

MTN-001: Unique Contributions

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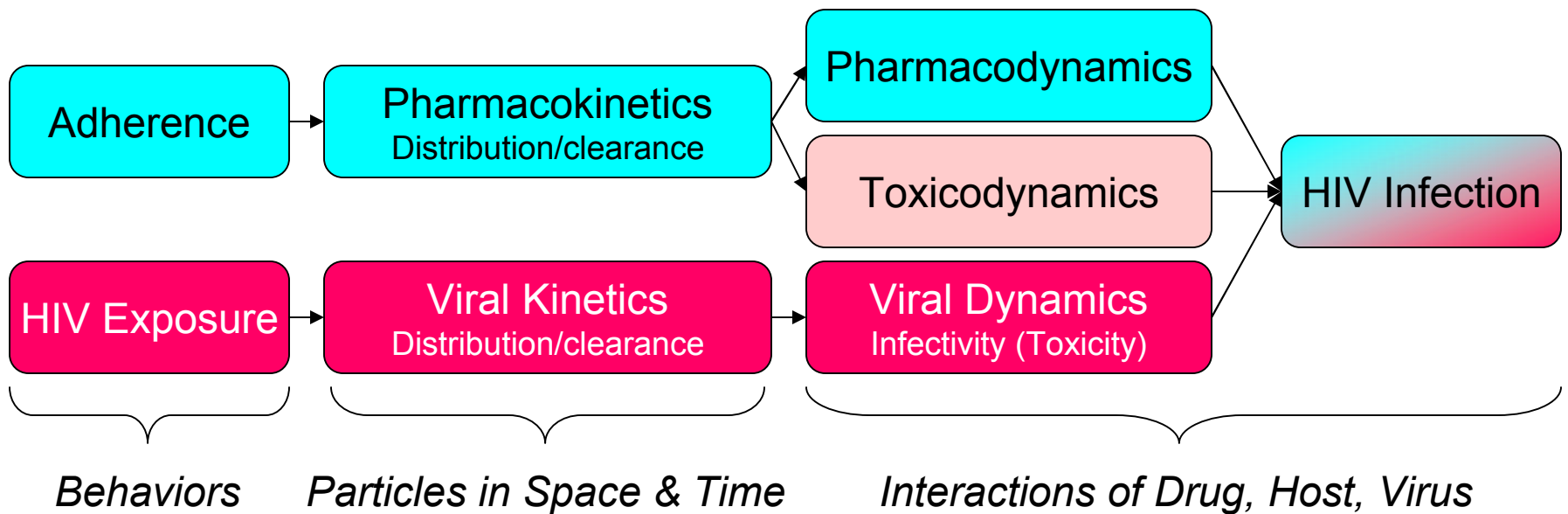
Unique Contributions

- Compare oral v. vaginal product adherence
- Impact of second product on adherence
- Comparison of oral v. vaginal PK
- Integrated multi-compartment PK model after oral dosing (blood cells, tissue, lumen)
- Additive effect of dual route dosing
- Comparison of observed v. unobserved PK to assess adherence
- Simulation of VOICE tissue intracellular TDP kinetics

Adherence



Importance of Adherence



Importance of Adherence

- Carraguard Trial

- N=6202

- Seroconversion: no significant difference
 - Active: 134
 - Placebo: 151

- Adherence 43%

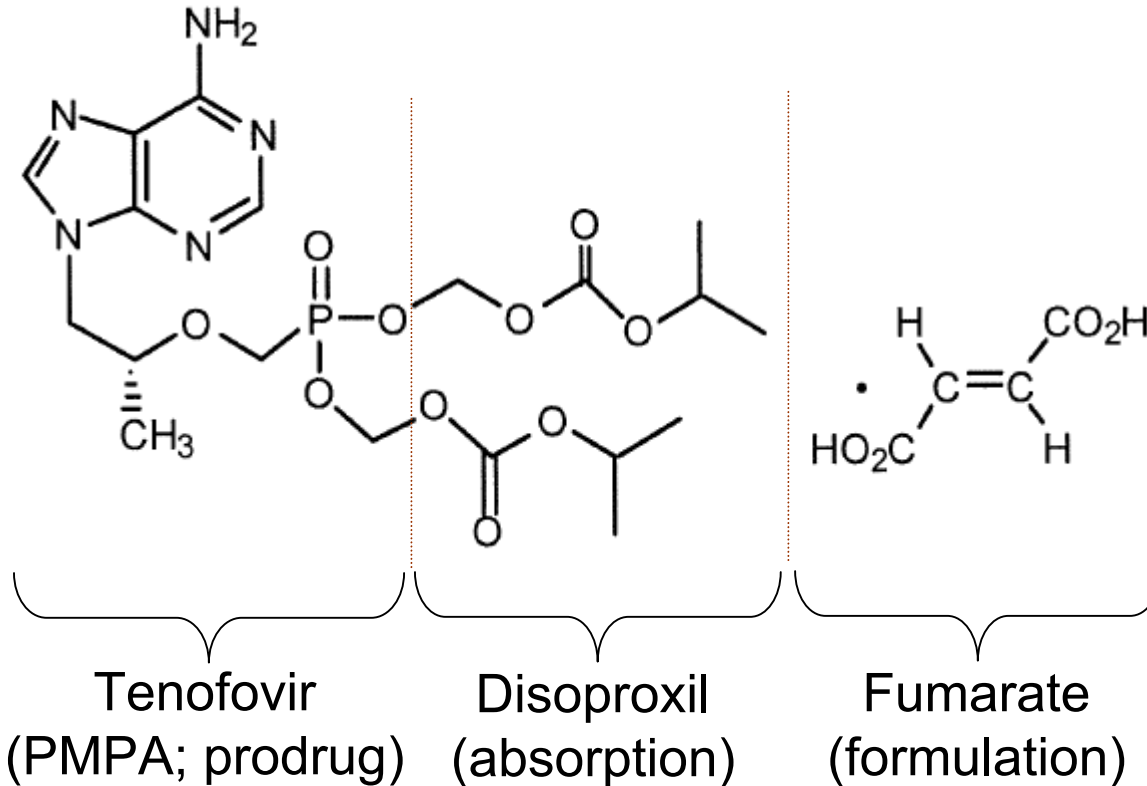
Adherence/Acceptability Objectives

- To compare adherence to and acceptability of three daily regimens of tenofovir (oral, vaginal, and dual use)
- To identify factors associated with product adherence, and whether these differ when women use one of three daily regimens of tenofovir (oral, vaginal, and dual use)
- To examine whether sexual activity or male condom use varies when women use one of three daily regimens of tenofovir (oral, vaginal, and dual use)
- To assess the timing of product use with sexual intercourse
- To determine the level of sharing of study products with non-participants (and to assess with whom products are shared)

Pharmacokinetics

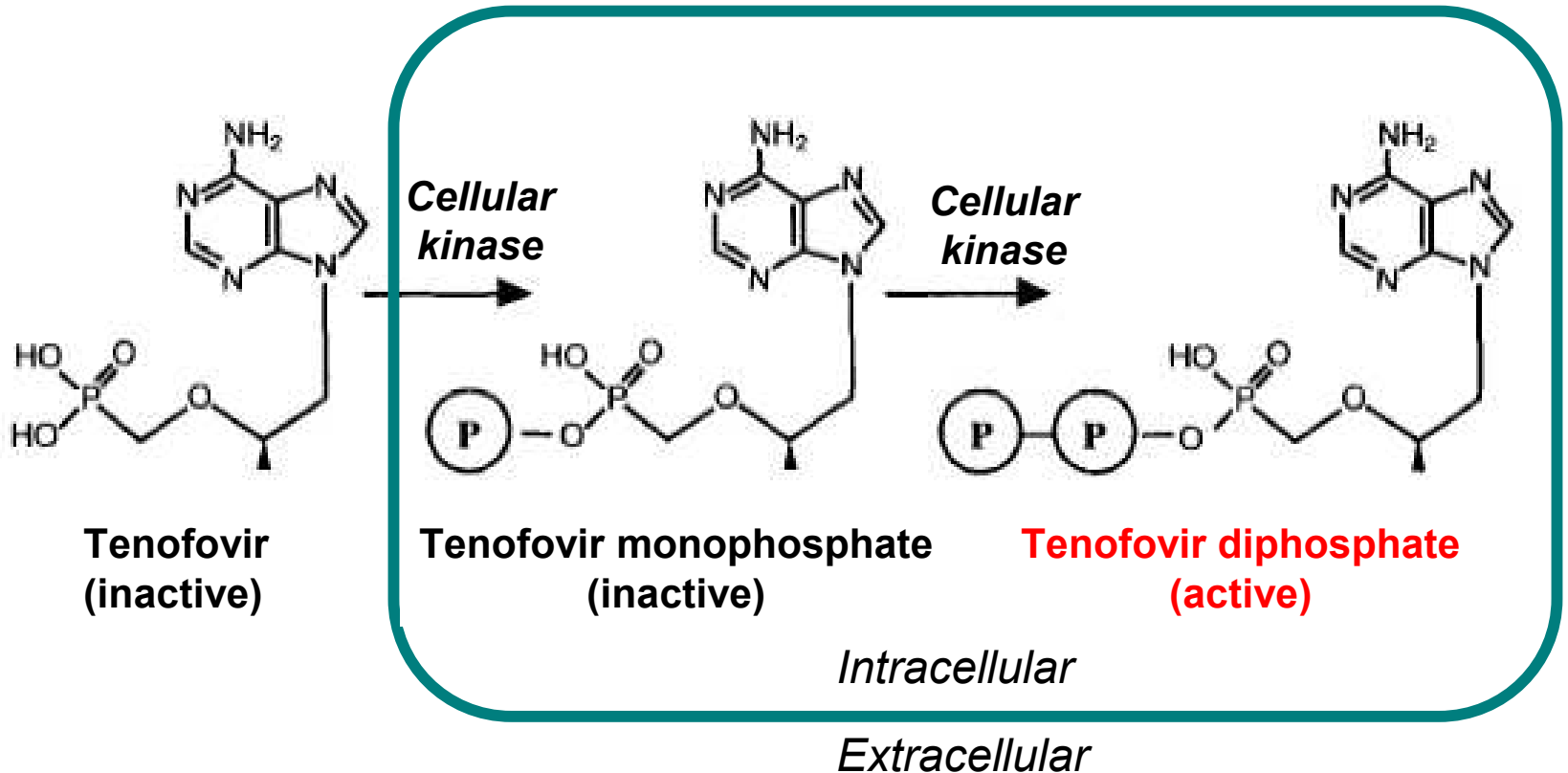


Tenofovir Disoproxil Fumarate



TDF: Inactive prodrug; only active after modification inside cells

Tenofovir Diphosphate

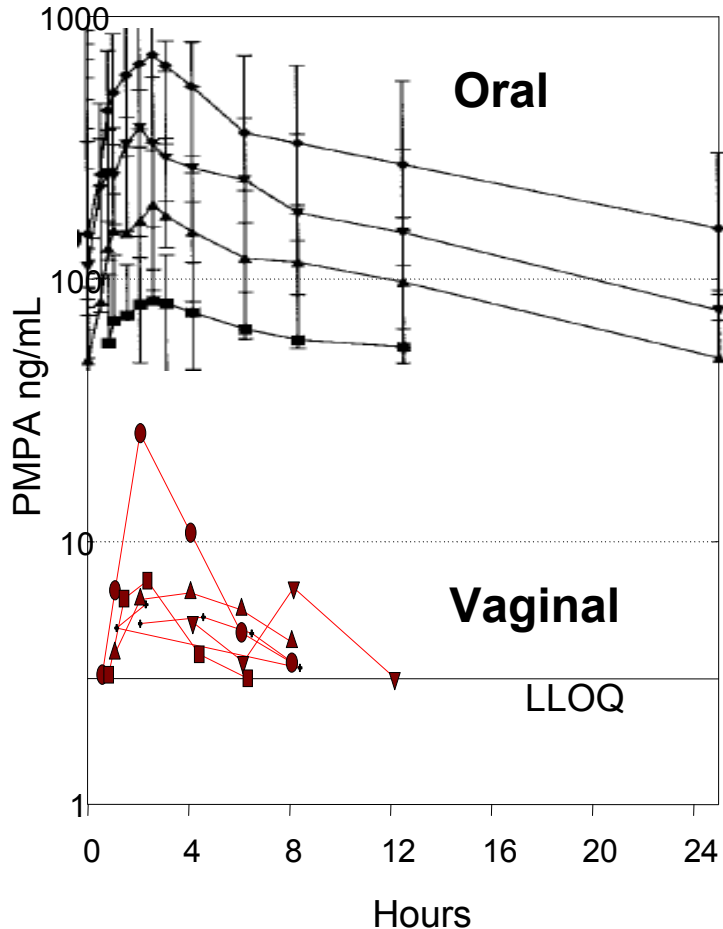


TDP: tenofovir diphosphate is active form; 2 phosphates added inside cells

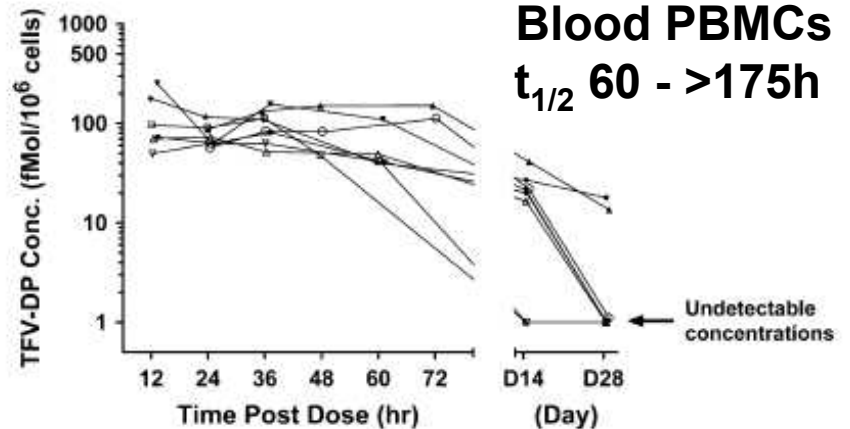
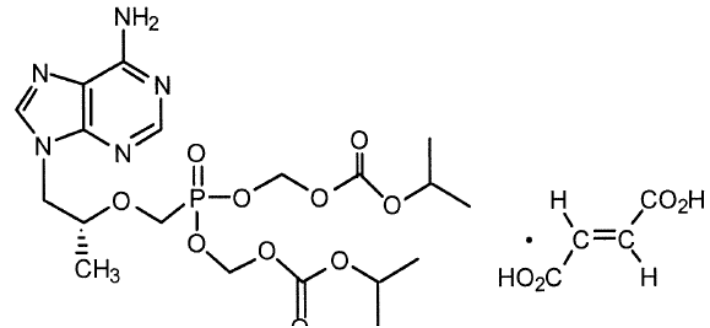
TDF: Inactive prodrug; only active after modification inside cells

Tenofovir Pharmacokinetics

Blood Plasma: $t_{1/2}$ 17 h



Prodrug of Active Diphosphate
Cellular kinases add 2 phosphates

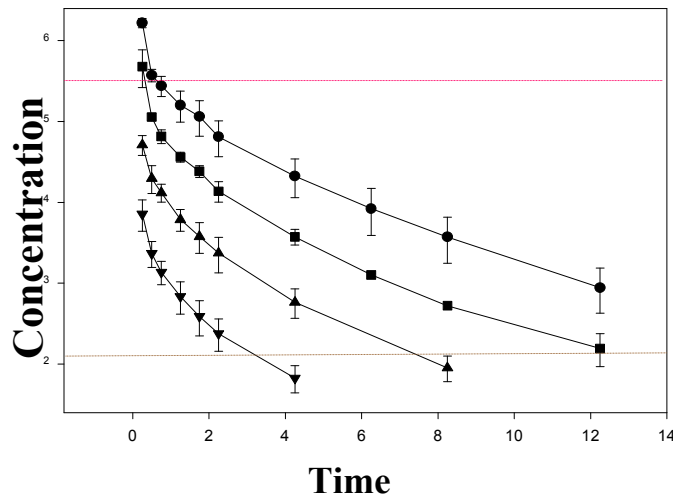


Blood PBMCs
 $t_{1/2}$ 60 - >175h

Definitions: PK & PD

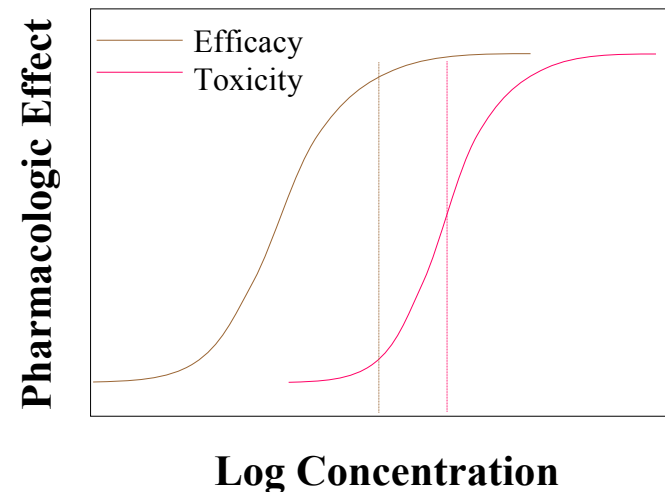
□ Pharmacokinetics (PK)

- Body effect on the drug
- Varying in drug conc'n in space and time
- Concentration-time data
- Hitting the target



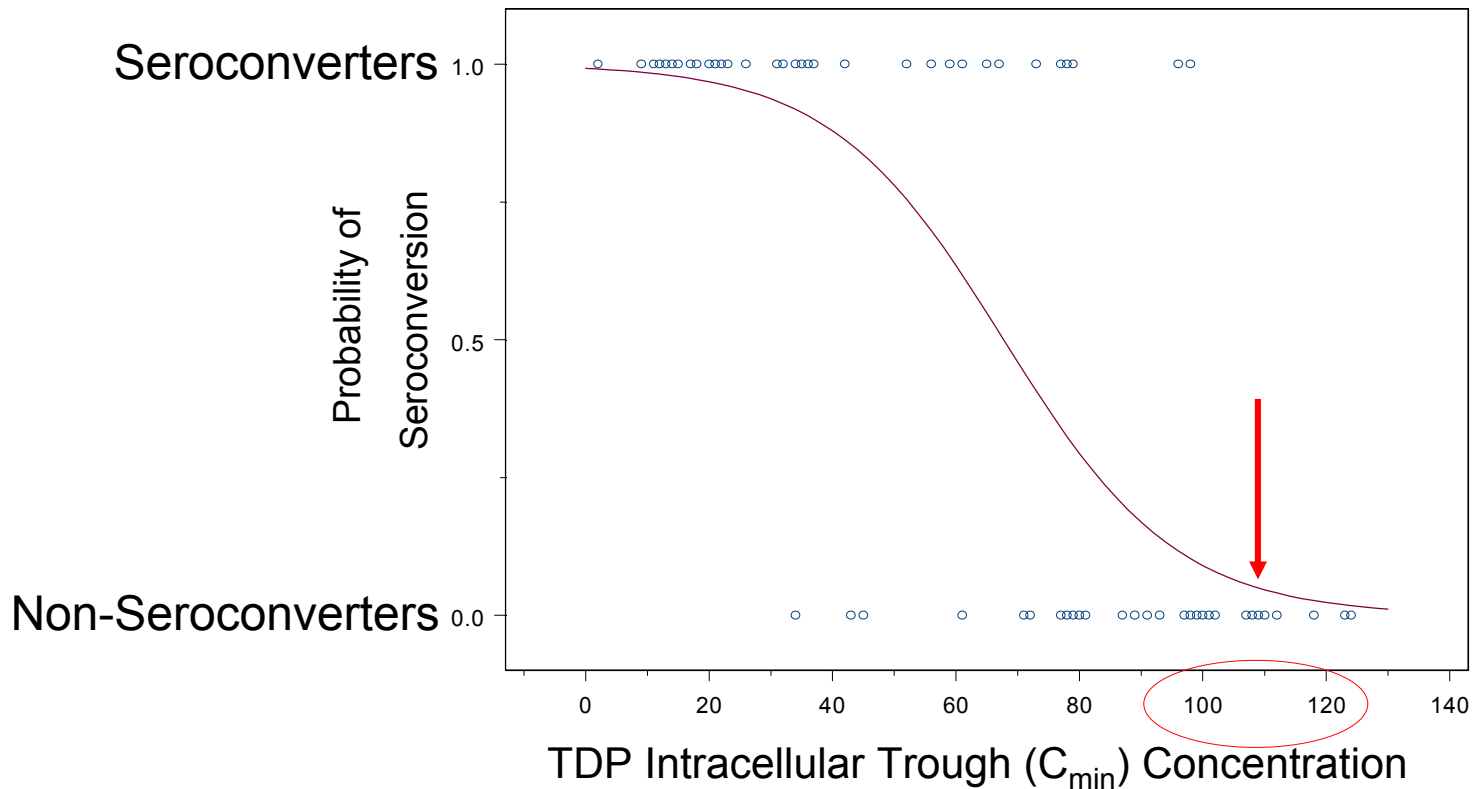
□ Pharmacodynamics (PD)

- Drug effect on body/pathogen
- Variation of drug effects with varying drug amount
- Concentration-response
- Deciding on the target



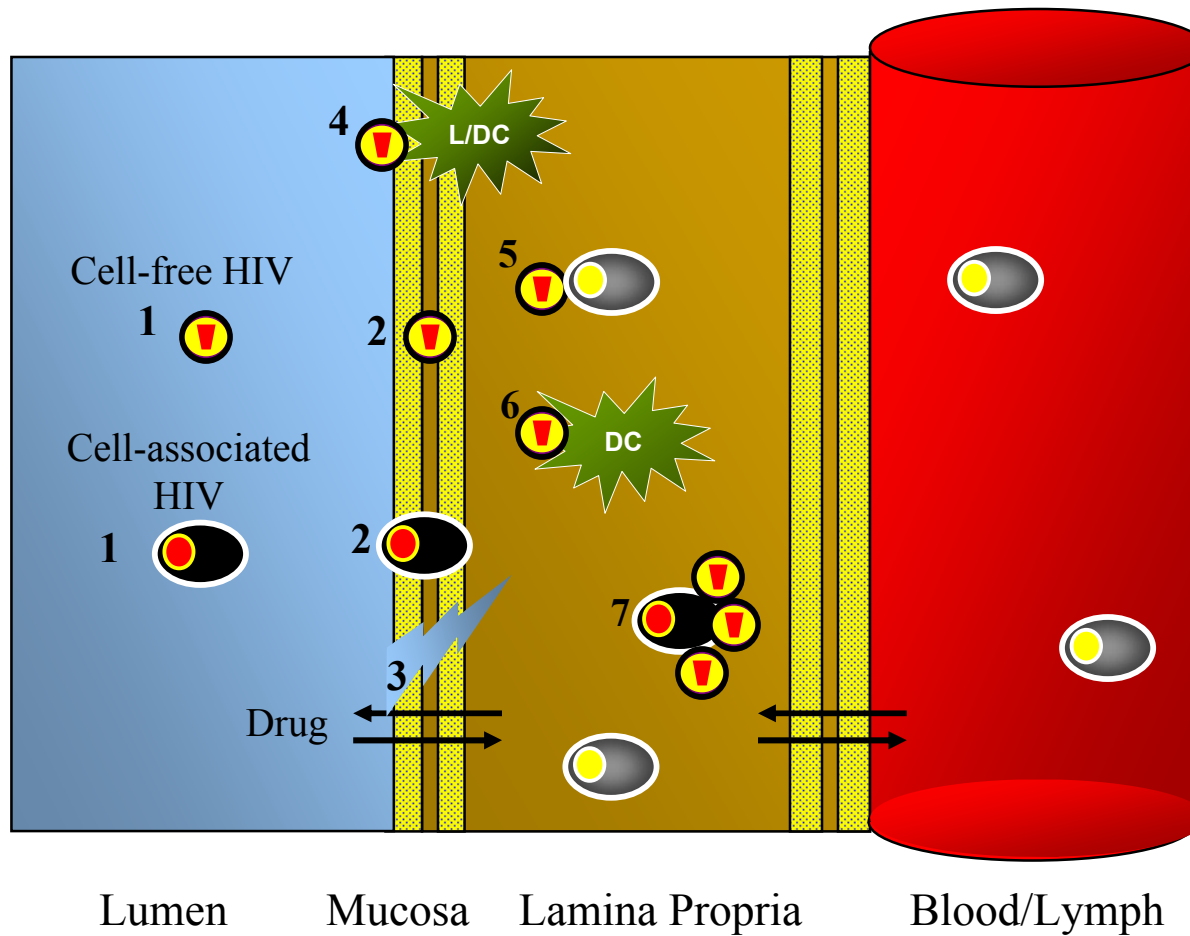
PD: Selecting Target

Pharmacodynamics

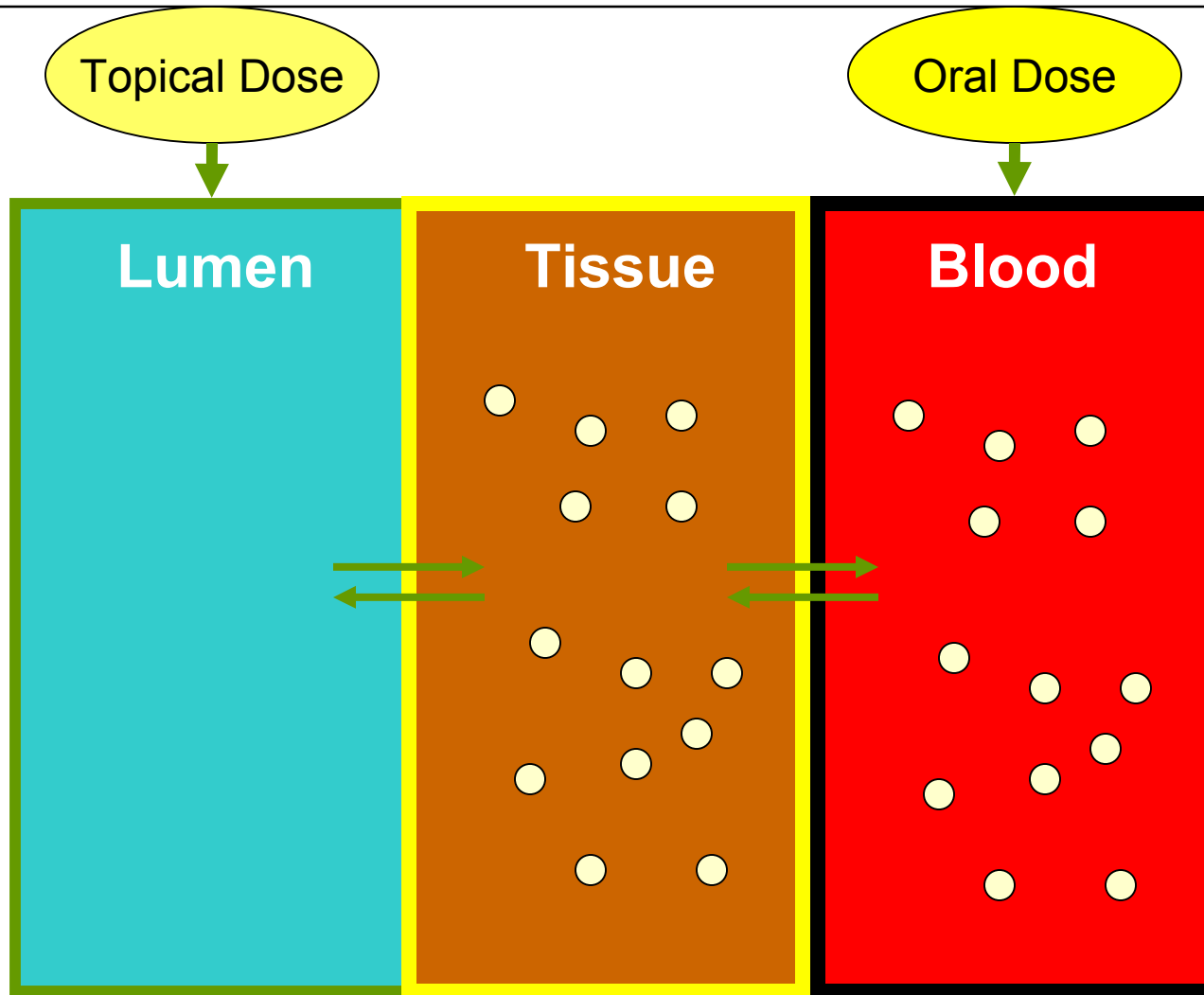


Pharmacokinetics

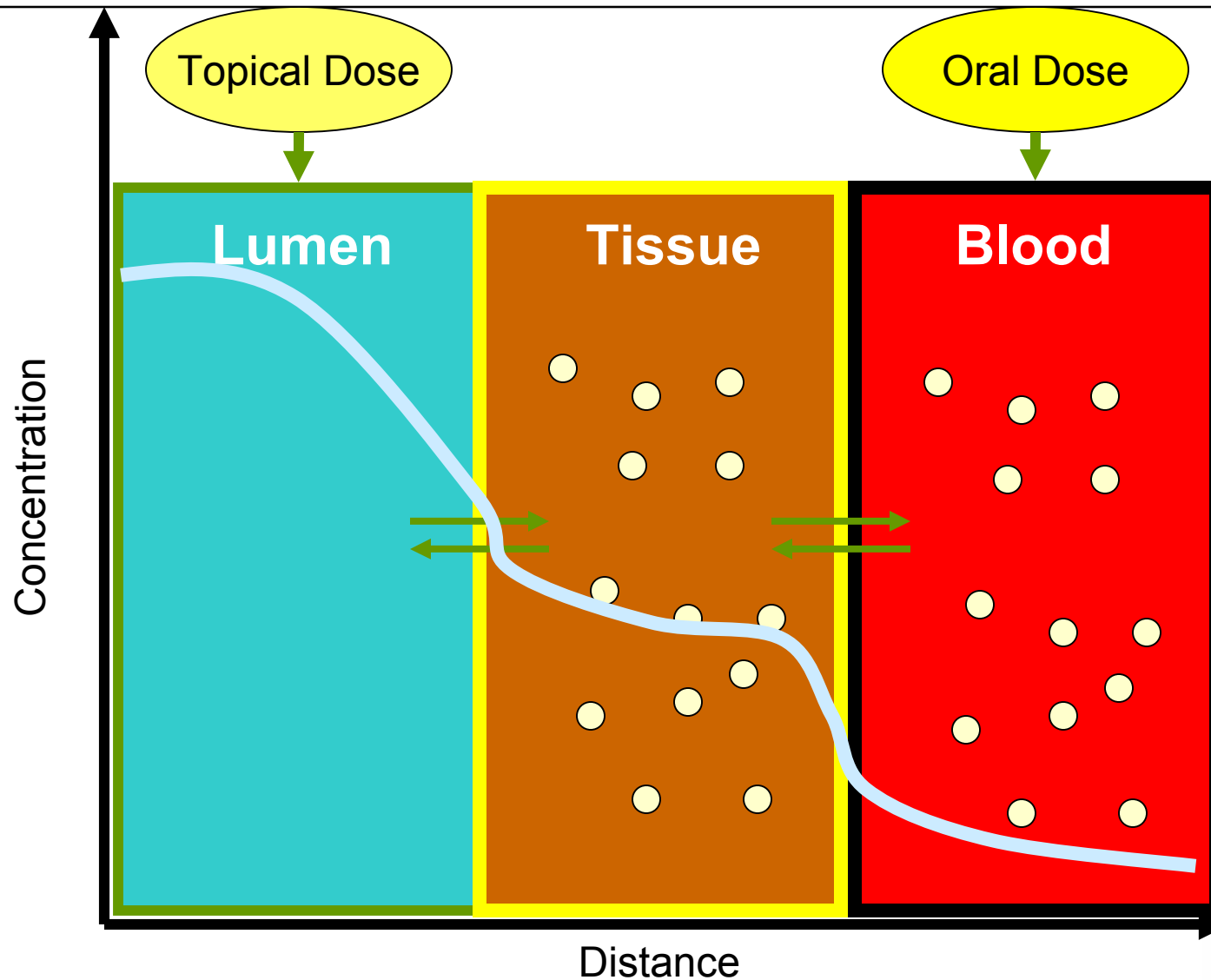
Site of Action



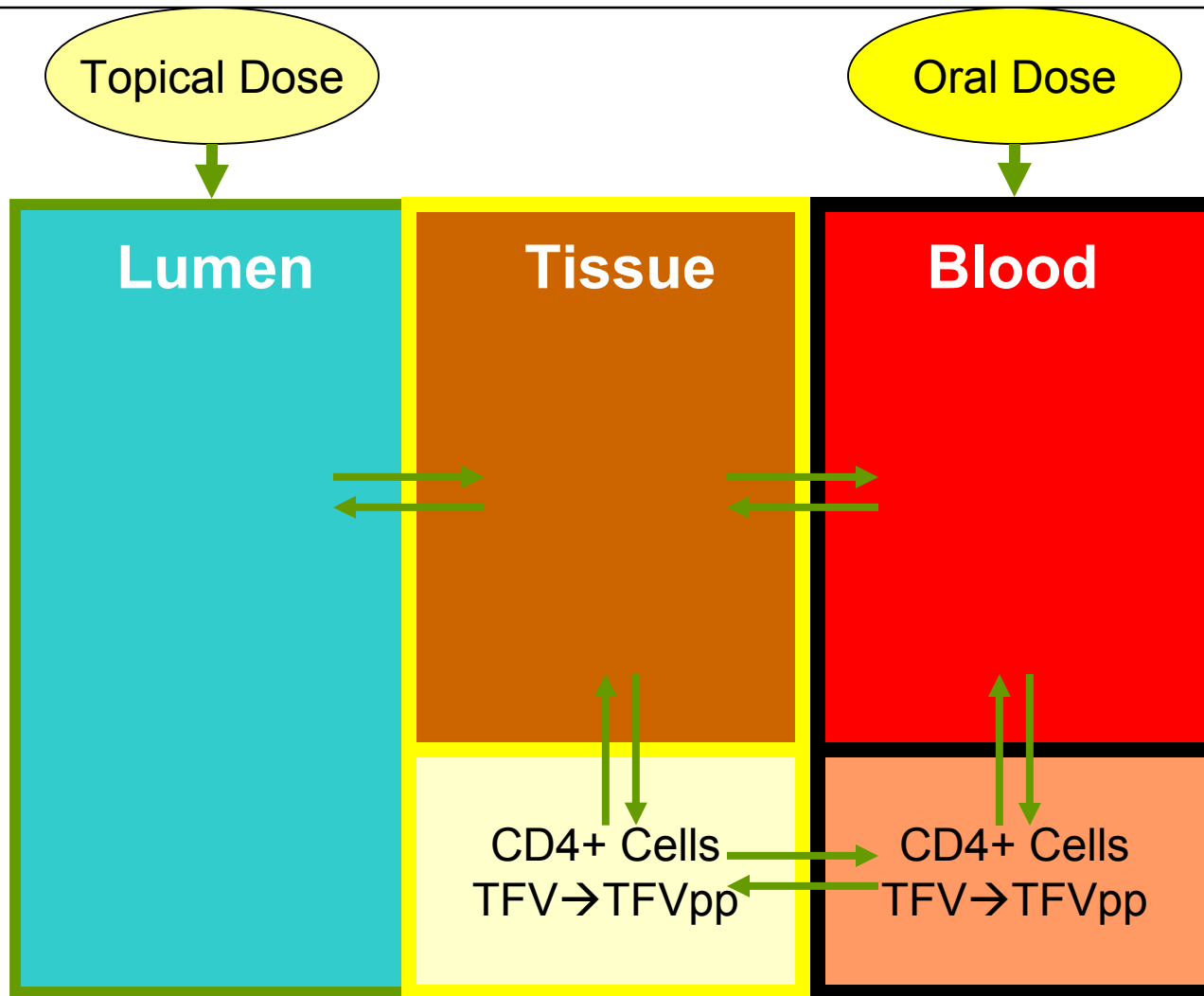
Drug Compartments



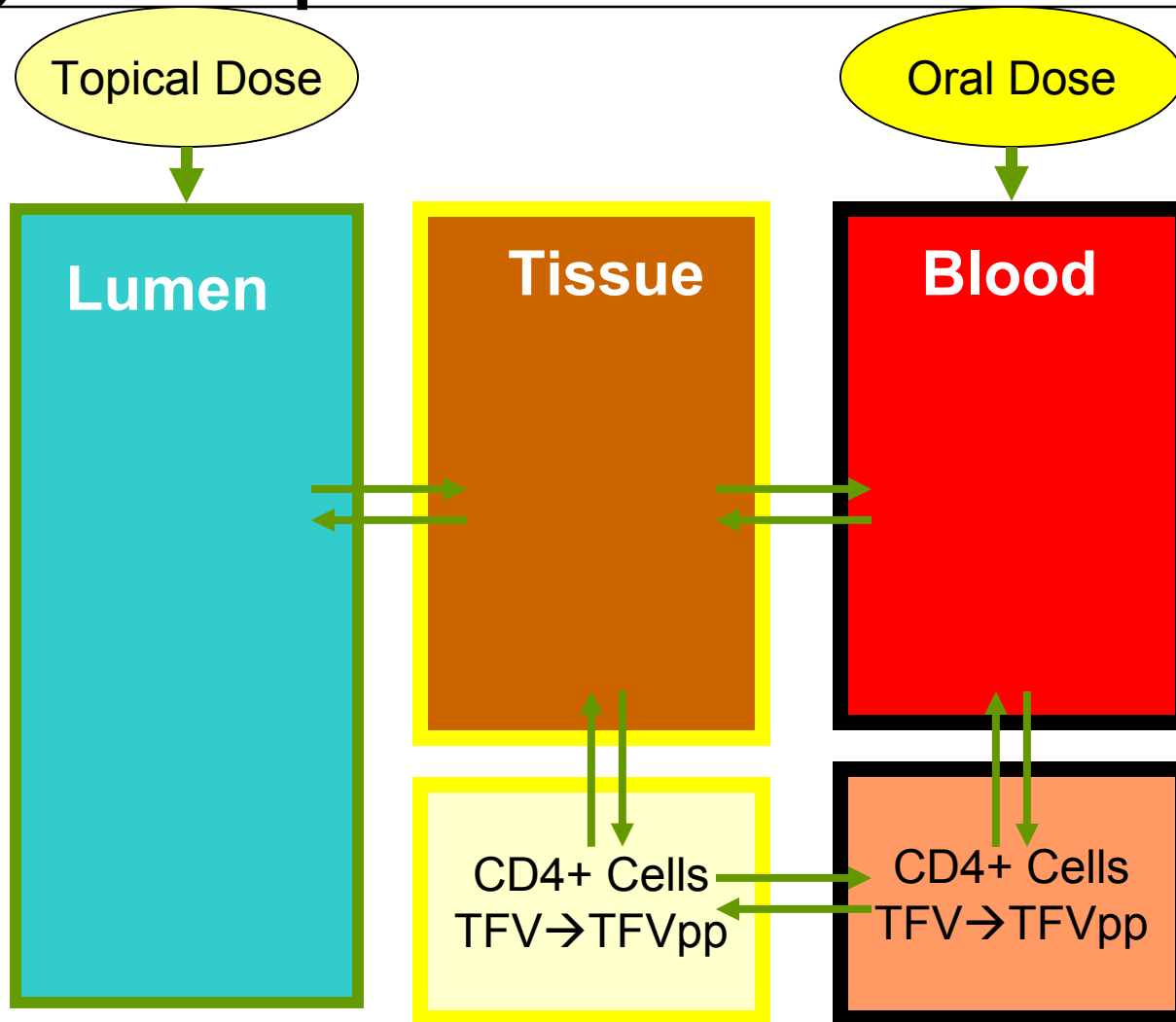
Drug Compartments



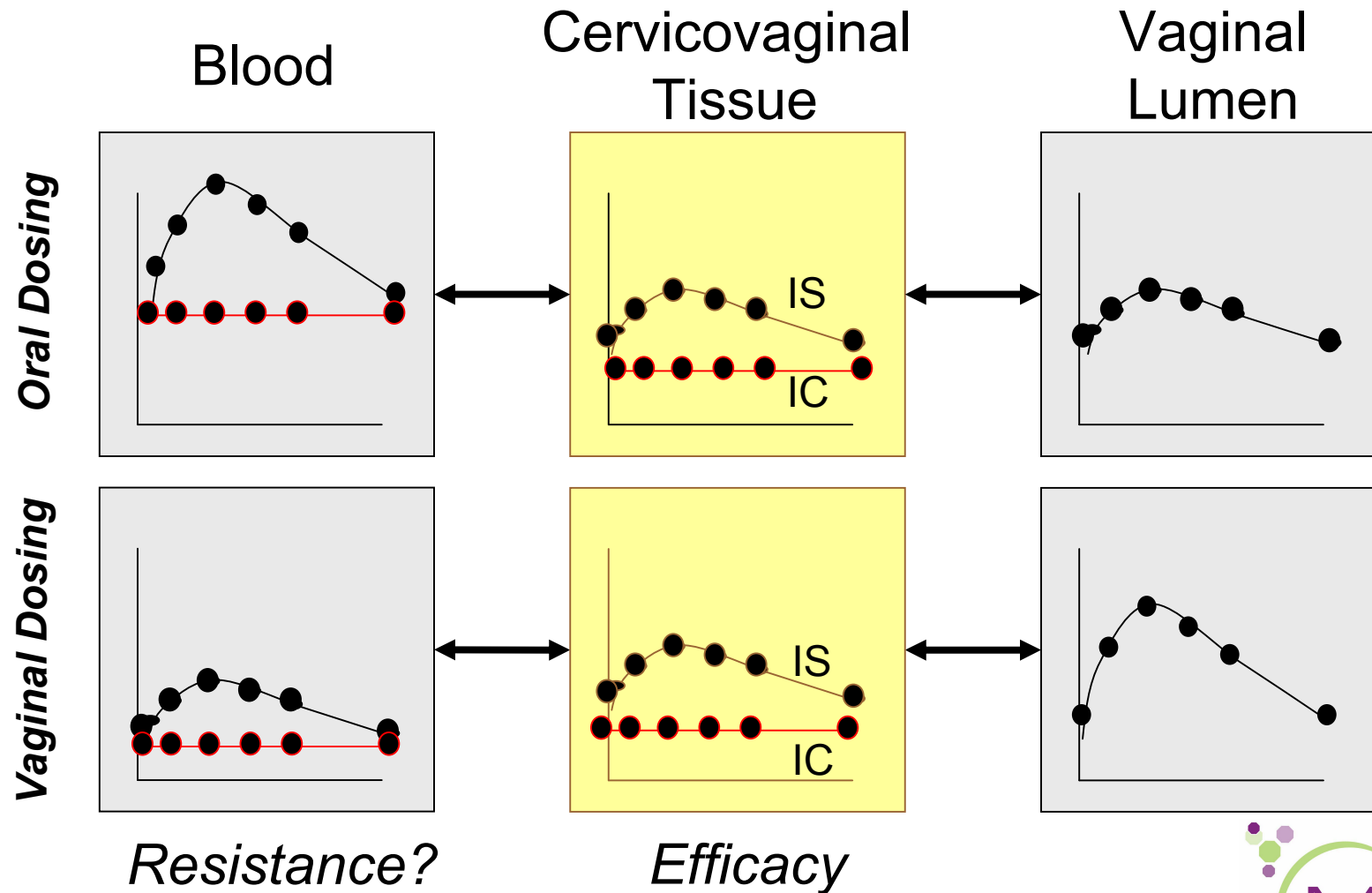
Drug Compartments



Drug Compartments



PK Model Building - Ideal



PK Model Building - Feasible

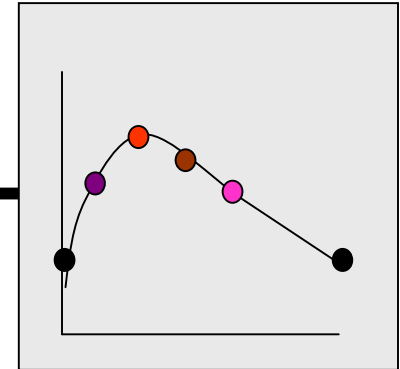
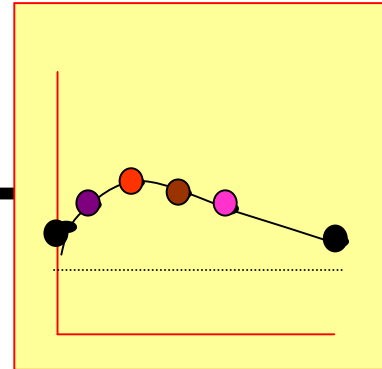
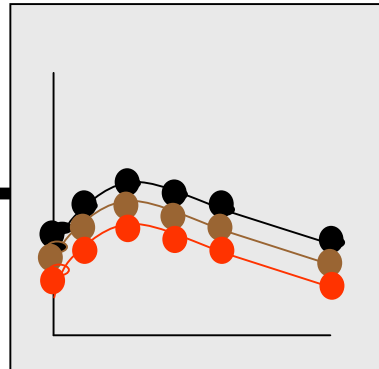
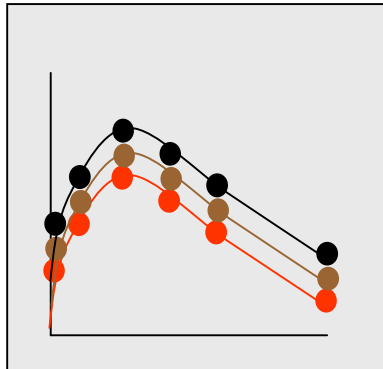
Blood
Plasma

Blood
PBMC

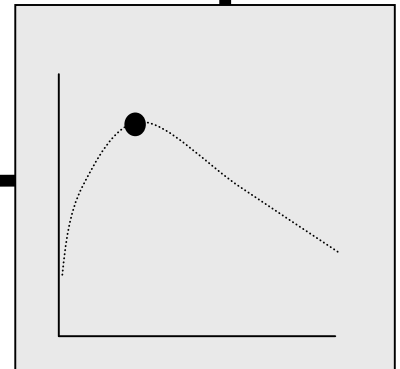
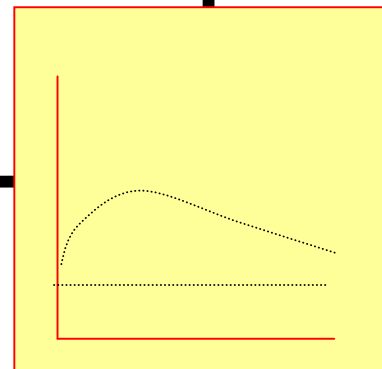
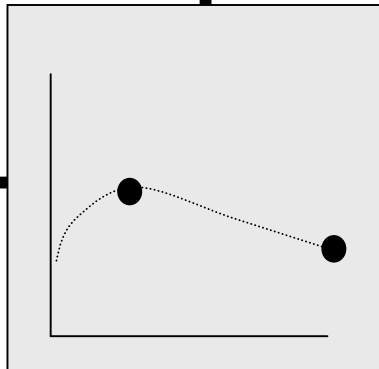
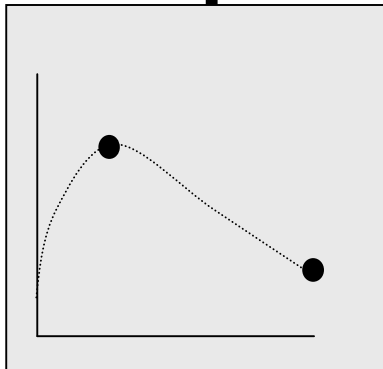
Cervicovaginal
Tissue

Vaginal
Lumen

Intensive Sites



Sparse Sites



Intensive PK Sampling

SPECIMEN	PRE-DOSE	POST-DOSE TIMING				
		1 HOUR	2 HOURS	4 HOURS	6 HOURS	8 HOURS
Blood draw <ul style="list-style-type: none"> • PBMC cell lysate (intracellular TFV-DP) • Tenofovir 	All	All	All	All	All	All
Blood draw <ul style="list-style-type: none"> • Flow cytometry 	All					
Cervical cytology brush <ul style="list-style-type: none"> • Cell lysates (TFV-DP) • Tenofovir 	12 ppts (Gp M)		12 ppts (Gp N)	12 ppts (Gp O)	12 ppts (Gp P)	
CVL <ul style="list-style-type: none"> • Tenofovir • Proteomics/Inflammation Mkr 	Gp M		Gp N	Gp O	Gp P	
Vaginal biopsies <ul style="list-style-type: none"> • Tenofovir 	Gp M		Gp N	Gp O	Gp P	

Sparse PK Sampling

<i>Sample</i>	<i>Pre-Dose</i>	<i>1-3 HOURS</i>	<i>3-5 HOURS</i>	<i>5-7 HOURS</i>
<i>Plasma for flow cytometry</i>	<i>All Sequences</i>			
<i>Plasma for tenofovir</i>	<i>All Sequences</i>	<i>1, 2*</i>	<i>3, 4*</i>	<i>5, 6*</i>
<i>CVL for tenofovir</i>		<i>1, 2*</i>	<i>3, 4*</i>	<i>5, 6*</i>

*Sequence

PK Multi-Site Model Building

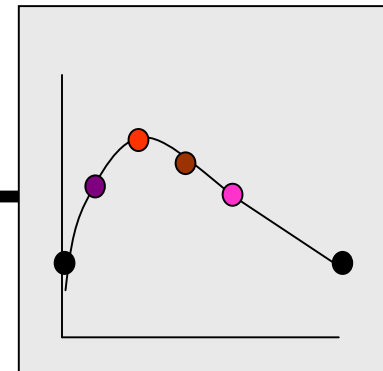
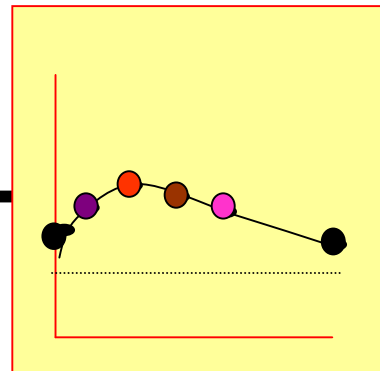
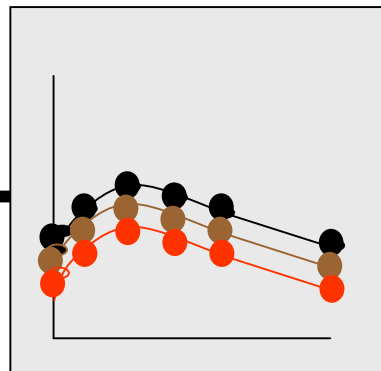
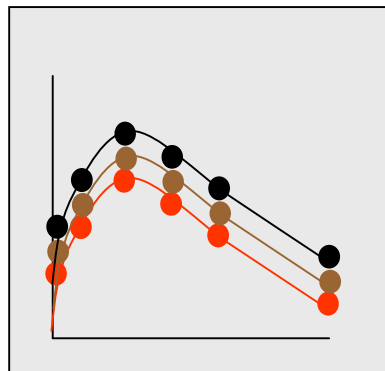
Blood
Plasma

Blood
PBMC

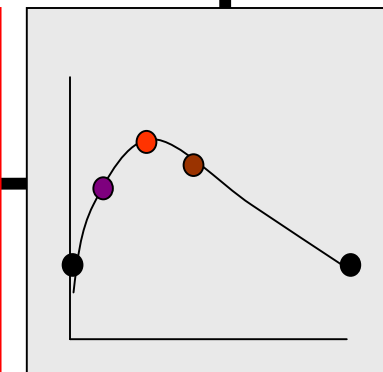
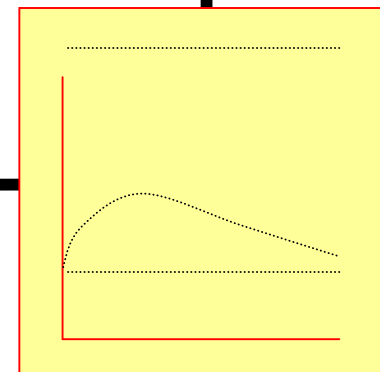
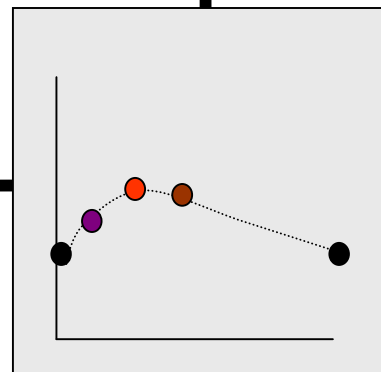
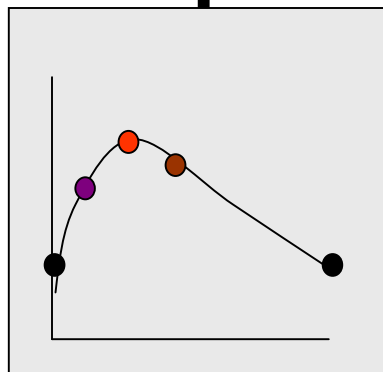
Cervicovaginal
Tissue

Vaginal
Lumen

Intensive Sites

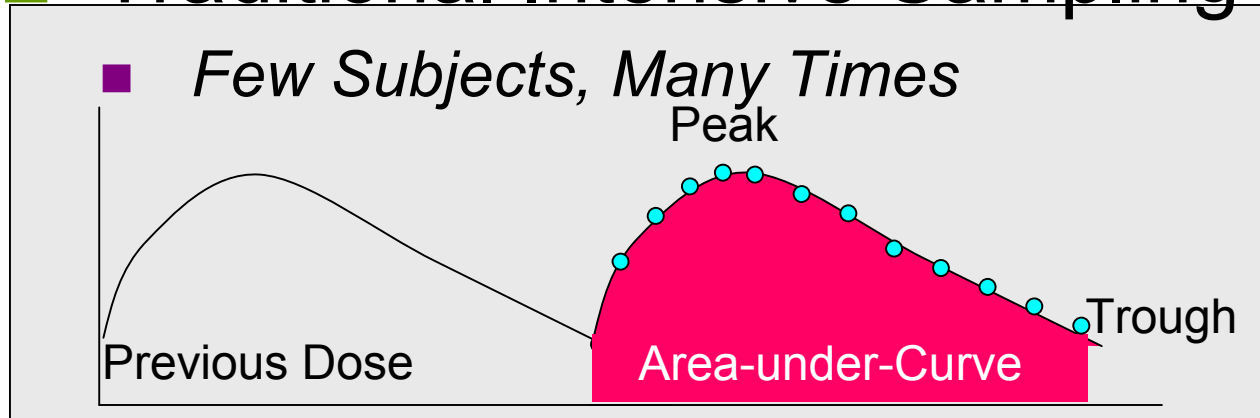


Sparse Sites

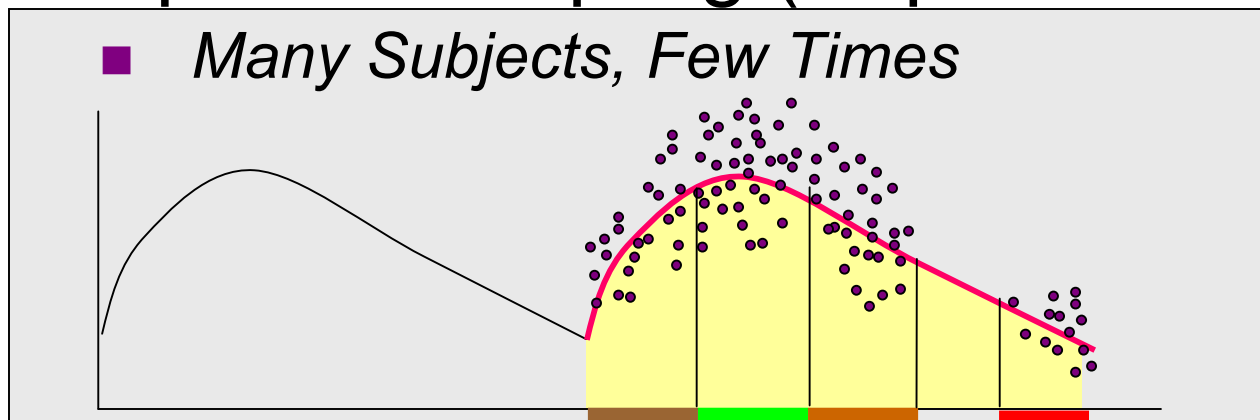


Complementary PK Sampling

□ Traditional Intensive Sampling



□ Sparse Sampling (Population PK)

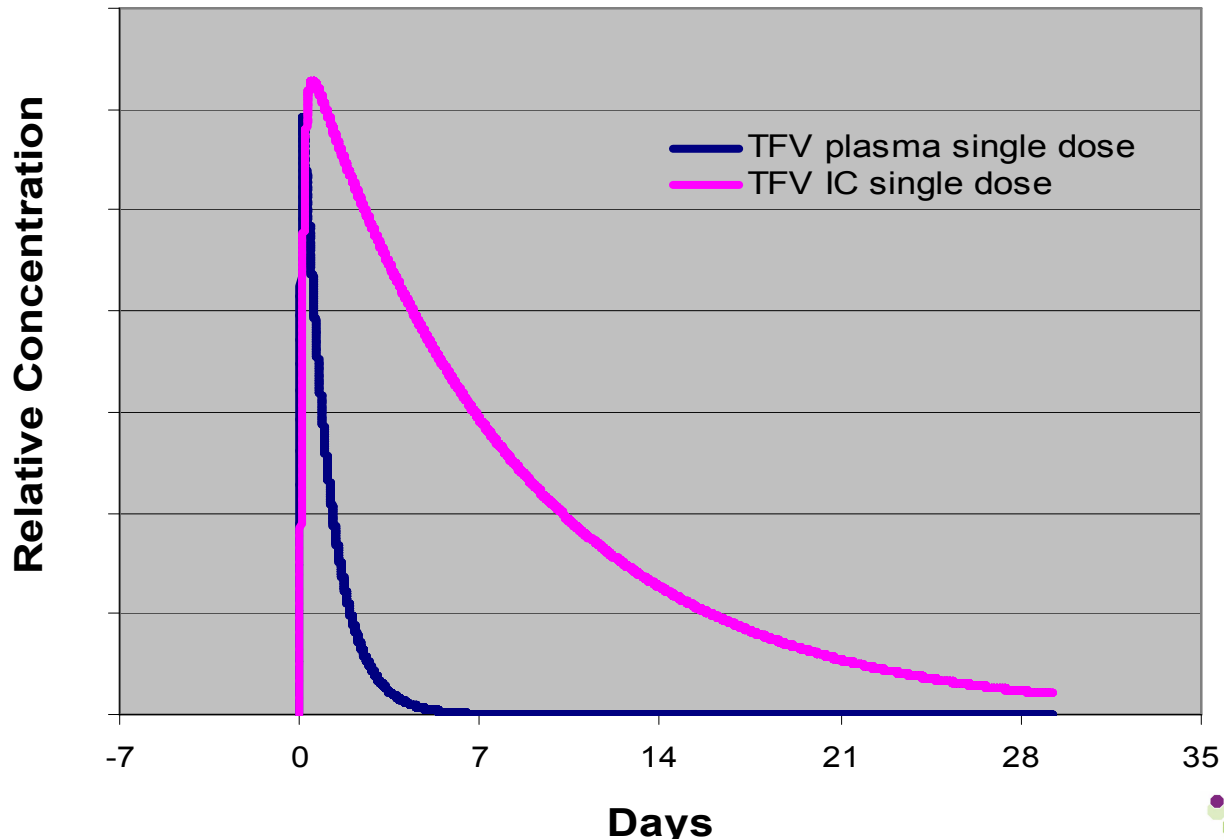


Value of PK Data After MTN-001

- Duration of concentration
 - dose frequency?
 - Coitally-Dependent Dosing?
- Route of Dosing
 - Oral or Topical most efficient?
- PK-PD Modeling in Efficacy Studies
 - What concentrations are associated with efficacy?

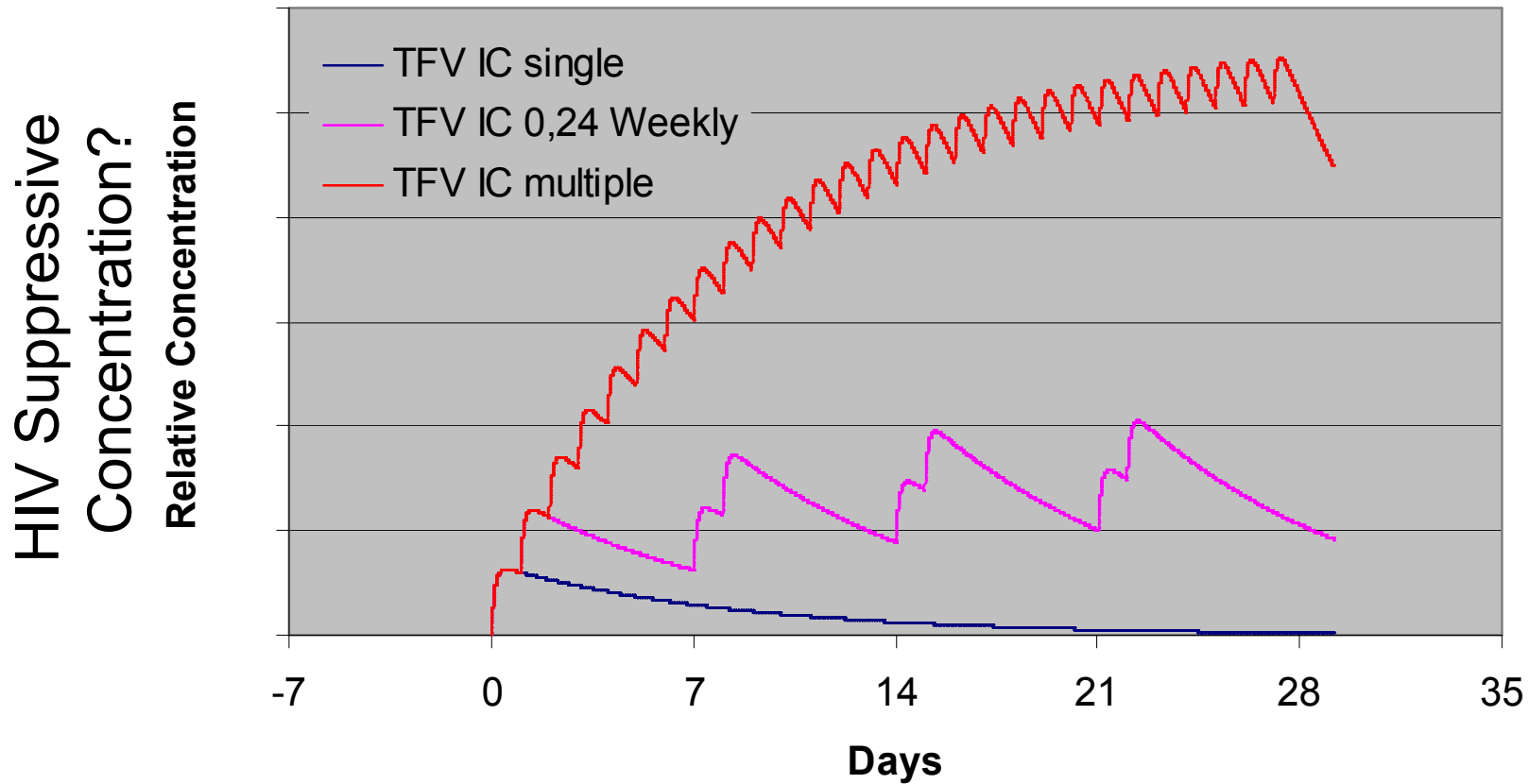
Dose & Frequency?

HIV Suppressive
Concentration?



HIV Half-Life ?

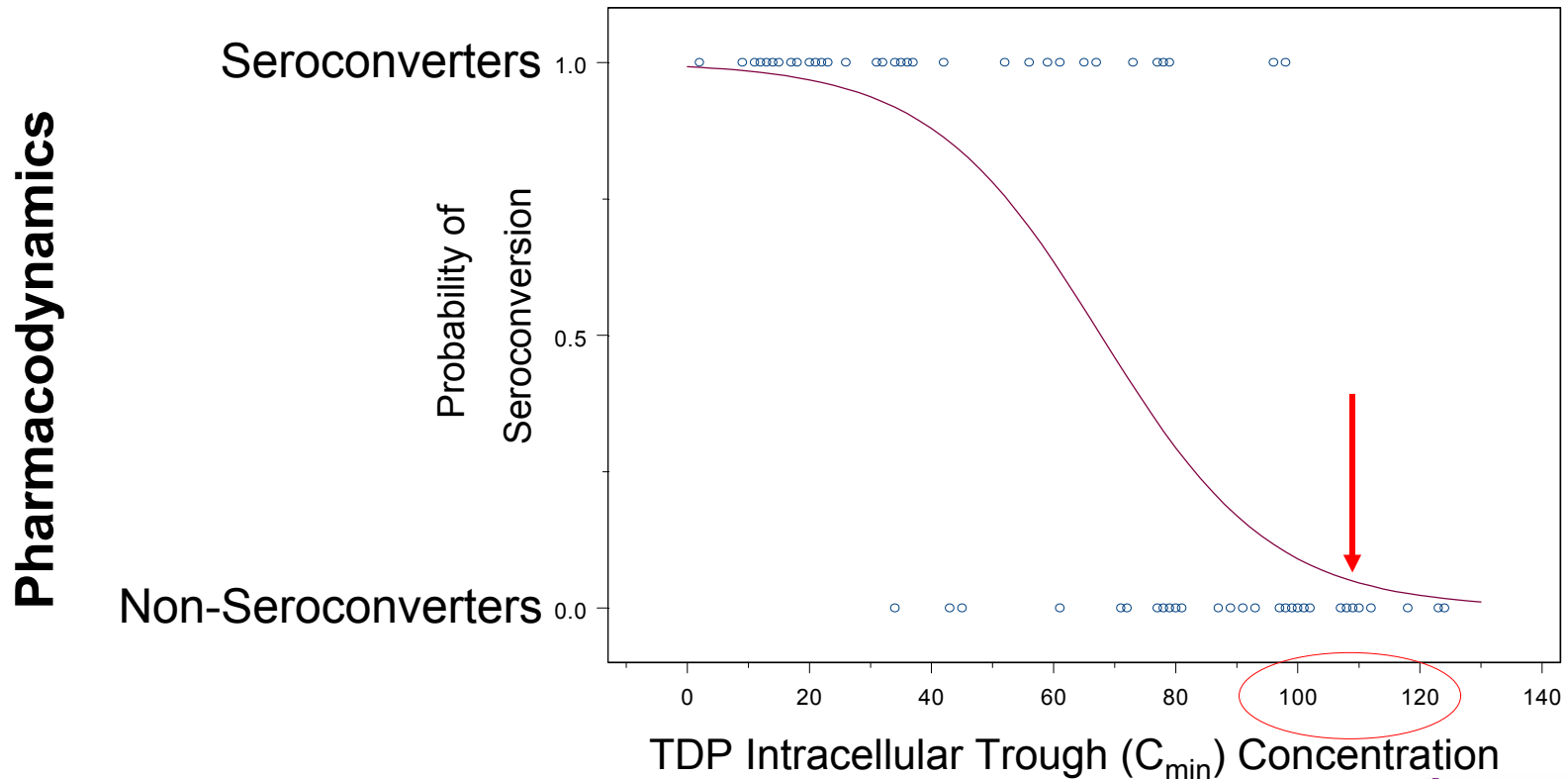
Coitally-Dependent v. Daily



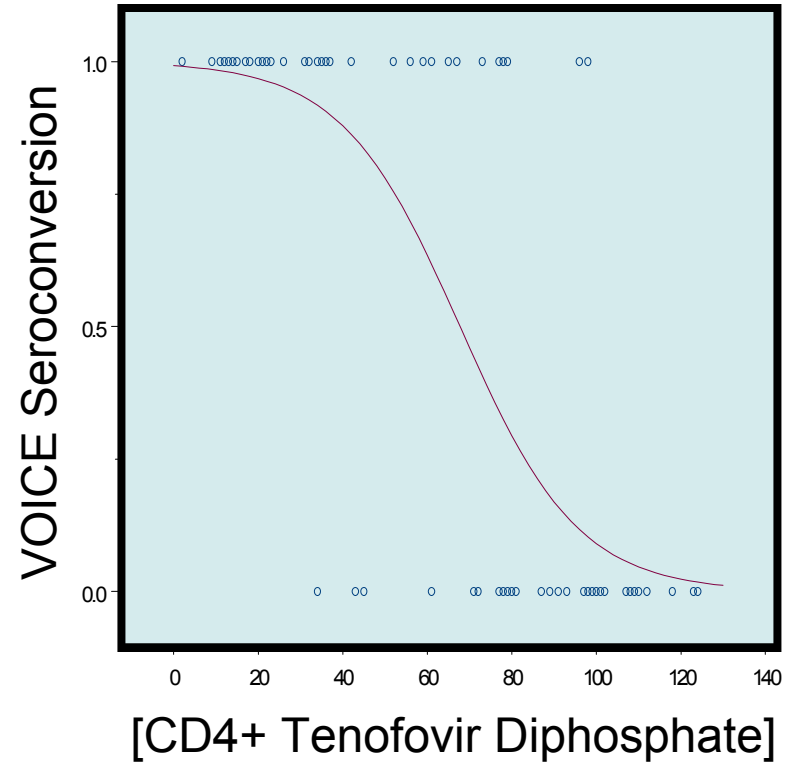
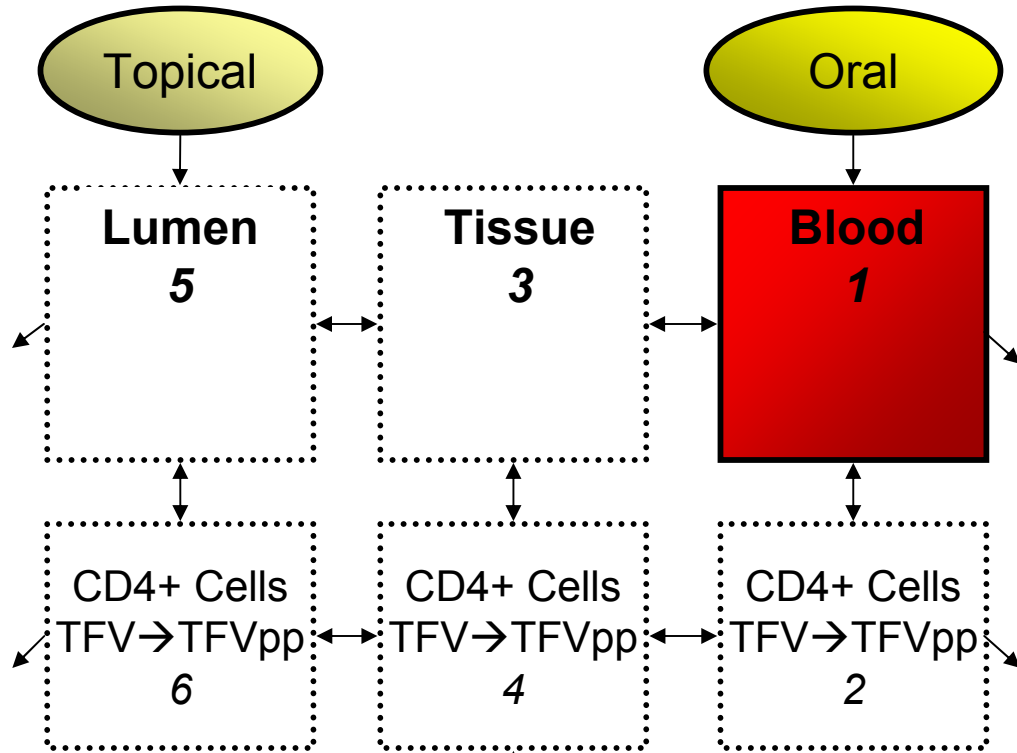
HIV Half-Life ?

VOICE: Ideal Finding

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

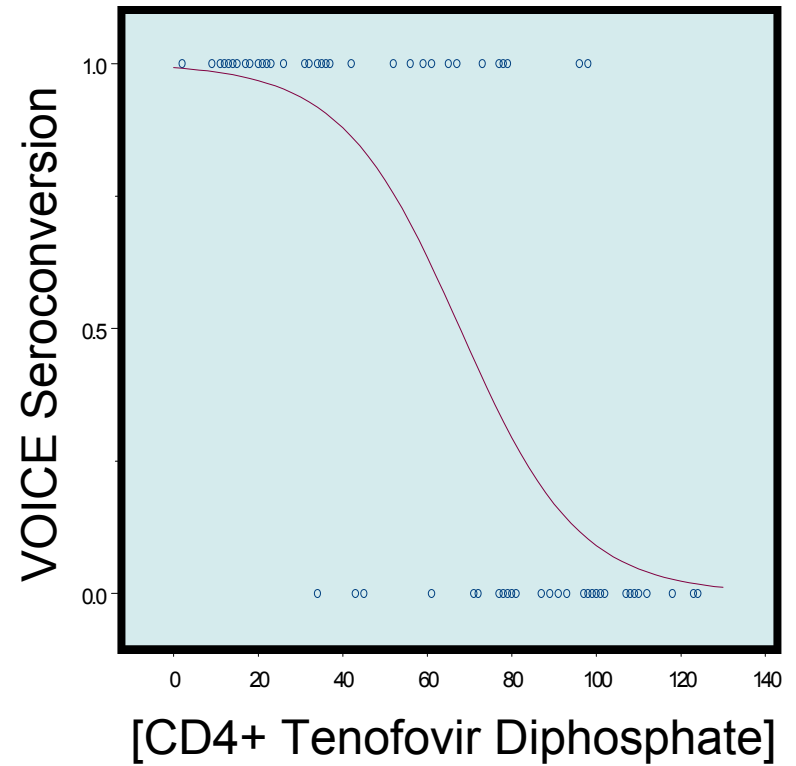
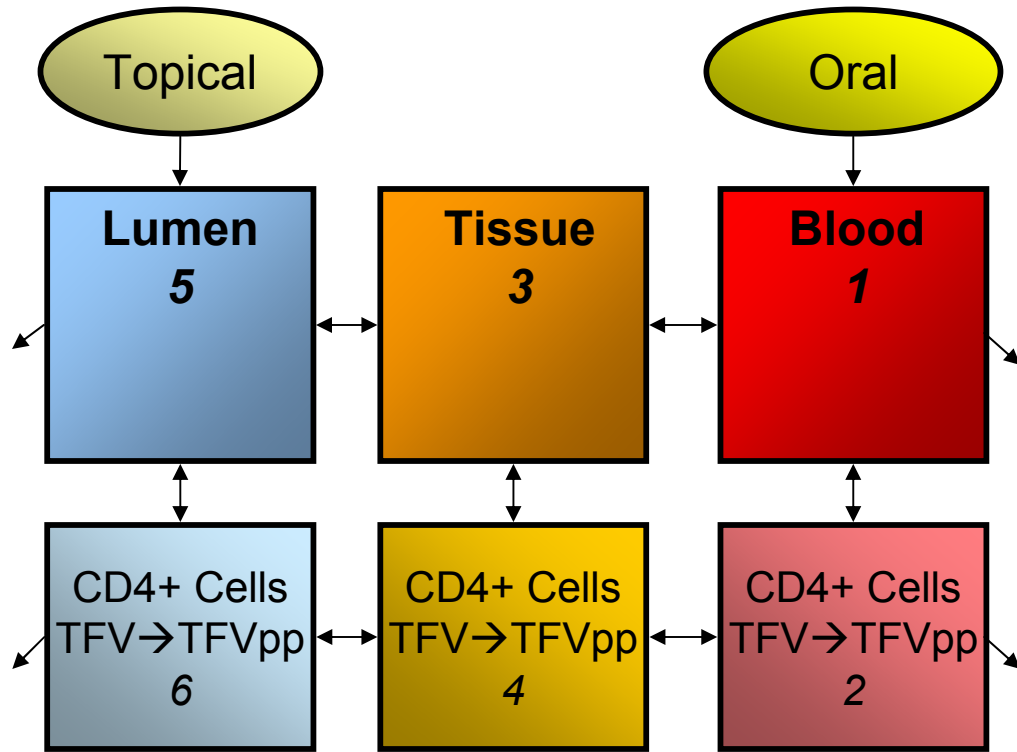


PK-PD: VOICE Alone



Pharmacokinetic – Pharmacodynamic Link

PK-PD: VOICE & MTN-001+



Pharmacokinetic – Pharmacodynamic Link

Unique Contributions

- Compare oral v. vaginal product adherence
- Impact of second product on adherence
- Comparison of oral v. vaginal PK
- Integrated multi-compartment PK model after oral dosing (blood cells, tissue, lumen)
- Additive effect of dual route dosing
- Comparison of observed v. unobserved PK to assess adherence
- Simulation of VOICE tissue intracellular TDP kinetics

Questions?



Tenofovir PK Data Sources

<i>Study</i>	<i>PK Data Available</i>	<i># on Drug</i>	<i>Route</i>	<i>Fluid</i>	<i>Blood Cellular PK</i>	<i>Tissue PK</i>	<i>Tissue Cellular PK</i>	<i>HIV - → +</i>
<i>HPTN 050</i>	Published	25	V	B	-	-	-	-
<i>HPTN 057</i>	Q1 2008	60	O	B,BM,CB	-	-	-	(60)*
<i>HPTN 059</i>	Q1 2008	100	V	B	-	-	-	-
<i>¹⁴C-TFV</i>	Q2 2008	3	O	B	CD4	R	CD4 ³	-
<i>CONRAD TFV</i>	Q2 2008	49	V	B	PBMC	V ²	MMC ^{2,3}	-
<i>MTN 002</i>	Q4 2008	12	V	B,CB,A	PBMC	V ² ,U	-	-
<i>MTN 001</i>	Q2 2009	144	V,O	B	PBMC	V ²	MMC ³	-
<i>CAPRISA 004</i>	Q1 2009	475	V	B	PBMC	V ²	V,Cx ³	68
<i>CDC PrEP</i>	Q3 2009	600	O	B	PBMC	-	-	125
<i>MTN 006</i>	Q3 2009	18	R,O	B	PBMC	R ²	MMC ³	-
<i>MTN 003</i>	Q3 2012	2520	V,O	B	-	-	-	217

¹Vertical transmission;

²Uncertain source of cells (cytobrush, biopsies)

³Uncertain sensitivity (MMC vagina, MMC colon, CD4 colon)