MTN-017: A Rectal Phase 2 Extended Safety and Acceptability Study of Tenofovir Reduced-Glycerin 1% Gel

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For the MTN-017 Protocol Team and Participants

MTN
microbicide trials network

Background

- Rectal microbicides have been in clinical development for over 10 years
- Topical gel products are used frequently by groups at high-risk of HIV during receptive anal sex
- Antiretroviral gel has demonstrated rectal protection in non-human primates and rectal explant *in vitro* models[1,2]
- The vaginal formulation of 1% tenofovir (TFV) gel was neither safe nor acceptable in the rectum[3]
- MTN-007 used a reduced-glycerin (RG) formulation of 1% TFV gel that was both safe and acceptable in the rectum following 7 consecutive daily doses[4]

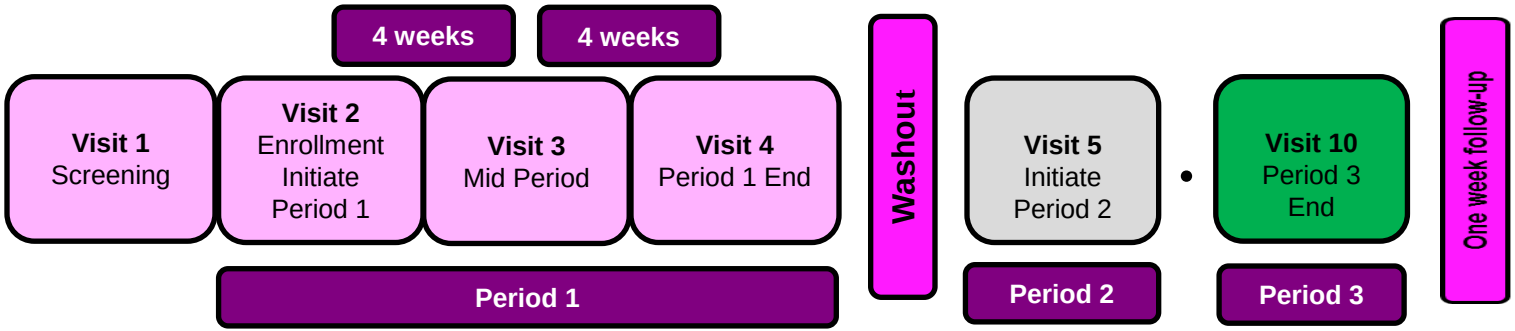
[1]Cranage PLoS Med 2008, [2]Dobard JID 2015, [3]Anton AIDS Res Hum Retroviruses 2012, [4]McGowan PLoS One. 2015

MTN-017 Population, Duration and Sites

- Study Population
  - 195 enrolled participants
  - HIV-uninfected
  - MSM or transgender females
  - Reported practicing receptive anal intercourse
  - Age 18 years or older
- Study Duration
  - 27 weeks per participant
- Sites
  - US (4)
  - Peru (1)
  - Thailand (2)
  - South Africa (1)

Study Design

- In a crossover design, each participant was randomized to follow all study regimens for eight weeks, with a one-week wash-out period between regimens
- Study regimens (randomized to one of 6 sequences)
  - Rectal RG 1% TFV gel used daily
  - Rectal RG 1% TFV gel used before and after receptive anal intercourse (RAI)
  - FTC/TDF tablet taken daily

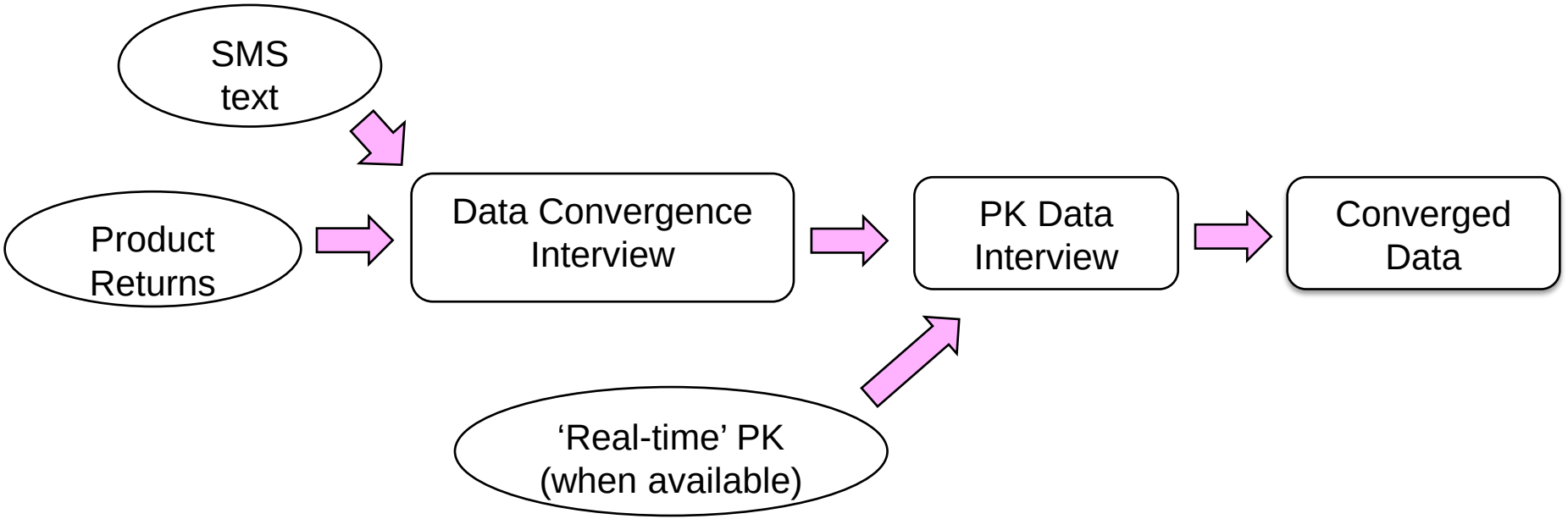


Study Endpoints

- Safety
  - Grade 2 or higher adverse events
- Acceptability
  - Participant self-report of ease of use, liking the product, and likelihood of product use if shown to be effective
- Pharmacokinetics
  - 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

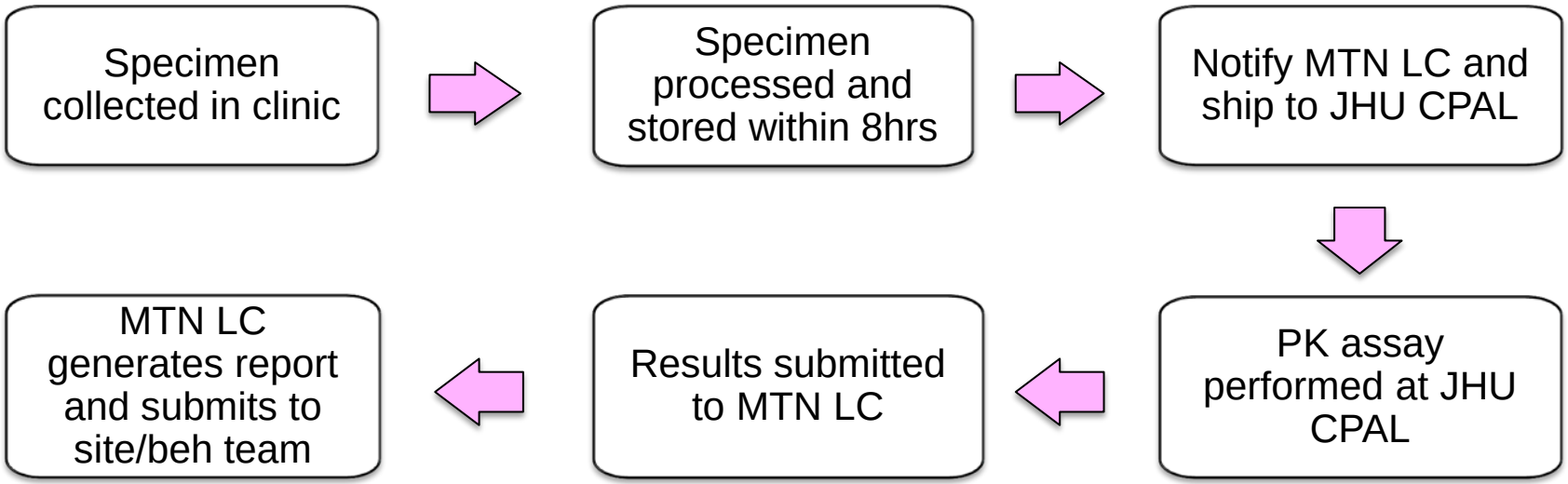
* Rectal tissue was collected on a subset of participants taking part in the rectal biopsy/fluid subset

MTN-017 Adherence Measurement



Adapted from Pool PLoS One 2010

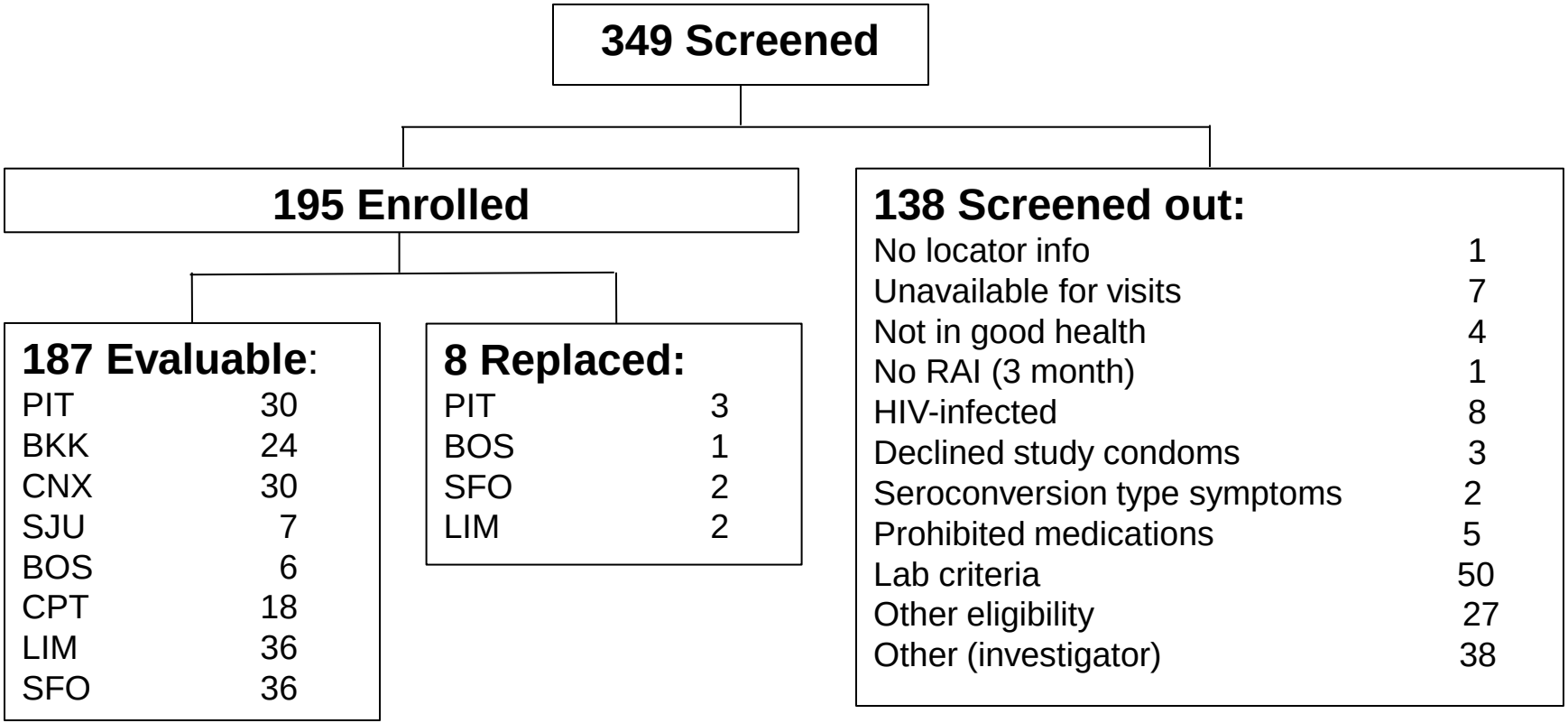
PK Specimen Flow Chart



Exploratory Objectives

- 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

Screening and Enrollment



Replacements

- Ppts with missing adherence data due to:
  - Participant was not dispensed study product
  - Participant did not report on study product use at least once in the daily gel period, the RAI gel period, or both
  - Loss-to-follow-up
  - Participant non-adherence or refusal of study product
  - Site-initiated product holds/discontinuations
- No participants were replace after full accrual

Study Conduct

- First enrollment to data lock
  - 23 months
- Adherence to visits and procedures
  - Over 98%
- Data quality
  - Checks on 6.2 per 100 records
- Retention
  - After replacements 185/187 (98.9%) exited study

Demographics

	LIM	SJU	CPT	BKK	CNX	BOS	PIT	SFO	All
Participants enrolled	38	7	18	24	30	7	33	38	**195**
Age (mean)	32.9	30.9	22.8	31.5	27.9	34.6	30.2	35.9	**31.1**
College education	27	6	5	21	25	4	32	36	**156 (80%)**
Male									**141 (73%)**
Female									**4 (2%)**
Transgender female									**19 (10%)**
Other/Declined									**30 (15%)**

Adverse Events

- 195 enrolled participants
- Grade 2 or higher AEs in:
  - Oral: 65/192* (34%)
  - Daily rectal: 64/192* (33%)
  - RAI rectal: 58/191** (30%)

	Reference	Estimated IRR	95% CI		P-value***
Daily Rectal	Oral	1.09	0.79	1.53	0.59
RAI Rectal	Oral	0.90	0.66	1.23	0.51

* 3 were not exposed
** 4 were not exposed
*GEE with Poisson link, person time offset, exchangeable correlation structure, robust errors, controlling for period of study

Acceptability

	Reference	Odds Ratio	95% CI		P-value*
Outcome: Overall Liking [Liked (1) vs. Disliked (0)]					
Daily Rectal	Oral	0.28	0.15	0.50	<0.001
RAI Rectal	Oral	0.37	0.20	0.70	0.002
Outcome: Overall Ease of Use [Easy (1) vs. Difficult (0)]					
Daily Rectal	Oral	0.56	0.29	1.08	0.08
RAI Rectal	Oral	0.76	0.37	1.56	0.46
Outcome: Intention to Use [Likely (1) vs. Unlikely (0)]					
Daily Rectal	Oral	0.38	0.22	0.65	<0.001
RAI Rectal	Oral	0.70	0.39	1.25	0.23

*GEE with binomial link, exchangeable correlation structure, robust errors, controlling for study period

‘Real Time’ Pharmacokinetics

- Qualitative results based on the lower limit of detection of TFV
- 187 evaluable participants, 2 tests per regimen at mid- and end-period visits

Regimen	Real-Time Plasma PK result			
	Negative	Positive	Not done/ not available	Total
Daily Rectal	66 (18.2%)	291 (80.2%)	6 (1.7%)	363
Oral	13 (3.5%)	346 (94.3%)	8 (2.2%)	367
Total	79 (10.8%)	637 (87.3%)	14 (1.9%)	730

Adherence (SMS and product return)

	Regimen		
	Oral	**Daily rectal**	**RAI**
Less than 80%	12 (6%)	31 (17%)	13 (7%)
At or greater than 80%	173 (94%)	153 (83%)	170 (93%)
Total	185	184	183

	Reference	**Odds Ratio**	**95% CI**		**P-value***
Daily Rectal	Oral	0.35	0.19	0.63	<0.001
RAI Rectal	Oral	0.89	0.43	1.81	0.74

*GEE with binomial link, exchangeable correlation structure, robust errors, controlling for study period

Oral PrEP in 017

- MTN-017 allowed initiation of oral PrEP with FTC/TDF
- 29 of 38 enrolled participants in SF chose to start oral PrEP at enrollment
- 16 (42%) remained on drug at study termination
- Of the 7 participants with social harms in SF,4 described negativity around PrEP use

Applicator

- Acceptability (product vs. applicator)
  - Daily gel p=0.008
  - RAI gel p=0.004

HIV Seroconversions

- Site A:
  - RAI/Oral/Daily Rectal. Positive test prior to Oral regime (no product taken due to suspicion for seroconversion). No resistance
- Site B:
  - Oral/Daily Rectal/RAI. Positive test at end of Daily Rectal regime. No resistance
  - RAI/Oral/Daily Rectal. Positive test 110 days after mid period Daily Rectal visit. NNRTI resistance K103N mutation
  - Daily Rectal/Oral/RAI. Positive test at end of Oral regime. NNRTI resistance E138A mutation

Summary

- Rectal 1% RG TFV gel was safe when used daily or with RAI in this population
- Use of 1% RG TFV with RAI was more acceptable than daily use
- There was high adherence to study product in all regimens
- These results support further study of 1% RG TFV as a rectal microbicide for HIV prevention in MSM and TGW

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