Assessing the Safety of Rectal Microbicides

Ian McGowan MD PhD FRCP
Center for Prevention Research
David Geffen School of Medicine at UCLA
Overview

- Why do we need rectal microbicides?
- What are the implications of AI on vaginal microbicide efficacy study?
- What do we know about the rectal safety profile of the microbicide portfolio?
- How will we assess rectal safety?
- How do we begin to integrate rectal microbicide into the bigger picture?
- Gap analysis
Why Do We Need Rectal Microbicides?
“The love microbicide that dare not speak its name...........

That it should be so, the world does not understand.

The world mocks at it and sometimes puts one in the pillory for it.”

Adapted from Oscar Wilde
Rectal Microbicides
Not Just For Cowboys?
So Who Is Having Anal Sex?

The Ultimate Guide to Anal Sex for Women, Tristan Taormino, Cleiss Press Inc. San Francisco 1998
Prevalence of AI
International Studies

Peru (1) Peru (2) China South Africa

Men
Women

CPR
## Prevalence of Anal Receptive Sex

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Prevalence of AI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM in EXPLORE study</td>
<td>4295</td>
<td>48 – 54%</td>
<td>Koblin et al. 2003</td>
</tr>
<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>

<table>
<thead>
<tr>
<th>Transmission Category</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM contact</td>
<td>18,203</td>
<td>47</td>
</tr>
<tr>
<td>IDU</td>
<td>5,962</td>
<td>15</td>
</tr>
<tr>
<td>MSM + IDU</td>
<td>1,372</td>
<td>4</td>
</tr>
<tr>
<td>High Risk Heterosexual contact</td>
<td>12,683</td>
<td>33</td>
</tr>
<tr>
<td>Other / not identified</td>
<td>335</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38,553</strong></td>
<td></td>
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</tbody>
</table>

* CDC data from 35 areas with HIV surveillance
UK HIV Infection by Transmission Category

Heterosexual subcategories

- undetermined
- infected in Africa
- infected abroad (not Africa)
- infected by high risk partner*
- infected in the UK

Sex between men
Rectosigmoid Anatomy
### Transmission Rates for HIV

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Risk of HIV Infection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Sex</td>
<td>0.0%</td>
<td>Page-Shafer K et al. 2002</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 0.015)</td>
<td></td>
</tr>
<tr>
<td>Vaginal Sex</td>
<td>0.001 – 0.02%</td>
<td>Kalichman S et al. 2002</td>
</tr>
<tr>
<td></td>
<td>(95% CI: NA)</td>
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</tr>
<tr>
<td>Anal Sex</td>
<td>0.25%</td>
<td>Vittinghoff E et al. 1999</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 0.06,0.49)</td>
<td></td>
</tr>
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</table>
Modeling Rectal Microbicide Efficacy

Adapted from Breban et al. (In Press)
What are the Implications of AI on Vaginal Microbicide Efficacy study?
## The Candidate Microbicides

<table>
<thead>
<tr>
<th>Phase</th>
<th>Membrane Disruption</th>
<th>Defense Enhancers</th>
<th>Entry Fusion Inhibitors</th>
<th>Replication Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Acidform™ Lime Juice Lactobacillus</td>
<td>VivaGel™ Cellulose acetate</td>
<td>PC-815 UC-781 TMC-120</td>
</tr>
<tr>
<td>1/2</td>
<td>Invisible Condom™</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(Praneem)</td>
<td></td>
<td></td>
<td>PMPA</td>
</tr>
<tr>
<td>2/2B</td>
<td>C31G</td>
<td>BufferGel™</td>
<td>PRO-2000</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>Carraguard® Cellulose Sulfate</td>
</tr>
</tbody>
</table>
Modeling the Impact of AI on Vaginal Microbicide Trials

- Randomization should balance AI across arms of the study but
- If study product has rectal toxicity you may see increased HIV infections in active arm
- Problem magnified by increased vulnerability of rectal vs. vaginal tissue
How Will We Assess Rectal Safety?
Rectal Safety Assessment

Vaginal Microbicide
(Cellulose sulfate)

Rectal Microbicide
(Product X)

Combination Microbicide
(Tenofovir)

Animal Toxicology

Phase 1 Rectal Safety

• Preclinical Evaluation
  • Cell lines
  • Explant studies
  • Animal models
  • Animal toxicology

• Human studies
  • Phase 1
  • Phase 2
  • Phase 2B/3
# Topical Rectal Cytotoxicity

<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>
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</table>

Sudol and Phillips. 2004
# Macaque Models

<table>
<thead>
<tr>
<th>Animal Species</th>
<th>Design</th>
<th>Agent</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td><em>M. nemestrina</em></td>
<td>Comparative description</td>
<td>N/A</td>
<td>Patton et al. 2000</td>
</tr>
<tr>
<td><em>H. sapiens</em></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>M. nemestrina</em></td>
<td>Safety</td>
<td>N-9</td>
<td>Patton et al. 2001</td>
</tr>
<tr>
<td><em>M. fasicularis</em></td>
<td>Efficacy: (SHIV89.6P)</td>
<td>Cyanovirin</td>
<td>Tsai et al. 2003</td>
</tr>
<tr>
<td><em>M. nemestrina</em></td>
<td>Safety / Efficacy (C. trachomatis)</td>
<td>BufferGel</td>
<td>Patton et al. 2004</td>
</tr>
<tr>
<td><em>M. nemestrina</em></td>
<td>Comparative description</td>
<td>N/A</td>
<td>Patton et al. 2004</td>
</tr>
<tr>
<td><em>M. fasicularis</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Epithelial Sloughing
Colorectal Explant System

Day 0

Day 1

Day 7
Toxicity of Topical Microbicides in Colorectal Explants

Dezzutti et al., 2005
Human Studies
# Pilot / Phase 1 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, +&gt;8hrs)</td>
<td>Phillips et al. 2004</td>
</tr>
</tbody>
</table>
N-9 Effect on Rectal Epithelium

Baseline

+ 15 minutes

+ 15 minutes

+ 2 hours

+ 2 hours

+ 8 hours

Phillips et al. 2004
What do We Know About the Rectal Safety Profile of the Microbicide Portfolio?
## Rectal Safety of Vaginal Microbicides

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Murine</th>
<th>Primate</th>
<th>Explant</th>
<th>Human</th>
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</thead>
<tbody>
<tr>
<td>N-9</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Buffergel</td>
<td>Neg</td>
<td>Neg</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>C31G</td>
<td>?</td>
<td>Neg</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Carraguard</td>
<td>Neg</td>
<td>Neg</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Cellulose sulfate</td>
<td>?</td>
<td>Neg</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>PRO 2000</td>
<td>?</td>
<td>?</td>
<td>Neg</td>
<td>?</td>
</tr>
<tr>
<td>SPL7013</td>
<td>?</td>
<td>Neg</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Octylglycerol</td>
<td>?</td>
<td>Neg</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>PMPA</td>
<td>?</td>
<td>Neg</td>
<td>Neg</td>
<td>?</td>
</tr>
<tr>
<td>TMC120</td>
<td>?</td>
<td>?</td>
<td>Neg</td>
<td>?</td>
</tr>
<tr>
<td>UC781</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>?</td>
</tr>
</tbody>
</table>
Where to Protect and What to Measure?

Hendrix et al., 2004
HPTN-056 Study Groups

- **Group 1**
  - HIV-1 negative / anal receptive (N = 4)

- **Group 2**
  - HIV-1 negative / not anal receptive (N = 4)

- **Group 3**
  - HIV-1 positive / anal receptive + plasma viral load > 10,000 (N = 4)

- **Group 4**
  - HIV-1 positive / anal receptive + plasma viral load < 50 (N = 4)
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
Experimental Endpoints

- Histopathology
  - Qualitative
  - Quantitative
- Flow cytometry
- Tissue cytokine mRNA
- Rectal secretion immunoglobulin
- Mucosal & rectal secretion viral load
Quantitative Histology

![Bar chart showing cell counts by group.](chart.png)

- **Cell Count**
  - Group G1: Lymphocytes, Plasma cells, Eosinophils, Total LP cell count.
  - Group G2: Lymphocytes, Plasma cells, Eosinophils, Total LP cell count.
  - Group G3: Lymphocytes, Plasma cells, Eosinophils, Total LP cell count.
  - Group G4: Lymphocytes, Plasma cells, Eosinophils, Total LP cell count.
T Cell Phenotype

Group

G1  G2  G3  G4

CD3  CD4  CD8

(%)
HIV Co-Receptor Expression

G1  G2  G3  G4

- CCR5/CD4
- CXCR4/CD4
- CCR5/CXCR4/CD4

(%)
Data Analysis

- Data analyzed by group means
- Subject variability around means explored
- Definitions:
  - Sig: within subject standard deviation
  - Tau: between subject standard deviation
  - Intra class correlation (ICC)
    \[ ICC = \frac{\text{Tau}^2}{\text{Tau}^2 + \text{Sig}^2} \]
- ICC thresholds
  - >0.75 shows strong stability
  - >0.5 shows moderate stability
## Flow Cytometry

<table>
<thead>
<tr>
<th>Mean</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>Sig</th>
<th>Tau</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3%</td>
<td>68</td>
<td>66</td>
<td>74</td>
<td>70</td>
<td>5.5</td>
<td>9.8</td>
<td>0.76</td>
</tr>
<tr>
<td>CD4%</td>
<td>42</td>
<td>41</td>
<td>12</td>
<td>29</td>
<td>4.0</td>
<td>8.0</td>
<td>0.81</td>
</tr>
<tr>
<td>CD8%</td>
<td>29</td>
<td>28</td>
<td>62</td>
<td>45</td>
<td>5.2</td>
<td>11.9</td>
<td>0.84</td>
</tr>
<tr>
<td>CD31%</td>
<td>68</td>
<td>66</td>
<td>73</td>
<td>70</td>
<td>5.6</td>
<td>9.9</td>
<td>0.76</td>
</tr>
<tr>
<td>CD19%</td>
<td>32</td>
<td>30</td>
<td>26</td>
<td>37</td>
<td>7.4</td>
<td>8.3</td>
<td>0.56</td>
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</table>
## Cytokines

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>Sig</th>
<th>Tau</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RANTES (log_{10})</td>
<td>4.1</td>
<td>4.5</td>
<td>4.9</td>
<td>4.1</td>
<td>0.28</td>
<td>0.49</td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>IFN-γ (log_{10})</td>
<td>2.7</td>
<td>3.2</td>
<td>3.3</td>
<td>3.0</td>
<td>0.29</td>
<td>0.50</td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>IL-10 (log_{10})</td>
<td>2.7</td>
<td>3.2</td>
<td>2.6</td>
<td>2.8</td>
<td>0.28</td>
<td>0.43</td>
<td></td>
<td>0.70</td>
</tr>
</tbody>
</table>
Effect of Osmolality on Mucosal Integrity

Fuchs et al. Microbicides 2006
Epithelial Denudation

Fuchs et al. Microbicides 2006
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
- Recovery interval
- Seven days of study drug
How Do We Begin To Integrate Rectal Microbicide Research Into the Bigger Picture?
## MTN Clinical Trials Portfolio

<table>
<thead>
<tr>
<th>ID</th>
<th>Task Name</th>
<th>Product(s)</th>
<th>Population</th>
<th>Phase</th>
<th>N</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>HPTN-005</td>
<td>BG, Pro2000</td>
<td>HIV Neg</td>
<td>2B</td>
<td>3220</td>
<td>1040 days</td>
</tr>
<tr>
<td>4</td>
<td>HPTN-059</td>
<td>PMPA</td>
<td>HIV Neg</td>
<td>2</td>
<td>200</td>
<td>330 days</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>MTN-001</td>
<td>PMPA</td>
<td>HIV Pos</td>
<td>1</td>
<td>45</td>
<td>330 days</td>
</tr>
<tr>
<td>7</td>
<td>MTN-002</td>
<td>NIA</td>
<td>HIV Neg</td>
<td>Prep</td>
<td>1500</td>
<td>523 days</td>
</tr>
<tr>
<td>8</td>
<td>MTN-003</td>
<td>TDF, PMPA</td>
<td>HIV Neg</td>
<td>2B</td>
<td>3000</td>
<td>1040 days</td>
</tr>
<tr>
<td>9</td>
<td>MTN-004</td>
<td>CCR5</td>
<td>HIV Neg</td>
<td>1</td>
<td>30</td>
<td>130 days</td>
</tr>
<tr>
<td>10</td>
<td>MTN-005</td>
<td>FI, CCR5</td>
<td>HIV Neg</td>
<td>2</td>
<td>300</td>
<td>330 days</td>
</tr>
<tr>
<td>11</td>
<td>MTN-006</td>
<td>FI</td>
<td>HIV Pos</td>
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<td>45</td>
<td>330 days</td>
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<tr>
<td>12</td>
<td>MTN-007</td>
<td>CCR5</td>
<td>HIV Pos</td>
<td>1</td>
<td>30</td>
<td>330 days</td>
</tr>
<tr>
<td>13</td>
<td>MTN-008</td>
<td>RTI, RTI</td>
<td>HIV Pos</td>
<td>1</td>
<td>30</td>
<td>330 days</td>
</tr>
<tr>
<td>14</td>
<td>MTN-009</td>
<td>RTI, RTI</td>
<td>HIV Neg</td>
<td>2</td>
<td>300</td>
<td>590 days</td>
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<tr>
<td>15</td>
<td>MTN-010</td>
<td>RTI</td>
<td>HIV Pos</td>
<td>1</td>
<td>45</td>
<td>330 days</td>
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<tr>
<td>16</td>
<td>MTN-011</td>
<td>RTI</td>
<td>HIV Pos</td>
<td>1</td>
<td>45</td>
<td>330 days</td>
</tr>
<tr>
<td>17</td>
<td>MTN-012</td>
<td>RTI, FI, CCR5</td>
<td>HIV Neg</td>
<td>2B</td>
<td>4900</td>
<td>730 days</td>
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<tr>
<td>18</td>
<td>MTN-013</td>
<td>RTI</td>
<td>HIV Neg + HIV Pos</td>
<td>1</td>
<td>50</td>
<td>520 days</td>
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<tr>
<td>19</td>
<td>MTN-014</td>
<td>Rectal TPO</td>
<td>HIV Neg</td>
<td>1</td>
<td>30</td>
<td>260 days</td>
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<tr>
<td>20</td>
<td>MTN-015</td>
<td>NIA</td>
<td>HIV Pos</td>
<td>Seroconverter</td>
<td>300</td>
<td>1712 days</td>
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<tr>
<td>21</td>
<td>MTN-016</td>
<td>NIA</td>
<td>HIV Pos</td>
<td>Registry</td>
<td>225</td>
<td>1712 days</td>
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Gap Analysis
## Rectal Microbicide Gap Analysis

<table>
<thead>
<tr>
<th>Area</th>
<th>Requirements</th>
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</thead>
<tbody>
<tr>
<td>Funding</td>
<td>Sponsors should integrate rectal studies into their microbicide study portfolio</td>
</tr>
<tr>
<td>Behavioral</td>
<td>Gather more information on the prevalence of AI in domestic and international settings</td>
</tr>
<tr>
<td>Regulatory</td>
<td>Develop regulatory guidelines for rectal studies</td>
</tr>
<tr>
<td>Design of Phase 1 studies</td>
<td>Simplify safety assessments</td>
</tr>
<tr>
<td>Surrogates for mucosal damage</td>
<td>Define approach for use in Phase 2 / efficacy studies</td>
</tr>
<tr>
<td>Rectal formulations</td>
<td>Design rectal specific formulation</td>
</tr>
</tbody>
</table>
Acknowledgements

**UCLA**
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NIH/NIAID/DMID  
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