

Mucosal Assays in Rectal Microbicide Trials

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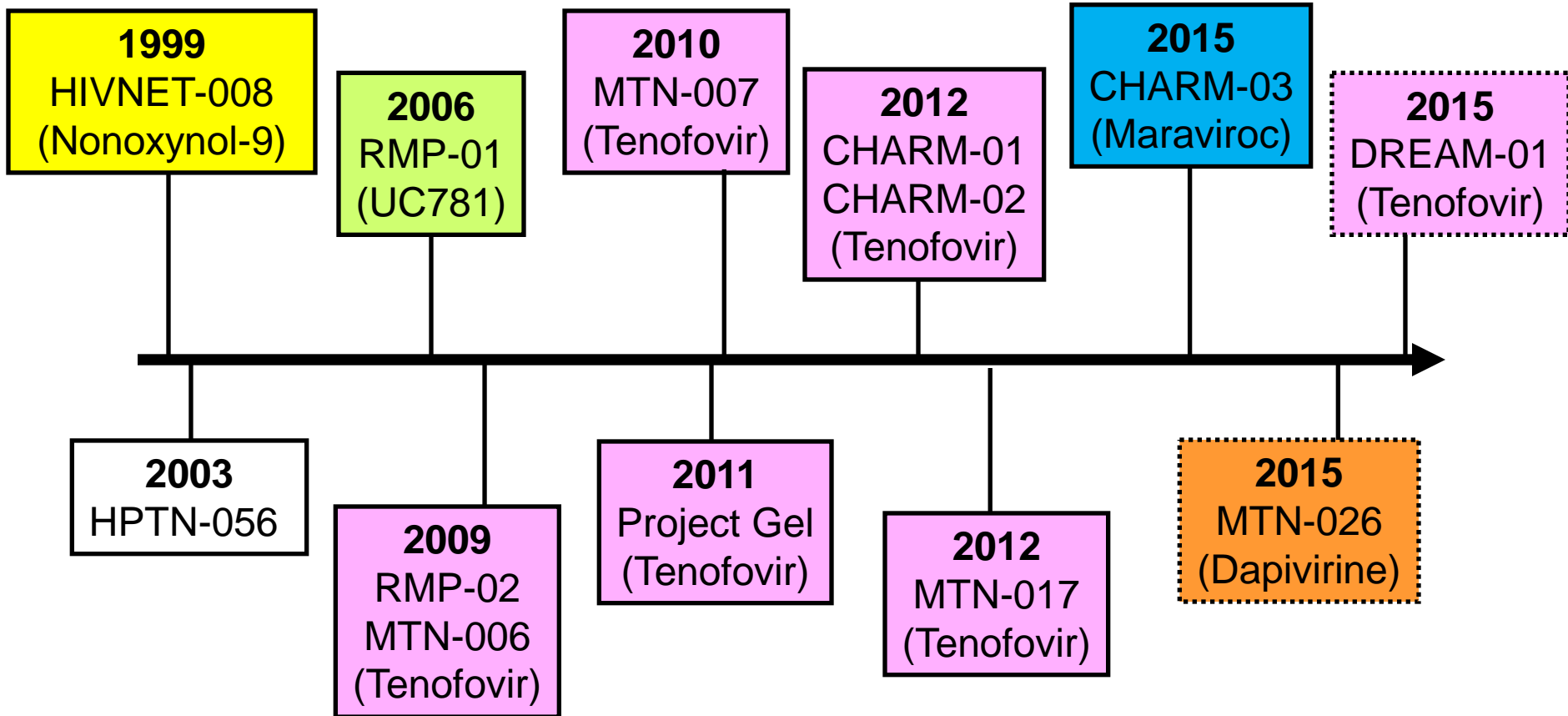
Overview

- A brief history of rectal microbicide research
- Integration of mucosal assays into rectal microbicide research
- Lessons learned about the performance and utility of mucosal assays in rectal microbicide trials



A Brief History of Rectal Microbicide Research

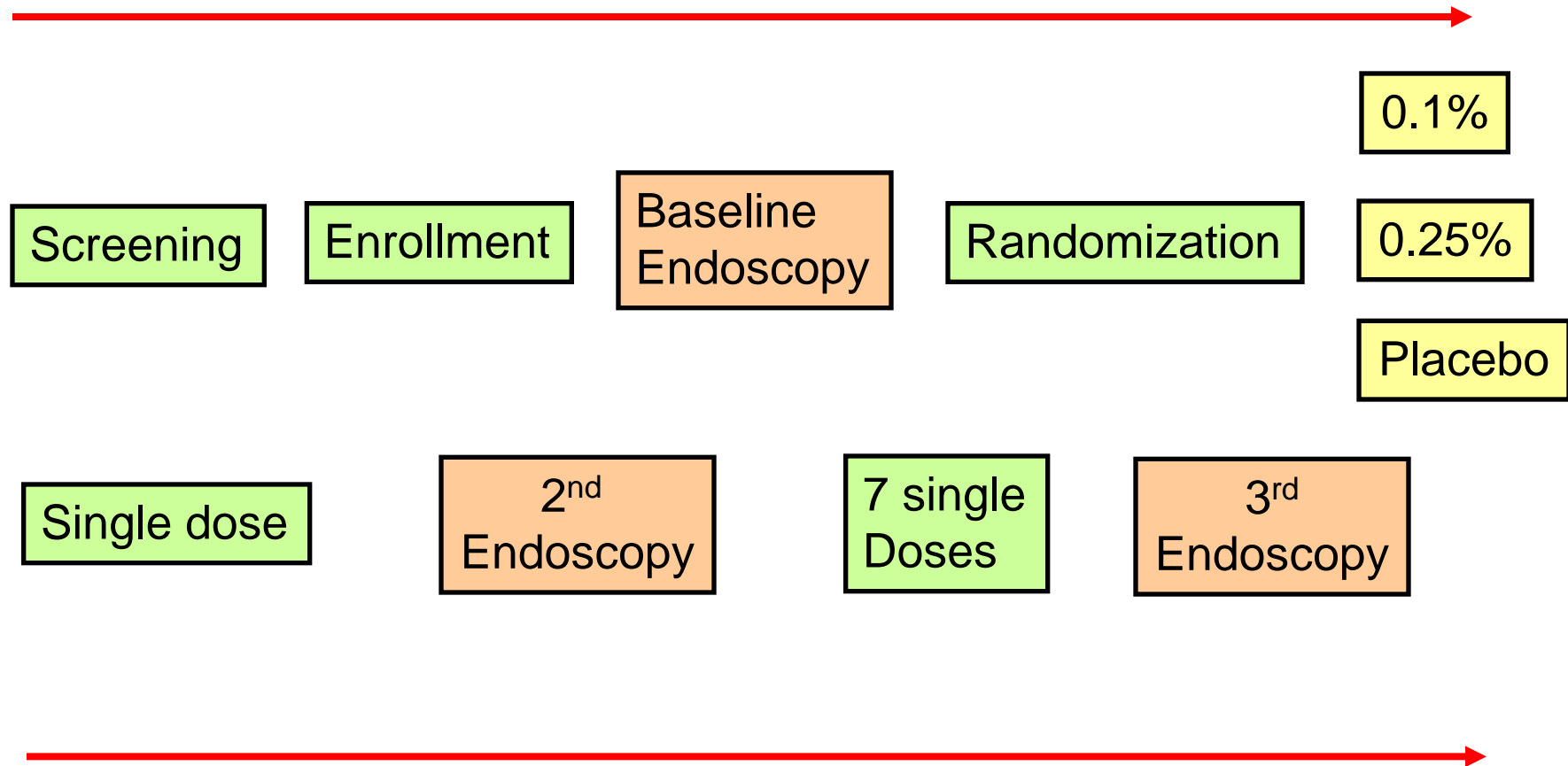
Rectal Microbicide Timeline



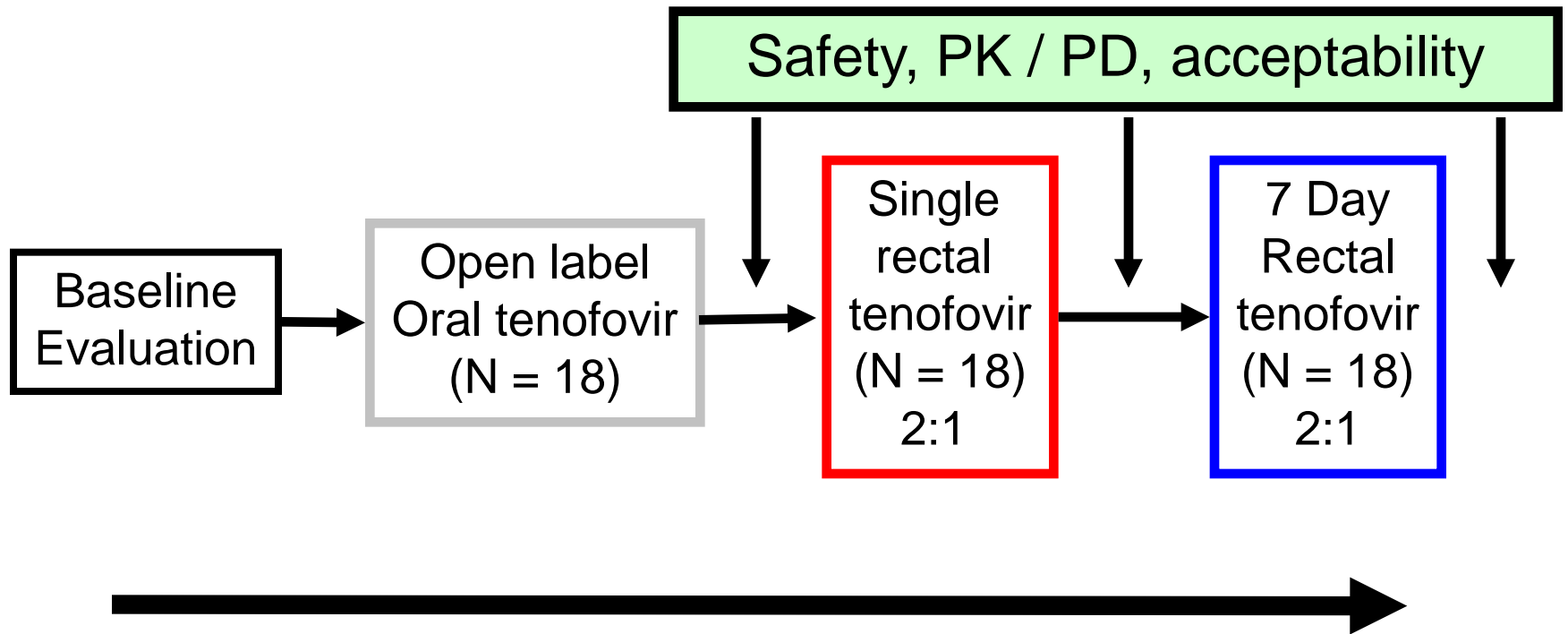
HIVNET-008

- Phase 1 evaluation of Advantage 24
 - 52.5 mg of N-9 in 1.5 ml of gel
- Conducted in Seattle during 1996 / 1997
- 35 seroconcordant sexually active couples
 - 25 HIV negative
 - 10 HIV positive
- Cohort dose escalation design
- Maximum exposure QD for five weeks + BID for one week
- Anal sex three times weekly

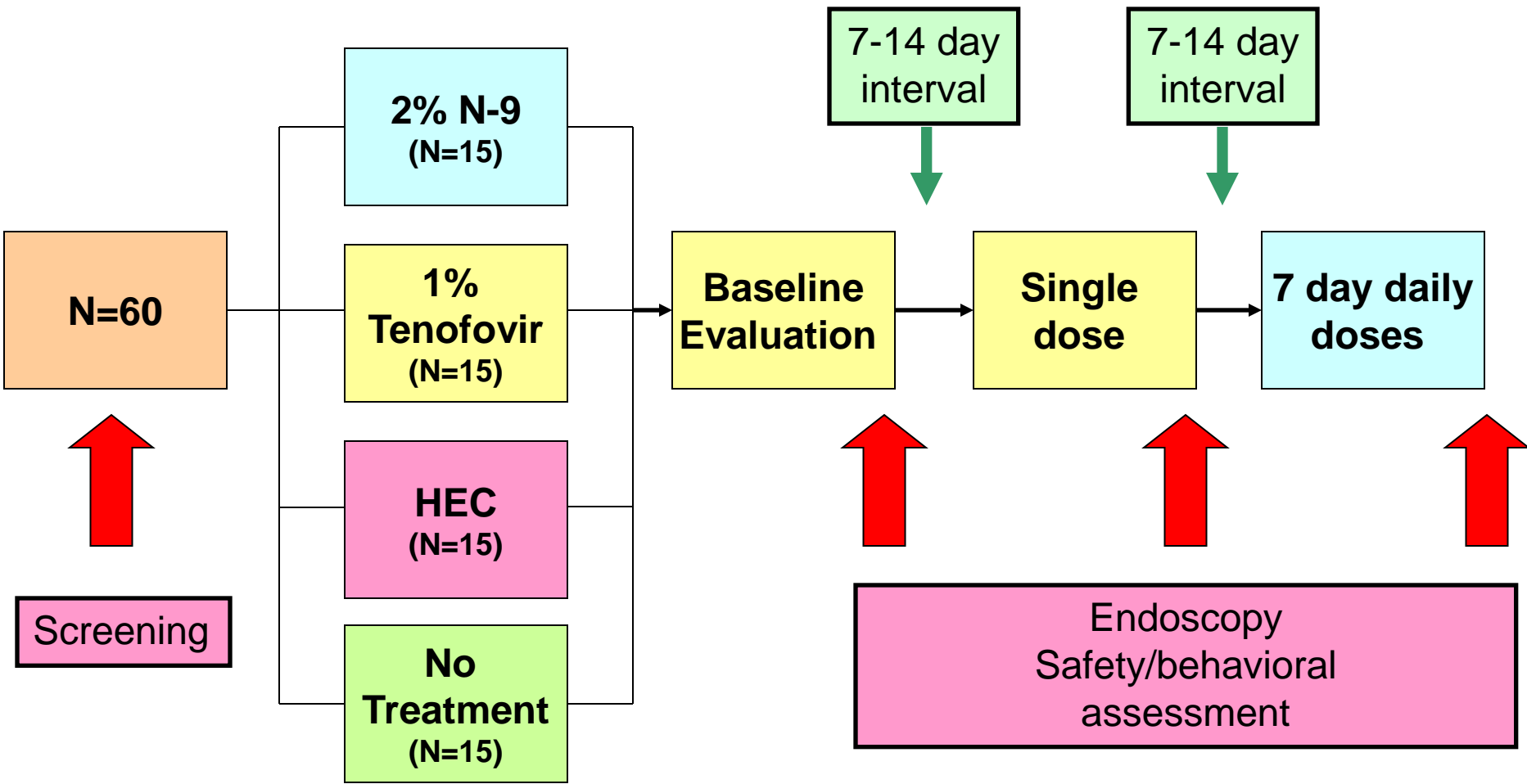
RMP-01 (UC781)



RMP-02/MTN-006



MTN-007



DAIDS Integrated Preclinical Clinical Program for HIV Topical Microbicides

- Microbicide Development Program
- CHARM Program
- Dual compartment Program
- DREAM Program
- PREVENT Program



MDP Program

- First IPCP focusing on rectal microbicide development
- Provided proof of concept in the SIV NHP model and development of explant platform
- Phase 1 clinical trials of the vaginal formulation of tenofovir gel
 - UC781 (RMP-01)
 - Tenofovir (RMP-02/MTN-006)
- Behavioral correlates of RAI



CHARM Program

- Combination HIV Antiretroviral Rectal Microbicide Program
- NIAID/DAIDS Integrated Preclinical Clinical Program
- Consortium
 - University of Pittsburgh
 - UCLA
 - Johns Hopkins
 - UNC
 - CONRAD / Gilead

CHARM-01

- Pre-Phase dose comparison of current formulations of tenofovir 1% gel
 - Vaginal formulation
 - Reduced glycerin formulation
 - Rectal specific formulation
- Endpoints
 - General and mucosal safety
 - PK/PD
- Current status
 - Completed



CHARM-02

- Pre-Phase 1 single dose comparison of current formulations of tenofovir 1% gel with and without simulated RAI
- Endpoints
 - Pharmacokinetics
 - Drug distribution using SPECT/CT imaging
- Current status
 - Completed

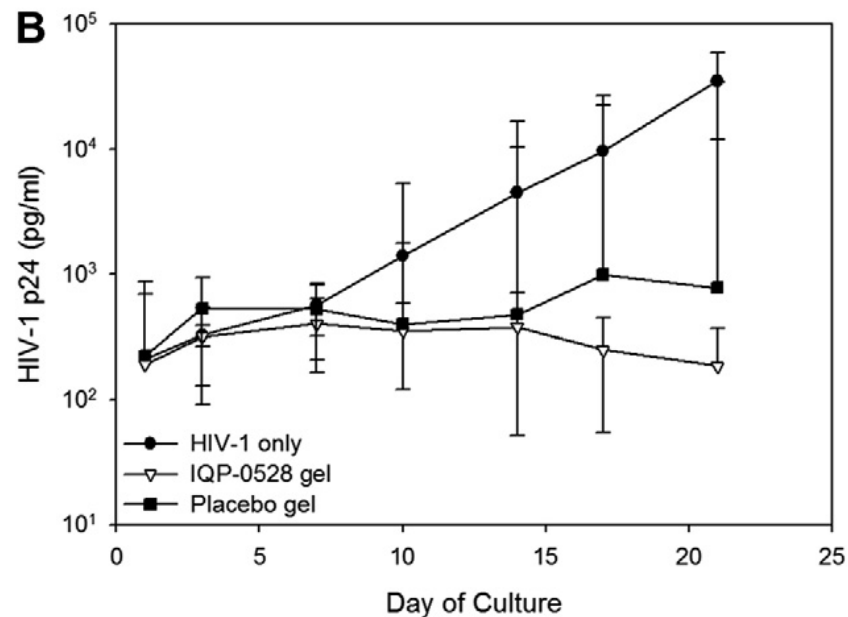


CHARM-03

- Pre-Phase 1 single dose comparison of oral and topical maraviroc
 - Rectal
 - Vaginal
- Endpoints
 - General and mucosal safety
 - PK/PD
- Current status
 - Enrolling

Dual Compartment Program

- Development and Evaluation of Dual Compartment Combination Microbicides
- Macaque, and human studies proposed
- Dual compartment and suppository formulations of IQP-0528 and tenofovir



PI: Robert Buckheit
Imquest Biosciences
Frederick, MD
Project start: June 2012
Project end: May 2017

DREAM Program

- **D**evelopment of **R**ectal **E**nama **A**s **M**icrobicide
- Murine, macaque, and three human studies proposed
- Candidates include
 - Tenofovir
 - TFV alafenamide fumarate
 - CMX157



PI: Craig Hendrix
Johns Hopkins University
Baltimore, MD
Project start: July 2014
Project end: June 2019

PREVENT Program

- Griffithsin-based Rectal Microbicides for **PRE**vention of **Viral ENT**ry
- To develop an antiviral lectin Griffithsin rectal gel
- Macaque, and one human study proposed



PI: Kenneth Palmer
University of Louisville
Louisville, KY
Project start: July 2014
Project end: June 2019

Project Gel



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projectgel

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or visit **www.microbicides.us**
for more information.



Microbicide Safety and Acceptability in Young Men



Project Gel

- NICHD R01
 - Pittsburgh, Boston, Puerto Rico
- Phase 1 safety and acceptability of tenofovir 1% gel
 - Ethnically diverse MSM (18-30)
 - Consensual RAI in last month
 - Unprotected RAI in last year

MTN-017

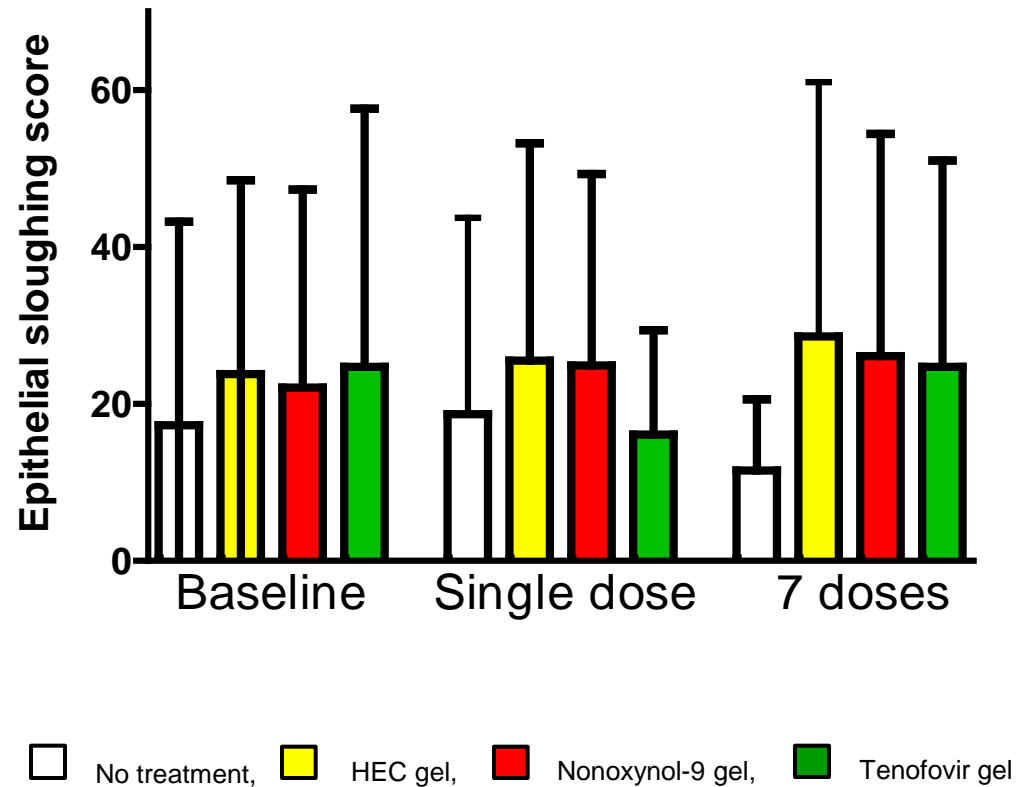
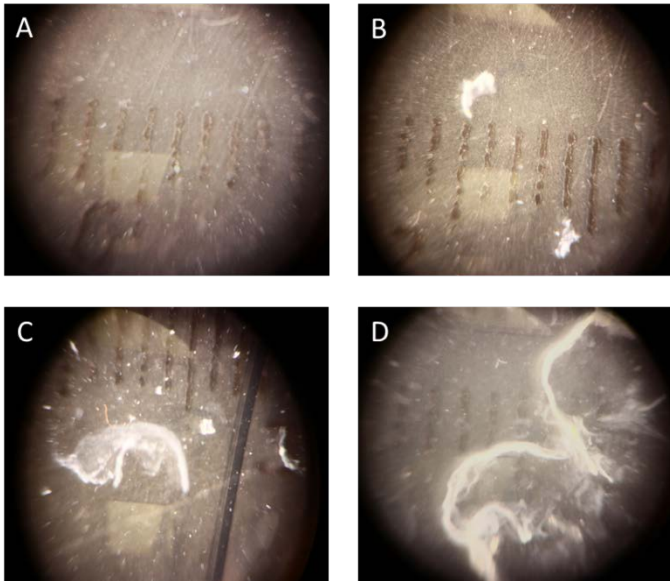


Integration of Mucosal Assays

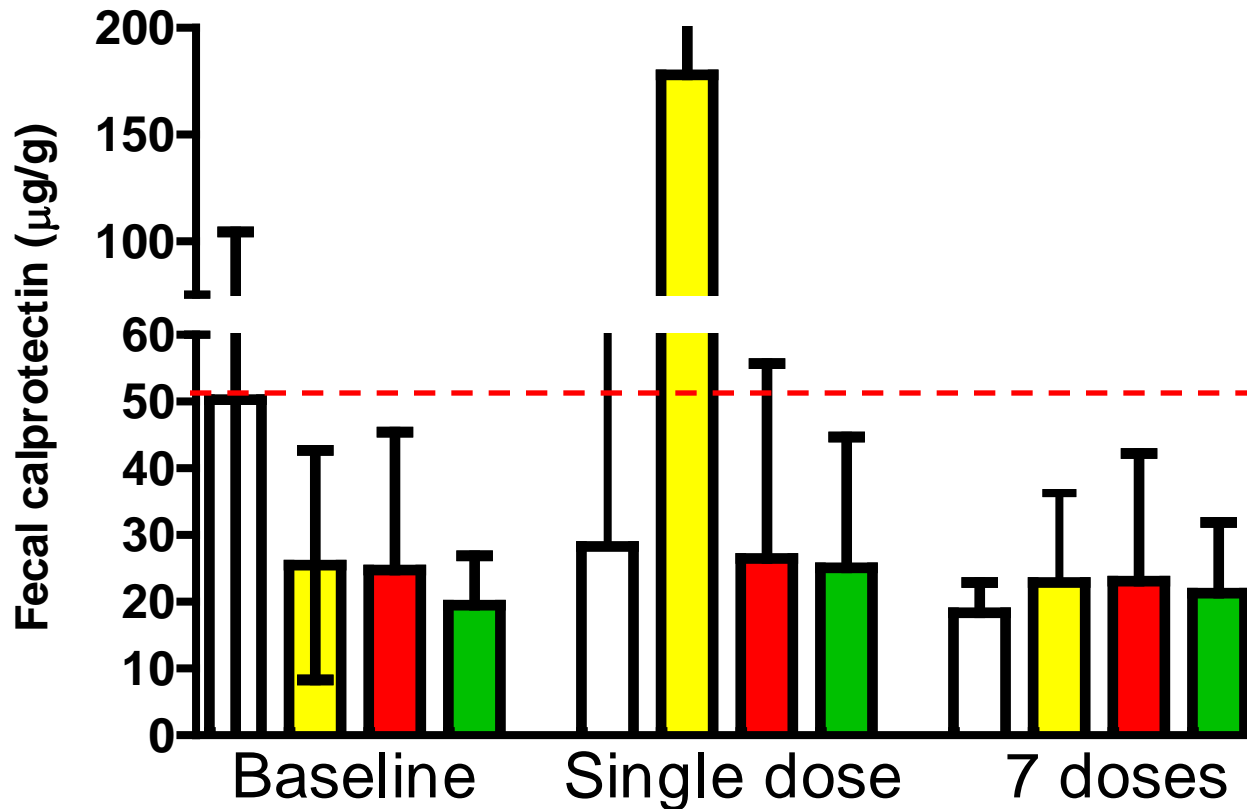
	HIV NET 008	RMP 01	RMP 02	MTN 007	Project Gel	MTN 017	CHARM 01	CHARM 03
Histology	X	X	X	X	X	X	X	X
Sloughing		X	X	X				
Immunoglobulins		X						
Microflora		X	X	X	X	X	X	X
Fecal calprotectin		X	X	X				
Cytokine (P)		X	X	X	X	X	X	X
Cytokine (GE)		X	X	X	X	X	X	X
GALT Flow		X	X	X	X	X	X	X
Tissue PK		X	X	X	X	X	X	X
Tissue PD		X	X	X	X	X	X	X
Transcriptomics				X	X	X	X	X
Proteomics				(X)	X	X	X	X

Lessons Learned

Epithelial Sloughing

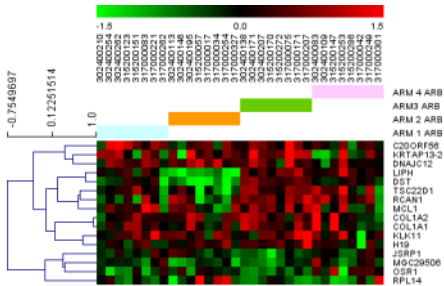


Fecal Calprotectin

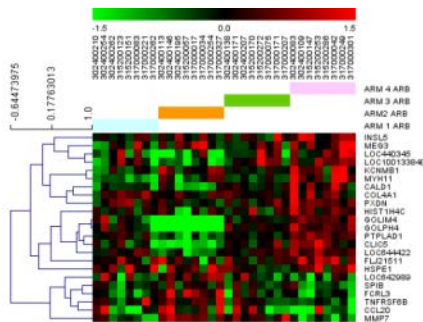


□ No treatment, ■ HEC gel, ■ Nonoxynol-9 gel, ■ Tenofovir gel

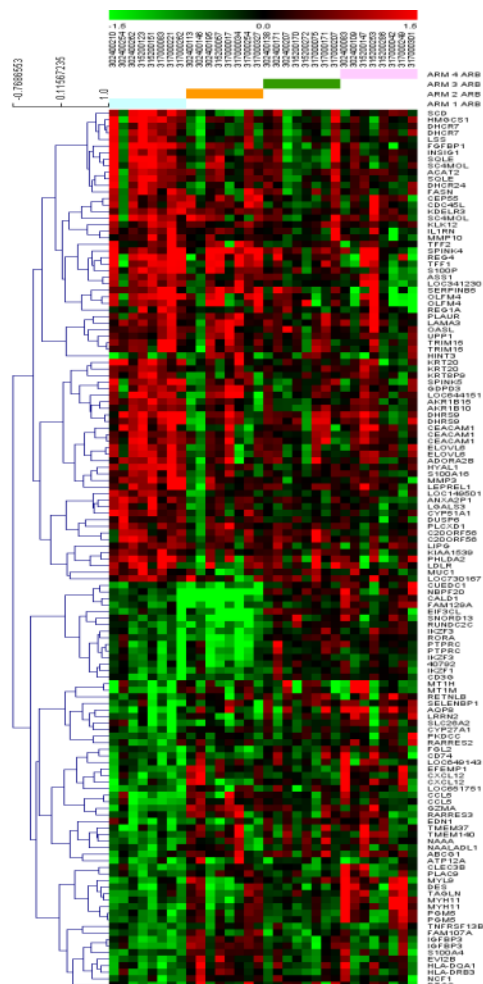
Microarray Data



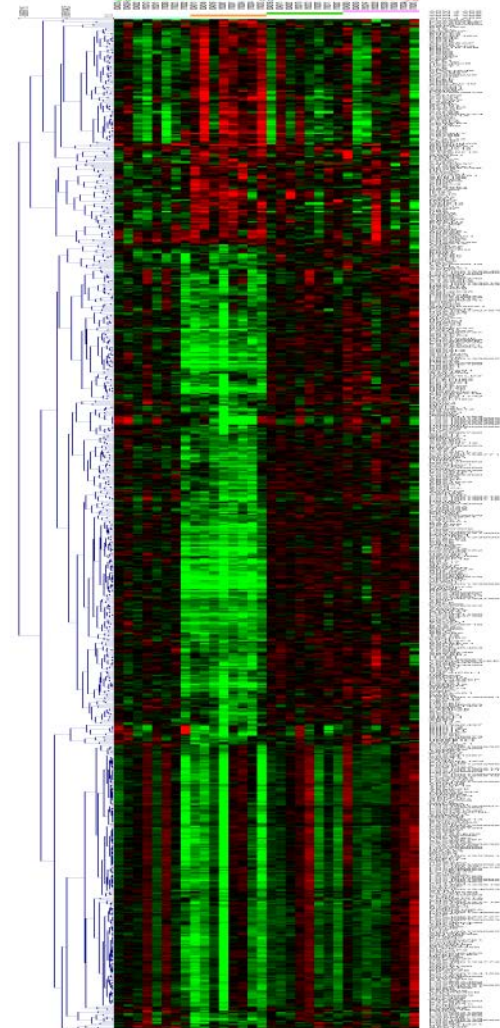
No Treatment



HEC placebo gel



Nonoxynol-9 gel



Tenofovir gel



Summary

- Rectal microbicides have moved from preclinical to Phase 2 clinical evaluation
- The current design of rectal microbicide Phase 1/2 trials commonly includes
 - Mucosal safety assays
 - Compartmental PK
 - Intestinal explant PD
- New assays under evaluation include transcriptomic and proteomic platforms

Acknowledgements

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