

# The Evolution and Implementation of MTN-017

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# MTN-017

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- 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

# Study Products

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□ Truvada®



□ 1% tenofovir RG Gel



Gilead Sciences (Foster City, CA), CONRAD (Arlington, VA)



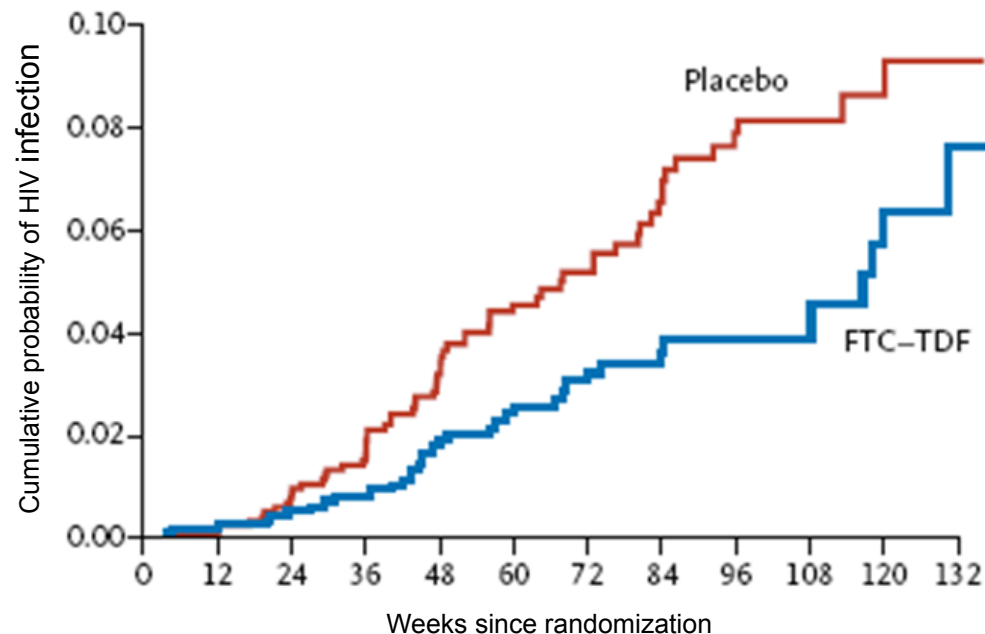
# iPrEx Study

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- Phase III multicenter trial of 2499 HIV negative MSM or transgender women randomized to receive placebo vs. FTC/TDF
- Median follow up 1.2 years
- Primary Endpoints:
  - AEs
  - HIV seroconversion

# iPrEx: HIV Seroconversion

- 44% effectiveness  
(95% confidence interval, 15 to 63;  $P=0.005$ )
- ~50% adherence to product



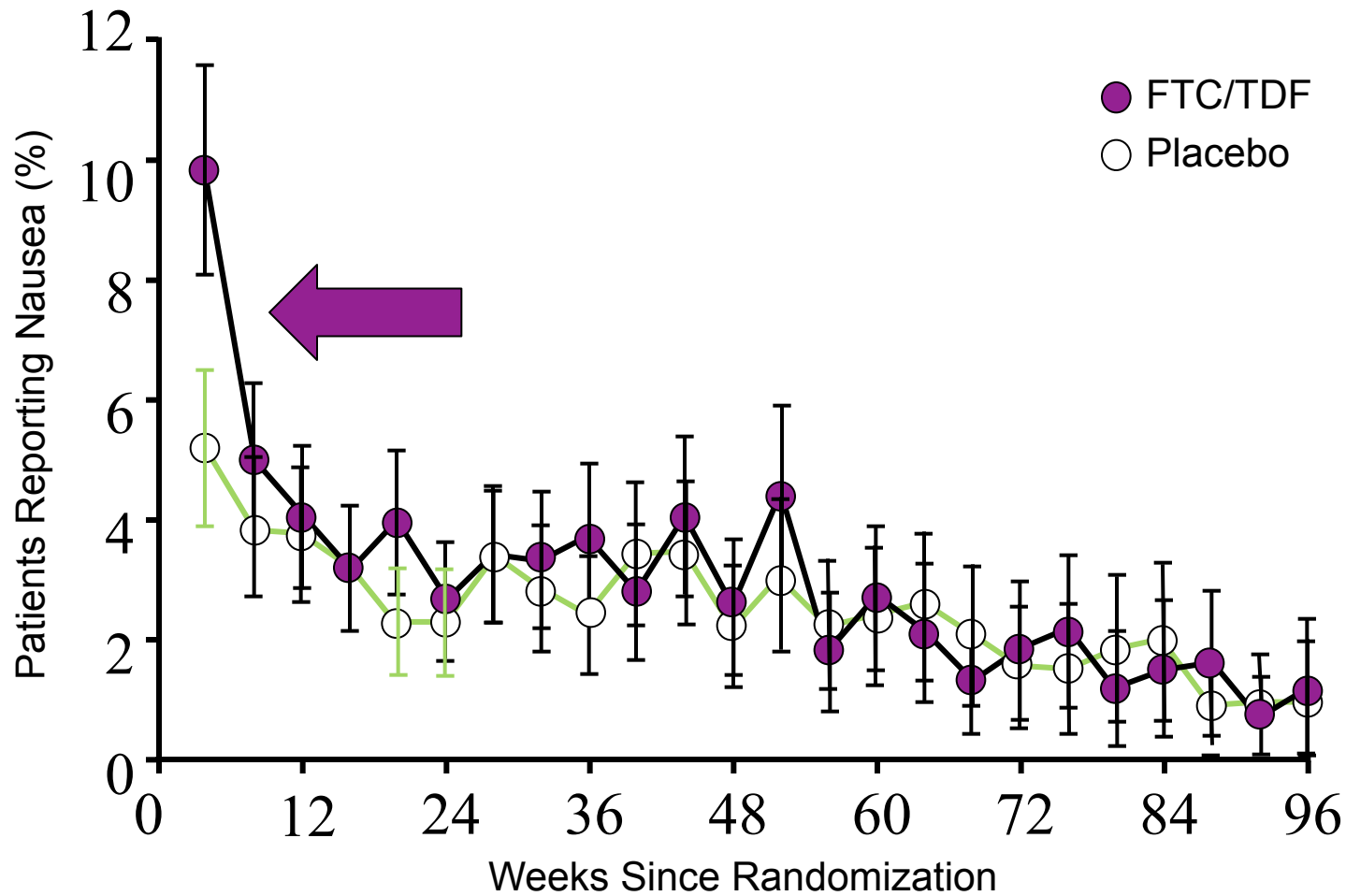
# iPrEx: Adverse Events

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- No significant differences between active and placebo arms for:
  - Any grade 3/4 event, death, SAE, elevated creatinine, creatinine elevation confirmed on next visit

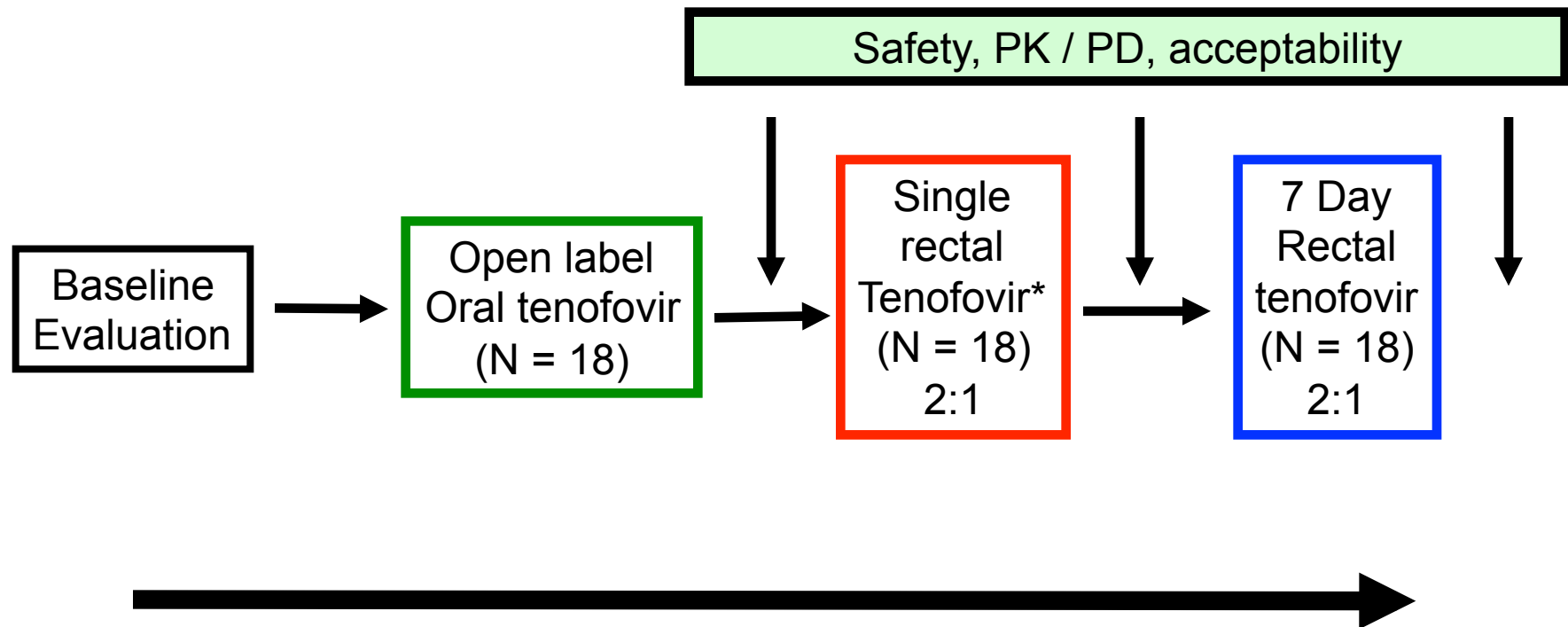
Adverse Event	FTC/TDF (n = 1251)		Placebo (n = 1248)		P Value
	%	Events	%	Events	
Nausea	2	22	<1	10	0.04
Weight decrease	2	34	1	19	0.04

# iPrEx: Nausea





# RMP-02/MTN-006 Study Design



\*1% tenofovir vaginal formulation

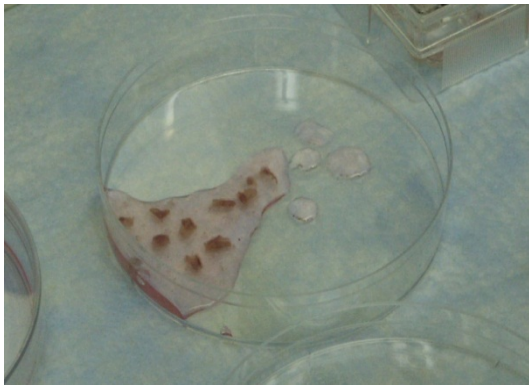


# RMP-02/MTN-006 Adverse Events

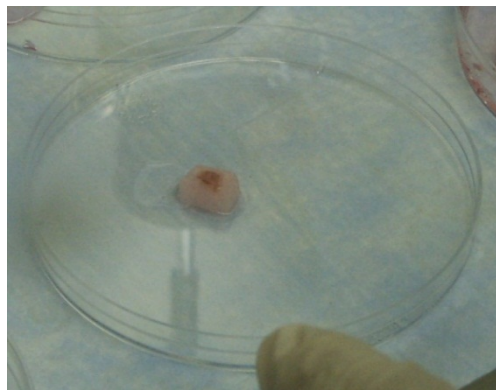
GI Adverse Events in the Tenofovir Arm	RMP-02/MTN-006 (N = 12) Vaginal Formulation	
	N	%
Abdominal pain	6	50%
Rectal urgency	5	42%
Bloating	5	42%
Nausea	4	33%
Diarrhea	7	58%
Flatulence	3	25%
Proctalgia	0	0%
Other	5	42%
<b>Total</b>	<b>35</b>	<b>-</b>

# Colorectal Explants

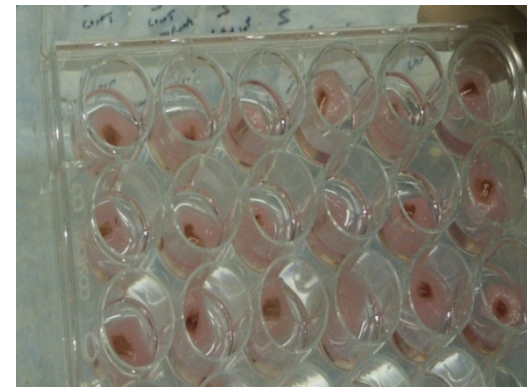
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Collect rectal biopsies  
From ppts previously  
exposed to Tenofovir gel

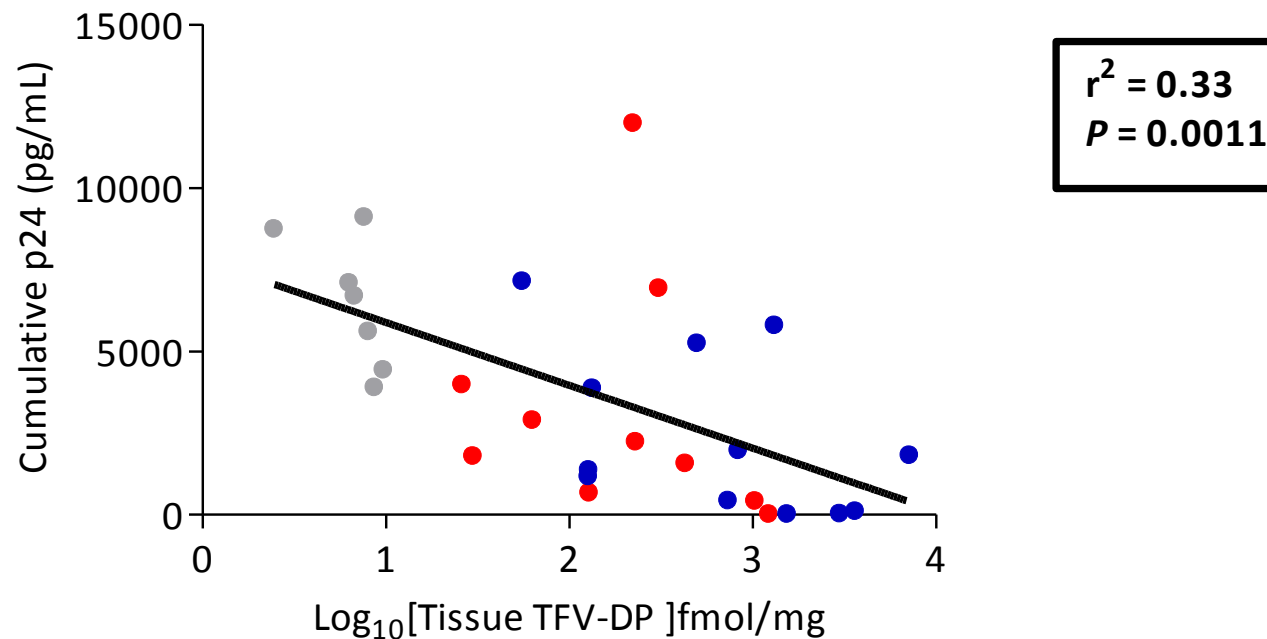


Place biopsy on raft



Expose to HIV and  
measure sequential  
p24 levels

# PK/PD Correlation in RMP-02/MTN 006



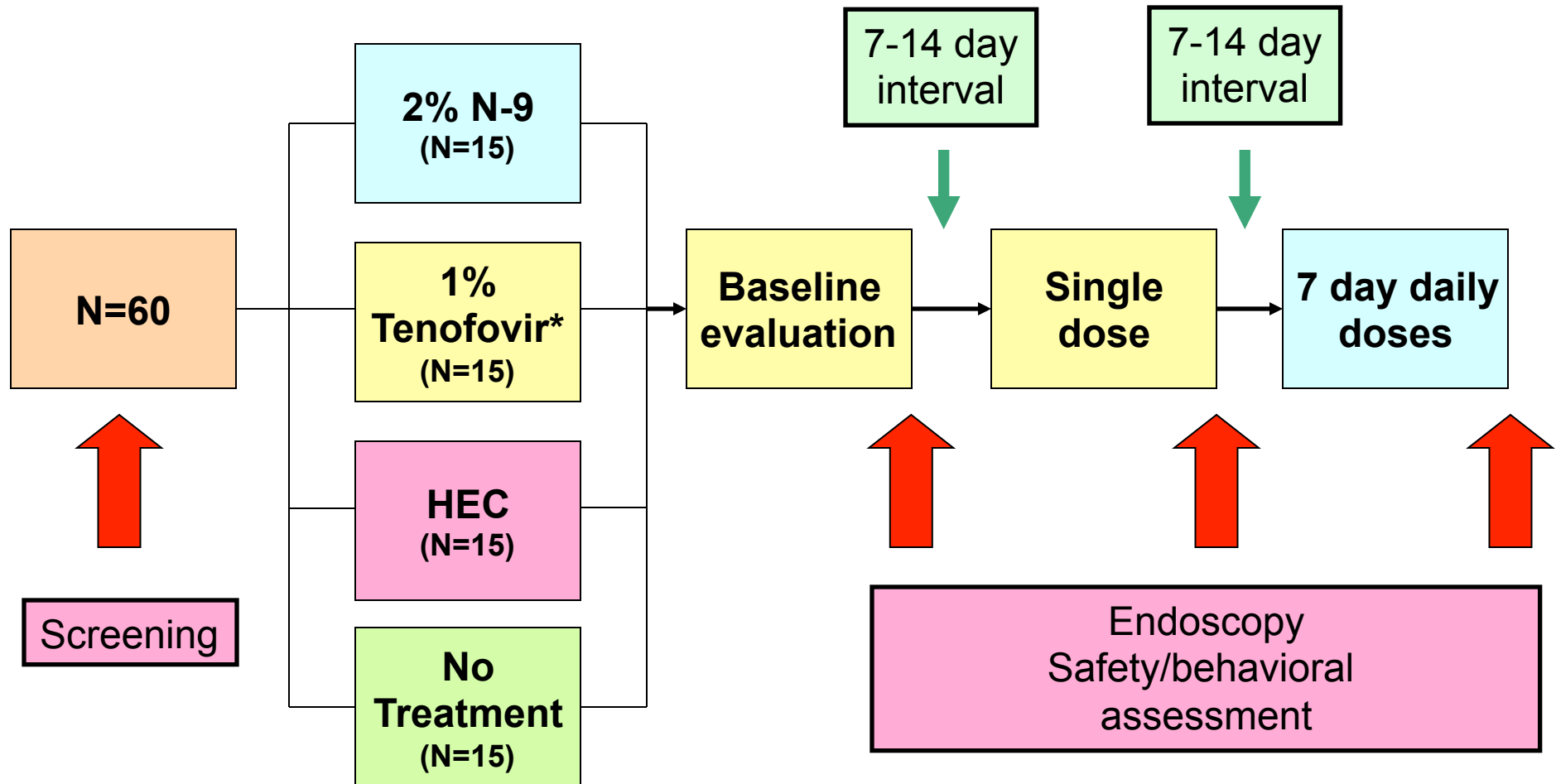


# Acceptability

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Product (N)	Like very much (%)
Tenofovir 1% gel (12)	25%
HEC Placebo (6)	50%

# MTN-007 Study Design



\*1% tenofovir reduced glycerin formulation

# 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%
<b>Total</b>	15	-



# Gastrointestinal Adverse Events

GI Adverse Events in the Tenofovir Arm	MTN-007 (N = 16) RG Formulation		RMP-02/MTN-006 (N = 12) Original Formulation	
	N	%	N	%
Abdominal pain	3	16%	6	50%
Rectal urgency	0	0%	5	42%
Bloating	0	0%	5	42%
Nausea	0	0%	4	33%
Diarrhea	1	6%	7	58%
Flatulence	6	38%	3	25%
Proctalgia	1	6%	0	0%
Other	4	25%	5	42%





# Acceptability

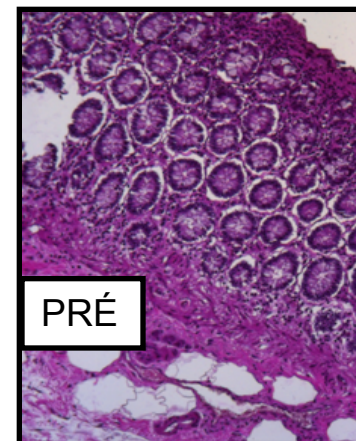
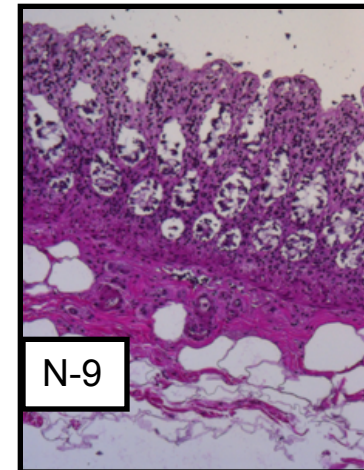
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Product (N)	Intention to Use (%)
RG Tenofovir (15)	87%
HEC Placebo (15)	93%
N-9 (16)	63%

# Mucosal Safety Endpoints

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- Epithelial sloughing
- Histopathology
- Mucosal mononuclear cell phenotype
- Mucosal cytokine mRNA
- Luminex
- Microarray gene expression
- Fecal calprotectin
- Rectal microflora



# MTN-007 Microarray Data

	Gene expression	
	Up	Down
N9	60	56
Tenofovir	138	490
HEC	12	4
No Rx	17	6

- Significant modulation of mucosal gene expression after 7 days of TFV gel
- Key pathways effected:
  - Mitochondrial function ↓
  - Innate immunity ↑



# MTN 017

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## □ Study Population

- Approximately 186 ppts
- HIV-uninfected
- MSM or transgender females
- Reported practicing receptive anal intercourse
- Age 18 years or older

## □ Study Duration

- Follow-up: 27 weeks per participant
- Accrual: Projected 6-9 calendar months at each site

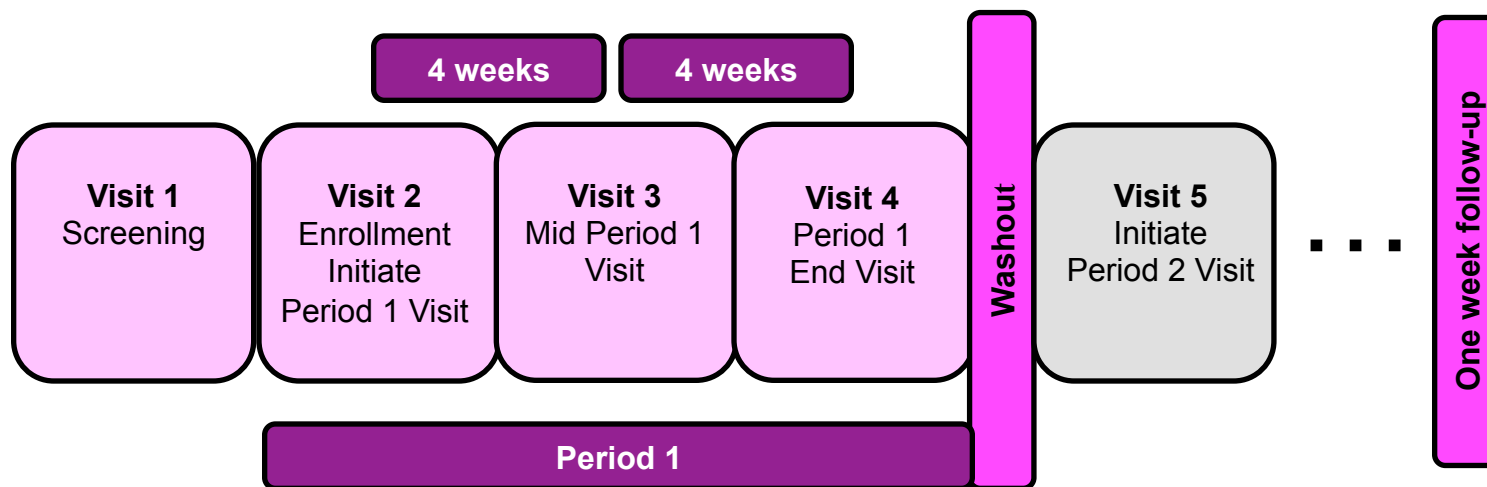


# MTN-017

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- Study regimens include:
  - Rectal tenofovir gel used daily
  - Rectal tenofovir gel used before and after sex (BAT 24)
  - 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

# 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 TDF/FTC		Daily rectal gel		Rectal gel before and after sex
2	31	Rectal gel before and after sex		Daily TDF/FTC		Daily rectal gel



# Primary Objectives/Endpoints

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## □ Safety

- Compare the safety profiles of rectal tenofovir gel used daily and before and after sex, and Truvada tablets
  - Grade 2 or higher adverse events

## □ Acceptability

- To evaluate and compare acceptability of rectal tenofovir gel used daily and before and after sex, and Truvada tablets
  - Participant self-report of ease of use, liking the product, and likelihood of product use if shown to be effective



# Secondary Objective/Endpoints #1

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- Pharmacokinetics
  - To compare systemic and local pharmacokinetics (PK)
    - Tenofovir concentrations
      - blood plasma, rectal tissue\* and rectal fluid
    - Tenofovir-diphosphate concentrations
      - peripheral blood mononuclear cell (PBMC) and rectal tissue\*
    - Emtricitabine concentrations
      - blood plasma, rectal tissue\* and rectal fluid
    - Emtricitabine-triphosphate concentrations
      - PBMC and rectal tissue\*

\* Rectal tissue will be collected on a subset of participants taking part in the Rectal Biopsy/Fluid Subset





# Secondary Objective/Endpoint #2

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- Adherence
  - Compare the safety profiles of rectal tenofovir gel used daily and before and after sex, and Truvada tablets
    - Percentage of prescribed doses taken orally or administered rectally in an 8-week period



# Exploratory Objectives

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- Characterize pharmacodynamic responses
- Characterize changes in mucosal immunity
- Assess correlation between PK and adherence measures
- Identify factors associated with product adherence and whether they differ by product used
- Examine whether sexual activity or condom use varies by product used
- Determine the level of sharing of study products with non-participants
- Determine the prevalence of behavioral practices associated with anal intercourse that may affect microbicide use

# Study Sites

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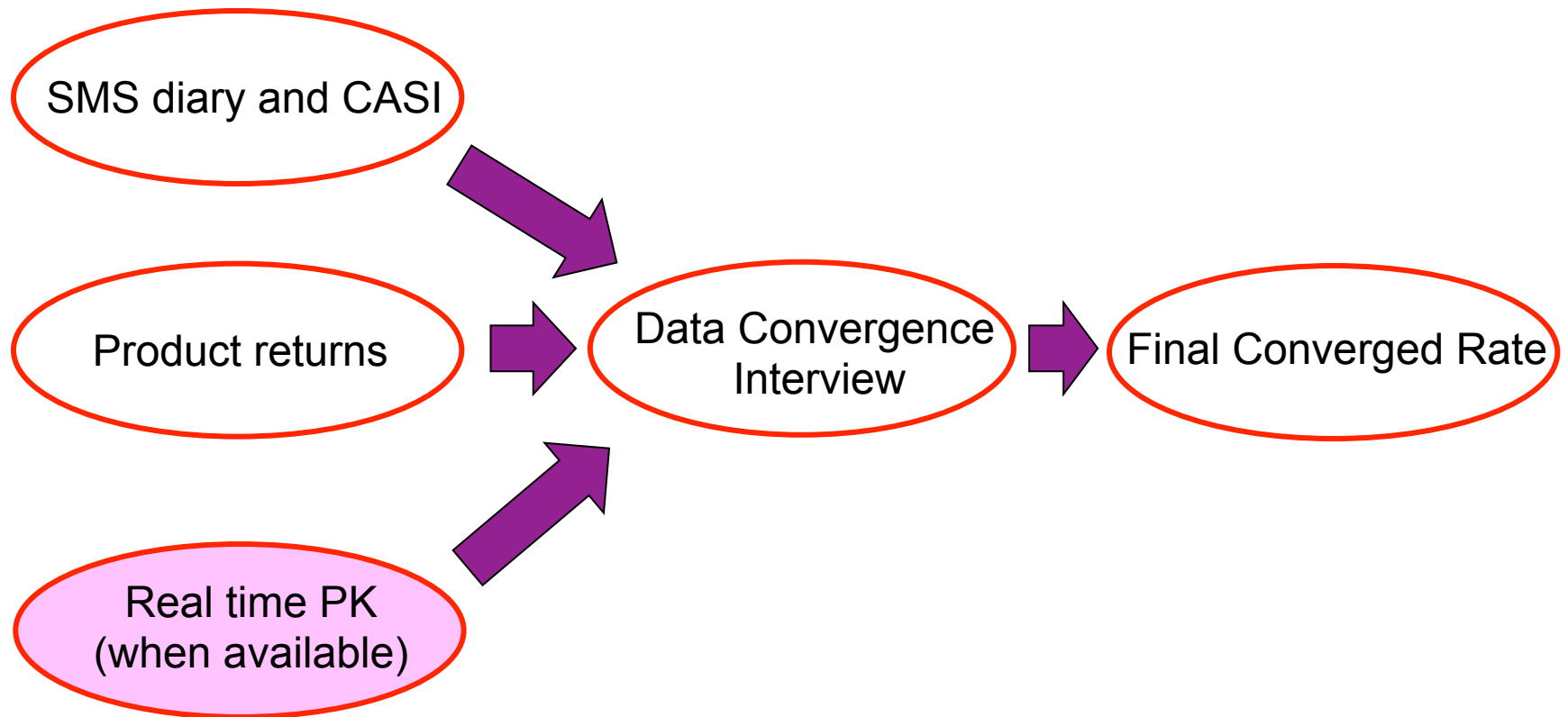
# Adherence in African PrEP Trials

Name	Population	Estimated Adherence		
		Self report	CPC	Drug level (in subset)
<b>TDF2</b>	557 ♀ & 662 ♂	94%	84%	80%
<b>Partners PrEP</b>	4758 sd ♀/♂ couples	98%	97%	82%
<b>Fem-PrEP</b>	2120 ♀	95%	85%	<40%
<b>VOICE</b>	5029 ♀			
• TDF		90%	87%	30%
• Truvada		91%	92%	29%
• TFV gel		91%	86%	25%

Ambia (review) 2013; Baeten (review) 2013; van der Straten 2012; Baeten CROI 2013; Marrazzo CROI 2013

# Measuring Adherence in 017

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# Timelines

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- Protocol development:
  - Protocol development meeting 09-28-11
  - Community consultations
    - Cape Town Oct 2011
    - Pittsburgh Dec 2011
    - Bangkok and Chiang Mai Jan 2012
    - Boston Mar 2012
    - Lima Mar 2012
  - PSRC 04-03-12
  - Version 1.0 07-13-12



# Site Activation

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□ Clinical Trial Agreement: 07-11-13

□ Sites:

■ Fenway	09-06-13
■ SFDH	09-24-13
■ Pittsburgh*	09-27-13
■ San Juan	11-15-13
■ Chiang Mai	01-06-14
■ Lima	01-15-14
■ Cape Town	03-03-14
■ Bangkok*	06-27-14

\*Mucosal immunology subset

# 017 Activity as of 02-02-15

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Site (n)	Screened	Screen Fail	Enrolled	Completed
Fenway (6)	11	4	7*	7*
SFDH (36)	100	62	38*	27*
Pittsburgh (30)	45	12	33*	25*
San Juan (6)	13	4	7*	7*
Chiang Mai (30)	56	27	30	22
Lima (36)	55	18	38*	26*
Cape Town (18)	47	29	18	7
Bangkok (24)	33	8	24	5
<b>TOTAL</b>	<b>360</b>	<b>164</b>	<b>195</b>	<b>126</b>

\* Including replacement ppt/s





# Anticipated Timeline

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Topic	Date of completion
Accrual	November 2014
Follow up (27 weeks)	June 2015
Data clean up	September 2015
Data lock	October 2015
Primary results	February 2016

# Rectal Microbicide Timeline\*

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Phase 1	→										
Phase 2				→							
Phase 3							→				
Review										→	
Available											→
Vaginal gel microbicide						?					

\*An approximation based on tenofovir 1% RG gel



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- CONRAD
- MTN-017 participants



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**Thank You!**