Clinical Pharmacology of Antiretrovirals for HIV Prevention: Implications for PrEP Efficacy and Adherence

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Pre-Exposure Prophylaxis

- PrEP ï prophylaxis for HIV susceptible
- Prevention control to receptive partner
- PMTCT precedent supported by animal models
- 1996-2009, 6 RCT luminally active vaginal gels failed
- 2010-2012, 6 RCT oral (TFV±FTC) & topical (TFV)
  - Efficacy demonstrated, but highly variable results
- 2012 FDA market approval for TDF/FTC (Truvada)
  - Combination with safer sex practices
  - Adults (men & women) at high risk of HIV infection
  - Single oral daily dose
  - Label emphasizes importance of adherence
- RCTs alone leave many unanswered questions

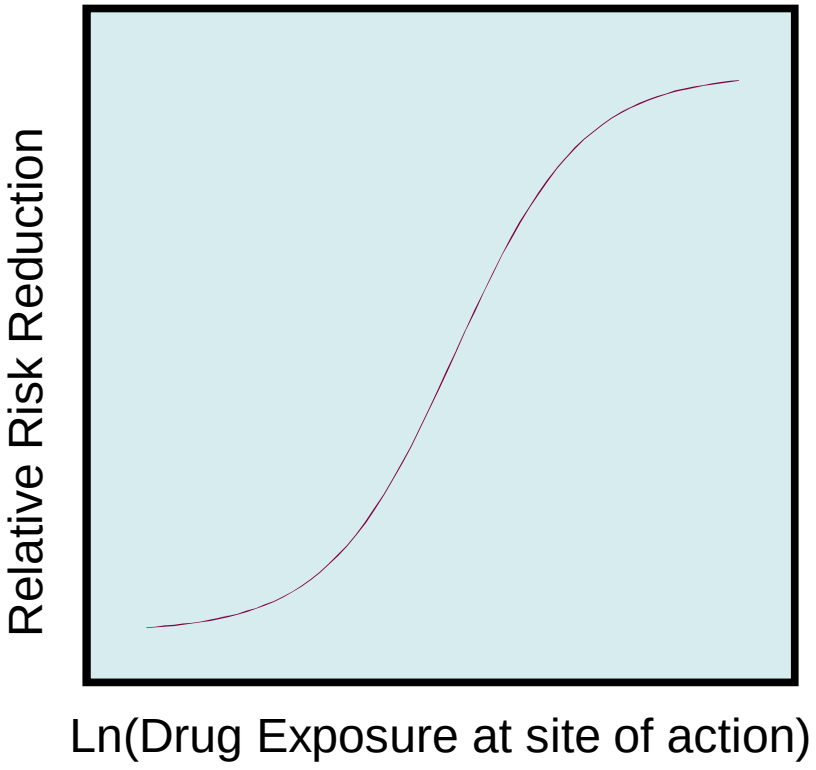
Outline

Clinical pharmacology studies informé

- é concentration-response relationship (target?)
- é how many doses before protection?
- é colon tissue ñadvantageò?
- é topical dosing advantage?
- é adherence source of study variability?
- é limitation of adherence estimates?
- é EMS and PK combination usefulness?

Concentration-response

- As drug concentration increases, efficacy increases
- Identify concentration target
- Informs dose & frequency
- Identify site of action (?)
- Poor concentration-response indicates additional variables
  - Clues to mechanism of action
  - Clues to management

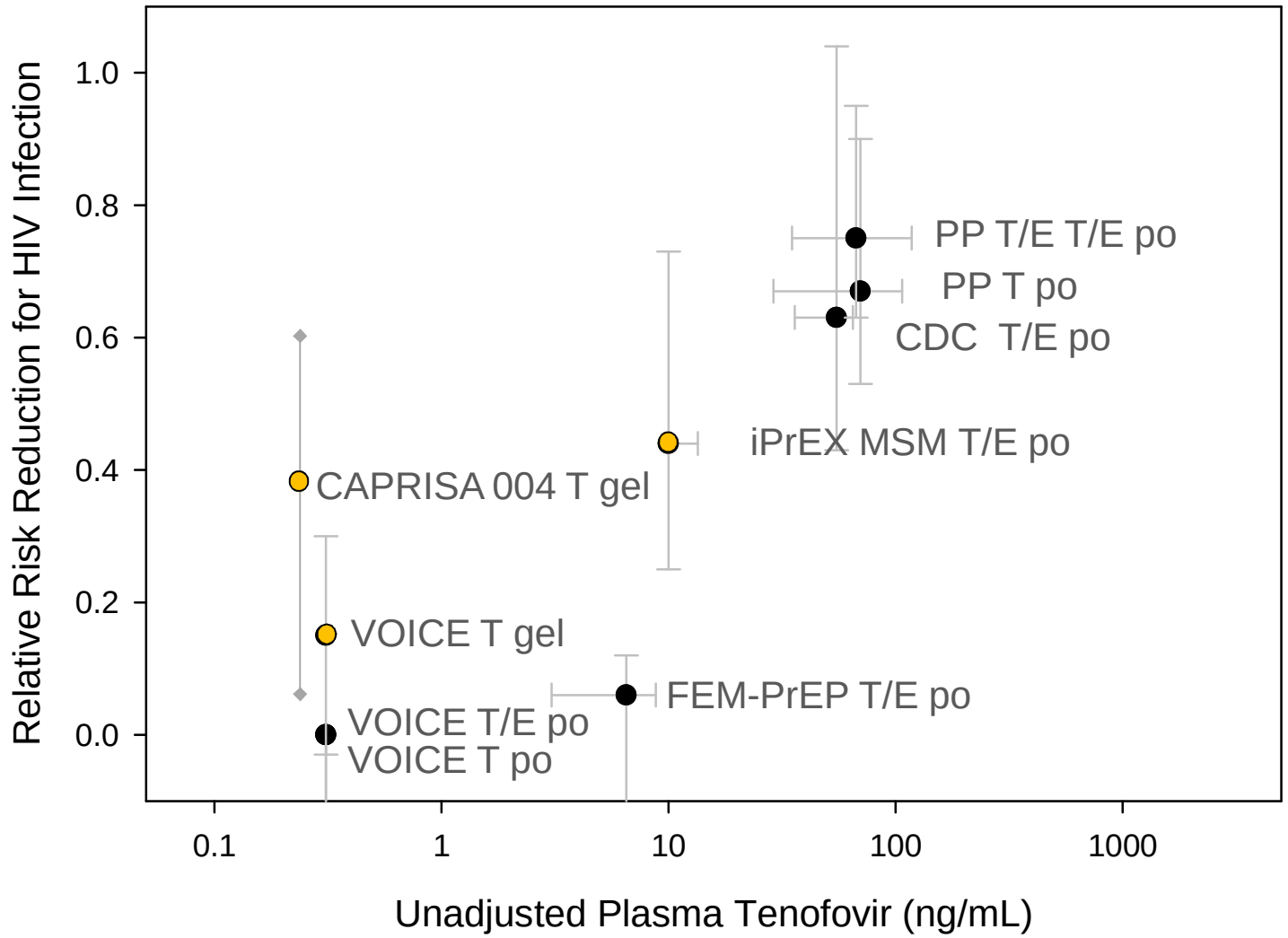


PrEP Concentration-Response

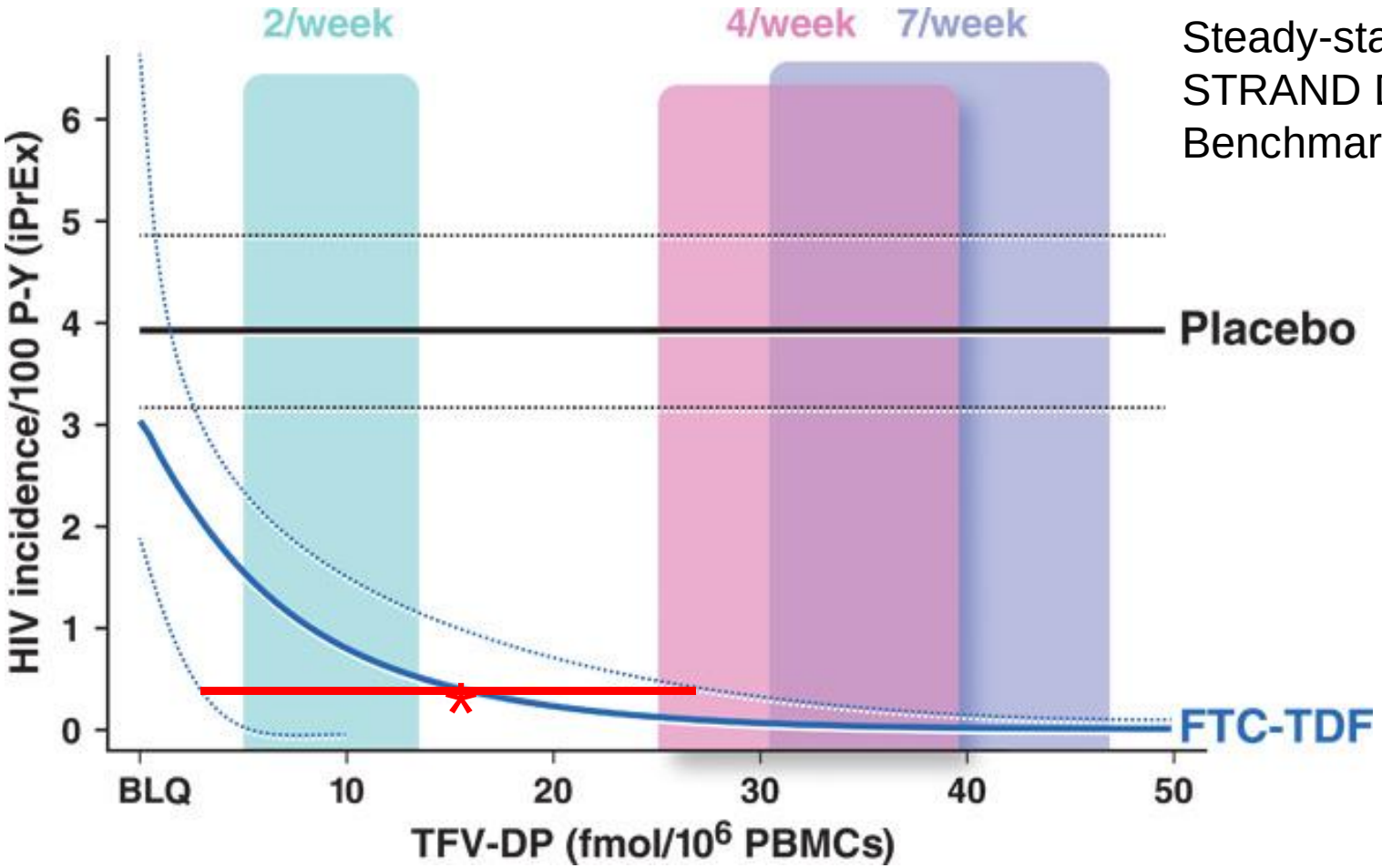
Study	Regimen	Relative Risk Reduction (95% CI)	
		All Subjects	Drug Detectible
Partners	TDF po qd	0.67 (0.44 ï 0.81)	0.86 (0.57ï 0.95); BLQ 0.3
	TDF/FTC po qd	0.75 (0.55 ï 0.87)	0.90 (0.56ï 0.98) ; BLQ 0.3
CDC TDF2	TDF/FTC po qd	0.62 (0.22 ï 0.83)	50% SC, 80+% NSC; BLQ 0.3
iPrEX	TDF/FTC po qd	0.42 (0.15 ï 0.63)	0.92 (0.40 ï 0.99) ; BLQ 10
FEM-PrEP	TDF/FTC po qd	0.06 (-0.41 ï 0.52)	No diff. 25% v 35%;BLQ 10
VOICE	TDF po qd	*-0.49 (-1.30 – 0.035)*	No difference; BLQ .0.3
	TDF/FTC po qd	*-0.04 (-0.50 – 0.30)*	
CAPRISA 004	TFV gel BAT24	0.39 (0.04 ï 0.60)	>1,000 CVF increased RRR
VOICE	TFV gel qd[e]	*0.15 (-0.20 – 0.40)*	No difference; BLQ 0.3

- Concentration-response among and within RCTs
- Plasma and CVF demonstrate concentration-response

Why no consistent pattern in the data?



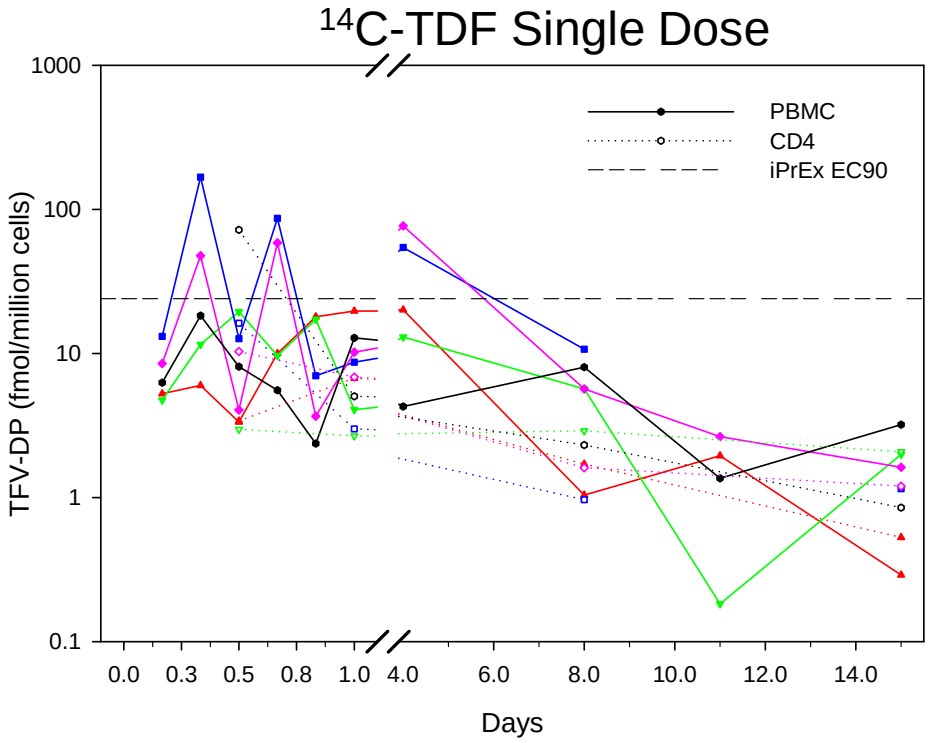
iPrEx-informed concentration target

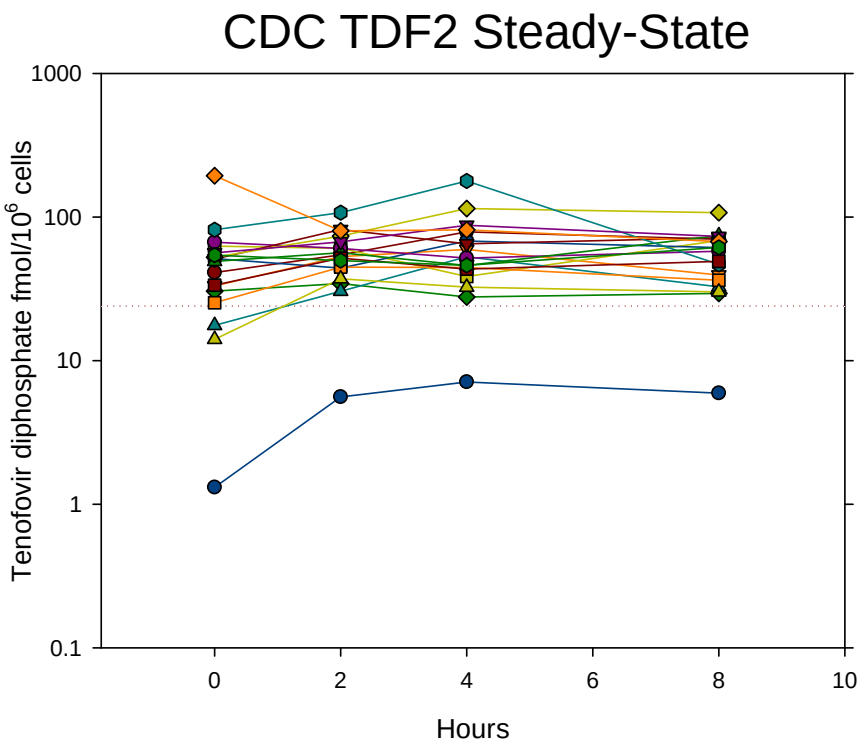


EC_{90} = 16 fmol/M (95%CI 3-28) viable cells (24-48 freshly lysed cells).

Anderson, *et al*. Sci Transl Med 2012

Can single oral dose achieve EC_{90}?





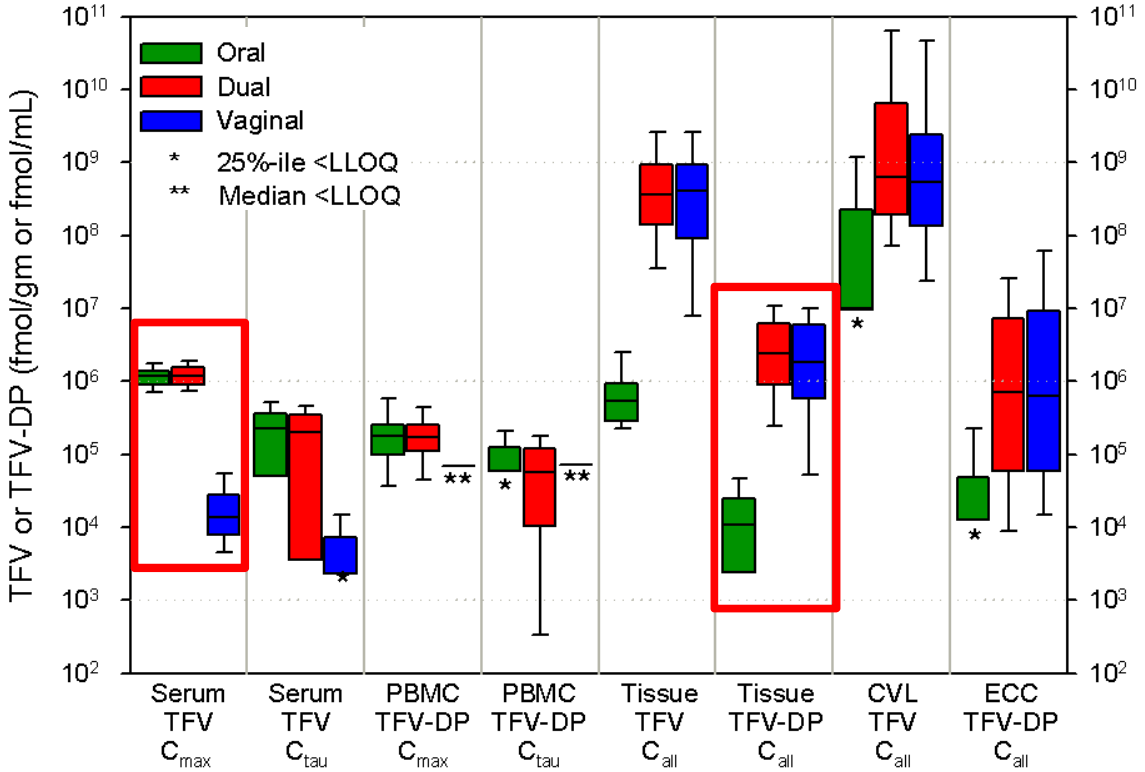
- Method differences require rescaling EC_{90} (16 viable = 24-48 freshly lysed)
- Most subjects below iPrEx EC_{90} with single dose (none sustained above)
- Most subjects above iPrEx EC_{90} at steady-state (3 weeks)

Louissaint, *et al*. ARHR 2013; Anderson, *et al*. Sci Transl Med 2012; CDC, data on file

MTN-001

Does dosing route affect concentrations?

- *144 women daily oral, vaginal, & combination dosing, 6 weeks each*



- *Vaginal tissue TFV-DP **Vaginal 130x > Oral** (topical tissue advantage)*
- *Serum TFV **Oral 56x >Vaginal** (serum doesn't reflect tissue)*

Hendrix, *et al*. *PLOS One* 2013

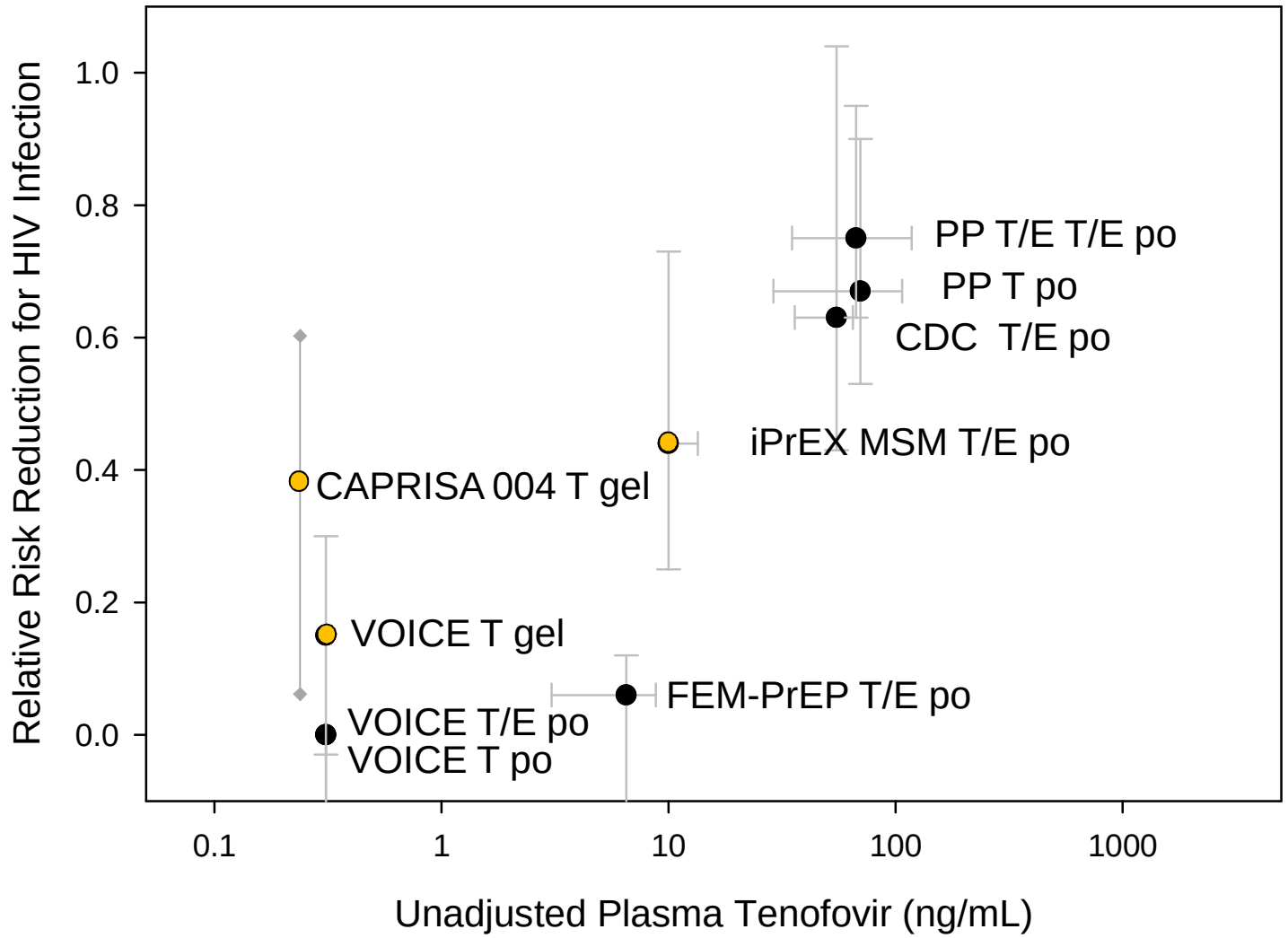
Are iPrEx targets the same for women?

- Single dose TDF, 6 women (paired across all matrices)
- Weekly tissue sampling x 2 weeks
- RV:VT TFV-DP homogenate c/w Patterson (STM 2011)
- RT:VT ratio varies with drug moiety & sample type
- Initial 24h colon:vaginal gradients not sustained
  - colon homogenate and CD4 cell half-life < vaginal tissue
- Rectal ñadvantageò clearest with > weekly dosing

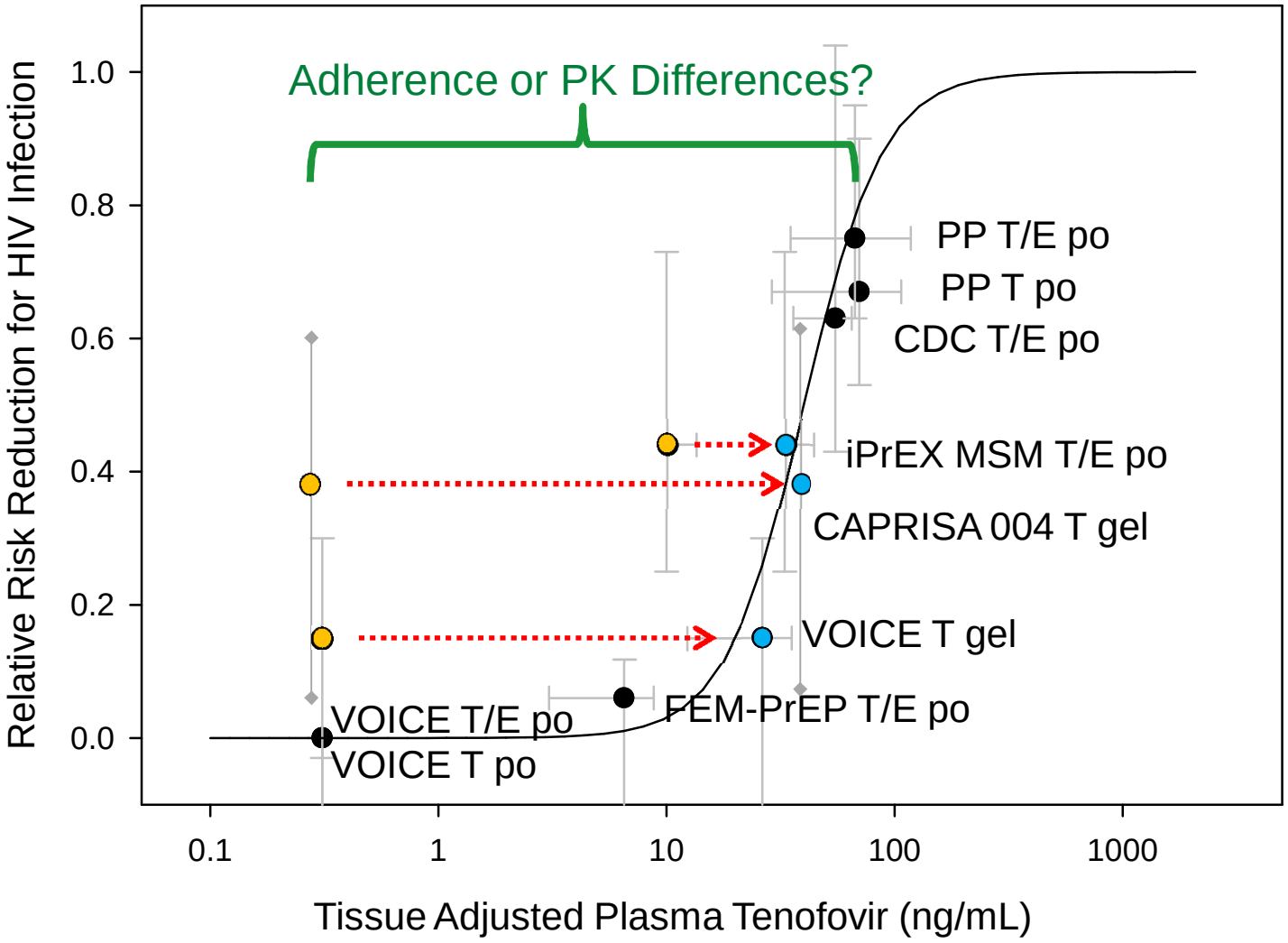
Day	RT:VT TFV Plasma Median (IQR)	RT:VT TFV-DP Homogenate Median (IQR)	RT:VT TFV-DP CD4 Cells Median (IQR)
1	33.8 (6.8, 37.8)	123.7 (8.4, 155.4)	19.20 (9.60, 28.8)
8	4.5 (0.9, 31.3)	1.7 (0.3, 2.8)	0.20 (0.17, 0.23)
15	0.3 (0.3, 0.3)	2.5 (2.5, 2.6)	0.15 (0.15, 0.15)

Louissaint, *et al*. ARHR 2013

Can tissue provide useful frame of reference?

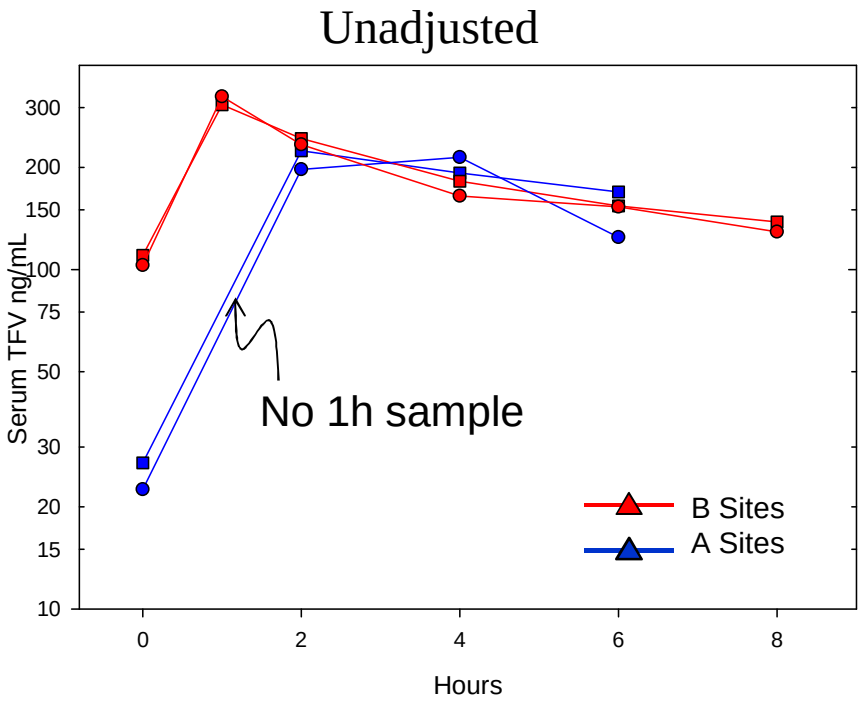


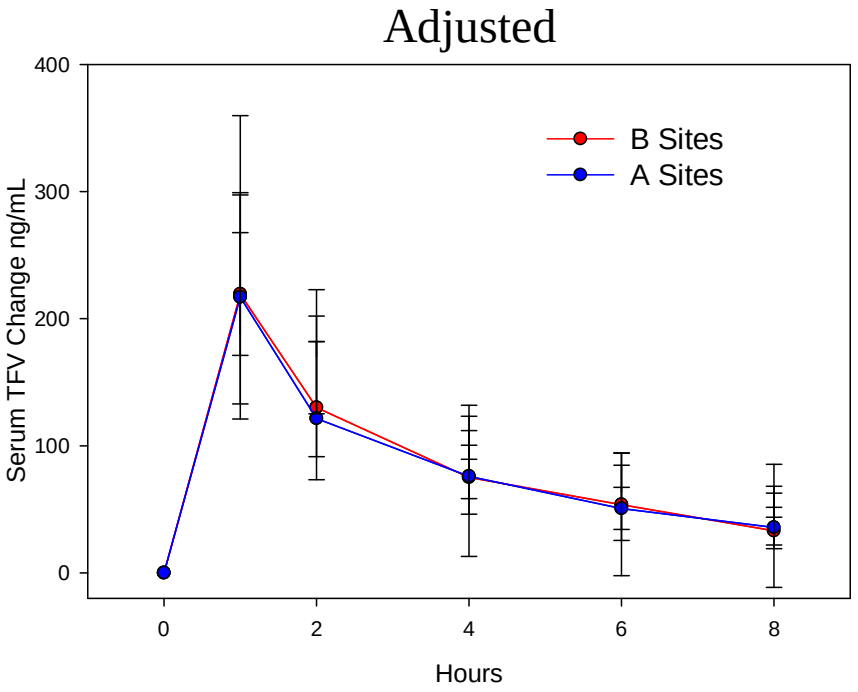
[Tissue] reference informs concôn-response



MTN-001

Variation in adherence or PK?





- Pre-dose concentration (adherence, PK) 5:1 ratio
- Decay (PK) same after observed dose
- Crude adjustment indicates similar PK across sites
- Formal Pop PK analysis confirms adherence>>PK variation
- Raised concern about potential for poor adherence at VOICE sites

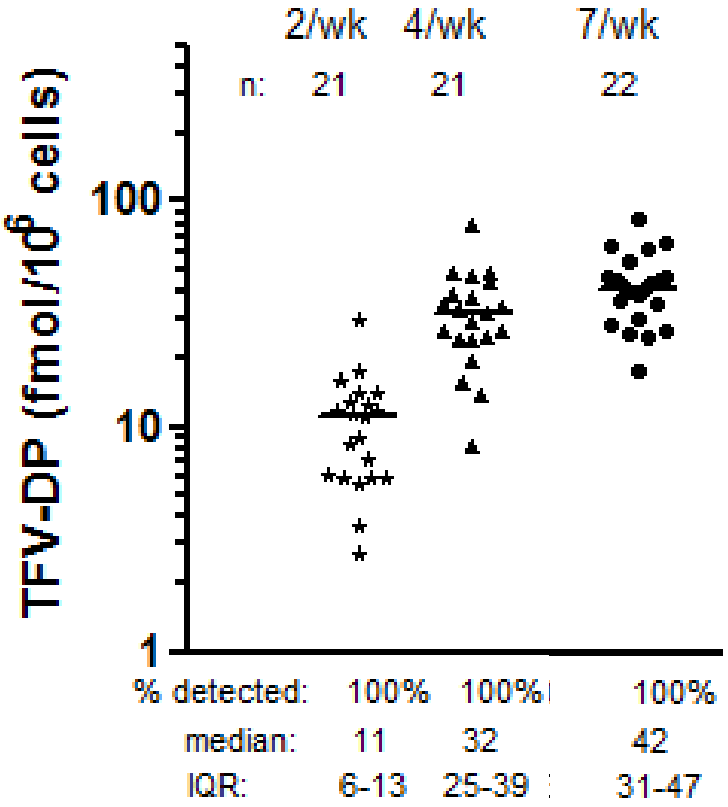
Uses of Adherence Data

- Interpret
  - Clinical study outcomes
- Intervene
  - Targeted adherence counseling
  - Real-time clinical site evaluation
- Optimize
  - Clinical trial simulation

DOT Benchmarks

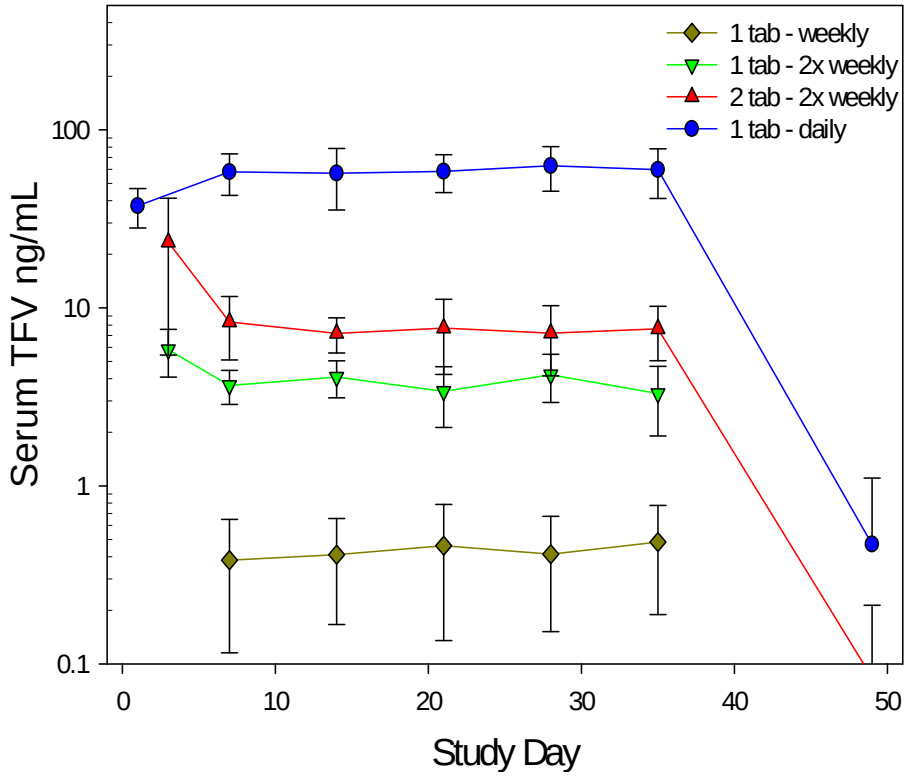
Expected Values as Reference

- STRAND



Anderson, *et al*. Sci Trans Med 2012

- HPTN 066



Donnell, . CROI 2012

HPTN 066 (DOT) Benchmark

Study	Daily	4/wk*	3/wk*	2x/wk	Weekly
HPTN066 Mean	*59*	*23*	*10*	*4*	*0.4*
HPTN066 L95%CI	*40*	*16*	*7*	*3*	*0.2*
Partners PrEP	~65 (67-75%)				
CDC TDF2	~55 (62%)				
iPrEx			~10 (42%)		
FEM-PrEP				<10 (0%)	
VOICE					<0.3(0%)

Figures are TFV plasma concentration ng/mL (% relative risk reduction)
*Model estimate

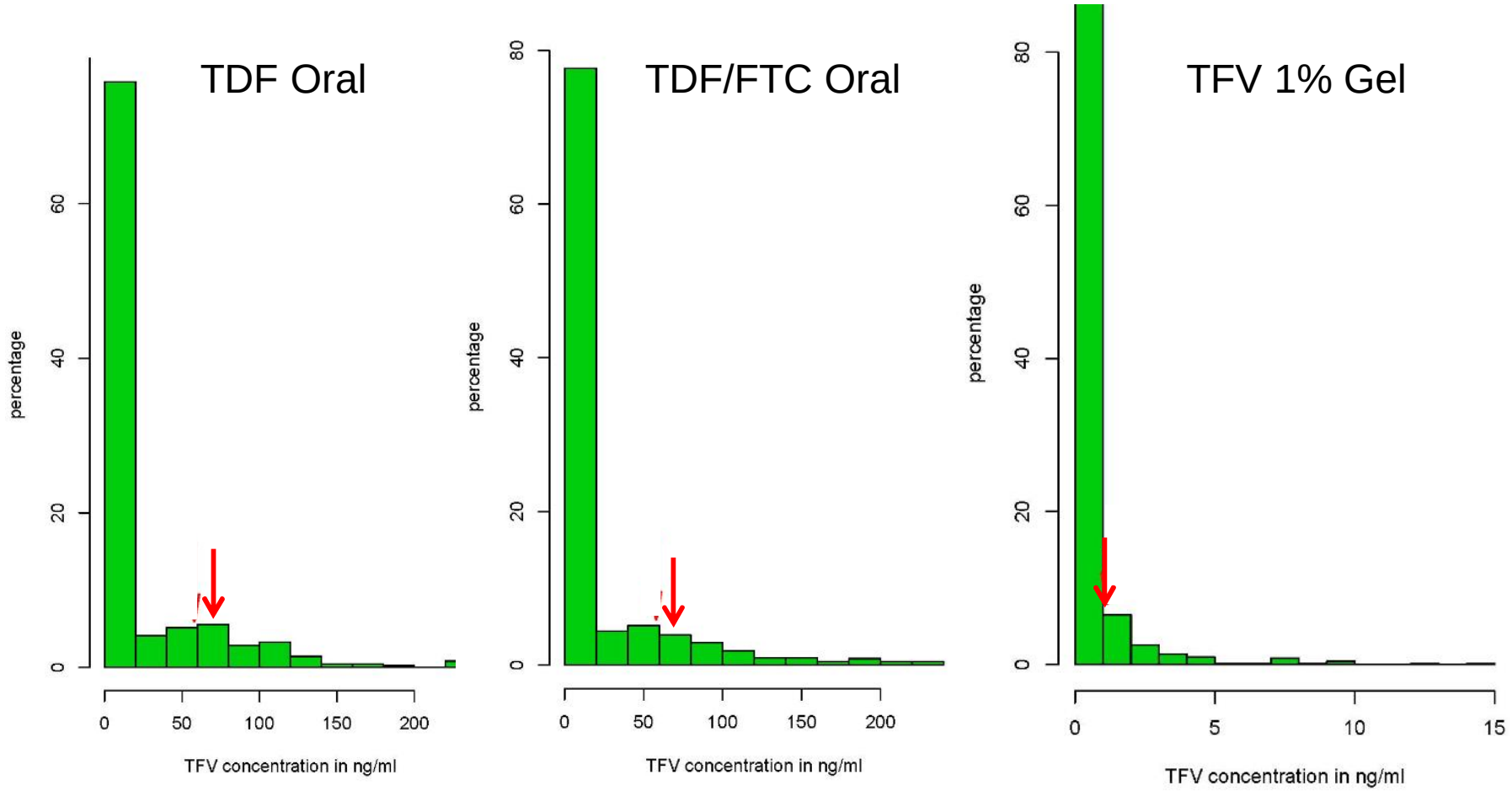
VOICE

Discordant Adherence Outcomes

Adherence Measure	TDF Oral	FTC/TDF Oral	TFV Gel
Product return	87%	92%	86%
Self report	90%	91%	90%
TFV ever detected (LLOQ 0.31 ng/mL)	42%	50%	45%
Samples with TFV >LLOQ (mean)	30%	29%	25%

VOICE

Was topical adherence worse than oral?



→ Expected 24 hour post-dose plasma TFV concentration with single dose

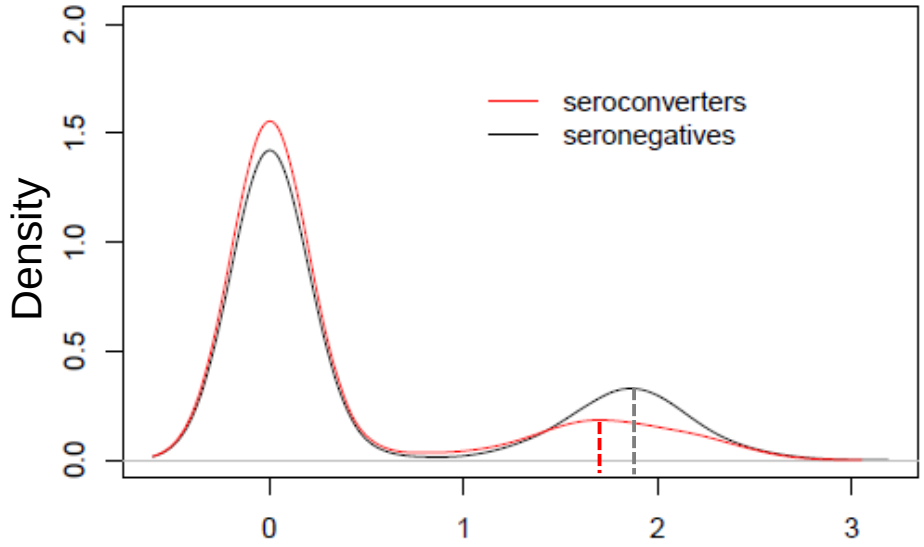
Requires adjustment to compare distributions of oral and vaginal dosing

Marazzo, *et al*., CROI 2013

VOICE

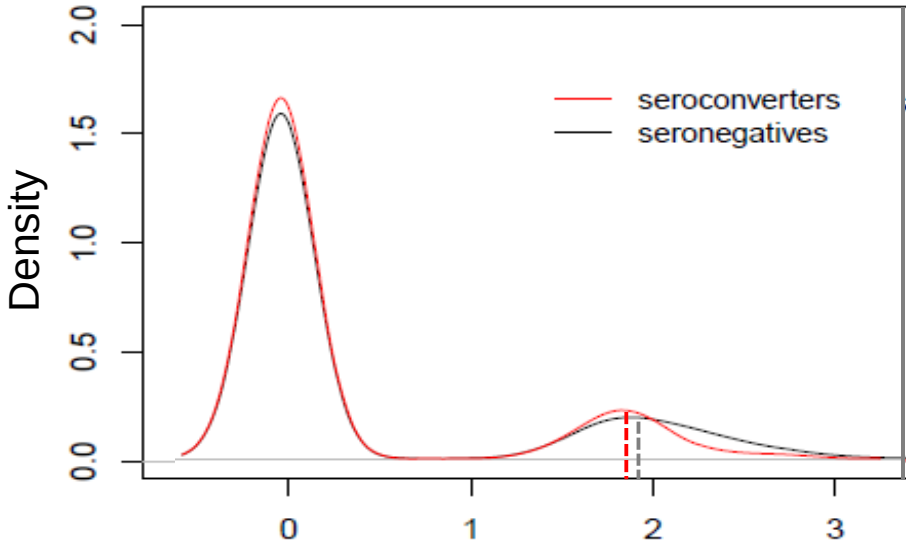
Dosing Route-adjusted TFV Concentrations

Oral TDF



log(1+TFV concentration)
Unadjusted plasma

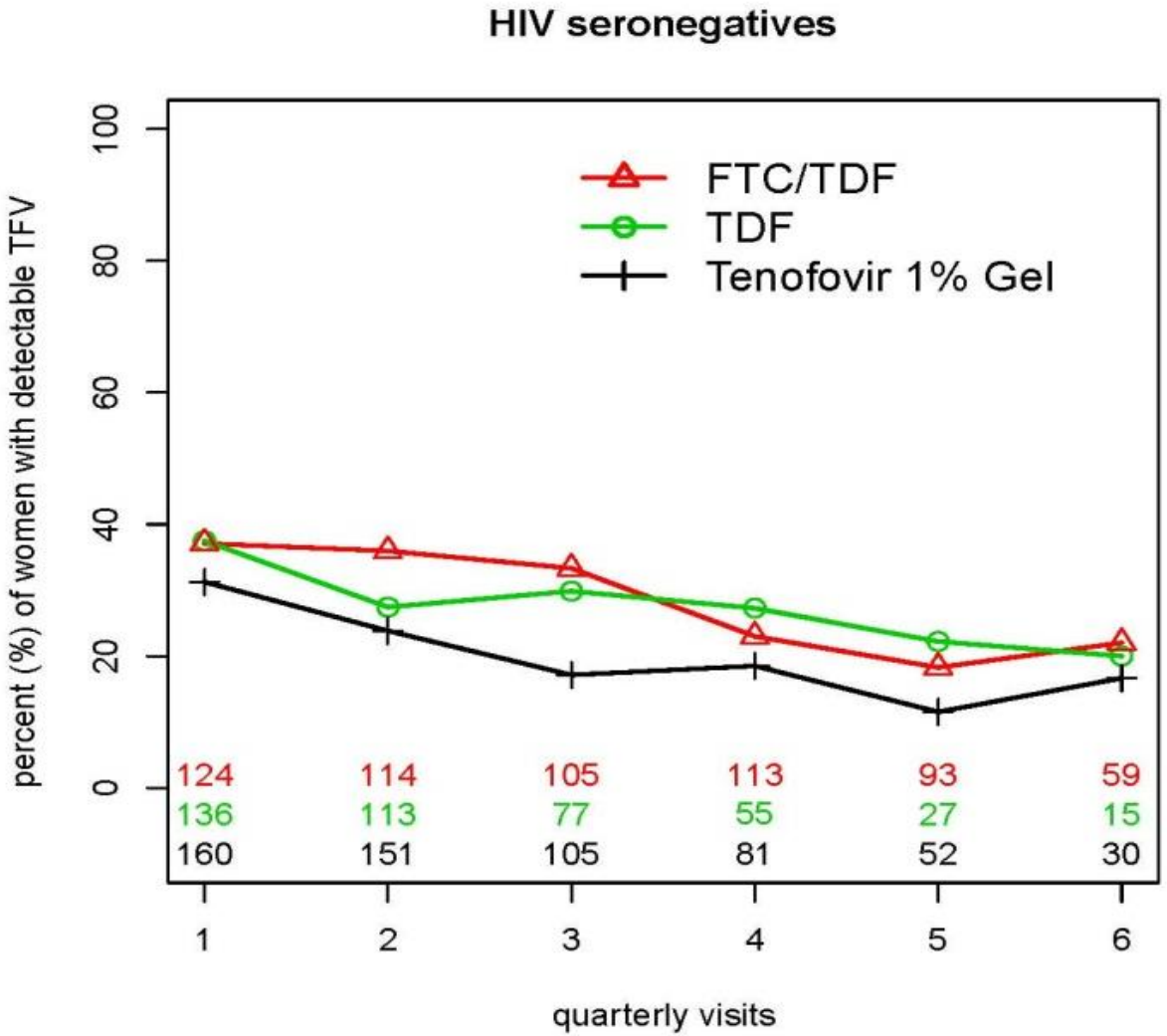
Vaginal 1% TFV Gel



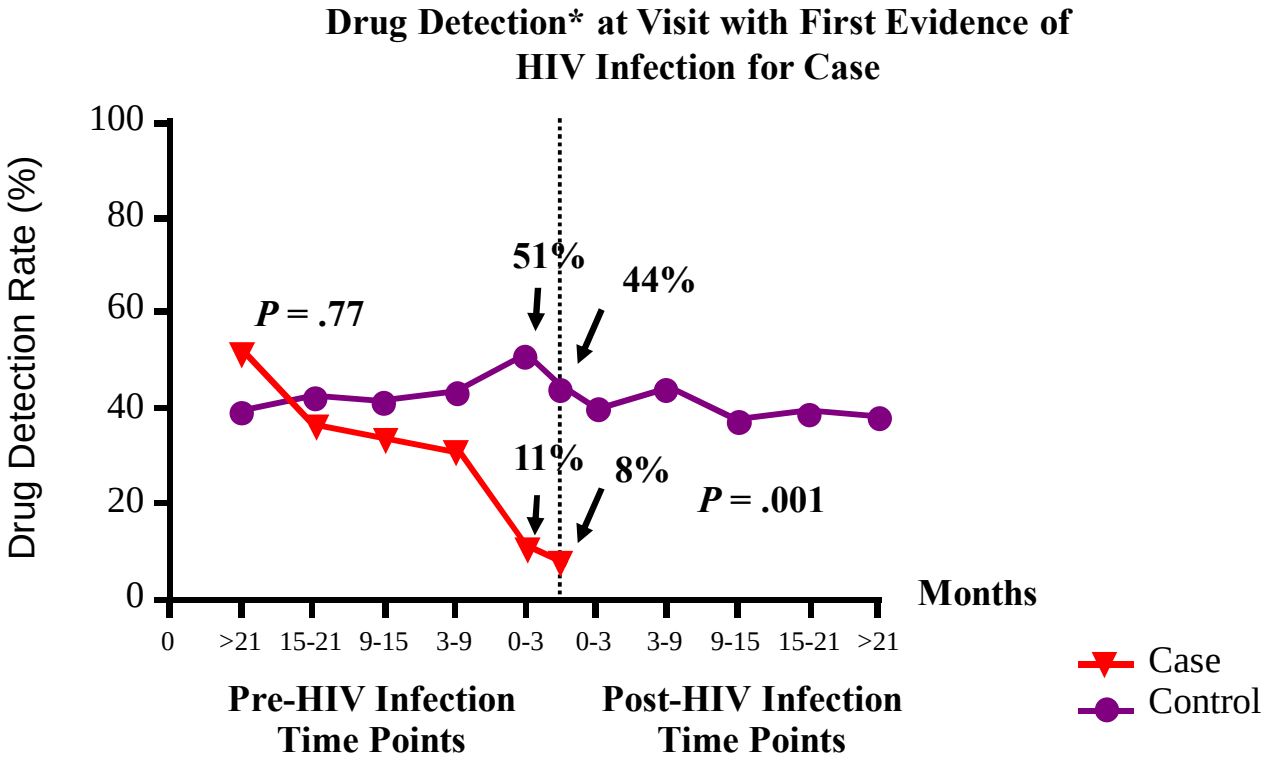
log(1+TFV concentration*56)
Tissue adjusted plasma

Oral v. vaginal dosing adjustment suggests similar oral and topical adherence.

VOICE: Temporal Adherence



iPrEx: Temporal Adherence



- Drug detected in <50% non-seroconverters
- LLOQ higher (10 ng/mL) compared to VOICE (0.31 ng/mL)
- HIV infection occurred during periods of low drug exposure

Anderson PL, *et al*. STM 2012.

Partners PrEP: Temporal Adherence

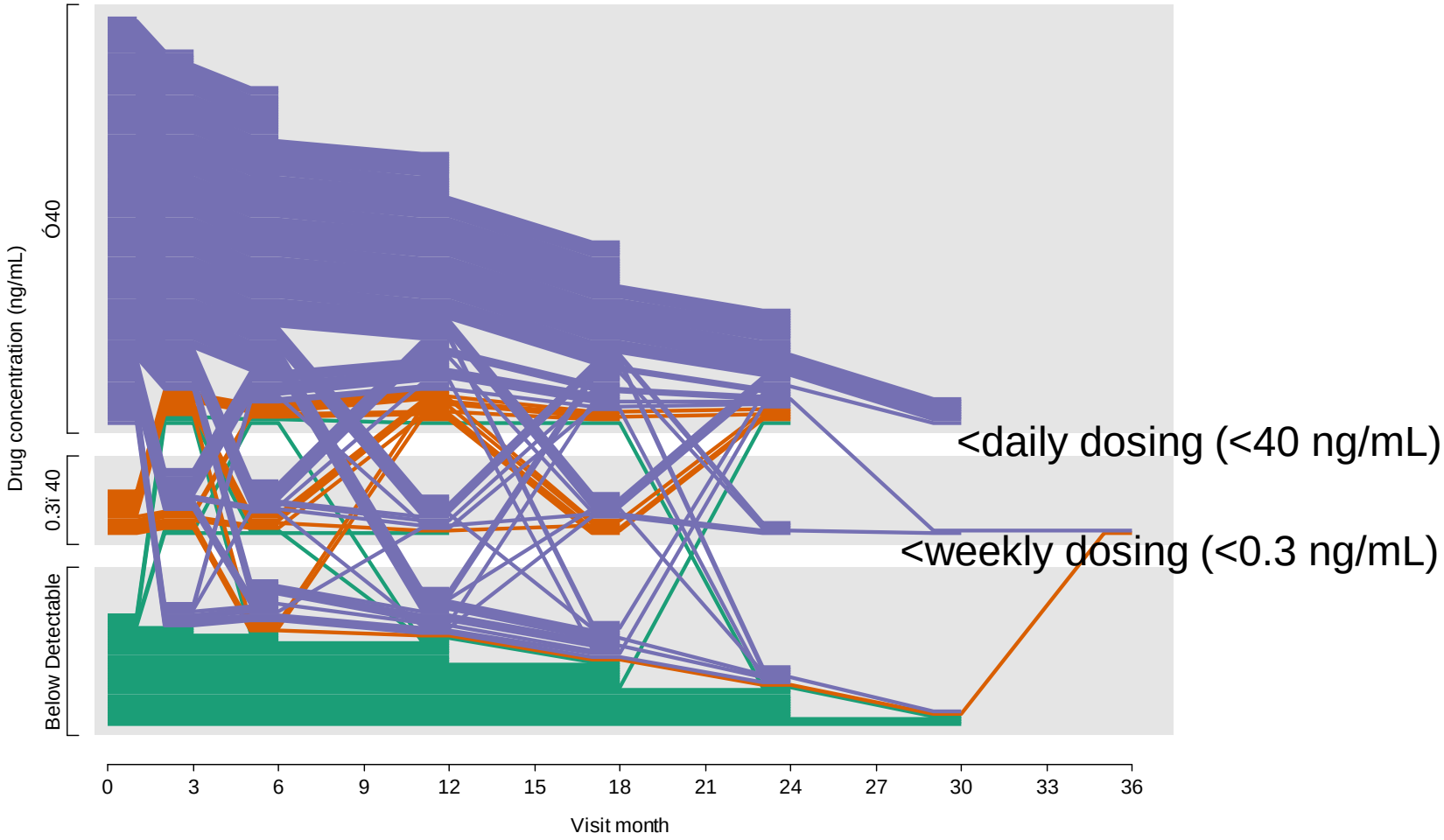
	Cases (TDF = 17, FTC/TDF = 12)				Cohort (N = 198)	
	Visits prior to seroconversion		Seroconversion visits		All visits	
TDF arm	35/63	**56%**	6/17	**31%**	363/437	**83%**
FTC/TDF arm	20/36	**56%**	3/12	**25%**	375/465	**81%**

- 25-31% of seroconverters had detectable levels of drug at seroconversion visit
  - Assay LLOQ limited explanatory capacity for outcomes
- 56% had detectable tenofovir earlier
- All 3 studies showed adherence erosion

Donnell, *et al*. CROI 2012

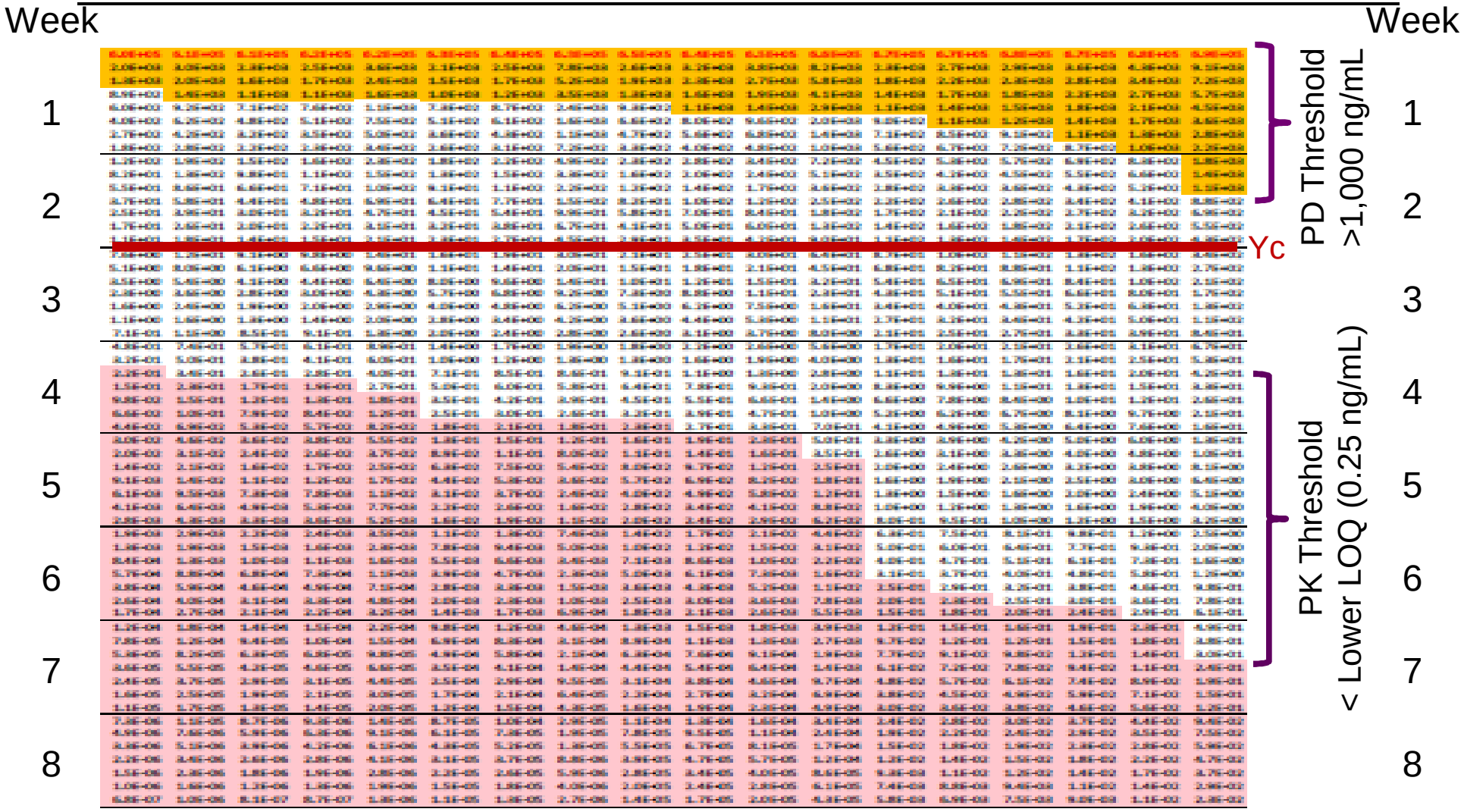
Partners PrEP

Beyond LLOQ adherence thresholds



ñAdherentò >40 ng/mL based on HPTN 066 lower 05% CI daily dosing
LLOQ 0.31 ng/mL
Donnell, *et al*. CROI 2011

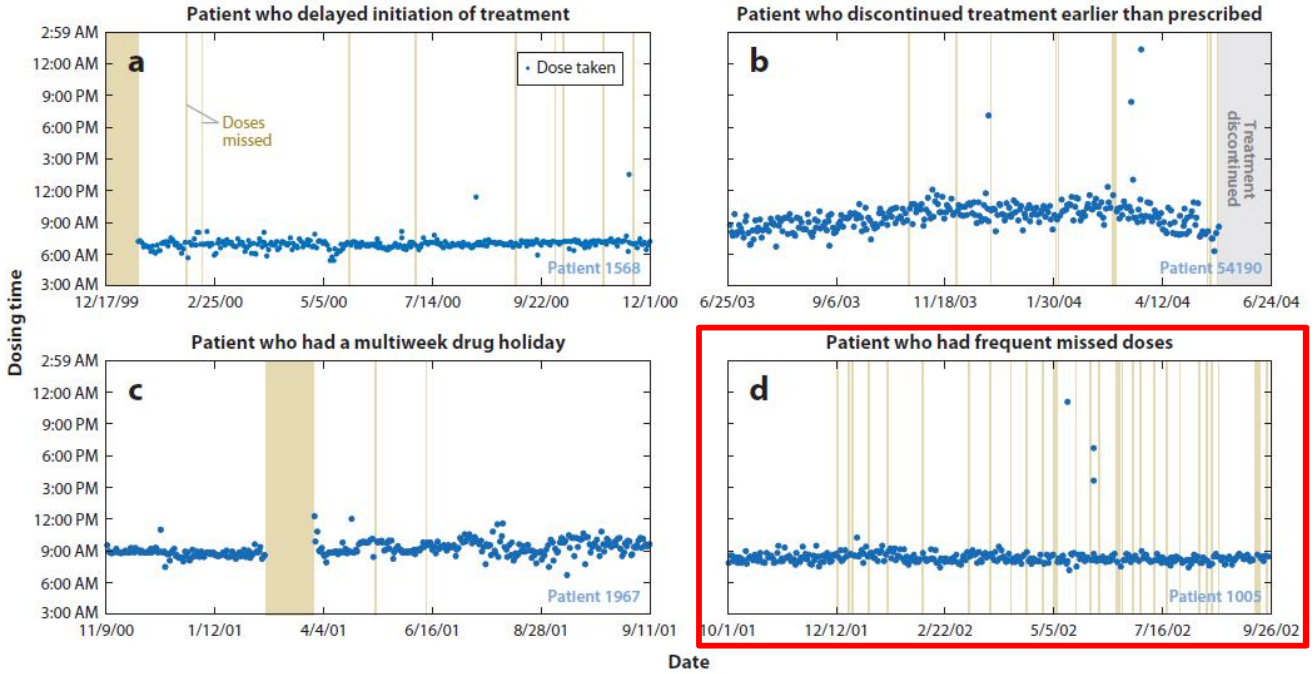
PK or PD based adherence threshold?



Adherence assessments using CVF PK (0.25) or PD (1,000) thresholds

Variable Patterns of Adherence

- ñ90% Adherenceòtakes many forms



- All PK matrices ñaverageòin holidays
  - Insensitive to holidays v. regular pattern

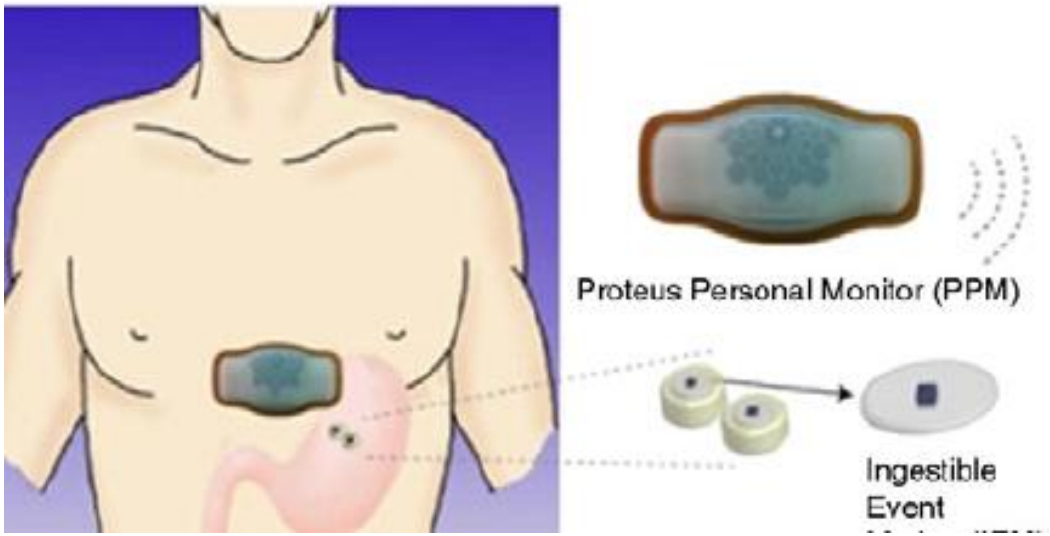
Blaschke, *et al*. Ann Rev Pharm Tox 2012

Electronic Event Monitoring Systems

MEMSCAP (micro-electromechanical systems)

Wisepill (SMS)

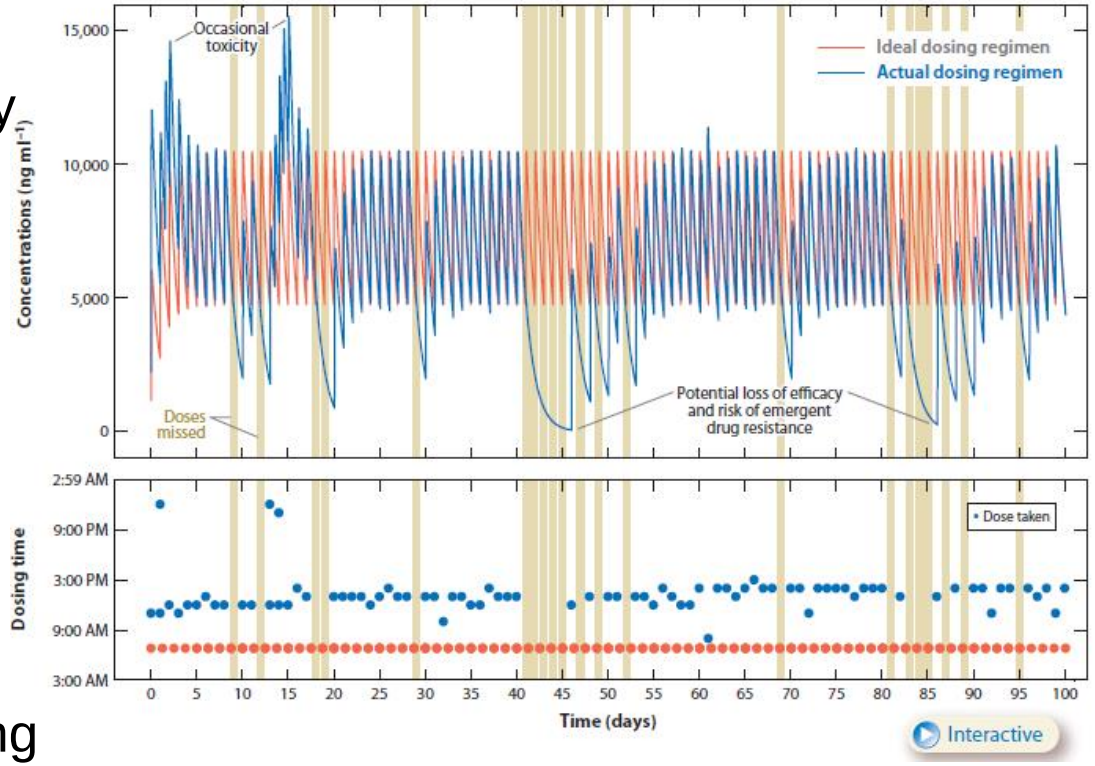
Proteus (SMS, swallowing, physiological)



Understanding Concentration-Response

Optimal: Combining EMS & PK_{IND}

- Adherence patterns vary
- Drug exposure varies widely
- Some patterns more permissive than others
- ñOn averageò adherence analyses may mislead regarding targets
- Need event monitoring for ***both drug and sexual exposure*** *(Yc).*
- EMS+Sparse PK_{IND} sampling enables simulation of concentration for entire study



Blaschke, *et al*. Ann Rev Pharm Tox 2012

- Powerful for understanding concentration-response (inform regimen)
- Enables clinical trial simulation to optimize future RCT study designs

Summary

Clinical pharmacology studies informé

- é concentration-response relationship (target)
- é multiple oral doses before protection
- é colon tissue ñadvantageò falls with dose frequency
- é topical dosing tissue advantage dose per dose
- é adherence greatest source of study variability
- é RCT adherence rates ñon averageò, miss holidays
- é EMS and PK combination needed

Thank You

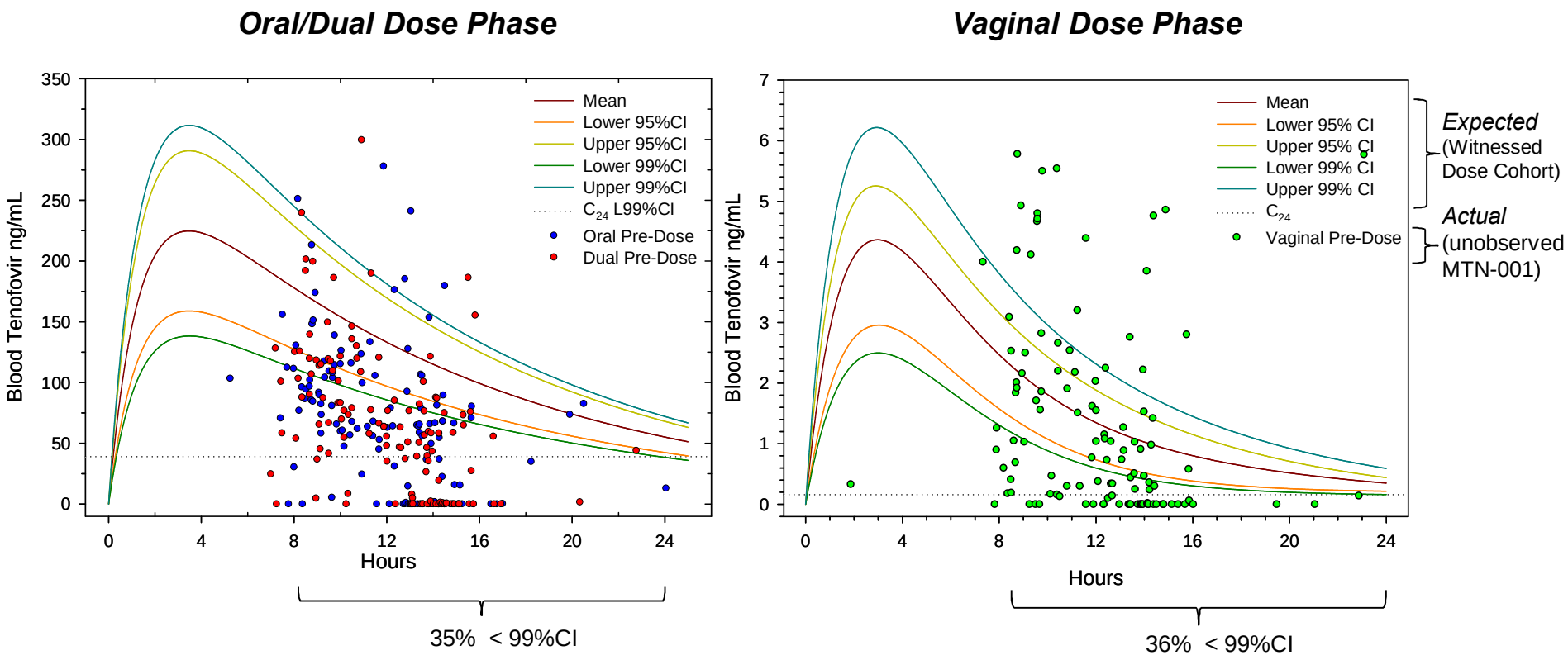
PK-based adherence intervention

- ñStudy Xò: 3 product, 8 week per product, cross-over study
- 4 & 8 week plasma ñreal timeòfor drug concentration
- How do I select Yes/No PK result to inform adherence counseling?

Route	Source	Sample Time	[TFV] Plasma X Days post dose (Dose Day = Day 0)								
			0	1	2	3	4	5	6	7	8
Oral	^{14}C-TDF SD	C_{max} Median	175.0	69.4	27.6	10.9	***4.3***	1.7	0.7	***0.3***	0.1
		C_{max} L25%	136.0	54.0	21.4	8.5	***3.4***	1.3	0.5	***0.2***	0.1
Vaginal	MTN-001 SS	C_{max} Median	3.9	1.5	0.6	0.2	0.1	0.0	0.0	0.0	0.0
		C_{max} L25%	2.2	0.9	0.3	0.1	0.1	0.0	0.0	0.0	0.0
Rectal	MTN-006 SD	C_{max} Median	6.6	2.6	1.0	0.4	0.2	0.1	0.0	0.0	0.0
		C_{max} L25%	4.6	1.8	0.7	0.3	0.1	0.0	0.0	0.0	0.0

- ñNon-Adherenceò (below limit quantitation - pink) varies with route
- Equivalent adherence - oral 10 ng/mL c/w topical 0.3 ng/mL
- PBMC, hair, DBS ï insensitive +/or Tss too long with 8 week/product

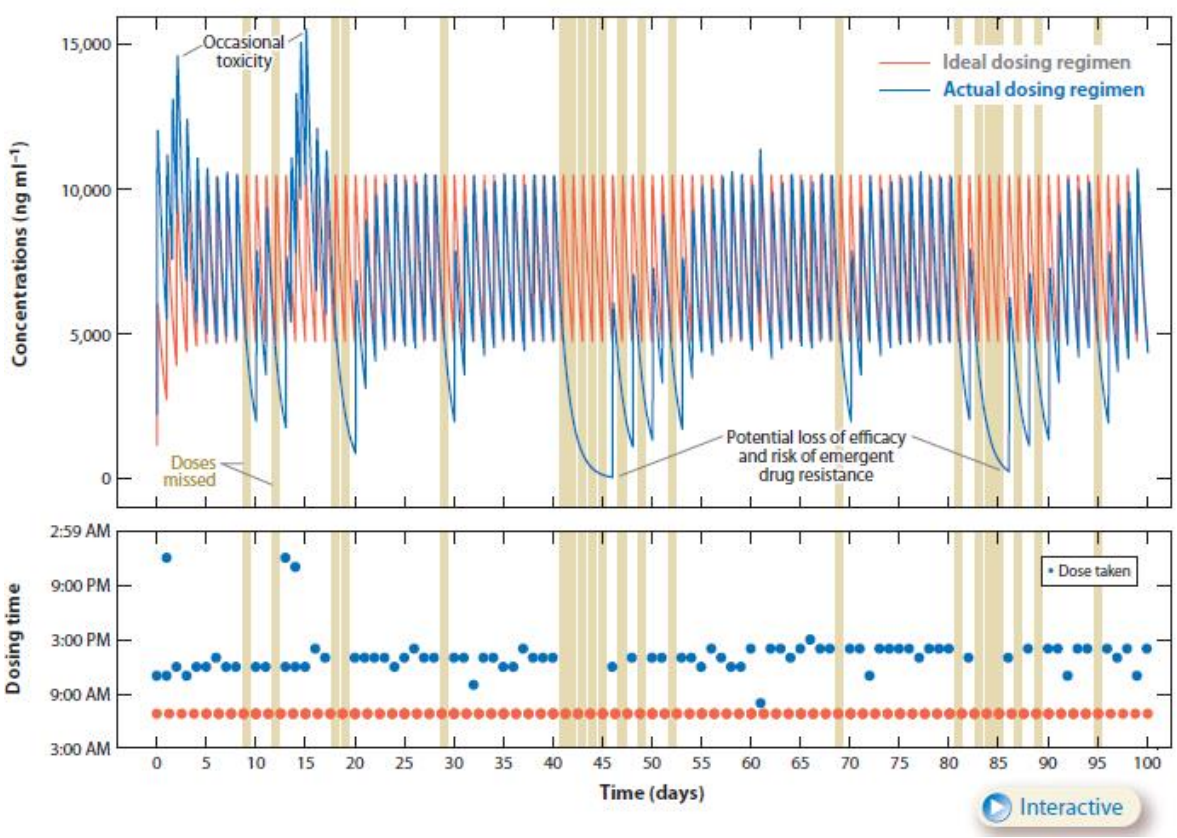
Observed v. Expected [TFV]



Individual data from MTN-001 shown in single data points overlayed on population estimates from single dose (underestimates, but directly observed) reference cohorts: JHU (ICTR, ^{14}C-TFV), MTN-006, CONRAD Gel Study (Jill Schwartz)

PK_{IND} Plus Event Monitoring

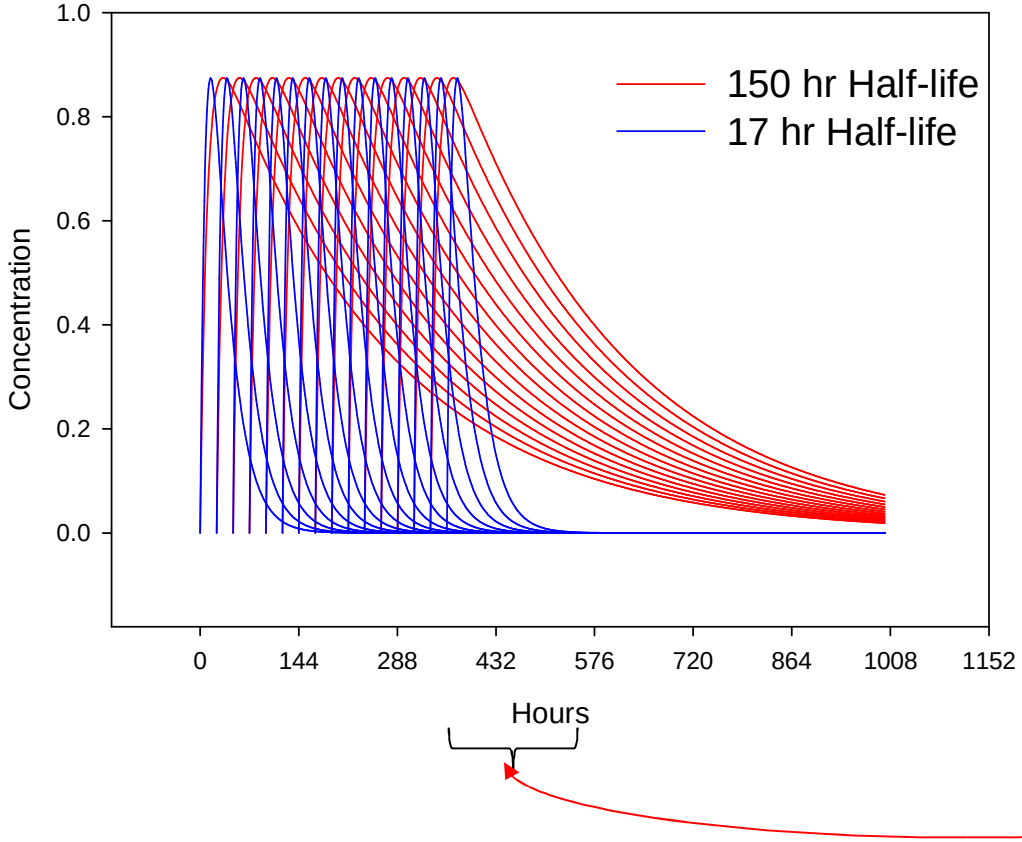
- Collect sparse PK data
  - to estimate PK_{IND}
- Collect drug taking events (MEMS)
- Estimate complete concn v. time curve
- Evaluate sensitivity of seroconversion to various patterns of drug exposure
- Provides
  - Explanatory value
  - Predictive value
- HIV exposure monitoring elusive

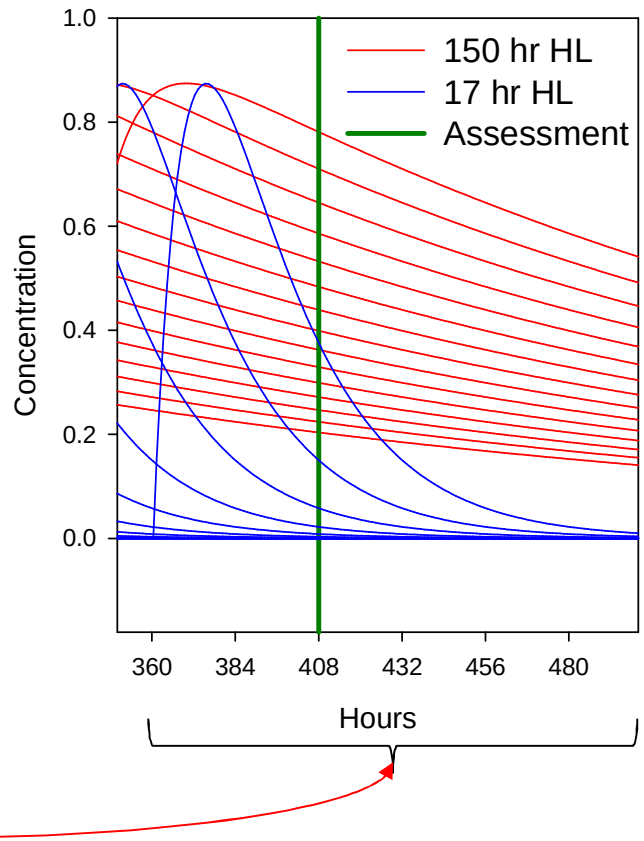


Blaschke, *et al*. Ann Rev Pharm Tox 2012

Influence of Matrix Half-Life

- ↑HL drug, more doses influence each observation
- ↓HL drug, more influence of most recent dose
- None sensitive to drug holidays unless recent (↓HL)





Future Directions

- PK/PD
  - Multi-compartment modeling (MTN-001) to bridge RCTs
  - Pooling RCTs to assess PK-PD (PP, TDF2, VOICE)
- Adherence
  - Other matrices (PBMC, DBS, hair)
  - VOICE, Partners, HPTN 067, IAVI
  - MEMS informed Markov modeling (Partners PrEP)
  - Real-time adherence assessment (MTN-020, -017)
- Clinical trial simulation
  - Optimize design of next generation PrEP RCTs
  - Sensitivity to varying patterns of adherence

Questions


National Institute of Allergy
and Infectious Diseases


NIMH
National Institute
of Mental Health


NATIONAL INSTITUTES
OF HEALTH


DEPARTMENT OF HEALTH & HUMAN SERVICES · USA


U.S. Department of
Health and Human Services
NATIONAL INSTITUTES OF HEALTH
NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE


HPTN
HIV Prevention Trials Network

RCT Cart before the PK/PD Horse

Generation	Pre-TFV	TFV			Post-TFV				
Drug	Many	TDF	TFV	TFV	DPV	MIV-150	RPV	MVC	IQP-0528
Route	Vaginal	Oral	Vaginal	Rectal	vaginal	vaginal	injectable	oral/vag/rect	vag/rect
Formulation	gel	tab	gel	gel/enema	ring/gel	ring/gel	injectable	tab/ring/gel	gel
MOA	det, anion	NRTI	NRTI	NRTI	NNRTI	NNRTI	NNRTI	CCR5	NNRTI>CCR5
animal PK - systemic	NA	pre	pre	pre	pre	pre	pre	pre	pre
animal PK - topical	no	post	post	pre	pre	pre	NA	pre	pre
animal PD	no	post	post	pre	pre	pre	???	pre	pre
human PK - Rx program	NA	pre	pre	pre	pre	NA	pre	pre	NA
human PK - topical	post	post	post	pre	pre	???	pre	pre	planned
human PK - adherence (objective)	no	post	post	pre	post	???	NA	planned	planned
human PD - dose/volume ranging	no	no	no	pre	no	???	pre	pre	planned
human PD - toxicity	post	post	post	pre	post	???	pre	pre	planned
human PD - *ex vivo*	no	post	post	pre	post	???	pre	pre	planned
human PD - *in vivo* POC	no	no	no	no	no	no	no	possible	possible
RCT - *in silico*	no	no	no	planned	no	no	planned	planned	planned
RCT - human	failed	mixed	mixed	future	ongoing	future	future	future	future

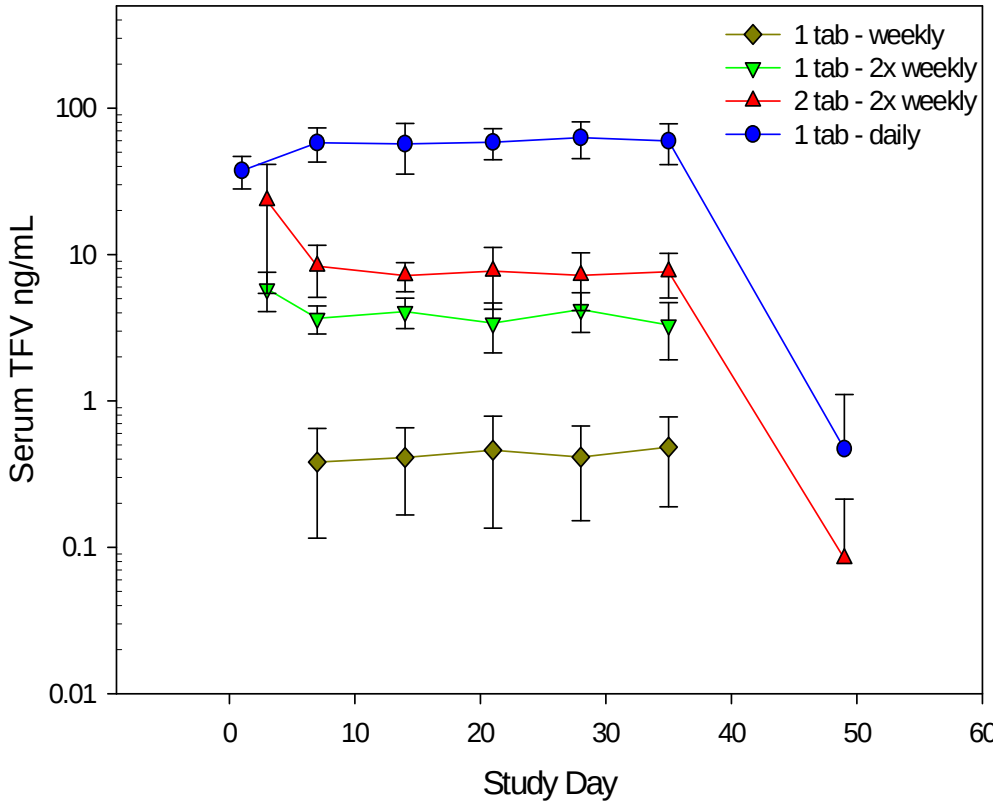
- Next Generation
  - Expansion of formulation types to enhance adherence (PK differs)
  - Different MOA (PK/PD may differ)
  - Need more PK → PK/PD → RCT progression

Added Variability of Non-Daily Dosing

- PD Threshold: 1,000 ng/mL CVF
  - 3-8 days post-last dose
  - So, 3 ï 8 days plus self-reported time since dosing
- Lower limit of quantitation
  - 3^{+} ï 7^{+} weeks post-last dose
  - So, 3^{+} ï 7^{+} wks plus self-reported time since dosing
- Added uncertainty of self-report for dosing
- Added uncertainty of self-report for exposure

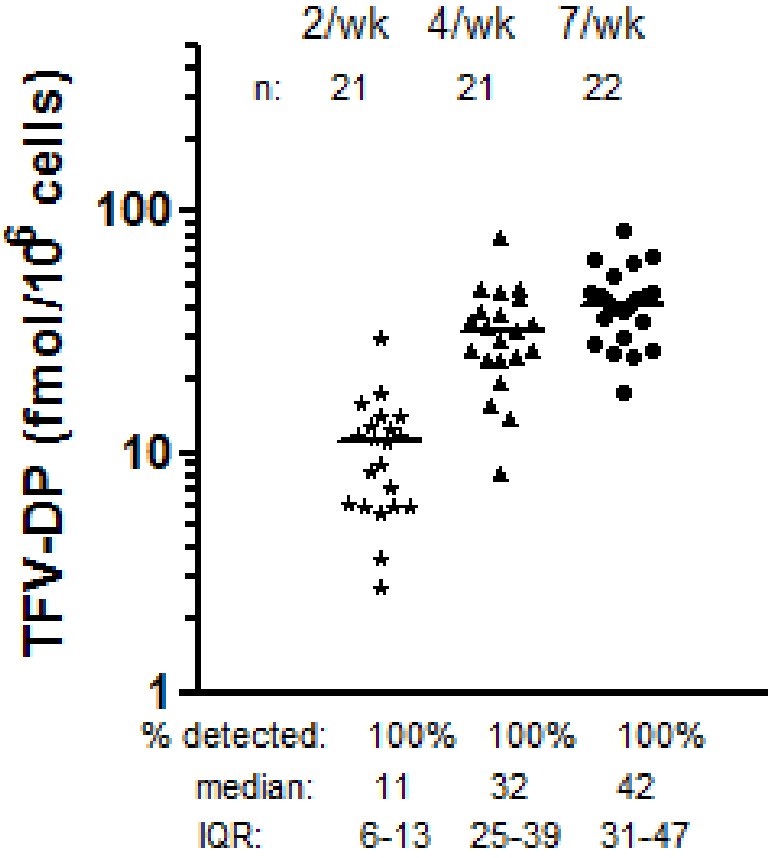
DOT: Benchmarks & Models

- HPTN 066



HPTN 066 (CROI 2012)

- STRAND



Anderson, *et al*. Sci Trans Med 2012

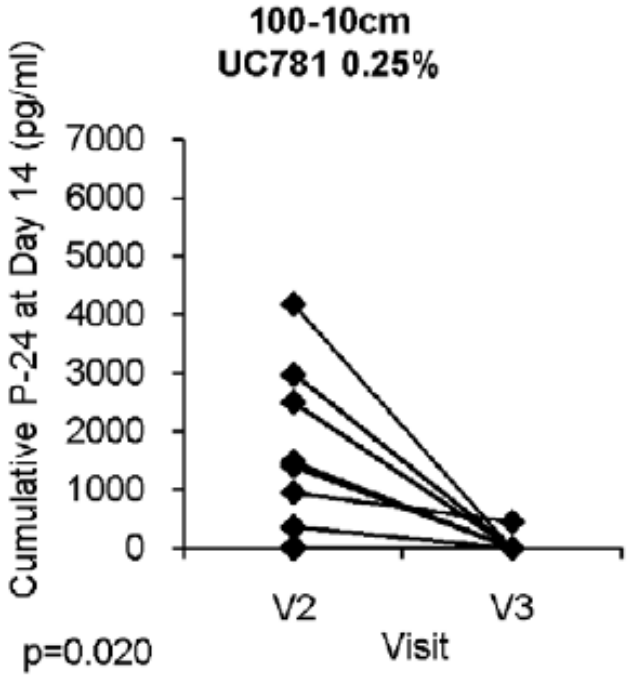
HPTN 066 (DOT) Benchmark

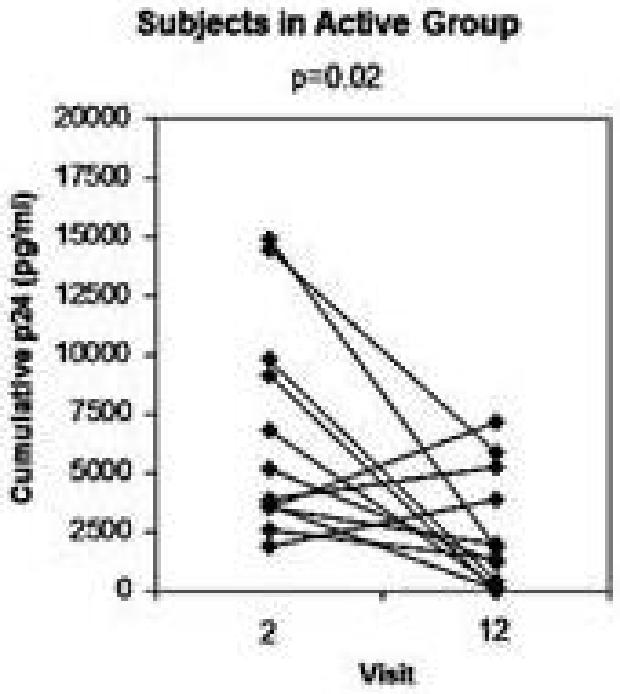
Study	Daily	4/wk*	3/wk*	2x/wk	Weekly
HPTN066 Mean	*59*	*23*	*10*	*4*	*0.4*
HPTN066 L95%CI	*40*	*16*	*7*	*3*	*0.2*
Partners PrEP	~65 (67-75%)				
CDC TDF2	~55(62%)				
iPrEx			~10 (42%)		
FEM-PrEP				<10 (0%)	
VOICE					<0.3(0%)

Figures are TFV plasma concentration ng/mL (% relative risk reduction)
*Model estimate

PD Effect: *Ex vivo* Explant Challenge

- UC781 (IP/CP-HTM)
- TFV (MTN-006)
- Rectal Vehicle (IP/CP-HTM)





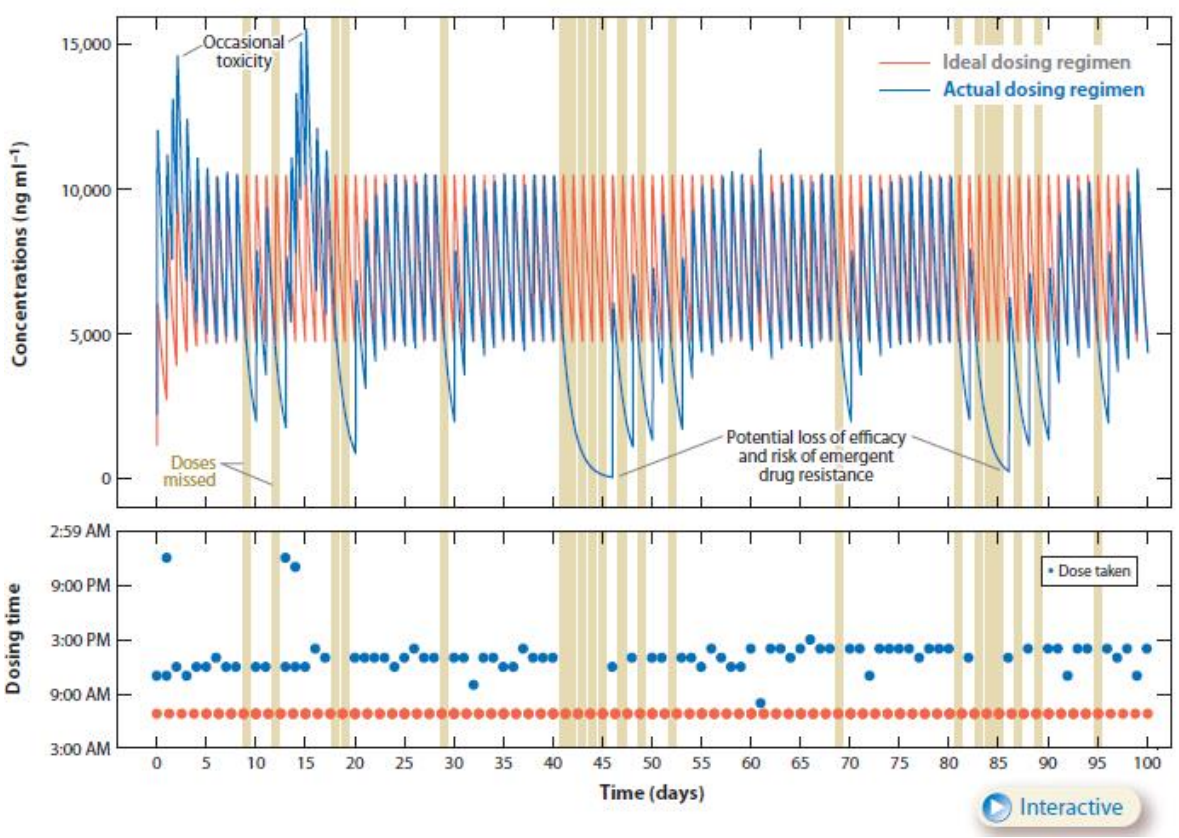
Product	Mean (95% CI)
BL	1
Aqueous fluid	0.71 (0.4-1.1)
Aqueous gel	0.61 (0.37-1.02)
Lipid fluid	1.74* (1.04-2.89)
Lipid gel	0.94 (0.5-1.5)

- Lipid gel Increased explant p24
- No histologic differences

Note: 3 examples of statistically significant changes in p24 ag in explant model (up and down)

PK_{IND} Plus Event Monitoring

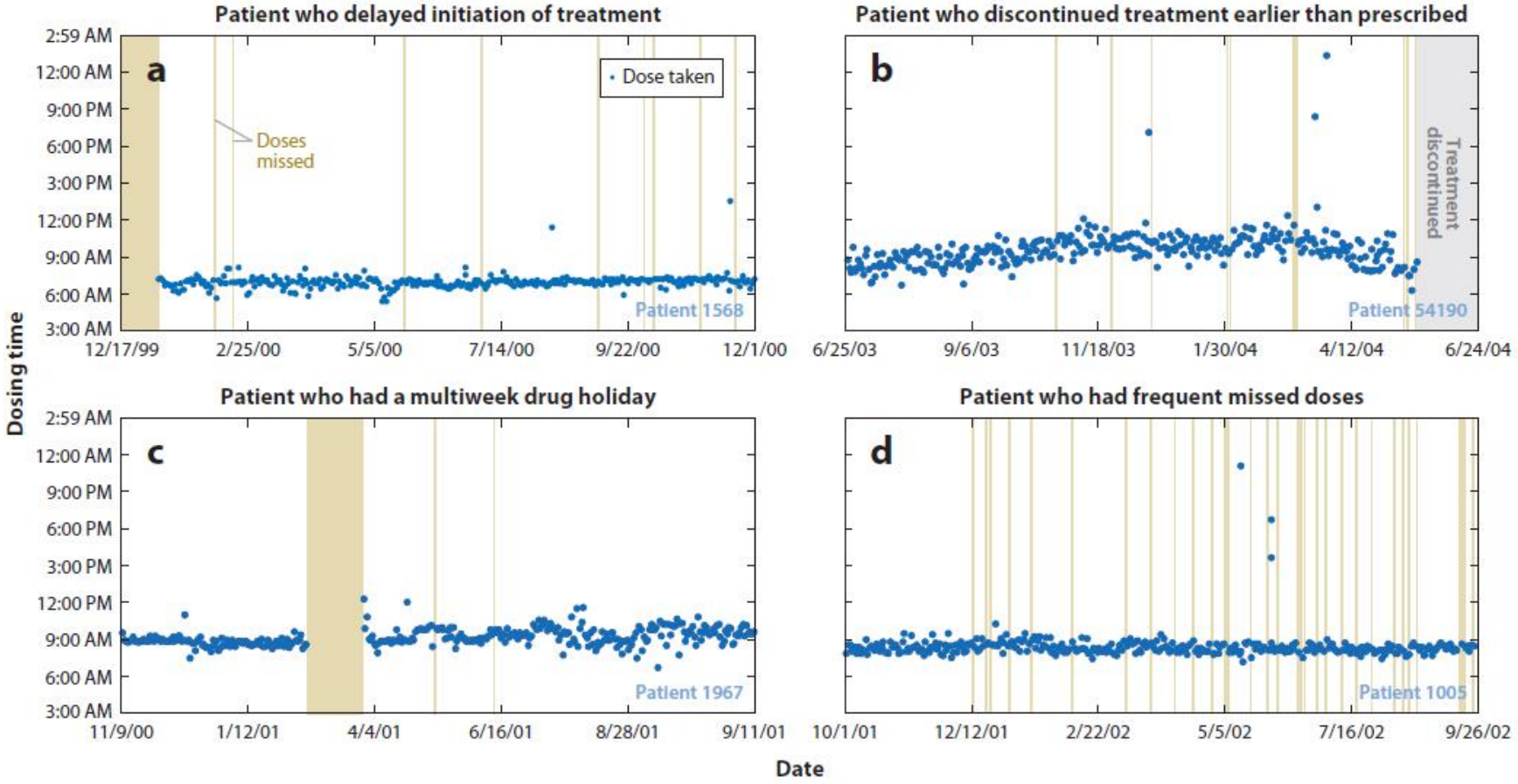
- Collect sparse PK data
  - to estimate PK_{IND}
- Collect drug taking events (MEMS)
- Estimate complete concôn v. time curve
- Evaluate sensitivity of seroconversion to various patterns of drug exposure
- Provides
  - Explanatory value
  - Predictive value



Blaschke, *et al*. Ann Rev Pharm Tox 2012

Variable Patterns of Adherence

- ñ90% Adherenceòtakes many forms

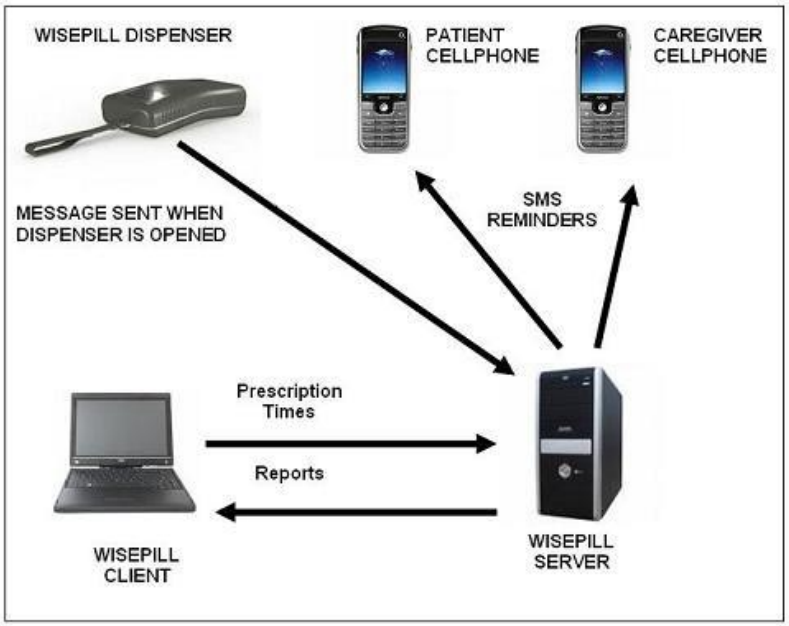


Blaschke, *et al*. Ann Rev Pharm Tox 2012

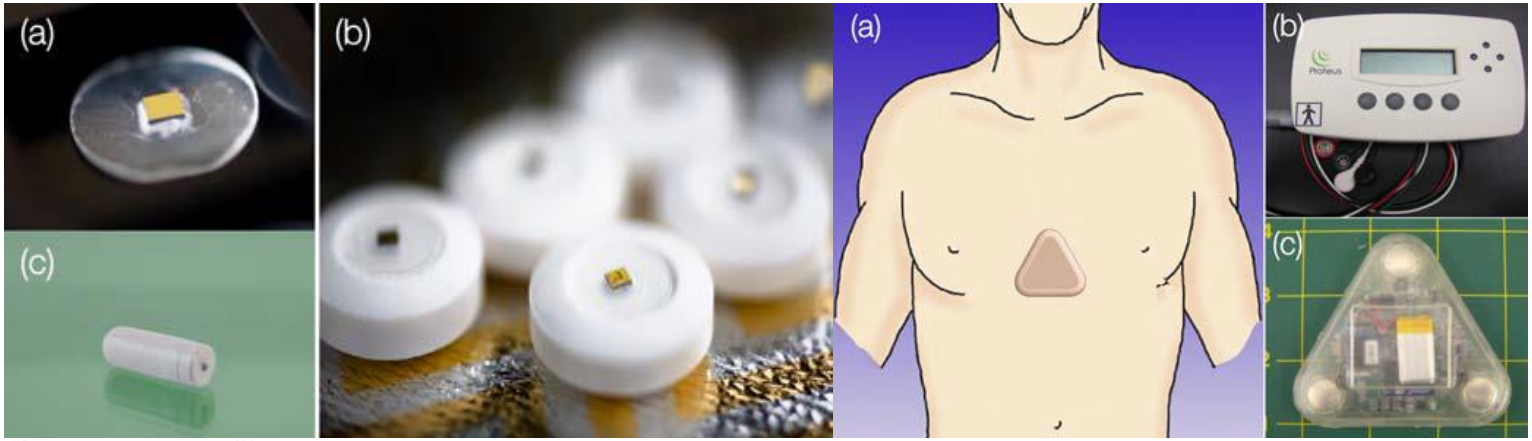
Electronic Event Monitoring

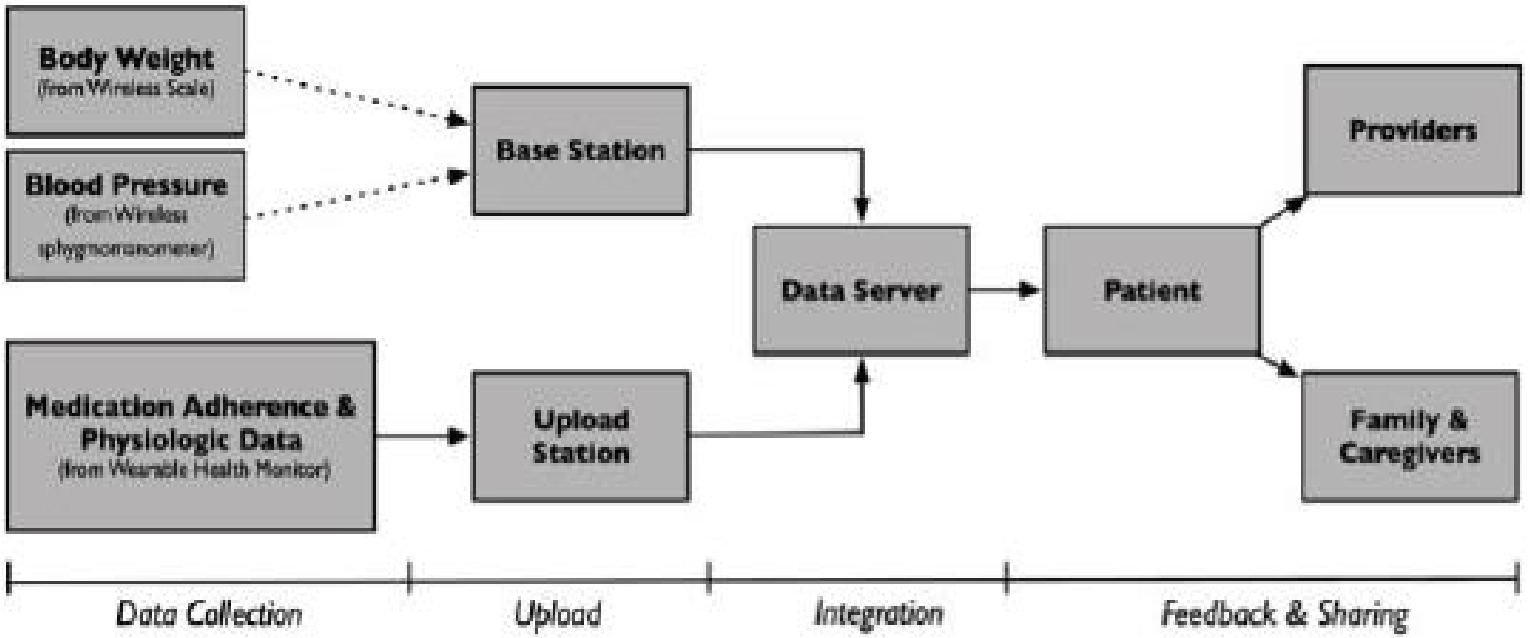
MEMSCAP (micro-electromechanical systems)

Wisepill



Electronic Event Monitoring





Au-Yeung et al., 2010 Proteus Biomed

Modeling Adherence for CTS

Markov Mixed Effect Regression

Table II. Estimates of $p(n)$ for ZDV data

Meaning	Parameter*	Estimate	95% CI of estimate	Interindividual† variability (−2SD, +2SD)
Model for $p(n_j = 0 \mid n_{j-1})$				
Intercept	θ_0^n	−2·45	−3·15, −1·74	−4·78, −0·11
$n_{j-1} = 0$	$\exp(\beta_{00})$	1·55	0·85, 2·82	0·23, 10·27
$n_{j-1} = 2$	$\exp(\beta_{20})$	2·03	1·49, 2·73	—
Weekend	$\exp(\theta_1^n)$	1·45	1·11, 1·89	0·65, 3·24
Midday	$\exp(\theta_2^n)$	3·24	2·19, 5·34	0·77, 15·2
Evening	$\exp(\theta_3^n)$	2·08	1·27, 3·39	0·37, 11·8
Age = 62	$\exp(\theta_4^n)$	0·31	0·08, 1·14	—
Age = 22	$\exp(-\theta_4^n)$	3·25	0·87, 12·1	—
Model $= p(n_j = 2 \mid n_{j-1})$				
Intercept	θ_5^n	−4·19	−5·32, −3·06	−7·79, −0·59
$n_{j-1} = 0$	$\exp(\beta_{02})$	3·67	1·02, 13·2	0·13, 106·32

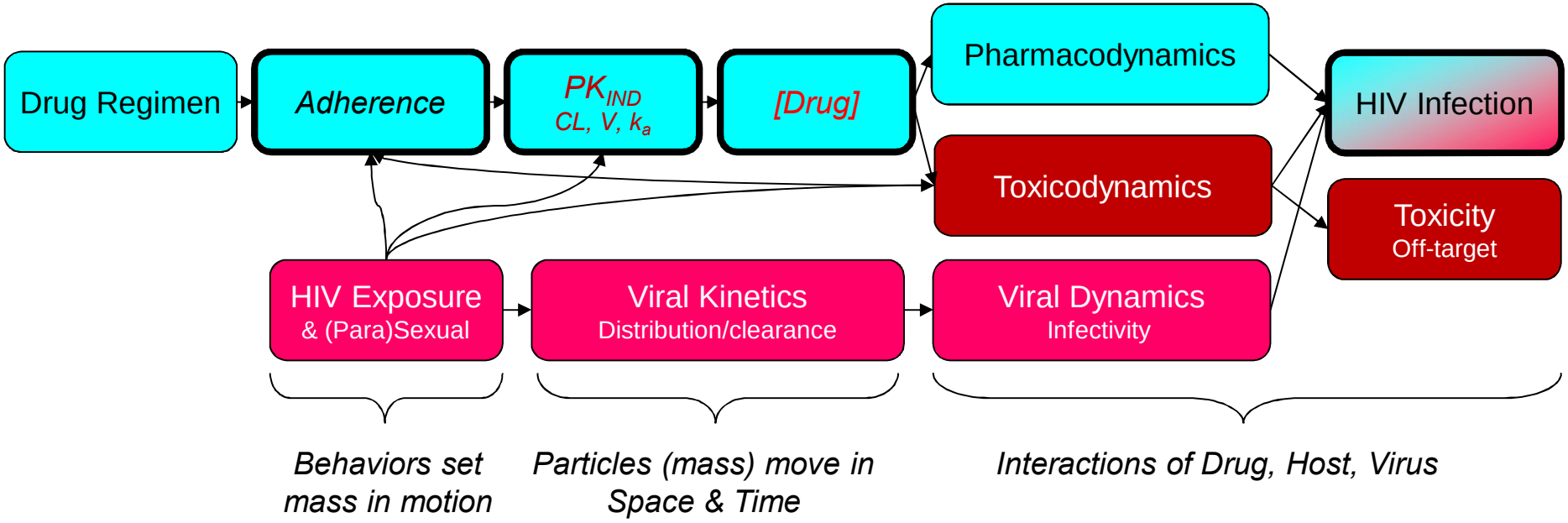
* Exponentiated parameters are odds ratios

† Based on estimates of θ^n and Ω^n only

Girard , *et al. Statisc Med* 1998

CLINICAL TRIAL SIMULATION

Clinical Trial Simulation



Why Clinical Trial Simulation?

- Forces identification of knowledge on hand and what is missing and uncertain
- Identify uncertainty impact on trial outcomes
- May result in cheaper, cost effective studies
- May result in trials with fewer adverse events
- Allows trial ñtest driveò on a computer
- Ask ñWhat if?òquestions

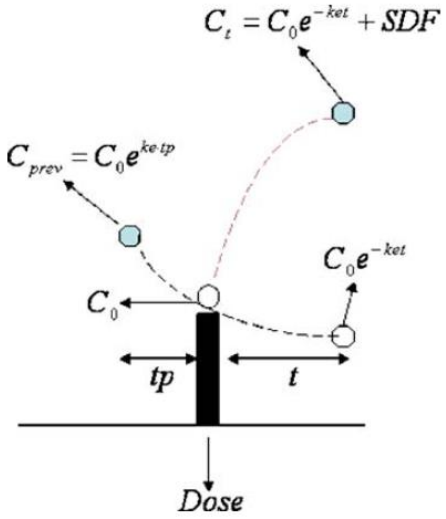
Key Points

- + Within study concentration-response
- + Between study concentration-response
- Caution extrapolating MSM results to others
- Adherence (mostly) explains concentration σ
- Target concentration needs more work
- Drug concentration cannot explain all

Pop PK Model: Adherence & PK

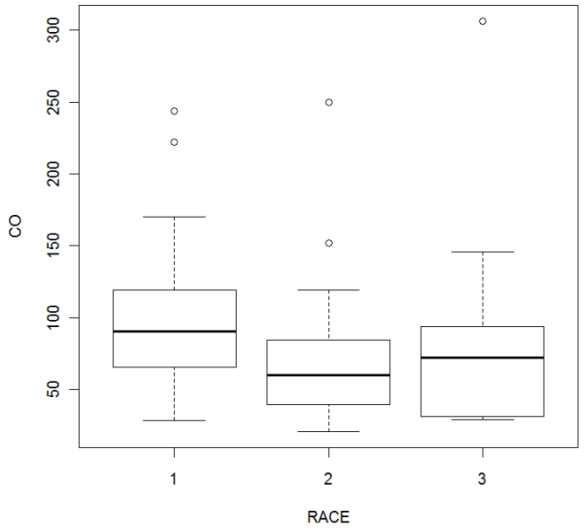
- MTN-001 non-linear mixed effects model
- Estimate PK (*Cl, V, Ka*) and adherence (C_0)
- No PK differences; sign. Adherence difference

PK Model

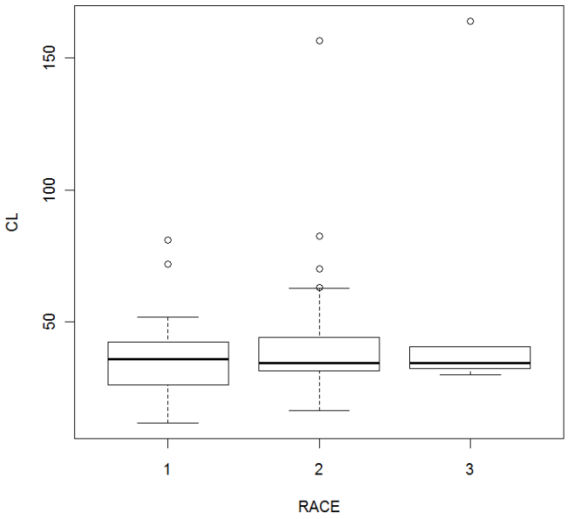


Gupta, *et al*. J PK PD 2008

Adherence Measure (C_0)

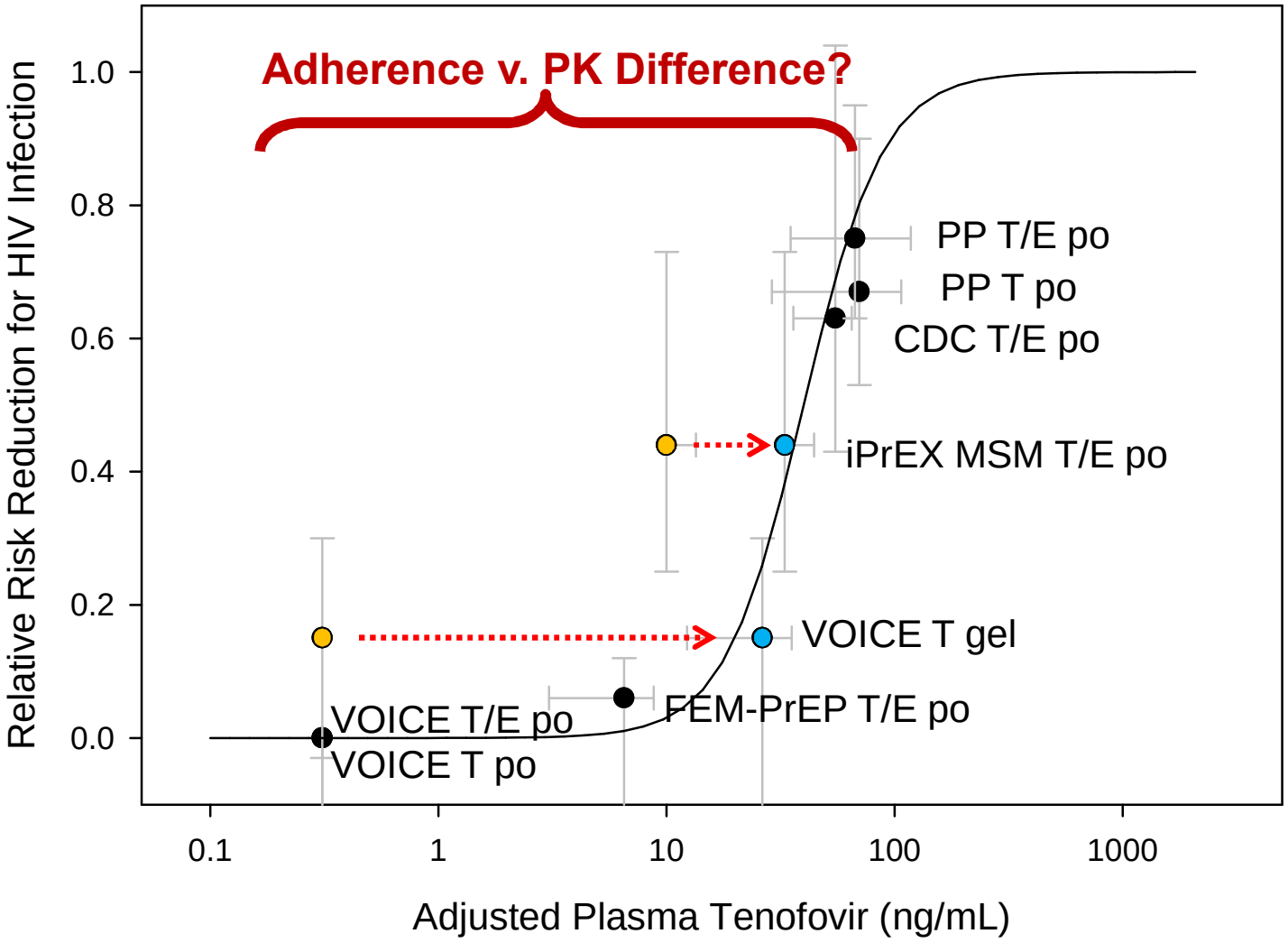


Clearance (*Cl*)



Chaturvedula, et al. 2012

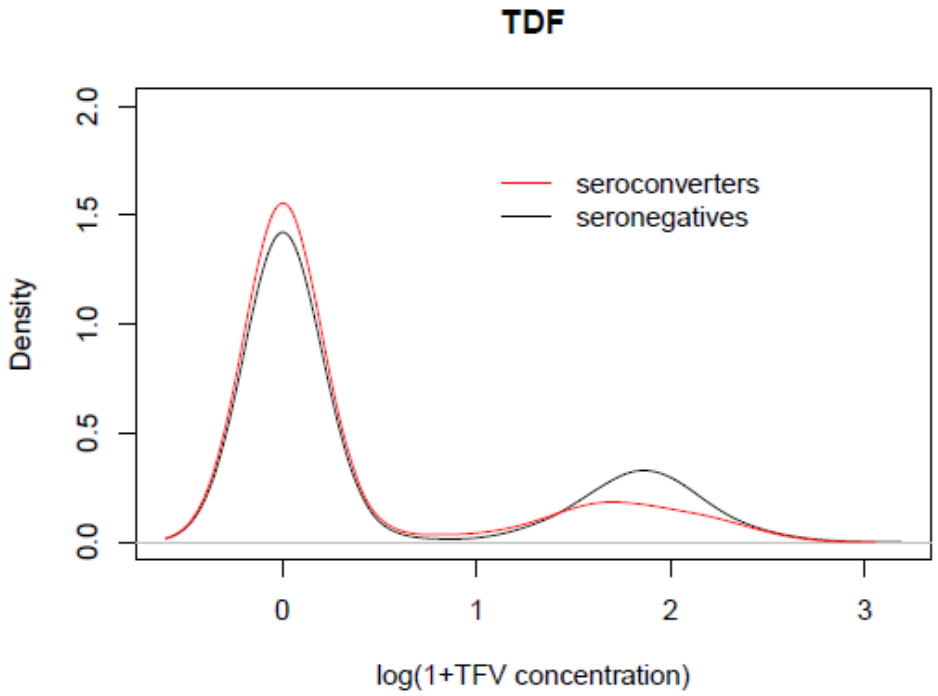
PrEP RCT PK-PD ï Informed by PK

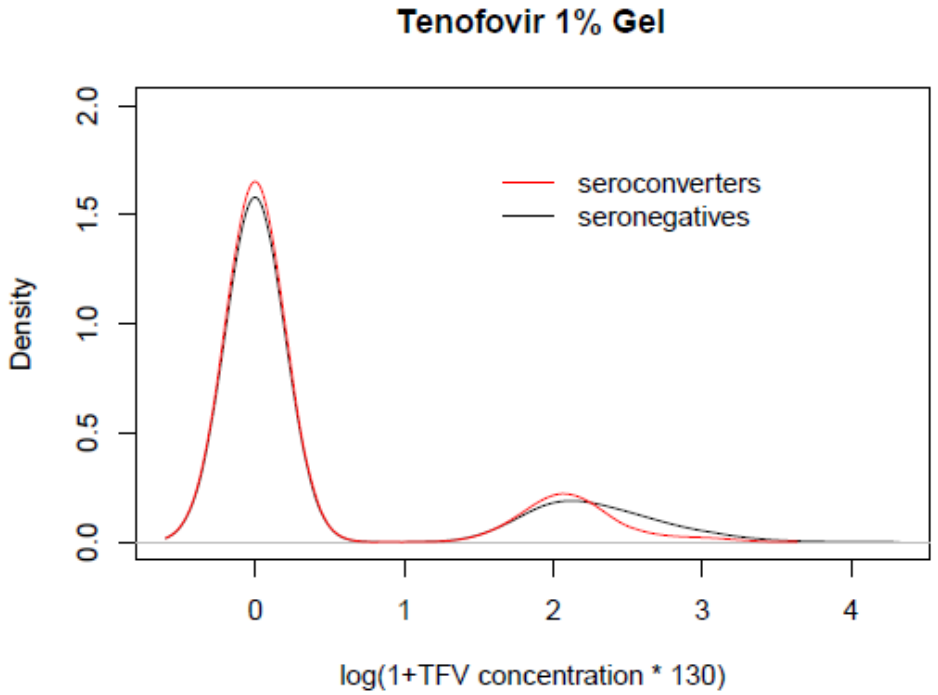


PK informed interpretation, not design

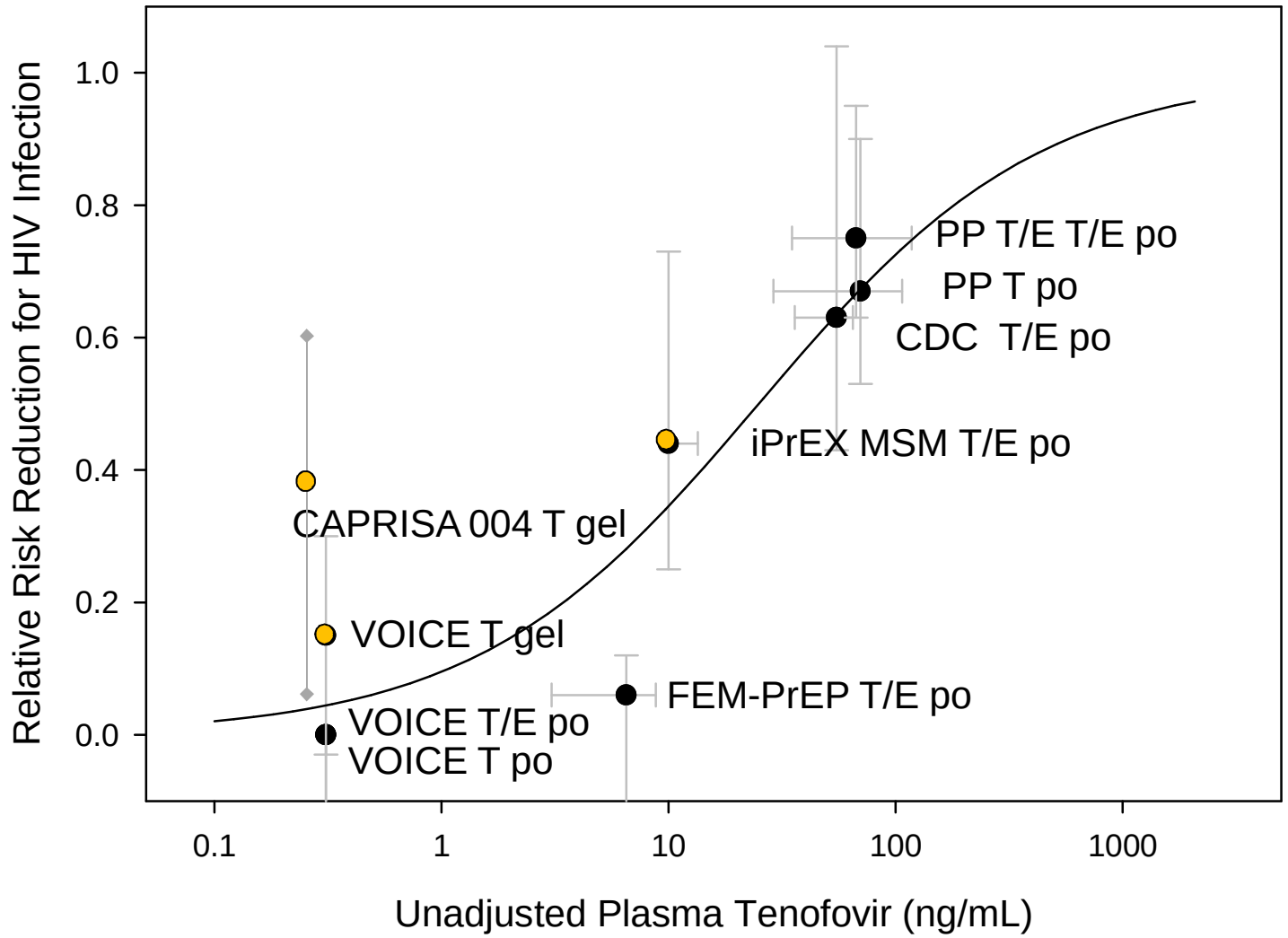
Study	Regimen	Relative Risk Reduction (95% CI)	
		All Subjects	Drug Detectible
Partners	TDF po qd TDF/FTC po qd	0.67 (0.44 ï 0.81) 0.75 (0.55 ï 0.87)	0.86 (0.57ï 0.95); BLQ 0.3 0.90 (0.56ï 0.98) ; BLQ 0.3
CDC TDF2	TDF/FTC po qd	0.62 (0.22 ï 0.83)	50% SC, 80+% NSC; BLQ 0.3
iPrEX	TDF/FTC po qd	0.42 (0.15 ï 0.63)	0.92 (0.40 ï 0.99) ; BLQ 10
FEM-PrEP	TDF/FTC po qd	0.06 (-0.41 ï 0.52)	No diff. 25% v 35%;BLQ 10
VOICE	TDF po qd TDF/FTC po qd	*-0.49 (-1.30 – 0.035)* *-0.04 (-0.50 – 0.30)*	No difference; BLQ .0.3
CAPRISA 004	TFV gel BAT24	0.39 (0.04 ï 0.60)	>1,000 CVF increased RRR
VOICE	TFV gel qd[e]	*0.15 (-0.20 – 0.40)*	No difference; BLQ 0.3

VOICE: Adjusted TFV Concentrations





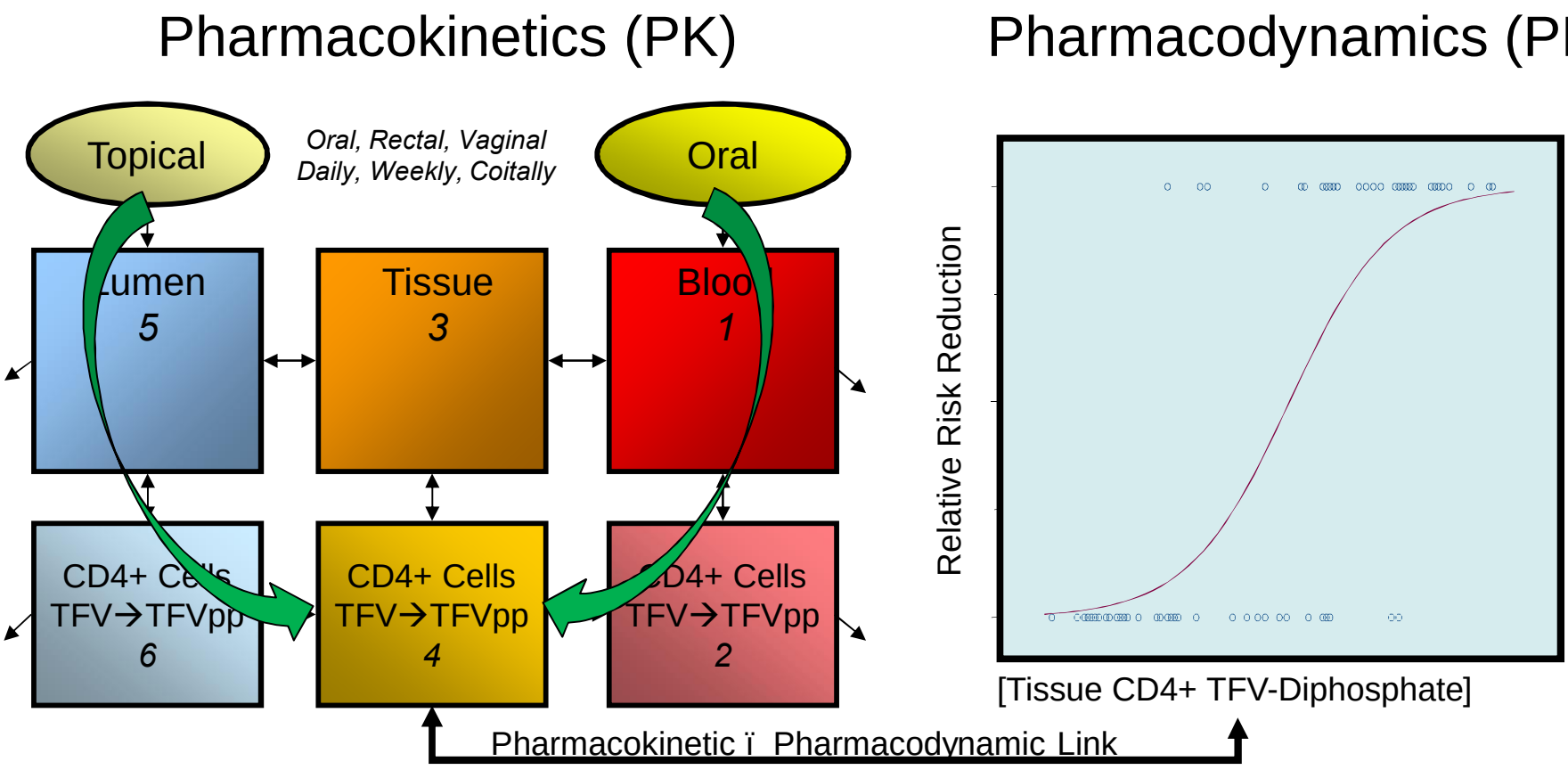
PrEP RCT PK-PD ï No Little Studies



How does clinical pharmacology inform?

- Concentration-response
  - Target concentration?
  - Target location?
  - Rational dosing
- Explain variable response among populations?
- Adherence assessment
  - *Post hoc* Interpretation of RCT outcomes?
  - Real-time study intervention?

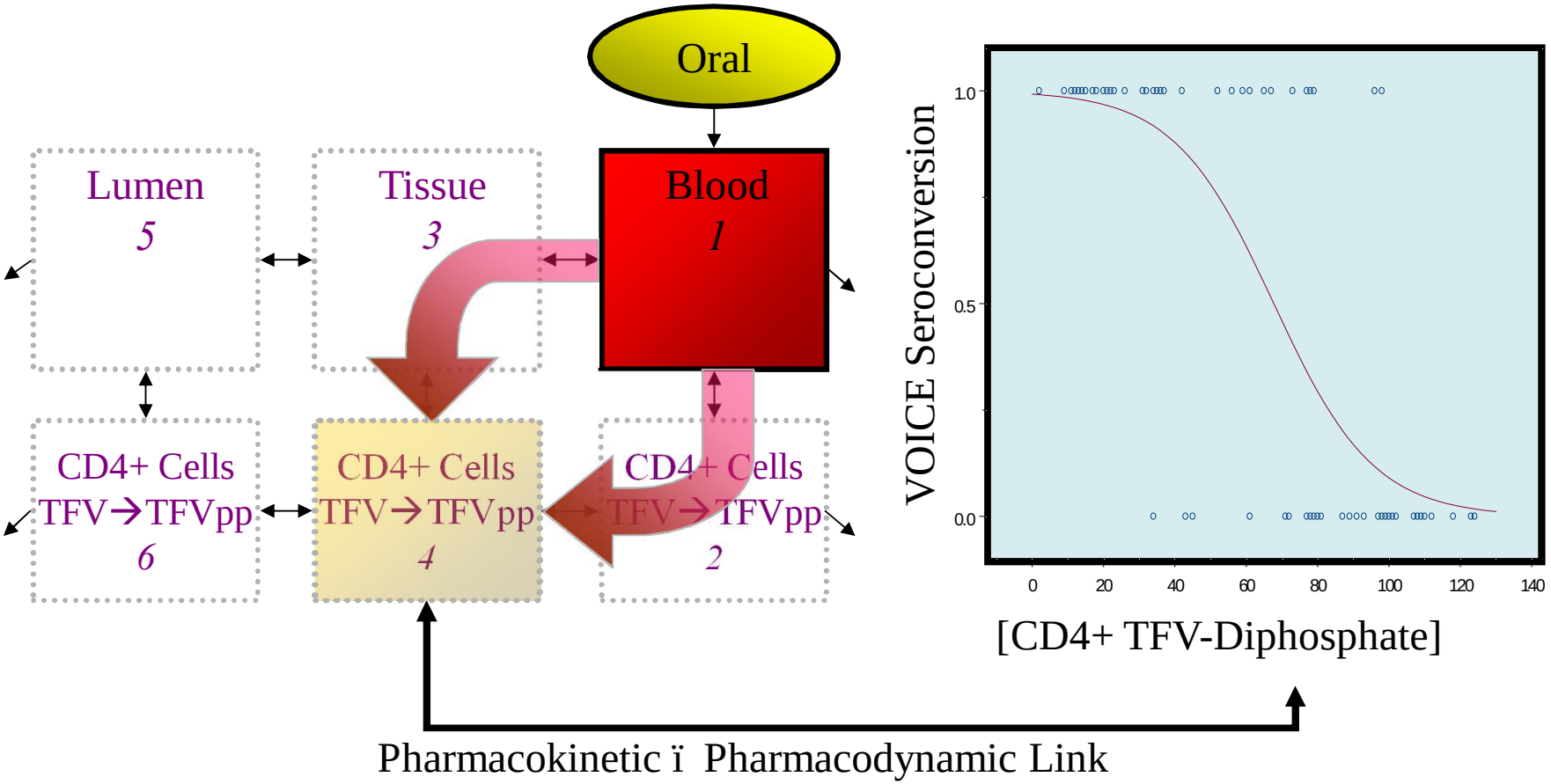
Site of Action: Tissue frame of reference



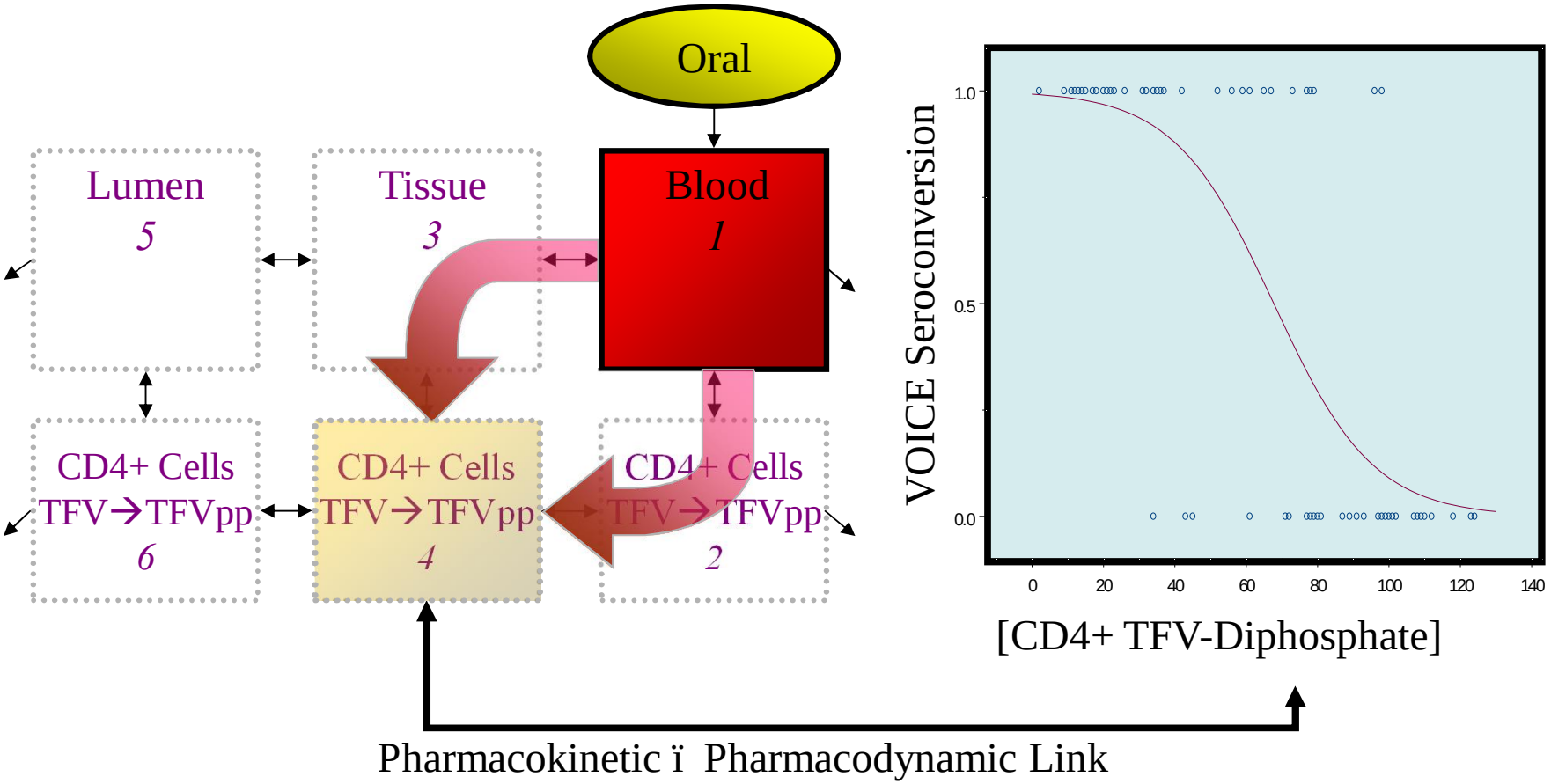
At the site of action oral and topical dosing achieves the same effective concentration (best PK/PD model fit).

Hendrix, *et al Ann Rev Pharm Toxicol* 2009

Distant Compartment Assessment

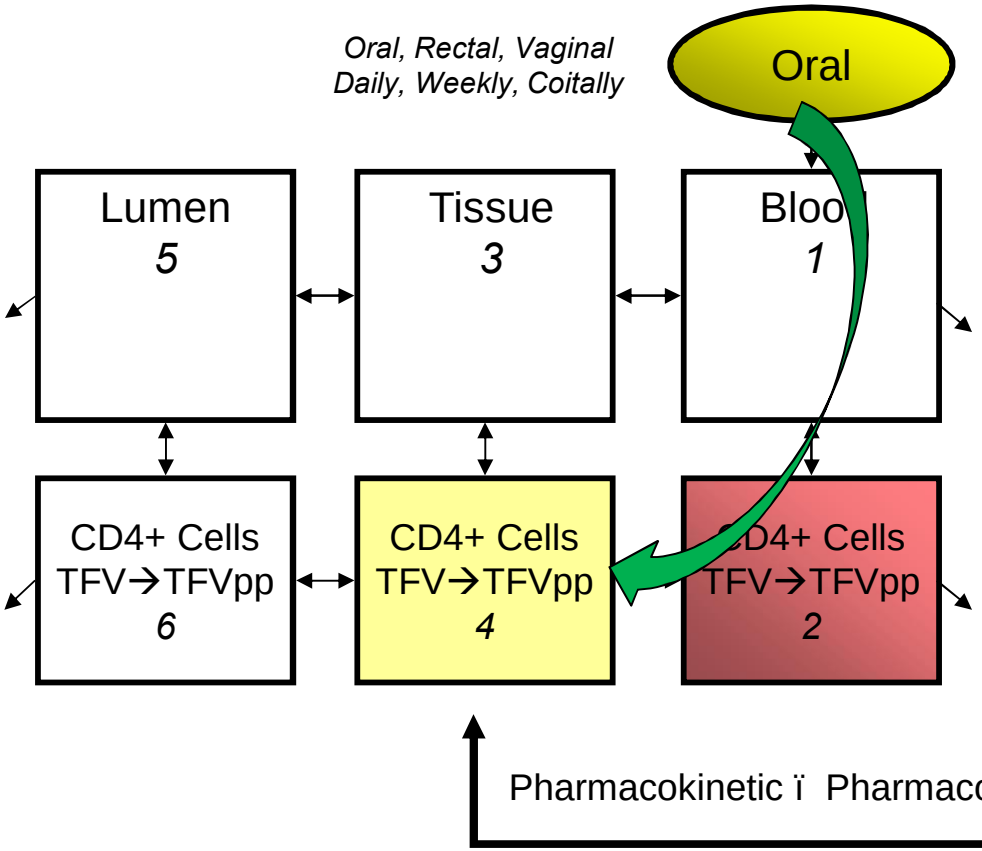


Distant Compartment Assessment

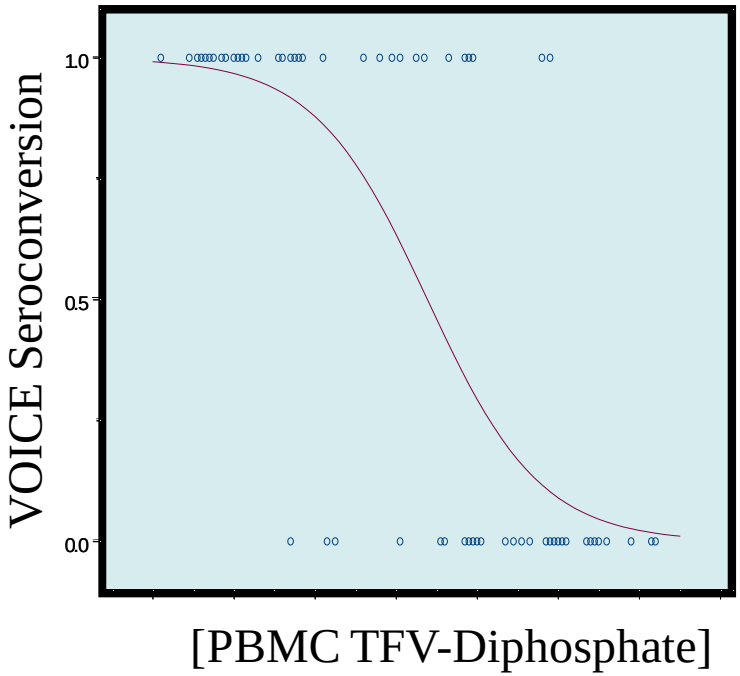


Distant Compartment PK Informative

Pharmacokinetics (PK)



Pharmacodynamics (PD)



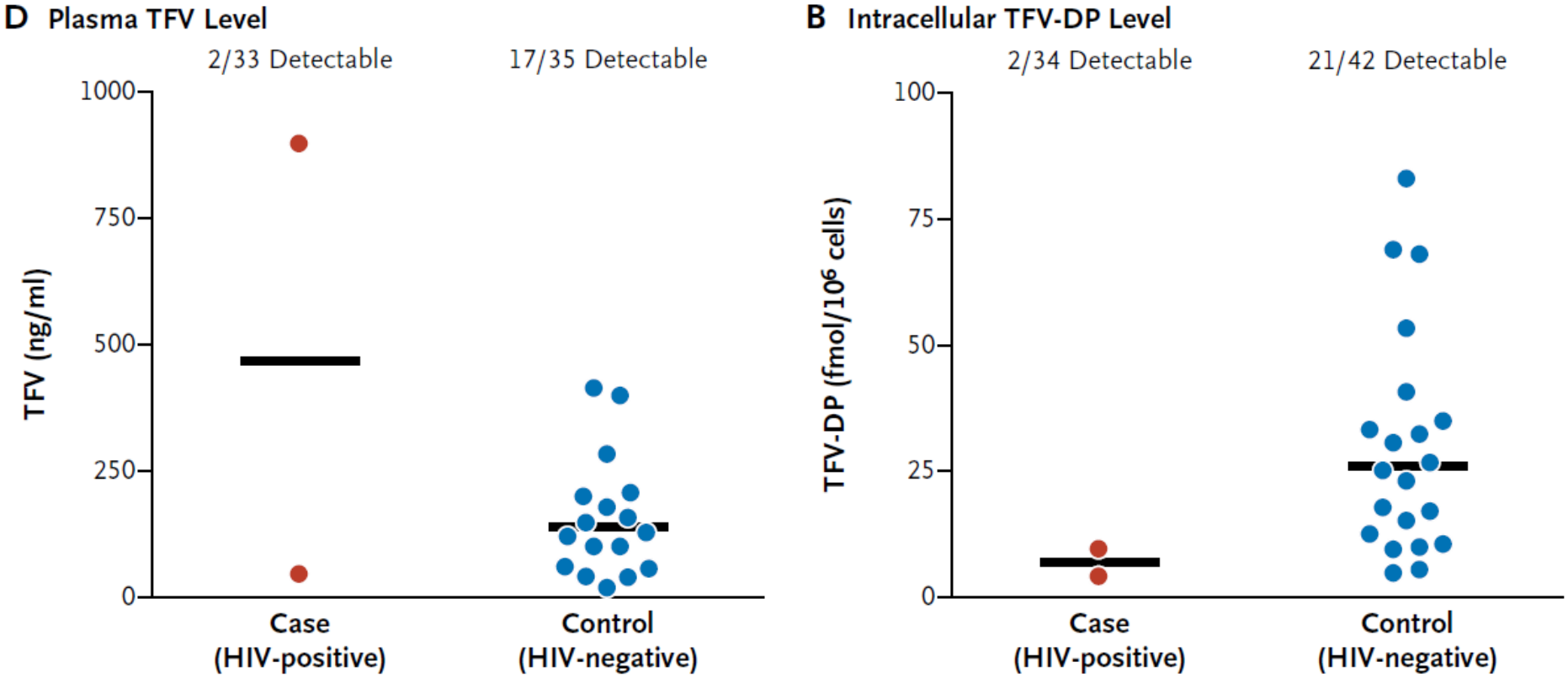
Pharmacokinetic ï Pharmacodynamic Link

Hendrix, *et al Ann Rev Pharm Toxicol* 2009

Does dosing route affect concentrations?

- 144 Women
- Africa, US
- Tenofovir daily
- Oral, Vaginal, Dual
- Cross-over design
- 6 weeks each regimen
- 6-compartment PK
  - Plasma TFV, PBMC TFV-DP 8 hours (US intense, Africa sparse)
  - Vaginal tissue homogenate TFV, TFV-DP
  - Cervicovaginal lavage TFV
  - Endocervical cytobrush TFV-DP

iPrEX: Contrasts womenôs cohorts

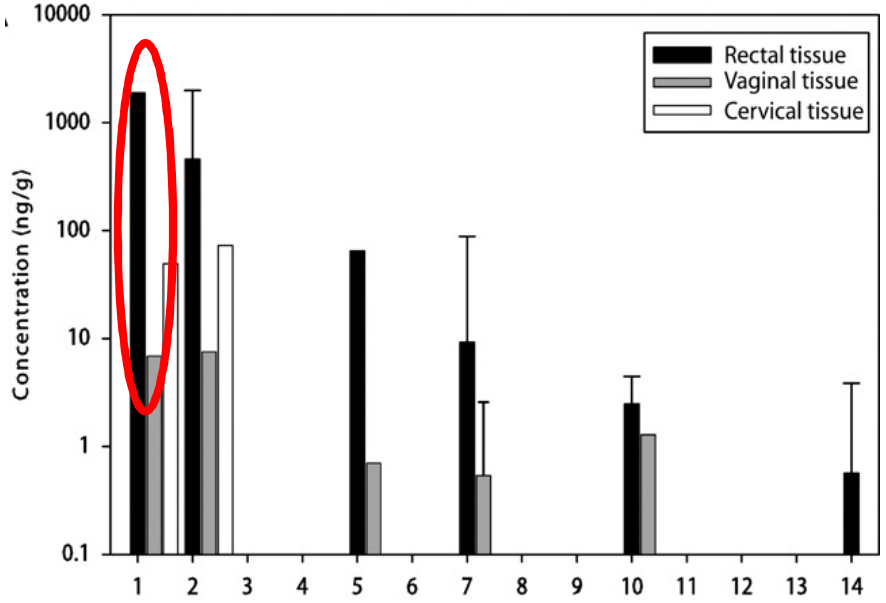


- Detection of drug relative reduction in HIV risk of 92% (95% CI 40-99)
- Only ½ had measurable drug ï far lower than oral womenôs studies (medians indicated are not medians)

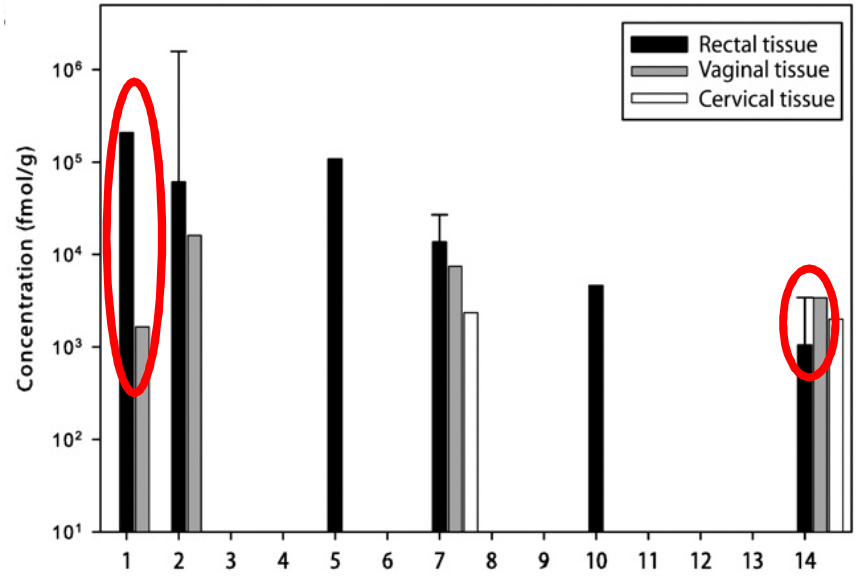
iPrEx (MSM) target similar for women?

- Single dose TDF
- 6 men; 6 women (unpaired)
- Semi-weekly tissue sampling x 2 weeks

TFV 24h RT:VT 2.5 Log_{10}



TFV-DP 24h RT:VT 2.2 Log_{10}



Patterson, *et al*. Sci Trans Med 2011

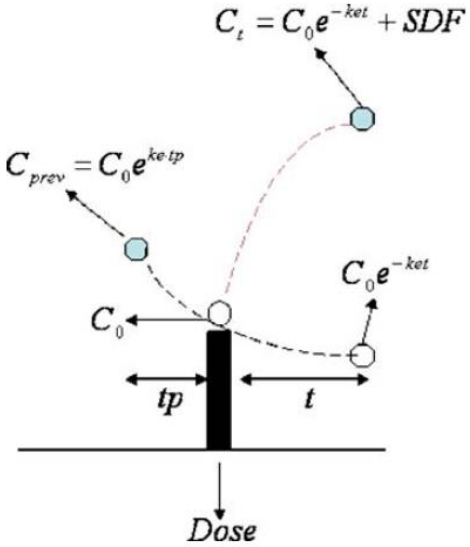
VOICE Adherence Assessments

- Product return (pill/vaginal applicator)
- Self-report using ACASI
- PK-related
  - Quarterly blood sampling planned for exposure-response analysis
  - Case-cohort design:
    - Random active arm subset (non-seroconverter + all seroconverters, N = 773
    - All samples from each participant, N = 3,298
    - Median number of samples 4; range 1 - 12
    - Small sample from placebo arms for blinding

Population PK: PK & Adherence

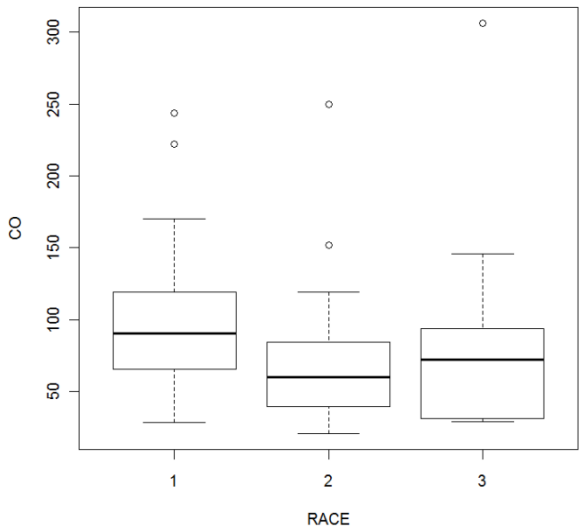
- Estimate PK (*CL, V, k_a*), adherence (C_0)
  - C_0 represents the concentration present in the system at the time of the most recent dose
  - $C=[SDF+ C_0^{-b\,t}]$
  - $SDF= Dose*(A*e^{(-a*t)}+B*e^{(-b*t)}-(A+B)*e^{-ka*t})$

PK Model

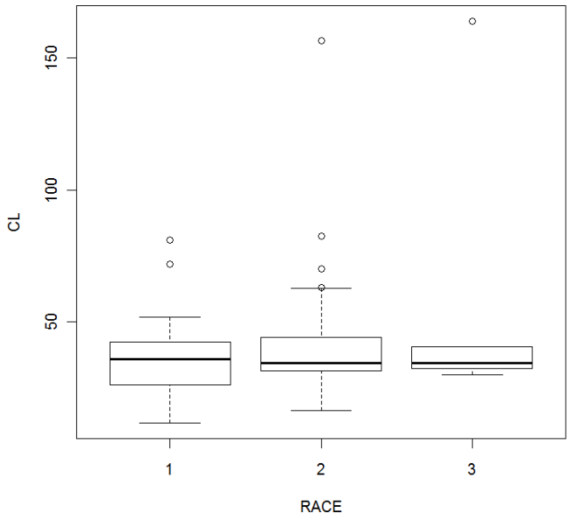


Gupta, *et al*. J PK PD 2008

Adherence Measure (C_0)



Clearance (*Cl*)



Chaturvedula, et al. 2012