On Demand, Behaviorally-Congruent Rectal Microbicide Douche

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MTN Annual Meeting 2018
Outline

• Describe need for rectal microbicides
  – Limitations to daily oral PrEP
  – Limitations to on demand rectal gel applicator

• Discuss microbicidal douche development
  – Community demand/readiness (next up - Alex!)
  – Vehicle development
  – Clinical Development
  – NHP SHIV challenge proof-of-concept
Rectal Microbicide Feasibility

- Oral PrEP *not* for everyone
- Product *options* improve adherence
- *On demand* oral TDF/FTC & vaginal PrEP efficacious; rectal gel high adherence
- *Behaviorally-congruent* ARV formulations “piggy-back” onto commonly used sex products
Rectal Microbicide Development

• Are rectal douches acceptable to those at risk?
• Can ARVs be delivered safely by rectal douche?
• Can douches provide protective concentrations?
• Can a rectal douche prevent HIV?
Enema Vehicle Selection

- 9 men, single dose cross-over
- Hyper-, iso-, hypo-osmolar enema
- Luminal PK, histology, acceptability favor iso-osmolar

Leyva, et al. ARHR 2013
Rectal Distribution: Microbicide & “HIV”

“Microbicide”\(^{(111} \text{In-DTPA)}\) \hspace{1cm} “HIV” \(^{(99m} \text{Tc-SC)}\) in Ejaculate

Rectal TFV gel (0h), simulated sex/ejaculation (1h), SPECT/CT (2h)

Hiruy, et al. ARHR 2015
Speeding Tissue Absorption

- Administered in isotonic (iso) or hypotonic (hypo) solution
- Fluorescent particle distribution mouse vagina 10’ post-dose
- Vaginal mucosal surface coverage varies with osmolality

DREAM Program

• Background
  – Adherence & choice greatest PrEP needs
  – On demand, behaviorally congruent widely desired
  – Enema behaviorally-congruent (67-75% RAI MSM)

• Objectives
  – Single dose TFV (prodrug) enema, 1 week protection

• Process
  – Sequential mice, macaque, human
  – Select best of TFV, TDF, TAF, CMX-157
  – Optimize formulation, osmolality, nano, gelling
Interspecies TFV-DP Comparisons

- Hypo-osmolar >5x increases in tissue TFV-DP in macaques
- Significant variability ($1\log_{10}$ range common)
- Target concentrations achieved by median low, exceeded by high doses

Xiao et al AAC 2017
Macaque Explant Protection

**Product B**
TFV 5.28 mg/mL Iso-osmolar

- Rectal explant culture: post-1 hr of DREAM product B
- Rectal explant culture: post-24 hr of DREAM product B
- Rectal explant culture: post-72 hr of DREAM product B

**Product C**
TFV 5.28 mg/mL Hypo-osmolar

- Rectal explant culture: post-1 hr of DREAM product C
- Rectal explant culture: post-24 hr of DREAM product C
- Rectal explant culture: post-72 hr of DREAM repeat product C

Time:
- 1 hr
- 24 hrs
- 72 hrs
DREAM-01 FIH Study

- Design: Phase I, single ascending dose study
- Goal: Identify dose achieving colon cell [TFV-DP] target
- Objectives: Safety, PK, PD (explant), & Acceptability
- Products (125 mL):
  - A: TFV 1.76 mg/mL (normal saline)
  - B: TFV 5.28 mg/mL (normal saline)
  - C: TFV 5.28 mg/mL (half-normal saline)
- Subjects: 18 MSM receive all 3 products sequentially
- Outcomes:
  - Safety: AEs, histology
  - PK: (intense) blood, (sparse), colorectal tissue, rectal fluid
  - Explore: colon proteomics & metabolomics, microbiome
Safety

AE: None > Grade 2

<table>
<thead>
<tr>
<th>Participants who experienced an AE</th>
<th>Total</th>
<th>Product A</th>
<th>Product B</th>
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<tbody>
<tr>
<td>Grade 1</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Grade 2</td>
<td>3</td>
<td>2</td>
<td>1</td>
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<tr>
<td><strong>Total</strong></td>
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<td><strong>5</strong></td>
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<table>
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<th>Total # of AE’s Reported</th>
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<tbody>
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<td>8</td>
<td>1</td>
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<tr>
<td>Grade 2</td>
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<td><strong>Total</strong></td>
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<td><strong>10</strong></td>
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Histology: No Change from Baseline

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<tr>
<th>Product</th>
<th>Time</th>
<th>Overall Grade (0-5)</th>
<th>Epithelial Denudation (0-3)</th>
<th>Lamina propria Hemorrhage (0-3)</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>Pre-Dose</td>
<td>0.5</td>
<td>1.0</td>
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<tr>
<td>Product A</td>
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<td>1.0</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>24 hrs</td>
<td>0.5</td>
<td>3.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>72 hrs</td>
<td>0.5</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Product B</td>
<td>1 or 3 hrs</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>24 hrs</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>72 hrs</td>
<td>1.0</td>
<td>0.0</td>
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</table>

Product C not shown – No AE > Grade 2 product related, histology no change from baseline
Colonic Luminal Distribution

Desired Colon Luminal Coverage

<table>
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<tr>
<th>J001</th>
<th>J002</th>
<th>J003</th>
<th>J004</th>
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<tr>
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<tr>
<td>Product B</td>
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</table>
Plasma TFV & PBMC TFV-DP PK

Low Systemic Exposure

Plasma Tenofovir (ng/mL)

Hours

0 12 24 36 48 60 72

Product A 220 mg/125 mL 0.9% NaCl
Product B 660 mg/125 mL 0.9% NaCl
Product C 660 mg/125 mL 0.45% NaCL
DREAM-01 Colorectal Tissue PK

Very High Colon Tissue Cell TFV-DP

[Graph showing MMC TFV-DP fmol/10^6 cells over time for different treatments and dosing frequencies.]
NHP Oral TDF v. TFV Douche PD

- Weekly intrarectal $10^3$ TCID$_{50}$ R5 SHIV
- Weekly plasma viral RNA by qPCR
- 2 vRNA values > 250/mL x 2 wks = infected

IP/CP-HTM DREAM U19, Francois Villinger, Univ Louisiana (Lafayette) CROI LB 2018
NHP Oral TDF v. TFV Douche PK

- Plasma TFV concentrations similar
- Colorectal tissue TFV-DP far higher with rectal dosing (not steady-state)
- Steady-state oral TDF NHP studies underway

Francois Villinger, Univ Louisiana (Lafayette) CROI LB 2018

TFV concentrations in plasma

TFV-DP concentrations in Rectal Tissues

- Plasma TFV concentrations similar
- Colorectal tissue TFV-DP far higher with rectal dosing (not steady-state)
- Steady-state oral TDF NHP studies underway

Francois Villinger, Univ Louisiana (Lafayette) CROI LB 2018
DREAM-01 Data to Come

- Proteomics (Adam Burgener)
- Metabolomics (Anne Le)
- Microbiome (Jaques Ravel)
- Acceptability (Alex Carballo-Dieguez & Rebecca Giguere)
- DREAM Grindr Survey (on deck)
Summary

• New methods developed to enable development
• Complex early studies informed development
• DREAM Pre-Clinical
  – Hypo-osmolar formulations increase tissue TFV-DP
  – Douche better than oral in NHP SHIV challenge
• DREAM-01 Clinical
  – ~85% complete, no safety signal
  – TFV-DP colon “target” exceeded by $2-3\log_{10}$ in 1-3 hrs
  – Plasma TFV below & colon TFV-DP above NHP
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