



# Nancy Padian, PhD

Women's Global Health Imperative

Department of Obstetrics, Gynecology & Reproductive Sciences

University of California, San Francisco (UCSF)

IOM HIV Prevention Trials Meeting

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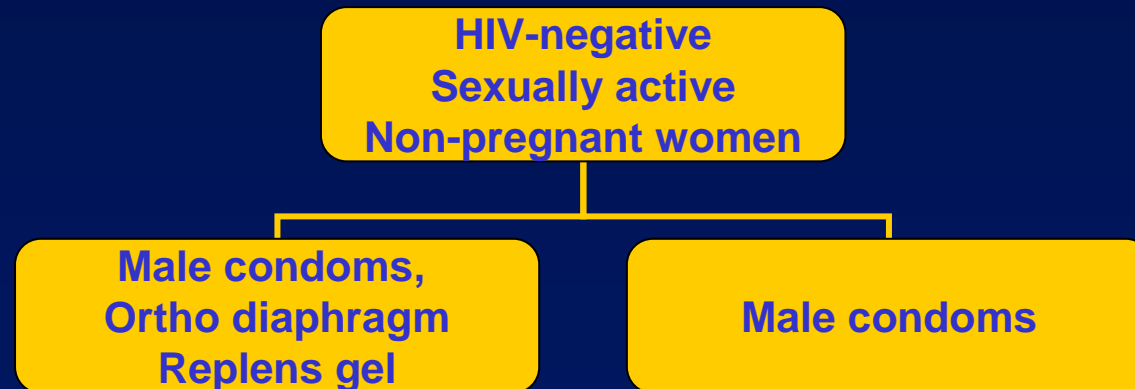
London, UK

# MIRA Study Investigators

- Nancy Padian (PI) & Ariane van der Straten, University of California San Francisco
- Tsungai Chipato & Taazadza Nhemachena, University of Zimbabwe-UCSF Collaborative Research Programme in Women's Health, Zimbabwe
- Gita Ramjee, Medical Research Council, RSA
- Guy de Bruyn, James McIntyre, & Glenda Gray, Perinatal HIV Research Unit, RSA
- Kelly Blanchard, Ibis Reproductive Health

# Trial Summary

- Open-label RCT to examine the effectiveness of the diaphragm and Replens lubricant gel for HIV/STI prevention
- Study design:



- All women receive risk reduction counseling, free male condoms and diagnosis and treatment of STI
- Women followed quarterly for 12-24 months

# MIRA Trial Sites



Total n = 5045

**UZ-UCSF**

Harare, Zimbabwe  
n=2499

**PHRU**

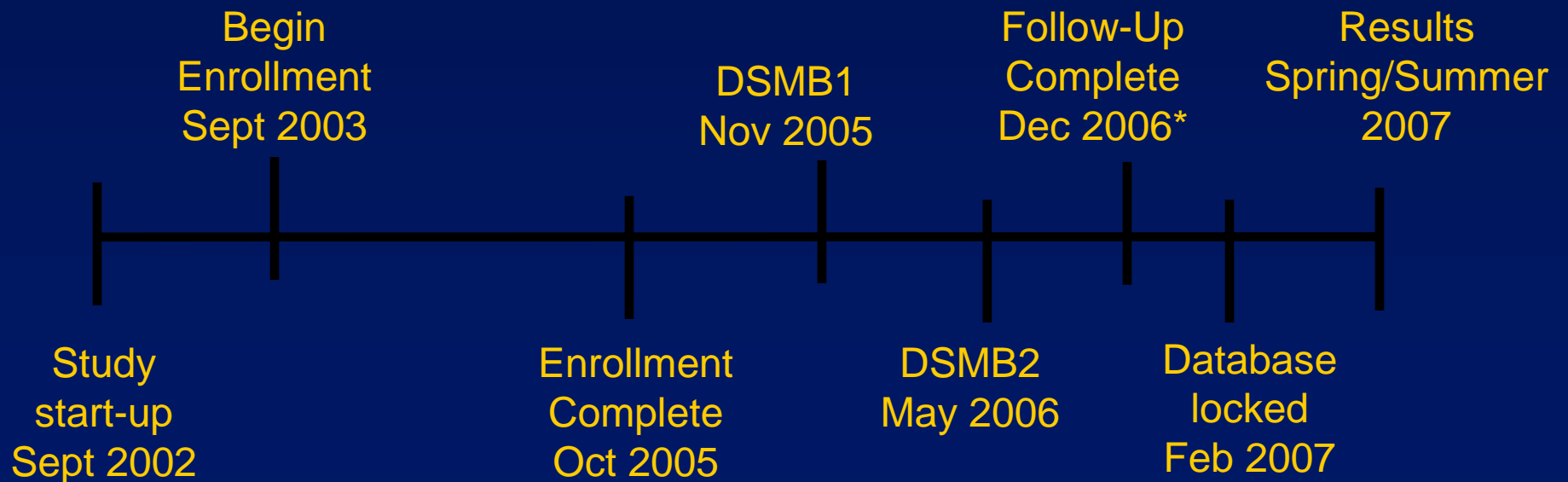
Soweto, South Africa  
n=1033

**MRC**

Durban, South Africa  
n=1513

# Trial Duration

- Trial duration: Sept 2002 – Dec 2006
- Release of results projected for May 2007



\*Last scheduled visit was done at the end of Sept 06; last ppt seen in Dec 06

# Primary & Secondary Objectives

## Primary:

- Effect on HIV incidence

## Secondary:

- Effect on STI incidence
  - Cervical STI: Chlamydia, Gonorrhoea
  - Other: Trichomoniasis, Genital herpes

# Estimating Sample size

## Original sample size → 4500 participants

- Assumptions:
  - Overall annual HIV incidence rate of 4% -> ~ estimated 293 seroconversions
  - Effectiveness of 33%
  - 90% power, two-tailed alpha (0.05)
  - Discontinuation rates of 6-7% per year for 3 years (~20%)

## Sample size increased in April 2005 → 5000 participants

- Review of incidence for an investigators' call in April 2005 revealed an observed incidence that was lower than expected
- Increased sample by 500 women
  - No other assumptions changed

## Final sample size → 5045

# Estimating HIV incidence

Site	Sample size	Protocol Estimated Incidence
Harare	2500	4%
Durban	1500	5%
Soweto	1000	3.5%
All	5000	~4%

# Sources for Estimating Incidence

- **Zimbabwe:** based on prevalence data & previous cohort (incidence) studies
  - HC-HIV (18-35 year old women) 4.1%
  - HPTN 016A (18+ year old women) 4.8%
- **Durban:** based on prevalence data from other studies done in the area (Pop Council study) and data from RSA government
- **Johannesburg:** based on modeling from prevalence studies (5-6%) and one incidence study (4.7%)

# Estimating pregnancy rates

- Eligibility criteria: woman not pregnant and not intending to get pregnant in next 24 months
- Participants are counseled on family planning methods and given free hormonal contraception at the MIRA clinics.
- Participants are reminded that contraceptive effectiveness of diaphragm+Replens is NOT known.
- Participants allowed to stay in study and on product if pregnant
- Lots of recruitment from well-baby clinics, therefore many participants had young babies and were breastfeeding
- Observations during the study
  - Many missed visits due to participants trying to “hide” pregnancy from study staff because they did not realize they could stay in the study if pregnant

# Product use and adherence

- Target: D&G used in at least 80% of all sex acts in intervention arm
- Plan for high D&G use (intervention arm):
  - All ppt required to successfully insert/remove D prior to randomization
  - Intensive education, counseling and role play at enrollment
  - Quarterly product adherence counseling and problem-solving at follow-up
- Plan for high condom use (intervention and control arm)
  - Condom demonstration and education at screening and enrollment
  - Quarterly safer sex counseling and problem solving at follow-up
  - Provision of standard and “fun” flavored novelty condoms
- Measured through quarterly ACASI (use at three time frames captured):
  - Use at last sex act (yes/no)
  - Frequency of use in the last 3 months (4 categories: never -> always)
  - Retrospective calendar: Use for every sex act in the past week

# Adherence challenges during trial

- Observed adherence lower than targeted
- Actions taken to address adherence rates
  - In-person meetings with study staff to try to identify their perception of lower than expected product use & gather ideas of how to address this (Jan & March 2006)
  - Assess staff's understanding of proper study product use to gauge any misperceptions (questionnaire at re-training)
    - Clarified proper amount of gel to use
    - Discussed how to respond to a ppt who reports that either she or her partner does not want to use some/all products (hierarchal counseling, discreet use, stress the importance of use for study results, role-playing, etc.)

# Adherence measurement challenges & responses

- Length of ACASI → Ppt inattention & fatigue\*
  - interview shortened and retrospective calendar only asked at 12-mo and exit visits
- Misreporting of Diaphragm use in condom arm\*
  - Pictures of each method were placed next to the questions and misreporting decreased
  - Ppt confused when reporting combined D & G use leading to possible under-reporting of gel use at last sex\*

\* These problems were identified through interim adherence reports and rapid qualitative follow-up research

# Challenges around condom use

- High intensity condom counseling (CC)
  - May mask effect of intervention products
  - May lead to more socially desirable responses
- Open label: CC may not be identical in both arms
- D&G and condom use may not be independent
- Protocol forbid monitoring of condom use by arm

# Retention

- Overall study retention rate: 95%
- Retention monitored by weekly site reports and monthly summaries from data center
- Important time, staff and energy resources committed to retention since study started

# Retention challenges & responses

- Addressed rumors in the community
  - Ongoing contacts through CABs to dispel misperceptions
- Political disruption in Zimbabwe: “Operation Clean-up”
  - Immediate tracking of all ppts, use of radio and outreach to displaced Ppts (~500), extending to rural areas
- Improve service for PPT at clinics
  - gold star system, evening/Saturday clinics, client liaison officer, childcare, movie in waiting room
- Staff training/motivation
  - Retention discussed on all monthly calls; yearly trainings, case-management approach to motivate outreach workers
- Proactive follow-up:
  - Reminder letters, phone calls, provision of transport, peer outreach, token gifts at visit milestones

# Interim analyses & DSMB

- Per protocol, the first DSMB convened to review an interim analysis after reaching the first 100 seroconversions
  - (November 2005, on data through July 15, 2005)
- Based on the results of the first interim analysis, the DSMB requested another interim analysis following an additional 100 seroconversions (reaching ~2/3 of the total expected cases)
  - (May 2006, on data through April 3, 2006)
- After both reviews, investigators were instructed to **proceed with the study**, with no protocol changes and no safety concerns

**Thank you!**