

MTN Response to the US Domestic Agenda

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The US HIV Epidemic in 2011

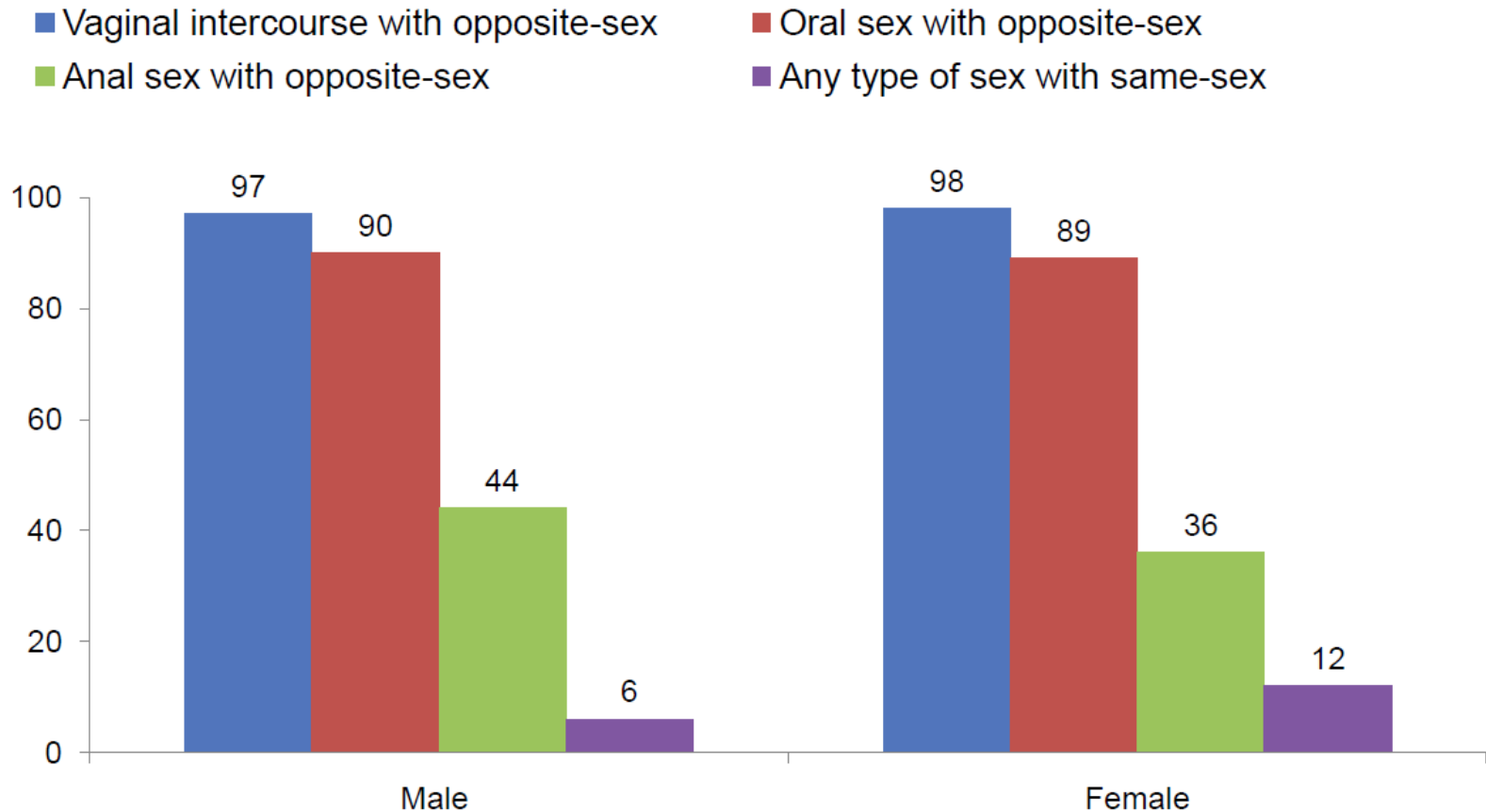
- Approximately 50,000 Americans are diagnosed with HIV infection each year
- Over one million Americans are currently living with HIV
- Medical costs are substantial, averaging approximately \$20,000 per year for each person in care
- 54 percent of HIV cases diagnosed in 2008 were transmitted by same-sex sexual contact among males



Sexual Behavior in the US

- 2006-2008 National Survey of Family Growth (NSFG).
- Survey of 13,495 males and females (15-44 years) in the household population of the United States using ACASI
- 36% of females and 44% of males ever had anal sex with an opposite-sex partner.

NSFG Data (2006 – 2008)





MTN Response to the US Epidemic

- MTN vaginal research program will be important for women at risk of HIV infection
 - Adolescents
 - (MTN-004 & MTN-021)
 - Sustained release vaginal products
 - (MTN-005, MTN-013 & MTN-020)
 - Pregnancy
 - (MTN-002, MTN-008, MTN-016, & MTN-019)

Rectal Microbicide Development



Rectal Microbicide Formulations



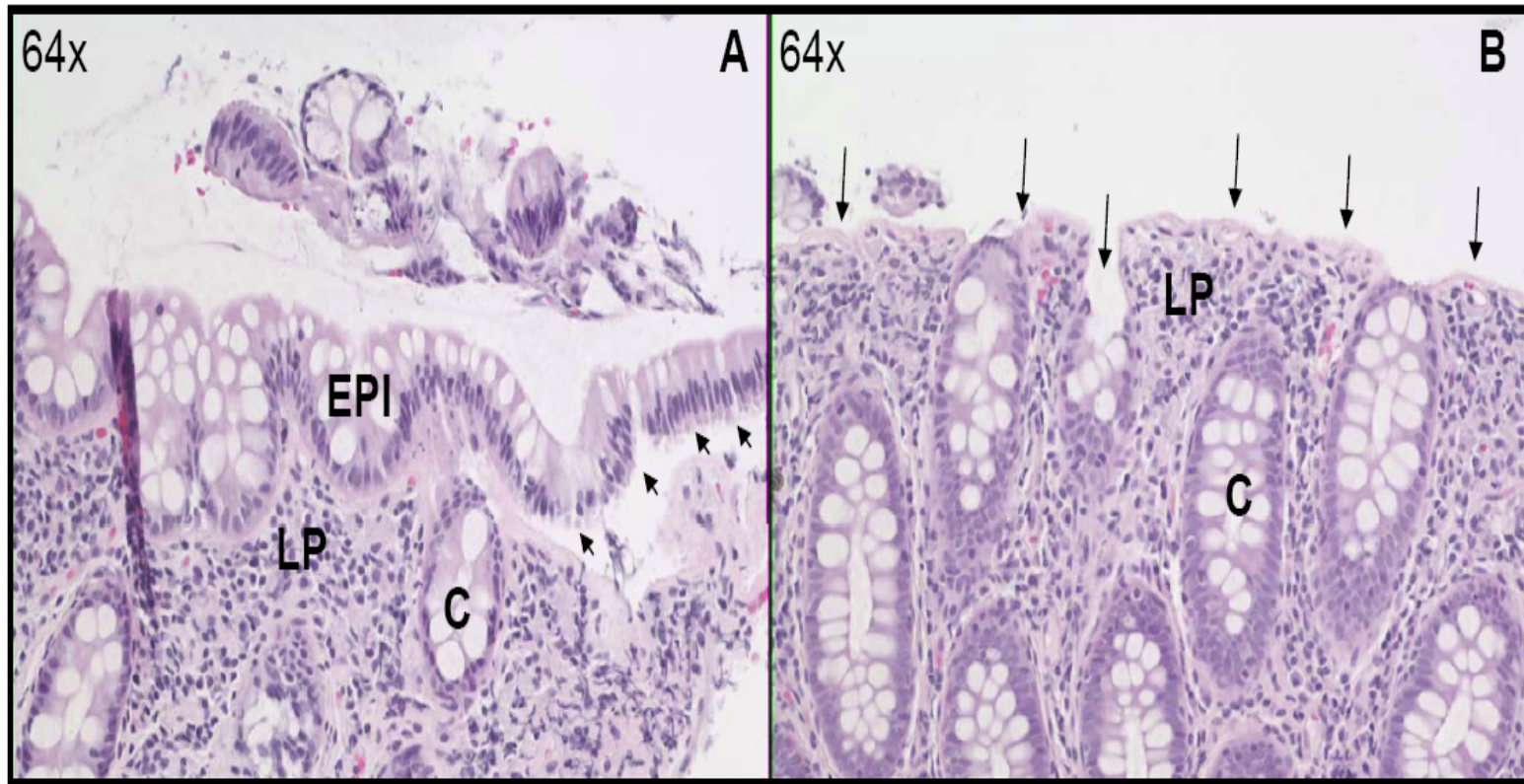
Formulation Characteristics

Lubricant	Osmolality (mmol/kg)	pH	Viscosity (cps, 10 rpm @ 25°C)
Semen	321	8.1	4
PRÉ	502	7.3	1683
KY Jelly	2510	4.5	5913
ID Glide	3150	5.2	751
Elbow Grease	3865	5.7	3159
Astroglide	6113	4.0	207
Gynol II (N9)	1245	4.7	1248
Wet Platinum	NA	NA	145

Osmolality & Mucosal Integrity

Iso-osmolar

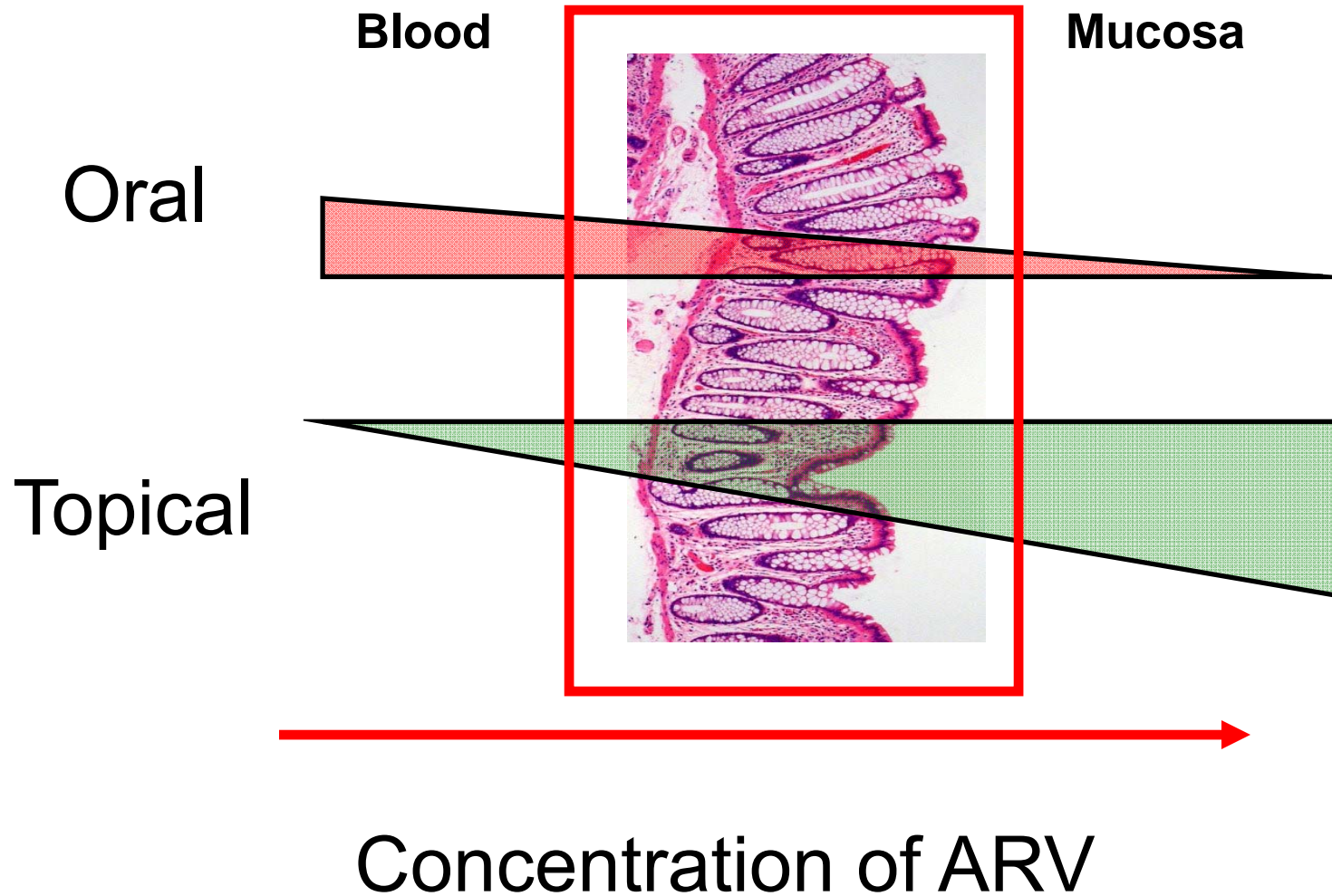
Hyperosmolar



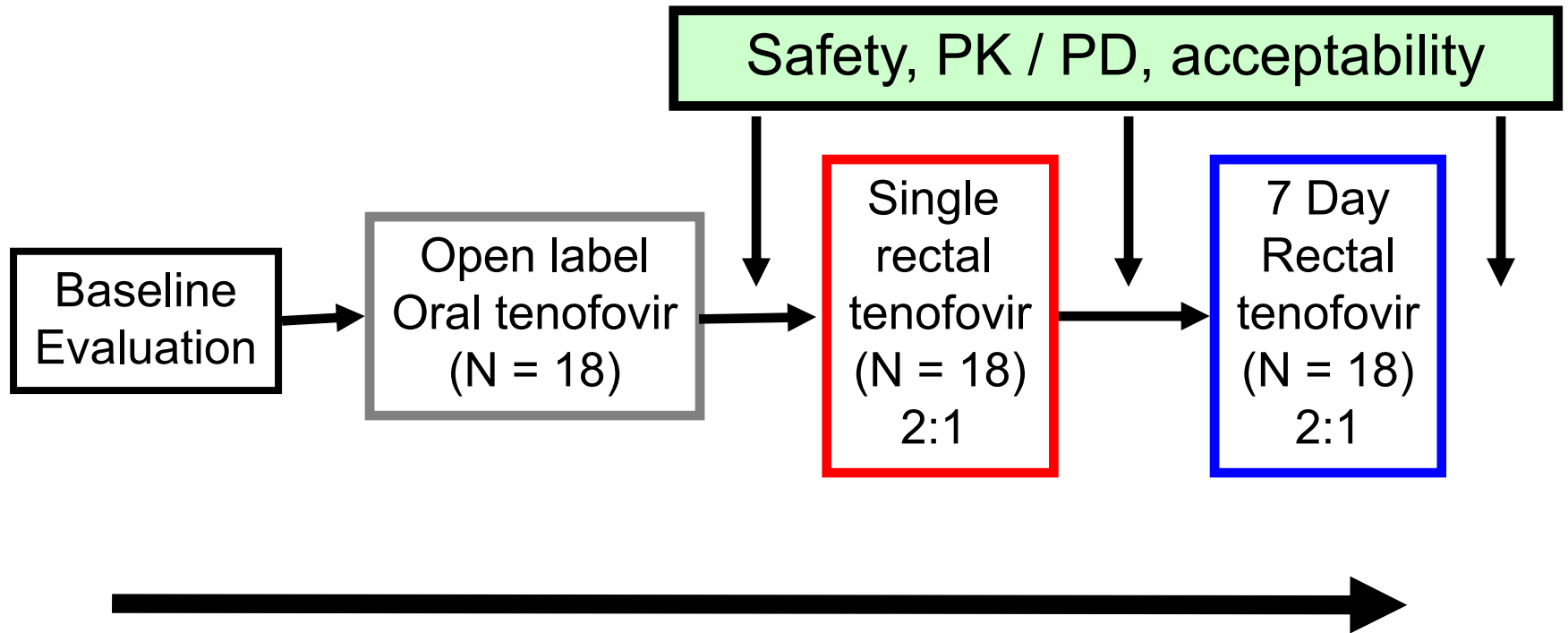


RMP-02 / MTN-006

Oral or Topical ARV PrEP?



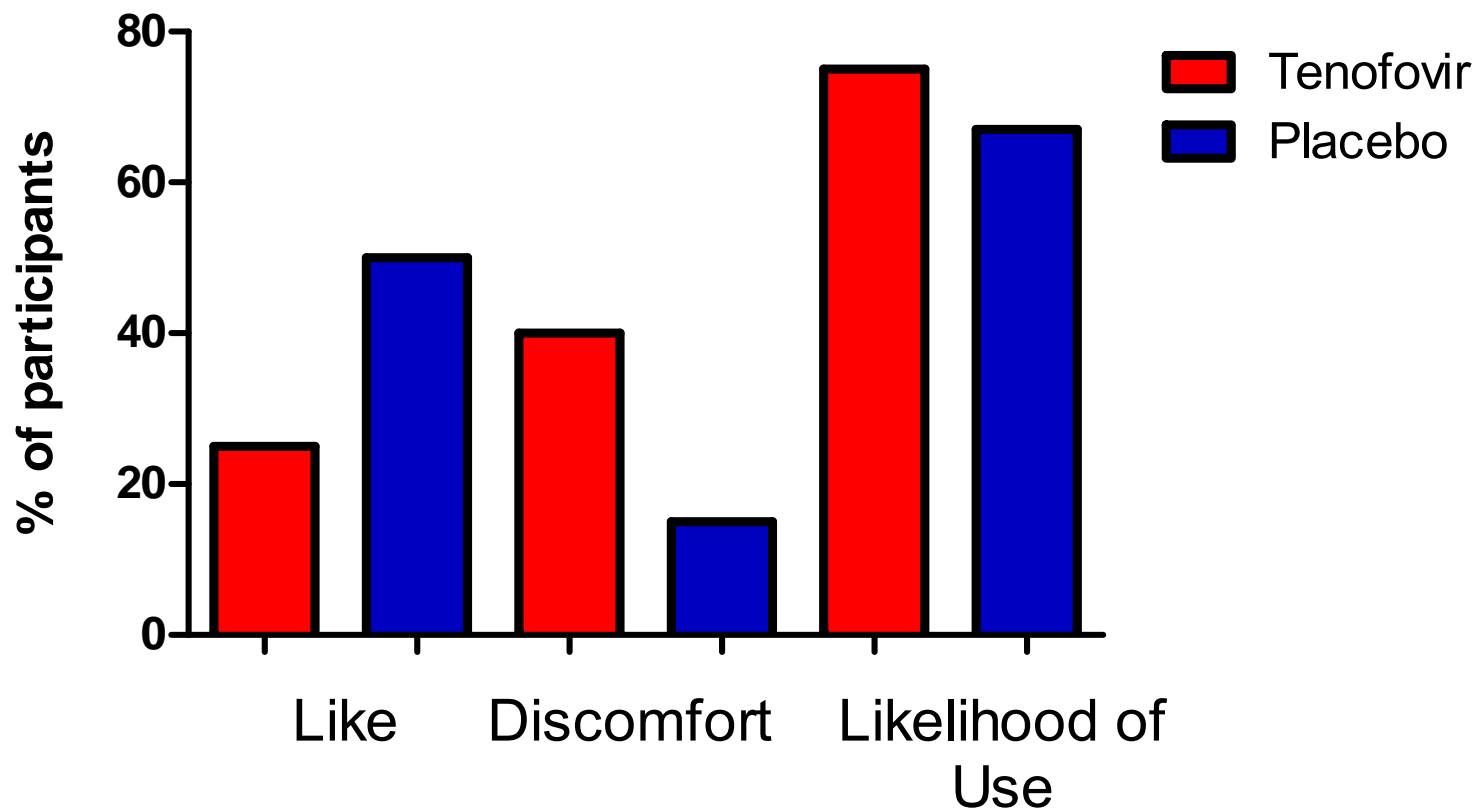
RMP-02/MTN-006



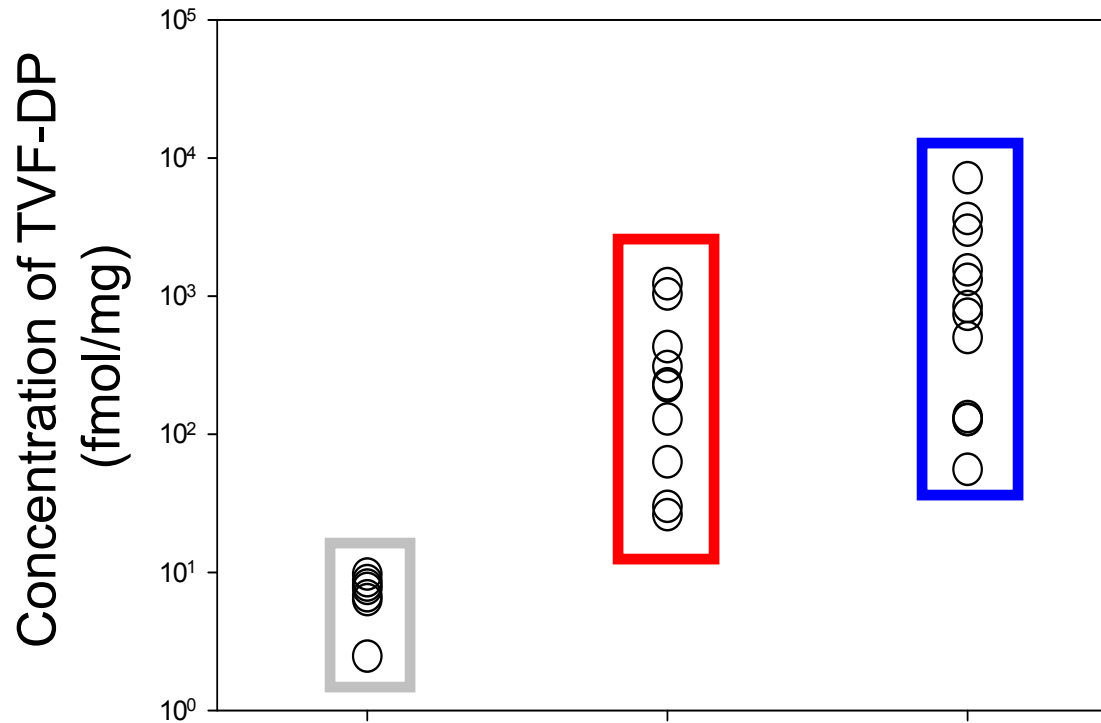
Safety

	n	GI System Events	
		Subjects	Events
Oral SD	18	7	15
Rectal SD Placebo	6	3	9
Rectal SD Tenofovir	12	6	10
Rectal 7-D Placebo	6	2	6
Rectal 7-D Tenofovir	12	12	37

Product Acceptability



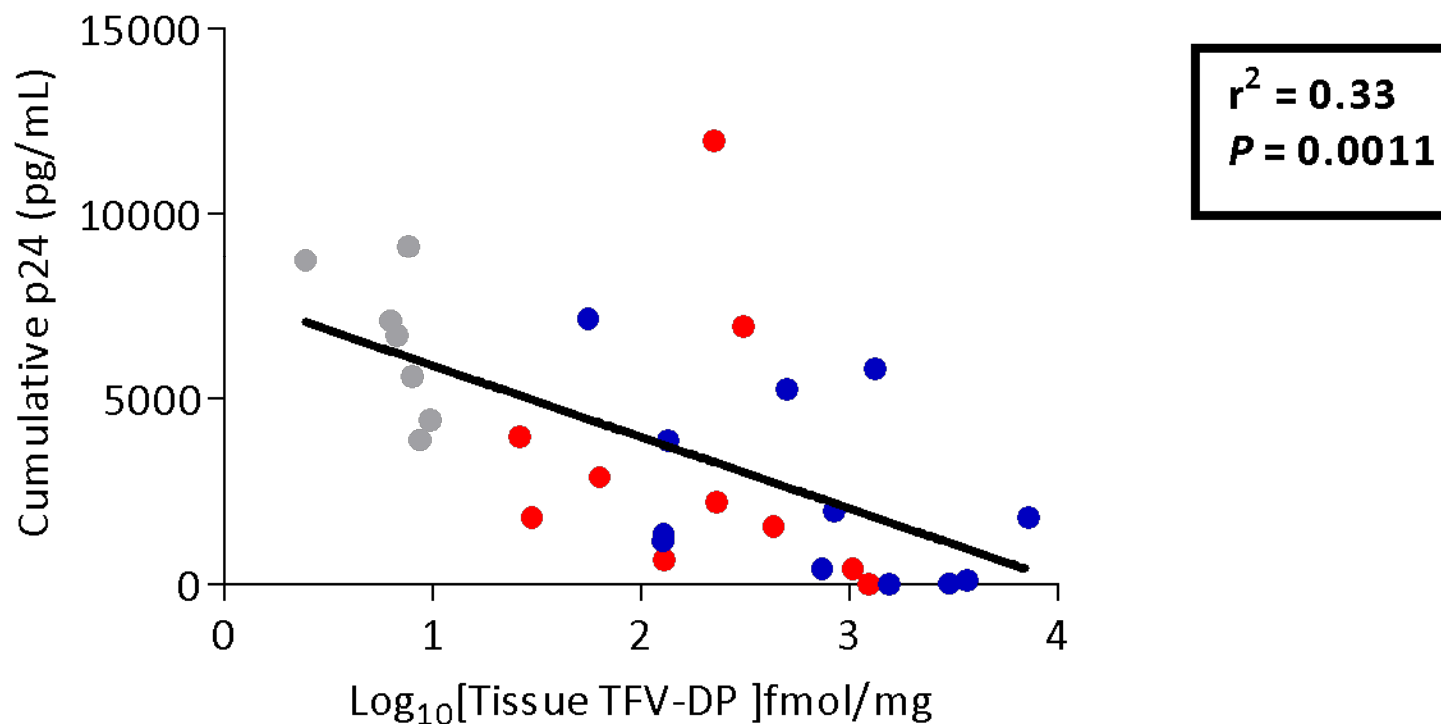
Pharmacokinetics in Tissue



Route	Oral	Rectal (S)	Rectal (7D)
N Detectable	7/18	10/12	12/12

PK/PD Relationship

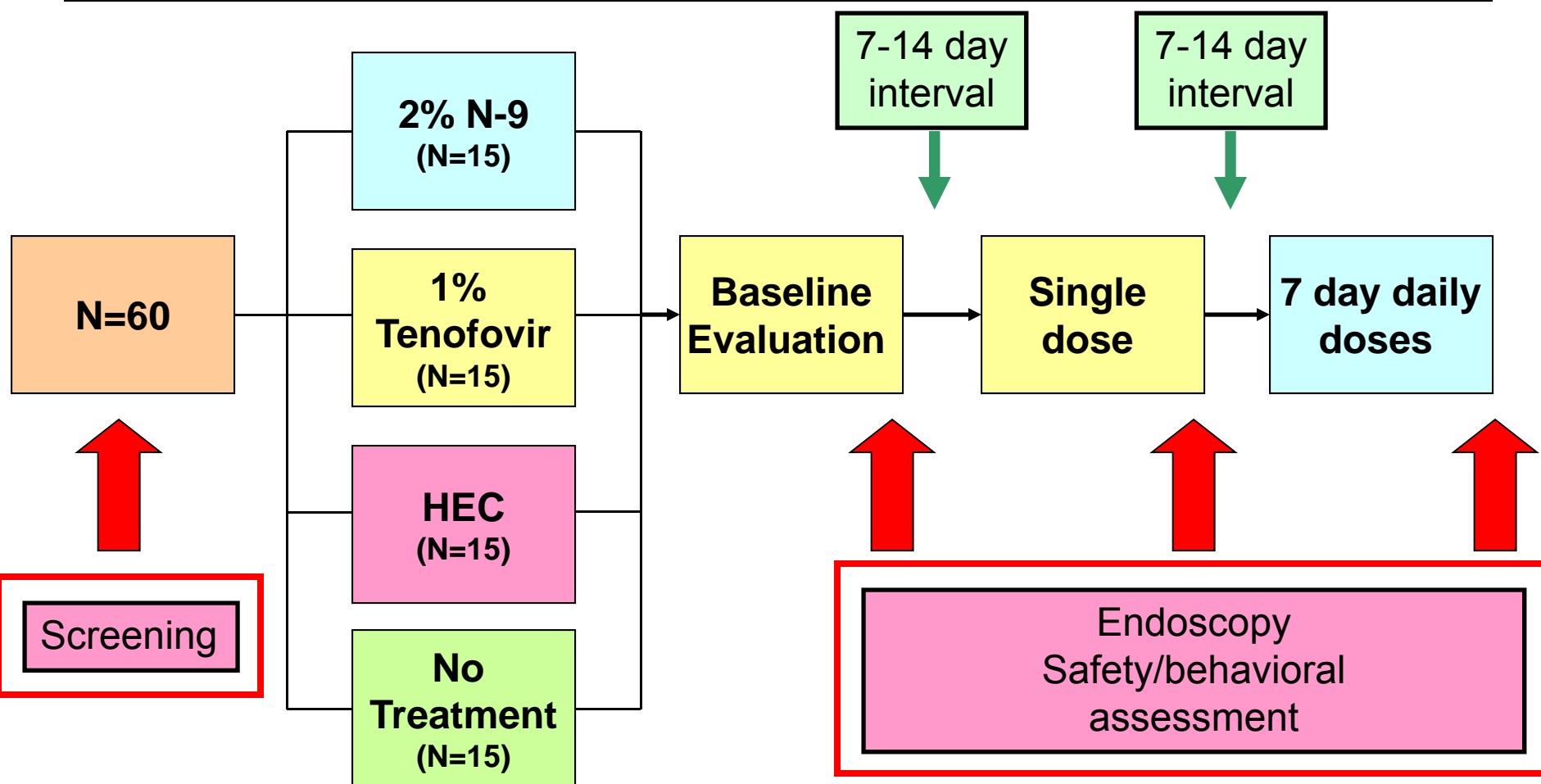
● Oral Dose ● Single Rectal Dose ● Multiple Rectal Dose



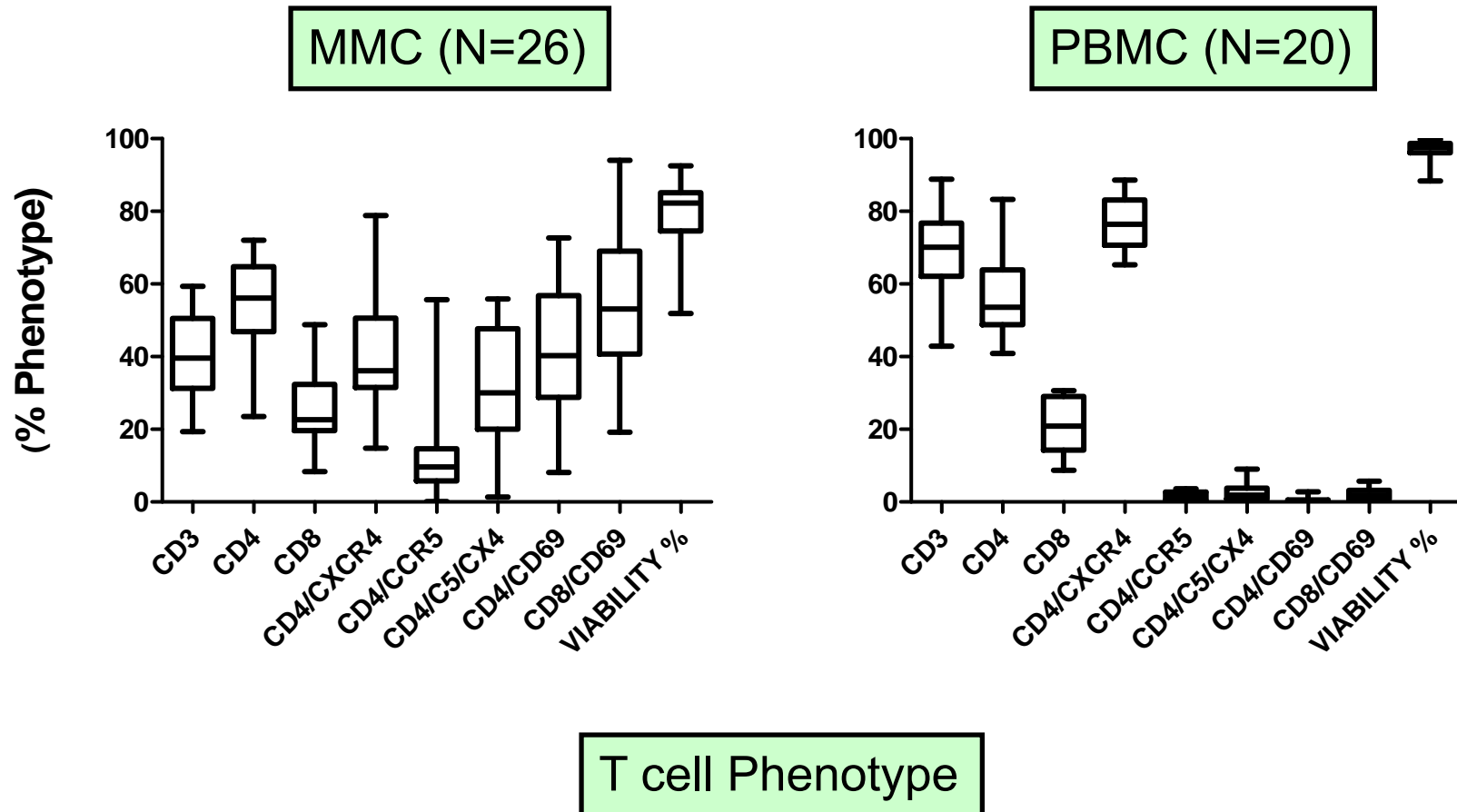


MTN-007

Design of MTN-007

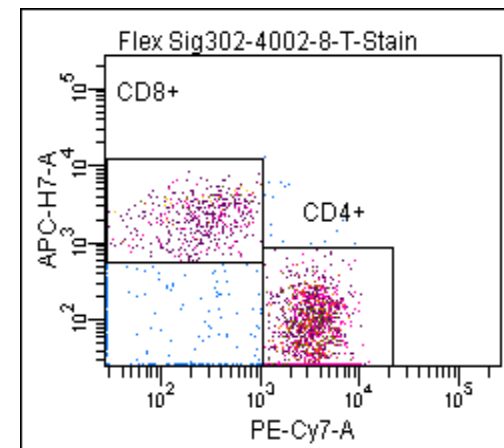
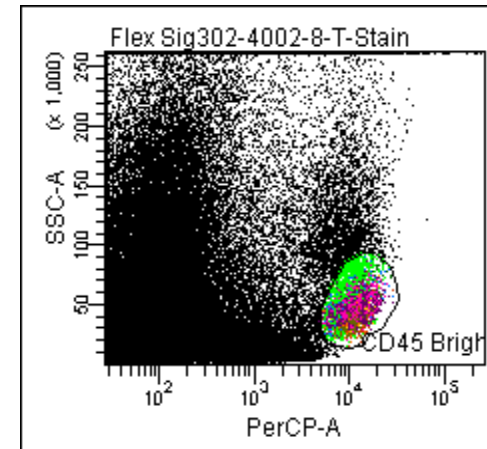
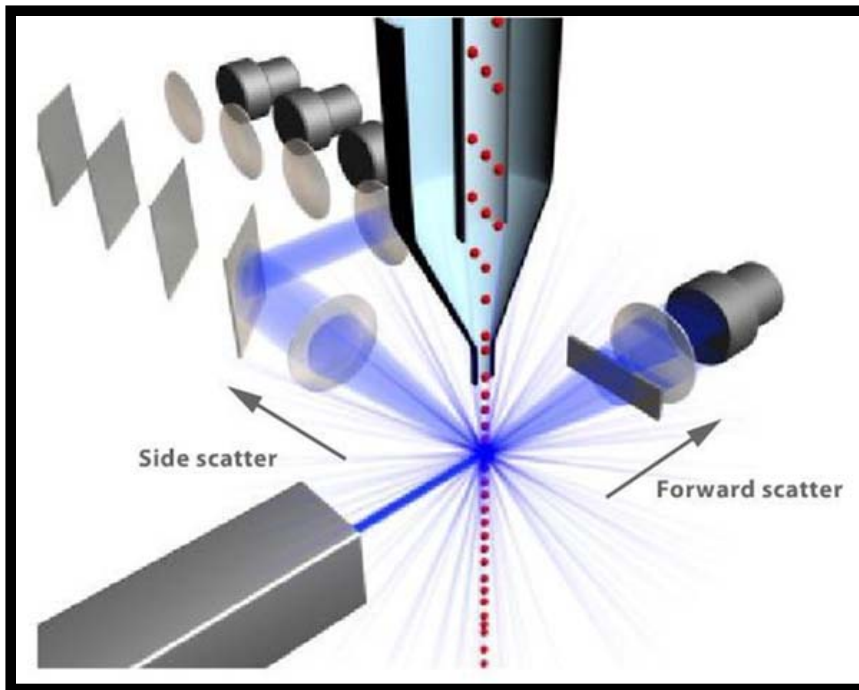


T Cell Phenotype in Blood & GALT



Unpublished Data

T Cell Phenotype Data



MTN-007 Flow Panel

- CD45
- CD3
- CD4
- CD8
- CCR5
- CXCR4
- CD69
- 180 samples at 9cm from anal margin
- 180 samples at 15 cm from anal margin
- Total of 240 baseline samples
 - Baseline + no intervention arm

HVTN Collaboration

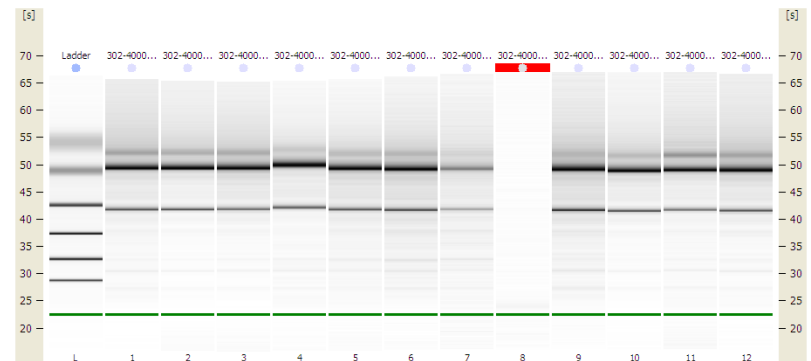
- Comparison of GALT flow data between UCLA and the University of Pittsburgh
- Consensus protocol controlling for:
 - Participants and tissue site Use of qPBMC
 - Standardized monoclonal antibodies
 - Gating strategy and analysis
- Flow panels
 - Phenotype (CD45, CD3, CD4, CD8, CCR5, CXCR4)
 - Memory (CD27, CD45RA)
 - Activation status (HLA-DR, CD69, CD38)
 - Intracellular cytokine stimulation (TNF- α , IFN- γ , IL-2)
 - PMA/ionomycin stimulation

MTN-007 Gene Expression

- 360 samples from 60 participants
 - qRT-PCR (Pittsburgh)
 - Microarray (Seattle)
- PCR Data normalized to 4 reference genes (GAPDH, β 2M, Actin and CD45)
- 12 Targets (CCR5, IL1 β , IL2, IL6, IL12p40, IL17, IL23, IFN γ , MIP1 α , MIP1 β , TNF α , RANTES)

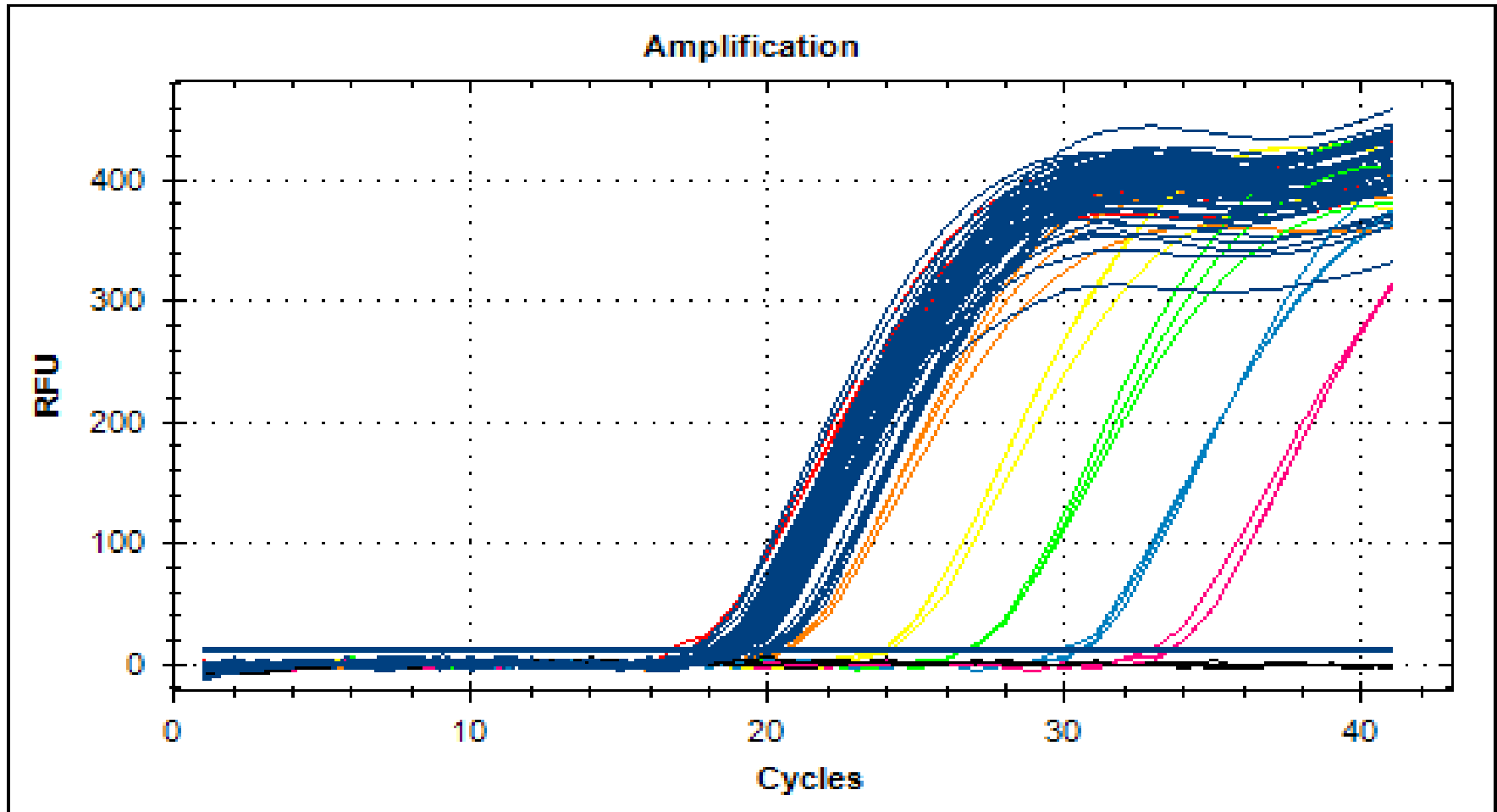
RNA Isolation from Biopsies

Biopsy	Total Yield	18s/28s Ratio	RIN#
Target	>2500ng	≥1.5	# ≥6.0
(1)	5750ng	1.90	8.85
(2)	6050ng	1.75	8.85
(3)	6700ng	1.75	8.10
(4)	8700ng	1.50	6.95
(5)	9800ng	1.85	8.55
(6)	11250ng	1.65	7.20
(7)	8750ng	1.75	8.20
(8)	12300ng	1.95	8.90
(9)	14800ng	2.00	9.10
(10)	11800ng	1.95	9.30
Average	9791ng	1.82	8.48

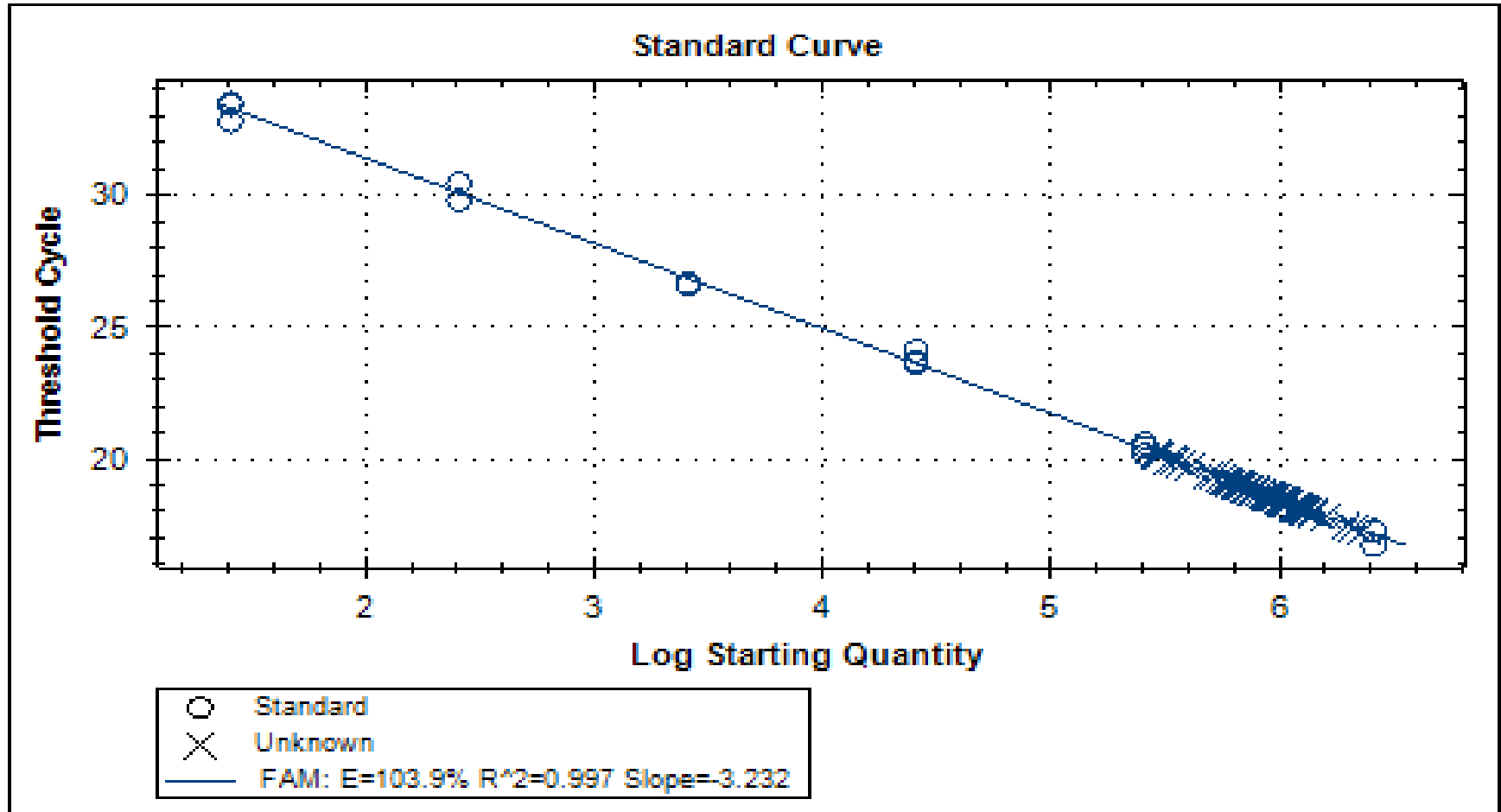


Agilent Ferrogram

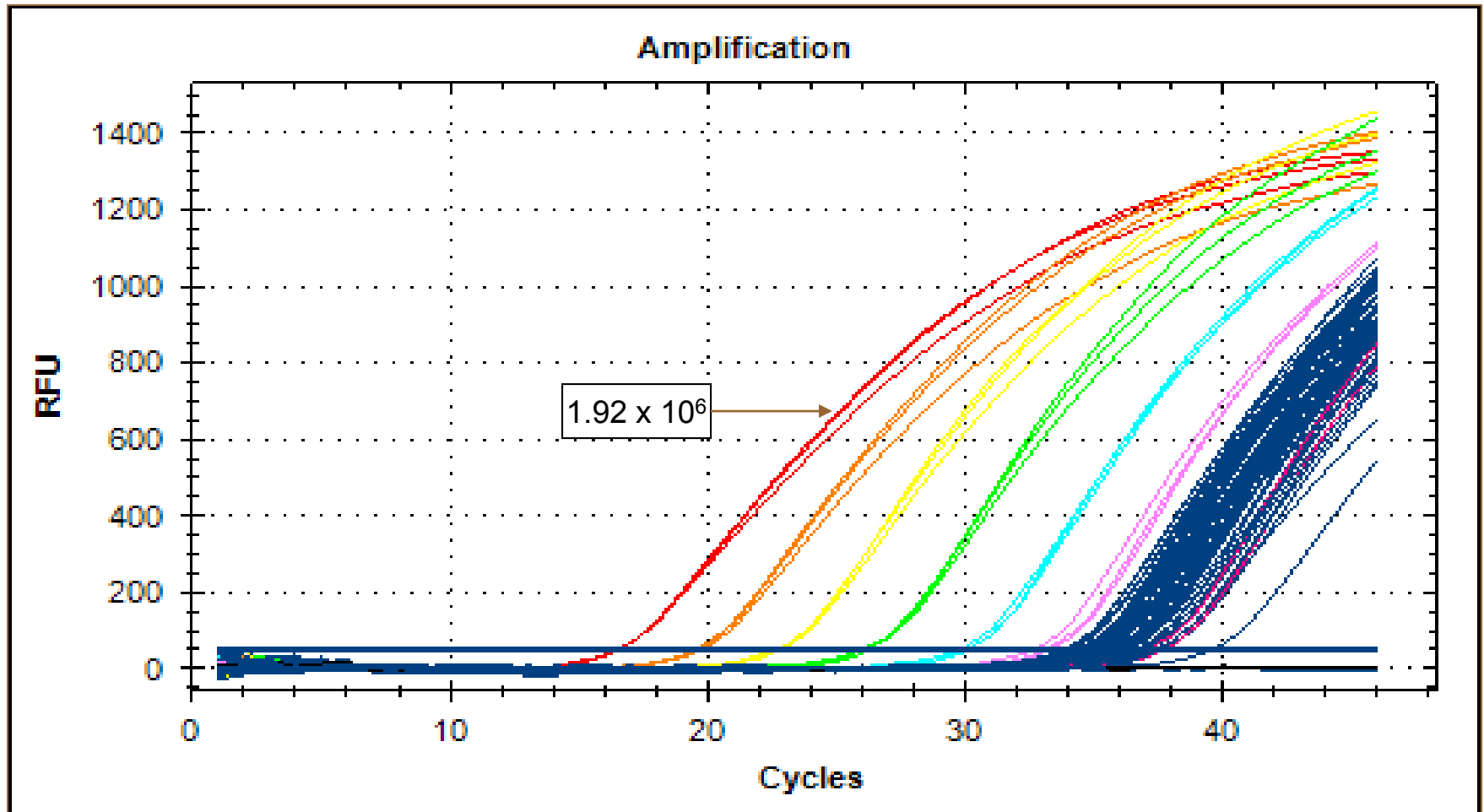
β 2 Microglobulin Gene Expression



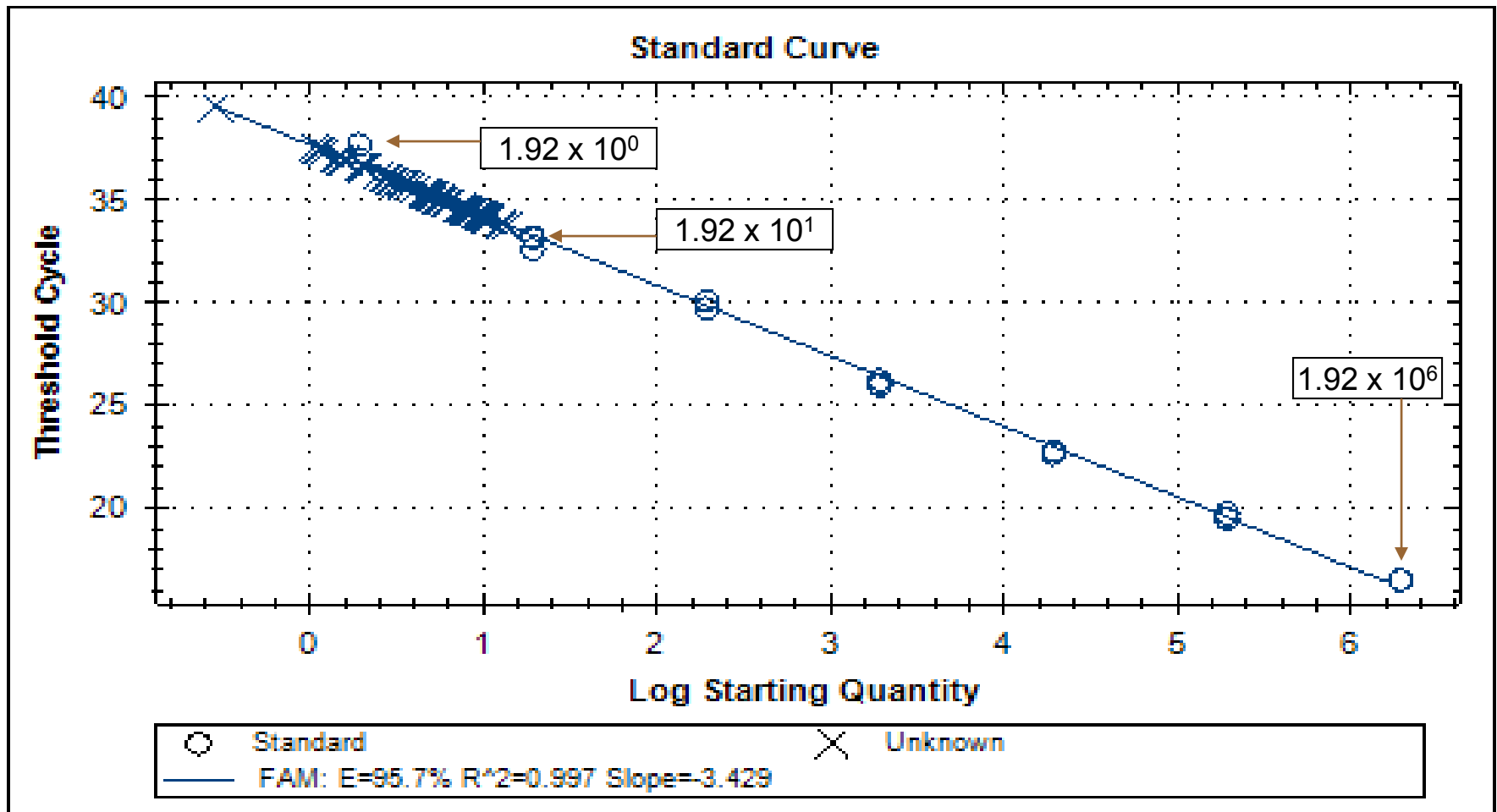
β 2 Microglobulin Standard Curve



Mucosal CCR5 Gene Expression



CCR5 Standard Curve





MTN-017

MTN-017







- Phase 2 Study
- International sites
 - United States
 - Thailand
 - South Africa
 - Peru
- Design: Crossover
- Endpoints
 - Safety
 - Adherence
 - Self report
 - Objective measures
 - Acceptability
 - PK/PD

MTN-017 Preliminary Design



Topical RGF tenofovir 1% gel	Washout	Oral Truvada	Washout	Oral Truvada + Topical RGF tenofovir 1% gel
4-6 weeks	2 weeks	4-6 weeks	2 weeks	4-6 weeks
N = ~ 100 - 120				
Safety and acceptability (All sites)				
Objective measures of adherence (All sites)				
Mucosal safety (Domestic site[s])				
PK/PD (Domestic site[s])				

Rectal Microbicide Timeline*

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

*An approximation based on 1% tenofovir gel



Conclusions

- Unprotected RAI is a common practice in the US and is associated with a very risk of HIV acquisition
- MTN is committed to advance the domestic HIV prevention research agenda through the development of safe and effective rectal microbicides
- The science is moving from Phase 1 to Phase 2 and hopefully soon to an effectiveness trial

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Thank You

