

Characterization of Mucosal Safety and Efficacy in Phase 1 Rectal Microbicide Studies

Ian McGowan MD PhD FRCP

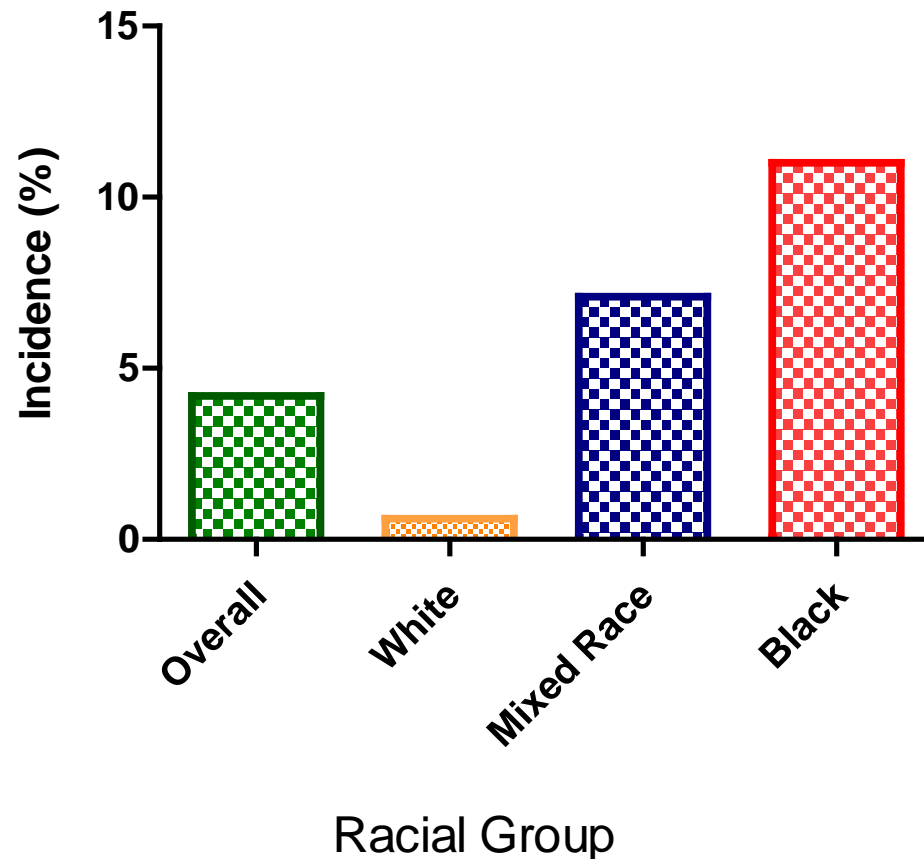
MTN Annual Meeting

Arlington, VA

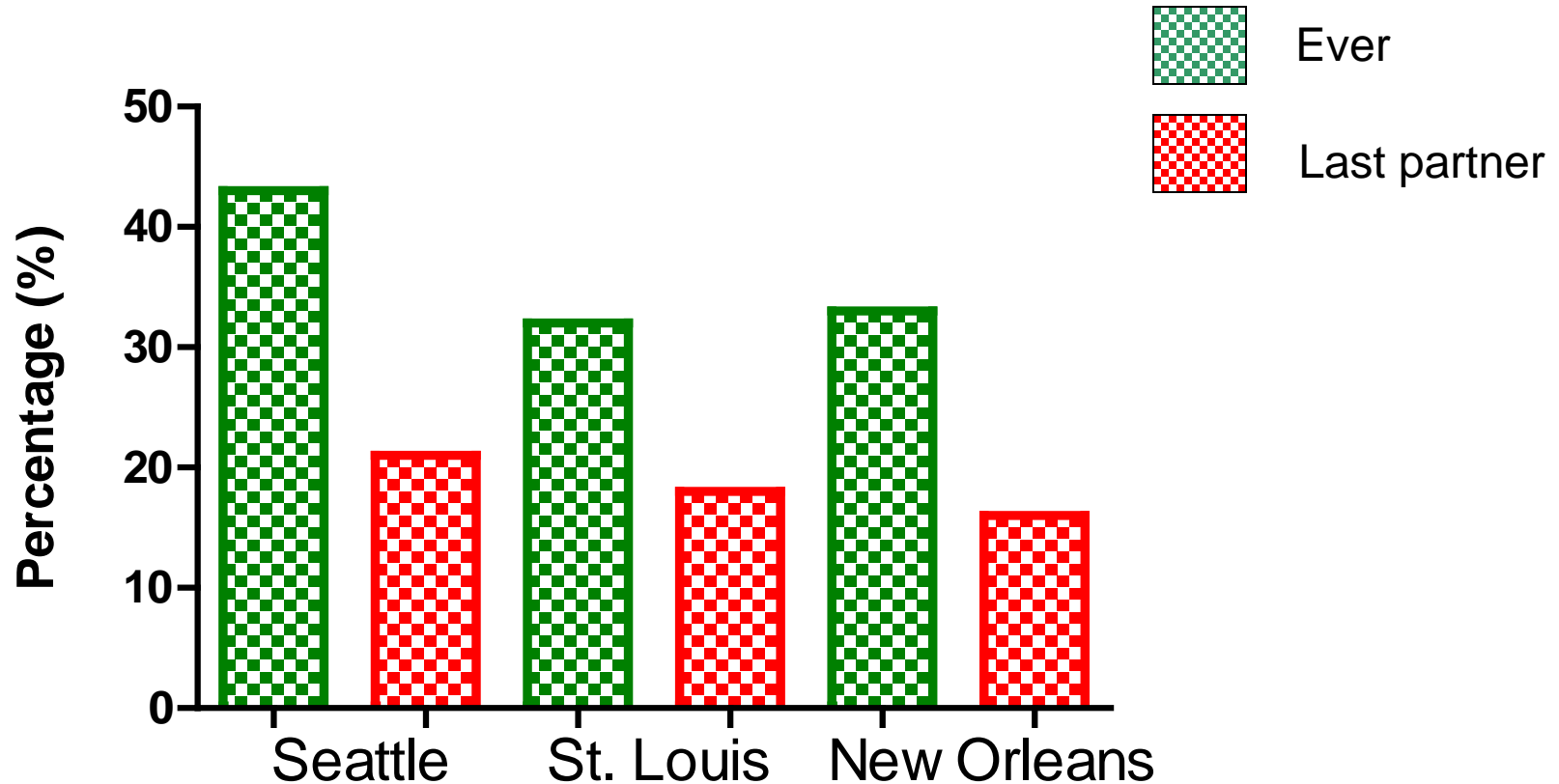
March 15th-17th, 2010



US HIV Incidence in MSM



Prevalence of AI in US Women



Gorbach PM et al. Sex Transm Dis, 2009 36(4):193-198.

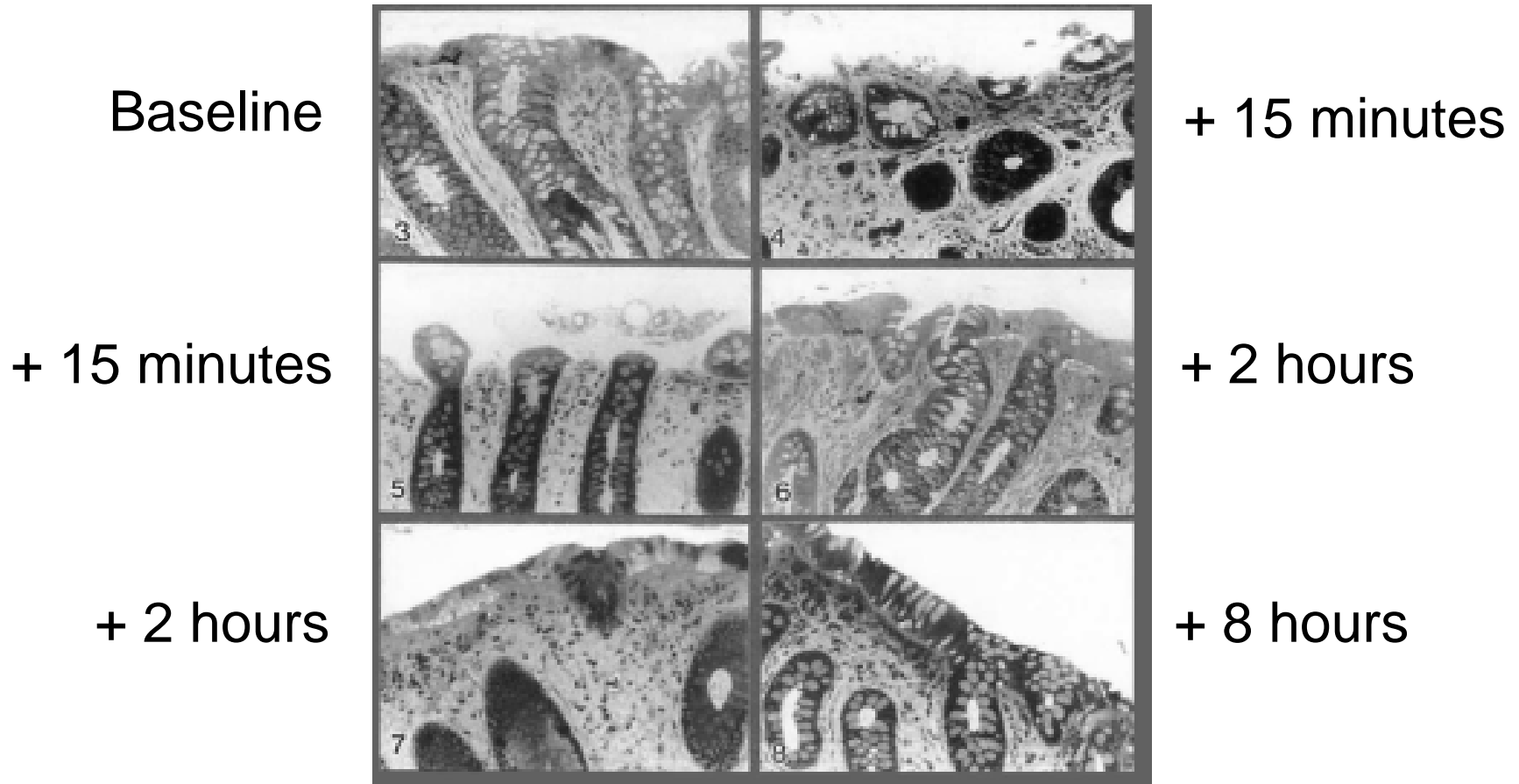
HIV Infection in African MSM

Country	Sample Size	HIV Prevalence	
		MSM \pm W	MSW
Senegal	943	21.6%	0.7%
Ghana	N/A	25.0%	1.4%
Nigeria	1961	13.5%	2.4%
Mauritania	21	19.0%	1.2%
Cote D'Ivoire	54	18.5%	2.9%
Kenya	1124	15.6%	7.5%
Tanzania	509	12.4%	5.9%
Uganda	19	42.1%	5.0%
Sudan	1119	8.8%	1.3%
Egypt	340	5.3%	0.02%
South Africa	574	15.3%	15.9%
Zambia	641	32.9%	15.7%
Malawi	201	21.4%	11.5%
Namibia	218	12.4%	10.8%
Botswana	117	19.7%	18.1%

Rectosigmoid Anatomy



N-9 Effect on Rectal Epithelium



Phase 1 Rectal Safety Studies

Product	Status	Timeline	Sponsor
UC781	Completed		NIAID/DAIDS
MTN-006	Ongoing	Q1 2009	NIAID/DAIDS
MTN-007	Planned	2010	NIAID/DAIDS
UC781 (NF)	Planned	2010	NICHD/R01
Tenofovir (RF)	Planned	2010	NIAID/DAIDS/ IPCP /U19 CHARM Program
UC781 (RF)	Planned	2011	
UC781 + TNF (RF)	Planned	2012	

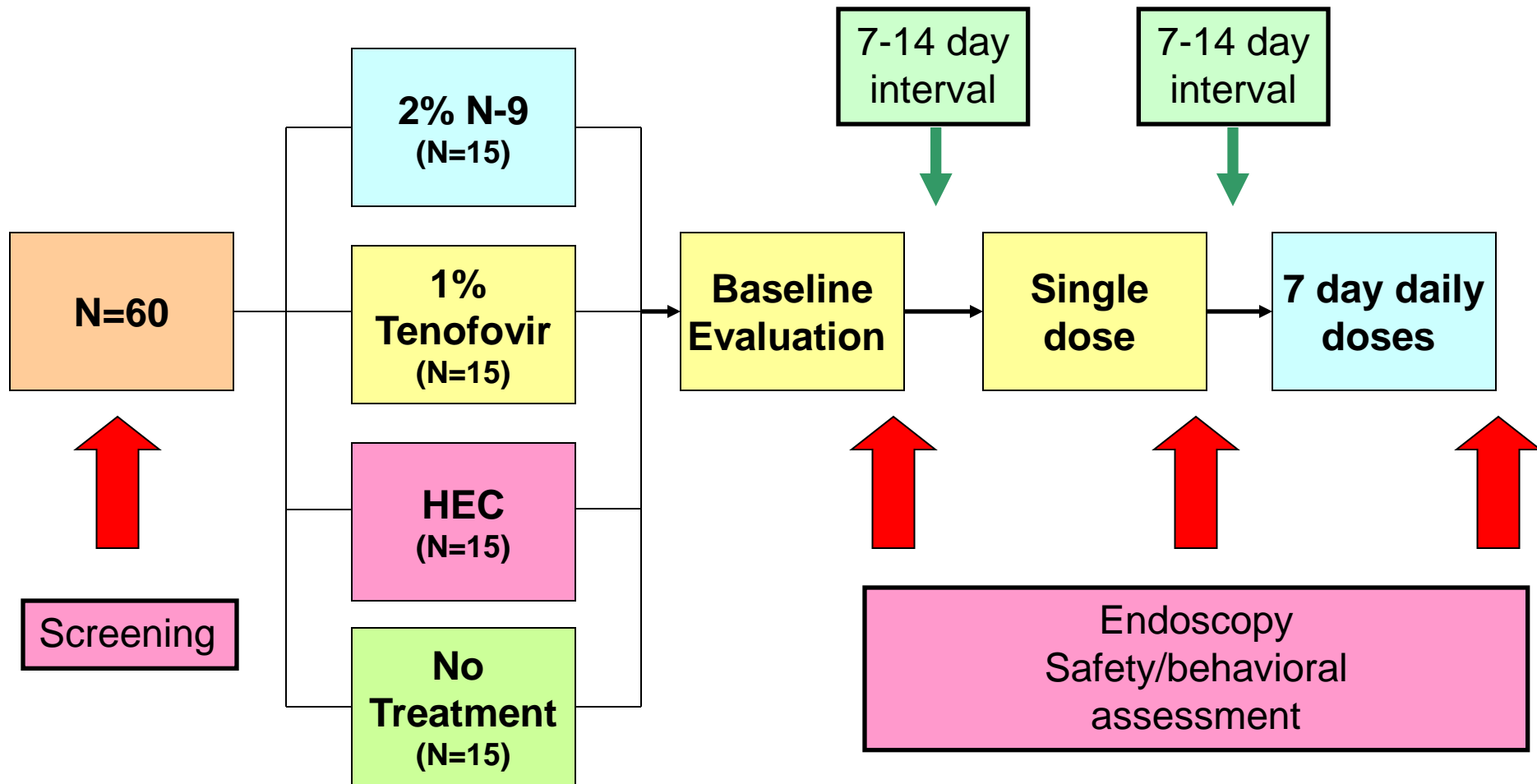


Mucosal Safety

Assessment of Mucosal Safety

- Traditional safety assessment in Phase 1/2 studies may not identify subtle product related mucosal injury
- Induction of T cell activation, release of proinflammatory cytokines / chemokines, or upregulation of GALT T cell HIV co-receptors may increase risk of HIV acquisition

MTN-007

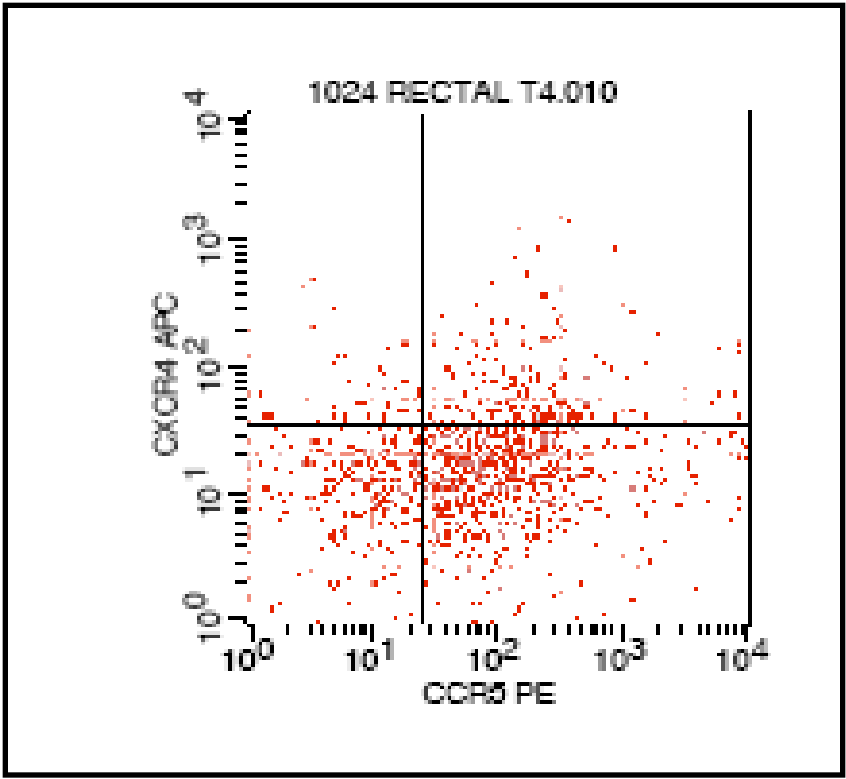
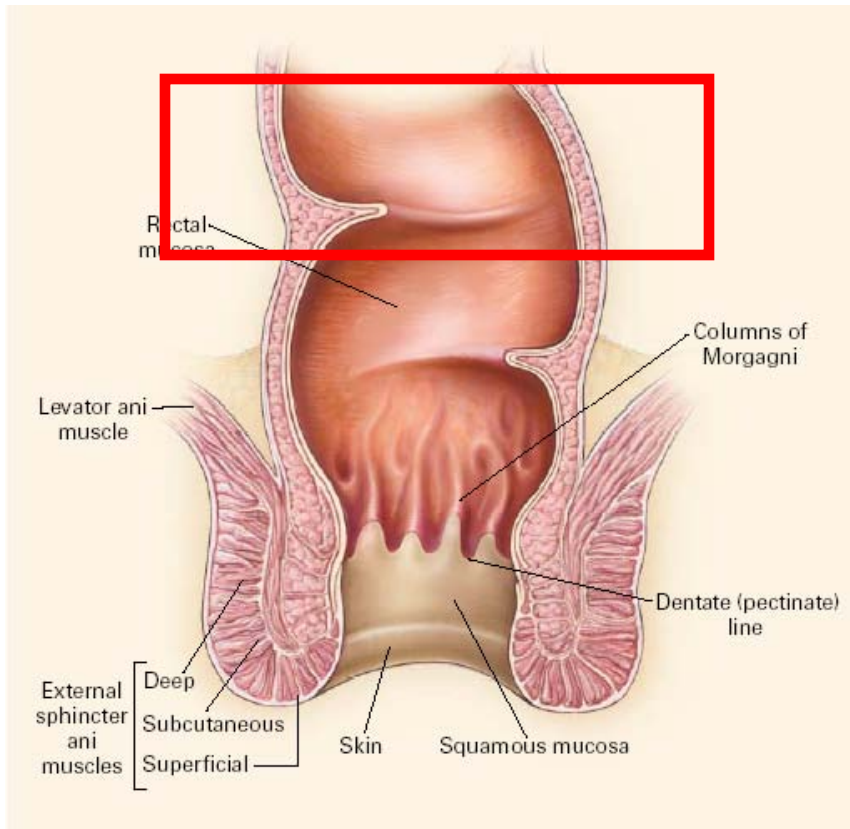


Mucosal Safety Endpoints in MTN-007

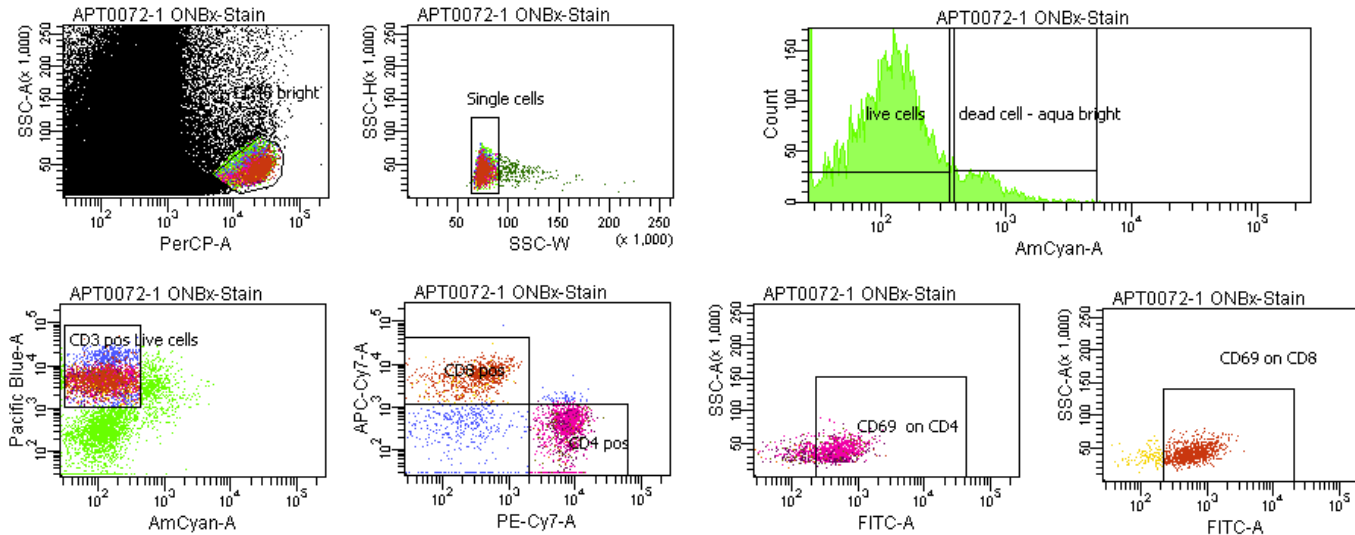
- Histology
- MMC phenotype
 - Activation
 - HIV Co-receptors
- Cytokine production
 - mRNA
 - Protein
- Gene array
- Fecal calprotectin
- Rectal microflora



Flow Cytometry

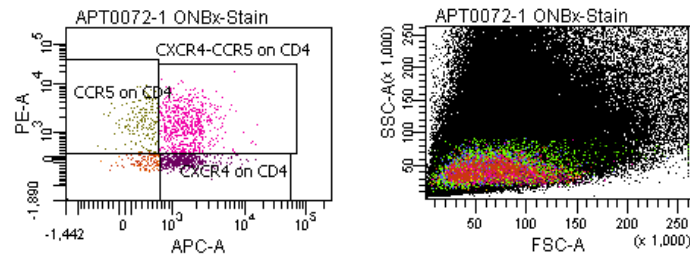


GALT T Cell Panel

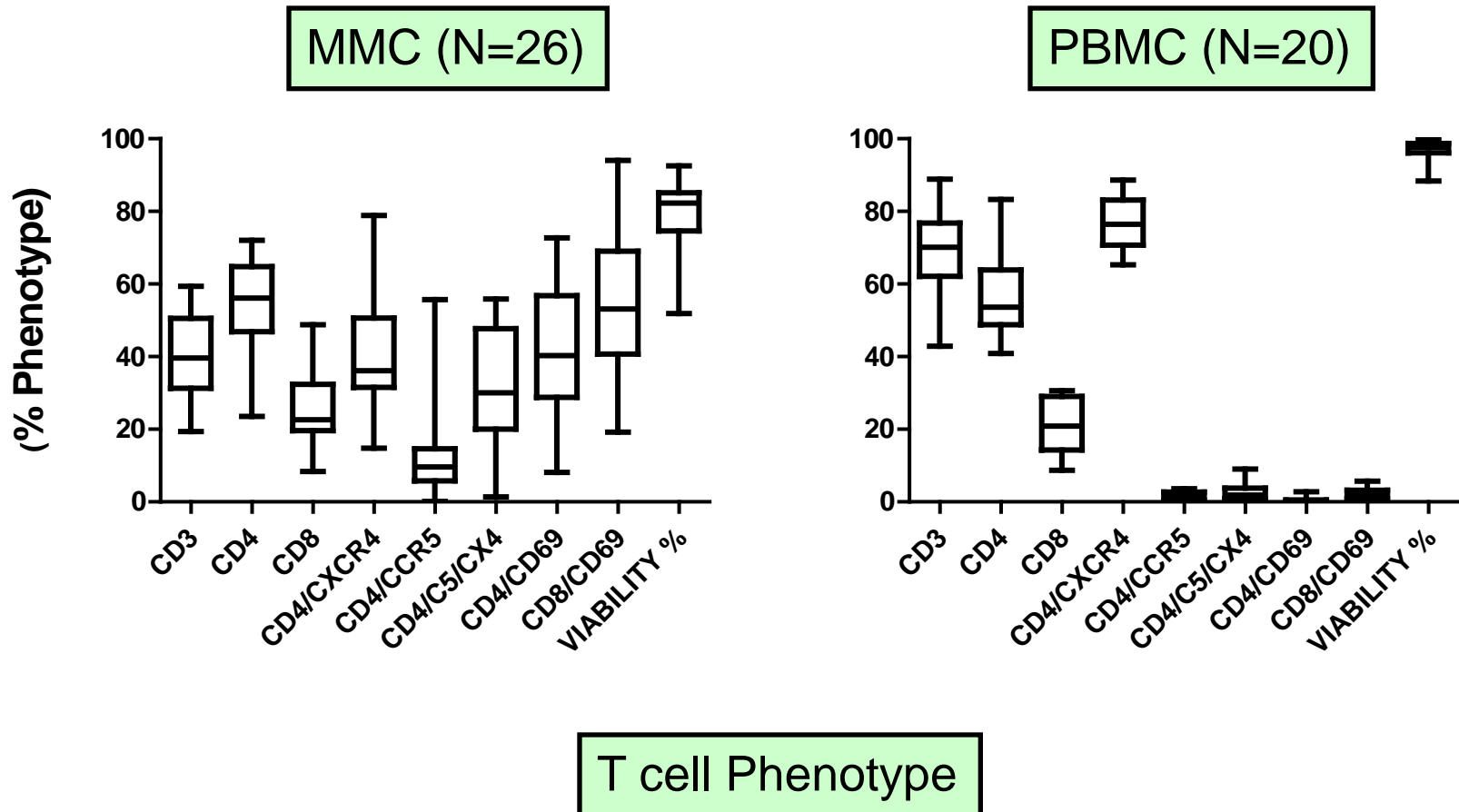


Tube: Stain

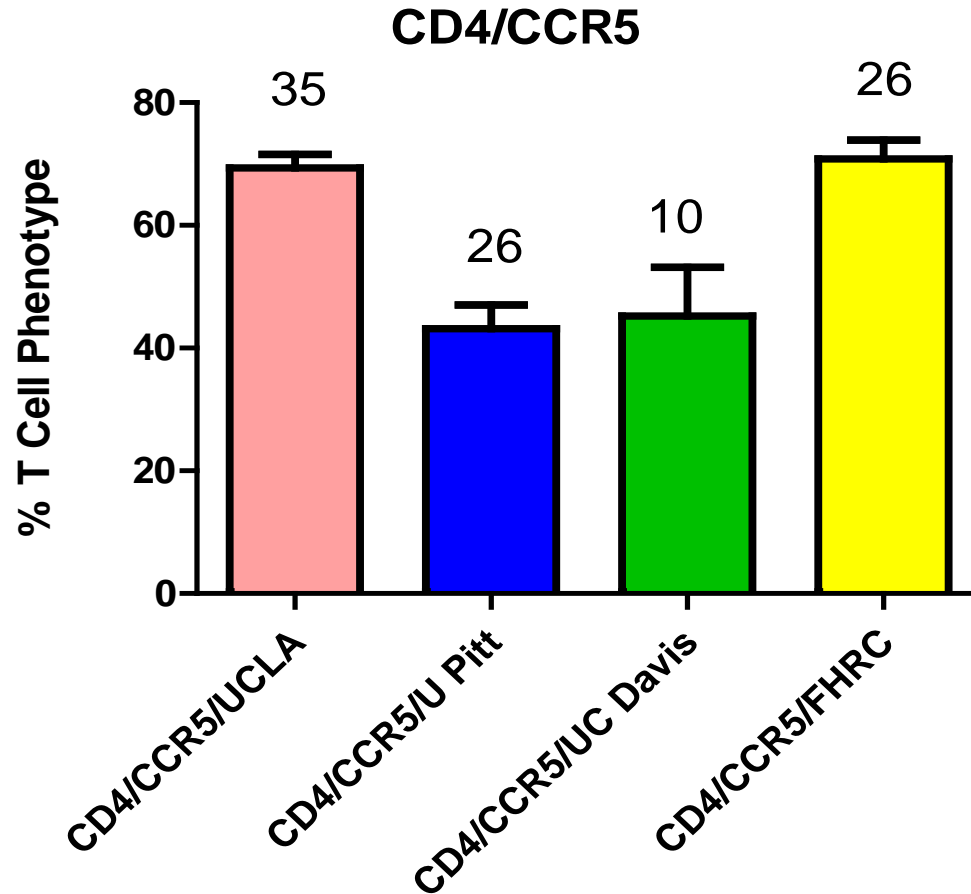
Population	#Events	%Parent	%Total
All Events	213,866	###	100.0
CD45 bright	7,756	3.6	3.6
Single cells	7,504	96.8	3.5
CD3 pos Live cells	3,256	43.4	1.5
CD4 pos	1,412	43.4	0.7
CD69 on CD4	1,041	73.7	0.5
CXCR4 on CD4	478	33.9	0.2
CCR5 on CD4	178	12.6	0.1
CXCR4-CCR5 on	671	47.5	0.3
CD8 pos	1,057	32.5	0.5
CD69 on CD8	906	85.7	0.4
dead cell - aqua bright	797	10.6	0.4
live cells	6,617	88.2	3.1



T Cells in Blood & GALT

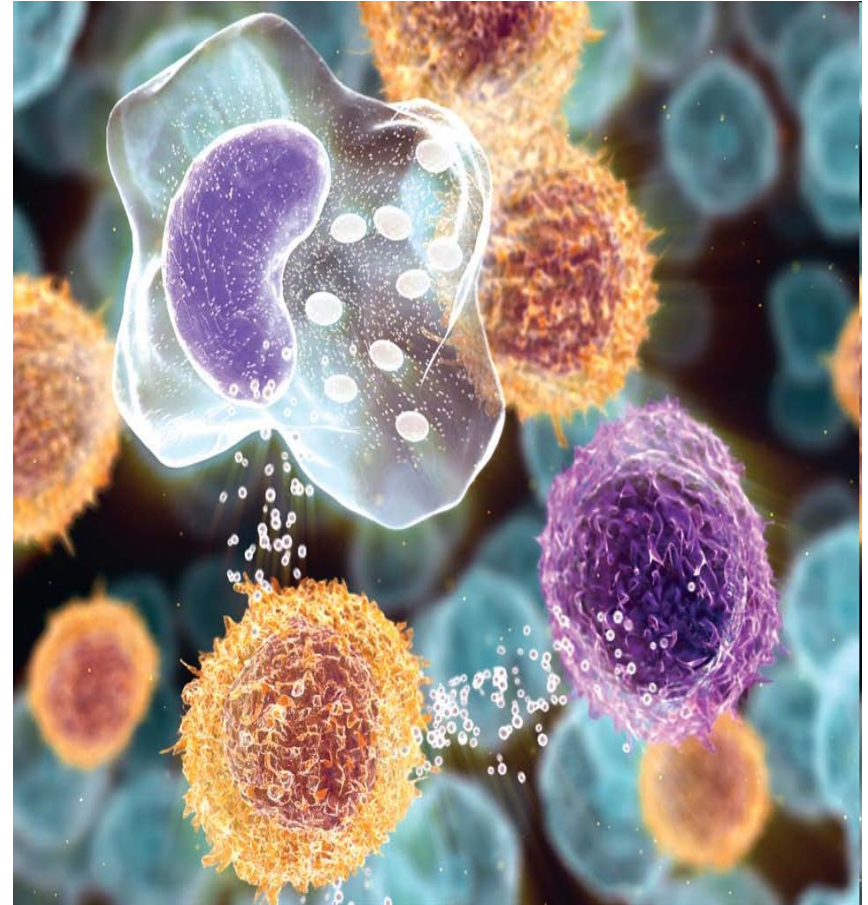


Normative Ranges for GALT T Cells

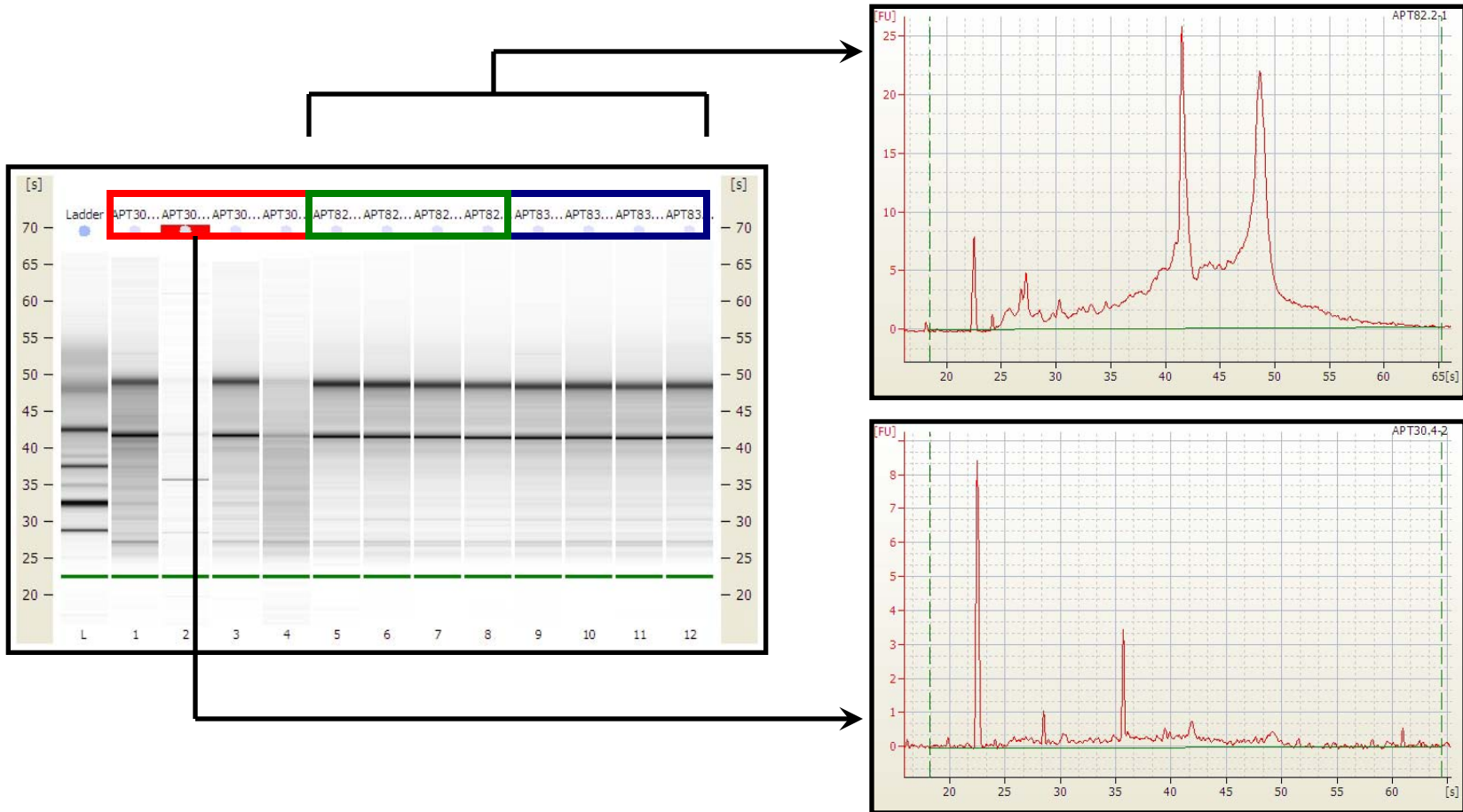


Cytokine Production (mRNA)

- Substances that are secreted by specific cells of the immune system which carry signals locally between cells, and thus have an effect on other cells including induction of inflammatory responses and recruitment of target cells



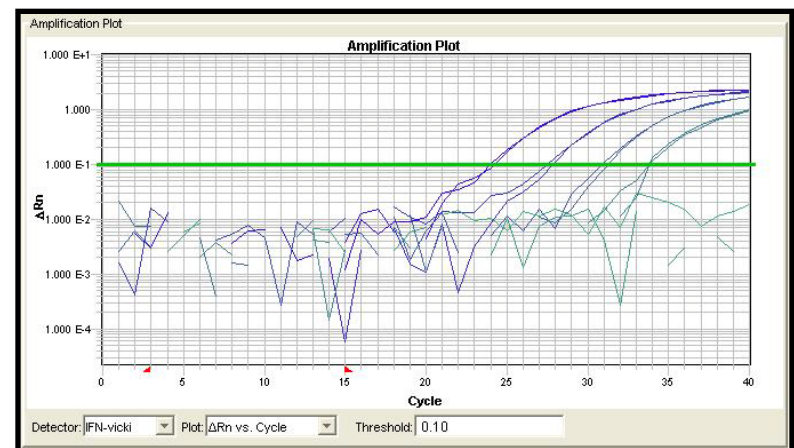
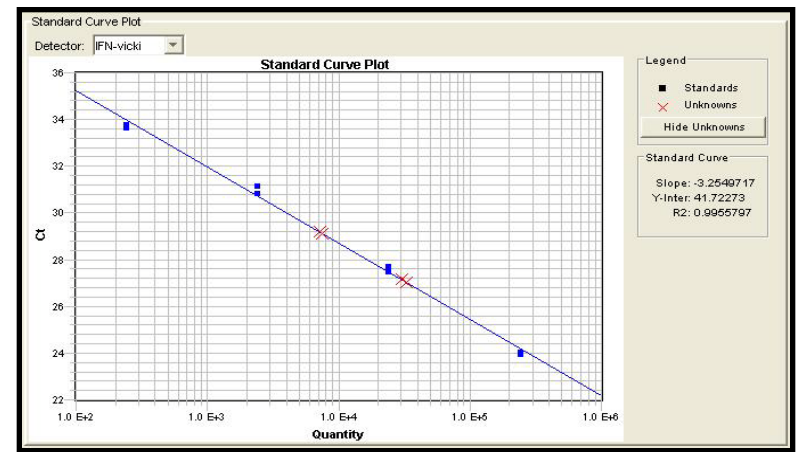
Evaluation of mRNA



Quantification of cytokine mRNA

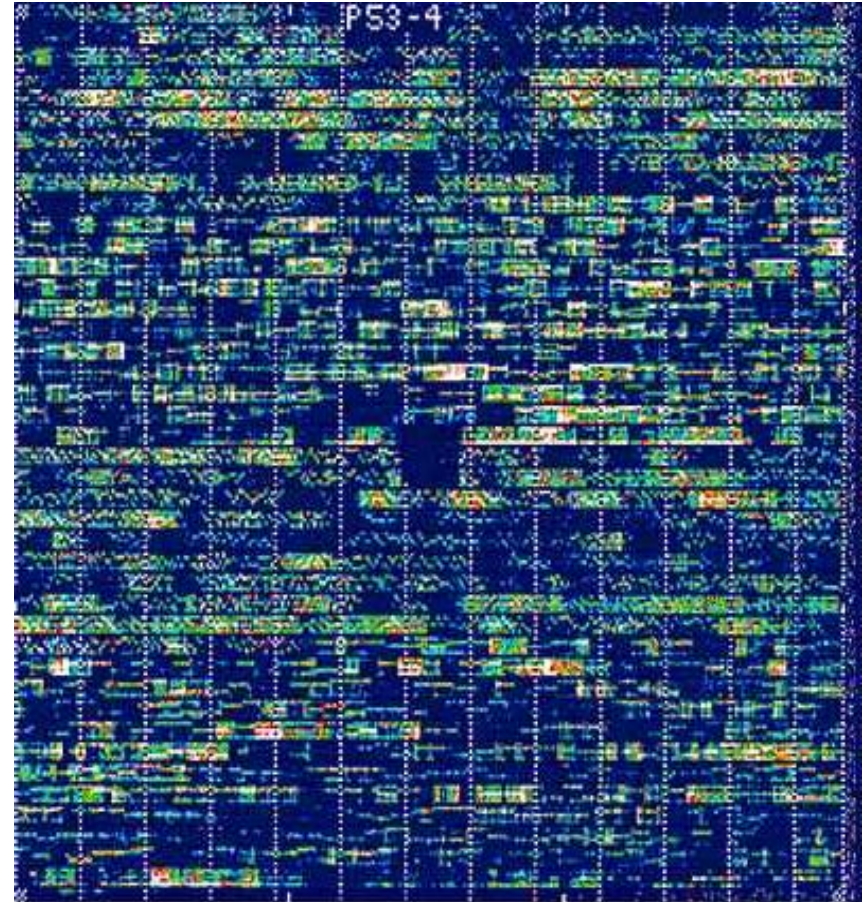
- Cytokine / chemokine mRNA will be quantified by RT-PCR
- A multiplex standard has been developed to provide quantitative mRNA data
- IL-1 β , IFN- γ , TNF- α , IL-6, IL-8, IL-12, IL-17, IL-23, MIP-1 α , MIP-1 β , RANTES, and CCR5

Interferon Gamma mRNA



Gene Array

- Gene arrays permit the measurement of 48,000 mRNAs simultaneously on a single high-density oligonucleotide microarray.
- This offers the opportunity to identify signature expression patterns of dozens or even hundreds of genes that correlate with microbicide side effects on the mucosa

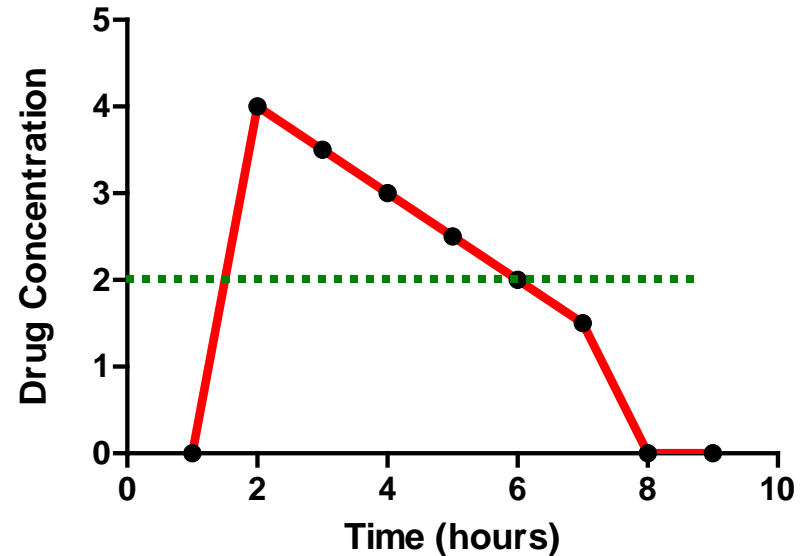




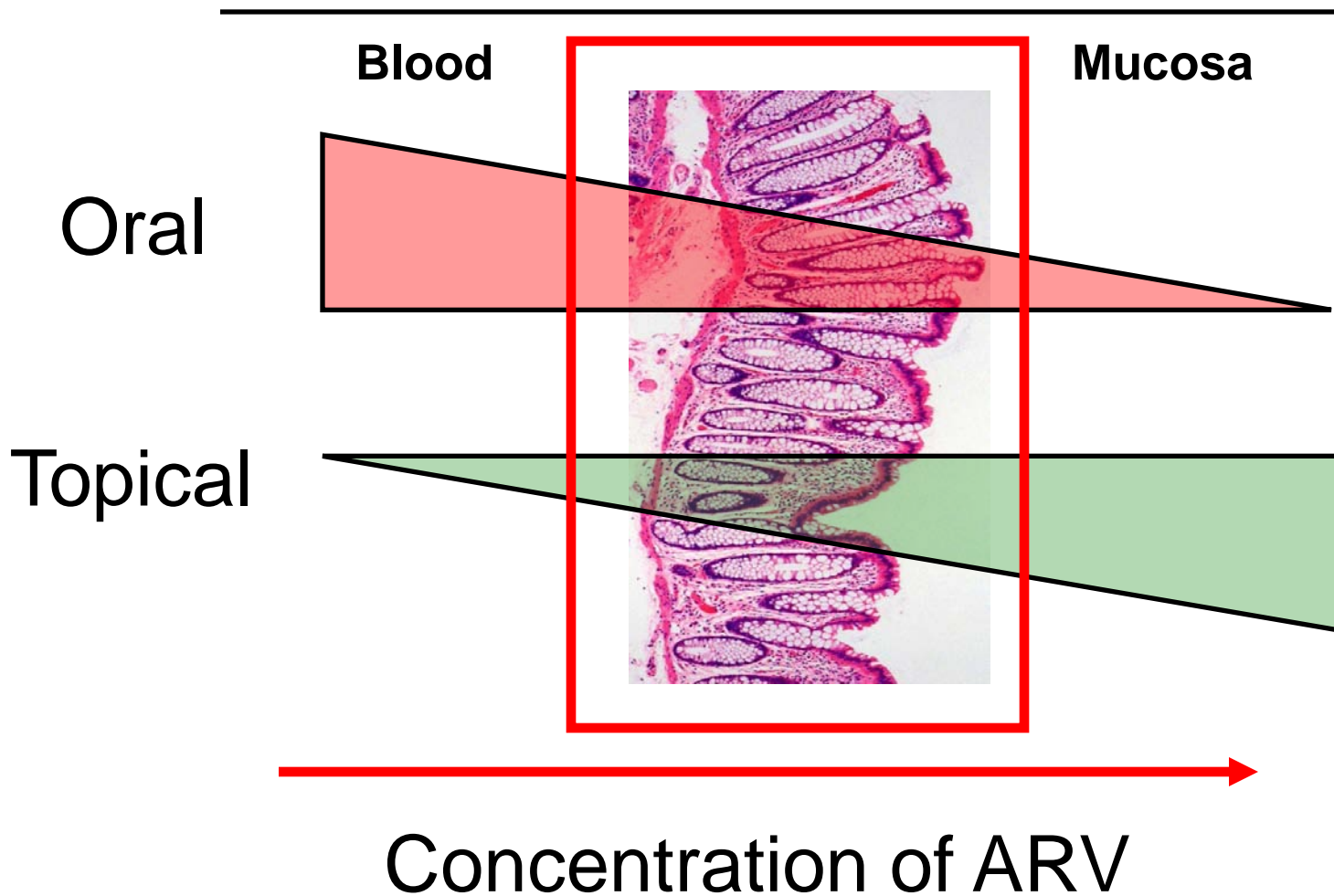
Pharmacokinetics

Pharmacokinetics

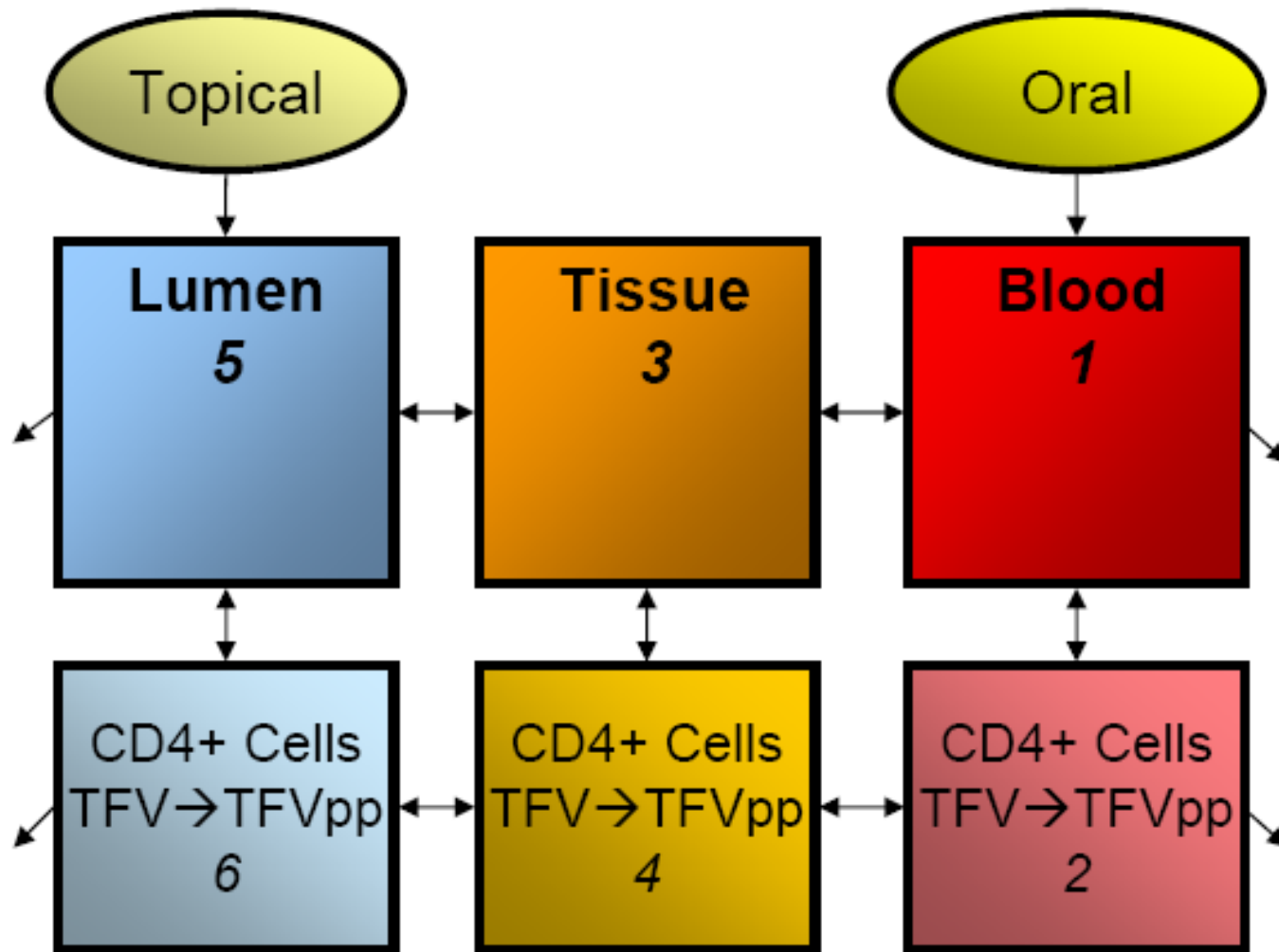
- Quantitative study of how drugs are taken up, biologically transformed, distributed, metabolized, and eliminated from the body



Oral or Topical ARV PrEP?

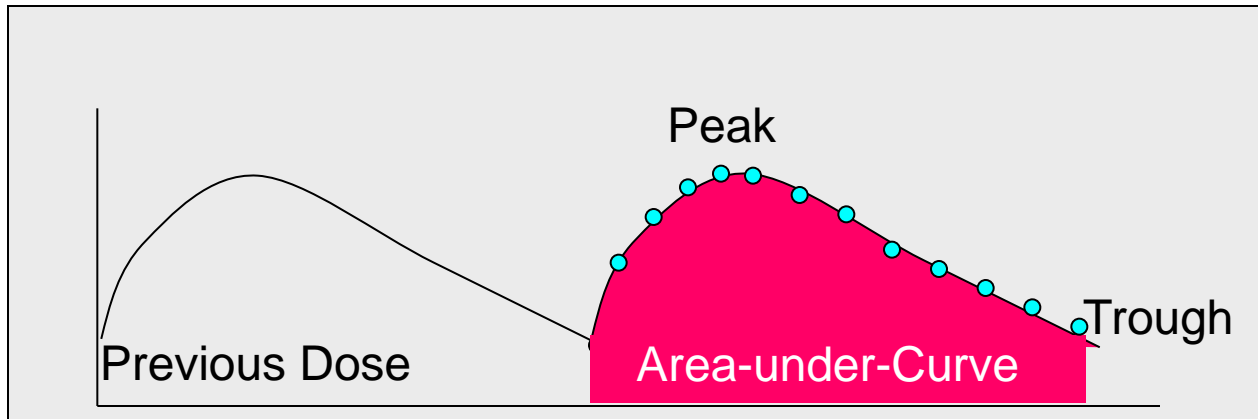


Compartments Sampled



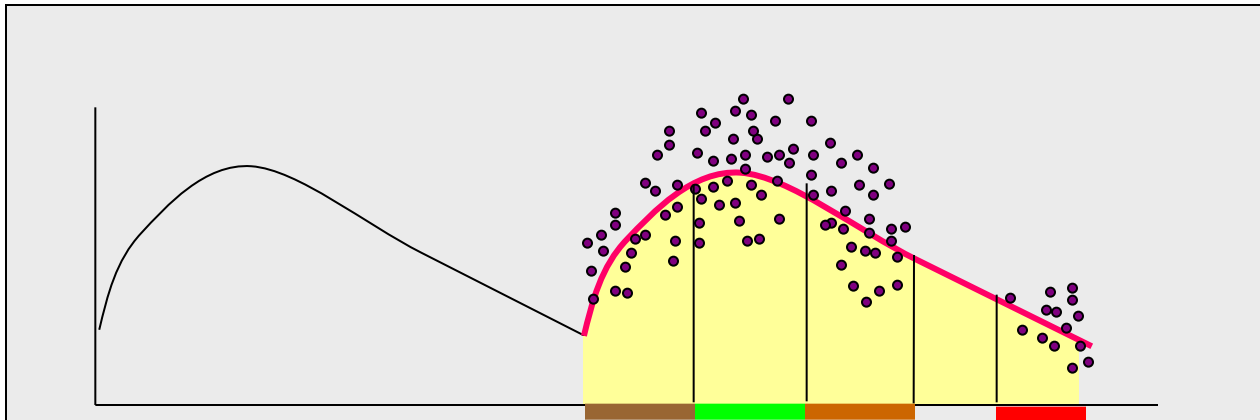
Approaches to PK (1)

- Traditional Intensive Sampling
 - *Few Subjects, Many Times*



Approaches to PK (2)

- Sparse Sampling (Population PK)
 - *Many Subjects, Few Times*



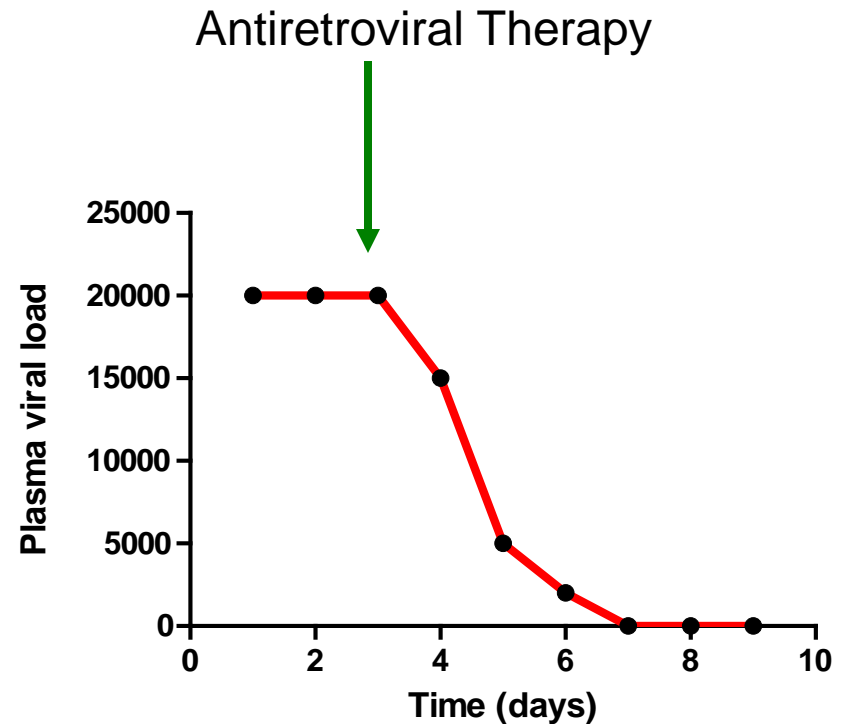
- MTN-006 tissue PK



Pharmacodynamics

Pharmacodynamics

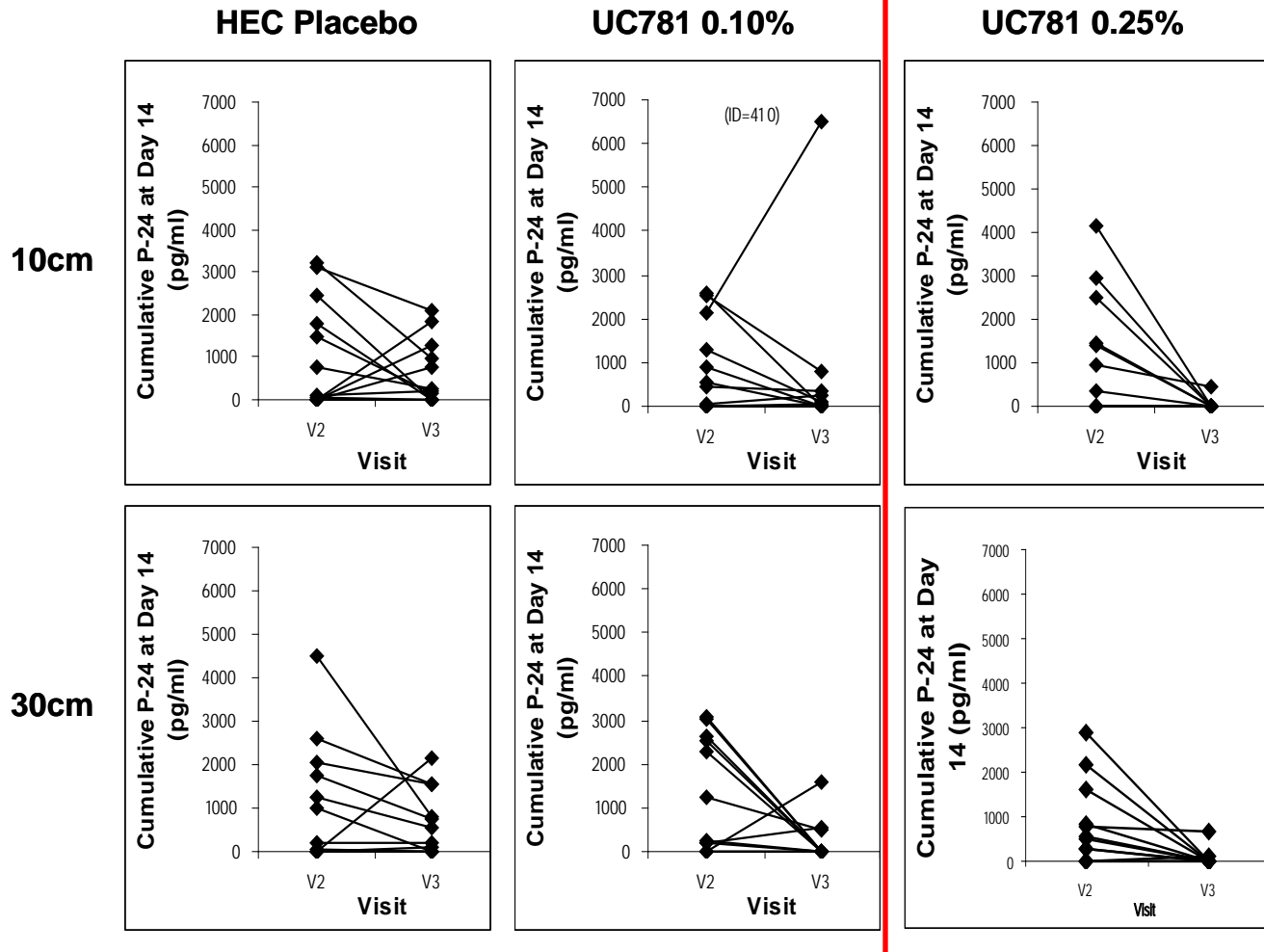
- The study of the physiological effects of drugs on the body or on microorganisms or parasites within or on the body





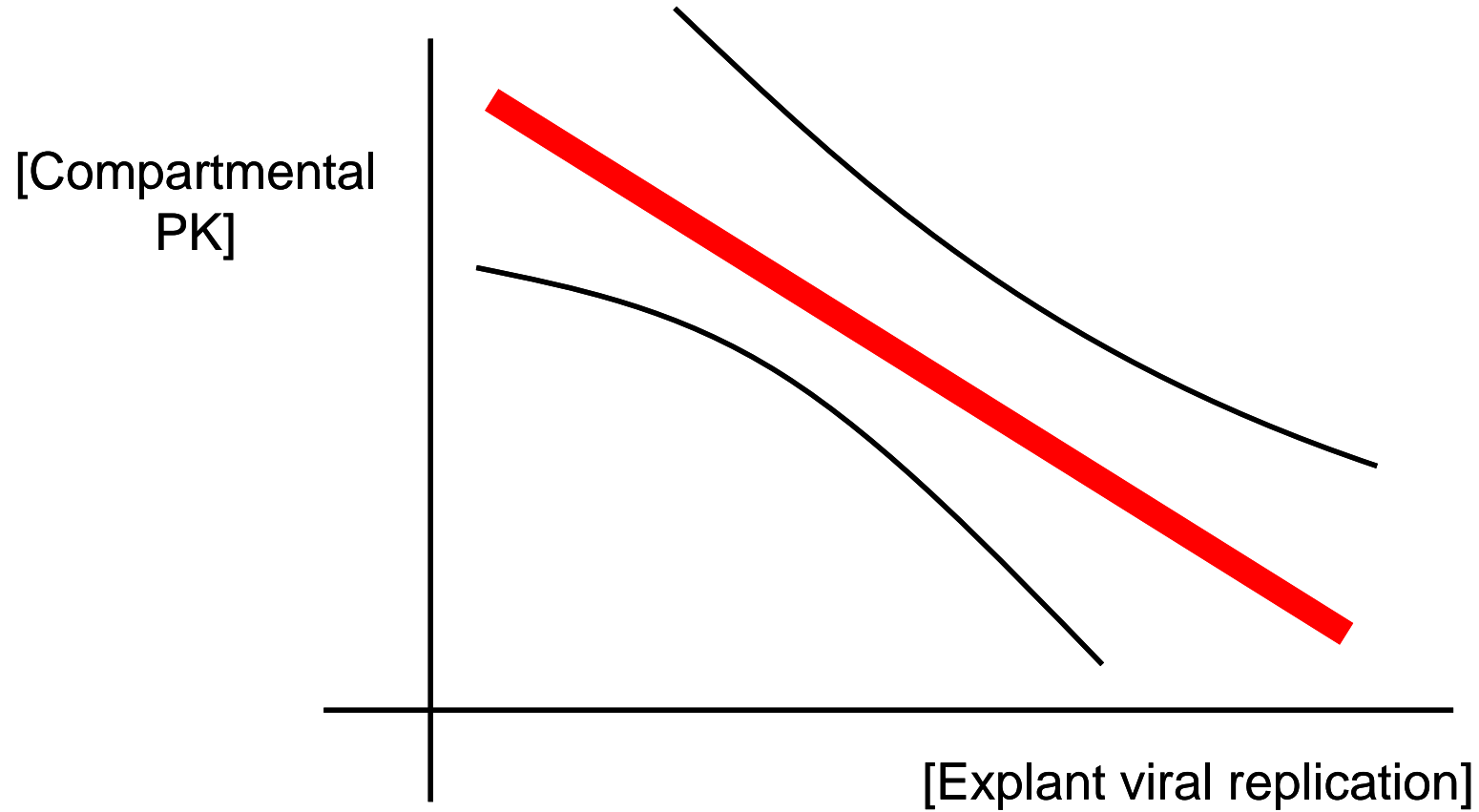
Linking PK with PD

Ex Vivo / In Vitro Explant Infection

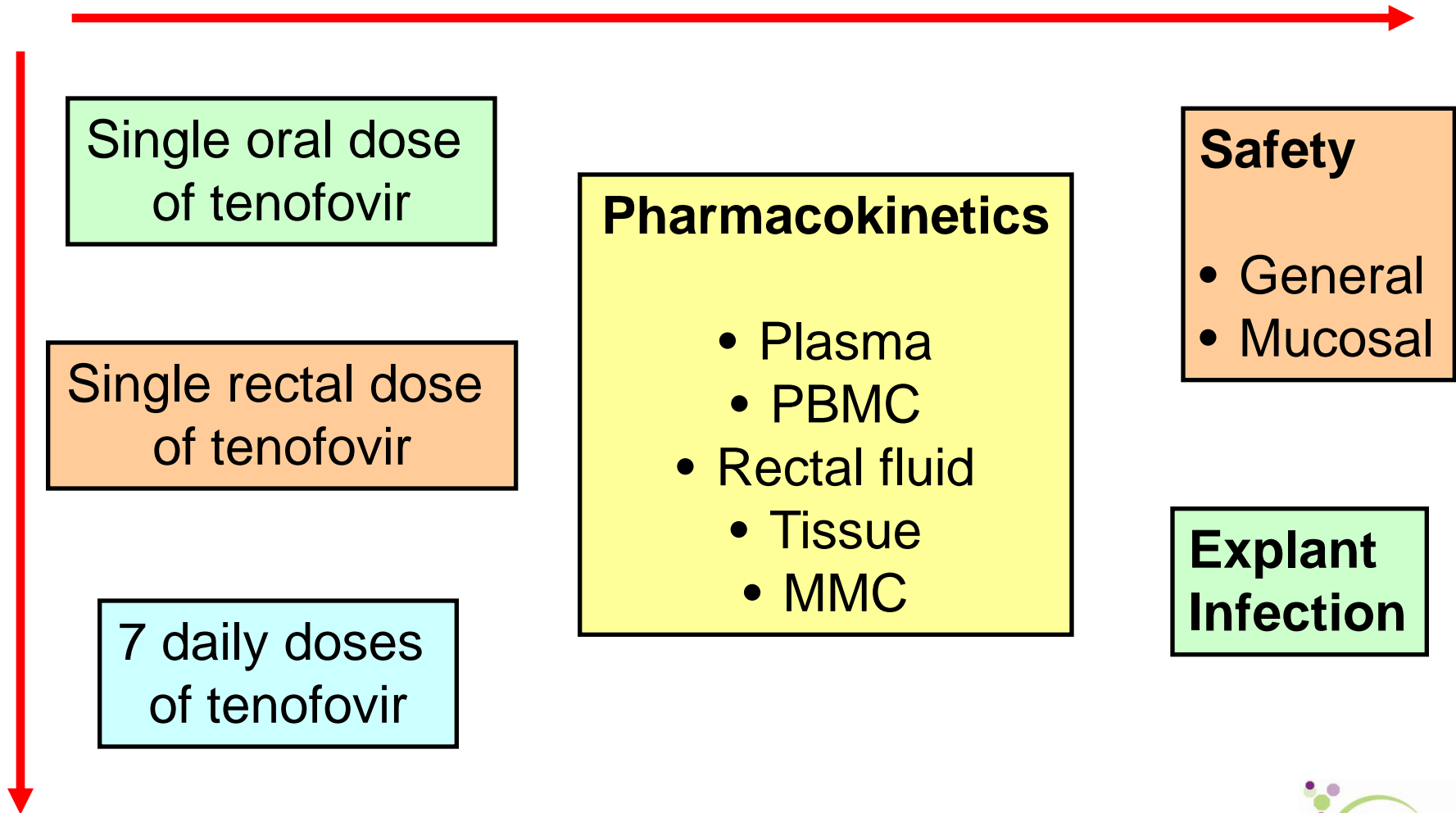


Anton: CROI 2009

Linking PK with PD



RMP-02/MTN-006



Conclusions

- Ongoing Phase 1/2 (MTN-001, 006, and 007) studies will provide critical data on:
 - PK, PD, and mucosal safety
- These data can be used to predict safety and efficacy of candidate products, route of delivery and the design of clinical trials:
 - Coital dependency versus daily dosing
 - Oral versus topical delivery
 - Vaginal versus rectal dosing
 - Intermittent dosing strategies



Thank You