The Rectal Microbicide Research Agenda

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Overview

- Rationale for rectal microbicide development
- Preclinical development of candidate rectal microbicides
- Evolving design of Phase 1 rectal safety studies
- Moving towards effectiveness studies

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Rationale for Rectal Microbicide Development

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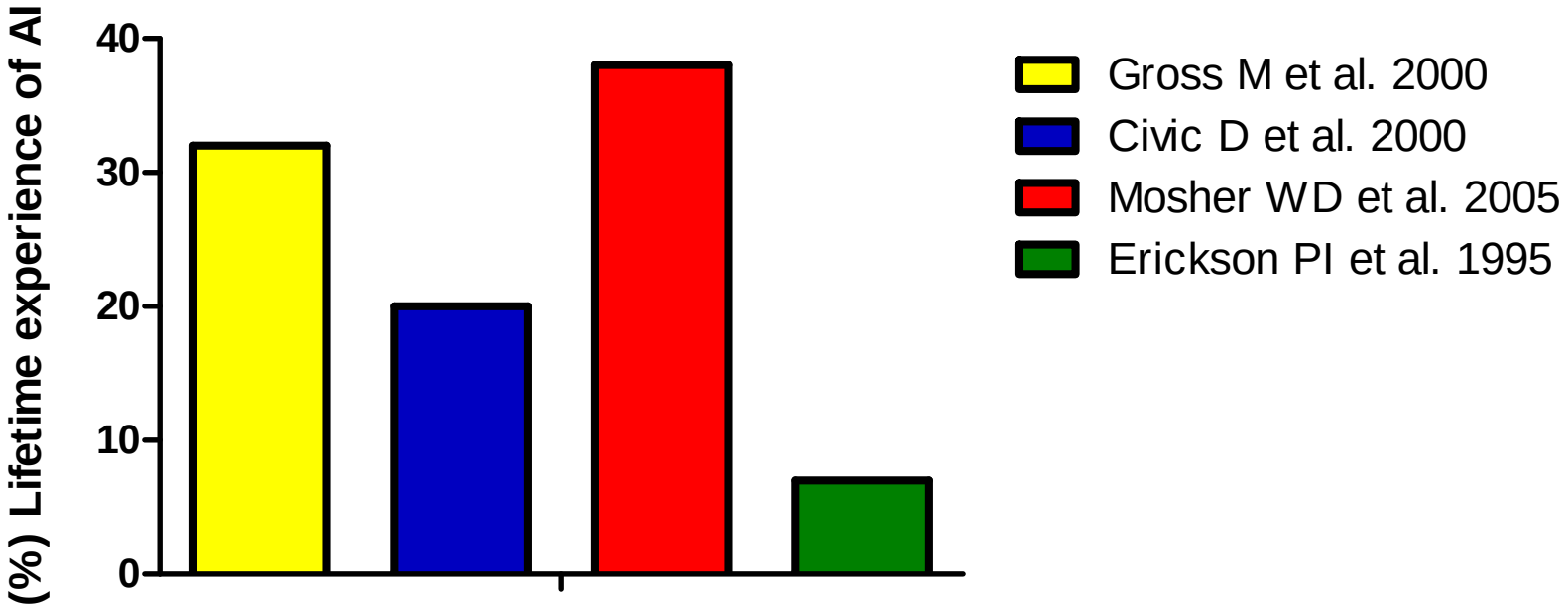
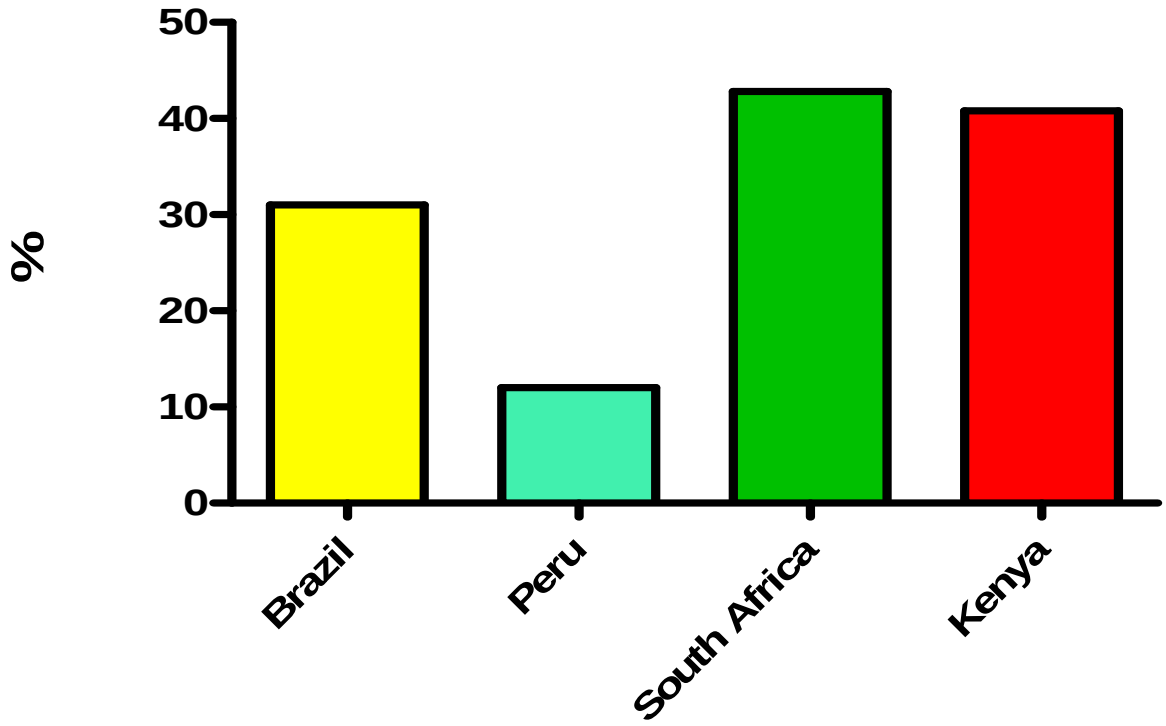
Anal Intercourse in US Women



Anal Intercourse in Women 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

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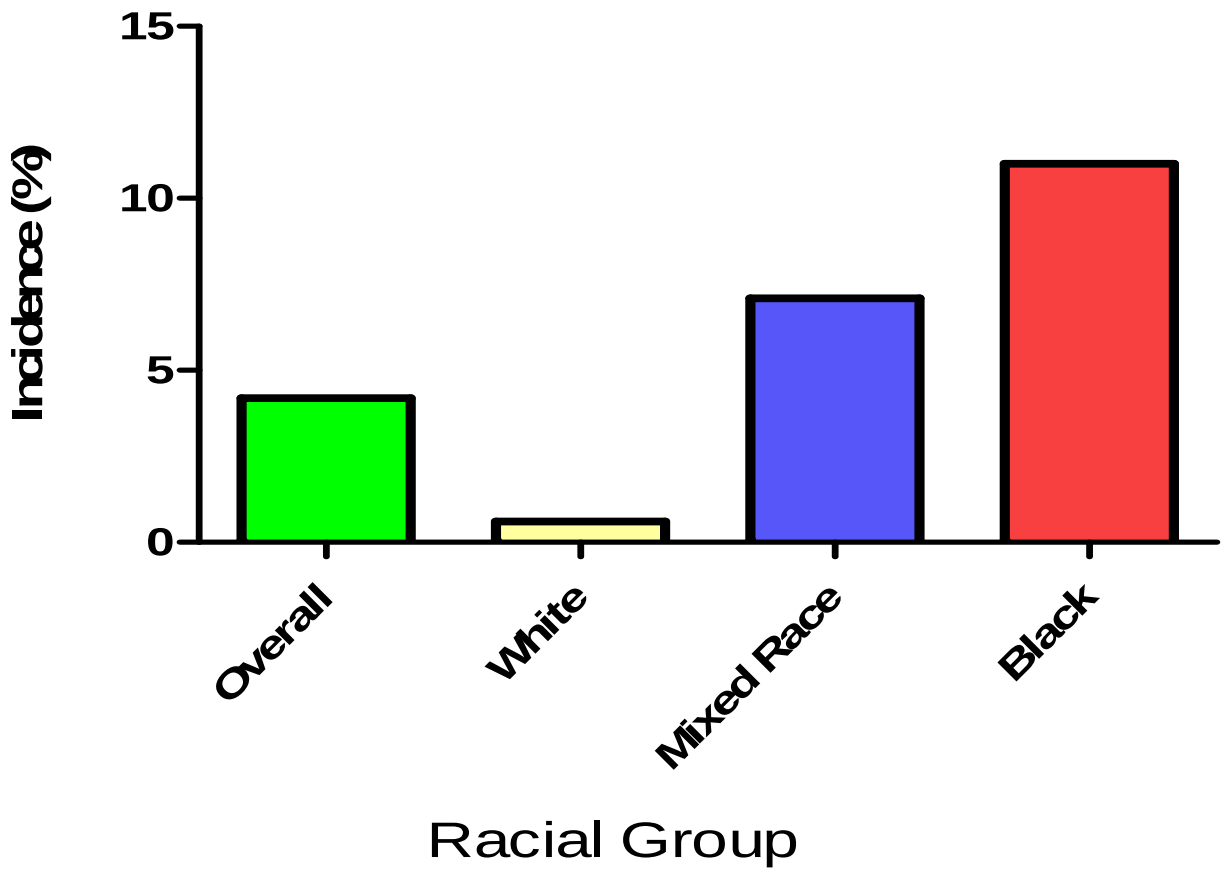
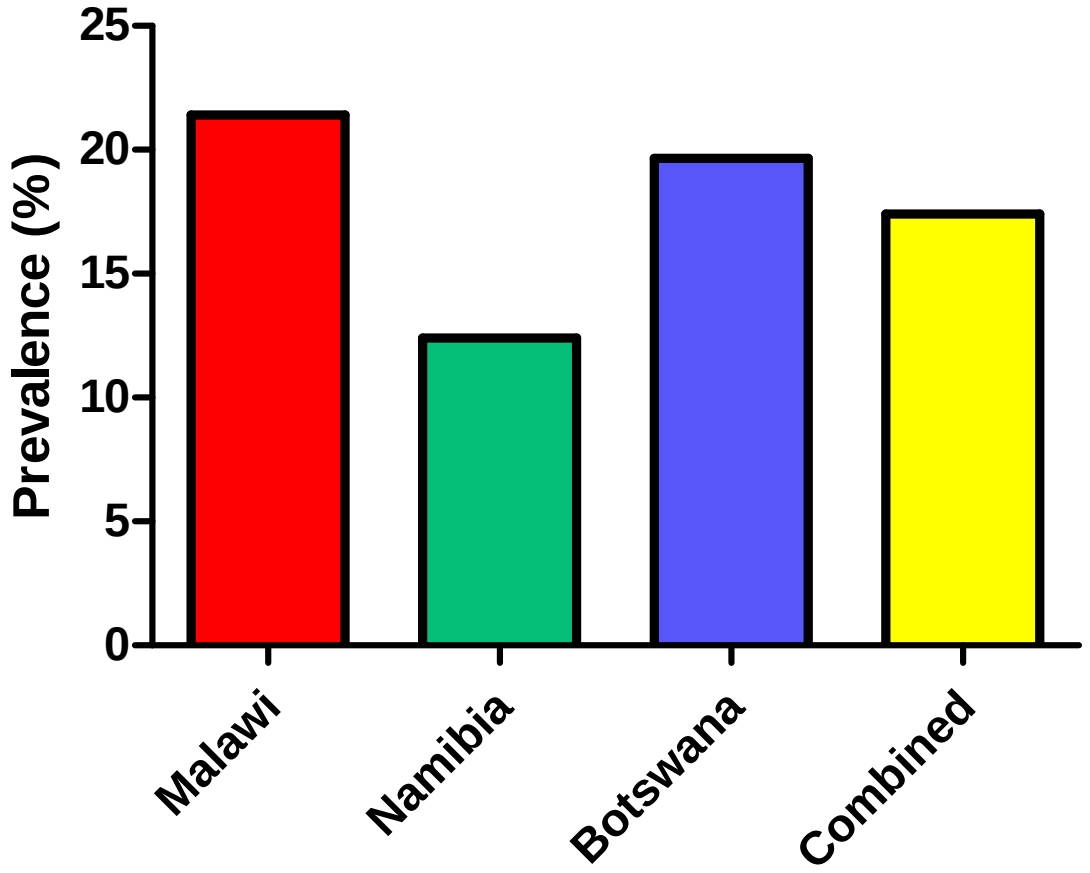
HIV Incidence in US MSM



Sifakis F et al. JAIDS 2007

HIV Prevalence in African MSM



Baral et al. PLoS One 2009

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Demographic Profile

- Mean age: 24.9 years
- Gay / homosexual: 49.5%
- Bisexual: 38.1%
- Found partner on the internet: 44.7%
- < 1:20 practiced safe sex
- Human rights abuse: 42.1%

Baral et al. PLoS One 2009

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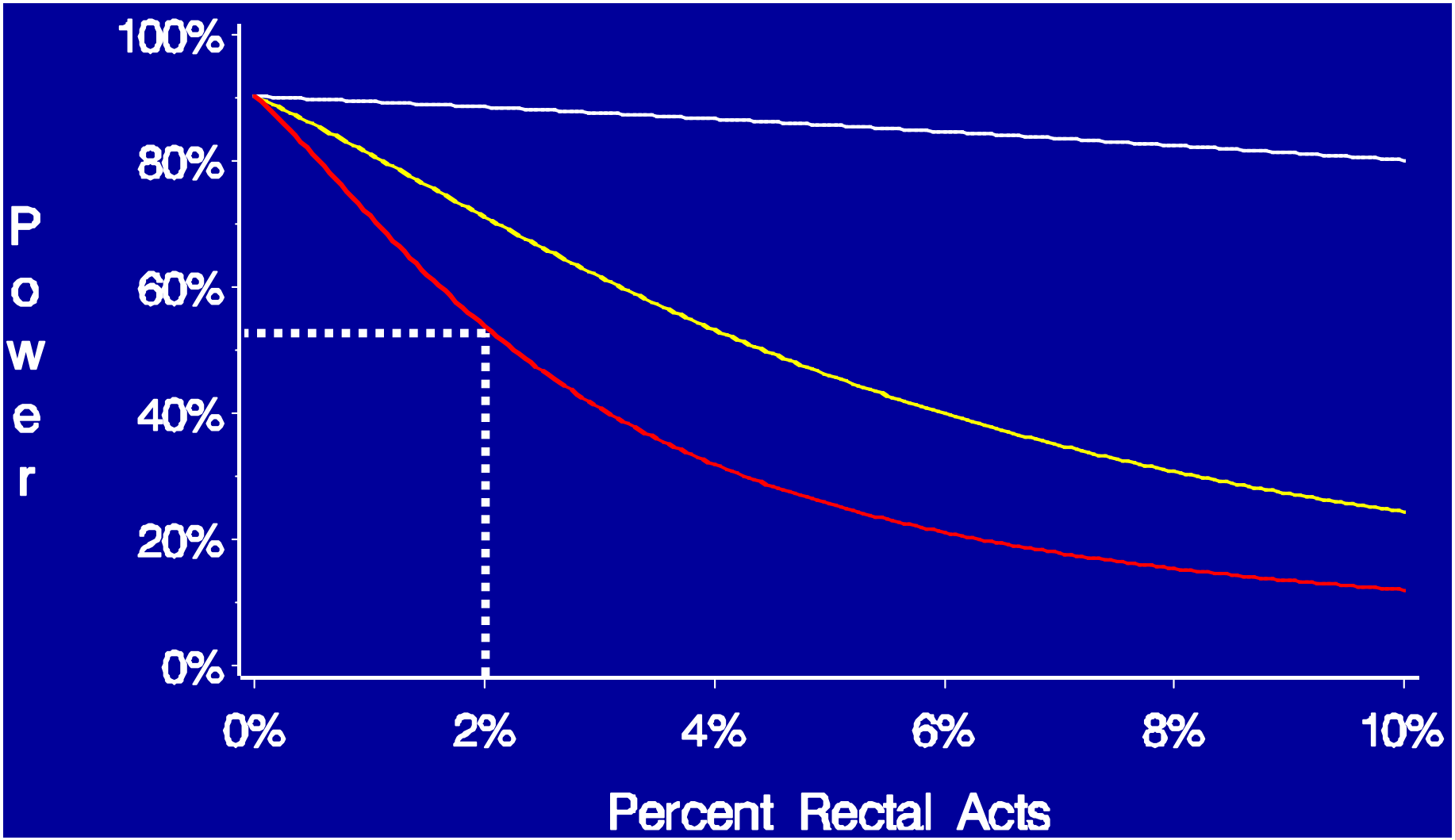
Effect of RAI in Microbicide Trials



Transmission Probability 1X 10X 20X

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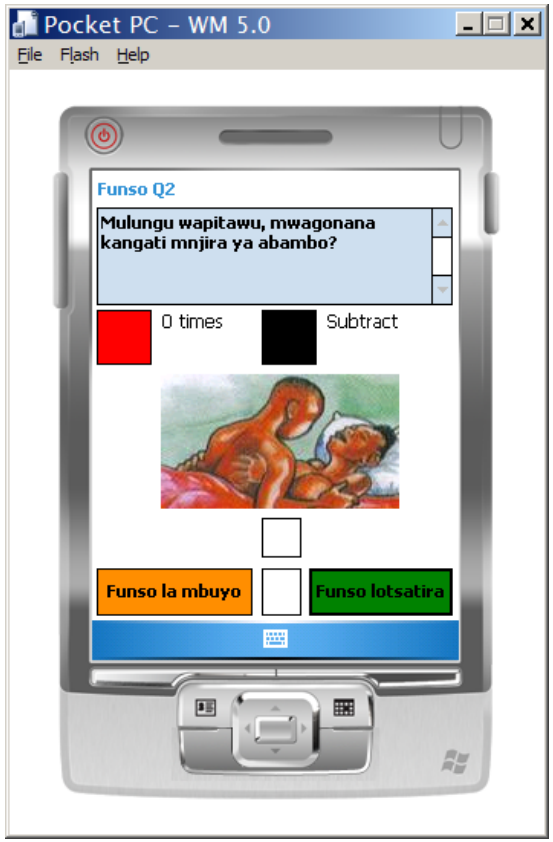
RAI in HPTN-059

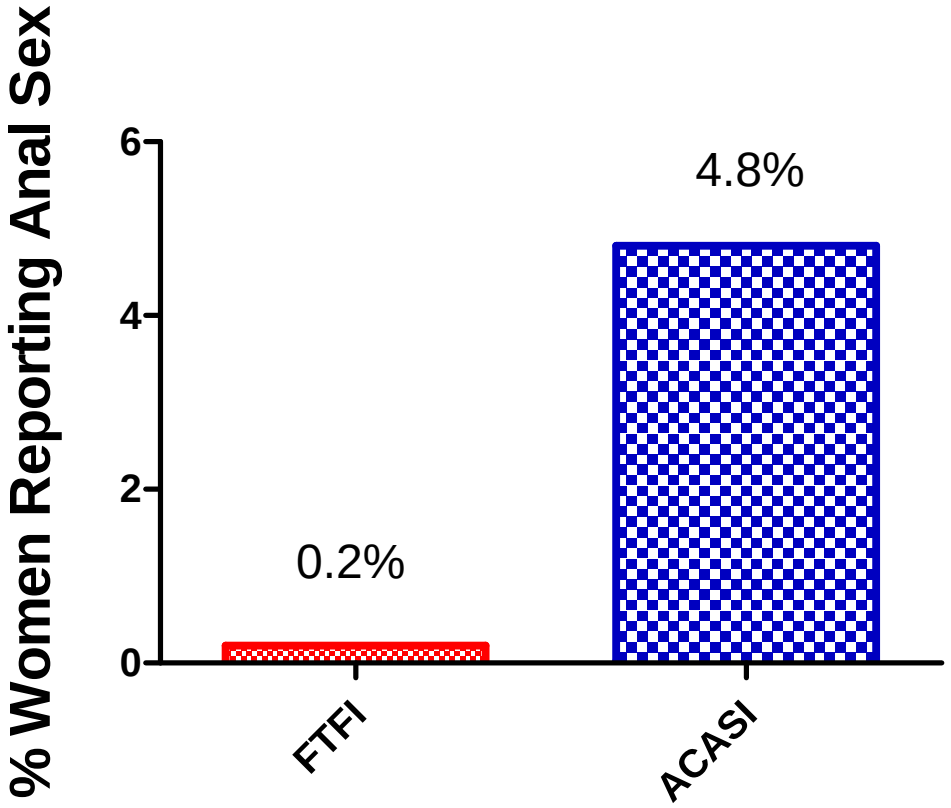
	Coitally Dependent		Daily Use	
	Tenofovir	Placebo	Tenofovir	Placebo
	N=50	N=51	N=49	N=50
Ever anal sex	24%	25%	33%	28%
Anal sex, (past 7 days)	2%	0%	4%	2%

RAI in HPTN-035

Baseline Characteristics			
Ever had anal sex			
BufferGel	PRO2000	Placebo	No Gel
4%	4%	5%	5%

HPTN-035B


Pocket PC – WM 5.0
File Flash Help
Funso Q2
Mulungu wapitawu, mwagonana kangati mnjira ya abambo?
0 times
Subtract
Funso la mbuyo
Funso lotsatira


% Women Reporting Anal Sex
6
4
2
0
0.2%
4.8%
FTFI
ACASI

Preclinical Development of Candidate Rectal Microbicides

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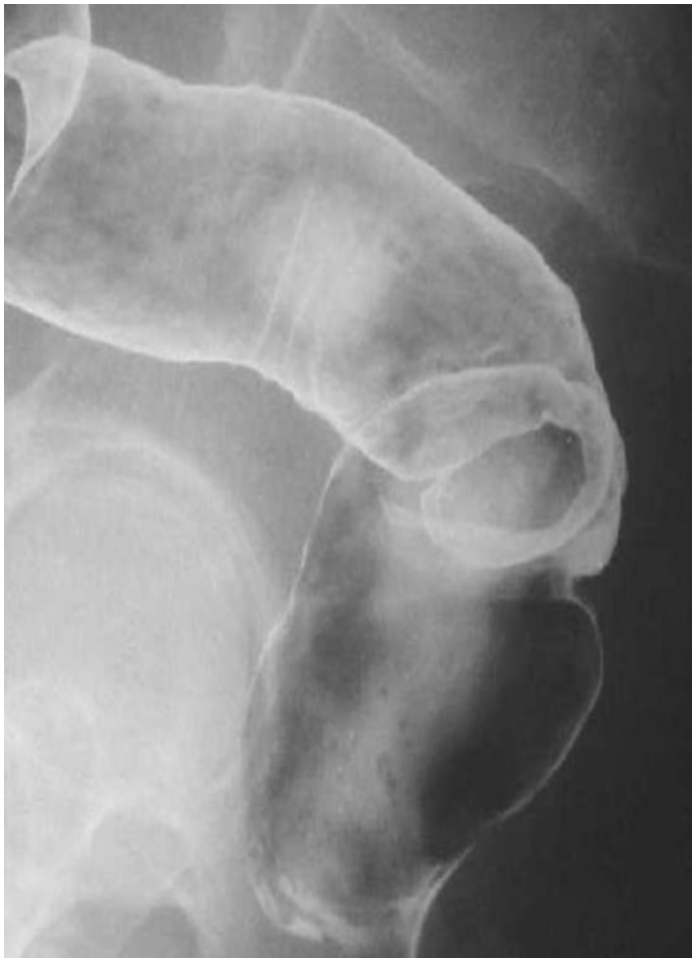
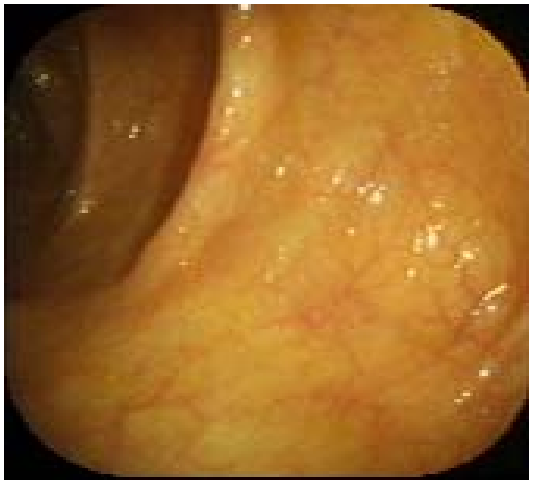
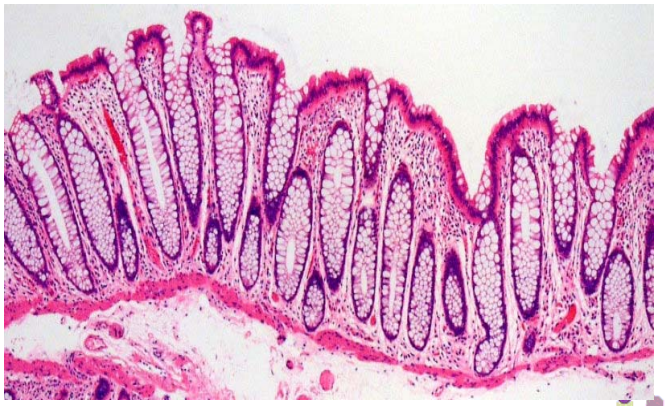
Rectosigmoid Anatomy

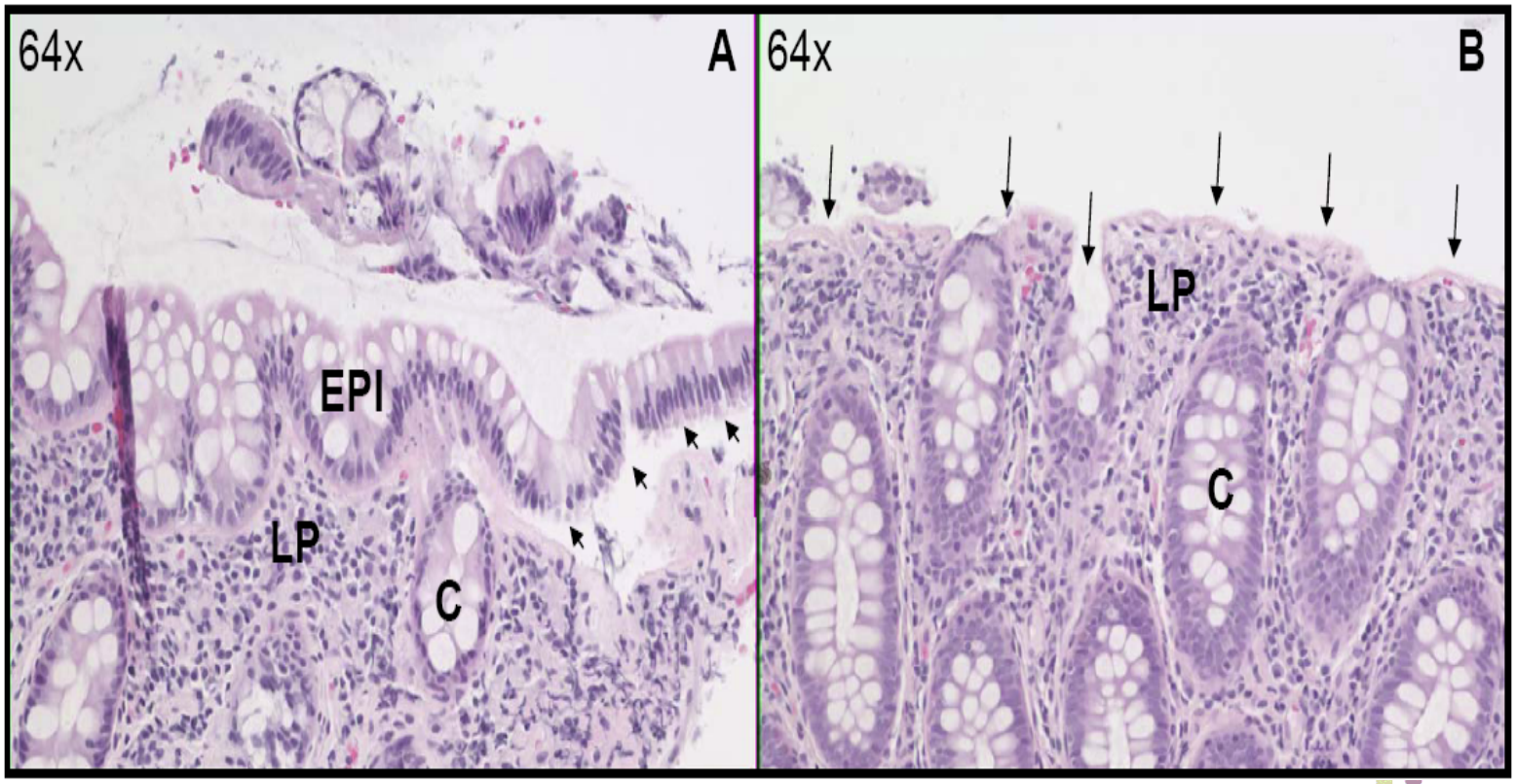






Effect of Osmolality on Mucosal Integrity

Iso-osmolar **Hyperosmolar**



Fuchs et al J Infect Dis 2007

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

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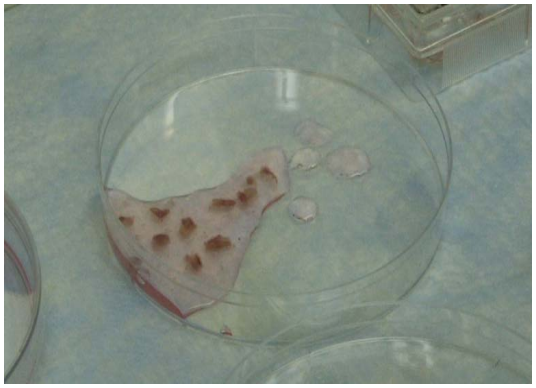
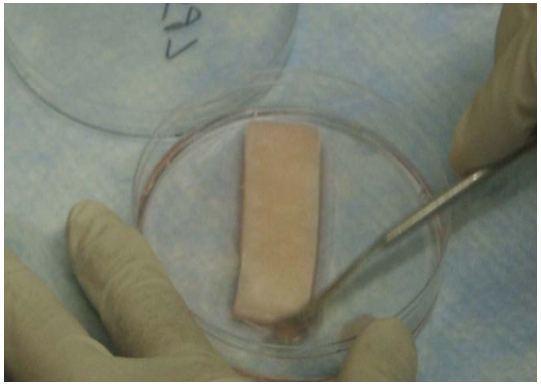
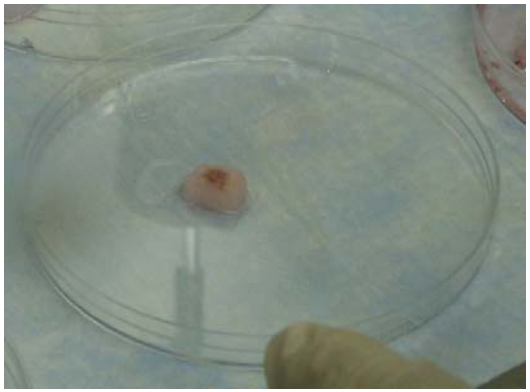
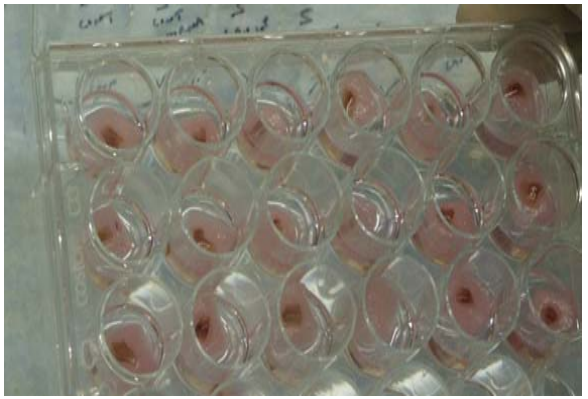
Colorectal Intestinal Explants





Endoscopic biopsies **+** **Absorbable gelatin sponge**





Abner SR et al. JID 2005, Fletcher P et al. AIDS 2006

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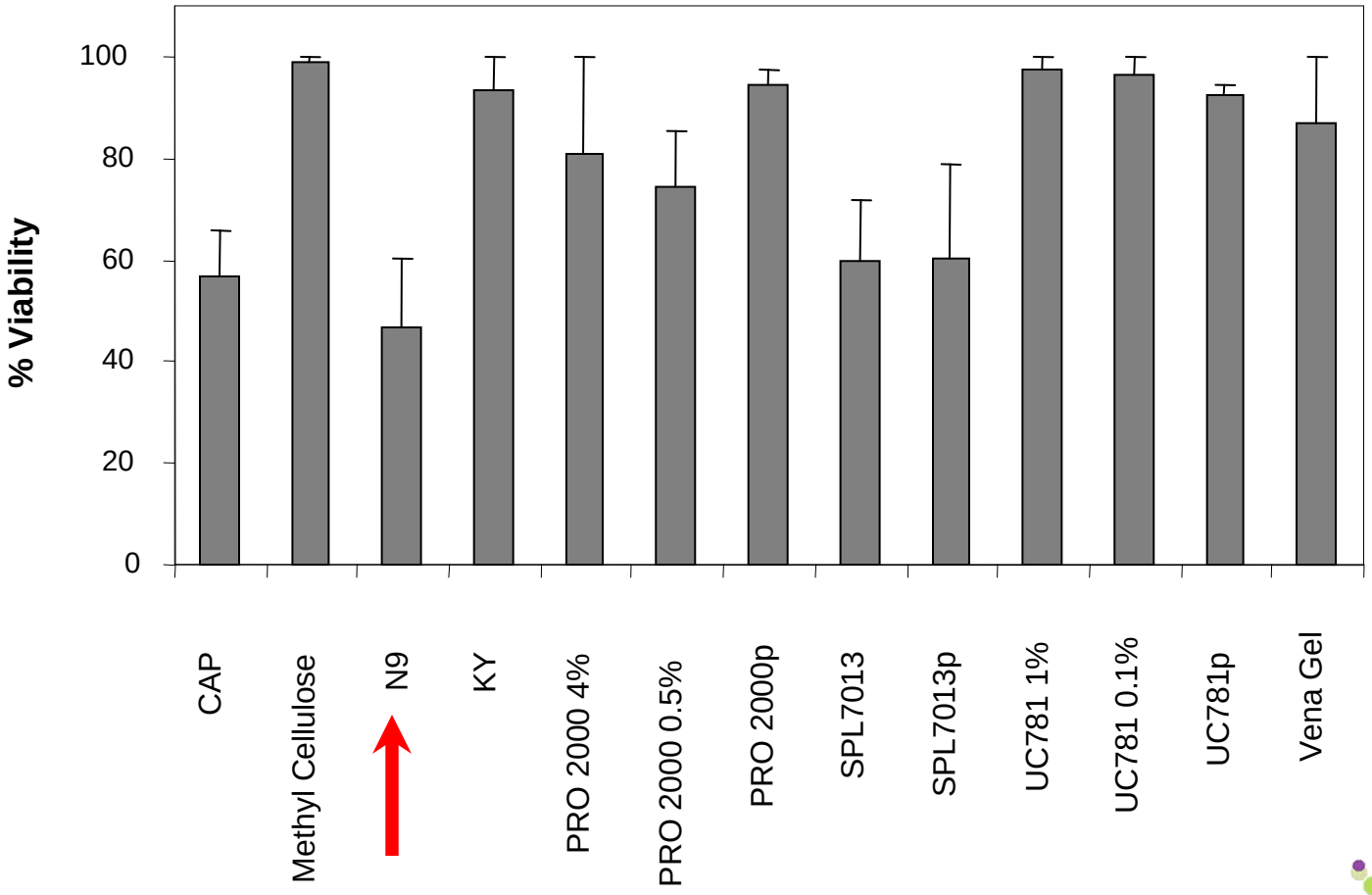
Toxicity of Topical Microbicides in Colorectal Explants



Dezzutti C et al., AAC 2004

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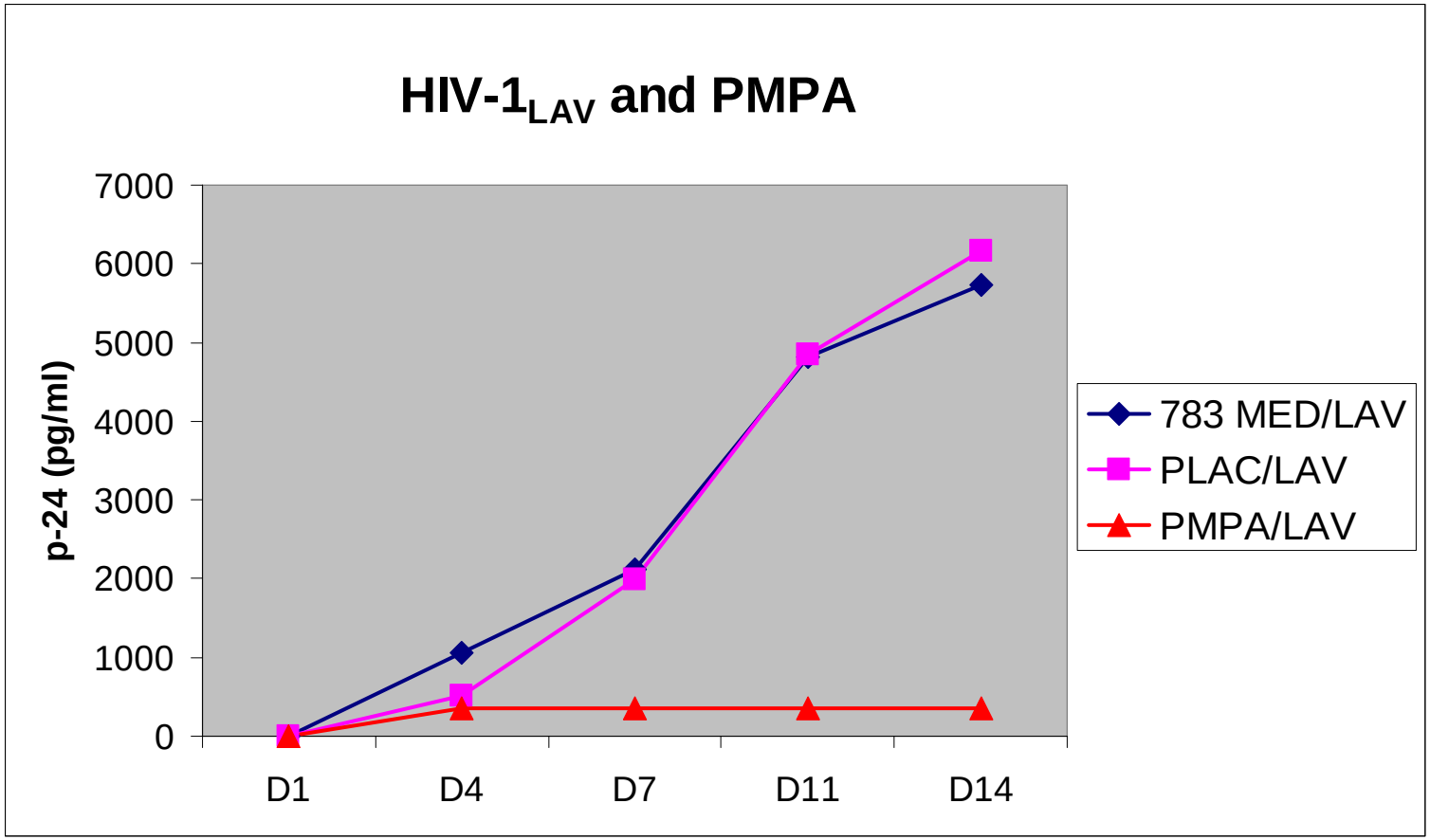
Tenofovir Explant Data



Rectal Model Development

Macaca nemestrina

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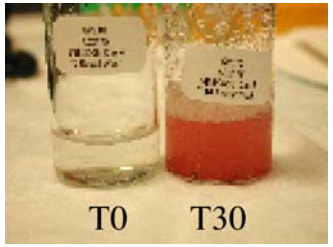
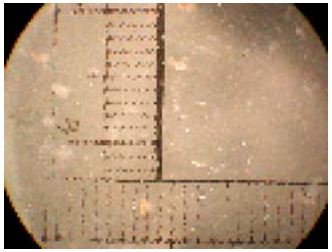
Rectal Lavage Assay

Lavage fluid

Day 4 **Combo** Animal

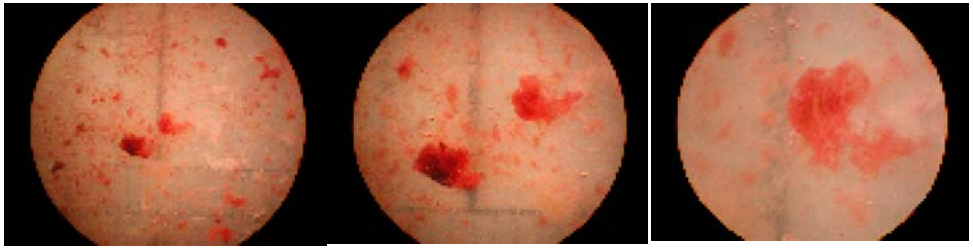


Day 4, T0 24 hrs post 3rd application



7X

Day 4, T30 post 4th application



7X 15X 30X

**Microbicides 2008 Poster #TA-057*

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Evolving Design of Phase 1 Rectal Safety Studies

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Tabet et al.

- Open label frequency escalation safety study of 3.5% nonoxynol-9 gel versus replens
- Population – monogamous couples
  - 25 HIV negative MSM
  - 10 HIV positive MSM
- Gel BID + RAI 3 times per week for 6 weeks
- 68 (97%) participants completed study
- Minor anoscopic or histological findings common

Tabet et al. STD 1999

Phillips et al.

- 2% Nonoxynol-9
- 18 participants - open label study
- Endpoint
  - Histology
- Sampling
  - Baseline
  - + 15 minutes
  - + 2 hours
  - + 8 hours

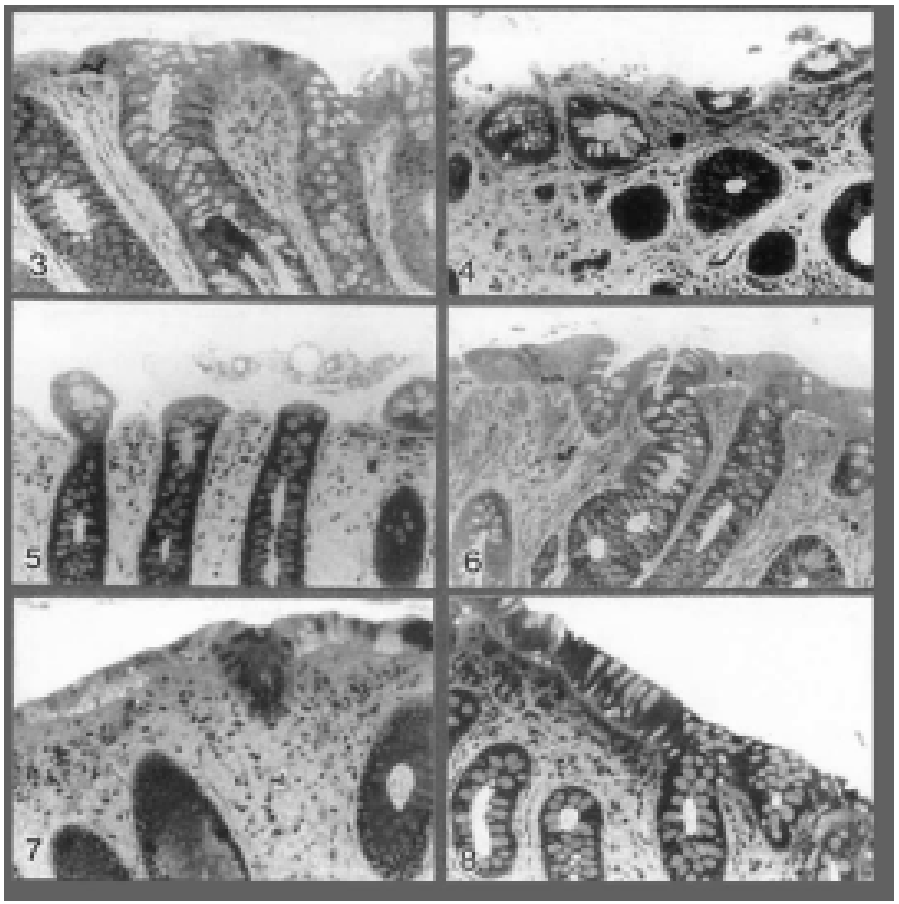
Phillips et al. Contraception 2004

Phillips et al.

Baseline

+ 15 minutes

+ 2 hours



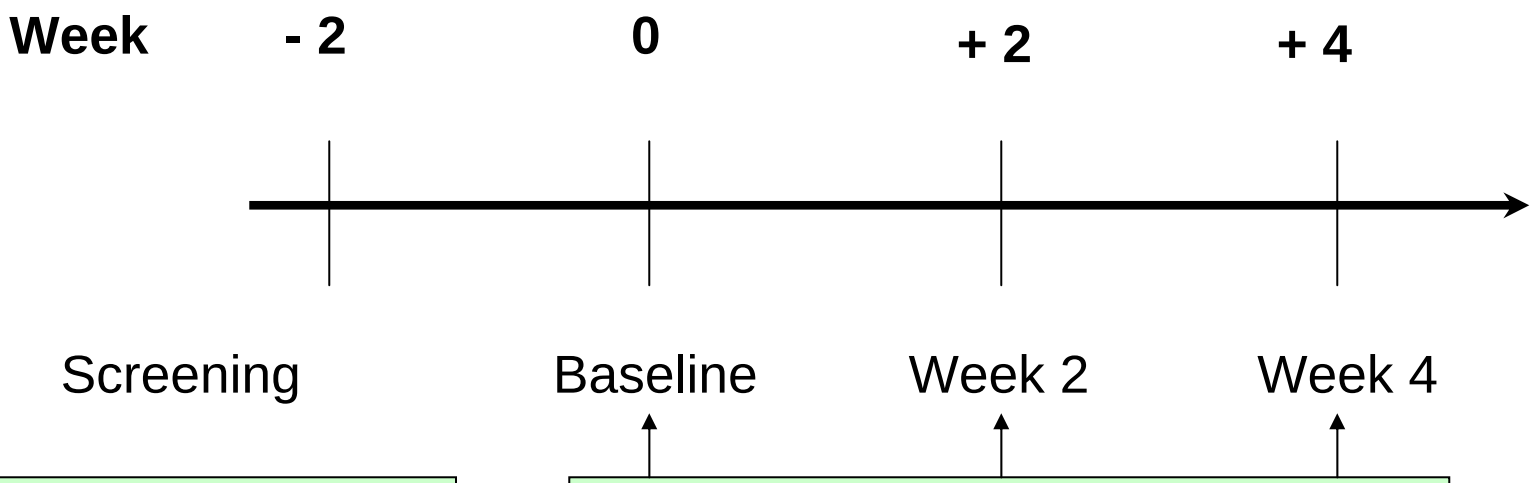
+ 15 minutes

+ 2 hours

+ 8 hours

Phillips et al. Contraception 2004

HPTN 056 Study Design



McGowan et al. JAIDS 2007

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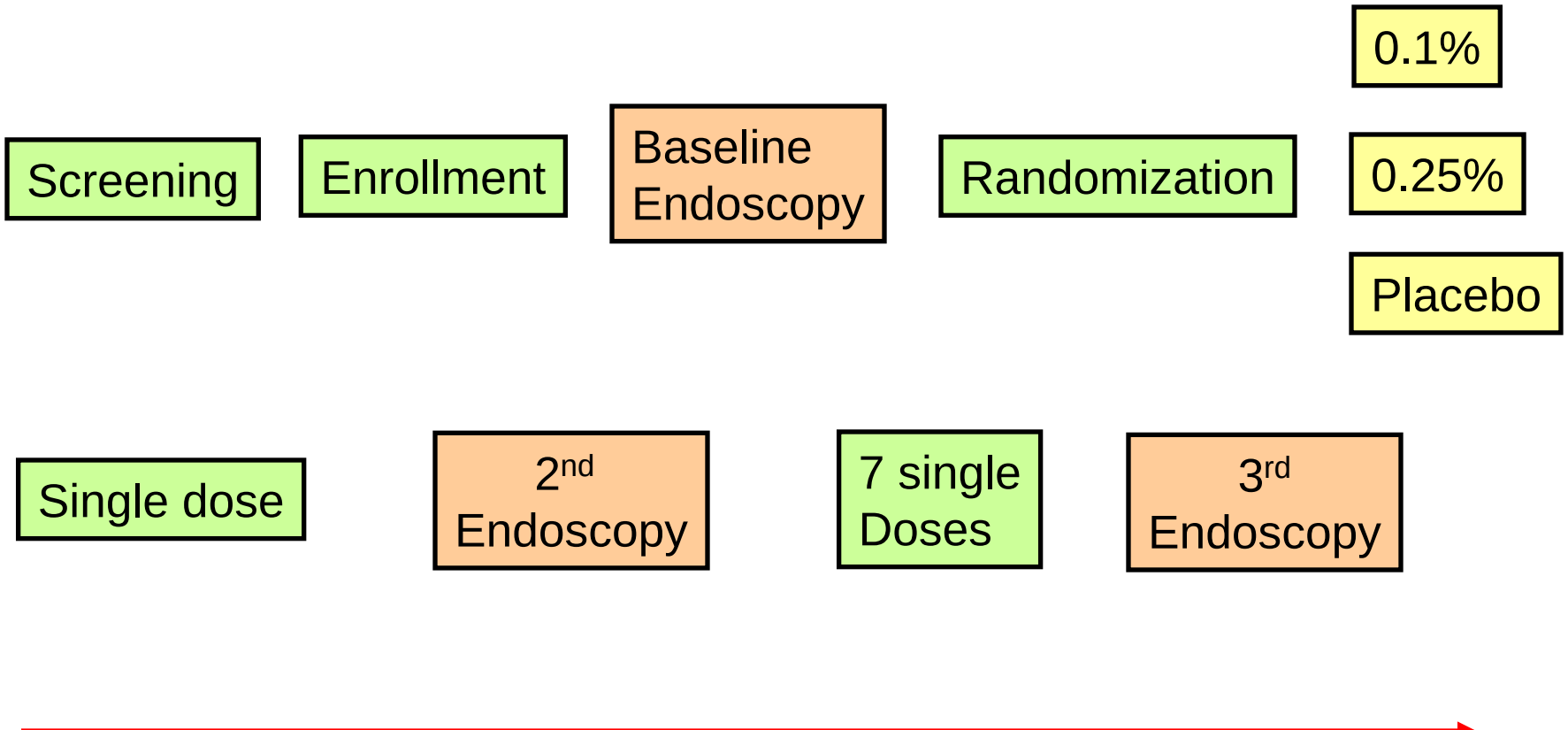
UC-781 Trial Design



Anton et al. CROI 2009

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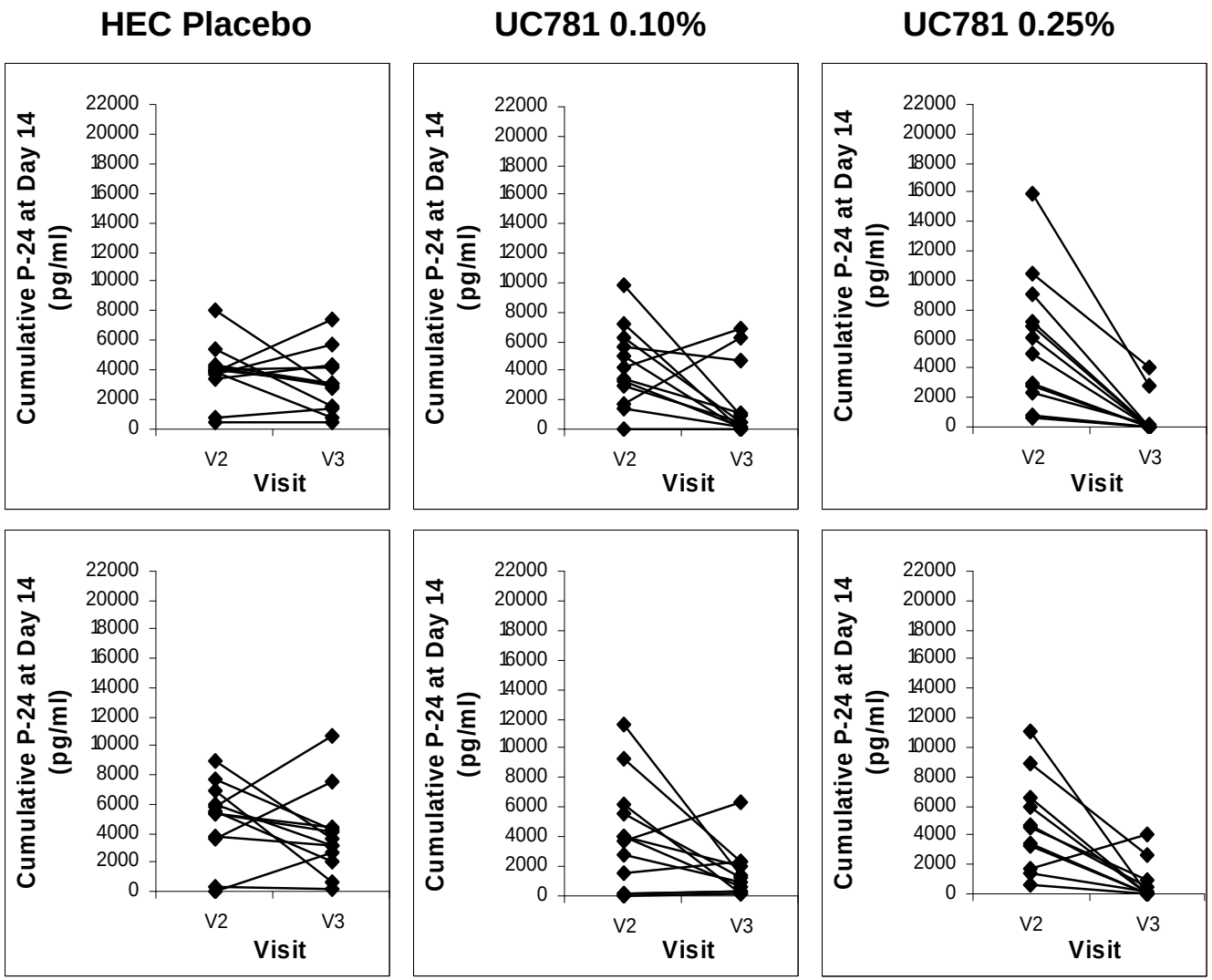
Explant Data



(HIV-1 BaL $TCID_{50}$ 10^4)

Future Phase 1 Rectal Microbicide Safety Studies

Product	Status	Timeline	Sponsor
UC-781	Completed		NIAID/DAIDS
MTN-007	Planned	Q2 2009	NIAID/DAIDS
RMP-02	Planned	Q2 2009	NIAID/DAIDS
VivaGel	Planned	Q4 2009	NIAID/DMID
PRO-2000	Planned	Q4 2009	MDP MRC-UK
UC-781 (RF)	Possible	Q4 2010	TBD

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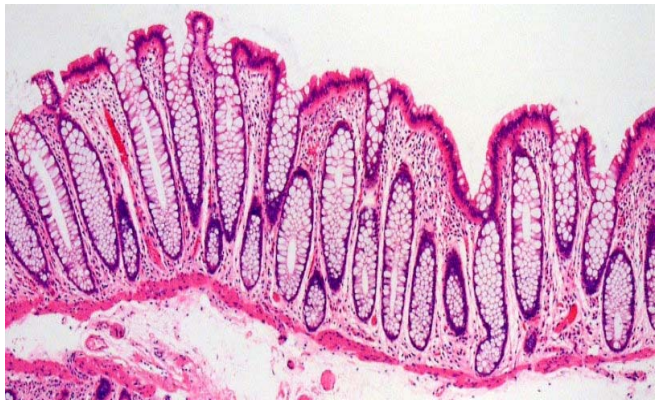
RMP-02 / MTN-006



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RMP-02 / MTN-006

- A Phase 1 rectal microbicide safety and acceptability trial of topically applied tenofovir compared with tablet
- Study population
  - 18 sexually abstinent HIV negative men and women
- Study products
  - Oral
    - Tenofovir
  - Topical
    - 1% vaginal formulation of tenofovir
    - Hydroxyethyl cellulose (HEC) placebo gel

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RMP-02 / MTN-006

Single oral dose of tenofovir

Single rectal dose of tenofovir

7 daily doses of tenofovir

Pharmacokinetics

- Plasma
- PBMC
- Rectal fluid
- Tissue
- MMC

Safety

- General
- Mucosal

Explant Infection

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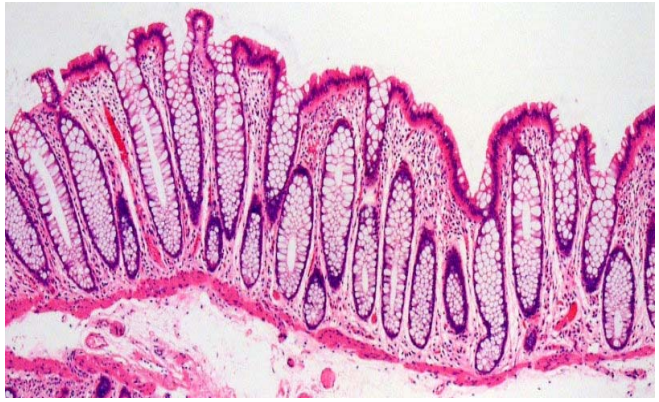
RMP-02 / MTN-006

- David Geffen School of Medicine at UCLA
  - IOR: Peter Anton MD
- Pittsburgh, PA
  - IOR: Ian McGowan MD PhD

MTN-007



MTN-007

- Phase 1 randomized, double-blinded, placebo-controlled rectal safety and acceptability study of tenofovir 1% gel
- Approximately 60 sexually (RAI) abstinent, HIV-negative adults men and women
- Four study arms:
  - 1% vaginal formulation of tenofovir
  - Hydroxyethyl cellulose (HEC) placebo gel
  - 2% nonoxynol-9 (Ortho-Gynol II)
  - No product arm

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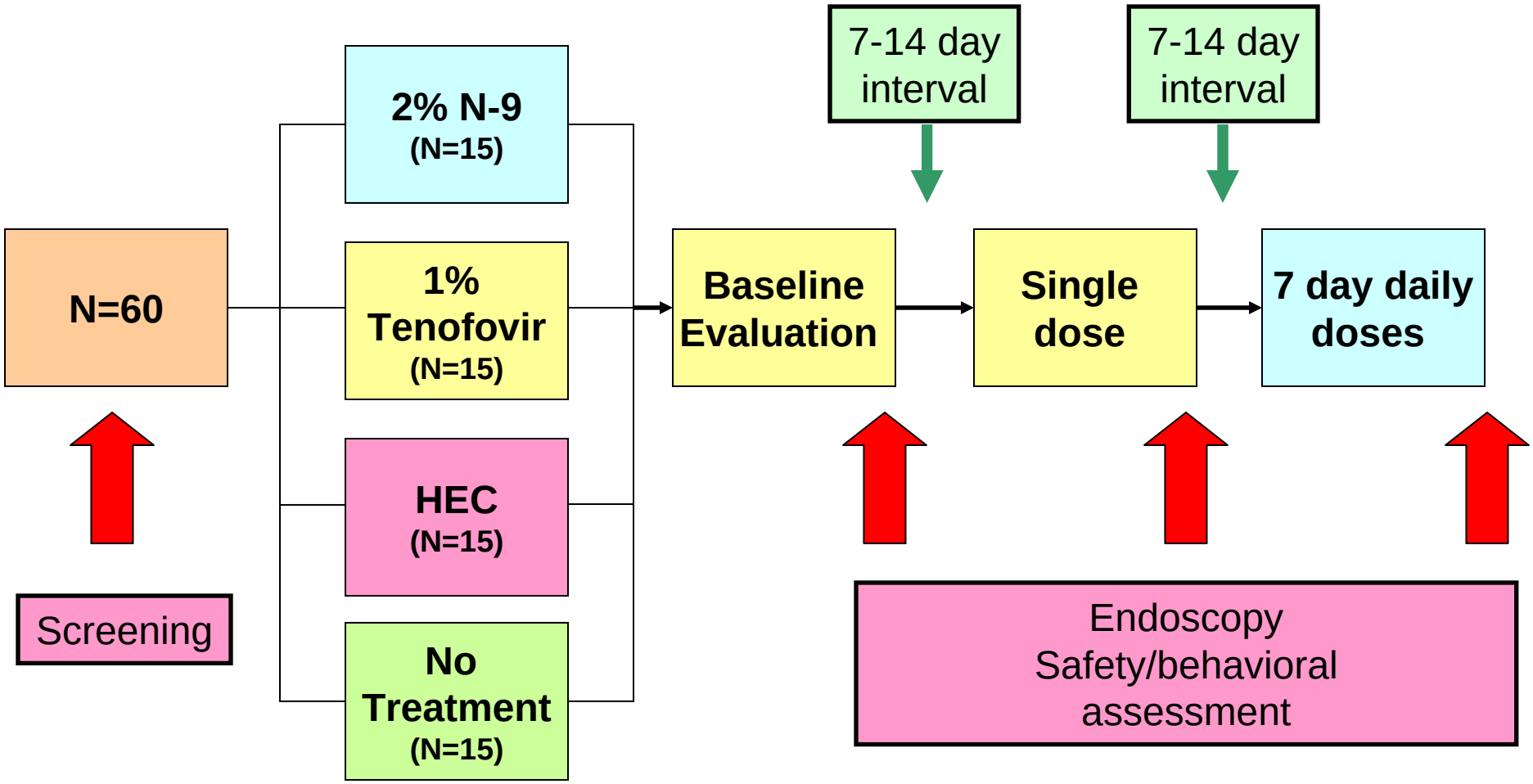
MTN-007 Design



Secondary Endpoints

- Mucosal safety parameters:
  - Epithelial sloughing
  - Intestinal histopathology
  - Intestinal mucosal mononuclear cell phenotype
  - Intestinal mucosal cytokine Intestinal mucosal gene expression arrays
  - Cytokine profile in rectal secretions
  - Fecal calprotectin
  - Microflora

MTN-007 Study Sites

- Pittsburgh, PA
  - IOR: Ross Cranston MD
- Birmingham, AL
  - IOR: Craig Hoesley MD
- Boston, MA
  - IOR: Ken Mayer MD

Why have an N-9 arm in MTN-007?

- Assessment of mucosal injury requires the use of esoteric and expensive assays
- Preliminary data from a UC-781 Phase 1 rectal safety study have not demonstrated changes in these mucosal safety parameters
- Rectal exposure to N-9 results in mild and transient epithelial disruption
  - Mice
  - Macaques
  - Humans

Is inclusion of an N-9 arm safe?

- Histological recovery occurs within 1-8 hours
  - Mice
  - Humans
  - Macaques
- Tabet et al. demonstrated minimal histological inflammation after up to 6 weeks treatment with a 3.5% formulation of N-9
- All participants in MTN-007 will be sexually abstinent

Moving Towards Effectiveness Studies

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U.S. Department of Health and Human Services

NIH News

National Institutes of Health

"For this reason, NIAID places a priority on developing HIV prevention tools that women can implement independently. One such method under study is a microbicide—a gel, cream or foam intended to prevent the sexual transmission of HIV when applied topically inside the vagina or **rectum**.

Statement of Anthony S. Fauci, M.D.
Director, National Institute of Allergy and Infectious Diseases
National Institutes of Health on National Women and Girls HIV/AIDS Awareness Day
March 10, 2009

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Next Steps

- Identify relevant population
- Develop rectal specific products
- Design rectal specific applicator
- Expanded safety study
- Effectiveness study

Populations for RM studies

- Phase 2 studies
  - RAI sexually active men and women
  - Higher risk populations
- Phase 2B studies
  - 3% seroincidence MSM populations
    - North America
    - Latin America
    - Africa

Microbicide Safety and Acceptability in Young Men

- NICHD R01
  - McGowan / Carballo-Dieguez
  - Pittsburgh, Boston, Puerto Rico
- Phase 1 safety and acceptability of VivaGel
  - Ethnically diverse MSM (18-30)
  - Consensual RAI in last month
  - Unprotected RAI in last year

Microbicide Safety and Acceptability in Young Men

Stage 1A

Screening

240 MSM

Consensual RAI in last month

URAI in last year

Stage 1B

3 month Acceptability & Adherence study with placebo gel

120 MSM

RAI in last 3 months

STI negative

Stage 2

Phase 1 VivaGel rectal safety study

42 MSM

80% adherence in Stage 1B

McGowan & Carballo-Dieguez 2009

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Rectal Specific Products

- CHARM Program
  - Combination HIV Antiretroviral Microbicide Program
  - DAIDS IPCP Program
  - PI: Ian McGowan MD PhD
  - Consortium
    - University of Pittsburgh
    - UCLA
    - Johns Hopkins
    - CONRAD

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Rectal Specific Applicators

- Incorporates Fleet ™ 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

Phase 2 Expanded Rectal Safety Study

- Double blind placebo controlled
- Population:
  - 300 RAI sexually active men and women with 6 month follow-up
- Three study arms:
  - Oral tenofovir + placebo tenofovir gel
  - Placebo oral tenofovir + tenofovir gel
  - Oral tenofovir + tenofovir gel
- Study endpoints
  - Safety
  - PK substudy
  - Explant efficacy substudy

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Phase 2B Rectal Safety and Effectiveness Study

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	Placebo Study
Study Arms	Oral tenofovir + Placebo gel
	Oral placebo + Tenofovir gel
	Oral tenofovir + Tenofovir gel
	Oral placebo + Placebo gel
Seroincidence	4%
Power	90%
Endpoints per pair wise comparison / total	90-100 2 pair wise comparisons Total: 180-200
Person years per endpoint	40-50
Follow-up	2 years
Sample size	3,500 – 5,000

	Placebo Study	Active Comparator Study
Study Arms	Oral tenofovir + Placebo gel	Oral tenofovir
	Oral placebo + Tenofovir gel	Oral tenofovir + Tenofovir gel
	Oral tenofovir + Tenofovir gel	
	Oral placebo + Placebo gel	
Seroincidence	4%	4%
Power	90%	90%
Endpoints per pair wise comparison / total	90-100 2 pair wise comparisons Total: 180-200	88 1 pair wise comparison Total: 88
Person years per endpoint	40-50	120
Follow-up	2 years	2 years
Sample size	3,500 – 5,000	5,000

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Summary

- There is a clear rationale for the development of rectal microbicides
- The design of rectal safety studies now includes immunotoxicity assays
- Rectal specific products and applicators are being developed
- It is time to move to the Phase 2 and beyond

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IAS Meeting, Cape Town, South Africa, July 2009

“Rectal Microbicide Development, An African Perspective”

Ian McGowan MD PhD
Chris Beyrer MD
James McIntyre MD
Jim Pickett

Sponsored by AVAC, IRMA, MTN

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Acknowledgements

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