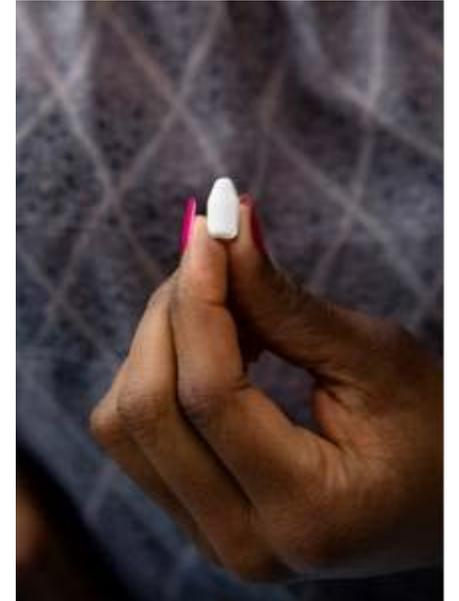
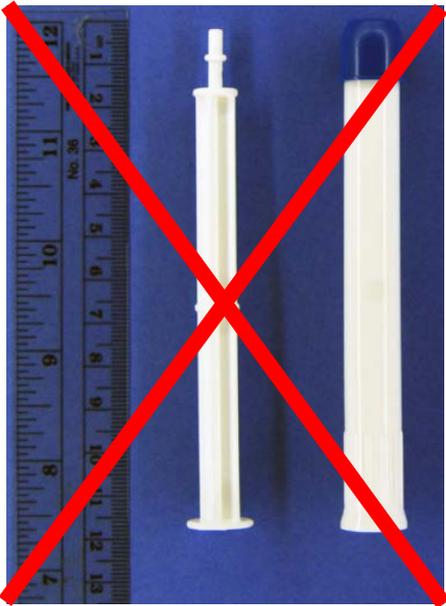


The Path Ahead for Rectal Microbicides



Craig W. Hendrix, MD
Wellcome Professor & Director, Clinical Pharmacology
Johns Hopkins University

Rectal Microbicide Need

- Not everyone wants to use oral PrEP
 - MTN-017 28% least liked daily oral TDF/FTC
- Multiple product options improve overall adherence
 - Contraceptive experience indicates more options → more prevention
- Behaviorally-congruent product: Medicated Lube or douche
 - Ardently desired by community
 - Least behavioral adaptation: change product, not behavior
- Commercial market analysis not well developed - liability

Rectal Microbicide Feasibility

- **On demand** oral PrEP (Truvada) efficacy high
 - Ipergay 86 % risk reduction
- **On demand** vaginal tenofovir efficacy modest
 - CAPRISA 004, FACTS 001 ~60% with good adherence
- Animal models: rectal tenofovir protects from anal monkey HIV
- **Behaviorally-congruent** formulations –
 - ARV-medicated sex lubricant or douche
 - “piggy-back” onto very common sex practices
 - less demanding of behavior change

Gaps in Knowledge

- Will any product deliver enough drug to the rectum?
- Can a product double as desirable lube or douche AND an effective microbicide?
- Does any product protect from other STIs as well as HIV?
- Can any drug protect both rectum & vagina with one dose?

To address these key questions ...

... the Rectal Road Continues

- 6 drugs, 4 formulations being tested as rectal microbicides in 8 studies
- 5 MTN rectal microbicide studies being developed, 2 expected to launch in 2017
- 3 Program Project grant studies ongoing or in development

... all funded by the DAIDS (Thank you!)



MTN-035 Study

- *Which formulation(s) are desirable in the sexual context?*
- Phase I acceptability, tolerability & adherence (placebo)
 - Douche (enema)
 - Insert (fast-dissolving tablet)
 - Suppository
- MSM & transgender women (N=210)
- Rectal products used in the context of sex
- Product use based acceptability, preference outcomes



MTN-033 Study

- *Is DPV gel both a desirable lube & potential microbicide?*
- Phase 1 DPV rectal gel as sexual lubricant
- Compare application of gel as sexual lubricant (using phallus & simulated anal sex) to applicator dosing of gel
- MSM & transgender women (N=16)
- Outcome: DPV concentration & distribution in colon

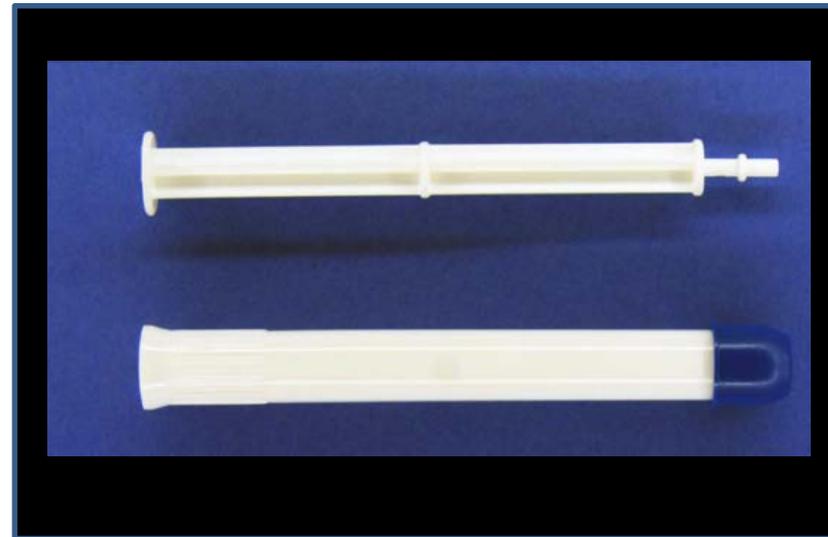
	N	Period 1	Washout	Period 2
Sequence A	8	DPV gel (2.5 g) applicator	2-4 weeks	DPV gel phallic device
Sequence B	8	DPV gel (10.0 g) phallic device		DPV gel applicator

Is Gel as Lube Feasible?

Douche
Saline-like 125 mL



Applicator Gel
HEC 10 mL



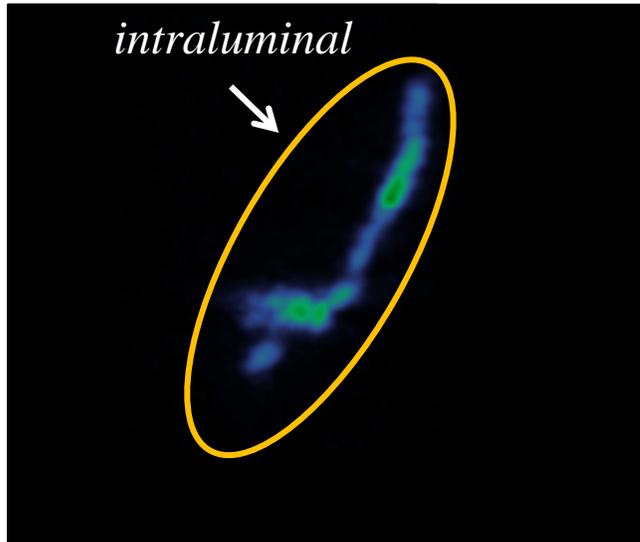
Manual Lube Application
Wet™ 10 mL



- How much product is delivered?
- Where is the gel distributed?

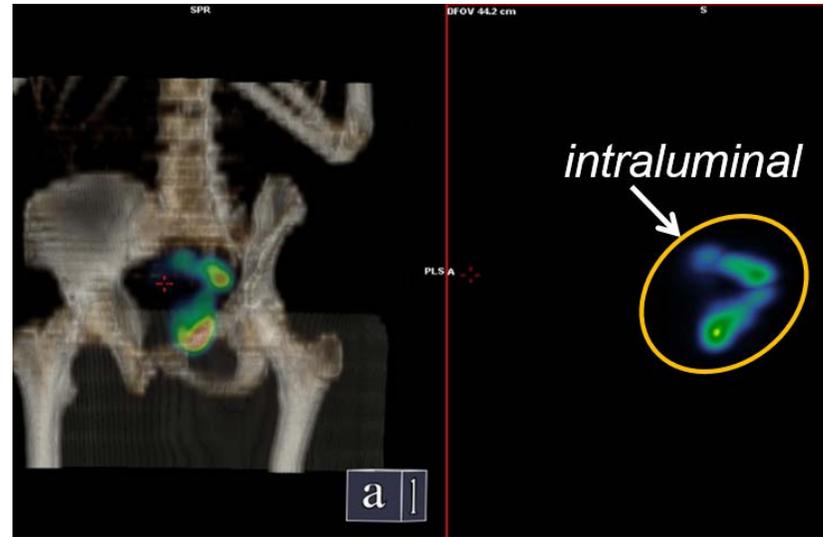
Is Gel as Lube Feasible?

Douche
Saline-like 125 mL



- Delivered: 60%
- Distribution: 60 cm

Applicator Gel
HEC 10 mL



- Delivered: 95%
- Distribution: 5.9–7.4 cm

Manual Lube Application
Wet™ 10 mL



- Delivered: 3% (10% of 3.5 mL)
- Distribution: 4.4–15.3 cm

*Sexual lubricant as Rectal Microbicide is feasible
IF we can increase the concentration of ARV in the gel*

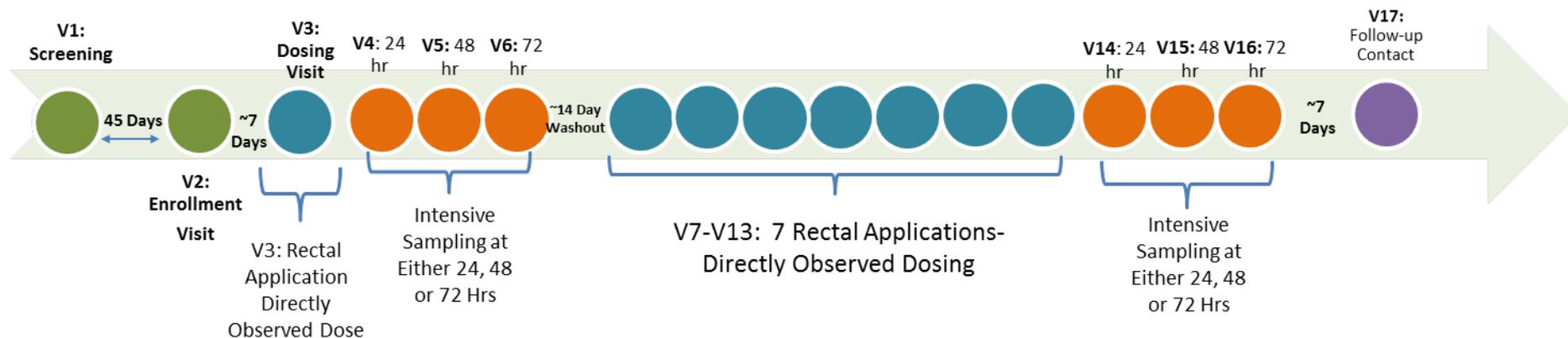
MTN-033 Study

- *Is DPV gel both a desirable lube & potential microbicide?*
- Phase 1 DPV rectal gel as lube
- Compare application of gel as sexual lubricant (using phallus & simulated anal sex) to applicator dosing of gel
- MSM & transgender women (N=16)
- Outcome: DPV concentration & distribution in colon tissue

	N	Period 1	Washout	Period 2
Sequence A	8	DPV gel (2.5 g) applicator	2-4 weeks	DPV gel phallic device
Sequence B	8	DPV gel (10.0 g) phallic device		DPV gel applicator

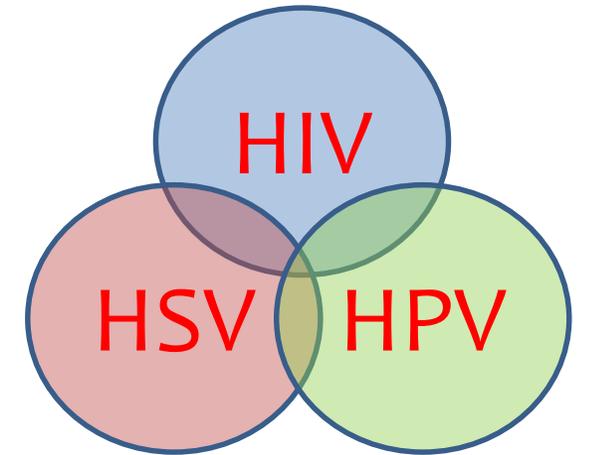
MTN-026 Study

- *How will Dapivirine (DPV) perform as a rectal gel?*
- Phase 1 rectal DPV 0.05% gel
- Dapivirine proven efficacy in women (vaginal ring)
- Safety, acceptability, drug concentration, tissue infectivity
- Men & women (cis & transgender) (N=27)



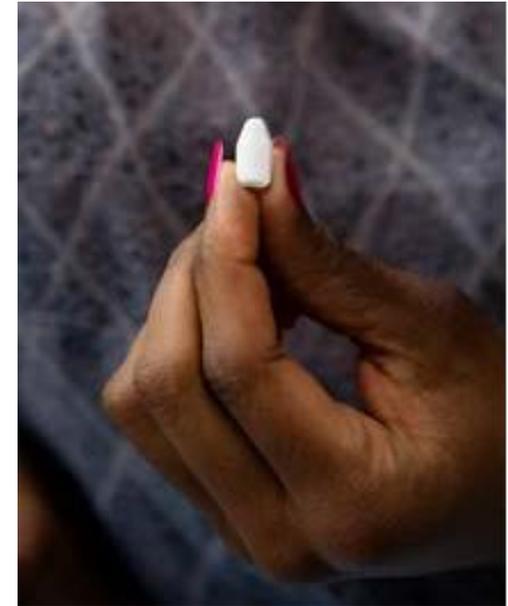
MTN-037 Study

- *Will multi-purpose antiviral achieve target concentrations?*
- Phase I MIV-150 / Carrageenan / Zinc gel
- Blocks HIV, HSV, & HPV in lab & animals
- Men & women (cis & transgender) (N=24)
- Single dose, volume escalation 4 mL to 32 mL
- Safety, acceptability, drug conc'n, tissue protection
- Population Council Collaboration (*also vaginal product*)



MTN-039 Study

- *Is a rectal insert feasible as rectal microbicide?*
- Phase 1 Elvitegravir (licensed for Rx) insert
- Men & women (cis & transgender) (N = 20)
- Single dose at two dose levels
- Safety, acceptability, drug concentration, biopsy susceptibility to infection
- CONRAD collaboration (*also vaginal product*)



Planned/Ongoing RM Clinical Studies

- 8 Studies
- 6 Drugs
- 4 Formulations
- All Start by 2018

Study	Drug	Formulation	Dose Levels	N drug (total)	TGW	CGW	TOX	PK	PD	ACC
MTN-035	No API	insert, supp, douche (PL)	NA	(150)	✓	-	✓			✓
MTN-026	DPV	gel (HEC)	1	18(27)	✓	✓	✓	✓	✓	✓
MTN-033	DPV	gel (appl v manual)	1	16	✓	-	✓	✓	✓	✓
MTN-037*	MIV-150	gel applicator	3	12	✓	✓	✓	✓	✓	✓
MTN-039**	EVG	inserts	2	30	✓	✓	✓	✓	✓	✓
DREAM U19	TFV	douche	3	18	✓	✓	✓	✓	✓	✓
ImQuest U19	IQP 0528	Duogel	1	16	✓	✓	✓	✓	✓	✓
PREVENT U19	Griffithsin	gel applicator	1	18	✓	✓	✓		✓	✓

*Partnership with Population Council; **Partnership with CONRAD

Each Study Fills Unique RM Gap

Active Drug	Gel w/ Applicator	Gel as Lube	Douche	Insert	Suppository
Placebo	√√√√	√	√, MTN-035 06/18-02/20	MTN-035 06/18-02/20	MTN-035 06/18-02/20
Tenofovir	√√√√√		DREAM 01 11/16-4/18		
Maraviroc	√				
Dapivirine	MTN-026 09/17-12/18	MTN-033 12/17-01/19			
Elvitegravir				MTN-039 05/18-07/19	
IQP-0528	ImQuest 02 09/17-10/18				
MIV-150/Zn/CG	MTN-037 01/18-05/19				
Griffithsin	PREVENT 2018-2019				

All end by Q1 2020

On Demand

Behaviorally-
Congruent

Multi-purpose STI

Vaginal & Rectal

√ completed study; √ Phase 2; Estimated start-completion dates for Enrolling & Planned studies

Study Timelines

Study	Drug	Formulation, niche	Q3 17	Q4 17	Q1 18	Q2 18	Q3 18	Q4 18	Q1 19	Q2 19	Q3 19	Q4 19	Q1 20	Q2 20	Q3 20	Q4 20
DREAM	TFV	Douche														
MTN-026	DPV	Appl. Gel														
IQP DuoGel	IQP-0528	Appl. gel														
MTN-033	DPV	Lube														
MTN-037*	MIV-150	Appl. Gel, MPT														
PREVENT	GRFT	Appl. Gel, luminal														
MTN-039**	EVG	Insert														
MTN-035	Placebo	Douche, Insert, Supp														

*Partnership with Population Council; **Partnership with CONRAD

Summary

- Rectal microbicide need & feasibility high
- Only one Phase 2 study (MTN-017) – no pivotal trial
- 8 phase I studies, 7 ARVs, 4 formulations, all done by Q1 2020
 - Integrate safety, acceptability, PK, & PD *in first study*
 - Include trans & cis women
- Community remains supportive of rectal microbicides, *BUT*
 - Desire a lubricant rather than an applicator delivered gel
 - Prefer on demand to daily dosing
- Challenge: How to choose among these candidates?

Acknowledgements

- Ian McGowan for his visionary leadership of RM development
- Jim Pickett & Matt Rose for teaching me about community
- Clare Collins for helping me to speak normally
- MTN: Judy Jones, Jennifer Thomas, Luis Duran
- FHI360: Sherri Johnson, Philip Andrew, Tara McClure
- Ross Cranston, Craig Hoesley, Sharon Riddler, Jose Bauermeister
- Amazing site teams, LC, SCHARP for dosing such complex studies



Thank You!

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. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.



CHARM Program TFV 1% Gels Compared

- TFV 1% gel Product Comparison (osmolality key variable)
 - VF 3,111 mOsm/kg
 - RGVF 836 mOsm/kg
 - RF 479 mOsm/kg

- Results
 - Acceptability: **RF = RGVF = VF** (unlike MTN-006)
 - Plasma TFV & Permeability: **VF > RGVF > RF**
 - Colon TFV-DP: **VF > RF ≥ RGVF**
 - Explant: **RF > RGVF**

Acceptability:

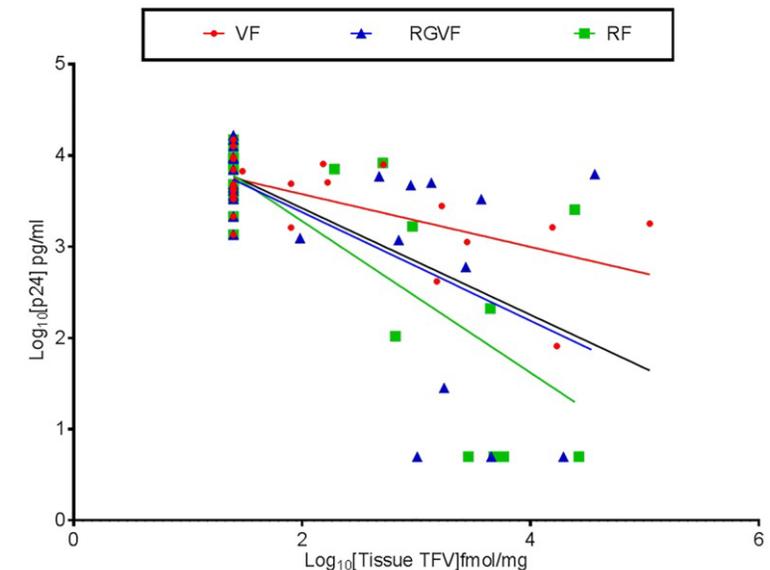
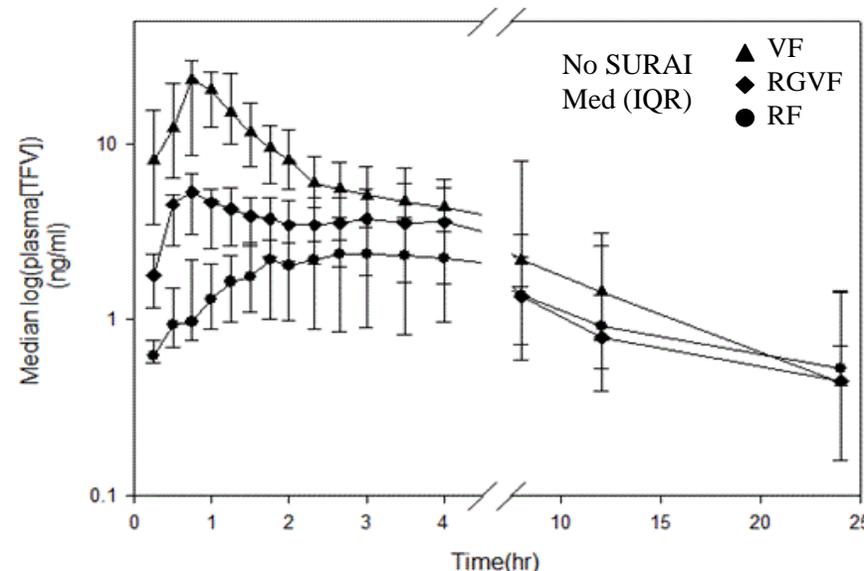
consistency, smell, taste, color, stickiness, lubrication, rectal feeling

Product acceptability ranges NS

RF 75%-100%

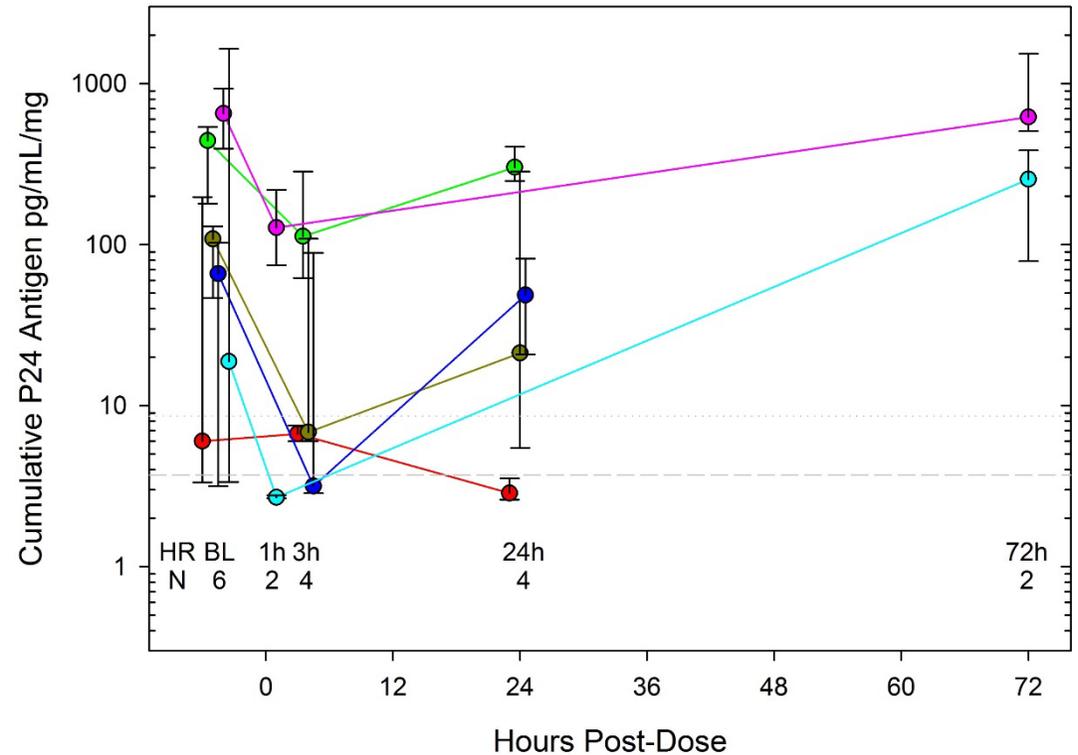
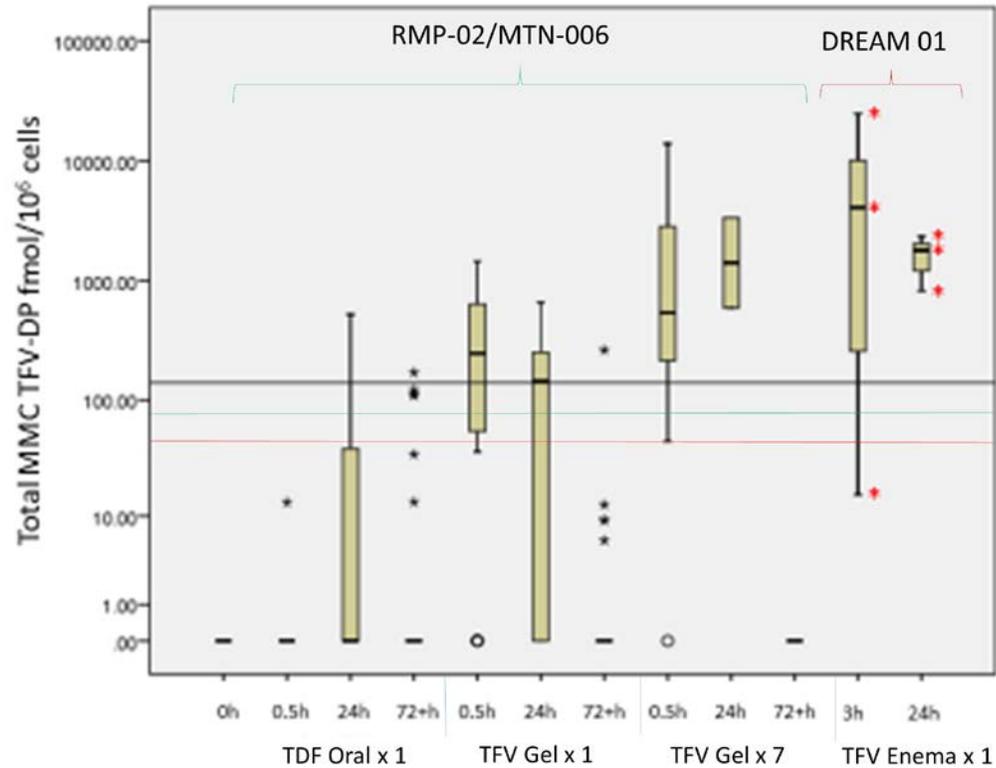
RGVF 82%-100%

VF 82%-100%



DREAM Program

- Behaviorally-congruent Episodic Use TFV Prodrug Enema (Douche)
- Preclinical - no superior prodrug, Hypo-osmolar up to 5X ↑colon TFV-DP
- Clinical – SAD 1st dose level preliminary data (below) – PK, PD, Tox, Accept

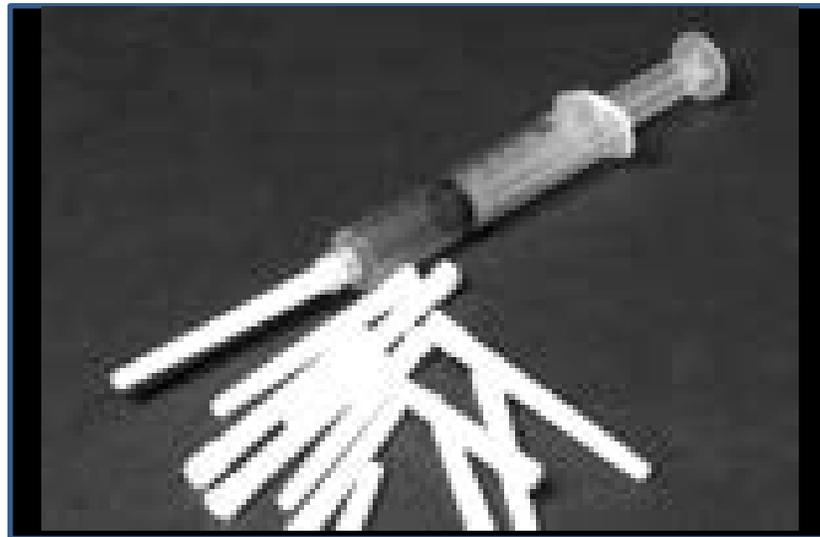


Is Gel as Lube Feasible?

Douche
Saline-like 125 mL



Applicator Gel
HEC 10 mL



Manual Lube Application
Wet™ 10 mL



- How much product is delivered?
- Where is the gel distributed?

TFV Microbicide Development To Date

Methods/Vehicle Development

JHU
"HIV" surrogate distribution

JHU
Tissue pharmacology methods

CDC
GI PK-D imaging development

MDP 2/2b
RF vehicle development

MDP 1
Enema vehicle development

JHU
Lube dosing feasibility

Drug Product Development

- Vaginal Formulation (VF)
 - 3,111 mOsm/kg
 - TFV 1%

- Reduced Glycerin (RGVF)
 - 836 mOsm/kg
 - TFV 1%

- Rectal Formulation (RF)
 - 479 mOsm/kg
 - TFV 1%

- Enema Formulation (EF)
 - Dose escalation
 - Iso- or hypo-osmolar

Phase I

HPTN 050
PK blood
AEs, culposcopy

RMP-02/MTN-006
PK blood/tissue
AEs, flow, histology

MTN-007
AE, flow, 'omics
no PK

CHARM 01/02 VF, RGVF, RF
PK blood/tissue, imaging, SURAI
ex vivo PD, microbiome
AE, histology, flow, permeability
Acceptability

DREAM 01/02 Dose escalation
PK blood/tissue, imaging, SURAI
AE, histology, 'omics
ex vivo PD
Acceptability

Phase II

HPTN 059
PK blood
AEs

No Phase II
• Safety
• AEs

MTN-017
Safety,
Adherence PK

Phase III

CAPRISA 004 BAT 24

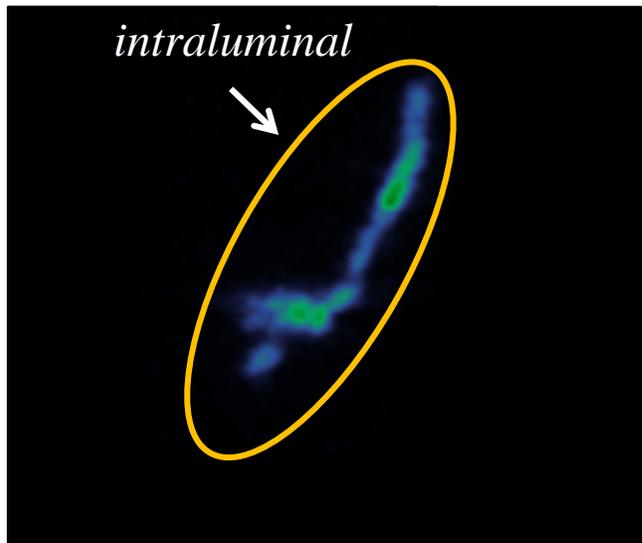
VOICE QD

FACTS 001 BAT 24

Future RCT ?
• Applicator
• Safety

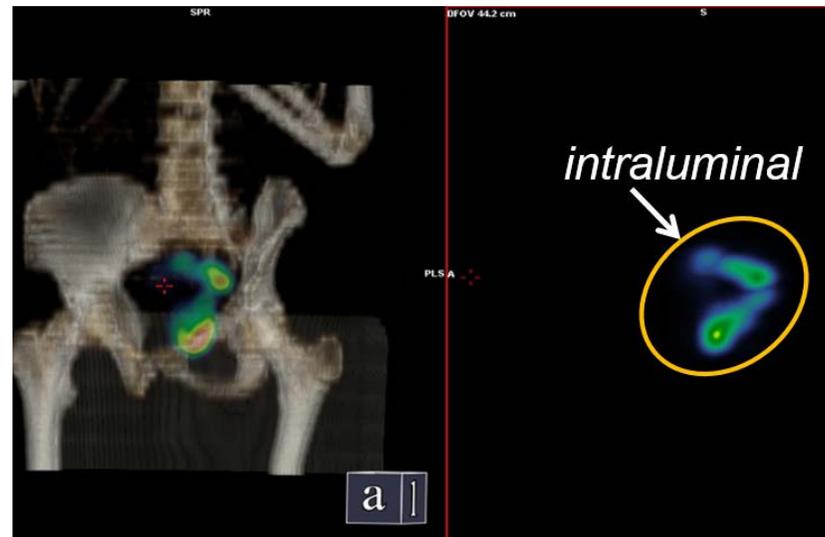
The Paths Ahead for Rectal Microbicides

Douche
Saline-like 125 mL



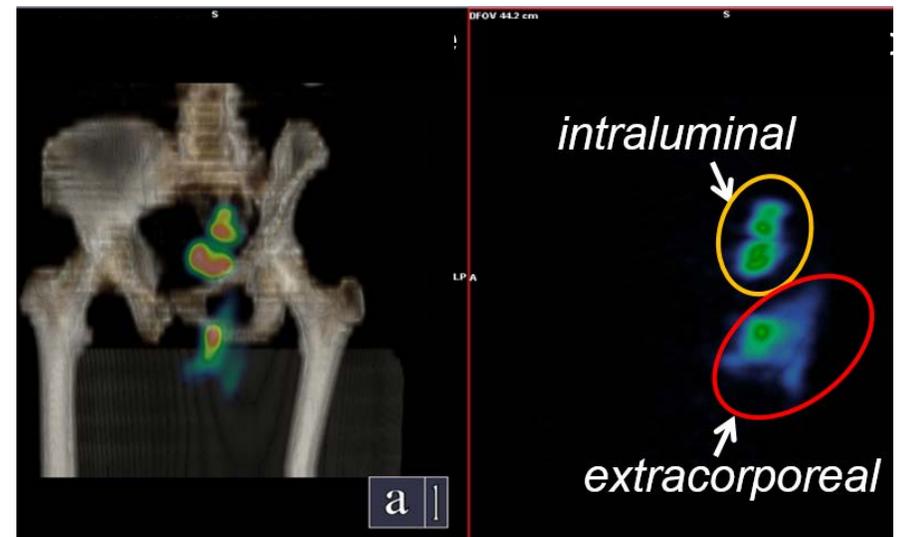
- Retention: 60%
- Distribution: 60 cm

Applicator Gel
HEC 10 mL



- Retention: 95%
- Distribution: 5.9–7.4 cm

Manual Lube Application
Wet™ 10 mL



- Retention: 3%
- Distribution: 4.4–15.3 cm

TFV Microbicide Development Future

Methods/Vehicle Development

JHU
"HIV" surrogate distribution

JHU
Tissue pharmacology methods

CDC
GI PK-D imaging development

MDP 2/2b
RF vehicle development

MDP 1
Enema vehicle development

JHU
Lube dosing feasibility

Drug Product Development

- Vaginal Formulation (VF)
 - 3,111 mOsm/kg
 - TFV 1%

- Reduced Glycerin (RGVF)
 - 836 mOsm/kg
 - TFV 1%

- Rectal Formulation (RF)
 - 479 mOsm/kg
 - TFV 1%

- Enema Formulation (EF)
 - Dose escalation
 - Iso- or hypo-osmolar

Phase I

HPTN 050
PK blood
AEs, culposcopy

RMP-02/MTN-006
PK blood/tissue
AEs, flow, histology

MTN-007
AE, flow, 'omics
no PK

CHARM 01/02 VF, RGVF, RF
PK blood/tissue, imaging, SURAI
ex vivo PD, microbiome
AE, histology, flow, permeability
Acceptability

DREAM 01/02 Dose escalation
PK blood/tissue, imaging, SURAI
AE, histology, 'omics
ex vivo PD
Acceptability

Phase II

HPTN 059
PK blood
AEs

No Phase II
• Safety
• AEs

MTN-017
Safety,
Adherence PK

Phase III

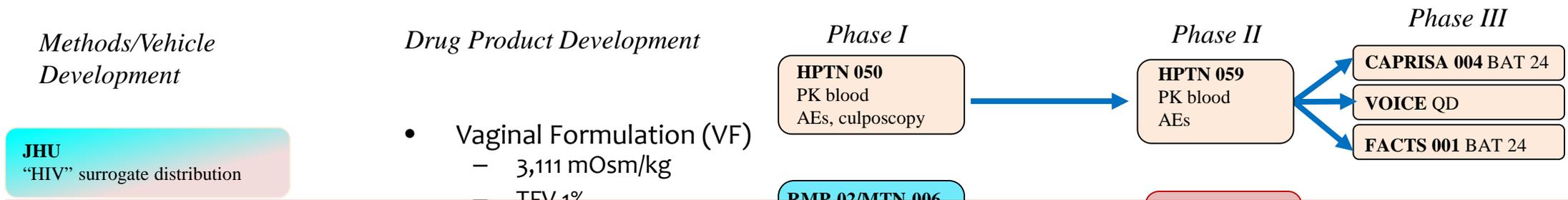
CAPRISA 004 BAT 24

VOICE QD

FACTS 001 BAT 24

Future RCT ?
• Applicator
• Safety

TFV Microbicide Development Future



Currently No TFV Study Planned by MTN

