Rectal Microbicide Development: Opportunities and Challenges

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Rectal compartment is particularly vulnerable to HIV transmission

- Single layer of columnar epithelium – easily damaged by RAI
- Several mechanisms of virus entry have been proposed
- Regional lymphoid tissue rich in activated cells providing environment for HIV amplification

Special considerations for rectal microbicides

- Some microbicides may be cytotoxic in the rectum
- Some microbicides may induce “immunological toxicity”
- Dynamics of absorption, local retention and clearance likely to be different to vaginal compartment
What might a rectal Microbicide look like?

Could potentially be made in many forms:

- gel or cream
- lubricant
- suppository
- tablet
- foam
- film
Any microbicide must be “safe, effective, cheap, user-friendly”

- **Safe** - must have no localized toxicity, including no damage to the rectal epithelium during sustained, repetitive use, with no localized inflammatory responses.

- **Effective** - must have a significant degree of efficacy in routine use.

- **Cheap** - pricing strategy must optimize distribution and availability.

- **User-friendly** - must be compatible with use during sex and must be used both consistently and reliably in a real life setting.
## Some Microbicides in the Pipeline

<table>
<thead>
<tr>
<th>PreClinical</th>
<th>Safety</th>
<th>Efficacy</th>
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<tbody>
<tr>
<td><strong>Entry/fusion inhibitors</strong></td>
<td>Cyanovirin Plant lectins BMS 806 Coreceptor antagonists gp41 inhibitors New polyanions (K5-N OS)</td>
<td>SPL7013 (dendrimer) CAP Polystyrene sulfonate</td>
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<tr>
<td><strong>NRTI</strong></td>
<td>PMPA</td>
<td></td>
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<tr>
<td><strong>NNRTI</strong></td>
<td>DABO UC781 TMC 120 MIV 150</td>
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<tr>
<td><strong>Membrane-disruptive agents</strong></td>
<td></td>
<td>C31G</td>
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<tr>
<td><strong>Unclassified</strong></td>
<td>Drug-expressing lactobacilli SiRNA</td>
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<td><strong>Combinations</strong></td>
<td>NRTI/NNRTI NRTI/Polyanion NNRTI/Polyanion NRTI/NNRTI/Polyanion CCR5-inhibitors/BMS806/C52L</td>
<td></td>
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First generation microbicides
(PRO2000, Carraguard, Cellulose Sulphate, Buffer gel)

Advantages
• Cheap \(\checkmark\) Broad activity \(\checkmark\)

Disadvantages
• No proof of concept in animal models (R5)
• Incomplete rectal safety studies
• Broad activity may reduce potency
• Need to be applied before UAI
  - high compliance burden
• May require large volume
ARV microbicides
(TMC-120, UC-781, MIV-150, PMPA)

Advantages
• **Cheap ✓** Highly active ✓ Could be formulated for sustained release.

Disadvantages
• Potential for resistance
• Unknown safety
• Lack of activity against other STDs
• Limited or lack of animal efficacy studies
NNRTIs show potent efficacy in rectal explant studies.
NNRTIs demonstrates significant memory effects

p24  provirus  DC-dissemination

TMC-120

May provide sustained protection in vivo (hours-days)
Entry inhibitor microbicides

(CMPD-167, BMS-806, PSC-RANTES)

Advantages
• Highly active  √ Could be formulated for sustained release.

Disadvantages
• Lack of activity against X4 virus
• Lack of activity against other STDs
• Unknown safety
• Lack of rectal animal efficacy studies, but potent protection when used vaginally
What’s been shown to work in animals?

1% Cyanovirin gel
7/7 protected

1% tenofovir gel
6/9 protected
(Martin Cranage M2006)

E.coli - C peptide
2/4 protected
(Dean Hamer M2006)
Funding gaps for preclinical studies

- Funding for early drug discovery
- Funding for novel formulation and sustained release technology specifically designed for rectal microbicides
- Funding for animal challenge studies
What would it take to demonstrate efficacy?

- Consistent use of product during every act of unprotected intercourse.
- High incidence of HIV-1 infection in control arms to provide sufficient statistical power.
- Multi-center trial involving 5-12 thousand participants
Unknowns for rectal microbicides

- The number of trial sites required to run a microbicide phase III trial
- The effect on incidence after counseling about safe sex practices in a rectal microbicide trial (site failure)
- The potential level of compliance by those not, or infrequently, using condoms
Why aren’t more products moving into clinical trails?

• Relatively few viable concepts
  – Polyanions, acid buffers and surfactants (unlikely to work for UAI)
  – Anti-retroviral drugs (most promising, but issues around resistance)
  – Entry inhibitors (unknown efficacy for rectal transmission)

• Phase I/II trials may raise issues of safety and or acceptability
Further Challenges

- **Strategies to deal with multiple failures/adverse events in vaginal trials** (fatigue/hostility - participants, investigators, activists, funders, politicians) - knock on effect for rectal microbicides?

- **Integrating with other prevention strategies** (Circumcision, PreP, HSV Suppression, vaccines)
The tipping point:
What would it take to make a difference

• What level of uptake and compliance would be required to have an impact on incidence rates?
• What level of effectiveness would encourage use? How would perceived risk influence uptake?
• How attractive is an HIV only product (other STIs, sexual pleasure?)

Can current concepts and trial design meet required characteristics?
What about the economic argument

• A vaginal microbicide trial costs 80 million dollars
• Could prevent 2.5 million infections in three years
• Would provide 2.7 billion savings in health care*
• Would have a target population of 10 million women

• A successful rectal microbicide trial would cost?
• Would prevent how many infections in three years?
• Would provide what level of savings?
• Would have a target population of?

*www.global-campaign.org/clientfiles/rep7_publichealth.pdf