PROTOCOL SYNOPSIS

TITLE

A two-part, cross-sectional and prospective, observational study to estimate HIV incidence among sexually active, adult females.

OBJECTIVES

Primary objectives:

Study A (Cross-sectional) and Study B (Cross-sectional and Prospective, Observational):

- To estimate Human immunodeficiency virus (HIV) incidence among sexually active, adult females in preparation for HIV microbicide efficacy trials.
  To detect acute HIV infections in study participants

Secondary objectives:

Study A:

- To describe demographic characteristics, HIV risk behaviors, contraception and condom use, Sexually Transmitted Infection (STI) symptomatic diagnoses, vaginal hygiene practices, and use of vaginally applied products among sexually active, adult females.
- To determine predictors of HIV prevalence at baseline, and for recent HIV infections as determined by the BED IgG-capture enzyme immunoassay (BED-CEIA) and Abbott AxSYM HIV 1/2gO Avidity Index assays.

Study B:

- To determine predictors of HIV prevalence at baseline, and for recent HIV infections as determined by the BED-CEIA and Abbott AxSYM HIV 1/2gO Avidity Index assays.
- To describe demographic characteristics, HIV risk behaviors, contraception and condom use, STI symptomatic diagnoses, vaginal hygiene practices, and use of vaginally applied products among sexually active, adult females.
- To estimate accrual and retention of women who might participate in future clinical trials of microbicides.
- To estimate the incidence of pregnancy in the study population when provided on-site contraception counseling.

THE DETERMINATION OF ENDPOINTS

Study A

HIV incidence is the primary endpoint for the study. Incidence will be calculated using data from the cross-sectional study. HIV incidence will be estimated by using the BED-CEIA and Abbott AxSYM HIV 1/2gO Avidity Index assays to differentiate between recent and chronic HIV infections from blood collected from HIV seropositive women. The secondary endpoints will be summarized by descriptive data and statistics.

Study B

HIV incidence is the primary endpoint for the study. This is a cross-sectional and prospective, observational study to estimate HIV incidence in consented sexually active, adult females. As in Study A, HIV incidence will be estimated by using the BED-CEIA and Abbott AxSYM HIV 1/2gO Avidity Index assays to differentiate between recent and chronic HIV infections from blood collected from HIV seropositive women enrolled into the cross-sectional study. HIV incidence in the observational prospective study component will be estimated by the number of HIV seroconversions per 100 woman years of follow-up at risk. Determination of seroconversion during follow-up of the prospective, observational study will be done according to the HIV test algorithm (Section 4.3).

The secondary endpoints will be summarized by descriptive data and statistics. Retention rates will be calculated and an incidence rate for pregnancy and STI symptoms will be computed. Pooled HIV Nucleic Acid Amplification Testing (NAAT) will be applied to all negative serology tests (HIV rapid tests) including the last visit of the study to determine the number of acute infections.

DESIGN

Study A is a cross-sectional study and Study B is a two part, cross-sectional and prospective, observational study. The main aim of both studies is to estimate HIV incidence among sexually active, adult females.

A Research Centre might be chosen to conduct either Study A or Study B.

Study A may be conducted for the following reasons:

- Selective data are available on HIV in the study population and/or;
- Verification of HIV data available or;
- Quick result turnaround to allow assessment to study feasibility.

Study B may be conducted for the following reasons:

- Data on HIV incidence in the study population are either outdated or not available and/or;
- To ensure research centre preparedness for Phase III Microbicide trials. This could include experience in Good Clinical Practice, community engagement and community mapping.

Study A
The cross-sectional study component, with a sample size of at least 800 and up to 1200 women, will estimate HIV incidence using the BED-CEIA and Abbott AxSYM HIV 1/2gO Avidity Index assays to differentiate between recent and chronic HIV infections from blood collected from HIV seropositive women.

Study B
The cross-sectional study component, with a sample size of a minimum of at least 800 and up to 1200 women, will estimate HIV incidence using the BED-CEIA and Abbott AxSYM HIV 1/2gO Avidity Index assays to differentiate between recent and chronic HIV infections from blood collected from HIV seropositive women at the screening visit. In addition, 300 of the screened participants who are HIV seronegative and meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into a prospective, observational study for a 12-month follow-up period and observed for HIV seroconversion at each quarterly follow-up visit. To detect acute infection, pooled HIV NAAT will be applied to all negative serology tests (HIV rapid tests) at all scheduled follow up visits.

STUDY POPULATION

Females ≥18 and ≤ 40 years of age who are currently sexually active, and meet study eligibility criteria.

EVALUATIONS AND FOLLOW-UP

Study A
Participants will provide written informed consent and will be assessed to obtain baseline information and to confirm eligibility. Eligible participants will undergo a screening process. All eligible participants screened will be considered enrolled into the cross-sectional HIV incidence study.

Study B
Participants will provide written informed consent for the prospective observational study and will be assessed to obtain baseline information and confirm eligibility. All participants screened will be considered enrolled into the cross-sectional HIV incidence study. Participants who are HIV-negative will be considered for enrolment into the prospective, observational study which will involve quarterly visits over a 12-month follow-up period. At each study visit, participants will be tested for HIV, counseled regarding HIV/STI risk reduction (including condom use), contraception use (except when a participant had undergone hysterectomy; surgical sterilization or tubal ligation), and asked to provide information such as behavioral risk factors, contraception and condom use, and vaginal hygiene practices.

STATISTICAL PLAN

A detailed statistical analysis plan will be developed prior to initiation of data analyses.

Study A

In the cross-sectional study, HIV incidence and 95% confidence intervals will be calculated using the most recent formulas published by the Centers for Disease Control and Prevention (CDC) and/or in the scientific literature for both the BED-CEIA and the Avidity Index assay.

Secondary endpoints will be summarized by descriptive statistics, and compared between relevant study population subgroups. Predictors for HIV prevalence and recent HIV infections will be determined by logistic regression models.

Study B

In the cross-sectional study, HIV-incidence and 95% confidence intervals will be calculated using the most recent formulas published by the CDC and/or in the scientific literature for both the BED-CEIA and the Avidity Index assay. In the prospective observational study, HIV incidence will be calculated by dividing the number of HIV seroconversion by the number of person-years of follow-up at risk. The number of acute HIV infections, defined as HIV antibody negative but NAAT positive, will also be described.

Secondary endpoints will be summarized by descriptive statistics, and compared between relevant study population subgroups. The study accrual process will be described and retention rates will be calculated. Incidence rates for pregnancy and STI symptoms will be computed and confidence intervals will be calculated based on Poisson distribution assumptions. Predictors for HIV and pregnancy incidence will be determined by Cox proportional hazard or Poisson models. Trends of HIV incidence over time will be determined by computing incidence rates for various time intervals and either comparing them directly (using McNamara's test) or including relevant time intervals in the Cox models. Methods to compare the various HIV incidence estimates will be described in the statistical analysis plan.

HIV PREVENTION CLINICAL TRIAL READINESS

In addition IPM will implement the following:

- Provide on-site Good Clinical Practice (GCP) training and experience to research centre staff in preparation for conducting future HIV prevention clinical trials using vaginal microbicide products. Intensive on-site GCP training will be provided at the beginning of the study after which, research centre staff will obtain accredited GCP certification. Theoretical and hands-on GCP training will be an ongoing process during each subsequent monitoring visit**.** A GCP readiness assessment tool will be applied to assess progress.

- Train the research centre in data quality control and measure quality of data by reviewing the number of data queries issued and compare to a standard of <5 data queries per 100 CRF pages over the duration of study conduct.

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OBJECTIVES

Primary objectives:

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- To detect acute HIV infections in study participants

Secondary objectives:

- To determine predictors of HIV prevalence at baseline, and for recent HIV infections as determined by the BED-CEIA and Abbott AxSYM HIV 1/2gO Avidity Index assays.
- To describe demographic characteristics, HIV risk behaviors, contraception and condom use, STI symptomatic diagnoses, vaginal hygiene practices, and use of vaginally applied products among sexually active, adult females.
- To estimate accrual and retention of women who might participate in future clinical trials of microbicides.
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THE DETERMINATION OF ENDPOINTS

HIV incidence is the primary endpoint for the study. This is a cross-sectional and prospective, observational study to estimate HIV incidence in consented sexually active, adult females. HIV incidence will be estimated by using the BED-CEIA and Abbott AxSYM HIV 1/2gO Avidity Index assays to differentiate between recent and chronic HIV infections from blood collected from HIV seropositive women enrolled into the cross-sectional study. HIV incidence in the observational prospective study component will be estimated by the number of HIV seroconversions per 100 woman years of follow-up at risk. Determination of seroconversion during follow-up of the prospective, observational study will be done according to the HIV test algorithm (Section 4.3).

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DESIGN

This is a two part, cross-sectional and prospective, observational study. The main aim of the study is to estimate HIV incidence among sexually active, adult females.

The study may be conducted for the following reasons:

- Accurate data on HIV incidence in Zimbabwe are either outdated or not available and/or;
- To ensure Africa University clinical research centre preparedness for Phase III Microbicide trials. This could include experience in Good Clinical Practice, community engagement and community mapping. Microbicides is one of the key priorities highlighted in the national HIV and AIDS research agenda for Zimbabwe (10).

The cross-sectional study component, with a sample size of a minimum of at least 800 and up to 1200 women, will estimate HIV incidence using the BED-CEIA and Abbott AxSYM HIV 1/2gO Avidity Index assays to differentiate between recent and chronic HIV infections from blood collected from HIV seropositive women at the screening visit. In addition, 300 of the screened participants who are HIV seronegative and meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into a prospective, observational study for a 12-month follow-up period and observed for HIV seroconversion at each quarterly follow-up visit. To detect acute infection, pooled HIV NAAT will be applied to all negative serology tests (HIV rapid tests) at all scheduled follow up visits.

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EVALUATIONS AND FOLLOW-UP

Participants will provide written informed consent for the prospective observational study and will be assessed to obtain baseline information and confirm eligibility. All participants screened will be considered enrolled into the cross-sectional HIV incidence study. Participants who are HIV-negative will be considered for enrolment into the prospective, observational study which will involve quarterly visits over a 12-month follow-up period. At each study visit, participants will be tested for HIV, counseled regarding HIV/STI risk reduction (including condom use), contraception use (except when a participant had undergone hysterectomy; surgical sterilization or tubal ligation), and asked to provide information such as behavioral risk factors, contraception and condom use, and vaginal hygiene practices.

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