

# Phase III Microbicide Trials Update

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# Objectives

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- **Primary:** effectiveness against male-to-female HIV transmission (vaginal sex)
- **Secondary:** effectiveness in preventing other STIs (most trials)

# Early Closures

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- ◆ SAVVY
  - ✓ Family Health International (USAID)
  - ✓ Nigeria: due to fertility
  - ✓ Ghana: lower than expected HIV incidence

# Early Closures (cont'd)

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## ◆ CELLULOSE SULFATE

- ✓ Multi-country CONRAD trial (USAID & Bill & Melinda Gates Foundation): potential harm observed in interim analysis presented to IDMC
- ✓ Nigeria FHI trial (USAID): did not observe same effect but based on the CONRAD results, IDMC recommended to also stop

# COMPLETED/ONGOING TRIALS

# POPULATION COUNCIL

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- ✓ USAID & BMGF
- ✓ Carraguard
- ✓ S Africa (Durban; Cape Town and Pretoria)
- ✓ Last study visit on 31 March 2007 – results by end 2007
- ✓ 6203 women enrolled
- ✓ 16-40 years
- ✓ At least one vaginal intercourse act in last three months
- ✓ Had three DSMB reviews

# MICROBICIDE DEVELOPMENT PROGRAMME (MDP)

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- ✓ UK Department for International Development (DfID)
- ✓ PRO 2000 0.5% and 2%
- ✓ S Africa: Durban; Mtubatuba and Johannesburg
- ✓ Tanzania, Mwanza
- ✓ Uganda, Masaka
- ✓ Zambia, Mazabuka

# MDP (continued)

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- ✓ Sample size: 9673
- ✓ First enrollment: 25 Oct. 2005
- ✓ 5259 women enrolled
- ✓ Estimated complete enrollment: 31 March 2008
- ✓ 16 years or older, except in S Africa and Zambia: 18years
- ✓ Likely to be sexually active
- ✓ Last IDMC meeting: 18 June 2007

# MICROBICIDE TRIAL NETWORK (MTN)

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- ✓ National Institutes of Health (USA)
- ✓ HPTN 035: PRO 2000 0.5%; BufferGel; Placebo and no gel arm
- ✓ Phase IIb trial
- ✓ Malawi, Blantyre and Lilongwe
- ✓ Zimbabwe, Chitungwiza and Harare
- ✓ S Africa: Durban and Hlabisa
- ✓ Zambia, Lusaka
- ✓ USA, Philadelphia

# MTN/HPTN 035 (continued)

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- ✓ Sample size: 3100 women
- ✓ 3032 women enrolled (at end of June, complete in some sites)
- ✓ Estimated date of complete enrollment: 31 July 2007
- ✓ 18 years or older
- ✓ At least once vaginal intercourse in three months prior to screening
- ✓ Last IDMC meeting: 15 June 2007

# CAPRISA 004

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- ✓ USAID and LIFELab (SA government)
- ✓ Tenofovir 1% gel
- ✓ Proof-of-concept trial (Phase IIb)
- ✓ S Africa (Durban and Vulindlela)
- ✓ Sample size: 980 women
- ✓ 18 years and older

# CAPRISA 004 (cont'd)

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- ✓ Family planning attendees, STI clinic clients and sex workers (3/2/1)
- ✓ Required to use contraception
- ✓ Enrollment started on 29 May 2007, 26 women enrolled mid June; estimated complete enrollment: September 2008
- ✓ Gel use within 12 hours before and 12 hours after sex, max. 2 applications within 24 hours

# PLANNED TRIALS

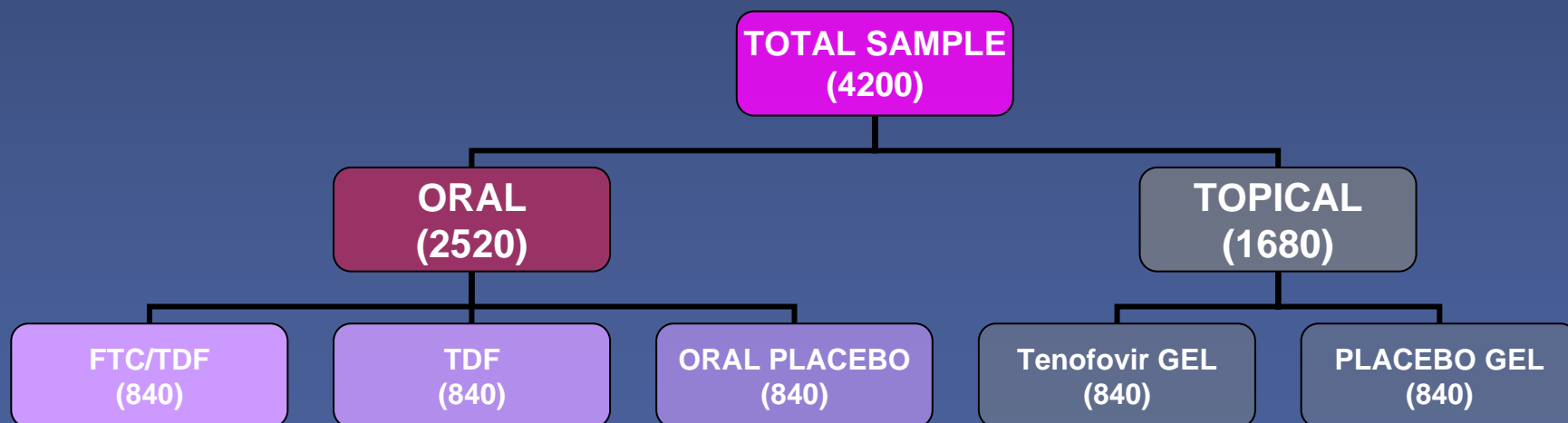
# INTERNATIONAL PARTNERSHIP for MICROBICIDES

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- ✓ Dapivirine, an NNRTI
- ✓ Design and delivery: adapted DOT in case of once daily gel and another form of monitoring for a monthly ring
- ✓ Statistical design parameters in progress
  - ✓ Licensure trials – no firm sample size calculations yet
  - ✓ Planned futility and safety stopping rules
- ✓ Planned start first trial at the end of 2008

# MTN: The VOICE Study

- ◆ NIH (USA)
- ◆ Tenofovir (TDF) 1% Gel, Tenofovir Tablet and Truvada (FTC/TDF) Tablet
- ◆ Phase 2B
- ◆ Five-arm, multi-site, randomized trial
- ◆ Will permit simultaneous assessments of different prevention strategies compared with appropriate controls
- ◆ Will also assess the selection of HIV-1 drug resistance in women who acquire HIV-1 infection while in the study



# Some Phase III challenges/issues and strategic responses

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- ◆ Lower than expected HIV incidence
- ◆ High pregnancy rates
- ◆ Low adherence to product use
- ◆ Retention
- ◆ Staff fatigue

# HIV incidence

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- ◆ Some trials had to increase their sample size or stop because of too low HIV incidence
- ◆ *Response*: how to predict HIV incidence?
- ✓ Incidence studies: no gold standard yet
- ✓ Pilot studies
- ✓ Adapt recruitment strategies
- ✓ Monitor incidence closely, and close and open sites as the trial goes on

# PREGNANCY

	Pregnancy rate (per 100 py)	Time off product
CS CONRAD	23	<10%
CS Nigeria	29	5%
Population Council	9	
MDP	11	
MTN/HPTN	13	7%
Savvy Ghana	64	10%
Savvy Nigeria	30	5%

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- ◆ Why worry? Participants go off product while staying in the trial (except Pop Council) → decrease of the study power
  - ◆ *Response:*
    - ✓ Most trials now provide contraception at clinics or do referrals
    - ✓ Segment III data would allow to keep pregnant women on product, but will make an intense follow-up necessary

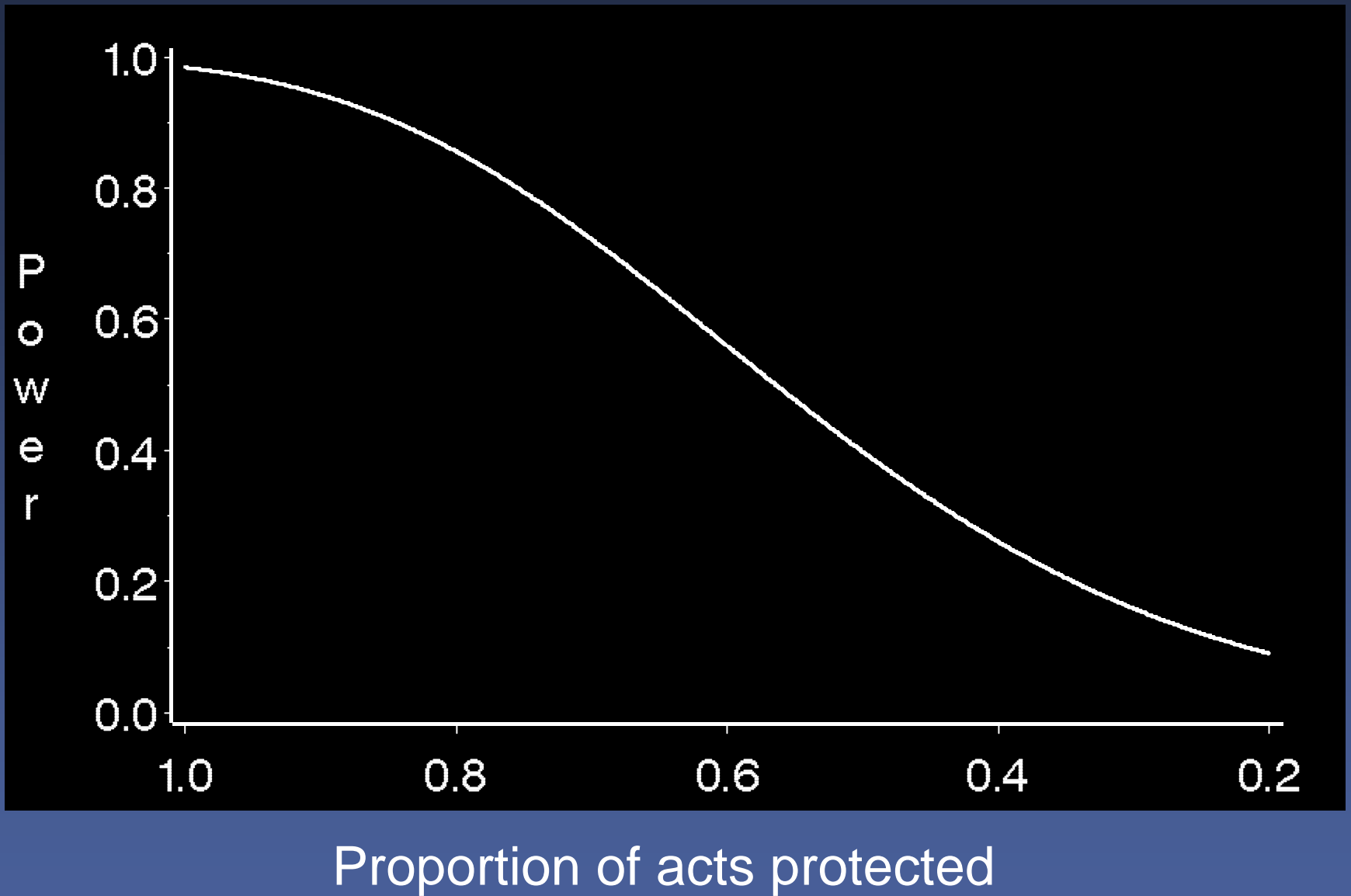
# ADHERENCE (1)

CS CONRAD	Condom use	96%
	Gel use	86%
	Gel when condom not used	45%
CS Nigeria	Condom use	88%
	Gel use	82%
	Gel when condom not used	53%
Savvy Ghana	Condom use	90%
	Gel use	79%
	Gel when condom not used	45%

# ADHERENCE (cont'd)

Savvy Nigeria	Condom use	87%
	Gel use	78%
	Gel when condom not used	62%
MDP	Condom use	>66%
	Gel use	>88%
	Gel when condom not used	>79%
MTN/HPTN	Condom use	72%
	Gel use	81%
	Gel when condom not used	78%

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- ◆ Despite objective of effectiveness above and beyond condom, gel has most potential impact in acts without condoms
  - ◆ No product use → power to detect any effect decreases a lot!
  - ◆ Difficult and challenging counseling on product use
  - ◆ *How do trials deal with this?*
  - ✓ Intensive and repeated training of staff
  - ✓ Intensive counseling of participants



Courtesy of D. Taylor, FHI, NC

# RETENTION (%)

CS CONRAD	90
CS Nigeria	70
Population Council	80
MDP	91
MTN/HPTN	90
Savvy Ghana	85
Savvy Nigeria	77

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- ◆ How do phase III teams try to obtain a high retention rate?
    - ✓ High medical care in trial
    - ✓ Good rapport with participants
    - ✓ Counseling on need for high retention
    - ✓ Flexible opening hours for clinics
    - ✓ Tracing after a missed visit (documented in notes)
    - ✓ Calls before a visit
    - ✓ Help of behavioral and social scientists
    - ✓ Sharing of experience across sites
    - ✓ Provision of meals and drinks during long waiting periods

# STAFF FATIGUE

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- ◆ Long term studies with many visits per day
- ◆ Many HIV positive women identified at screening
- ◆ Routine

What to do?

- ◆ Incentives
- ◆ Extra training
- ◆ Staff rotation
- ◆ Extra opportunities (e.g. education)

# WHAT DO WE KNOW?

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- ◆ Effectiveness trials are difficult, but
- ◆ Each “current” trial group is/was creative in addressing challenges encountered
- ◆ Each planned trial is taking those challenges into account

# WHAT NEXT AND WHY

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- ◆ Clear from all prevention research that there is no magic bullet
- ◆ Same framework applies to microbicide strategies--no magic bullet for HIV prevention
- ◆ Thus continuous clinical research is necessary on:
  - ✓ Coitally-dependent, topical products (gels)
  - ✓ Topical products, not coitally-dependent (rings, daily dosing regimes)
  - ✓ Oral tablets

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Thanks to all study participants,  
collaborators, and donors