

A feasibility study in preparation for Phase III microbicide trials in the Hlabisa sub-district, South Africa

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1 SUMMARY

This study aims to investigate the feasibility of conducting Phase III trials of vaginal microbicides in the Africa Centre Demographic Surveillance Area (ACDSA) in the Hlabisa sub-district of Umkhanyakude in northern KwaZulu Natal, South Africa.

A cohort of HIV-uninfected and HIV-infected women who are sexually active and not intending to become pregnant in the next 12 months will be recruited at 6 primary health care (PHC) clinics and a family planning clinic. Women will be recruited from family planning and immunisation clinics at the PHC clinics.

The feasibility of conducting Phase III trials of vaginal microbicides is assessed by measuring HIV incidence and the ability to recruit, follow and retain women over time. In addition, this feasibility study will be an opportunity to measure the prevalence of HIV and other sexually transmitted diseases (STDs) in this cohort, and to describe sexual practises, condom use, and disclosure of HIV status among these subjects. Reasons for refusal and loss to follow up, validation of the informed consent process, and the acceptability of microbicide products will also be explored.

The goal is to enrol 700 person years of follow-up among HIV negative women for this study. Enrolment will occur in 2003 and women will be followed for a period of up to 1 year, making an effort to arrange follow-up visits to coincide with family planning and immunization needs. Follow-up visits after enrolment will be scheduled at week 2, at 3 months and then 3 monthly thereafter.

At each follow-up visit, with the exception of week 2, all HIV negative women will be retested for HIV. Data on sexual behaviour and condom use, signs and symptoms of STDs, and disclosure of HIV status will be collected for all women. Women will receive syndromic management for sexually transmitted diseases. At week 2, a subgroup of women will be tested for STDs. At 6 and 12 months, all women will have a pelvic examination. If this setting is found to be suitable for a Phase III trial, in terms of HIV incidence, recruitment, follow-up and retention, further work will investigate the acceptability of the vaginal microbicide preparations and delivery systems to women and their partners.

2 INTRODUCTION

By the end of 2001, 40 million people were estimated to be living with HIV-1 worldwide¹, with sub-Saharan Africa continuing to be the region most severely affected. In this region, approximately 3.4 million new infections occurred in 2001, mostly through vaginal sexual intercourse, bringing the total number of people living with HIV/AIDS there to be approximately 28.1 million. Women in this region are at particular risk, accounting for 55% of HIV infections. Not only is heterosexual HIV transmission more efficient from men to women than from women to men, but women more often have undiagnosed and untreated STDs, which further increases their risk of infection².

Antenatal HIV prevalence in the rural district of Hlabisa mirrors infection rates in the rest of the Kwa-Zulu-Natal province. In 2000, antenatal HIV prevalence in a more urban clinic of Hlabisa sub-district was 42% (95% CI 38.3-46.0%)³. Amongst a sample of women bringing

their children to immunisation clinics in the district, HIV prevalence was 28%, with age-specific prevalence as high as 37% in young mothers between the ages of 21 and 25 years⁴. The current HIV prevalence in the Hlabisa sub-district therefore appears to be higher than that reported from other African field sites including Mwanza and Rakai⁵.

There is no empirical data on HIV incidence in South Africa. The study among women attending immunization clinics, described above by Rollins et al, found that 2% of women who did not have antibodies were in the phase of acute sero-conversion (HIV ELISA negative, RNA positive)⁴. Crudely modeling this as sero-conversion lasting 6 weeks, suggests an incidence rate of 17% per year. Methods have also been proposed to identify individuals in the period of early infection as a surrogate for incidence estimates⁶. In one study, 3551 serum samples were collected from antenatal attendees in KwaZulu-Natal as part of a national survey in 1999. Of the positives, 8.5% (91/1073) were determined to be recent infections using a modified EIA as the detuned assay⁷. Assuming that this reflects new cases sero-converting within the previous 200 days, this equates to an annual incidence rate of 6.5% in 1999. Mathematical models have also been used to estimate age-specific incidence from antenatal prevalence data^{8,9}. However, it is clear that empirical data on HIV incidence is urgently needed since all these methods of estimating incidence are based on assumptions that may limit their value.

One possible reason for the explosive local epidemic is the high prevalence of STDs in this population. Amongst women attending an antenatal clinic in Hlabisa sub-district in 2000, 17.9% (95% CI 15.0-21.0%) were infected with *Trichomonas vaginalis*, 9.2% (95% CI 7.1-11.6%) with *Neisseria gonorrhoea* and 9.9% (95% CI 7.8-12.5%) with *Chlamydia trachomatis*³. A population-based survey done in Hlabisa in 1995 detected *Neisseria gonorrhoea* in 4.5%, *Chlamydia trachomatis* in 6.1% and active syphilis in 8.8% of 228 women tested by molecular methods¹⁰. This contrasts with data from the population-based Rakai cohort where STI prevalence rates were much lower: 1.5% of women were found to have *N.gonorrhoea* and 2.4% *C. Trachomatis*¹¹.

Other factors likely to contribute to the high levels of HIV infection among the population of Hlabisa sub-district include high levels of circular migration¹²; and, low rates of marriage and co-habitation in young adults. Approximately 50% of adult women aged 40-44 have never married. More than 60% of unmarried women aged 18-24 reported having a regular sexual partner¹³.

It is clear that urgent interventions are needed to curb the explosive HIV epidemic in South Africa. Condom use is an effective method of preventing HIV transmission¹⁴, and in some African countries its use has increased¹. However, women are often unable to negotiate the use of condoms by their male partners^{15,16}. In addition, condoms are contraceptive, and in many African communities a non-contraceptive barrier product that can protect against HIV and other STDs would be highly desirable. Vaginal microbicides, topical chemical agents designed to inhibit the sexual transmission of HIV and other disease pathogens, may meet the needs in this setting. Potentially, they can be applied vaginally to prevent both male-to-female and female-to-male transmission of HIV. They also offer a female-controlled prophylactic option in cases where male condom use cannot be negotiated.

Nonoxynol-9 (N-9) is the only microbicide that has been evaluated in Phase III trials. The results of three trials showed that N9 did not protect against HIV^{17,18}, and may even have

increased HIV transmission due to local genital toxicity¹⁹. As a result of these trials, there is a renewed emphasis on the safety of microbicide candidates. Two of the most promising agents are dextrin sulphate (DS)²⁰ and PRO 2000²¹. Both DS and PRO 2000 appear to be very well tolerated, and unlike N9, do not induce histological evidence of inflammation in the vagina. The safety profiles of DS and PRO 2000 are currently being examined in a Phase II study in Uganda and Cote D'Ivoire. Should safety trials be successful, the UK Medical Research Council (MRC) intends to proceed to a phase III trial of these two products, as part of a large programme of research for developing microbicides for the prevention of HIV infection, funded by the UK Department of International Development.

Prior to launching such a large multi-centred trial, it is necessary to estimate the suitability of sites for such a phase III clinical trial through a feasibility study. A feasibility study measures HIV incidence and assesses the site's ability to recruit, follow and retain women over time. In addition, a feasibility study provides an opportunity to measure the prevalence of HIV and other sexually transmitted diseases (STDs) in a cohort, and to describe sexual practises, condom use, and disclosure of HIV status among these subjects. These data would then allow assessment of whether it is likely to be feasible and cost-effective to conduct a Phase III trial in this area. The feasibility study would also facilitate the design of any future phase III trial.

The Africa Centre for Health and Population in Hlabisa District, Kwa-Zulu Natal Province has been selected by the UK MRC as a site to participate in a multi-centre series of feasibility studies. Other sites are in South Africa, Tanzania, Zambia, Uganda and Cameroon. Since January 2000, the Africa Centre Demographic Information System (ACDIS) has followed a population of approximately 89,000 household members every 4 months, collecting data on demographic events (births, deaths, migrations) and detailed pregnancy and reproductive histories from all women of reproductive age²². In addition, information on the health and socio-economic status of homesteads and households are also collected²³. All homesteads and facilities are geo-referenced. This surveillance is currently funded until 2006.

3 OVERVIEW OF STUDY DESIGN & METHODS

3.1 Overall objective:

To investigate the feasibility of conducting a randomised controlled Phase III trial of vaginal microbicides amongst women in the Africa Centre Demographic Surveillance Area (ACDSA) in the Hlabisa sub-district of Umkhanyakude in northern KwaZulu Natal, South Africa.

3.2 Specific Objectives:

3.2.1 Primary objectives:

To determine the following parameters amongst women aged 15 and above attending family-planning or immunization clinics at 7 primary health-care facilities serving the ACDSA in Hlabisa, South Africa.

1. The incidence of HIV-infection

2. The prevalence of HIV-infection
3. The prevalence of sexually transmitted diseases (STDs)
4. Rates of successful health-facility-based follow-up

3.2.2 Secondary objectives

- 1 To characterise and estimate sexual behaviour among women and their sexual partners including
 - a. Condom use and use of other contraceptives
 - b. Patterns of sexual behaviour (sexual activity, multiple partners, douching, anal sex practice, vaginal inserts for dry/wet sex etc)
 - c. Risk perceptions
 - d. Health seeking behaviour and perception of quality of care
 - e. Partner relations and communication
 - f. Community's attitudes on HIV/AIDS and other STDs
- 2 To explore the acceptability of regular gynaecological examinations in this cohort
- 3 To explore the acceptability of repeat HIV testing
- 4 To monitor ethical issues and to understand factors that may encourage or discourage participation
 - i. Understanding of informed consent for individual women
 - ii. Community mobilization and acceptance of the project.
 - iii. Acceptance of clinical procedures
 - iv. Compliance with study procedures
- 5 To determine the acceptability of microbicide products among women and their sexual partners
 - i. Acceptability of vaginal gel.
 - ii. Preferences for applicators (pre-filled or tube plus applicator)
 - iii. Optimum presentation of the product, e.g. packaging, price, placement
 - iv. Characteristics of sexual behaviour among women and their sexual partners.
 - v. Social contextual factors of sexual behaviour among women and their sexual partners that might impact the acceptability of microbicide products
- 6 To explore the reasons for refusing an HIV test and reasons for refusing to receive HIV test results
- 7 To explore patterns of disclosure of HIV test results among both HIV negative and HIV positive women
- 8 To explore the role of family in adapting to HIV among women who are HIV positive and their families

3.3 Study Design

The study is a prospective cohort study.

3.4 Study Population

HIV-uninfected and HIV-infected women who are sexually active and attend family planning and immunisation clinics will be enrolled in the study. Enrolment into the study will be strictly sequential and will continue until the target of 805 HIV negative women enrolled is reached.

3.5 Inclusion and Exclusion Criteria

Whilst this study is primarily interested in women who are HIV-uninfected at screening, we will also include 10% of the HIV positive women. This helps avoid creating stigma by excluding women who are HIV positive at screening, but also allows us to compare sexual behaviour and disclosure with HIV negative women. In addition, we will not invite 5% of the women who screen HIV negative to the study. In this way, we will be able to communicate to the community that enrolment status does not infer any information regarding HIV status. A similar process has successfully been used in the Africa Centre's mother to child transmission study where although endpoints relate to HIV positive women and their infants, a percentage of HIV negative women have also been enrolled.

Enrolling a number of HIV positive women in this feasibility study will allow us to examine the responses and needs of newly identified HIV positive women and their families²⁴. There can be many issues within families around the disclosure of disease status and symptoms. These include stigma about revealing within the family, overcoming obstacles in the past relationship between the seropositive woman and her family, and changing roles. For example, an adult who for many years was independent needs to be reintegrated into the family for care. The Household Dynamic project at the Africa Centre have been addressing some of these issues in their ethnographic study of households coping with HIV / AIDS. In the microbicide feasibility study, the role of the family in adapting to HIV will be investigated among the enrolled HIV positive women in collaboration with Dr. Hosegood and her ethnographic team. This information will inform the design of strategies for those who are identified as HIV positive during the screening for the Phase III trial.

There has been very little research on the factors related to disclosure of HIV status among women in Africa²⁵. The characteristics of HIV positive or negative women who choose to disclose their test result are not well understood. In Kenya, partner notification of serostatus among HIV-infected pregnant women was significantly associated with marriage, young age, and low socioeconomic status. Heyward et al reported nearly universal intention to disclose to partners among seronegative women (94%) but far lower willingness to disclose among seropositive women (47%)²⁶. However, whether the intention of disclosure represents full disclosure is unknown. This study will provide information on disclosure patterns among HIV negative and positive women over time.

This study is interested in women who are likely to be sexually active during the follow-up period. Since traditionally, women in the Hlabisa area are expected to abstain from sex for several months after delivery, only women who are attending the immunization clinic for their baby's week 14 vaccination or later will be invited to enroll in the study

3.5.1 Inclusion Criteria

- Females aged 15 years or more
- Intending to use the clinic for her and her child's health care over the next 12 months

- Willing to attend the clinic for repeat visits as part of the study
- Willing to answer questions about sexual behaviour
- Previously / currently sexually active and likely to remain sexually active during follow-up
- Willing to be screened for sexually transmitted diseases
- Willing to undergo repeat HIV test on venous blood at screening and at intervals throughout the study
- Willing to receive HIV test result at screening
- Willing to have urine tested during follow-up to test for pregnancy
- Willing and able to give informed consent

3.5.2 Exclusion Criteria

- Unwilling to receive result of HIV test at screening
- Pregnant or intending to be pregnant in the next 12 months
- Intending to move away from this area over the next 12 months so that she could not attend the district clinics anymore

3.6 **Community Preparation**

At the outset, all Africa Centre research projects are explained to the community by the Africa Centre's community liaison office. New projects or changes to existing study protocols are presented to a Community Advisory Board (CAB) for their input and approval. The CAB consists of about 30 members nominated by the community and meets on a regular basis. In addition, the approval and understanding of community leaders is sought so as to ensure the smooth running of studies in this rural community.

Community preparation will include consultations with various stakeholders in the study area for the purpose of raising awareness about the study. A situation analysis of the study community will be carried out, focussing on health and social services available to identify community-based organisations that can be included in a referral network for support for those women who sero-convert during the study, as well as those who are identified as HIV positive through the screening / recruitment process. In addition, this process will facilitate a greater awareness for the study and mobilise the community to support the feasibility study. Information sheets, similar to the participant information sheet, presenting details of the study will be distributed to all the organisations contacted. A database of organisations will be developed and maintained and used to create a directory of referral services. There will also be leaflets / information sheets in the clinics informing clients of the study and a description of the study has been included in the Umbiko, Africa Centre's quarterly newsletter to the community.

3.7 **Recruitment Process**

Study staff will be based full-time at the 7 clinics. They will address groups of women attending family-planning clinics and immunisation clinics whilst they wait to be seen. All women will be given information about the prevention of HIV and STDs in Zulu. They will be informed about the purpose of the study as well as the requirements for blood, cervical and vaginal specimen collection and follow up at regular intervals. Women will have the opportunity to obtain more information about the study from the study staff in private. Male

partners will be welcomed at information-sessions for the study and will be offered individual voluntary counselling and testing for HIV as well. The social science team will assess the recruitment process by focusing on how well women are informed about different aspects of the study.

Recruitment at immunisation clinics will differ slightly from that at family planning clinics in that many or most women attending immunisation clinics will have been tested for HIV during their recent pregnancies and may therefore be aware of their HIV status. If women are found to be HIV-uninfected following testing during pregnancy, they will be informed of the study during post-test HIV counselling (by Africa Centre counsellors involved in the prevention of mother-to-child transmission of HIV (PMTCT) programme). They will be made aware of the study and asked to see the microbicide study staff when they return for their 6-week and 14-week immunisations to obtain further information about the study and to discuss possible enrolment. They will be told that if they remain interested in participating in the study, they will be retested for HIV at 14 weeks. They will be asked to discuss their possible entry into the study with their partners, if they feel comfortable in doing so. They may visit the study staff for further information at any time.

4 STUDY PROCEDURES

See Appendix 1 for summary of all visits and procedures.

4.1 Prior to recruitment starting

Comprehensive data on sexual partnerships and practices are crucial to the study. However, such data are notoriously difficult to capture. Several qualitative and quantitative methods will be combined to characterise and estimate the sexual behaviour of the population of women participating.

At the beginning of the study, focus group discussions (FGDs) will be used to characterise sexual behaviour in the Hlabisa sub-district and to also solicit opinions and views about collecting information on sexual practices in a study. These FGDs will inform the design of instruments and data collection procedures to be used in the study to examine sexual behaviour, specifically the coital log and the sexual behaviour questionnaire.

Table 1 shows that women attending immunisation and family planning clinics will be selected for different FGDS based on their age and whether they live in a rural or urban area. Selection based on these criteria is intended to encourage more open communication during the discussions. Two focus groups will be held for each of these sub-groups of the target population, with 8-10 participants in each, for a total of 8 FGDs.

Table 1: *Sub-groups of the target population for focus group discussions*

Group	Residence type	Age group
1	Rural	Younger women (teens & 20s)
2		Older women (30s and 40s)
3	Urban	Younger women (teens & 20s)
4		Older women (30s and 40s)

Basic demographic details, including information about their partners, will be collected for each participant of the FGDs. The information obtained will inform the selection for FGDs of males from the community who are considered to be representative of partners of potential study participants. The holding of 8 FGDs among men has two goals - the first is to ensure that we have men's perspectives on the same questions discussed with the women in FGDs (themes listed below), the second is to make them aware of the study and to increase their support of women's enrollment in such a study. The second goal is important since past experience with Africa Centre studies targeting women has shown that men may be unsupportive when their partners are recruited in a study that they have no information about. We are aware it is difficult to recruit men for FGDs in the study area, so a combination of channels to reach them will be used such as flyers, the Africa Centre newsletter *Umbiko* and sports activities.

The FGDs will be based on the following five themes:

1. HIV awareness and attitude- general perception of people in the community about HIV/AIDS
 - What are the issues regarding HIV/AIDS that people talk about?
 - What is the magnitude of the problem?
 - How does the community treat people with HIV/AIDS- within the context of a family? within the general community?
 - Are people doing anything to protect themselves from HIV?
 - Are people willing to be tested and get their results?
 - How do people feel about getting results on the same day that they are tested?
2. Partnerships and gender relations- the common type of sexual partnerships in the community, eg. Marriage, regular, casual
 - Who generally initiates sexual relationships?
 - Who generally decides on use of contraception, condom use and childbearing in a sexual relationship?
 - Can a woman say no to sex?
 - Is it OK for a woman to enjoy sex?
3. Sexual practices
 - Are people generally free to talk about sexual experiences with others? Who do they talk to? What sort of issues do they talk about?
 - Do people in this community do anything to enhance sexual pleasure? What do they do? Who does it? Why do they do it?
 - Is the practice of anal sex common in this community? Under what circumstances is it practised? Who does it? Are condoms used in these acts?
4. Genital hygiene (women only)
 - Do women usually clean inside their vagina? When do they do it? Why do they do it? What do they use for cleaning? How do they do it?
5. Collection of sexual behaviour data
 - Are coital diaries a practical way of collecting sexual behaviour information?
 - What are the potential problems in the use of the coital logs?
 - What are people's reactions to the drafted sexual behaviour form?

- What are peoples' reactions to the method of secret voting vs face-to-face interviews?

4.2 HIV screening visit

Any woman expressing an interest in the study will be allocated a personal identification (PID) number to maintain confidentiality. This PID number, the woman's name and the woman's civilian ID number will be recorded in the study register. This PID number will be used on all forms and specimens collected from that individual. The study register at each clinic will be the source of linkage between each woman's name and her PID number for the study staff at the clinic. Each woman will be asked to consent to answering questions about herself and will be given pre-test counselling for HIV, specifically designed for rapid testing. Demographic details will be collected among those who have consented to answer questions.

Once a woman has received pre-test counselling, and the counsellor is satisfied that she understands the implications of testing for HIV and the purpose of the study, she will be asked to consent to HIV screening. If the woman agrees to be tested, her written consent will be documented prior to testing and to all other investigations. The eligibility checklist will be administered among those who consent to HIV screening, after which she will be sent to the nurse for HIV screening. The nurse will take venous blood samples (2 x 5ml) for HIV and perform rapid HIV tests using the Determine HIV- 1/2 (Abbott Diagnostics Division, Japan) and Smartchek (White Star Diagnostics) tests concurrently using blood from one sample. She will also ask the woman about her last menstrual period (LMP) date. If indicated by the LMP date, the nurse will carryout a pregnancy test on a urine sample to exclude pregnancy and tell the woman her pregnancy test result.

After 15 minutes, the HIV rapid test results are recorded by the nurse. She will also have the random list of numbers, for HIV positives and negatives separately, which will indicate whether the next client of a certain HIV status should be invited to enrol, assuming they meet all of the eligibility criteria. These randomly generated lists will identify for enrolment 10% of the women who are HIV positive at screening, and will identify 5% of the women who test HIV negative at screening that should not be invited to enrol.

Once the HIV test results have been documented, the nurse will return the client to the same counsellor that gave her pre-test counselling, and the nurse will provide the counsellor with the results of the rapid tests. The nurse will also indicate to the counsellor whether or not this client should be invited to join the study, based on the random enrolment list. The nurse does not tell the participant her result directly. Instead, the counsellor will ask the client whether she wishes to be told the result of her HIV test the same day, or another day, and will be given the option of *not* being told her HIV test result. Regardless of the rapid test results, each participant will be given individual, client centred post-test counseling (risk-reduction counseling), aimed at explaining the results and their implications, in order to draw up an individualized risk reduction plan with the participant. Additional counseling sessions, support and referral to local services and networks for care will be offered as required. Women who choose not to enrol or who were not asked to enrol will be provided information about STD syndromic management and condom distribution available in the clinics.

The rapid test results will be interpreted by the nurse as follows:

- 1 If both tests give negative results, the woman will be considered HIV negative.
- 2 If both tests give positive results, the woman will be considered HIV positive.
- 3 If the two tests give discordant results, the woman will be told that the tests are not giving the same answer about whether she has HIV infection, and that we must wait to receive the EIA test results. She will be given an appointment for one week later and the counsellor will invite the client to ask any questions she might have concerning the discordant results.
- 4 If the control is not read on one of the tests then that test will be repeated until the control appears on the test, and that result will be communicated to the counsellor.

Both blood samples will be sent to the Centre's laboratory directed by Professor Sharon Cassol of the University of Oxford. The laboratory is located at the University of Natal in Durban approximately 2½ hours drive from Mtubatuba. Refrigerated transport is available daily to transport samples to Durban. At Prof. Cassol's lab, 100% of the rapid HIV test results will be confirmed using EIA testing on the 2nd sample. These samples will also be stored and used later to conduct a series of small immunologic studies of HIV positive and negative blood that will provide normative values of different immunologic markers and form a baseline for future trials in this region of South Africa.

There will be no study nurse based at Esiyembeni, Gunjaneni or Machibini PHC clinics because the number of women eligible for recruitment is expected to be low at these clinics and there are insufficient resources for a nurse to be based there. At these clinics, the HIV counsellor will perform a finger-prick test for rapid HIV-testing and will store a sample of blood on filter paper which will be sent to the lab to confirm the HIV rapid test results. Women at these clinics who agree to receive their HIV test results, will be invited to enrol but will be referred to Mtubatuba family planning clinic for their follow-up visits.

4.3 Study enrollment visit

Following post-test counselling of women who wish to know their HIV results, women will be invited, on the same day, to enrol in the study, according to the random enrolment lists. Women who do not wish to know their results (i.e. HIV-infected and uninfected) will not be invited to enrol. Additional counseling services will be available if a participant wants more time to consider whether to participate in the study. However, enrollment must occur within 14 days of the screening visit. Otherwise, another HIV test must be performed if the woman was initially HIV negative.

Any woman who agrees to enrol will be asked to give written consent. At that time, permission will be sought to make home visits if, during the study, she misses a follow-up visit. However, it will be made clear to each woman that she is free to join the study without giving consent for home visits. Once the woman has given written informed consent, the date of enrolment for that woman will be added to the study register.

The contact details of each woman who agrees to be enrolled and other personal information will be recorded on the last page of the eligibility form. Women who live within the ACDSA will be asked to provide their Bounded Structure Identification number (BSID) by which all dwellings are documented and mapped in the ACDIS database. If it is not already known, a woman will be asked to bring her household BSID number with her to the next visit, 2 weeks later. A detailed map cue will be taken, asking for directions using landmarks such as

schools and churches. This page will be kept at the Africa Centre, not at the clinic, and will only be available to study trackers, if a woman has missed her appointment and had previously given consent to being traced at home. This page will be the only location where information linking the study ID number to any personal information regarding the participant is recorded.

A coital log (section 4.4.4) will be given to each enrollee to take home. They will be asked to bring it to the next visit, 2 weeks later. They will be given instructions as to how to fill the log before they leave the clinic.

If enrolment is not on the same day as screening, contact details will be updated, another pregnancy test will be administered if indicated, and each woman's eligibility for enrolment will be reassessed before enrolment takes place.

4.4 Follow-Up Visits

At every follow-up visit information regarding the study's purpose, the role of the participant and the procedures involved will be reviewed and the participant will be asked whether she is willing to remain in the study before any other scheduled questionnaire or procedure is administered. Contact details will also be updated. Each visit will also include HIV/STI education and counselling, information on the importance of regular condom usage for both the woman and her partner(s), and hypo-allergenic non-spermicidal lubricated condoms. Women who do not return for follow-up visits will be traced at home, if they had previously given informed consent. She will be interviewed to find out the reasons for her missed appointment and her continued participation in the study will be encouraged.

4.4.1 Week 2

After the initial discussion that occurs at the beginning of every visit, the counselor will administer the disclosure form and the sexual behaviour questionnaire (see section 4.4.4). In addition, the coital log given at the enrolment visit will be reviewed with the participant, using the weekly history form as a guide, and any difficulties with using the log will be discussed. The weekly history form will be completed even among those who did not return their coital log. After this interview, the woman will be directed to the study nurse.

Venous blood (10 ml) will be drawn from all women for syphilis and herpes simplex virus (HSV) testing and sent to Prof. Sturm's lab for testing. Syphilis serology will be analysed using the Determine test as a screening test, followed by a quantitative Rapid Plasma Reagin (RPR) test for the positives. HSV testing will be performed using a focus test.

The nurse will use the clinical questionnaire to establish any history of sexually transmitted diseases (STDs). Any woman reporting current symptoms will be examined and treated syndromically if discharge and / or ulcers are found, and given nystatin if candida is found.

A random subgroup at week 2 will be chosen to receive full STD testing. The nurse will perform a pelvic examination that includes a clinical assessment of the external genitalia, vagina and cervix to detect any abnormality. A vaginal swab will be taken to test for bacterial vaginosis and trichomoniasis. A swab will also be collected to test for Chlamydia trachomatis and Neisseria gonorrhoea infections using PCR technology, specifically

Probetec SDA (strand displacement assay). In addition, one more vaginal swab and an endocervical swab will be taken and sent to Prof. Cassol's lab to be stored and used later to conduct a series of small studies that would provide information about cytokines in the vaginal fluids of HIV negative women and characterise how HIV is compartmentalised in the vagina among HIV positive women; information that will form a baseline for future trials in this region of South Africa.

STD test results will be given 2 weeks later and women will be treated appropriately. Individuals who have a phone contact will be told that they will be called and asked to return to the clinic if they have positive test results and require treatment. Their specific results will not be given over the phone. Instead, an appointment to come in will be given. Those who report not to have a phone or contact number will be given an appointment 2 weeks later to return to the clinic. Male-partner notification will be encouraged. A referral note will be given to the participant to give to their partner for treatment of any infections they may have at a local clinic.

Before the woman leaves the clinic at week 2, her 3 month appointment will be scheduled.

4.4.2 3 month and 9 month visits

After the initial discussion that occurs at the beginning of every visit, the counselor will administer the disclosure form and then the sexual behaviour questionnaire. Those who were HIV negative at their last test will then be pre-test counselled by the counsellor and given another HIV test by the study nurse using the same two rapid tests and procedures used during the enrolment visit. While waiting for the test results, the nurse will provide syndromic management for STDs and, if indicated by the date of the participant's last menstrual period, administer a pregnancy test on a urine sample to exclude pregnancy. Once the test results have been documented, the nurse will return the client to the same counsellor that gave her pre-test counselling and will provide the documented results to the counselor. Post-test counselling will then occur. Women who sero-convert during the study will be counselled and referred to local HIV support services. They will also continue to be followed for the rest of their scheduled visits.

4.4.3 6 month and 12 month visits

After the initial discussion that occurs at the beginning of every visit, the counselor will administer the disclosure form and then the sexual behaviour questionnaire. Those who were HIV negative at their last test will be pre-test counselled by the counsellor. All women will have blood drawn by the nurse for syphilis testing, and those who were previously HIV negative will have additional blood drawn so that they can also be tested for HIV. The tube of blood taken for syphilis testing will also be tested for HSV if the woman was HSV negative previously. Women will be contacted regarding their syphilis results 2 weeks later.

While waiting for the HIV test results, the nurse will perform a pelvic examination on all women that includes a clinical assessment of the external genitalia, vagina and cervix to detect any abnormality. If abnormal discharge or ulceration is noted during the clinical examination or reported by the client, appropriate treatment will be given based on syndromic management. In addition, an additional vaginal swab and an endocervical swab will be taken from a subgroup of women and sent to Prof. Cassol's lab.

Once the HIV test results have been documented, the nurse will return the client to the same counsellor that gave her pre-test counselling and will provide the documented results to the counselor. Post-test counselling will then occur. Women who sero-convert during the study will be counselled and referred to local HIV support services.

4.4.4 Sexual behaviour information during the study

Several different data collection methods will be used and compared, as shown in table 2, to collect data on contraceptive and condom use, sexual relationships, vaginal inserts, and genital hygiene practices.

Table 2: *Methods of collection of sexual behaviour data*

Method	Completed by who?	Given when?	Contents
Coital Log	Self-completed	Enrolment	Type of sexual act Frequency of sexual acts Condom use Partner type
Face to Face Questionnaire	Counselor	Every follow-up visit	Contraceptive use Condom use Sexual relationships Genital hygiene (at wk 2 only) Vaginal inserts (at wk 2 only)
Secret voting	Self completed	Every follow-up visit	Sexual relationships Type of sexual act Frequency of sexual acts
Sexual history form	Counselor	Every follow-up visit	Comparison of sexual activity from coital logs/self-reports Type of sexual act Frequency of sexual acts Condom use Partner type Partnership duration Use of vaginal inserts

Coital logs are self-completed by women at home over a two week period. The rationale for using coital logs is to record events close to the time that they happen, and minimise recall bias. Coital logs have been used in a number of studies of contraceptive and microbicide use or acceptability in high risk populations such as sex workers and adolescents²⁷⁻³⁰. We are not aware of any published report of the value of using coital logs in women from the general population attending immunization and family planning clinics. Such women may be more likely to have stable relationships in which it may be more difficult to record such information at home on a daily basis. Our research will inform us about the difficulties in using this instrument.

Two types of logs have been designed for this study, one with words and the other with images. The pictorial logs have been made to avoid difficulties with literacy and make them easy for women to complete. Half of the women at the first visit will be given word logs,

and the other half pictorial logs. Although we anticipate the possibility of illiteracy, it should be noted that this population has a high literacy rate and good school enrolment³¹. We therefore, expect that most women will be able to understand and use written material.

It is evident from data sources such as the Demographic and Health Survey that data collected in face-to-face interviews are unreliable due to factors such as social desirability bias. The sexual behaviour form incorporates a proposed “secret voting” data collection method designed to maximise privacy and confidentiality. The questions are constructed so as to elicit simple yes/no/don't know or numerical responses and while the interviewer reads out the question, the participant self-records her response, thereby minimizing non-participation and response errors. The methodology has been shown to reduce social desirability bias and provide more reliable data on the behavioural determinants of the spread of HIV and other STDs. It has proved acceptable to other rural, basic-literate populations in sub-Saharan Africa³². The method is already being employed in the ACDIS and the experience from a pilot study has shown that respondents appreciate the added level of confidentiality that “secret voting” provides.

A random sample of women will be interviewed face-to-face for the questions usually asked by secret voting. We hypothesize that the information reported in the secret voting method will be more accurate than that reported in face-to-face interviews particularly with respect to the number of partners and anal sex. To test this hypothesis, at two consecutive visits, women who have an interview using one method at the first visit will be asked through the other method the second visit.

The final section of the sexual behaviour questionnaire at each visit requires the interviewer to guide the participant through a sexual history form that covers a period of 2 weeks. The hypothesis is that collecting data in this way assists women in recalling sexual acts that they may otherwise have forgotten to report and provides more complete data through the prompting of the interviewer.

4.4.5 Monitoring ethical issues and acceptability of the clinical trial

Interviews with individuals will explore the participants' understanding of the following in order to ensure informed consent and appropriate participation:

- What are the services offered and who can access them in this study?
- What is the importance of condom usage?
- What are the main objectives of this research?
- What questions will be asked at routine visits?
- What clinical data will be collected at routine visits?
- What will be done with specimens?
- What rights do individuals have to refuse to participate and to withdraw from the study?
- When might a woman be tracked at home?

We will explore factors that may encourage or discourage continued participation in the study. It is hypothesized that a range of social circumstances may affect willingness and ability to participate. In-depth interviews (IDIs) with a sample of those who have refused to

take part, those who have not returned for follow-up (non-compliers), and those who have completed follow-up (compliers), will be conducted.

It is important to assess the clinic context. Interviews among clinic and study staff will enable them to share their experiences, make recommendations and raise issues. Interactions between clinic staff and women in the study during enrolment, informed consent, collection of specimen, HIV testing and counselling, will also be observed directly and used to identify any need for changes in procedures.

4.4.6 Determining the acceptability of a microbicide product among women and their sexual partners

Placebo gel and samples of the two types of applicators will be made available towards the end of the feasibility period. At this time, sixteen FGDs, based on the sub-groups in Table 1, and gender, will be conducted. During the FGDs, participants will be provided with placebo gel and applicators to examine and asked to comment on them. The following will be raised to explore how the cultural aspects of sexual behaviour affect the use of microbicide products:

- How does a male's physical and economic power alter negotiations for safe sex by the woman with different types of partners?
- What are the local attitudes to the amount of vaginal lubrication desirable for sexual pleasure and/or to increase or decrease the time to male ejaculation?
- How do the concepts of trust and fidelity influence condom use in regular/ non-regular relationships?
- What contraceptive/ prophylactic precautions are used with each type of sexual partner?
- How would attitudes and practices regarding genital and menstrual hygiene alter the use of a microbicide product?
- How would perceptions of personal risk of HIV alter the use of a microbicide product?
- Would women tell their partners that they were using a microbicide product?
- Would men expect their partners to inform them that they are using microbicide products? Would men support women using a microbicide product?

A sample of the participants in the FGDs will be asked to take part in IDIs. In addition, 10 IDIs with women and their partners together will be conducted on the same topics.

4.5 Completeness of follow-up

The ACDIS infrastructure is equipped to track individuals who migrate within the AC DSA or who leave the area. It will be possible to continue follow-up of any women who migrate internally using the ACDIS field staff. Study participants can change to a different study clinic if they change their place of residence. Participants who live outside of the AC DSA and have missed a visit will be traced at home if they have consented to a home visit. When participants leave the area they may continue to make regular return visits to their previous residence. Efforts will be made to continue follow-up by flexible appointments.

4.6 Payment

It is not the general policy of the Africa Centre to offer payment to study participants. However, where participants need to travel to a clinic for study visits and no intervention is offered, a R40 food voucher is given as reimbursement for travel costs.

4.7 Participant Withdrawal

Participants may withdraw from the study at any time without jeopardising the care they receive from the health services. The reason, if given, will be recorded. If consent had been granted at enrolment for home visits, a follow-up visit will be made. If the study sponsors or government or regulatory authorities terminate the study prior to its planned end date, follow-up of participants might end.

4.8 Informed Consent

The informed consent is required at two points in the enrolment process. Before a participant is screened, every effort will be made to ensure that the participant understands the purpose of the study, including the requirement for HIV testing, and the risk and benefits of being screened for HIV. At this first informed consent stage, the participant will be asked to answer questions and / or HIV testing. Women who are HIV tested and receive their HIV results, as well as meet all the eligibility criteria, will be told again the purpose of the study, the procedures to be followed (including the requirement for repeat HIV testing), and the risk and benefits of participating in the study. Specific issues that will be discussed with each woman include:

- That they are free to withdraw at any time without jeopardizing their medical care.
- That screening for STDs other than HIV will be carried out during the study.
- That screening for STDs may be carried out by reported history alone or may include an examination and collection of specimens.
- That they do not have to pay for any STD treatment during the study.
- That they are advised to discuss the study with their sexual partner(s) but the consent of their partner is not essential.

Women will be told that they can return at any time to obtain more information or have further questions answered. They will then be asked to go through the consent form with a staff member before enrolling them in the study. The signed informed consent will become a permanent part of the participant's study records.

4.9 Data collection

All interviews will be conducted in Zulu, and the accuracy of translation will be verified by independent back-translation of forms. Data will be collected on the case record form appropriate to the visit. These data will include demographic data, contraceptive history, sexual behaviour and information about disclosure of HIV status.

Participant names will not appear on any forms, instead they will be identified by a PID number. All forms will be reviewed prior to data entry for accuracy, consistency and completeness by designated study staff. Data entry will be performed using EpiInfo 6.0.

4.10 Record Storage and Archive

Each participant will have a clinic record, identifiable by the PID only, to maintain confidentiality, containing details of visit dates, signed consent, laboratory results and details of clinical management (for example, treatment dispensed). These records will be kept in locked files in the study nurse's examination room at each clinic. A copy of all the completed questionnaires for each woman will also be kept at the Africa Centre. All locator information will be kept at the Africa Centre, separate from all other study documents.

Two registers will be maintained at each clinic. One will record the name and PID number of women who enrol in the study, as well as the date of their enrolment, and will record dates that they completed each follow-up visit and when those visits occurred. This register will provide the link between name and PID number for the study staff in the clinic. The second register will be a weekly register that will be used to schedule visits and to identify women who miss their visits.

4.11 Statistical considerations

4.11.1 Sample size

It is anticipated that the real incidence in the study populations lies between 0% and 5%. If 700 person years of data are collected then the precision around the incidence estimates of 1%, 2%, 3% and 5% will be as follows:

1%	+/	0.76
2%	+/	1.07
3%	+/	1.31
5%	+/	1.69

Loss to follow up is expected to be no higher than 15%. We assume that those lost to follow-up drop out at 6 months, on average. Pregnancy rates are likely to be low in this population, and are likely to add < 1% to the total sample required for enrolment. Further assuming that the prevalence of HIV in the population is approximately 30%, then 1130 participants would need to be identified as eligible for enrollment and willing to be enrolled in order to enroll 752 HIV negative women (since 5% of the HIV negative women will not be invited to enrol) and to achieve 700 person years of data among HIV negative women by the end of the study. Our process of randomly selecting 10% of HIV positive women at screening for enrolment will result in an additional 34 women being followed.

Socio-demographic data will be collected at screening for all women. Data from those women who are not eligible, do not wish to receive their result or, are not selected through the randomisation process, will be compared with those who enroll in order to examine differentials with respect to sexual activity and socio-economic status.

Enrolment will be primarily on Tuesdays in all of the PHC clinics (the day for family planning and immunisation clinics). Enrolment will occur every day at Mtubatuba family planning clinic. It is anticipated that staff at the Mtubatuba clinic will see on average 6 participants per day (conservative estimate) while enrolment at the other clinics will average 20 per week (conservative estimate) overall. The adequate length of time required to achieve

capacity is unknown. It is estimated that recruitment will be at a slower rate over the first month and progress over the next 3 months. Follow-up visits will be arranged on other days to reduce congestion in the clinics.

4.11.2 Analysis

Descriptive analyses will be carried out to determine the frequencies and distribution of key demographic and HIV exposure variables (number of partners, sexual practices, sexually transmitted infections). When the use of descriptive statistics to assess group characteristics or differences is required, the following methods are to be used:

- For categorical variables: the number and percent in each category, chi-square or Fishers exact test.
- For continuous variables, the mean, median and standard deviations, quartiles and range (min, max), appropriate test or the non-parametric equivalent

An estimate of HIV incidence will be calculated from the number of serologically confirmed HIV infections during the 12-month period of follow up. It may be possible to examine age-specific HIV incidence rates but with less precision (log rank or binomial).

The proportion of women in follow-up at 12 months will be presented. Rates of follow up will be explored for association with other risk factors.

A crude estimate (% of sexual acts protected) of condom use at each visit will be made using data collected regarding use in the sexual behaviour form. This will also be presented by age for each site, and a measure of association between these two parameters (age and condom use) will be made.

Finally, a table of sample sizes for a randomised placebo-controlled phase III microbicide trial will be drawn up for a range of efficacy levels and Type I/II error rates, using the age-related HIV incidence at one year and the likely follow-up at one year for each site.

5 ETHICAL CONSIDERATIONS:

Full medical confidentiality will be preserved. No names will be used on the samples or forms in the study. All HIV samples and results will be identified only by a barcode and a linking PID number.

The study will be conducted according to MRC GCP guidelines (based on ICH guidelines). The Africa Centre subscribes to the Declaration of Helsinki (South Africa 1996) and Local Investigators will abide by this protocol.

The Africa Centre Community Advisory board acts as consultative mechanism for representatives of the ACDSA. These individuals, who are elected by their communities, are consulted on all studies proposed for ACDIS. Concerns related to the study will be addressed at meetings before and during the study. Community education around the study will form part of a broader HIV/AIDS education effort in ACDIS.

Prior to implementation, the protocol, informed consent forms and participant information forms, the questionnaires, and any other requested documents – and any subsequent

modifications - must be reviewed and approved by the Research Ethics Committee of the University of Natal. The local principal investigator (or designated representative) is responsible for preparation of all submission documents and periodic reports required by the ethical review committee.

6 COMPENSATION AND INDEMNITY

All the staff conducting the interviews and collecting the samples will hold contracts with the Africa Centre for Health and Population Studies and the University of Natal.

THE SPONSOR will indemnify against claims made by subjects or their dependants, which are proven a result of participating in the study described in this protocol.

APPENDIX 1: Schedule of visits, procedures and assessments

VISITS	Screening Visit	Enrollment Visit ¹	Week 2	Follow-Up Visit (3, 9, Months)	Follow up visit (6, 12 Months)
PROCEDURES					
Provide study information	X	X	X	X	X
Obtain informed consent for screening (HIV testing and / or answering questions)	X				
Collect demographic information	X				
Obtain / update contact information	X	X	X	X	X
Provide HIV pre-test counselling (if applicable)	X			X	X
Collect venous blood specimens for HIV rapid tests	X			X	X
Provide HIV post test counselling + test results (as applicable)	X			X	X
Obtain informed consent for enrollment		X			
Distribute coital log with instructions		X			
Next visit scheduled		X	X	X	X
Collect disclosure information			X	X	X
Review coital log			X		
Administer sexual behaviour & history questionnaire			X	X	X
Administer clinical questionnaire	X		X	X	X
Collect venous blood specimen for syphilis testing			X		X
Collect venous blood specimen for HSV testing			X		X ²
Collect urine specimen for pregnancy test (if indicated)	X		X	X	X
Pelvic examination using a speculum			X		X
Perform genital exam for STIs (as indicated)			X	X	X
Collect Swabs for STI assessment			X		
Collect swabs for storage / further study			X		X
Syndromic management or treatment for lab diagnosed infections			X	X	X
Dispense condoms and instructions for use		X	X	X	X
HIV rapid tests	X			X	X
HSV-2 serology			X		X ²
Syphilis serology			X		X
Cervical gonorrhoea and chlamydia PCR			X		
Vaginal swab Gram stain for BV, yeasts			X		
Vaginal swab for trichomonas culture (and/or PCR)			X		
Reimbursement for transport			X	X	X

¹ If an HIV negative woman wishes to enrol more than 14 days after completing the screening process, she must agree to another HIV test first. Enrollment can be on the same day as screening.

² Blood screened for HSV at 12 months only, and only among those who tested negative at week 2.

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