

# Committee on Methodological Challenges in HIV Prevention Trials

Institute of Medicine

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# Carraguard<sup>®</sup> Basics

- Derived from a seaweed extract
- Carrageenan used in food and cosmetics
- Generally Recognized As Safe (GRAS)
- Not likely to be absorbed
- In vitro: blocks HIV & range of pathogens
- Animal models: HSV-2, gonorrhea, HPV

# Carraguard Basics, cont.

- Non-contraceptive
- Compatible with latex condoms
- Odorless, tasteless, colorless
- Inexpensive, stable, widely available
- Favorable reproductive toxicology file (segments I & II)

# Site Selection

- Phase 2 Expanded Safety (1999-2002)
  - » South Africa, Thailand
  - » 400 women followed for one year
  - » Safety, acceptability, feasibility
  - » Incidence in SA: 4% overall
  - » Incidence in Thailand: 0%
- Phase 1 Safety in HIV positive men and women (2003-2004)
  - » 60 people enrolled, Medical Research Council- SA

# Building Capacity

- Renovated clinics
  - » 5-6 counseling rooms
  - » 5-6 clinician rooms
  - » On site laboratory (SANAS equivalent)
  - » Temperature controlled room for storage of gel and other medications
- Staff on site trained in GCP
- Community Advisory Groups/Outreach
- DataFax machines and training
- Requires funds, time and ongoing research

# Endpoints

- HIV seroconversion
  - » HIV-positive by 2 rapid tests and confirmation EIA
    - If at M1 or M3, enrollment sample must be negative by PCR RNA/DNA
  - » Time of seroconversion: midpoint between most recent negative HIV test, and positive HIV test
- Long term safety
  - » Abnormal epithelial findings, STI's, other AE's and SAE's

# Study Design

- Randomized, double blind, placebo controlled

Carraguard +  
condoms

VS.

Placebo  
(methylcellulose) +  
condoms

- N= 6639, endpoints= 194
- Assumes 3.5% HIV incidence rate in the placebo group
- 80% power to detect 33% difference
- p value = 0.05

# Study Design, cont.

- Women enroll for 18 months
- Participate for a minimum of 9 months and a maximum of 24
- Total study duration: 3 years
- 80% completion rate assumed

# Eligibility

- Female
- HIV negative
- Not pregnant
- Sexually active (once in the last 3 months)
- Living in catchment area
- 16 – 40 years old (originally, no upper age limit)

# Steps for participants

- Quarterly visits
  - » HIV tests, pregnancy tests, pelvic exams
  - » Regular STI tests (& if clinically indicated)
  - » Annual Pap smears
- Gel use
  - » One applicator/act (round)
  - » Up to an hour before sex
  - » Vaginal use only

# Progress

- Screened: 9662
- Enrolled: 6203
- Follow up ongoing until March 31
  - » 1662 completed study on time
  - » 1258 early discontinuations
  - » 3273 still active
- Retention of 84.3% at 12 months, 79% at 18 months

# HIV prevalence/incidence

- HIV Prevalence rates
  - » UCT, Cape Town: 18%
  - » MEDUNSA, Soshanguve: 24%
  - » MRC, Isipingo: 43%

# Challenge: Pregnancy

- Younger women who are at risk, hardest to maintain
- Quarterly pregnancy tests
- Women are censored at first positive pregnancy test, and discontinued from the study
- Pregnancy rates declined from 12% to current 9% with provision of contraception at all sites

# Challenge: Adherence

- No surrogate endpoint or biomarker
- Behavioral data carries reporting bias
- Exit interviews re: acceptability and use
- Dye to detect vaginal mucous (“applicator test”) on returned applicators
  - » Low tech, low cost
  - » Good accuracy, quality control
  - » Does not indicate gel use in relation to sex act

# Interim Analyses

- DSMB members
  - » Demographer/Economist, Statistician, Clinical gynecologist, Infectious Disease Specialist
- DSMB dates
  - » August 2005; 33 endpoints; safety
  - » March 2006; 93 endpoints; safety
  - » September 2006; 191 endpoints; safety and efficacy

# Analysis Populations

- Intent to treat – no exclusions (all randomized)
- Efficacy - excludes if all gel unopened and/or HIV+ at enrolment
- Per protocol, compliant set- excludes at specific time points for missed visits; injection drug use. Stratified based on adherence calculation:

$$\text{ADHERENCE} = \frac{\text{AVG INSERT/WK}}{\text{AVG SEX/WK}}$$

# Thank You

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