
KEEP
CALM
AND
MIND THE
GAP
KeepCalmAndPosters.com

The Big Picture

- Rectal microbicide development has made significant advances since 2001
- Tenofovir 1% gel is currently the lead candidate for Phase 3 development
- MTN-017 is ongoing and will provide critical data for making decisions about progression to Phase 3
  - Safety and acceptability
  - Preferences
  - PK/PD

MTN-017

- Phase 2 rectal safety study of tenofovir gel
- N = 186
- International sites
  - United States (4)
  - Thailand (2)
  - South Africa (1)
  - Peru (1)

- Endpoints
  - Safety
  - Adherence
    - Self report
    - Real time PK
  - Acceptability
  - PK/PD

PI: Ross Cranston, University of Pittsburgh

MTN-017 Recruitment

Site	Total No. Screened	Screen Fails	Enrolled	Accrual Target
Bangkok, Thailand				24
Cape Town, South Africa	12	9	2	24
Boston, USA	11	4	7**	6
Chiang Mai, Thailand	24	11	13	24
Lima, Peru	21	3	15	24
Pittsburgh, USA	22	5	15	30
San Francisco	51	30	20	30
San Juan, Puerto Rico	8	2	6	24
TOTAL	149	64	**78**	**186**

May 12th, 2014

Timeline for Phase 3

	2012	2013	2014	2015	2016	2017	2018	2019
Phase 1								
MTN-017								
Phase 3								
Review								
Available								
Vaginal microbicides					?			

Where are the Gaps?

- Formulation
- Dosing
- Adherence
- Safety and acceptability
  - General
  - Mucosal
- Efficacy
- Phase 3 study design
- Alternative PrEP strategies

Formulation

- There are three tenofovir gels that have been evaluated in rectal microbicide clinical trials

Product	MTN-006	MTN-007	CHARM-01/02	MTN-017
Vaginal TFV	X			
Reduced glycerin TFV		X	X	X
Rectal specific TFV			X	

- Alternate formulations
  - Douche or suppository

Dosing

- MTN-017 will evaluate two dosing schedules
  - Daily
  - Before & after sex
- Which schedule should be advanced into Phase 3?
- Importance of Phase 1 PK studies

Adherence

- What is the best mechanism to track adherence in future studies?
  - Behavioral reports
  - Real time PK
  - Unblinding issues
- Can we develop novel adherence biomarkers for use in Phase 3?

Safety & Acceptability

- Rectal tenofovir appears generally safe
- Data from MTN-007 suggest that repeated exposure to tenofovir results in mucosal changes
  - Mitochondrial function
  - Changes in innate immunity
- Biological significance unclear
- More data will be available from MTN-017

Efficacy

- Traditionally microbicide products advance to Phase 3 based on appropriate safety and acceptability data
- Increasingly we have preclinical / non-human primate and explant efficacy data
- Can these PK/PD data be used further to optimize Phase 3 dosing

Populations for RM

- Licensure population
  - MSM & transgender
- Post licensure populations
  - Men and women practicing RAI
  - Higher risk subgroups
    - MSM with STI
- HIV positive individuals with non-ARV products

Phase 3 Study Design

- Design considerations
  - Dosing
  - Use of placebo or deferred exposure design
  - Provision of oral PrEP
  - Optimization of HIV testing process
  - Use of screening period with placebo products
- Populations
  - Geography (MTN-017 regions)
  - MSM & transgender populations

Other Issues

- Where is the TPP/STP/TMP for tenofovir gel?
- What do we really know about end user perspectives on rectal microbicides?
- What do we know about funders willingness to support roll-put of a rectal microbicide?
- What is the overall development plan for tenofovir gel?

Alternative RM Candidates

- Discovery phase
  - MIV-150 / Zn / Carageenan
  - 5P12 RANTES
  - Griffithsin
- Phase 1
  - Maraviroc

Alternative PrEP Strategies

- Oral PreP is licensed in the US
- Uptake still quite limited but improving

Unique PrEP users n (%)	2,319
Mean age in years	38 (12)
Younger < 25 y/o	12.3%
Female	48.8%
Medicaid	9.9%

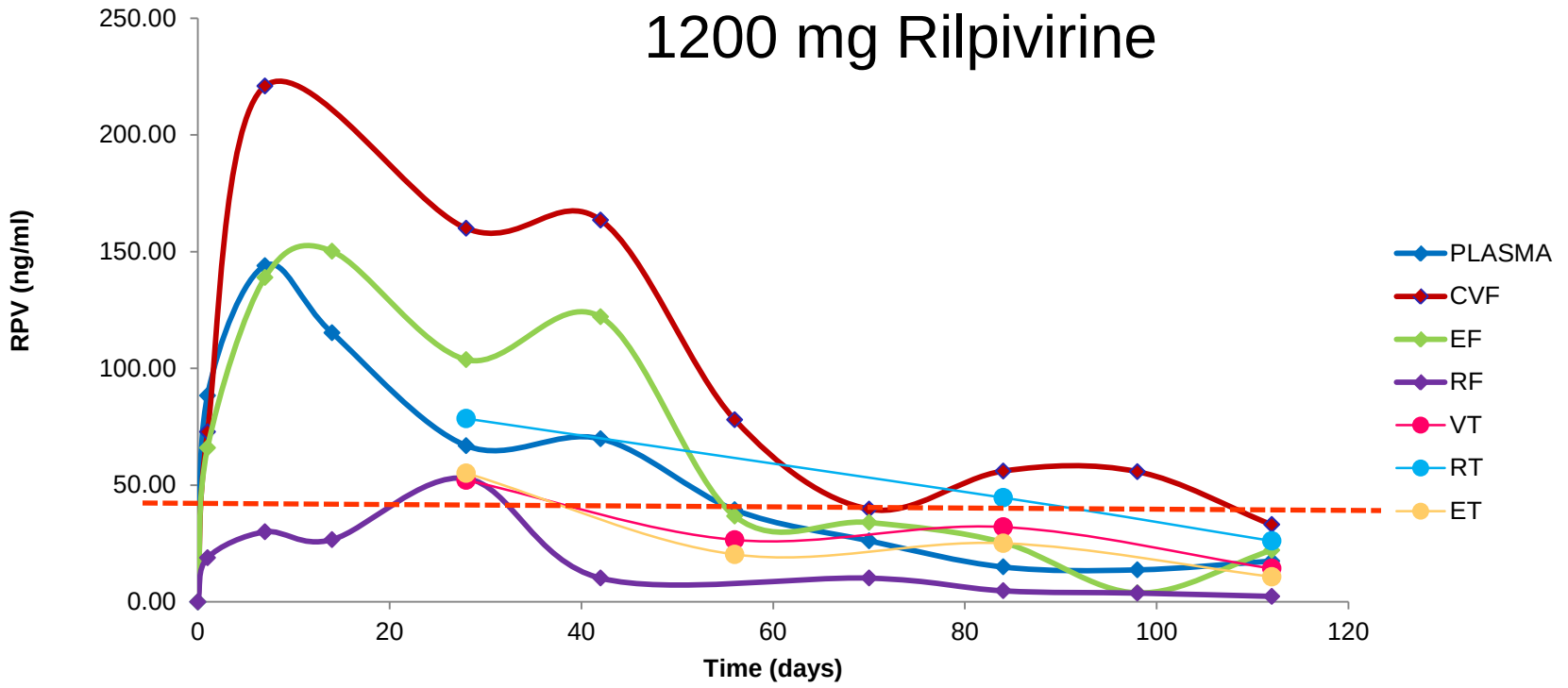
January 2012 – September 2013 / 55% of US pharmacies

Mera Robertino et al. HIV Drug Therapy in the Americas, 2014

Alternatives to Rectal Microbicides?

- Two products under evaluation
- Rilpivirine (NNRTI)
- 744 (Integrase)
- IM injection
- Potential for 1-3 month delivery
- Supportive NHP data for 744
- Phase 1 PK/PD studies ongoing for TMC278
  - MWRI-01

PK Profile in MWRI-01



MWRI-01 PK/PD

Who Is Sailing the TFV RM Ship?

CONRAD

DAIDS

Gilead

MTN

IPM

Summary (1)

- Many of the critical questions related to development of a TFV rectal microbicide will be addressed in MTN-017
- A Phase 3 study could start in Q4 2016
  - Planning needs to start now!
  - The landscape will be challenging
- We need continued efforts to create desire within a Phase 3 program and beyond

Summary (2)

- Undertake modelling of:
  - Clinical trial design
  - Effectiveness in subpopulations
  - Cost effectiveness
- Put comprehensive TFV RM development plan together including a target product profile
- Further assessment of end user needs and funding agency interest

Thank You