

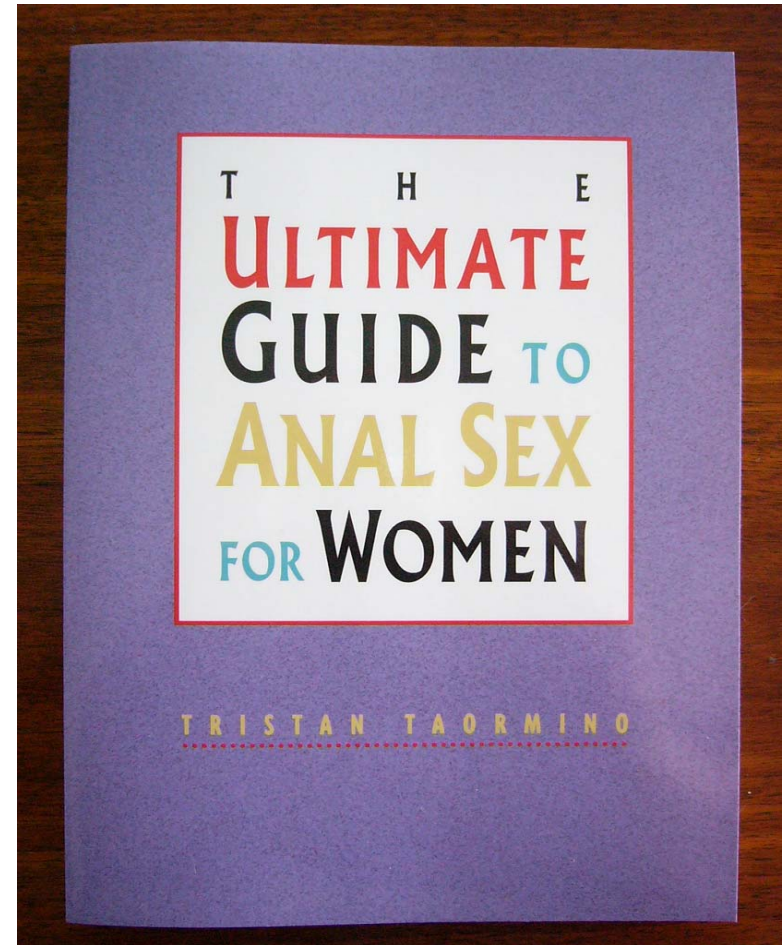
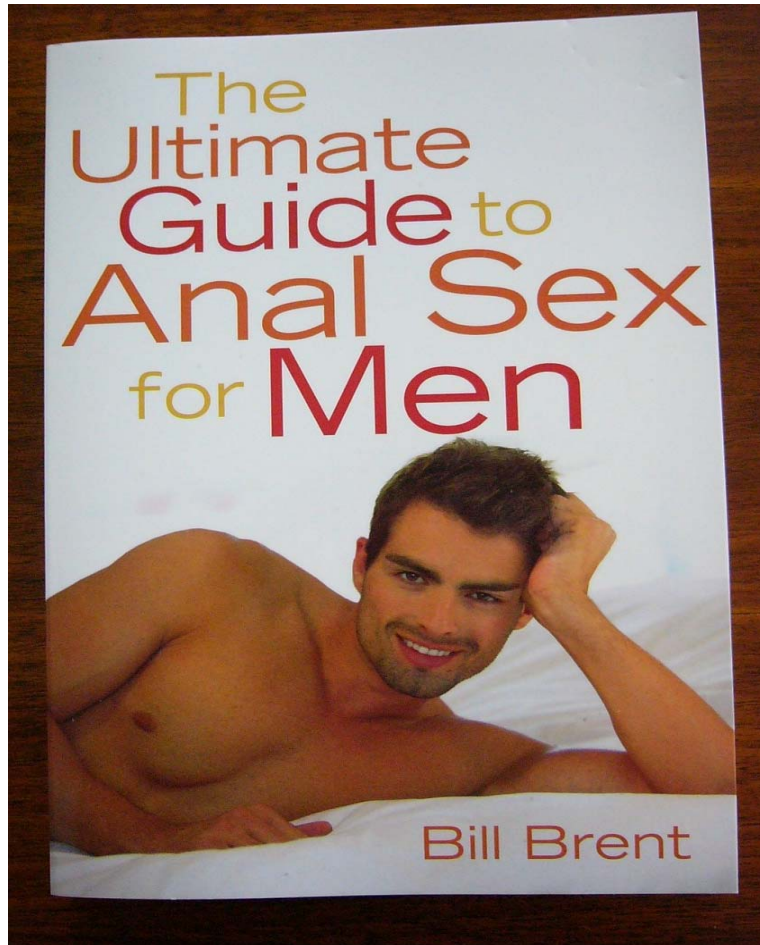
# A Preview of New Rectal Microbicides Safety Studies

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Magee Womens Research Institute  
University of Pittsburgh, USA



# So Who Is Having Anal Sex?



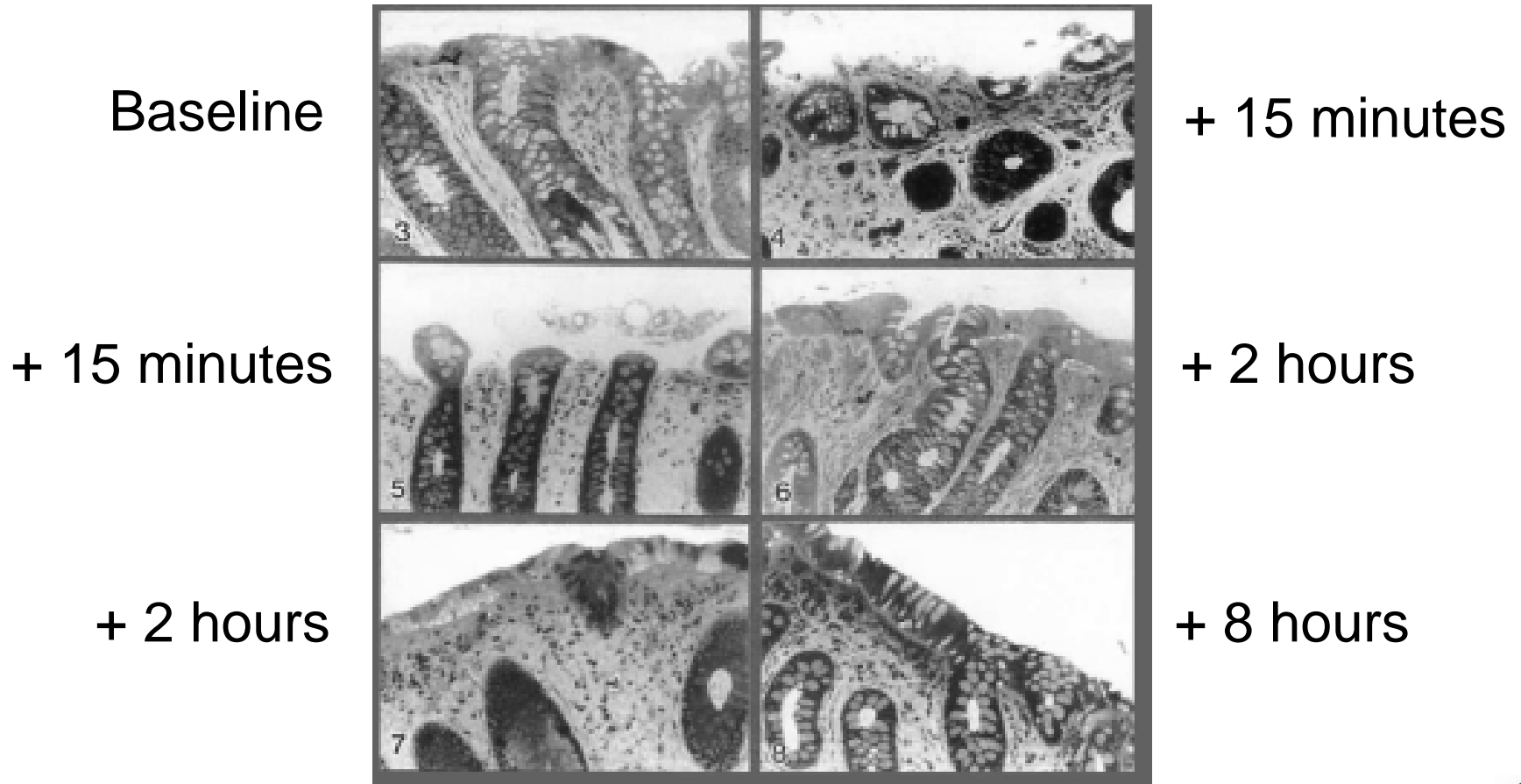
The Ultimate Guide to Anal Sex for Men. Bill Brent. Cleiss Press Inc. San Francisco 2002  
The Ultimate Guide to Anal Sex for Women, Tristan Taormino, Cleiss Press Inc. San Francisco 1998



# Rectosigmoid Anatomy



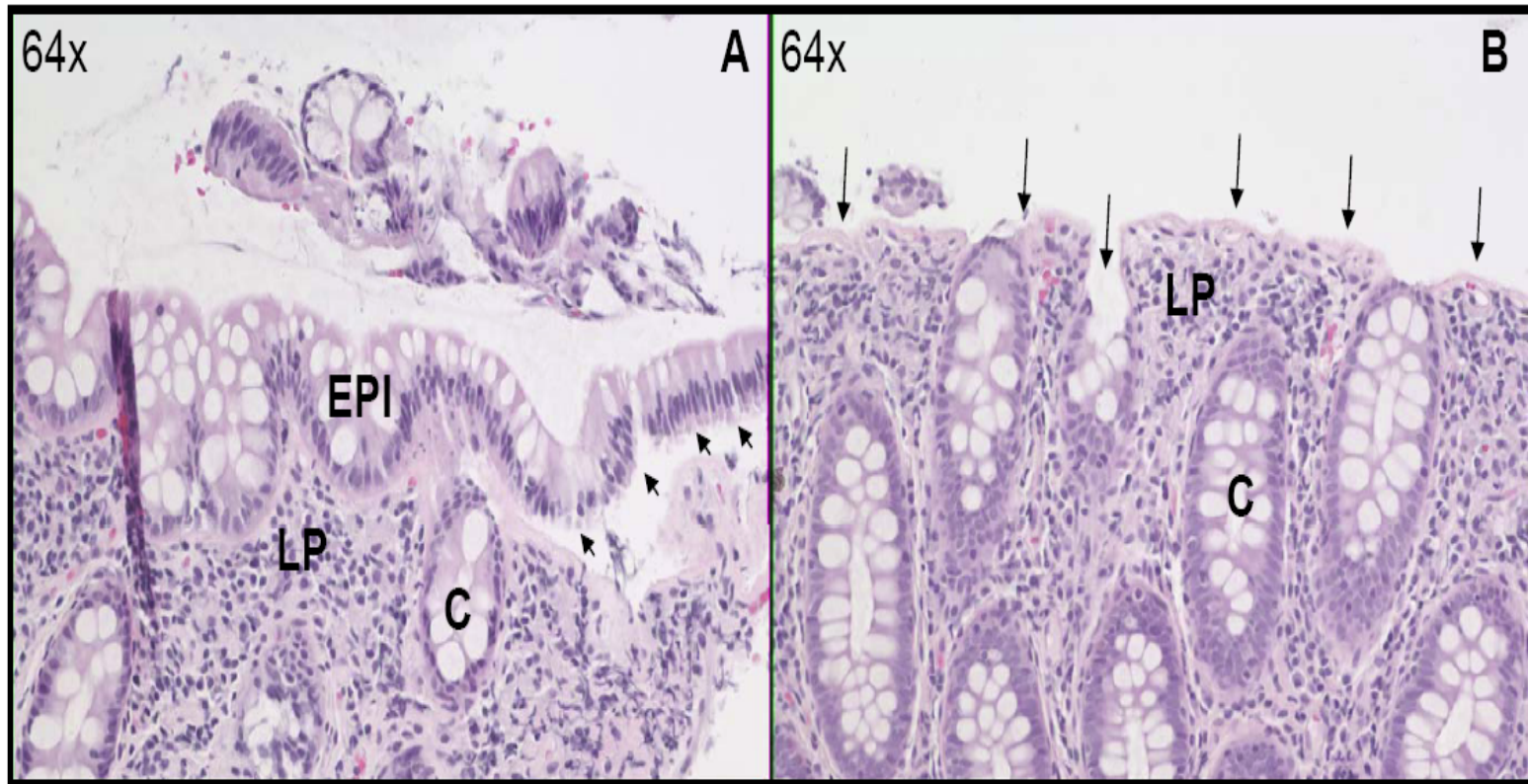
# N-9 Effect on Rectal Epithelium



# Effect of Osmolality on Mucosal Integrity

Iso-osmolar

Hyperosmolar



# Lubricants Vary in Osmolality

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



# Evaluation of Rectal Safety

- Preclinical
  - Cell lines
  - Animal models
  - Formal GLP animal toxicology
- Clinical
  - Phase 1
  - Phase 2
  - Phase 3
- Post licensure surveillance

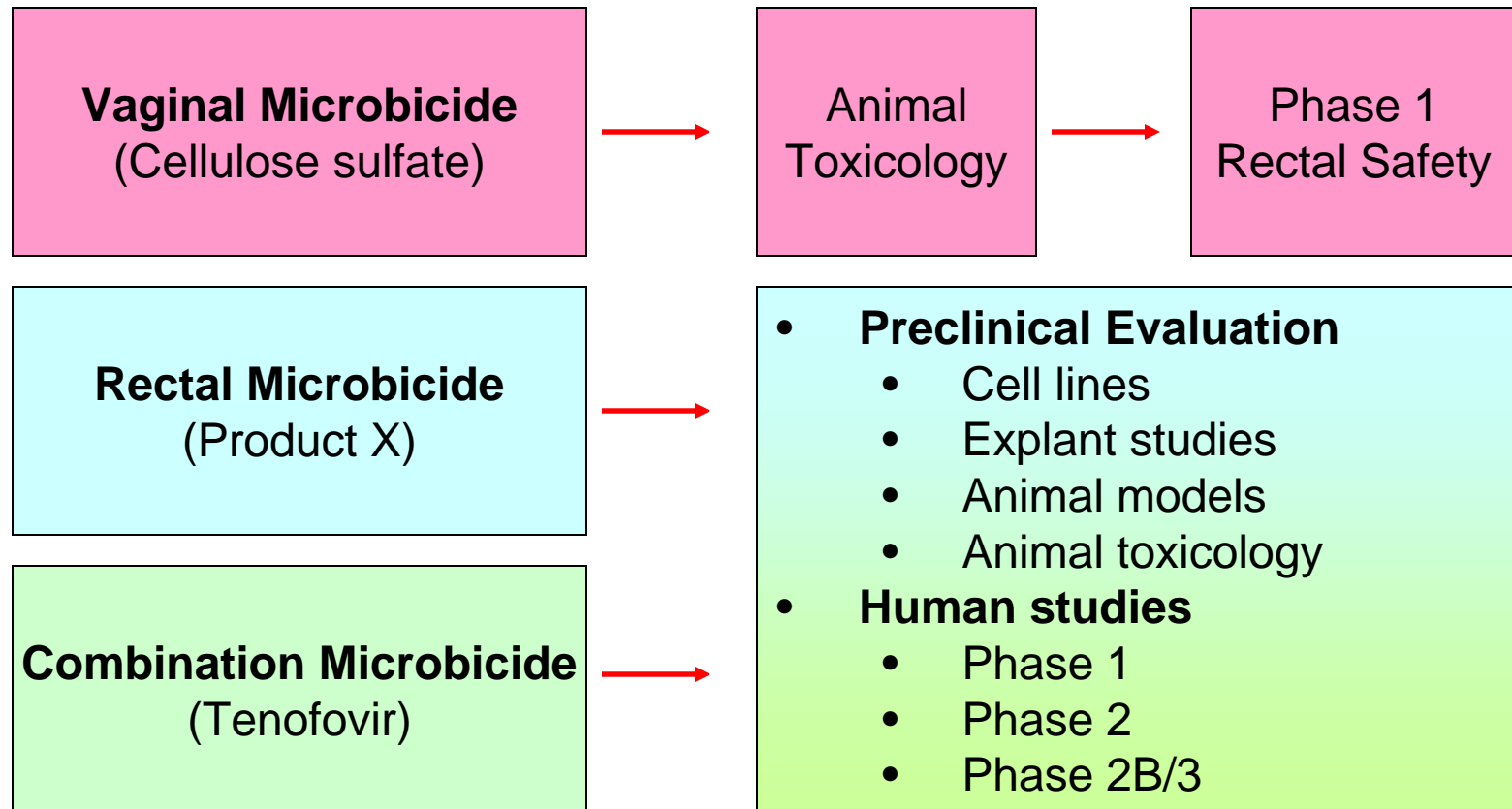


# Regulatory Issues

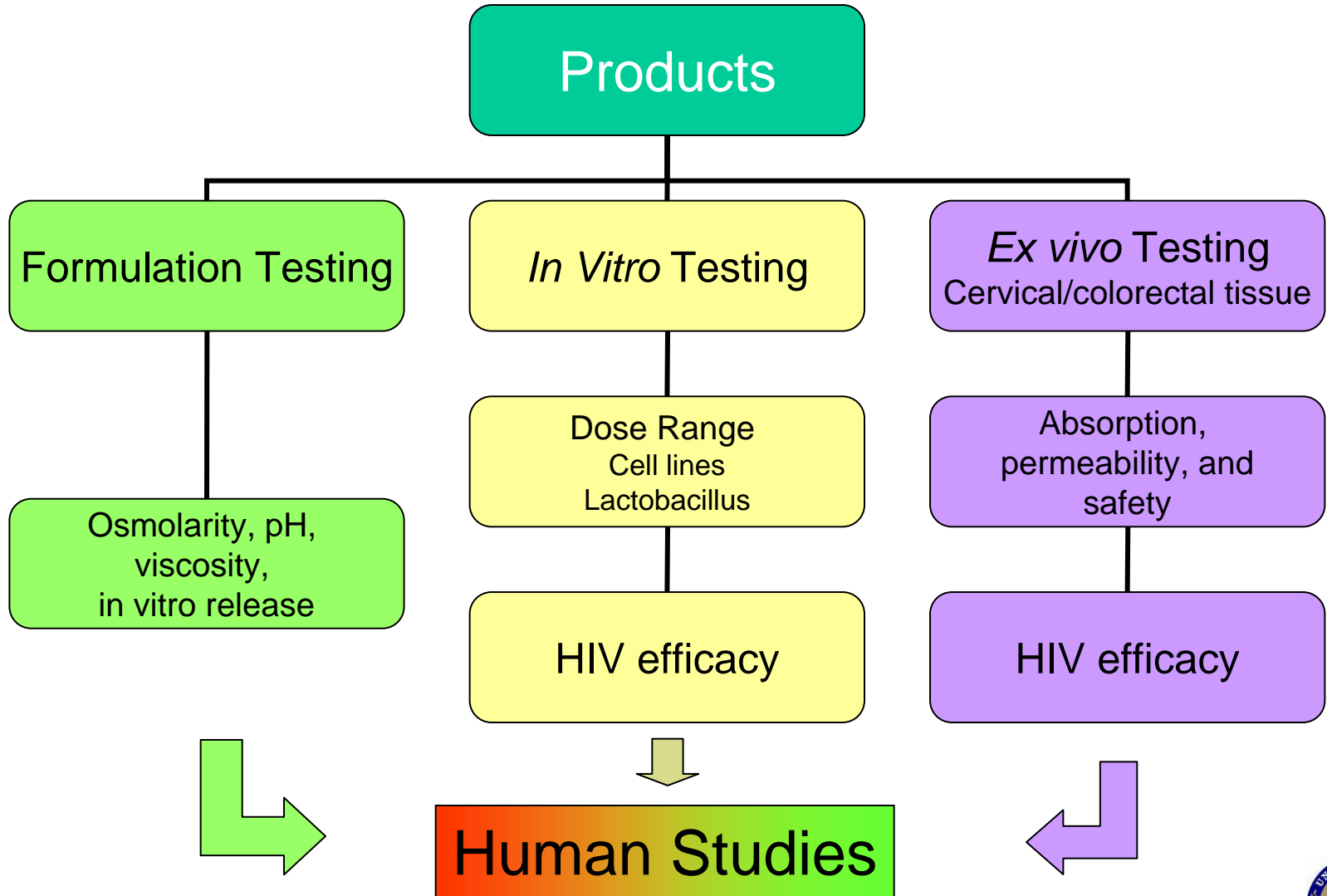
- No specific guidance for rectal microbicide development
- Ongoing Phase 1 studies linked to vaginal microbicide IND
- FDA seems to want Phase 1 rectal safety study for any vaginal microbicide
- Rectal specific microbicide will probably need its own IND



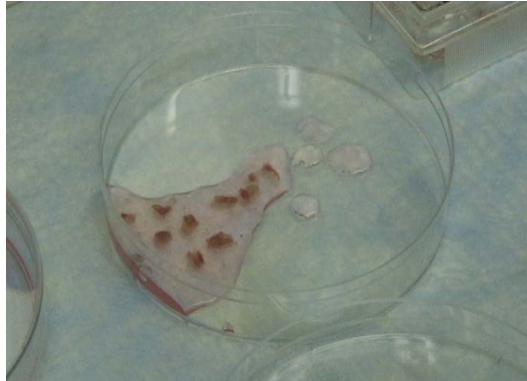
# Rectal Safety Assessment



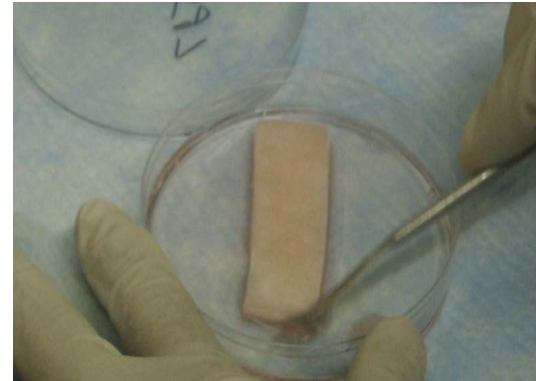
# Preclinical Safety



# Colorectal Intestinal Explants

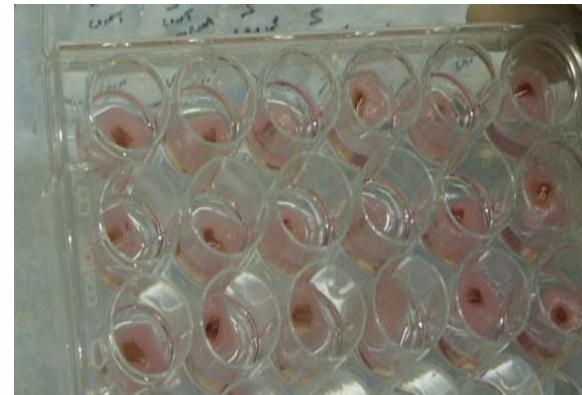
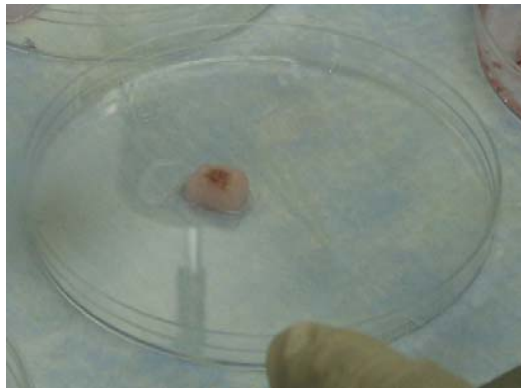


**Endoscopic biopsies**



**Absorbable gelatin sponge**

**+**



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



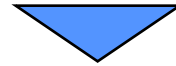


Rectal Model  
Development  
*Macaca  
nemestrina*

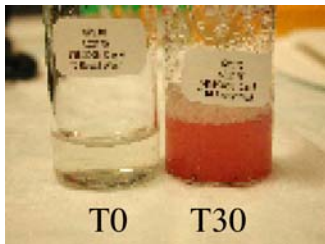


# Rectal Lavage Assay

Lavage  
fluid

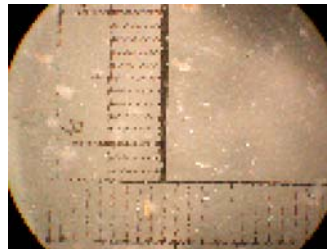


Day 4  
**Combo**  
Animal



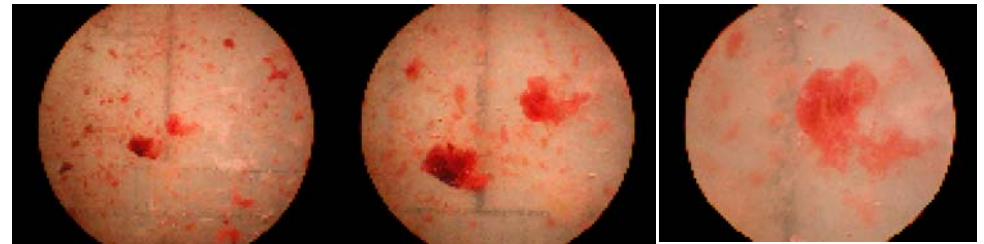
T0 T30

Day 4, T0  
24 hrs post  
3rd application



7X

Day 4, T30 post 4th application



7X

15X

30X

# Design of Phase 1 Rectal Safety Studies



# Previous Human Rectal Studies

- Tabet et al. 1999
  - Nonoxynol-9
- Phillips et al. 2004
  - Nonoxynol-9
- McGowan et al. 2007
  - HPTN-056
- Anton et al. 2008
  - UC-781 Phase 1 rectal safety study



# 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



# Phillips et al.

- Double blind study with four participants
- Products
  - 1% nonoxynol-9
  - 2% nonoxynol-9
  - Methyl cellulose
  - PC-515 (carrageenan)
- Endpoint
  - Saline lavage 15 minutes after exposure
  - Histology and EM



# Lavage Fluid

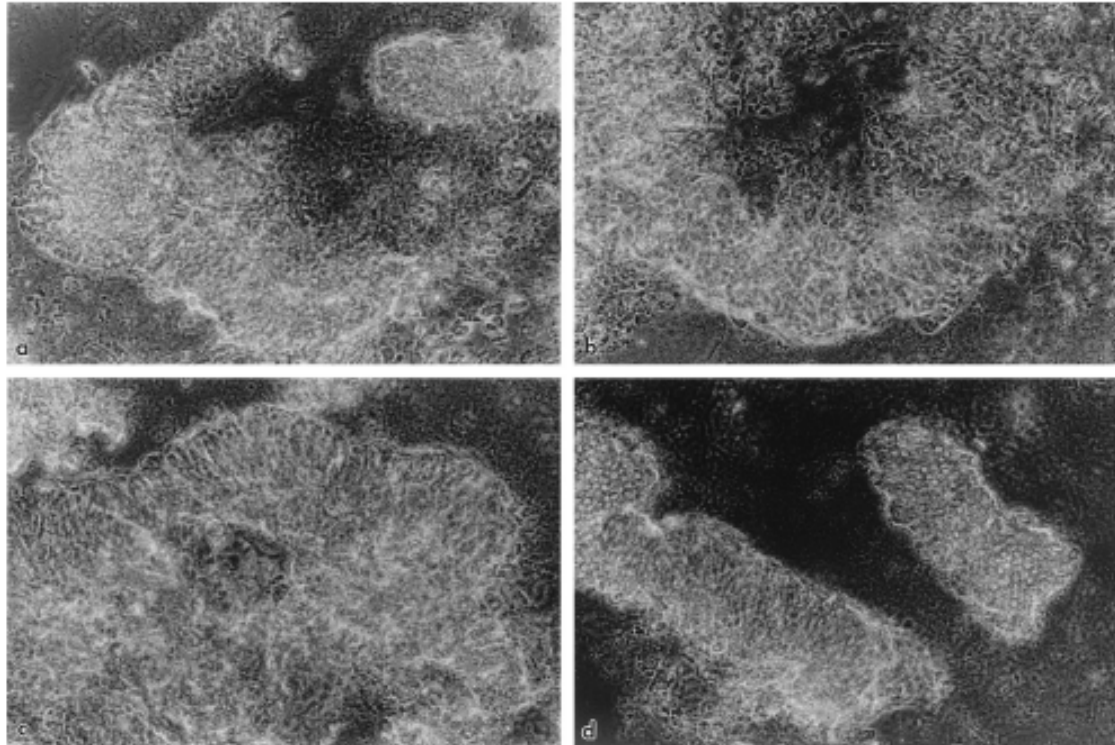


Fig. 1. (a-d) Phase contrast micrographs of sheets of rectal epithelium cells from the four specimens taken 15 min following the application of K-Y<sup>®</sup>Plus N-9 product. Each sheet of epithelium contains hundreds of cells.

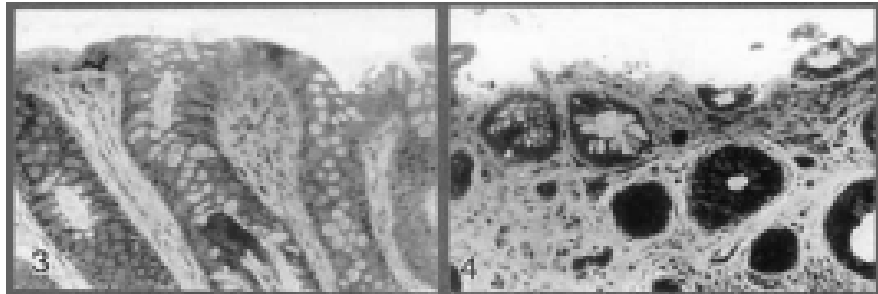
# Phillips et al.

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



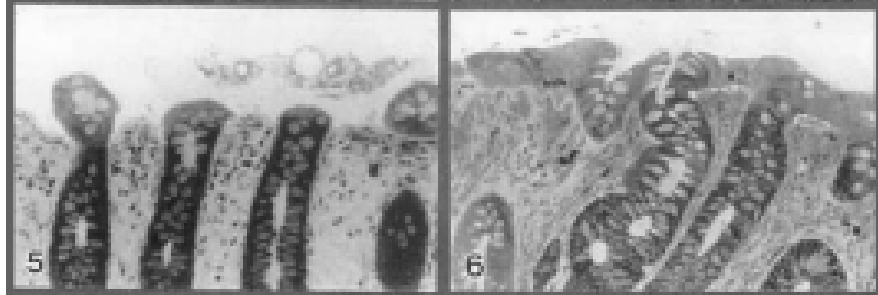
# Phillips et al.

Baseline



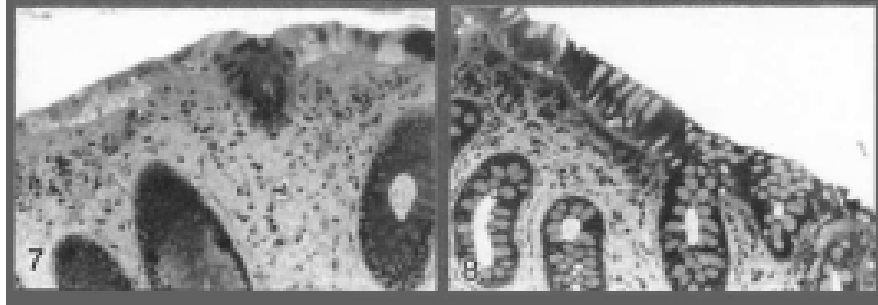
+ 15 minutes

+ 15 minutes



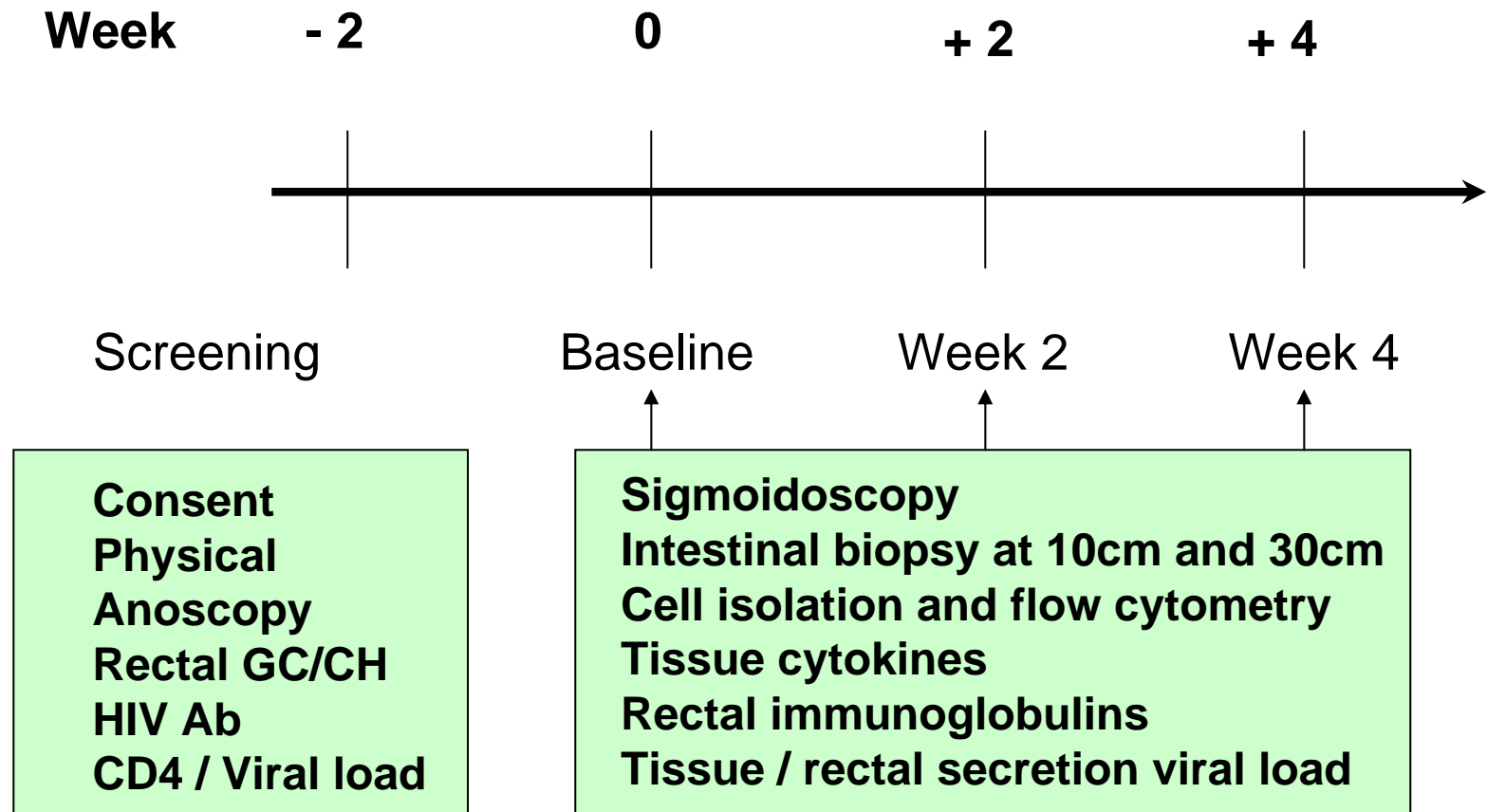
+ 2 hours

+ 2 hours

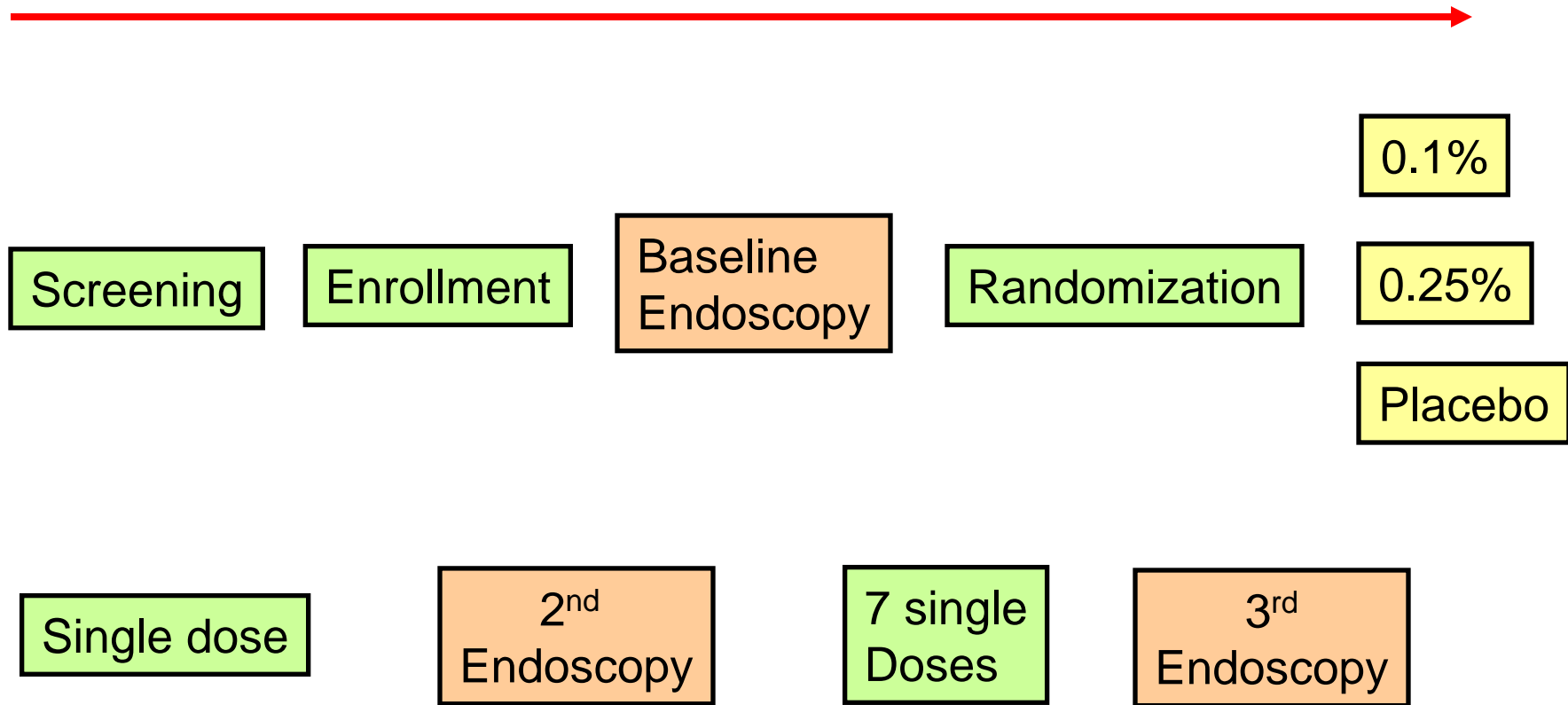


+ 8 hours

# HPTN 056 Study Design



# UC-781 Trial Design



# Future Phase 1 Rectal Microbicide Safety Studies

Product	Status	Timeline	Sponsor
UC-781	Completed		NIAID/DAIDS
MTN-007	Planned	Q2 2009	NIAID/DAIDS
MTN-006	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



# 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



# Primary Objective

- To evaluate the safety of tenofovir 1% gel when applied rectally



# Primary Endpoint

- Grade 2 or higher AEs as defined by:
  - The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004
  - Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies)



# Secondary Objectives

- To evaluate the acceptability of tenofovir 1% gel when applied rectally
- To evaluate the safety of HEC gel when applied rectally
- To determine whether use of tenofovir 1% gel is associated with rectal mucosal damage
- To determine whether use of 2% Nonoxynol-9 gel (Gynol-II®) is associated with rectal mucosal damage



# Secondary Endpoints (1)

- Acceptability:
  - The proportion of participants who at their Final Clinic Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during receptive anal intercourse.



# Secondary Endpoints (2)

- Safety:
  - Grade 2 or higher adverse events in the HEC gel arm
  - Mucosal safety



# Secondary Endpoints (3)

- 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



# Exploratory Objective

- To determine whether regional heterogeneity exists between mucosal endpoints in samples collected at 9 cm and 15 cm for all parameters examined
- To determine whether there is a correlation between histological abnormality and changes in mucosal biomarkers

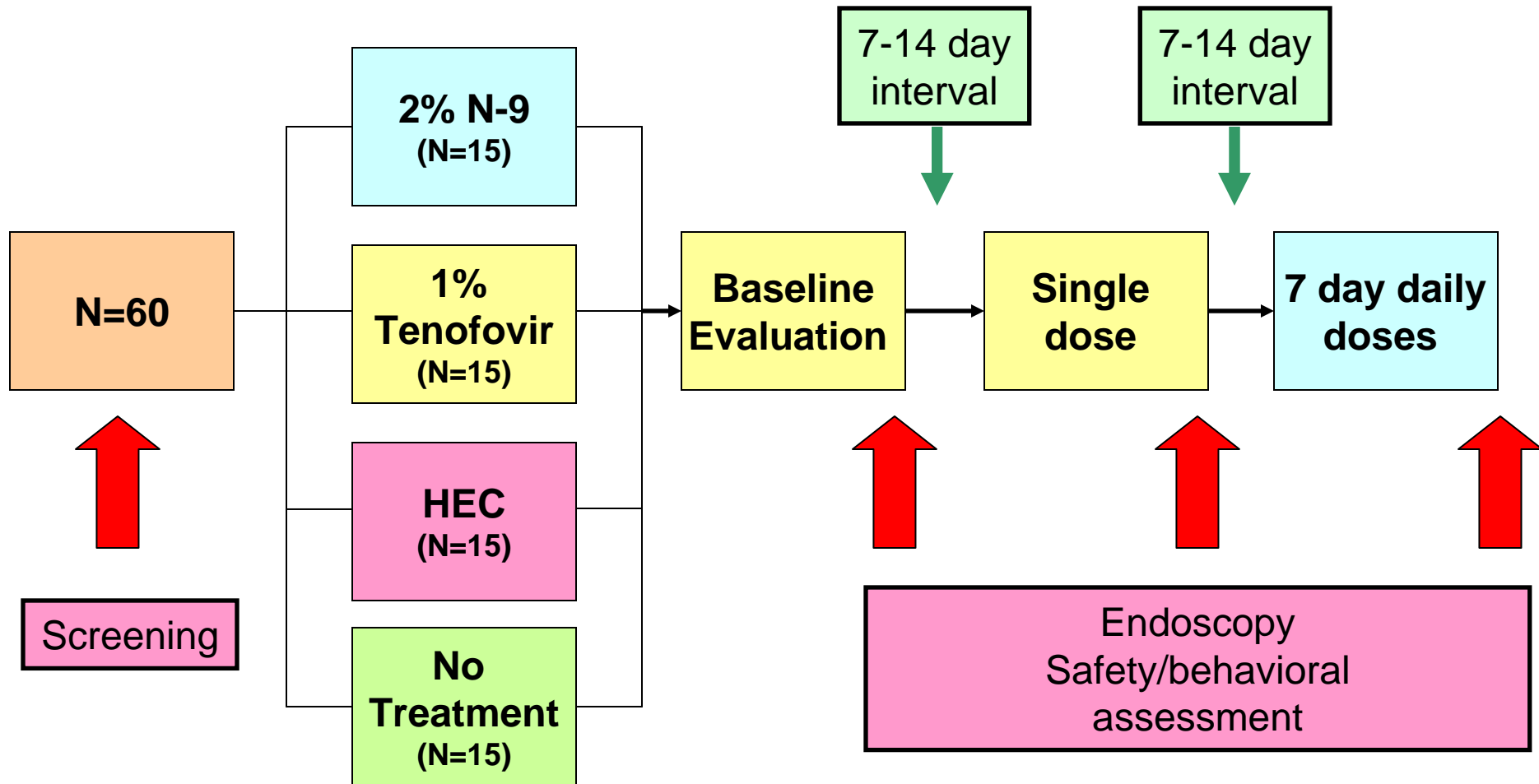


# Exploratory Endpoints

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



# MTN-007 Design



# MTN-007 Study Sites

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

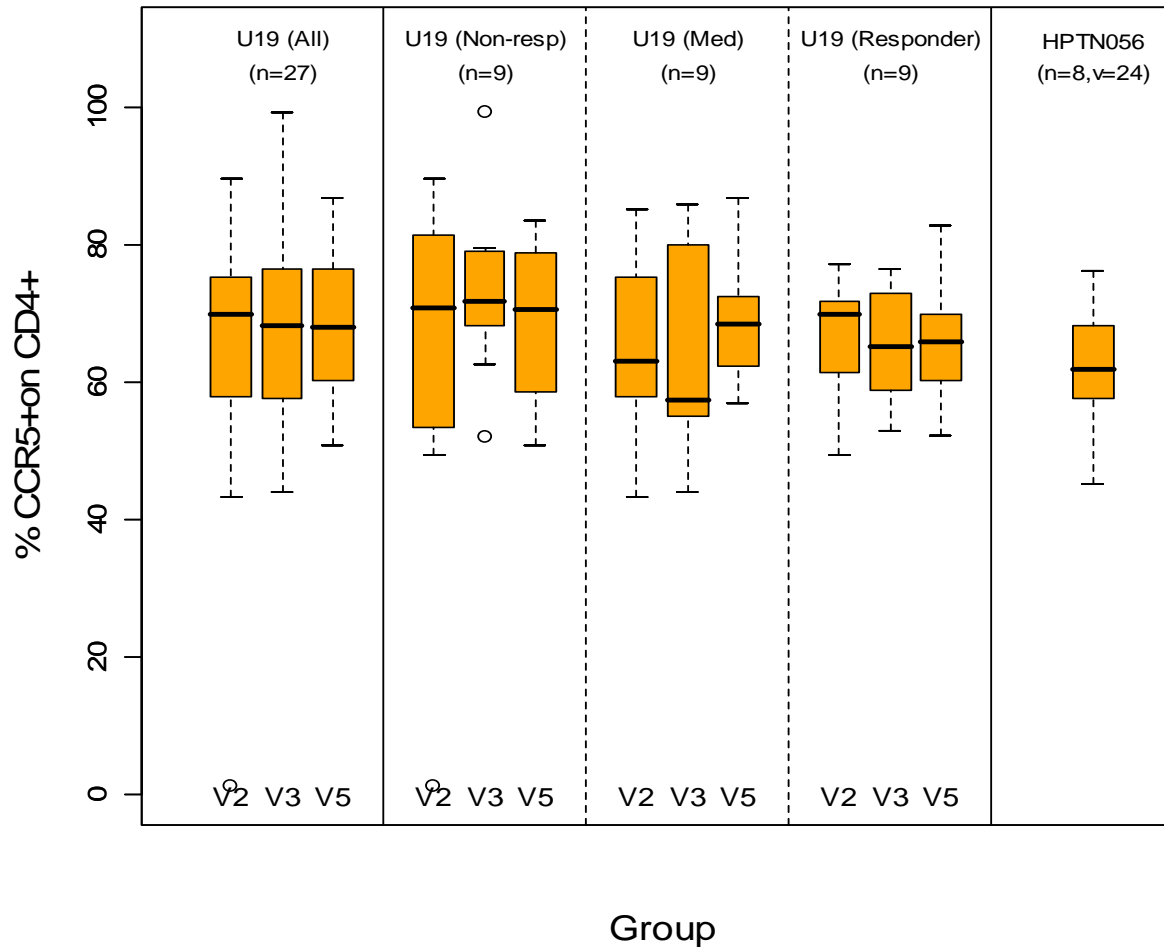


# Why have an N-9 arm in MTN-007?

- 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



# Safety Biomarkers



# 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

# Current Status of MTN-007

- Protocol completed
- Undergoing regulatory review
- Anticipated enrolment starts
  - July 2009
- Completion
  - June 2010



# Acknowledgements

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Bargello Museum, Florence, Italy

