The Road to MTN-017

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Microbicides

- Microbicides are products that can be applied to the vaginal or rectal mucosa with the intent of preventing or significantly reducing the risk of acquiring STIs including HIV

What Do They Look Like?

- Possibilities:
  - Gel
  - Vaginal ring
  - Film
  - Foam
  - Suppository
  - Enema

Lubricant Use and Anal Intercourse

- In San Francisco MSM
  - 89% reported always using lubricant for AI
- 59% of 6,124 men and women reporting AI reported always using commercial lubricant in large internet survey
  - Non-use:
    - Used saliva
    - Lubricant not available

Carballo-Dieguez AIDS Behav 2007, Javanbakht J Sexual Health 2010

Enemas/Lubricants and HIV Risk

- 1980's epidemiology papers site HIV risks other than RAI as:
  - Enemas/douching before sex
- Increased HIV risk in female sex workers using N9 in an early vaginal microbicide study
- Rectal epithelial loss following N9 lubricant use

Coates RA, Moss AR, Chmiel JS Am J Epidemiology 1987 and 1988, Phillips Contraception 2000/2004, Van Damme Lancet 2002

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Enema/Lubricant Characteristics

Product	Median mOsm/kg
Tap water	3
Semen	340
K-Y plus (2% N9)	2037
Fleet enema	2127
K-Y jelly	2424
ID Glide	3429

Personal lubricant ingredients are categorized by the US FDA as a medical device and GRAS

CFR 172.515

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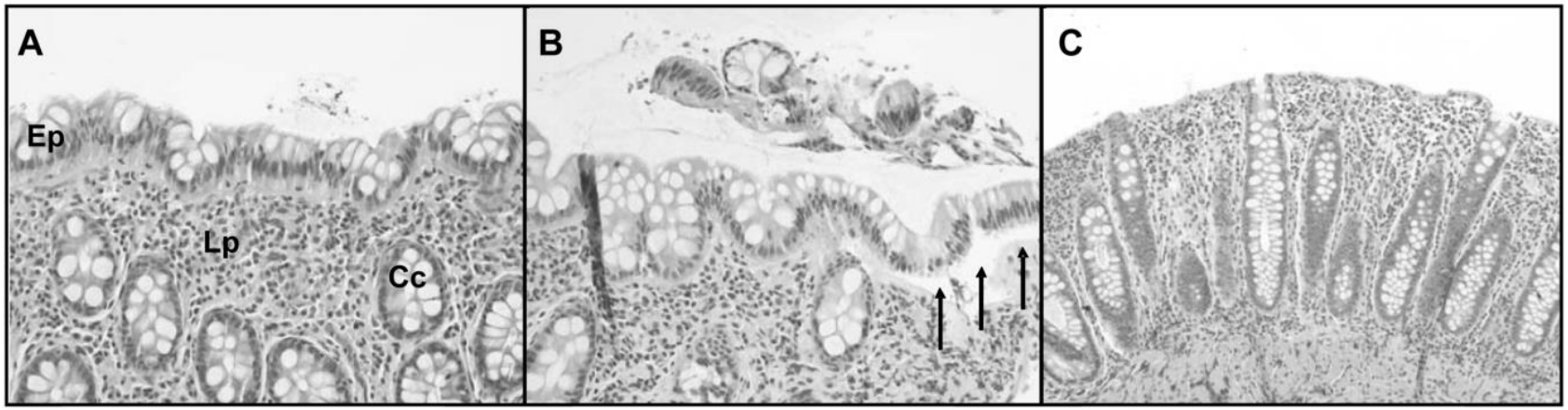
Rectal Exposure to Lubricant



Normal iso-osmolar gel hyperosmolar gel

- Hyperosmolar lubricant is associated with
  - Loss of epithelial integrity
  - Increased luminal secretion
- Increased HIV risk *in vivo*?

Fuchs JID 2007

Non Human Primate Efficacy

Dosing	Infected	Not Infected
Tenofovir	3	6
No tenofovir	7	1

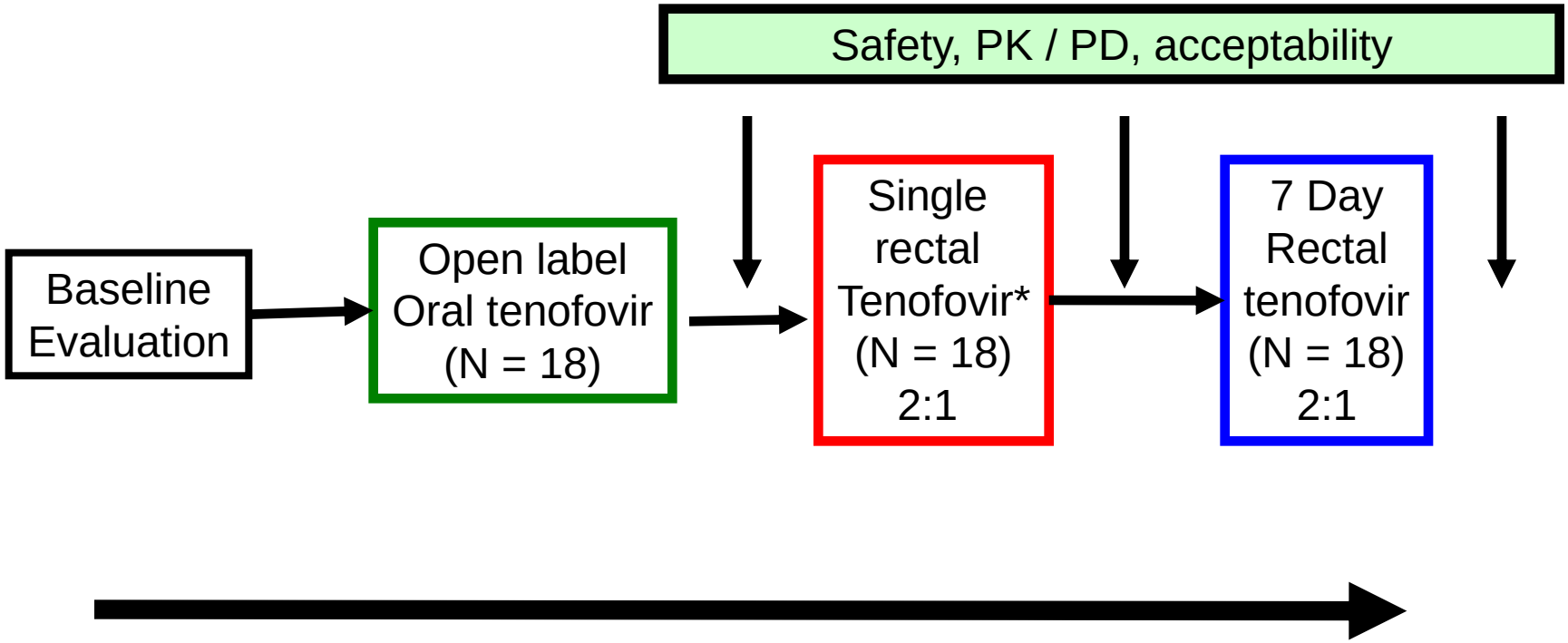
Rectal challenge with SIV with and without previous rectal tenofovir administration (P=0.05)

Cranage M et al., PLOS Med, 2008

Phase 1 Development

- Tenofovir (original formulation) (RMP-02/MTN-006 study)
- Tenofovir (reduced glycerin formulation) MTN-007

RMP-02/MTN-006 Study Design



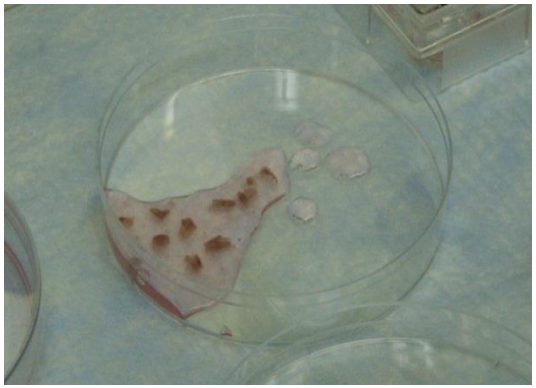
*1% tenofovir vaginal formulation

Anton AIDS Res Hum Retroviruses 2012

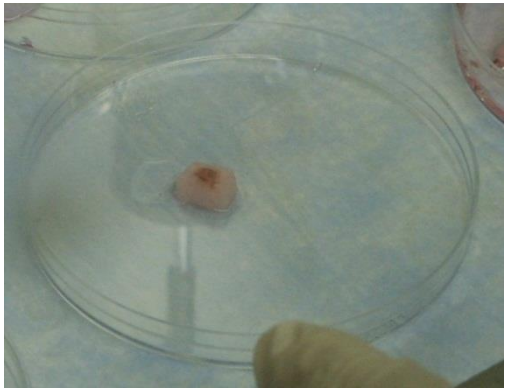
RMP-02/MTN-006 Adverse Events

GI Adverse Events in the Tenofovir Arm	MTN-006 (N = 12) Vaginal Formulation	
	N	%
Abdominal pain	6	50%
Rectal urgency	5	42%
Bloating	5	42%
Nausea	4	33%
Diarrhea	7	58%
Flatulence	3	25%
Proctalgia	0	0%
Other	5	42%
Total	35	-

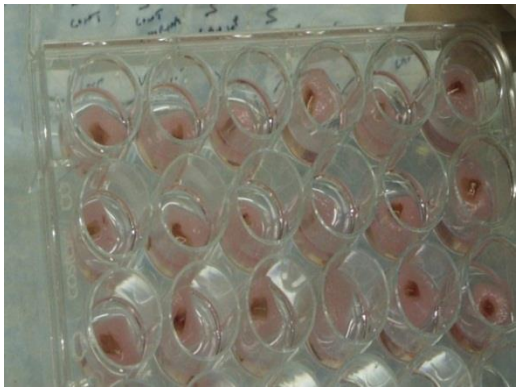
Colorectal Explants



Collect rectal biopsies Previously exposed to Tenofovir gel



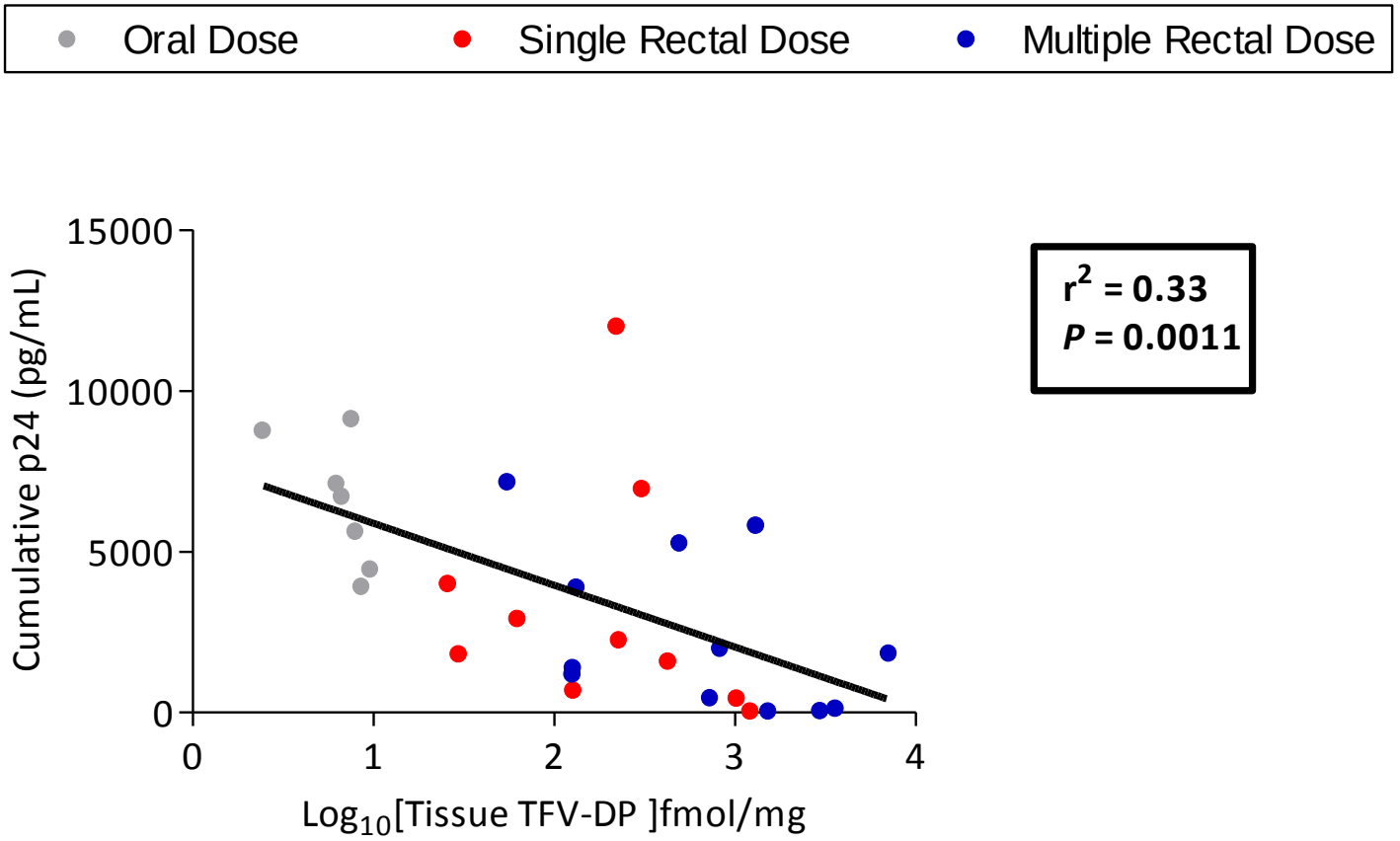
Place biopsy on raft



Expose to HIV and measure sequential p24 levels

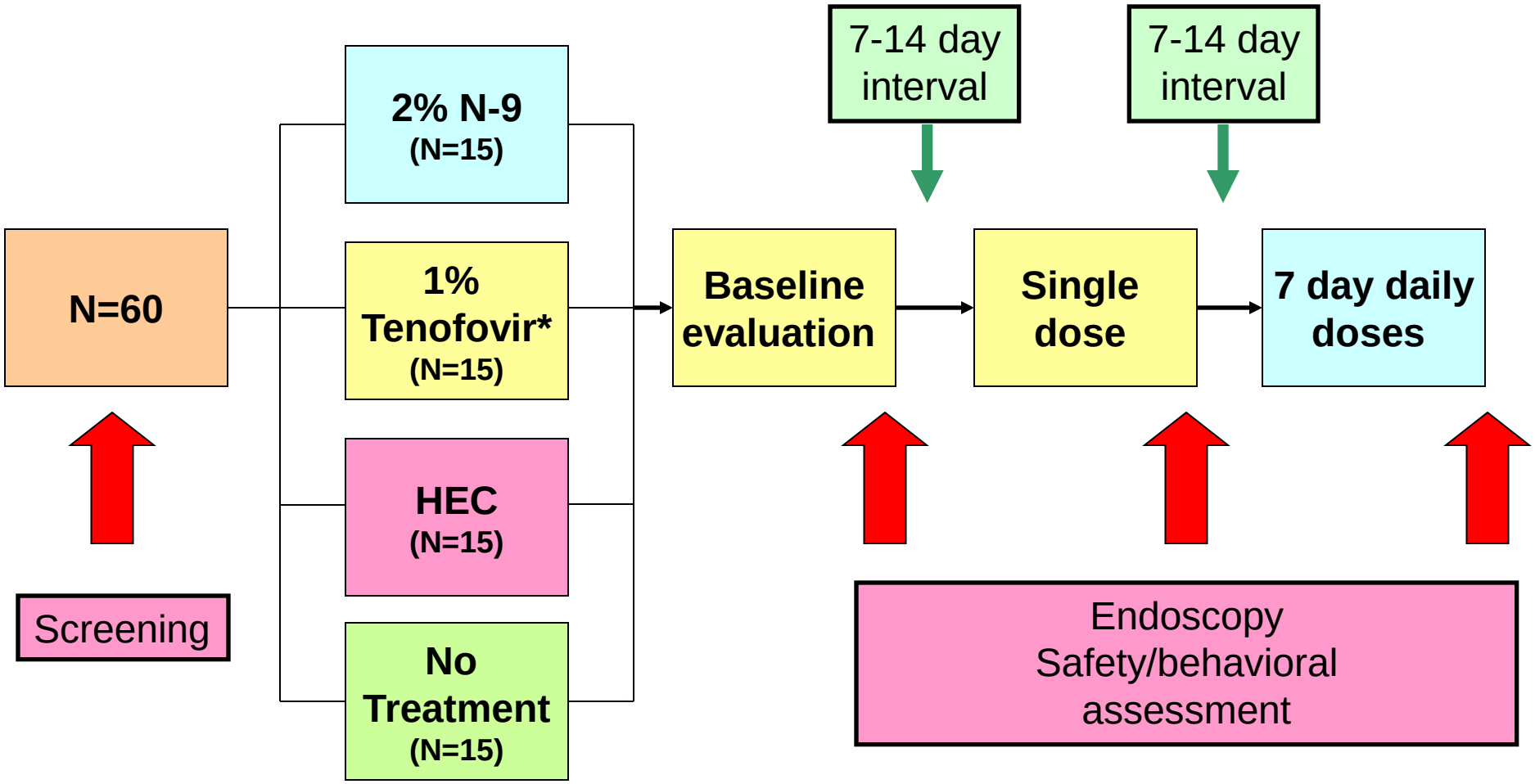
Abner SR et al., *JID*, 2005, Watts P et al., *AIDS*, 2006

PK/PD Correlation in RMP-02/MTN 006



Anton et al. *AIDS Res Hum Res,* 2012

MTN-007 Study Design



*1% tenofovir reduced glycerin formulation

McGowan PLoS One 2013

MTN-007 Adverse Events

GI Adverse Events (Tenofovir Arm)	MTN-007 (N = 16) RG Formulation	
	N	%
Abdominal pain	3	16%
Rectal urgency	0	0%
Bloating	0	0%
Nausea	0	0%
Diarrhea	1	6%
Flatulence	6	38%
Proctalgia	1	6%
Other	4	25%
Total	15	-

MTN-017

- A Phase 2 Randomized Sequence Open Label Expanded Safety and Acceptability Study of Oral Emtricitabine/Tenofovir Disoproxil Fumarate Tablet and Rectally-Applied Tenofovir Reduced-Glycerin 1% Gel

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Participants and Locations

- N = 186
- Participants: Men who have sex with men and transgender women
- Study sites
  - United States (4)
  - Thailand (2)
  - South Africa (1)
  - Peru (1)

MTN-017

- Study regimens include:
  - Rectal tenofovir gel used daily
  - Rectal tenofovir gel used before and after sex
  - Truvada tablets taken daily
- Each participant will follow all of the study regimens for eight weeks, with a weeklong break between regimens when no product will be used
  - The order in which participants follow study regimens will be based on random assignment
- All participants will receive standard HIV prevention package

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MTN-017 Study Design

Product Sequence	N	Period 1 (8 weeks)	Product Break (1 week)	Period 2 (8 weeks)	Product Break (1 week)	Period 3 (8 weeks)
1	31	Daily Truvada		Daily rectal gel		Rectal gel before and after sex
2	31	Rectal gel before and after sex		Daily Truvada		Daily rectal gel
3	31	Daily rectal gel		Rectal gel before and after sex		Daily Truvada
4	31	Daily rectal gel		Daily Truvada		Rectal gel before and after sex
5	31	Daily Truvada		Rectal gel before and after sex		Daily rectal gel
6	31	Rectal gel before and after sex		Daily Rectal gel		Daily Truvada

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About the Study Products

- Truvada tablets
  - Brand name for combination drug containing tenofovir and emtricitabine
  - iPrEx study showed Truvada reduced the risk of HIV infection among MSM by nearly 44 percent when used daily compared a placebo tablet
  - Licensed for HIV prevention

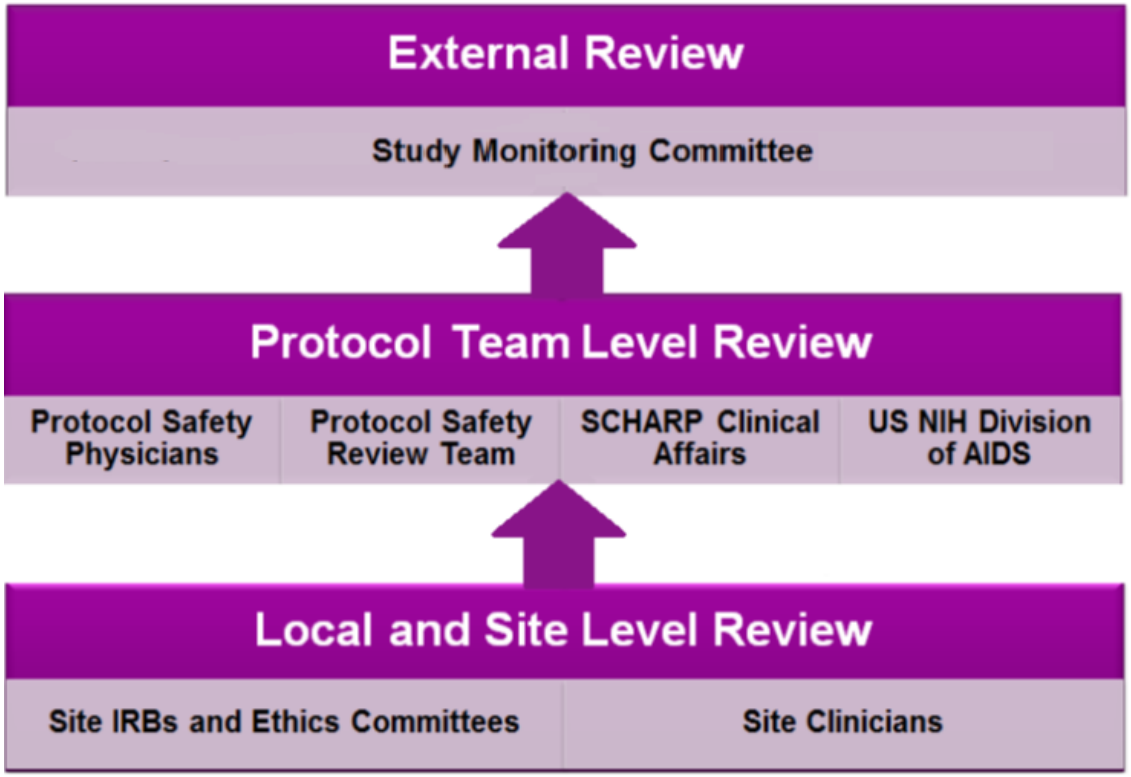
- Tenofovir gel
  - Rectal-friendly formulation evaluated in MTN-007

Photo courtesy of: Microbicide Trials Network, University of Pittsburgh and Magee-Womens Research Institute

Primary Objectives

- Safety
  - Compare the safety profiles of rectal tenofovir gel used daily and before and after sex, and Truvada tablets
- Acceptability
  - Evaluate and compare the acceptability of Truvada tablets to rectal tenofovir gel, i.e., did they like the product?; would they use it in the future, if available?

Layers of Safety Monitoring



Secondary Objectives

- Estimate adherence to the products, i.e. ppts use the product?
- Examine whether sexual activity or condom use varies by product type
- Determine the level of product sharing with non-participants
- Determine practices associated with anal sex that could detract from microbicide effectiveness, i.e. lubes, douching

Adherence

Adherence

- iPrEx ~50%
- VOICE ~20%
- MTN 017
  - PK monitoring
  - ‘Real time’ PK
  - Layered approach to monitoring
    - SMS
    - Product returns
    - CASI

Study Visits and Procedures

- Screening visit
  - Informed consent
  - Physical and rectal exams
  - HIV risk reduction counseling
- Enrollment visit
  - Randomization of participants
- Follow-up visits
  - Monthly
- Visit procedures
  - Physical exams
  - Rectal exams
  - Urine and blood tests
  - Rectal biopsies (flexible sigmoidoscopy) at some sites
  - Behavioral surveys

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017 is Here!

- Formal announcement of the study opening by DAIDS this week
- 3 sites activated
- 1 ppt enrolled

Acknowledgements

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Thank You!

Project GEL: Gel use during sex

- Overall, participants used gel on about 4 out of 5 RAI occasions
  - Based on CASI (N=83):
    - Median 12 occasions RAI
    - 82.4% adherence to gel use with RAI
  - Based on IVRS (N=88)
    - Median 10.5 occasions RAI
    - 87.9% adherence to gel use with RAI