Rectal Microbicides in 2014

Ian McGowan MD PhD FRCP
Creating Desire Meeting
Arlington, VA
13th May, 2014
Microbicides are products that can be applied to the **vaginal** or **rectal** mucosa with the intent of preventing or significantly reducing the risk of acquiring **STIs** including **HIV**.
Microbicide Mechanism of Action

- Viral disruption
- Prevention of STDs
- Maintenance of normal microflora
- Gel/cream: physical barrier, lubrication
- Inhibition of reverse transcriptase
- Inhibition of HIV uptake by dendritic cells (e.g., anti-DC-SIGN)
- Fusion/absorption inhibition (e.g., polyanions, co-receptor antagonists)

Microbicides
A Brief History of Rectal Microbicides
Early Events

1999: Beyond condoms - life after latex Michael Scarce

1999: Microbicides: Anna Forbes & Polly Harrison

Second LGBTI Health Summit. Colorado

2000: Rectal Microbicides: Anna Forbes
Creating a Research and Development Agenda for
Rectal Microbicides that Protect Against HIV Infection

Report from the Workshop:
Baltimore, Maryland, June 7-8, 2001

This report was published by the American Foundation for AIDS Research.
Goals of the 2001 Symposium

- Establish the current state of knowledge across those disciplines that bear on rectal microbicide research and development
- Identify biomedical and behavioral research priorities for advancing an understanding of rectal physiology, particularly in the context of sexual acts, mechanisms of HIV transmission, and the potential role of topical agents in conferring protection against rectal HIV infection
- Outline key considerations associated with studies of **product acceptability**, including applicator design
- Propose an appropriate **clinical strategy** for rectal microbicides
What Happened Next?
Key Events in RM Development

- **2004**
  - MDP Program
  - U19 IPCP
  - Grant

- **2005**
  - IRMA
  - MTN
  - MTN-006
  - MTN-007
  - MTN-017

- **2006**
  - MTN

- **2009**
  - Project Gel

- **2014**
  - MTN

- **2014**
  - DREAM Program
  - U19 IPCP
  - Grant

- **2009**
  - CHARM Program
  - U19 IPCP
  - Grant

- **2014**
  - PREVENT Program
  - U19 IPCP
  - Grant
Are Rectal Microbicides Needed in 2014?
Diagnoses of HIV Infection among Adults and Adolescents, by Transmission Category, 2008–2011—United States and 6 Dependent Areas

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting.

* Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

b Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.
Would Anyone Use a Rectal Microbicide?
Lubricant Use is Common Among MSM

Where is the Science?
Non Human Primate Studies

- Cyanovirin-N / SHIV89.6P
  - Tsai CC et al., *AIDS Res Hum Retroviruses*, 2003

- Tenofovir / SIVmac251/32H
  - Cranage M et al., *PLOS Med*, 2008

- MIV-150 / SIVmac239

- Maraviroc
  - Dobard C et al., Abstract, 2013
Colorectal Intestinal Explants

Endoscopic biopsies + Absorbable gelatin sponge

Abner SR et al., JID, 2005
Watts P et al., AIDS, 2006
Maraviroc *In Vitro* Colorectal Explant Efficacy Data

Dezzutti C et al., CHARM Project 1, unpublished data
Product Distribution

Phase 1 Development

- Nonoxynol-9 (HIVNET-008 study)
  - Tabet S et al., *Sex Transm Infect*, 1999
- UC781 (RMP-01 study)
  - Anton PA et al., *PLOS ONE*, 2011
- Tenofovir (original formulation) (RMP-02/MTN-006 study)
- Tenofovir (reduced glycerin formulation) MTN-007
  - McGowan I et al. *PLOS ONE*, 2013
## Adverse Events in Trials

<table>
<thead>
<tr>
<th>GI Adverse Events in the Tenofovir Arm</th>
<th>MTN-007 (N = 16)</th>
<th>RMP-02/MTN-006 (N = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>3 16%</td>
<td>6 50%</td>
</tr>
<tr>
<td>Rectal urgency</td>
<td>0 0%</td>
<td>5 42%</td>
</tr>
<tr>
<td>Bloating</td>
<td>0 0%</td>
<td>5 42%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 0%</td>
<td>4 33%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 6%</td>
<td>7 58%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>6 38%</td>
<td>3 25%</td>
</tr>
<tr>
<td>Proctalgia</td>
<td>1 6%</td>
<td>0 0%</td>
</tr>
<tr>
<td>Other</td>
<td>4 25%</td>
<td>5 42%</td>
</tr>
<tr>
<td>Total</td>
<td>9 56%</td>
<td>12 100%</td>
</tr>
</tbody>
</table>
PK/PD Relationship

Oral Dose

Single Rectal Dose

Multiple Rectal Dose

Log$_{10}$[Tissue TFV-DP] fmol/mg

Cumulative p24 (pg/mL)

$r^2 = 0.33$

$P = 0.0011$

CHARM U19 Program Grant

- Combination HIV Antiretroviral Rectal Microbicide Program
  - Preclinical evaluation
  - Humanized mouse model
  - Phase 1 studies
    - CHARM-01 (TFV)
    - CHARM-02 (TFV)
    - CHARM-03 (MVC)

PI: Ian McGowan
Project Gel

GUYS EXPERIENCING LUBE

projectgel

IS NOW ENROLLING

Call 412.641.3380
or visit www.microbicidesc.us
for more information.

Pls: Alex Carballo-Diéguez & Ian McGowan
MTN-017

- Phase 2 rectal safety study of tenofovir gel
- N = 186
- International sites
  - United States (4)
  - Thailand (2)
  - South Africa (1)
  - Peru (1)

Endpoints
- Safety
- Adherence
  - Self report
  - Real time PK
- Acceptability
- PK/PD

PI: Ross Cranston, University of Pittsburgh
### MTN-017

<table>
<thead>
<tr>
<th></th>
<th>8 weeks</th>
<th>8 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BL</strong></td>
<td>TFV Gel</td>
<td>TFV Gel</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Daily</td>
<td>With sex</td>
<td>Truvada</td>
</tr>
<tr>
<td><strong>BL</strong></td>
<td>TFV Gel</td>
<td>TFV Gel</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>With sex</td>
<td>Daily</td>
<td>Truvada</td>
</tr>
<tr>
<td><strong>BL</strong></td>
<td>Oral</td>
<td>TFV Gel</td>
<td>TFV Gel</td>
</tr>
<tr>
<td></td>
<td>Truvada</td>
<td>With sex</td>
<td>Daily</td>
</tr>
</tbody>
</table>

*Mucosal PK/PD subset (N = 36)*
Phase 3 Development

- Contingent upon supportive data from MTN-017
- Placebo controlled trial of RG-TFV gel on expanded prevention package including access to oral PrEP
- N = 5,000 MSM & transgender women
- One year follow-up period
- US, Latin America, Asia, ± Europe
Why Are We Here Today?
Vaginal Gel Adherence Data

Marrazzo J et al. CROI 2013
Meeting Priorities

- How can we increase desire for rectal microbicide use within clinical trials
  - At an individual level
  - At a community level
- What can we learn from previous studies
- What can be done over the next 2-3 years to maximize the success of product roll-out
- Where are the research gaps?
Funding

- NIH/NIAID/DAIDS
  - U19 AI060614
  - U19 AI082637
  - U01AI068633-01
  - UM1AI068633
- NIH/NIAID/DMID
  - U01 AI066734
- NIH/NICHD & NIH/NIMH
  - R01 HD059533-01A1
Thank You