The Need for Parallel Development of Rectal Microbicides

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Overview

- Rationale for conducting Phase 1 rectal safety studies of vaginal microbicides
- Update on the design of rectal safety studies
  - UC-781 Phase 1 rectal safety study
- The rectal Phase 1 pipeline
- Development of rectal-specific microbicides
- Update on rectal microbicide advocacy
Rectosigmoid Anatomy
Mucosal Targets for HIV Infection

McGowan, Biologicals 2006
Rationale for Conducting Phase 1 Rectal Safety Studies of Vaginal Microbicides
# Heterosexual Anal Intercourse is Common in the US

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Prevalence of AI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk women</td>
<td>1268</td>
<td>32%</td>
<td>Gross M et al. 2000</td>
</tr>
<tr>
<td>College students</td>
<td>210</td>
<td>20%</td>
<td>Civic D 2000</td>
</tr>
<tr>
<td>US Survey 15 – 44 years NSFG</td>
<td>12,571</td>
<td>35-40%</td>
<td>Mosher WD et al. 2005</td>
</tr>
<tr>
<td>Californian residents</td>
<td>3545</td>
<td>6-8%</td>
<td>Erickson PI et al. 1995</td>
</tr>
</tbody>
</table>
## Women and RAI Outside the US

<table>
<thead>
<tr>
<th>Country</th>
<th>Ever Experienced RAI (%)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>31.0</td>
<td>Guimares MD et al. 1995</td>
</tr>
<tr>
<td>Peru</td>
<td>12.0</td>
<td>Caceres C et al. 1997</td>
</tr>
<tr>
<td>South Africa</td>
<td>42.8</td>
<td>Karim SS and Ramjee G 1998</td>
</tr>
<tr>
<td>Kenya</td>
<td>40.8</td>
<td>Schwandt M et al. 2006</td>
</tr>
</tbody>
</table>
# Limited Preclinical Rectal Safety Data

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Murine</th>
<th>Primate</th>
<th>Explant</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-9</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Buffergel</td>
<td>?</td>
<td>(±)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>PRO 2000</td>
<td>?</td>
<td>?</td>
<td>(±)</td>
<td>Pending</td>
</tr>
<tr>
<td>Carraguard</td>
<td>Neg</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>VivaGel</td>
<td>?</td>
<td>Neg</td>
<td>(±)</td>
<td>Pending</td>
</tr>
<tr>
<td>PMPA</td>
<td>?</td>
<td>?</td>
<td>Neg</td>
<td>?</td>
</tr>
<tr>
<td>UC-781</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
# Rectal Cytotoxicity is a Problem

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cellular toxicity</th>
<th>Enhanced HSV-2 Infection</th>
<th>Rectal Sloughing</th>
</tr>
</thead>
<tbody>
<tr>
<td>KY-Plus</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Delube</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Astroglide</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Vagisil</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Viamor</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Carraguard</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Methylcellulose</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PBS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Sudol and Phillips. 2004
N-9 Effect on Rectal Epithelium

Baseline

+ 15 minutes

+ 15 minutes

+ 2 hours

+ 2 hours

+ 8 hours

Phillips et al. Contraception 2004
## Lubricants Vary in Osmolality

<table>
<thead>
<tr>
<th>Product</th>
<th>Osmolality (Median mOsm/Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tap water</td>
<td>3</td>
</tr>
<tr>
<td>Femglide</td>
<td>42</td>
</tr>
<tr>
<td>Semen</td>
<td>340</td>
</tr>
<tr>
<td>Gynol II</td>
<td>1182</td>
</tr>
<tr>
<td>Fleet enema</td>
<td>2127</td>
</tr>
<tr>
<td>KY Jelly</td>
<td>2424</td>
</tr>
<tr>
<td>Astroglide</td>
<td>3126</td>
</tr>
<tr>
<td>Prepair</td>
<td>4026</td>
</tr>
</tbody>
</table>

Fuchs et al J Infect Dis 2007
Effect of Osmolality on Mucosal Integrity

Iso-osmolar

Hyperosmolar

Fuchs et al J Infect Dis 2007
Epithelial Denudation Score

Average Grade of Surface Denudation

- 10 cm
- 40 cm
- 10 cm
- 40 cm

Iso-osmolar

Hyperosmolar

$p = 0.009$

$p = 0.007$

Fuchs et al J Infect Dis 2007
Update on the Design of Rectal Safety Studies
## Rectal Safety Studies

<table>
<thead>
<tr>
<th>Products</th>
<th>N</th>
<th>Safety Assessment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-9 (3.5%)</td>
<td>35</td>
<td>Anoscopy</td>
<td>Tabet et al. 1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rectal biopsy &amp; qualitative histology (+12 hrs)</td>
<td></td>
</tr>
<tr>
<td>N-9 (1% &amp; 2%), Carraguard, methycellulose</td>
<td>4</td>
<td>Qualitative lavage Electron microscopy</td>
<td>Phillips et al. 2000</td>
</tr>
<tr>
<td>N-9 (2%)</td>
<td>18</td>
<td>Histology (BL, +2hrs, +8hrs) Lavage (+15min, + &gt;8hrs)</td>
<td>Phillips et al. 2004</td>
</tr>
</tbody>
</table>
Rectal Safety Assessment

- Preclinical
  - Cell lines
  - Animal models
  - Explant systems

- Clinical
  - Symptoms
  - Signs
  - Histology
  - Experimental endpoints
  - Immunological toxicity
HPTN 056 Study Design

Week -2  0   +2   +4

Screening

Consent
Physical
Anoscopy
Rectal GC/CH
HIV Ab
CD4 / Viral load

Baseline

Sigmoidoscopy
Intestinal biopsy at 10cm and 30cm
Cell isolation and flow cytometry
Tissue cytokines
Rectal immunoglobulins
Tissue / rectal secretion viral load

Week 2  Week 4
Design of UC-781 Phase 1 Rectal Safety Study

- Three arms (Men and women with history of RAI)
  - 0.1% UC-781 (N = 12)
  - 0.25% UC-781 (N = 12)
  - Placebo (N = 12)
- Single dose followed by 7 days of study drug
Design of UC-781 Phase 1 Rectal Safety Study

- **Primary objective:** To evaluate the safety and acceptability of 0.1% and 0.25% UC-781 vaginal microbicide gel versus placebo when applied rectally.

- **Endpoints:**
  - Frequency of ≥Grade 2 adverse events
  - Acceptability
Randomization: 0.1% UC-781, 0.25% UC-781, or placebo

Visit 1: Screening
Visit 2: Baseline
Visit 3: Single-dose Clinical Eval
Visit 4: 7 Daily doses Clinical Eval
Visit 5: Phone interview
UC-781 Phase 1 Rectal Safety 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 - Mucosal cytokine mRNA and susceptibility to HIV infection
Applicator Design

Courtesy of Dr. Alex Carballo-Diegunz/amfAR
The Rectal Phase 1 Pipeline
## Phase 1 RM Safety Studies

<table>
<thead>
<tr>
<th>Product</th>
<th>Status</th>
<th>Timeline</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC-781</td>
<td>Ongoing</td>
<td></td>
<td>NIAID/DAIDS</td>
</tr>
<tr>
<td>TBN</td>
<td>Planned</td>
<td>Q3 2007</td>
<td>NIAID/DMID</td>
</tr>
<tr>
<td>PRO-2000</td>
<td>Planned</td>
<td>Q1 2008</td>
<td>MDP MRC-UK</td>
</tr>
<tr>
<td>UC-781 (Rectal formulation)</td>
<td>Possible</td>
<td>Q4 2010</td>
<td>TBD</td>
</tr>
</tbody>
</table>
Development of Rectal-specific Microbicides
Is There a Need?

- High prevalence of unprotected RAI among heterosexual and MSM population
- MSM still most affected demographic in Western Europe and the Americas
- 88% of MSM use lubricants for RAI*
- 26% are still using N-9 products*

*Carballo-Dieuguez et al. AIDS Behav 2007
Where to Protect and What to Measure?

Hendrix et al., 2004
Colonic Distribution of Microbicicides

Tc-SC (HIV Surrogate)  In-DTPA Microbicide ARV Surrogate

Hendrix et al. Microbicides 2006
Direct Endoscopic Sampling

SPECT/CT S004 @ 4 HR

Cytology brush (20 ml) @ 4 HR

Hendrix et al. Microbicides 2006
Update on Rectal Microbicide Advocacy
International Rectal Microbicide Working Group (IRMWG)

- Founded in Spring 2005
- Current membership 360 advocates from 35 countries on 5 continents

http://www.irmwg.org/
Conclusions
Conclusions

- Vaginal microbicides being considered for effectiveness studies should be evaluated for rectal safety
- Phase 1 rectal safety studies have begun and will increase in number
- Design methodology is still in evolution but moving towards simplified studies
- Rectal microbicide advocacy is increasing and will include demands for rectal safety and effectiveness
Bargello Museum, Florence, Italy