

# Rectal Microbicides

Ian McGowan MD PhD FRCP

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Magee Womens Research Institute

University of Pittsburgh, USA

# Overview

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- Rationale for rectal microbicide development
- Design of Phase 1 rectal safety studies
- Rectal microbicide advocacy
- Implications for vaginal microbicide development

# **Rationale for Rectal Microbicide Development**

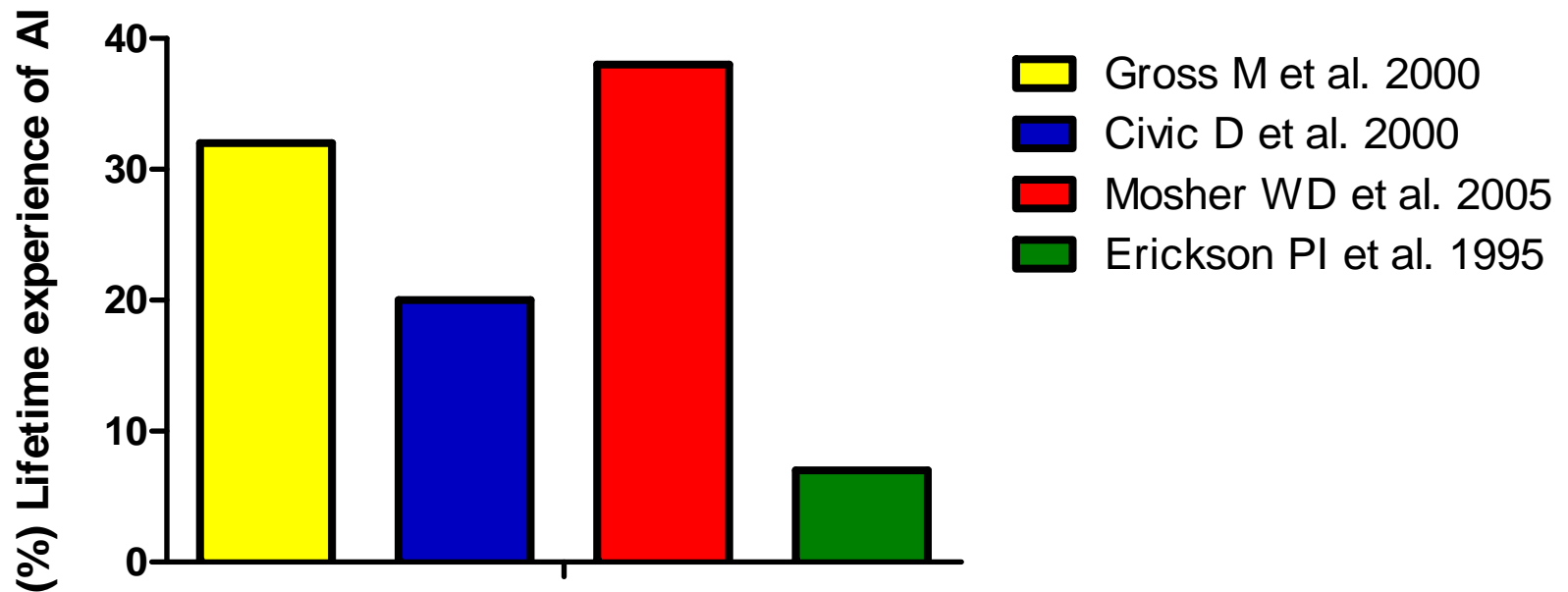
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# Rectosigmoid Anatomy

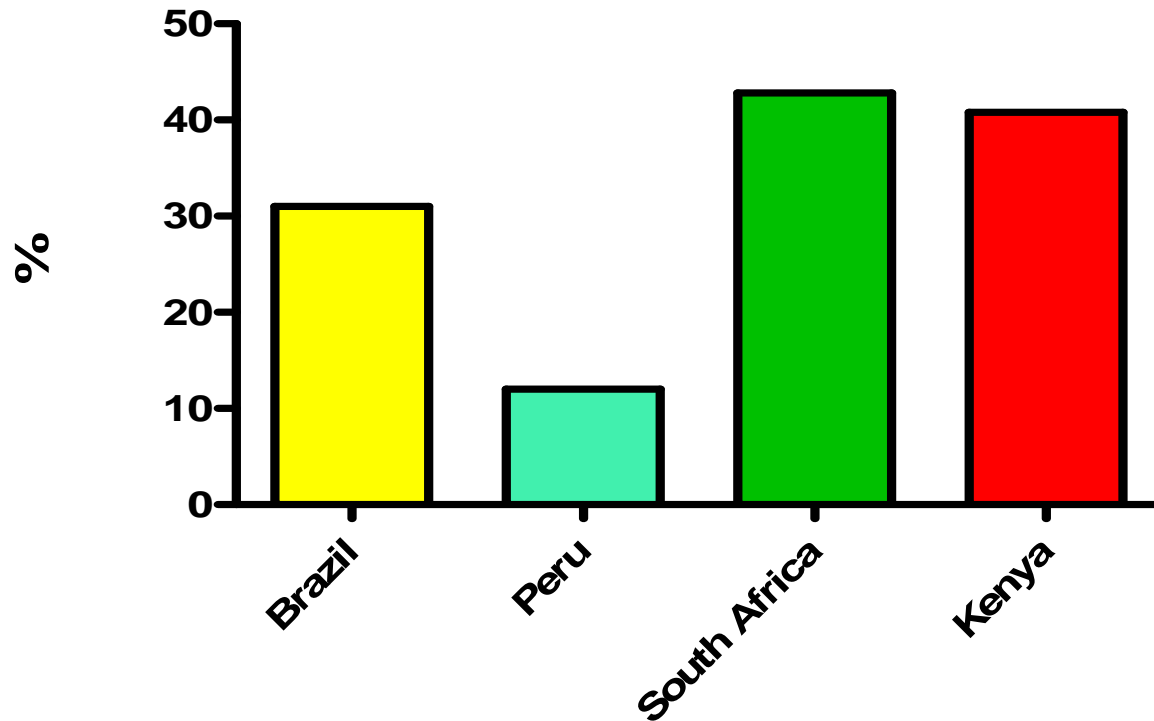
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# Heterosexual AI in the US



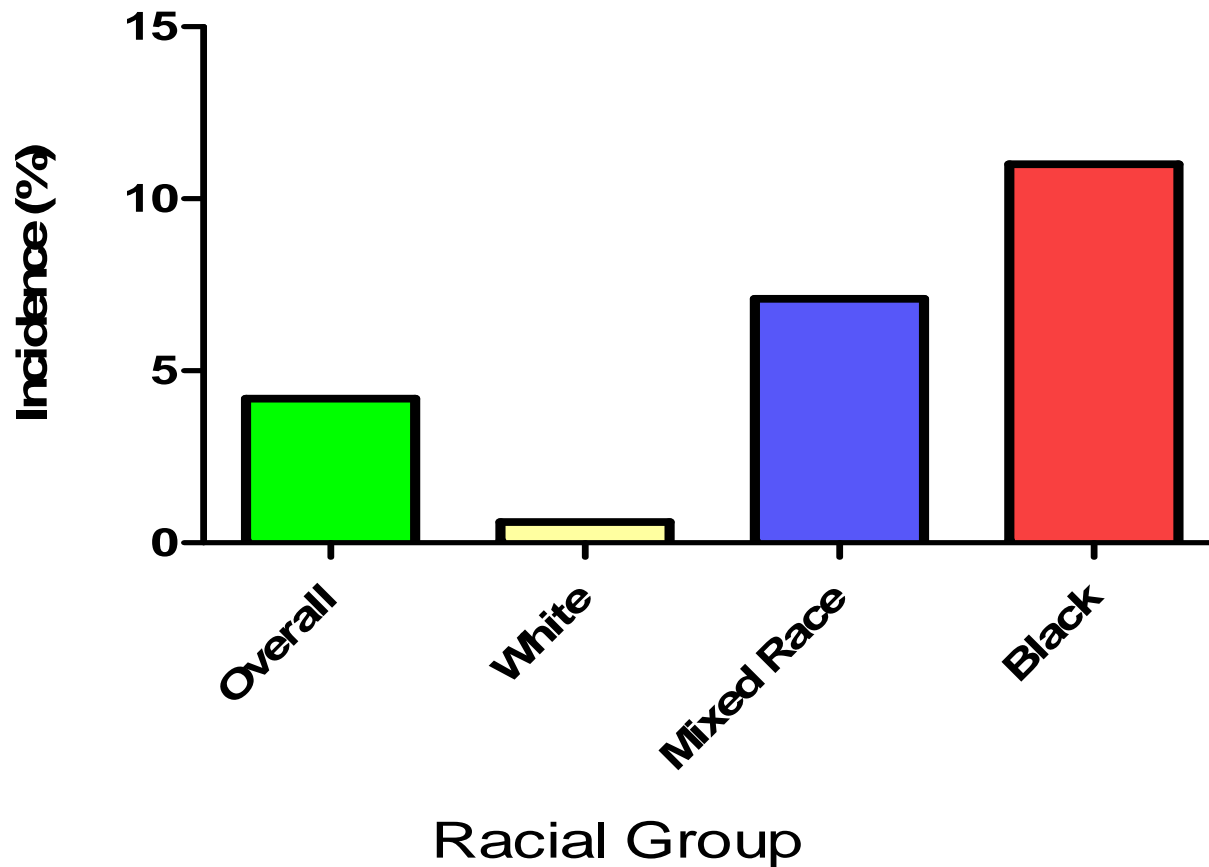
# Heterosexual AI Outside the US



**Brazil:** Guimares MD et al. 1995,  
**Peru:** Caceres C et al. 1997,

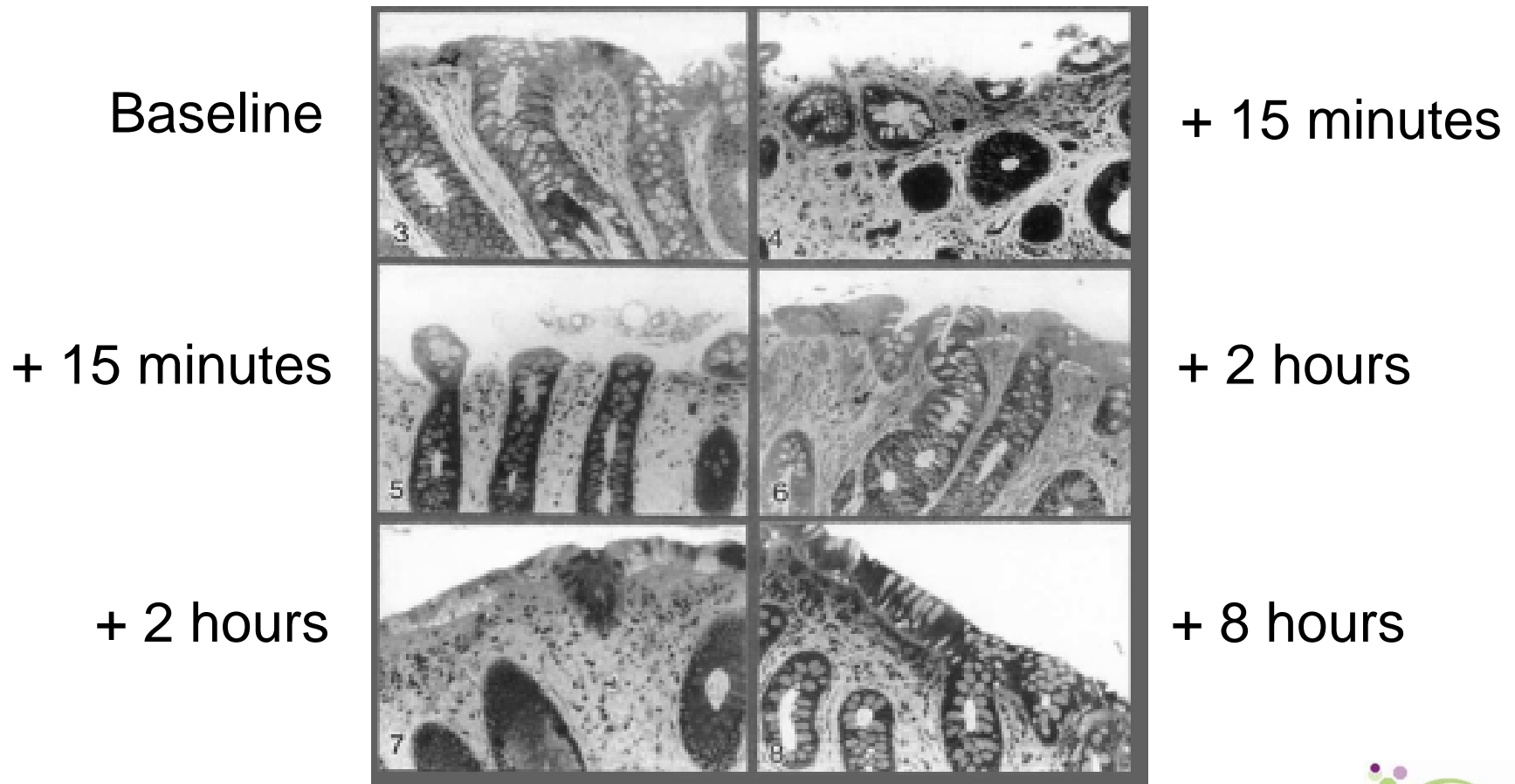
**South Africa:** Karim SS and Ramjee G 1998  
**Kenya:** Schwandt M et al. 2006

# US HIV Incidence in MSM



Sifakis F et al. JAIDS 2007

# Nonoxynol-9 Rectal Toxicity

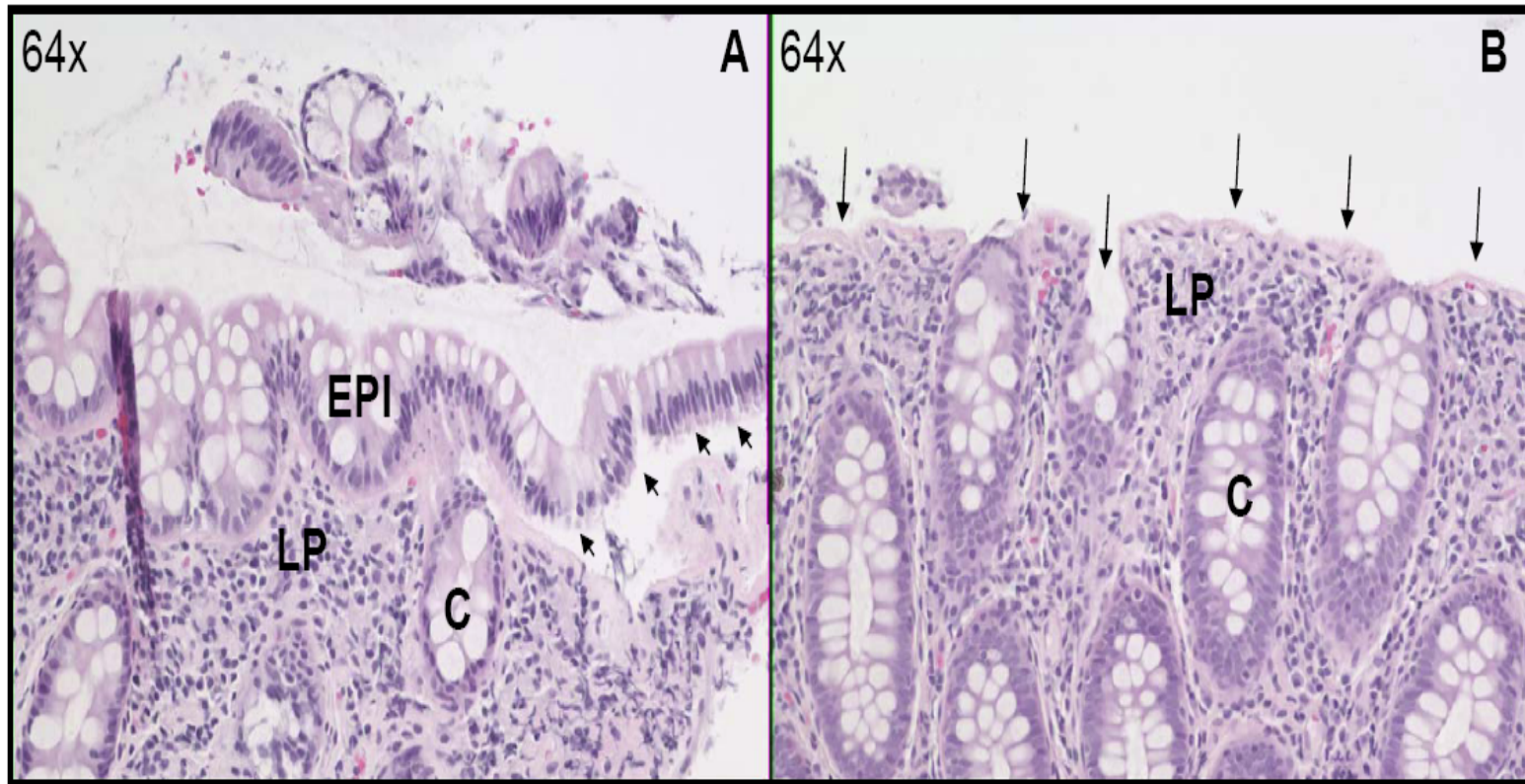




# Sexual Lubricants

Iso-osmolar

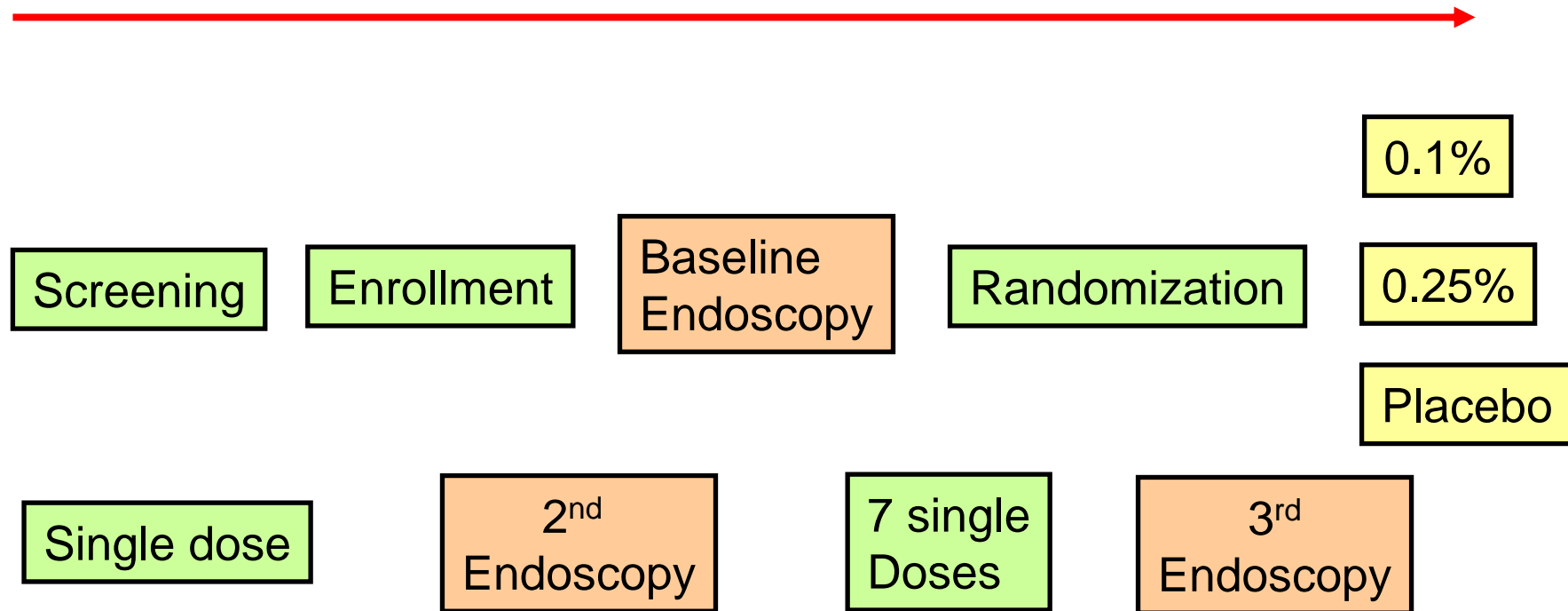
Hyperosmolar



# **Design of Phase 1 Rectal Safety Studies**

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# UC-781 Trial Design



# UC-781 Study

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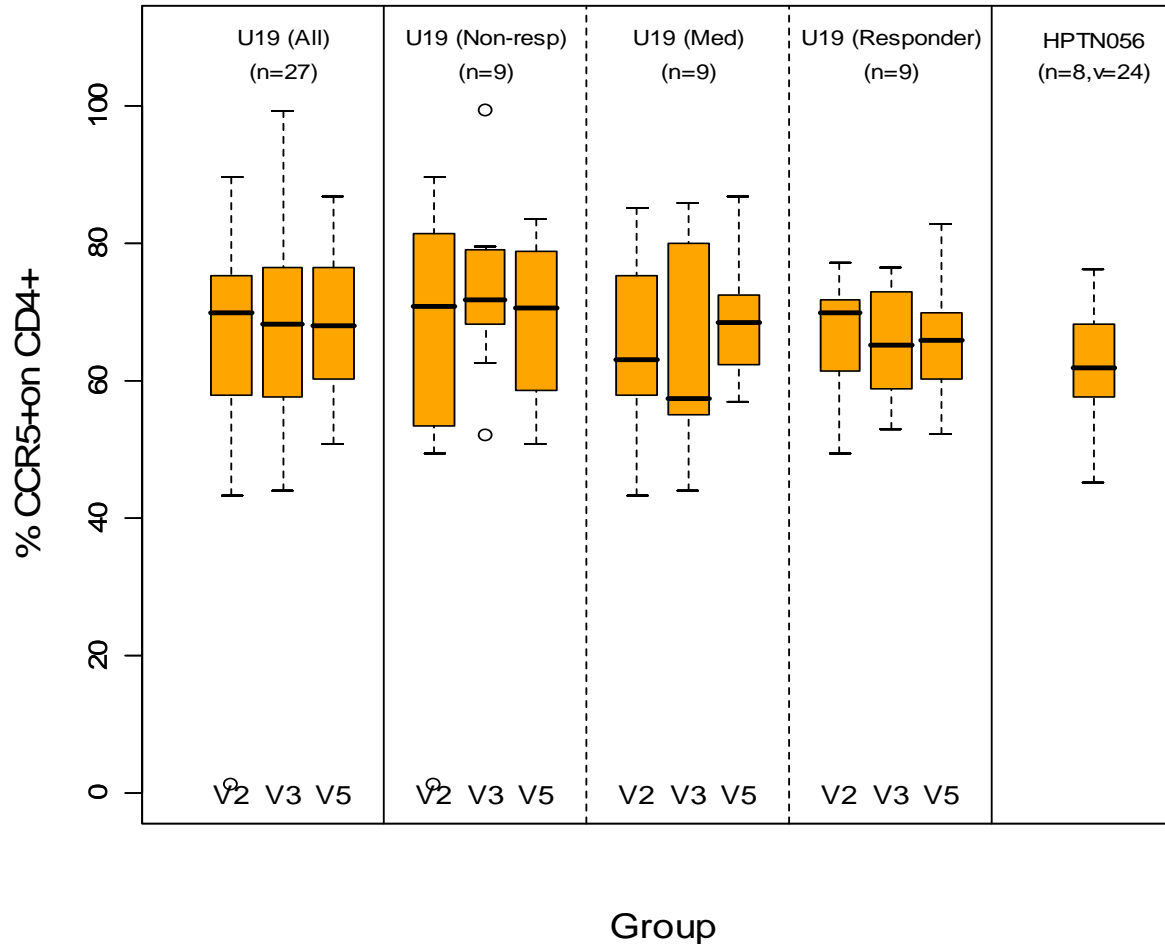
- **Secondary Objective:**
  - To determine whether use of study product is associated with rectal mucosal damage
  
- **Endpoints:**
  - Epithelial sloughing
  - Histopathology
  - Mucosal mononuclear cell phenotype
  - Mucosal cytokine mRNA
  - Mucosal immunoglobulins
  - Fecal calprotectin
  - Explants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

# Interim Results

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- Appears safe and well-tolerated
- Subjects highly compliant
- Procedures well tolerated
- No drop outs/withdrawals
- No Grade 3 or 4 AE
- No procedure related AE
- 7 Grade 2 AE reported in 4 of 19 individuals completing

# Safety Biomarkers



# Rectal Safety Studies

Product	Status	Timeline	Sponsor
UC-781	Completed		NIAID/DAIDS
Polyanion	Planned	Q1 2009	NIAID/DMID
PRO-2000	Planned	Q3 2008	MDP MRC-UK
MTN-007	Planned	Q1 2009	NIAID/DAIDS
MTN-006	Planned	Q1 2009	NIAID/DAIDS
UC-781 (RF)	Possible	Q4 2010	TBD

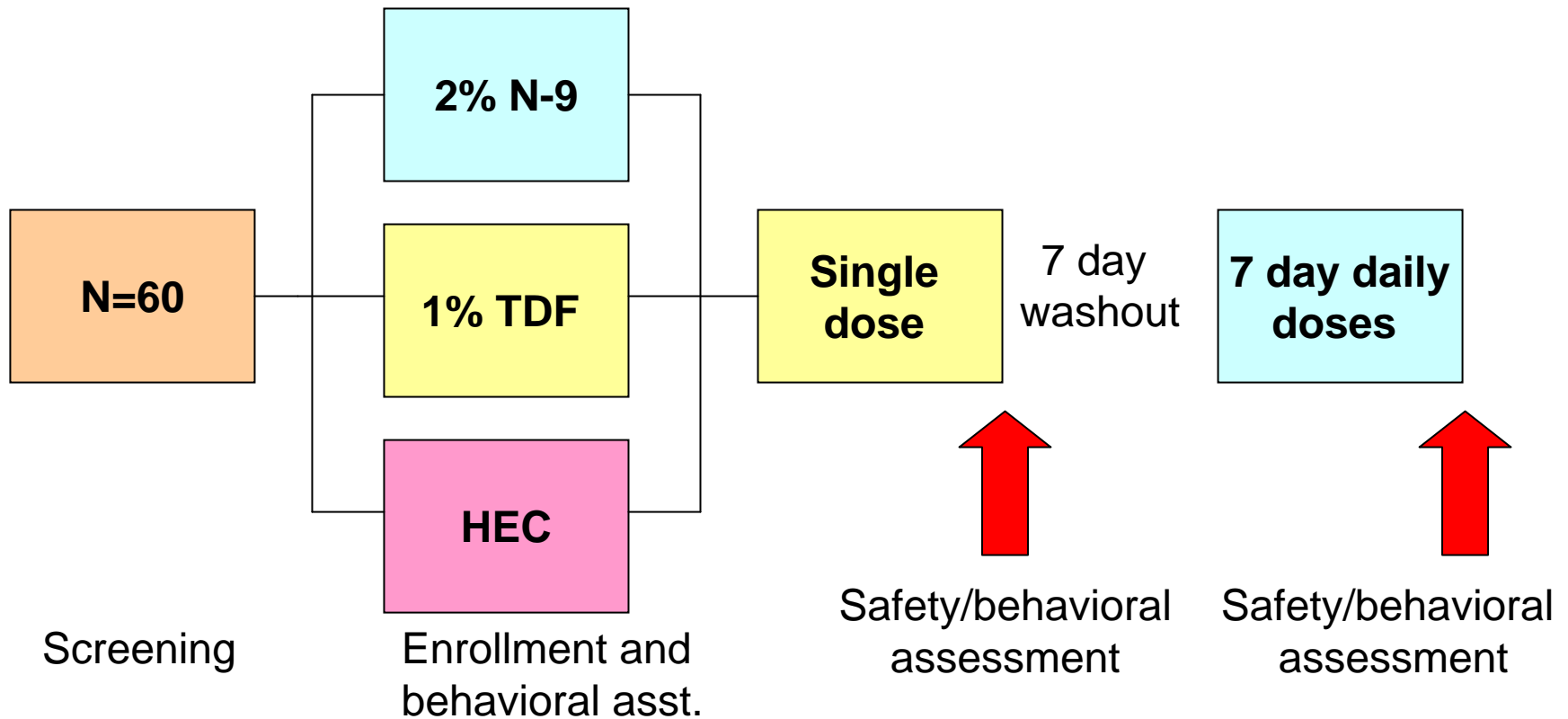
# MTN-007

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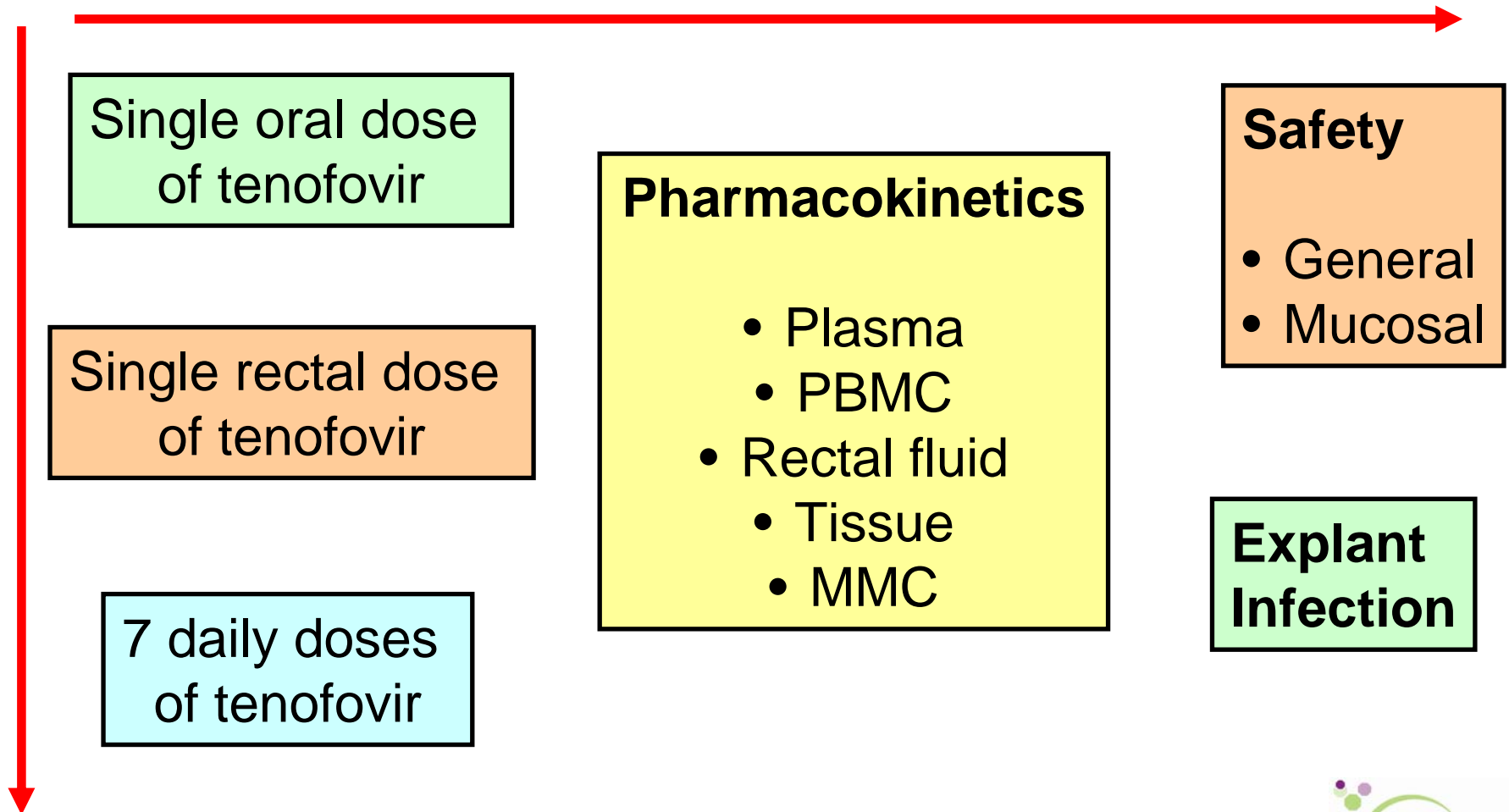
- Phase 1 rectal safety study
- Randomized blinded, placebo-controlled trial:
  - 1% vaginal formulation of tenofovir
  - Hydroxyethyl cellulose (HEC) placebo gel
  - 2% nonoxynol-9 (Ortho-Gynol II)



# MTN-007 Study Design



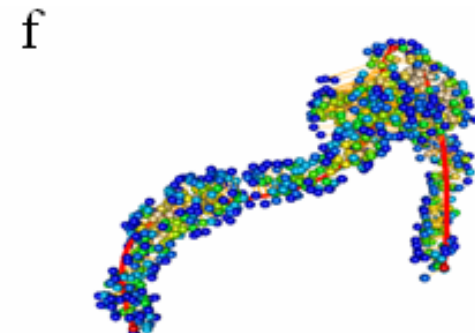
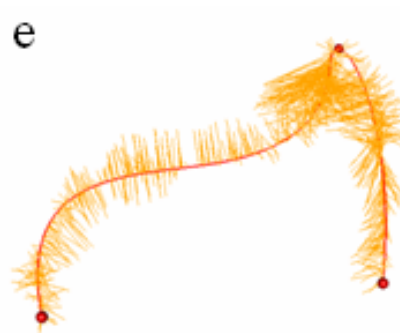
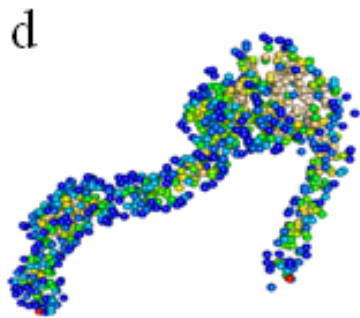
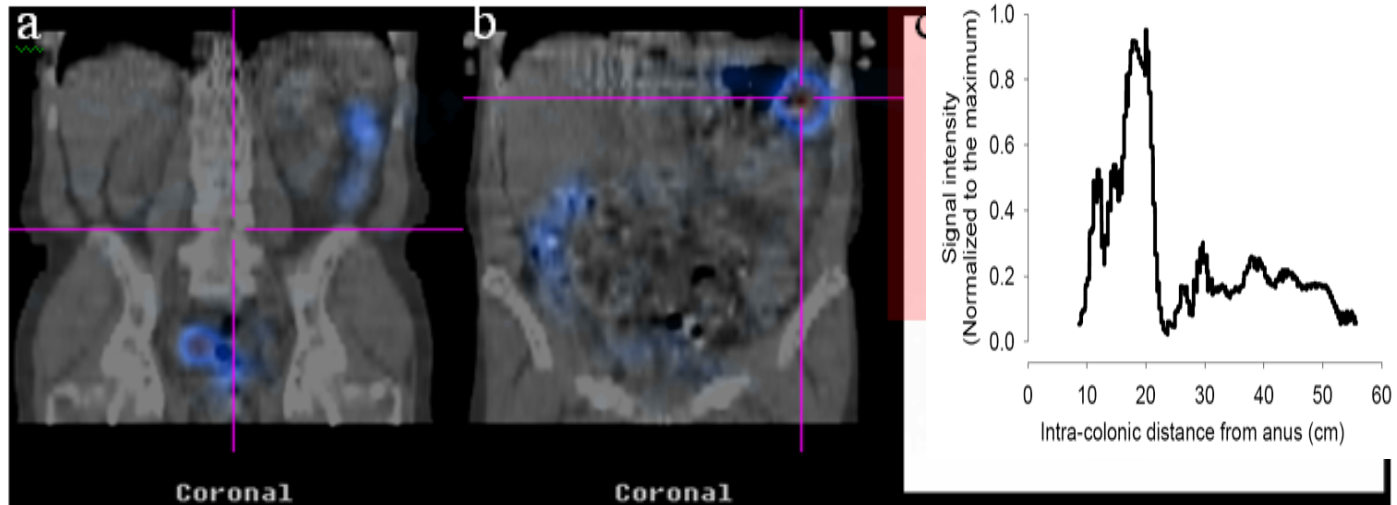
# MTN-006 Study Design



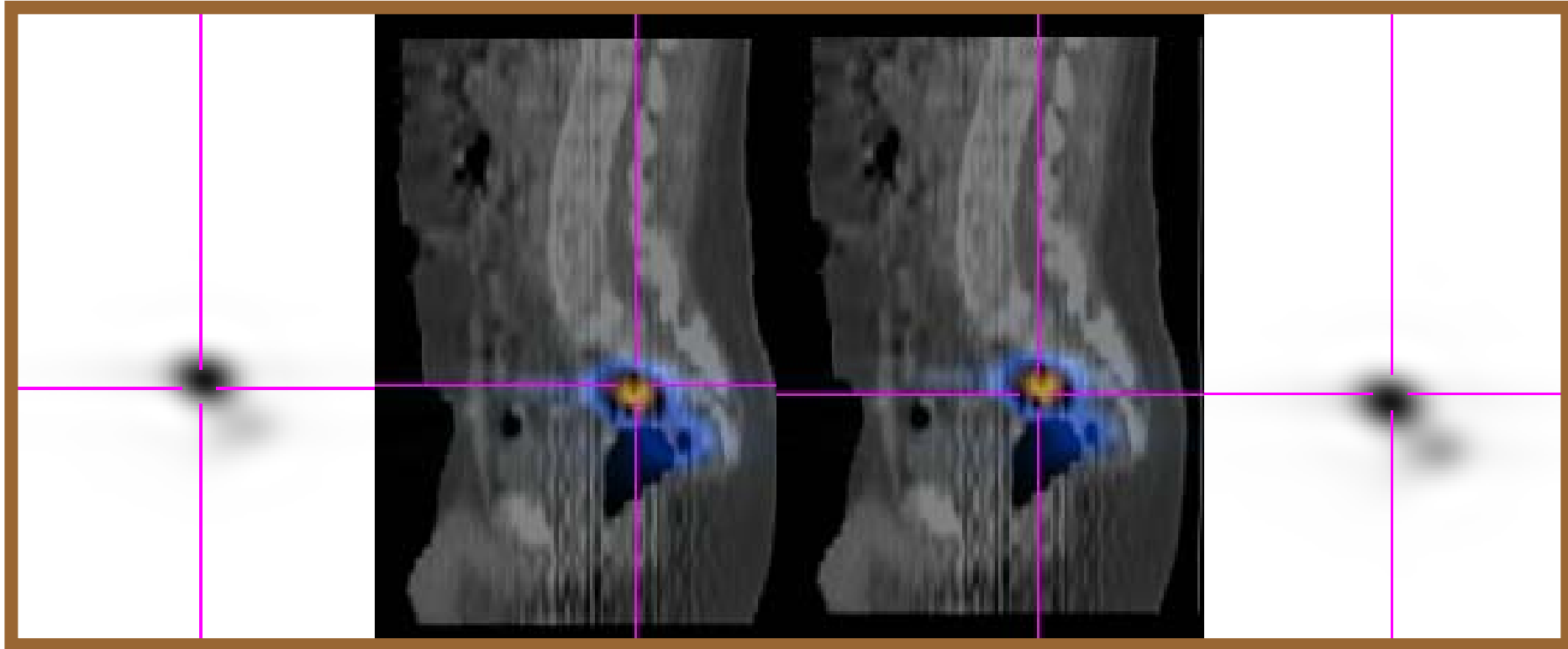
# **Moving Towards RM Effectiveness studies**

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# Imaging Microbicide Distribution



# Rectal Lymphocyte Distribution



$^{99m}\text{Tc}$ -Sulfur Colloid  
Cell-free HIV Surrogate

$^{111}\text{In}$ -Lymphocytes  
Cell-Associated HIV Surrogate

# Rectal Specific Applicators

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- Incorporates Fleet <sup>TM</sup> tip
- Can be operated with one hand
- Has grips for the fingers
- Can deliver a precise dose up to 10 ml
- Used across clinical trials, this MDD will reduce sources of acceptability and adherence variability
- Can be manufactured in gray color



# **Rectal Microbicide Advocacy**

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# IRMA



[www.rectalmicrobicides.org](http://www.rectalmicrobicides.org)

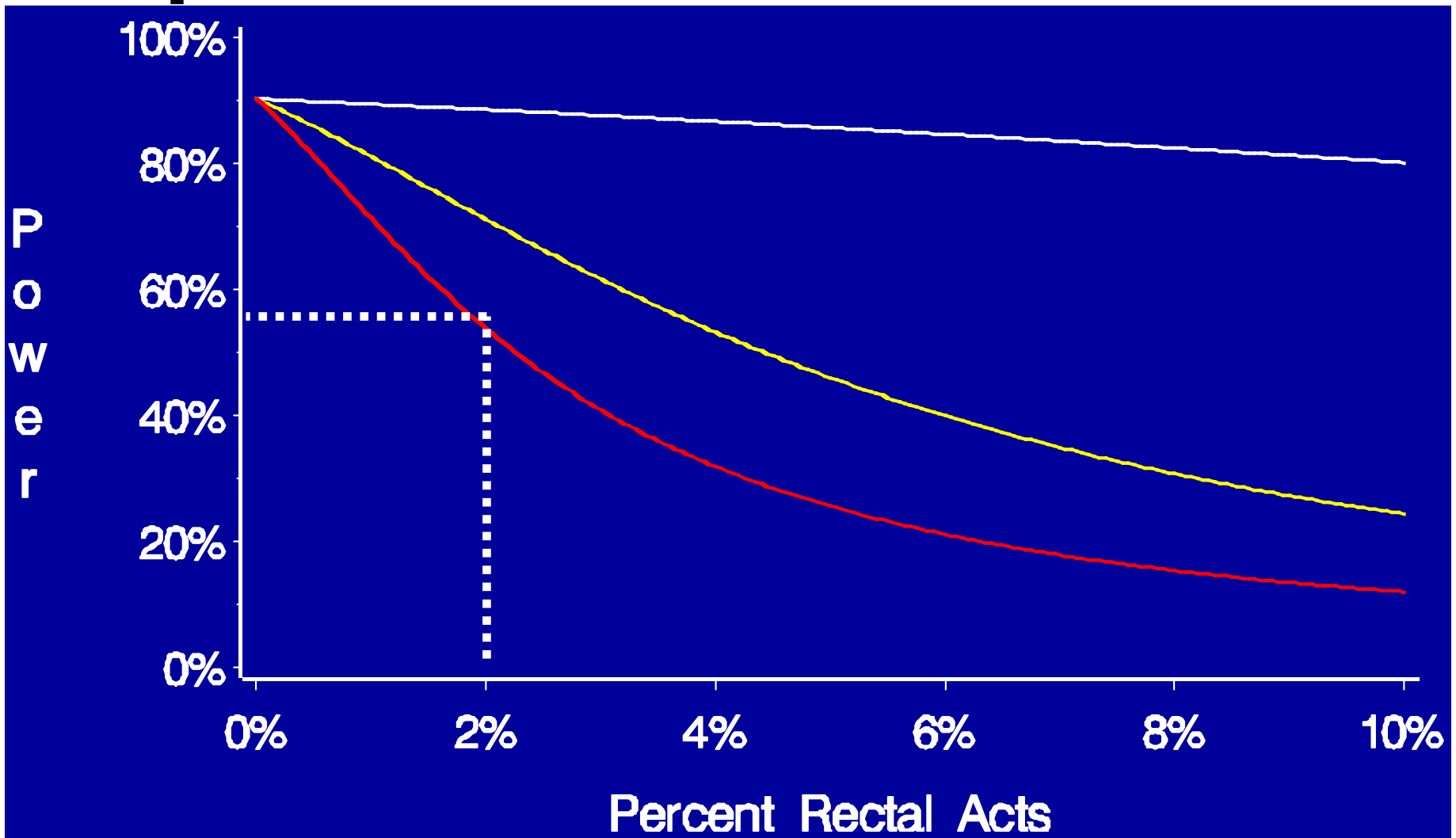




# **Implications for Vaginal Microbicide Development**

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# Impact of Rectal Sex on Power



Transmission Probability

1X

10X

20X

# Anal Intercourse in HPTN-059

	Coitally Dependent		Daily Use	
	Tenofovir	Placebo	Tenofovir	Placebo
	N=50	N=51	N=49	N=50
Ever anal sex	24%	25%	33%	28%
Anal sex, (past 7 days)	2%	0%	4%	2%

# Summary

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- Increasing evidence of RAI in heterosexuals and MSM
- Phase 1 RM safety design evolving
- MTN RM portfolio
  - MTN-006
  - MTN-007
- Research focus needs to shift from safety to efficacy