Pharmacological Approach to Monitoring Drug Adherence

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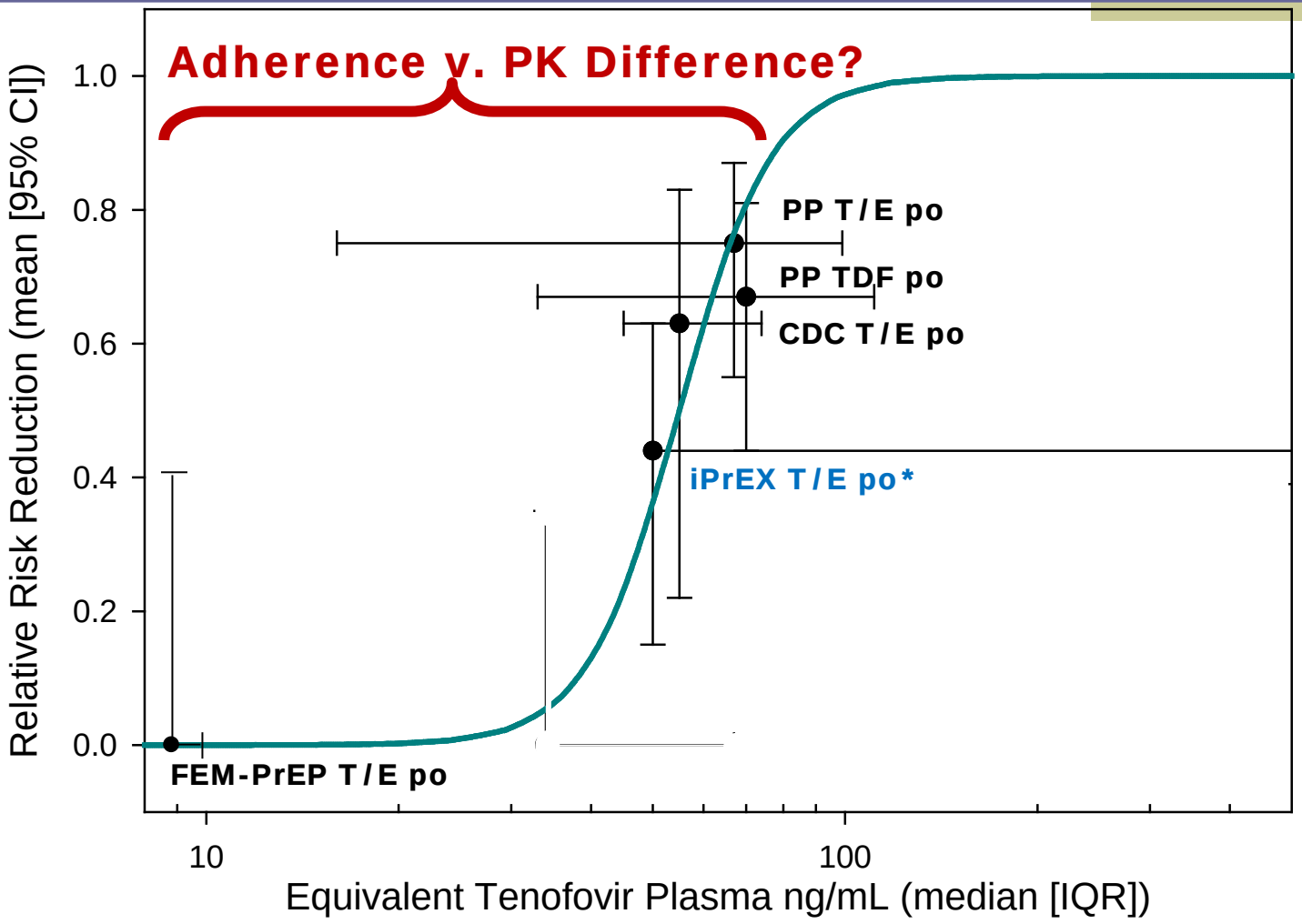
[Drug] - Adherence Questions

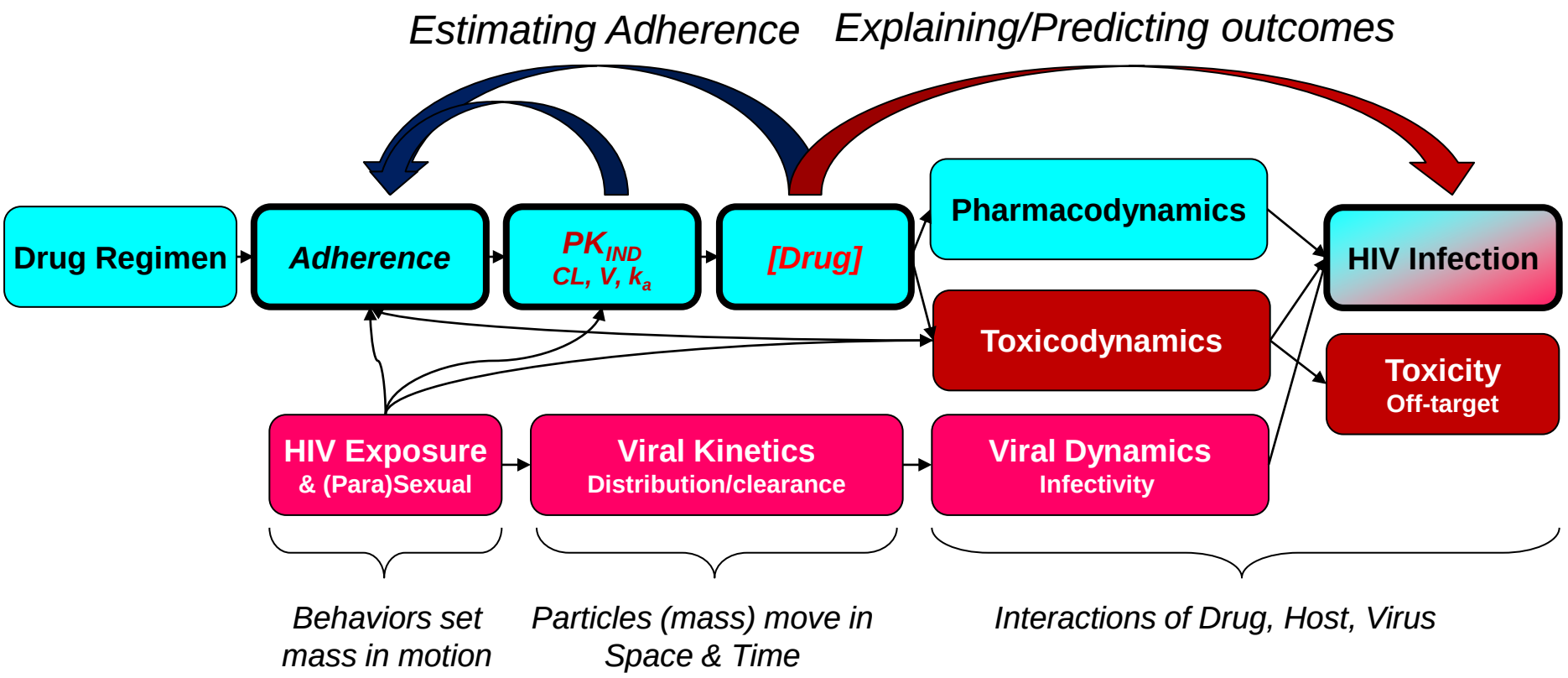
- How much of [drug] variation is adherence?
- Can [drug] quantitatively assess adherence?
  - Population level?
  - Individual level?
- How might [drug] be used to target adherence interventions?

Conc'n-Response *Among* RCTs



*Adjusted for 66x → increased colon tissue concentration & 20x ← greater anal transmission risk

Adherence-PK-PD Connections



- [Drug] 2 steps from adherence
- [Drug] + PK_{IND} next to adherence
- [Drug] 2 steps from seroconversion PLUS many other variables

Population or individual level assessment?

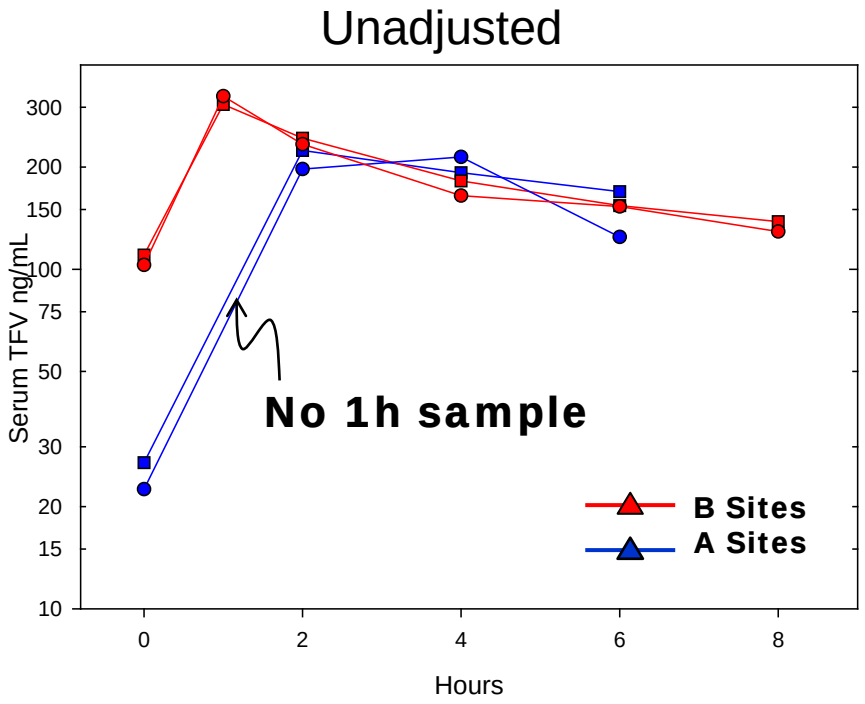
Quantitative Adherence PK_{POP}

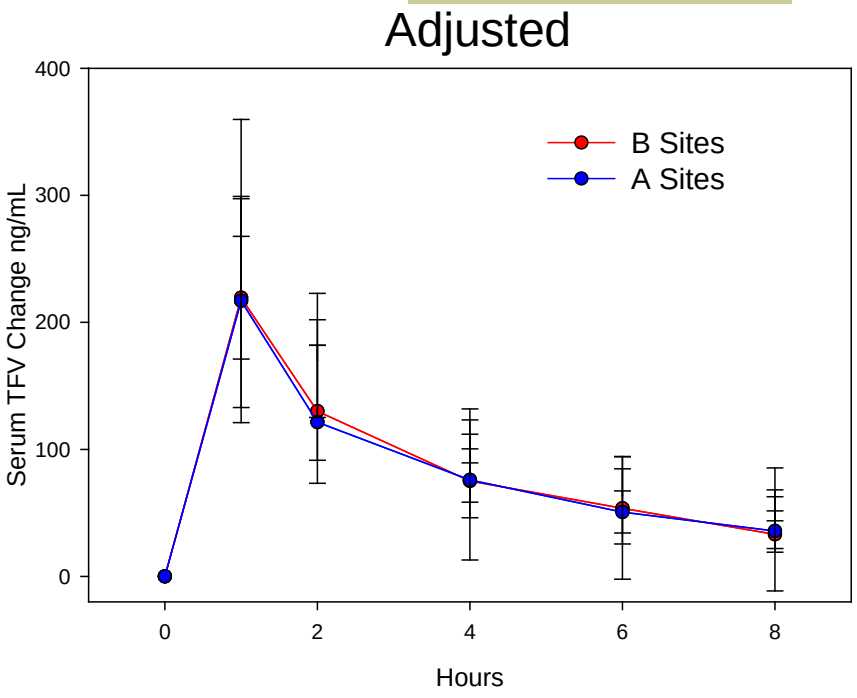
- Collect biological specimen
- Assay for drug concentration
- Relate to 100% adherence standard

%Adherence = (Observed/Expected)●100 + σ + ε

- Observed – collect sample, assay sensitivity?
- Expected – population benchmark?
- Variables – are they known?

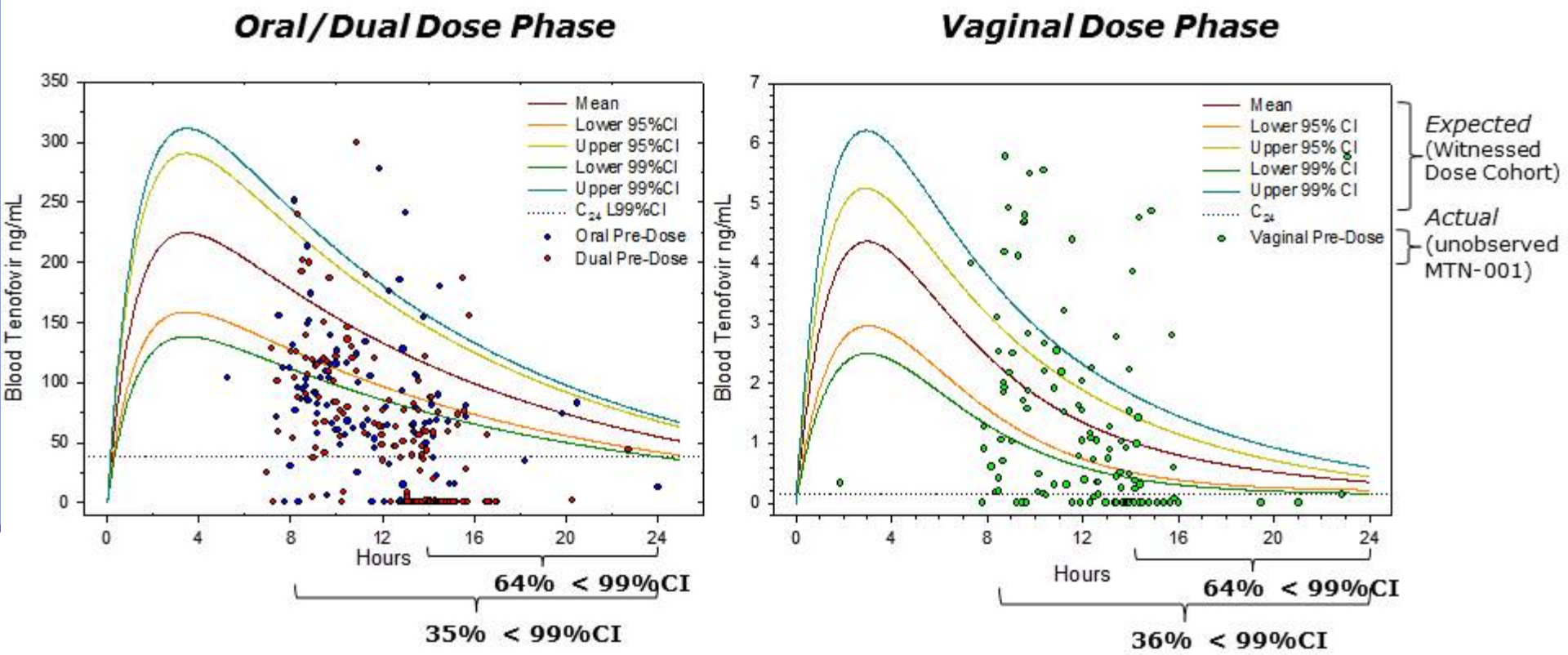
Adherence or PK_{POP}?





- Decay (PK) same after observed dose
- Pre-dose concentration (adherence, PK) 5:1 ratio
- Crude adjustment indicates same PK

Observed v. Expected [TFV]



How much of the low concentration is a result of PK_{IND}?

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)

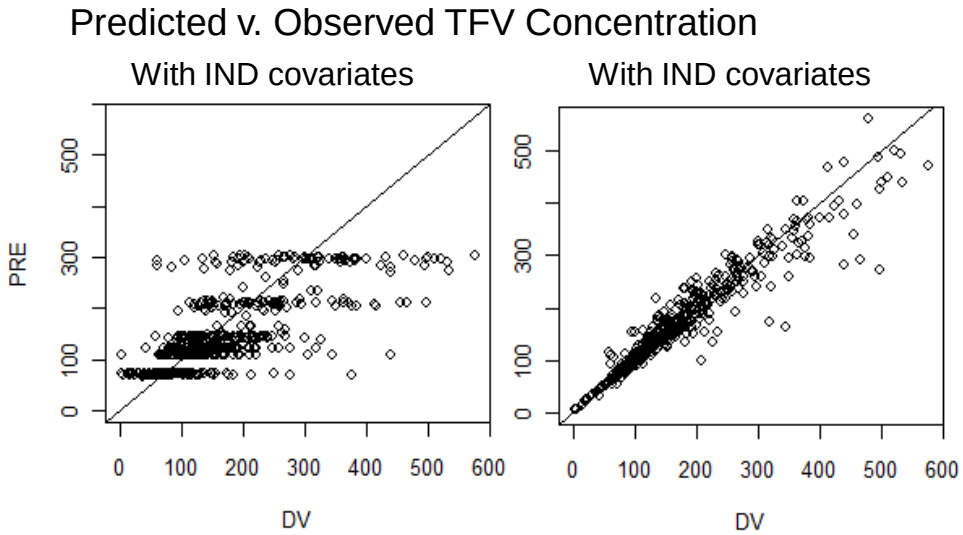
Quantitative Adherence PK_{IND}

- Expected Phase
  - Directly observe initial dose
  - Sample once or twice before second dose
  - Population PK analysis estimate PK_{IND}
  - Estimate expected value with 100% adherence
- Observed Phase
  - Subjects take meds without observation
  - Adherence assessment at intervals
- Data Analysis

%Adherence = (Observed/Expected)●100 + σ + ε

Estimating IND Expected Values

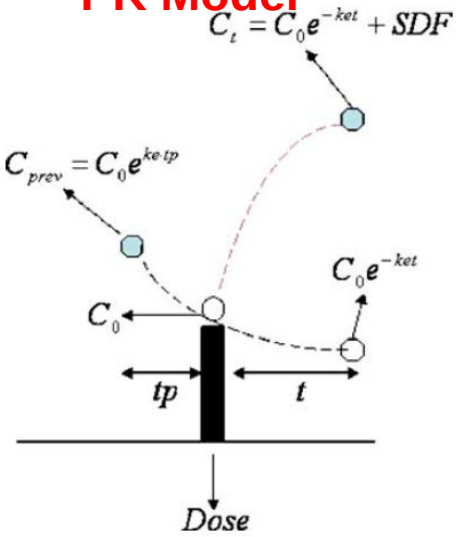
- Goal: Estimate individual concentration-time course based on 1-2 concentrations, individual covariates
- Population PK models
  - Estimate pop's PK (CL, V)
  - Estimate effect of individual covariates
    - CrCl, Age, Wt, gender, genetics , conmeds
  - Improve individual prediction



Adherence or PK_{IND}?

- Build non-linear mixed effects model
- Estimate PK (*CL, V, k_a*) and adherence (C_0) & influential covariates
- PK_{IND} (CL, V) covariates
  - CrCl, Age (*significant)*
  - Race (NS)
  - Location (NS)
  - Contraceptives (NS)
- Adherence (C_0)
  - Location (*significant)*

PK Model



Gupta, *et al*. J PK PD 2008

A. Chaturvedula, *manuscript in preparation*

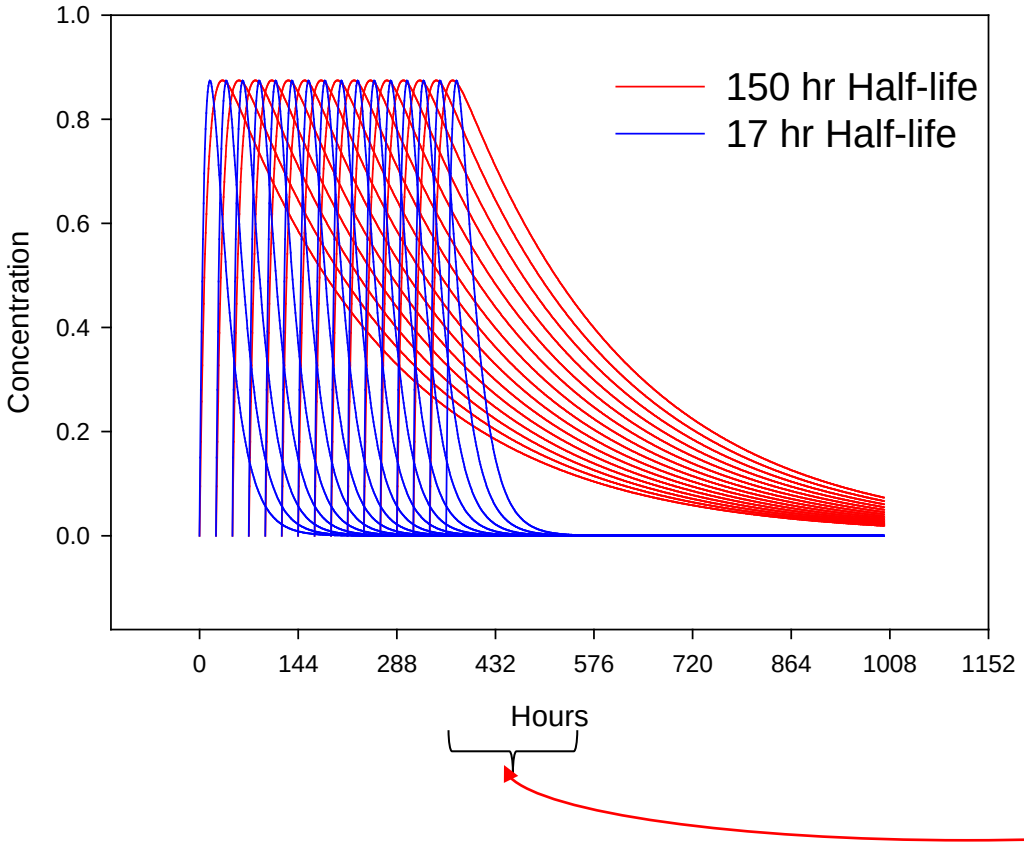
Sources of variation

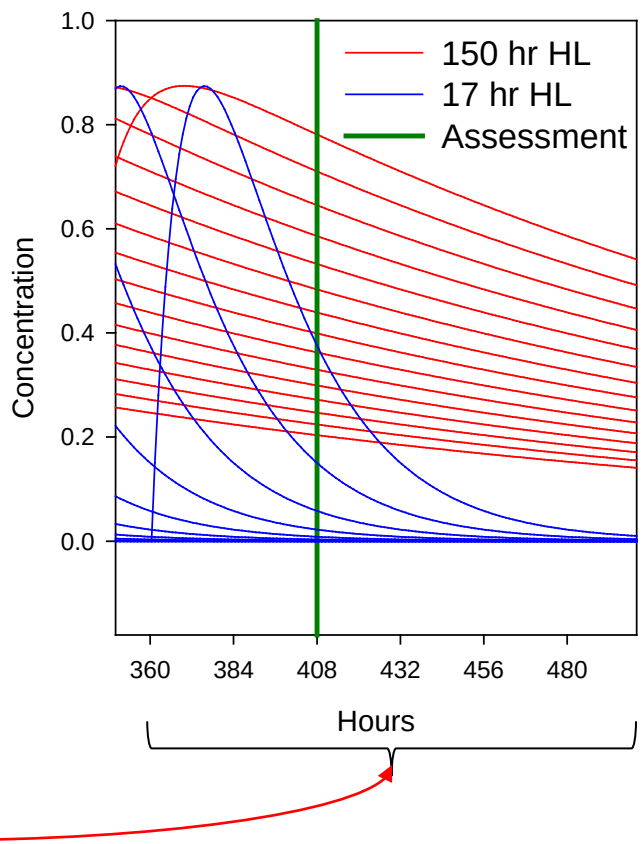
Variables (Obstacles)

- What variables complicate quantitative adherence monitoring by [drug]?
  - Dose-proportionality
  - Dynamic range
  - Patterns of adherence
  - White coat effect
  - Intra-subject variability
  - Inter-subject variability
  - PK_{IND} Covariates
    - gender, age, meds, CrCl, PGx, hair color/Rx

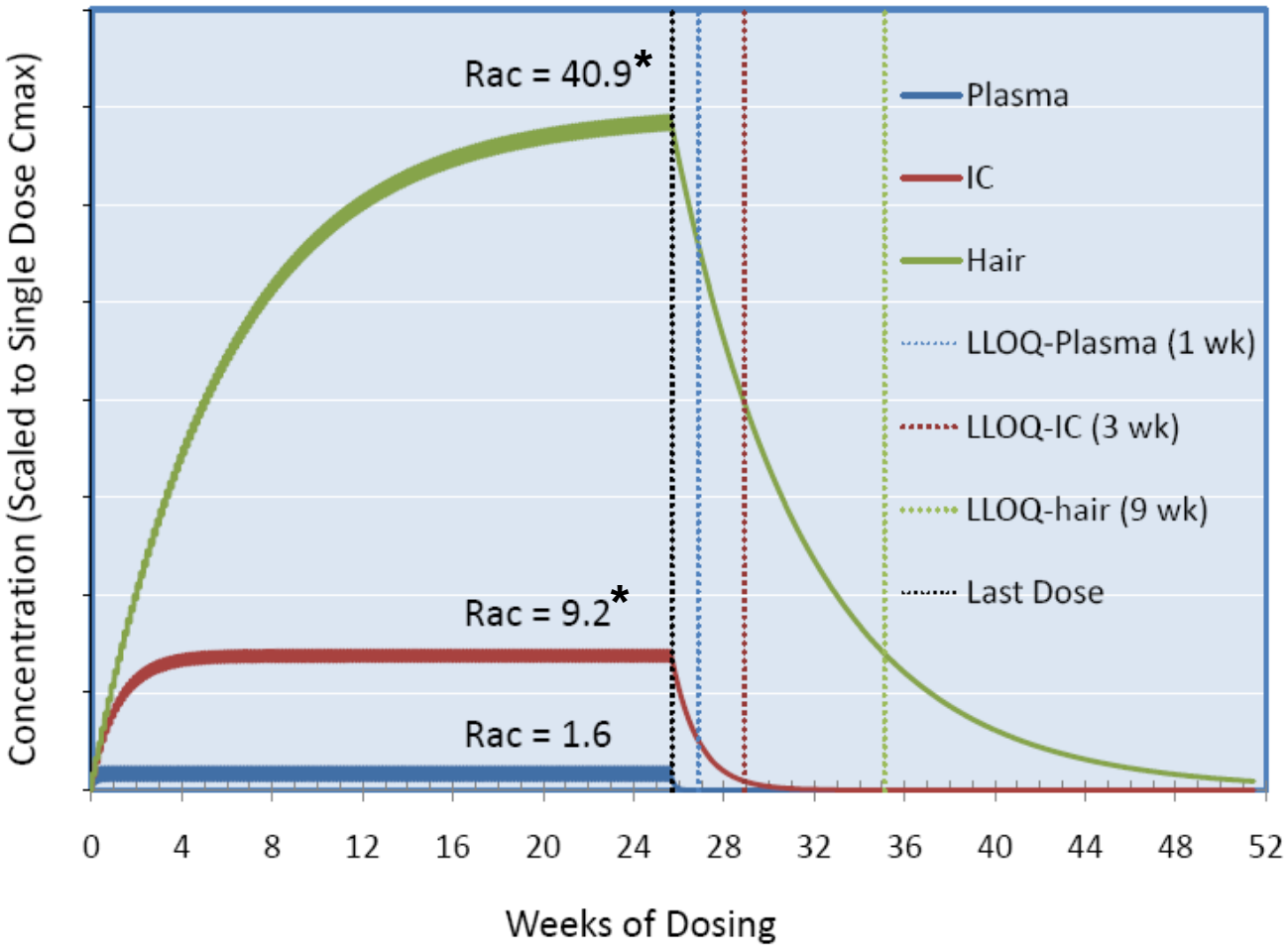
Influence of Matrix Half-Life

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





Matrix Selection
Dynamic Range, LLOQ, T_{ss}



*conjecture, estimated to be far greater than plasma

Dynamic range,
- adherence σ > biological/assay σ

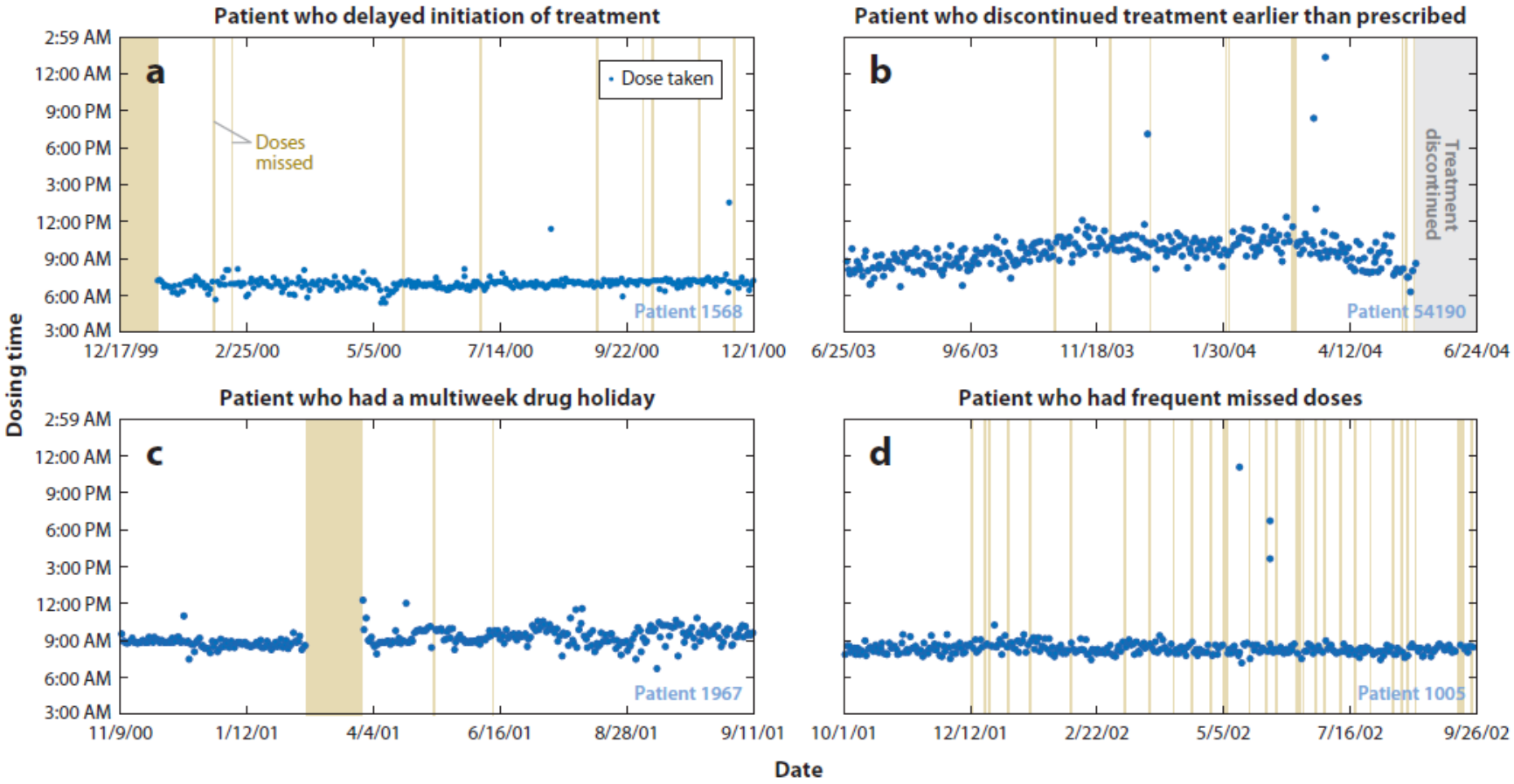
Time to SS
- time before comparable

Time to LLOQ
- lookback duration
- holiday sensitivity

Assay Sensitivity
- ? Topical dosing

Variable Patterns of Adherence

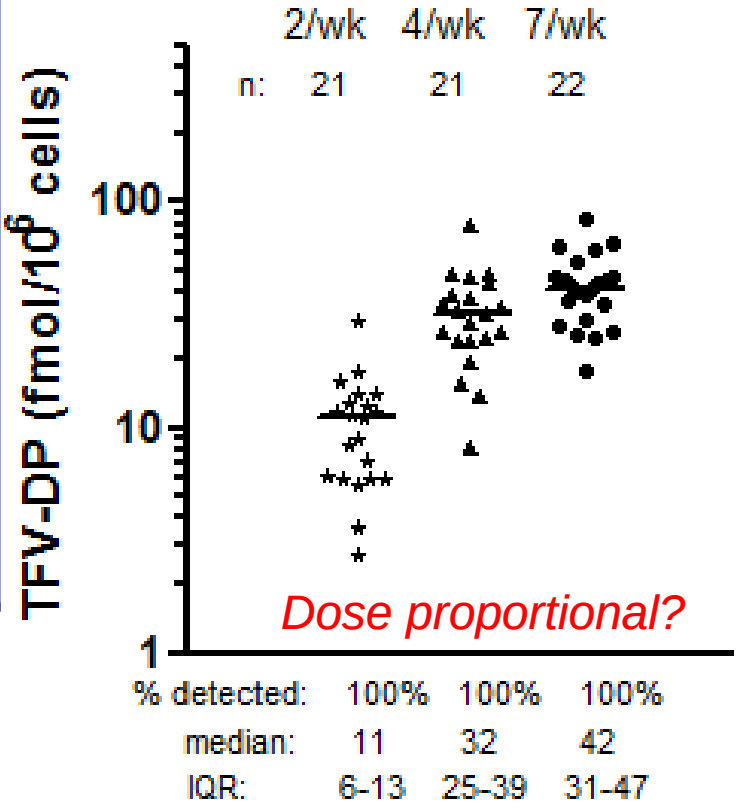
- "90% Adherence" takes many forms



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

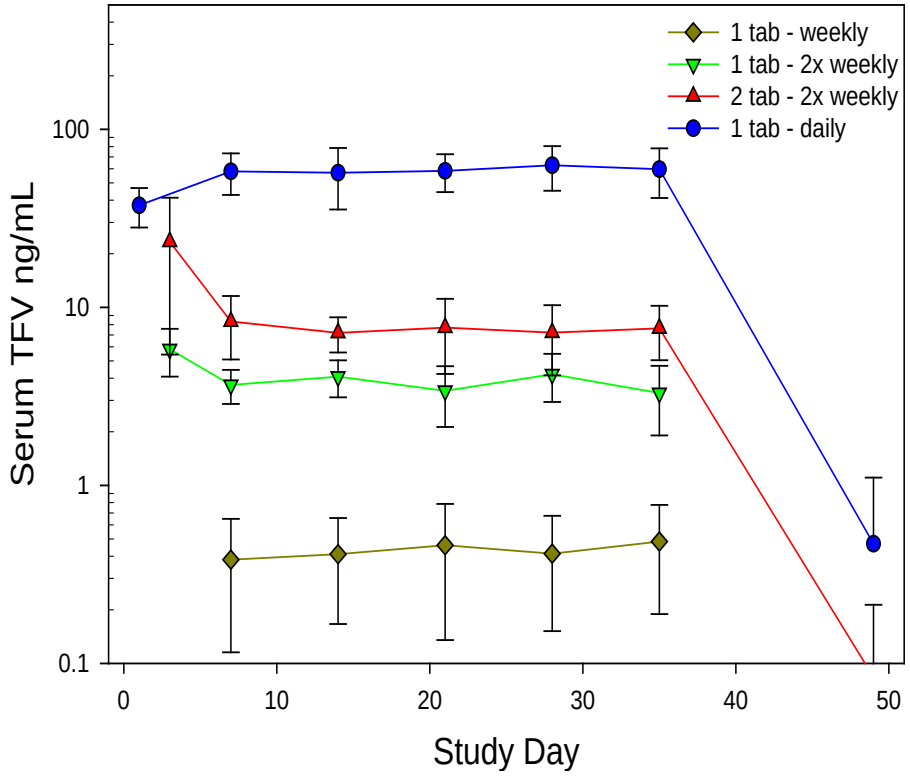
DOT Benchmarks

- STRAND



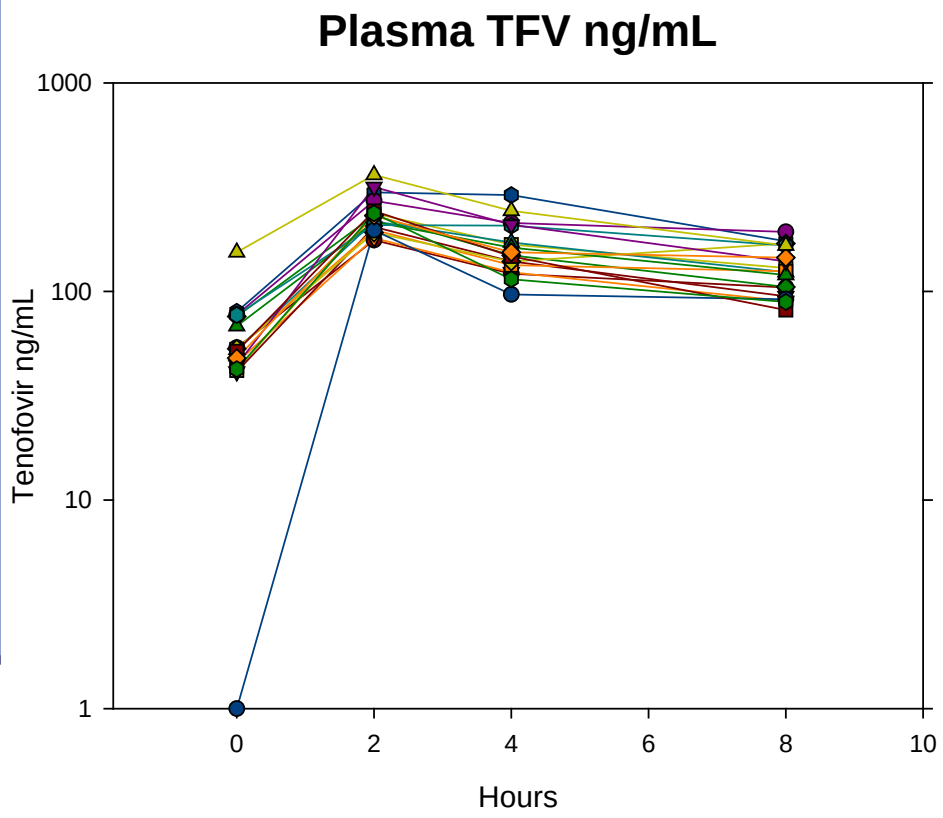
Anderson, *et al*. Sci Trans Med 2012

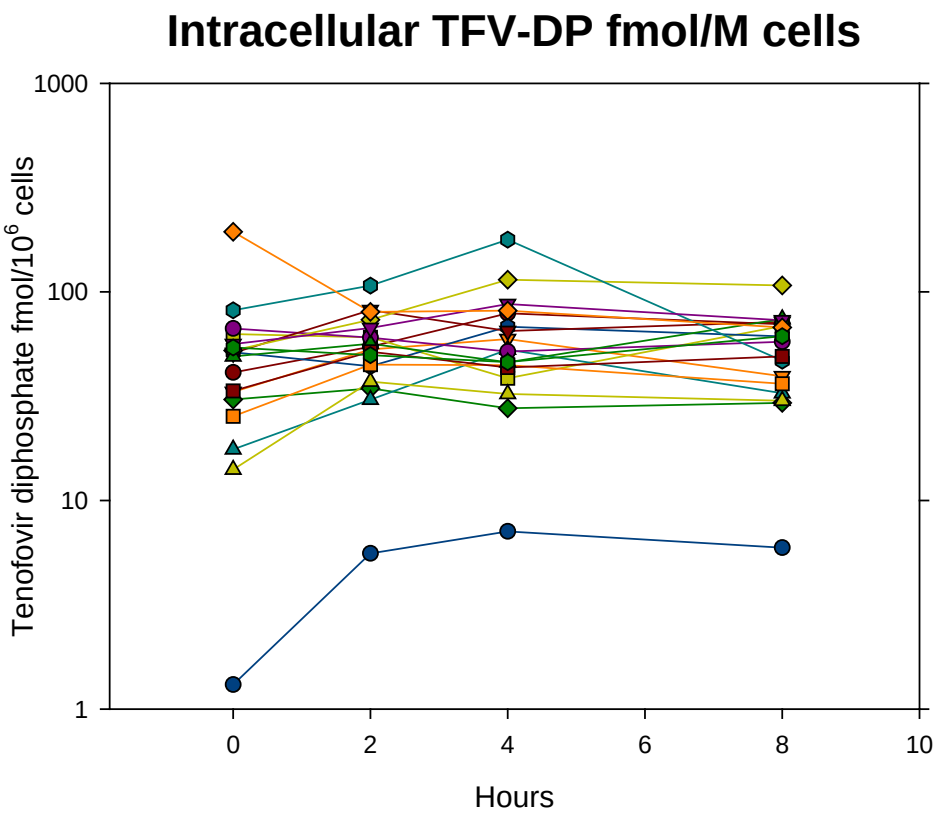
- HPTN 066



HPTN 066 (CROI 2012)

White Coat Effect & Matrix





Note "*white coat adherence*" in subject still seen in TFV-DP, but not plasma after dosing, plasma; due to difference in *time to steady-state* and *accumulation index*.

Source: TDF2 (CDC Botswana PrEP, TDF 300 mg qd, steady-state, men & women)

Target adherence interventions?

PK-Targeted Interventions

- Both PK_{POP} & PK_{IND} data may be useful to target adherence interventions
- Different individuals "non-adherent" depending on method

Pop PK Calculation	Total (n=137)	A Sites (n=68)	B Sites (n=69)
Below 20% Predicted IND	43 (31.4%)	34 (50%)	9 (13.0%)
Below 99% CI Population	49 (35.8%)	38 (55.9%)	11 (15.9%)
>1.5 x Population Lower 25%	36 (26.3%)	28 (41.2%)	8 (11.6%)

Model based on MTN-001 Population PK model

PK_{POP}-Adherence Example

- MTN-017: 3 product, 8 week per product cross-over study
- 4 & 8 week plasma PK sample "real time"
- Yes/No PK results informs 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

- "Non-Adherence" @ assay LLOQ (pink) varies with route
- Quantitative Adherence - oral 10 ng/mL c/w topical 0.3 ng/mL
- PBMC, hair, DBS – insensitive +/or Tss too long
- *Future: Single observed dose PLUS 1-2 samples enables individualized adherence thresholding (PK_{IND})*

Summary

- Adherence can be differentiated from PK
- Dose-proportionality, Tss, variability data growing
- Individual PK data improves adherence estimates
- Matrix depends on route of dosing, study duration
- Estimating adherence
  - Informs need for adherence intervention
  - Identify poor performer, improve or remove
- Problematic implementation with placebo trials
- Most matrices insensitive for topical dosing
- EMS superior/complementary to PK for adherence
  - Continuous + sensitive to holidays
  - Logistical, financial feasibility?

Acknowledgements

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Questions?