The Need for Parallel Development of Rectal Microbicides

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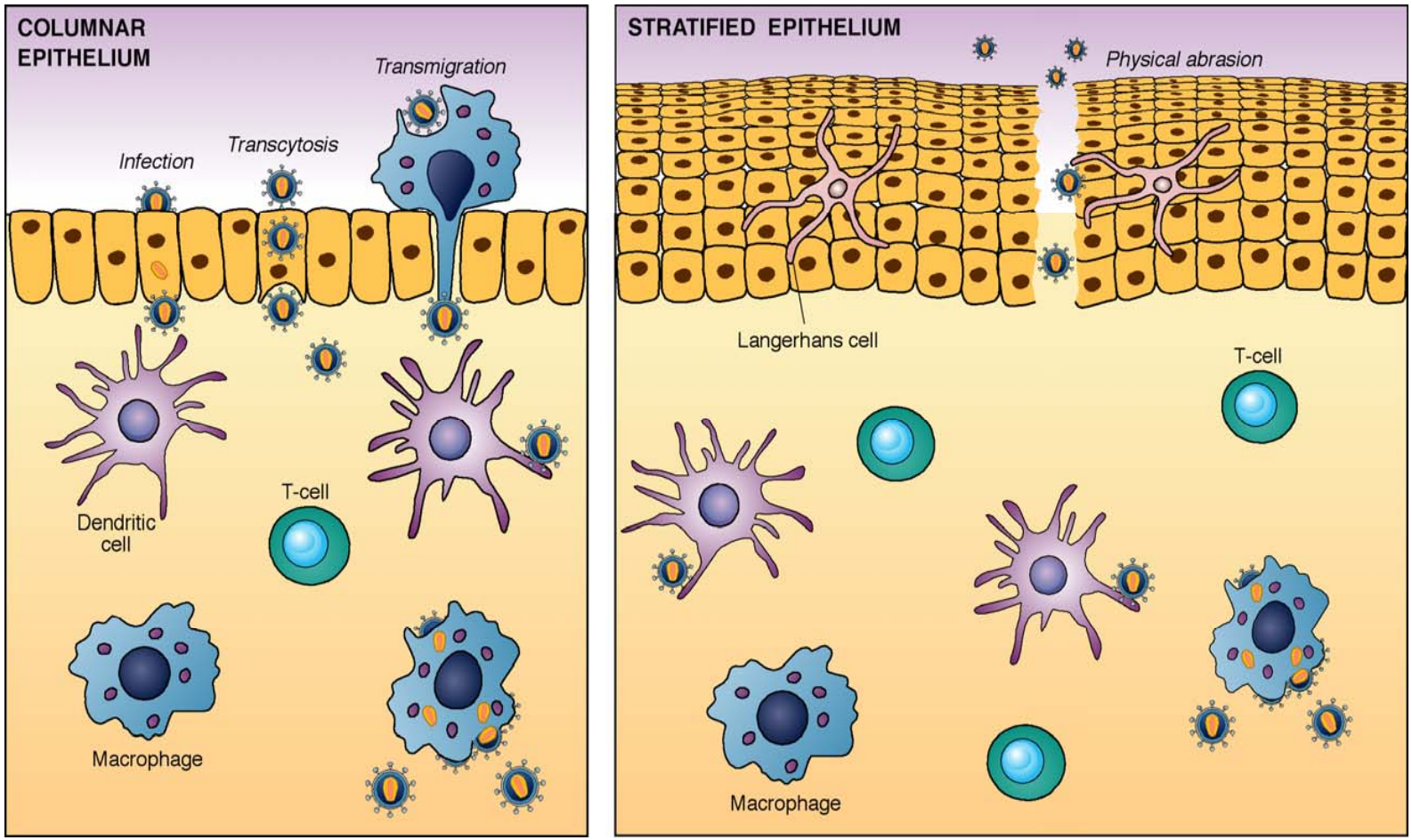
Overview

- Rationale for conducting Phase 1 rectal safety studies of vaginal microbicides
- Update on the design of rectal safety studies
  - UC-781 Phase 1 rectal safety study
- The rectal Phase 1 pipeline
- Development of rectal-specific microbicides
- Update on rectal microbicide advocacy

Rectosigmoid Anatomy

Mucosal Targets for HIV Infection



McGowan, Biologicals 2006

Rationale for Conducting Phase 1 Rectal Safety Studies of Vaginal Microbicides

Heterosexual Anal Intercourse is Common in the US

Population	N	Prevalence of AI	Reference
High risk women	1268	32%	Gross M et al. 2000
College students	210	20%	Civic D 2000
US Survey 15 – 44 years NSFG	12,571	35-40%	Mosher WD et al. 2005
Californian residents	3545	6-8%	Erickson PI et al. 1995

Women and RAI Outside the US

Country	Ever Experienced RAI (%)	Source
Brazil	31.0	Guimares MD et al. 1995
Peru	12.0	Caceres C et al. 1997
South Africa	42.8	Karim SS and Ramjee G 1998
Kenya	40.8	Schwandt M et al. 2006

Limited Preclinical Rectal Safety Data

Candidate	Murine	Primate	Explant	Human
N-9	+++	+++	+++	+++
Buffergel	?	(±)	?	?
PRO 2000	?	?	(±)	Pending
Carraguard	Neg	?	?	?
VivaGel	?	Neg	(±)	Pending
PMPA	?	?	Neg	?
UC-781	Neg	Neg	Neg	Ongoing

Rectal Cytotoxicity is a Problem

Compound	Cellular toxicity	Enhanced HSV-2 Infection	Rectal Sloughing
KY-Plus	++++	++++	++++
Delube	++++	++++	++++
Astroglide	++	++	++
Vagisil	++	++	++
Viamor	+	++	++
Carraguard	-	-	-
Methylcellulose	-	-	-
PBS	-	-	-

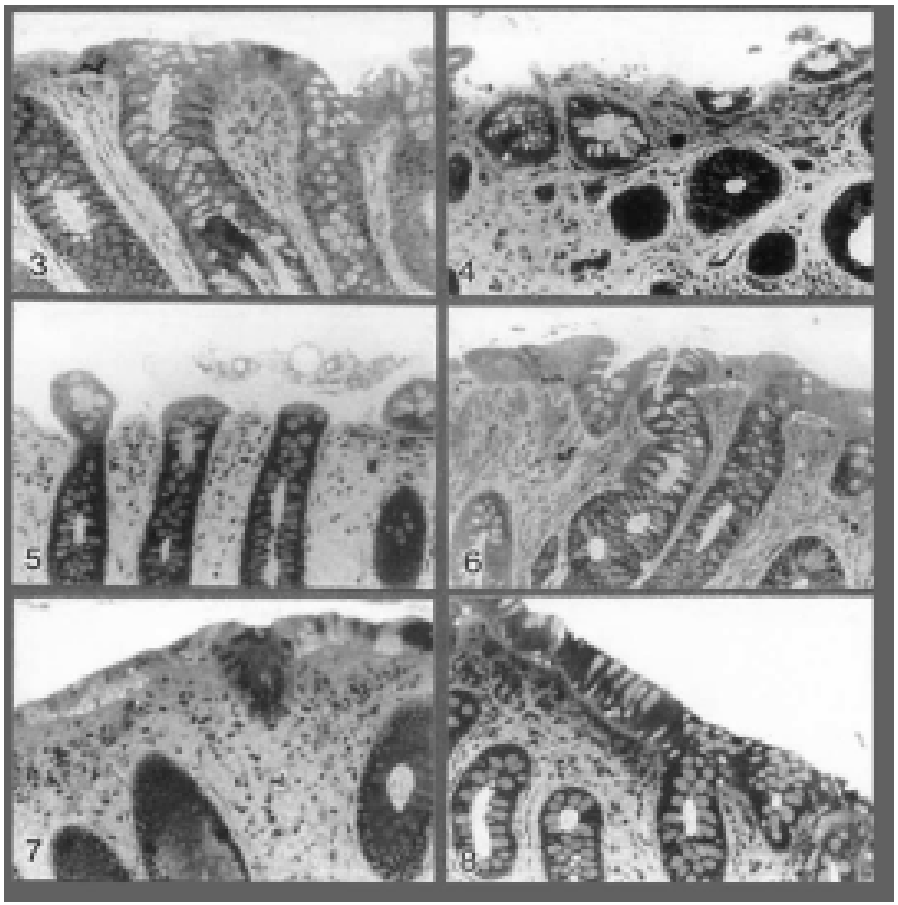
Sudol and Phillips. 2004

N-9 Effect on Rectal Epithelium

Baseline

+ 15 minutes

+ 2 hours



+ 15 minutes

+ 2 hours

+ 8 hours

Phillips et al. Contraception 2004

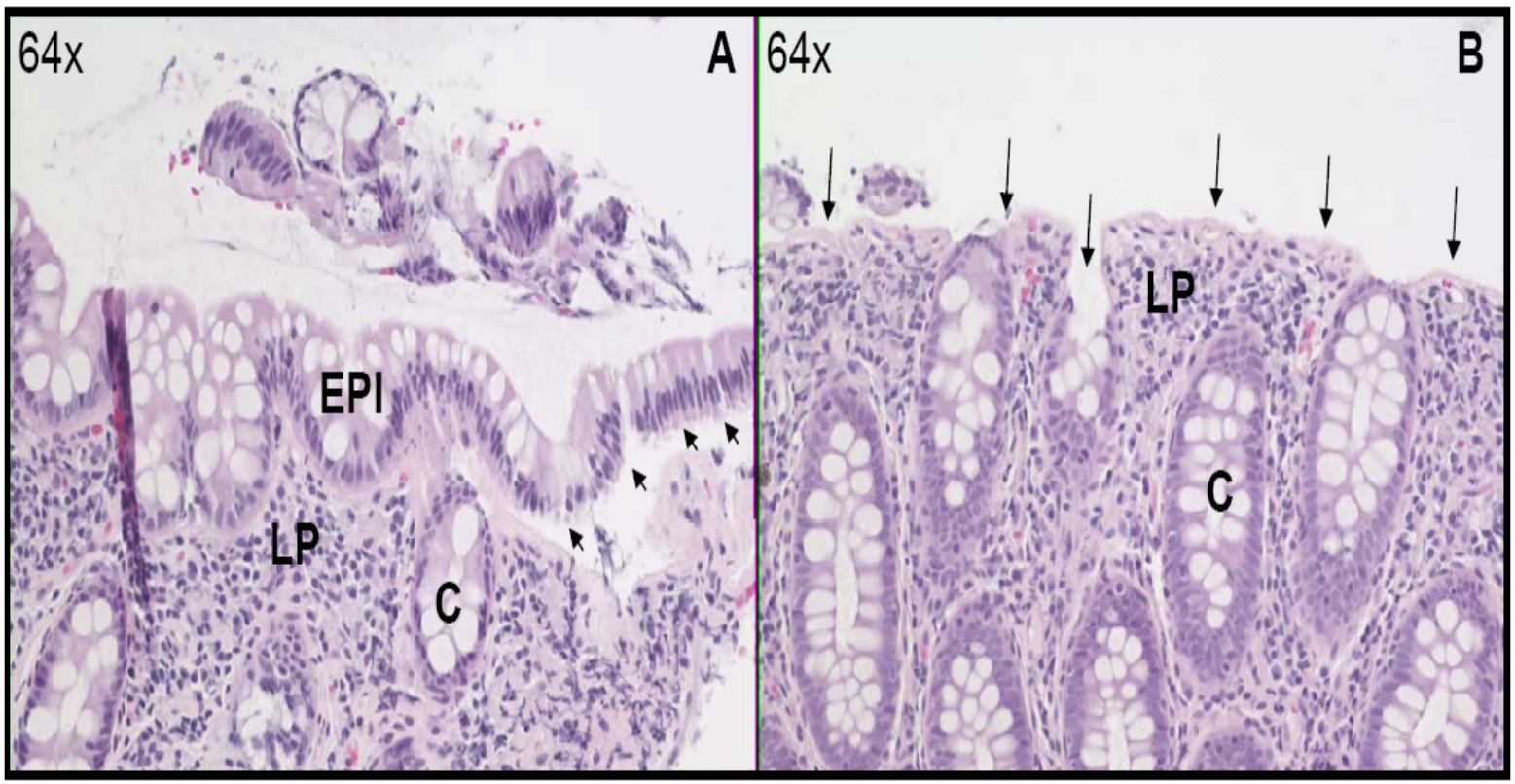
Lubricants Vary in Osmolality

Product	Osmolality (Median mOsm/Kg)
Tap water	3
Femglide	42
Semen	340
Gynol II	1182
Fleet enema	2127
KY Jelly	2424
Astroglide	3126
Prepair	4026

Fuchs et al J Infect Dis 2007

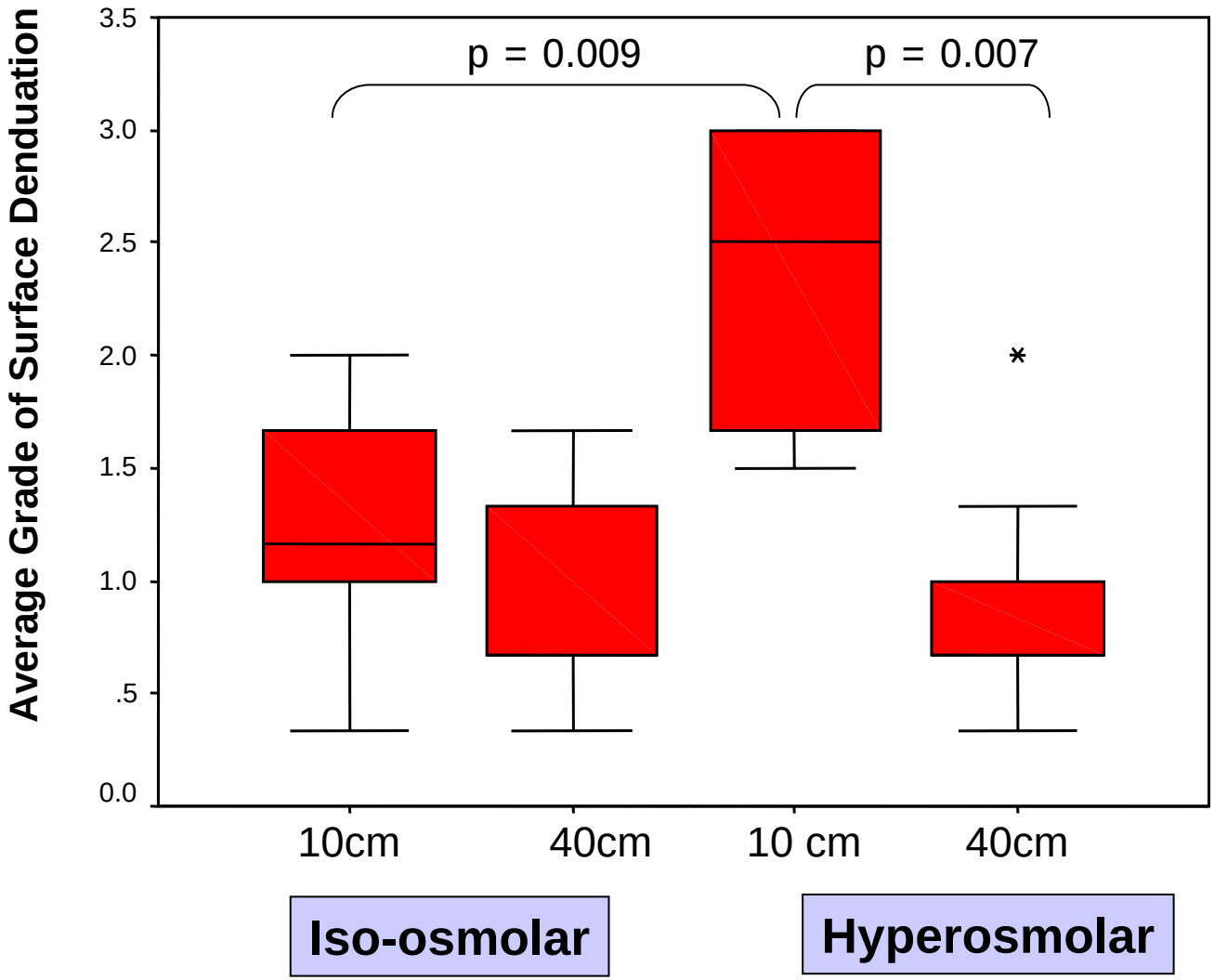
Effect of Osmolality on Mucosal Integrity

Iso-osmolar **Hyperosmolar**



Fuchs et al J Infect Dis 2007

Epithelial Denudation Score



Fuchs et al J Infect Dis 2007

Update on the Design of Rectal Safety Studies

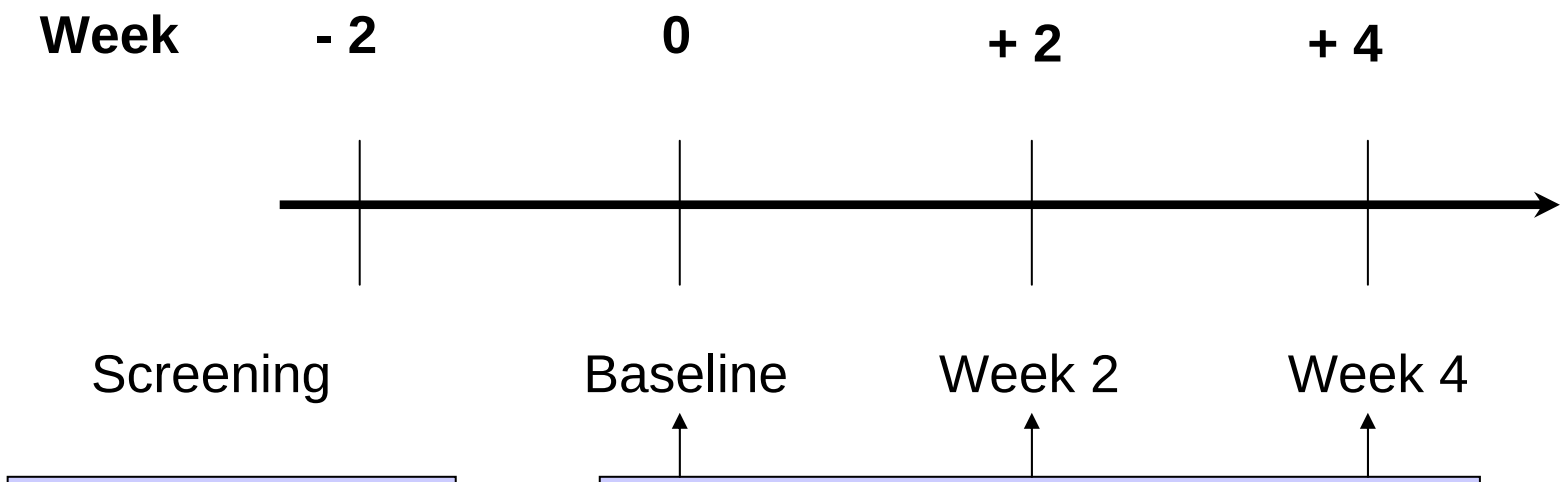
Rectal Safety Studies

Products	N	Safety Assessment	Reference
N-9 (3.5%)	35	Anoscopy Rectal biopsy & qualitative histology (+12 hrs)	Tabet et al. 1999
N-9 (1% &2%), Carraguard, methycellulose	4	Qualitative lavage Electron microscopy	Phillips et al. 2000
N-9 (2%)	18	Histology (BL, +2hrs, +8hrs) Lavage (+15min, +>8hrs)	Phillips et al. 2004

Rectal Safety Assessment

- Preclinical
  - Cell lines
  - Animal models
  - Explant systems
- Clinical
  - Symptoms
  - Signs
  - Histology
  - Experimental endpoints
  - Immunological toxicity

HPTN 056 Study Design



Design of UC-781 Phase 1 Rectal Safety Study

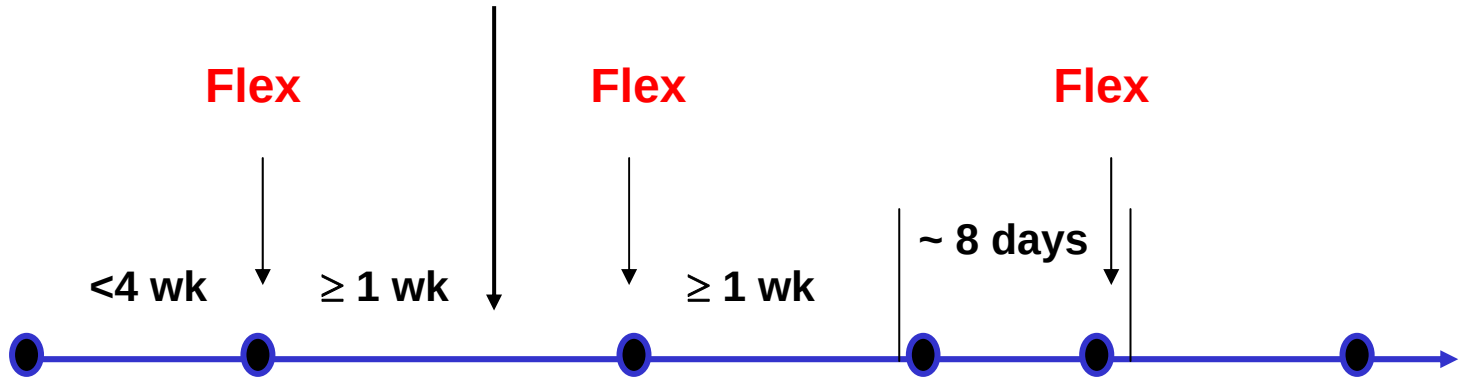
- Three arms (Men and women with history of RAI)
  - 0.1% UC-781 (N = 12)
  - 0.25% UC-781(N = 12)
  - Placebo (N = 12)
- Single dose followed by 7 days of study drug

Design of UC-781 Phase 1 Rectal Safety Study

- **Primary objective:** To evaluate the safety and acceptability of 0.1% and 0.25% UC-781 vaginal microbicide gel versus placebo when applied rectally
- **Endpoints:**
  - Frequency of ≥Grade 2 adverse events
  - Acceptability

UC-781 Trial Design

Randomization: 0.1% UC-781, 0.25% UC-781, or placebo



Visit 1	Visit 2	Visit 3	Outpatient	Visit 4	Visit 5
Screening	Baseline	Single-dose Clinical Eval	7 Daily doses	Clinical Eval	Phone interview

UC-781 Phase 1 Rectal Safety Study

- **Secondary Objective:** To determine whether use of study product is associated with rectal mucosal damage
- **Endpoints:**
  - Epithelial sloughing
  - Histopathology
  - Mucosal mononuclear cell phenotype
  - Mucosal cytokine mRNA
  - Mucosal immunoglobulins
  - Fecal calprotectin
  - Explants- Mucosal cytokine mRNA and susceptibility to HIV infection

Applicator Design

Courtesy of Dr. Alex Carballo-Dieguez/amfAR

The Rectal Phase 1 Pipeline

Phase 1RM Safety Studies

Product	Status	Timeline	Sponsor
UC-781	Ongoing		NIAID/DAIDS
TBN	Planned	Q3 2007	NIAID/DMID
PRO-2000	Planned	Q1 2008	MDP MRC-UK
UC-781 (Rectal formulation)	Possible	Q4 2010	TBD

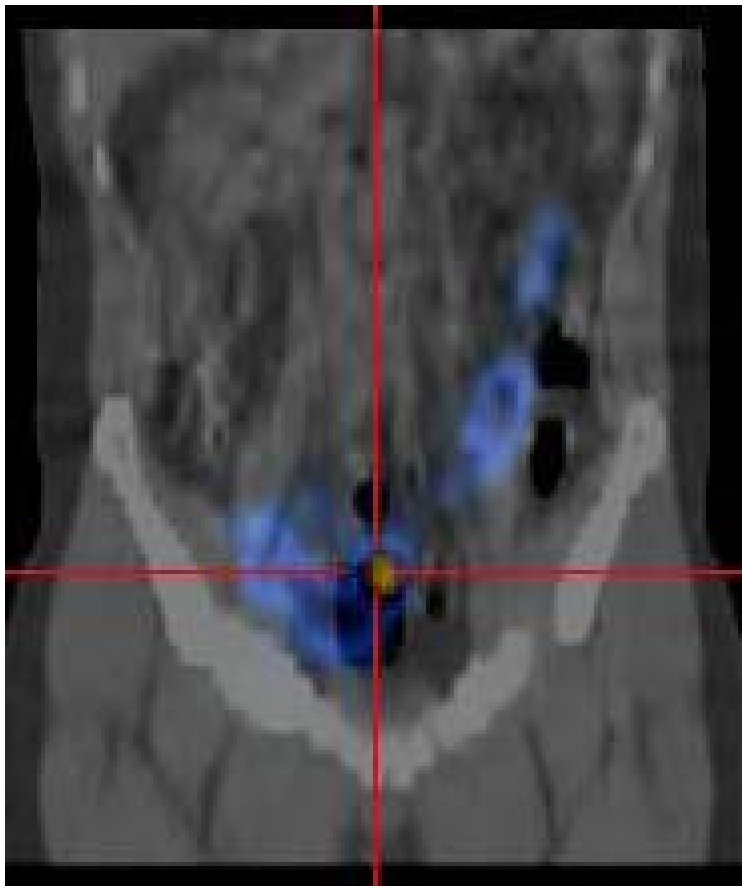
Development of Rectal-specific Microbicides

Is There a Need?

- High prevalence of unprotected RAI among heterosexual and MSM population
- MSM still most affected demographic in Western Europe and the Americas
- 88% of MSM use lubricants for RAI*
- 26% are still using N-9 products*

*Carballo-Dieguez et al. AIDS Behav 2007

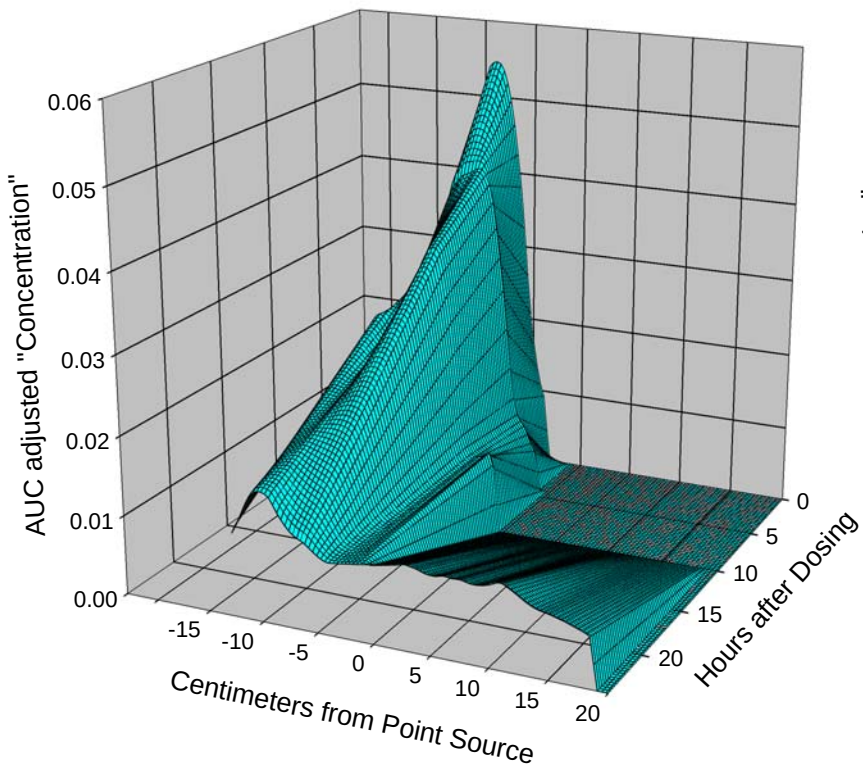
Where to Protect and What to Measure?



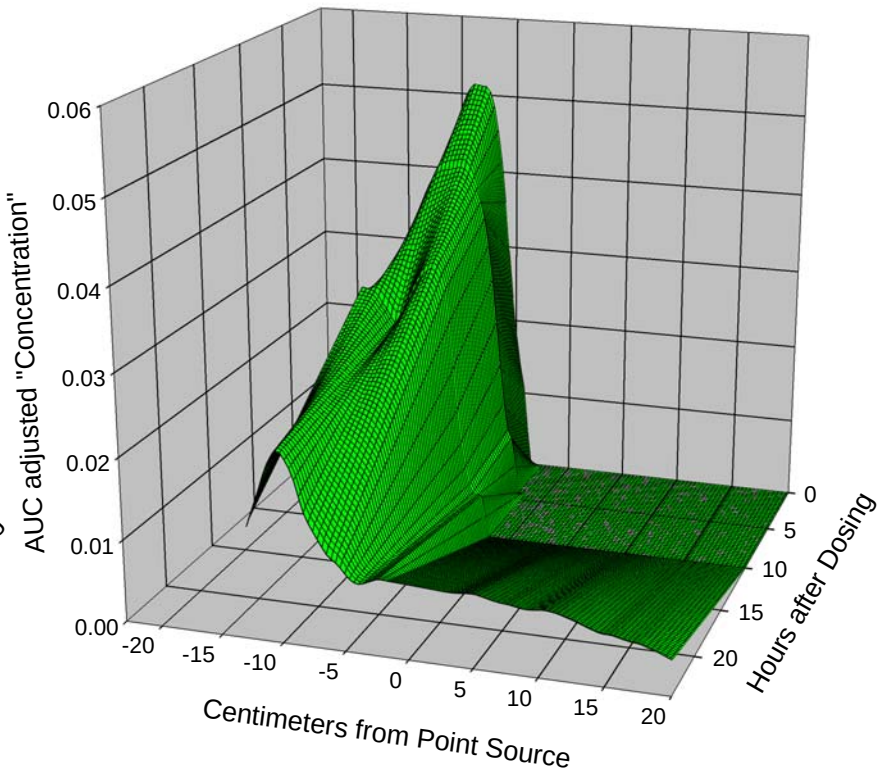
Hendrix et al., 2004

Colonic Distribution of Microbicides

Tc-SC (HIV Surrogate)



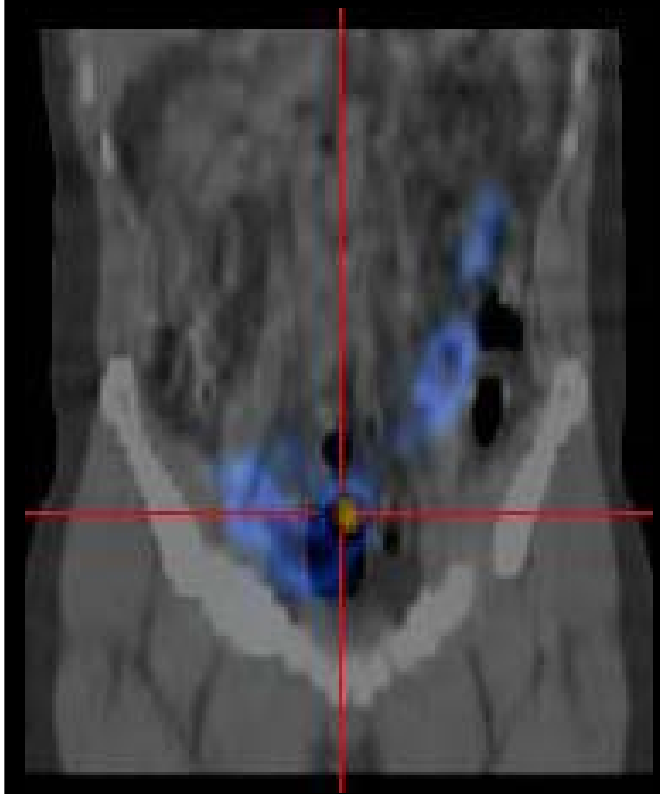
In-DTPA Microbicide ARV Surrogate



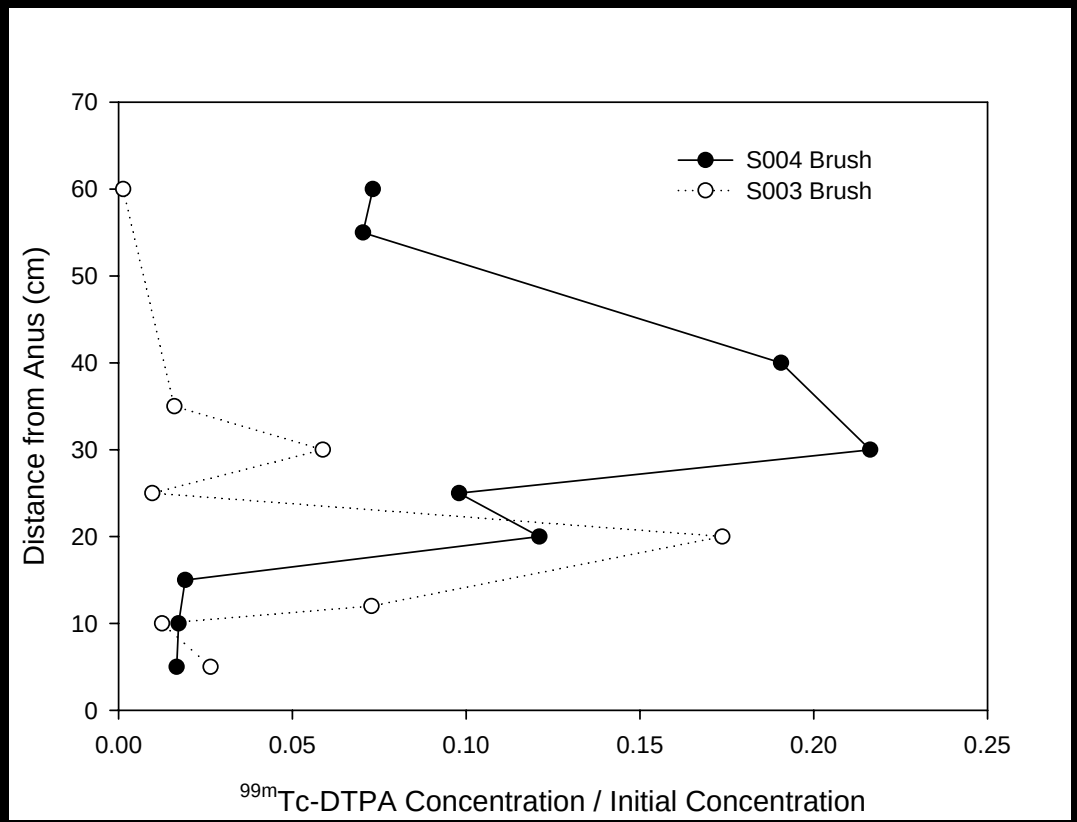
Hendrix et al. Microbicides 2006

Direct Endoscopic Sampling

SPECT/CT S004 @ 4 HR



Cytology brush (20 ml) @ 4 HR



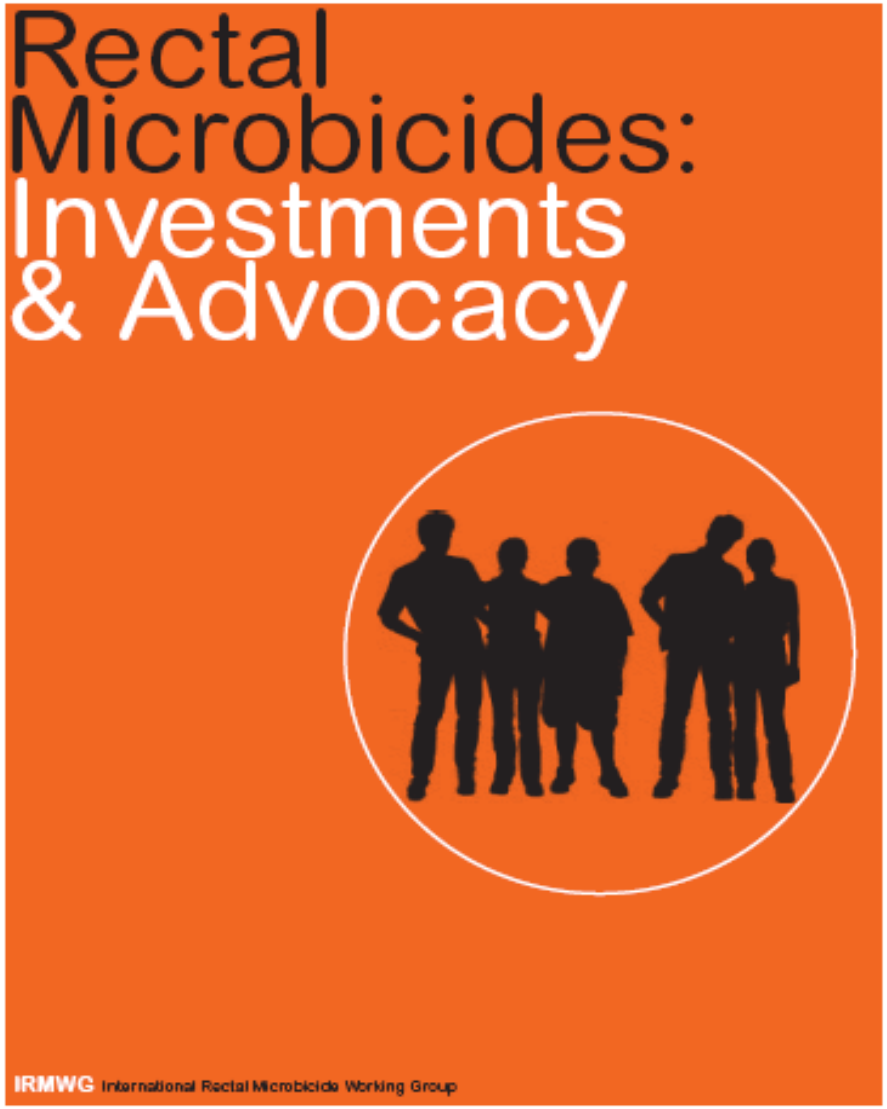
Hendrix et al. Microbicides 2006

Update on Rectal Microbicide Advocacy

International Rectal Microbicide Working Group (IRMWG)

- Founded in Spring 2005
- Current membership 360 advocates from 35 countries on 5 continents

http://www.irmwg.org/

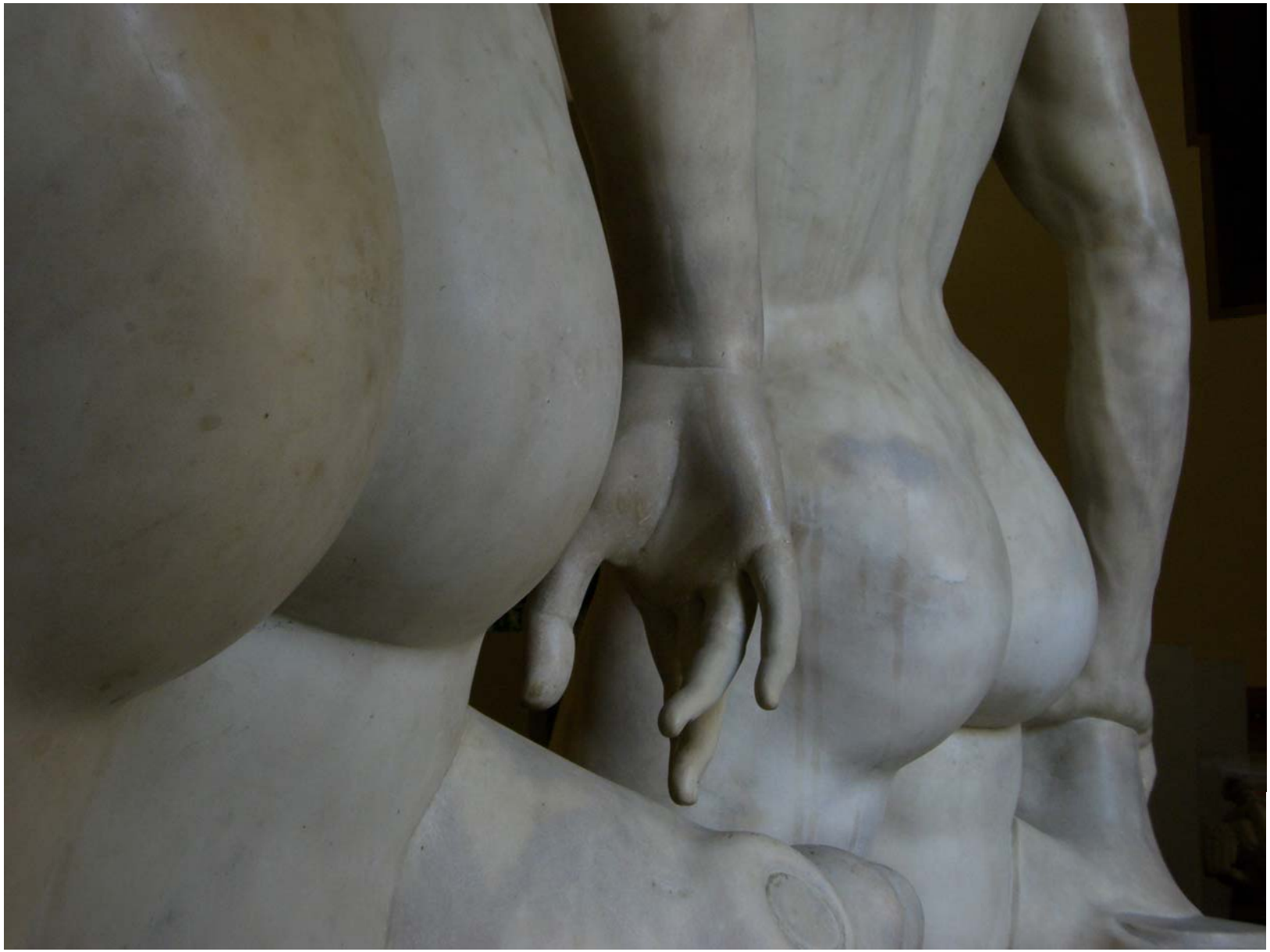


http://www.lifelube.org/

Conclusions

Conclusions

- Vaginal microbicides being considered for effectiveness studies should be evaluated for rectal safety
- Phase 1 rectal safety studies have begun and will increase in number
- Design methodology is still in evolution but moving towards simplified studies
- Rectal microbicide advocacy is increasing and will include demands for rectal safety and effectiveness



Bargello Museum, Florence, Italy