MTN-007

A Phase I Randomized, Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of 1% Tenofovir Gel and 2% Nonoxynol-9 Gel

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Introduction

- Once vaginal microbicides are licensed they are likely to be used in the context of vaginal **and** anal intercourse
- There are critical epithelial differences between the cervicovaginal and rectal mucosa
- It is important to assess the rectal safety of vaginal microbicides
- The design of Phase 1 rectal microbicide safety studies is in rapid evolution and emphasizes immunological safety

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Tenofovir gel

- Tenofovir gel is being developed as a vaginal microbicide
- The tenofovir portfolio needs a rectal safety study

Completed	Ongoing	Planned
HPTN-050	CAPRISA 04	MTN-001
HPTN-059		MTN-002
		MTN-003
		MTN-006
		MTN-007

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- Phase 1 rectal safety study
- Randomized blinded, placebo-controlled trial:
  - 1% vaginal formulation of tenofovir
  - Hydroxyethyl cellulose (HEC) placebo gel
  - 2% nonoxynol-9 (Ortho-Gynol II)

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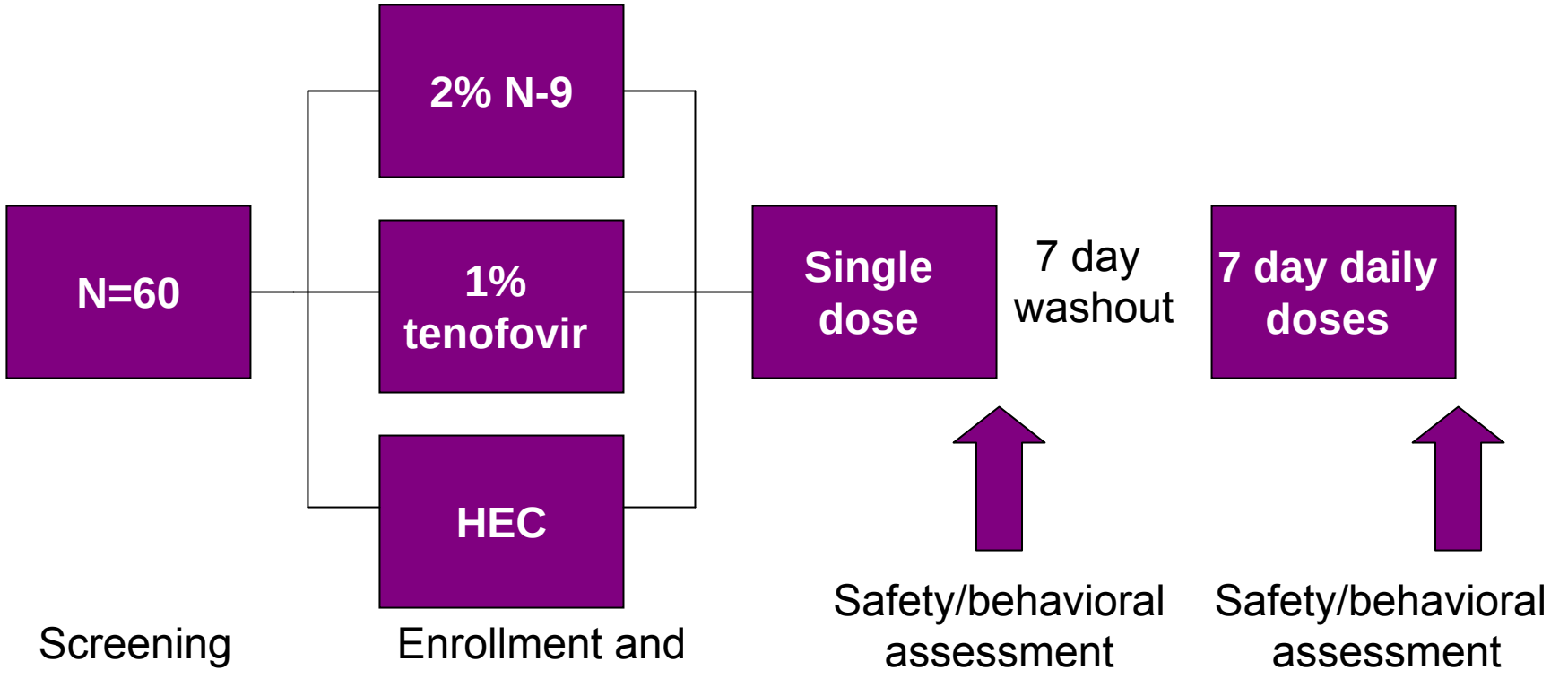
- Population:
  - Approximately 60 sexually (anally) abstinent, HIV-negative adults (male and female)
- Duration:
  - Participant accrual will take approximately 6-9 months and each participant will be on study for approximately 4-8 weeks. The total duration of the study will be approximately 12 months.

MTN-007 Study design



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- Primary objectives
  - To evaluate the safety of 1% tenofovir gel, 2% N-9 gel or HEC gel when applied rectally
  - To evaluate the acceptability of 1% tenofovir gel, 2% N-9 gel or HEC gel when applied rectally

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- Primary endpoints
  - Frequency of ≥ Grade 2 adverse events as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004, Addendum 3 (Rectal Grading Table for Use in Microbicide Studies).
  - Acceptability assessments
- Secondary endpoints
  - To determine whether use of study product is associated with rectal mucosal damage

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- Measured secondary endpoint parameters
  - Epithelial sloughing
  - Histopathology
  - Mucosal mononuclear cell phenotype
  - Mucosal cytokine mRNA
  - Weck cell cytokine
  - Mucosal immunoglobulins
  - Fecal calprotectin

Why include an N-9 arm?

- Rectal exposure to N-9 results in epithelial disruption
  - Mice
  - Macaques
  - Humans
- Histological recovery occurs within 1-8 hours
- Tabet et al. demonstrated minimal histological inflammation after up to 6 weeks treatment with a 3.5% formulation of N-9

The need for a positive control

- Assessment of mucosal injury following application of microbicide candidates requires the use of esoteric and expensive assays
- Preliminary data from a UC-781 Phase 1 rectal safety study have not demonstrated changes in these mucosal safety parameters
- Interpretation:
  - The product is safe?
  - The assay is insensitive?

MTN-007 Timeline

Activity	Timeline
Protocol concept approval	Completed
Site selection	Q2 2008
Version 0.1 protocol	Q2 2008
Face-to face meeting	Q3 2008
Pre-PSRC review	Q4 2008
PSRC review	Q4 2008
Site activation	Q1 2009
FPI	Q1 2009
LPO	Q3 2009
Manuscript	Q4 2009

Summary

- 1% tenofovir gel is a promising candidate vaginal microbicide
- Safety assessment of 1% tenofovir in the rectum is necessary as epidemiological evidence suggests its' likely use in this compartment
- Previous rectal microbicide studies have shown little change in signal from histological or inflammatory safety markers
- MTN-007 will use both placebo and positive control to assess safety

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