

PK/PD: Gut vs Genital Tract

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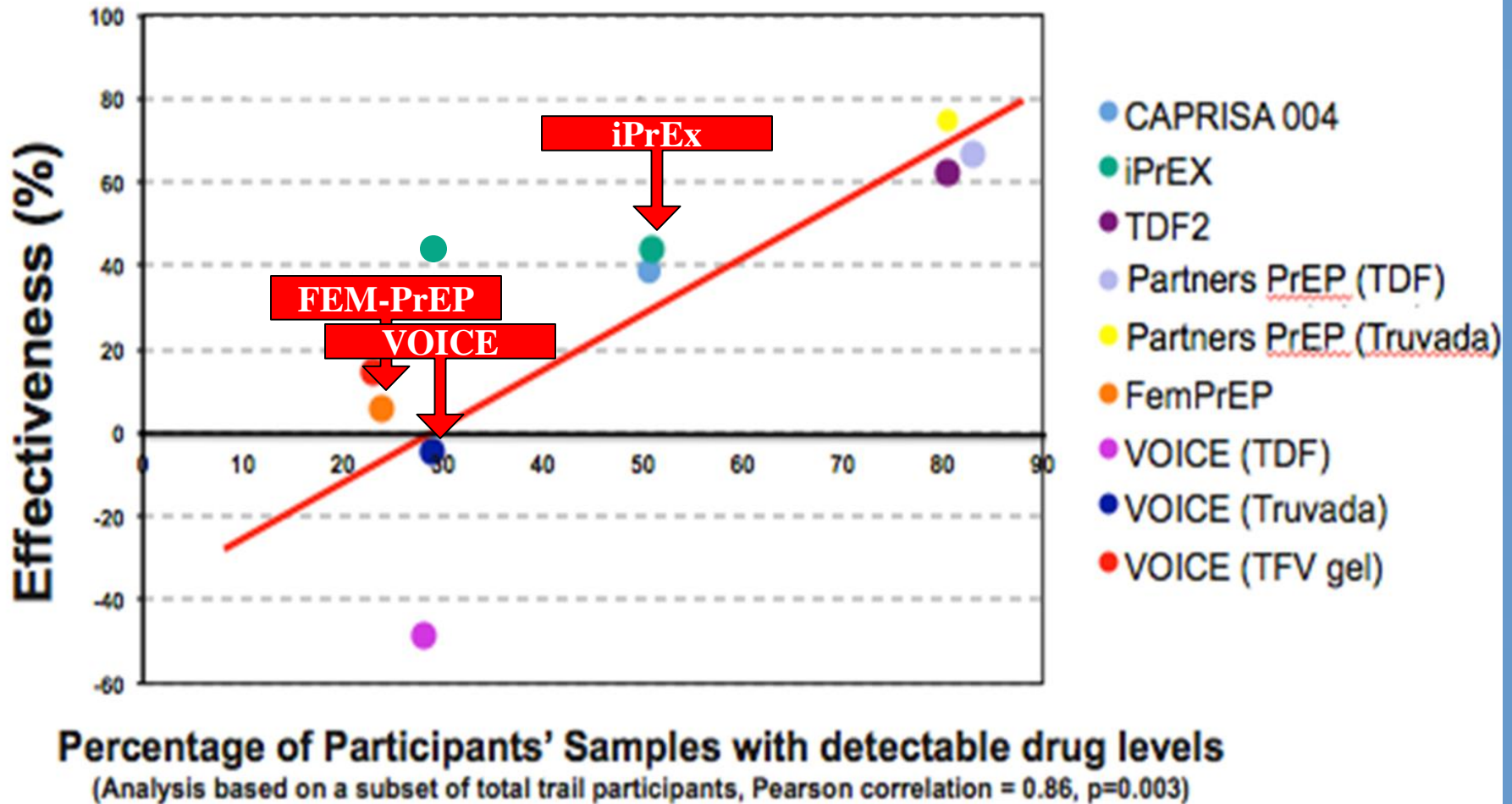


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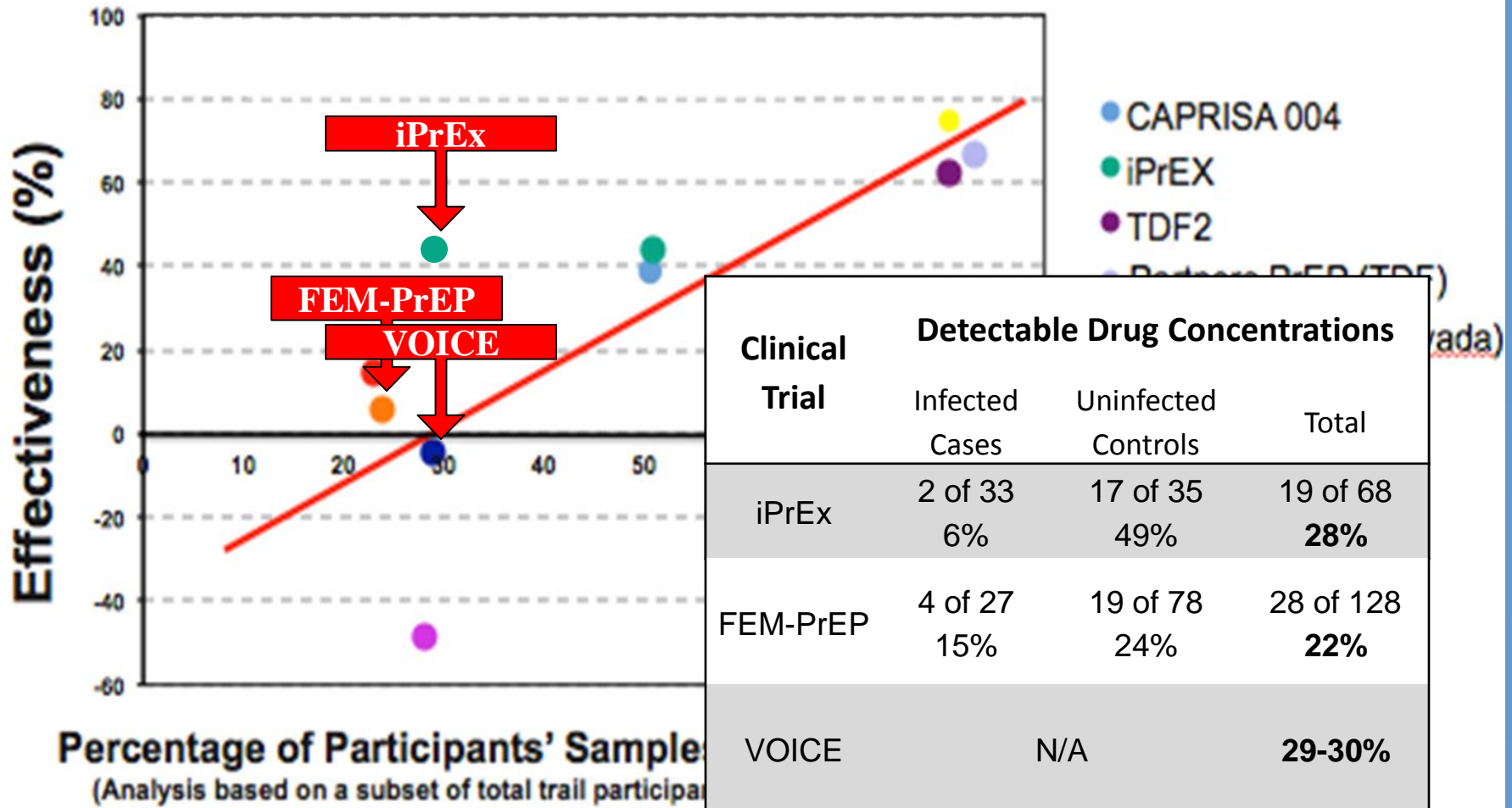
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Adherence Correlates with Clinical Trial Results



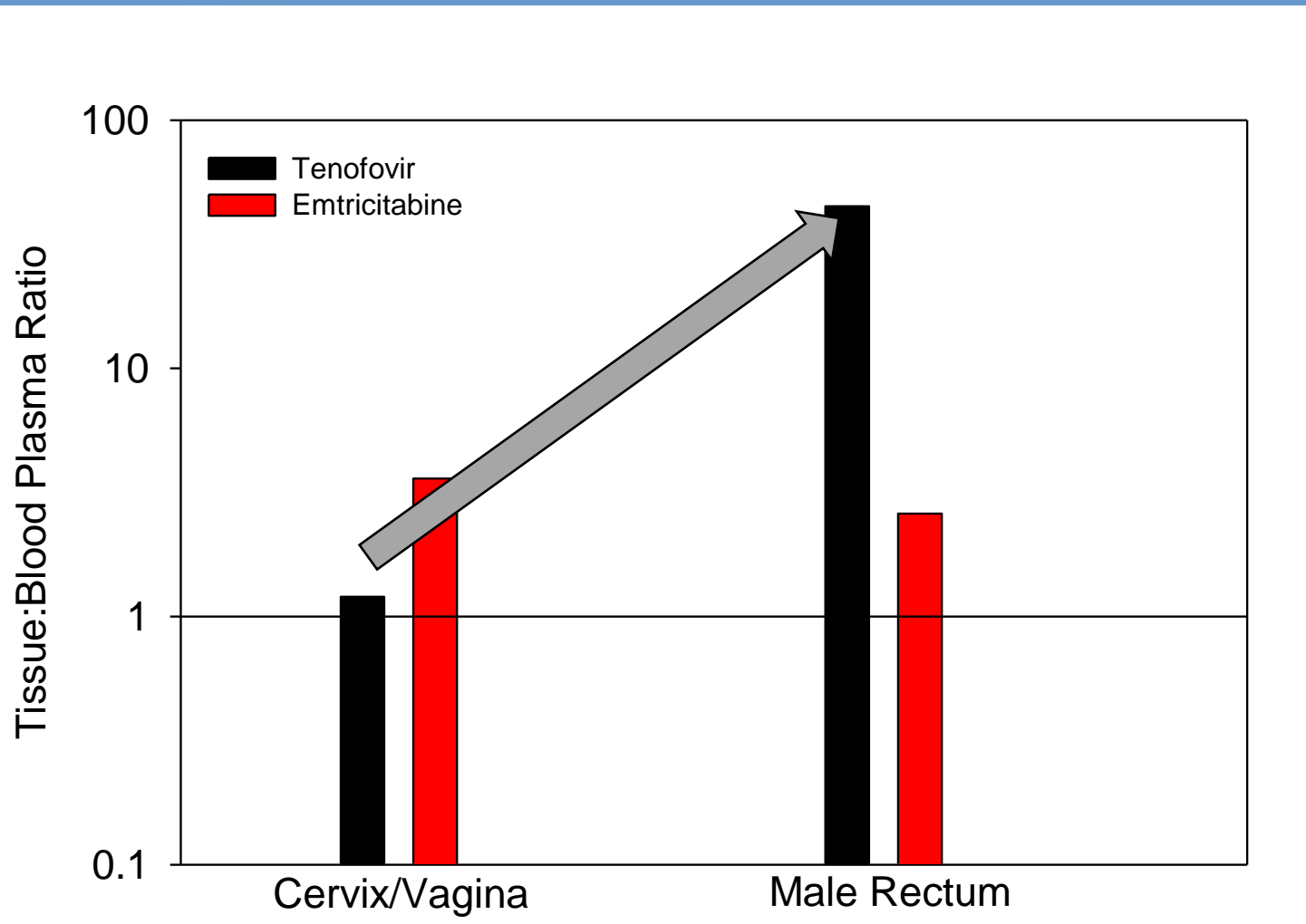
SS Abdool Karim, personal communication

Adherence Correlates with Clinical Trial Results

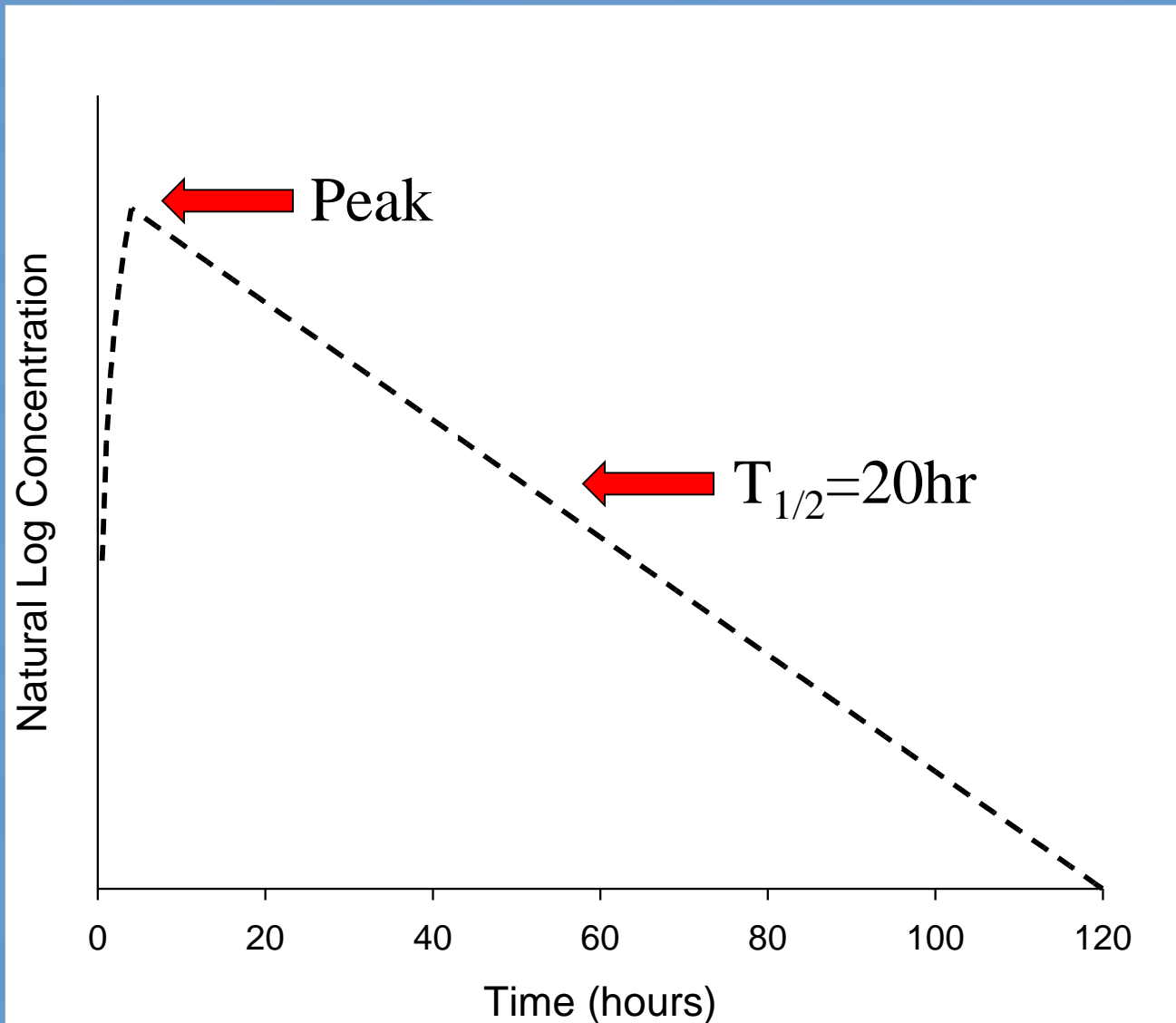


SS Abdool Karim, personal communication

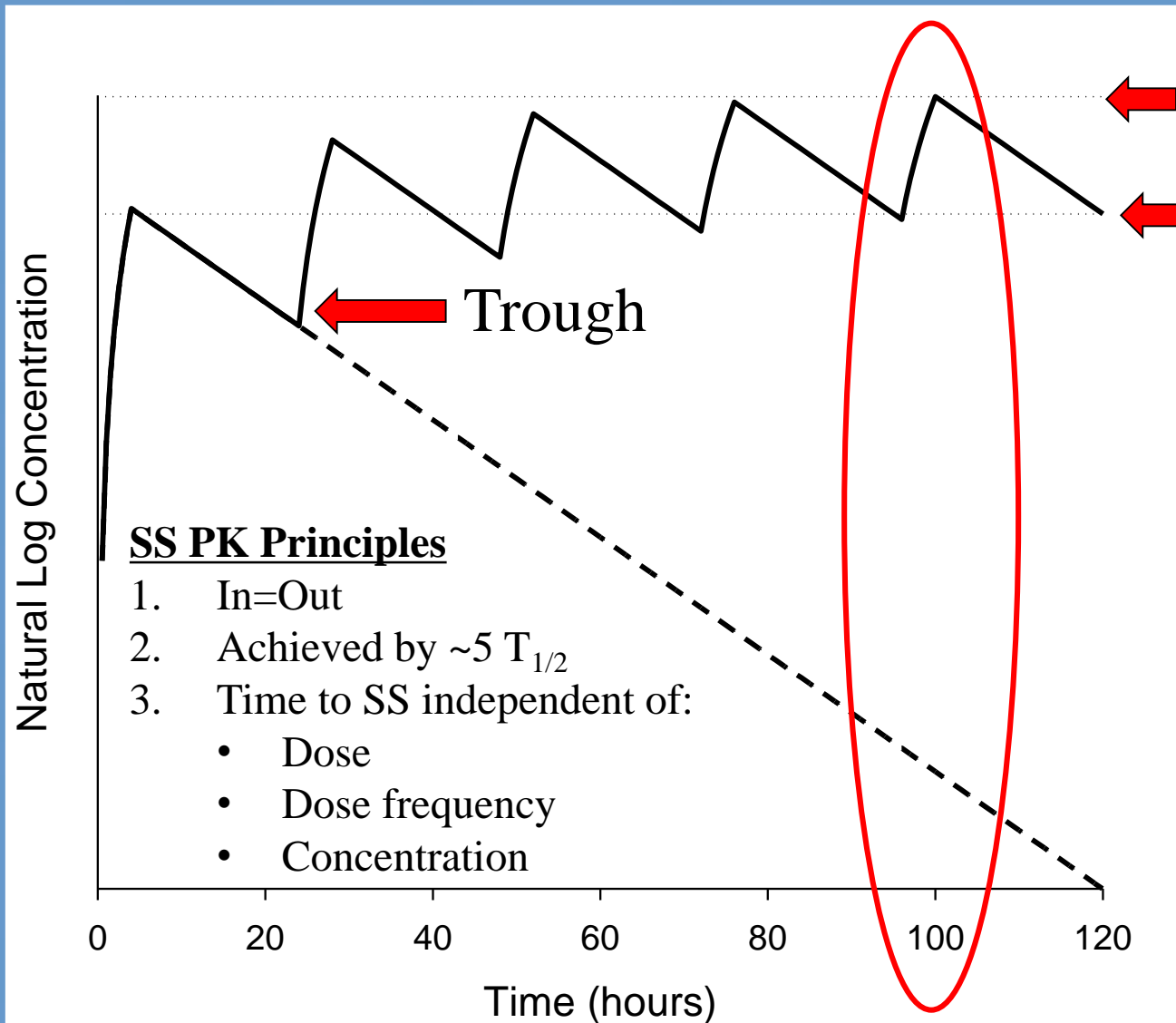
NRTI Pharmacology Differs by Exposure Site



PK Principles: Time to Steady State



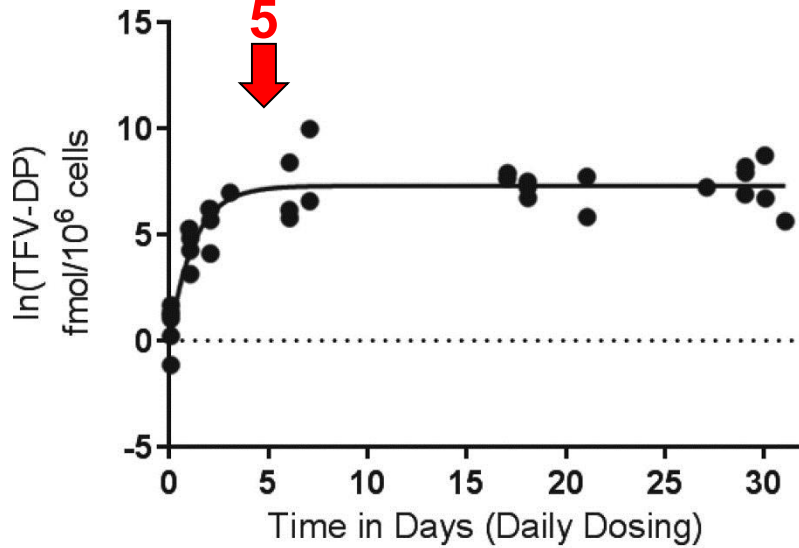
PK Principles: Time to Steady State



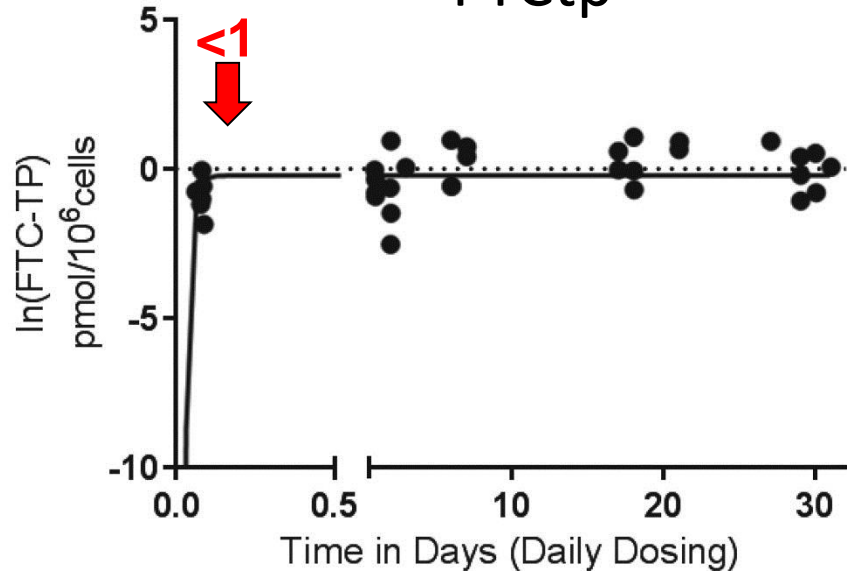
Time to Steady State in Tissues

Rectal (N=40)

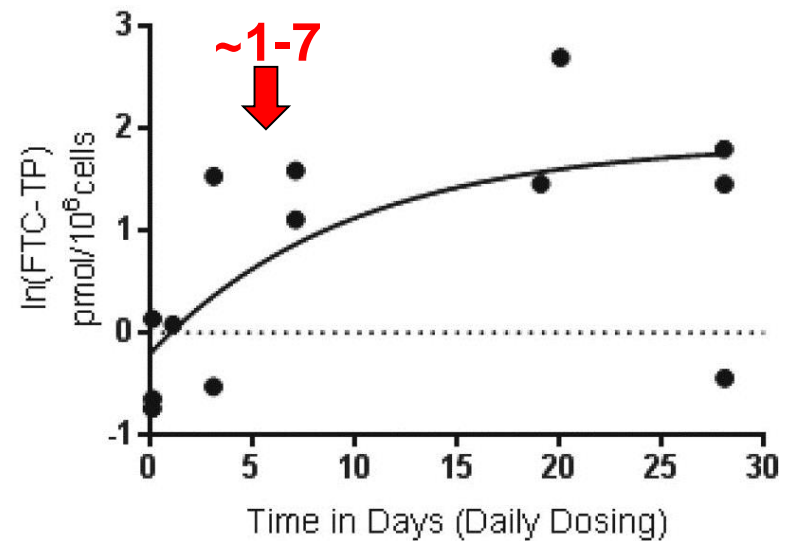
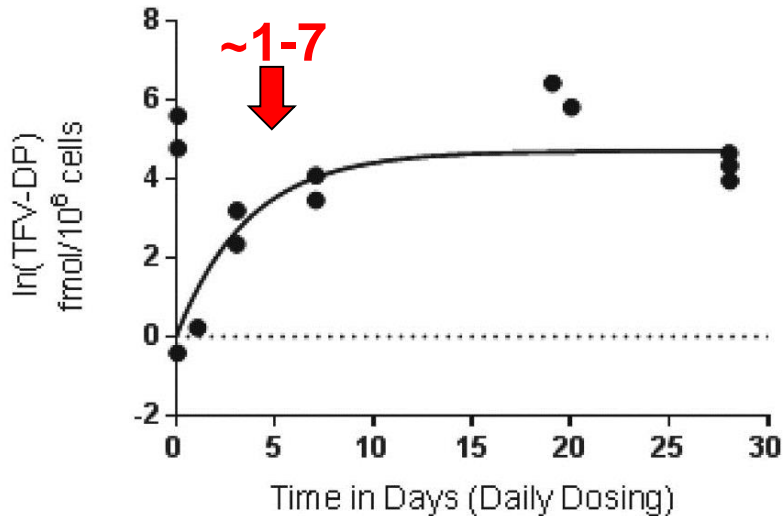
TFVdp



FTCtp

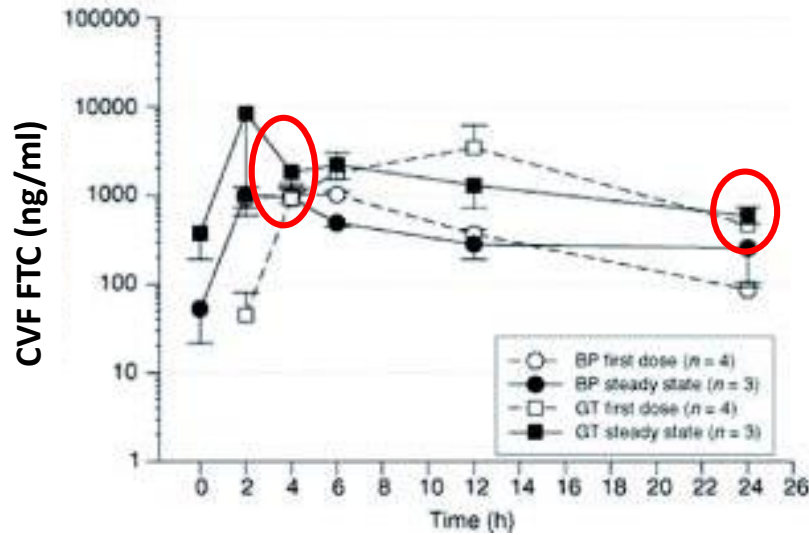


Cervical (N=13)

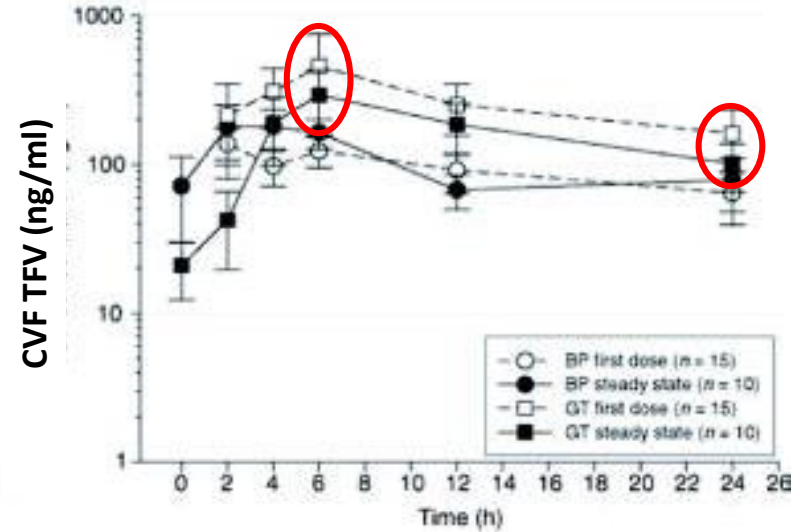


Time to Steady State in CVF

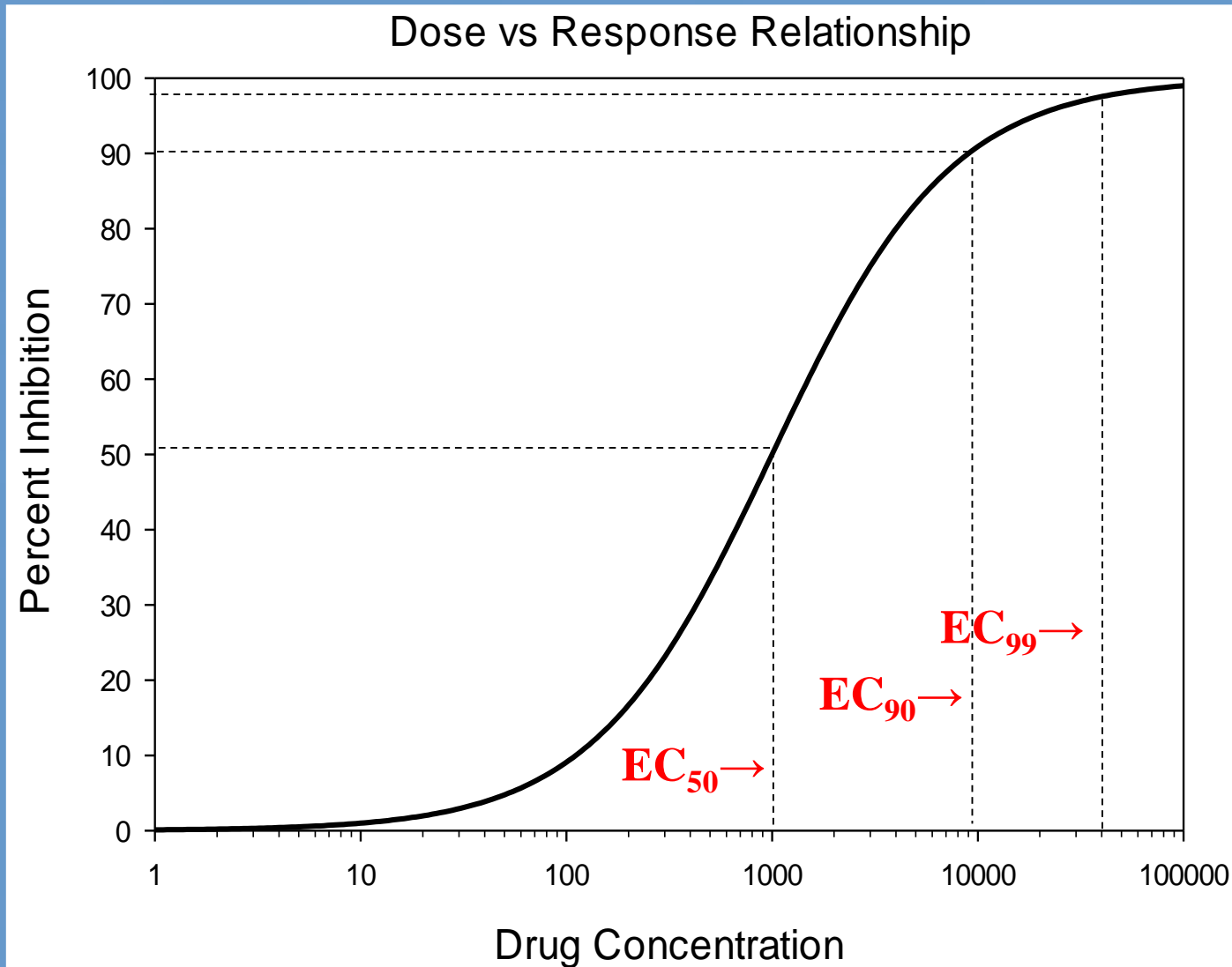
FTC



TFV

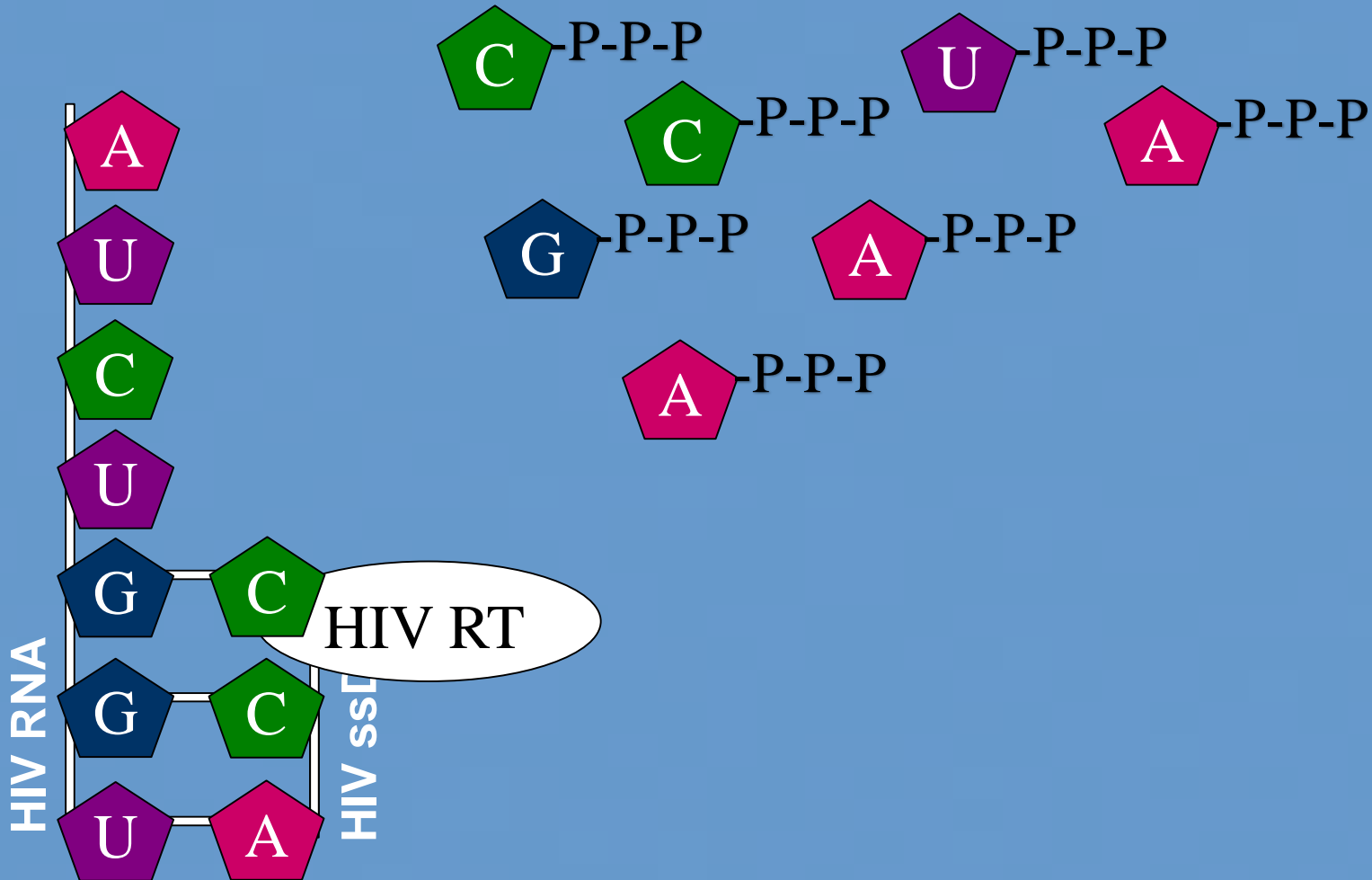


PK Principles: Effective Concentrations



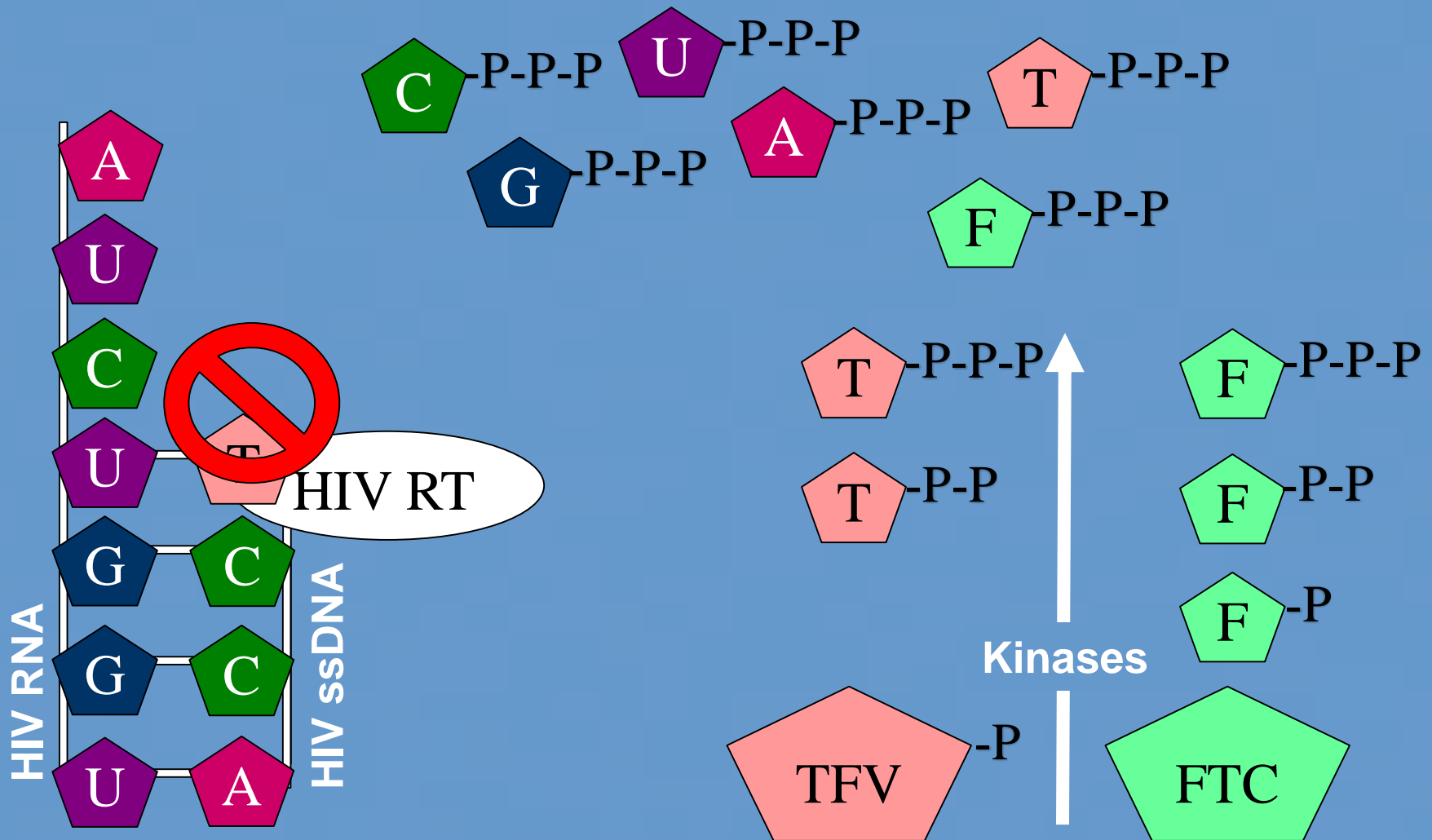
TDF/FTC PrEP Mechanism of Action

Host Endogenous Nucleotide Pool



TDF/FTC PrEP Mechanism of Action

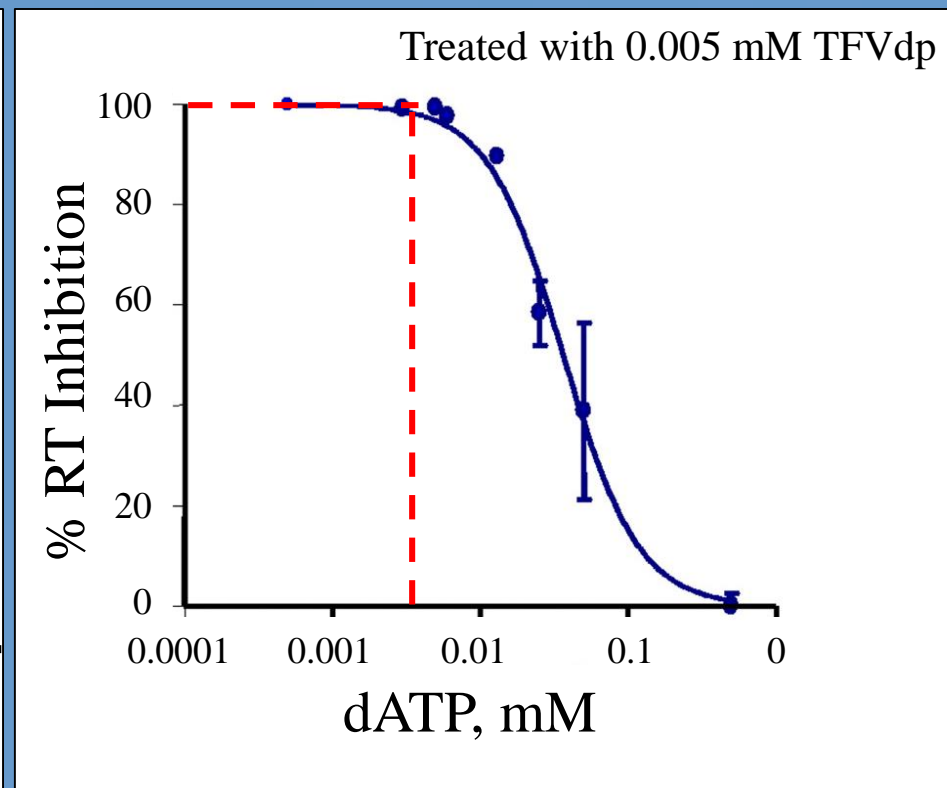
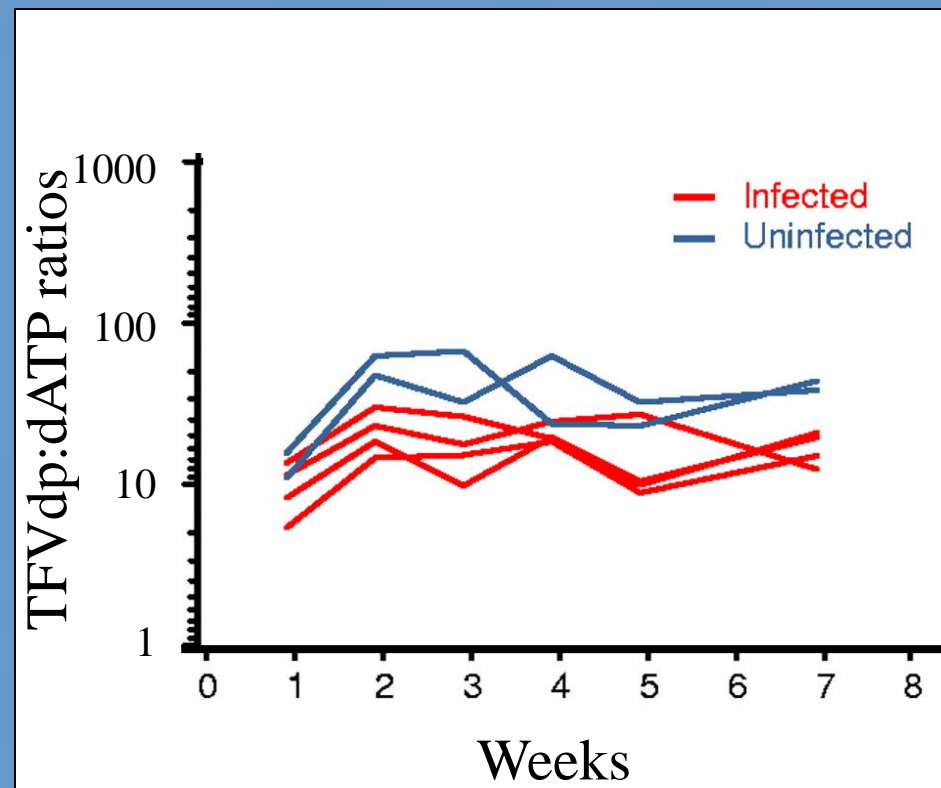
Host Endogenous Nucleotide Pool



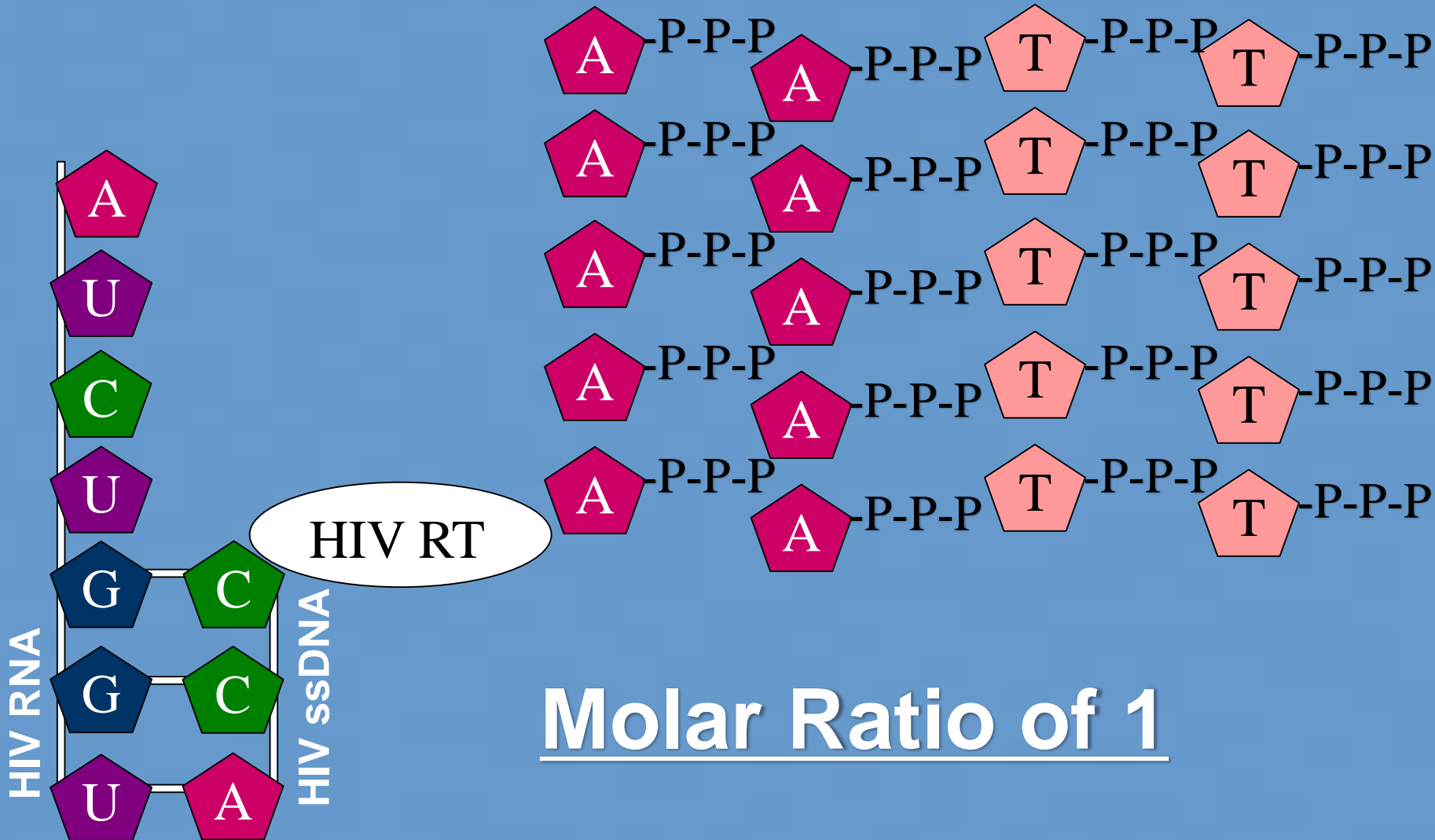
Endogenous Substrates Affect NRTI Potency

Lower TFVdp:dATP associated with infection in 4/6 macaques dosed with tenofovir PrEP

Molar TFVdp:dATP ratio of ≥ 1 associated with 100% reverse transcriptase inhibition



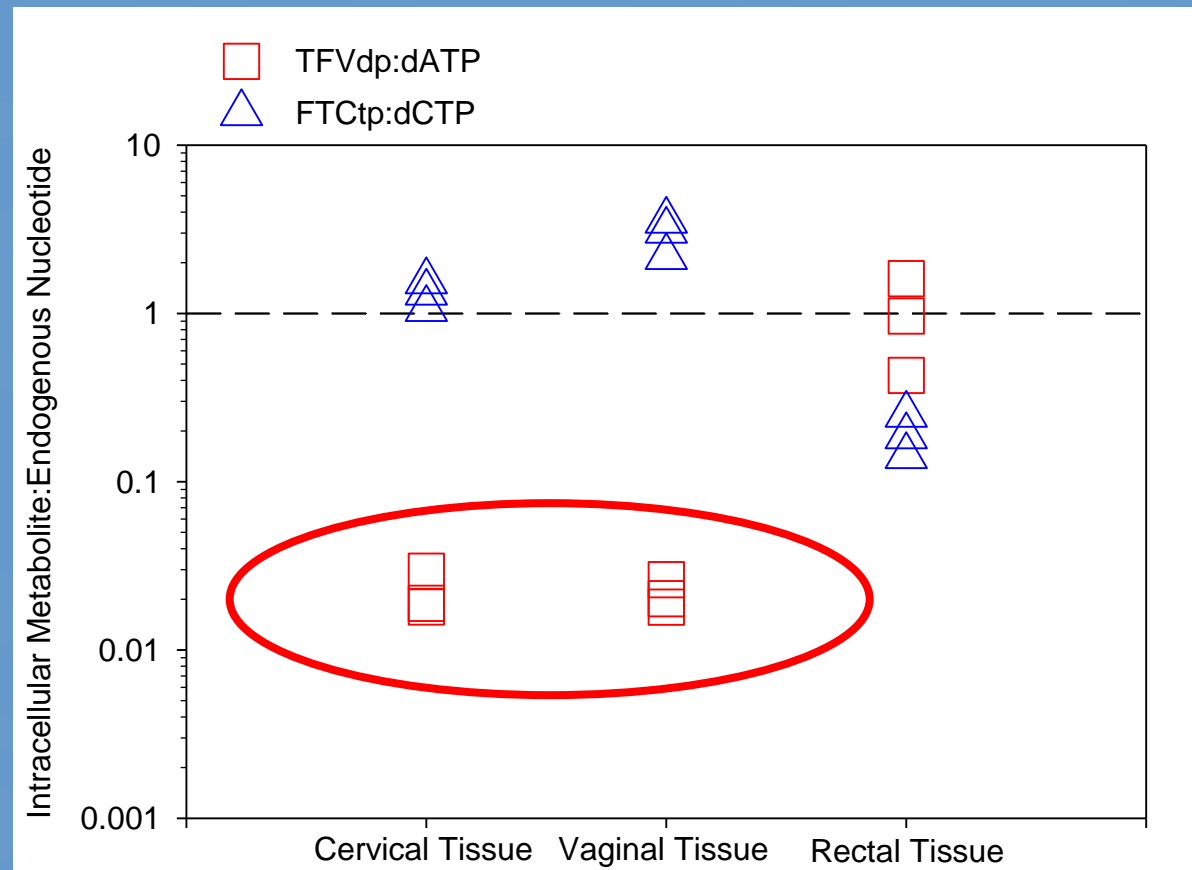
Intracellular Metabolite:Endogenous Nucleotide as an Efficacy Target



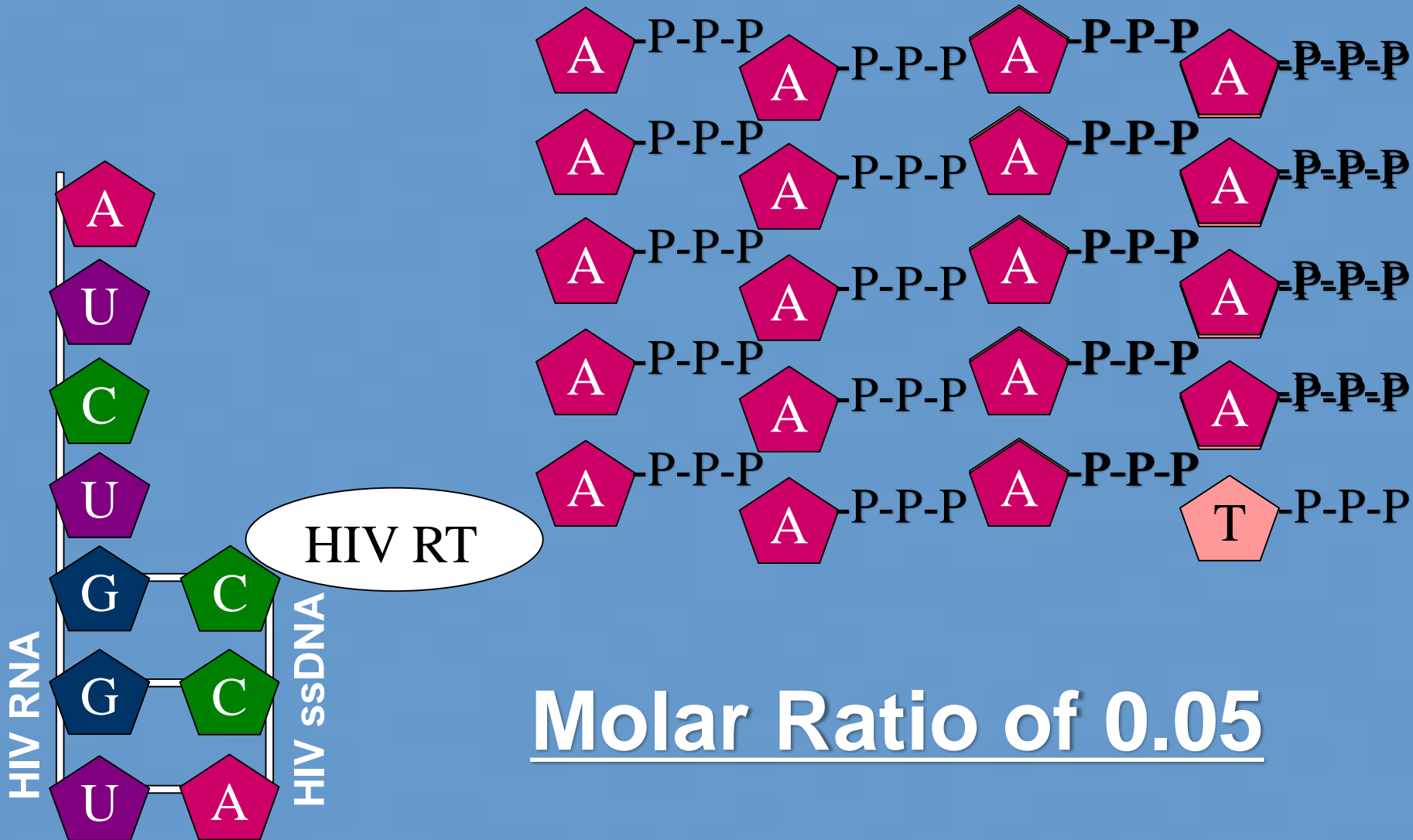
Ratios Differ Between Mucosal Tissues

Phase I Study Design

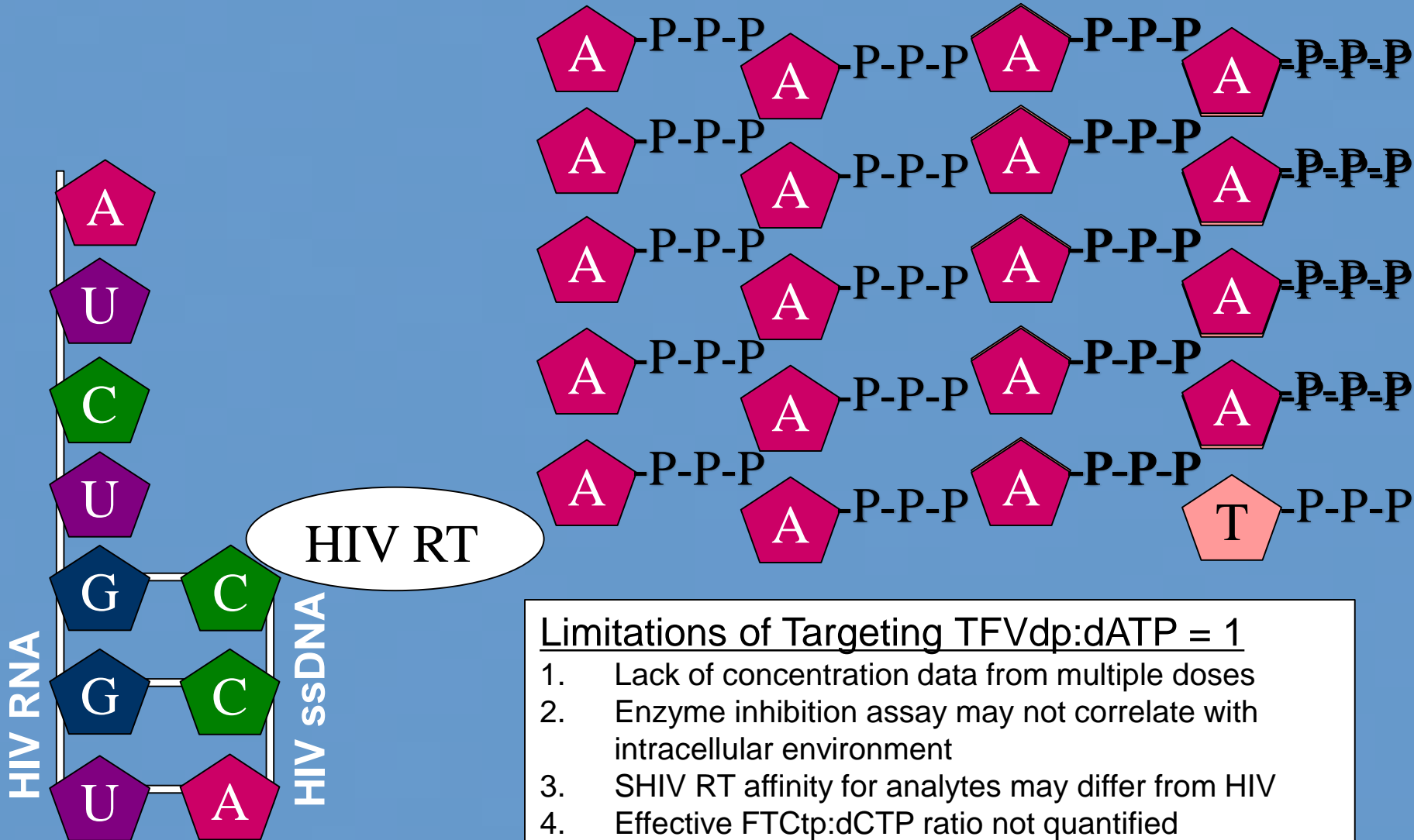
- 48 healthy female volunteers
- Single dose of either:
 - Tenofovir-DF 150, 300, 600mg
 - Emtricitabine 100, 200, 400mg
- Sample collection:
 - 12 blood plasma samples over 48 hours
 - Tissue at 6, 12, 24, OR 48 hours



Intracellular Metabolite:Endogenous Nucleotide as an Efficacy Target



Intracellular Metabolite:Endogenous Nucleotide as an Efficacy Target

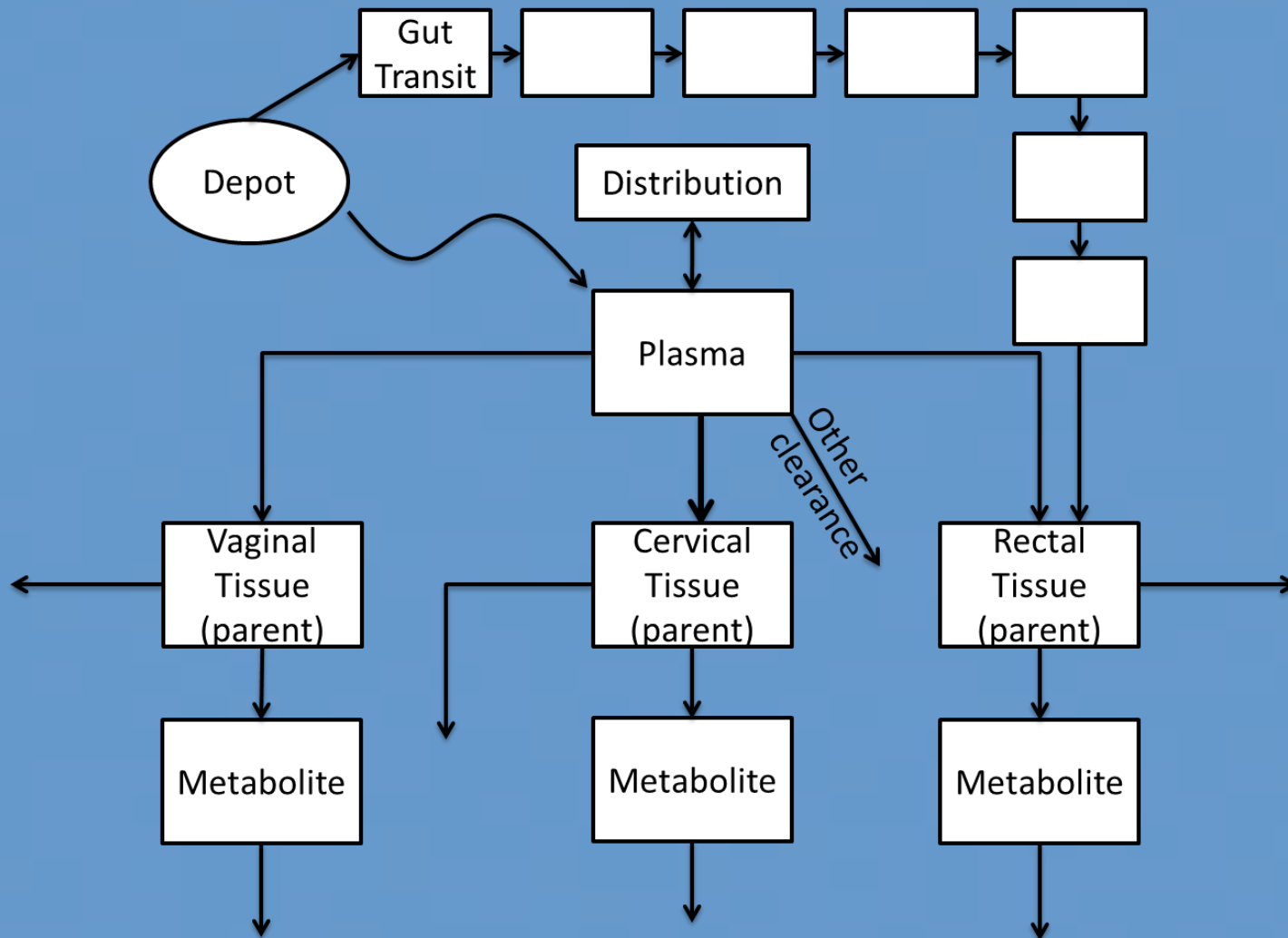


Limitations of Targeting TFVdp:dATP = 1

1. Lack of concentration data from multiple doses
2. Enzyme inhibition assay may not correlate with intracellular environment
3. SHIV RT affinity for analytes may differ from HIV
4. Effective FTCTp:dCTP ratio not quantified
5. Interaction between TFVdp and FTCTp not described

Modeling Population Pharmacokinetics

8 Compartment PK Model Describes Tissue PK

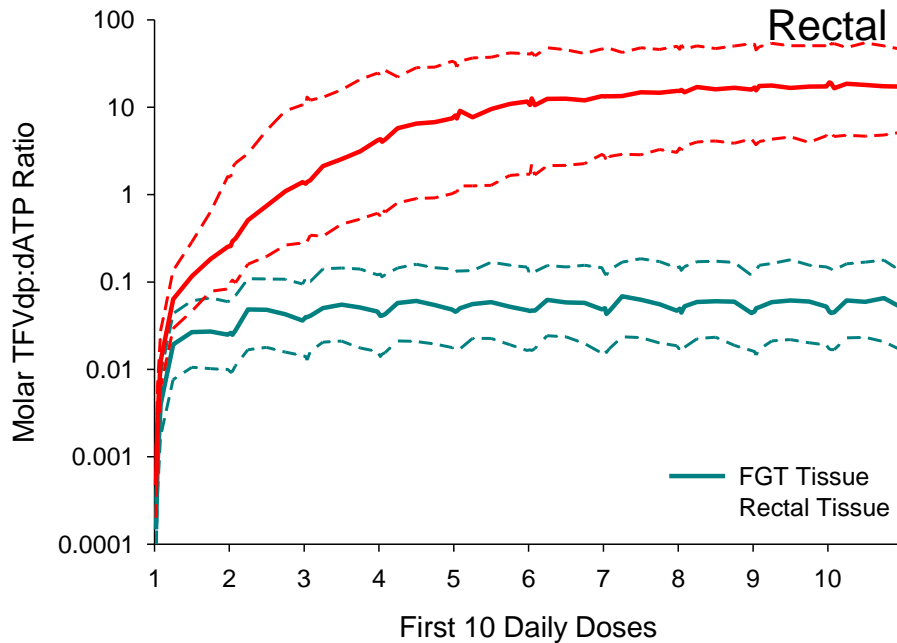


Modeling Population Pharmacokinetics

Simulated Mucosal Tissue Molar Ratios

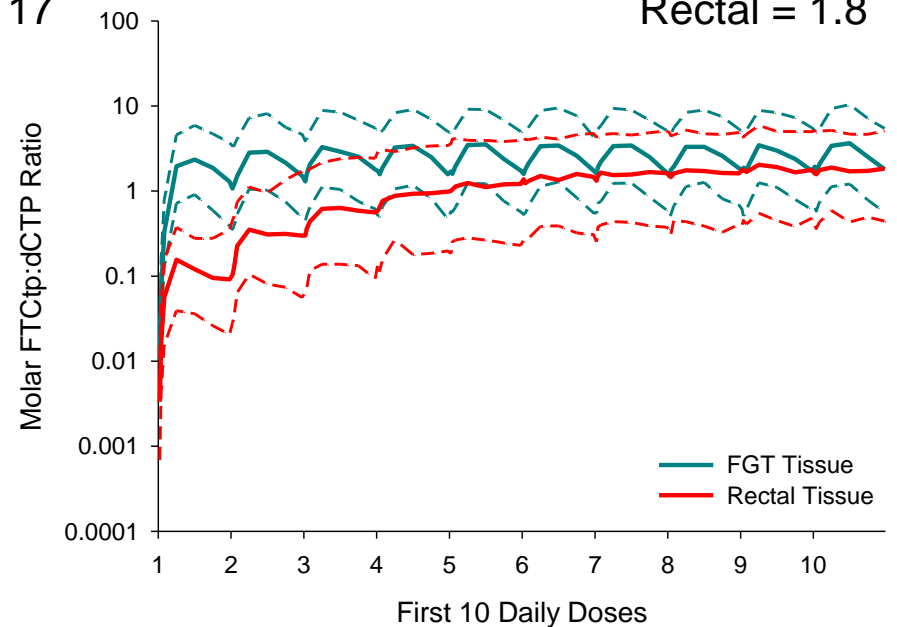
TFVdp:dATP

Trough SS Ratio
FGT = 0.051
Rectal = 17



FTCtp:dCTP

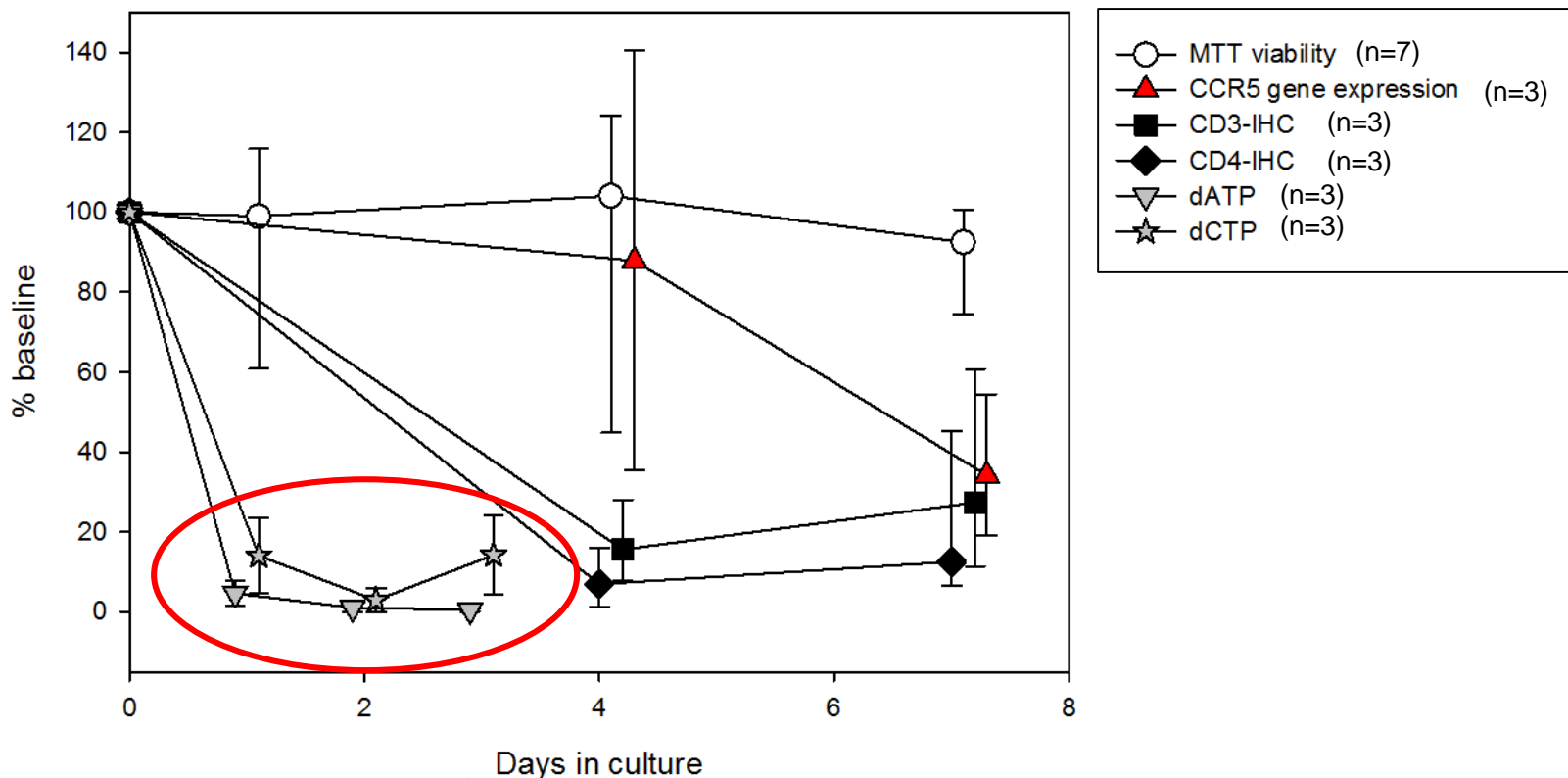
Trough SS Ratio
FGT = 1.8
Rectal = 1.8



Finding Efficacy Target for Prevention

Selecting the Right *In Vitro* Model

Altered Microenvironment in Cultured Tissue Explants

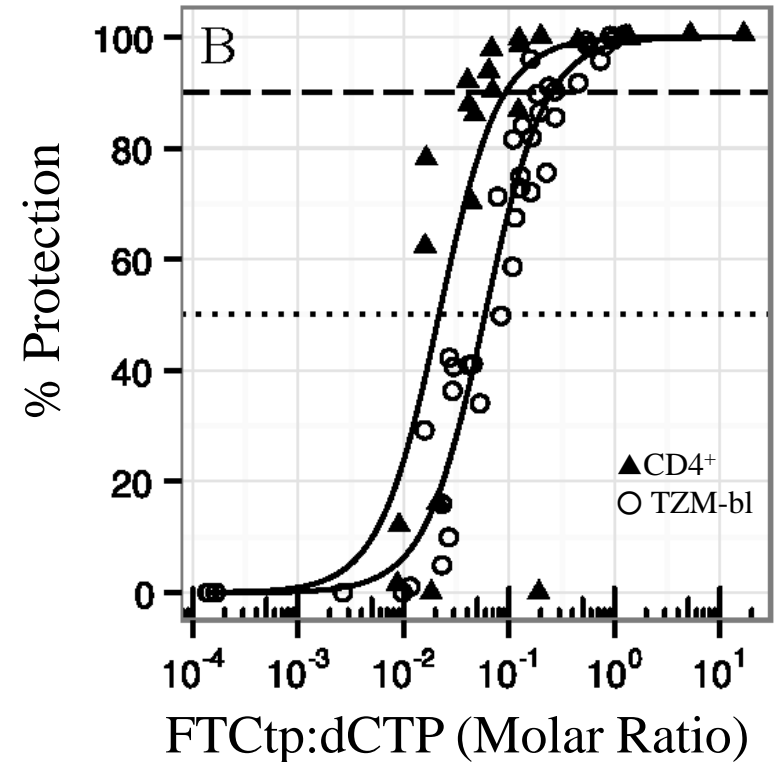
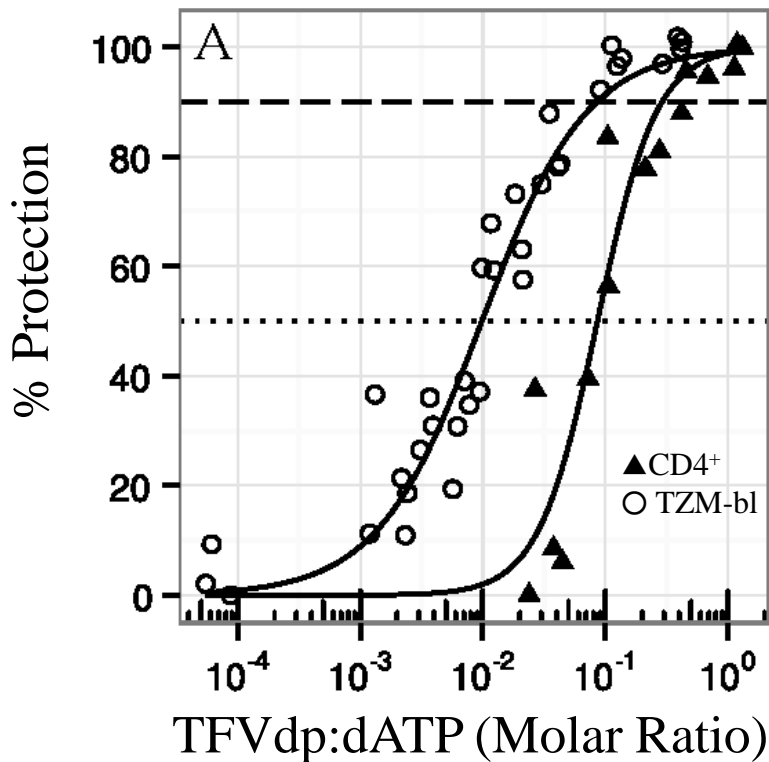


Finding Efficacy Target for Prevention

In vitro Exposure vs Response Model

Cell	EC50 (\pm SE)	Hill (\pm SE)	EC90
TZM-bl	0.01 (\pm 0.001)	1.02 (\pm 0.11)	0.086
CD4 ⁺	0.086 (\pm 0.011)	1.81 (\pm 0.39)	0.29

Cell	EC50 (\pm SE)	Hill (\pm SE)	EC90
TZM-bl	0.059 (\pm 0.004)	1.42 (\pm 0.11)	0.27
CD4 ⁺	0.022 (\pm 0.005)	1.86 (\pm 0.67)	0.07



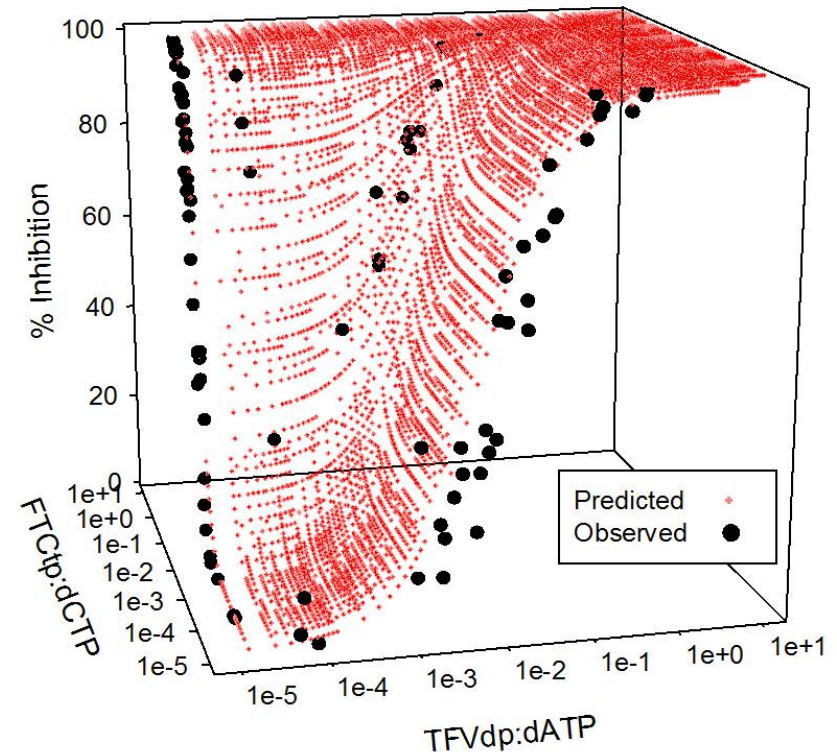
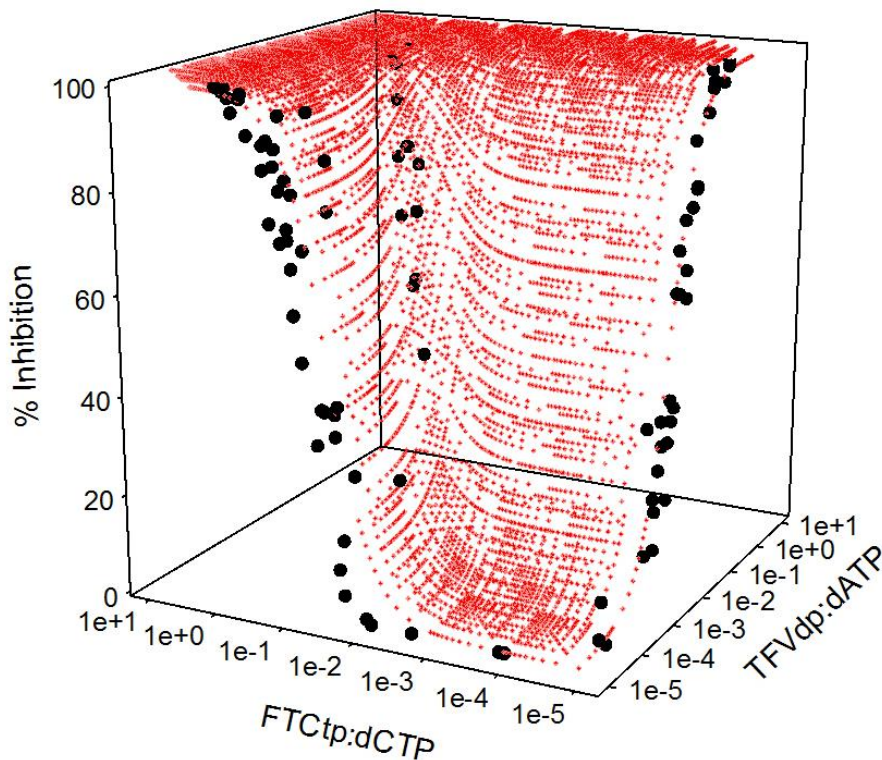
Modeling Additivity/Synergy

In vitro TFVdp:dATP/FTCtp:dCTP Interaction Model

$$E = \frac{\frac{TFV}{\psi \times EC_{50,TFV}}^{Y_{TFV}} + \frac{FTC}{\psi \times EC_{50,FTC}}^{Y_{FTC}} + (1) \times \frac{TFV}{\psi \times EC_{50,TFV}}^{Y_{TFV}} \times \frac{FTC}{\psi \times EC_{50,FTC}}^{Y_{FTC}}}{1 + \frac{TFV}{\psi \times EC_{50,TFV}}^{Y_{TFV}} + \frac{FTC}{\psi \times EC_{50,FTC}}^{Y_{FTC}} + \frac{TFV}{\psi \times EC_{50,TFV}}^{Y_{TFV}} \times \frac{FTC}{\psi \times EC_{50,FTC}}^{Y_{FTC}}}$$

Chakraborty A and Jusko W. J Pharm Sci. 2002;91(5):1334-1342.

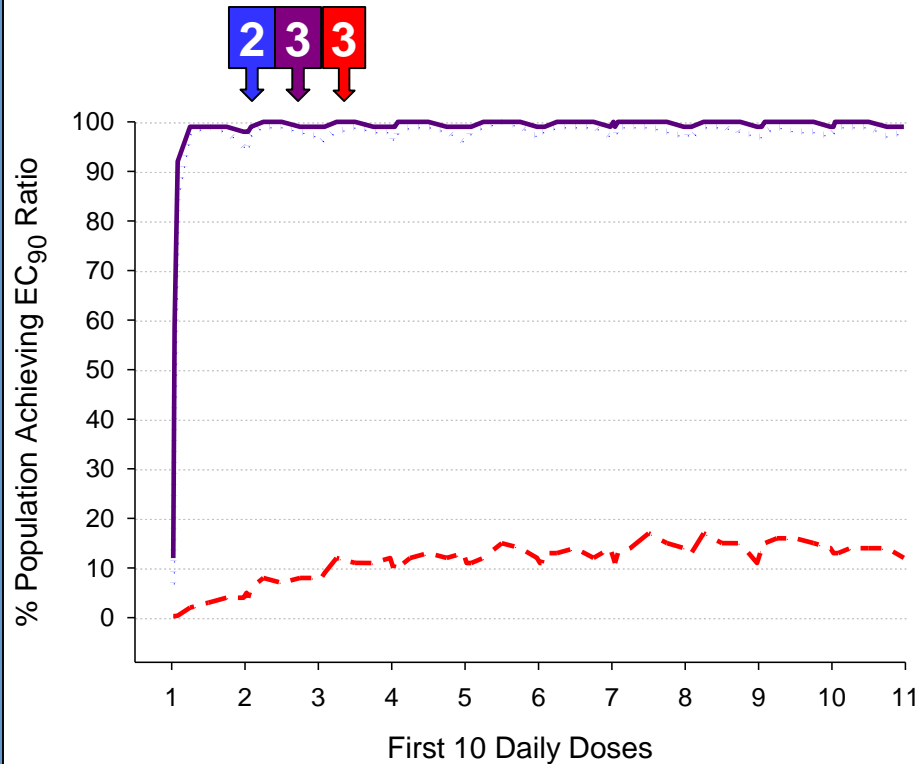
$\Psi=0.632 (\pm 0.074; p<0.001)$



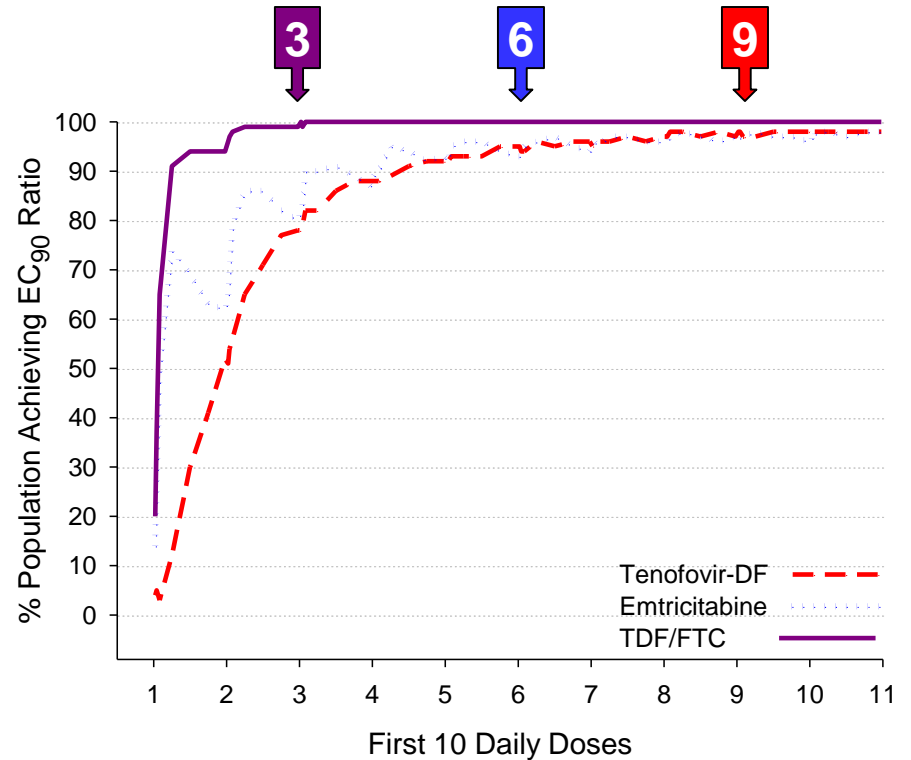
Making PK-PD Predictions

First 10 Daily Doses

Lower FGT Tissue



Rectal Tissue

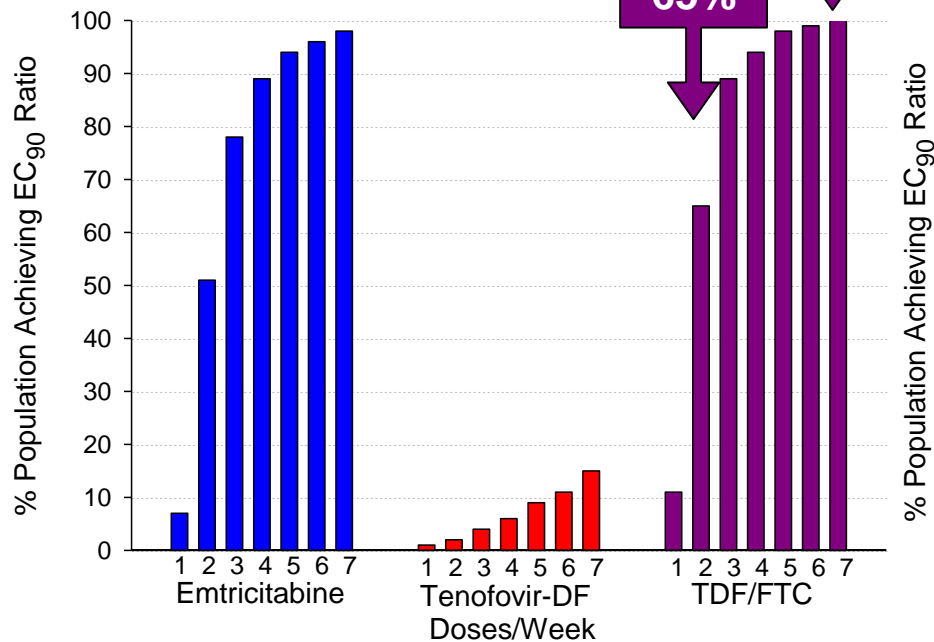


Model Parameters: TFVdp:dATP EC90=0.29; FTCtp:dCTP EC90=0.07; $\Psi = 0.632$

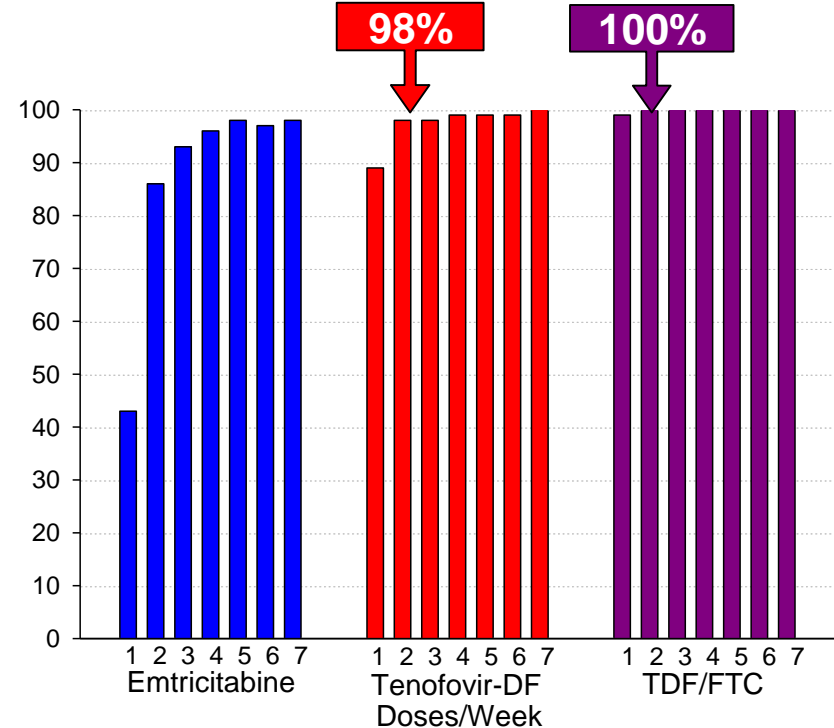
Making PK-PD Predictions

Scenarios of Imperfect Adherence

Lower FGT Tissue



Rectal Tissue



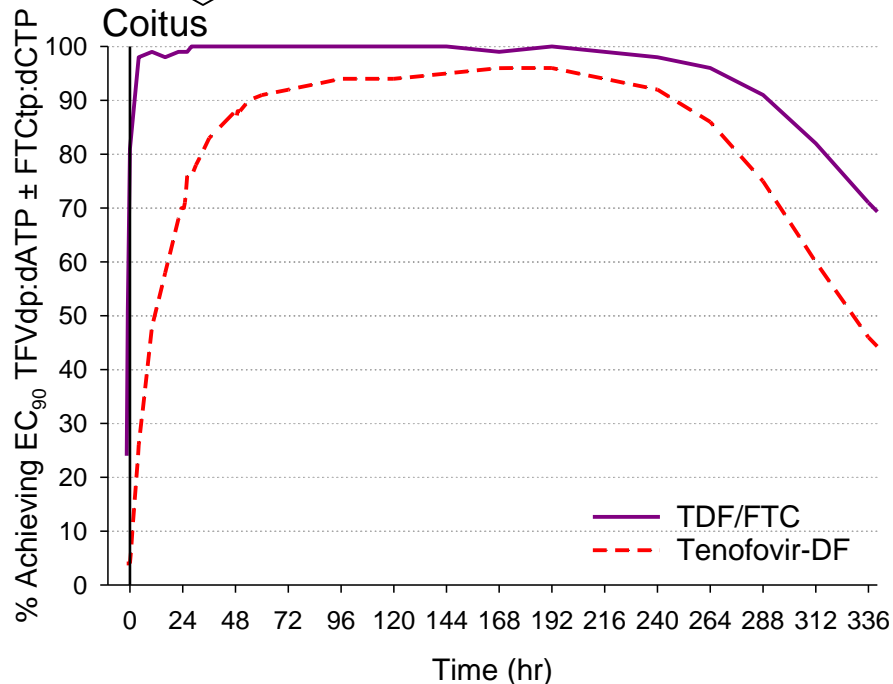
Model Parameters: TFVdp:dATP EC₉₀=0.29; FTCtp:dCTP EC₉₀=0.07; $\Psi = 0.632$

Making PK-PD Predictions

Pericoital Dosing

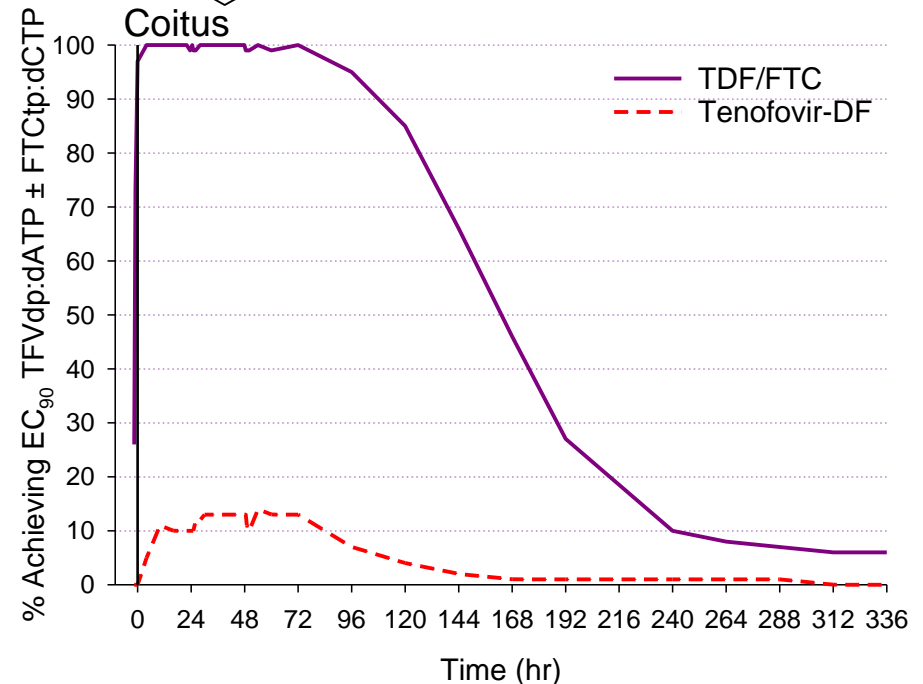
Rectal Tissue

-24 to -2hrs Take #2 Tabs
Coitus
24hrs Take #1 Tab
48hrs Take #1 Tab



Lower FGT Tissue

-24 to -2hrs Take #2 Tabs
Coitus
24hrs Take #1 Tab
48hrs Take #1 Tab



Model Parameters: TFVdp:dATP EC_{90} =0.29; FTCtp:dCTP EC_{90} =0.07; Ψ =0.632

Conclusions

- **Time to Protection**
 - Steady State achieved by 5-7 days in rectal cells from Cell PrEP Study and within ~1-7 days in cervical cells but data less conclusive
 - PK/PD Model predicts effective exposure achieved by third dose of TDF/FTC in both female genital and lower gastrointestinal tract tissues
- **Minimal Required Adherence**
 - 100% Adherence (Daily TDF/FTC): 100% at target in both female genital and lower gastrointestinal tract tissues
 - 30% Adherence (~Twice weekly TDF/FTC): 65% vs 100% at target in female genital and lower gastrointestinal tract, respectively
- When pharmacokinetics and pharmacodynamics are characterized drug dosing strategies can be efficiently explored in silico, along with estimates of efficacy prior to Phase III studies.

Acknowledgements



UNC CFAR Clinical Pharmacology and Analytical Chemistry Core Members

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Nicholas J Shaheen, MD
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