

# **HIV Prevention Clinical Research: Update on Microbicides**

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Sept 23, 2010

# Why is HIV Prevention Important?

## Globally

- Prevention programs are available to 1 in 5 people who need them
- For every person put on antiretroviral therapy, 2 to 3 people are newly infected with HIV globally

## Country Context

- Every day in South Africa, 1,500 people become infected with HIV—around one person every minute
- Every 9 ½ minutes someone in the U.S. is infected



DFID (2009); CDC (2009); Fauci & Folkers, (2009)

# Presentation Overview

- **Overview of selected topics in HIV prevention clinical research**
  - **STIs**
  - **Male Circumcision**
  - **Vaccines**
  - **PREP**
  - **ART**
- **Microbicide research trials update**

# HIV PREVENTION 2010

## DECREASE SOURCE OF INFECTION

- Barrier protection
- Blood screening
- IDU harm reduction
- Antiretroviral Therapy
  - PMTCT
  - Rx infected partners
- STI Treatment

## DECREASE HOST SUSCEPTIBILITY


- Barrier protection
- Infection Control
- Circumcision
- PEP
- Oral PREP
- Topical Microbicides
- Vaccines
- STI Treatment

## ALTER BEHAVIOR

- Condom and HIV testing promotion
- Individual interventions
- Couples interventions
- Community-based interventions
- Structural interventions (e.g., economic)

**Where are we in STI, Male  
Circumcision, and HIV  
Vaccine Research?**

# STIs: Community-Level Intervention Trials

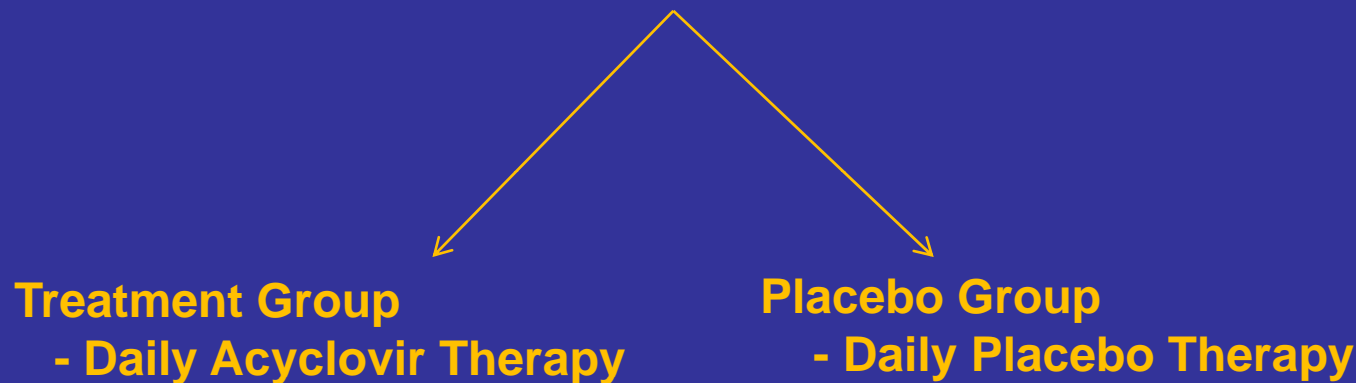
- **Mwanza Trial:** Improved STI case management for *symptomatic* STIs versus routine care; evolving HIV epidemic (n=12,000)  38% reduction in HIV
- ~~**Rakai Trial:** Intensive STI control with mass antibiotics versus MVI *asymptomatic* STIs q 10 mo x 3; HIV epidemic stable (n=14,000)~~
- ~~**Masaka Trial:** Information/education (I/E) alone versus I/E + STI interventions versus routine services; HIV epidemic stable (n=20,000)~~

Grosskurth (1995); Wawer (1999); and Kamali (2003)

# STIs: “Partners in Prevention”

## HSV-2 Suppression to prevent HIV

3408 Randomized HIV Sero-discordant Couples  
One partner was both HIV+ and HSV2+



## Results

- daily acyclovir therapy did not reduce the risk of transmission of HIV-1
- reduction in plasma HIV-1 RNA of 0.25 log<sub>10</sub> copies/ml
- 73% reduction in genital ulcers due to HSV-2

# Adult Male Circumcision Trials

**3 RCTs on HIV acquisition by men: 11,054 HIV-negative, uncircumcised men enrolled**

- **ANRS 1265 (S. Africa):** 18-24y men (n= 3,274)
- **Rakai, Uganda:** 15-49 y (n=4,996)
- **Kisumu, Kenya:** 18-24 y (n=2,784)

The above trials found a 51-60% lower incidence of HIV infection among circumcised vs. uncircumcised men

# Adult Male Circumcision Trials

## 1 RCT on HIV transmission from men to women

- Circumcision of HIV-positive men did not reduce HIV transmission to their HIV-negative female sexual partners (n=922)

# HIV Vaccine Trials

- **Overview:**

- **STEP Study:** Phase IIb trial of V520 vaccine that led to an overall increase in HIV infection risk in vaccine vs placebo recipients [HR 1.6 to 2.0] (n=3,000)



- **Thailand Vaccine Trial:** Largest HIV vaccine efficacy trial → 31% reduction in HIV to placebo group (n=>16,000); modest, statistically significant finding could have been due to chance

# PREP with ART

# PrEP Clinical Trials: 2010

<u>Study Name</u> <u>Location</u>	<u>Funder</u>	<u>Population</u>	<u>Intervention</u>	<u>Findings</u>
<b><u>CDC 4940</u></b> <b>Botswana</b>	<b>CDC</b>	<b>1,200 Het. Men &amp; Women</b>	<b>Daily Oral TDF, TDF/FTC</b>	<b>Amended Research Question Results 2011</b>
<b><u>CDC 4323</u></b> <b>USA</b>	<b>CDC</b>	<b>400 MSM</b>	<b>Daily Oral TDF</b>	<b>Safe &amp; Acceptable</b>
<b><u>CDC 4370</u></b> <b>Thailand</b>	<b>CDC</b>	<b>2400 IDU</b>	<b>Daily Oral TDF</b>	<b>2012</b>
<b><u>CAPRISA 004</u></b> <b>South Africa</b>	<b>USAID</b>	<b>900 Women</b>	<b>Pre/Post Coital 1% TFV Gel</b>	<b>Incidence Reduced by 39%</b>
<b><u>IPREX</u></b> <b>Peru, Ecuador, Brazil, USA, Thailand, South Africa</b>	<b>NIH, BMGF</b>	<b>3,000 MS</b>	<b>Daily Oral TDF/FTC</b>	<b>Results December 2010</b>

# PrEP Clinical Trials: Beyond 2010

<u>Study Name</u> Location	<u>Funder</u>	<u>Population</u>	<u>Intervention</u>	<u>Status</u>
<u>Partners Prep</u> Kenya, Uganda	BMGF	3,900 Het. Discord. Couples	Daily Oral TDF	2012
<u>Fem Prep</u> Kenya, Malawi, South Africa, Tanzania, Zambia	USAID, BMGF	3,900 Women	Daily Oral TDF	2012
<u>CDC 4370</u> South Africa, Uganda, Zambia, Zimbabwe	MTN/NIH	5,000 Women	Daily Oral TDF, TDF/FTC, and Tenofovir Gel	Enrolling Results 2012

# Partners Study: HIV transmission and ART initiation

## • Overview

- Assess effect of ART use by HIV-infected patients on risk of transmission to their uninfected partners
- 3,381 couples from an RCT were eligible for analysis
- **Primary Outcome:** genetically-linked HIV transmission

## • Results

- 349 participants initiated ART during the study
- Transmission rates by ART vs. no ART initiation:
  - 0.37 (0.09-2.04) vs. 2.24 (1.84-2.72) per 100 PY

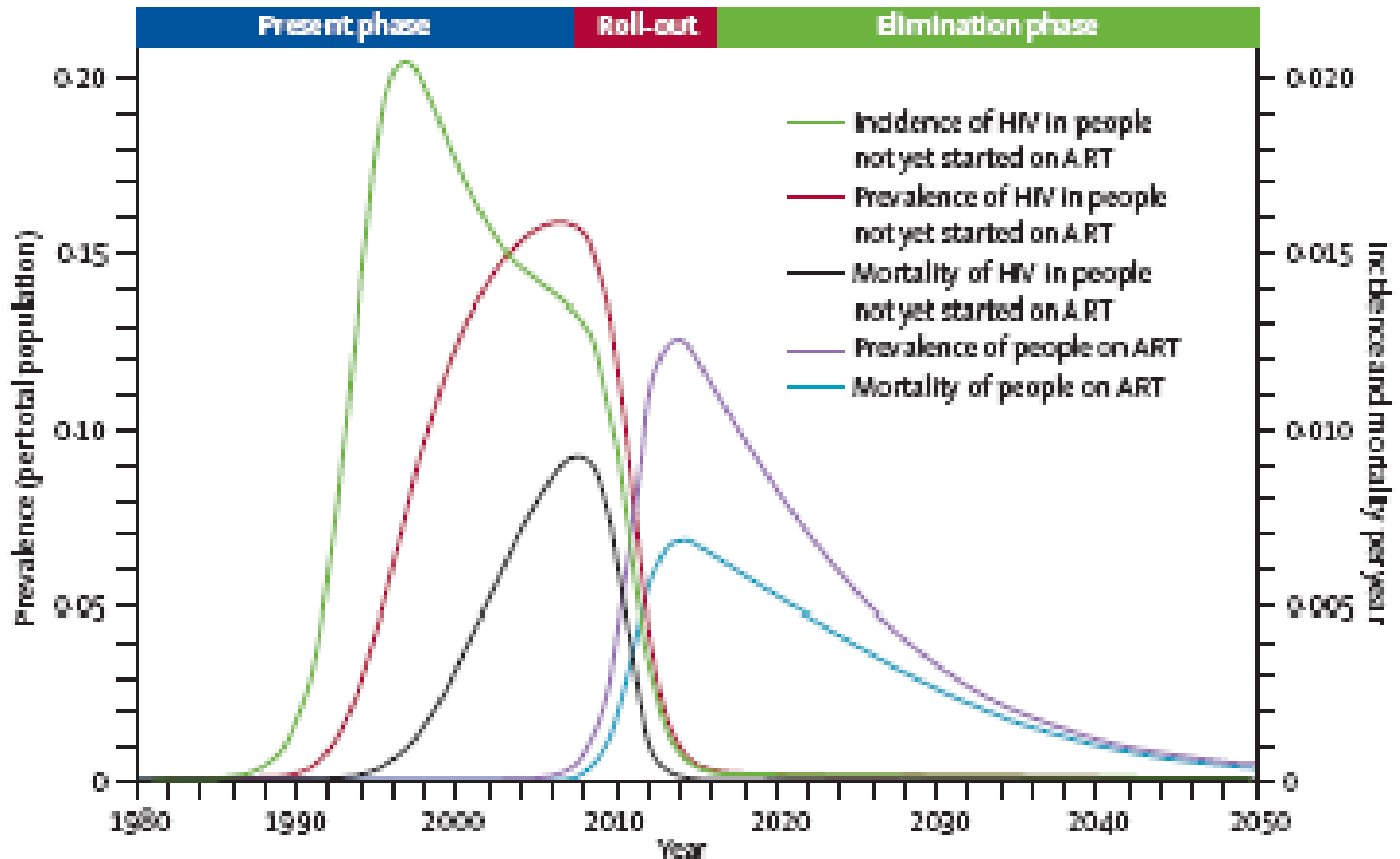
## • Conclusion

- Provision of ART could be an effective strategy to achieve population level reduction in HIV-1 transmission
- Caution with observational cohort

# Test & Treat Model

Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

Reuben M Granich, Charles F Gilks, Christopher Dye, Kevin M De Cock, Brian G Williams



## Slide 15

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**MB6** pull out the figures and make them into a slide just by themselves  
- put the text in the notes and make the slide the graph

(done)

New Admin, 11/16/2010

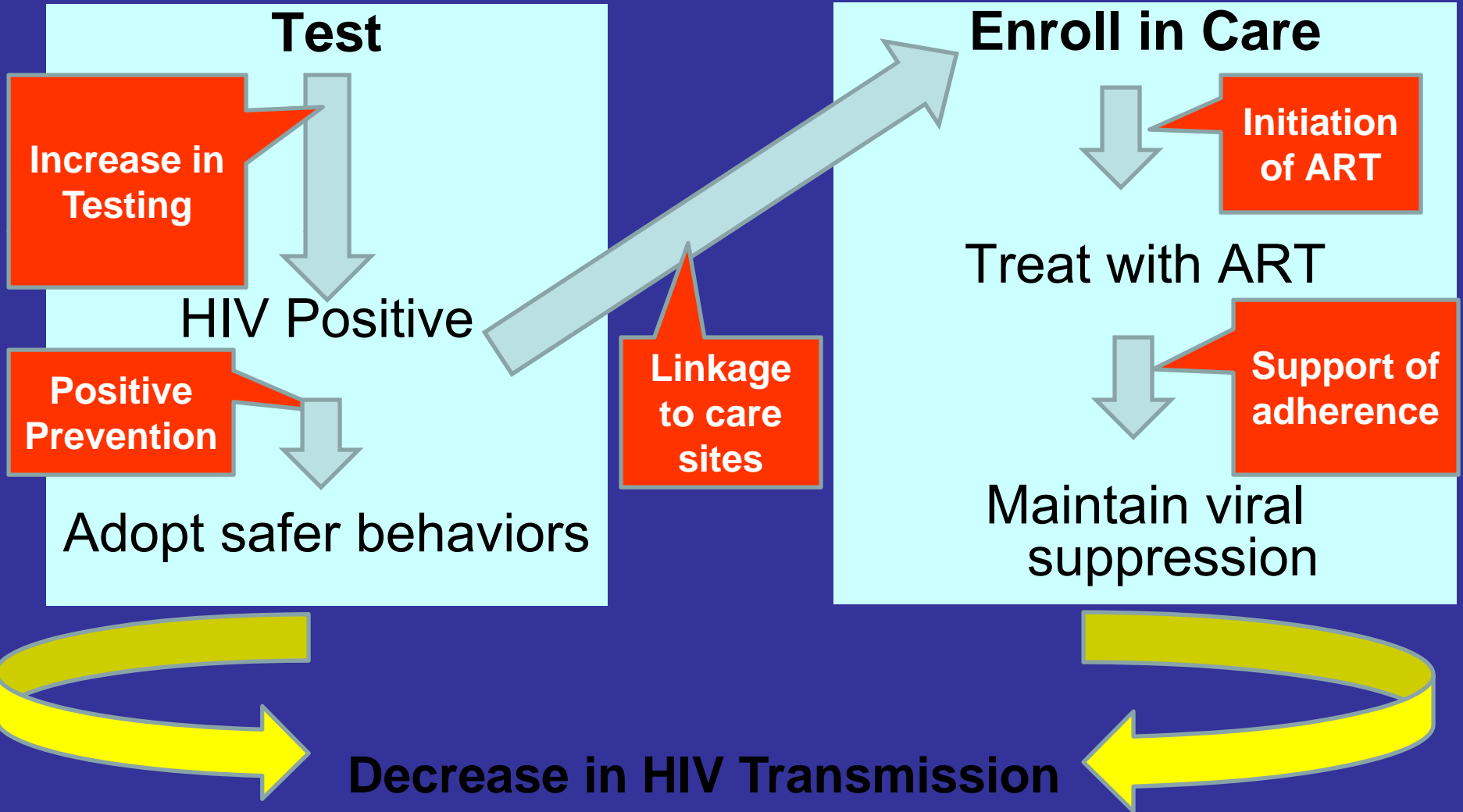
# Test & Treat (HPTN 065 TLC-Plus)

- **Overview:**

- Evaluate the feasibility of an enhanced community-level HIV test, link-to-care, plus treat strategy in US
- **Intervention Communities:** DC and Bronx, NY
- **Comparison Communities:** Houston, TX, Philadelphia, PA, Chicago, IL, and Miami, FL
- **Outcomes:**
  1. Proportion of newly identified HIV+ patients from HIV test sites who complete two clinical visits at HIV care sites
  2. Proportion of patients at HIV care site achieving and maintaining viral suppression

***\*\*TLC-Plus is not designed to measure a change in HIV incidence***

# Test & Treat (HPTN 065 TLC-Plus) Study Concept



# Microbicide Research

# What is a microbicide?

- A microbicide is any substance that can substantially reduce transmission of sexually transmitted infections (STIs), including HIV, when topically applied in the vagina or the rectum
- All microbicides are investigational at this time



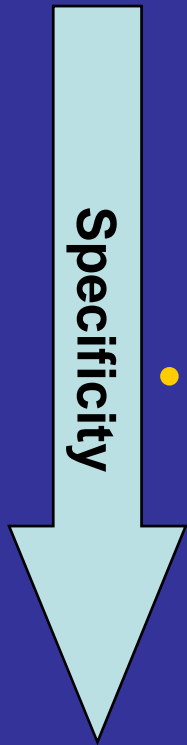
# Microbicides

- **Initial Strategies:**

- *Physical disruption of virus:* surfactants
- *Boost normal microflora:* acidifying agents
- *Prevent viral entry:* sulfated polyanions

- **Recent Strategies:**

- *Prevent replication cycle:* antiretroviral agents (NRTIs, NNRTIs)
- *Prevent viral entry:* entry inhibitors (CCR5 inhibitors)



# Product Development: Clinical Trial Stages

-Pre-clinical: in vitro and animal model

-Clinical:

– Phase 1

- Preliminary safety

– Phase 2

- Extended safety +/- preliminary efficacy

– Phase 3

- Efficacy

Clinical Trial Efficacy  $\neq$  Real Life Effectiveness

# Phase I microbicide studies

- Small numbers of participants (10-50)
- Highly selective
- Short duration –14 days
- Local toxicity endpoints
  - pelvic exam
  - colposcopy + digital imaging
  - cervical / vaginal biopsy
- Acceptability endpoints



# Phase II and III studies

## Phase II

- more participants (50-200)
- product used for a longer time period
- Extended use safety and acceptability endpoints
- Phase IIb: powered for preliminary efficacy endpoints

## • Phase III

- a large number (500-5,000)
- HIV seroincidence as primary endpoint

# Placebos used in microbicide trials

- **K-Y Jelly**
  - Available since 1917. Initials are a mystery.
  - Water-based gel with HEC, glycerin, chlorhexidine, etc.
- **Conceptrol**
  - Anti HIV effects due to nonoxynol 9 ingredient
- **RePlens**
  - Water-based gel with carbopol 974P (buffering agent)
- **Hydroxyethylcellulose (HEC)**
  - Derived from cellulose, no antiHIV effect, no buffering effect, proposed as the “universal placebo”
- **Methylcellulose (MEC)**
  - Derived from cellulose, used as a thickener and emulsifier in food products, used to treat constipation (Citrucel), used in artificial tears
- **Condom-only comparison**
  - Lack of blinding vs ability to assess placebo effect

# About Adverse Events (AEs)

- High prevalence of vaginal symptoms (81%), even in absence of gel use (Priestley, 1997)
- High prevalence of AEs with placebo gels
  - KY gel 75%
  - Conceptrol (nonoxynol-9) 75% (Mauck, 2001)
- Applicator trauma, speculum trauma
- Intermenstrual bleeding common
- Standardization of genital AE assessments

# MANUAL FOR THE STANDARDIZATION OF COLPOSCOPY FOR THE EVALUATION OF VAGINAL PRODUCTS

## STEPS TO BE CARRIED OUT WHEN PERFORMING COLPOSCOPY

**Prior to the examination:** Everything needed for the procedure should be in place before the study participant is brought into the room. This includes working equipment, spare bulbs, and adequate specula that have been inspected to make sure there are no rough edges that could induce epithelial injury. A Standard Operating Procedure written by each site helps ensure that these steps are taken.

### 1. PARTICIPANT POSITIONING:

The participant should lie on a soft examination table in the lithotomy position with leg supports so that the perineum and vulva can be inspected. At all times, the physical and emotional comfort and privacy of the woman should be ensured.

### 2. NAKED EYE AND COLPOSCOPIC EXAMINATIONS OF EXTERNAL GENITALIA:

Examine the external genitalia with the naked eye and record findings. Then, using appropriate magnification (usually 4-10X), examine the external genitalia again and record findings.

### 3. INSERTION OF SPECULUM:

Use a speculum with sufficiently long blades to permit adequate visualization of the vagina and cervix. If necessary, apply a small amount of the lubricant specified in the protocol to the external surfaces of the blades. Gently insert and open the speculum so as to prevent trauma and position it so that the cervix and upper vagina can be seen clearly.

The position of the cervix relative to the vagina and the least traumatizing type/size of speculum should be recorded on the source document during the first examination for reference at later examinations. This information should be reviewed prior to subsequent examinations to reduce the chance of causing iatrogenic injury.

### 4. NAKED EYE EXAMINATION OF VISIBLE EPITHELIUM:

Naked eye inspection of visible epithelial surfaces should be performed without manipulation. Record findings.

### 5. AUXILIARY VAGINAL TESTS:

If a vaginal specimen, such as a wet preparation, pH test, or vaginal microbiological test is collected, the sample should be obtained after the speculum is placed and initial visual examination is made, but prior to lavage. The sample should be taken from the vaginal pool or lateral vaginal wall (or as directed by the protocol) away from any apparent abnormal areas. The area from which the wet preparation is taken should be excluded from the subsequent examination, or findings should be noted as "probably iatrogenic - wet preparation site."

### 6. LAVAGE:

Using a syringe, gently lavage the cervix and vaginal walls with normal saline to remove mucus and cellular debris. Avoid contact between the tip of the syringe and the epithelium. The lateral fornices may be lavaged without manipulation by directing the stream into them.

Aspirate the fluid with the tip of the syringe against the inner surface of the posterior blade of the speculum. Do not permit contact between the syringe and the epithelium. Dry swabs may be used to remove obscuring fluid from the posterior blade that cannot be removed by aspiration. (Do not use dry swabs in any other manner during the colposcopic exam.)

If the product obscures findings, it should be lavaged away as gently and completely as possible using a medium specified in the protocol. All unobscured epithelial surfaces should be examined. If lavage alone does not adequately remove the study product, a saline-soaked swab may be used. Record any observations not noted on previous naked eye examination.

Some protocols may require collection of lavage fluid for measurement of inflammatory markers. If this is felt to be of higher priority than collection of vaginal specimens, it may be collected first; this should be specified in the protocol.

### 7. COLPOSCOPIC EXAMINATION OF CERVIX:

Inspect the cervix under appropriate magnification (usually 4-10X) and record findings.

### 8. AUXILIARY CERVICAL TESTS:

Cervical specimens are generally collected after colposcopic examination of the cervix since their collection is likely to induce minor trauma which may be erroneously attributed to product use.

### 9. COLPOSCOPIC EXAMINATION OF FORNICES:

Under appropriate magnification (usually 4-10X), examine the anterior, right lateral, left lateral, and posterior fornices and adjacent cervical trunk and record findings. Additional irrigation and/or slight manipulation of the speculum may be necessary to clearly visualize the fornices. The lateral fornices are best exposed by placing a saline-moistened swab in the contralateral fornix and pressing toward the head and laterally. For example, to view the right lateral fornix, place a saline-soaked swab in the left lateral fornix and press gently toward the woman's head and left side. Record findings.

### 10. COLPOSCOPIC EXAMINATION OF VAGINA:

To examine the rest of the vagina, move the colposcope to bring the lateral vaginal walls into focus. Slowly withdraw the speculum, relaxing the blades as necessary for the comfort of the woman and refocusing as needed, to view the anterior and posterior vaginal walls. Record findings.

## TABLE 1. TERMINOLOGY FOR COLPOSCOPIC FINDINGS

The results of the colposcopic examination should be documented using the terms in Table 1 and by recording the status of the epithelium and blood vessels for each numbered finding.

Term	Status of epithelium*	Status of blood vessels	Comments
Erythema	Intact	Intact	Distinguished by color (erythema being redder than normal, edema either normal or paler than normal, and grossly white findings being white). Grossly white findings are sharply demarcated whereas edema and erythema may be sharp or diffuse.
Edema	Intact	Intact	
Grossly white finding	Intact	Intact	
Petechiae	Intact	Disrupted	< 3mm > 3mm Color of finding is red or purple.
Echymosis	Intact	Disrupted	
Peeling	Disrupted, superficial	Intact	Fragment of disrupted epithelium may remain attached to the area from which it has peeled off. Generally has well demarcated outline. Underlying epithelium looks normal.
Ulcer	Disrupted, superficial or deep	Intact or disrupted	May include sloughing at base. Generally round or oval with sharply demarcated outline. Superficial ulcers are more accurately called erosions.
Abrasion	Disrupted, superficial or deep	Intact or disrupted	Distinguished from other findings in this class by diffuse or poorly demarcated outline.
Laceration	Disrupted, superficial or deep	Intact or disrupted	Sharply demarcated linear finding includes fissures. Lacerations appear to be the result of trauma. Fissures appear to be linear "pulling apart" or wearing away of tissue.

\*Superficial epithelial disruption does not penetrate into the subepithelial tissue. Deep epithelial disruption penetrates into and exposes the subepithelial tissue and possibly blood vessels. If bleeding from the finding is present, the disruption should be recorded as deep.



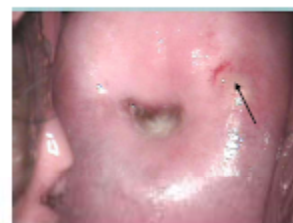
Normal



Erythema



Petechiae



Echymosis



Abrasion



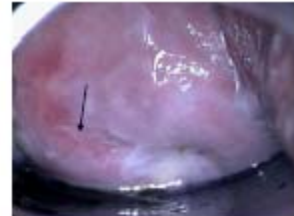
Laceration



Edema



Grossly White Finding



Peeling



Ulcer



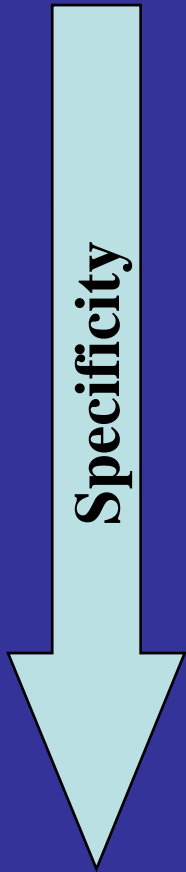
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Speculum Trauma

# Initial Microbicide Strategies

- Physical disruption: Surfactants
  - N-9, C31G (Savvy), sodium lauryl sulfate
- Boost normal microflora: Acidifying Agents
  - BufferGel, Acidform, exogenous lactobacilli
- Prevent viral entry: Polyanions
  - PRO2000, Carraguard, cellulose sulfate,
  - VivaGel, cellulose acetate phthalate



# Initial Microbicide Strategies

- Physical disruption: Surfactants
  - ~~N-9~~, ~~C31G~~ (Savvy), sodium lauryl sulfate
- Boost normal microflora: Acidifying Agents
  - ~~BufferGel~~, Acidform, exogenous lactobacilli
- Prevent viral entry: Polyanions
  - ~~PRO2000~~, ~~Carraguard~~, ~~cellulose sulfate~~,
  - ~~VivaGel~~, cellulose acetate phthalate



Specificity

# Recent Microbicide Strategies

- Prevent replication cycle: Antiretroviral agents
  - NtRTI: Tenofovir
  - NNRTIs: TMC-120, UC-781
- Prevent viral entry: Entry inhibitors (CCR5 inhibitors)
  - PSC-RANTES
  - CMPD 167, BMS-378806, C52-L
- Fusion Inhibitors – Cyanovirin-N
  - From Cyanobacterium
  - Binds high Mannose residues in HIV envelope
- Unknown Mechanism
  - Praneem – Spermicide from Neem tree, advancing to Phase III trials.

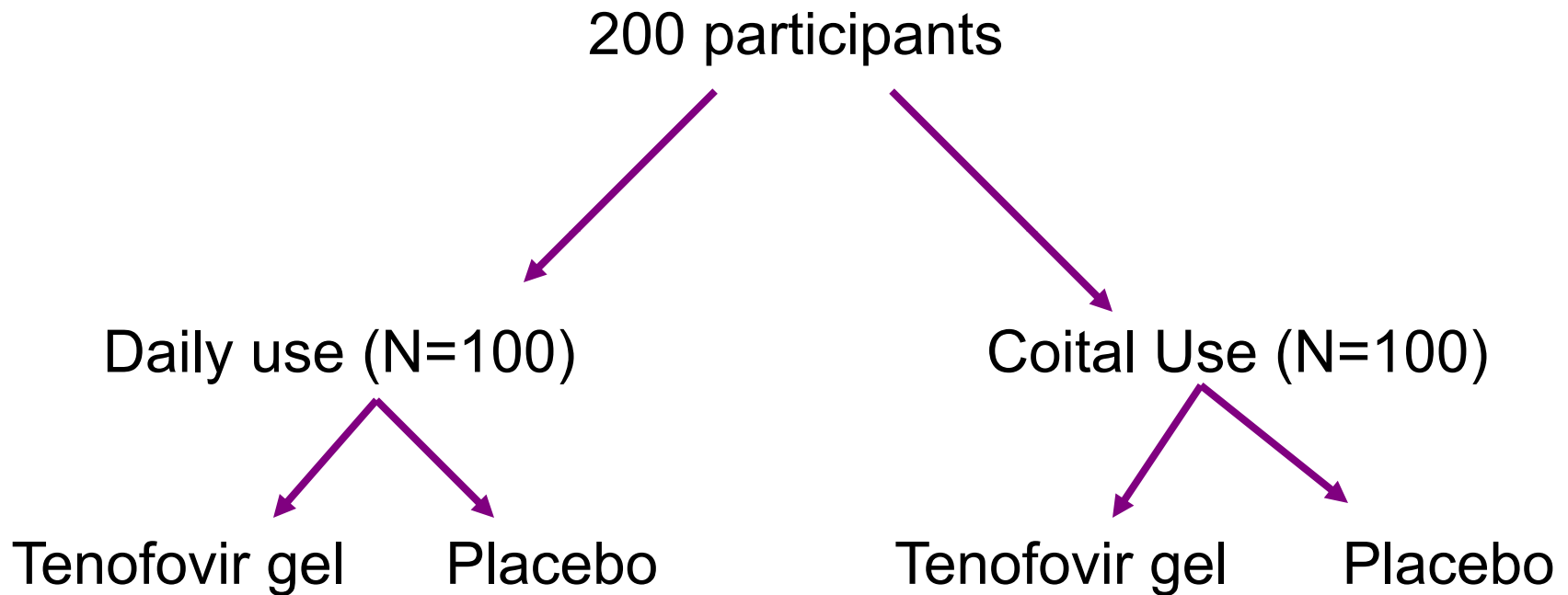
# HPTN 050: Vaginal Tenofovir Gel

## First Phase I study of ART agent as a microbicide

- Open label, 0.3% or 1%, QD or BID x 14 days
- Sexually abstinent and sexually active HIV- and HIV+ women
- Many mild adverse events
  - At least one AE: 92% ppts; 87% of AEs were mild
  - Most AEs r/t genital tract (70%) or GI tract (32%)
  - No life-threatening AEs or deaths reported
- PK substudy: Half of participants had low serum levels & no clear dose–response relationship
- Safe and well-tolerated

*Mayer, KH, et al. AIDS 2006 20: 543-51*

# HPTN 059: Safety and Acceptability Study of Vaginal Microbicide 1% Tenofovir Gel



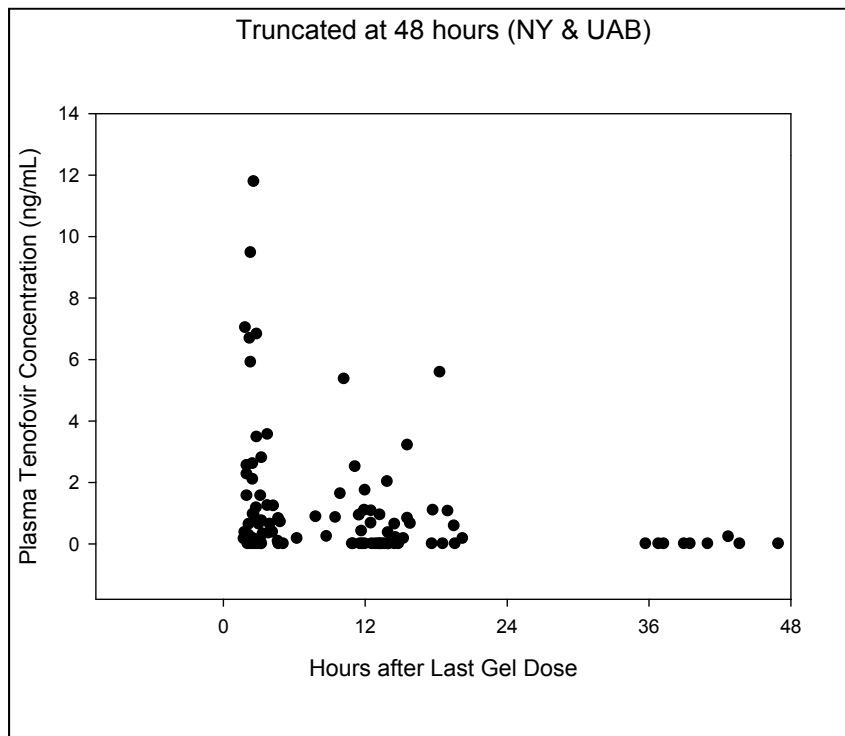
Full safety and acceptability assessments:

Baseline  
1 month  
3 months  
6 months

# Incidence of Genital Symptoms During Follow-up of 198 Women

	Daily Use		Coital Use	
	Tenofovir	Placebo	Tenofovir	Placebo
Itching	33%	35%	18%	27%
Burning	25%	14%	22%	16%
Bleeding	13%	4%	22%	6%
Odor	6%	10%	8%	2%
Pain with sex	4%	8%	2%	2%
No statistically significant differences in genital symptoms, genital infections, and lab safety monitoring				

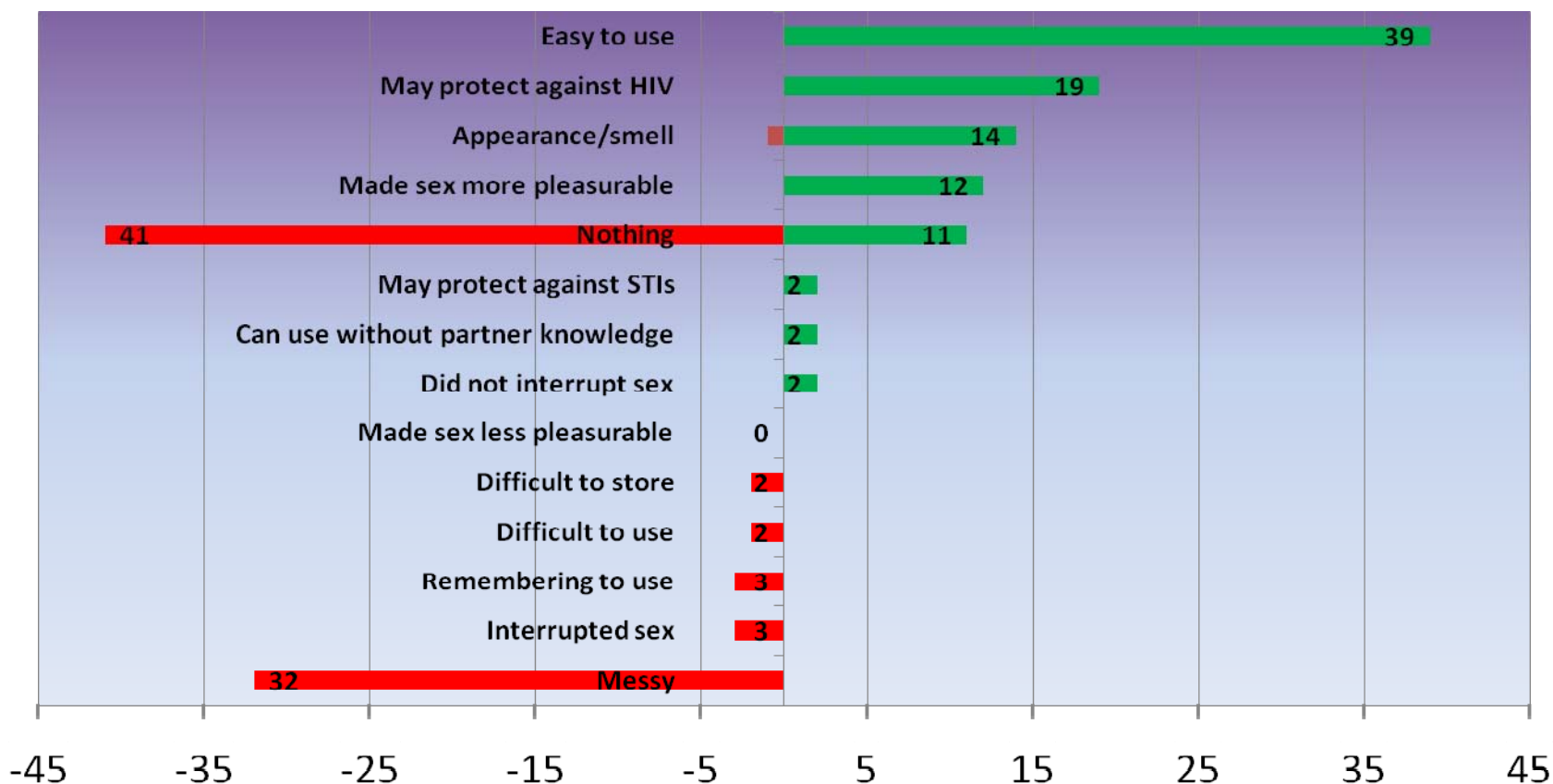
# Plasma tenofovir vs Last Gel Use



Category	Total	n, Detectable	% Detectable
0-24 hours	91	64	70%
0-12 hours	61	48	79%
12-24 hours	30	16	53%
>24 hours	41	5	12%
coital use	69	30	43%
daily use	65	39	60%

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# Gel Acceptability at Study Exit



What Women Didn't Like

What Women Liked

# HPTN-059 Conclusions

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- **Safety:** Daily or coitally dependent 1% tenofovir gel no different from placebo
- **Adherence:** Coitally dependent adherence within 2 hours of sex: 80%; 83% of daily doses reported used
- **Acceptability:** Daily and coital use highly acceptable to women
- **PK:** Timing of dose-response relationship



## MTN 001: Ph 2 Adherence and PK Study of Oral and Vaginal Preparations of Tenofovir

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- Three daily regimens – tenofovir gel, tenofovir tablet and the two taken together
- 21-week study, with each regimen used for six weeks
- Pharmacokinetic studies of plasma, vaginal fluid, vaginal tissue and rectal fluid.
- N = 144 sexually active HIV-negative women enrolled from sites in Uganda, South Africa and the United States
  - 72 women enrolled at the two U.S. sites were involved in more intensive assessments of each approach.

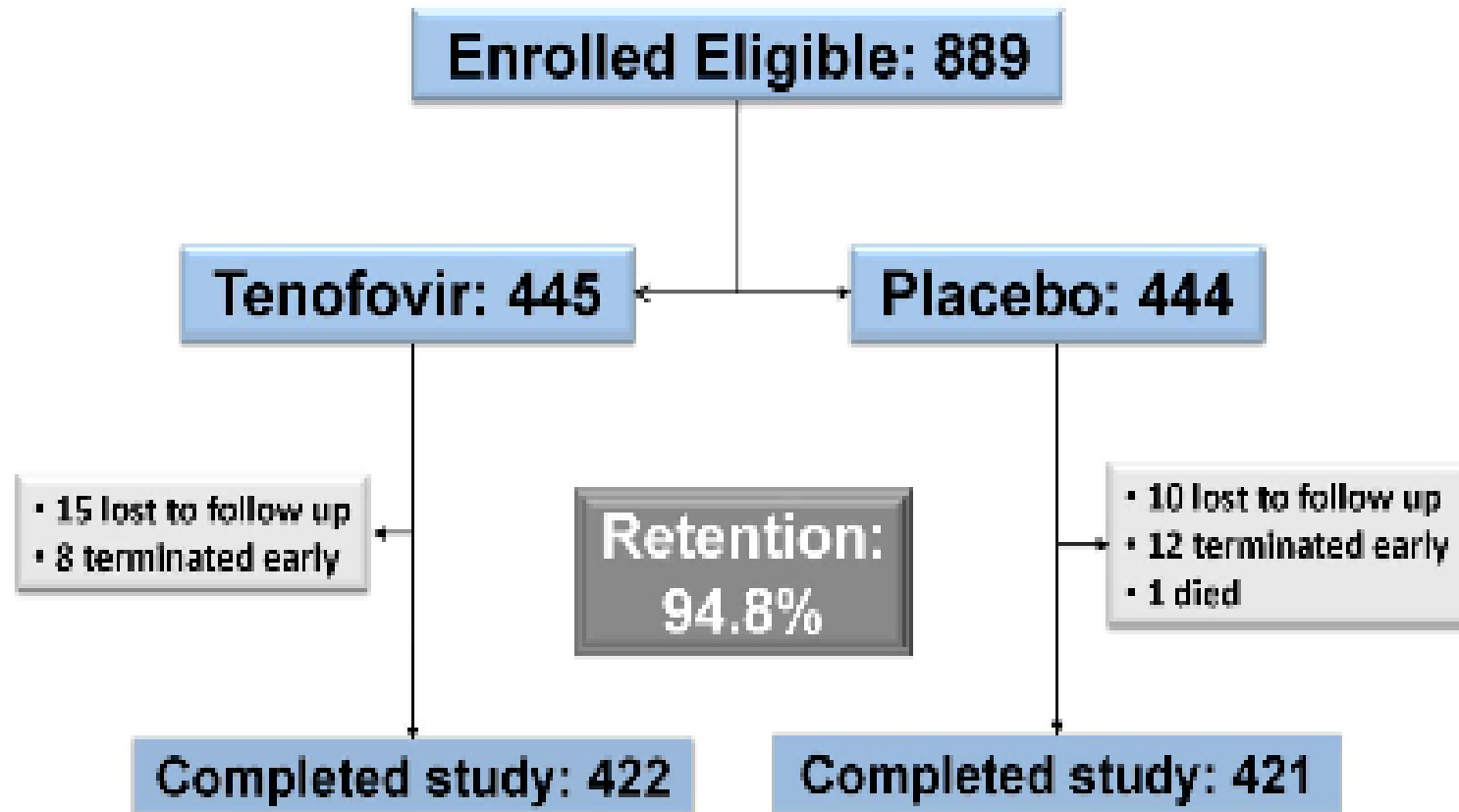
# CAPRISA 004



- **Overview**

- Phase IIb trial evaluating the coital use of 1% tenofovir gel
  - Once within 12 hours before sex and again 12 hours after sex, no more than two doses in a 24 hour period
  - designed for women whose partners are home for short periods of time, modeled after sd NVP
- 889 women, 18-40 y in 2 sites (rural and urban) in South Africa, 2007
- Randomized to tenofovir or placebo (HEC) gel
- 94.8% retention, 30 months F/U
- Monthly assessments for HIV and pregnancy

# Enrollment & Retention



# CAPRISA 004 Results

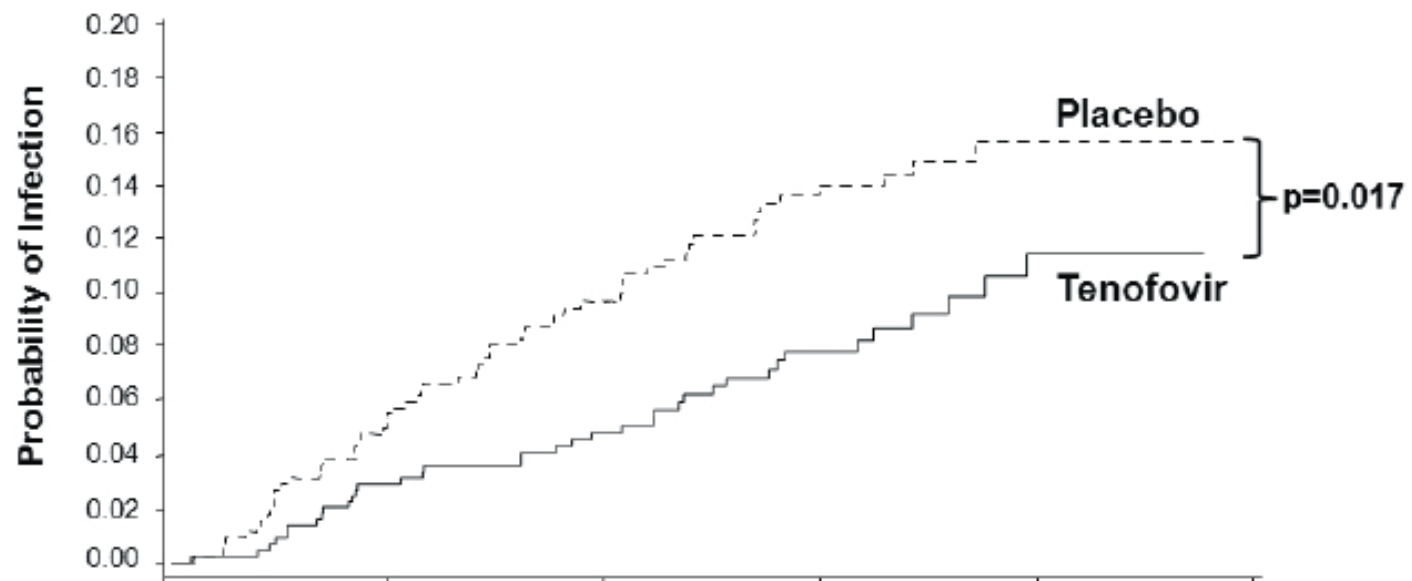
## Effectiveness of tenofovir gel in preventing HIV infection

	Tenofovir	Placebo
<b># HIV infections</b>	<b>38</b>	<b>60</b>
Women-years (# women)	680.6 (445)	660.7 (444)
<b>HIV incidence</b> (per 100 women-years)	<b>5.6</b>	<b>9.1</b>

**Incidence rate ratio: 0.61 (CI: 0.4 to 0.94); p = 0.017**

**39% lower HIV incidence in tenofovir gel group**

# Kaplan-Meier estimates of cumulative probability of HIV infection in the tenofovir and placebo gel arms



Months of follow-up	6	12	18	24	30
Cumulative HIV endpoints	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 10.2	5.6 vs 9.1
<b>Effectiveness (p-value)</b>	<b>47% (0.064)</b>	<b>50% (0.007)</b>	<b>47% (0.004)</b>	<b>40% (0.013)</b>	<b>39% (0.017)</b>

# CAPRISA 004 Results (cont'd)

**Dose-response trend:  
54% vs 28%  
reduction among  
women who  
reported high vs  
low adherence to  
product use**

## Impact of adherence on effectiveness of tenofovir gel

	# HIV	N	HIV incidence		Effect
			TFV	Placebo	
High adherers (>80% gel adherence)	36	336	4.2	9.3	<b>54%</b>
Intermediate adherers (50-80% adherence)	20	181	6.3	10.0	<b>38%</b>
Low adherers (<50% gel adherence)	41	367	6.2	8.6	<b>28%</b>

# CAPRISA 004: More Results

- HSV-2 protection:
  - 434/889 women HSV-2 negative at baseline
  - IRR for HSV-2: 0.49,  $p = 0.003$  or 51% protective
- PK data:
  - Tenofovir levels detectable in plasma of 12% seroconverters vs 50% of those who remained HIV-seronegative
  - Tenofovir levels detectable in CVL of 45% seroconverters vs 96% of those who remained HIV-seronegative

# How safe was tenofovir gel in Caprisa 004?

- No major safety concerns
  - More diarrhea in the tenofovir gel group
- No tenofovir resistance identified
  - Resistance tests checked in seroconverters (n=35) an average of 20 weeks after estimated date of infection
- Safe in Hepatitis B virus infected women
  - Evidence from physical exams and laboratory tests of the liver
- No evidence of increased risk behavior, i.e. “risk compensation”

# VOICE Study: Vaginal and Oral Interventions to Control the Epidemic

- **Overview**

- First study to compare the oral vs topical PrEP for prevention of sexual transmission of HIV

- Phase 2b trial with 5 arms (all once a day)

- 1) tenofovir gel vaginally

- 2) placebo gel vaginally

- versus

- 3) tenofovir pill and a placebo pill

- 4) tenofovir/emtricitabine pill and a placebo pill

- 5) two placebo pills

- 4,200 HIV-negative women

- 18-45 years of age at 10 sites in Uganda, South Africa, Zambia, and Zimbabwe and Malawi

- **Results: TBD in late 2013**

# VOICE & CAPRISA 004

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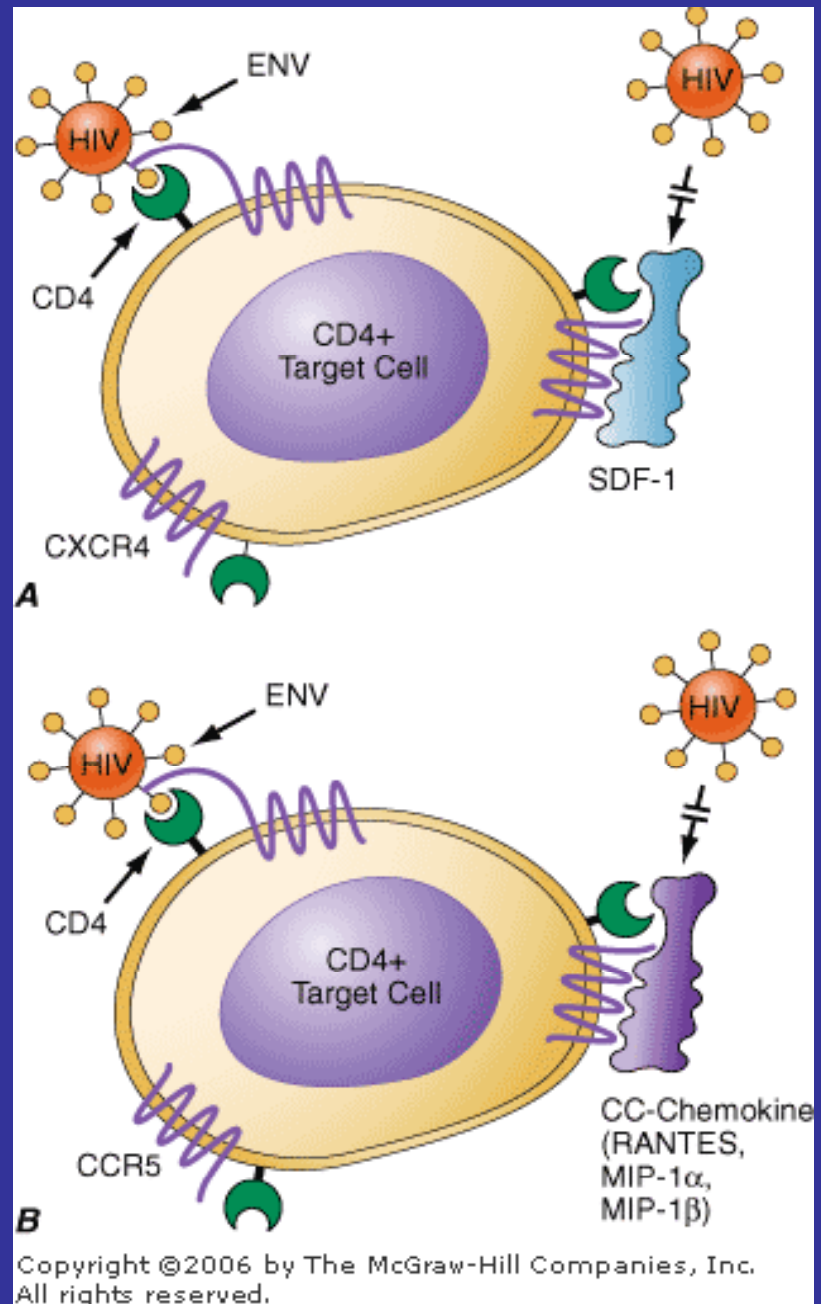
	<b>VOICE</b>	<b>CAPRISA 004</b>
Location	S. Africa, Zimbabwe, Uganda, Malawi	S. Africa (Durban area)
Participants	~5000 women 18 - 40 years	889 women 18 - 40 years
Inclusions	Intercourse last 3 months	Intercourse >2 times, last 30 days
Exclusions	Similar	Similar
Study product dosing strategy	DAILY	BEFORE & AFTER SEX

# Why continue with VOICE Study?

- Single study result of 39% (with estimate between 6 and 60%) not considered enough for licensure of product
  - Could we get a higher level of effectiveness?
- More diverse study population
- Chance to learn about preferences (tablet vs gel)

# Co-Receptors CCR5 & CXCR4

- Receptors for natural chemokines
- Used by HIV along with CD4 for binding, fusion and entry
  - R5 strains use CCR5
  - X4 strains use CXCR4
- Most transmitted HIV strains are R5
- Maraviroc CCR5 inhibitor  
FDA approved for therapy



# Maraviroc (MVC): A New CCR5 Inhibitor

## • Overview

- Rhesus macaques challenged with a high-dose of a CCR5-using virus (SHIV-162P3) with or without MVC vaginal gel, derived from MVC tablets

## • Results

- Dose-dependent protection
- Duration of protection transient
  - Less protection with longer delays between MVC application and virus challenge (T<sub>1/2</sub> ~ 4h)

# Rectal Microbicides

- Receptive anal intercourse (RAI) is a common practice in a significant proportion of the US population
  - In a 1993-2000 study of 813 female college students in a university in California, 32% of women reported that they had ever engaged in anal intercourse (Flannery et al., 2003)
  - In a population-based survey (1997-2000) of 202, 18-24 year old African American and Latino women in a Brooklyn neighborhood, 14% reported unprotected anal sex with men in the last year (Friedman, 2001)
- RAI is estimated to be riskier than other sexual practices
  - Choosing insertive fellatio rather than insertive anal sex decreases the relative risk of HIV-infection 13-fold (Varghese et al., 2002)

# Rectal Microbicide Trials

## Results Pending:

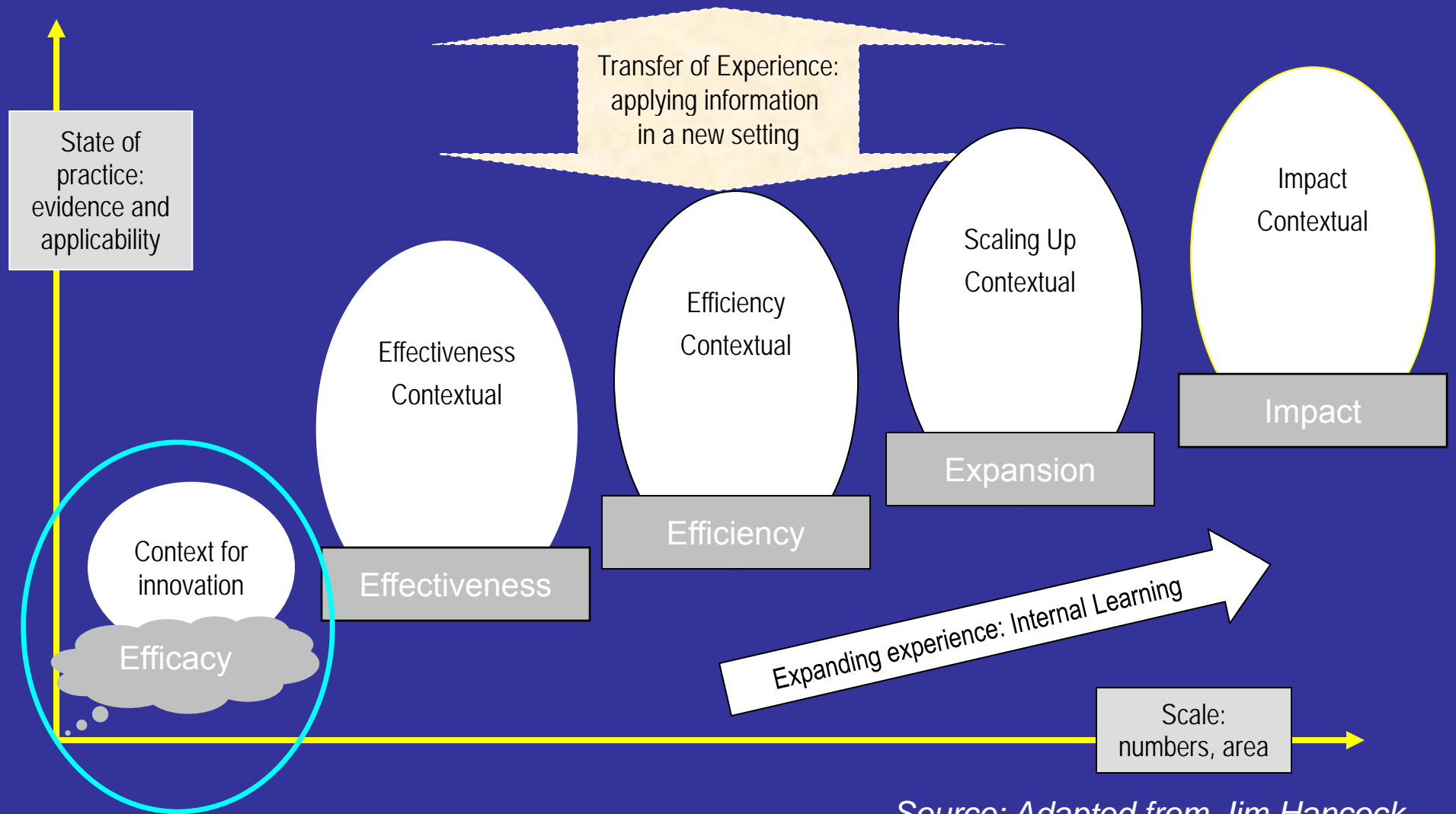
- RMP-02/MTN 006
  - Phase I RCT
  - 18 HIV-negative, abstinent participants randomized to receive:
    - 1) 0.1% tenofovir gel
    - 2) placebo gel
- MTN 007
  - Phase I RCT
  - 60 participants randomized to receive:
    - 1) 0.1% tenofovir gel
    - 2) 0.2% nonoxynol-9 (N-9) gel
    - 3) placebo gel

## Completed:

- **UC781 Gel**
  - Phase I trial (2007-2008)
  - 36 Participants, randomized to receive
    - 1) 0.1% UC781 gel
    - 2) 0.25% UC781 gel
    - 3) placebo gel
  - **Results**
    - 54% (CI .38-.70) favorable rating both immediately after insertion and 49% (CI .33-.65) 30 minutes after insertion

Candidate	Current Status—Phase
Nonoxynol-9	No protection
PRO2000(5%)	No protection
Carraguard	No protection
Cullulose Sulfate	No protection
C31G/Savvy	2 trials stopped for fertility
Truvada Oral	Ongoing Phase III
Viread Oral	Ongoing Phase III
TMC120	Phase III planned
Sodium laurel sulfate (Invisible Condom)	Phase II/III planned
Tenofovir	Protection; Ongoing Phase iib
Dapivirine Gel	Completed Phase I (Safe and well Tolerated)
VivaGel	Completed Phase I (low acceptability)
Acidform/Amphora	Ongoing Phase I
UC781	Ongoing Phase I
Dapivirine Ring	Ongoing Phase I
MIV-150+gel (Gel + Ring)	Phase I planned

# The Scale-up Ramp



Source: Adapted from Jim Hancock

# Impact of HIV Prevention Programs is More Important than Specific Intervention Used



- Regardless of what intervention is recommended, it must get to and be accepted by the target population
  - In 2008, only 45% of known HIV-infected pregnant women in LRC received ART for PMTCT



- Program impact is more related to the effectiveness of the cascade than the efficacy of the intervention

*Source: Mofenson (2009)*

# Acknowledgements

-Wafaa El-Sadr, Ken Mayer, Sharon Hillier and many other colleagues

-Bronx-Lebanon study office

-Allison Goldberg and Montina Befus

-HPTN, MTN, FHI and NIH

-the contributions of the women and their male partners who volunteer for these trials



Proud Woman  
Letwin Mugavezi

# Thank you

For more info on microbicide trials:

[www.mtnstopshiv.org](http://www.mtnstopshiv.org)

[www.avac.org](http://www.avac.org)