Rectal Microbicides

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Overview

- Epidemiology of anal intercourse
- Rectal transmission of HIV infection
- Phase 1 rectal safety studies of vaginal microbicides
- Development of rectal-specific microbicides
- Update on rectal microbicide advocacy
Epidemiology
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>
Lifetime Experience of RAI in Women

**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
Rectal Transmission
Rectosigmoid Anatomy
Mucosal Targets for HIV Infection

McGowan, Biologicals 2006
The Anal Canal as a Target for HIV Infection

Cranston et al. WEPEA040
Anal Tissue Infection in Vivo

- **PVL < 50**
- **PVL > 10,000**

![Graph showing VL Log10 vs Subject Number with different symbols for PVL, AVL, and RVL.]
T Cell Phenotype in Anal Tissue

Rectal Tissue

Anal Tissue

CXCR4

CCR5
Ex Vivo / In Vitro Infection of Anal Explants

Rectal Tissue

Anal Tissue

HIV-1 R5

HIV-1 X4
Preclinical Studies
# 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

Fuchs et al. J Infect Dis 2007

Iso-osmolar

Hyperosmolar

A

B

EPI

LP

C

LP

C
Phase 1 Rectal Safety Studies
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
Key Findings from HPTN-056

- High adherence rates are possible in studies with mucosal sampling
- Stability of safety assays variable
  - **Good**: T cell phenotype, cytokine mRNA
  - **Poor**: Quantitative histology
- Modest differences between samples collected at 10 and 30 cm

McGowan I JAIDS 2007 (In Press)
## 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, Rectal biopsy &amp; qualitative histology (+12 hrs)</td>
<td>Tabet et al. 1999</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, +8hrs)</td>
<td>Phillips et al. 2004</td>
</tr>
</tbody>
</table>
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 $\geq$ Grade 2 adverse events
  - Acceptability
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
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
UC-781 Trial Design

Screening → Enrollment → Baseline Endoscopy → Randomization → Placebo

0.1% 0.25% Placebo

Single dose 2nd Endoscopy 7 single Doses 3rd Endoscopy
<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>Polyanion</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</td>
<td>Possible</td>
<td>Q4 2010</td>
<td>TBD</td>
</tr>
<tr>
<td>(Rectal formulation)</td>
<td></td>
<td></td>
<td></td>
</tr>
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</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-Dieguez et al. AIDS Behav 2007
## Rectal Macaque PMPA Data

+-  Tx: SIVmac32H
  20 MID\(_{50}\) l.r.

<table>
<thead>
<tr>
<th>-2</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>6</th>
<th>week</th>
<th>12</th>
<th>16</th>
<th>20</th>
</tr>
</thead>
</table>

- PK

PBMC (VI & PCR); Plasma (vRNA); Serum (anti-SIV antibodies)

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Animal No.</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6</td>
<td>D3, D30, D37, D39, D43, D79</td>
<td>PMPA 15 min prior to virus challenge</td>
</tr>
<tr>
<td>B</td>
<td>4</td>
<td>C57, D26, D9, D68</td>
<td>Placebo 15 minutes prior to virus challenge</td>
</tr>
<tr>
<td>C</td>
<td>4</td>
<td>D77, D83, E73, E81</td>
<td>No treatment</td>
</tr>
<tr>
<td>D</td>
<td>3</td>
<td>D14, D56, D69</td>
<td>PMPA 2 hours prior to virus challenge</td>
</tr>
<tr>
<td>E</td>
<td>3</td>
<td>D15, D18, D29</td>
<td>PMPA 2 hours after virus challenge</td>
</tr>
</tbody>
</table>

Cranage et al. CROI 2007
## Rectal Macaque PMPA Data

<table>
<thead>
<tr>
<th>Week</th>
<th>D3</th>
<th>D30</th>
<th>D37</th>
<th>D39</th>
<th>D43</th>
<th>D79</th>
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</thead>
<tbody>
<tr>
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<td>- - -</td>
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<td>- - -</td>
<td>- - -</td>
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<tr>
<td>2</td>
<td>+ + +</td>
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<td>- - -</td>
<td>- - -</td>
<td>- - -</td>
<td>- - -</td>
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<tr>
<td>6</td>
<td>+ + +</td>
<td>+ + +</td>
<td>- - -</td>
<td>- - -</td>
<td>- - -</td>
<td>- - -</td>
</tr>
<tr>
<td>12</td>
<td>+ + +</td>
<td>+ + +</td>
<td>+ + +</td>
<td>- - -</td>
<td>- - -</td>
<td>- - -</td>
</tr>
<tr>
<td>16</td>
<td>+ + +</td>
<td>+ + +</td>
<td>+ + +</td>
<td>+ + +</td>
<td>- - -</td>
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<tr>
<td>20</td>
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<td>+ + +</td>
<td>+ + +</td>
<td>+ + +</td>
<td>+ + +</td>
<td>- - -</td>
</tr>
</tbody>
</table>
Rectal Macaque PMPA Data

- **Proviral DNA**
- **Viral RNA**
Where to Protect and What to Measure?

Hendrix et al., 2004
Colonic Distribution of Microbicides

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. Microbicicides 2006
Applicator Design

Courtesy of Dr. Alex Carballo-Dieeguez/amfAR
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
Acknowledgements

- NIH/NIAID/DAIDS IPCP Program
- NIH/NIAID/DMID
- amfAR
- Gilead Sciences
- CONRAD
- International Partnership for Microbicides
- UCLA CPR