Rectal Microbicide Development: Opportunities and Challenges

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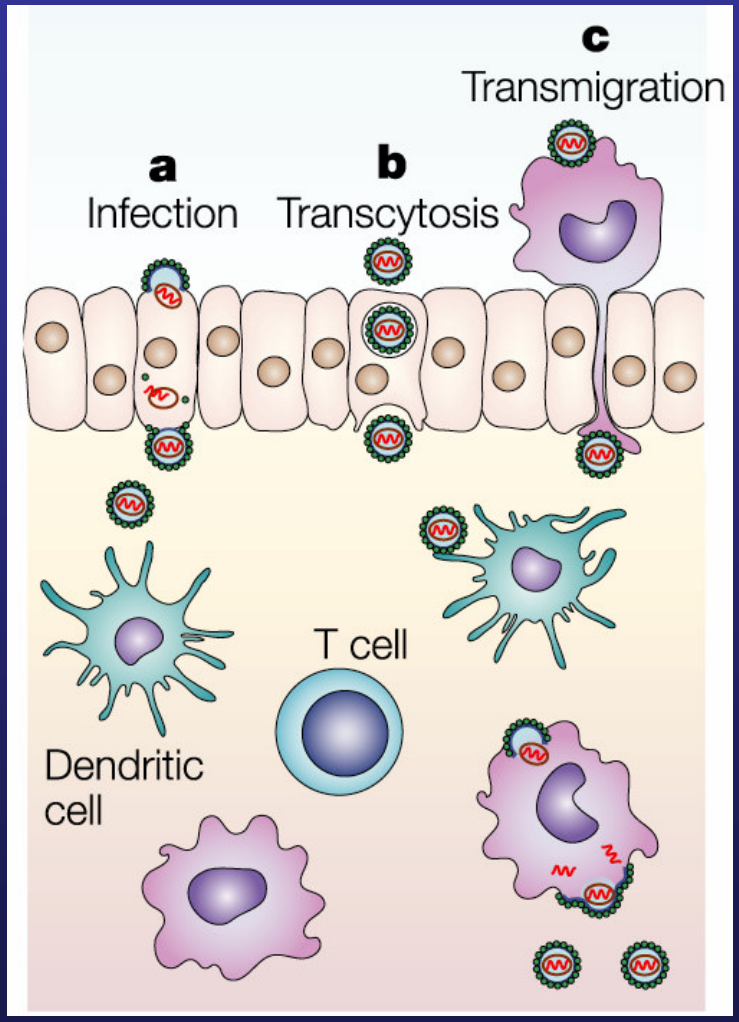
Rectal transmission of HIV: use of rectal microbicides



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

	PreClinical	Safety	Efficacy
Entry/fusion inhibitors	Cyanovirin Plant lectins BMS 806 Coreceptor antagonists gp41 inhibitors New polyanions (K5-N OS)	SPL7013 (dendrimer) CAP Polystyrene sulfonate	PRO2000 Carraguard Cellulose sulfate Buffer gel
NRTI		PMPA	
NNRTI	DABO	UC781 TMC 120 MIV 150	
Membrane-disruptive agents			C31G
Unclassified	Drug- expressing lactobacilli SiRNA		
Combinations	NRTI/NNRTI NRTI/Polyanion NNRTI/Polyanion NRTI/NNRTI/Polyanion CCR5-inhibitors/BMS806/C52L		

First generation microbicides

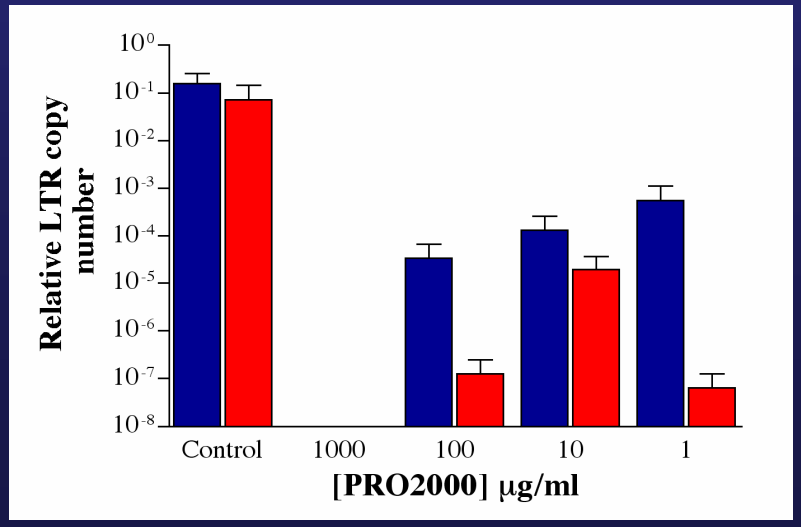
(PRO2000, Carraguard, Cellulose Sulphate, Buffer gel)

Advantages

- Cheap √ Broad activity √

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

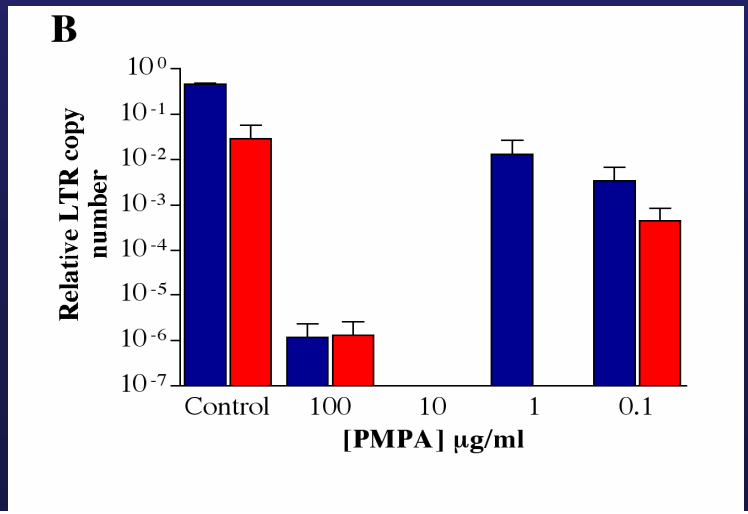
(TMC-120, UC-781, MIV-150, PMPA)

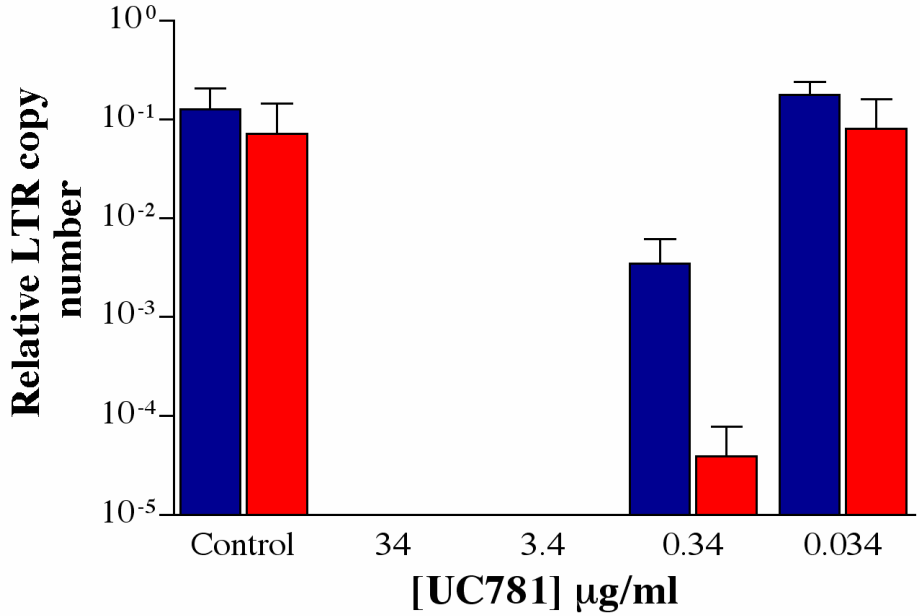
Advantages

- **Cheap √ Highly active √ Could be formulated for sustained release.**

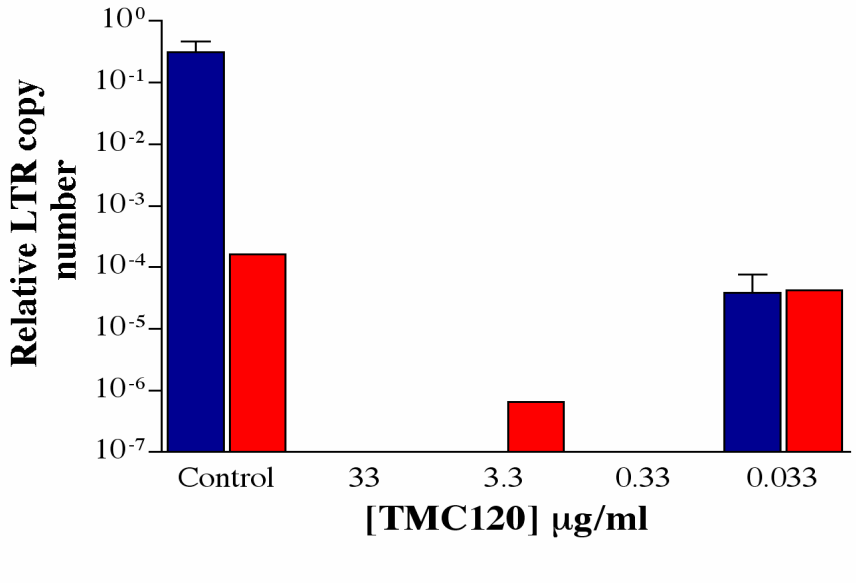
Disadvantages

- **Potential for resistance**
- **Unknown safety**
- **Lack of activity against other STDs**
- **Limited or lack of animal efficacy studies**



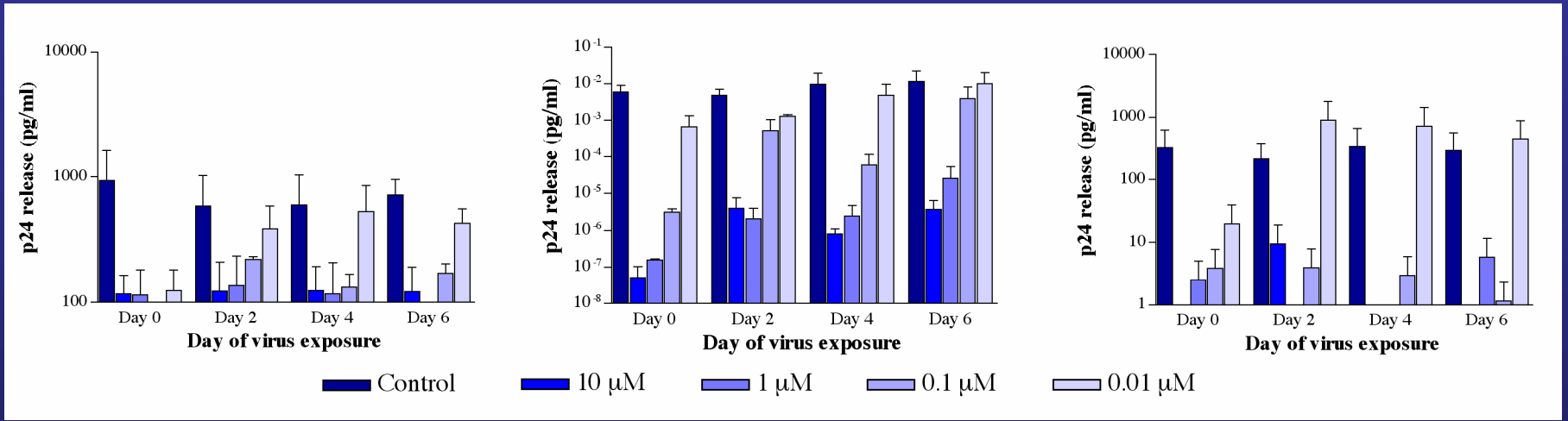


NNRTIs show potent efficacy in rectal explant studies



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

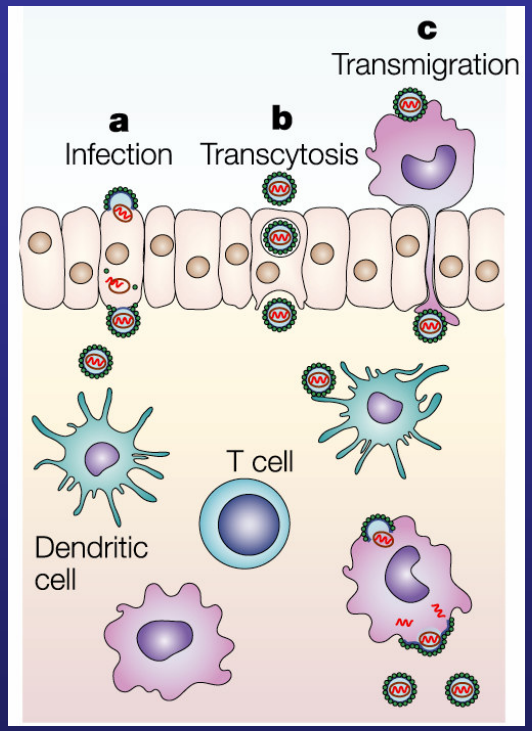
- Highly active √ Could be formulated for sustained release.

Disadvantages

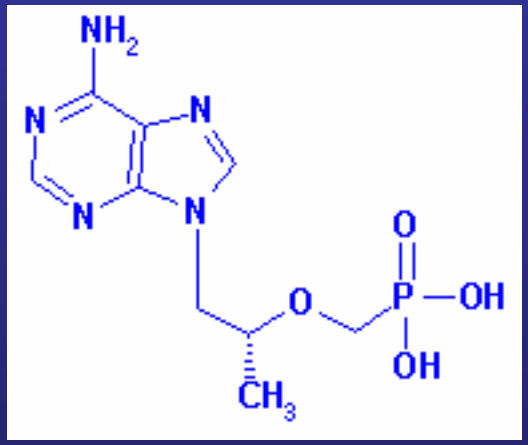
- Lack of activity against X4 virus
- Lack of activity against other STDs
- Unknown safety
- Lack of rectal animal efficacy studies, but potent protection when used vaginally

PlosMedicine 2006 August 15 (http://dx.doi.org/10.1371/journal.pmed.0030351)

What's been shown to work in animals?



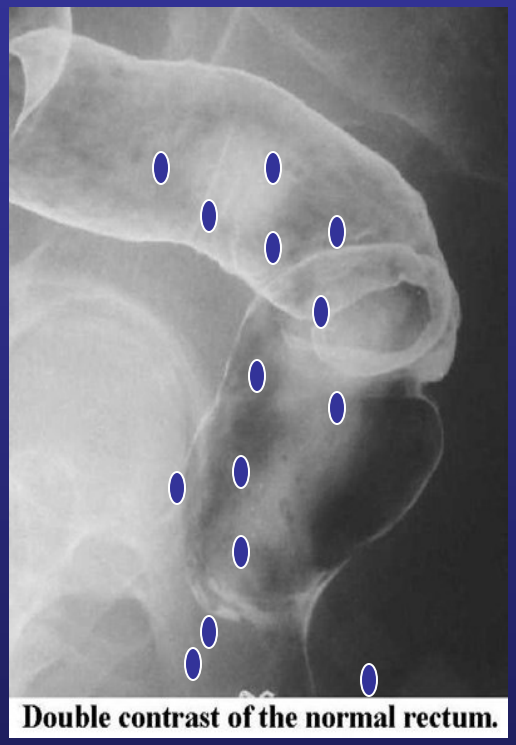
1% Cyanovirin gel
7/7 protected



1% tenofovir gel

6/9 protected

(Martin Cranage M2006)


Double contrast of the normal rectum.

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