Rectal Microbicides

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Overview

- Rationale for rectal microbicide development
- Design of Phase 1 rectal safety studies
- Rectal microbicide advocacy
- Implications for vaginal microbicide development
Rationale for Rectal Microbicide Development
Rectosigmoid Anatomy
Heterosexual AI in the US

Gross M et al. 2000
Civic D et al. 2000
Mosher WD et al. 2005
Erickson PI et al. 1995

(%) Lifetime experience of AI

Gross M et al. 2000: Yellow
Civic D et al. 2000: Blue
Mosher WD et al. 2005: Red
Erickson PI et al. 1995: Green

(%) Lifetime experience of AI

0 10 20 30 40

MTN
Heterosexual AI Outside the US

Brazil: Guimares MD et al. 1995,
Peru: Caceres C et al. 1997,
South Africa: Karim SS and Ramjee G 1998
Kenya: Schwandt M et al. 2006
US HIV Incidence in MSM

Sifakis F et al. JAIDS 2007
Nonoxynol-9 Rectal Toxicity

Baseline
+ 15 minutes

+ 15 minutes
+ 2 hours

+ 2 hours
+ 8 hours

Phillips et al. Contraception 2004
Sexual Lubricants

Iso-osmolar

Hyperosmolar

Fuchs et al J Infect Dis 2007
Design of Phase 1 Rectal Safety Studies
UC-781 Trial Design

Screening  Enrollment  Baseline Endoscopy  Randomization

0.1%  0.25%  Placebo

Single dose  2nd Endoscopy  7 single Doses  3rd Endoscopy

Anton et al. Microbicides 2008
UC-781 Study

- **Secondary Objective:**
  - To determine whether use of study product is associated with rectal mucosal damage

- **Endpoints:**
  - Epithelial sloughing
  - Histopathology
  - Mucosal mononuclear cell phenotype
  - Mucosal cytokine mRNA
  - Mucosal immunoglobulins
  - Fecal calprotectin
  - Explants infection
Interim Results

• Appears safe and well-tolerated
• Subjects highly compliant
• Procedures well tolerated
• No drop outs/withdrawals
• No Grade 3 or 4 AE
• No procedure related AE
• 7 Grade 2 AE reported in 4 of 19 individuals completing

Anton et al. Microbicides 2008
Safety Biomarkers

- % CCR5+ on CD4+

<table>
<thead>
<tr>
<th>Group</th>
<th>U19 (All)</th>
<th>U19 (Non-resp)</th>
<th>U19 (Med)</th>
<th>U19 (Responder)</th>
<th>HPTN056</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(n=8, v=24)</td>
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<tr>
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<td>(n=9)</td>
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<td>(n=9)</td>
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<td>(n=9)</td>
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<td>(n=9)</td>
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</table>

Group:
- V2
- V3
- V5
## Rectal Safety Studies

<table>
<thead>
<tr>
<th>Product</th>
<th>Status</th>
<th>Timeline</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td>UC-781</td>
<td>Completed</td>
<td></td>
<td>NIAID/DAIDS</td>
</tr>
<tr>
<td>Polyanion</td>
<td>Planned</td>
<td>Q1 2009</td>
<td>NIAID/DMID</td>
</tr>
<tr>
<td>PRO-2000</td>
<td>Planned</td>
<td>Q3 2008</td>
<td>MDP MRC-UK</td>
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<tr>
<td>MTN-007</td>
<td>Planned</td>
<td>Q1 2009</td>
<td>NIAID/DAIDS</td>
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<tr>
<td>MTN-006</td>
<td>Planned</td>
<td>Q1 2009</td>
<td>NIAID/DAIDS</td>
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<tr>
<td>UC-781 (RF)</td>
<td>Possible</td>
<td>Q4 2010</td>
<td>TBD</td>
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</table>
MTN-007

- Phase 1 rectal safety study
- Randomized blinded, placebo-controlled trial:
  - 1% vaginal formulation of tenofovir
  - Hydroxyethyl cellulose (HEC) placebo gel
  - 2% nonoxynol-9 (Ortho-Gynol II)
MTN-007 Study Design

N=60

2% N-9

1% TDF

HEC

Screening

Enrollment and behavioral asst.

Single dose

7 day washout

Safety/behavioral assessment

Safety/behavioral assessment

7 day daily doses
MTN-006 Study Design

- Single oral dose of tenofovir
- Single rectal dose of tenofovir
- 7 daily doses of tenofovir

Pharmacokinetics
- Plasma
- PBMC
- Rectal fluid
- Tissue
- MMC

Safety
- General
- Mucosal

Explant Infection
Moving Towards RM
Effectiveness studies
Imaging Microbicide Distribution

Hendrix et al. Microbicides 2008
Rectal Lymphocyte Distribution

$^{99m}$Tc-Sulfur Colloid
Cell-free HIV Surrogate

$^{111}$In-Lymphocytes
Cell-Associated HIV Surrogate

Hendrix et al. Microbicicides 2008
Rectal Specific Applicators

- Incorporates Fleet™ tip
- Can be operated with one hand
- Has grips for the fingers
- Can deliver a precise dose up to 10 ml
- Used across clinical trials, this MDD will reduce sources of acceptability and adherence variability
- Can be manufactured in gray color

Carballo-Dieguez et al. Microbicides 2008
Rectal Microbicide Advocacy
IRMA

Less Silence More Science
Advocacy to Make Rectal Microbicides a Reality

www.rectalmicrobicides.org
Implications for Vaginal Microbicide Development
Impact of Rectal Sex on Power Transmission Probability

Transmission Probability

- 1X
- 10X
- 20X
### Anal Intercourse in HPTN-059

<table>
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<tr>
<th></th>
<th>Coitally Dependent</th>
<th>Daily Use</th>
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<tbody>
<tr>
<td></td>
<td>Tenofovir</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=50</td>
<td>N=51</td>
<td>N=49</td>
</tr>
<tr>
<td>Ever anal sex</td>
<td>24%</td>
<td>25%</td>
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<tr>
<td>Anal sex, (past 7 days)</td>
<td>2%</td>
<td>0%</td>
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Summary

- Increasing evidence of RAI in heterosexuals and MSM
- Phase 1RM safety design evolving
- MTN RM portfolio
  - MTN-006
  - MTN-007
- Research focus needs to shift from safety to efficacy