Development of Rectal Microbicides

Ian McGowan MD PhD FRCP

Magee Womens Research Institute
University of Pittsburgh, USA
Overview

• Rationale for rectal microbicide development
• Preclinical development of candidate rectal microbicides
• Formulation considerations
• Design of Phase 1 rectal safety studies
• Moving towards effectiveness studies
Rationale for Rectal Microbicide Development
Why Do We Need Rectal Microbicides?

• Unprotected receptive anal intercourse (RAI) is the highest risk sexual activity for HIV transmission
• Men and women in the developed and developing world practice RAI
• Murine and non human primate studies have shown proof of concept that rectal application of ARV microbicides can prevent SIV/HIV infection
Rectosigmoid Anatomy
Preclinical Development of Candidate Rectal Microbicides
Rectal Model Development

Macaca nemestrina
Rectal Lavage Assay

Lavage fluid

Day 4 Combo Animal
Day 4, T0 24 hrs post 3rd application
Day 4, T30 post 4th application

*TMicrobicides 2008 Poster #TA-057
# Microbicide Toxicity in NHP Model

<table>
<thead>
<tr>
<th>Product</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BufferGel</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Nonoxynol-9</td>
<td>Acceptable</td>
</tr>
<tr>
<td>C31G</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Octylglycerol</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Polystyrene sulfate</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Cellulose sulfate</td>
<td>Acceptable</td>
</tr>
<tr>
<td>VivaGel</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Carraguard</td>
<td>Acceptable</td>
</tr>
<tr>
<td>UC781</td>
<td>Acceptable</td>
</tr>
<tr>
<td>VivaGel + BufferGel</td>
<td>Unacceptable</td>
</tr>
</tbody>
</table>

Patton DL et al. Sex Trans Dis 2009
Colorectal Intestinal Explants

Endoscopic biopsies + Absorbable gelatin sponge

Tenofovir Explant Data

HIV-1\textsubscript{LAV} and PMPA

<table>
<thead>
<tr>
<th>p-24 (pg/ml)</th>
<th>D1</th>
<th>D4</th>
<th>D7</th>
<th>D11</th>
<th>D14</th>
</tr>
</thead>
<tbody>
<tr>
<td>783 MED/LAV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLAC/LAV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMPA/LAV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MTN
Aptamer Explant Data

HIV-1 p24 pg/mL at Day 15

- Aptamer 1
- Aptamer 2
- Aptamer 3
- Aptamer 4
- UC781
- Dextrin sulfate

Microbicide
Formulation Considerations
## 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>Fem glide</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>Prep air</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
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.
Design of 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

McGowan et al. JAIDS 2007
UC-781 Trial Design

- Screening
- Enrollment
- Baseline Endoscopy
- Randomization
- Placebo
- 0.1%
- 0.25%
- Single dose
- 2nd Endoscopy
- 7 single Doses
- 3rd Endoscopy

Anton et al. CROI 2009
Colorectal Explant Data

HEC Placebo  
UC781 0.10%  
UC781 0.25%

Anton et al. CROI 2009
# Phase 1 Rectal Microbicide 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>Completed</td>
<td></td>
<td>DAIDS</td>
</tr>
<tr>
<td>MTN-007</td>
<td>Planned</td>
<td>Q3 2009</td>
<td>DAIDS</td>
</tr>
<tr>
<td>RMP-02 /MTN-006</td>
<td>Planned</td>
<td>Q3 2009</td>
<td>DAIDS</td>
</tr>
<tr>
<td>VivaGel</td>
<td>Planned</td>
<td>Q3 2010</td>
<td>NICHD</td>
</tr>
<tr>
<td>PRO-2000</td>
<td>Planned</td>
<td>Q1 2010</td>
<td>MRC-UK</td>
</tr>
<tr>
<td>Tenofovir (RF)</td>
<td>Planned</td>
<td>Q4 2010</td>
<td>DAIDS</td>
</tr>
</tbody>
</table>
RMP-02 / MTN-006

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
MTN-007

N=60

2% N-9 (N=15)

1% Tenofovir (N=15)

Baseline Evaluation

Single dose

7 day daily doses

7-14 day interval

HEC (N=15)

No Treatment (N=15)

Endoscopy Safety/behavioral assessment

Screening
Moving Towards Effectiveness Studies
“For this reason, NIAID places a priority on developing HIV prevention tools that women can implement independently. One such method under study is a microbicide—a gel, cream or foam intended to prevent the sexual transmission of HIV when applied topically inside the vagina or rectum.

Statement of Anthony S. Fauci, M.D.
Director, National Institute of Allergy and Infectious Diseases
National Institutes of Health on National Women and Girls HIV/AIDS Awareness Day
March 10, 2009
Next Steps

- Identify relevant populations
- Develop rectal specific products
- Design rectal specific applicator
- Expanded safety study
- Effectiveness study
Populations for RM studies

• Phase 2 studies
  – RAI sexually active men and women
  – Higher risk populations

• Phase 2B studies
  – 3% seroincidence MSM populations
    • North America
    • Latin America
    • Asia
    • Africa
Microbicide Safety and Acceptability in Young Men

• NICHD R01
  – McGowan / Carballo-Dieguez
  – Pittsburgh, Boston, Puerto Rico

• Phase 1 safety and acceptability of VivaGel
  – Ethnically diverse MSM (18-30)
  – Consensual RAI in last month
  – Unprotected RAI in last year
Microbicide Safety and Acceptability in Young Men

Stage 1A
Screening
240 MSM
Consensual RAI in last month
URAI in last year

Stage 1B
3 month Acceptability & Adherence study with placebo gel
120 MSM
RAI in last 3 months
STI negative

Stage 2
Phase 1 VivaGel rectal safety study
42 MSM
80% adherence in Stage 1B

McGowan & Carballo-Dieguez 2009
Rectal Specific Products

- CHARM Program
  - Combination HIV Antiretroviral Microbicide Program
  - DAIDS IPCP Program
  - PI: Ian McGowan MD PhD
- Consortium
  - University of Pittsburgh
  - UCLA
  - Johns Hopkins
  - UNC
  - CONRAD
Phase 2 Expanded Rectal Safety Study

- Double blind placebo controlled
- Population:
  - 300 RAI sexually active men and women with 6 month follow-up
- Three study arms:
  - Oral tenofovir + placebo tenofovir gel
  - Placebo oral tenofovir + tenofovir gel
  - Oral tenofovir + tenofovir gel
- Study endpoints
  - Safety
  - PK substudy
  - Explant efficacy substudy
Phase 2B Rectal Safety and Effectiveness Study
<table>
<thead>
<tr>
<th>Study Arms</th>
<th>Placebo Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral tenofovir + Placebo gel</td>
<td></td>
</tr>
<tr>
<td>Oral placebo + Tenofovir gel</td>
<td></td>
</tr>
<tr>
<td>Oral tenofovir + Tenofovir gel</td>
<td></td>
</tr>
<tr>
<td>Oral placebo + Placebo gel</td>
<td></td>
</tr>
<tr>
<td>Seroincidence</td>
<td>4%</td>
</tr>
<tr>
<td>Power</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Endpoints per pair wise comparison / total</strong></td>
<td>90-100</td>
</tr>
<tr>
<td></td>
<td>2 pair wise comparisons</td>
</tr>
<tr>
<td></td>
<td>Total: 180-200</td>
</tr>
<tr>
<td><strong>Person years per endpoint</strong></td>
<td>40-50</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>2 years</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>3,500 – 5,000</td>
</tr>
<tr>
<td>Study Arms</td>
<td>Placebo Study</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Oral tenofovir + Placebo gel</td>
<td>Oral tenofovir</td>
</tr>
<tr>
<td>Oral placebo + Tenofovir gel</td>
<td>Oral tenofovir + Tenofovir gel</td>
</tr>
<tr>
<td>Oral tenofovir + Tenofovir gel</td>
<td>Oral tenofovir + Tenofovir gel</td>
</tr>
<tr>
<td>Oral placebo + Placebo gel</td>
<td>Oral tenofovir + Tenofovir gel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Seroincidence</th>
<th><strong>4%</strong></th>
<th><strong>4%</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Power</td>
<td><strong>90%</strong></td>
<td><strong>90%</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoints per pair wise comparison / total</th>
<th><strong>90-100</strong></th>
<th><strong>88</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 pair wise comparisons</td>
<td>1 pair wise comparison</td>
</tr>
<tr>
<td></td>
<td>Total: 180-200</td>
<td>Total: 88</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Person years per endpoint</th>
<th><strong>40-50</strong></th>
<th><strong>120</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td><strong>2 years</strong></td>
<td><strong>2 years</strong></td>
</tr>
<tr>
<td>Sample size</td>
<td>3,500 – 5,000</td>
<td><strong>5,000</strong></td>
</tr>
</tbody>
</table>
Summary

• There is a clear rationale for the development of rectal microbicides
• The design of rectal safety studies now includes immunotoxicity assays
• Rectal specific products and applicators are being developed
• It is time to move to the Phase 2 and beyond
Acknowledgements

MTN is funded by NIAID (5U01AI068633-03), NICHD and NIMH, all of the U.S. National Institutes of Health.
SAVE THE DATE!
May 22-25, 2010
Pittsburgh, Pennsylvania, USA

M2010

MICROBICIDES:
Building Bridges in HIV Prevention

www.microbicides2010.org