Protocol

CAPRISA 008

Open-Label Randomized Controlled Trial to Assess the Implementation Effectiveness and Safety of 1% Tenofovir Gel Provision through Family Planning Services in KwaZulu-Natal, South Africa

Centre for the AIDS Programme of Research in South Africa (CAPRISA),
University of KwaZulu-Natal, Durban, South Africa,

In collaboration with
CONRAD, FHI360 & IHI

Principal Investigator
Quarraisha Abdool Karim, PhD

Co-Principal Investigators
Salim S. Abdool Karim, MBChB, MMed, FFPHM, PhD
Leila E Mansoor, BPharm, PhD

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PROTOCOL TEAM ROSTER:

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA (CAPRISA)

Quarraisha Abdool Karim, PhD
Principal Investigator
CAPRISA, Nelson R Mandela School of Medicine, University of KwaZulu-Natal , Private Bag 7, Congella 4013, Durban, South Africa
abdoolq2@ukzn.ac.za
T: 27-31-260-4208
F: 27-31-260-4566

Salim S. Abdool Karim, MBChB, FFPHM, PhD
Co-Principal Investigator
CAPRISA, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Private Bag 7, Congella 4013, Durban, South Africa
karims1@ukzn.ac.za
T: 27-31-260-4550
F: 27-31-260-4549

Leila E Mansoor, PhD
Co-Principal Investigator
CAPRISA , Nelson R Mandela School of Medicine, University of KwaZulu-Natal , Private Bag 7, Congella 4013, Durban, South Africa
mansoor@ukzn.ac.za
T: 27-31-260-4641
F: 27-31-260-4549

Cheryl Baxter, MSc
Research Associate
CAPRISA , Nelson R Mandela School of Medicine, University of KwaZulu-Natal , Private Bag 7, Congella 4013, Durban, South Africa
baxterc1@ukzn.ac.za
T: 27-31-260-4559
F: 27-31-260-4549

Bonginkosi Mdluli, MBChB
Vulindlela Site Principal Investigator
CAPRISA Vulindlela Clinic
Mafakatini
Vulindlela, South Africa
mdluli@ukzn.ac.za
T: 27-31-260-6875
F: 27-33-997-1425

Kathryn Mngadi, MBChB
eThekwini Site Principal Investigator
CAPRISA eThekwini Clinic
University of KwaZulu-Natal, Private Bag 7,
Congella 4013, Durban, South Africa
mngadik@ukzn.ac.za
T: 27-31-260-1927
F: 27-33-260-4566

Silvia Maarchalk, MSocSci
Vulindlela Site Project Director
CAPRISA Vulindlela Clinic
Mafakatini
Vulindlela, South Africa
maarschalk@ukzn.ac.za
T: 27-31-260-6861
F: 27-33-997-1425

Janet Frohlich, DCurMSocSci
Vulindlela Site Director
CAPRISA Vulindlela Clinic
Mafakatini
Vulindlela, South Africa
frohlichj@ukzn.ac.za
T: 27-31-260-6861
F: 27-33-997-1425

Tanuja Gengiah, MClinPharm, MS (Epi)
Protocol Pharmacist
CAPRISA, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Private Bag 7, Congella 4013, Durban, South Africa
gengiaht1@ukzn.ac.za
T: 27-31-260-4262
F: 27-31-260-4549

Sengeziwe Sibeko, MBChB, FCOG, MS (Epi)
Project Gynecologist
CAPRISA, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Private Bag 7, Congella 4013, Durban, South Africa
sibekos1@ukzn.ac.za
T: 27-31-260-4453
F: 27-31-260-4566

Ayesha BM Kharsany, PhD
Microbiologist
CAPRISA, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Private Bag 7, Congella 4013, Durban, South Africa
kharsany@ukzn.ac.za
T: 27-31-260 4558
F: 27-31-260 4566

Anneke Grobler, MSc
Protocol Statistician
CAPRISA, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Private Bag 7, Congella 4013, Durban, South Africa
grobler@ukzn.ac.za
T: 27-31-260 4392
F: 27-31-260 4566

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COLLABORATING ORGANIZATIONS:

CONRAD
Henry Gabelnick, PhD
Executive Director,
Janet Schafer
Administrator, Clinical and Regulatory Affairs
Jill Schwartz, MD, MPH.
Medical Director
CONRAD, 1911 Fort Myer Drive., Ste. 900,
Arlington, VA 22209,
hgabelnick@conrad.org
jschafer@conrad.org
jschwartz@conrad.org
T: 1-703-276 3904
F: 1-703-524 4744

FHI360
Kristine Torjesen, MD, MPH, FAAP
Scientist
Mario Chen, PhD
Statistician
FHI, PO Box 13950, Research Triangle Park, NC 27709, USA
ktorjesen@fhi360.org
mchen@fhi360.org
T: 1-919-544 7040 ext. 11521
F: 1-919-544 0207

Institute for Health Care Improvement (IHI)
Kedar S. Mate, MD
Senior Researcher
Pierre Barker, MBChB, MD, MRCP, FAAP
Senior Vice President
Institute for Healthcare Improvement
Weill Cornell Medical College
20 University Road, 7th Floor
Cambridge, MA 02138
kmate@ihi.org
pbarker@ihi.org
T: 1-617-301-4800
F: 1-617-301-4865

Packaged tenofovir & placebo gel supplies provided by:
CONRAD
Attn: **Henry Gabelnick, PhD**
Executive Director, CONRAD
1611 North Kent St., Suite. 806
Arlington, VA 22209,
hgabelnick@conrad.org
T: 1-703-276 3904
F: 1-703-524 4744

Tenofovir active product ingredient provided by:
Gilead Sciences
Attn: **James F. Rooney, MD**
Vice President, Medical Affairs
Gilead Sciences, 333 Lakeside Drive
Foster City, CA 94404
jrooney@gilead.com
T: 650-522-5708
F: 650-522-5854

ETHICS OVERSIGHT:
University of KwaZulu-Natal Biomedical Research Ethics Committee
Attn: **Douglas Wassenaar**
Faculty of Health Sciences Ethics Committee of the Nelson R Mandela School of Medicine, University of KwaZulu-Natal
brec@ukzn.ac.za
T: 27-31-260 4495
F: 27-31-260 4410

REGULATORY OVERSIGHT
South African Medicines Control Council
Attn: **Portia Nkambule**
Acting Director, Clinical Evaluations and Trials
MCC
Private Bag X828
Pretoria, 0001
nkambp@health.gov.za
T: 27-12-395-8126
F: 27-12-312-3129

STUDY MONITOR:
CAPRISA Clinical Monitoring Department
CAPRISA , Nelson R Mandela School of Medicine,
University of KwaZulu-Natal , Private Bag 7,
Congella 4013, Durban, South Africa
T: 27-31-260 4012
F: 27-31-260 4566

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CAPRISA 008

Signatures of Approval:

Co-Principal Investigator Quarraisha Abdool Karim, PhD	Date of Signature
Co-Principal Investigator Salim S. Abdool Karim, MBChB, PhD	Date of Signature
Co-Principal Investigator Leila E Mansoor, PhD	Date of Signature

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ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ANC	Antenatal Care
APR	Antiretroviral Pregnancy Register
ARV	Antiretroviral
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BREC	Biomedical Research Ethics Committee
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CAT	CAPRISA AIDS Treatment
CDC	(United States) Center for Disease Control and Prevention
CEC	CAPRISA eThekwini Clinic
CI	Confidence Interval
C_{max}	Maximum Concentration
CP	Community Programme
CRSG	Community Research Support Group
CRF	Case Report Form
CVC	CAPRISA Vulindlela Clinic
CVF	Cervico Vaginal Fluid
DSMB	Data and Safety Monitoring Board
ELISA	Enzyme-linked Immunosorbent Assay
FACTS	Follow on African Consortium for Tenofovir studies
FDA	(United States) Food and Drug Administration
FIV	Feline Immunodeficiency Virus
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HEC	Hydroxyethylcellulose
HIV	Human Immunodeficiency Virus
HBsAg	Hepatitis B Virus surface antigen
HBV	Hepatitis B Virus
HPTN	HIV Prevention Trials Network
HPV	Human Papillomavirus
HSV-2	Herpes Simplex Virus-2
ICH	International Conference on Harmonization
IDU	Intravenous Drug Users
IHI	Institute for Health Care Improvement
IPM	International Partnership for Microbicides
IRR	Incidence Rate Ratio
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
LPHC	Lancers Road Primary Health Care
MCC	Medicines Control Council
MDP	Microbicide Development Programme
MPHC	Mafakathini Primary Health Care
MSM	Men who have Sex with Men
OCR	Optical Character Recognition
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PCZCDC	Prince Cyril Zulu Communicable Disease Clinic
PDSA	Plan-do-study-act
PHC	Primary Health Care
PID	Participant identification
PK	Pharmacokinetics
PMPA	9-[(R)-2-(phosphonomethoxy)propyl]adenine monohydrate (tenofovir)
pMTCT	Prevention of Mother-to-Child Transmission
QI	Quality Improvement
RNA	Ribonucleic Acid

RT	Reverse Transcriptase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SIV	Simian Immunodeficiency Virus
SOP	Standard Operating Procedures
SSP	Study Specific Procedures
STI	Sexually Transmitted Infection
TDF	Tenofovir Disoproxil Fumarate
UKZN	University of KwaZulu-Natal
UNAIDS	Joint United Nations Programme on HIV/AIDS
USA	United States of America
VCT	Voluntary counseling and testing
w/w	Weight per Weight
w/v	Weight per Volume
w-y	Women years

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STUDY SCHEMA

Purpose: To assess the effectiveness of an implementation model which integrates tenofovir gel provision into existing family planning services

Background: The CAPRISA 004 trial demonstrated 39% reduction in HIV infection, with 54% HIV reduction in women who used tenofovir gel consistently, highlighting the importance of gel adherence for effectiveness against HIV.

Confirmatory studies are expected to report their results in early to mid- 2013, and it is anticipated that they will provide the information needed to support licensure of tenofovir gel. Hence, the next 2-3 years are a critical window of opportunity to prepare for and devise effective strategies for the future policy and programmatic scale-up of tenofovir gel provision. Since mathematical modeling suggests that tenofovir gel can change the course of the HIV epidemic in southern Africa, it is vital that preparations for large-scale provision begin as soon as possible so that rapid scale-up can be achieved once tenofovir gel is licensed.

A significant gap can exist between the prevention effectiveness achieved in clinical trials and subsequent performance of the health system in real-life clinical settings. A potential programmatic approach to making tenofovir gel available within the public health sector is to integrate its provision into family planning services using a quality improvement (QI) approach, which utilizes small scale rapid cycles of improvement designed by local providers to develop reliable processes for service delivery. This approach, which has been shown to improve the performance of prevention of mother-to-child HIV transmission programs in South Africa, offers a locally sustainable approach to integration of tenofovir gel provision into existing health care services.

Integrating HIV prevention and family planning services using a health systems strengthening approach has several advantages:

- Large numbers of sexually active women, who would benefit from tenofovir gel provision, already utilize family planning services at regular intervals
- Family planning staff are knowledgeable about reproductive health and have experience providing counseling and adherence support
- With minimal additional resources, the existing family planning service delivery systems could be substantially enhanced using a QI approach
- HIV prevention services could help strengthen family planning services and utilization.

Empiric evidence is needed to assess whether integrating tenofovir gel into family planning services can achieve similar levels of effectiveness as observed in the CAPRISA 004 trial.

Study Design: Two-arm, open-label, randomized controlled trial

Study Sites: CAPRISA eThekwini and CAPRISA Vulindlela Clinics and their neighboring public sector family planning services in KwaZulu-Natal, South Africa

Study Population: Consenting sexually active, HIV-uninfected women aged 18 years and older who previously participated in an antiretroviral (ARV) prevention study

Study Duration: Maximum duration of follow-up of 30 months

Study Product: 1% tenofovir gel provided to both study arms

Study Intervention: Participants will be randomized to receive 1% tenofovir gel through either:

- Public sector family planning services with 2-3 monthly provision and monitoring of 1% tenofovir gel and the use of QI methodology to promote reliable service delivery (intervention arm), or
- The CAPRISA research clinics with monthly provision and monitoring of 1% tenofovir gel (control arm).

All women in the trial will be provided with the standard package of HIV prevention and reproductive health services.

Sample Size: A maximum sample size of 700 women is anticipated. This provides 90% power to demonstrate whether gel use in women attending family planning services is similar to, but no more than 20% lower than, gel use among women attending the CAPRISA research clinics, stratified by study population and adjusted for 10% loss to follow-up.

Treatment Regimen: Participants in both study arms will be provided with a supply of single-use, pre-filled applicators of 1% tenofovir gel. While in the study, participants will be advised and supported to follow the CAPRISA 004 pre- and post-dosing strategy, namely BAT24, where the first dose of tenofovir gel is applied within 12 hours before anticipated coitus and a second dose as soon as possible but within 12 hours after coitus, with a maximum of two doses of gel in a 24-hour period.

Primary Objective: To assess the effectiveness of an implementation model for tenofovir gel provision through family planning services.

Primary Endpoint: Mean number of returned used applicators per participant per month

Secondary Objectives: **To compare women receiving tenofovir gel through family planning services with women receiving tenofovir gel through clinical trial clinics for the following:**

1. Safety of tenofovir gel measured by clinical and laboratory adverse event rates, including pregnancy rates and outcomes
2. HIV incidence rates
3. The estimated proportion of reported sex acts covered by two gel doses, self-reported adherence to the tenofovir gel dosing strategy and factors influencing gel use in relation to sexual activity, condom use, and intravaginal practices
4. Self-reported service acceptability and completion rates of quarterly (or 2 monthly in Nur-isterate users) HIV and pregnancy testing
5. HIV viral load among HIV seroconverters
6. Tenofovir resistance of HIV strains from HIV seroconverters
7. Vaginal cytokines to assess the role of genital inflammation in HIV acquisition
8. HSV-2 and human papillomavirus (HPV) incidence rates
9. Tenofovir levels
10. Self-reported product acceptability

1. INTRODUCTION

1.1 The need for HIV prevention that women can use and control

The Joint United Nations Programme on HIV/AIDS and the World Health Organization, estimate that nearly half of the 33.4 million people living with Human Immunodeficiency Virus (HIV)/Acquired immunodeficiency disease syndrome (AIDS) in the world are women[1]. In sub-Saharan Africa, women account for 59% of all infected adults. Young women are especially vulnerable. Worldwide, 60% of the 15- to 24-year olds with HIV are women and between 70 and 90% of all HIV infections among women are due to heterosexual intercourse. In sub-Saharan Africa, women aged 15 to 24 years with HIV represent 76% of the total cases in that age group, outnumbering their male peers by three to one[2-3].

In addition to biological factors[4-6] that make women more vulnerable than men to acquiring HIV during sex, various sexual coupling patterns place young women at high risk, including partnering with older men who are more likely to be infected[7], multiple concurrent relationships[8], low marriage rates[9], low consistent condom use rates[10-11], and limited skills in negotiating safer sex practices. Gender-based violence increases vulnerability[12], and poverty increases reliance on transactional sex for survival[13]. Women are often unable to convince their male partners, especially husbands and regular partners, to use condoms or to be monogamous or faithful. Despite the greater vulnerability of women, they have few options to reduce the transmission and acquisition of HIV. New technologies to prevent the sexual transmission of HIV in women, such as topical microbicides, are urgently needed.

1.2 A brief history of microbicides

Topical microbicides, an HIV prevention strategy that women can initiate or control, were first proposed almost two decades ago[14]. Since then several candidate microbicides have entered effectiveness trials to assess their impact on the prevention of HIV infection. These candidate microbicides ranged from products that disrupt cell membranes (surfactants such as nonoxynol-9 and C31G) or prevent attachment to target cells in the vagina (polyanions), to products (e.g. BufferGel) that maintain low vaginal pH in the presence of ejaculate. Most of the candidate microbicides that have been tested in late stage prevention trials have not shown protection against HIV infection[15-20], and some products were even potentially harmful [15, 21-22]. It is noteworthy that surfactants, polyanions and acid buffers are less anti-HIV specific compared to antiretrovirals[23]. Further, the antiviral activity of previous microbicide candidates was in the vaginal lumen compared to antiretroviral drugs, which act at an intracellular level against HIV replication in vaginal CD4 positive target cells.

Currently, research on microbicides is focused on assessing potential antiretroviral agents in various formulations and dosing strategies for their ability to prevent HIV infection. The agent in the most advanced stages of effectiveness testing is tenofovir gel, (PMPA, 9-[(R)-2-(phosphonomethoxy)propyl]adenine monohydrate (tenofovir), manufactured by Gilead Sciences, Inc., and licensed to CONRAD and International Partnership for Microbicides (IPM). Tenofovir, a nucleotide analog (nucleoside monophosphate) with potent activity against retroviruses [24], was initially developed and tested as a prophylactic in monkeys and was subsequently formulated for oral use as tenofovir disoproxil fumarate (Viread®), which has been approved for the treatment of HIV-1 infection since 2001 in the United States of America (USA), 2002 in Europe, and more recently in several resource constrained settings. Several hundred thousand HIV infected patients have received treatment with tenofovir disoproxil fumarate (TDF).

Tenofovir's efficacy in suppressing viral replication, favorable safety profile, long half-life [25] and accessibility made it an ideal choice to be formulated into a microbicide gel. *In vitro* and *in vivo* assessments of the 1% concentration of tenofovir in a gel formulation have demonstrated its potential as a microbicide [25]. Tenofovir has shown efficacy against viral challenge in animal models when administered as pre- or post-exposure prophylaxis [26-27]. In monkey challenge studies, tenofovir gel has shown protection from SIV infection with intermittent dosing and with a single pre-exposure dose [28]. In early stage clinical trials, tenofovir gel was well tolerated in both HIV negative and HIV positive women [29], and both daily and coitally-related use of the gel was found to be acceptable and safe [30].

1.3 Safety and effectiveness of tenofovir gel: Results of the CAPRISA 004 trial

The CAPRISA 004 trial, a Phase IIb, double-blind, randomized, placebo-controlled trial demonstrated a 39% protective effect of 1% tenofovir gel in preventing HIV infection among women in KwaZulu-Natal, South Africa[31]. A total of 889 rural and urban sexually active, HIV-uninfected women aged 18 to 40 years were included in the trial; 445 randomly assigned to the tenofovir gel arm, and 444 to the placebo gel arm. A pre-

and post-coital dosing strategy, also referred to as BAT 24, was used. Study participants were counseled and supported throughout the study to apply the first dose of the assigned study gel within 12 hours **b**efore anticipated sex; a second dose as soon as possible but within 12 hours **a**fter sex and to apply no more than **two** gel doses in **24** hours.

The intent-to-treat analysis demonstrated that the HIV incidence rate in the tenofovir gel arm was 5.6 per 100 women-years (w-y), compared to 9.1 per 100 w-y in the placebo gel arm (Incidence Rate Ratio (IRR)=0.61; p=0.017). There was a 50% reduction in HIV acquisition in the first 12 months of follow-up with a steady reduction in protection over the remaining duration of the study, reaching 39% at 30 months or study exit.

A unique feature of the CAPRISA 004 adherence measurement approach was monthly reconciliation of applicators to establish the number of returned used applicators as a real-time measure of adherence. Women in the trial were asked to return all applicators, used and unused at each month's study visit. A total of 181,340 applicators were dispensed to women during follow-up in the CAPRISA 004 trial; 95.2% of these applicators were returned, either as used or unused. Returned used applicators, which provided an advance on the self-reported gel use used in past microbicide trials, were found to be a useful indicator of adherence and correlated with effectiveness against HIV infection. Exploratory analysis of the relationship between adherence and efficacy shows a clear dose response related to level of adherence to the BAT 24 regimen with high adherers (defined as gel adherent in >80% of coital acts) demonstrating 54% protection (p=0.025) compared to 38% in intermediate adherers (defined as gel adherent in 50-80% of coital acts) and 28% in low adherers (defined as gel adherent in < 50% of coital acts). All three approaches used in the CAPRISA 004 trial to calculate gel adherence demonstrate a compelling relationship between the number of applicators returned as used and the level of effectiveness.

Tenofovir gel was also shown to be 51% effective in preventing herpes simplex type 2 (HSV-2) virus acquisition (p=0.003) [32]. Given the high prevalence and incidence rates of genital herpes in these settings and the role of genital herpes in increasing HIV acquisition rates this is a significant additional benefit of tenofovir gel.

In CAPRISA 004, there were 4692 adverse events reported during the study, with 94.3% (838/889) of the study participants reporting at least one adverse event. Twenty of these events (1%) were *probably* related and 100 (2%) were *possibly* related to use of tenofovir gel. Adverse event rates were 3.55 per w-y in the tenofovir gel arm and 3.44 per w-y in the placebo gel arm (p=0.265). There were 39 serious adverse events in the intent-to-treat population, including one death. Mild, self-resolving diarrhea and gastrointestinal infections were reported by more women in the tenofovir gel group than in the placebo gel group (16.9% vs 11.0%, p=0.015). Compared to placebo gel recipients, women in the tenofovir gel arm were no more likely to have elevated hepatic enzymes, abnormal renal function, hematological or bone abnormalities. The pregnancy rate was similar in both arms, and the proportion of pregnancies resulting in live births was 66.7% in the tenofovir gel arm as compared to 51.9% (p=0.38) in the placebo gel group.

Given the safety and effectiveness findings from CAPRISA 004, tenofovir gel could potentially fill an important HIV prevention gap, especially for women unable to successfully negotiate mutual monogamy or condom use. Based on mathematical modeling of the CAPRISA 004 results on the South African epidemic, tenofovir gel has the potential to alter the course of the HIV epidemic. It is estimated that over the next two decades, tenofovir gel could prevent 1.3 million new HIV infections and over 800,000 deaths in South Africa alone [33]. These estimates do not take into account the added benefit of preventing HSV-2 infection that doubles the risk of acquiring HIV[34]. Thus, implemented on a broader scale, tenofovir gel could save millions of lives over time, thereby helping to ease the global burden of providing HIV treatment and care.

1.4 Next steps towards licensure and implementation of tenofovir gel for HIV prevention

The CAPRISA 004 study findings are a first step in offering women an HIV preventive technology that they can initiate and use to protect themselves from acquiring HIV. Additional studies are urgently needed to confirm and/or extend the findings of this study in other epidemic settings and populations as well as in other formulations and dosing strategies, in order to advance product licensure as a critical next step in terms of women getting access to a safe and effective product. The Microbicide Trials Network's VOICE study is a crucial multi-country, five-arm randomized controlled trial testing daily dosing of oral and topical formulations of tenofovir and oral formulation of a tenofovir/FTC combination (also known as Truvada) for preventing HIV acquisition in sexually active African women. The results of the VOICE trial are anticipated in 2013 and will provide critically important information on the safety and effectiveness of daily dosing of oral and topical formulations of tenofovir for preventing HIV infection as well as the impact of adding FTC to tenofovir on HIV acquisition rates.

In addition to the ongoing VOICE study, two other placebo-controlled effectiveness studies are being proposed, each of which could provide valuable data needed for meeting the diverse needs of women who would benefit from such a product. The first is the proposed Follow-on African Consortium for Tenofovir Studies (FACTS) 001 study, which is a two-arm placebo-controlled safety and effectiveness study of 1% tenofovir gel utilizing the CAPRISA 004 BAT 24 coitally-related dosing strategy and includes 16-30 year old HIV-uninfected, sexually active women across six South African sites. The second is the Microbicide Development Programme (MDP) four-arm placebo-controlled trial testing the CAPRISA 004 BAT 24 dosing strategy with a single pre-sex dose of tenofovir gel. In addition to VOICE, FACTS001 and MDP 003, several other trials testing daily dosing of oral formulations of tenofovir alone or in combination with emtricitabine (Truvada) in men who have sex with men (MSM), injection drug users (IDU) and women at high risk of acquiring HIV in a number of different epidemic settings are anticipated to be completed by 2013. If shown to be effective, the results of these studies will strengthen the generalizability and validity of the protective effect of prophylactic use of ARVs and will support licensure of prophylactic use of ARVs in various dosing strategies, formulations and drug combinations, thereby expanding the HIV prevention toolbox for populations at high risk of acquiring HIV. A key gap following policy formulation will be programmatic access to product that ensures safety and effectiveness is maintained.

1.5 Rationale for the CAPRISA 008 trial

CAPRISA 004 established proof of concept that tenofovir gel is safe and effective in preventing HIV infection in a rigorous clinical trial. Translating these findings into health service programs poses many challenges that can be exacerbated in the context of weak health care delivery systems. This was evident with nevirapine-based prevention of mother-to-child transmission (PMTCT) programs in KwaZulu-Natal where clinics showed on average a 16% reduction in perinatal HIV transmission compared to the 50% seen in clinical trials. This proposed study is an opportunity to answer critically important implementation questions about how best to incorporate tenofovir gel into routine family planning health services and how to make it accessible to women who would benefit most from this product. Undertaking this study now, as opposed to three years from now, will enable us to be better prepared for widespread roll-out access following licensure of tenofovir gel and simultanosly meet our post-trial ethical obligations to trial participants. The population level effectiveness of tenofovir gel may drop if we do not provide adequate adherence support and safety monitoring in users and ensure adequate product supplies at health care delivery sites. A good understanding of the current health system delivery strengths and challenges prior to anticipated roll-out of new interventions is key to success. One approach to programmatic scale-up of tenofovir gel within the public sector health service in South Africa is to integrate its provision into family planning services. Integrating HIV prevention and family planning services has several advantages, including:

i. Large numbers of sexually active women, who would benefit from tenofovir gel provision, already utilize family planning services and attend these services at regular intervals over long periods;
ii. Family planning staff are knowledgeable about reproductive health and have experience providing counseling and adherence support;
iii. Primary Health Care (PHC) policy requires that family planning service is integrated into all PHC services as part of a minimum package of services provided at no cost through the public sector health care delivery system. As a result, family planning services are widely available in South Africa;
iv. Family planning services are provided as a sexual and reproductive health package for women, which includes contraceptive provision with counseling, HIV risk reduction counseling, HIV testing, screening for STIs, condom distribution and PAP smears.;
v. HIV prevention services could enhance provision of comprehensive contraceptive counseling and services.

Empiric evidence is needed to assess whether integrating tenofovir gel provision into family planning services can achieve similar levels of safety and gel use (if not better than that) observed in the CAPRISA 004 trial. The next 3 years are a critical window of opportunity to prepare and devise effective strategies for informing future policy and programmatic scale-up of tenofovir gel provision. A priority population for access to tenofovir gel is the participants from the CAPRISA 004 trial who remain HIV-uninfected and are willing to use tenofovir gel. In addition to the personal benefit for individual study participants, important ongoing data on the long-term safety of tenofovir gel will be generated. Tenofovir gel will be made available to HIV-uninfected women who previously participated in an ARV prevention study and willing to use tenofovir gel through this open-label study at the CAPRISA Vulindlela and eThekwini Clinics and their neighboring family planning services.

Existing family planning services vary in the quality of services provided to clients. Simply requesting or instructing family planning services to add tenofovir gel provision to their existing workload may lead to highly

variable outcomes. Hence, a structured and evidence-based approach is needed to facilitate the process of integrating tenofovir gel into existing family planning services. A quality improvement (QI) approach will be utilized to assist public sector family planning services to expand their current service delivery to include tenofovir gel provision. The QI approach strengthens health systems using small scale, rapid cycles of improvement that are designed and implemented by local providers to develop reliable processes for service delivery through mentored coaching and support. With minimal additional resources, the existing family planning service delivery systems could be substantially strengthened using a QI approach and serve as a strong base to introduce tenofovir gel to the family planning clients. A key strength of the QI approach is its nurturing of critical thinking and problem solving skills among clinic staff at the front lines of service delivery. Promoting ownership for the quality of service delivery is empowering for healthcare providers in the face of overwhelming service delivery challenges and allows them to rapidly witness data-supported benefits to clinical practice.

1.6 What is a Quality Improvement (QI) Approach?

The QI approach is based on methodology that is grounded in operations research and management science, two well-established fields that have, for more than 90 years, combined the disciplines of statistics, psychology, systems engineering, and iterative learning, to have major impact on systems performance across countries and industries [35]. This approach seeks to design systems for maximum effectiveness, efficiency, and adaptability and to actively disseminate the best models for health service delivery at the most rapid rate possible [36-37]. Specialized, evidenced-based tools aimed at rapid-cycle iterative testing of changes, networked collaborative learning, development of institutional capability for continuous improvement and frameworks to guide large-scale change have been developed [38-40] to facilitate this process (Figure 1). The QI approach supports a shift in provider attitudes and practice from a prescriptive mode to one that supports critical thinking and problem solving skills with continuous review and improvement of service provision.

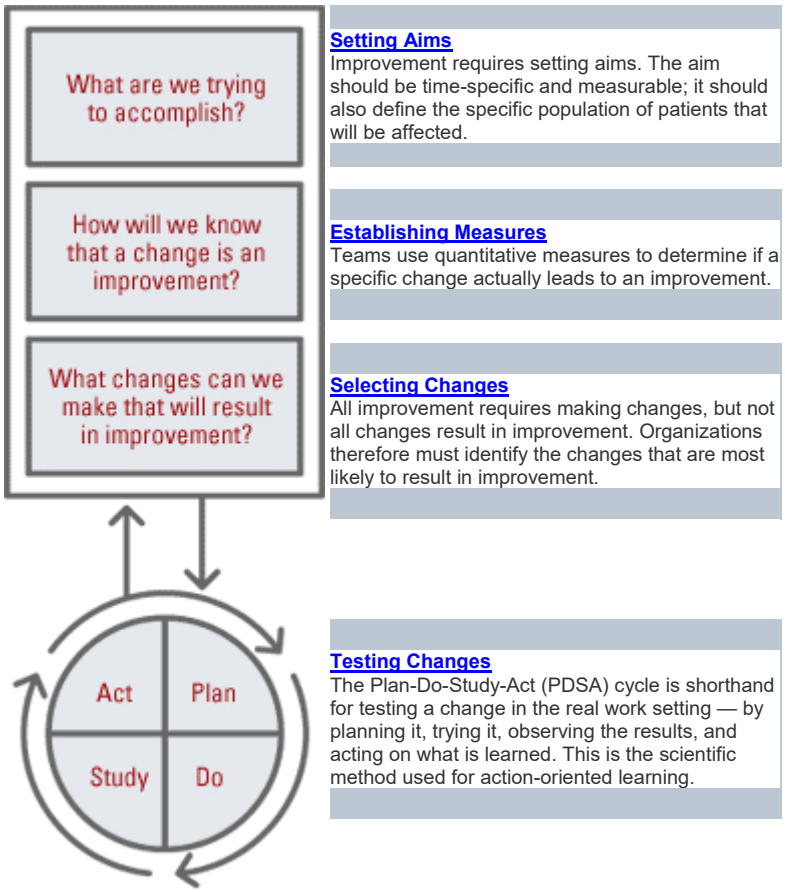

Figure 1: Model for improvement

Health care quality improvement principles and the Model for Improvement (Figure 1) provide an effective approach to help close the gap between evidence-based knowledge and the ability of health systems to implement large-scale programs[35, 37]. This approach places a premium on data driven front line decision-

making, peer-to-peer knowledge exchange, local adaptation of clinical protocols, and highly participative management [41]. Originally developed in the United States and widely adopted in the United Kingdom and other high-income nations, these efforts have increasingly found their way, with appropriate modifications, into global health applications in low and middle income countries [42-43].

Application of the QI approach to health systems of low and middle income countries shows considerable promise. Efforts in the Russian federation have reduced neonatal mortality by 60% [44]; in Niger, malnutrition-related fatality was halved in a single year [45]; in Ecuador, an essential obstetric care collaborative substantially reduced the incidence of post-partum hemorrhage [46]; in projects in South Africa, rapid scale-up of access to HIV care and treatment services and falling rates of mother-to-child transmission of HIV at a district level have been demonstrated [47-48].

Traditionally this approach is used following policy formulation and where some program implementation experience has already been established. This often means that health care providers have to unlearn what they have been doing for years and replace with new enabling and empowering approaches that involve critical thinking and problem solving skills, which have the added advantage of application to other health challenges facing the facility or service. CAPRISA 008 will be testing this model in a rigorous manner through strengthening existing family planning services as a foundation to introduce a new health technology even prior to licensure and importantly pave the way for more rapid, efficient, safe and effective access to a much needed product to women who would benefit most. A strengthened family planning service and more engaged providers will benefit existing family planning services, overall health care delivery in these facilities and most importantly support and benefit the clients of these services. .

2. STUDY GOAL AND OBJECTIVES

2.1 Primary objective

To assess the effectiveness of an implementation model which integrates tenofovir gel provision into existing family planning services

2.2 Secondary objectives

To compare women receiving tenofovir gel through family planning services with women receiving tenofovir gel through clinical trial clinics for the following:

1. Safety of tenofovir gel measured by clinical and laboratory adverse event rates, including pregnancy rates and outcomes
2. HIV incidence rates
3. The estimated proportion of reported sex acts covered by two gel doses, self-reported adherence to the tenofovir gel dosing strategy and factors influencing gel use in relation to sexual activity, condom use, and intravaginal practices
4. Self-reported service acceptability and completion rates of quarterly (or 2 monthly in Nur-isterate users) HIV and pregnancy testing
5. HIV viral load among HIV seroconverters
6. Tenofovir resistance of HIV strains from HIV seroconverters
7. Vaginal cytokines to assess the role of genital inflammation in HIV acquisition
8. HSV-2 and HPV incidence rates
9. Tenofovir levels
10. Self-reported product acceptability

3. METHODS

3.1 Study overview

This is a two-arm, open-label, randomized, controlled trial. A maximum of 700 sexually active, HIV-uninfected women aged 18 years and older who previously participated in an ARV prevention study will be enrolled from an urban and rural site in KwaZulu-Natal. The study's Data and Safety Monitoring Board (DSMB) will monitor the parameters used to estimate the sample size and may, if needed, recommend changes, during the study, in the sample size and/or follow-up duration. The primary endpoint of gel use will be assessed as the mean number of returned used applicators per participant per month. The sample size is estimated to provide 90% power to demonstrate whether gel use in women attending family planning services is similar, but no more than 20% lower than, gel use among women attending the CAPRISA research clinics, stratified by study population and adjusted for 10% loss to follow-up. Safety will be

assessed by the frequency of adverse events using laboratory and clinical markers. While this study is not specifically designed to use HIV incidence rates to assess non-inferiority of the family planning clinic arm, HIV incidence rates observed in the trial as a secondary endpoint will be used to assist in the interpretation of the primary outcome of the trial. The acceptability of family planning services for tenofovir provision will be assessed using self-report and clinic attendance rates.

The anticipated total study duration is approximately 30 months, with accrual requiring approximately 12 months and follow-up continuing for approximately 18 months after the end of the accrual period. Potential study participants will be screened for eligibility and eligible participants will be enrolled in the study within 30 days of screening. At each of the two sites, consenting eligible participants will be randomly assigned to receive 1% tenofovir gel through either family planning services (intervention arm) or the CAPRISA clinics (control arm) at both study sites.

Provision of tenofovir gel and study monitoring for women enrolled in the intervention arm will be done through local family planning services where QI methodology will be used to promote reliable delivery of tenofovir gel and family planning services. Participants in the intervention arm will have monthly visits for the first three months post-enrollment; thereafter, gel provision and monitoring will be scheduled to coincide with each participant's routine family planning visit (typically every 2-3 months). Study visits in the intervention arm will be scheduled no longer than 3 months apart.

Women assigned to the control arm will have monthly scheduled visits at the CAPRISA urban or rural clinic where they will be provided with 1% tenofovir gel.

HIV and pregnancy testing will be performed at each study visit in both study arms. HIV/sexually transmitted infection (STI) risk reduction messages and condoms will be provided to all participants using consistent prevention messages. Similarly, family planning services, tenofovir gel and counseling on product adherence will be provided to all participants. Participants in both study arms will be requested to return all used and unused applicators at each study visit.

Clinical safety will be assessed pre-, during- and post-enrollment. Laboratory safety assessments will be done at enrollment, months 6, 12, 18, 24, study exit and additionally if indicated. At these visits, blood samples will be collected for urea, electrolytes, creatinine, liver function tests, full blood count, calcium and phosphate levels. Pelvic examinations, including naked eye examination of the external genitalia and speculum examination of the vagina and cervix will be conducted at enrollment, months 6, 12, 18, 24, study exit and additionally if indicated. These visits will also include collection of blood for storage of serum and plasma and genital specimens for storage to assess for markers of safety, risk exposure, product adherence, potential post-trial assessments of activity against STIs, and tenofovir resistance. For symptoms experienced between scheduled visits, the participant will be counseled to report to their assigned study site as soon as possible.

Participants identified with an STI or other treatable reproductive tract infection at a scheduled or participant-initiated visit will be provided counseling and clinical care at the study sites in accordance with the South African Department of Health guidelines. Participants with STIs will be encouraged to refer their partners for treatment.

While contraceptive services will be provided to all CAPRISA 008 participants, those who become pregnant during the study will discontinue product use while they are pregnant. Pregnant women will be advised to continue with their follow up visits. When these participants no longer have a positive pregnancy test, the pregnancy outcome will be documented and they will be re-started on tenofovir gel should they wish to continue with study participation.

Participants infected with hepatitis B virus (HBV) at enrollment will be closely monitored clinically and using laboratory diagnostics especially during episodes of product hold. Any participant needing further treatment for HBV will be referred to a health care provider for further follow-up.

Participants who become HIV infected during study follow-up will be referred to the CAPRISA Acute Infection Study (CAPRISA 002), the CAPRISA Treatment Study (CAPRISA 009) and/or the CAPRISA AIDS Treatment (CAT) Programme for ongoing care, antiretroviral treatment and follow-up. Participants who do not wish to enroll in CAPRISA studies will be provided with information on other sources of care and support available in the community or appropriate health facilities serving the catchment populations.

3.2 Study setting

This study will be conducted at the urban and rural CAPRISA Clinics that participated in the CAPRISA 004 study and their neighboring public sector primary health care (PHC) clinics where family planning services are provided in KwaZulu-Natal, South Africa

3.2.1. CAPRISA Vulindlela and Mafakathini Clinics

The CAPRISA Vulindlela Clinic (CVC) is situated in the sub-district of Vulindlela, a rural community, with approximately 90,000 residents in the KwaZulu-Natal midlands, about 150 km 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 (VCT). The CVC adjoins the Mafakathini PHC clinic (MPHC), which has an average of 500 clients per month seeking family planning services. The intervention arm for CAPRISA 008 in the rural community will be conducted in the MPHC and the control arm will be undertaken at the CAPRISA Vulindlela Clinic (CVC).

3.2.2 HIV prevalence and incidence rates in Vulindlela

Temporal trends in HIV infection in the Vulindlela district are monitored through annual, anonymous, cross-sectional HIV prevalence surveys conducted in clients utilizing antenatal services for their first visit at the seven PHC clinics. These surveys coincide with the National ANC surveys conducted by the Ministry of Health between October and December each year and have been undertaken since 2001. The prevalence of HIV infection in pregnant women in Vulindlela increased from 32.4% (95% CI 27.6-37.6%) in 2001, to a peak of 42.6% in 2004, and was 37.2% in 2009. Data on temporal trends in HIV infection overall and by age from 2004-2009 are presented in Table 1.

Table 1: Temporal trends in overall and age-specific HIV prevalence among pregnant women attending antenatal clinics in Vulindlela, 2004-2009

Age group (years)	2004 N=552 HIV Prev% (95%CI)	2005 N=361 HIV Prev% (95%CI)	2006 N=333 HIV Prev % (95%CI)	2007 N=361 HIV Prev % (95%CI)	2008 N=389 HIV Prev % (95%CI)	2009 N=379 HIV Prev % (95%CI)
<20	26.8 (20.6-32.8)	22 (14.2-29.8)	16.6 (9.2-24.2)	13.0 (7.2-18.8)	20.8 (13.0-28.4)	18.2 (12.0- 26.5)
20-24	54.8 (47-62.4)	37.8 (28.8-46.8)	48.4 (38.6-58.4)	36.4 (26.8-46)	39.2 (30.8-47.6)	37.4 (28.7- 47.0)
25-29	66.2 (56-76.4)	50.8 (38.2-63.4)	51.0 (36.8-65.4)	60.4 (47.8-73)	60.8 (49.6-72.0)	55.0 (41.7- 67.7)
30-34	53.8 (41.8-66.0)	56.8 (42.2-71.4)	51.4 (34.8-68)	55.6 (39.4-71.8)	59.6 (45.6-73.6)	62.5 (47.3- 75.7)
>35	9.8 (0.6-18.8)	34.2 (18.6-50)	33.4 (15.6-51.2)	42.2 (26.4-57.8)	39.3 (21.2-57.4)	42.3 (24.0- 62.8)
Overall	42.6 (38.4-46.6)	37.4 (32.4-42.4)	37.6 (32.4-42.8)	34.4 (29.4-39.2)	40.9 (36.0-45.8)	37.2 (32.4- 42.3)

CI: Confidence interval

Using a pooling algorithm for HIV-1 ribonucleic acid (RNA) testing in these ANC clients the HIV incidence rate was estimated as 11.2% per year (95% CI 0.3–22.1) in 2007 and 2008[49].

A pre-CAPRISA 004, prospective cohort study was conducted in the CVC between March 2004 and April 2005 to determine the feasibility of undertaking longitudinal studies utilizing volunteers recruited from the Mafakathini Clinic and to establish HIV incidence rates in this population. Consenting, sexually active HIV-uninfected women utilizing family planning and ANC services were enrolled into this study. A total of 981 women were screened and HIV prevalence at baseline in this cohort was 35.7% (95% CI: 32.7–38.8). After 492.8 w-y of follow-up the HIV incidence rate in this cohort was 6.5 (95% CI 4.4–9.2) per 100 w-y[50].

3.2.3 CAPRISA eThekwini, PCZCDC and Lancers Road Clinics

The CAPRISA eThekwini Clinic (CEC), the urban control site for CAPRISA 008, 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. In addition family planning services are also offered. The PCZCDC and CEC are conveniently situated in the Warwick triangle in the metropolitan region of Durban which is a public transportation hub with the central bus, “minibus” taxi station and rail station all within a 500 meter radius of the CEC and PCZCDC. The majority of the PCZCDC clients live within the eThekwini municipality. Annually, approximately 40 000 cases of STIs are treated at this clinic, about 36 000 of which are new cases. The majority of the male and female STI clients accessing

these facilities are self-referred either symptomatic with genital ulceration and/or vaginal discharge syndrome or as contacts of patients with an STI diagnosis. 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[51].

The Lancers Road PHC clinic (LPHC) is a Durban City Health Department facility and is located very close (within a 5 minute walk) to the CEC and PCZCDC. The LPHC is a nurse-managed facility providing comprehensive services including ANC, family planning, childhood immunization, STI treatment, minor ailment care, and HIV VCT services. The LPHC and PCZCDC clinics have an average of 250 and 100 family planning clients a month respectively and will serve as the urban intervention clinics for CAPRISA 008.

3.2.4 HIV prevalence and incidence rates in the CAPRISA eThekwini and PCZCDC Clinics

Between July and December 2005, as part of a provider-initiated HIV testing program, 2439 women utilizing the PCZCDC STI clinic were tested for HIV infection. Data from this program are presented in Table 2 and demonstrate an overall HIV prevalence of 56.5% (95% CI: 54.5-58.5) with the highest prevalence in the 30-39 year age groups.

Table 2: Age-specific HIV prevalence in female STI clinic attendees at the PCZCDC in 2005

Age (years)	n/N	Prevalence (%) (95% CI)
< 19	79/213	37.1 (30.7-43.9)
20-24	394/859	45.9 (42.5- 49.3)
25-29	438/669	65.5 (61.7-69.1)
30-34	256/350	73.1 (68.1-77.7)
35-39	121/173	69.9 (62.4-76.6)
>= 40	90/175	51.4 (43.8.-59.0)
Total	**1378/2439**	**56.5 (54.5-58.5)**

A pre-CAPRISA 004, prospective cohort study undertaken at the CEC between May 2005 and December 2005, screened 1259 volunteers recruited from the PCZCDC STI clinic. The HIV prevalence in volunteers at screening was 59.3%. After 52 women years of follow-up the HIV incidence rate in this cohort was 5.8 per 100 w-y (95% CI 0-12.3)[50].

A second cohort of self-identified sex workers (CAPRISA 002) was established at the CAPRISA urban clinic. The HIV prevalence was 59.4% in the 776 women screened between 2004 and 2005. The HIV incidence rate was 7.2 (95% CI: 4.5 to 9.8) per 100 person-years. The age-specific HIV incidence rate in the CAPRISA 002 cohort is presented in Table 3[52].

Table 3: Age-specific prevalence of HIV infection among a cohort of high risk women (CAPRISA 002), 2005-2006

Age group (years)	HIV prevalence (%)	Follow-up (W-Y)	Incidence Rate (95% CI)
18-19	53.4	16.2	18.6 (0.0 – 37.6)
20-24	67.7	32.6	6.1 (0.0 – 14.5)
25-29	73.0	24.8	0
30-39	62.2	61.0	11.5 (3.0 – 20.0)
40-49	39.1	63.4	7.8 (0.9 – 14.1)
50+	29.0	20.2	0
Total	59.4	216	7.9 (4.1 – 11.6)

More recent data on HIV incidence rates in the urban and rural sites is available from the CAPRISA 004 trial, where an overall HIV incidence rate of 9.1 per 100 w-y (95% CI 6.9-11.7) was observed in the placebo gel arm[31].

These HIV prevalence and incidence rate data from the eThekwini and Vulindlela settings in KwaZulu-Natal, South Africa underscore the generalized nature of the HIV pandemic in this region of the world. The high HIV prevalence and continued high HIV incidence rates particularly in younger women highlight the hyper-endemic characteristic of the epidemic and the importance of targeting young women to alter HIV epidemic trajectories in this setting.

4. STUDY POPULATION

The study will include a maximum of 700 consenting sexually active, HIV-uninfected women aged 18 years and older who previously participated in an ARV prevention study and willing to use tenofovir gel through this open-label study at the CAPRISA Vulindlela and eThekwini Clinics and their neighbouring primary care clinics.

4.1 Inclusion criteria

Women must meet all of the following criteria at enrollment (determined by self-report, unless otherwise indicated) in order to be eligible for inclusion in this study:

- Age 18 years and older
- Women who previously participated in an ARV prevention study
- Currently utilizing or agreeing to attend designated public sector family planning services
- Able and willing to provide first person informed consent to be screened for, and to enroll in, the study
- Able and willing to provide adequate locator information for study retention purposes
- Sexually active (at least one coital act in the last 3 months prior to screening)
- HIV negative (by HIV testing performed by study staff within 30 days of enrollment - see Appendix I)
- Negative pregnancy test performed by study staff within 21 days of enrollment[a]
- Agree to use a non-barrier form of contraceptive
- Agree to adhere to study visits and procedures

4.2 Exclusion criteria

Volunteers who meet any of the following criteria (by self-report, unless otherwise indicated) will be excluded from the study:

- Has a creatinine clearance <50ml/min, as estimated using the method of Cockcroft and Gault[53].
- Has any other condition that, based on the opinion of the Investigator or designee, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.3 Recruitment, screening, and enrollment

4.3.1 Sources for study participants

Only HIV-uninfected women who previously participated in an ARV prevention study will be offered participation in this study. Given the high HIV prevalence and incidence rates in Vulindlela and Durban, women from these communities could derive substantial public health benefit from reduced HIV transmission from an effective microbicide.

4.3.2 Cohort recruitment and accrual

Eligible participants will be enrolled over approximately 12 months. At regular intervals, the Principal Investigators, in consultation with the study team, will assess progress in accrual and retention at each of the sites and may reallocate enrollment numbers and targets across the sites, as deemed necessary to achieve the goals of this trial efficiently.

4.3.3 Screening and enrollment

Eligibility for the study will be assessed in a step-wise manner at Screening and Enrollment (described in Section 7). Although all required procedures may be completed in one or two visits, additional visits may be conducted if needed. Regardless of the number of visits required, all screening and enrollment procedures will be completed within a 30-day period. If a participant is not enrolled within 30 days of providing informed consent for screening, the participant will be re-consented for screening and the screening process will be repeated, in which case the results of the last screening prior to enrollment will be considered applicable for trial purposes. All potential participants will be screened, enrolled and randomized at the urban or rural CAPRISA Clinics. Once randomized, those assigned to the intervention arm will be escorted to the respective family planning services, either MPHC, LPHC and/or PCZCDC, for completion of post-randomization enrollment visit procedures.

[a] *Note: Breastfeeding is not exclusionary*

Screening

Screening will be completed in a step-wise manner. Firstly, potential participants will be invited to screen for the study and asked to provide informed consent for screening (Appendix IIa). Potential study participants will be assigned a screening number, receive pre-test counseling, and two rapid HIV tests will be performed. Post-test counseling will be provided and those testing positive or indeterminate on at least one rapid test will be referred to one of several AIDS treatment programs including the urban and rural CAT Program at the CVC and CEC. HIV testing may be repeated prior to enrollment if >30 days have elapsed between the HIV rapid test result and the date of enrollment. If both HIV test results are negative, the potential participant will be invited to continue with the screening process and will be asked to provide demographic information, behavioral eligibility information, locator information, blood for creatinine levels and undergo urine pregnancy testing. Participants deemed eligible based on the above procedures will be offered an appointment for enrollment.

Enrollment

Potential participants will be informed of their creatinine clearance test results and if they remain eligible, will undergo a physical and pelvic examination with genital specimen collection for storage. Women who meet all the study eligibility criteria will be requested to provide their informed consent for participation in the trial and thereafter enrolled in the study. Consent for specimen storage will also be sought (Appendix IIc). Blood will be drawn for hematology, liver function tests, blood chemistry tests, serology, HBV assays, serum and plasma archive (Appendix III). After completion of randomization procedures, participants who are randomized to the intervention arm will be escorted to the neighboring family planning clinic for adherence counseling and gel dispensation.

4.4 Co-enrollment guidelines

Participants in this study may not take part in any other concurrent research studies that would interfere with the objectives of this study. The determination of whether participation in another study would be exclusionary for a given participant will be made by the Principal Investigators. Approved co-enrollment in other concurrent protocols will be documented.

4.5 Participant retention

The target retention rate will be 90% per annum. The Protocol Team will track retention rates. Once a participant is enrolled in the study, study staff will make every reasonable effort to ensure adequate locator information is available for follow-up tracking. A missed visit in either arm will prompt a single telephonic reminder, where the participant is spoken to directly and reminded of her clinic visit. A home visit will be triggered if a second clinic visit is missed. A home visit will be considered complete when the participant is met in person. A maximum of 3 attempts will be made to complete a home visit. Retention efforts will be conducted by the same team for both arms and have been standardized across study arms.

4.6 Participant withdrawal

Participants may voluntarily withdraw from the study for any reason at any time. Designated study staff may also withdraw participants from the study in order to protect their safety. Participants may also be withdrawn if the South African MCC or the University of KwaZulu-Natal's (UKZN) Biomedical Research Ethics Committee (BREC) 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. Study staff will record the reason(s) for all withdrawals in participants' study records.

5. STUDY INTERVENTION

Participants randomized to the intervention arm will receive tenofovir gel through the MPHC in Vulindlela and the LPHC and/or PCZCDC in eThekwini. In the event that either of these clinics is closed or is no longer able to participate in this trial, it will be replaced by an alternate nearby PHC clinic with family planning services. Following completion of the randomization procedures at the CAPRISA clinics, participants assigned to the intervention arm will be escorted to their designated family planning services, where they will be followed-up monthly for the first three months and 2-3 monthly thereafter.

At enrollment and throughout the trial, enrolled participants will be provided at each scheduled study visit with:

- HIV risk reduction counseling and male and female condoms
- Contraception counseling and provision of contraceptive method of choice as needed
- Tenofovir gel supplies with adherence support counseling
- Advice to contact study staff with questions about the study, requests for additional counseling, requests for additional condoms and gel, requests for contraception, as needed, and/or to reports adverse events (AEs)

As part of the study intervention for CAPRISA 008, a QI approach will be used to assist the family planning services to expand their current services to include tenofovir gel provision. An experienced QI advisor will work with the staff at the MPHC in Vulindlela and the LPHC and/or PCZCDC in eThekwini to conduct a gap analysis of existing family planning service provision prior to the enrollment of study participants at these sites. External and internal ideas will be carefully vetted to improve the quality of family planning service delivery in the areas of family planning counseling and contraception provision, STI/HIV counseling and treatment, and general clinic processes (e.g. clinic flow, documentation, follow-up). The QI advisor will undertake ongoing monitoring of the quality of each of the two family planning services. Once the initial QI process has been completed at the participating family planning services, a site initiation assessment will be undertaken to ensure procedures are in place for the study including procedures for dispensing tenofovir gel. Once each family planning service meets the requirements for site initiation, study participants will be enrolled and the same QI approach will be used to integrate reliable tenofovir gel provision and monitoring into the family planning programs.

Specific steps used in the QI approach to be implemented in both PHC clinics to initially strengthen family planning services include:

- Acknowledgement that family planning services need to be strengthened and improved
- Clear commitment by facility-based staff to specific time-limited aims to ensure improvements to the quality of family planning services to be provided
- Completion of a facility audit to identify nature of challenges and bottlenecks in system that impede service delivery
- Establishment of a clinic-based multi-disciplinary “improvement team”
- Goals and timelines for rapid improvement of outcomes set
- Mapping of relevant clinic-based processes for family planning service provision with identification of critical milestones and timelines
- Development of systems tools to support the QI process
  Development and testing of specific changes to the system using the Model for Improvement and PDSA cycles
- Establishment of logs and data collection forms to monitor progress
- Rapid feedback of clinic data to enable the clinic QI team to identify ongoing challenges and develop solutions

The introduction of tenofovir gel into family planning services will build on QI strengthened family planning service delivery.

- Family planning staff will be provided with detailed information on what is known about tenofovir gel and strategies for providing individualized user support
- With support from the experienced QI advisor, the clinic QI team will:
  - Set clear goals for service delivery improvement
  - Map out the critical steps required for provision of tenofovir gel to family planning clients
  - Develop system tools to support tenofovir gel provision including data collection tools to monitor progress
  - Oversee implementation of the tenofovir gel delivery plan
  - Review data and feedback to family planning staff to develop solutions to challenges

This two-step approach of initially strengthening the family planning services and introducing the tenofovir gel using a QI framework will create a cadre of service providers who can remain vigilant about the quality of services provided and cope with unexpected or unanticipated situations, in contrast to a more traditional prescriptive, top-down approach of service delivery.

Control arm
Participants randomized to the control arm will receive tenofovir gel with monthly follow-up visits through the CEC or CVC. Their study visits and procedures will be similar to those followed in the CAPRISA 004 protocol. There will not be any additional QI effort in the control clinics beyond what is routinely done by the research clinics.

At enrollment and throughout the trial, participants in the control arm will be provided with the following at each monthly study visit:
- HIV risk reduction counseling and condoms
- Contraception counseling and provision of contraceptive method of choice, as needed
- Tenofovir gel supplies with adherence support counseling
- Advice to contact study staff with questions about the study, requests for additional counseling, requests for additional condoms and gel, requests for contraception, as needed, and/or to reports AEs

Similarities and differences between the intervention and control arms
Women in both the intervention and control arms receive:
- A comprehensive prevention package comprising education, counseling, condom promotion, STI treatment, HIV testing
- Family planning and reproductive health services
- Tenofovir gel
- Intensive 6 monthly monitoring visits
- Safety monitoring at every study visit

Women in the intervention arm receive the following, which is not available to control arm participants:

Intervention arm	Control arm
• Attend the *QI-strengthened Family planning services* throughout the study	• Attend *CAPRISA clinics* throughout the study
• Receive all services, including tenofovir gel provision, *from FP clinic staff, under the guidance of a quality mentor*	• Receive all services, including tenofovir gel provision *from CAPRISA clinic staff*
• Clinic visits are *3 monthly*, except for women on Nur-isterate where visits are 2 monthly	• Clinic visits are *monthly*
• Tenofovir gel provision is *integrated into FP service* provision	• Tenofovir gel is *provided separately* not integrated into FP service provision

6. STUDY PRODUCT CONSIDERATIONS

6.1 Product formulation

Tenofovir gel is a clear, transparent, viscous gel at a concentration of 1% (w/w) formulated in purified water with edentate disodium, citric acid, glycerin, methylparaben, propylparaben, hydroxyethylcellulose (HEC), and pH adjusted to 4-5. The gel will be administered as a 4mL dose. (More detailed information on tenofovir gel is provided in the Investigator's Brochure).

6.2 Product use regimen

The CAPRISA 004 dosing strategy, referred to as BAT 24, will be utilized in the intervention and control arms of this study. Participants will be advised to:
- Insert first gel up to 12 hours **BEFORE** sex
- Insert second gel as soon as possible, within 12 hours **AFTER** sex
- Not to insert more than **TWO** gels in a **24 hour** period

Participants will also be advised to:

- Only apply the gel vaginally.
- Not douche or otherwise clean the vagina, or insert other objects or vaginal products for 2 hours after gel insertion. If a women plans to douche after coitus, she will be advised to insert the gel after douching. Note - this restriction does not apply to the use of female condoms.
- Not distribute or share their gel to other women.
- Not alter their gel in any way.
- Properly store their gel in a cool dry place out of direct sunlight.
- Use gel whether or not a condom is used.

As part of risk reduction counseling, participants will also be informed of the increased risk of HIV acquisition associated with anal sex compared with vaginal sex and will be encouraged to use a condom with all vaginal or anal coital acts.

Information on mechanics of gel use as well as storage will be provided to all participants in the intervention and control arms.

6.3 Product management

6.3.1 Supply

CONRAD will oversee the production and shipping of tenofovir gel to CAPRISA. All study gel will be produced, filled and packaged under Good Manufacturing Practices (GMP) conditions. The delivery volume, microbial limit, chemical and physical properties of the pre-filled applicators will be verified by the manufacturer prior to shipping the clinical supplies. CONRAD will supervise the clinical supply operational procedures and review the GMP documents before authorizing shipment of the supplies to CAPRISA.

Tenofovir gel will be packaged in single-use, pre-filled opaque applicators containing approximately 4 ml of gel. Each applicator will be individually wrapped and labeled. The Study Pharmacist will obtain tenofovir gel from CONRAD according to ordering instructions provided by CONRAD. The Study Pharmacist will maintain full accountability records in accordance with Good Clinical Practice (GCP) and legal requirements. These will include pharmacy specific participant logs as well as stock accountability records.

6.3.2 Storage

Study product will be securely stored at controlled room temperature with excursions permitted from 15°C-30°C until required for administration. Tenofovir gel should be stored away from direct sunlight.

6.3.3 Dispensing

Tenofovir gel will be dispensed either directly (control arm) or indirectly (intervention arm) by designated individuals to enrolled study participants as per Standard Operating Procedures (SOPs) in quantities expected to be sufficient until the participant's next follow-up visit.

In the event that a participant needs additional supplies between visits, she will be instructed to contact the study clinic to request additional supplies. Study participants will be asked to return all previously dispensed applicators at each visit. All returned used and unused applicators will reconciled with the number dispensed to the participant and the outcome logged, All returned applicators will be stored until checked by the study monitors and thereafter disposed of in accordance with Good Pharmacy Practice. Unused applicators that were never dispensed will be stored at the study pharmacy until destroyed. Further details of the dispensing procedures are outlined in the Study Specific Pharmacy Procedures Manual.

6.4 Adherence counseling

Adherence counseling will be provided to study participants upon enrollment and additionally at each study visit. Adherence counselors / nurses will be provided with a set of job aids, including a reference guide to assist with and standardize adherence support counseling. Techniques based on motivational interviewing will be used to address such topics as participant-centered strategies to remember to use the products before and after sex, to ensure the availability of the products both in the home and away from home, and to identify and discuss various challenges and situations that may impede product use. Counseling will include reminders to contact study staff with questions about gel use and requests for additional supplies. For participants experiencing adherence challenges, every effort will be made to identify customized strategies to increase their rates of product use throughout the course of the study.

6.5 Adherence assessment

Data on adherence to the gel use regimen will be collected at each study visit via brief interviewer-administered instruments. Additionally, genital specimens collected during the trial at study months 6, 12, 18 24, study exit and from suspected HIV seroconvertors will be archived for analysis of markers of product adherence to enhance interpretation of the results of the trial.

6.6 Discontinuation of product

Study participants will be discontinued from using tenofovir gel by the Principal Investigators and their designees in the event that they experience a Serious Adverse Event (SAE) that is judged by the study clinician or designee to be related to gel use (see Section 8.2). Participants who become pregnant will discontinue gel use and will only resume gel use when their pregnancy test reverts to negative. The Principal Investigators and designees also may at their discretion discontinue gel use — temporarily or permanently — among participants who:

- Experience an AE judged to be related to gel use.
- Have a pelvic examination finding involving deep epithelial disruption that is not resolving.
- Are unable or unwilling to comply with required study procedures.
- Otherwise might be put at undue risk to their safety and well-being by continuing gel use.

Gel use will be permanently discontinued when HIV infection has been confirmed according to the algorithm in Appendix I.

For participants who temporarily discontinue gel use, every effort will be made to complete all protocol-specified follow-up visits and procedures (except study product dispensing procedures). Designated staff will document all changes in gel regimen, and the reason for the change, on applicable Case Report Forms (CRFs).

6.7 Concomitant medications

Enrolled study participants may continue use of all concomitant medications, including prescription, non-prescription, traditional, and other preparations during this study. As noted in Section 6.2, participants will be encouraged to avoid douching and the use of vaginally-applied medications/preparations. All concomitant medications used by participants throughout the course of the study will be reported on applicable CRFs.

7. STUDY PROCEDURES

The schedule of evaluations for the two study arms are provided in Appendix IV. Study specific training will be provided to all study staff to ensure that study procedures are undertaken in a standardized manner. The protocol, SOPs and Study Specific Procedures (SSP) manual will guide this process. Following study initiation, study specific training will be undertaken annually and/or if there are any protocol and/or procedural changes.

7.1 Screening visit (up to day -30)

If all the required screening procedures cannot be completed in a single visit, then multiple visits may be conducted as necessary. For potential participants who do not meet the study eligibility criteria, the screening process will be discontinued when ineligibility is determined.

Screening will be completed in a stepwise manner. The first step includes the provision of introductory study information and obtaining informed consent for screening procedures. HIV testing in the context of pre- and post-test counseling will be done and only HIV negative participants will continue with the screening process.

The following procedures will be completed:

7.1.1 Administrative, behavioral, and regulatory procedures

- Informed consent for screening
- Assignment of a screening number
- Collection of the following:
    - Demographic information

- Locator information
- Eligibility assessment
- HIV/STI risk reduction counseling and provision of condoms

7.1.2 Clinical procedures

- Focused medical and menstrual history and ascertainment of concomitant medications
- Physical examination
- Assessing for STIs and other genitourinary symptoms requiring treatment
- Pelvic examination (only if indicated)
- Blood draw

7.1.3 Laboratory procedures

- Urine pregnancy testing
- HIV rapid testing
- Creatinine level (serum)

7.2 Enrollment visit (day 0)

Women found to be eligible after screening, will be scheduled for an enrollment visit. Informed consent for study participation will be administered once eligibility for enrolment has been confirmed; thereafter enrollment (or "on-study") procedures will be conducted.

7.2.1 Administrative, behavioral, and regulatory procedures

- Confirm eligibility
- Informed consent for enrollment and stored specimens
- Update locator information
- HIV/STI risk reduction counseling and provision of condoms
- Randomization and participant identification (PID) number allocation
- Baseline data collection including sexual behavior
- Family planning counseling
- Product adherence counseling

7.2.2 Clinical procedures

- Review/update pre-existing conditions
- Inventory and documentation of concomitant medications
- Physical examination
- Pelvic examination
- Genital specimen collection
- Blood draw
- Demonstration of product use and onsite gel insertion

7.2.3 Pharmacy-related procedures

- Provision of tenofovir gel and instructions
- Update accountability log

7.2.4 Laboratory procedures

- Urine pregnancy testing if no negative pregnancy test result in last 21 days prior to enrollment
- Serum and plasma archive
- HBV assay
- HSV-2 assay
- Hematology – full blood count
- Chemistry – creatinine, urea and electrolytes, calcium and phosphate
- Liver function tests
- Genital specimen archive

7.3 Follow-up visits

Women randomized to the intervention arm will attend monthly visits for the first 3 months of study participation. Thereafter, gel provision and monitoring will be scheduled to coincide with each participant's

routinely scheduled family planning visits (typically every 2-3 months). Follow-up visits for women enrolled into the control arm are scheduled throughout the study follow-up period on a 28-day schedule. The visit window around a study visit is 14 days on either side. In addition to the regular follow-up requirements, additional procedures are done at study months 6, 12, 18, 24 and study exit for all participants. For participants 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. However, for participants who miss their month 6, 12, 18 or 24 visits, the study procedures specified to take place at these visits will be conducted at the participants' next visit.

Participants who become pregnant during the study will be followed as usual, but gel will be withheld until they have a negative pregnancy test. For participants who become HIV infected during the study, product will be permanently discontinued once diagnosis of a HIV positive status is confirmed. HIV seroconvertors in the trial will be referred to the CAPRISA 002 Acute Infection study and/or the CAPRISA 009 treatment study for further care and follow-up. For women opting not to enroll in the CAPRISA 002 or CAPRISA 009 study they will be referred to the CAT Programme at the urban or rural site as appropriate or to other sources of care and support available to these communities.

Follow-up study visits occur monthly for the first 3 months and 2-3 monthly thereafter up to and including the study exit visit for participants in the intervention arm and monthly up to and including the study exit visit for participants in the control arm. The following study procedures will be performed during study follow-up:

7.3.1 Administrative, behavioral, and regulatory procedures

- Locator information update:
  - Each study visit
- HIV/STI risk reduction counseling:
  - Each study visit
  - Additionally when clinically indicated
- Distribution of condoms:
  - Each study visit
- Inventory and documentation of concomitant medications:
  - when indicated and at study exit
- Sexual behavioral and study product reconciliation:
  - Each study visit
- Family planning counseling:
  - Each study visit
- Service acceptability assessment:
  - At months 6,12, 18, 24 and study exit
- Product acceptability assessment:
  - At months 6, 12, 18, 24 and study exit

7.3.2 Clinical procedures

- Interval (i.e. since last visit) medical and menstrual history including detailed intermenstrual bleeding history and AE assessment and concomitant medication review
  - Each study visit
  - Additionally when indicated
- Pelvic examination
  - At months 6, 12, 18, 24 and study exit
  - Additionally when indicated
- Genital specimen collection
  - At months 6, 12, 18, 24 and study exit
  - If indicated, at the time of suspected or confirmed HIV seroconversion
- Blood draw
  - At months 6, 12, 18, 24 and study exit
  - Additionally when clinically indicated

7.3.3 Pharmacy procedures

- Supply of tenofovir gel
  - Each study visit (except at study exit)
  - Additionally when indicated
- Collection of unused and used applicators from participant
  - Each study visit

- Updating product accountability log
    - Each study visit
    - Additionally when indicated

7.3.4 Laboratory procedures

- Urine pregnancy test:
    - Each study visit
    - Additionally when clinically indicated
- HIV rapid tests
    - Each study visit
    - Additionally when clinically indicated
- HIV confirmatory RNA Polymerase Chain Reaction (PCR)
    - If indicated
- HIV confirmatory Western Blot and/or ELISA
    - If indicated
- Serum, plasma archive
    - Months 6, 12, 18, 24 and at study exit
- HBV assays
    - At study exit
- HSV-2 assays
    - At months 6, 12, 18, 24 and study exit
- Creatinine levels
    - At months 6, 12, 18, 24 and study exit
- Safety bloods (see appendix III for tests)
    - At months 6, 12, 18, 24 and study exit
    - Additionally when clinically indicated
- Genital specimen archive
    - Months 6, 12,18, 24 and study exit

7.4 Interim contacts and visits

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

- For administrative reasons, e.g., a participant may have questions for study staff or may need to re-schedule a follow-up visit.
- For product-related reasons, e.g., a participant may need additional tenofovir gel or want to discuss problems with adherence to gel use.
- In response to AEs. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and with laboratory and/or relevant diagnostic investigations if indicated and provide or refer the participant to appropriate medical care.
- For interim STI counseling and or treatment in response to STI symptoms.
- For interim HIV counseling and testing in response to presumed exposure to HIV or seroconversion symptoms.
- Family planning counseling and/or contraception provision.
- To provide participants with the results of confirmatory HIV test results (Appendix I).
- For other reasons at participant request.

The procedures performed at an interim visit will depend on the reasons for the visit. At the minimum, an interim visit CRF will be completed.

8. SAFETY MONITORING AND ADVERSE EVENT REPORTING

8.1 Adverse events and reporting requirements

An AE is defined as any untoward medical or social occurrence in a clinical research participant which may or may not have a causal relationship with the study product. Study product refers to tenofovir gel. New information regarding symptoms or conditions that occur during the screening period, but prior to randomization will be recorded in the participant's medical history as pre-existing conditions. All new or

worsening symptoms or conditions that occur following randomization will be considered AEs and will be recorded on the appropriate CRF.

8.2 Adverse event reporting

Study participants will be provided contact telephone numbers and instructed to contact study staff to report any AEs they may experience, except for life-threatening events for which they will be instructed to seek immediate emergency care. Depending on the severity of the event, the study staff will instruct the participant to present to their assigned study site (for mild events) or to a hospital casualty department (for serious events) for immediate evaluation. With appropriate permission of the participant, records from all non-study medical providers related to AEs will be obtained and required data elements will be recorded on study CRFs. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline) or stabilizes. AEs that are ongoing at the time of study exit will be followed up for up to 30 days after study exit and then, if not resolved, will be referred to a health care provider for further follow-up.

Designated study staff will determine the severity of the AE and document it on the appropriate CRF. Each adverse event that the participant is aware of will be graded for severity using the most current DAIDS severity grading system.

An AE **does not** include:

- Pre-existing diseases or conditions present or detected prior to start of study product administration, which do not worsen.
- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); the condition that led to the procedure is the adverse event.
- Elective hospitalization for surgery, social and/or convenience admissions or situations where an untoward medical occurrence has not occurred.

For each AE, an assessment of the relatedness to the study product will be made using the criteria and scale as outlined in the SSP manual. All AEs will be captured regardless of the association or otherwise to tenofovir gel and reported on the appropriate CRF in accordance with the SSP. All AE reports will contain at least the date the AE occurred, a brief description of the event, the relationship to study product, the action taken, the outcome, date resolved, and the seriousness of the event.

8.3 Serious adverse event (SAE) reporting

An SAE includes any experience that is fatal or life-threatening, results in persistent or significant disability/incapacity, requires or prolongs hospitalization, or is a congenital anomaly. A life-threatening AE means that the participant was, in the view of the designated study staff, at immediate risk of death from the condition as it occurred. Notification of deaths will be recorded by reflecting the medical condition that led to the death on the appropriate CRF. Reporting SAEs may require additional detailed reports and follow-up.

All serious adverse events will be reported to CONRAD, the South African MCC and the UKZN BREC.

8.4 Safety monitoring

Designated study staff will be responsible for continuous close safety monitoring of all study participants. The study statisticians will prepare routine study progress reports for review by the Protocol Team. In addition, the study statisticians will prepare routine study progress reports which include reports of AEs experienced by study participants for review by the DSMB. The membership, scope of responsibility, role and modus operandi of the DSMB will be outlined in the SSP and will include safety monitoring of enrolled participants infected with HBV. DSMB members will meet in-person and/or via teleconference regularly throughout the period of study implementation. Any deaths of study participants or other SAEs will be reviewed and final decision taken by the DSMB documented. Following its review of the data during the trial, the DSMB may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. The CAPRISA 008 DSMB will conduct interim reviews of study progress (pooled across both study arms), including rates of participant accrual, retention, completion of primary and relevant secondary endpoint assessments, and clinical and laboratory adverse events including the SAE rate.

9. STATISTICAL CONSIDERATIONS

9.1 Review of study design

This is a two-arm, open-label, randomized, controlled trial among a maximum of 700 sexually active, HIV-uninfected women aged 18 years and older who previously participated in an antiretroviral (ARV) prevention study, currently utilizing or agreeing to attend family planning clinics neighboring the CAPRISA sites. A total study duration of approximately 30 months is planned, with accrual requiring approximately 12 months

9.2 Endpoints

9.2.1 Primary endpoint

Gel use is essential for the effectiveness of tenofovir gel in preventing HIV infection. The level of gel use was a strong predictor of effectiveness in the exploratory adherence analysis of the CAPRISA 004 trial. Gel use on its own and in relation to coitus were both predictors of the level of protection. Based on the CAPRISA 004 trial which demonstrated a correlation between the number of returned used applicators and the level of effectiveness against HIV infection, the primary endpoint is:

- Mean number of returned used applicators per participant per month

9.2.2. Secondary endpoints

The following secondary endpoints will be assessed:

- Clinical and laboratory adverse event and pregnancy rates
- HIV incidence rates.
- Self-reported adherence to the tenofovir gel dosing strategy (and factors influencing gel use in relation to sexual activity, condom use, and intravaginal practices)
- Self-reported service acceptability and completion rates of quarterly HIV and pregnancy testing
- HIV viral load among HIV seroconverters.
- Tenofovir resistance among HIV seroconverters.
- Vaginal cytokines.
- HSV-2 and HPV incidence rates
- Tenofovir levels (and their correlation with HIV and HSV-2 infection rates)
- Self-reported product acceptability.

9.3 Accrual, follow-up, and sample size

A maximum of 700 women (350 in each arm) will be enrolled over approximately 12 months of the total 30 month study duration. The study's DSMB will monitor key parameters that may affect the study's statistical power and sample size calculations and may therefore recommend changes to the target accrual or duration of follow-up.

The primary endpoint is gel use as assessed by the mean number of returned used applicators per participant per month. In the CAPRISA 004 trial, the mean number of returned used applicators per participant per month was 5 and the standard deviation was 3. We would like to exclude a greater than 20% (i.e., more than 1 applicator per participant per month) difference in gel use between the two study arms. A maximum sample size of 700 provides > 90% power to demonstrate whether gel use in women attending family planning services is similar to, but no more than 20% lower than gel use by women attending the CAPRISA research clinics, adjusted for 10% loss to follow-up.

9.4 Random assignment

The trial randomization plan outlines the procedures for randomization. In summary, the procedures are as follows: Enrolled participants will be assigned at random to one of the two study treatment arms in a 1:1 ratio. The randomization list used to assign individual study participants to one of the two treatment arms will be generated by a randomization statistician who is not otherwise involved in the study. This statistician will use a randomly permuted block design, stratified by site. Two or more pre-specified block sizes will be recorded on a formal randomization request form, but they will not be written in the protocol or communicated to the clinical staff in order to reduce the chance of the clinical staff anticipating the assignment of the next participant. Electronic copies of the randomization schedule and the programs used to generate the randomization schedule will be limited in access and password protected. Paper copies of the randomization schedule will be locked in a secure location at the CAPRISA office, where no unauthorized study staff will have access to them.

The randomization statistician will provide the site with sealed, opaque randomization envelopes, sequentially labeled by a PID. These envelopes will be assigned in sequential order to eligible study participants. Upon opening the envelope, the staff member will add his or her name and signature as well as the time and date the envelope was opened. Study arm allocation will be concealed until after a participant is deemed eligible to participate in the study. Once a PID is assigned, the participant will be regarded as enrolled and randomized and the randomization envelope can be opened after the PID is assigned. This is an open label trial and there will be no blinding after the envelope is opened.

9.5 Data analysis

A Statistical Analysis Plan (SAP) will outline the planned analyses. The following is a summary of the planned analyses. Any deviations to be made from this summary plan will be documented in the detailed SAP.

This is a non-inferiority study with the primary objective being to show that gel use, as measured by the mean number of returned used applicators per participant per month, in the family planning arm is not more than 20% lower than the CAPRISA clinic arm.

The analyses will be performed on an intention-to-treat (ITT) basis and on the per-protocol and as-treated populations. For the ITT analysis, participants will be analyzed according to the study arm, even if the participant did not follow the assigned procedures. The only participants excluded from this primary analysis population will be women with no post-randomization visit and no data collected. The ITT analysis could increase the chances of declaring equivalence in a non-inferiority study. We will therefore do both the ITT and the per-protocol analyses and compare the findings of both analyses. The assumption is made that the ITT and per-protocol population will give similar results. If that is not the case, the differences in the two analyses will be investigated. In a non-inferiority trial, the ITT population is not necessarily the most conservative analysis and consideration will be given to trial conduct before the decision is made to regard the ITT population as the primary population. For example, in instances with many protocol violations or low adherence to visit schedule, the per protocol analysis might be more appropriate.

The number of used applicators returned will be compared between the two treatment arms using an appropriate longitudinal method, such as generalized estimating equations or linear mixed models, adjusted for site. The null hypothesis will be that the difference between the mean in the CAPRISA arm and the mean in the family planning arm differ by more than or equal to 20%. The alternative hypothesis will be that this difference between the means is smaller than 20%. This will be a one-sided test.

The analyses of the primary and secondary objectives will be described in detail in the SAP.

9.6 Data management

Data will be collected on standardized CRFs which will be developed by the study team. Site study staff will be trained in the correct completion of CRFs. If data entered on the CRFs are taken from an external source (e.g., laboratory reports, patient records), the source documents will be maintained in the participant's medical chart or study file at the site, and will be available for review. The CRFs will be faxed into the database management system which is DataFax version 4.0.0 (or higher) running on SUSE linux V 11. DataFax has optical character recognition (OCR) which will read the check boxes and numerical fields on the CRFs and store them in the study database. Any fields not recognized by the OCR system will be entered manually by the data encoders. Data encoders will verify all data by cross-checking the faxed version to what is entered into the database.

Queries arising during validation of the data will be recorded in quality control (QC) reports sent to the sites on a regular basis. Any queries resulting in a change to the database will be documented and attached to the original CRF. The data management center staff will perform periodic quality control and validation checks on the data. Database files will be password-protected and access to the files will be limited to authorized study staff members only. All data will be backed up at regular intervals, and backups will be stored in secure areas with limited access.

The original CRFs and related documents will be stored securely at the sites, both during and after the completion of the study. At all sites the forms will be stored in locked cupboards in a secure room with restricted access. Upon completion of the study, the close-out site monitoring visit and finalization of the database for analysis, the original forms will placed in long term storage. More detail on how the data will be managed will be contained in the study's data management plan.

10. HUMAN SUBJECTS CONSIDERATIONS

10.1 Regulatory and ethical review

This study will be conducted under the regulatory oversight of the South African MCC. It will be performed in accordance with International Conference on Harmonization (ICH) guidance and GCP standards.

The study also will be conducted under the ethical oversight of the UKZN's BREC. The study will only be initiated after it has been approved by the MCC and UKZN's BREC. The study will be conducted in accordance with all conditions of approval by the ethics and regulatory committees.

An important key recommendation from extensive consultations with ethicists, communities where the trial was conducted, national and international advocacy groups including WHO and UNAIDS was extending access of tenofovir gel to include women from CAPRISA 004 communities. Since these communities were involved in supporting the study and have high HIV incidence rates,there was widespread support to extend post-trial access to tenofovir gel beyond the women who participated in the CAPRISA 004 to include women from the participating communities. This approach was supported and approved by the UKZN BREC. However, the study team is not able to implement this as the MCC has explicitly instructed the Study team not to provide access of tenofovir gel to non-research participants.

10.2 Informed consent

Informed consent will be obtained from each study participant in English or Zulu prior to screening and enrollment, in accordance with GCP guidelines. Participants will be provided with copies of their informed consent forms if they are willing to receive them. An impartial witness is required for the entire informed consent process with any participant who is illiterate or whose literacy is limited. Documentation of the presence of a witness will be achieved through their signature on the informed consent document. Illiterate participants will indicate their consent via use of their mark (finger/thumb print) on the informed consent documents.

10.3 Risks

The study clinical procedures are similar to those experienced by women in routine gynecological examinations. Study participants may experience discomfort when having pelvic examinations and/or undergoing phlebotomy for this study. During phlebotomy, participants may feel dizzy or faint, and/or develop a bruise, swelling, or infection where the needle is inserted. Participants may become embarrassed, worried, or anxious when completing their HIV-related interviews and/or receiving HIV/STI counseling. They also may become worried or anxious while waiting for their HIV test results or after receiving HIV-positive test results. Trained study staff will be available to help participants deal with these feelings.

Study personnel will make every effort to protect participant privacy and confidentiality, but it is possible that participants may disclose their HIV status to non-study participants and could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities. Participants also could have problems in their partner relationships associated with use or attempted use of condoms and/or the study product.

Data on participant risk behaviors and the occurrence of other potential social harms will be collected from all participants. The Protocol Team will monitor trends in risk behaviors over time based on these data, as well as the occurrence of social harms, and initiate any required follow-up action.

Available clinical trial evidence indicates that 1% tenofovir gel is safe and well tolerated.

There is a theoretical possibility of tenofovir resistance in HIV strains from women who acquire HIV infection while using tenofovir gel. Limited resistance data from the HIV Prevention Trials Network (HPTN) 050 study showed that no new resistance mutations evolved in plasma or cervicovaginal lavage specimens after 14 days of tenofovir gel use[54]. No participant had high level tenofovir mutations (e.g., K65R). Similarly, there were no tenofovir-related resistant viruses detected in 35/38 women who became infected in the CAPRISA 004 trial[55] and where we were able to isolate virus in sufficient quantities for the assay..

Some of the possible side effects of the study gel are diarrhea, dryness, burning, itching, cervical ulceration, abrasion, ecchymosis, erythema, sub epithelial and/or petechial hemorrhage, inflammation, or pain in the

genital area. In CAPRISA 004 only a mild self-resolving diarrhea was statistically significantly observed among women in the tenofovir gel arm.

10.4 Benefits

10.4.1 To the individual:

Study participants from the tenofovir gel arm of CAPRISA 004 will benefit from longer term monitoring of prophylactic exposure to tenofovir. All study participants will benefit from access to tenofovir gel, an investigational new formulation of tenofovir with demonstrated protection against HIV and HSV-2 infection. Participants in this study will benefit from HIV education and prevention messages. They will receive free HIV, STI, and hepatitis serologic testing and free medical treatment for diagnosed curable STIs and gynecological evaluations. Contraceptive method of choice will be available to all study participants. For participants who have a diagnosed curable STI, their partners will be offered free STI testing and treatment. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Study participants will also receive condoms and risk reduction counseling and will be reimbursed for transport and refreshment costs for each scheduled visit. Participants who acquire HIV infection during the study will be referred to the CAPRISA 002 Acute Infection Study and/or the CAPRISA 009 Treatment Study for ongoing care and support including laboratory testing and monitoring of immune function, virological changes, tenofovir resistance, and access to antiretroviral therapy (ART) either provided directly at the CAPRISA clinic or through active linkage with local clinics in accordance with national policies regarding HIV treatment.

10.4.2 To the community and public at large:

Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study could enhance the scale-up and implementation of tenofovir gel for HIV prevention when licensed.

10.5 Access to HIV-related care

10.5.1 HIV counseling and testing

HIV counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study, and to all enrolled participants at each study visit. HIV test results will be provided with post-test counseling. Male and female condoms will be provided to participants throughout the duration of their participation in the trial.

10.5.2 Care for participants identified as HIV-infected

Potential study participants who volunteer to undergo HIV testing as part of the study screening process may discover that they are HIV positive. Study staff will provide all HIV test results with post-test counseling. Potential study participant who have been identified as HIV positive will be referred to local AIDS treatment services. Such services include the CAPRISA–based as well as other local facilities that provide medical and psychosocial AIDS care and support.

HIV-uninfected study participants who become infected during follow-up will be referred to one of the long-term CAPRISA cohort studies on acute infection or AIDS treatment; these studies have excellent provisions for care, antiretroviral therapy and support for those infected with HIV. For those who do not wish to continue in any of these studies post-seroconversion, they will be referred to their preferred HIV/AIDS care provider, which could include the CAT Programme, or either government or non-governmental HIV/AIDS care services for ongoing clinical management and care.

10.6 Community involvement and consultation:

The CAPRISA Community Program (CP) has, through a consultative process, established CAPRISA Community Research Support Groups (CRSGs) at both the CAPRISA Sites where this study will be conducted. The CRSG membership includes local community leaders, traditional leaders, leadership of local HIV/AIDS organizations, previous study participants, local health service provider representatives and HIV positive local community members. The CAPRISA CP in partnership with the CRSGs will involve the community and local community based organizations in preparation for this trial. Specifically, the CAPRISA CP will inform, educate and mobilize the community to enhance community input into the research process. The local CRSGs in Vulindlela and eThekwini play an active role as an interface between the researchers and community members serving as advocates for the community's best interests and ensuring that the researchers are aware of any concerns within the community about the research being conducted. The CRSGs also play an important role in reviewing study educational materials, consent forms and Zulu

translations of documents, which will be shared with study participants. The QI team in the intervention clinics will provide additional and ongoing input into this study from a provider and another key stakeholder perspective.

10.7 Confidentiality

Every effort will be made to protect participant privacy and confidentiality to the extent permitted by law. Study-related information will be stored securely at the CAPRISA clinical research sites. All participant information will be stored in lockable file cabinets in areas with access limited to study staff. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified by a coded number only, to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study 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 PID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Participant study data, as identified by PID number only, will not be released without the participant's written permission, except as necessary for review and monitoring by:

- Authorized study representatives
- South African MCC
- UKZN's BREC
- Study Monitors

10.8 Study Discontinuation

This study may be discontinued at any time by the South African MCC, UKZN's BREC, or the Protocol Team (e.g., in response to recommendations from the DSMB).

11. LABORATORY CONSIDERATIONS

The study laboratory plan will include the procedures for specimen management (e.g., chain of custody, handling, labeling and transport), assay procedures, proficiency testing and quality assurance procedures, and specimen storage procedures.

11.1 Laboratory specimens

The following types of specimens will be collected for testing:

- Urine for pregnancy testing
- Blood for hematology and chemistry
- Blood for HIV testing by rapid tests, confirmatory RNA PCR assays, Western blots and/or ELISAs
- Blood for HBV testing
- Blood for HSV-2 testing
- Blood and genital specimens from suspected seroconvertors for tenofovir levels and tenofovir resistance assays
- Blood for plasma and serum archive
- Genital specimens for archive

All the above specimens will be collected following Good Clinical and Laboratory Practice standards and as described in the SOPs for collection of specimens.

11.2 On site testing

The study laboratory plan will detail the procedures to be followed for on-site testing as well as proficiency testing for all on-site testing (i.e. urine pregnancy tests and HIV rapid tests).

11.3 Collection and shipping of specimens

All specimens (blood, urine and genital) will be collected according to methods described in the SOPs for proper collection, processing, labeling, and transport of specimens to the laboratories conducting the assays.

11.4 Specimen storage for quality assurance and potential future research testing

Serum, plasma, and genital specimens will be stored for assessments of markers of safety, risk exposure, product adherence, activity against STIs, and tenofovir resistance. In addition, stored plasma will be used for retrospective RNA PCR or Western blot testing to confirm whether early incident cases of HIV infection during the trial occurred post-randomization. Where possible, stored specimens will be re-tested to assess the validity of unusual or unexpected assays results. For those participants who do not consent to long-term storage of their specimens, any residual specimens will be destroyed at the end of the study after all protocol-required and quality assurance testing has been completed.

11.5 Laboratory quality control and quality assurance procedures

The laboratories involved in the study will follow the quality assurance and quality control procedures outlined in the study laboratory plan. For the on-site tests, the quality assurance personnel from the CAPRISA laboratory will conduct periodic visits to the study clinics in Vulindlela and eThekwini to assess the implementation of on-site quality control procedures, including maintenance of laboratory testing equipment, use of appropriate reagents, proficiency testing records and quality checks of on-site testing procedures.

12. ADMINISTRATIVE PROCEDURES

12.1 Protocol compliance

The study will be conducted in full compliance with the protocol. Amendments to the protocol will be required to follow a SOP which stipulates the levels of approval required prior to submission to regulatory bodies and the steps to be followed prior to implementation of a protocol amendment.

12.2 Protocol deviations and violations

Protocol deviations and violations are broadly defined as any departure from the procedures described in the study protocol. They may impact subject safety, affect the integrity of study data, affect subject's willingness to participate in the study, and/or provide evidence of willful or knowing misconduct or non-compliance on the part of the site investigator(s) will be documented and reported. Protocol deviations and violations may be identified by any of the study staff or by the study monitor. The procedures for documenting these will be specified in the monitoring plan.

Some examples of protocol violations include:

- Omission or inadequate administration of informed consent
- Inclusion/exclusion errors, including legal age limit
- Missing or incorrectly timed study procedures and assessments
- Failure to discontinue product use due to protocol criteria

In an emergency, the Investigator may make departures from the protocol to eliminate an apparent immediate hazard for a particular participant. In such a case, he/she will notify the UKZN's BREC in writing as soon as possible and document reasons for the violation (unless solely caused by participant non-compliance such as not attending for study visits).

12.3 Quality assurance and study monitoring

Quality assurance in the trial will be undertaken according to the Study Quality Assurance Plan. The Quality Assurance Plan will include ongoing monitoring of study progress and safety by the Protocol Team, study monitoring in accordance with GCP guidelines. The Investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. The Investigators will also allow inspection of all study-related documentation by authorized representatives of the South Africa MCC and UKZN's BREC. A site visit log will be maintained at the study site to document all visits.

12.3.1 Study monitoring

Study monitoring will be conducted by the CAPRISA Clinical Monitoring Unit. Pre-initiation site monitoring will be undertaken to establish study site readiness for study initiation. Thereafter ongoing monitoring will be undertaken after enrollment of the first participants and at regular intervals thereafter. A site visit log will be maintained at the study site to document all visits. Monitor findings will be documented per CAPRISA

monitoring SOPs. The Principal Investigators will be notified of the findings. If the monitor discovers issues related to safety, he/she is to report their findings immediately to the Principal Investigators or designee.

12.4 Study records

Complete, accurate, and current study records will be maintained and stored in a secure manner throughout the study. All study records will be maintained for at least 5 years after the termination of the trial and extended to 2 years following the date of marketing approval for the study product for the indication in which it was studied and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of the development of the study product. Gilead Sciences and CONRAD will be consulted by the Principal Investigators to determine if this storage period needs to be extended.

12.5 Use of information and publications

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

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APPENDICES

I. HIV Antibody Testing Algorithm
IIa. Informed Consent Form for Screening Participants
IIb Informed Consent Form for Enrolling Participants
IIc Informed Consent Form for Specimen Storage and Possible Future Research Testing
III. Safety Laboratory Evaluations to be performed in Study Months 1-3
IV. Schedule of Study Visits and Procedures

Appendix I: HIV Antibody Testing Algorithm

The HIV testing algorithm at baseline and at each follow-up visit is provided below.

At screening, participants will undergo two rapid tests for HIV antibodies. Those who are negative on both tests and meet all eligibility criteria as assessed within a 30-day period since screening will be enrolled in the study.

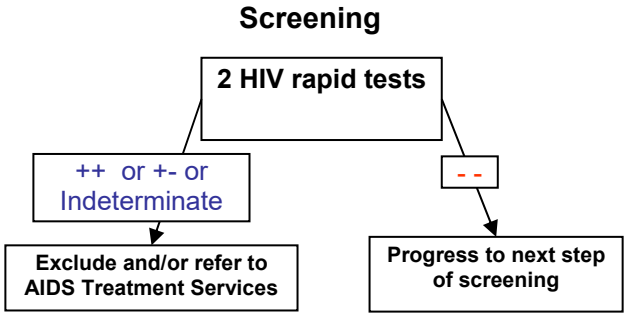
At enrollment participants will not be re-tested for HIV, but plasma samples taken at this time will be stored for future testing among those who seroconvert early in the trial in order to confirm that HIV infection and seroconversion occurred post-randomization.

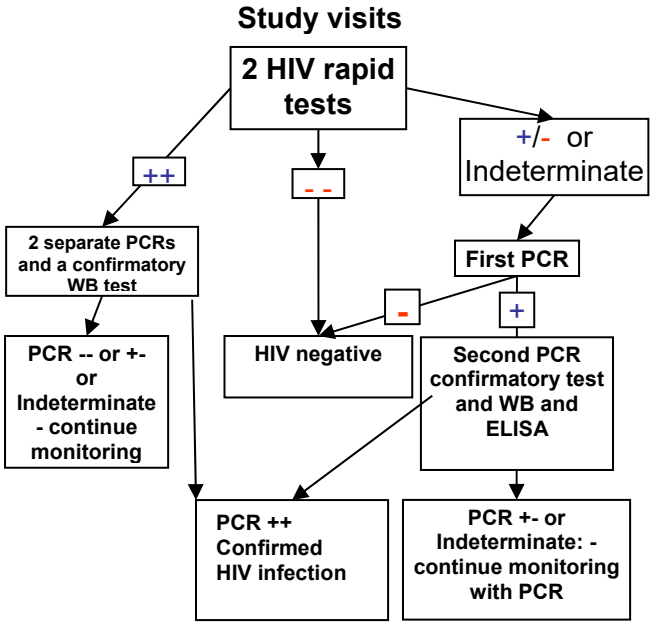
At each study visit, participants will be tested for HIV antibodies with two rapid HIV tests. Participants with two negative rapid tests will continue follow-up in the study. If both tests are not negative i.e. either of these tests is positive or indeterminate, then the participant is considered a suspected seroconvertor. HIV RNA PCR testing will be performed on suspected seroconvertors to confirm HIV status and a follow-up visit will be scheduled for a week later. If the RNA PCR test is positive, a second blood sample will be drawn to confirm HIV status using RNA PCR during the scheduled visit a week later and another follow-up visit will be scheduled for a week thereafter to present results. Western blots and ELISAs will be performed on all suspected seroconvertors to provide additional confirmatory information on the presence / absence of HIV infection. HIV infection is defined as two positive PCR tests from independent samples. Participants will continue using gel product until HIV infection status is confirmed.

Upon request, participants can be tested for HIV between scheduled study visits if they feel they have been exposed or are experiencing symptoms of HIV infection.

At the end of the study all new HIV infections will be confirmed by RNA PCR on stored plasma for quality assurance purposes and samples of plasma stored from enrollment will also be tested by RNA PCR to confirm that seroconversion occurred post-randomization. Non-incident cases will be excluded from the analysis for the primary objective.

Participants who become infected with HIV will be offered counseling and referral, as appropriate, to the CAPRISA acute infection study (CAPRISA 002) and/or treatment programs or other HIV/AIDS care services.


Screening
2 HIV rapid tests
++ or +- or Indeterminate
- -
Exclude and/or refer to AIDS Treatment Services
Progress to next step of screening


Study visits
2 HIV rapid tests
++
- -
+/- or Indeterminate
2 separate PCRs and a confirmatory WB test
First PCR
-
+
PCR -- or +- or Indeterminate - continue monitoring
HIV negative
Second PCR confirmatory test and WB and ELISA
PCR ++ Confirmed HIV infection
PCR +- or Indeterminate: - continue monitoring with PCR

Appendix IIa: Informed Consent Form for Screening Participants (separate document)

Appendix IIb: Informed Consent Form for Enrolling Participants (separate document)

Appendix IIc: Informed Consent Form for Specimen Storage and Possible Future Research Testing (Separate document)

Appendix III: **Safety Laboratory Evaluations**

Performed at enrollment and at Study Months 6, 12, 18, 24 and study exit

Hematology Tests
Full (Complete) blood count

Blood Chemistry
Liver Function Tests:
Alkaline phosphatase
ALT
AST
Total bilirubin

Renal Function Tests
Urea
Creatinine
Serum electrolytes (Na+, K+, PO4-, Ca++)

Serum amylase

Appendix IV: Schedule of evaluations

	Screening	Enrol	Follow-up																												Exit
Intervention arm																															
Control arm																															
Administrative, Behavioural and Regulatory Procedures																															
Informed consent for screening	X																														
Obtain screening number	X																														
Informed consent for storage		X																													
Informed consent for enrolment		X																													
Demographic information	X																														
Locator information	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Eligibility assessment	X	X																													
Risk reduction counselling and condom supplies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Document concomitant medication	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Obtain random assignment and PID		X																													
Baseline data including sexual behavior		X																													
Product adherence and familiy planning counseling		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Sexual behaviour & study product reconciliation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Service ans product acceptability assessment								X					X						X						X						X
Clinical Procedures																															
Focused medical and menstrual history	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X																													
Pelvic examination	0	X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X
Genital specimen collection		X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X
Scheduled blood draws	X	X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X
Provide test results	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demonstration of product use and onsite gel insertion		X	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Pharmacy procedures																															
Provide study product & instructions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Update accountability log		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collection of used and unused product			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Perform laboratory evaluations:																															
Urine pregnancy test	X	0[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV serology (rapid tests)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV RNA PCR, and Western blot[e]			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Plasma and serum archive[c, e]		X						X					X						X						X						X
Hepatitis B assays[e]		X																													X
HSV-2 assay		X						X					X						X						X						X
Creatinine level[e]	X							X					X						X						X						X
Safety bloods[e] (hematology and chemistry)		X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X
Genital specimen for archive[c]		X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X	0	0	0	0	0	X
Viral load in seroconvertors[d]																															
Resistance testing in seroconvertors[d]																															
Maximum amount of blood collected (mls):	5[e]	60	60[e]	60[e]	60[e]	60[e]	60[e]	95[e]	60[e]	60[e]	60[e]	60[e]	60[e]	95[e]	60[e]	60[e]	60[e]	60[e]	60[e]	95[e]	60[e]	60[e]	60[e]	60[e]	60[e]	95[e]	60[e]	60[e]	60[e]	60[e]	60[e]	105

[a] if no negative pregnancy test result in last 21 days prior to enrolment

[c] The stored serum, plasma and cytobrush specimens will be used for assessments for markers of safety, risk exposure, product adherence and tenofovir resistance. In addition, stored plasma will be used for retrospective RNA PCR testing to confirm whether incident cases of early HIV infection during the trial occurred post-randomisation. [d] Performed on first positive HIV rapid specimen and repeated at 3 months later.

[e] Blood volumes: Confirmatory tests (WB) (20ml) (only if indicated), Creatinine (5 mls); Safety bloods (20 mls), HBV assays (10 mls); Storage (20 mls), tenofovir resistance assays (20 ml) (only if indicated), HSV-2 testing (10ml for storage)

0 =if indicated

[f] HBsAg positive participants will have a liver function test performed

schedule for women on depo and other contraceptive methods - note will need to receive injection at study month 3

schedule for women on nuristurate - note will need to receive injection at study month 2

all women enrolled in FPS arm