they will undergo screening and consenting procedures relevant for those studies.



**Figure 2:** Peer adherence support

## **8 SCALING UP PREP PROVISION**

Based on experiences of PrEP provision in the rural, urban and peri-urban settings, a strategy for PrEP introduction through public sector facilities will be developed. This will include components as described below.

### **8.1 Development of PrEP messages: Public Awareness & Demand Creation**

Formative research of understanding women's preferences on oral PrEP will be conducted and various communication messages will be developed and tested as resources for public awareness and demand creation. This will ensure the use of various communication strategies for demand creation. For example, the use of emotions and desire for status, which are often key drivers in decision-making, will be explored for relevance and adaptation in communication messages. Framing of messages that promote positive benefits of self-esteem, confidence, responsibility and self-control will be integrated into the messaging. Other communication approaches such as entertainment, education and extended parallel process model (perceived risk and perceived efficacy) will be explored for the public awareness.

### **8.2 Community Mobilisation**

Integration of the community in the demonstration of oral PrEP will ensure the support of instant and new-adopters. Community mobilisation, engagement and community dialogues will encourage the active participation and support of the community for adopters, ensuring that they can become agents of support to adolescent girls and young women. An active and continuous community mobilisation programme ensures that communities become partners to HIV prevention instead of gatekeepers to new prevention technologies.

Through community mobilisation, the appropriate population will be accessed and retained in CAPRISA 084. The importance of community in individual's life will be taken into consideration by reaching to the community through presenting PrEP and HIV prevention information, and product demonstration in community meetings. The CAPRISA Community Program (CP) will inform, educate and mobilize the community to increase awareness and uptake of oral PrEP.

### **8.3 Development of resources for demand creation and providers**

Information, Education and Communication (IEC) materials, will be developed using participatory methodologies that engage PrEP clients in the various stages of research, design, development and testing. These resources will be designed as a catalyst for public awareness raising and demand creation. They will further facilitate a knowledge sharing platform for informing, educating and communicating with providers and clients on access to PrEP.

A comprehensive IEC package promotes understanding, awareness and demand for PrEP with potential clients, and the development of relevant resources for training providers in public health care settings for the promotion, administration and support of PrEP use.

### **8.4 Capacity Building for providers**

Training and capacity building of staff based at the government PHC clinics will continue in parallel with the demonstration project so that providers in the three public sector districts can acquire the necessary skills to integrate PrEP provision into existing health services. Staff will be trained using the various communication resources with a specific focus on oral PrEP. Staff training will include individual and small group adherence counselling skills. The last 6 months of the project will be utilized to consolidate the experiences in the three settings of PrEP provision for health care provider use, with the development of manuals and supporting material for awareness raising and user friendly adherence support interventions.

Some of the specific capacity building topics include:

- Product information on oral PrEP options
- Recruitment, screening and enrolment procedures
- Patient journey - monitoring and follow-up

- Adherence counselling
- Referrals
- Integrated prevention package options
- Comprehensive SRH, HIV and STI services

Workshops will be hosted with clients and providers facilitated by the project team to aid the process of enhancing materials development for clients and providers.

### **8.5 Marketing to popularize PrEP**

Aspects of social marketing will be adapted to encourage awareness of, and PrEP product recognition. Informed by instant adopters and rejecters of oral PrEP, product identity will be professionally designed as a visual representation, logo and slogan for PrEP as part of the demonstration project. This phase of the project will use the communicative process of a culture-centred approach to understand what clients think and know about oral PrEP, and their perceptions of PrEP. The development of a brand identity will ensure that clients are able to translate their knowledge, attitudes and positive perceptions of oral PrEP into a visual representation and slogan.

### **8.6 Monitoring and Evaluation of the Impact of PrEP provision**

Routinely collected data on HIV infection and pregnancy rates in young women utilizing antenatal and family planning services will be used to monitor the impact of PrEP provision within the context of SRH service provision. Population based data and school attendance rates, if available, will be utilized to determine impact at a population level. Data on patterns of PrEP use will be utilized to generate profiles of potential adherent PrEP clients to facilitate programmatic access.

## **9 PRIVACY AND USE OF PROJECT INFORMATION**

### **9.1 Confidentiality**

Every effort will be made to protect user privacy and confidentiality to the extent permitted by law. All user and project related information will be stored in lockable file cabinets in areas with access limited to project staff. Data collection, process, and administrative forms, and other reports will be identified by a coded number only, to maintain user confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from records identified by code number. All databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link UID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

User data, as identified by UID number only, will not be released without the user's written permission, except as necessary for review and monitoring by:

- Authorized project representatives
- University of KwaZulu-Natal's Biomedical research Ethics Committee
- Project Monitors

### **9.2 Use of information and publications**

Presentation and publication of the results of this study will be governed by CAPRISA's publication policy.



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## **APPENDICES**

- I. Schedule of Evaluation
- IIa. Informed Consent Form for participation in the CAPRISA 084 daily, oral PrEP Demonstration Project
- IIb. Informed Consent Form for Specimen Storage
- III. CAPRISA 084: DoH Oral PrEP pamphlet
- IV. Current GCP, HSP and HPCSA Certificates for all investigators

## Appendix I: Schedule of Evaluations

Procedure	Screen	Enrol	Follow-up				Exit
	Screening (up to 30 days)	Enrolment (day/month 0)	(Optional Follow up – 7 days after PrEP initiation)	Optional Follow up visit – 14 days after initiation	Monthly follow-up (months 1, 2 & 3)	Quarterly follow-up (month 4 onwards <sup>a</sup> )	Exit visit
	V0	V1	V2	V3	V4, V5, V6	V7 - V22	V23
<b>Administrative, Behavioural and Regulatory Procedures</b>							
Informed consent for participation	X						
Obtain Unique Identifier	X						
Eligibility assessment	X	X					
Demographic information	X						
Locator information	X	X	X	X	X	X	X
HIV pre/post-test counselling and risk reduction counselling	X	X		X	X	X	X
Provision of HIV prevention options (i.e.: condoms)	0	0	0	0	0	0	0
Fertility control (if indicated)	0	0	0	0	0	0	0
HIV self-testing home kits (if indicated)						0	0
HIV risk perception and behavioural assessment		X		X	X	X	X
Assessment of PrEP Adherence and adherence support counselling (Pill counts)			X	X	X	X	X
Peer Adherence support (if indicated)						0	0
Schedule next visit	X	X	X	X	X	X	
<b>Clinical Procedures</b>							
Medical history	X	X					X
Assessment of PrEP side effects			X	X	X	X	X
Pelvic exam and Genital specimen collection		X			X (month3 only)	X	X
Phlebotomy	X	x			X	X	
Provide test results if applicable		X			X	X	X
Prescription for oral PrEP		X		X	X	X	
<b>Perform Laboratory Evaluations</b>							
HIV serology (rapid tests)	X	X			X	X	X
Urine pregnancy test	X	X			X	X	X
Creatinine Clearance Levels	X				X (first quarter)	X (annually)	
Hepatitis B surface antigen (HBsAg), Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST)	X						
Tenofovir Drug level testing (DBS)					X	X	X
Vaginal pH testing	X	X			X	X	X
STI diagnostic testing <sup>c</sup> (urine, plasma and or genital specimens <sup>b</sup> )		X			X	X	X
<b>Pharmacy Procedures</b>							
Provision of PrEP		X		X	X	X	X
Amount of blood collected <sup>d</sup> in mls:	5ml	5 ml			10ml	15ml	15ml
<b>Footnotes and abbreviations:</b> DBS = dried blood spots; <sup>a</sup> This quarterly visit schedule will continue until clients are exited from this study; <sup>b</sup> Five vaginal swabs will be collected by nurses from each woman: one for wet prep, KOH, and pH, one for Gram staining, one for Trichomonas culture, one for DNA extraction (microbiome), and one for storage. <sup>c</sup> Two genital swabs will be collected from men, one for STI testing and One for storage. <sup>d</sup> Those who are STI positive will be offered counselling, treatment and partner(s) referral (if appropriate); <sup>e</sup> Blood volumes: Creatinine clearance (5ml); Drug level testing (DBS); 0 = if indicated							

**Appendix IIa: Informed Consent Form for participation in the CAPRISA 084 daily, oral PrEP Demonstration Project (separate document)**

**Appendix IIb: Informed Consent Form for Specimen Storage (Separate document)**

**Appendix III: . CAPRISA 084: DoH Oral PrEP pamphlet**

**Appendix IV: Current GCP, HSP and HPCSA Certificates for all investigators  
(separate document)**