Why PK/PD Matters

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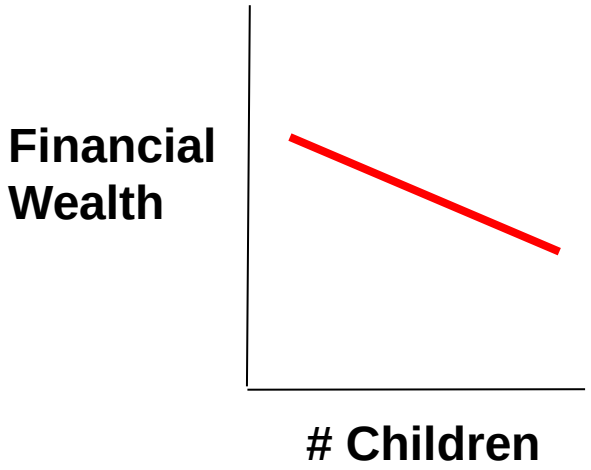
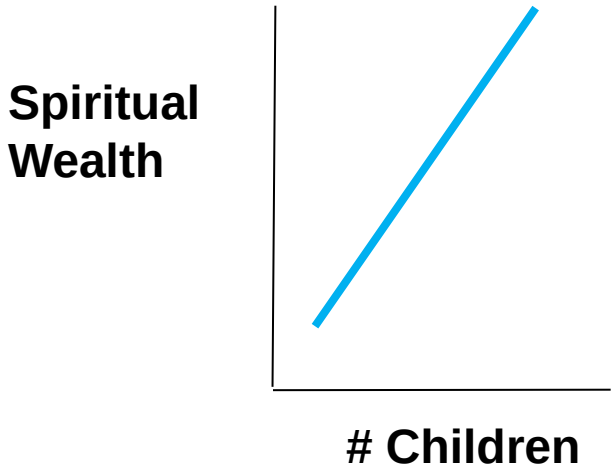
Uses of PK/PD Data

- Select critical concentration (PD)
- Planning study regimen
- Explanatory variable after study
- Forecasting efficacy outcomes
- Adherence measure
- Clinical trial simulation

Models & Equations

- Models are mathematical descriptions of observations.



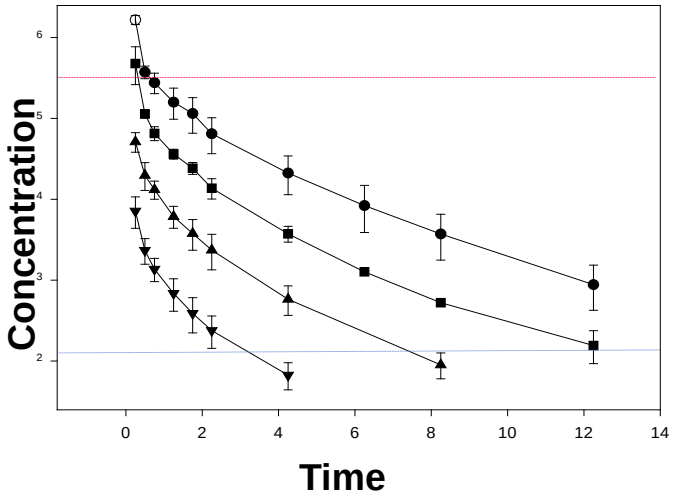


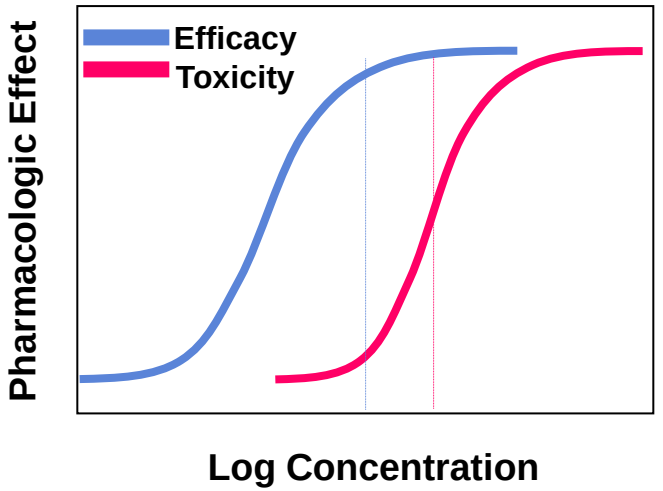
Y = slope● x-axis + intercept

- Helpful to quantitatively relate variables observed.
  - How does slope differ for financial & spiritual wealth
- Useful to predict what might happen.
- “All models are wrong. Some are useful.”

Definitions: PK & PD

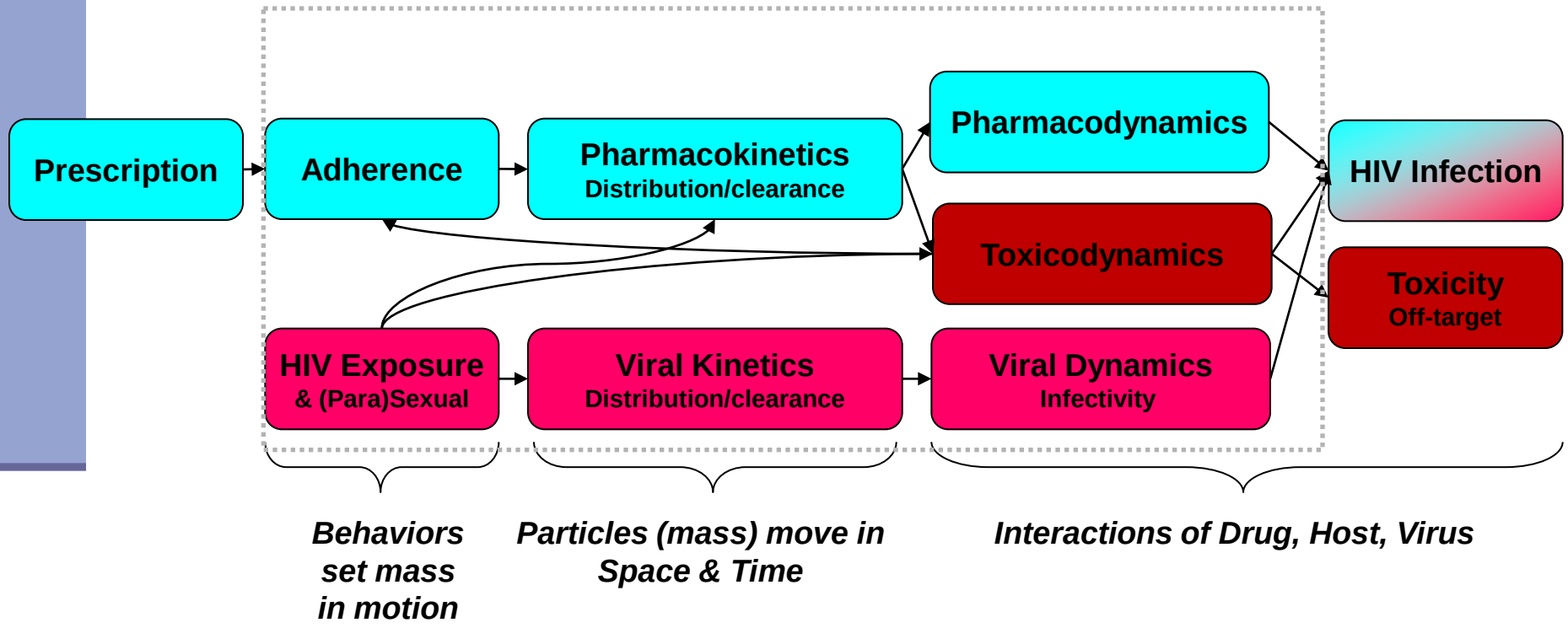
- **Pharmacokinetics (PK)**
  - Body effect on the drug
  - Variation in drug conc'n in space and time
  - Concentration-time
  - ***Hitting the target***
- **Pharmacodynamics (PD)**
  - Drug effect on body/HIV
  - Variation of drug effect with varying amount
  - Concentration-response
  - ***Deciding on the target***





HIV Chemoprevention Development
Empiric Approach

HIV Chemoprevention Development
Mechanistic Approach

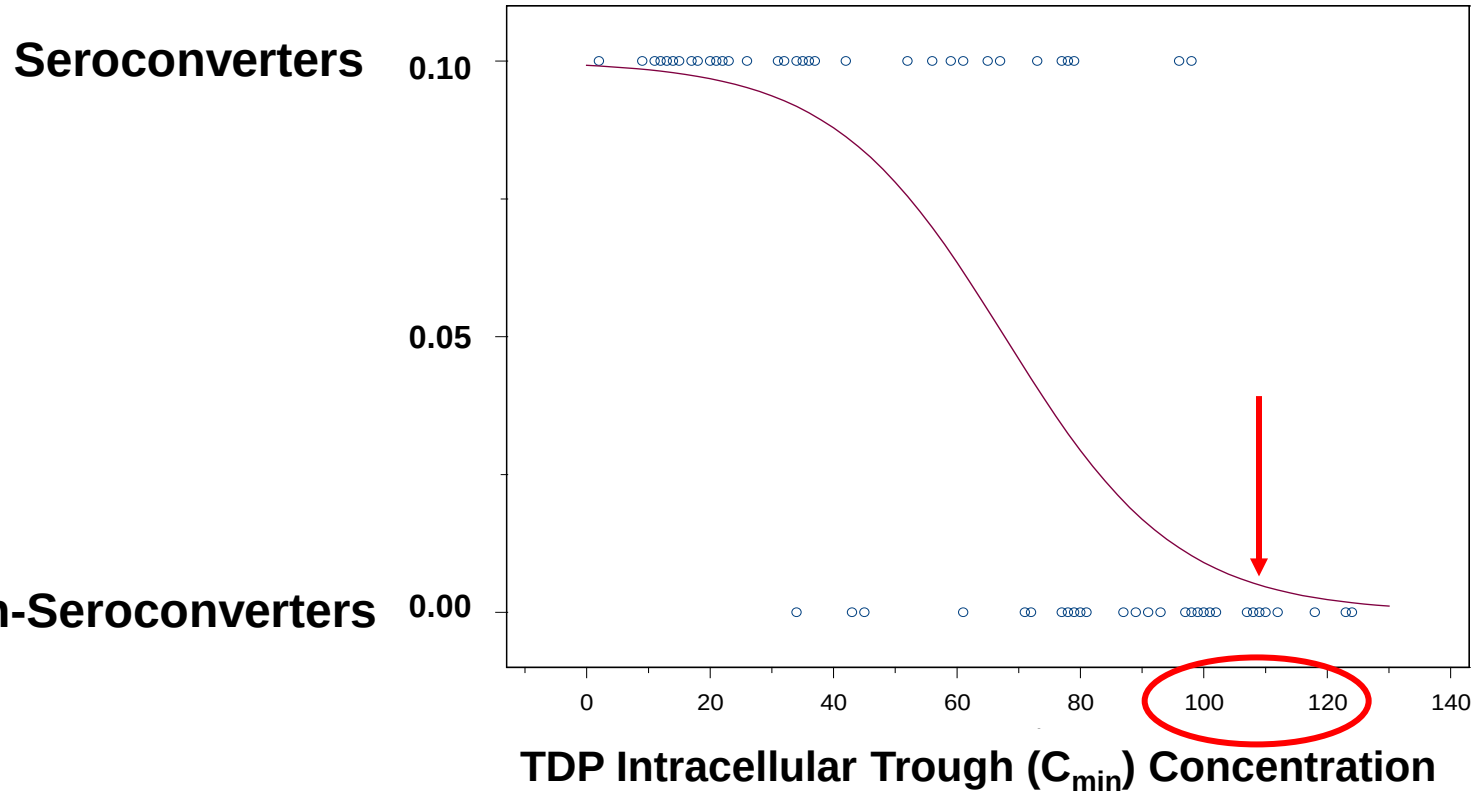


Critical Concentration

What is the critical concentration (PD)?

Critical Concentration

Identification of "Critical" concentration of active drug at site of action provides guidance for interpretation of results and planning future studies



MTN
microbicide trials network

Choosing Microbicide Targets

- Pharmacokinetics (exposure-time)
  - Lumen, tissue, blood?
  - Fluid, intracellular?
  - Peak, Trough, AUC?
- Pharmacodynamics (exposure-response)
  - Seroconversion
  - HIV challenge *in vivo*
  - HIV challenge *ex vivo*
  - Animal protection
  - *In vitro* protection

•Optimal variables for concentration and response are guided by those that best fit the data

•Biological plausibility is critical

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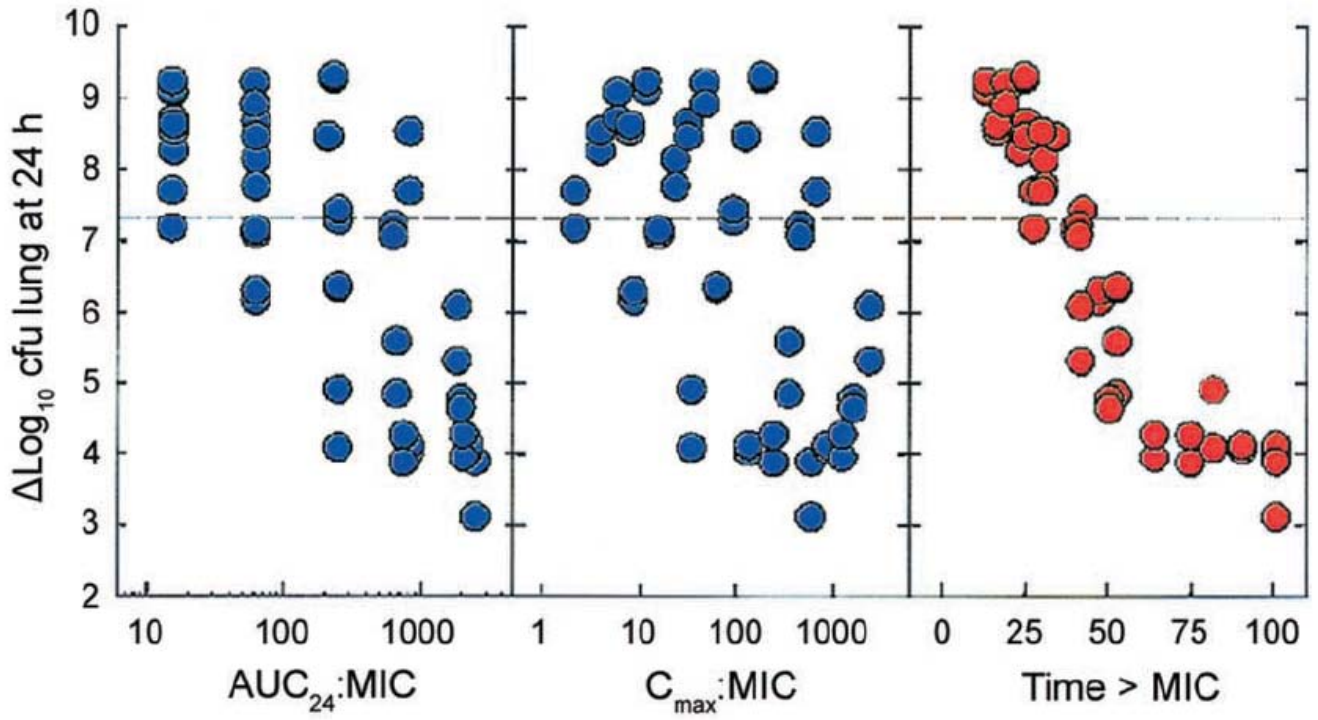
microbicide trials network

Informative PD Variables

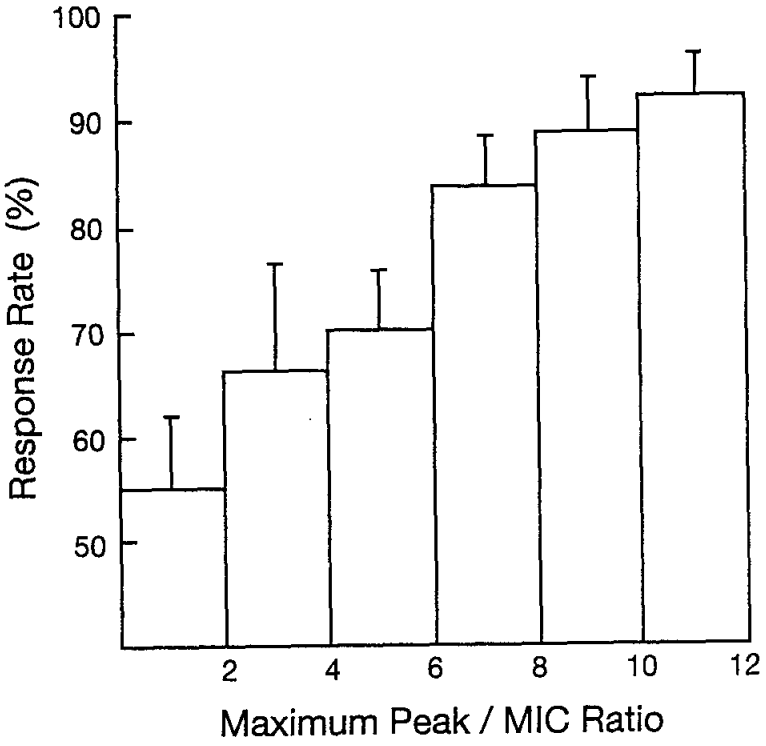
- *K. pneumoniae* pneumonia animal model
- Ceftazidime (β-lactam antibiotic)



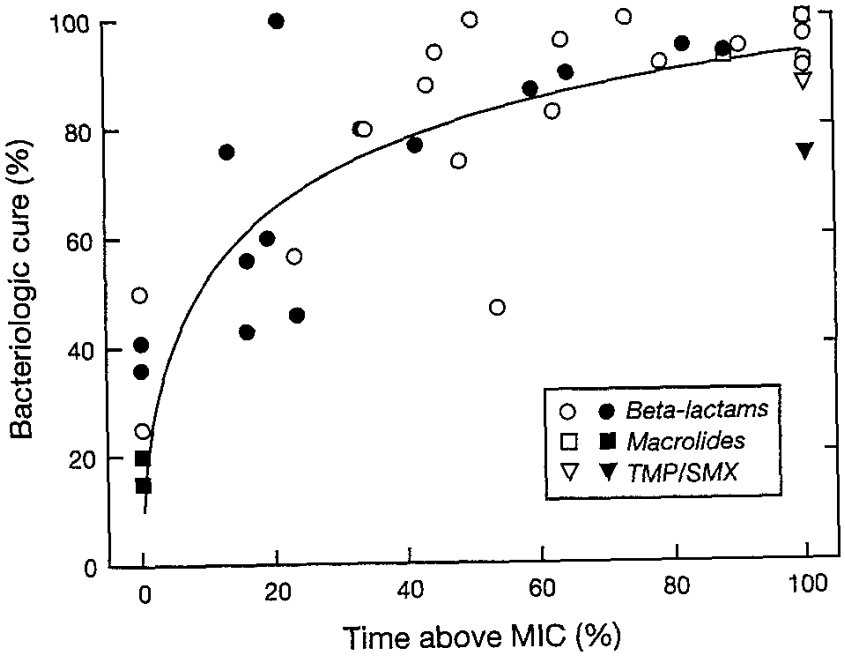
Craig WA. Diagn Microbiol Infect Dis 1995; 22:89–96.

Informative PD Variables

Concentration-Dependent (Aminoglycosides)



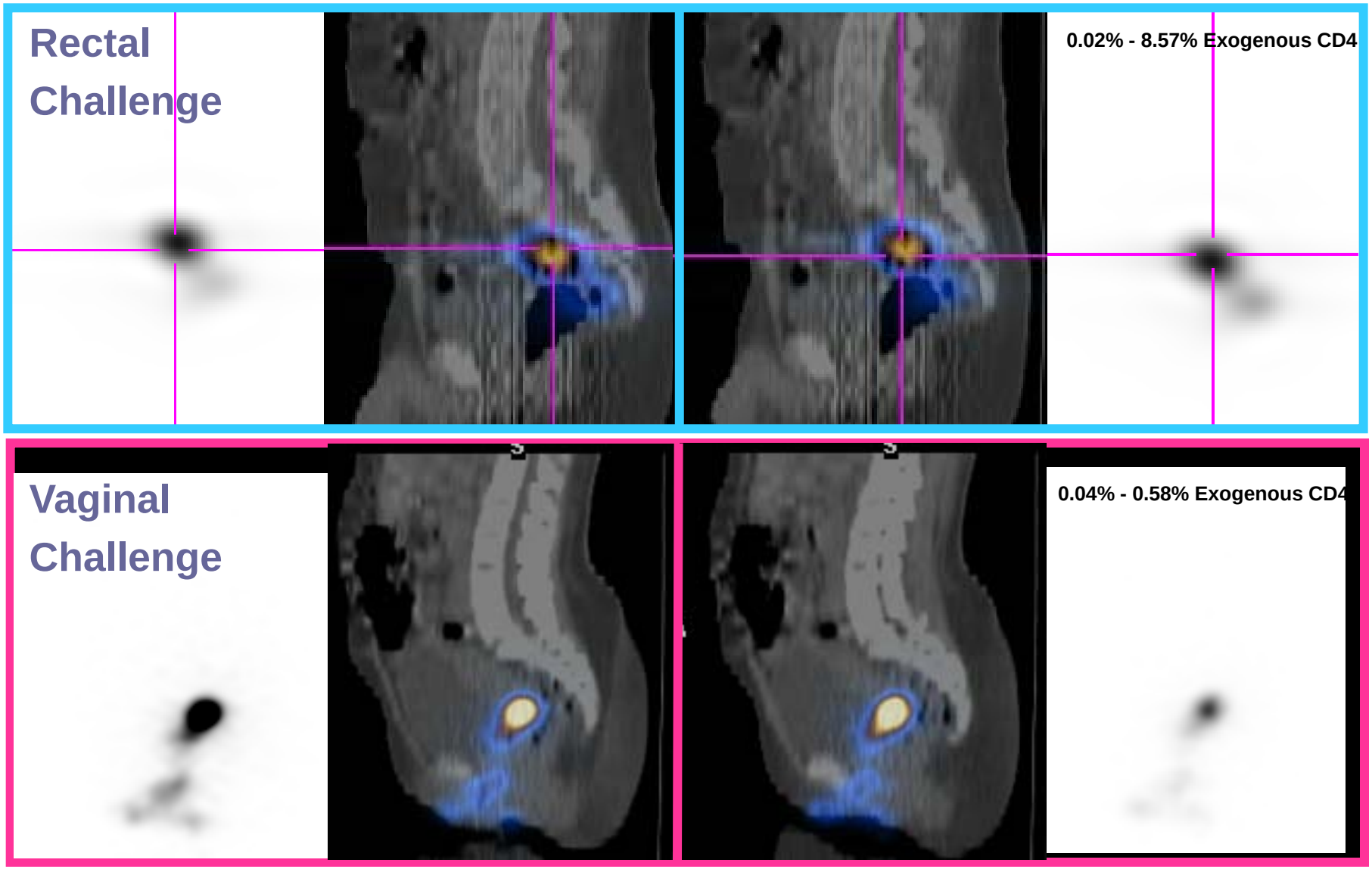
Time-Dependent (β-lactam, MAC, Trim/Sulfa)



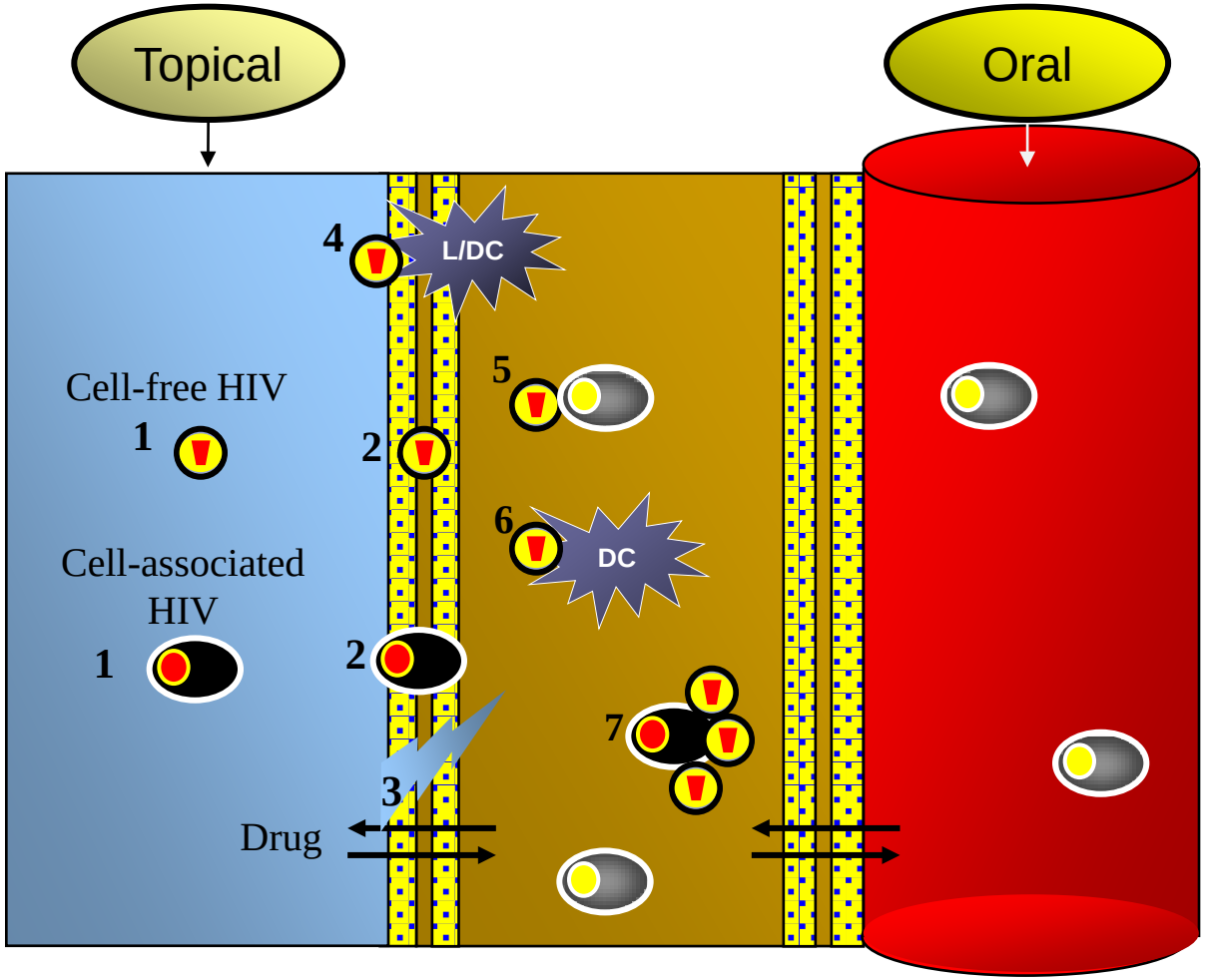
Planning Study Regimen

How to achieve (PK) the critical concentration at the critical site?

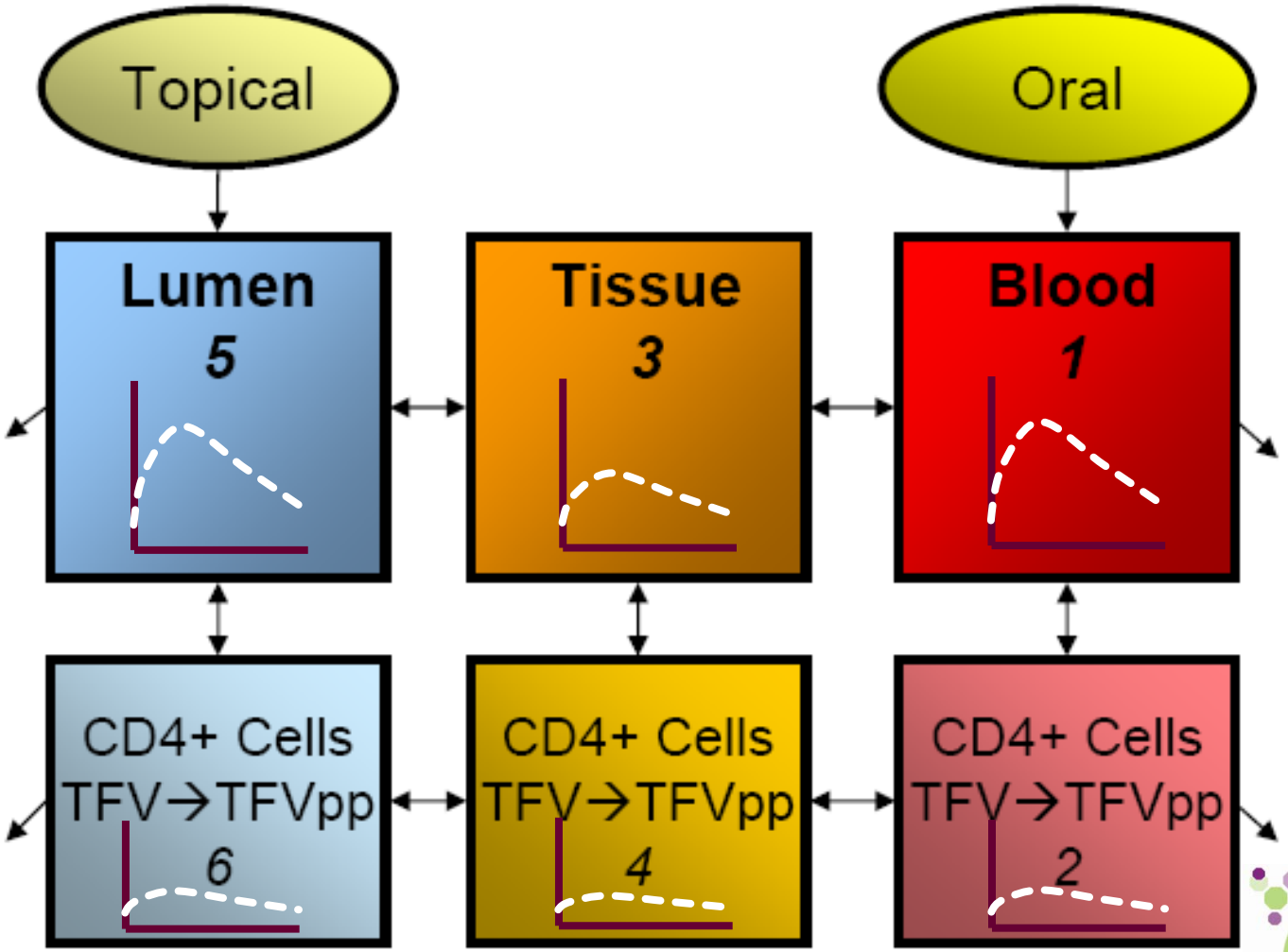
Assess HIV Surrogate Distribution



Drug Moving in Space

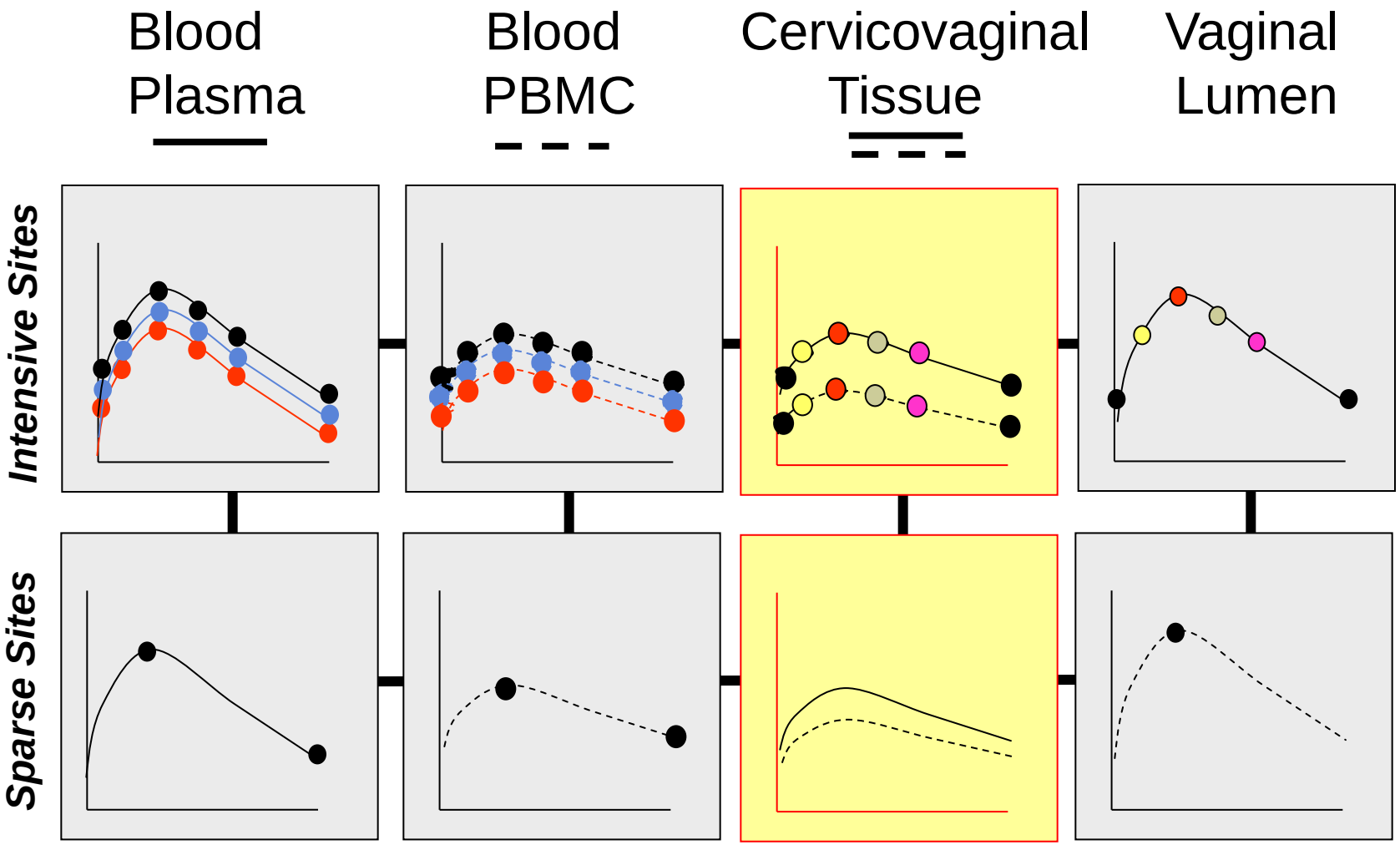


Drug Moving in Space & Time

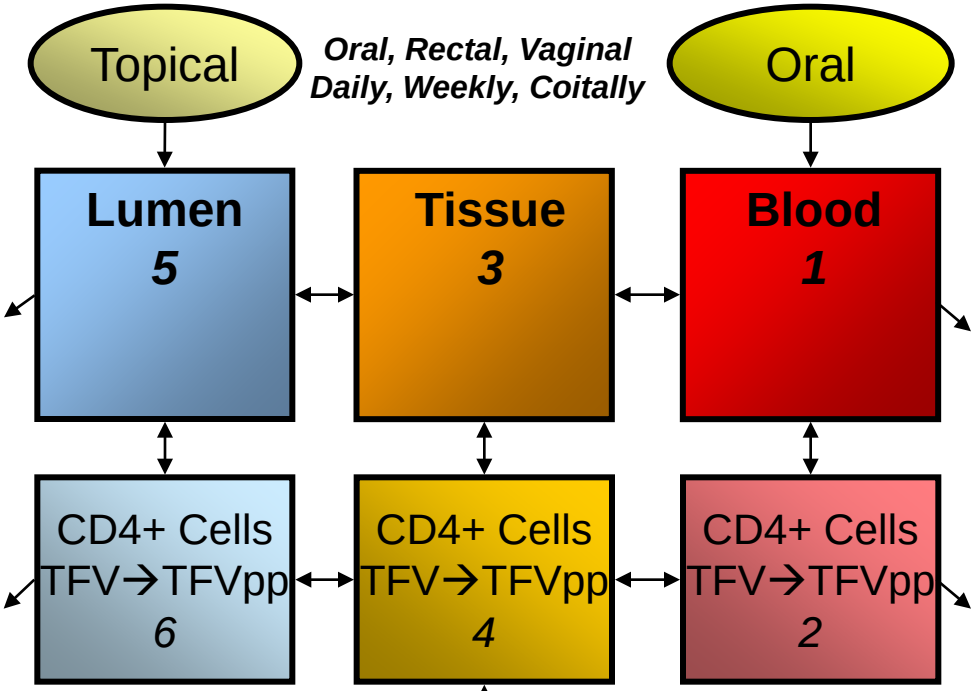


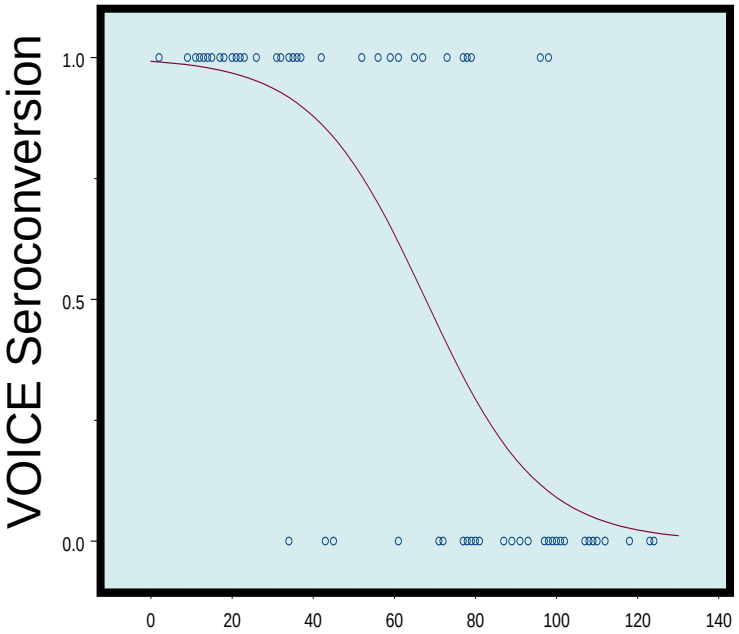
MTN
microbicide trials network

MTN-001
Populating the Space-Time Model



PK Model Informs Regimen to Hit Target





Pharmacokinetic – Pharmacodynamic Link

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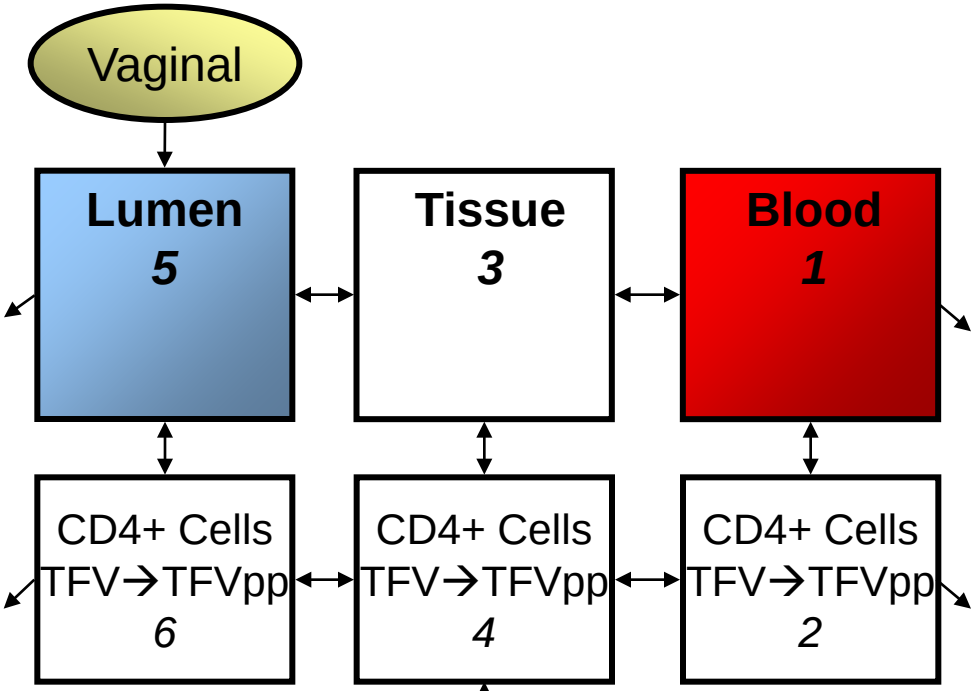
Explanatory Variable

Does concentration predict efficacy?

CAPRISA 004
Linking PK-PD: Qualitative (LOQ)



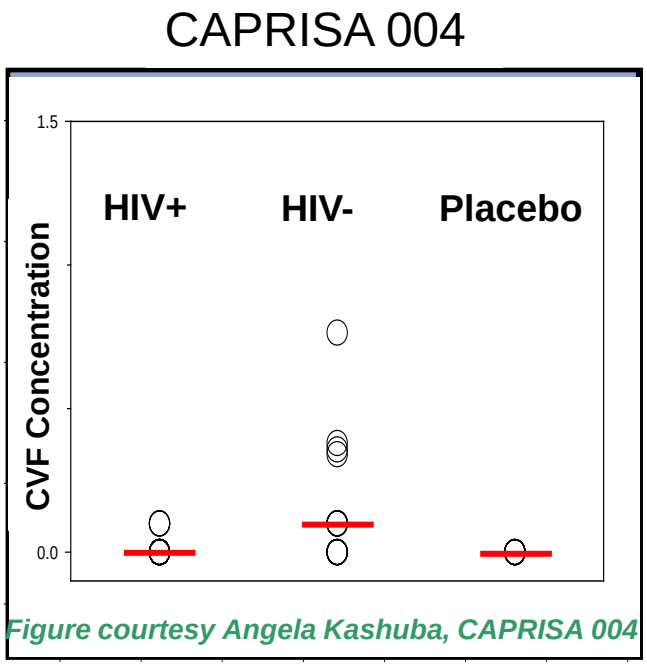


Figure courtesy Angela Kashuba, CAPRISA 004

Pharmacokinetic – Pharmacodynamic Link

Qualitative

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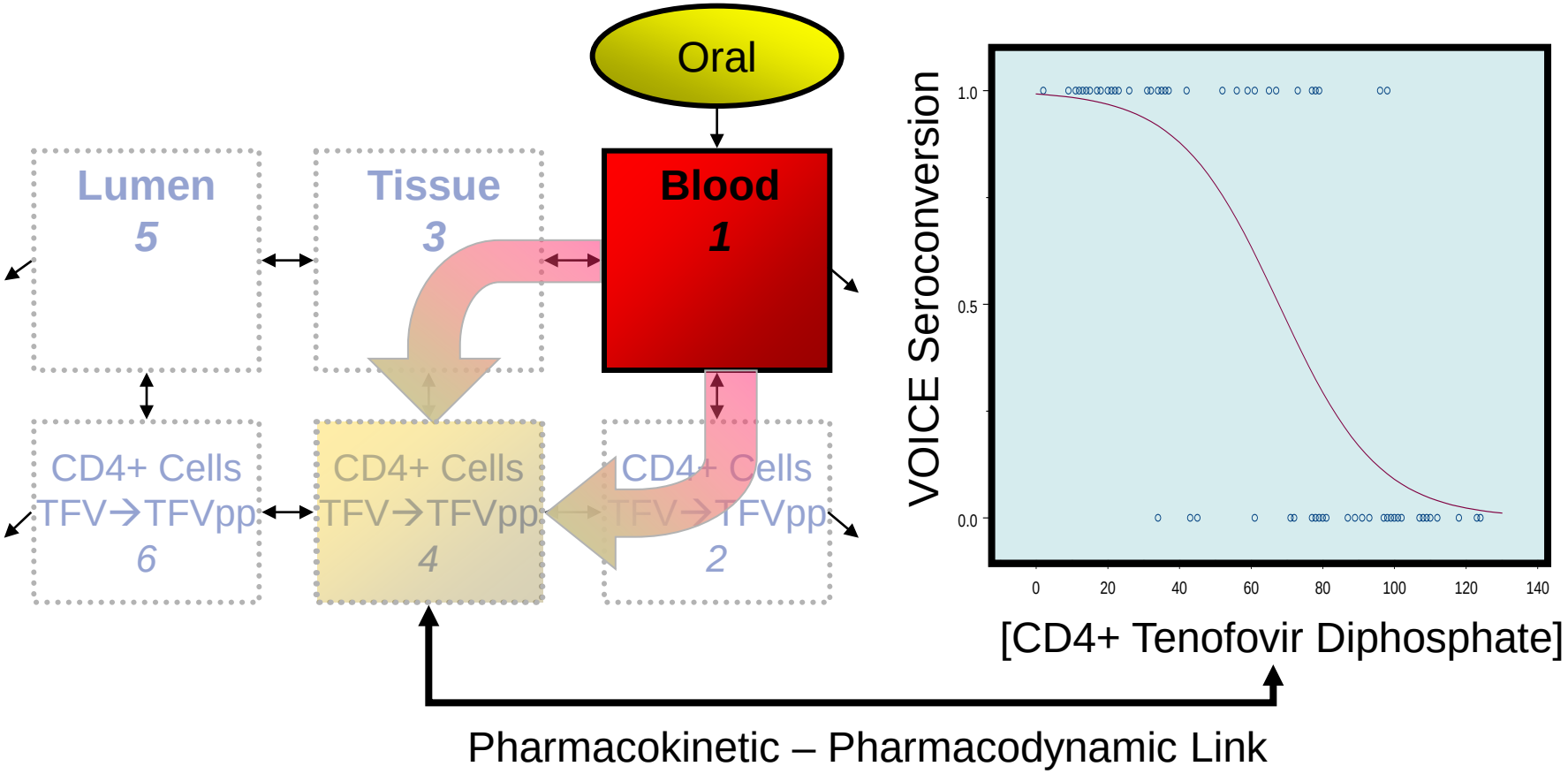
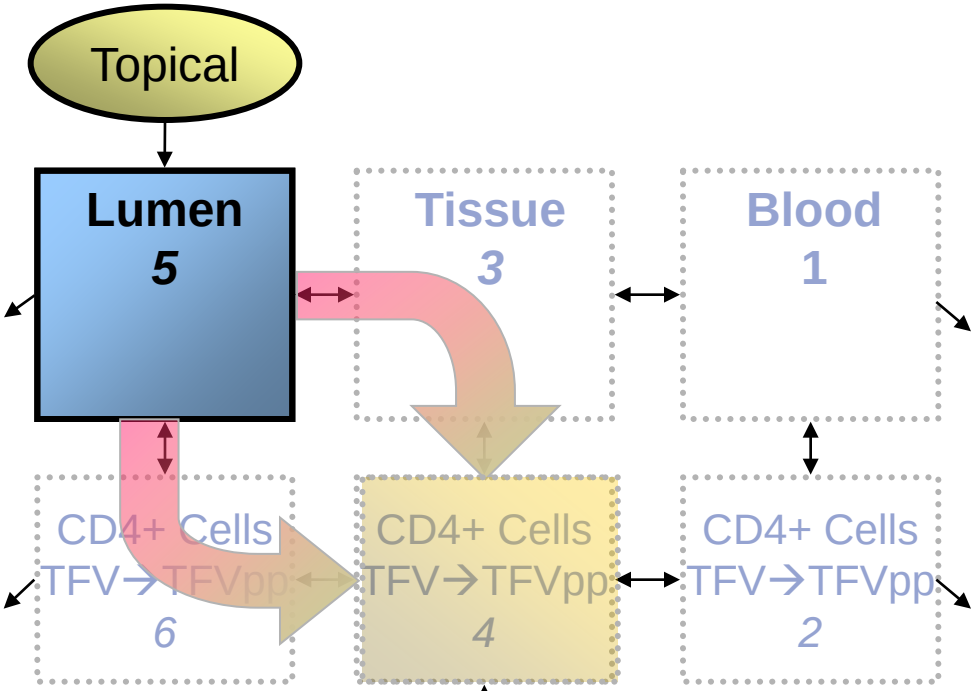
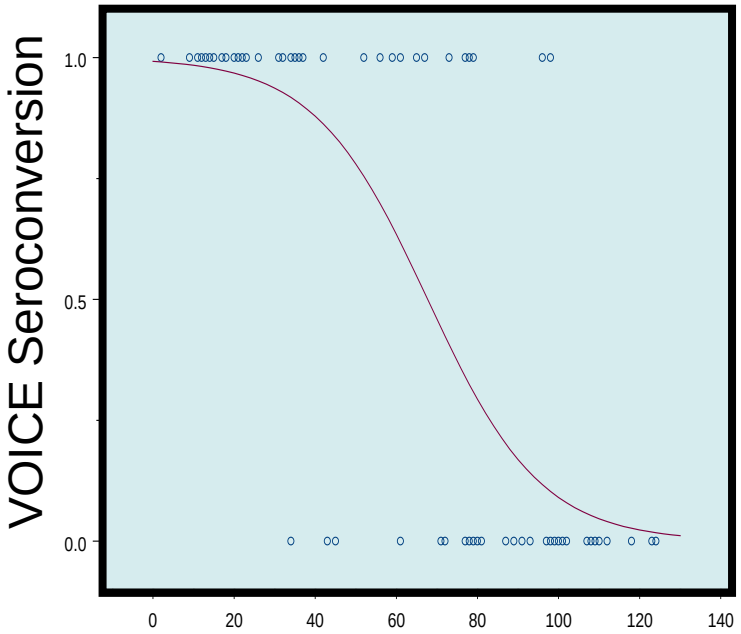
PK Model Estimates Unmeasured Compartments



PK Model Estimates Unmeasured Compartments





Pharmacokinetic – Pharmacodynamic Link

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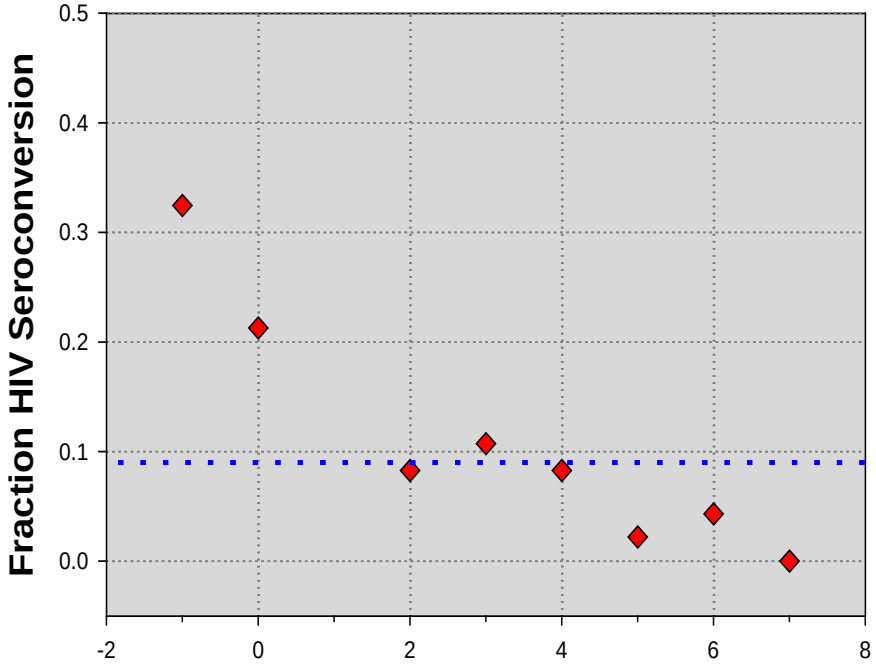
CAPRISA 004
CVF [TFV] v. Seroconversion



CAPRISA 004							CVF Log 10 [TFV]								
	Study Total		# Assayed*		#Adjusted		-1	0	1	2	3	4	5	6	7
Total	889		57		299		49	28		36	37	12	45	46	11
HIV+	98	**11%**	33	**58%**	33	**11%**	16	6		3	4	1	1	2	0
HIV-	791	**89%**	24	**42%**	**266**	**89%**	*33*	*22*		*33*	*33*	*11*	*44*	*44*	*11*
% HIV Seroconversion (Adjusted)							*32%*	*21%*		*8%*	*11%*	*8%*	*2%*	*4%*	*0%*

Raw data courtesy Angela Kashuba, CAPRISA 004

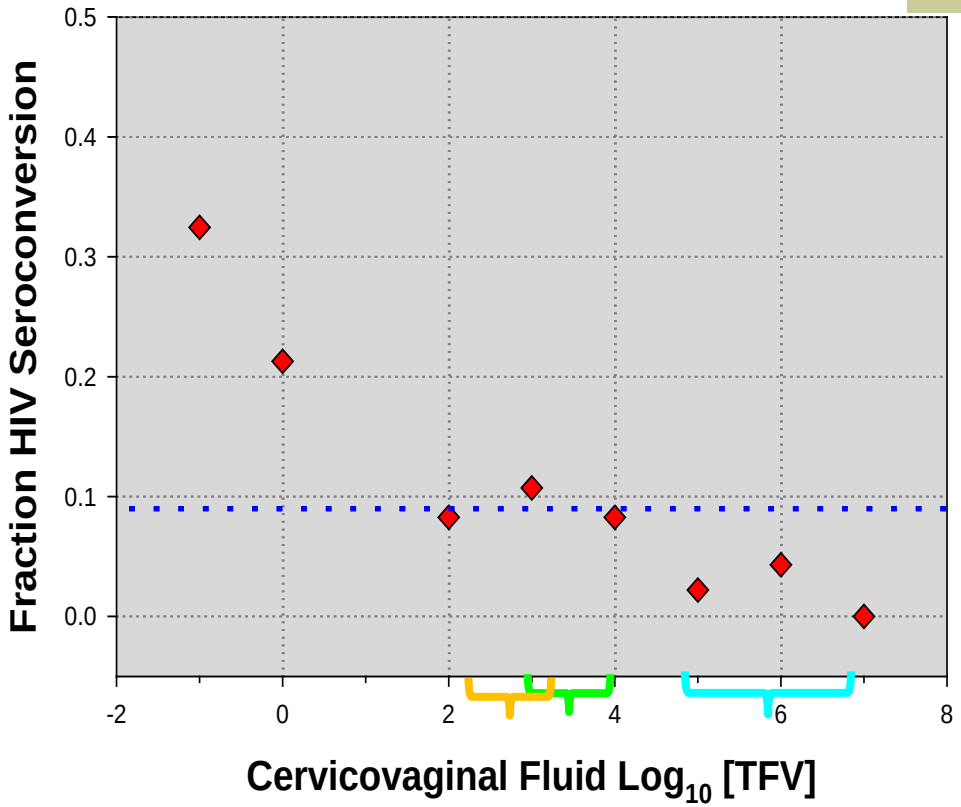
Interpretation of CAP 004 Seroconversions

- Failure due to inadequate concentration; perfect adherence as prescribed
  - Solution: increase the dose frequency to increase concentration at time of exposure
- Failure due to inadequate adherence; concentrations fully protective if taken as prescribed
  - Solution: increase the dose frequency to increase concentration at time of exposure
- Failure due to inadequate placement of dose
  - Solution: Develop options for rectal dosing

Forecasting Efficacy

What results with different regimen?

CAPRISA 004 "Forecasting"
CVF [TFV] v. Seroconversion



Voice Topical
- Daily
- 2d HL
- 60% adh.
- 90% sex loss
- 10:1 CVF:VT

Voice Oral
- Daily
- 17h HL
- 60% adh.
- 1-2:1 BP:CVF
- Route adjust.

Weekly Oral*

CAPRISA 004							CVF Log 10 [TFV]								
	Study Total		# Assayed*		#Adjusted		-1	0	1	2	3	4	5	6	7
Total	889		57		299		49	28		36	37	12	45	46	11
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% HIV Seroconversion (Adjusted)							*32%*	*21%*		*8%*	*11%*	*8%*	*2%*	*4%*	*0%*

*Low estimate; depends on magnitude of dilutional effect of anal sex

Route of Infection

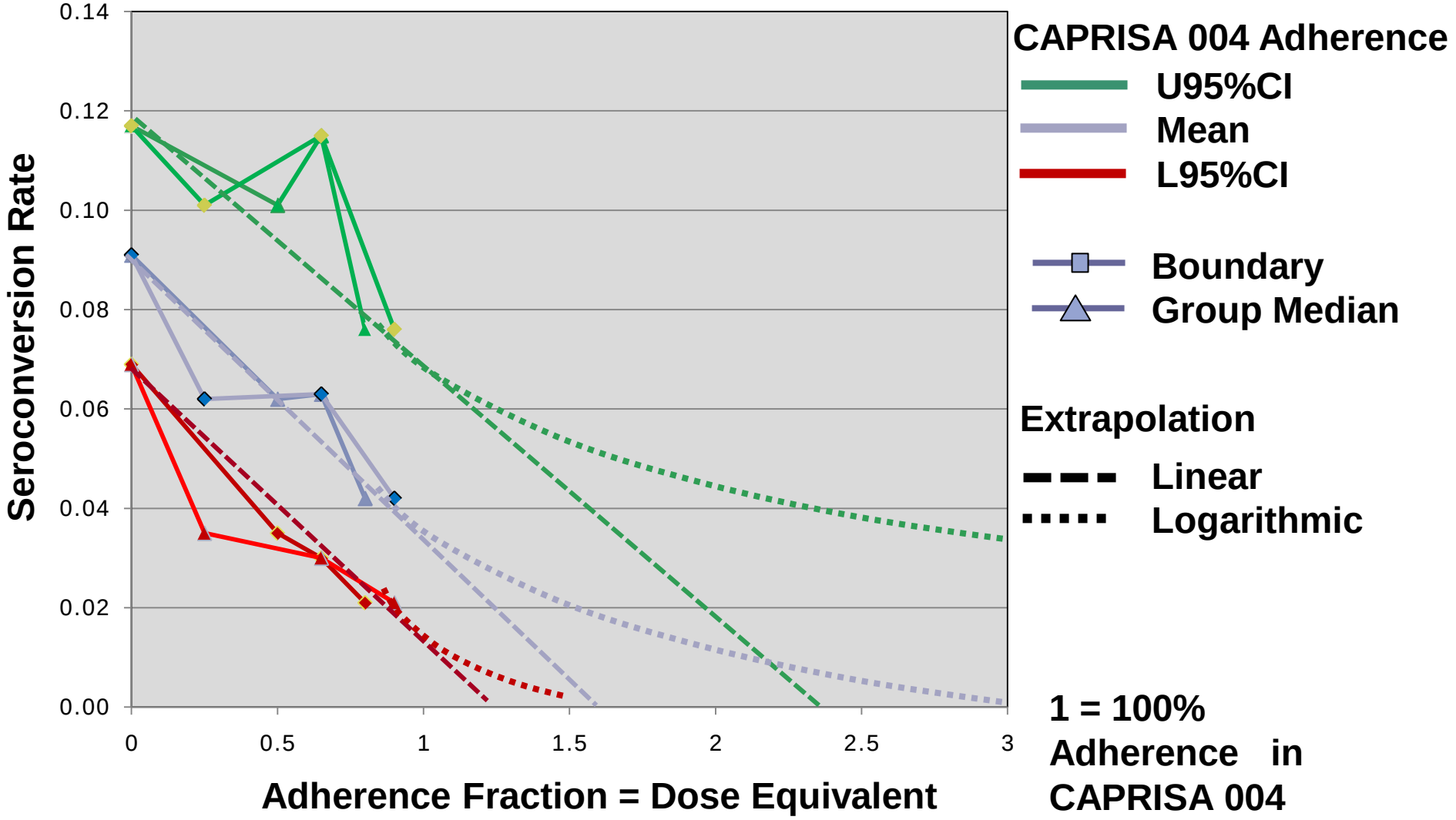
- PK-PD estimates are route dependent
  - Route of dosing
  - Route of transmission
- Anal sex dilutional effect may be less for oral dosing
  - CAPRISA 004 PK-PD may underestimate impact of oral dosing
  - VOICE may show narrower oral–topical difference than tissue concentrations predict (based on CAPRISA 004)

Impact of adherence on effectiveness of tenofovir gel

	# HIV	N	HIV incidence		Effect
			TFV	Placebo	
High adherers (>80% gel adherence)	36	336	4.2	9.3	**54%**
Intermediate adherers (50-80% adherence)	20	181	6.3	10.0	**38%**
Low adherers (<50% gel adherence)	41	367	6.2	8.6	**28%**

Slide courtesy Salim Abdool Karim, CAPRISA 004

Inadequate Adherence or Dose



Mean dose associated with 100% Adherence in CAPRISA 004 (10 doses/mo.) is 1/3 the dose of VOICE at 100% adherence or equivalent to 33% VOICE adherence.

Adherence Measure

Can [TFV]…

…quantitatively estimate adherence?

…target adherence interventions?

Rationale

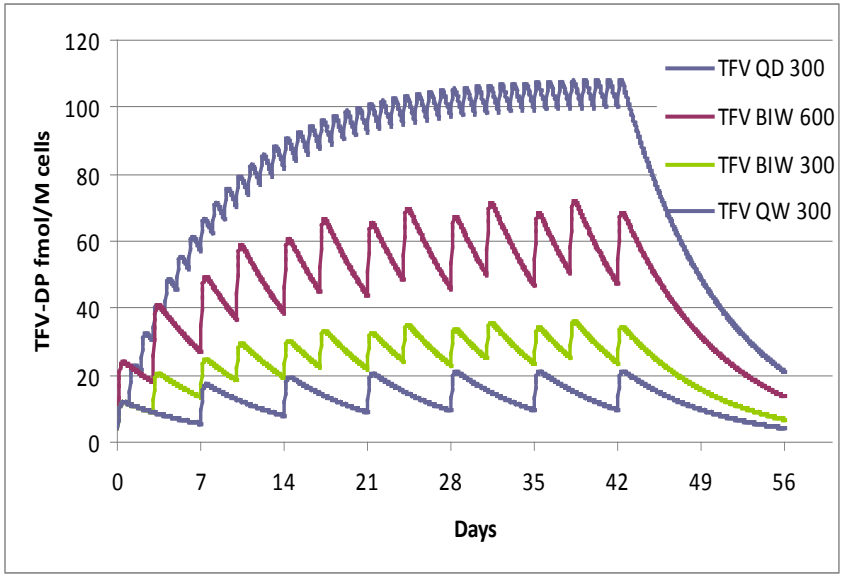
- Adherence has a major impact on drug exposure and outcome
- Adherence assessments are lacking
- Drug concentration as adherence measure
  - Quantitative
  - Relevant to outcomes

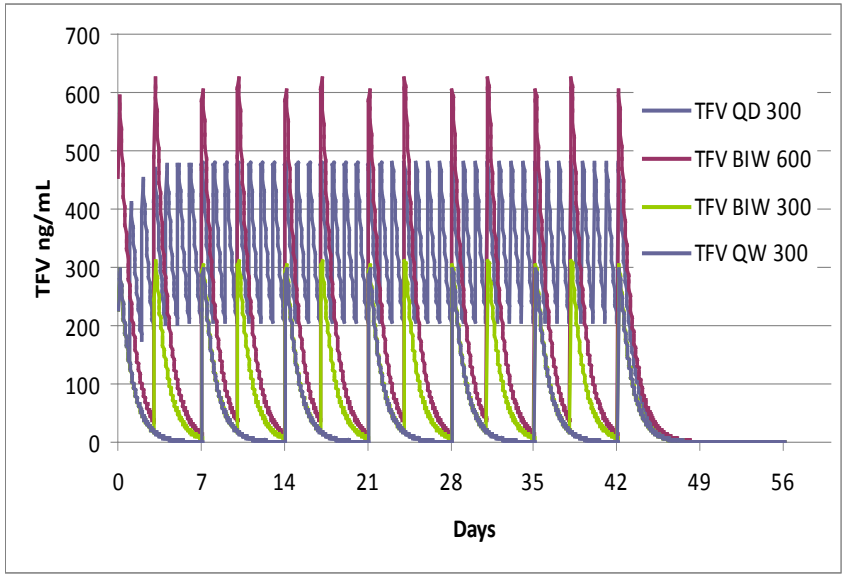
$$(Observed/Expected) \bullet 100 = \%Adherence + \sigma + \varepsilon$$

- Several drug variables remain unknown
  - Dose-proportionality
  - Intra-individual variability

HPTN 066
Adherence: Matrix Sensitivity

- Contrast TFV-DP and TFV Variability





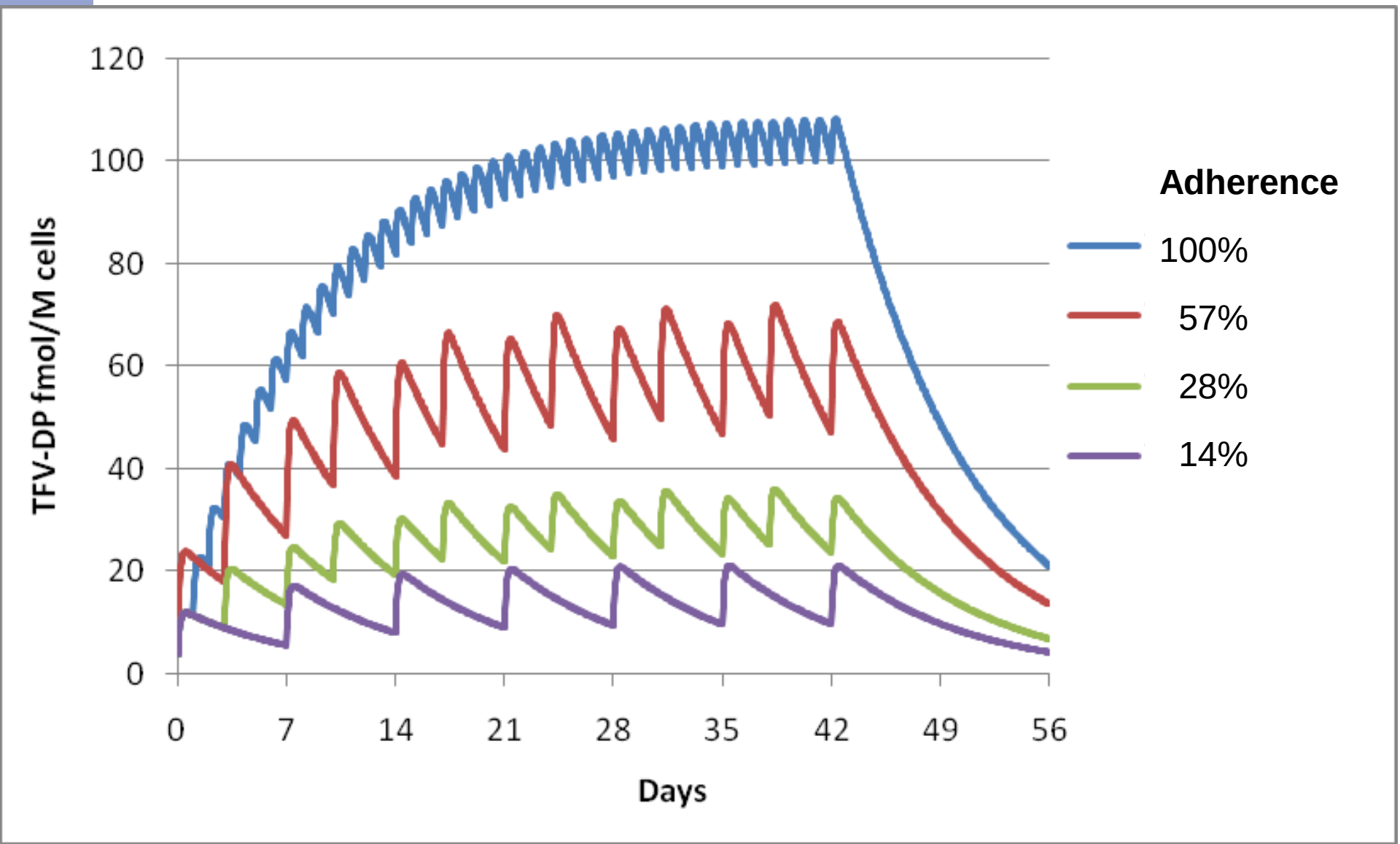
HPTN 067
Selecting a PK Adherence Matrix

Characteristic	TFV plasma	TFV-DP	TFV hair
Half-life	17 hours	6 days	>1 month (?)
Time to Steady-state	3-4 days	4-5 weeks	4-5 months
Time Sensitivity	Days	Weeks	Months
White coat effect	Susceptible	Not susceptible	Not susceptible
Holidays (week)*	Insensitive	Sensitive	Insensitive
Holidays (month)*	Insensitive	Insensitive	Sensitive
Pharmacodynamics	Pro-drug	Active moiety	Pro-drug
Covariates	PK (ht, wt, CrCl)	PK (ht, wt, CrCl)	PK, hair color/Rx
Variability	Low	Modest (cell #)	Modest (hair length)
Specimen Processing	Centrifuge	Spin, count, lyse	Mark end, foil wrap
Storage	Freezer	Freezer	Room temp

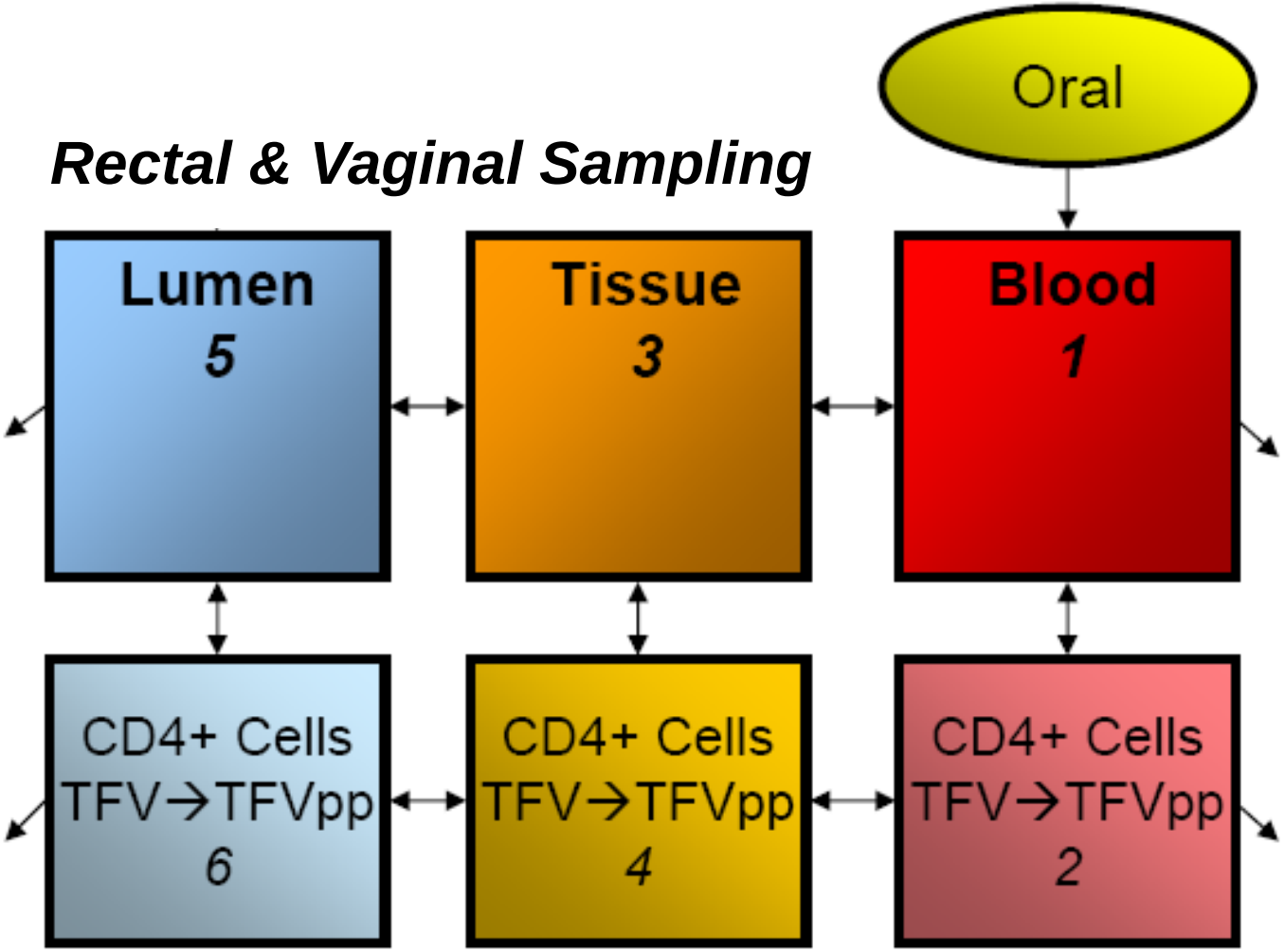
***Sensitive indicates the matrix detects an adherence difference due to drug holiday of given length. Insensitive indicates matrix does not show change despite holiday of given length.**

HPTN 066

100% Adherence Standard…



HPTN 066
...in All Compartments Sampled



MTN
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HPTN 067
Overall Approach

- Expected Phase

  (Investigator-Controlled Lead-In)
  - Directly observe all doses given
  - Measure [TFV] to describe typical concentration-time course and variability after dosing
- Observed Phase

  (Patient-Controlled On-Study)
  - Subjects take meds without observation
  - Adherence assessment at intervals
- Analysis of Data

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

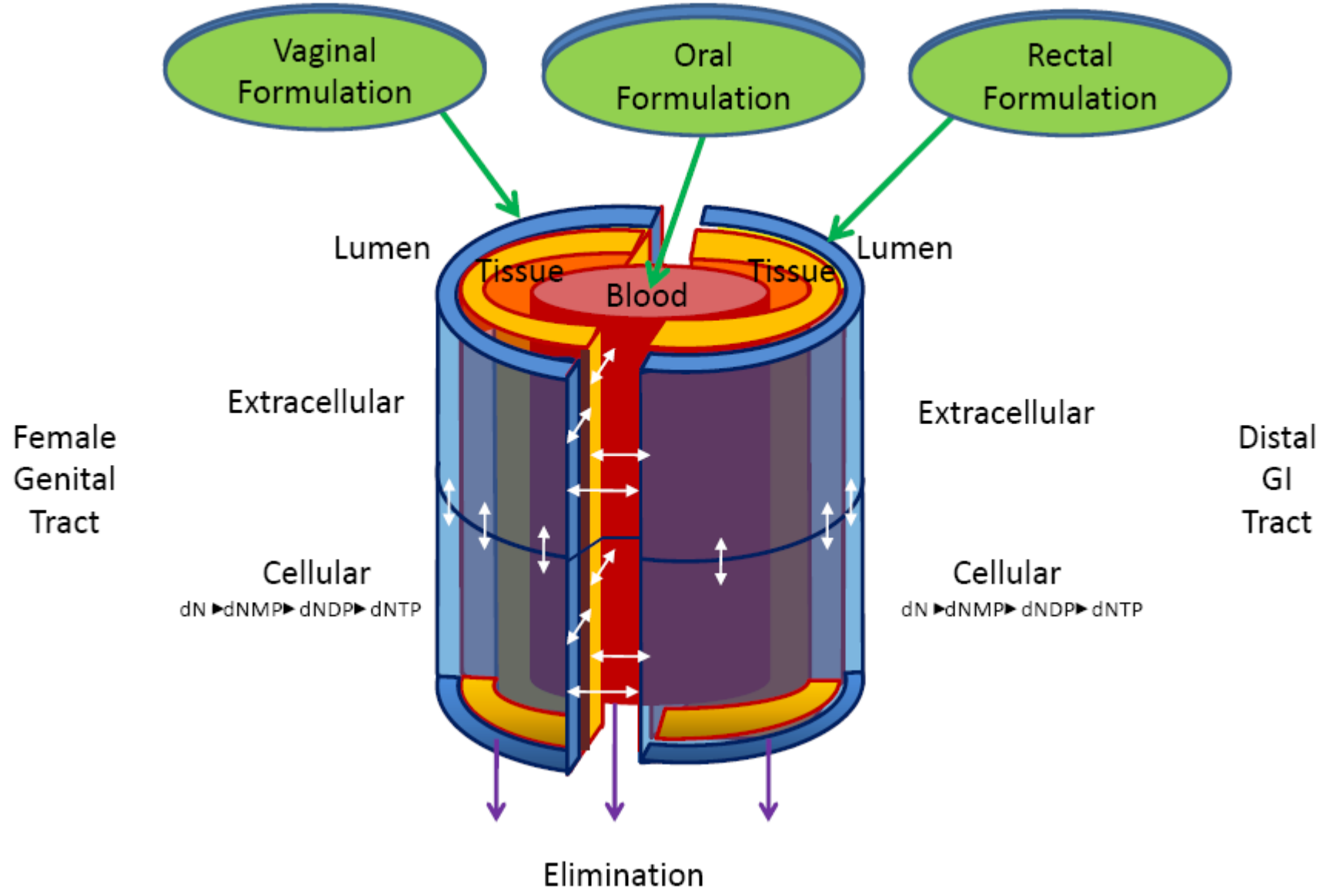
PK as Adherence Measure

- Developmental Studies

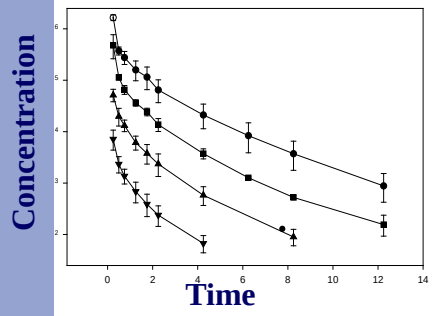
- MTN-001
- HPTN 066
- HPTN 067
- IAVI (Kenya, Uganda)
- Partners PrEP

Clinical Trial Simulation

Surrogate for RCT?

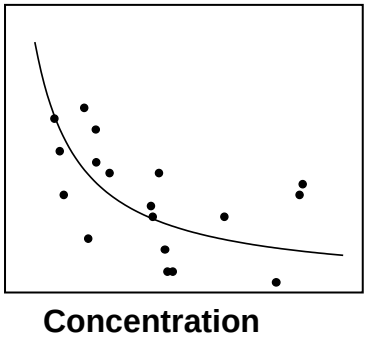

Vaginal Formulation
Oral Formulation
Rectal Formulation
Lumen
Tissue
Blood
Tissue
Lumen
Extracellular
Extracellular
Female Genital Tract
Distal GI Tract
Cellular
dN ▶dNMP▶ dNDP▶ dNTP
Cellular
dN ▶dNMP▶ dNDP▶ dNTP
Elimination

Clinical Trial Simulation



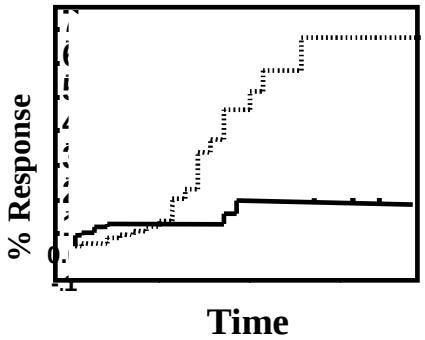
- Population Pharmacokinetics Model

$$Ce = \frac{D \cdot k_{1e}}{V_c \cdot (k_{e0} - k_e)} \left(e^{-k_e t} - e^{-k_{e0} t}\right)$$



- Pharmacodynamics Model

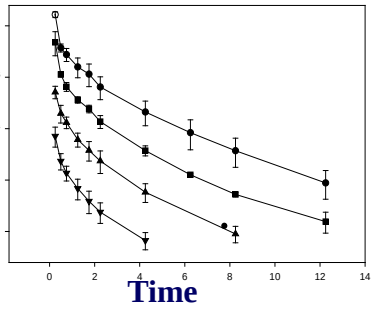
$$E_{SLOPE} = \frac{E_{max} \cdot (k_{e0} \cdot C_e / k_{1e})^{\gamma}}{EC_{50}{}^{\gamma} + (k_{e0} \cdot C_e / k_{1e})^{\gamma}}$$

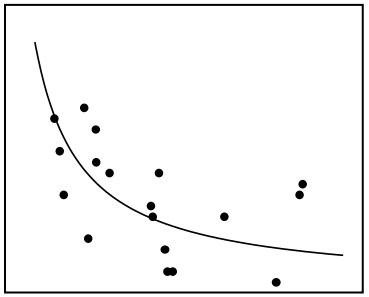


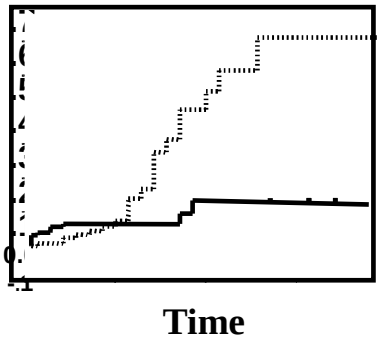
- Disease Progression Model

$$S(t) = S_0 + [E_{SLOPE}(C_e) + \alpha] \cdot t$$

Clinical Trial Simulation







$$Ce = \frac{D \cdot k_{1e}}{V_c \cdot (k_{e0} - k_e)} \cdot (e^{-k_e t} - e^{-k_{e0} t})$$

$$E_{SLOPE} = \frac{E_{max} \cdot (k_{e0} \cdot C_e / k_{1e})^{\gamma}}{EC_{50}{}^{\gamma} + (k_{e0} \cdot C_e / k_{1e})^{\gamma}}$$

$$S(t) = S_0 + [E_{SLOPE}(C_e) + \alpha] \cdot t$$

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Questions?