The Path Ahead for Rectal Microbicides

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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

<table>
<thead>
<tr>
<th>N</th>
<th>Period 1</th>
<th>Washout</th>
<th>Period 2</th>
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<tbody>
<tr>
<td>Sequence A</td>
<td>8 DPV gel (2.5 g) applicator</td>
<td>2-4 weeks</td>
<td>DPV gel phallic device</td>
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<tr>
<td>Sequence B</td>
<td>8 DPV gel (10.0 g) phallic device</td>
<td></td>
<td>DPV gel applicator</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Sequence</th>
<th>N</th>
<th>Period 1</th>
<th>Washout</th>
<th>Period 2</th>
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<td>DPV gel (10.0 g) phallic device</td>
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<td>DPV gel applicator</td>
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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**

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Formulation</th>
<th>Dose Levels</th>
<th>N drug (total)</th>
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*Partnership with Population Council; **Partnership with CONRAD*
## Each Study Fills Unique RM Gap

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<th>Active Drug</th>
<th>Gel w/ Applicator</th>
<th>Gel as Lube</th>
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☑️ completed study; ☑️ Phase 2; Estimated start-completion dates for Enrolling & Planned studies

All end by Q1 2020

- On Demand
- Behaviorally-Congruent
- Multi-purpose STI
- Vaginal & Rectal
# Study Timelines

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*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

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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%

CHARM-01: McGowan PLOS One 2015; CHARM-02: Hiruy ARHR 2015
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 059: PK blood, AEs, culposcopy
- RMP-02/MTN-006: PK blood/tissue, AE, flow, histology
- MTN-007: AE, flow, ’omics, no PK
- CHARM 01/02: VF, RGVF, RF, PK blood/tissue, imaging, SURAI, ex vivo PD, microbe, AE, histology, flow, permeability, Acceptability

**Phase II**
- No Phase II
- MTN-017: Safety, Adherence PK

**Phase III**
- Future RCT?
  - Applicator
  - Safety

**Future RCT?**
- HPTN 059: PK blood, AEs
- JHU: 'HIV' surrogate distribution
- CDC: GI PK-D imaging development
- MDP 2/2b: RF vehicle development
- MDP 1: Enema vehicle development
- JHU: Lube dosing feasibility
Is Gel as Lube Feasible?

The Path Ahead for Rectal Microbicides

Douche
Saline-like 125 mL

Applicator Gel
HEC 10 mL

Manual Lube Application
Wet™ 10 mL

- Retention: 60%
- Distribution: 60 cm

- Retention: 95%
  Distribution: 5.9–7.4 cm

- 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 059**
  - 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

Methods/Vehicle Development

JHU
“HIV” surrogate distribution

Drug Product Development

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

• Reduced Glycerin (RGVF)
  – 836 mOsm/kg
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• 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

Phase II

HPTN 059
PK blood
AEs

Phase III

CAPRISA 004 BAT 24

VOICE QD

FACTS 001 BAT 24

Currently No TFV Study Planned by MTN

Methods/Vehicle Development

MDP 1
Enema vehicle development

JHU
Lube dosing feasibility

HPTN 059
PK blood
AEs, culposcopy

RMP 02/MTN 006

Acceptability

DREAM 01/02 Dose escalation
PK blood/tissue, imaging, SURAI
AE, histology, ’omics
e x vivo PD
Acceptability

Future RCT?