

# **PROTOCOL**

## **CAPRISA 082**

### **Prospective Study of HIV Risk Factors and Prevention Choices in Young Women in KwaZulu-Natal, South Africa**

#### **Study Design and Conduct:**

Centre for the AIDS Programme of Research in South Africa (CAPRISA)

#### **Study Sites:**

CAPRISA eThekweni, Vulindlela and Umlazi Research Clinics

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# Prospective Study of HIV Risk Factors and Prevention Choices in Young Women in KwaZulu-Natal, South Africa

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**Prospective Study of HIV Risk Factors and Prevention Choices in Young Women in  
KwaZulu-Natal, South Africa**

**CAPRISA 082**

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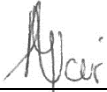
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15 January 2016

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# Prospective Study of HIV Risk Factors and Prevention Choices in Young Women in KwaZulu-Natal, South Africa

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# Prospective Study of HIV Risk Factors and Prevention Choices in Young Women in KwaZulu-Natal, South Africa

## ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
BREC	Biomedical Research Ethics Committee
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CI	Confidence Interval
CP	Community Programme
CRSG	Community Research Support Group
CRF	Case Report Form
ELISA	Enzyme-linked Immunosorbent Assay
FACTS	Follow-on Consortium for Tenofovir Studies
FDA	(United States) Food and Drug Administration
FP	Family Planning
FTC	Emtricitabine
GCP	Good Clinical Practice
HCT	HIV Counselling and Testing
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
ICH	International Conference on Harmonization
LA	Long-acting
MCC	Medicines Control Council
MSM	Men who have Sex with Men
PCR	Polymerase Chain Reaction
PCZCDC	Prince Cyril Zulu Communicable Diseases Clinic
PEP	Post-exposure Prophylaxis
PHC	Primary Health Care
PID	Participant Identification
PrEP	Pre-exposure Prophylaxis
QC	Quality Control
RNA	Ribonucleic Acid
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
STI	Sexually Transmitted Infection
TASP	Treatment as Prevention
TDF	Tenofovir Disoproxil Fumarate
UKZN	University of KwaZulu-Natal
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States (of America)
VOICE	Vaginal and Oral Interventions to Control the Epidemic
WHO	World Health Organization

# Prospective Study of HIV Risk Factors and Prevention Choices in Young Women in KwaZulu-Natal, South Africa

## STUDY SUMMARY

- Purpose:** To assess HIV risk factors and prevention choices in young women in KwaZulu-Natal, South Africa.
- Design:** Prospective observational cohort study: Potential study participants will be screened for eligibility and eligible participants will be enrolled in the study within 30 days of screening. Participants will have monthly visits for the first three months post-enrolment, thereafter visits will be scheduled every three months.
- Study population:** HIV uninfected women aged 18 to 30 years from Durban, Vulindlela and Umlazi in South Africa
- Target sample size:** Up to 2,500 women
- Study duration:** An open cohort will be maintained for up to 5 years. Participants may be simultaneously enrolled in or may transition to other studies as appropriate.
- Primary objective:** To identify risk factors for HIV acquisition in healthy young women in KwaZulu-Natal, South Africa.

### Secondary objectives:

- To measure the acceptability of, uptake and adherence to the range of behavioural and biomedical prevention options, including pre-exposure prophylaxis (when available).
- To measure HIV and other sexually transmitted infection incidence rates.
- To assess trends in sexual behaviour.
- To measure pregnancy rates.

### Study sites:

- CAPRISA eThekweni Research Clinic, Durban, South Africa (Urban Site)
- CAPRISA Vulindlela Research Clinic, KwaZulu-Natal, South Africa (Rural Site)
- CAPRISA Umlazi Research Clinic, Umlazi, South Africa (Peri-urban Site)



## 1. BACKGROUND AND RATIONALE

### 1.1 The HIV epidemic in sub-Saharan Africa and the need for HIV prevention methods that women can control

The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO), estimate there are about 380 000 new HIV (Human Immunodeficiency Virus) infections among young women aged 15–24 years every year<sup>1</sup>. In 2013, almost 60% of all new HIV infections, in those aged between 15–24 years, occurred among adolescent girls and young women<sup>2</sup>. In sub-Saharan Africa, women acquire HIV infection at least 5–7 years earlier than men<sup>1</sup>. Adolescents and young women in sub-Saharan Africa are therefore especially vulnerable to HIV acquisition, which occurs mostly as a result of unprotected heterosexual intercourse<sup>3</sup>.

In addition to biological factors<sup>4–6</sup> 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<sup>3</sup>, multiple concurrent relationships<sup>7</sup>, low marriage rates<sup>8</sup>, low consistent condom use rates<sup>9,10</sup>, and limited skills in negotiating safer sex practices. Gender-based violence increases vulnerability<sup>11</sup>, and poverty increases reliance on transactional sex for survival<sup>12</sup>. 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. There is an urgent need for new technologies to prevent HIV infection in young women.

### 1.2 Antiretrovirals (ARVs) for HIV prevention

Since 2010, the HIV prevention landscape has been transformed, principally through oral and topical use of ARVs and pre-exposure prophylaxis (PrEP) or through early ARV treatment initiation in HIV infected individuals (Treatment as Prevention/TasP).

ARVs were first shown to reduce sexual HIV acquisition in the CAPRISA 004 Tenofovir Gel Trial. This trial, conducted among 889 rural and urban South African women, showed that tenofovir gel used before and after sex reduced acquisition of HIV infection in women by 39% (95% Confidence Interval (CI): 6;60) overall, and by 54% in women who used the gel consistently<sup>13</sup>. Thereafter, the iPrEX trial showed that daily oral tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) combination (Truvada) reduced HIV incidence by 44% (95% CI 15;63) among 2,499 men or transgender women who have sex with men<sup>14</sup>.

Further, the effectiveness of daily oral PrEP in heterosexual men and women was shown in the Partners PrEP trial<sup>15</sup> and the Botswana TDF2 trial<sup>16</sup>. The Partners PrEP trial, which included 4,758 HIV discordant couples from Kenya and Uganda showed that daily oral TDF and TDF/FTC reduced HIV incidence by 67% (95% CI 44; 81) and 75% (95% CI 55; 87) respectively, while the Botswana TDF2 trial, conducted among 1,200 heterosexual men and women from the general population, found that daily oral TDF-FTC reduced HIV incidence by 62% (95% CI 22; 83).

The use of ARVs for treatment of HIV-infected patients has also recently been shown in a randomized clinical trial to prevent onward transmission of HIV to their uninfected partners (TasP). The HIV Prevention Trials Network (HPTN) 052 trial, conducted among 1,763 HIV-discordant couples from 9 countries, showed that HIV transmission was reduced by 96% (95% CI, 73;99.5) when antiretroviral therapy (ART) was initiated in patients with CD4 counts between 350 and 550 cells/mm<sup>3</sup>,<sup>17</sup>.

This series of breakthroughs in HIV prevention, combined with the recent approval of the first ARV drug (Truvada<sup>®</sup>) for reducing the risk of sexually acquired HIV infection by the South African Medicines Control Council (MCC)<sup>18</sup> and the WHO guidelines recommending PrEP for all populations at substantial risk of HIV (HIV incidence >3%)<sup>19</sup>, has led to PrEP being regarded as part of a comprehensive HIV prevention package.

The implementation of PrEP, however, will not be straightforward. Adherence to the daily dosing regimens has emerged a significant challenge that directly impacts on the effectiveness of the intervention. Some PrEP trials that have been conducted among women have failed to show efficacy due to suboptimal adherence<sup>20,21</sup>. In the FEM-PREP trial<sup>20</sup>, only 24% of the women allocated to the daily oral TDF/FTC group had detectable drug levels. Similarly, in the VOICE trial, only 25%, 29%, and 30% of women allocated to the daily tenofovir gel, daily oral TDF/FTC and daily oral TDF groups respectively had detectable drug levels<sup>21</sup>. Therefore, the implementation of PrEP will need to be accompanied by intensive adherence counselling.

To overcome some of these adherence challenges, novel PrEP agents and innovative delivery systems such as long-acting ARV intravaginal rings and long-acting ARV injectable drugs are being developed. These products may potentially improve adherence as they are less dependent on user compliance compared with oral or gel formulations. Results of trials on the dapivirine intravaginal ring<sup>22,23</sup>, which release drugs slowly over a 28 day period, are anticipated in early 2016. Studies on long-acting ARV injectable agents such as rilpivirine (TMC278)<sup>24</sup> and cabotegravir (GSK1265744)<sup>25</sup>, which can be administered every 2 to 3 months, are ongoing.

### **1.3 Study rationale**

Longitudinal studies are essential to characterise the epidemiology of and trends in HIV infection. Assessing known HIV risk factors and identifying new risk factors for HIV acquisition is important for the development of appropriate risk reduction programmes. As risk factors vary over time, a prospective cohort approach is being employed in this study to monitor risk factors, HIV incidence and transmission patterns in women from KwaZulu-Natal.

The HIV prevention landscape is rapidly expanding and now includes oral PrEP in South Africa. Over time other ARV based formulations, such as intravaginal rings, long-acting injectables, implants and vaccines, may become available. As the PrEP product options and formulations expand and new evidence of efficacious prevention products emerge, women's preferences within the range of available HIV prevention methods will need to be assessed and monitored for service planning and provision. Further, this study provides an opportunity to measure uptake and adherence of different prevention options.

## **2. STUDY SETTING**

This study will be conducted at three Research Clinics in KwaZulu-Natal, South Africa and will enrol HIV uninfected women in Durban, Vulindlela and Umlazi.

### **2.1 CAPRISA eThekweni Research Clinic**

The CAPRISA eThekweni Research Clinic is located adjacent to the Prince Cyril Zulu Communicable Disease Centre (PCZCDC), a designated PHC of the Durban City Health Department, for the diagnosis and treatment of sexually transmitted infections (STIs) and tuberculosis. The clinic is conveniently situated in the Warwick triangle in the metropolitan region of Durban which serves as the nucleus of the public transportation with the central bus, "minibus" taxi station and rail station all within a 500 metre radius of the clinic building. This clinic is readily accessible in terms of the transport infrastructure. This clinic provides free STI and tuberculosis treatment. Annually, approximately 40 000 cases of STIs are treated at this clinic, approximately 36 000 of which are new cases. The majority of the STI patients accessing these facilities are self-referred either symptomatic with genital ulceration and/or vaginal discharge syndrome or as contacts of patients with a diagnosis of a STI and include both males and females. Given the high prevalence of HIV infection in South Africa and the strong association between STIs and HIV acquisition, these patients are at an increased risk of acquiring and transmitting HIV through sex.

Overall HIV prevalence in women attending the CAPRISA eThekweni Research Clinic is 23 % (95% CI 21.3 - 25.6).

### **2.2 CAPRISA Vulindlela Research Clinic**

The CAPRISA Vulindlela Research Clinic 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 Primary Health Care (PHC) services are provided through seven clinics in the sub-district. These nurse-managed services provide antenatal care, family planning, childhood immunizations, STI treatment, minor ailment care, tuberculosis treatment and HIV counseling and testing (HCT). The closest referral hospitals are Grey's, Northdale and Edendale. The CAPRISA Vulindlela Research Clinic adjoins the Mafakathini PHC Clinic.

Overall HIV prevalence in pregnant women in Vulindlela increased from 35.3% (95% CI 32.3-38.3) in 2001-2003 to 39.3% (95% CI 37.2-41.4) in 2009-2013.

CAPRISA has a long established relationship with the Vulindlela community, which has participated in several studies, including the CAPRISA 004 trial and the recently completed CAPRISA 008 trial.

## **2.3 CAPRISA Umlazi Research Clinic**

The CAPRISA Umlazi Research Clinic is a well-established research facility that has been conducting HIV prevention research with a particular focus on Prevention of Mother to Child Transmission for the past 9 years. Umlazi, which is the largest township in KwaZulu-Natal, has a population of about 400,000 and is divided into sections using alphabets from A to Z. About 30% of the houses are informal housing. There are 40 secondary schools in the Umlazi district. This district is serviced by one district hospital, the Prince Mshiyeni Memorial Hospital, and there are 17 provincial clinics that are linked to the hospital with an additional 3 municipal clinics in the area.

More than 40% of prenatal clinic attendees in Umlazi are HIV positive.

These HIV prevalence and incidence rate data from the eThekweni, Vulindlela and Umlazi 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 developing HIV prevention technologies for young women in this setting.

## **3. STUDY OBJECTIVES AND DESIGN**

### **3.1 Primary objective**

To identify risk factors for HIV acquisition in healthy young women in KwaZulu-Natal, South Africa.

### **3.2 Secondary objectives**

- To measure the acceptability of, uptake and adherence to the range of behavioural and biomedical prevention options, including pre-exposure prophylaxis (when available).
- To measure HIV and other sexually transmitted infection incidence rates.
- To assess trends in sexual behaviour.
- To measure pregnancy rates.

### **3.3 Study overview**

This is a prospective observational cohort study.

Up to 2,500 sexually active, HIV-uninfected women between the ages of 18 and 30 years will be enrolled from an urban, a peri-urban and a rural site in KwaZulu-Natal, South Africa. Potential study participants will be screened for eligibility and eligible participants will be enrolled in the study within 30 days of screening. Participants will have monthly visits for the first three months post-enrollment, thereafter visits will be scheduled every three months.

HIV and pregnancy testing will be performed at each study visit and the incidence of pregnancy, as well as HIV and other STIs will be assessed. HIV/STI risk reduction messages and HIV prevention methods (e.g. condoms) will be offered to all participants using consistent prevention messages. It is anticipated that PrEP use will increase during this study. Uptake and adherence to PrEP and other HIV prevention modalities will be assessed during follow up. A HIV risk perception and behavioural assessment using an interviewer administered questionnaire will be conducted at each visit. In addition, an acceptability assessment of expanded HIV prevention options (oral tablets, rings, injectables and implants) will be conducted through an interviewer administered questionnaire at enrolment and study exit. Blood and genital specimens will be collected and stored every three months and will be used for potential post-study assessments for markers of safety, risk exposure, PrEP adherence and resistance. In addition, stored plasma will be used for retrospective RNA PCR testing to confirm whether incident cases of early HIV infection during the study occurred post-enrolment.

An open cohort will be maintained for up to 5 years. Participants may be simultaneously enrolled in or may transition to other studies as appropriate.

Overviews of the study visit and procedures schedules are presented in Appendix I: Schedule of Evaluations.

## 4 STUDY POPULATION

Women, between the ages of 18 and 30 years will be recruited through outreach activities in the community. The aim will be to identify up to 2,500 volunteers, who meet the inclusion criteria for the study and are likely to adhere to study procedures and the study visit schedule.

### 4.1 Inclusion criteria

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

- Female
- Age 18-30 years (inclusive)
- Able and willing to provide written informed consent to be screened for, and to enrol in, the study
- Able and willing to provide adequate locator information for study retention purposes
- Sexually active (sexual intercourse at least three times in the last 3 months)
- HIV negative on testing performed by study staff
- Have a negative pregnancy test performed by study staff
- Agree to adhere to study visits and procedures

### 4.2 Exclusion criteria

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

- Known HIV positive status
- Any medical condition or other factors which would preclude study participation as per principal Investigator's or designee's decision
- Any mental health condition which, in the opinion of the investigator, would preclude comprehension of informed consent, or preclude study participation.

### 4.3 Recruitment, screening, and enrolment

#### 4.3.1 Sources for study participants

At the eThekwini research clinic, potential participants will be enrolled from STI clients utilizing the PCZCDC, as well as PHC clinics in eThekwini. In Vulindlela, potential study participants will be recruited from among clients utilizing the PHC clinics in Vulindlela. In Umlazi, potential participants will be recruited from among clients attending the Prince Mshiyeni Memorial Hospital, as well as the provincial and municipal clinics that are linked to the hospital. Community-based outreach activities will also be utilized to recruit participants in all three areas.

#### 4.3.2 Screening and enrolment

Eligibility for study participation will be assessed at the study Screening and Enrolment visits. Although all required procedures may be completed in these visits, additional visits may be conducted if needed. Regardless of the number of visits required, all screening and enrolment 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 enrolment will be considered applicable for study purposes.

##### 4.3.2.1. Screening

Potential participants will be invited to screen for the study and asked to provide written informed consent for screening (Appendix IIa). Potential study participants will be assigned a screening number, receive pre-test counselling, and two rapid HIV tests will be performed. Post-test counselling will be provided and those testing positive or indeterminate on at least one HIV rapid test will be referred to an HIV/AIDS treatment programme. 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, behavioural eligibility information, locator information, a medical history, undergo a physical examination and undergo urine pregnancy testing. Potential participants will also be evaluated by research staff for STI symptoms and will be offered syndromic

treatment as per South African Department of Health guidelines. Participants deemed eligible based on the above procedures will then be invited for enrolment.

#### **4.3.2.2 Enrolment**

Women who meet all the study eligibility criteria will be requested to provide their written informed consent for participation in the study (Appendix IIb) and thereafter enrolled in the study. Consent for specimen storage will also be sought (Appendix IIc). Baseline behavioural data and acceptability of HIV prevention options will be collected. Blood will be drawn for dry blood spots, STI testing, CD3/CD4/CD8 counts, as well as serum and plasma archive. In addition, a pelvic examination and genital specimen collection will be conducted.

At enrolment and throughout the study, all enrolled participants will be provided with:

- HIV risk reduction counselling, supplies of male and female condoms and any other approved HIV prevention measures (e.g. oral/topical PrEP once licensed in South Africa)
- Contraception counselling and provision of contraceptive methods, as needed
- Instructions to contact study staff with questions about the study, requests for additional counselling, requests for additional condoms and requests for contraception, as needed.
- Study visit adherence counselling

#### **4.4 Co-enrolment guidelines**

Participants in this study may take part in other CAPRISA studies. Participants may not co-enrol in any non-CAPRISA studies. Within CAPRISA studies, co-enrolments are readily identifiable and are allowed only when the Principal Investigators of both studies approve. Principal Investigator approval is based on whether the co-enrolment would or would not interfere with the objectives of both studies involved. Approved co-enrolment 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 and take any required action to address below-target retention rates. If volunteers do not adhere to scheduled pre-enrolment visits, screening may be discontinued at the discretion of the Principal Investigator or designee. Once a participant is enrolled in the study, study staff will make every reasonable effort to retain her in follow-up. This may include obtaining and checking locator data, home visits, issuing telephonic and in-person reminders of scheduled visits, and maintaining a scheduler of enrolled participants as part of a strategy to achieve the target.

#### **4.6 Participant withdrawal**

Participants may voluntarily withdraw from the study for any reason at any time. The Principal Investigator or designee may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Continued participation in the study may be terminated by the Principal Investigator or designee based on advice from the University of KwaZulu-Natal's (UKZN) Biomedical Research Ethics Committee (BREC). Study staff will record the reason(s) for all withdrawals in participants' study records.

### **5. STUDY PROCEDURES**

Overviews of the study visit and procedures schedules are presented in Appendix I: Schedule of Evaluations. Study staff will be trained to conduct study procedures in a standardised manner. In addition, SOPS will guide this process.

#### **5.1 Targeted recruitment**

Study staff may conduct targeted recruitment, by focusing study outreach and recruitment efforts on women likely to be between 18 and 30 years of age. All possible efforts will be made to maintain the confidentiality of eligibility criteria, so as not to encourage artificial responses from volunteers being screened or to encourage them to change their behaviour in order to be eligible for the study.

## **5.2 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 if 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 written informed consent for screening procedures. HIV testing including pre- and post-test counselling will be done and only HIV negative participants will continue with the screening process.

The following procedures will be completed:

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

- Informed consent for screening
- Assignment of a screening number
- Collection of the following:
  - Demographic information
  - Locator information
- Eligibility assessment
- HIV pre- / post-test counselling and HIV/STI risk reduction counselling
- Provision of HIV prevention methods (e.g. condoms)
- Provide reimbursement
- Schedule next visit

### **5.2.2 Clinical procedures**

- Medical history
- Targeted physical examination
- Pelvic examination (if needed)
- Provision of test results

### **5.2.3 Laboratory procedures**

- HIV rapid testing
- Urine pregnancy testing

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

The enrolment visit will only be commenced for participants who are found to be eligible. Written informed consent for study participation will be obtained before any enrolment (or “on-study”) procedures are conducted.

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

- Review eligibility
- Informed consent for enrolment and stored specimens
- Assignment of a participant identification (PID) number
- Update locator information
- HIV pre- / post-test counselling and HIV/STI risk reduction counselling
- Contraceptive counselling
- Provision of HIV prevention methods (e.g. condoms)
- Collect HIV risk perception and baseline behavioural data
- Assess acceptability of HIV prevention options
- Provide reimbursement
- Schedule next visit

### **5.3.2 Clinical procedures**

- Medical history
- Targeted physical examination
- Pelvic examination
- Genital specimen collection
- Blood draw
- Provision of test results

### **5.3.3 Laboratory procedures**

- HIV rapid testing
- Urine pregnancy testing
- Collection of dry blood spots
- CD3/CD4/CD8 count
- STI testing (Urine, Plasma and/or genital specimen)
- Serum and plasma archive
- Genital specimen archive

## **5.4 Follow-up visits**

Monthly follow-up visits are scheduled on a 28-day schedule for the first three months, with a 14-day visit window on either side. Thereafter visits will be scheduled on an 84-day schedule (every three months), with a 28-day visit window on either side. For 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.

HIV-uninfected study participants who become infected during follow-up will be referred to one of the long-term CAPRISA Acute Infection cohort studies, which have provisions for care, ART and support for those infected with HIV. These services are provided at no cost to the participant. For those who do not wish to continue in any of these studies post-seroconversion, participants will be referred to their preferred AIDS care provider which could include government or non-governmental AIDS care services for ongoing clinical management and care.

Participants who become pregnant during follow-up may be maintained in this study, however follow-up procedures may be modified according to guidelines specified in the study-SOPs, i.e. the principal change will be the discontinuation of pelvic examinations and genital specimen collection after 24 weeks of pregnancy.

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

- Update locator information
- HIV pre- / post-test counselling and HIV/STI risk reduction counselling
- Contraceptive counselling
- Provision of HIV prevention methods (e.g. condoms)
- Collect HIV risk perception and behavioural data
- Provide reimbursement
- Schedule next visit

### **5.4.2 Clinical procedures**

- Medical history
- Targeted physical examination
- Blood draw (at quarterly follow-up visits only or if indicated, e.g. at the time of suspected HIV seroconversion)
- Provision of test results
- Pelvic examination (at quarterly follow-up visits only or if indicated, e.g. at the time of suspected HIV seroconversion)
- Genital specimen collection (at quarterly follow-up visits only or if indicated, e.g. at the time of suspected HIV seroconversion)

### **5.4.3 Laboratory procedures**

- HIV rapid testing
- Urine pregnancy testing
- Collection of dry blood spots
- HIV confirmatory tests – RNA PCR, CD3/CD4/CD8 counts, Western Blot and/or ELISA (only if indicated)
- STI testing (only if indicated)
- Serum and plasma archive (at quarterly follow-up visits only or if indicated, e.g. at the time of suspected HIV seroconversion)
- Genital specimen archive (at quarterly follow-up visits only or if indicated, e.g. at the time of suspected HIV seroconversion)

## **5.5 Study Exit Visit**

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

- Update locator information
- HIV pre- / post-test counselling and HIV/STI risk reduction counselling
- Contraceptive counselling
- Provision of HIV prevention methods (e.g. condoms)
- Collect HIV risk perception and behavioural data
- Assess acceptability of HIV prevention options
- Provide reimbursement

### **5.5.2 Clinical procedures**

- Medical history
- Targeted physical examination
- Blood draw
- Provision of test results
- Pelvic examination (at quarterly follow-up visits only or if indicated, e.g. at the time of suspected HIV seroconversion)
- Genital specimen collection (at quarterly follow-up visits only or if indicated, e.g. at the time of suspected HIV seroconversion)

### **5.5.3 Laboratory procedures**

- HIV rapid testing
- Urine pregnancy testing
- Collection of dry blood spots
- STI testing
- Serum and plasma archive
- Genital specimen archive
- HIV confirmatory tests – RNA PCR, CD3/CD4/CD8 counts, Western Blot and/or ELISA (only if indicated)

## **5.6 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 interim STI counselling and or treatment in response to STI symptoms.
- For interim HIV counselling and testing in response to presumed exposure to HIV or seroconversion symptoms.
- Contraception counselling and/or provision
- To provide participants with the results of confirmatory HIV test results, per algorithm in Appendix III.
- For other reasons – at the request of study staff or the participant.



## **6 STATISTICAL CONSIDERATIONS**

### **6.1 Sample size**

A sample size of 2,500, allowing for 10% loss to follow-up, will be large enough to identify known and new risk factors of HIV infection. Multivariate models will be fitted with numerous co-variables to determine which risk factors are associated with HIV infection. This sample size will also allow sufficient power within subgroups (i.e. women who prefer various prevention options and women in various age groups) and will enable us to compare risk factors between various groups.

### **6.2 Data analysis**

#### **6.2.1 Primary analysis**

To assess the risk factors for HIV infection proportional hazards regression models will be used to estimate the hazard rate ratio, along with a 95% confidence interval, controlling for the selected baseline prognostic variables. Behavioural variables measured over time after baseline will be included in the analysis as time-dependent covariates.

Date of HIV infection will be estimated as the midpoint between the last negative HIV test date and the first confirmed positive HIV test date. Participants who do not become HIV infected before their last study visit will be censored on the day of their last negative HIV test. Time to HIV infection, in days, will be computed as the difference between the estimated date of HIV infection, and the enrolment date, plus one. Time to censoring will be computed as the difference between the date of censoring and the enrolment date, plus one.

#### **6.2.2 Secondary analysis**

Acceptability of HIV prevention options will be measured using acceptability questionnaires administered during interviews with the participants. These interviews will include questions about the uptake of different prevention options. Prevention choices will be described by giving the number and percentage of participants who prefer various prevention options at different time points. The acceptability and uptake of the HIV prevention options will be summarised at different time points. The acceptability and uptake in different age groups will be compared using Fisher's exact test.

Adherence to prevention options will be measured as appropriate according to the prevention method; for example oral tablets will be measured using pill counts and drug level data. Adherence will be summarised at various time points, by giving the percentage adherence. For pill counts adherence will be calculated as the number of pills taken according to pill count (number dispensed minus number returned) divided by the number of pills prescribed in the time period. Adherence for other options may be defined as a binary variable: adherent, not adherent – based on some predefined criteria. The proportion adherent participants will then be summarised at various time points.

STIs will be measured using laboratory assessments of urine, plasma and/or genital specimens. The incidence rate of the various STIs (including HIV) will be calculated as the number of new infections over the time on study. A Poisson distribution will be assumed for the confidence intervals of incidence rates.

Sexual behaviour will be ascertained through interviews with the enrolled participants where questions about sexual behaviour related to HIV risk (e.g. number of partners, condom use and use of HIV prevention interventions, etc.) will be asked. Trends in sexual behaviour will be summarised over time using means and proportions at the various time points. If needed longitudinal mixed models will be fit to determine whether there are changes over time.

Pregnancy will be defined as a positive pregnancy test. The pregnancy incidence rate will be calculated as the number of new infections over the time on study. A Poisson distribution will be assumed for the confidence intervals of incidence rates.

### **6.3 Data management**

Data will be collected on data collection forms (CRFs), which will be developed by the study team. All research clinic 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 study file at the research clinic, and will be available for review. The data will

be entered into the database management system which is DataFAX running on a four node Dell R730 Virtual SAN Cluster within a SUSE Linux operating system environment on a VMWare Enterprise Virtualised Platform.

Queries arising during validation of the data will be recorded in quality control (QC) reports sent to the research clinics 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 QC and validation checks on the data. Database files will be password-protected and access to the files will be limited to authorised study staff members only. All data will be backed up at regular intervals, and backups will be stored in secure areas with limited access.

All documents will be stored securely at the research clinics and both during and after the completion of the study. At all research clinics the forms will be stored in locked cupboards in a secure room with restricted access. Upon completion of the study, the close-out research clinic monitoring visit and finalisation of the database for analysis, the original forms will be bound and kept for long term storage.

## **7 HUMAN SUBJECTS CONSIDERATIONS**

### **7.1 Regulatory and ethical review**

This study will be conducted under the oversight of the UKZN's BREC in accordance with International Conference on Harmonization (ICH) standards of Good Clinical Practice (GCP). CAPRISA will be responsible for reporting study-related information to the UKZN BREC. The study will only be initiated after it has been approved by the UKZN BREC. The study will be conducted in accordance with all conditions of approval by the ethics committee.

### **7.2 Informed consent**

Written informed consent will be obtained from each study participant in English or *isiZulu* prior to screening and enrolment, in accordance with 21 CFR Part 50 and ICH 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 for 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.

### **7.3 Risks**

The study clinical procedures are similar to those experienced by women in routine gynaecological 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 counselling. They also may become worried or anxious while waiting for their HIV test results or after receiving HIV-positive test results. Trained counsellors 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 participation in the study.

### **7.4 Benefits**

There may be no direct benefits to participants in this study. However, participants and others may benefit in the future from information learned from this study.

Study participants will receive HIV and STI counselling and testing, a physical examination, and gynaecological assessments. Contraception will also be available to study participants. They will be provided syndromic STI treatment free-of-charge, and will be offered STI treatment for their partners. 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 be provided with available HIV prevention methods (e.g. condoms) and risk reduction counselling and will be reimbursed for time, transport and inconvenience costs for each scheduled visit.

## **7.5 Access to HIV-related care**

### **7.5.1 HIV prevention for study participants**

HIV counselling 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 follow-up HIV testing time point. HIV test results will be provided with post-test counselling. Condoms will be provided to participants throughout the duration of their participation in the study.

All study participants will be provided with any newly approved HIV prevention measures (e.g. oral PrEP) once licensed.

### **7.5.2 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 counselling. Potential study participants who have been identified as HIV positive will be referred to local AIDS treatment services, which will provide medical and psychosocial AIDS care and support.

A participant who has a positive or discordant HIV rapid test will complete all tests required for that visit (per the Schedule of Evaluations), including blood for HIV confirmatory tests (RNA PCR, CD3/CD4/CD8 + cell counts, Western Blot and/or ELISA) and virologic resistance testing. Participants would then return one week later to receive their test results. Should the confirmatory tests indicate a seroconversion event, the participant would have additional blood drawn for a second set of confirmatory results. Participants with two sets of positive confirmatory tests will be scheduled for a study exit visit as detailed in the Schedule of Evaluations. Please see appendix III for more details regarding HIV antibody testing.

HIV-uninfected study participants who become infected during follow-up will be referred to one of the long-term CAPRISA Acute Infection cohort studies, which have provisions for care, ART and support for those infected with HIV. These services are provided at no cost to the participant. For those who do not wish to continue in any of these studies post-seroconversion, participants will be referred to their preferred AIDS care provider which could include government or non-governmental AIDS care services for ongoing clinical management and care.

## **7.6 Community involvement and consultation**

The CAPRISA community programme (CP) has, through a consultative process, established CAPRISA Community Research Support Groups (CRSGs) at all CAPRISA research clinics where this study will be conducted. The CRSG membership includes local community leaders, traditional leaders, leadership of local HIV/AIDS organisations, previous study participants, local health service provider representatives and HIV-positive local community members. The CAPRISA CP in partnership with the CRSG's will involve the community and local community based organisations in preparation for this study. Specifically, the CAPRISA CP will inform, educate and mobilise the community to enhance community input into the research process. The local CRSGs in eThekweni, Vulindlela and Umlazi 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.

## **7.7 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 study research clinic. 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.

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

- Authorized study representatives
- UKZN BREC
- Authorized monitors / auditors

## **8 LABORATORY CONSIDERATIONS**

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

### **8.1 Laboratory specimens**

The following types of specimens will be collected for testing:

- Urine for pregnancy testing.
- Blood, urine and/or genital specimens for STI testing
- Blood for HIV testing by rapid tests, confirmatory RNA PCR assays and CD3/CD4/CD8 counts, Western blots and ELISAs
- Blood for dry blood spots, as well as plasma and serum archive.
- Genital specimens for archive

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

### **8.2 On site testing**

The study laboratory SOPs 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).

### **8.3 Collection specimens**

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

### **8.4 Specimen storage for quality assurance and potential future research testing**

Serum, plasma and genital specimens will be stored for potential post-study assessments for activity against STIs, assessment of vaginal microbiome, markers of safety, risk exposure, PrEP adherence and resistance. In addition, stored plasma will be used for retrospective RNA PCR and/or other confirmatory testing to confirm whether early incident cases of HIV infection during the study occurred post-enrolment. 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.

### **8.5 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 SOPs. For the on-site tests, the quality assurance personnel from the CAPRISA laboratory will conduct periodic visits to the eThekweni, Vulindlela and Umlazi Research Clinics 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.

## **9 ADMINISTRATIVE PROCEDURES**

### **9.1 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.

### **9.2 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 participant safety, affect the integrity of study data, affect participant'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

In an emergency, the Principal Investigator or designee 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).

### **9.3 Quality assurance**

Quality assurance in the study will be undertaken according to the Study Quality Assurance Plan. The Quality Assurance Plan will include ongoing monitoring of study progress by the Protocol Team, as well as study monitoring in accordance with ICH GCP guidelines by trained authorized monitoring staff.

Investigators also will allow inspection of all study-related documentation by authorized representatives of UKZN BREC, if required.

#### **9.3.1 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 enrolment 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.

### **9.4 Study records**

Complete, accurate, and current study records will be maintained and stored in a secure manner, throughout the study. Study records include administrative documentation, including all reports and correspondence relating to the study, as well as documentation related to each participant screened for and/or enrolled in the study, including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

### **9.5 Use of information and publications**

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

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## **APPENDICES**

- Appendix I: Schedule of evaluations
- Appendix IIa: Informed consent form for screening participants
- Appendix IIb :Informed consent form for enrolling participants
- Appendix IIc Informed consent form for specimen storage and possible future research testing
- Appendix III: HIV antibody testing algorithm

## Appendix I: Schedule of evaluations

Procedure	Screen	Enrol	Follow-up		Exit
	Screening (up to 30 days)	Enrolment (day/month 0)	Monthly follow-up (months 1 & 2)	Quarterly follow- up (month 3 onwards <sup>a</sup> )	Study exit visit
	V0	V1	V2, V3	V4 - V22	V23
<b>Administrative, Behavioural and Regulatory Procedures</b>					
Informed consent for screening	X				
Obtain screening number	X				
Eligibility assessment	X	X			
Demographic information	X				
Informed consent for enrolment		X			
Informed consent for specimen storage		X			
PID assignment		X			
Locator information	X	X	X	X	X
HIV pre- / post-test counselling and risk reduction counselling	X	X	X	X	X
Contraception provision and counselling		X	X	X	X
Provision of HIV prevention methods	X	X	X	X	X
HIV risk perception and behavioural assessment		X	X	X	X
Assessment of acceptability of HIV prevention options		X			X
Provide reimbursement	X	X	X	X	X
Schedule next visit	X	X	X	X	
<b>Clinical Procedures</b>					
Medical history, including targeted physical examination	X	X	X	X	X
Pelvic examination		X	0	X	X
Genital specimen collection		X	0	X	X
Phlebotomy		X	0	X	X
Provide test results	X	X	X	X	X
<b>Perform Laboratory Evaluations</b>					
HIV serology (rapid tests)	X	X	X	X	X
Urine pregnancy test	X	X	X	X	X
Dry blood spots		X	X	X	X
HIV RNA PCR, Western blot and/or ELISA <sup>b</sup>		0	0	0	0
CD3 / CD4 / CD8 count <sup>b</sup>		X	0	0	0
Plasma and serum archive <sup>b,c</sup>		X	0	X	X
STI testing (Urine, Plasma and/or genital specimen) <sup>b</sup>		X	0	0	X
Genital specimen for archive <sup>c</sup>		X	0	X	X
Amount of blood collected <sup>c</sup> in mls:	0	75 (90)	0 (20)	50 (70)	80 (100)
<b>Footnotes:</b> <sup>a</sup> This quarterly visit schedule will continue until participants are exited from this study.					
<sup>b</sup> Blood volumes: HIV confirmatory tests (PCR, WB and/or ELISA) (15ml); CD3, CD4, CD8 (5ml); Storage (50ml); STI testing (10ml).					
<sup>c</sup> The stored serum, plasma and genital specimens will be used for potential post-study assessments for markers of safety, risk exposure, PrEP adherence and resistance. In addition, stored plasma will be used for retrospective RNA PCR testing to confirm whether incident cases of early HIV infection during the study occurred post-enrolment.					
( ) = includes additional bloods for suspected seroconverters (i.e. HIV confirmatory tests and CD3/CD4/CD8 counts).					
0 = if indicated					



**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: 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 enrolment, participants will undergo two rapid tests for HIV antibodies. In addition plasma samples taken at this time will be stored for future testing among those who seroconvert early in the study in order to confirm that HIV infection and seroconversion occurred post-enrolment.

At each follow-up 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 seroconverter.

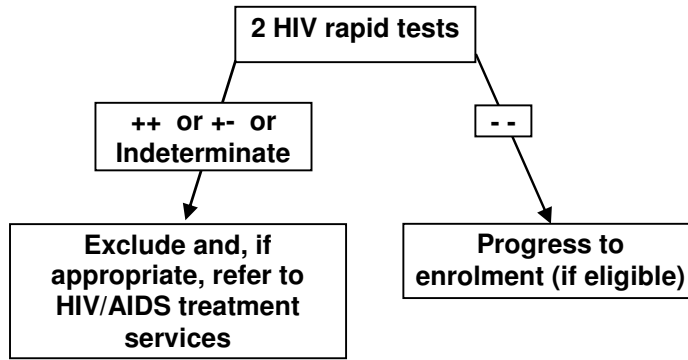
HIV RNA PCR testing will be performed on suspected seroconverters to confirm HIV status and a follow-up visit will be scheduled for a week later. If the RNA PCR test is positive, a second blood sample will be drawn to confirm HIV status using RNA PCR during the scheduled visit a week later and another follow-up visit will be scheduled for a week thereafter to provide these results to the study participant.

Western blots and / or ELISAs will be performed on all suspected seroconverters to provide additional confirmatory information on the presence / absence of infection. HIV infection is defined as two positive PCR tests from independent samples.

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

Participants who become infected with HIV will be offered counselling and referral, as appropriate, to the CAPRISA acute infection study (CAPRISA 002) or other HIV/AIDS care services, where immediate ART initiation will be made available to the participant.

### Screening



### Study visits

