Rectal Microbicides

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Magee-Womens Research Institute
University of Pittsburgh
Questions About Rectal Microbicides

- Are they needed?
- Would anyone use them?
- Would they work?
- Where is the science?
- How would they fit into the HIV prevention landscape?
Are Rectal Microbicides Needed?
US HIV Incidence in MSM

Sifakis F et al. JAIDS 2007
HIV Prevalence in African MSM

Beyrer Lancet 2012
Would Anyone Use a Rectal Microbicide?
Lubricant Use is Common Among MSM

Potential Rectal Microbicide Use

• Prevention preparedness studies
  – Gross et al. Sex Transm Dis 1998
• Conjoint analysis in Peruvian MSM
  – Kinsler et al. Int J STD AIDS 2010
• Community advocacy
  – International Rectal Microbicide Advocates
    – 1,100 advocates on six continents
    – http://www.rectalmicrobicides.org/
 Would Rectal Microbicides Work?
Non Human Primate Studies

- Cyanovirin-N / SHIV89.6P
  - Tsai et al. AIDS Res Hum Retroviruses 2003
- Tenofovir / SIVmac251/32H
- MIV-150 / SIVmac239
Rectal Macaque Tenofovir Data

- Proviral DNA
- Viral RNA

Colorectal Intestinal Explants

Endoscopic biopsies + Absorbable gelatin sponge

Colorectal Explant Infection

HIV-1 RNA/DNA & p24 (Mean ± SD)

- Malnati (DNA)
- Li/Wong (DNA)
- Rouet (RNA)
- Drosten (RNA)
- HIV-1 p24

Day 4  Day 7  Day 11  Day 14
Maraviroc In Vitro Colorectal Explant Efficacy Data

Dezzutti et al. CHARM Project 1
Ex vivo / In Vitro Challenge Model

Where is the Science?
Preclinical Development

• *In vitro* assessment of safety and efficacy
  – TZM-bl & PBMC
  – Explants

• Animal models of safety and efficacy
  – Humanized mice
  – Non-human primates

• Preclinical toxicology
  – Rabbits
  – Rats
Formulation Studies

• Formulation preference: gel and suppository
  – Carballo-Dieguez et al. Sex Transm Infect 2008

• Formulation volume
  – Carballo-Dieguez et al. Sex Transm Dis 2007

• Rectal specific formulation development and assessment
  – Wang et al. AIDS Res Ther 2011
Product Distribution

Phase 1 Development

- Nonoxynol-9 (HIVNET-008 study)
  - Tabet et al. *Sex Transm Infect* 1999

- UC781 (RMP-01 study)
  - Anton et al. *PLoS ONE* 2011

- Tenofovir (original formulation) (RMP-02/MTN-006 study)

- Tenofovir (reduced glycerin formulation) MTN-007
  - McGowan et al. *CROI* 2012
Key Findings from HIVNET-008

- Low-dose (52.5 mg/ml) N-9 was not associated with macroscopic rectal ulceration
- GI symptoms such as rectal fullness common after exposure to placebo and N-9
- High rates of histological abnormality after placebo and N-9 gels
- N-9 acceptability inconclusive and warranted further study of redesigned applicators and ways to minimize rectal side effects.

Gross M et al. Sex Trans Dis 1999
UC781 (RMP-01)

- Phase 1 study
- NNRTI
- Single & 7 day exposure
- Safe and acceptable
- Significant viral suppression in explant challenge

Anton et al. PLoS ONE 2011
RMP-02/MTN-006

Baseline Evaluation

Open label Oral tenofovir (N = 18)

Safety, PK / PD, acceptability

Single rectal tenofovir (N = 18) 2:1

7 Day Rectal tenofovir (N = 18) 2:1

Anton PA et al. CROI 2011
PK/PD Relationship

![Graph showing the PK/PD relationship between cumulative p24 (pg/mL) and Log_{10}[Tissue TFV-DP]fmol/mg for different dose forms: Oral Dose, Single Rectal Dose, and Multiple Rectal Dose. The graph includes a regression line with r^2 = 0.33 and P = 0.0011.](image)

Anton et al. *AIDS Res Hum Res* 2012
### Phase 1 GI Adverse Events

#### RMP-02/MTN-006 (N = 12)

<table>
<thead>
<tr>
<th>GI Adverse Events in the Tenofovir Arm</th>
<th>N</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>6</td>
<td>50%</td>
</tr>
<tr>
<td>Rectal urgency</td>
<td>5</td>
<td>42%</td>
</tr>
<tr>
<td>Bloating</td>
<td>5</td>
<td>42%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>33%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>58%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3</td>
<td>25%</td>
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<tr>
<td>Proctalgia</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>42%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>12</td>
<td>100%</td>
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</tbody>
</table>
MTN-007

N=65

1% TFV (N=16)

2% N-9 (N=17)

Baseline Evaluation

Single dose

7-14 day interval

7-14 day interval

Endoscopy Safety/behavioral assessment

Screening

No Treatment (N=16)

HEC (N=16)
# Phase 1 GI Adverse Events

<table>
<thead>
<tr>
<th>GI Adverse Events in the Tenofovir Arm</th>
<th>MTN-007 (N = 16)</th>
<th>RMP-02/MTN-006 (N = 12)</th>
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</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Rectal urgency</td>
<td>0</td>
<td>5</td>
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<tr>
<td>Bloating</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>4</td>
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<tr>
<td>Diarrhea</td>
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<td>7</td>
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<tr>
<td>Flatulence</td>
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<td>3</td>
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<tr>
<td>Proctalgia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>12</td>
</tr>
</tbody>
</table>

- Abdominal pain: 3 (16%) vs. 6 (50%)
- Rectal urgency: 0 (0%) vs. 5 (42%)
- Bloating: 0 (0%) vs. 5 (42%)
- Nausea: 0 (0%) vs. 4 (33%)
- Diarrhea: 1 (6%) vs. 7 (58%)
- Flatulence: 6 (38%) vs. 3 (25%)
- Proctalgia: 1 (6%) vs. 0 (0%)
- Other: 4 (25%) vs. 5 (42%)
- Total: 9 (56%) vs. 12 (100%)
Mucosal Safety Endpoints

- Epithelial sloughing
- Histopathology
- Mucosal mononuclear cell phenotype
- Mucosal cytokine mRNA
- Luminex
- Microarray gene expression
- Fecal calprotectin
- Rectal microflora
MTN-007 Gut T Cell Phenotype

- **CD45**: Common antigen leukocyte
- **Single Cell Population of the CD45+**
- **Live CD3+ Cell of the Single Cells**
- **CD4+ / CD8+ of the Live CD3+ Cells**
- **CXCR4+ & CCR5+ on CD4+**
- **CD69+ on CD4+**
- **CXCR4+ & CCR5+ on CD8+**
- **CD69+ on CD8+**
MTN-007 Microarray Data

No Treatment

HEC placebo gel

Nonoxynol-9 gel

Tenofovir gel
MTN-007 Microarray Data

- Significant modulation of mucosal gene expression after 7 days of TFV gel
- Key pathways effected:
  - Mitochondrial function ↓
  - Innate immunity ↑

<table>
<thead>
<tr>
<th></th>
<th>Up</th>
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<tbody>
<tr>
<td>N9</td>
<td>60</td>
<td>56</td>
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<td>Tenofovir</td>
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<td>6</td>
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</table>
Phase 2: 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
  - Objective measures
  - Acceptability
  - PK/PD

PI: Ross Cranston
## MTN-017

<table>
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<td>Oral Truvada</td>
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<tr>
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**Mucosal PK/PD subset (N = 36)**
Phase 3 Development

- Contingent upon supportive data from MTN-017
- Placebo controlled trial of RG-TFV gel on expanded prevention package including oral PrEP
- N = 5,000 MSM & transgender women
- One year follow-up period
- US, Latin America, and Thailand
CHARM U19 Program Grant

- Combination HIV Antiretroviral Rectal Microbicide Program
  - Preclinical evaluation
  - Humanized mouse model
  - Phase 1 studies
    - CHARM-01 (TFV)
    - CHARM-02 (TFV)
    - CHARM-03 (MVC)

PI: Ian McGowan
GUYS EXPERIENCING LUBE

Project Gel

IS NOW ENROLLING

Call 412.641.3380
or visit www.microbicicides.us
for more information.
Microbicide Safety and Acceptability in Young Men

**Stage 1A**
Screening
240 MSM
Consensual RAI in last month
URAI in last year

**Stage 1B**
3 month Acceptability & Adherence study with placebo gel
120 MSM
RAI in last 3 months
STI negative

**Stage 2**
Phase 1 Tenofovir rectal safety study
24 MSM

PI: McGowan
Where Do Rectal Microbicides Fit in the HIV Prevention Landscape?
Combination Prevention

Conventional HIV Prevention Package + PrEP

SC ± Oral ± Rectal ± Vaginal

± HIV Vaccine
# Rectal Microbicide Timeline*

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*An approximation based on tenofovir 1% gel
Summary

• There is a clear rationale for the development of rectal microbicides
• The design of rectal safety studies includes extensive mucosal immunotoxicity, PK, and PD assays
• Rectal specific products and applicators are being developed
• It is time to move to start preparing for efficacy studies
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CONRAD
Leaders in Reproductive Health and HIV Prevention

GILEAD

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