MTN
microbicide trials network

Rectal Microbicides

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Questions About Rectal Microbicides

- Are they needed?
- Would anyone use them?
- Would they work?
- Where is the science?
- How would they fit into the HIV prevention landscape?

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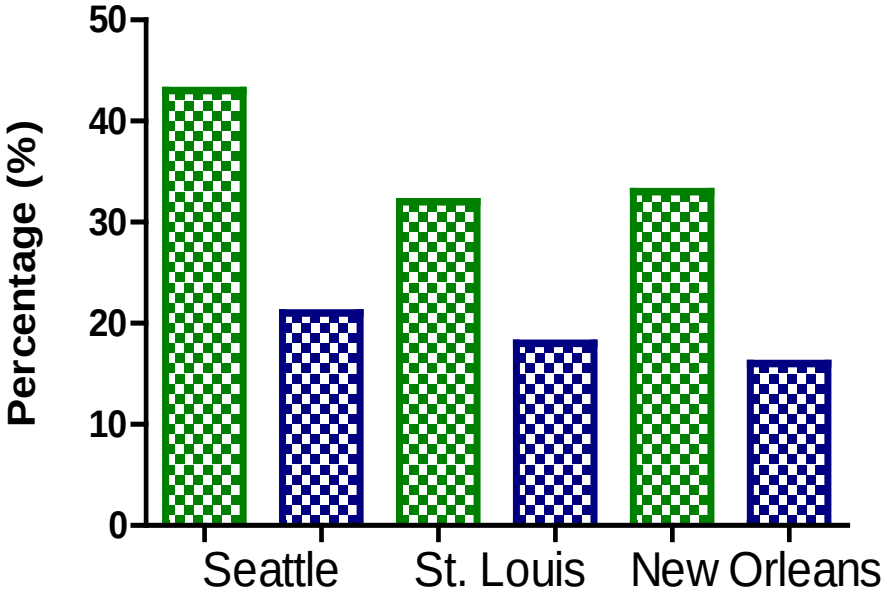
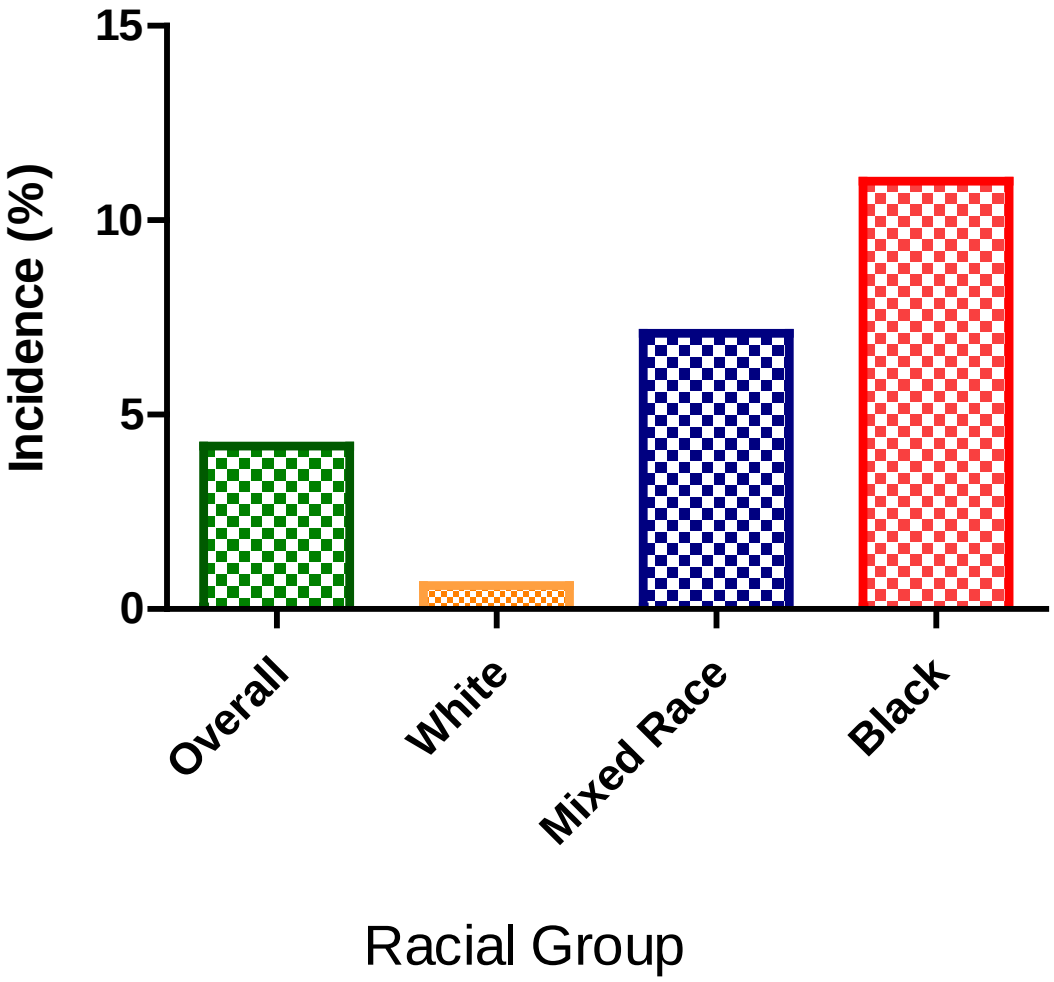
Are Rectal Microbicides Needed?



PROJECT ARM

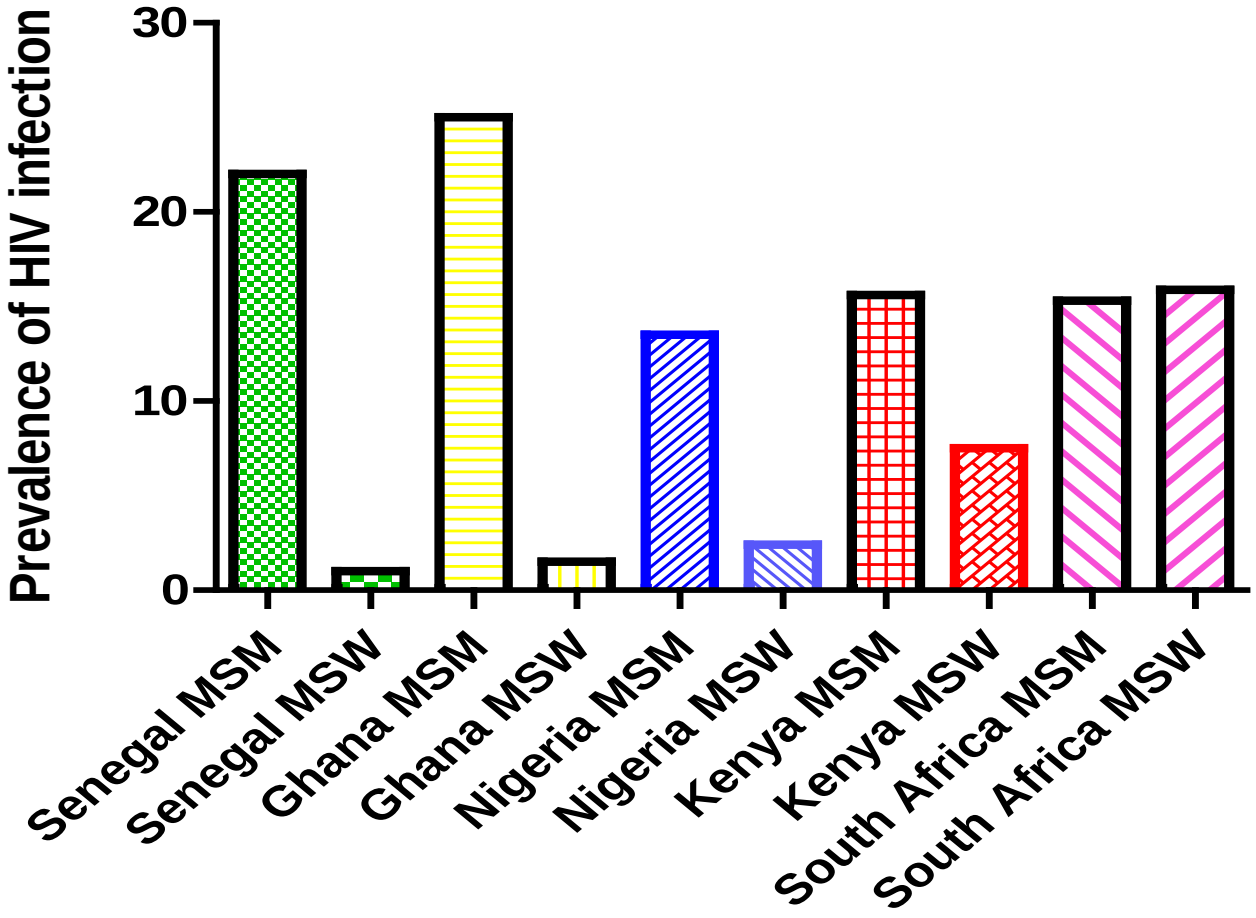
AFRICA FOR RECTAL MICROBICIDES

US HIV Incidence in MSM



Sifakis F et al. JAIDS 2007

HIV Prevalence in African MSM



Beyrer Lancet 2012

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Would Anyone Use a Rectal Microbicide?

Lubricant Use is Common Among MSM

Carballo-Dieguez et al. *Am J Pub Health* 2000

Potential Rectal Microbicide Use

- Prevention preparedness studies
  - *Gross et al. Sex Transm Dis* 1998
- Conjoint analysis in Peruvian MSM
  - Kinsler et al. *Int J STD AIDS* 2010
- Community advocacy
  - International Rectal Microbicide Advocates
  - 1,100 advocates on six continents
  - http://www.rectalmicrobicides.org/

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Would Rectal Microbicides Work?

Non Human Primate Studies

- Cyanovirin-N / SHIV89.6P
  - Tsai et al. *AIDS Res Hum Retroviruses* 2003
- Tenofovir / SIVmac251/32H
  - Cranage M et al. *PLoS Med* 2008
- MIV-150 / SIVmac239
  - Singer R et al. *J Virol* 2011

Rectal Macaque Tenofovir Data

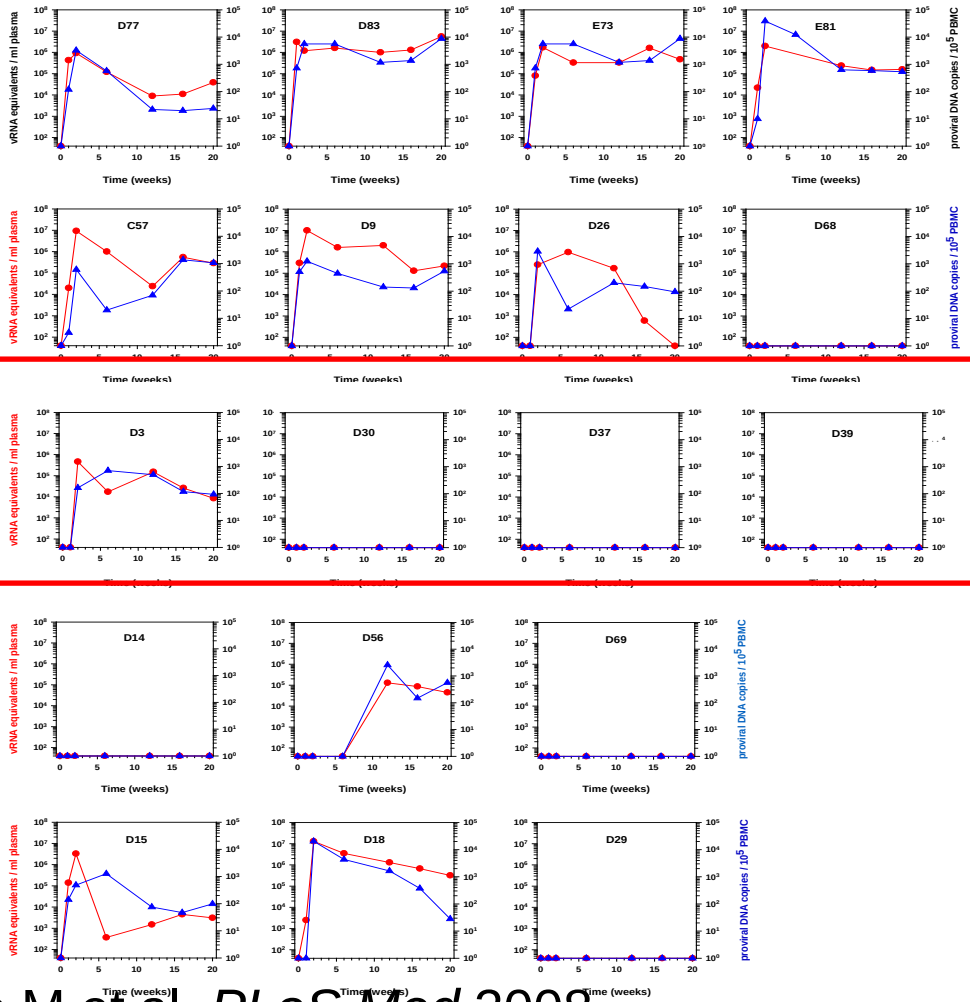
No Rx

Placebo
-15 min

PMPA
-15 min

PMPA
-2 hrs

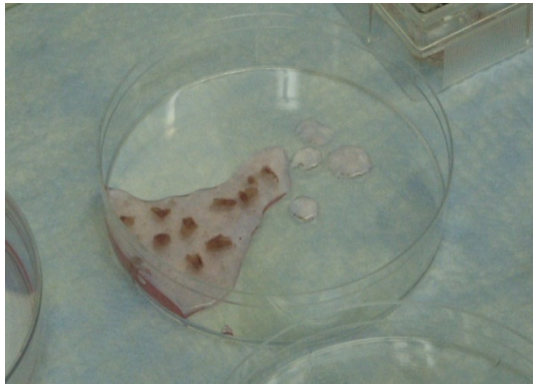
PMPA
+ 2 Hrs



- Proviral DNA
- Viral RNA

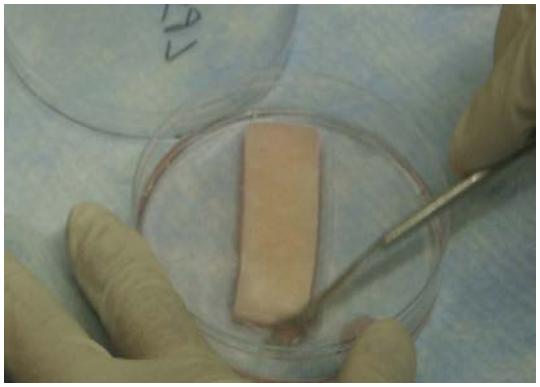
Cranage M et al. *PLoS Med* 2008

Colorectal Intestinal Explants

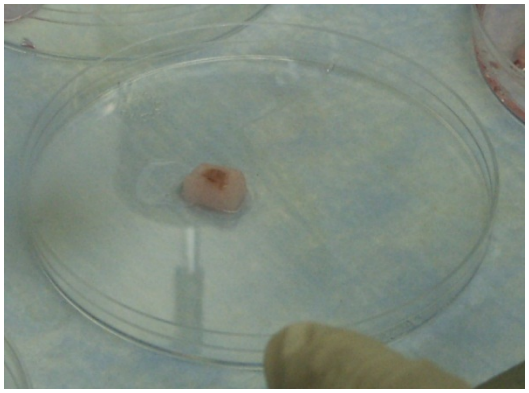


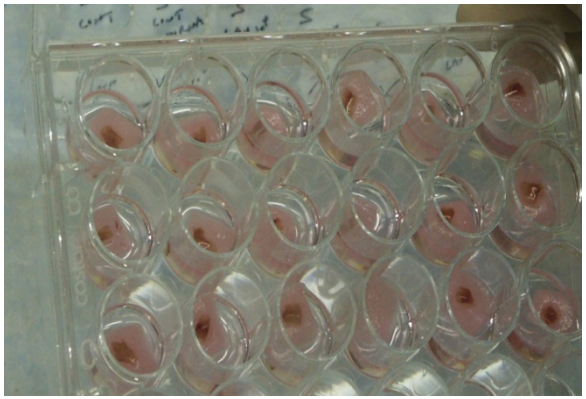
Endoscopic biopsies

+



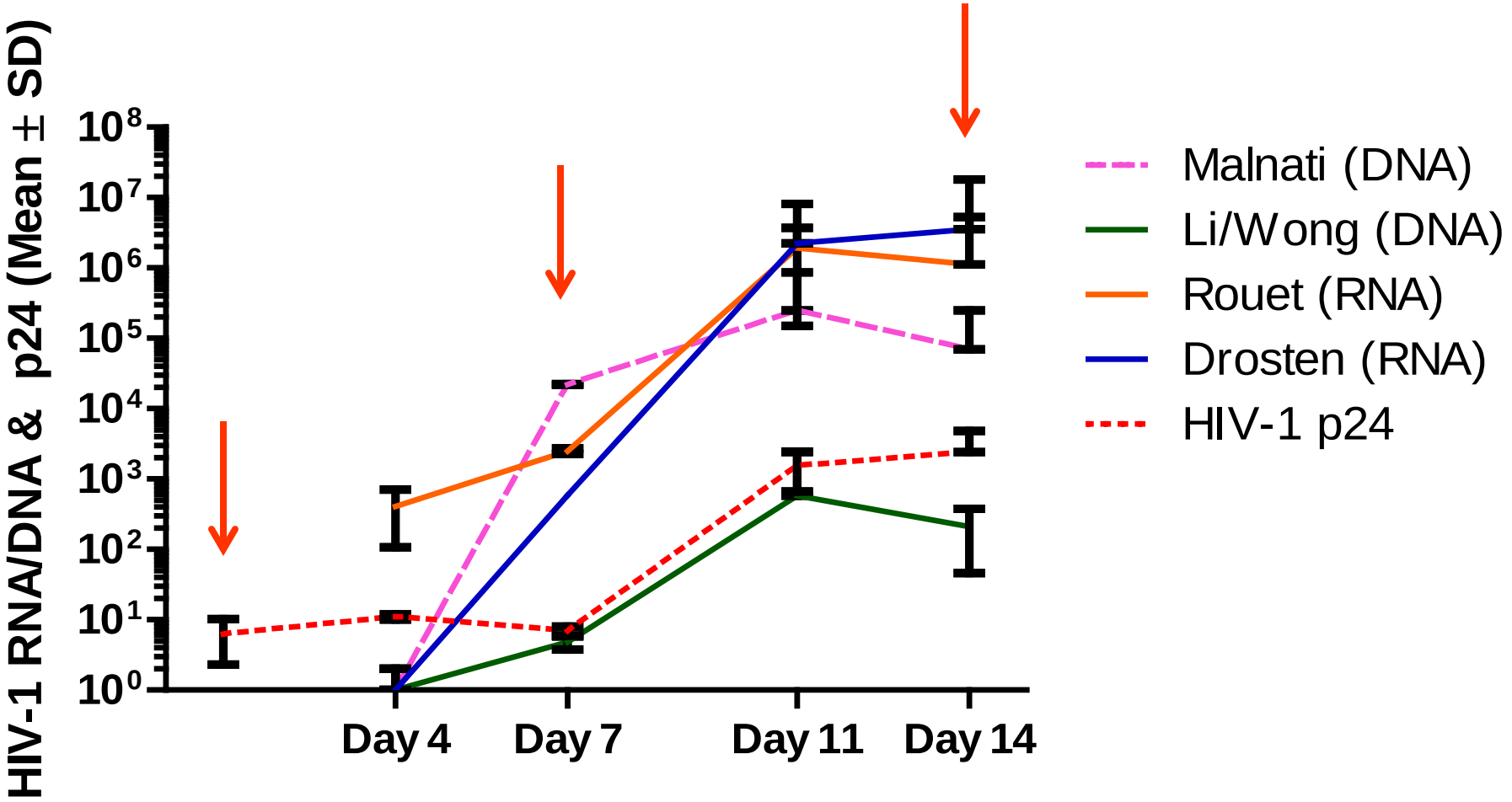
Absorbable gelatin sponge



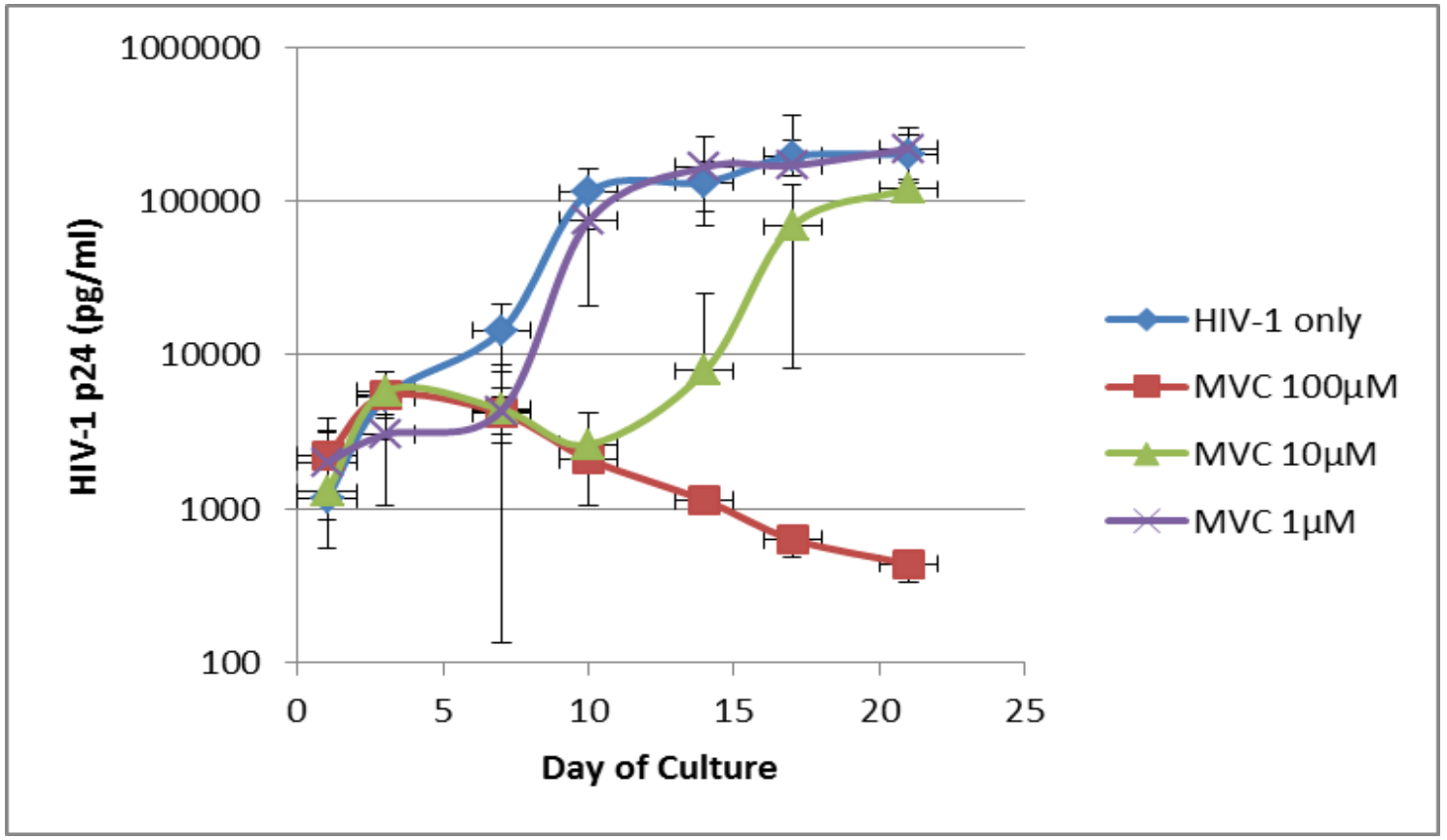


Abner SR et al. JID 2005, Watts P et al. AIDS 2006

Colorectal Explant Infection

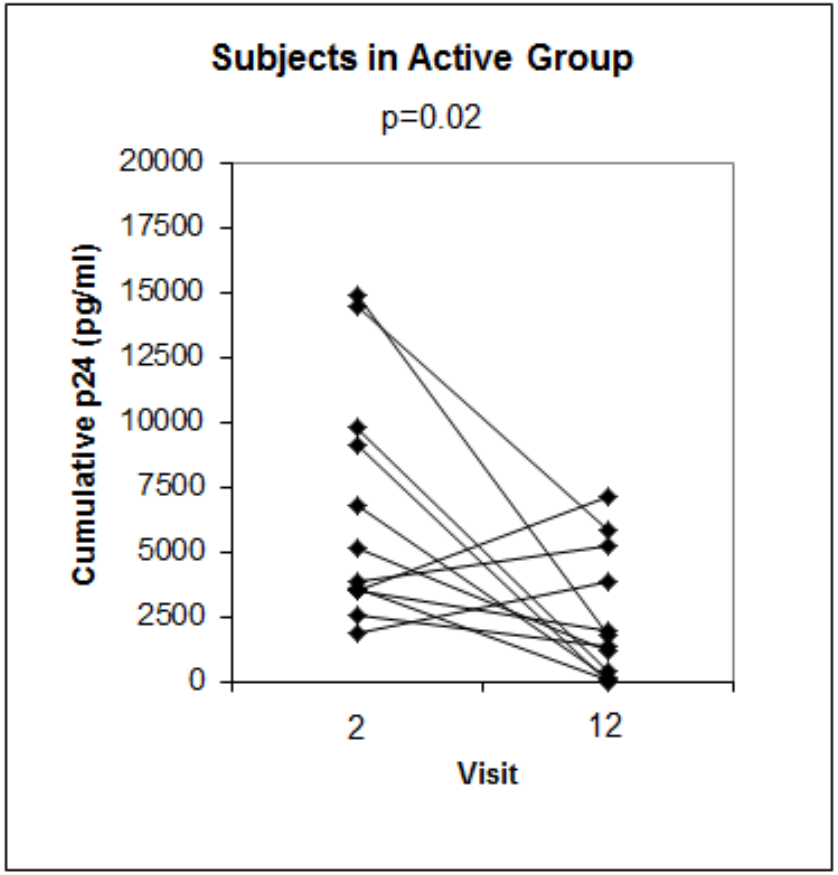


Maraviroc *In Vitro* Colorectal Explant Efficacy Data



Dezzutti et al. CHARM Project 1

Ex vivo / In Vitro Challenge Model



Tenofovir: Anton et al. *AIDS Res Hum Res* 2012

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Where is the Science?

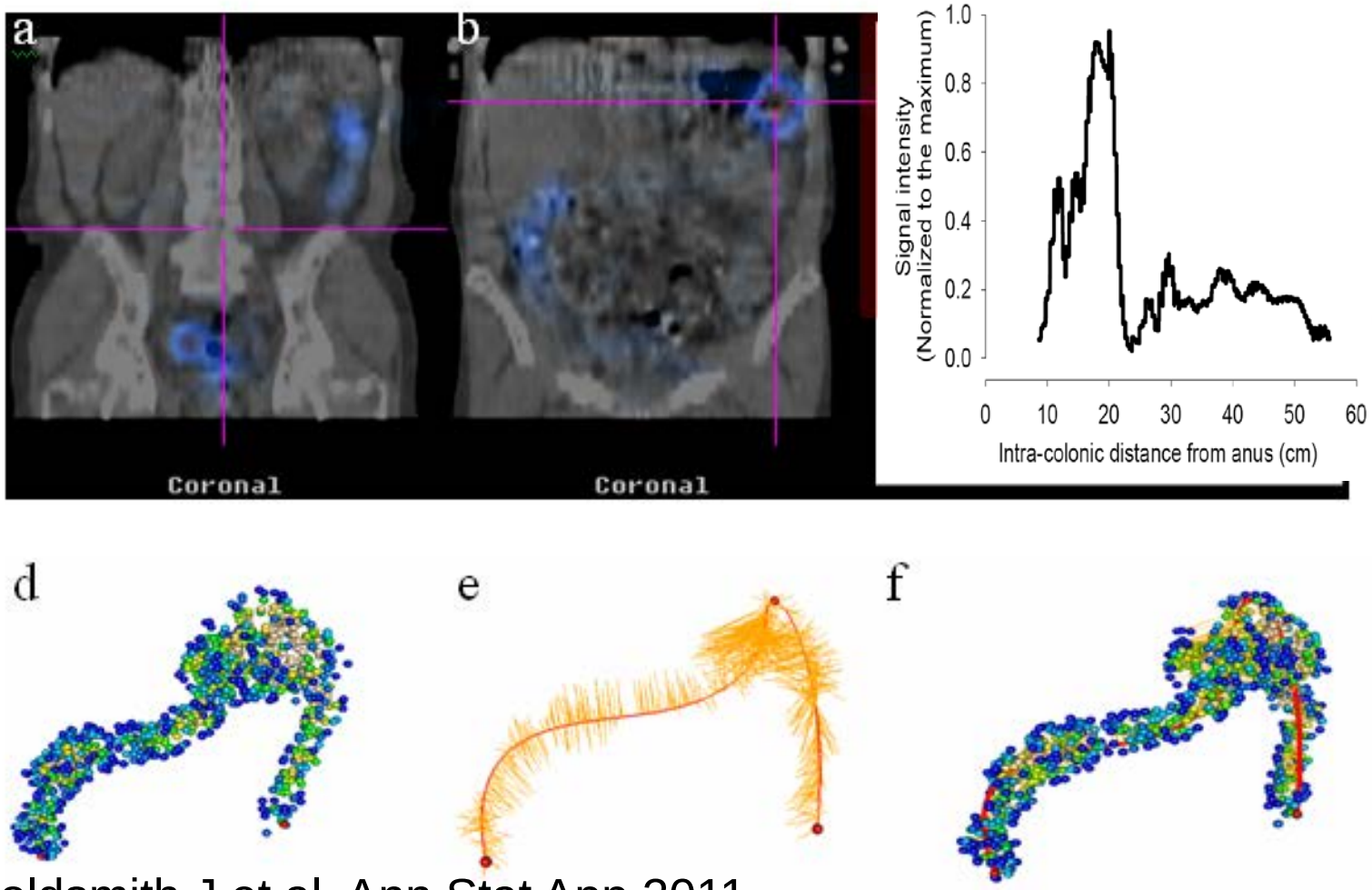
Preclinical Development

- *In vitro* assessment of safety and efficacy
  - TZM-bl & PBMC
  - Explants
- Animal models of safety and efficacy
  - Humanized mice
  - Non-human primates
- Preclinical toxicology
  - Rabbits
  - Rats

Formulation Studies

- Formulation preference: gel and suppository
  - Carballo-Dieguez et al. *Sex Transm Infect* 2008
- Formulation volume
  - Carballo-Dieguez et al. *Sex Transm Dis* 2007
- Rectal specific formulation development and assessment
  - Wang et al. *AIDS Res Ther* 2011

Product Distribution



Goldsmith J et al. Ann Stat App 2011

Phase 1 Development

- Nonoxynol-9 (HIVNET-008 study)
  - Tabet et al. *Sex Transm Infect* 1999
- UC781 (RMP-01 study)
  - Anton et al. *PLoS ONE* 2011
- Tenofovir (original formulation) (RMP-02/MTN-006 study)
  - Anton et al. *AIDS Res Hum Res* 2012
- Tenofovir (reduced glycerin formulation) MTN-007
  - McGowan et al. CROI 2012

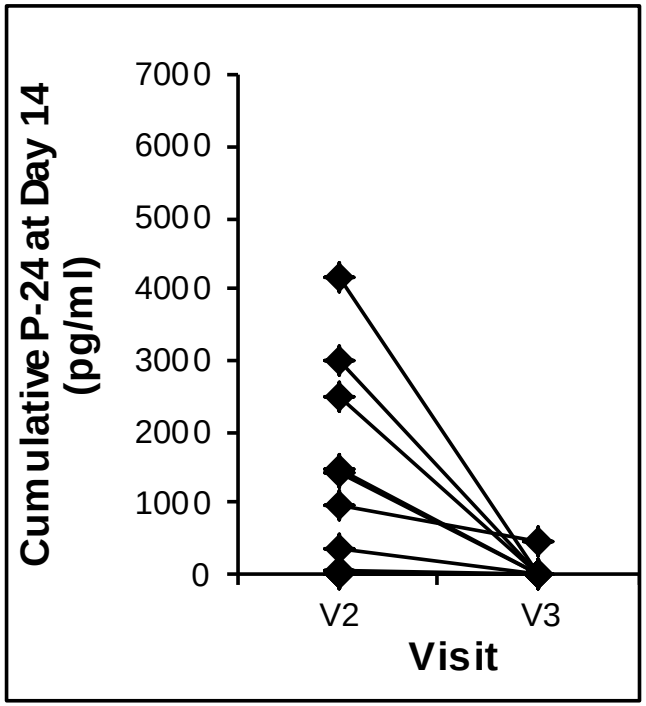
Key Findings from HIVNET-008

- Low-dose (52.5 mg/ml) N-9 was not associated with macroscopic rectal ulceration
- GI symptoms such as rectal fullness common after exposure to placebo and N-9
- High rates of histological abnormality after placebo and N-9 gels
- N-9 acceptability inconclusive and warranted further study of redesigned applicators and ways to minimize rectal side effects.

Gross M et al. Sex Trans Dis 1999

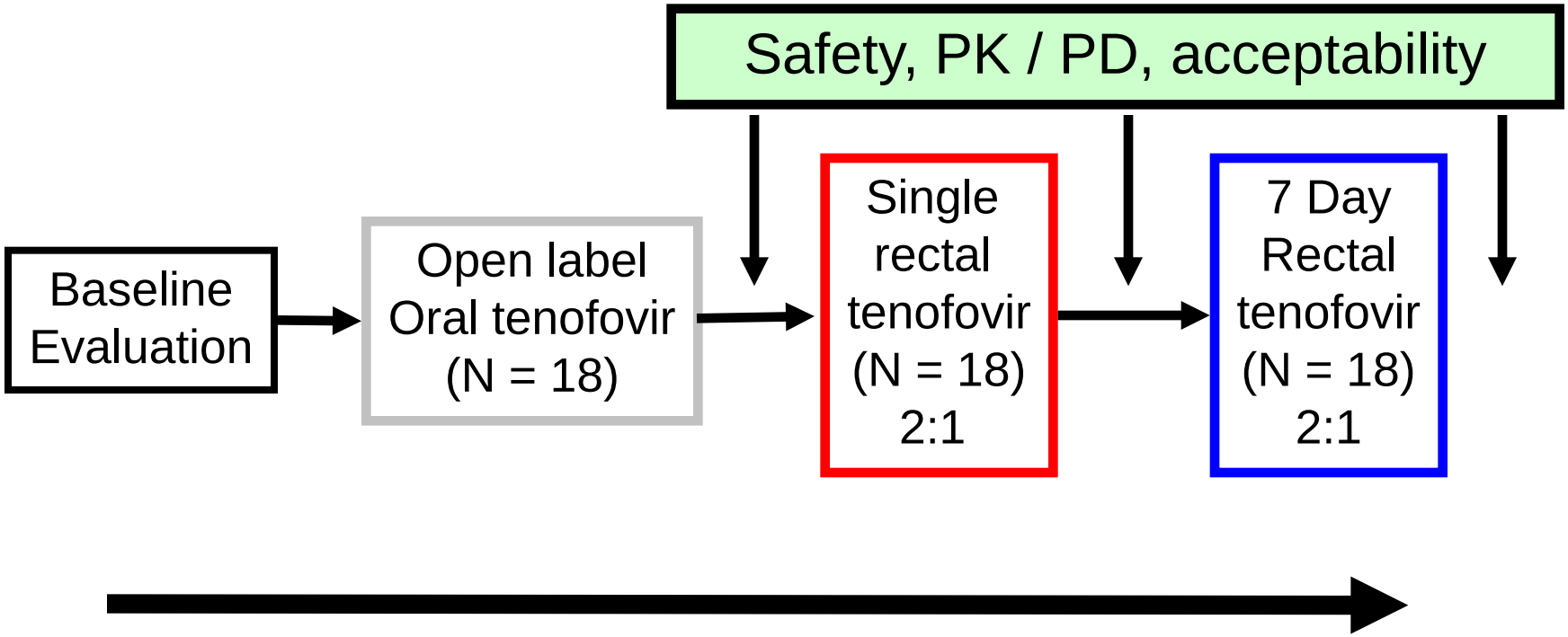
UC781 (RMP-01)

- Phase 1 study
- NNRTI
- Single & 7 day exposure
- Safe and acceptable
- Significant viral suppression in explant challenge



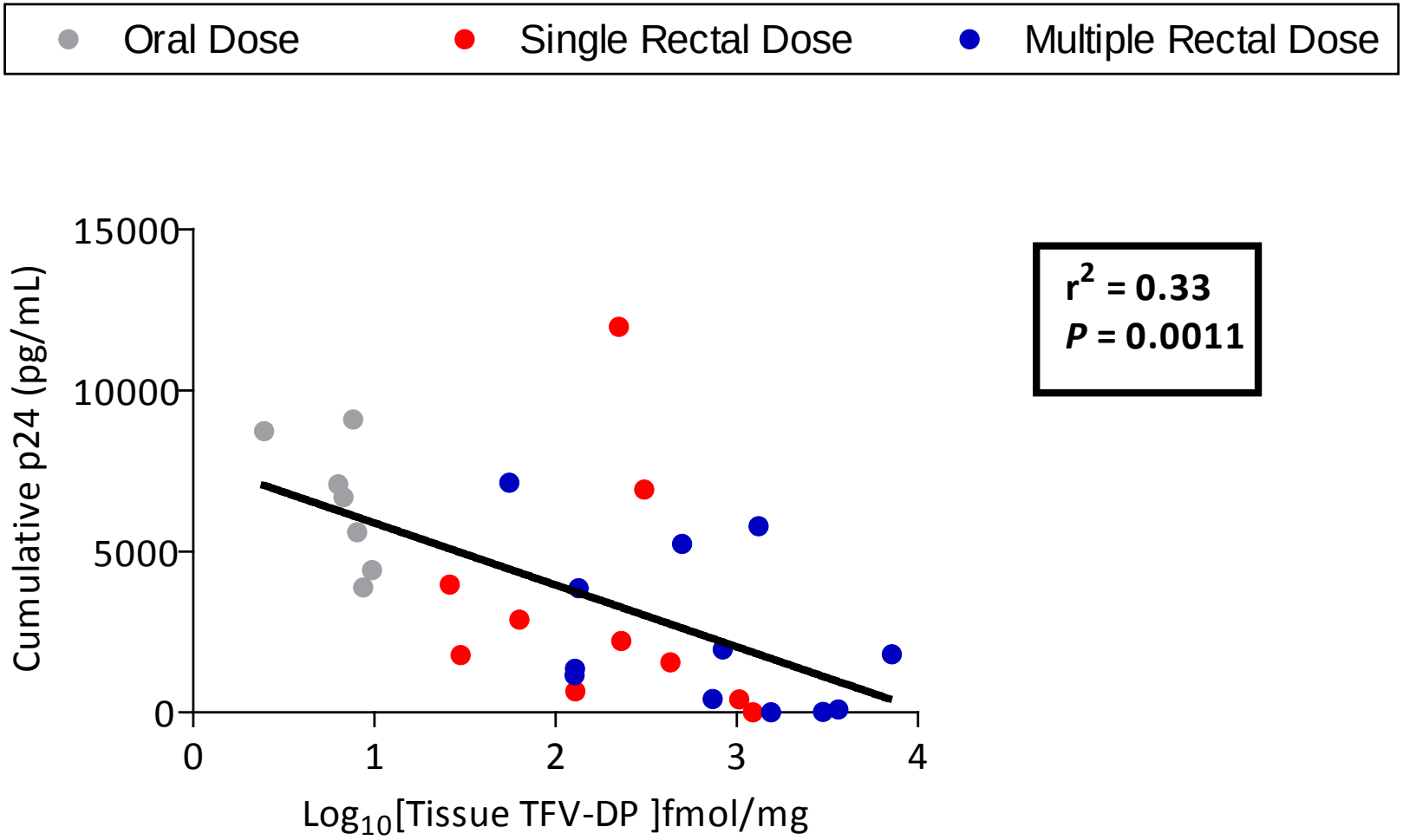
Anton et al. *PLoS ONE* 2011

RMP-02/MTN-006



Anton PA et al. CROI 2011

PK/PD Relationship

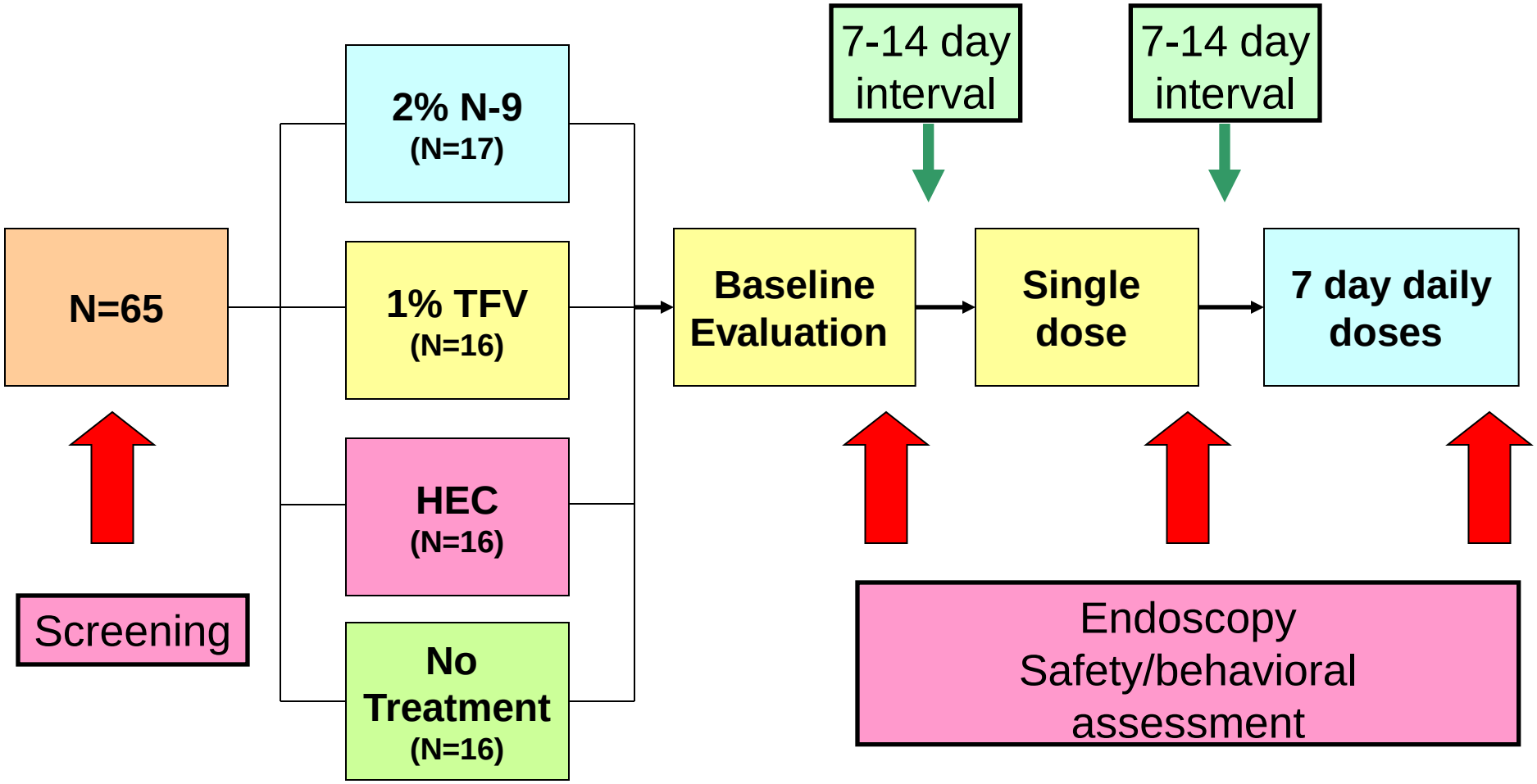


Anton et al. *AIDS Res Hum Res* 2012

Phase 1 GI Adverse Events

GI Adverse Events in the Tenofovir Arm			RMP-02/MTN-006 (N = 12)	
			N	%
Abdominal pain			6	50%
Rectal urgency			5	42%
Bloating			5	42%
Nausea			4	33%
Diarrhea			7	58%
Flatulence			3	25%
Proctalgia			0	0%
Other			5	42%
Total			**12**	**100%**

MTN-007

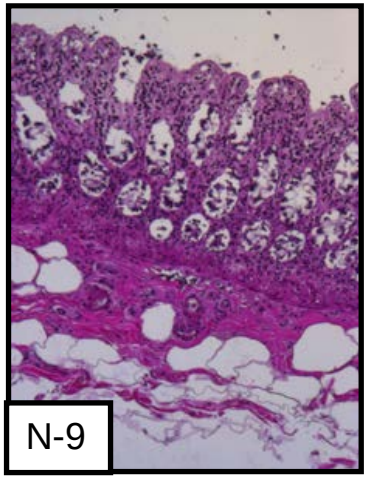

7-14 day interval
7-14 day interval
2% N-9 (N=17)
1% TFV (N=16)
HEC (N=16)
No Treatment (N=16)
N=65
Baseline Evaluation
Single dose
7 day daily doses
Screening
Endoscopy
Safety/behavioral assessment

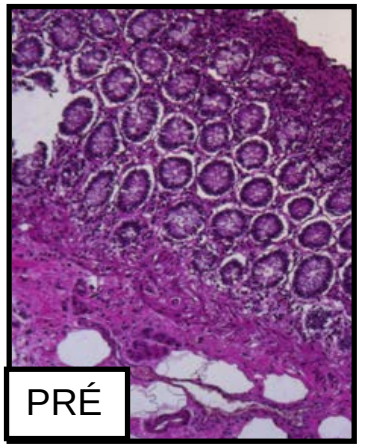
Phase 1 GI Adverse Events

GI Adverse Events in the Tenofovir Arm	MTN-007 (N = 16)		RMP-02/MTN-006 (N = 12)	
			N	%
Abdominal pain	3	16%	6	50%
Rectal urgency	0	0%	5	42%
Bloating	0	0%	5	42%
Nausea	0	0%	4	33%
Diarrhea	1	6%	7	58%
Flatulence	6	38%	3	25%
Proctalgia	1	6%	0	0%
Other	4	25%	5	42%
Total	**9**	**56%**	**12**	**100%**

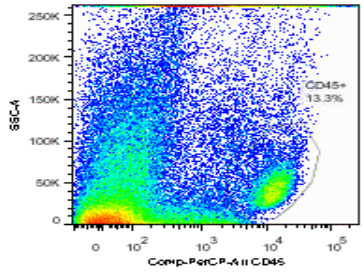
Mucosal Safety Endpoints

- Epithelial sloughing
- Histopathology
- Mucosal mononuclear cell phenotype
- Mucosal cytokine mRNA
- Luminex
- Microarray gene expression
- Fecal calprotectin
- Rectal microflora

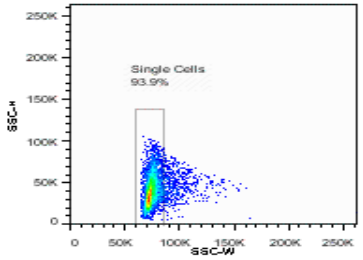




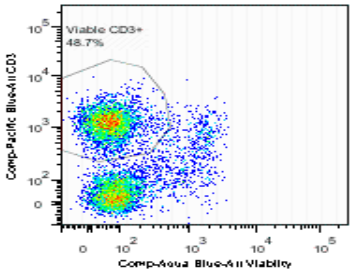
MTN-007 Gut T Cell Phenotype



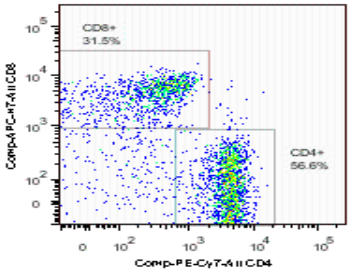
CD45+ COMMON ANTIGEN LEUKOCYTE



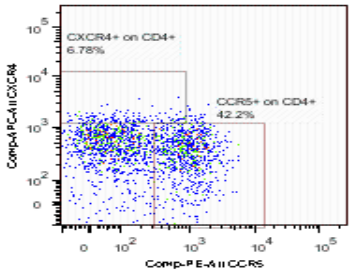
SINGLE CELL POPULATION OF THE CD45+



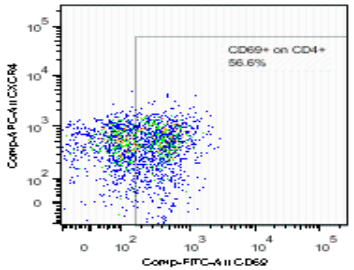
LIVE CD3+ CELL OF THE SINGLE CELLS



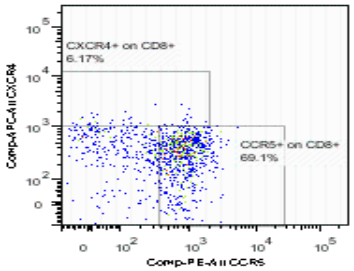
CD4+ /CD8+ OF THE LIVE CD3+ CELLS



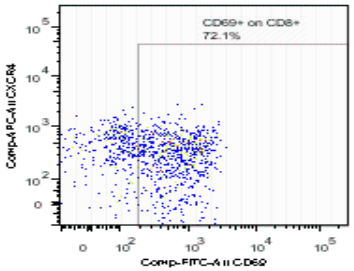
CXCR4+ & CCR5+ ON CD4+



CD69+ ON CD4+

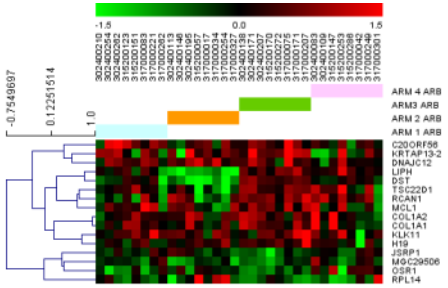


CXCR4+ & CCR5+ ON CD8+

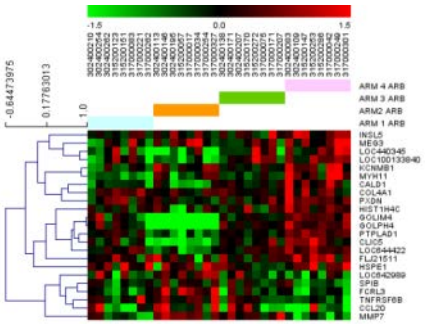


CD69+ ON CD4+

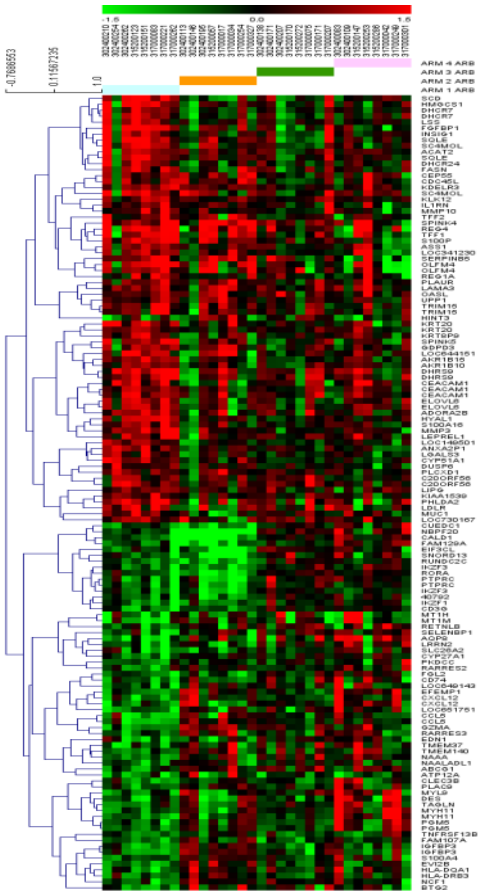
MTN-007 Microarray Data



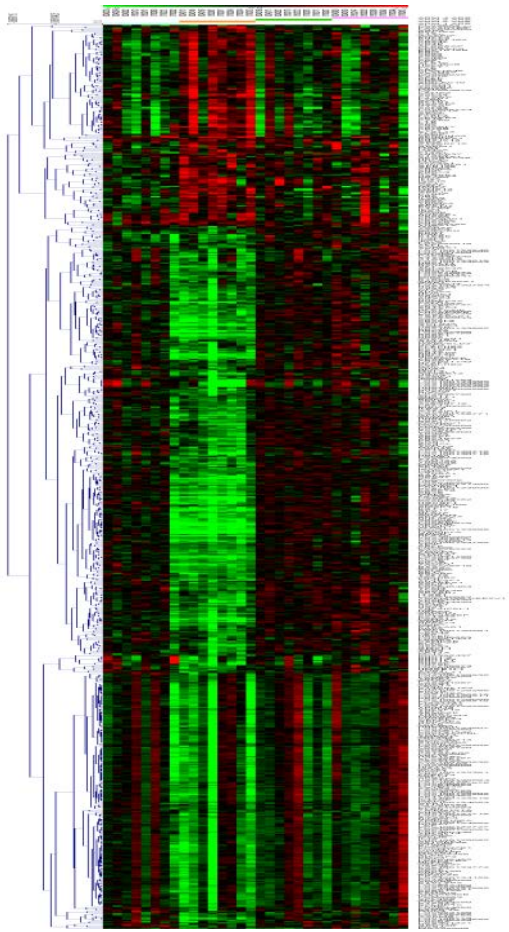
No Treatment



HEC placebo gel



Nonoxynol-9 gel



Tenofovir gel

MTN-007 Microarray Data

	Up	Down
N9	60	56
Tenofovir	138	490
HEC	12	4
No Rx	17	6

- Significant modulation of mucosal gene expression after 7 days of TFV gel
- Key pathways effected:
  - Mitochondrial function ↓
  - Innate immunity ↑

Florian Hladik, University of Washington

Phase 2: MTN-017

- Phase 2 rectal safety study of tenofovir gel
- N = 186
- International sites
  - United States (4)
  - Thailand (2)
  - South Africa (1)
  - Peru (1)
- Endpoints
  - Safety
  - Adherence
    - Self report
    - Objective measures
  - Acceptability
  - PK/PD

PI: Ross Cranston

MTN-017

	8 weeks		8 weeks		8 weeks	
BL	TNF Gel Daily		TNF Gel With sex		Oral Truvada	
BL	TNF Gel With sex		TNF Gel Daily		Oral Truvada	
BL	Oral Truvada		TNF Gel With sex		TNF Gel Daily	

Mucosal PK/PD subset (N = 36)

Phase 3 Development

- Contingent upon supportive data from MTN-017
- Placebo controlled trial of RG-TFV gel on expanded prevention package including oral PrEP
- N = 5,000 MSM & transgender women
- One year follow-up period
- US, Latin America, and Thailand

CHARM U19 Program Grant

- Combination HIV Antiretroviral Rectal Microbicide Program
  - Preclinical evaluation
  - Humanized mouse model
  - Phase 1 studies
    - CHARM-01 (TFV)
    - CHARM-02 (TFV)
    - CHARM-03 (MVC)

PI: Ian McGowan

Project Gel


GUYS EXPERIENCING LUBE
projectgel
IS NOW ENROLLING
Call 412.641.3380
or visit www.microbicides.us
for more information.

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 Tenofovir rectal safety study

24 MSM

PI: McGowan

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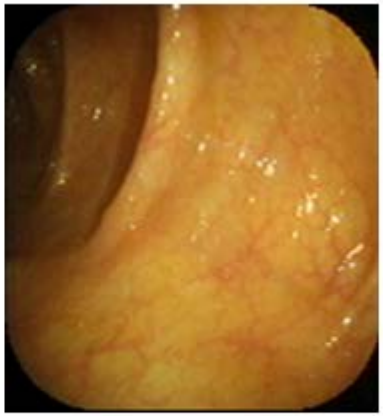
Where Do Rectal Microbicides Fit in the HIV Prevention Landscape?

Combination Prevention

Conventional HIV Prevention Package + PrEP






SC ± Oral ± Rectal ± Vaginal

± HIV Vaccine

Rectal Microbicide Timeline*

	2010	2011	2012	2013	2014	2015	2016	2017	2018
Phase 1	→	→							
Phase 2			→	→					
Phase3						→	→		
Review								→	
Available									→
Vaginal microbicides						?			

*An approximation based on tenofovir 1% gel

Summary

- There is a clear rationale for the development of rectal microbicides
- The design of rectal safety studies includes extensive mucosal immunotoxicity, PK, and PD assays
- Rectal specific products and applicators are being developed
- It is time to move to start preparing for efficacy studies

Acknowledgements

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