The World Needs Rectal Microbicides

A global approach to rectal microbicide advocacy
GLMA, San Francisco, 13 October 2006
Dr. Ian McGowen
Marc-André LeBlanc
Jim Pickett
Objectives for this session

- Latest in rectal microbicide research
- The (new) Microbicide Trials Network
- Lubricant safety
- International advocacy efforts
- Quiz – how did you do?
Rectal Microbicide Development

Ian McGowan MD PhD FRCP

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<th>Transmission Category</th>
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* CDC data from 35 areas with HIV surveillance
Modeling Rectal Microbicide Efficacy

Adapted from Breban R et al. Mathematical Biosciences & Engineering 2006
Where to Protect and What to Measure?

Hendrix et al., 2004
## Topical Rectal Cytotoxicity

<table>
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<tr>
<th>Compound</th>
<th>Cellular Toxicity</th>
<th>Enhanced HSV-2 Infection</th>
<th>Rectal Sloughing</th>
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<tr>
<td>KY-Plus</td>
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<tr>
<td>Carraguard</td>
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<td>Methylcellulose</td>
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<td>PBS</td>
<td>-</td>
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Sudol and Phillips. Contraception 2004
## Rectal Safety of Vaginal Microbicides

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<tr>
<th>Candidate</th>
<th>Murine</th>
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<td>Octylglycerol</td>
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<td>PMPA</td>
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<td>UC781</td>
<td>Neg</td>
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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
Macaque Models
Epithelial Sloughing
Colorectal Explant System

Day 0

Day 1

Day 7
Toxicity of Topical Microbicides in Colorectal Explants

Abner et al., JID 2005
Effect of Osmolality on Mucosal Integrity

Iso-osmolar

Hyperosmolar

Fuchs et al. Microbicicides 2006
<table>
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<th>Products</th>
<th>N</th>
<th>Safety Assessment</th>
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<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>
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<td>N-9 (1% &amp; 2%), Carraguard, methycellulose</td>
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<td>Qualitative lavage, Electron microscopy</td>
<td>Phillips et al. 2000</td>
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<td>N-9 (2%)</td>
<td>18</td>
<td>Histology (BL, +2hrs, +8hrs), Lavage (+15min, +&gt;8hrs)</td>
<td>Phillips et al. 2004</td>
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</table>
HPTN 056 Study Design

**Week -2**
- Screening
  - Consent
  - Physical
  - Anoscopy
  - Rectal GC/CH
  - HIV Ab
  - CD4 / Viral load

**Week 0**
- Baseline
  - Sigmoidoscopy
  - Intestinal biopsy at 10cm and 30cm
  - Cell isolation and flow cytometry
  - Tissue cytokines
  - Tissue immunoglobulins
  - Rectal immunoglobulins
  - Tissue / rectal secretion viral load

**Week +2**

**Week +4**

UC-781 Phase 1 Safety Study (1)

- Phase 1 study of UC-781 vaginal microbicide gel (0.1% and 0.25%) when rectally administered in HIV-1 seronegative adults
- N = 36
- Single site at David Geffen School of Medicine at UCLA
- Population
  - HIV negative men and women with a history of RAI
- Design
  - Stage 1 – Single dose
  - Stage 2 – Seven daily doses
UC-781 Phase 1 Safety Study (2)

- Primary endpoints
  - Frequency of ≥ Grade 2 adverse events
  - Acceptability

- Secondary endpoints
  - Epithelial sloughing
  - Histopathology
  - Microflora
  - Mucosal mononuclear cell phenotype
  - Mucosal cytokine profile
  - Mucosal immunoglobulins
  - Fecal calprotectin
  - Explant susceptibility to HIV infection
## Rectal Microbicide Gap Analysis

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<th>Area</th>
<th>Requirements</th>
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<td>Funding</td>
<td>Sponsors should integrate rectal studies into their microbicide study portfolio</td>
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<tr>
<td>Behavioral</td>
<td>Gather more information on the prevalence of AI in domestic and international settings</td>
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<tr>
<td>Regulatory</td>
<td>Develop regulatory guidelines for rectal studies</td>
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<tr>
<td>Design of Phase 1 studies</td>
<td>Simplify safety assessments</td>
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<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>
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Update on the Microbicide Trials Network (MTN)
The mission of the Microbicide Trials Network is to reduce the sexual transmission of HIV through the development and evaluation of products applied topically to mucosal surfaces or administered orally.

The goal is to conduct scientifically rigorous and ethically sound clinical trials of safety and effectiveness that will support licensure of topical microbicide products.
From the HPTN to the MTN

- First microbicide trials conducted in HIVNET 1995-2000
- Microbicide research agenda expanded in HPTN 2000-present
- MTN proposed as an independent network because of growing research agenda in a high priority area
- Drug development paradigm for microbicides differs significantly from other HIV prevention research
- No duplication in scientific portfolio with other DAIDS Networks
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MTN Priorities

- Successful completion of ongoing microbicide trials within regulatory environment required for licensure:
  - HPTN-035
  - HPTN-059

- Assess readiness of new sites to determine whether formal prep studies will be required
  - Kampala, Cape Town, and Durban

- Development of new protocols
  - Phase 1 (MTN-004, MTN-001)
  - Seroconverter protocol (MTN-015)
  - Tenofovir tissue / plasma PK studies
Key Scientific Issues (1)

Retention
- Provision of contraceptive services
- Evaluation of incident pregnancy

Adherence

Safety monitoring
- Use of safety physicians
- Evaluation of cytokines
- Cross agency safety meetings
- Development of new toxicity tables
Antiretroviral resistance
  Phase 1 studies in HIV-positive women
  MTN-015 & MTN-016
Topical versus systemic microbicides
  (MTN-003)
Strategic alliances to provide additional candidate microbicides
Single versus multiple or combination agents
Accrual*
- 3308 subjects screened
- 1560 subjects enrolled
- Accrual overall is slightly behind target, mainly due to delays in site initiation
- Once initiated, sites have generally met monthly targets

Retention*
- 6757 monthly follow-up visits completed:
  - 93% retained at Mo 3
  - 92% retained at Mo 6
  - 92% retained at Mo 9
  - 92% retained at Mo 12
  - 89% retained at Mo 15

*Week ending October 6th, 2006
HPTN-035 Workload

Visits, Fax Pages, and AEs

- Patient screening
- Patient enrollment
- Total Visits
- Data Fax Pages
- Adverse Events

Screening and Enrollment

0 10 20 30 40 50 60 70 80 90

2005 2006 2007 2008 2009

Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1

0 10000 20000 30000 40000 50000 60000 70000

0 100 200 300 400 500 600 700 800 900
Defining Success for the MTN

- Rapid evaluation of microbicide safety in seropositive and seronegative women
- Evaluation of safety and effectiveness of oral versus vaginal ART (tenofovir)
- Screening of safe candidates for efficacy (rank selection trials)
- Prove efficacy of one or more microbicides
Lubricant Safety

Results of studies:
- Broad range in the degree of toxicity
- No lubricants appears protective for HSV-2 (rectal, mouse assays)

Next steps for researchers and advocates
- Disseminate results of studies
- Test more products
- Use as “test-run” for RM messaging
Lubricant Safety

Sudol/Phillips studies

3 sets of tests:
- Cytotoxicity
- Sloughing of rectal epithelium
- Challenge with HSV-2

Advocacy

How we facilitate moving rectal microbicides from laboratory test tubes to the shelves at Walgreens Pleasure Chest, and CBOs around the world…
In this section we will cover…

- Who needs rectal microbicides? Who is having anal intercourse (AI)?
- What are the resources needed?
- Who is doing the advocacy work?
- What is the agenda?
- What can WE do?
Who needs rectal microbicides?

- **Women/hetero**
  - U.S. – 35% report at least one episode of anal intercourse (AI) in lifetime
  - U.S. – 6.7% het couples practice AI at least once/mo.
  - 30% of het pop in many cultures practice AI (virginity, contraception)
  - Volume unprotected AI (UAI) 7x higher in het compared to gay/MSM

- **Gay men/MSM**
  - Among U.S. gay and MSM, most report practicing AI: 76-90%
  - U.K.: 48.8% UAI (Gay Men’s Sex Survey 2002)
  - U.S.: 48-54% UAI (EXPLORE Study 2003, n = 4,295)
  - STD rates confirm high prevalence of UAI
  - Higher prevalence of HIV compared to heterosexual population = more risk per act of UAI
Global Campaign for Microbicides

A worldwide effort co-sponsored by groups working on
- HIV/AIDS
- Reproductive health
- Gay health
- Women’s empowerment
- Prevention

Working to educate, raise awareness and generate collective advocacy for increased political and public investment in microbicide development in the states and the global north and south. Visit the website, endorse the campaign, sign up for their newsletter, host a talk…get involved!

www.global-campaign.org
The Alliance for Microbicide Development is a global, non-profit organization whose sole mission is to speed the development of safe, effective, and affordable microbicides to prevent sexually transmitted infections, most critically HIV/AIDS. The Alliance envisions a world in which all individuals have the power and tools they require to protect themselves from HIV and other sexually transmitted diseases.

www.microbicide.org
IRMWG formed June 2005
Over 280 advocates, scientists and policy makers from 32 countries
Global listserv
Conference calls featuring scientific presentations, next is Oct 30
Advocacy agenda supporting the research and development of safe, effective rectal microbicides
Published “Rectal Microbicides: Investments and Advocacy” in April 2006, M2006 in Cape Town.

www.lifelube.org – more info
jpickett@aidschicago.org – sign up
The IRMWG mission

- To promote and facilitate the research and development of safe and effective rectal microbicides for all those that need them
- To promote rectal safety studies on all Phase III vaginal microbicide candidates
- To support the research of other new prevention technologies, such as vaccines and oral prevention (PrEP)
- To promote and disseminate lubricant safety research
- To place rectal microbicides within sexual harm reduction
- To serve as a central forum for exchange, debate, networking on these ideas
- To convene diverse perspectives and scientific disciplines to improve understanding and action
Rectal investments

- Total 2000 – 2006 = $34M
  - 2000 = $2M
  - 2006 = $7.2M (estimated)
Rectal investments

- Public Sector
  - **U.S.** = $33.1M, 00-06, 97.4%
  - **NIH** = $30.8M, 00-06
    - 06 = $6.6M
    - .023% of overall budget
    - 07 = $5.5M (projected)
  - **CDC** = $2.3m, 01-06
    - “The Evaluation of Topical Microbicides in Men Who Have Sex With Men”
    - CDC vaginal - $2.4M, 01-06
  - 12 cents per capita

- Europe?
  - Funds not apportioned specifically, VM $?, Britain’s Microbicide Development Programme - Phase 1 rectal safety study in 06 but investment totals could not be confirmed, other spending too elusive to track…
Rectal investments

**Philanthropic Sector**
- $739,649 - 00-06
  - Approx. 2.2% total funds
  - Trend from 00-06
    - 00 = $337,455
    - 01 = $268,194
    - 02 = $99,000
    - 03 = $0
    - 04 = $10,000
    - 05 = $0
    - 06 = $25,000
- **amfAR** primary investor
  - No dedicated RM stream, funding levels fluctuate. RFP released this year for 250k.
  - Direct research support, meeting support.

**Commercial sector**
- $100,000 - 06
  - Most support in-kind
  - Time spent, pipeline compounds, infrastructure.
  - Likely waiting for proof of concept before fiscal risk.
  - Biosyn 06 – $100,000 – in kind
  - Gilead – no figure given
Estimate of rectal funding needs

- Conservatively, rectal field probably needs 5 candidates over 10 – 15 year period
- Will require minimum $350M, or at least $35M/year for 10 years
- Annual rectal spending needs to increase 5-fold
FUND THE GAP
Whatever the strategy, the securing of public and private funding for every stage of rectal microbicide R&D must be a priority.
Donors must:

- Provide a minimum of $350 million for targeted RM research funding over the next 10 to 15 years, or an average of at least $35 million per year to build a comprehensive RM research program.
- Provide transparency and an increase in institutional commitment to explicitly fund RM development.
- Commit to supporting phase 1 rectal safety studies for all vaginal microbicide candidates being evaluated in phase 2B/3 efficacy trials.
Recommendations from report

- **Intl nongovernmental orgs must:**
  - Form a body to specifically track RM development, to ensure funding, and to coordinate research, regulatory approval, and advocacy.

- **Researchers must:**
  - Recruit new scientists to the field and promote RM research within the scientific community.
  - Initiate ideas for grant proposals to create demand for funding.
Advocates must:

- Reach out to affected communities to educate and to promote RM trial preparedness.
- Promote global, national, and regional surveillance efforts to determine percentage of HIV infections attributed to AI in order to better assess the need for RM development.
- Raise awareness, educate, and mobilize communities to foment a stronger, more visible demand for RM and to elevate the profile of microbicides among policymakers.
- Ensure linkages to the broader microbicide movement and to advocates working on other prevention technologies.
Regulatory agencies like the U.S. FDA, the EMEA, and others must:

- Develop support and development guidelines to accelerate the study and licensure of RM.
- Request that all New Drug Applications for vaginal microbicides include at least one rectal safety study as part of the submission package.
The U.S. Congress must:

- Pass the Microbicide Development Act, and other countries should consider similar legislation.
Contact info

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- Marc-André LeBlanc
  - maleblanc27@yahoo.ca

- Jim Pickett
  - jpickett@aidschicago.org

- LifeLube – International Rectal Microbicide Working Group
  - www.lifelube.org

- Global Campaign for Microbicides
  - http://www.global-campaign.org/
Thank You!