MTN 014: What Questions will it Answer?

Gonasagrie Nair
CAPRISA/University of Kwa -Zulu Natal/Durban

MTN Regional Meeting

Cape Town, SA

October 2014

MTN-014

Phase 1 Crossover Trial Evaluating the Pharmacokinetics of Tenofovir Reduced-Glycerin 1% Gel in the Rectal and Vaginal Compartments in Women

Study Population

14 women at the Bronx Prevention Center CRS in Bronx, NY, USA

Background

- Microbicide research: thus far focus on safety/ effectiveness of vaginal microbicides
- Receptive Anal Intercourse (RAI) is associated with increased risk of HIV acquisition -10 to 20x more risk than receptive vaginal intercourse
- RAI may impact the potential to identify a safe and effective vaginal Microbicide
- Women are 7 times more likely to engage in unprotected AI than MSM
- The development of a safe and effective Microbicide that offers dual protection is critical

Background

- the practice of RAI varies by geographical location:
- Prevalence in South Africa:
  - Seth Kalichman' s data: 10% of 1818 women in Cape Town reported anal sex in the prior 3 months (2009)
  - VOICE data: 17% of 5,029 women enrolled in VOICE reported anal sex in the prior 3 months (2012)
  - Lut Van Damme (Col 1492 N9 study) 75% of 140 women/sex workers in Durban reported anal sex during the study (2002)
- Prevalence in USA:
  - 2006-2008 National survey of family growth: 36% of adult women indicated ever having engaged in RAI
  - In high risk areas of NY – 38% of women reported practicing anal sex in the past year

Background

- Limited data of tenofovir levels in the rectal compartment following vaginal application and vice versa
  - Non-human primate study showed significant levels of tenofovir in secretions and tissues of animals dosed either vaginally or rectally in the opposite compartment (Nuttall, et al)
  - Exact mechanism unknown
  - Actual concentration of drug required for protection unknown
  - Human studies required to show same rapid transfer of drug to opposite compartment

Background/Rationale

- MTN-001 evaluated levels of tenofovir in blood, vaginal tissue and rectal/vaginal lumens following different routes of administration – oral/vaginal/ combination
- demonstrated rectal fluid tenofovir concentrations after vaginal dosing periods were higher than concentrations measured in the oral only dosing period ($p<0.03$) raising the potential that a vaginal dosing route might provide some level of protection from receptive anal intercourse (Hendrix, et al)

Why the Reduced-Glycerin TFV 1% Gel formulation (RGF)?

- RMP-02/MTN-006 and MTN-007 first rectal safety studies
- The vaginal formulation of 1% TFV gel was sub-optimal for clinical safety and acceptability when rectally applied- associated GIT intolerance
- Secondary to higher osmolality of tenofovir 1% vaginal gel in comparison to RGF
- Osmolality vaginal formulation: 3111mOsmol/kg vs osmolality of RGF: 836 mOsmol/kg

Why the Reduced-Glycerin TFV 1% Gel formulation (RGF)?

- MTN 007: RGF tenofovir gel/HEC placebo gel/2% N9/ no treatment arm
- Rectal administration of reduced glycerin formulation of TFV 1% gel was found safe and acceptable in MTN-007
- No significant difference in prevalence of AES across the 4 arms of the study
- AES – generally mild (80%) or moderate (18%)
- The grade3/4 AES reported occurred in no treatment arm or preceded product use

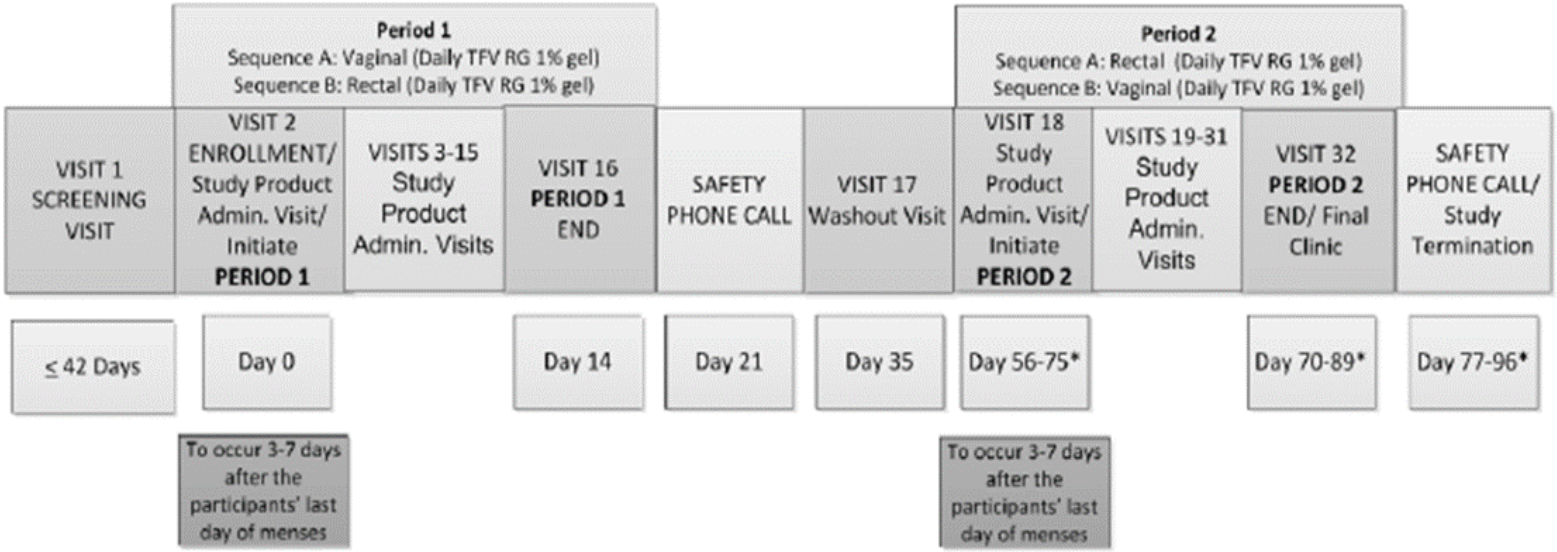
MTN 014

- 14 study participants intended to complete a 14 day study period each of rectal and vaginal dosing in a randomly assigned order
- Study product: 4ml (42mg) of tenofovir RG gel inserted daily under direct observation

sequence	n	Period 1 (2 weeks)	Washout (6 weeks)	Period 2 (2 weeks)
A	7	vaginal		rectal
B	7	rectal		vaginal

MTN-014 Study Design

- Duration of participation: 10-13 weeks
- Dependent on participants menstrual schedule



* Visit schedule will vary based upon participants' menses.

Directly Observed Dosing (DOD) Rationale

- Data from MTN-003 (VOICE) demonstrates low adherence based on detection of tenofovir in plasma samples
- Self reported adherence of 90% vs tenofovir levels evident only in 25% of samples tested
- DOD guarantees participant inserts product daily
  - Adherence will not serve as confounding factor in PK analysis

Primary Objective and Endpoint: PK

To compare local and systemic pharmacokinetics of tenofovir reduced-glycerin 1% gel after 2 weeks of daily rectal use and after 2 weeks of daily vaginal use

*Drug levels in blood, vaginal fluid samples, cervical cytobrush, rectal fluid samples, cervicovaginal lavage, vaginal and rectal tissue samples**

Secondary Objective and Endpoint: Safety

To assess the safety of tenofovir reduced-glycerin 1% gel after 2 weeks of daily rectal use and after 2 weeks of daily vaginal use

Adverse events Grade 2 or higher

- Defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009)
- Addendum 1, Female Genital Grading Table for Use in Microbicide Studies
- Addendum 3, Rectal Grading Table for Use in Microbicide Studies (Clarification dated May 2012)

Exploratory Objectives and Endpoints

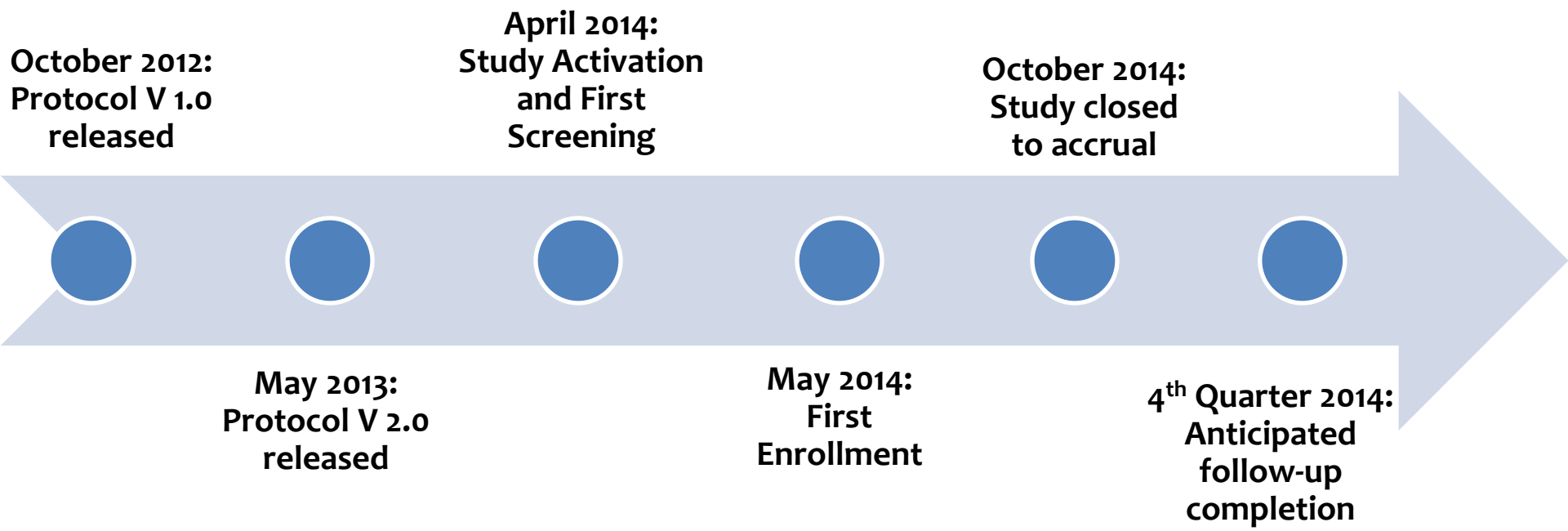
Correlation of drug levels in rectal and genital fluids with drug potency

Inhibition of HIV by drug in rectal and genital fluids

Determination of changes in microflora, biomarkers and gene expression

Changes in pH, microflora, biomarkers and gene expression

Study Timeline/Status

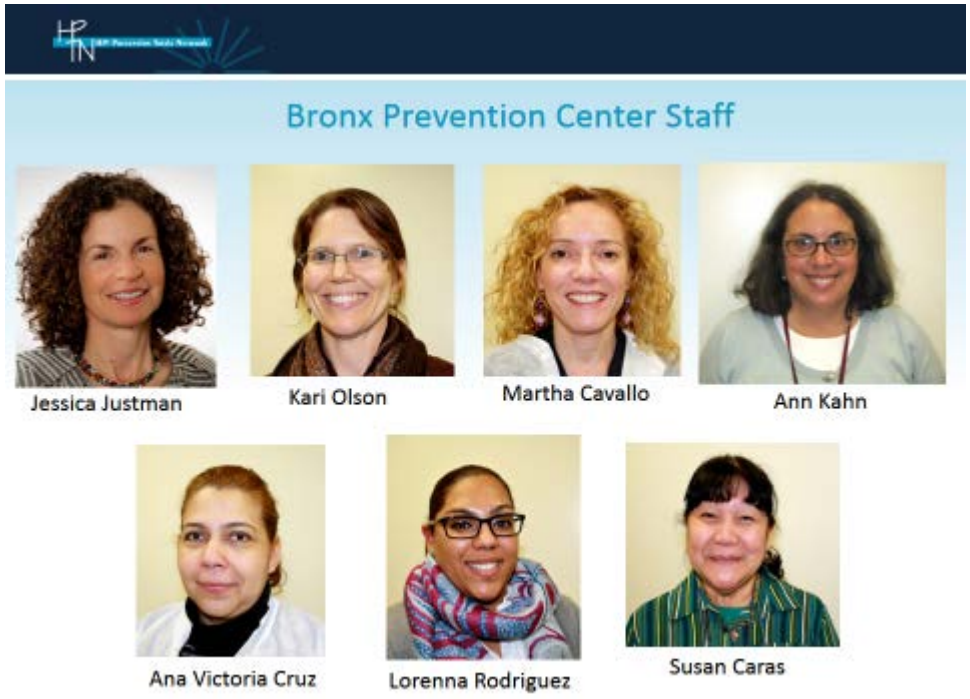


Summary

- MTN 014: investigating the vaginal and rectal application of tenofovir RG 1% gel for the prevention of HIV infection
- Potential to provide evidence of protective effect of vaginal/rectal dosing in the opposite compartment
- Provide evidence of the safety of the RGF of 1% tenofovir gel following vaginal application

Acknowledgements

- Lisa Levy – FHI 360
- BRONX team



Acknowledgements

The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI106707), with co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health.

MTN
microbicide trials network