Rectal Microbicide Development: Measuring Gel & Virus Distribution

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Outline
Measuring Gel & Virus Distribution

- Research Objectives
- Conceptualization of Problem
- Pharmacologic Methods – Gel Distribution
  - MRI
  - SPECT/CT
  - Endoscopy
- Future Studies – HIV Spread & Challenge
Objectives

Long Term

- Locate the virus following sex
- Develop a microbicide to *outdistance* and *outlast* the virus
Conceptualization
Gel & Virus Distribution

Anus

Microbicide

HIV

Success

Failure

Rectum

Colon

Ano-Rectal Distance

Concentration
Conceptualization
Rectal Microbicide Development

Enhanced Adherence & Spread
Research Plan

Gel & HIV Distribution

- Demonstrate feasibility of simulating
  - Receptive anal intercourse
  - Ejaculation
- Demonstrate feasibility of imaging surrogates for
  - Semen
  - Microbicide vehicle gel
- Validate surrogates with CD4 cells & HIV
Distal GI PK
Distal Gastrointestinal Tract Studies

- Coital Behaviors
- Simulated Coitus
- Concentration – Distance – Time
  - Magnetic Resonance Imaging
  - SPECT/CT
  - Endoscopic Sampling
Methods
Focus Groups: Anal Sex Characterization

◆ Design
  – CDC funded/approved as part of methods development contract
  – 2 focus groups; 16 participants; RAI; 63% white
  – Structured questions; Open discussion format

◆ Questions
  – Duration
  – Frequency
  – Positions
  – Lubricants
  – Enemas
  – Study willingness

◆ Results
  – Few minutes up to 8 hours
  – 60 cps initiation; 80 cps later; few 112 cps
  – Supine, Prone, Lateral
  – 100%; K-Y, Wet; Reapplication q5-20 min.
  – 63% sometimes or always
  – ~ One third later volunteered
### Distal GI PK

#### Methods: Surrogate Gels

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Microbicide Vehicle</th>
<th>Semen Simulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>10 mL</td>
<td>5 mL</td>
</tr>
<tr>
<td>Gel</td>
<td>K-Y® Jelly (2400 mOsm)</td>
<td>K-Y® Jelly 1:1 NS (viscosity ~ semen; 1200 mOsm)</td>
</tr>
<tr>
<td>MR contrast</td>
<td>1:100 Gd-DTPA</td>
<td>1:100 Gd-DTPA</td>
</tr>
<tr>
<td>Isotope</td>
<td>500 μCi $^{99m}$Tc Sulfur Colloid</td>
<td>500 μCi $^{99m}$Tc Sulfur Colloid (100 nm ~ HIV particle size)</td>
</tr>
<tr>
<td>Administration</td>
<td>Microbicide Vehicle</td>
<td>Semen Simulant</td>
</tr>
</tbody>
</table>

- Coital Dynamic Simulator
- Vaginal Dilator
## Distal GI PK

### Coital Simulation Schema

<table>
<thead>
<tr>
<th>Sequence of Events</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enema</td>
<td>+/-</td>
</tr>
<tr>
<td>Microbicide (10 mL)</td>
<td>+/-</td>
</tr>
<tr>
<td>Coitus (5' @ 1 cps)</td>
<td>+/-</td>
</tr>
<tr>
<td>Ejaculate (5 mL)</td>
<td>+/-</td>
</tr>
<tr>
<td>Coitus (10 @ 1 cps)</td>
<td>+/-</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>+</td>
</tr>
<tr>
<td>Dosimeter measurements</td>
<td>+</td>
</tr>
<tr>
<td>SPECT/CT</td>
<td>0 hr</td>
</tr>
<tr>
<td>MRI</td>
<td>1 hr</td>
</tr>
<tr>
<td>SPECT/CT</td>
<td>4 hr</td>
</tr>
<tr>
<td>MRI</td>
<td>5 hr</td>
</tr>
<tr>
<td>SPECT/CT</td>
<td>10 hr</td>
</tr>
<tr>
<td>MRI</td>
<td>11 hr</td>
</tr>
<tr>
<td>SPECT/CT</td>
<td>24 hr</td>
</tr>
<tr>
<td>MRI</td>
<td>25 hr</td>
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</tbody>
</table>
**Distal GI PK**

**Coital Simulation: Dosing Efficiency**

<table>
<thead>
<tr>
<th></th>
<th>% Initial Dose Administered</th>
<th>% Administered Dose Retained</th>
<th>μCi Administered Dose Retained</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median</strong></td>
<td>92 %</td>
<td>99 %</td>
<td>488</td>
</tr>
<tr>
<td><strong>IQR</strong></td>
<td>83 – 96 %</td>
<td>95 – 100 %</td>
<td>422 – 545</td>
</tr>
</tbody>
</table>
Rectal Microbicide PK
Effect of Coital Simulation: MRI
Distal GI PK
Vehicle & Semen Simulant Distribution

Study: Subject F001
T₁-weighted spin echo, fat suppression, sagittal view.
1 L tap water enema 4 hours before dosing
Distal GI PK

“Simultaneous” Nuclear Medicine/CT

GE Hawkeye System

Parallel Rotating SPECT Detector Panels

Computed Tomography Tunnel
Distal GI PK
Semen Simulant No Enema 3D SPECT
Distal GI PK

Concentration Distribution

First Hour Post-Dose (0803 HRS)

SPECT / CT Fusion

“Concentration”

SPECT / CT Fusion

Fourth Hour Post-Dose (1139 HRS)

“Concentration”

Subject F003: CDS SS 0E

5 mL semen simulant @ 0734 HRS
Distal GI PK
Post-/coital SPECT/CT Quantification
Distal GI PK
Post-/coital SPECT/CT Quantification

Ratio T2 / T1
Median (Range)
1.7 (1.0 – 3.4)

Ratio T2 / T1
Median (Range)
2.5 (1.0 – 6.4)
Distal GI PK
MRI Compared to SPECT/CT

Magnetic Resonance Imaging
SPECT/CT Fused
24 hours
**Microbicide Development Methods**

**Dual Isotope Imaging**

\[ \text{Location Relative to Iliac Crest (cm)} \]

-18 -16 -14 -12 -10 -8 -6 -4 -2 0 111In - DTPA 290 mOsm
99mTc-SC 360 mOsm

99mTc-SC as HIV surrogate (blue)
111In-DTPA as microbicide (green)
Fractional change from administered concentration of $^{99m}$Tc-SC, 4 hours after dosing, along the length of the distal colon beginning at the anus (0 cm), extending up toward the splenic flexure (60 cm).
Summary

“Microbicide” & “Semen” Spread

- “Virus” in gel spreads up to 60 cm (splenic flexure)
- Variable with no clear trends: enema, volume, gel
- Stool not obvious impediment to proximal spread
- 1/3 – 2/3 enema fluid retained
- Gas introduced with “sex”; displaced signal upward
- Bowel movement clears up to 98% of gel
Next Steps

Putting the Methods Together

Diagram showing the relationship between microbicide efficacy, toxicity, and HIV infection over time, with distances in anorectal and vaginal-cervical regions.
Next Steps

HIV Spread & Challenge Studies

- HIV Spread over time
  - HIV Labeling
  - HIV Distribution
    » Colon
    » Mucosal Penetration

- HIV Challenge Study (Proof-of-Concept)
  - Measure HIV penetration
  - Measure HIV penetration following microbicide
# Collaborators – School of Medicine

<table>
<thead>
<tr>
<th>Name</th>
<th>Department</th>
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<tbody>
<tr>
<td>Ed Fuchs</td>
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<td>Medicine/Radiology - ClinPharm Post-Doctoral Fellow</td>
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<td>Kasia Macura</td>
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<td>Richard Wahl</td>
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<td>Jeff Leal</td>
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<tr>
<td>David Clough</td>
<td>Radiology - Nuclear Medicine</td>
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<tr>
<td>Mike Torbenson</td>
<td>Pathology - Anatomic</td>
</tr>
<tr>
<td>James Hildreth</td>
<td>Pharmacology</td>
</tr>
<tr>
<td>Jean Anderson</td>
<td>Obstetrics and Gynecology</td>
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Questions?