

Phase 3 Trials of 6% CS Gel

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Phase 3 Trials of 6% CS Gel

FHI trial in Nigeria

- Funded by USAID

CONRAD trial in India, Benin, Uganda, and South Africa

- Co-funded by USAID and Gates

CS-Nigeria (FHI)

Principle Investigator in Lagos

- Folasade Ogunsola, MD

Principle Investigator in Port Harcourt

- Orikomaba Obunge, MD

FHI Project Leader

- Vera Halpern, MD

Design

- 2160 HIV anti-body negative participants in Lagos and Port Harcourt (1080 at each site)
- 1:1 allocation ratio at each site, CS: placebo
- 12 months of product use for each participant
- Monthly counseling (product and condom use, HIV and STI risk reduction)
- Product discontinued during pregnancy

Key Eligibility Criteria

- Willing to give informed consent
- 18 to 35 years old
- Average ≥ 3 sexual acts per week
- ≥ 2 sexual partner in the previous 3 months
- Not pregnant or desire pregnancy in next 12 months
- Willing to participate for 12 months

Power and Study Size

80% power to detect a 50% reduction in HIV rate

- HIV incidence of 5 per 100 women-years in the placebo group
- $\geq 80\%$ retention at 12 months
- Targeted 66 incident infections
- Expand recruitment if pooled incidence too low (blinded assessment)

Outcomes Assessment

HIV: Monthly OMT anti-body testing, confirmed by Elisa and Western Blot

- Pre-study infection ruled out *via* PCR on stored enrollment specimen if seroconversion occurs in the first 3 months of follow-up
- Final visit PCR test for all antibody-negative women

GC/CT: Monthly vaginal swab tested by SDA

Pregnancy: Monthly urine pregnancy testing

Pelvic exam: at baseline and as needed

Contraception and Pregnancy

- Condoms provided at all study visits
- Family planning counseling
- Referred to Planned Parenthood Centers
- No other contraception provided
- No assessment of pregnancy rates prior to trial

Statistical Methods (HIV)

Test for effectiveness

One-sided ($\alpha=.025$ level), stratified log-rank test.
Type I error controlled using spending function approach

Test for harm or futility

Not tightly controlled. DMC to provide guidance if p-value < 0.10 at an interim look

Secondary analysis methods

PH Regression to evaluate effects of site, site-by-treatment, and pre-specified covariates

Timeline

1 st participant enrolled	December 2004
Interim analysis (16 events)	September 2006
Last participant enrolled	November 2006
Early closure	January 2007

Screening and Enrollment

Screened	3618
Enrolled	1644 (45%)
Screened but not enrolled:	1974 (55%)
• OMT reactive	584 (16%)
• Pregnant	260 (7%)

Baseline Contraception Use

None	~ 20%
Oral, Injectables, IUD	~ 20%
Condom	~ 55%
Other	~ 5%

Interim Self-reported Adherence Data

Condom use

at screening

~60% of acts

at follow-up

~90% of acts

Gel use

at follow-up

~80% of acts

HIV Rate

- ~ 2 per 100 women-years, despite dynamic enrollment efforts
- Trial stopped enrolling women in Nigeria in November 2006
- Plans to add additional sites in Pretoria and Cape Town, South Africa

Pregnancy Rate

- ~ 30 per 100 women-years (overall, both sites)
- ~ 5% of all recorded follow-up time was off-product due to pregnancy
- Impact on study power depends on HIV risk during pregnancy and numbers of infections while off product

Challenges

- Lower than anticipated HIV rates
- High pregnancy rates
- Follow-up of high risk populations
- Difficulties working in Delta region of Nigeria

CS-CONRAD

Cotonou, Benin

Michel Alary, MD

Kampala, Uganda

Florence Mirembe, MD

Durban, South Africa

Gita Ramjee, MD

CONRAD Project Leader

Lut Van Damme, MD, PhD

Chennai, India

Suniti Solomon, MD

Bangalore, India

Marissa Becker, MD

Design

- **2574** HIV-negative participants (unequally distributed across the five study sites)
- 1:1 allocation ratio at each site, CS: placebo
- 12 months of product use for each participant
- Monthly counseling (product and condom use, HIV and STI risk reduction)
- Product discontinued during pregnancy

Key Eligibility Criteria

- Willing and able to give informed consent
- 18 years **or older**
- Average ≥ 3 sexual acts per week
- **≥ 3** sexual partners in the previous 3 months
- Not pregnant or desire pregnancy in next 12 months
- Willing to participate for 12 months

Contraception and Pregnancy

- Condom provided at all study visits
- Family planning counseling
- Protocol amended (and implemented) to provide contraception as part of study
- No assessment of pregnancy rates prior to trial

Power and Study Size

80% power to detect a 50% reduction in HIV rate

- HIV incidence of **4** per 100 women-year in the placebo group
- $\geq 80\%$ retention at 12 months
- Targeted 66 incident infections
- Expand recruitment if incidence too low (blinded assessment prior to first interim analysis)

Outcomes Assessment

HIV: finger prick rapid testing at months 1, 3, 6, 9, and 12, confirmed on second sample

- Pre-study infection ruled out *via* PCR on stored enrollment specimen if seroconversion in the first 3 months of follow-up
- Final visit PCR test for all seronegative women

GC/CT: quarterly vaginal swab tested by SDA

Pregnancy: Monthly urine pregnancy testing

Pelvic Exam: quarterly

Statistical Methods (HIV)

Test for effectiveness

One-sided ($\alpha=.025$ level), stratified log-rank test.
Type I error controlled using spending function

Test for harm or futility

Not tightly controlled. DMC to provide guidance if
 $p\text{-value} < 0.10$ at interim look

Secondary analysis methods

PH Regression to evaluate effects of site, site-by-treatment, and limited pre-specified covariates

Timeline

1 st participant enrolled	July 2005
Interim analysis (35 events)	January 2007
Last participant enrolled	January 2007
Early closure	January 2007

Interim Screening and Enrollment Data

Screened	2733
Enrolled	1333 (49%)
Screened but not enrolled:	1400 (51%)
• HIV-positive	1020 (37%)
• Pregnant	94 (3%)

Baseline Contraception Use

None	~ 10%
Oral, Injectables, IUD	~ 20%
Sterilization	~ 20%
Condom	~ 60%

Interim Pregnancy Rate

- Varied by site
- Impact on study power depends on HIV risk during pregnancy and numbers of infections while off product
- Pregnancy was the most documented reason for time off-product

HIV Rate

- Burkina Faso never initiated, and Chennai stopped enrolling early, due to low expected incidence
- Two additional sites would have been added (Durban and Zimbabwe) in order to achieve target enrollment
- Study size re-assessment, based on crude estimates of pooled incidence rates, conducted prior to first planned interim analysis
- No need to expand enrollment beyond 2574

Challenges

- High pregnancy rates in some sites (not all)
- Need for more accurate measures of adherence and HIV status of partners to better understand product effectiveness