MTN-001

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On behalf of the MTN001 Team

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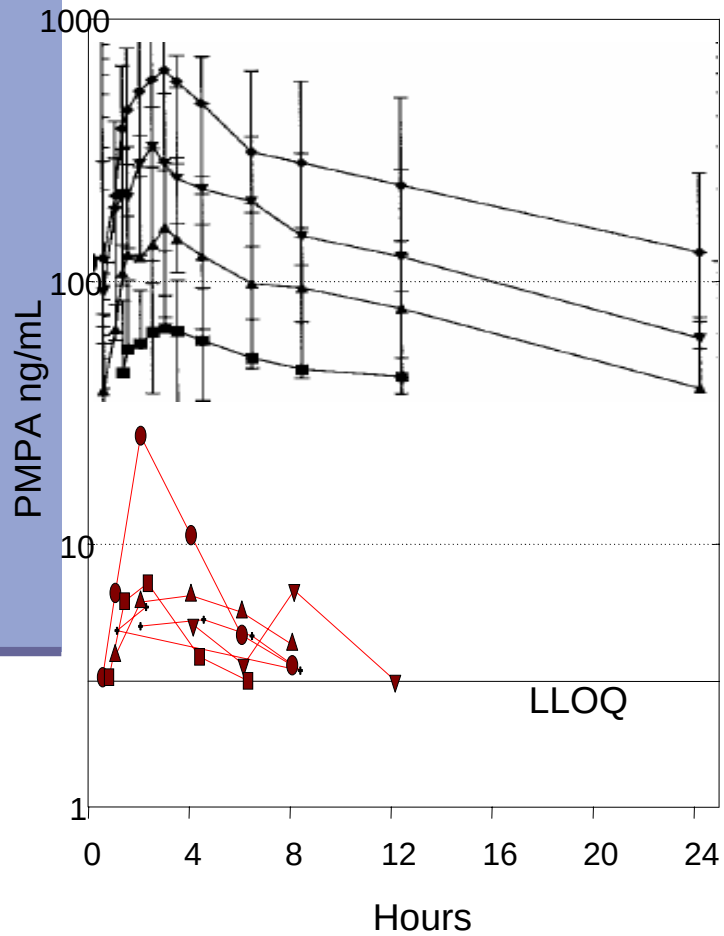
- Randomized, controlled, Phase II trial
- Comparing Adherence & Pharmacokinetics
- Once daily vaginal PMPA 1% gel
- Once daily oral tenofovir disoproxil fumarate (TDF) 300 mg tablet

MTN001 Rationale

- Head-to-head comparison of oral versus vaginal prevention dosing strategies
- Inform the design of 003 Tenofovir Efficacy Trial
  - Adherence estimates
  - Drug level estimates
- Activate new sites rapidly

Oral v. Vaginal Tenofovir



Route	Dose (mg)	Cmax (ng/mL)	Cmax per 100 mg	AUC (ng*hr/mL)	AUC per 100 mg	Relative F (C_{max}, AUC)
Oral	270	618	2.29	3,372	12.5	100%
	135	240	1.78	2,093	15.5	
Vaginal	40	3.4	0.09	46	1.2	<4%, <2%

Figure Legend

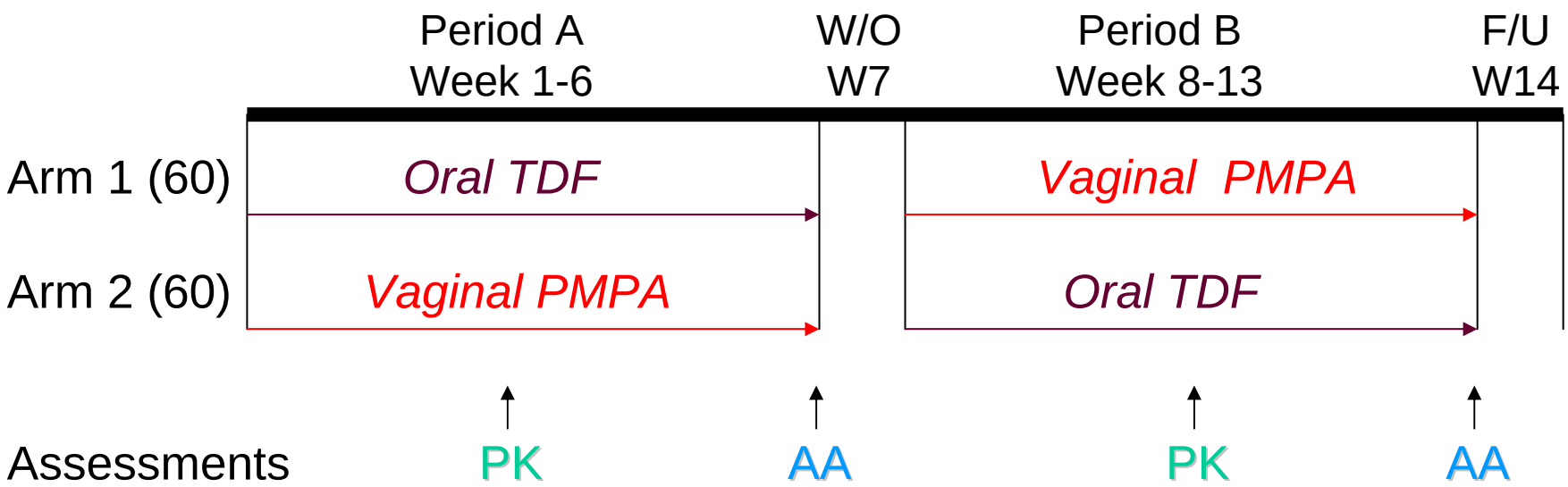
270 mg PMPA QD PO
135 mg PMPA QD PO
68 mg PMPA QD PO
34 mg PMPA QD PO
[*Barditch-Crovo AAC 2001*]

40 mg PMPA (1%) single dose vaginal
[*HPTN 050*: N=6; Subj. w/ 3+ points]

Hypotheses

- Adherence and acceptability will be similar in both arms
- Tissue levels of PMPA will be similar irrespective of the route of administration
- Oral TDF will be associated with higher concentrations of PMPA in the blood compared to topical administration of PMPA

Study Schema



Primary Objectives

- Comparison of oral tenofovir with vaginal PMPA in domains of
  - Adherence
  - Acceptability
  - Pharmacokinetics (tissue)

Secondary Objectives

- Intracellular pharmacokinetics in blood
- Comparison of adverse effects

Procedures

- Adherence measures
- Behaviorally focused quantitative surveys
- Pharmacokinetic studies
  - Blood, vaginal fluid, vaginal biopsy*, intracellular*
- Laboratory measures of systemic safety

*PK Substudy Cohort only

Study Population

- Sexually active (weekly) women
- HIV-uninfected
- 18 to 45 years of age
- No active disease

Exclusion Criteria

- Acute or chronic hepatitis
- Renal disease (CrCl >70 mL/min)
- Any clinically relevant systemic disease
- History of pathologic fracture
- Pregnancy
- Breastfeeding

Sample size

- 120 women (60 in each arm)
- Paired analysis

- Detect difference in adherence rate of Oral versus Vaginal regimen of
  - 7.5% Difference, 83% Power, 0.0 rho*
  - 5.0% Difference, 78% Power, 0.5 rho

*rho is magnitude of intra-individual correlation between arms.

Study Duration

- Approximately 98 days per participant
- Ten calendar months of accrual
- Eleven months total planned study duration

Sites

- Case Western Reserve University
- University of Pittsburgh
- University of Cape Town
- Makarere University/Johns Hopkins University
- TBD
- TBD