

**Protocol**  
**CAPRISA 009**

**Open Label Randomized Controlled Trial to Assess the Impact of prophylactic exposure to tenofovir gel on the efficacy of subsequent tenofovir-containing antiretroviral therapy on viral suppression**

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

**Principal Investigator**  
**Nivashnee Naicker, MBChB**

**Co-Principal Investigators**  
**Salim S Abdool Karim, MBChB, MMed, FFPHM, PhD**  
**Anushka Naidoo, BPharm, MMed Sc**

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**PROTOCOL TEAM ROSTER:  
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA (CAPRISA)**

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**Nivashnee Naicker, MBChB**

Principal investigator / Study clinician  
CAPRISA, Nelson R Mandela  
School of Medicine,  
University of KwaZulu-Natal, Private Bag 7,  
Congella, 4013, Durban, South Africa  
[naickern1@ukzn.ac.za](mailto:naickern1@ukzn.ac.za)  
T: 27-31-260 1949  
F: 27-31-260 1963

**Salim S. Abdool Karim, MBChB, MMed, 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](mailto:karims1@ukzn.ac.za)  
T: 27-31-260 4550  
F: 27-31-260 4549

**Anushka Naidoo, BPharm, MMed Sc**

Co- principal investigator / Protocol Pharmacist  
CAPRISA, Nelson R Mandela School of  
Medicine,  
University of KwaZulu-Natal, Private Bag 7,  
Congella, 4013, Durban, South Africa  
[naidooa2@ukzn.ac.za](mailto:naidooa2@ukzn.ac.za)  
T: 27-31-260 1963  
F: 27-31-307 7138

**Quarraisha Abdool Karim, PhD**

Co-Investigator  
CAPRISA, Nelson R Mandela School of  
Medicine,  
University of KwaZulu-Natal, Private Bag 7,  
Congella, 4013, Durban, South Africa  
[Abdoolq2@ukzn.ac.za](mailto:Abdoolq2@ukzn.ac.za)  
T: 27-31-260 4208  
F: 27-31-260 4566

**Kogieleum Naidoo, MBChB**

Co-Investigator  
CAPRISA, Nelson R Mandela School of  
Medicine,  
University of KwaZulu-Natal, Private Bag 7,  
Congella, 4013, Durban, South Africa  
[Naidook45@ukzn.ac.za](mailto:Naidook45@ukzn.ac.za)  
T: 27-31-260 4687/1922  
F: 27-31-260 4566

**Bonginkosi Mdluli, MBChB**

Vulindlela Study Clinician  
Vulindlela Clinic, Mafakatini Primary Health  
Care  
Clinic, Mafakatini, Vulindlela,  
South Africa  
[mdluli@ukzn.ac.za](mailto:mdluli@ukzn.ac.za)  
T: 27-31-260 6851  
F: 27-33-997-1425

**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](mailto:grobler@ukzn.ac.za)  
T: 27-31-260 4392  
F: 27-31-260 4566

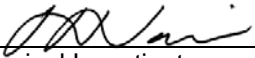
**Jacqueline Kasavan**

Laboratory Technician  
CAPRISA, Nelson R Mandela School of  
Medicine,  
University of KwaZulu-Natal, Private Bag 7,  
Congella, 4013, Durban, South Africa  
[kasavan@ukzn.ac.za](mailto:kasavan@ukzn.ac.za)  
T: 27-31-260 4555  
F: 27-31-260 4566

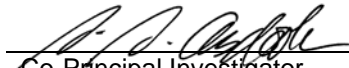
**Open Label Randomized Controlled Trial to Assess the Impact of prophylactic exposure to tenofovir gel on the efficacy of subsequent tenofovir-containing antiretroviral therapy on viral suppression**

**CAPRISA 009**

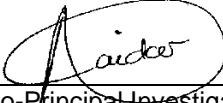
Signatures of Approval:

  
\_\_\_\_\_  
Principal Investigator  
Nivashnee Naicker, MBChB

27 January 2011  
Date of Signature

  
\_\_\_\_\_  
Co-Principal Investigator  
Salim S. Abdool Karim, MBChB, PhD

27 January 2011  
Date of Signature

  
\_\_\_\_\_  
Co-Principal Investigator  
Anushka Naidoo, BPharm, MMed Sc

27 January 2011  
Date of Signature

# Open Label Randomized Controlled Trial to Assess the Impact of prophylactic exposure to tenofovir gel on the efficacy of subsequent tenofovir-containing antiretroviral therapy on viral suppression

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# Open Label Randomized Controlled Trial to Assess the Impact of prophylactic exposure to tenofovir gel on the efficacy of subsequent tenofovir-containing antiretroviral therapy on viral suppression

## ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ABC	Abacavir
ARVs	Antiretrovirals
AZT	Zidovudine
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CAT	CAPRISA AIDS Treatment
CD4	Cluster of differentiation 4
CDC	Communicable Disease Centre
CRF	Case Report Form
CRS	Clinical Research Site
DAIDS	Division of Acquired Immunodeficiency Syndrome
EFV	Efavirenz
FBC	Full blood count
FTC	Emtricitabine
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HBV	Hepatitis B Virus
ITT	Intention to treat
LFT	Liver function test
LPV/r	Lopinavir/Ritonovir
NRTI	Nucleotide Reverse Transcriptase Inhibitor
PEPFAR	Presidents Emergency Plan For AIDS Relief
PHC	Primary health care
PrEP	Pre-Exposure Prophylaxis
PID	Participant identification
QA	Quality assurance
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedures
STI	Sexually transmitted infection
TDF	Tenofovir disoproxil fumarate
WHO	World Health Organisation

## Open Label Randomized Controlled Trial to Assess the Impact of prophylactic exposure to tenofovir gel on the efficacy of subsequent tenofovir-containing antiretroviral therapy on viral suppression

### STUDY SCHEMA

<b>Purpose:</b>	To determine whether prophylactic exposure to tenofovir gel alters the therapeutic response to a tenofovir containing antiretroviral regimen				
<b>Study design:</b>	Open label, two-arm, randomised controlled trial				
<b>Study population:</b>	Women who become infected with HIV while participating in the CAPRISA 004 and CAPRISA 008 trials. There are 3 study populations: <i>Study population 1:</i> HIV positive women from the CAPRISA 004 tenofovir gel arm and HIV positive women from the clinical trial tenofovir gel provision arm of CAPRISA 008 <i>Study population 2:</i> HIV positive women in the placebo arm of CAPRISA 004 <i>Study population 3:</i> HIV positive women from the family planning service arm of CAPRISA 008				
<b>Study sites:</b>	CAPRISA eThekweni and CAPRISA Vulindlela clinics.				
<b>Study duration:</b>	3 years				
<b>Study intervention:</b>	Enrolled women will be initiated on their assigned antiretroviral therapy regimen when they reach any of the following criteria: <ul style="list-style-type: none"><li>• reach a CD4+ count of less than 350 cell/mm<sup>3</sup></li><li>• acquire an AIDS defining illness</li><li>• become pregnant - women in any of the three study populations who become pregnant during follow-up will be initiated on their assigned treatment regimen, as appropriate, for prevention of mother-to-child transmission of HIV.</li></ul> <p>At enrolment women in each of the three study populations will be assigned randomly to one of the two following antiretroviral regimens</p> <table><tr><td><i>Intervention Arm:</i></td><td>Tenofovir, lamivudine and efavirenz</td></tr><tr><td><i>Control arm:</i></td><td>Zidovudine, lamivudine and efavirenz</td></tr></table>	<i>Intervention Arm:</i>	Tenofovir, lamivudine and efavirenz	<i>Control arm:</i>	Zidovudine, lamivudine and efavirenz
<i>Intervention Arm:</i>	Tenofovir, lamivudine and efavirenz				
<i>Control arm:</i>	Zidovudine, lamivudine and efavirenz				
<b>Sample size:</b>	The projected sample size is 90 women. The number of women in each stratum is as follows: Study population 1: n = 40 Study population 2: n = 30 Study population 3: n = 20				
<b>Primary endpoint:</b>	The primary endpoint is the antiretroviral treatment failure rate at 12 months. Treatment failure is defined as viral load > 50 copies/ml, antiretroviral regimen changes for treatment failure or death				
<b>Secondary Endpoints:</b>	<ol style="list-style-type: none"><li>1. Change in CD4+ cell count from the earliest post-infection timepoint to the time of randomisation to 12, 24 and 36 months post-randomisation</li><li>2. Tenofovir resistance, defined as presence of K65R, K70E or any of the TAMS mutations.</li><li>3. Reported adverse events with severity grades 3 and 4 based on the DAIDS toxicity grading tables</li><li>4. Cellular and humoral immune responses</li><li>5. Genital viral shedding (viral load on tear flow)</li></ol>				
<b>Ancillary Endpoint</b>	Mother-to-child HIV transmission rates as determined by PCR on infant at 6 weeks.				

# Open Label Randomized Controlled Trial to Assess the Impact of prophylactic exposure to tenofovir gel on the efficacy of subsequent tenofovir-containing antiretroviral therapy on viral suppression

## 1. Background and Rationale:

The HIV/AIDS pandemic remains among our greatest public health challenges. The overall number of people living with HIV is increasing as new infections continue to occur and AIDS deaths are prevented by increasingly available antiretroviral therapy (ART). Globally, there were an estimated 33.2 million people living with HIV infection or AIDS and annual incidence of new HIV infections was an estimated 2.7 million in 2007 [1] emphasizing the urgent need for safe and effective methods of HIV prevention especially in Africa, a region which accounts for 70% of the global burden of disease[1]. In the absence of an effective vaccine, focus has shifted to other prevention strategies such as pre-exposure prophylaxis.

Tenofovir, an adenosine nucleotide analog with potent activity against retroviruses[2], was initially developed and tested as a prophylactic in monkeys and was subsequently formulated for oral use as tenofovir disoproxil fumarate (Viread®), which is now widely used for HIV treatment. The efficacy of Viread® has been demonstrated in treatment-experienced and naïve patients.[3, 4] In antiretroviral-naïve patients, the combination of tenofovir with lamivudine and efavirenz has been classified as a preferred regimen in the Department of Health and Human Services treatment guidelines[5], and has been adopted by the South African Department of health as the first line regimen in treatment-naïve HIV infected patients since April 2010. The durability of antiviral response, favourable resistance profile, once daily dosing, and excellent long term safety profile of tenofovir [6], makes this drug an attractive option in both treatment and prevention regimens and its long half-life [7], made it an ideal choice as the first antiretroviral drug to be formulated as a microbicide gel.

Tenofovir has been used in the majority of prevention studies testing the concept of Pre-exposure Prophylaxis (PrEP) as a prevention strategy to date. Currently there are five large- scale trials assessing oral pre-exposure prophylaxis with tenofovir or tenofovir-emtricitabine.[8] The results of the CAPRISA 004 study conducted in South Africa released in July 2010 which tested the effectiveness and safety of 1% tenofovir gel showed that the use of tenofovir in a gel formulation reduced HIV acquisition by 39% overall, and by 54% in women with high gel adherence.[9] The Microbicides Trial Network (MTN 003 trial) is assessing the effectiveness of daily tenofovir gel, tenofovir oral or tenofovir-emtricitabine oral tablets.[10]

There have been concerns raised regarding the use of tenofovir in both PrEP and treatment regimens due to the potential for selection of viral mutations and development of resistance in patients who have become HIV-infected while on PrEP.

Previous experience with the use of antiretroviral drugs in both prevention and treatment of HIV comes largely from the use of nevirapine (NVP) in prevention of mother to child transmission (PMTCT) programs, especially in resource limited settings. Prophylactic use of NVP readily selects viral mutations that promote resistance to non nucleoside reverse-transcriptase inhibitors (NNRTIs)[11-14] that are recommended as part of first line adult treatment regimens.[15] NVP added to short-course zidovudine treatment resulted in reduced viral suppression 6 months after the commencement of therapy in a randomized trial from Thailand.[16] A subsequent study from seven African countries found that treatment with a NVP-sparing regimen was superior to a regimen containing NVP in women with prior exposure peripartum single-dose NVP.[17] The superiority of the NVP-sparing regimen was present both in women who had and did not have detectable resistance to NVP [17]. A study from Zambia reported that sdNVP exposure occurring 16 months before therapy was initiated had no impact on clinical outcomes or CD4 cell count.[18] The proportion of women who have detectable viral drug-resistance mutations decreases after exposure to NVP, providing a rationale for these findings.[14, 19, 20] A study conducted in Johannesburg found that exposure to single dose nevirapine in the prior 18-36 months was not associated with a reduced likelihood of achieving and sustaining viral suppression while receiving NNRTI based therapy. [21]

There have been no studies conducted to determine whether the use of tenofovir in pre-exposure prophylaxis affects treatment outcomes in patients who subsequently use tenofovir, which is part of the first line antiretroviral therapy regimen of many countries including South Africa. Resistance to tenofovir is associated with the K65R mutation in the reverse transcriptase gene. A separate pattern of tenofovir resistance is conferred by 3 or more thymidine analogue resistance mutations (TAMS), particularly M41L or L210W. The T69S insertion mutations, associated with resistance to multiple nucleoside analogues is also associated with resistance to tenofovir. An *in vitro* study suggested that subtype C viruses have a higher propensity to develop the K65R mutation compared to subtype B viruses, when cultured in the presence of TFV alone [22] but these findings remain controversial. It is not known if the development of viral resistance mutations in persons on PrEP may lead to less fit viruses, which may be rapidly replaced by wild virus, and therefore the future ARV treatment options are difficult to predict.

In a PrEP trial conducted in Ghana, no tenofovir-related resistance mutations were found in one seroconverter in the tenofovir arm.[23] In a Phase II trial of 1% tenofovir gel (HPTN 050), no new resistance mutations were detected in plasma and cervicovaginal lavage after 14 days of product use in HIV-infected women.[24]. Similarly, no tenofovir-related resistance mutations were found in the CAPRISA 004 tenofovir gel trial.[9]

This study aims to determine whether prophylactic exposure to tenofovir gel alters the therapeutic response to a tenofovir containing antiretroviral regimen

## **2. Study Objectives**

### **2.1 Primary Objective:**

To determine whether prophylactic exposure to tenofovir gel at the time of infection alters the subsequent therapeutic response to a tenofovir containing antiretroviral regimen

### **2.2 Secondary Objectives:**

1. To assess whether prophylactic exposure to tenofovir gel at the time of infection alters the rate of CD4+ cell count decline (HIV disease progression) and subsequent rebound following initiation of tenofovir containing or tenofovir-sparing antiretroviral treatment
2. To assess the role, if any, of tenofovir resistance on the therapeutic response to tenofovir containing antiretroviral treatment
3. To assess the safety of tenofovir containing antiretroviral treatment in women exposed to tenofovir gel at the time of HIV acquisition
4. To assess whether exposure to tenofovir gel at the time of HIV acquisition alters the subsequent humoral and cellular immune responses following antiretroviral treatment initiation
5. To assess whether prophylactic exposure to tenofovir gel at the time of HIV acquisition influences genital viral shedding and the prevalence of tenofovir resistance in genital tract viruses

### **2.3 Ancillary objective**

To assess whether tenofovir containing antiretroviral treatment regimen following prophylactic exposure to tenofovir gel at the time of HIV acquisition, is effective in preventing HIV transmission in pregnancy

### **2.4 Primary endpoint:**

The primary endpoint is the antiretroviral treatment failure rate at 12 months. Treatment failure is defined as viral load > 50 copies/ml, antiretroviral regimen changes for treatment failure or death

### **2.5 Secondary endpoint:**

1. Change in CD4+ cell count from the earliest post-infection timepoint to the time of randomisation to 12, 24 and 36 months post-randomisation
2. Tenofovir resistance, defined as presence of K65R, K70E or any of the TAMS mutations.
3. Reported adverse events with severity grades 3 and 4 based on the DAIDS toxicity grading tables
4. Cellular and humoral immune responses
5. Genital viral shedding (viral load on tear flow)



## 2.6 Ancillary Endpoint

Mother-to-child HIV transmission rates as determined by PCR on the infant at 6 weeks.

## 3. Methods

### 3.1 Study Overview

This study is an open label, two-arm, randomised control trial comparing treatment outcomes in women previously exposed to tenofovir gel at the time of HIV acquisition, who are randomised to either a tenofovir containing or a tenofovir-sparing antiretroviral treatment regimen. Comparisons in treatment outcomes will also be made between tenofovir gel exposed and tenofovir gel unexposed women following tenofovir containing antiretroviral treatment initiation. Approximately 90 women who have seroconverted while in the active or placebo arms of the CAPRISA 004 (Phase IIb Trial to Assess the Safety and Effectiveness of the Vaginal Microbicide 1% tenofovir Gel for the Prevention of HIV Infection in Women in South Africa) study and the CAPRISA 008 (Phase IIIb Open-Label Randomized Controlled Trial to Assess the Effectiveness and Safety of Tenofovir Gel Provision through Family Planning Services in KwaZulu-Natal, South Africa) study will be enrolled. Enrolment into the study will coincide with eligibility for ART initiation. Following enrolment, at which the assigned ART regimen is initiated, women will be followed up at week 1, month 1, 3, 6, 12, 18, 24, 30 and 36. The primary endpoint is the antiretroviral treatment failure rate at 12 months. Treatment failure is defined as viral load > 50 copies/ml, antiretroviral regimen changes for treatment failure or death. In addition CD4+ monitoring, viral resistance testing, adverse event reporting and blood and mucosal immunology assays will be conducted to fulfil the secondary objectives of the study. The anticipated total study duration is approximately 36 months of follow-up after ART initiation.

### 4. Study setting:

CAPRISA eThekweni Clinical Research site, Durban, South Africa:

CAPRISA eThekweni CRS is located adjacent to the Prince Cyril Zulu Communicable Disease Centre (CDC), a designated PHC of the Durban City Health Department, for the diagnosis and treatment of STIs and tuberculosis.

CAPRISA Vulindlela Clinical Research Site, KwaZulu-Natal, South Africa:

The Vulindlela CRS is situated in the sub-district of Vulindlela, a rural community, with approximately 250,000 residents in the KwaZulu-Natal midlands, about 150 km north-west of Durban.

### 5. Study Population:

Women who become infected with HIV while participating in the CAPRISA 004 and CAPRISA 008 trials.

There are 3 study populations:

- Study population 1:* HIV positive women from the CAPRISA 004 tenofovir gel arm and HIV positive women from the clinical trial tenofovir gel provision arm of CAPRISA 008
- Study population 2:* HIV positive women in the placebo arm of CAPRISA 004
- Study population 3:* HIV positive women from the family planning service arm of CAPRISA 008

Women in any of the three study populations who become pregnant during follow-up will be initiated on their assigned treatment regimen, as appropriate, for prevention of mother-to-child transmission of HIV.

#### 5.1 Inclusion Criteria:

1. Age 18 years or older
2. Previously enrolled in the CAPRISA 004 or CAPRISA 008 study – placebo or active arms
3. Able and willing to provide informed consent to be screened for, and to enrol in, the study
4. Able and willing to provide adequate locator information for study retention purposes
5. Confirmed HIV infection in the CAPRISA 004 or 008 trial
6. Agree to adhere to study visits and procedures

#### 5.2 Exclusion criteria:

1. Currently on antiretroviral therapy (including PMTCT prophylaxis)

2. 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.

### **5.3 Recruitment:**

Participants who have seroconverted while enrolled in the CAPRISA 004 study or the CAPRISA 008 study will be recruited for study participation. Participants who acquired HIV infection while in follow-up in the CAPRISA 004 study are currently in follow up in the CAPRISA 002 study (Viral Set Point and Clinical Disease Progression in HIV-1 subtype C infection: the role of immunological genetic and viral factors over the course of disease and during antiretroviral therapy, acute and early infection). All participants who become infected with HIV while in the CAPRISA 008 study will be referred to the CAPRISA 002 study for follow-up. When participants in CAPRISA 002 become eligible for antiretroviral therapy, they will be referred to this study for screening and enrolment.

### **5.4 Screening, Enrolment and Randomisation:**

Study participants will be screened for eligibility and participants meeting eligibility criteria will be enrolled in the study. Eligibility will be confirmed prior to enrolment. PID assignment will be done at enrolment. Enrolment into the study will coincide with ART initiation. Randomisation to either the intervention or control arm will be done at enrolment/ART initiation in a 1:1 ratio (see section 9.2).

### **5.5 Follow up:**

Follow up visits will follow the study schedule of evaluations (Appendix 1). Participants will be followed up for a maximum period of 36 months post antiretroviral treatment initiation following which participants will be transitioned into CAPRISA 002 phase V or the CAPRISA AIDS treatment (CAT) programme where antiretroviral treatment and clinical care will continue.

### **5.6 Retention:**

The CAPRISA DataFax system will serve as an electronic tracking system to allow study staff to monitor and track participants who have missed scheduled study visits. Participants will be contacted telephonically to follow up missed visits. If unable to contact participant telephonically a tracking team will conduct home visits and assist participants who require transport to clinic.

### **5.7 Participant Withdrawal**

Participants may voluntarily withdraw from the study for any reason at any time. Participants may be withdrawn from the study by designated staff in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures following consultation with the PIs. Participants may also be withdrawn if the study is terminated prior to its planned end date.

## **6. Co-enrolment**

Co-enrolment in other studies, either observational or experimental, will only be permitted following approval by the Principal Investigator.

## **7. Study Intervention:**

Antiretroviral therapy will be initiated when any one of the following criteria are met:

- reach a CD4+ count of less than 350 cell/mm<sup>3</sup>
- acquire an AIDS defining illness
- become pregnant

At enrolment women in each of the three study populations will be assigned randomly to one of the two following antiretroviral regimens

Intervention Arm:	Tenofovir, Lamivudine and Efavirenz (TDF/3TC/EFV)
Control arm:	Zidovudine, Lamivudine and Efavirenz (ZDV/3TC/EFV)

### **7.1 Treatment considerations:**

- The current South African antiretroviral treatment guidelines, 2010, prescribe as first line regimen for all new patients needing treatment, including pregnant women, initiation on Tenofovir,

Lamivudine or Emtricitabine, and Efavirenz or Nevirapine. Patients with a contraindication to tenofovir should be initiated on zidovudine [25].

- In this study abacavir will be reserved as an alternative nucleotide reverse transcriptase inhibitor (NRTI) for drug switches if required or if there are contra-indications to using Zidovudine.
- If a participant becomes pregnant during the study follow up she will be switched from efavirenz to nevirapine if still in the first trimester.
- For patients with TB co-infection a regimen containing efavirenz is the preferred choice [25].
- Participants who are found to be anaemic at screening will be commenced on haematinics and haemoglobin will be re-evaluated prior to enrolment
- Participants found to have a creatinine clearance of <60ml/min at screening will be investigated and re-assessed over three months. If the creatinine clearance remains <60ml/min, then the potential participant will not be eligible for this study
- Participants failing first line regimen because of virological failure or virological together with immunological or clinical failure will be commenced on an appropriate second line regimen. Participants will be commenced on a NRTI not used in the first line regimen together with lamivudine or emtricitabine and lopinavir/ritonavir [25].

## **8. Summary of Assessments:**

### **8.1 Counselling**

Participants will receive risk reduction counselling at enrolment and all scheduled follow up visits. Adherence support counselling (ASP) will be provided at screening and at ART initiation. ASP will be provided during follow up if there is any indication that a participant may have low compliance to ART.

### **8.2 Behavioural Assessment**

Questionnaires on HIV risk and quality of life will be administered at specified visits according to the schedule of evaluations.

### **8.3 Clinical assessment**

Participants will have a medical history taken at every scheduled visit. A physical examination, including vital signs will also be done at every scheduled visit. A morphological examination will be done at enrolment and 6 monthly thereafter, Pelvic examinations will be done on visits requiring genital specimen collection or if clinically indicated. Participants will be monitored for side effects experienced following ART initiation, compliance on ART and the development of new opportunistic conditions. All grade 3 and 4 adverse clinical events will be documented and graded according to the DAIDS toxicity grading system. Serious adverse events including deaths will be reported to the BREC in writing. Pregnancies will be documented and outcomes including HIV status of the infant will be followed up. All clinical events will be managed by the study clinician. Participants will be referred to their a local hospital for any problem that cannot be managed at the clinical research site. Clinical data will be captured on CRFs.

### **8.4 Laboratory Assessment**

Laboratory assessments will follow the schedule of evaluations:

- Urine pregnancy test at every visit
- FBC (full blood count), U+E(urea and electrolytes) and Creatinine at baseline and 6monthly intervals
- Cholesterol, LFT (liver function tests) iron studies, Vitamin B12 and folate and calcium, magnesium phosphate at baseline and yearly intervals
- Blood specimens for STI screen at baseline and yearly intervals.
- Genital specimens for STI screen at baseline and yearly intervals
- Genital specimens for mucosal immunology at every visit
- Blood for virology , immunity assays, storage, resistance testing and storage to be collected at every visit

## 9. Statistical Considerations

### 9.1 Sample Size:

The total number of women with HIV infection in the CAPRISA 004 and CAPRISA 008 studies is anticipated to be approximately 120 in the tenofovir gel exposed group. In addition 60 participants seroconverted in the 004 study on the placebo treatment arm.

If 50% of these participants need to be initiated on ART within the next 3 years, we would be able to randomise approximately 60 participants who were exposed to tenofovir gel to ART assignment. We also anticipate that 30 participants who seroconverted on the placebo arm will be eligible for randomisation to treatment assignment in the next 3 years (Table 1).

There are 3 study populations:

*Study population 1:* HIV positive women from the CAPRISA 004 tenofovir gel arm and HIV positive women from the clinical trial tenofovir gel provision arm of CAPRISA 008

*Study population 2:* HIV positive women in the placebo arm of CAPRISA 004

*Study population 3:* HIV positive women from the family planning service arm of CAPRISA 008

Participants will be randomised in each of the tenofovir gel exposed groups and the placebo gel exposed groups to either a tenofovir containing antiretroviral regimen or a tenofovir-sparing antiretroviral regimen.

The primary treatment outcome, treatment failure (treatment failure includes viral load > 50 copies/mL at 12 months, regimen changes for treatment failure within the first 12 months or death within the first 12 months), will be analysed in four different comparisons.

#### Comparison A:

Hypothesis: The proportion of women with treatment failure on tenofovir containing antiretroviral treatment is different than that in women on tenofovir-sparing antiretroviral treatment.

This includes study population 1 and 3, i.e. only women who were in the tenofovir gel arm of a trial at the time they acquired HIV infection. The proportion of treatment failures in women on a tenofovir containing regimen will be compared to the proportion of treatment failures in women on a tenofovir-sparing regimen.

#### Comparison B:

Hypothesis: In women on tenofovir antiretroviral treatment, longer intervals for HIV testing while on tenofovir gel, lead to different treatment failure rates.

This comparison includes women in the tenofovir containing antiretroviral treatment arms of study populations 1 and 3. Treatment failure rates in the tenofovir containing antiretroviral treatment arm of study population 1 will be compared to the treatment failure rates in the tenofovir containing antiretroviral arm of study population 3.

#### Comparison C:

Hypothesis: Prior exposure to tenofovir gel leads to different treatment failure rates.

This comparison involves the tenofovir containing antiretroviral treatment arms of all three study populations. The treatment failure rate in the tenofovir containing antiretroviral treatment arm of study populations 1 and 3 will be compared to the treatment failure rate in the tenofovir containing antiretroviral treatment arm in study population 2.

#### Comparison D:

Hypothesis: Prior exposure to tenofovir gel has no influence on treatment failure rates when a tenofovir-sparing regimen is used.

This comparison involves study populations 1, 2 and 3. The treatment failure rate in the tenofovir-sparing antiretroviral arm of study populations 1 and 3 will be compared to the treatment failure rate in the tenofovir-sparing antiretroviral treatment arm in study population 2.

#### Power

Comparison A: We anticipate that there will be 30 and 30 participants in the two arms.

Comparison B: We anticipate that there will be 20 and 10 participants in the two arms.

Comparison C: We anticipate that there will be 30 and 15 participants in the two arms.

Comparison D: We anticipate that there will be 30 and 15 participants in the two arms.

Power for Comparison A:

A Fisher's exact test with a 0.05 two-sided significance level will have 70% power to detect the difference between a Group 1 proportion, of 0.9 and a Group 2 proportion, of 0.6 when the sample size in the two groups is 30.

Power for Comparison B:

A Fisher's exact test with a 0.05 two-sided significance level will have 25% power to detect the difference between a Group 1 proportion, of 0.9 and a Group 2 proportion, of 0.6 when the sample sizes are 10 and 20, respectively.

Power for Comparison C and D:

A Fisher's exact test with a 0.05 two-sided significance level will have 43% power to detect the difference between a Group 1 proportion, of 0.9 and a Group 2 proportion, of 0.6 when the sample sizes in the two groups are 15 and 30 respectively.

**Table 1:** Statistical power estimates for comparison A based on a range of sample sizes and potential treatment failure rates

Sample size	Proportion with treatment failure			
	0.10 vs 0.30	0.10 vs 0.40	0.05 vs 0.40	0.10 vs 0.50
40/30	44	77	93	94
30/30	37	70	89	91
30/25	34	64	86	86
30/20	28	57	79	82
40/15	28	55	77	79
30/15	22	47	68	72
30/10	15	34	53	56
20/15	18	41	59	67

**9.2 Random assignment**

Enrolled participants will be assigned at random to one of the two study treatment arms in a 1:1 ratio at the time of ART initiation. Randomization will be stratified by study population. 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 and study population. 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 randomisation statistician will provide the site with sealed, opaque randomization envelopes, sequentially labelled by participant identification number (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 randomised 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.

**9.3 Data analysis plan**

A Statistical Analysis Plan (SAP) will outline the statistical 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.

A Fisher's exact test will be used to compare the proportion of participants with treatment failure in each of the two arms. We will also do a stratified Mantel Haenszel test where the stratum is the study arm a participant who seroconverted while randomised to tenofovir was in (004, 008 CAPRISA arm or 008 family planning arm). Placebo arm patients will not be stratified.

In addition, treatment failure at 24 and 36 months will be compared between the treatment arms using the same statistical methods as for the primary comparison at 12 months.

All primary analyses will be performed on an intention-to-treat (ITT) basis with additional analyses performed on the per protocol and as treated populations. For the ITT analysis, participants will be analysed 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-randomisation visit and no data collected. All primary and secondary analyses will be two-sided and will be performed at the 0.05 level of significance.

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

#### **9.4 Data collection**

Case report forms will be provided for each patient. Participants will be identified by a PID provided by CAPRISA data management centre upon enrolment. The PID is used on all CRFs to identify the participant during the study.

#### **9.5 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 centre 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 be 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**

The study will be conducted under the oversight of the University of KwaZulu-Natal, Nelson R Mandela School of Medicine Biomedical Research Ethics Committee (BREC). The Principal investigator will provide progress reports and all other information required by the ethics committee to conduct its reviews.

#### **10.2 Informed Consent Process**

Written informed consent will be obtained from each study participant prior to enrolment (see Appendix 2). Written informed consent will also be obtained for long-term specimen storage and possible future testing

(see Appendix 2). However, consent for specimen storage is not a pre-condition for study participation. Participants will be provided with a copy of their informed consent forms. Study informed consent forms will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The informed consent forms will also be translated into *isiZulu* and the accuracy of the translation will be verified through independent back-translation. The study consent process will include an assessment of each potential participant's understanding of the study and the risks and benefits of study participation, which are essential for an informed decision. Participants who are not able to demonstrate adequate understanding of key concepts will not be enrolled in the study.

### **10.3 Participant 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
- University of KwaZulu-Natal Biomedical Research Ethics Committee
- Study Monitors

### **11. Laboratory Considerations**

The study laboratory plan will include operating procedures for specimen management i.e. specimen collection, chain of custody, handling, labelling, transport; on-site testing; assay procedures; quality assurance procedures and storage procedures.

### **12. Pharmacy**

Study drug will be dispensed from the CAPRISA site pharmacies to study participants. Appropriate accountability of all study product will be maintained at the study pharmacy in accordance with GCP requirements.

### **13. Administrative procedures**

#### **13.1 Protocol compliance**

The study will be conducted in full compliance with the protocol. Amendments to the protocol will be required to follow an 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.

#### **13.2 Protocol 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 wilful 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

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 Ethics Committee 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).

### **13.3 Quality assurance**

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 study sponsors. A site visit log will be maintained at the study site to document all visits.

### **14. Use of information and Publications**

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



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## Appendix 1: Schedule of evaluations

	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
	Scr	Enr	W1	M1	M 3	M 6	M12	M18	M24	M30	M36
<b>CONSENT/ADMIN</b>											
Informed Consent	X	X									
Storage consent		X									
Locator Info	X	X	X	X	X	X	X	X	X	X	X
Risk Reduction		X	X	X	X	X	X	X	X	X	X
Eligibility assessment	X	X									
Randomisation		X									
Adherence support counselling	X	X									
<b>CLINICAL</b>											
Pregnancy test	X	X	X	X	X	X	X	X	X	X	X
FBC	X	X				X	X	X	X	X	X
U+E and Creatinine	X	X				X	X	X	X	X	X
Cholesterol, Trig		X					X		X		X
LFT		X					X		X		X
Fe/B12/Fol		X					X		X		X
Ca/Mg/PO4		X					X		X		X
<b>STI</b>											
RPR		X					X		X		X
HSV & HBV		X					X		X		X
BV		X					X		X		X
GC/CT-VVS		X					X		X		X
<b>VIROLOGY</b>											
RT-PCR/VL		X	X	X	X	X	X	X	X	X	X
Viral isolation		X	X	X	X	X	X	X	X	X	X
Seq (RNA/DNA)		X	X	X	X	X	X	X	X	X	X
Seq mucosal (CVL)		X					X		X		X
<b>IMMUNITY ASSAYS</b>											
	X	X	X	X	X	X	X	X	X	X	X
<b>STORAGE</b>											
Storage-Serum		X	X	X	X	X	X	X	X	X	X
Storage-PBMC		X	X	X	X	X	X	X	X	X	X
<b>MUCOSAL IMMUNOLOGY</b>											
Tear Flo Strips		X					X		X		X
Cytobrush		X					X		X		X
<b>RESISTANCE TESTING</b>											
ARV resistance plasma		X	X	X	X	X	X	X	X	X	X
Tenofovir resistance: Cytobrush		X					X		X		X
<b>Approximate Blood Draw Volumes</b>	<b>13ml</b>	<b>117ml</b>	<b>95ml</b>	<b>95ml</b>	<b>103ml</b>	<b>112ml</b>	<b>117ml</b>	<b>112ml</b>	<b>117ml</b>	<b>112ml</b>	<b>117ml</b>

Note:

1. Enrolment coincides with day of ART initiation
2. These are the study visits. In addition participants will be seen every month for the first 6 months following ART initiation
3. Any test may be performed when clinically indicated

## **Appendix 2: Informed Consent Forms**

- Informed consent form for enrolment, Version 2.0, 27 January 2011
- Informed consent for specimen storage for possible future research, Version 2.0, 27 January 2011

## CAPRISA 009

### Open Label Randomized Controlled Trial to Assess the Impact of Prophylactic Exposure to Tenofovir Gel on the Efficacy of Subsequent Tenofovir-Containing Antiretroviral Therapy On Viral Suppression

Version 2.0, 27 January 2011

#### INFORMED CONSENT FORM FOR ENROLMENT

If the volunteer cannot read, this form must be read to the volunteer exactly as written, in the volunteer's language of choice, and a witness must sign this form to confirm that the correct information was given to the volunteer and that the volunteer freely consents to be in this study.

#### PRINCIPAL INVESTIGATORS:

Dr Nivashnee Naicker, Prof. Salim S Abdool Karim , Ms Anushka Naidoo  
2<sup>nd</sup> Floor Doris Duke Medical Research Institute  
Nelson R Mandela School of Medicine  
Private Bag 7, Congella 4013, Durban, South Africa  
Telephone: 031-260 4550

#### INTRODUCTION

You are being asked to volunteer to be screened for enrolment into CAPRISA 009 because you may have previously participated in the CAPRISA 004 or CAPRISA 008 studies and you are infected with the HIV virus and you now need to be initiated on or start antiretroviral therapy. The purpose of this study is to assess whether exposure to 1% tenofovir gel at the time of infection with the HIV virus affects how well the antiretroviral therapy that you will be taking to treat your HIV infection works by checking your viral load and CD4 cell counts at regular intervals. We will also check if you have any resistance to tenofovir and if you have any side effects to the antiretroviral drugs used to treat you

This consent form is the first step to establish if you are eligible to be enrolled into the CAPRISA 009 study. No study procedures will be undertaken until you have read (or have read to you) this enrolment consent and voluntarily agree to participate in CAPRISA 009. After you have agreed to participate in CAPRISA 009, the screening procedures will be undertaken. If you are found to be eligible, the enrolment procedures will then be completed. The screening and enrolment procedures can happen on the same day or on different days.

A second informed consent that will request your permission to utilise any remaining specimens collected as part of your participation in CAPRISA 009 and after all CAPRISA 009 testing has been completed for other studies that may be undertaken in the future. We will start today with the screening and enrolment consent.

#### YOUR PARTICIPATION IS VOLUNTARY

You are being asked to volunteer in the research study named above. In order to be sure that you have sufficient information about this study and your consent is voluntary we are asking you to read (or have read to you) this consent form in the language of your choice.

You are being asked to sign this consent form (or make your mark in front of a witness) if you agree to participate in this study. We will give you a copy of this form to keep or we can store your copy for you. This consent form might contain some words or ideas or terms that are you may not understand or be unsure about its meaning. Please stop me at any time during this process and ask me to explain anything you may not understand.

Before you learn about the study, it is important that you know the following:

- Your participation is entirely voluntary. You may decide not to participate in the study, but you are still eligible for antiretroviral therapy and you may decide to obtain your HIV care through your own medical provider or the CAPRISA AIDS Treatment Program (CAT).
- You may decide not to take part or to withdraw from the study at any time. You will not lose the benefits of your routine medical care at this clinic.
- If you decide to not take part in this research study, you can still take part in another research study, if one is available and you meet the study requirements.
- You can expect to be informed of any new information that may arise, which could affect your decision to remain a part of this study.

Before you decide if you want to be a part of this study, we want you to know about the study.

### **WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to learn whether using tenofovir gel to prevent HIV infection affects the use of tenofovir to treat HIV infection when antiretroviral therapy is required. This is a open label, two arm randomized controlled trial wherein eligible, consenting women will have an equal chance to be randomized to an antiretroviral drug regimen containing, tenofovir, efavirenz and lamivudine or a regimen containing zidovudine, lamivudine and efavirenz, at the CAPRISA eThekweni or Vulindlela Clinics. It will not be possible to change the group to which you are randomized or assigned.

The study will assess if your viral load, CD4+ cell count and side effects experienced are affected by being exposed to tenofovir gel at time of infection or not. We will also check if you have HIV virus which is resistant to tenofovir or if exposure to tenofovir gel at time of HIV infection affects transmission of HIV to your baby if you fall pregnant during the course of the study.

### **WHAT IS THE DURATION OF THE STUDY?**

The study will be conducted over approximately 3 years (36 months).

### **HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**

About 90 people will take part in this study.

### **WHAT DO I HAVE TO DO IF I PARTICIPATE IN THIS STUDY?**

If you join this study, we will ask you to come into the clinic for examinations, interviews, and laboratory tests frequently. We will ask you to attend the clinic at your enrolment visit, week 1 and month1, thereafter you are required to come to the clinic once every 3 months for approximately three years. If you miss appointments, the persons you named will be contacted or field workers will be sent to your home. Please inform a study staff member, should you wish not to be visited at home.

Any time that results of exams and laboratory tests such as viral load (which measures how much HIV virus is in your blood), CD4+ T cell counts (immune cells that help fight infection such as HIV), and safety tests are known, they will be given to you. There may be times that you must come for additional visits if these exams or tests show abnormal results. Some of the blood drawn and genital specimens collected throughout the study may be stored. You can expect to be asked for your permission to store the blood and genital specimens for future research and asked to sign a separate consent form if you agree to do this. You may still participate in the study if you do not agree to have blood stored.

### **Screening Visit (today)**

After you complete the informed consent process and if you agree to participate in the CAPRISA 009 study the following will be done:

The study staff will determine if you are eligible to take part in the study.

We will ask you to have a physical examination and will be asked questions about your medical history and any medicines that you have taken. We will ask you to give urine for a pregnancy test and get the results; you may still take part in the study if you are pregnant. About 15 ml (about 3 teaspoons) of blood will be drawn, with a needle from your arm, for routine tests and CD4+ cell count. As part of the routine tests that will be done on your blood, we will check if your kidneys are working correctly and you will be given the results of these tests. The haemoglobin levels in your blood will also be checked to ensure that you can take antiretroviral drugs which may affect your haemoglobin blood levels.

Counselling regarding HIV and risk reduction will be provided.

We will ask you to provide information on where you live and how to keep in contact with you.

### ***Enrolment and Scheduled Follow-up Visits***

You will have a physical exam and bloods drawn at the enrolment visit and then at every scheduled study visit and additionally when clinically indicated. About 117ml (about 8 tablespoons) of blood will be drawn, with a needle

from your arm, for routine tests, CD4+ cell counts, viral load and other study related tests You will be told your test results throughout the study.

Bloods will be taken from you at enrolment and some of your blood will be stored for future HIV-related testing including a test for HIV resistance.

If you are a woman, and able to become pregnant, you can expect to be asked to provide some urine for a routine pregnancy test.

You are to commence on antiretroviral therapy in the study arm to which you are randomized, if you meet eligibility criteria. It is not possible to change the arm to which you are assigned or randomized but the investigator may change the drugs that you are taking if these affect your health adversely or cause serious side effects, do not work correctly to treat your HIV infection or are deemed inappropriate by the investigator for any other reason.

We will ask you to have pelvic exams done at enrolment and then every 12 months thereafter.

Counselling regarding adherence to study drugs will be provided.

You can expect to be screened and counselled about other infections that may be passed during sex. These other infections may cause a vaginal discharge or ulcers in your genital tract. Some examples of these infections are syphilis, gonorrhoea and chlamydia. If you have an ulcer or discharge because of these infections we will give you medicine to treat them today. If you have an infection that your partner may also have, you may bring him here for treatment that he may need too. This will be at no cost to you or your partner.

If you are admitted to hospital, you can expect to be asked questions about the reasons for your stay there.

#### **USE OF STORED SAMPLES**

The stored samples may be used for future research, to confirm test results, or to do additional testing. Your samples will not be sold or used in products that make money for the researchers. You will be asked to sign a separate form asking for your consent to have your samples stored. Should you decide not to have your samples stored; this will not affect your ability to take part in the study.

#### **WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT?**

You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC).
- The investigator or study staff feels that staying in the study may be harmful to you.
- You are not able or willing to attend study visits or to complete the study procedures.

#### **WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?**

Instead of being in this study you have the choice of:

- Participation in the CAT programme.
- Treatment with ART through the South African national rollout program.
- No treatment

Antiretroviral medications, laboratory tests to monitor the effectiveness of these medications, and quality medical care for HIV/AIDS may or may not be available to you outside the study. The clinic staff will discuss with you other treatment choices in your area and the risks and the benefits of all the choices.

#### **WHAT ABOUT CONFIDENTIALITY?**

Your medical records, personal information, and the results of your HIV tests and other medical and laboratory evaluations will be kept strictly confidential within the extent of South African law. Only your doctor and/or nurse will know the results of your tests. Your records will be identified by a study code. Any publication of this study will not use your name or identify you personally.

Every effort will be made to protect your confidentiality but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may also be reviewed by regulatory authorities, namely the Biomedical Research Ethics Committee, Medicines Control Council and study staff.

**WHAT ARE THE RISKS AND DISCOMFORTS ASSOCIATED WITH THE STUDY?**

Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, light-headedness, and in rare cases, fainting or infection. Many people do not understand the facts about infection with the AIDS virus. Being HIV positive can be a very stressful experience. You may be treated badly by friends and family if you are HIV positive and your HIV status becomes known to others.

**WHAT HAPPENS IF I BECOME PREGNANT?**

If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices and refer you to a provider of prenatal care if you do not have one. You may still continue to be part of the study and your antiretroviral therapy may be changed to the most appropriate drugs that may be used during pregnancy. All female patients who participate in this study will be offered a pregnancy test at every study visit. We will check if exposure to tenofovir gel at time of HIV infection affects transmission of HIV to your baby..

**WHAT ARE THE BENEFITS ASSOCIATED WITH THE STUDY?**

If you participate in this study, there may be a direct benefit to you, but no guarantee can be made. Your health will be followed more closely than usual while you are on the study, which may help you to feel better.

**WILL I RECEIVE ANY PAYMENT?**

Participants will be reimbursed R150 at enrolment in the study and for every scheduled study visit thereafter.

**WHAT ARE THE COSTS TO ME?**

There is no cost to you for taking part in this study.

**WHAT HAPPENS IF I AM INJURED?**

It is very unlikely that you will become injured as a result of involvement in this study. However, in the case of a research related injury, you will be given the immediate necessary treatment for your injuries at the CAPRISA Clinical Research sites or referred to an appropriate health care facility for treatment. The cost of this treatment will be borne by the research team. There is, however, no compensation provided for research related injuries. You do not give up any legal rights by signing this consent form.

If you ever have any questions about your participation in this study you should contact Dr Nivashnee Naicker at 031-260 1949 at the CAPRISA eThekweni Clinic , Professor Salim S Abdool Karim at 031-260 4550, CAPRISA, Second Floor Doris Duke Medical Research Institute, Durban or Dr Bonginkosi Mdluli at 033-260 6851 at the CAPRISA Vulindlela Clinics, Mafakathini.

If you have questions about your rights as a research participant, you should contact the Biomedical Research Ethics Administration, University of KwaZulu-Natal, Research Office, Westville Campus, Govan Mbeki Building, Private Bag X 54001, Durban, 4000, KwaZulu-Natal, South Africa. Tel: 27 31 2604769 - Fax: 27 31 2604609, Email: [BREC@ukzn.ac.za](mailto:BREC@ukzn.ac.za)



**SIGNATURE PAGE:**

If you have read the informed consent (or if you have had it read to you) and understand the information, and you voluntarily agree to join this study, please sign your name below. .

\_\_\_\_\_  
Participant's name  
(print as in ID book or birth certificate)

\_\_\_\_\_  
Participant's signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of staff member who  
administered consent (print)

\_\_\_\_\_  
Staff member's signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Witness' name (print)

\_\_\_\_\_  
Witness' signature

\_\_\_\_\_  
Date

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***The section below is to be completed by the person who administered the informed consent***

Was a copy of the signed copy given to the volunteer:  
If no, why not:

Yes

No

**CAPRISA 009**  
**Open Label Randomized Controlled Trial to Assess the Impact of prophylactic exposure to tenofovir gel  
on the efficacy of subsequent tenofovir-containing antiretroviral therapy on viral suppression**

**Version 2.0**  
**27 January 2011**

**INFORMED CONSENT FOR SPECIMEN STORAGE FOR POSSIBLE FUTURE RESEARCH**

If the volunteer cannot read, this form must be read to the volunteer exactly as written, in the volunteer's language of choice, and a witness must sign this form to confirm that the correct information was given to the volunteer and that the volunteer freely consents to be in this study.

**PRINCIPAL INVESTIGATORS:**

Dr Nivashnee Naicker, Prof. Salim S Abdool Karim, Ms Anushka Naidoo  
2<sup>nd</sup> Floor Doris Duke Medical Research Institute  
Nelson R Mandela School of Medicine  
Private Bag 7, Congella 4013, Durban, South Africa  
Telephone: 031-260 4550

**INTRODUCTION:**

You have decided to participate in the CAPRISA 009 study. During this study blood and other biological samples will be taken from you for testing. Some of these samples may be kept for future research relating to the study of HIV. This consent form gives you information about this storage and the use of samples. You are being asked to consent to the storage of your blood and other samples. The study staff will discuss this with you. Please ask if you have any questions. If you agree to the storage of your blood and other samples, you will be asked to sign this consent form. You will be given a copy of this form to keep.

You can still take part in CAPRISA 009 even if you decide not to sign this form. If you decide not to sign this form the specimens described below will be collected from you and after all the study related testing has been completed all remaining specimens will be destroyed.

Please note that:

- Your participation in this study is entirely voluntary. You may decide not to participate in the study, but you are still eligible for anti-retroviral therapy. You may decide to obtain your HIV care through your own medical care provider.
- You may stop taking part in the study at any time and this will not affect the care you receive through the CAPRISA AIDS Treatment Program.

**BLOOD AND BIOLOGICAL SAMPLES**

**HOW WILL YOU GET THE BLOOD AND BIOLOGICAL SAMPLES FROM ME?**

Blood samples will be taken from you at every scheduled study visit. At these visits we will take about 117ml (about 8 tablespoons) will be taken with a needle from your arm for the study. This blood is needed to carry out the regular tests for the research study. If you agree to have your specimens stored for possible future research, we will store the remainder of this blood after the tests for this study have been completed for possible future research that is not related to this study. As with your other samples, only a number, not your name, will be used to identify these samples. These samples may provide valuable information in the future when different immune system and HIV tests become available and for possible future research that is not related to this study.

In addition, as part of this study, you will have a pelvic examination when you come for the following study visits: at enrolment, month 12, month 24 and month 36 and we will collect genital specimens. These specimens will be stored and may be used during, or at the end of the study, to recheck or conduct additional tests to help us understand how the gel works better. If you have not agreed to your specimens being stored for future testing not related to this study, these specimens will be destroyed after all the study related tests have been

completed. If you agree to have your specimens stored for possible future research, these genital specimens will be kept and used for possible future research that is not related to this study.

### **HOW WILL YOU USE MY STORED SAMPLES?**

The stored samples may be used for future research, to confirm test results, or to do additional testing. If new methods of testing become available, the samples may be used to see if these new tests give the same results. We may test your cells, proteins, other chemicals in your body and your genes (DNA). Some of the samples will also be tested to see how your nutritional status may be interacting with HIV infection. Your samples may be analysed in laboratories outside of South Africa. Your blood or genital specimens will not be sold or used in products that make money for the researchers or anyone else. Virus obtained from your sample may be used in vaccine research and development. Any studies that use your specimens in future research will be reviewed by the Biomedical Research Ethics Committee of the Nelson R. Mandela School of Medicine, University of KwaZulu-Natal.

The researchers do not plan to contact you or your regular doctor with any results that are done on the stored samples after the study has been completed. This is because research tests are often done with experimental procedures so the results from one study are generally not useful for making decisions on managing your health. Should a rare situation come up where the researchers decide that a specific test result would provide important information for your health, the researchers will notify the study doctor who will try to contact you or your regular doctor. If you wish to be notified of this type of test result, you need to make sure that you contact the study nurse or doctor with any changes to your phone number or address. If you want your regular doctor to be told about this kind of test result, you need to provide the study team with the contact details of your regular doctor.

### **HOW LONG WILL YOU KEEP MY BLOOD AND BIOLOGICAL SAMPLES?**

There is no time limit on how long your blood and biological samples will be stored.

### **HOW WILL MY BLOOD AND BIOLOGICAL SAMPLES BE STORED?**

Your samples will be stored at laboratories that are specially designed to keep stored samples safely. Only approved researchers working on this project and related projects will be able to access your samples. The people who work at these laboratories will have access to your samples when they store them and keep track of them, but they will not know who you are as your samples will be stored by number. There is no time limit on how long your samples may be stored. Should you decide during the study that you do not want the samples to be stored, you do have the right to request that your samples be destroyed. A study staff member will ask you to sign a form documenting your decision. Deciding to withdraw consent to have your samples stored will not affect the quality of care and attention that you receive within the study.

### **WHAT ARE THE BENEFITS TO HAVING MY SAMPLES STORED**

There is no direct benefit to you through having your samples stored and tested later. There may be benefits to society of doing research on your stored blood or biological samples. These benefits may include learning more information about HIV infection or other diseases and may help others who have HIV/AIDS, as well as for publication in a scientific medical journal.

### **RISKS**

There is very little risk to you when you have your samples stored. There is a small risk that others may find out information about your HIV status from stored samples. This risk is reduced as your sample is stored under a study number, and not your name. You are entitled to the same protections of confidentiality and privacy for stored samples as you are for the samples that are drawn and used during the study. It is possible that tests that have yet to be developed may tell us things about your health we cannot currently test for. Results from these tests may cause distress to you.

### **WHAT ABOUT PREGNANCY?**

All female patients who participate in this study will be offered a pregnancy test at every study visit. If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices and refer you to a provider of prenatal care if you do not have one. You may still continue to be part of the study.

**WHAT ARE THE BENEFITS ASSOCIATED WITH THE STUDY?**

If you participate in this study, there may be a direct benefit to you, but no guarantee can be made. Your health will be followed more closely than usual while you are on the study, which may help you to feel better.

**WHAT ABOUT CONFIDENTIALITY?**

The results of future tests of your samples will not go into your medical record. Although every effort is made to make sure that your samples are stored confidentially (by number and not name), we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may also be reviewed by regulatory authorities the University of KwaZulu Natal Biomedical Research Ethics Committee (BREC), study staff and study monitors.

**WHAT ARE MY RIGHTS AS A PARTICIPANT**

The decision to allow your samples to be stored is completely voluntary. If you do not allow your samples to be stored, you may still participate in the main study. You may decide not to allow your samples to be stored after the tests that are needed for this study have been done or you decide to stop participating in the study. If you do decide to allow your samples to be stored, you can change your mind at any time and still participate in the main study. You must contact the study doctor or nurse and let them know that you do not want your samples to be stored any more. If you decide to do this, your samples will no longer be stored. You will then be asked if you want all stored samples to be destroyed. In this case, any samples that have been stored will be destroyed. You will then be asked to sign this form again under the section, "Withdrawal of Consent" so that there is a record of your decision. At the end of the study you will also be given the opportunity to review your consent for the storage of your samples.

**WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?**

If you ever have any questions about the storage of your blood or genital specimens you should contact Dr Nivashnee Naicker at 031-260 1949 at the eThekweni Clinic, Professor Salim S Abdool Karim at 031-260 4550, CAPRISA, Second Floor Doris Duke Medical Research Institute, Durban or Dr Bonginkosi Mdluli at 031- 260 6851 at the CAPRISA Vulindlela Clinic, Mafakathini.

If you have questions about your rights as a research participant, you should contact the Biomedical Research Ethics Administration, University of KwaZulu-Natal, Research Office, Westville Campus, Govan Mbeki Building, Private Bag X 54001, Durban, 4000, KwaZulu-Natal, SOUTH AFRICA. Tel: 27 31 2604769 - Fax: 27 31 2604609, Email: [BREC@ukzn.ac.za](mailto:BREC@ukzn.ac.za).

**SIGNATURES**

Please carefully read the statements below and think about your choice. No matter what you decide it will not affect your care or your participation in CAPRISA 008.

I agree to have blood and genital specimens taken for the purpose of storage and testing for future research related to HIV and other infections.

\_\_\_\_\_ Yes

\_\_\_\_\_ No

\_\_\_\_\_  
Participant Name  
(Print)

\_\_\_\_\_  
Participant Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Staff Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Witness Name  
(print)  
(If participant is unable to provide a signature)

\_\_\_\_\_  
Witness Signature

\_\_\_\_\_  
Date

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***The section below is to be completed by the person who administered the informed consent***

Was a copy of the signed copy given to the volunteer:       Yes       No  
If no, why not:

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