The Rectal Microbicide Research Agenda

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Overview

• Rationale for rectal microbicide development
• Preclinical development of candidate rectal microbicides
• Evolving design of Phase 1 rectal safety studies
• Moving towards effectiveness studies
Rationale for Rectal Microbicide Development
Anal Intercourse in US Women

- Gross M et al. 2000
- Civic D et al. 2000
- Mosher WD et al. 2005
- Erickson PI et al. 1995

(% Lifetime experience of Al)

MTN
Microbicide Trials Network
Anal Intercourse in Women Outside the US

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
HIV Incidence in US MSM

Sifakis F et al. JAIDS 2007
HIV Prevalence in African MSM

Demographic Profile

- Mean age: 24.9 years
- Gay / homosexual: 49.5%
- Bisexual: 38.1%
- Found partner on the internet: 44.7%
- < 1:20 practiced safe sex
- Human rights abuse: 42.1%

Effect of RAI in Microbicide Trials

Transmission Probability

- 1X
- 10X
- 20X
### RAI in HPTN-059

<table>
<thead>
<tr>
<th></th>
<th>Coitally Dependent</th>
<th>Daily Use</th>
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<tbody>
<tr>
<td></td>
<td>Tenofovir</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=50</td>
<td>N=51</td>
<td></td>
</tr>
<tr>
<td>Ever anal sex</td>
<td>24%</td>
<td>25%</td>
</tr>
<tr>
<td>Anal sex, (past 7 days)</td>
<td>2%</td>
<td>0%</td>
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</tbody>
</table>
## RAI in HPTN-035

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Ever had anal sex</th>
</tr>
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<tbody>
<tr>
<td>BufferGel</td>
<td>PRO2000</td>
</tr>
<tr>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>
HPTN-035B

% Women Reporting Anal Sex

- FTFI: 0.2%
- ACASI: 4.8%
Preclinical Development of Candidate Rectal Microbicides
Rectosigmoid Anatomy
Effect of Osmolality on Mucosal Integrity

Iso-osmolar

Hyperosmolar

Fuchs et al J Infect Dis 2007
# Lubricants Vary in Osmolality

<table>
<thead>
<tr>
<th>Product</th>
<th>Osmolality (Median mOsm/Kg)</th>
</tr>
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<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>
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</tbody>
</table>

Fuchs et al J Infect Dis 2007
Colorectal Intestinal Explants

Endoscopic biopsies + Absorbable gelatin sponge

Toxicity of Topical Microbicides in Colorectal Explants

Dezzutti C et al., AAC 2004
Tenofovir Explant Data

HIV-1\textsubscript{LAV} and PMPA

- 783 MED/LAV
- PLAC/LAV
- PMPA/LAV

p-24 (pg/ml)

D1 D4 D7 D11 D14
Rectal Model Development

*Macaca nemestrina*
Rectal Lavage Assay

Lavage fluid

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

Day 4 Combo Animal

*TMicrobicides 2008 Poster #TA-057*
Evolving Design of Phase 1 Rectal Safety Studies
Tabet et al.

- Open label frequency escalation safety study of 3.5% nonoxynol-9 gel versus replens
- Population – monogamous couples
  - 25 HIV negative MSM
  - 10 HIV positive MSM
- Gel BID + RAI 3 times per week for 6 weeks
- 68 (97%) participants completed study
- Minor anoscopic or histological findings common

Tabet et al. STD 1999
Phillips et al.

• 2% Nonoxynol-9
• 18 participants - open label study
• Endpoint
  – Histology
• Sampling
  – Baseline
  – + 15 minutes
  – + 2 hours
  – + 8 hours

Phillips et al. Contraception 2004
Phillips et al. Contraception 2004

Baseline

+ 15 minutes

+ 15 minutes

+ 2 hours

+ 2 hours

+ 8 hours

Phillips et al. Contraception 2004
HPTN 056 Study Design

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 0 +2 +4

McGowan et al. JAIDS 2007
UC-781 Trial Design

Screening  Enrollment  Baseline Endoscopy  Randomization  Placebo

Single dose  2nd Endoscopy  7 single Doses  3rd Endoscopy

Anton et al. CROI 2009
Explant Data

HEC Placebo  UC781 0.10%  UC781 0.25%

10cm

30cm

(CUMULATIVE P-24 AT DAY 14 (pg/ml))

(HIV-1 BaL TCID_{50} 10^4)
# Future Phase 1 Rectal Microbicide Safety Studies

<table>
<thead>
<tr>
<th>Product</th>
<th>Status</th>
<th>Timeline</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td>UC-781</td>
<td>Completed</td>
<td></td>
<td>NIAID/DAIDS</td>
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<tr>
<td>MTN-007</td>
<td>Planned</td>
<td>Q2 2009</td>
<td>NIAID/DAIDS</td>
</tr>
<tr>
<td>RMP-02</td>
<td>Planned</td>
<td>Q2 2009</td>
<td>NIAID/DAIDS</td>
</tr>
<tr>
<td>VivaGel</td>
<td>Planned</td>
<td>Q4 2009</td>
<td>NIAID/DMID</td>
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<tr>
<td>PRO-2000</td>
<td>Planned</td>
<td>Q4 2009</td>
<td>MDP MRC-UK</td>
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<tr>
<td>UC-781 (RF)</td>
<td>Possible</td>
<td>Q4 2010</td>
<td>TBD</td>
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</table>
RMP-02 / MTN-006

• A Phase 1 rectal microbicide safety and acceptability trial of topically applied tenofovir compared with tablet

• Study population
  – 18 sexually abstinent HIV negative men and women

• Study products
  – Oral
    • Tenofovir
  – Topical
    • 1% vaginal formulation of tenofovir
    • Hydroxyethyl cellulose (HEC) placebo gel
RMP-02 / MTN-006

Pharmacokinetics
- Plasma
- PBMC
- Rectal fluid
- Tissue
- MMC

Safety
- General
- Mucosal

Explant
Infection

Single oral dose of tenofovir

Single rectal dose of tenofovir

7 daily doses of tenofovir
RMP-02 / MTN-006

• David Geffen School of Medicine at UCLA
  – IOR: Peter Anton MD

• Pittsburgh, PA
  – IOR: Ian McGowan MD PhD
MTN-007

- Phase 1 randomized, double-blinded, placebo-controlled rectal safety and acceptability study of tenofovir 1% gel
- Approximately 60 sexually (RAI) abstinent, HIV-negative adults men and women
- Four study arms:
  - 1% vaginal formulation of tenofovir
  - Hydroxyethyl cellulose (HEC) placebo gel
  - 2% nonoxynol-9 (Ortho-Gynol II)
  - No product arm
MTN-007 Design

N=60

2% N-9 (N=15)

1% Tenofovir (N=15)

HEC (N=15)

No Treatment (N=15)

Baseline Evaluation

Single dose

7-14 day interval

7-14 day interval

7 day daily doses

Endoscopy Safety/behavioral assessment

Screening
Secondary Endpoints

• Mucosal safety parameters:
  – Epithelial sloughing
  – Intestinal histopathology
  – Intestinal mucosal mononuclear cell phenotype
  – Intestinal mucosal cytokine Intestinal mucosal gene expression arrays
  – Cytokine profile in rectal secretions
  – Fecal calprotectin
  – Microflora
MTN-007 Study Sites

- Pittsburgh, PA
  - IOR: Ross Cranston MD
- Birmingham, AL
  - IOR: Craig Hoesley MD
- Boston, MA
  - IOR: Ken Mayer MD
Why have an N-9 arm in MTN-007?

- Assessment of mucosal injury requires the use of esoteric and expensive assays
- Preliminary data from a UC-781 Phase 1 rectal safety study have not demonstrated changes in these mucosal safety parameters
- Rectal exposure to N-9 results in mild and transient epithelial disruption
  - Mice
  - Macaques
  - Humans
Is inclusion of an N-9 arm safe?

- Histological recovery occurs within 1-8 hours
  - Mice
  - Humans
  - Macaques
- Tabet et al. demonstrated minimal histological inflammation after up to 6 weeks treatment with a 3.5% formulation of N-9
- All participants in MTN-007 will be sexually abstinent
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.
Next Steps

• Identify relevant population
• 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
    • Africa
Microbicide Safety and Acceptability in Young Men

• NICHD R01
  – McGowan / Carballo-Dieeguez
  – 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-Diequez 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
    • CONRAD
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
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>
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<th>Placebo Study</th>
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<td>Seroincidence</td>
<td>4%</td>
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<tr>
<td>Power</td>
<td>90%</td>
</tr>
<tr>
<td>Endpoints per pair wise</td>
<td>90-100</td>
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<td>comparison / total</td>
<td>2 pair wise comparisons</td>
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<td></td>
<td>Total: 180-200</td>
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<td>Person years per endpoint</td>
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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
IAS Meeting, Cape Town, South Africa, July 2009

“Rectal Microbicide Development, An African Perspective”

Ian McGowan MD PhD
Chris Beyrer MD
James McIntyre MD
Jim Pickett

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