

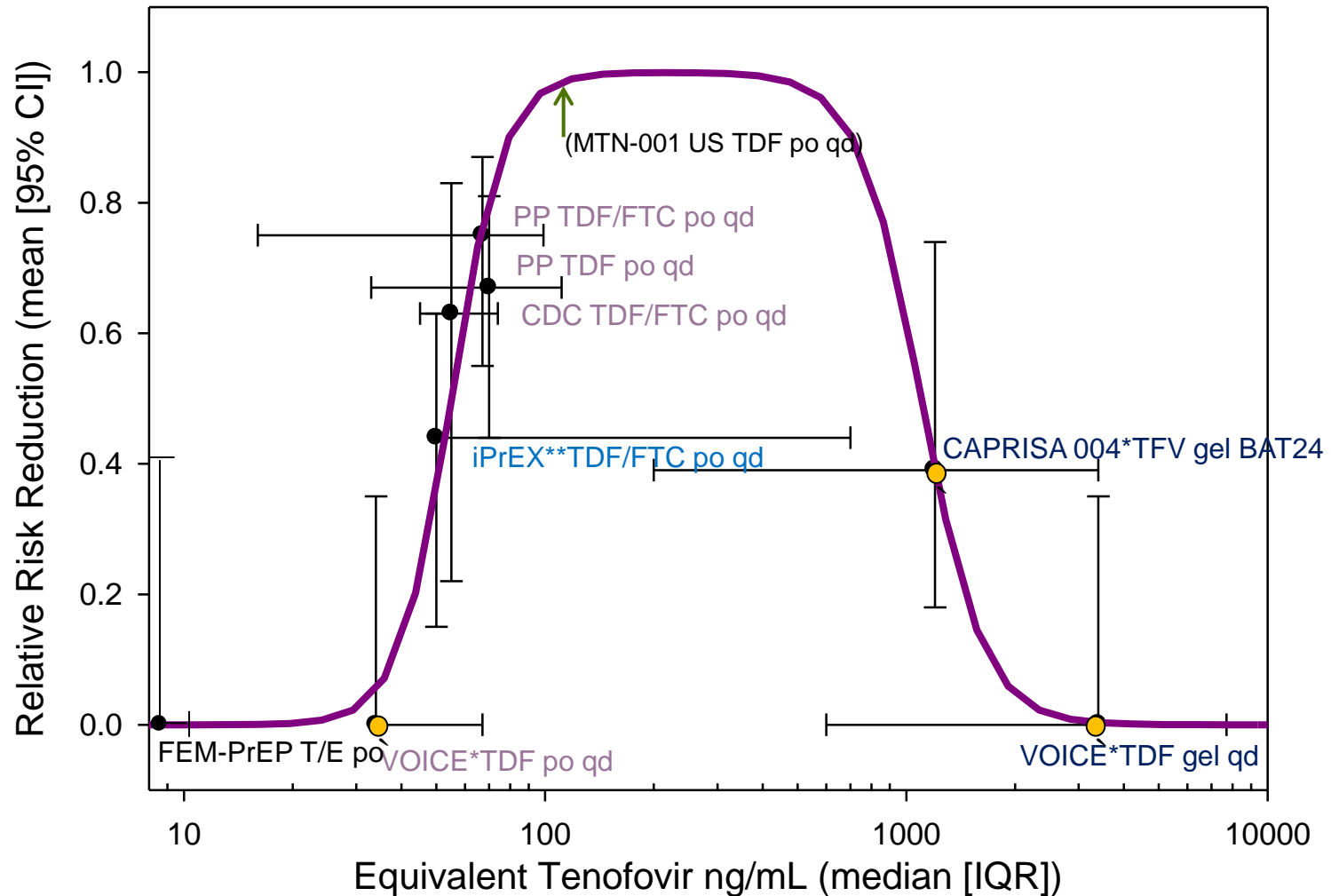


# Antiretroviral Pharmacology for PrEP: Enhancing RCT Understanding with Small Intensive Studies

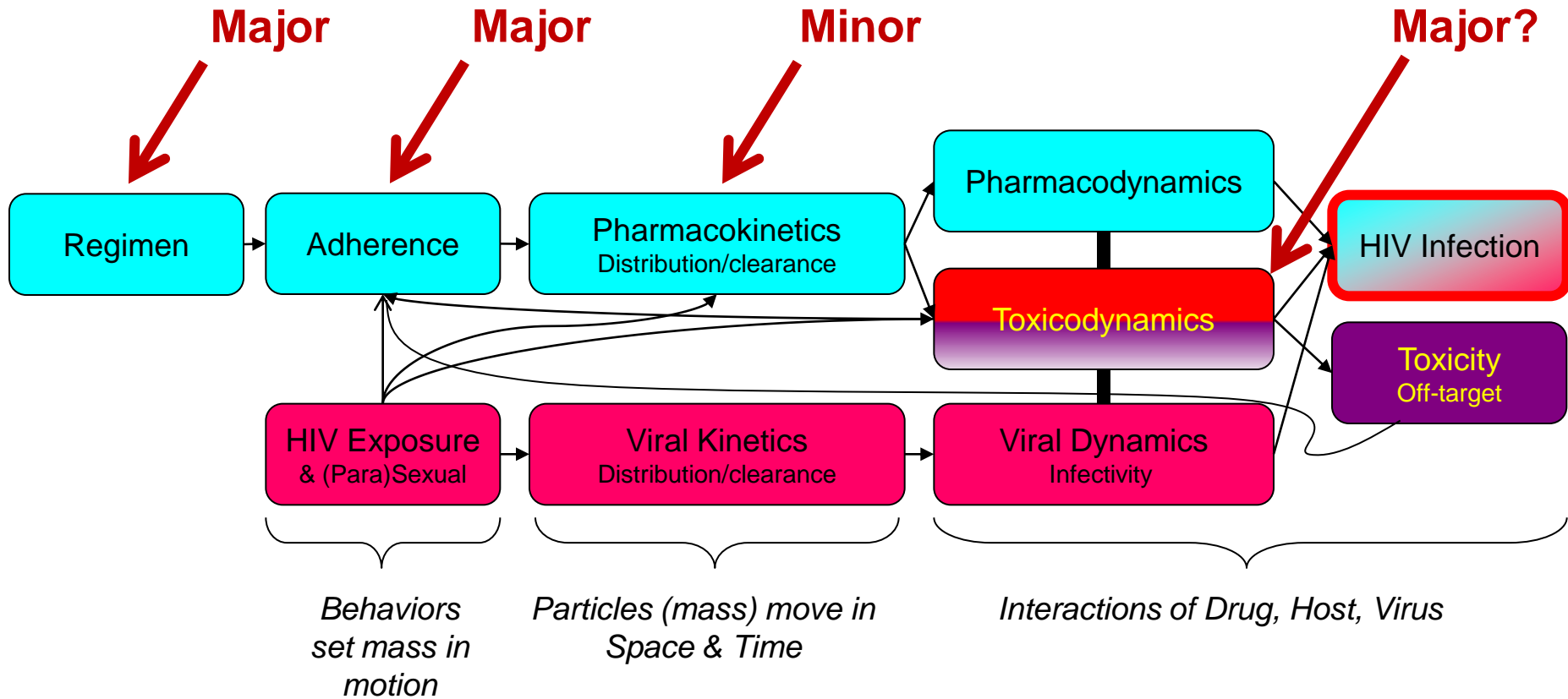
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# PrEP Concentration-Response



# Variables Influencing Infection





# Key Points

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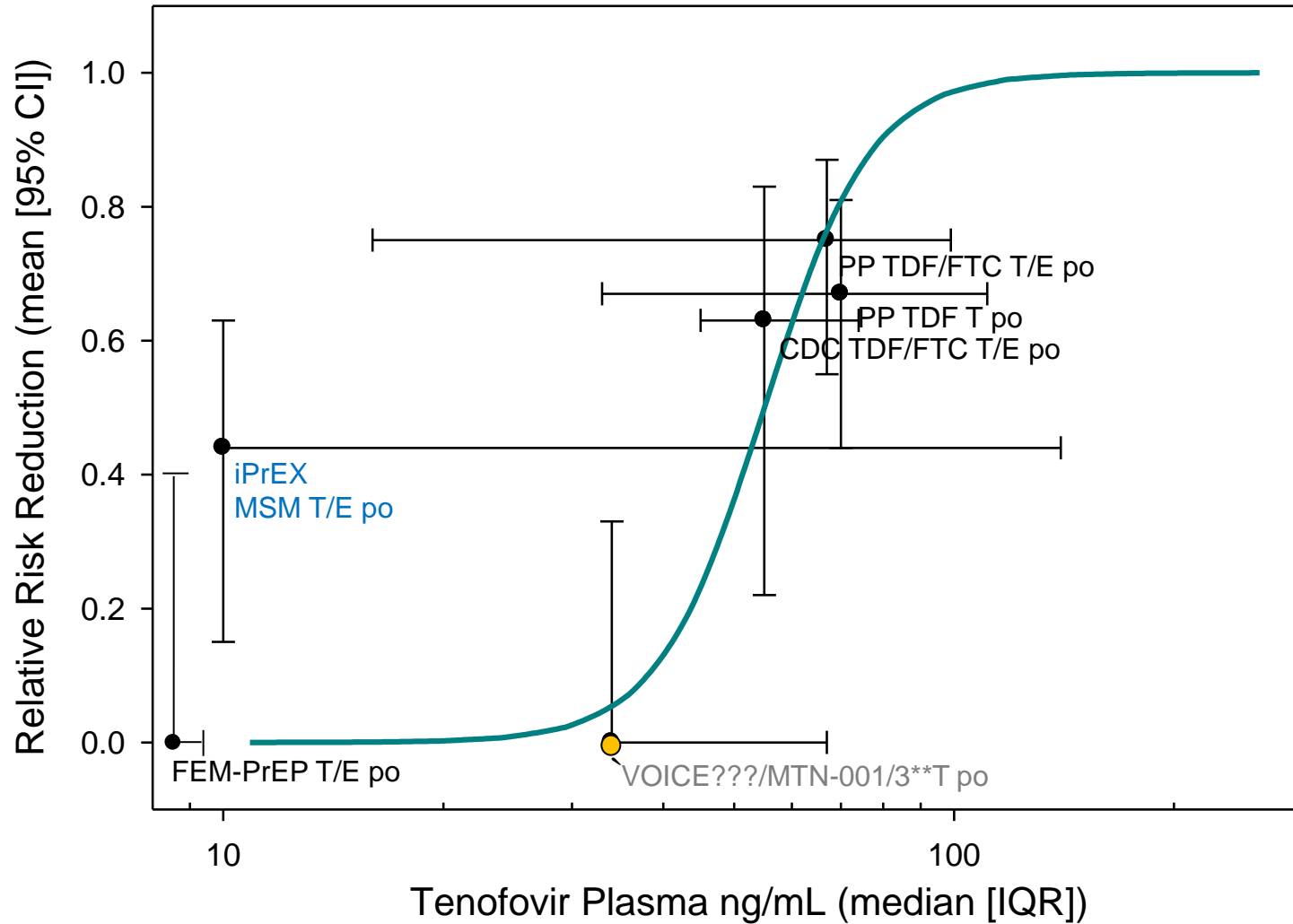
- Within study concentration-response
- Between study concentration-response
- Caution extrapolating MSM results to others
- Adherence (mostly) explains concentration  $\sigma$
- Seroconverter adherence wanes with time
- Target concentration needs more work
- Drug concentration cannot explain all
- Daily regimen affords greatest protection

# Within Study Concentration-Response

Study	Regimen	Relative Risk Reduction (95% CI)		
		All Subjects	Drug Detectible	Adherence
CAPRISA 004	TFV gel BAT24	0.39 (0.04 – 0.60)	>1,000 CVL <sup>b</sup>	0.54 (0.20 – 0.96) <sup>a</sup>
VOICE	TFV gel qd <sup>e</sup>	0.0 (-0.35 – 0.35)	<i>In Analysis</i>	
iPrEX	TDF/FTC po qd	0.42 (0.15 – 0.63)	0.92 (0.40 – 0.99) <sup>c</sup> ; BLQ <b>10</b>	
Partners	TDF/FTC po qd	0.75 (0.55 – 0.87)	0.90 (0.58–0.98) <sup>c</sup> ; BLQ <b>0.3</b>	
	TDF po qd	0.67 (0.44 – 0.81) <sup>d</sup>	0.86 (0.67–0.94) <sup>c</sup> ; BLQ <b>0.3</b>	
CDC TDF2	TDF/FTC po qd	0.63 (0.22 – 0.83)	<i>In Analysis</i>	0.78 (0.41 – 0.94) <sup>e</sup>
FEM-PrEP	TDF/FTC po qd	0.0 (-0.73 – 0.42)	No difference	
VOICE	TDF po qd <sup>e</sup>	0.0 (-0.35 – 0.35)	<i>In Analysis</i>	

<sup>a</sup>High adherence (>80% self-report); CVL>1,000 log-rank significant; <sup>c</sup>Detectable drug; <sup>d</sup>TDF v TDF/FTC NS; <sup>e</sup>Available supply of study drug

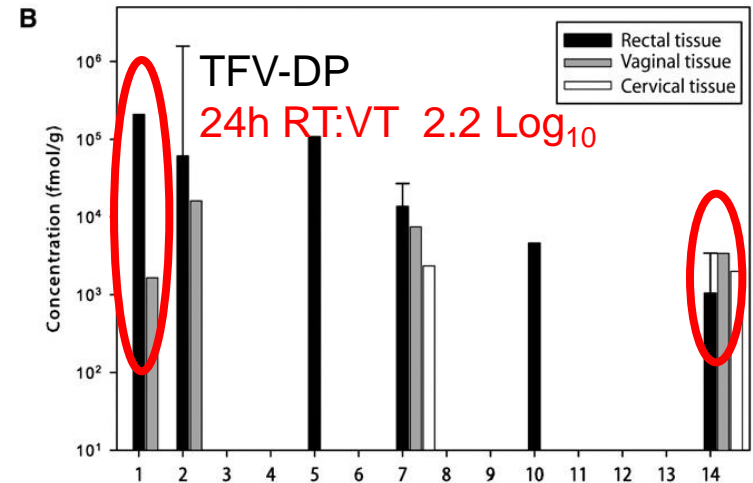
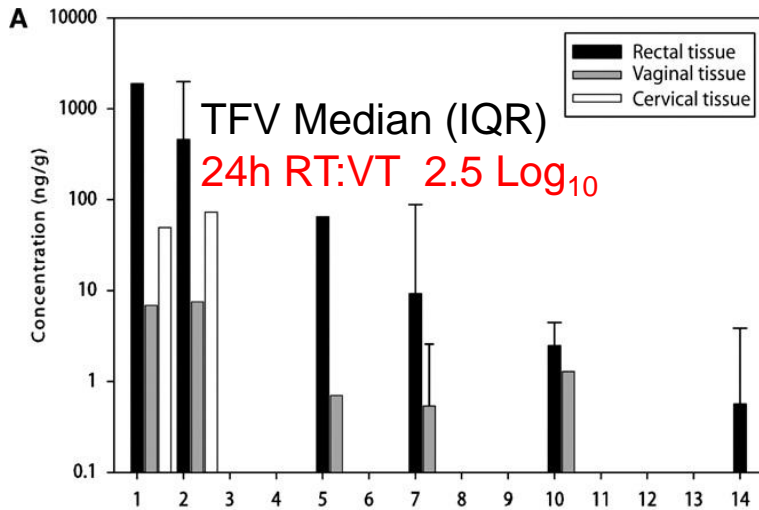
# Among Study Concentration-Response



\*\*VOICE simulated by MTN-001 African sites

# Rectal:Vaginal Tissue Comparison

Patterson, *et al.* Sci Trans Med 2011



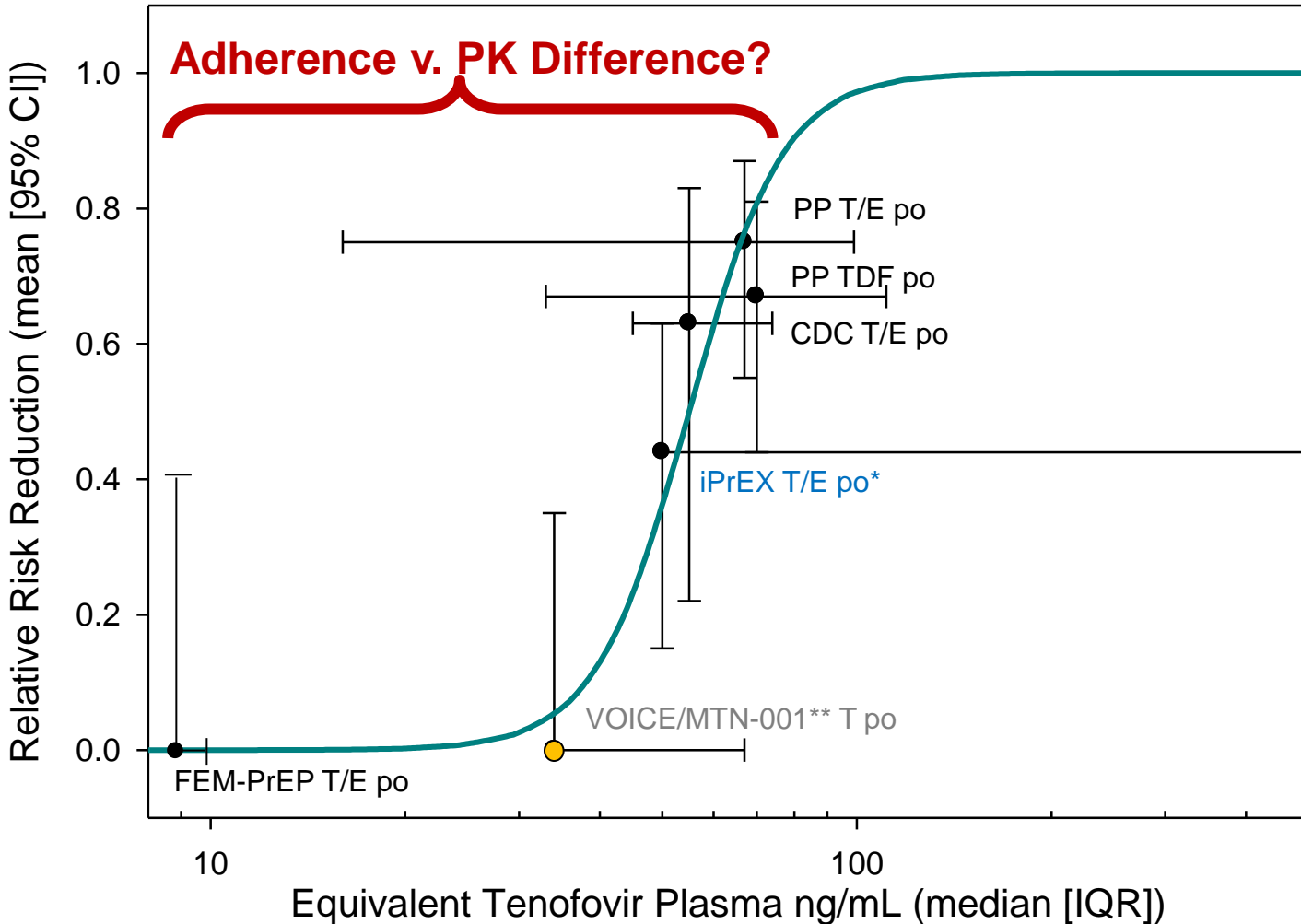
Louissaint, *et al.* Keystone 2011

Day	RT:VT TFV Median (IQR)	RT:VT TFV-DP Homogenate Median (IQR)	RT:VT TFV-DP CD4 Cells Median (IQR)
1	33.8 (6.8, 37.8)	123.7 (8.4, 155.4)	19.20 (9.60, 28.8)
8	4.5 (0.9, 31.3)	1.7 (0.3, 2.8)	0.20 (0.17, 0.23)
15	0.3 (0.3, 0.3)	2.5 (2.5, 2.6)	0.15 (0.15, 0.15)

TFV-DP RT:VT Gradient

- RT > 100x VT @ 24h
- Not sustained
- CD4 gradient smaller

# Among Study Concentration-Response

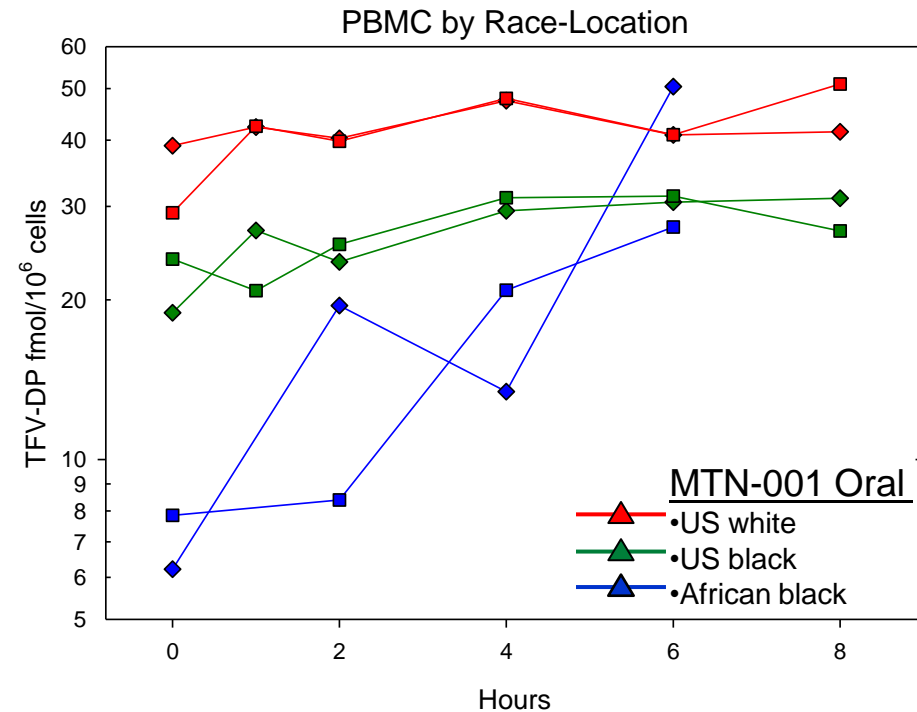
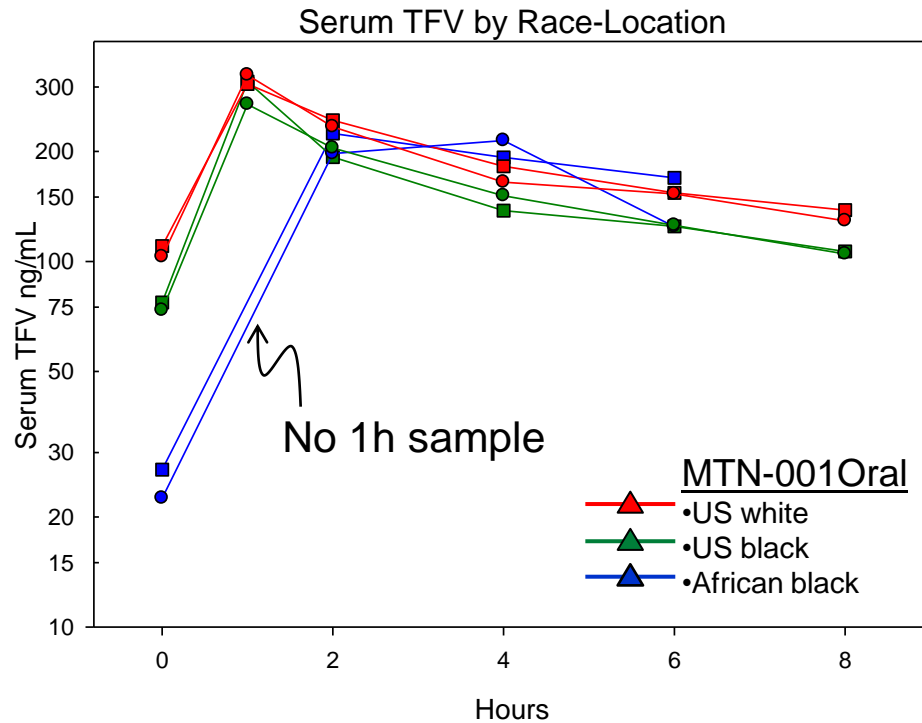


\*Adjusted for 66x increased colon tissue concentration (→) and 20 times greater anal transmission risk (←)

\*\*VOICE simulated by MTN-001 African sites



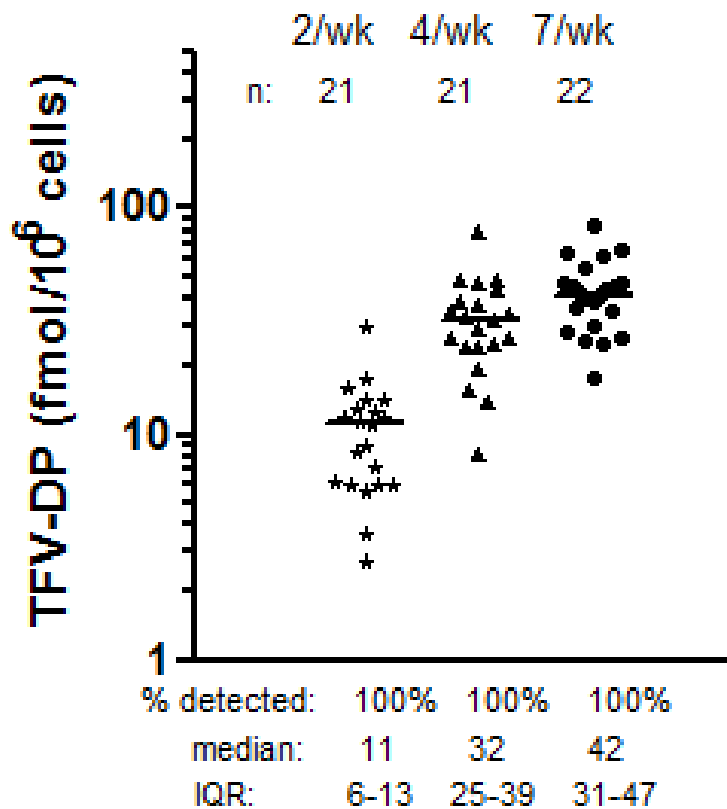
# [TFV] Variation: Adherence or PK?



- Decay (PK) same after observed dose
- Pre-dose concentration (adherence) 5x different
- TFV catches up in 1 hr; TFV-DP in 8 hrs.

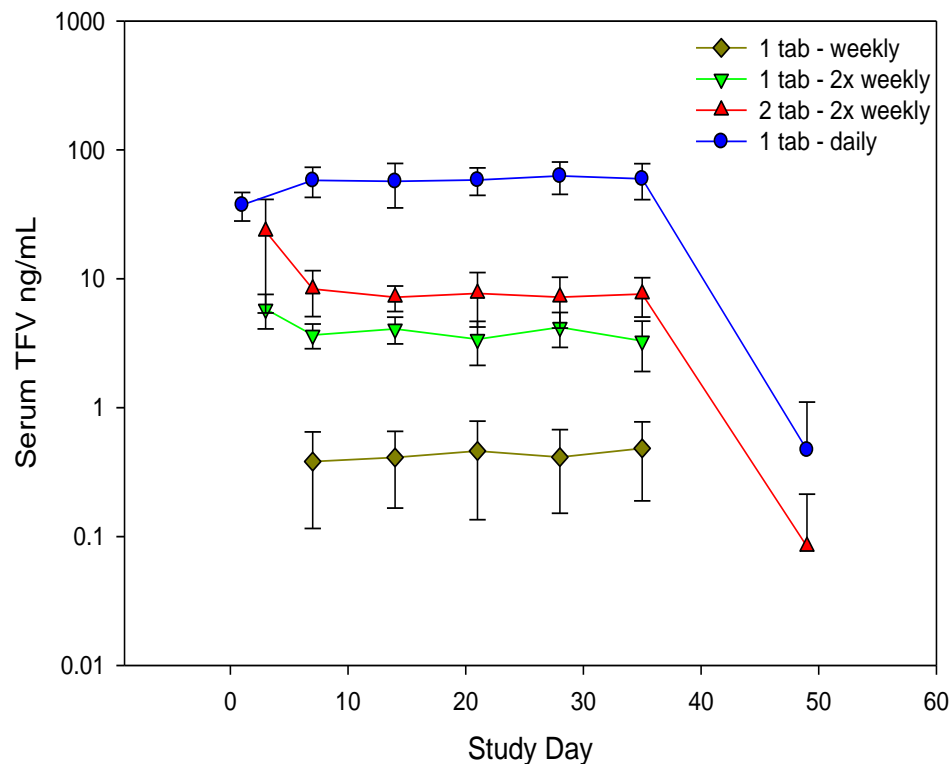
# DOT: Benchmarks & Models

## STRAND



Anderson, et al. CROI 2012

## HPTN 066

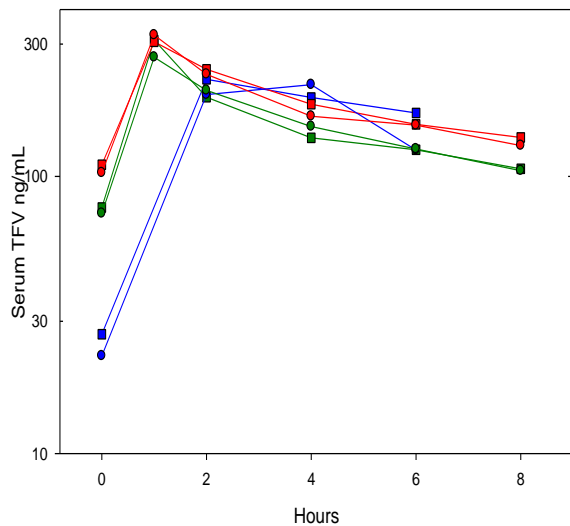


HPTN 066 Study Team (Donnell CROI 2012)

# Population PK: Adherence & PK

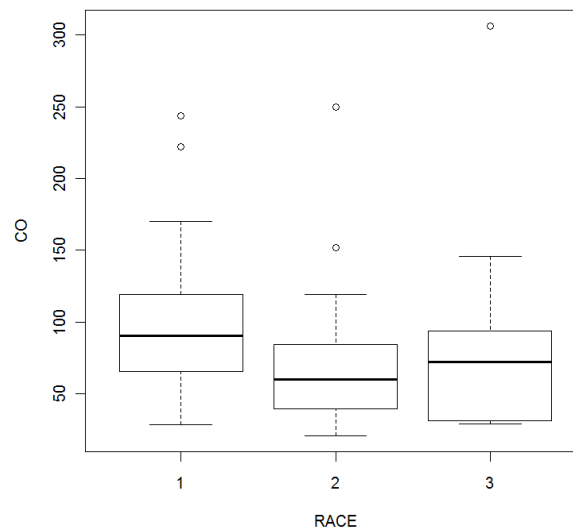
- Combine data from HPTN 066 & MTN-001
- Build non-linear mixed effects model
- Estimate PK ( $Cl$ ,  $V$ ,  $Ka$ ) and adherence ( $C_0$ )

Observational Data

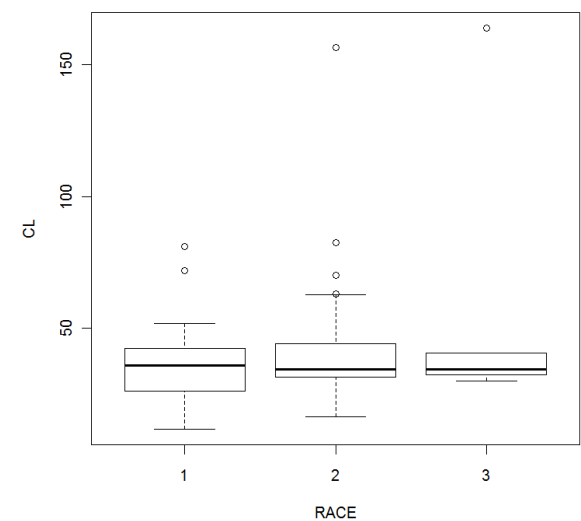


US White, US Black, Africa Black  
Oral dosing (MTN-001)

Adherence Measure ( $C_0$ )

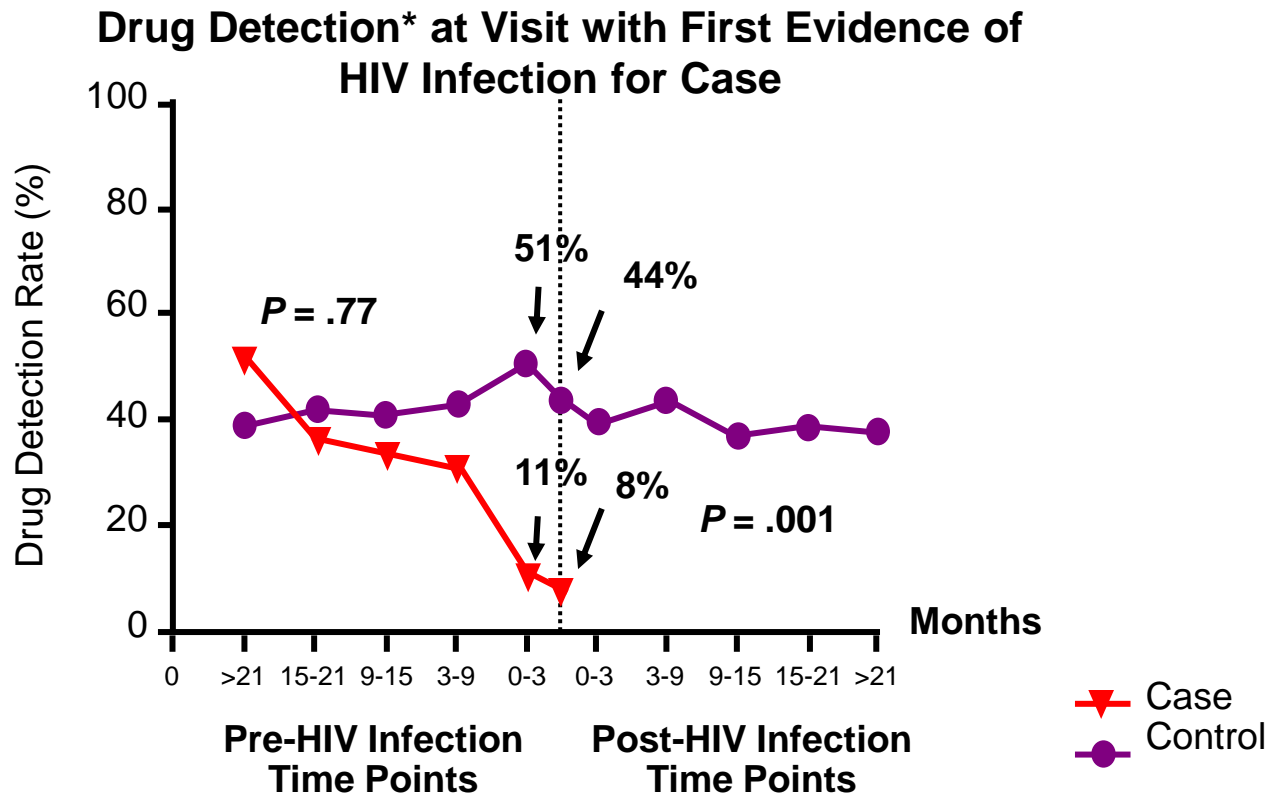


Clearance ( $Cl$ )



# iPrEx: [Drug] Falls in Seroconverters

Temporal pattern consistent with adherence change, but not PK change

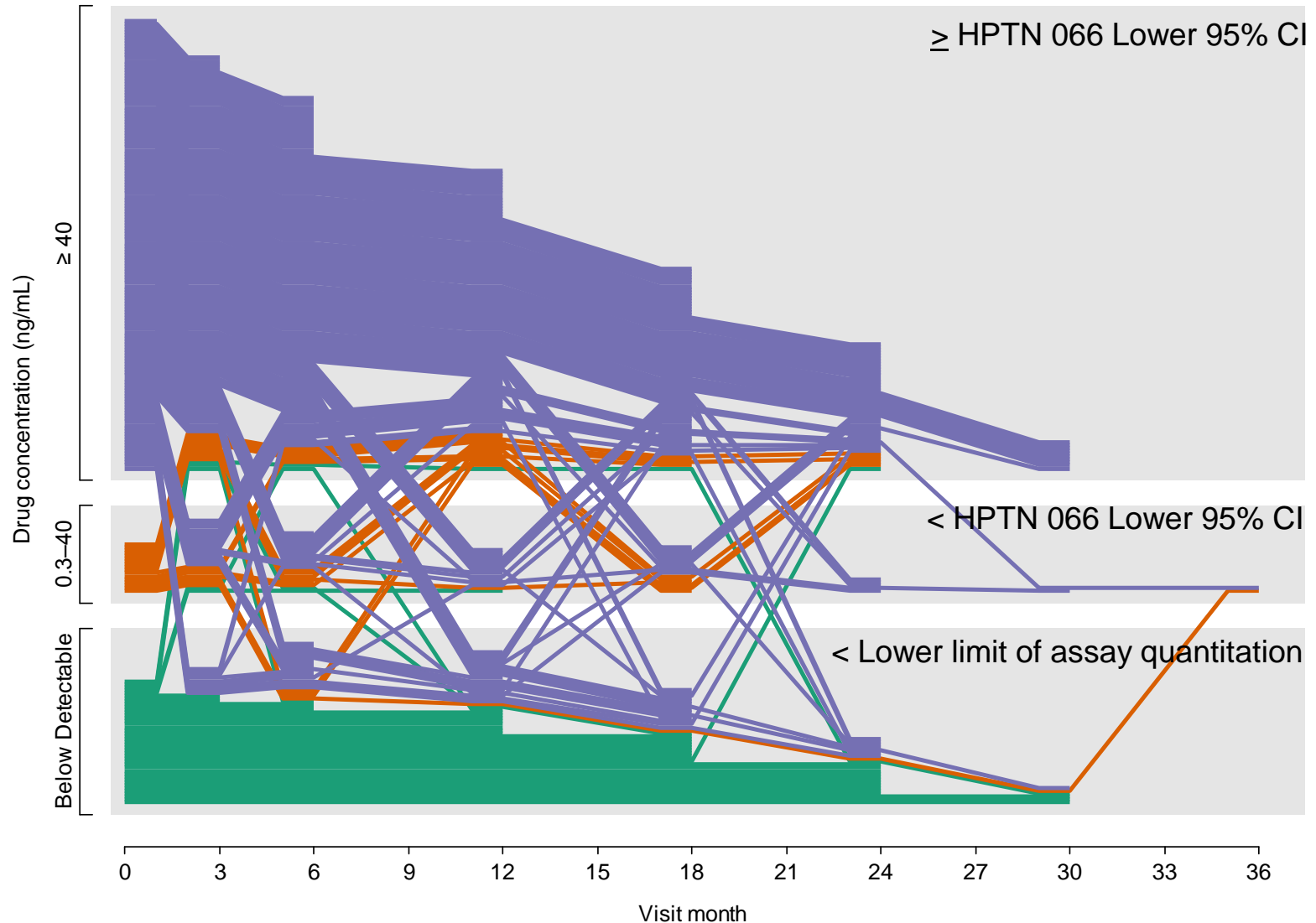


-<50% drug detected in non-seroconverters

-HIV infection occurred during periods of low drug exposure

Anderson PL, *et al.* CROI 2012. Abstract 31LB.

# Partners: Transients in Non-seroconverters



# HPTN 066 Plasma TFV Comparisons

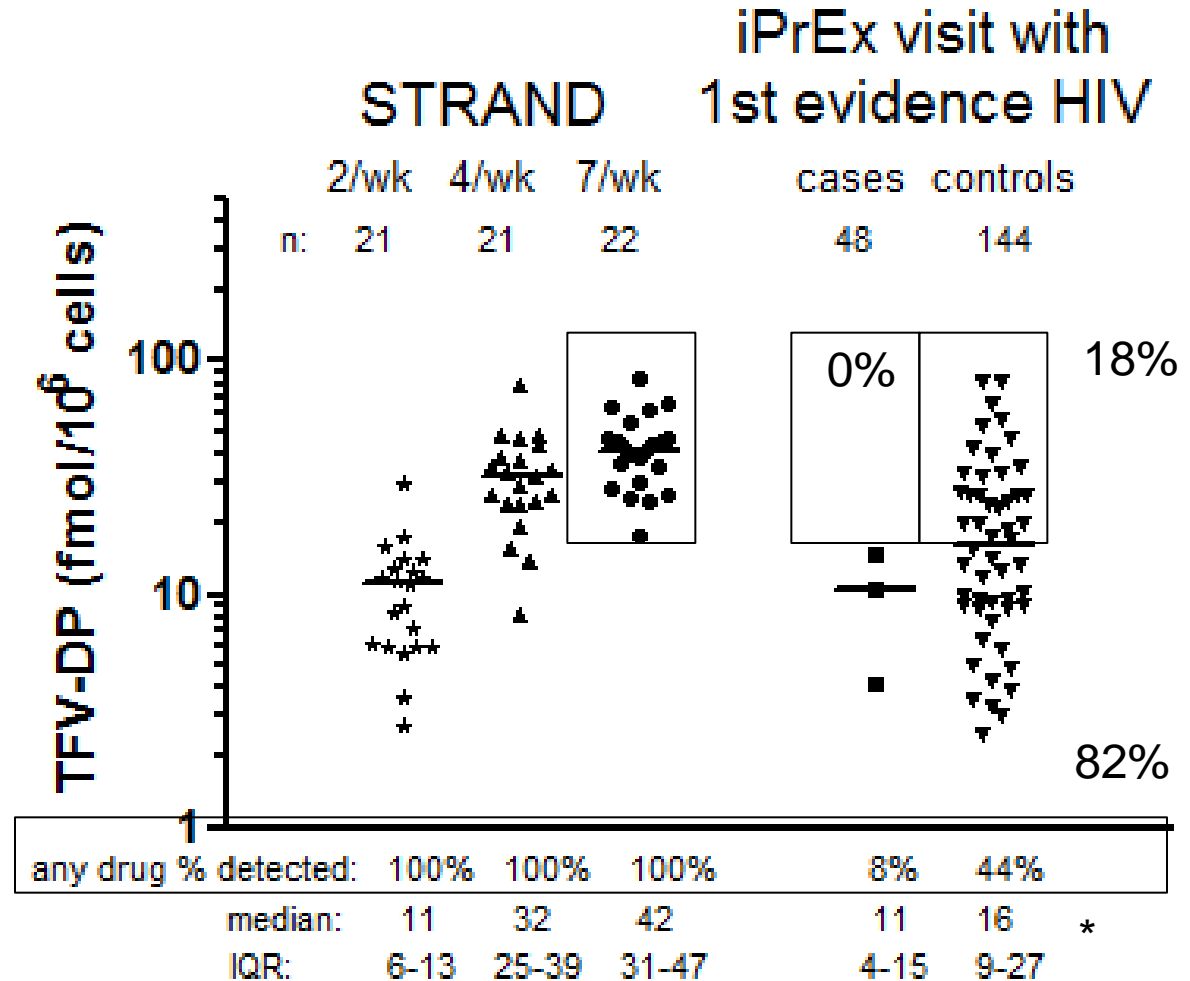
Study	Daily	4x/week*	2x/week	Weekly
<i>DOT HPTN 066 Mean</i>	59	23.4	3.7	0.4
<i>DOT HPTN 066 L95%CI</i>	40	15.9	2.5	0.2
MTN-001 US	~100			
Partners PrEP	~ 65 (67-75%)			
CDC TDF2	~ 55 ( 62% )			
MTN-001 Africa		~25		
iPrEX			~ 10 (42%)	
FEM-PrEP			<10 ( 0%)	
<i>VOICE</i>	?	?	?	?

Figures are mean/median TFV plasma concentration ng/mL (% relative risk reduction)

\*Model estimate

# iPrEx vs STRAND Benchmarks

- Low % detection suggests < 2 doses/week.
- 0% cases, 18% controls in range of daily dosing.
- The majority of active arm dosing < daily, still the overall iPrEx trial efficacy was 42%.



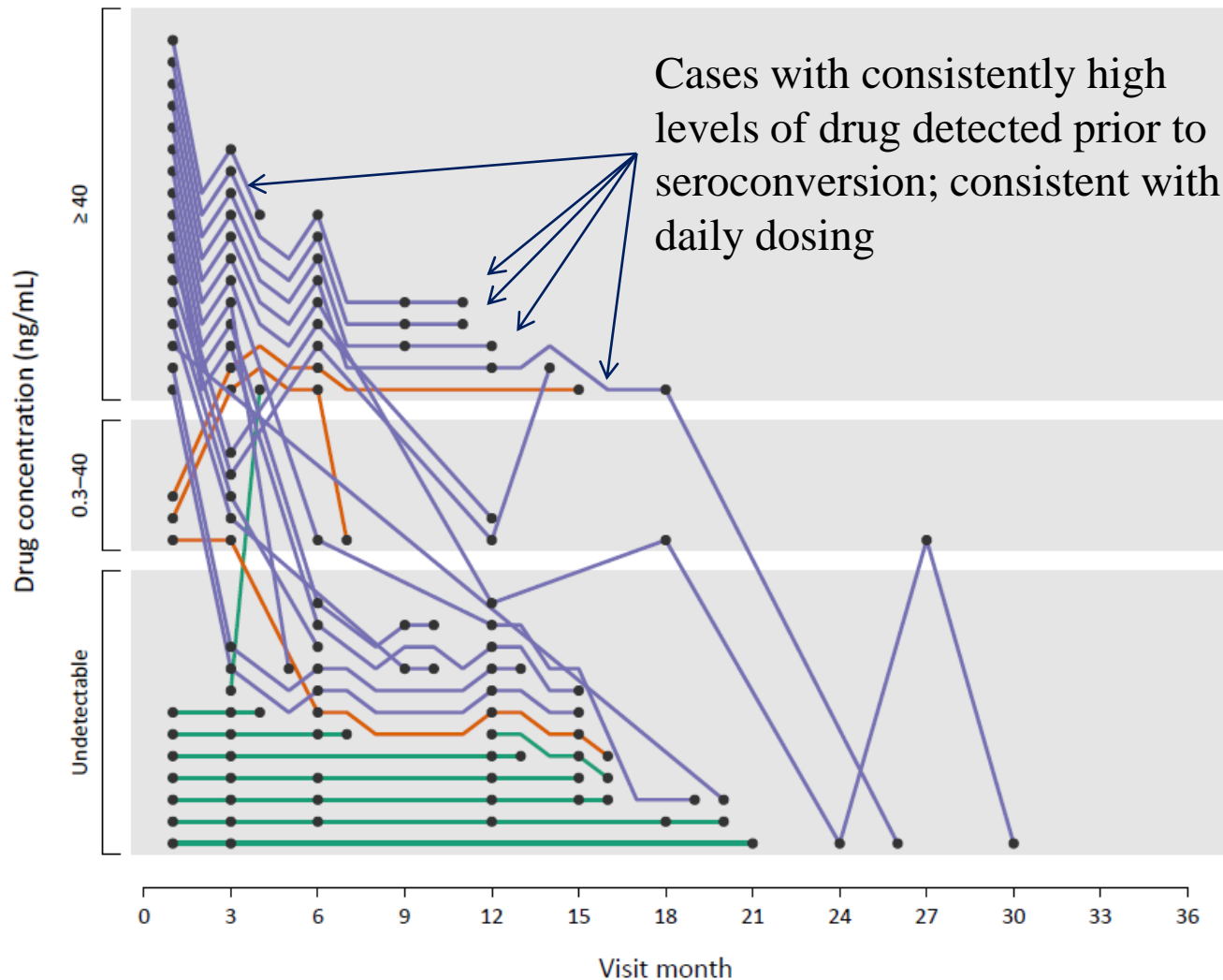
# iPrEX Risk Reduction & STRAND Dosing

Adherence (STRAND)	iPrEx model estimate for HIV Relative Risk Reduction (95% CI)
2 doses/wk	76% (56 to 96%)
4 doses/wk	96% (90 to >99%)
7 doses/wk	99% (96 to >99%)

90% effective TFV-DP ( $EC_{90}$ ) = 16 (95% CI, 3 to 28) fmol/million viable PBMC.  
TFV-DP levels from STRAND analyzed with regression model from iPrEx.  
Anderson CROI 2012



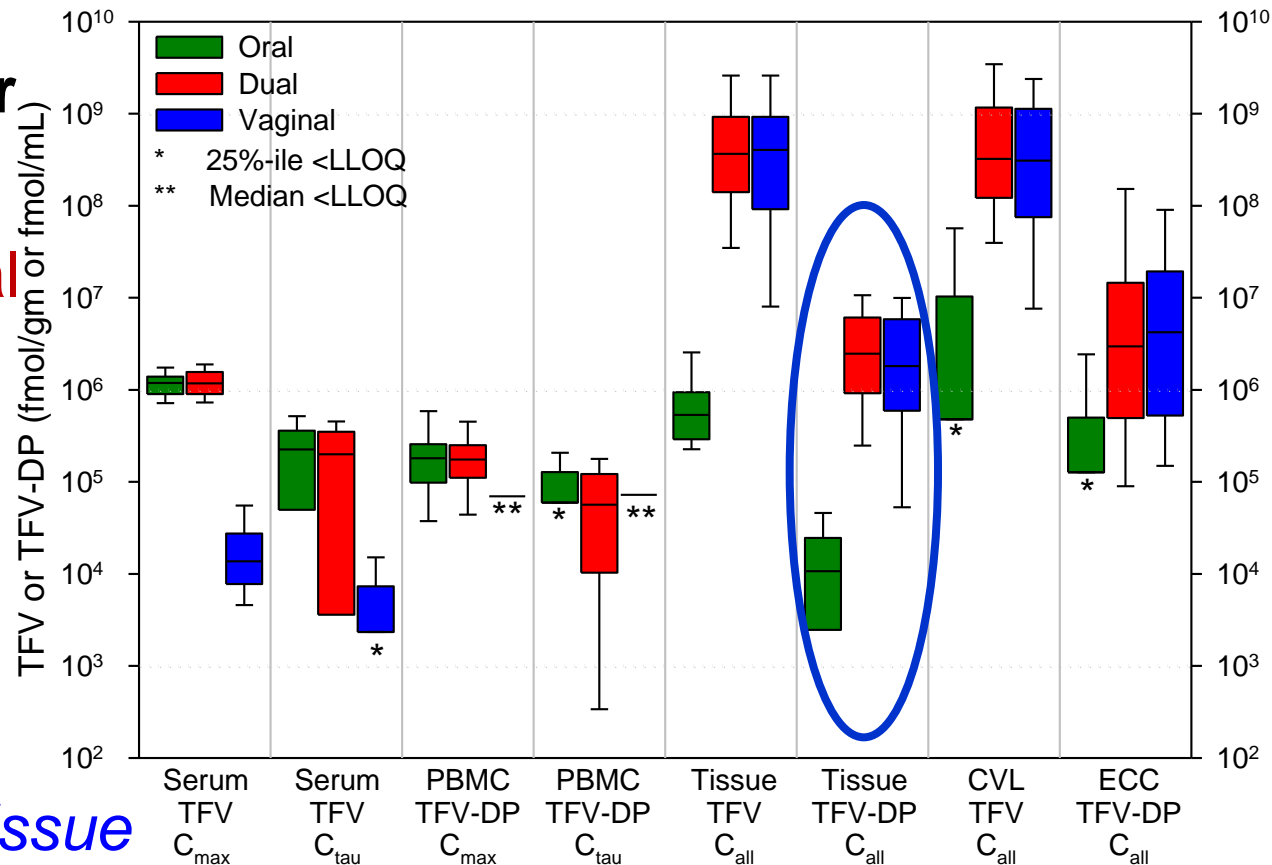
# Partners Seroconverters: More than [TFV]



# Relating Oral to Topical Dosing

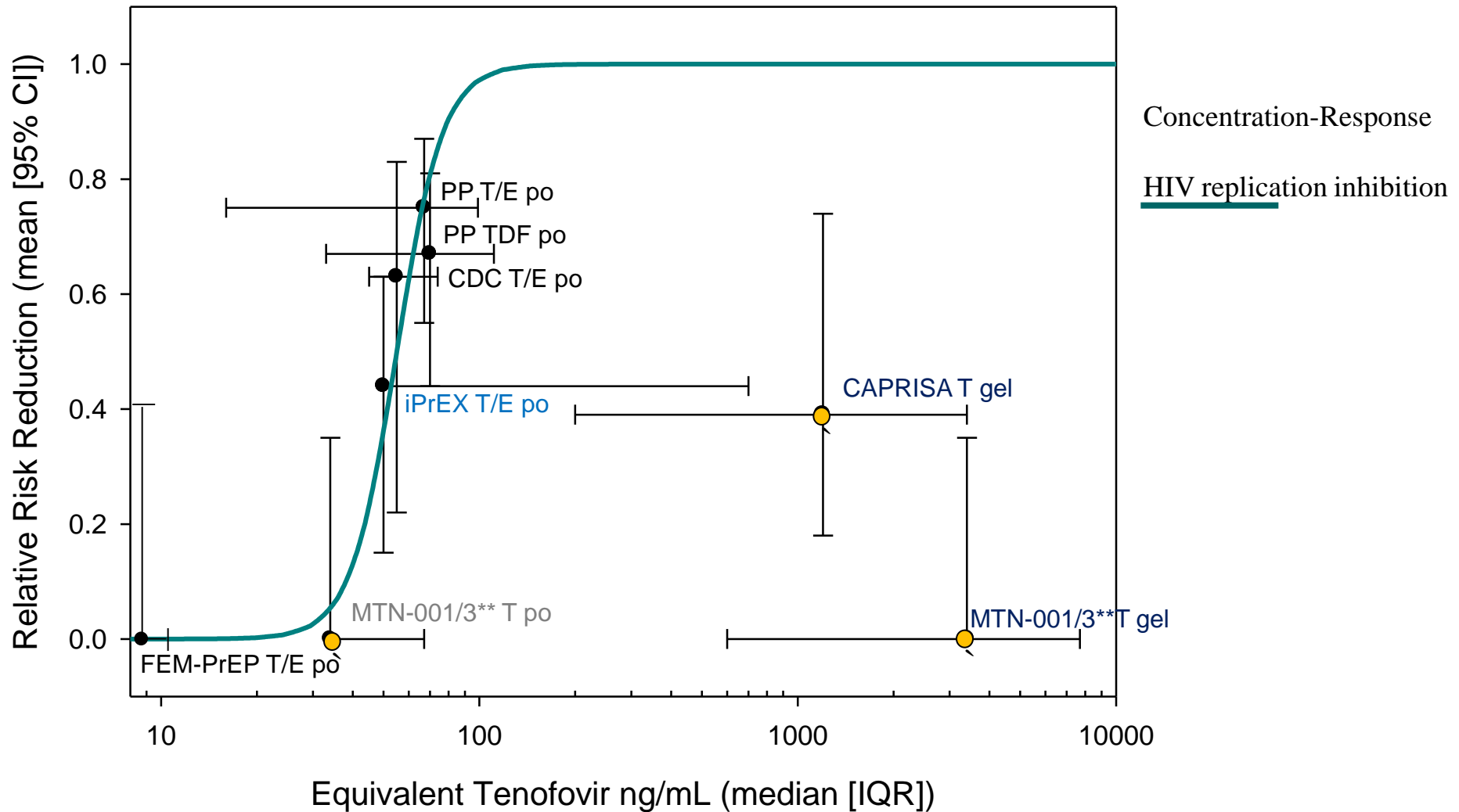
## MTN-001 Cross-Over

- TFV daily
- Oral, Vaginal, Dual
- Cross-over design
- 144 Women
- Africa, US
- Multi-site PK



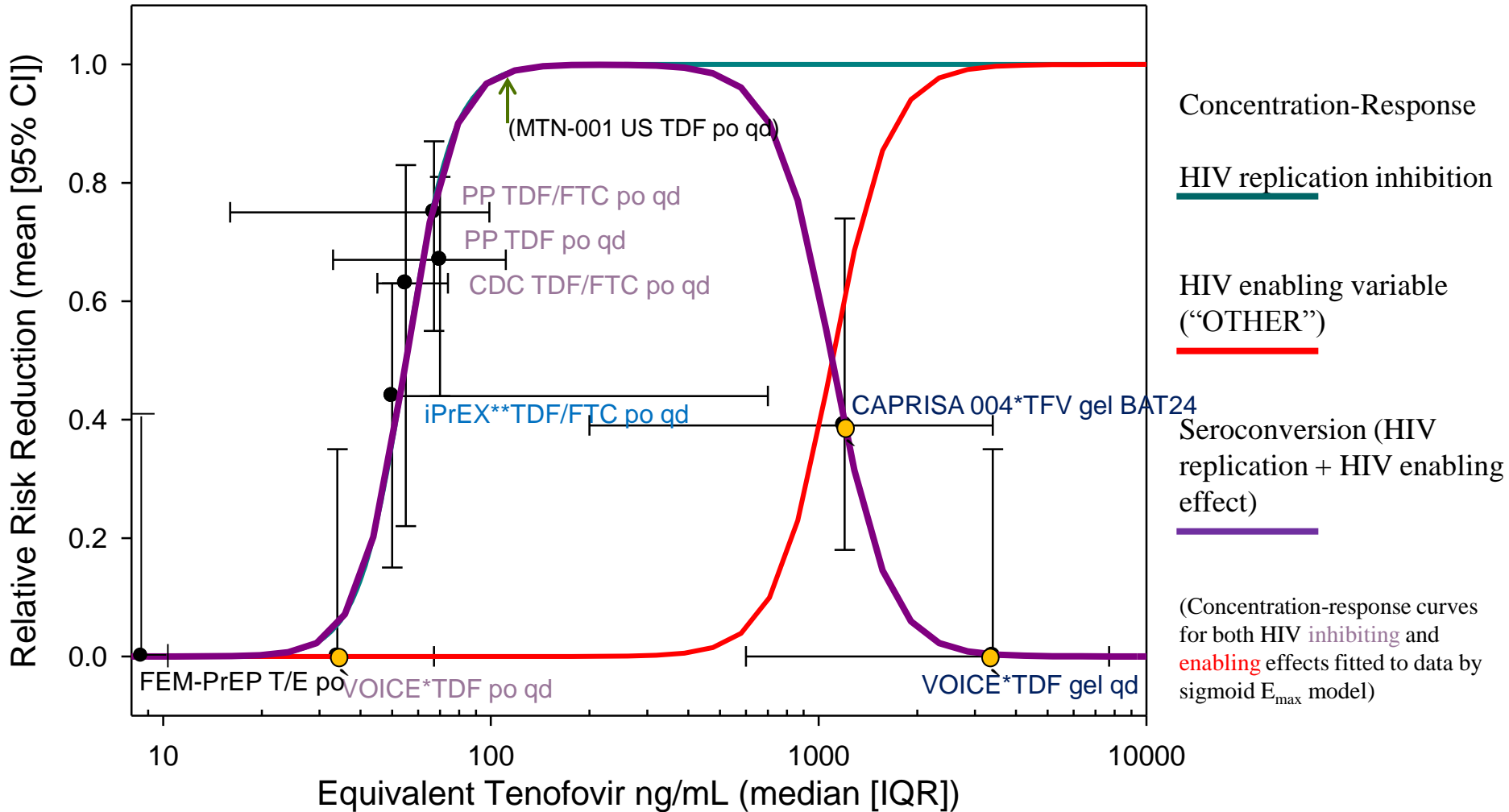
- *Relate Serum to tissue*
- *Vaginal tissue TFV-DP 100x higher with vaginal dosing*
- *Expect vaginal >> oral efficacy*

# Reconciling Oral & Topical Results



\*\*VOICE simulated by MTN-001 African sites

# Adherence (Oral) & HIV-Enabling? (Topical)





# Key Clinical Pharmacology Points

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- Clear within study concentration-response
- Clear between study concentration-response
- Caution extrapolating MSM results to others
- Adherence mostly explains concentration
- Seroconverter adherence wanes with time
- Critical concentration needs additional work
- Daily regimen affords greatest protection



# Thank You

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- Research Participants
- Pete Anderson, iPrEX
- Lut van Damme, FEM-PrEP
- Deborah Donnell, Partners PrEP Co-Is
- Mike Thigpen, Lynn Paxton, CDC TDF2 Co-Is
- Kris Patterson, Ken Mayers, HPTN 066 Co-Is
- MTN-001 Study Team
- Johns Hopkins Clinical Pharmacology