What's Happening with Tenofovir Gel?

Trials Update and Overview

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Next Steps for HIV Prevention in Women: Tenofovir Gel and Beyond

Joint Civil Society and MTN Community Working Group Meeting

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Overview

- Why Tenofovir Gel?
- CAPRISA 004
- VOICE
- FACTS 001
- CAPRISA 008
- Supporting studies

Tenofovir Gel

- Active ingredient is ARV tenofovir
  - Has specific action against HIV (unlike earlier microbicides)
- Furthest along in clinical testing of ARV-based microbicides
- Effectiveness Studies
  - CAPRISA 004 (CAPRISA 008)
  - VOICE
  - FACTS 001

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Tenofovir Gel

- Developed by Gilead Sciences, Inc.
- Assigned royalty-free license to CONRAD and International Partnership for Microbicides (IPM) in 2006
- Experience to date suggests the gel is safe
  - Side effects with gel considered mild to moderate

CAPRISA-004

A major milestone

- **The first study to demonstrate the effectiveness of a vaginal microbicide for preventing HIV**

- Phase IIb study that involved 889 sexually active women 18 years and older at two sites in KwaZulu-Natal, SA
- Women were randomized to use either tenofovir gel or placebo gel in a regimen timed before and after sex (BAT-24)

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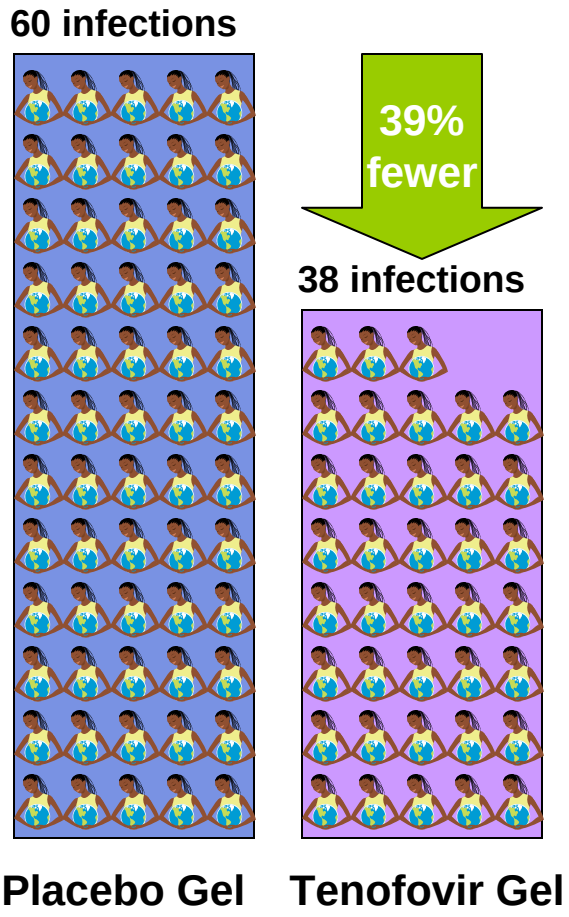
CAPRISA 004 Results

- Tenofovir gel was 39% more effective than placebo gel for protecting against HIV
- Result is statistically significant, but with a wide “confidence interval”
  - True level of effectiveness could be as low as 6% or as high as 60%



Additional Results

- More effective with greater adherence
  - 54% reduction in HIV among women who followed regimen most closely
- 50% decrease in genital herpes (HSV-2) infections among women randomized to tenofovir gel

A Major Milestone…

- But…
  - One trial can't provide all the answers
  - Tested specific regimen (before and after sex)
  - More women need to be studied
- But also…
  - Affirmed importance of VOICE
    - Already ongoing and testing *daily* use
  - Indicated need for second study of *same regimen*
    - Can the results be replicated or improved?
  - Started discussions about possible approval

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VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC

- Phase IIb safety and effectiveness trial evaluating two ARV-based HIV prevention approaches:
  - *Daily* ARV tablet (oral PrEP)
    or
  - *Daily* application of tenofovir gel
- The only trial that involves ***both*** oral and vaginal products
- Funded by U.S. National Institutes of Health (NIH)
  - Study products provided by CONRAD, Gilead Sciences

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VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC

- Started September 2009
- Fully enrolled with 5,029 women at 15 sites in SA, Uganda and Zimbabwe
  - Diverse – single and married, average age 25
- Planned completion in 2012; results early 2013
- “Powered” to support licensure of tenofovir gel if effect size adequate
  - Conducted under IND which is required for U.S. FDA to consider approval of the gel
  - FDA said it will consider data from CAPRISA 004 and VOICE

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15 VOICE Sites – 5,029 women

UGANDA - 322 participants

- Makerere Univ./JHU, Kampala (1 site)

ZIMBABWE – 630 participants

- UZ-UCSF, Harare (1 site)
- UZ-UCSF, Chitungwiza (2 sites)

SOUTH AFRICA – 4,077 participants

Durban Area

- Medical Research Council (7 sites)
- CAPRISA eThekwini (1 site)

Johannesburg Area

- WRHI (1 site)
- PHRU Soweto (1 site)

Klerksdorp Area

- Aurum Institute (1 site)

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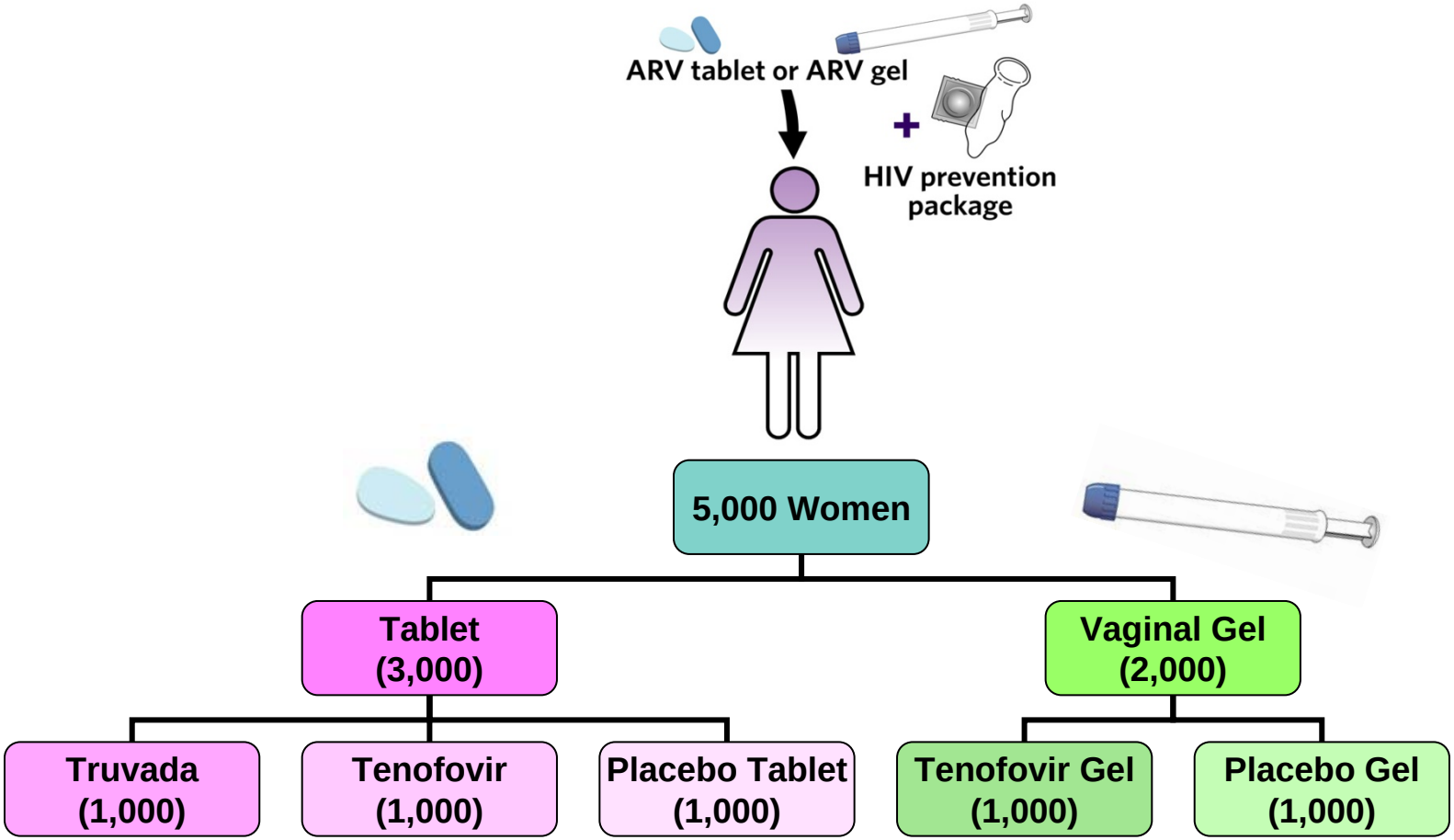
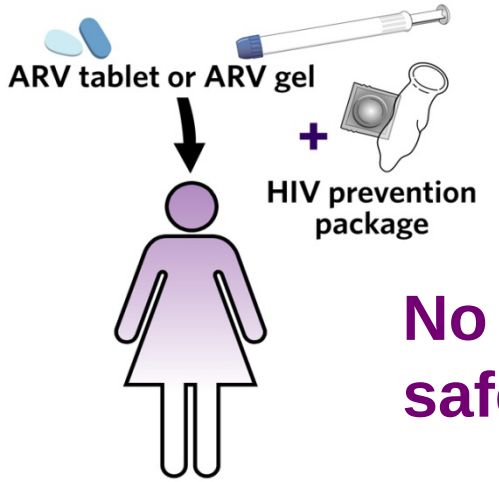
VOICE Study Design



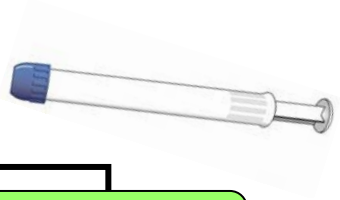
Five study groups

VOICE Study Post DSMB

Sept. 16 DSMB – closed the oral tenofovir arm because not possible to show it is effective in VOICE



No concerns about safety of any product



- **5,000 Women**
  - **Tablet (3,000)**
    - **Truvada (1,000)**
    - ~~**Tenofovir (1,000)**~~
    - **Placebo Tablet (1,000)**
  - **Vaginal Gel (2,000)**
    - **Tenofovir Gel (1,000)**
    - **Placebo Gel (1,000)**

Five study groups

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FACTS-001

- Phase III study of same regimen in CAPRISA 004 – gel used before and after sex
- Minimum of 2,200 women will be enrolled at up to 9 sites in SA
  - Focus on younger women (age 18-30)
- Just starting; expect to have results before end of 2013
- Funded by USAID, SA Dept. of Science and Technology and SA Dept. of Health

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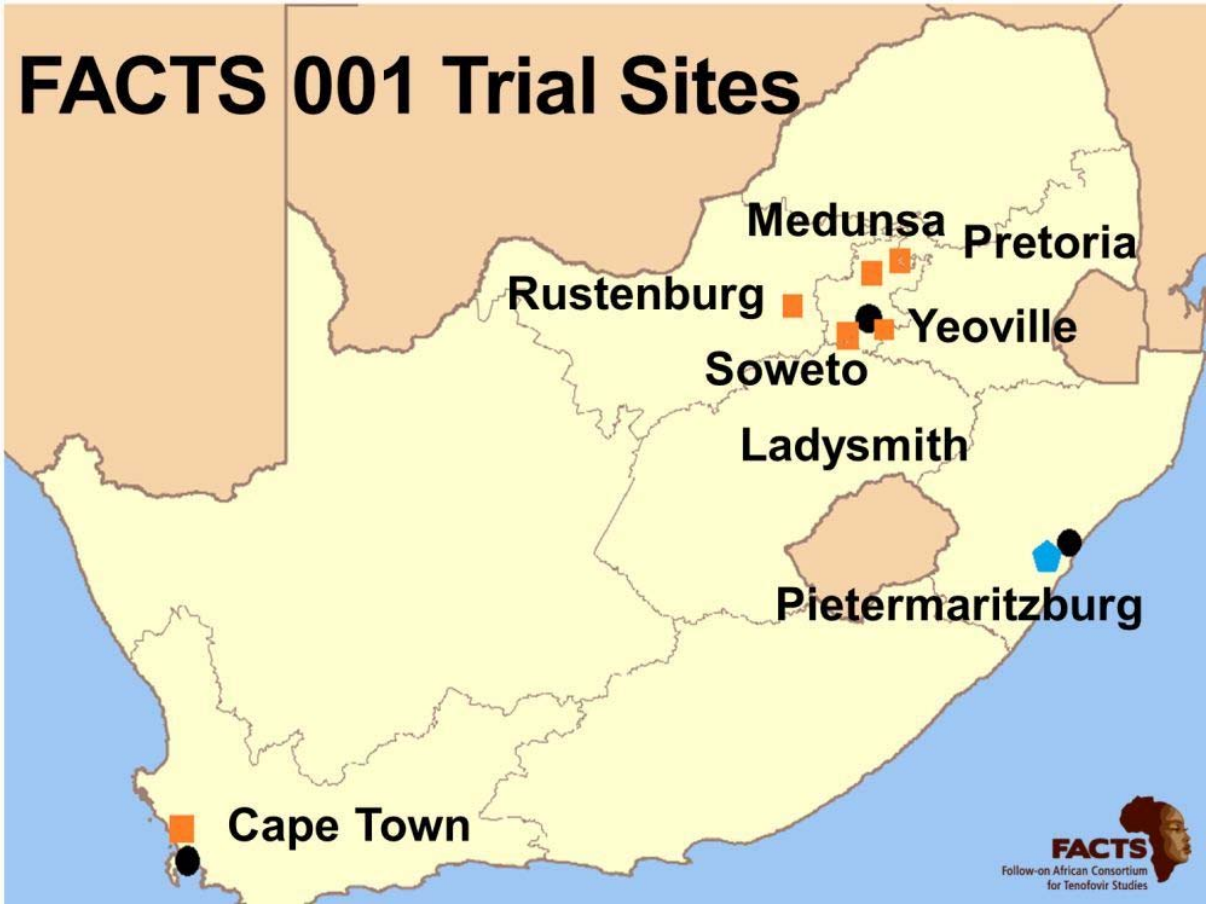
FACTS-001



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CAPRISA 008

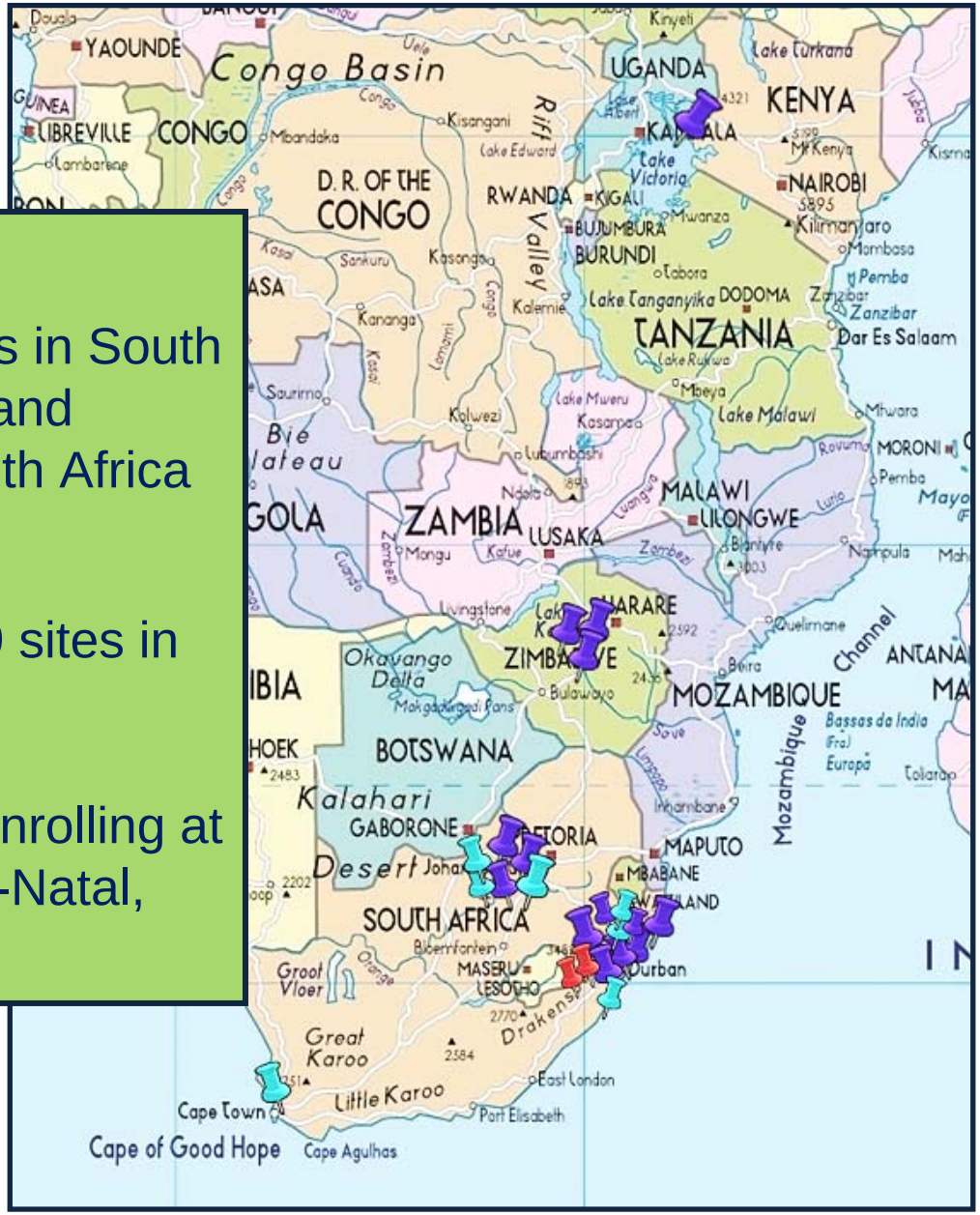
- Open-label randomized control trial with former CAPRISA 004 participants who are HIV-negative
- To assess the effectiveness of tenofovir gel implementation strategies
- One group – Receive tenofovir gel monthly in CAPRISA clinic (same as standard CAPRISA 004 trial process)
- Second group – Receive tenofovir gel quarterly in family planning clinic
- Starting soon?

Tenofovir Gel 2011-2012

VOICE –
Ongoing at 15 sites in South Africa, Zimbabwe and Uganda; 11 in South Africa

FACTS 001 –
Enrolling at up to 9 sites in South Africa

CAPRISA 008 – Enrolling at 2 sites in KwaZulu-Natal, South Africa



Will tenofovir be approved?

It all depends on what the results are

- U.S. FDA said it will review data from CAPRISA 004 and VOICE (when available)
- South African Medicines Control Council (MCC) has expressed interest in results of FACTS 001, with CAPRISA 004 data
- Other studies are also critical
  - Pregnancy
  - Safety and drug absorption
  - Adolescent safety
  - Extended safety

Tenofovir Gel Pregnancy Studies

MTN-002

- First microbicide study in pregnancy
  - How does pregnancy affect drug absorption?
  - Is the drug transferred to the fetus?
- Gel applied as one-time dose in 16 HIV-negative U.S. women prior to scheduled C-section
- Results:
  - Only small amounts of drug absorbed into mother's bloodstream, amniotic fluid and umbilical cord (fetal) blood

Tenofovir Gel Pregnancy Studies

MTN-008

- Ongoing at 2 U.S. sites
- Safety and drug absorption in women in third trimester and breastfeeding

MTN-019

- Phase II study to be conducted in U.S. and Africa
- Women in second and third trimesters and breastfeeding

MTN-016 (EMBRACE)

- Registry of women and babies to evaluate safety and risks associated with product exposure in pregnancy

MTN-018 (CHOICE) Sub-studies

- **CHOICE B** -Open-label follow-up study to VOICE for breastfeeding women if products effective
- **CHOICE C** - for pregnant women

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Adolescent Safety

MTN-021

- Phase II expanded safety and tolerability study of tenofovir gel used daily for 12 weeks
- To enroll 90 adolescent girls ages 15-18 in the U.S.

- Being conducted in collaboration with the Adolescent Medicine Trials Network for HIV/AIDS Interventions of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD).

Extended Safety and Open-label

Committed to Having Options for Interventions to Control the Epidemic

CHOICE

- Open-label follow-up study to VOICE if any product is found effective
- Designed to provide additional safety data required for licensure of tenofovir gel
- Designed to help in understanding women's preferences for the gel and tablet (if both are effective) and their use by women in more real-world settings

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MTN Rectal Safety Studies

- MTN-006
  - Phase I safety, acceptability and drug absorption study of vaginal tenofovir gel applied rectally18 HIV-negative adults at 2 U.S. sites
  - Found safe but resulted in reformulation of the gel
- MTN-007
  - Phase I follow-up study to MTN-006
  - 60 HIV-negative men and women at 3 U.S. sites
  - Study completed; results expected early 2012
- MTN-017
  - Planned Phase II study in MSM in U.S., South Africa (Cape Town), Thailand and Peru

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