PrEP and Microbicides

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WRI 2011, March 17-20, 2011.

What is Choice?

- Choice is rational, and can be in opposition to desire. Choice is not wishing for things one does not believe can be achieved, such as immortality, but rather always concerning realistic aims. Choice is also not simply to do with opinion, because our choices make us the type of person we are, and are not simply true or false. What distinguishes choice is that before a choice is made there is a rational **deliberation** or thinking things through

Aristotle

Contraceptives: Many Choices

HIV Prevention Options which May Not be Viable Choices for Some Women

- Abstinence, be faithful
- Male condoms
- Female condoms
- Male circumcision

The HIV Prevention Research Landscape is Changing Quickly

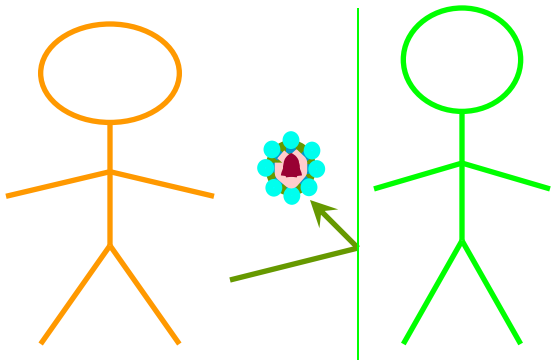
Women will have new choices for HIV prevention

Overview

- What are the key lessons from iPrEX and CAPRISA-004?
- Which other studies of PrEP and microbicide effectiveness are underway?
- What do we know so far about use of topical ARVs as microbicides during pregnancy, and is there a path to support their licensure?
- After the first prevention tools are proven to work in trials, can and will they be implemented?

Pre-Exposure Prophylaxis (PrEP)

In PrEP, an HIV uninfected individual takes antiretroviral medication (oral or topical) ahead of ongoing HIV exposures. By having these medications in the bloodstream/tissues, HIV may be unable to establish infection.



Slide courtesy of Jared Baeten, MD

Oral and Topical PrEP Effectiveness Trials Completed in 2010

Topical PrEP:

- **CAPRISA-004 (USAID, FHI, CONRAD)**

  Abdool Karim et al, Science 329:1168

Oral PrEP

- **iPrEX (UCSF/NIAID/BMGF)**

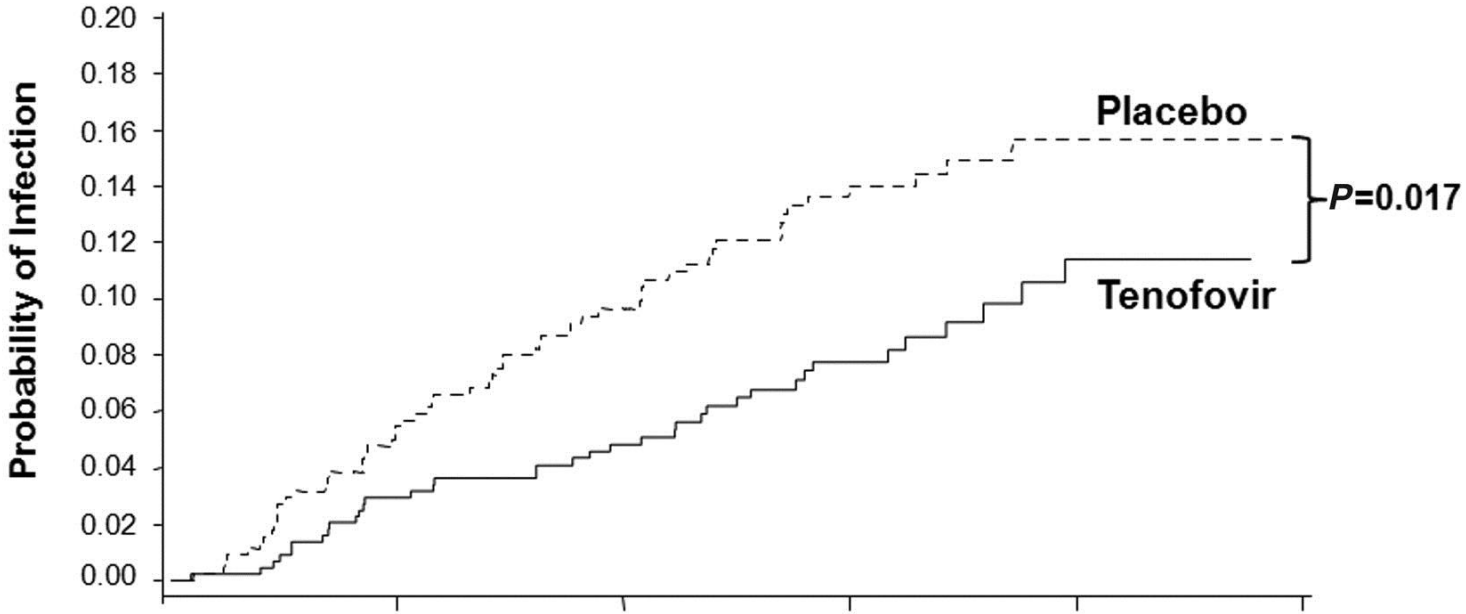
  Grant RM et al. N Engl J Med 2010;363:2587-2599

CAPRISA-004 Study of 1% Tenofovir

- ✓ Proof-of-concept trial (phase 2B trial) in 889 women 18 years and older in Durban, SA
- ✓ Required to use contraception
- ✓ Coitally dependent: gel use within 12 hours before and 12 hours after sex, max. 2 applications within 24 hours
- ✓ Study population primarily young (mean age 23 years), unmarried, sexually active women from rural (69%) or urban (31%) communities

Abdool Karim et al, Science July 20, 2010

HIV Incidence in CAPRISA 004

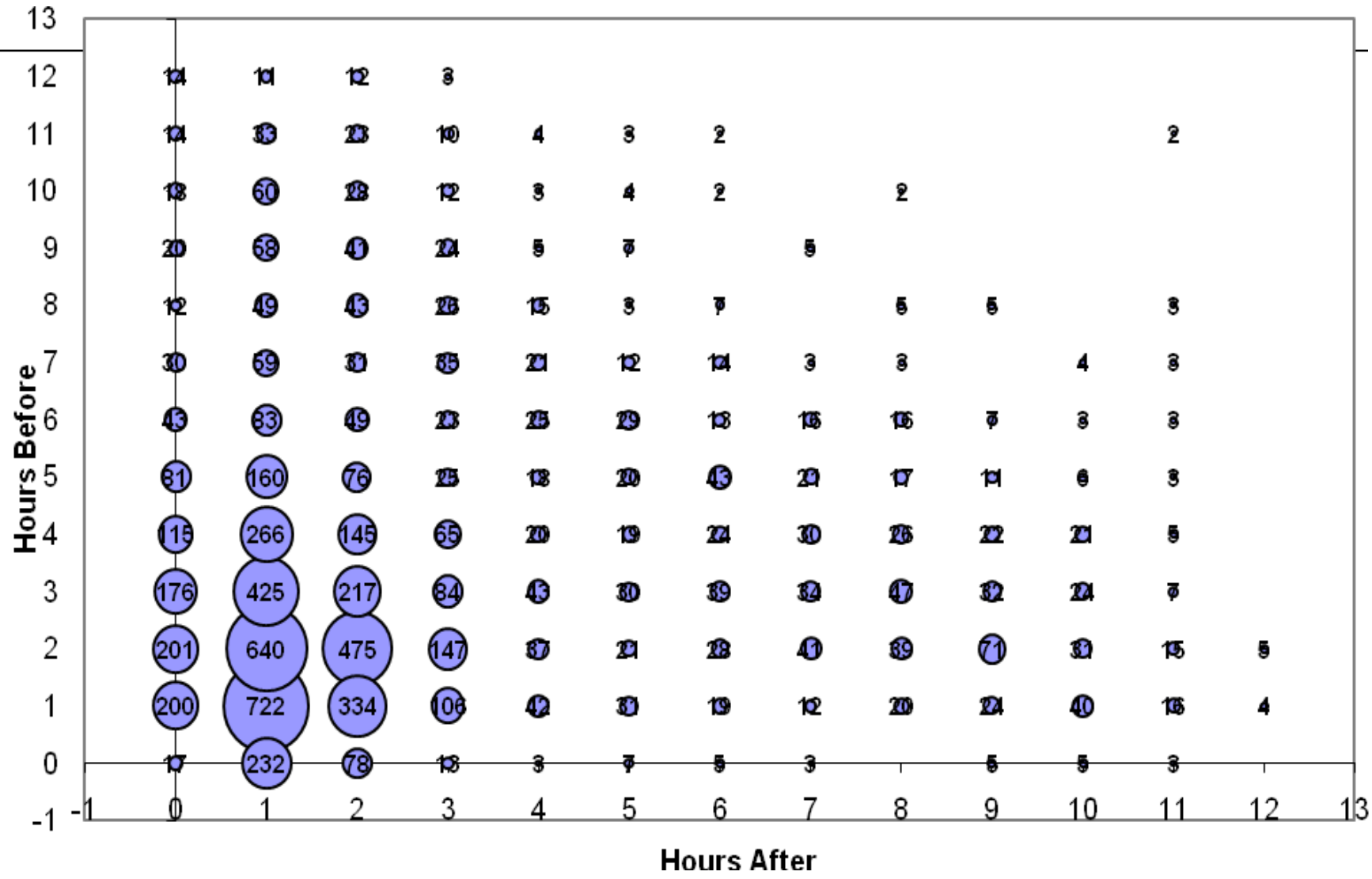


Months of follow-up	6	12	18	24	30
Cumulative HIV endpoints	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 10.2	5.6 vs 9.1
Effectiveness (*P*-value)	**47% (0.064)**	**50% (0.007)**	**47% (0.004)**	**40%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

No K65R resistance mutations among seroconverters – by standard sequencing

Q Abdool Karim et al.
Science 2010;329:1168-1174

Self-reported Timing of Tenofovir Gel Use



CAPRISA 004 Incidence by Adherence

- High (>80% gel adherence), n=336:
  Tenofovir gel: 4.2%
  Placebo gel: 9.3 % P=0.025, **54% effective**
- Intermediate (50-80% adherence), n=181
  Tenofovir gel: 6.3%
  Placebo gel: 10.0% P=.343, **38% effective**
- Low (<50% gel adherence), n=367
  Tenofovir gel: 6.2%
  Placebo gel: 8.6 % P=.303, **28% effective**

Abdool Karim et al, Science July 20, 2010

CAPRISA 004 and HSV-2 incidence

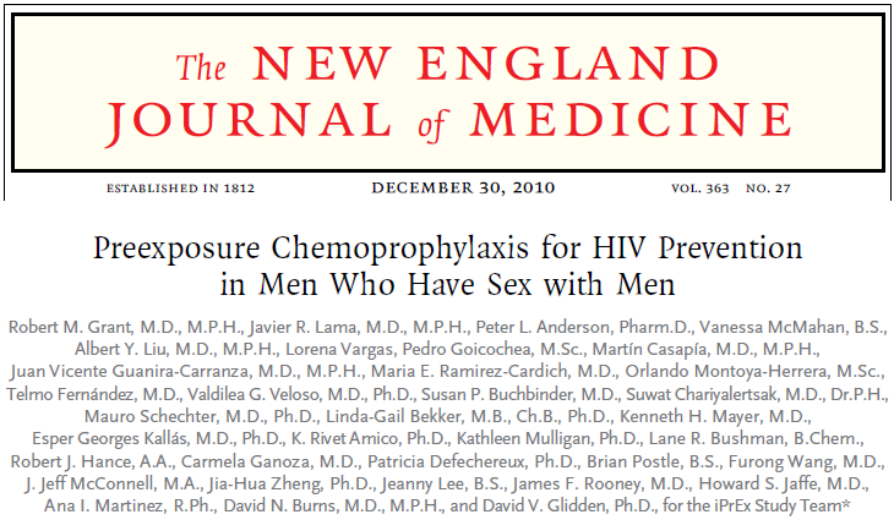
	Tenofovir gel n = 202*	**Placebo gel n = 224***
# HSV-2 infections	**29**	**58**
Women-years of followup	292.3	287.3
HSV-2 incidence per 100 wy (95% CI)	**9.9** (6.6, 14.2)	**20.2** (15.3, 26.1)

51% protection against HSV-2 by 1% TDF gel (95% CI: 22% - 70%)

Abdool Karim et al, IAS 2010

The iPrEX Study

- Agent: Oral daily emtricitabine-tenofovir in MSM



The NEW ENGLAND JOURNAL of MEDICINE

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Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H., Peter L. Anderson, Pharm.D., Vanessa McMahan, B.S., Albert Y. Liu, M.D., M.P.H., Lorena Vargas, Pedro Goicochea, M.Sc., Martín Casapía, M.D., M.P.H., Juan Vicente Guanira-Carranza, M.D., M.P.H., Maria E. Ramirez-Cardich, M.D., Orlando Montoya-Herrera, M.Sc., Telmo Fernández, M.D., Valdilea G. Veloso, M.D., Ph.D., Susan P. Buchbinder, M.D., Suwat Chariyalertsak, M.D., Dr.P.H., Mauro Schechter, M.D., Ph.D., Linda-Gail Bekker, M.B., Ch.B., Ph.D., Kenneth H. Mayer, M.D., Esper Georges Kallás, M.D., Ph.D., K. Rivet Amico, Ph.D., Kathleen Mulligan, Ph.D., Lane R. Bushman, B.Chem., Robert J. Hance, A.A., Carmela Ganoza, M.D., Patricia Defechereux, Ph.D., Brian Postle, B.S., Furong Wang, M.D., J. Jeff McConnell, M.A., Jia-Hua Zheng, Ph.D., Jeanny Lee, B.S., James F. Rooney, M.D., Howard S. Jaffe, M.D., Ana I. Martinez, R.Ph., David N. Burns, M.D., M.P.H., and David V. Glidden, Ph.D., for the iPrEx Study Team*

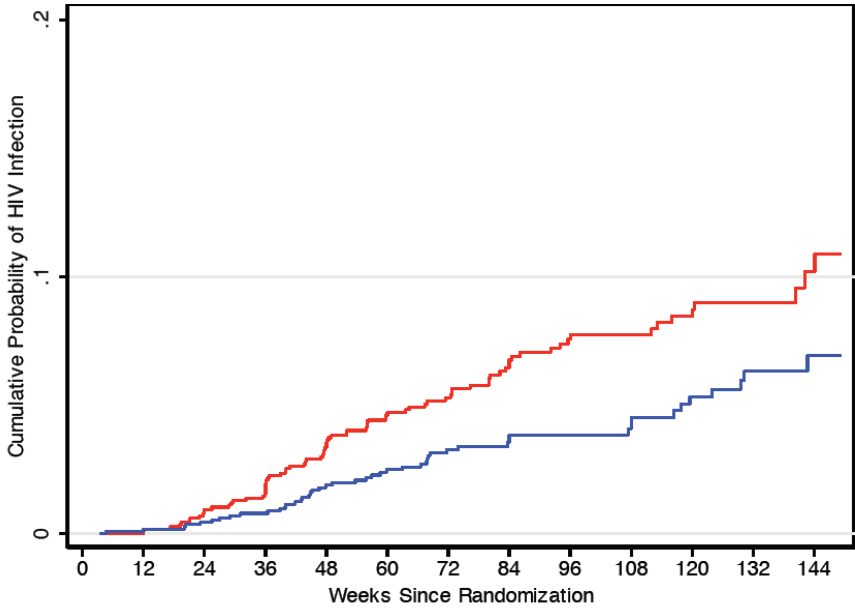
- 2499 high risk MSM, randomized 1:1 daily oral FTC/TDF vs placebo
- 11 sites (Brazil, Ecuador, Peru, South Africa, Thailand, US); 70% from Andean sites
- Young high risk MSM:
  - 50% <25 yrs
  - Median18 partners in 12 wks prior to enrollment
  - 60% with unprotected receptive anal sex in prior 12 wks
  - ↑ nausea 1st month
  - Small decrease in bone mineral density (Mulligan, CROI 2011)

Updated iPrEx Efficacy

131 infections after randomization

48 on FTC/TDF

83 on placebo



Updated efficacy estimate (mITT):
42% reduction in HIV acquisition
(95% CI 18%-60%)

No reduction in HSV-2 acquisition (Lama, CROI 1002)

- TDF-DP drug levels in blood << EC_{50} for HSV

Grant et al, Updated data presented at CROI 2011

iPrEx: Adherence is critical to efficacy

Efficacy by as-treated analysis

(data as of Nov 21, 2011)

High (≥ 90% adherence; 49% of visits)

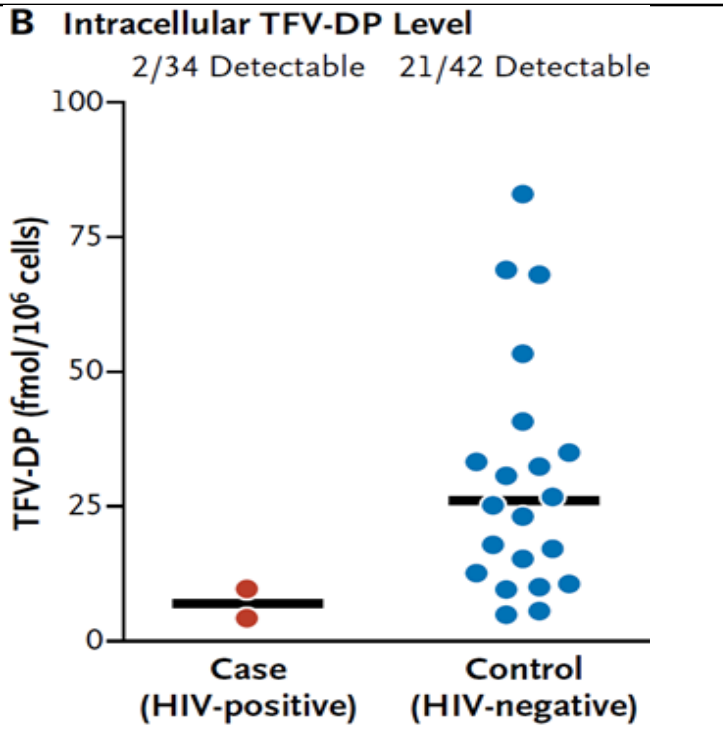
68% efficacy

Intermediate (50-90% adherence; 33% of visits)

34% efficacy

Low (< 50% adherence;18% of visits)

16% efficacy



- 9% of seroconverters had detectable drug at first HIV+ visit - vs 51% of nonseroconverters

Grant et al, NEJM 2010

Key Lessons from CAPRISA-004 and iPrEX

- ARVs (oral Truvada, 1% topical tenofovir gel) are moderately effective at blocking HIV among MSM and heterosexual women
- Efficacy is driven by adherence to drug
- Safety profile good among healthy people
- ARV resistance not observed among seroconverters; need to monitor for acute infection at study entry

Overview

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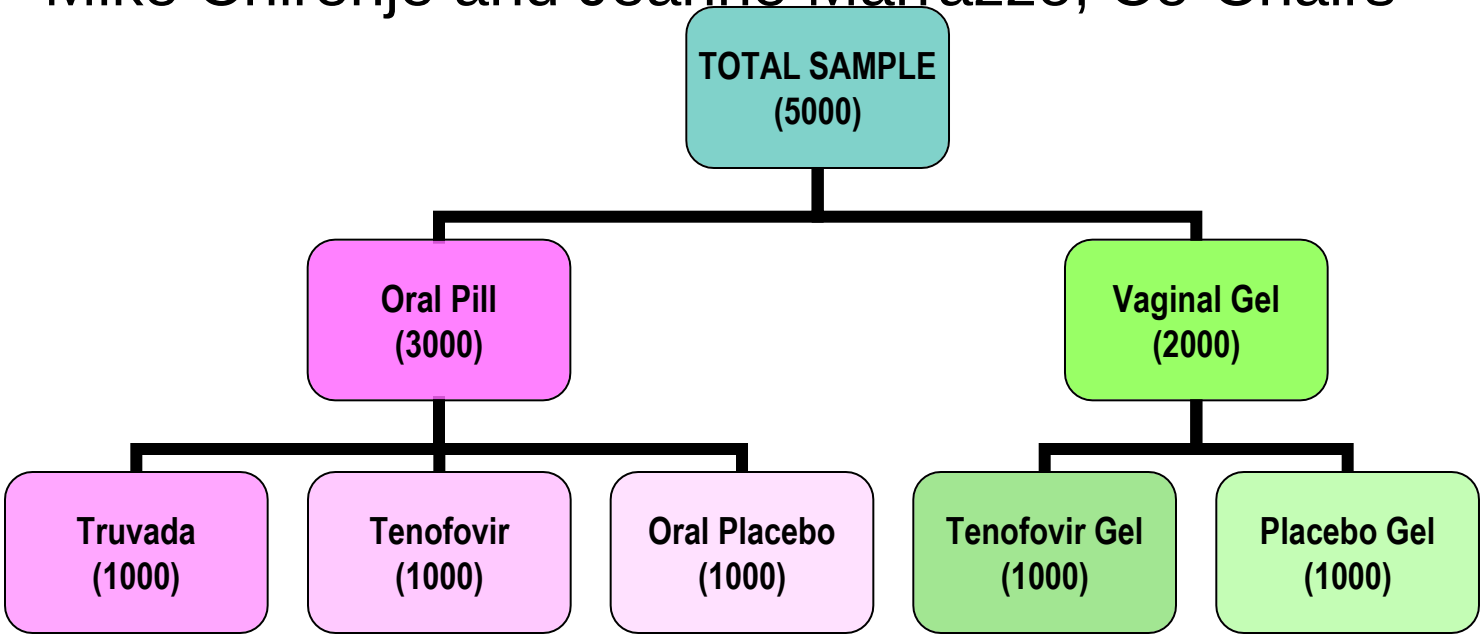
- Which other studies of PrEP and microbicide effectiveness are underway?
- What do we know so far about use of topical ARVs as microbicides during pregnancy, and is there a path to support their licensure?
- After the prevention tools are proven to work in trials, can and will they be implemented?

Ongoing PrEP efficacy studies

Location	Sponsor/ Funder	Population	N	PrEP Agent	Status
Thailand *Bangkok Tenofovir Study*	CDC	IDU	2400	TDF	Fully enrolled Results 2012
Kenya, Uganda *Partners PrEP Study*	UW / BMGF	HIV discordant couples	4758	TDF, FTC/TDF	Fully enrolled Results 2012
Kenya, South Africa , Tanzania, Zimbabwe *FEM-PrEP*	FHI / USAID & BMGF	Women	3900	FTC/TDF	50% enrolled Results 2013
South Africa, Uganda, Zimbabwe *VOICE / MTN 003*	MTN / NIH	Women	5000	TDF, FTC/TDF, Vaginal tenofovir gel (daily)	75% enrolled Results 2012-3

VAGINAL + ORAL INTERVENTIONS
TO CONTROL THE EPIDEMIC

- Safety and effectiveness study of tenofovir gel, and tenofovir and Truvada tablet for prevention of HIV
- Women will use product for average of 24 months
- Mike Chirenje and Jeanne Marrazzo, Co-Chairs



VOICE & CAPRISA 004

	VOICE VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC	**CAPRISA 004**
Location	S. Africa, Zimbabwe, Uganda, Malawi (± Zambia)	Durban, S. Africa
Participants	4,950 women 18 - 40 years 217 endpoints	892 women 18 - 40 years 92 endpoints
Inclusions	Intercourse last 3 months	Intercourse >2 times, last 30 days
Exclusions	Similar	Similar
Study product dosing strategy	DAILY	BEFORE & AFTER SEX

VOICE

VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC

Tenofovir Tablets

Tenofovir Gel

Truvada Tablets

Which is effective?
Is each safe?
Which will women use?

MTN microbicide trials network

What Do We Know About Women's Preferences for Pills or Gels?

- In the contraceptive arena, pills taken daily are dominant, but also least expensive option for US women
- Vaginal rings growing segment in the US, while injectables common in low resource settings

MTN-001Phase 2 Adherence and Pharmacokinetic Study of Oral and Vaginal Preparations of Tenofovir

Craig Hendrix, Alexandra Minnis, Vijayanand Guddera, Sharon Riddler, Robert Salata, Clemensia Nakabiito, Craig Hoesley, Jessica Justman, Lydia Soto-Torres, Katherine Bunge, Karen Patterson, Sharavi Gandham, Kailazarid Gomez, Barbra Richardson, and the MTN-001 Study Group

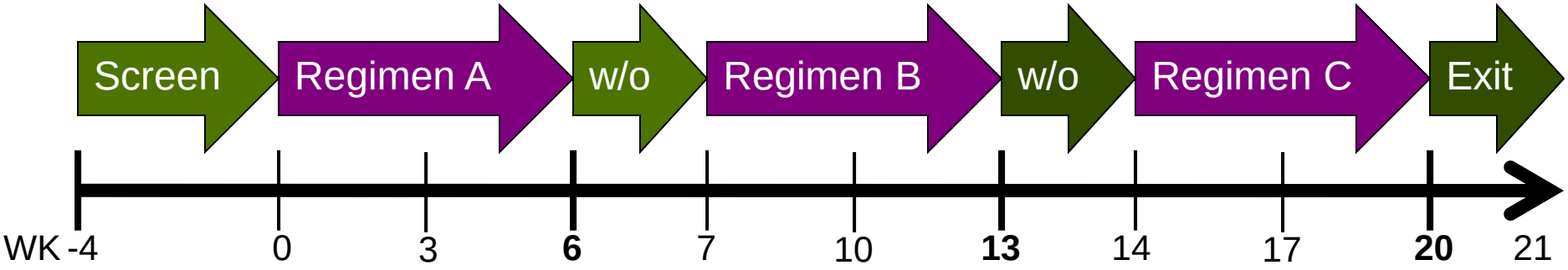
CROI 2011 LB

Questions: Informing RCT Outcomes

- Acceptability
  - Preference for oral tablets or vaginal gel?
- Adherence
  - Vary between oral and vaginal dosing forms?
- Pharmacokinetics
  - Active site concentrations vary with dosing form?
  - Is there an additive effect of dosing oral tablet and vaginal gel together?

MTN-001 Study Design

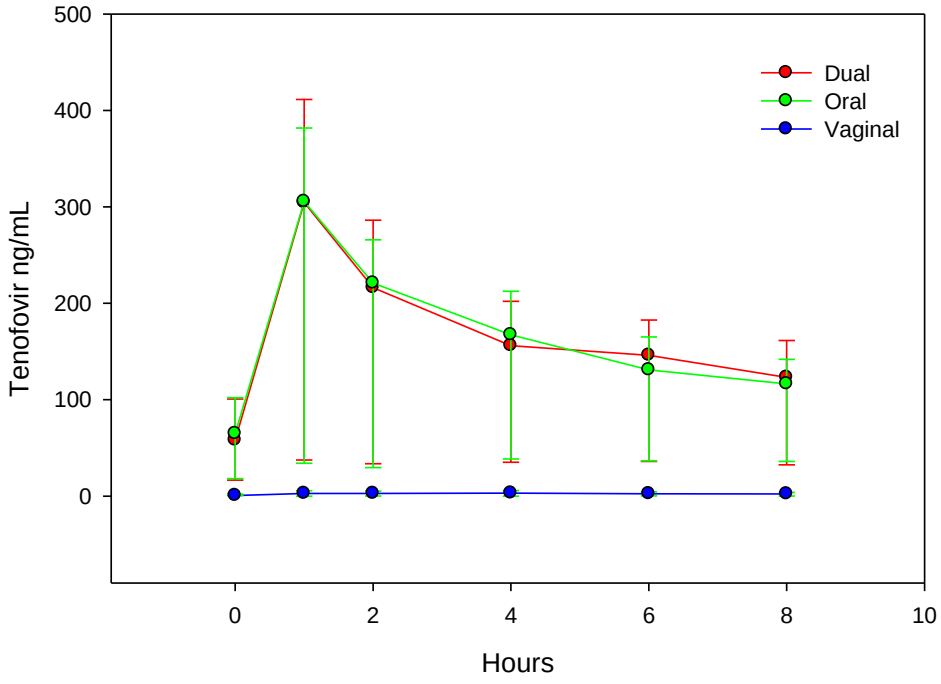
- Three period, open label crossover study
- All receive oral, vaginal, dual – sequence randomized
  - Tenofovir disoproxil fumarate (TDF) 300 mg oral tablet daily
  - Tenofovir 1% (TFV, 40 mg) vaginal gel daily
- 144 sexually active, HIV- women, 18-45 y.o., 7 sites
- 21 weeks (3, 6-week periods; 1 week washout)



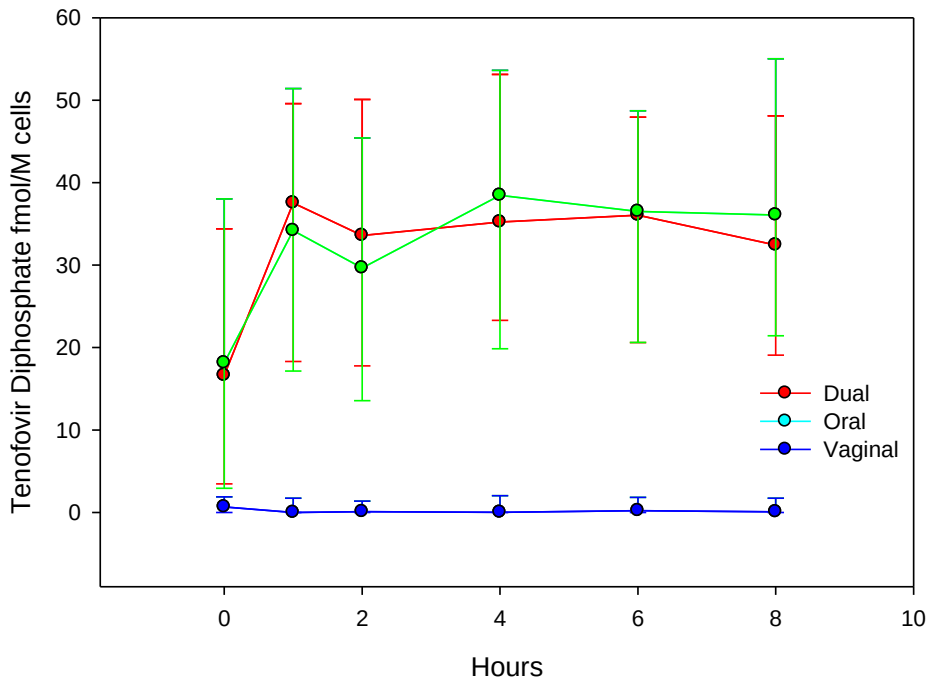
- Safety, adherence, acceptability, PK each visit

Serum TFV & PBMC TFV-DP

Serum TFV (median, IQR)



PBMC TFV-DP (median, IQR)



All other sites sampled lacked temporal trends over 8 hour interval.

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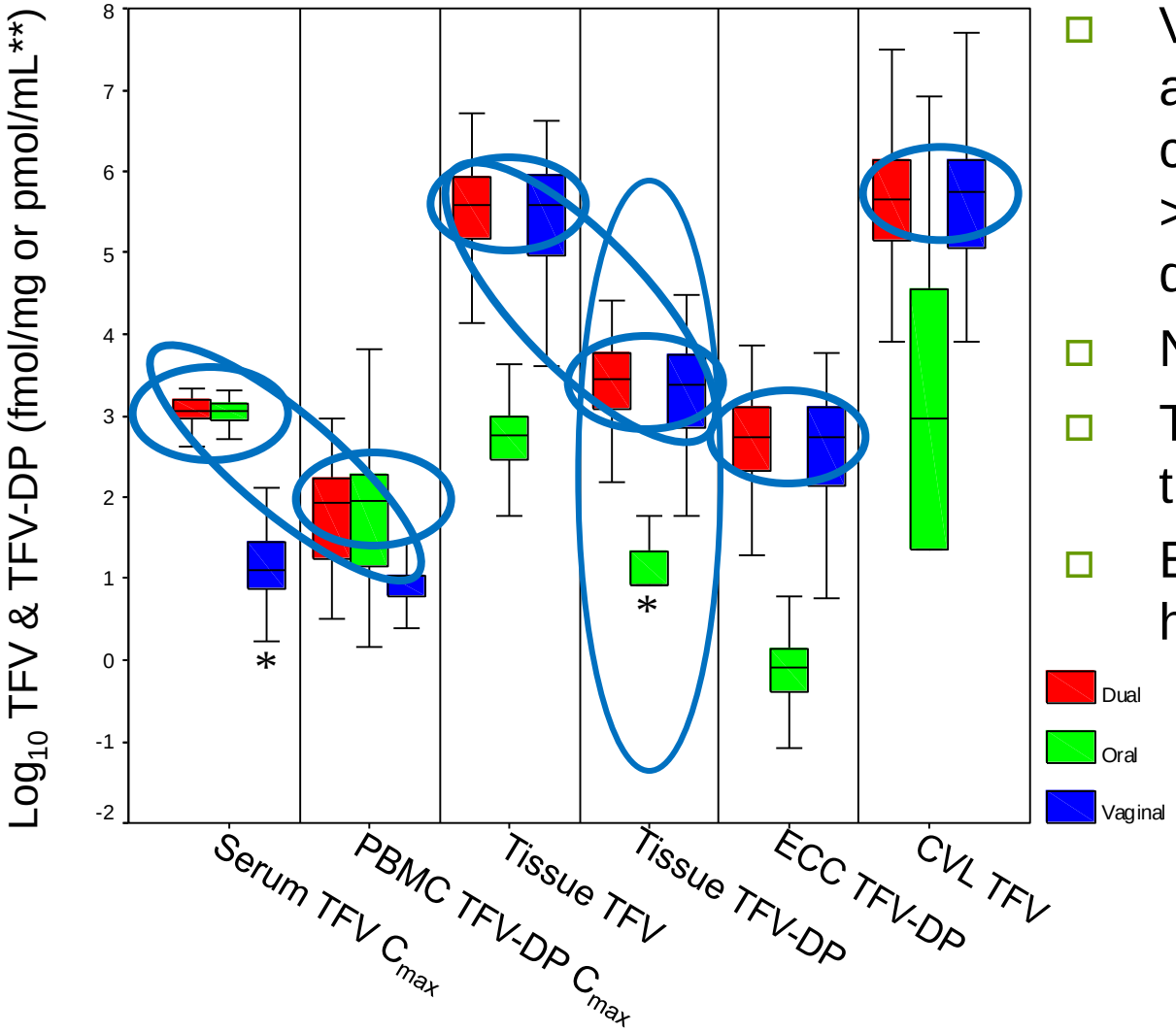
TFV & TFV-DP by Route & Site



- Vaginal dosing achieves active drug (TFV-DP) concentrations in tissue >100x higher than with oral dosing
- No additive effect of Dual
- TFV-DP ~1-10% of TFV in the same compartment
- Effective concentrations have not been established

*Median <LLOQ, assigned BLQ/2 for median; value **Molar equivalent units assumptions: gm = mL, 10^6 cells = 0.2uL

Self-Reported Product Adherence

	Overall	Vaginal Gel	Oral Tablets	Dual
	N=851‡	N=285	N=282	N=284
	%	%	%	%
Adherence Measures				
% daily doses taken (mean, SD)†	94.0 (10.8)	94.4 (12.2)	93.9 (10.1)	93.8 (10.2)
>=90% doses taken	81	85	79	79

†p=0.8 (mixed effect model with Gaussian link and fixed effects for treatment, period, sequence; random effect of participant within sequence).
‡N=visits among 144 participants; maximum of 864 possible visits.

No differences in adherence among regimens or across study sites, but
drug levels suggest about 50% adherence!

Pill vs Gel Acceptability

- Likely future use, if effective:
  - 93% oral tablet; 83% gel (p=0.002)
  - Difference driven by lower, different US rates
- Preferences differed by location

	Overall (%)	Africa (%)	US (%)
Vaginal Gel	28	42	14
Oral Tablets	57	40	72
Both liked equally	10	14	7
Both disliked	5	3	7

- Gel perceived to improve sex by many African women (Qualitative interviews)

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MTN-001 Summary

- Active drug concentrations (TFV-DP) in vaginal tissue >100-times higher with gel, but “enough” for prevention is yet to be defined
- Dual dosing does not increase concentrations
- US women prefer tablet; African women have equal preference & high likelihood of use for both products
- TFV concentrations indicate poor adherence in contrast to self-report, but no difference noted between regimens

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Overview

- What are the key lessons from iPrEX and CAPRISA-004?
- Which other studies of PrEP and microbicide effectiveness are underway?
- What do we know so far about use of topical ARVs as microbicides during pregnancy, and is there a path to support their licensure?
- After the prevention tools are proven to work in trials, can and will they be implemented?

What Do We Need to Allow Microbicide Use During Pregnancy?

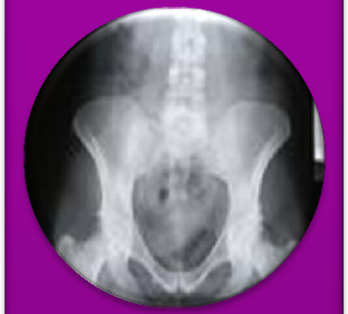
- HIV prevention trials enroll sexually active women
  - Pregnancy natural consequence of sexual activity and highly desired by many women
    - 85% per year – Non-contraceptive users
    - 0.5-15% per year – Typical users of all different methods
    - Pregnancy rate: 16-64/100 woman-years
- Microbicides :
  - Prevent HIV/STI's among sexually-active women
  - Have widespread availability
  - Optimal if could be used for pregnant and breastfeeding women

Darroch. Fam Planning Perspect 1999;31. Trussel Contraception 2004;70.
Ranjit. Fam Planning Perspect 2001;33. Raymond. STD's 2007;34
Lagakos. National Academies Press,2008.

What Do We Need to Allow Microbicide Use During Pregnancy?

- Pharmacokinetic data showing whether vaginal drugs are absorbed differently among pregnant women
- Safety data showing that use of the microbicides does not alter vaginal microflora or inflammatory mediators
- Long term follow up data for women who became pregnant while using products showing whether exposure to products during early pregnancy had any impact on pregnancy outcome and infant outcomes

VOICE - Related Studies



MTN-003B

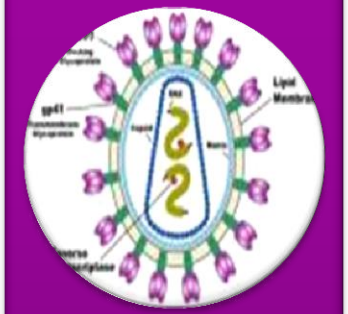
Bone Toxicity

MTN-003C

Community Perceptions

MTN-016

Pregnancy



MTN-009

Resistance

MTN-015

HIV Seroconverter

Drawing data from VOICE sites concurrently with VOICE

MTN-002: First Microbicide Study in Pregnant Women

- Primary:
  - Assess term pregnancy maternal single-dose pharmacokinetics (PK) of Tenofovir (TFV) 1% vaginal gel
- Secondary:
  - Characterize the systemic safety profile of single-dose TFV gel in term gravidas
  - Compare 3rd trimester absorption of TFV gel to absorption in non-pregnant recent historic controls
  - Assess cord blood, amniotic fluid, endometrial tissue and placental tissue levels following single-dose TFV gel

Beigi, et al, Microbicides 2010

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MTN-002 Protocol

- Enrollment
  - Screening visit ≤ 4 weeks before planned Cesarean (C/S) Delivery
    - Healthy term, aged 18-45, singleton pregnancy, no co-morbidites
      - Demographic data, confirm eligibility criteria, undergo informed consent
      - Targeted pelvic: Trichomonas Culture, GC/CT by SDA
      - Blood:
        - Serum creatinine, AST/ALT, Rapid HIV test with counseling
        - *Confirmatory Testing for HIV, *HBsAg, *RPR, *Confirmatory Testing for Syphilis (* When needed)
- Single-dose Tenofovir (TFV) 1% gel (40 mg)
  - Placed vaginally in Pre-operative holding area within 8 hrs prior to C/S

Beigi, et al, Microbicides 2010

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Pregnancy Studies of Tenofovir: Summary

- PK of single-dose TFV gel in term pregnancy shows levels similar to nonpregnant women
- Tenofovir applied topically does get to fetal compartment but at 40X lower levels than with oral dosing (Beigi, et al, Microbicides 2010)
- Multiple dosing of tenofovir gel in the 3rd trimester among HIV negative to begin April 2011 (MTN-008)
- Data on safety of first trimester exposure being accumulated during effectiveness studies (MTN-016)

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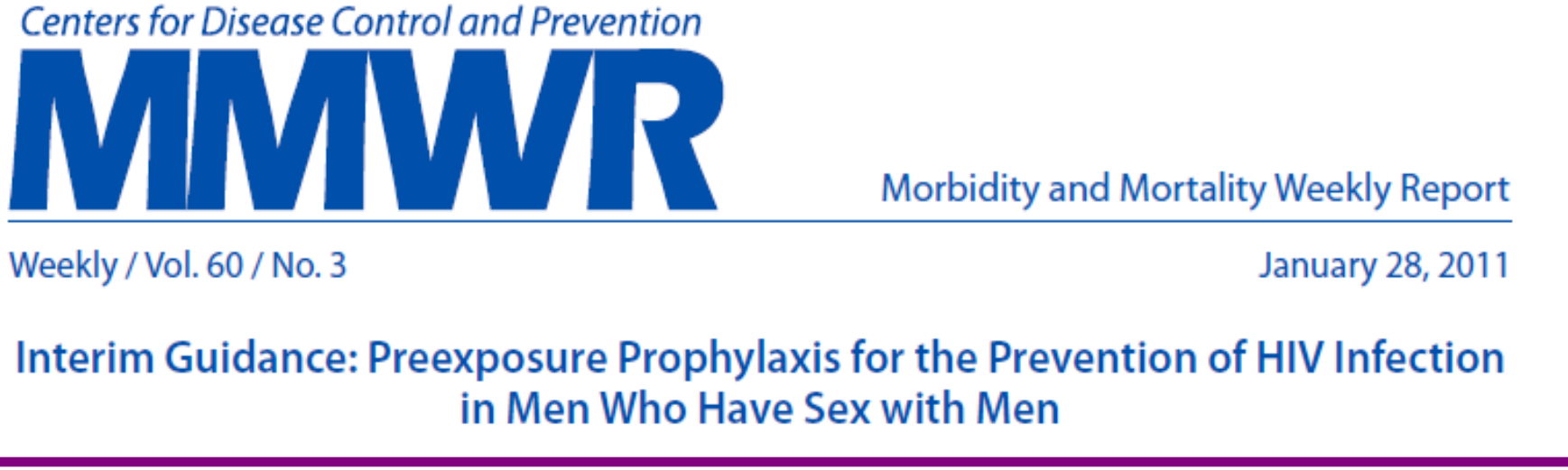
- Which other studies of PrEP and microbicide effectiveness are underway?
- What do we know so far about use of topical ARVs as microbicides during pregnancy, and is there a path to support their licensure?
- After the prevention tools are proven to work in trials, can and will they be implemented?

Who Will Get PrEP or Microbicides?

- How should microbicides and PrEP be provided and to whom? MSMs? Serodiscordant couples? Young women?
- For how long?
- For oral PrEP, how do we balance the need for treatment against use of these agents for prevention?
- What will people prefer- Oral or topicals?
- Implementation studies will be critical to ensure that these questions are answered

CDC Interim Guidelines



Phase 3B: Peri-Approval Trials

- Conditional approval: restricted license
  - Often done at request of regulatory agency
  - Product might be deemed OK to market despite some information missing
  - Conducted just before or during reg. filing
- Better understanding of benefit/risk ratio
- Safety and efficacy in real world settings
- Address outstanding adherence issues once people know they are getting active and not placebo

iPrEx OLE

- Open label extension aimed at providing additional safety data regarding long-term PrEP use among those rolling over from the active arm

- Rationale:
  - Information about PrEP efficacy might decrease perception of HIV risk
  - Risk compensation: increased risk behavior (decreased use of condoms or more sex partners)
  - Information about PrEP safety and efficacy may increase pill use and drug exposure

- The iPrEx Open Label Extension will provide unique opportunities to address questions about how information on PrEP safety and efficacy might affect risk behavior and pill use

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CHOICE (MTN-018)

- Phase 3b open-label study to provide post-trial access to tenofovir gel, Truvada tablet and/or TDF tablet to former VOICE participants

- All women will be allowed to choose whether they prefer an oral or a topical ARV. How often will they switch?
- Participants will be randomized to one of two strategies for follow-up: **monthly** or **quarterly** follow-up.
- MTN-018 will obtain additional safety data on VOICE study products desired by regulators
- Will contribute 500 woman-years of safety data on tenofovir gel towards the FDA requirement for submission of tenofovir gel NDA

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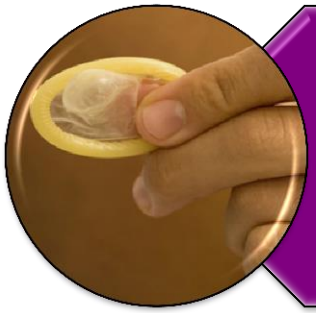
How Will Microbicides or PrEP be Delivered?

Like managing hypertension treatment?

Like getting Depo-Provera?



Like buying condoms?

How Can We Make Prevention Products More Fun to Use?

Is intermittent PrEP feasible?

- Intermittent dosing: periods of risk (e.g., periconception), event-driven, or scheduled fixed dosing
- Do we know enough about PK and PD to predict frequency of fixed, intermittent dosing or optimal timing of dosing pre-exposure?
  - May vary by drug & by compartment (vaginal, rectal, blood)
- How much sex is planned, & could be protected by event-driven PrEP?
- Would adherence be higher with fixed intermittent dosing than daily dosing?

Human studies of intermittent PrEP

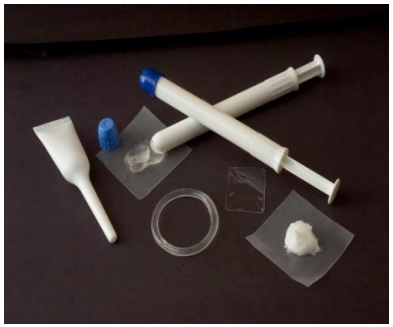
- **IAVI E001/E002**: **Daily, twice weekly & post-coital dosing of FTC/TDF** (Mutua, IAS 2010)
  - Adherence measured by MEMS

Dosing strategy	HIV discordant couples, Uganda (N=72)	High risk women & MSM, Kenya (N=72)
Daily dosing, adjusted rate	96-97%	82-92%
Fixed twice weekly dosing	91%	55%
Post-coital dosing	45%	26%

  - Highest adherence: daily dosing & among discordant couples
  - Post-coital dosing significantly lower than twice weekly dosing

Topical & Systemic Delivery: More Options

Pill



Gel with applicator

Vaginal film

Vaginal ring (sustained delivery)

Injectable (long-acting)

- ✓ Ideal: long acting, safe, effective, low cost and user-friendly
- ✓ Maximize choice & optimize effectiveness
- ✓ Potential for combination ARVs to increase effectiveness
- ✓ Potential to combine ring or injections with contraception

Candidate drugs in PrEP pipeline

Phase III

- **NNRTIs:** Long half-life, resistance concerns
  - Efficacy trials of **dapivirine ring** 2011 (IPM & partners)

Phase II

- **Entry inhibitors:** Block HIV entry; no efficacy for X4 viruses
  - **Oral maraviroc +/- FTC/TDF** (HPTN 069)

Phase I

- **NNRTIs**
  - **Monthly rilpivirine (TMC-278) injectable** (BMGF)
  - **Maraviroc & dapivirine vaginal ring** (IPM, MTN)

Animal Studies

- **Integrase inhibitors:** Act late in life cycle, long half-life, use for PEP?
  - **Topical & oral raltegravir:** Protection in macaque & humanized mice (Dobard CROI 30; Neff PLoS One 2010)

- **Future: separate drugs or classes for HIV prevention**
- **Combinations may have greater efficacy, lower resistance**

Summary and Conclusions

- Current studies have provided proof-of concept that topical and oral PrEP can prevent HIV
- Ongoing studies, if confirmatory, will lead to first FDA approved products for prevention of HIV. Likely 2012-2014.
- Adherence is key; providing more choice could be critical to uptake

- “It is only when you exercise your right to choose that you can also exercise your right to change.”