Pharmacokinetics in Microbicide Development

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Objectives

How does PK inform microbicide development?

- Describe, Explain, Predict Concentration-Response
- Give examples through
  - Concentration-time-distance relationships (PK)
  - Concentration-response relationship (PK/PD)
  - Regimen selection
  - Clinical trial interpretation
  - Clinical trial simulation
- Identify optimized PK study design approaches to microbicide development

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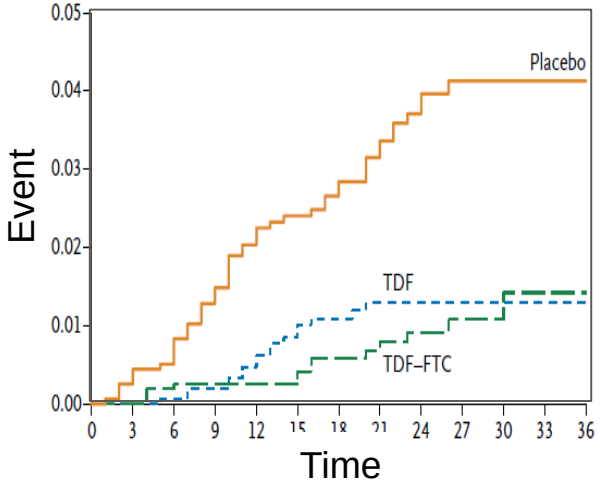
Sample Handling & Analyte Quantitation

- Development of assay begins with plasma
- Validation per FDA Bioassay Guidance
  - Precision & accuracy
  - Stability benchtop, e.g., maraviroc tissue
  - Stability freezer
  - Stability post-freezer, e.g., TFV-DP tissue
- All biological matrices require separate validation
- All collection devices require separate validation

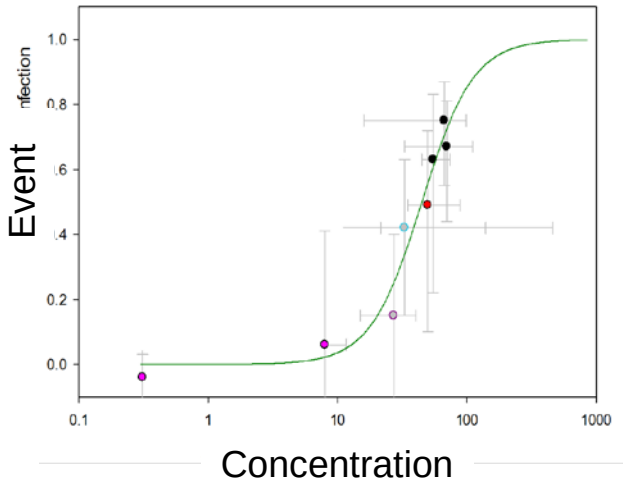
What's the goal of PK-PD Studies?

Relating Conc'n, Distance, Time, & Outcome

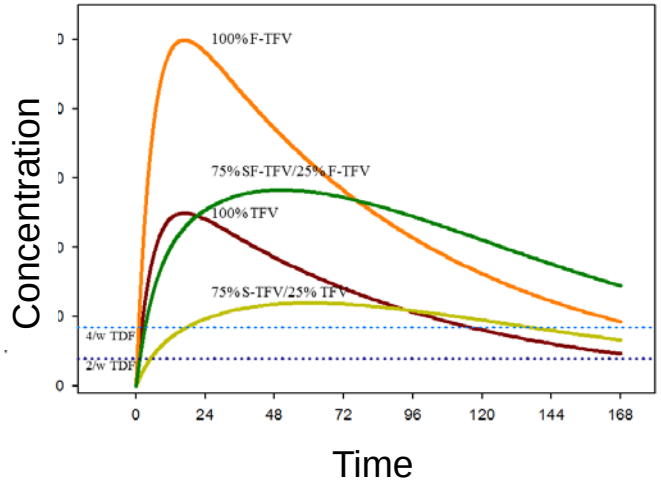
Survival Analysis
event v. time



Pharmacodynamics
event v. concentration



Pharmacokinetics
concentration v. time



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

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

$$C_e = \frac{D \cdot k_{1e}}{V_c \cdot (k_{e0} - k_e)} (e^{-k_e t} - e^{-k_{e_0} t})$$

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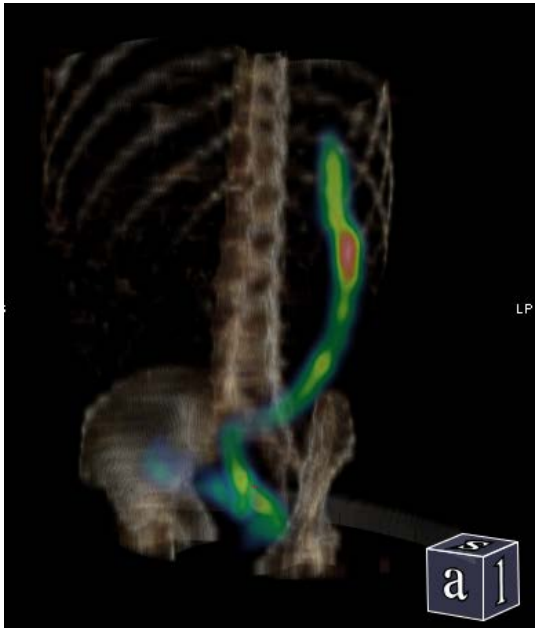
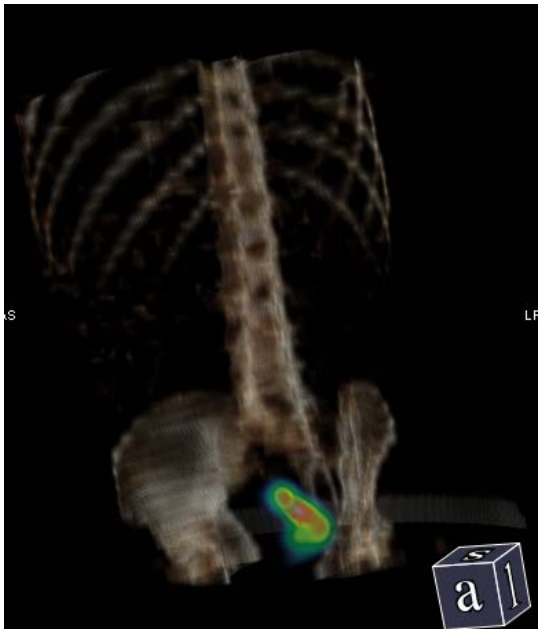
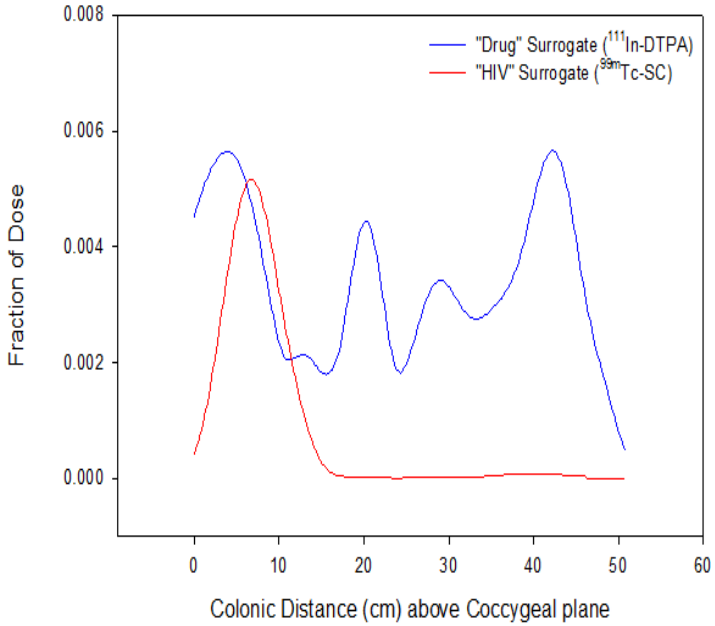
Luminal Distribution

Does rectal gel adequately cover “HIV”?

“Microbicide”(^{111}In-DTPA) “HIV” (^{99m}Tc-SC) in Ejaculate Relative surrogate Distribution







Rectal TFV gel (0h), simulated sex/ejaculation (1h), SPECT/CT (2h)

- PK-distance parameters indicate “HIV” surrogate within “microbicide” luminal distribution
- Voxel-by-voxel “HIV” covered by “microbicide” 86% (SD 0.19)
- Guides sampling sites for colon biopsies

CHARM 02 (Hiruy, et al. ARHR 2015)

Luminal Distribution

Which rectal formulation covers best?

Study	CDC Imaging*	P5-Aim 2**	P5-Aim 2**	P5-Aim 1***
Formulation	gel	gel	fluid	enema
Volume	10 mL	10 mL	10 mL	125 mL
Osmolality	hyper-osmolar	iso-osmolar	iso-osmolar	iso-osmolar
Post-dose	4h	4h	4h	4h
D_{max}	14.0 (9.0–63)	12.9 (11.6, 20)	23.1 (14.9, 25.1)	38.6 (23.8–41.7)
DC_{max}	6.0 (2.0–14)	5.1 (2.0, 8.3)	5.3 (3.3, 7.2)	17.5 (8.2–24.1)
D_{ave}	6.7 (3.2–29)	6.4 (4.7, 7.5)	6.8 (4.7, 10.2)	19.6 (9.8–23.6)
D_{min}	-	-2.6 (-3.5, 0.8)	-3.8 (-3.8, -3.5)	2.0 (−1.3–3.4)

median and range for CDC Imaging (BJCP 2012), IQR for all others.
D_{max}, greatest proximal distance at which radiolabel is detected
DC_{max}, distance at which greatest radiolabel concentration is detected
D_{ave}, mean residence distance (similar to mean residence time)
D_{min}, most distal location of radiolabel
All distances are relative to coccyx

Rectal HIV ~10-15 cm (relative to coccyx)

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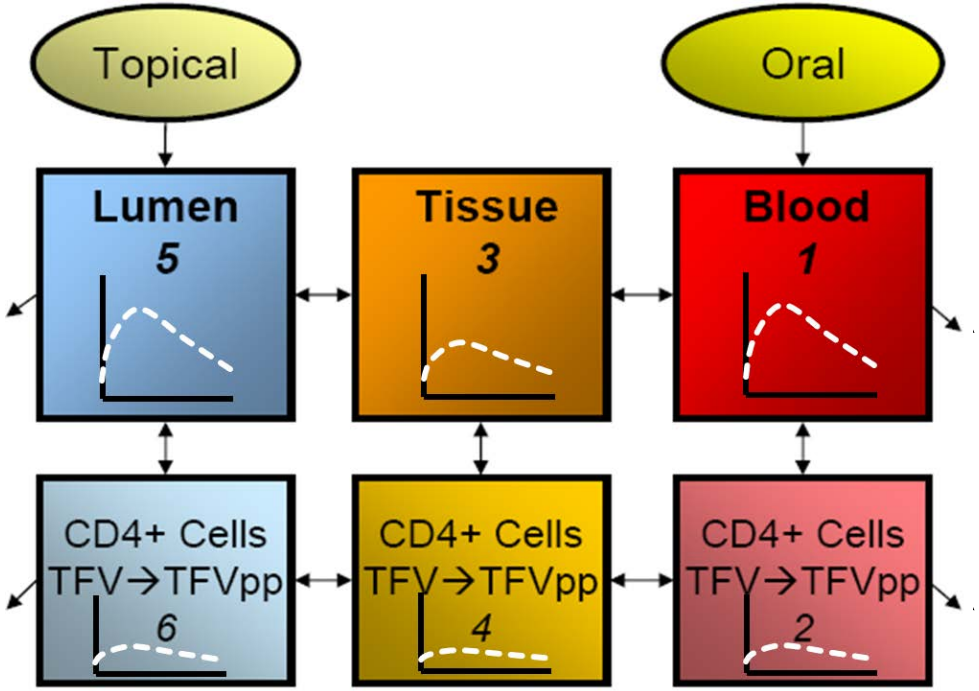
*Cao, et al BR J Clin Pharm 2012; **MDP Aim 2/2b Leyva, et al. ARHR 2015; ***MDP-Aim 1 Leyva, et al., ARHR 2013

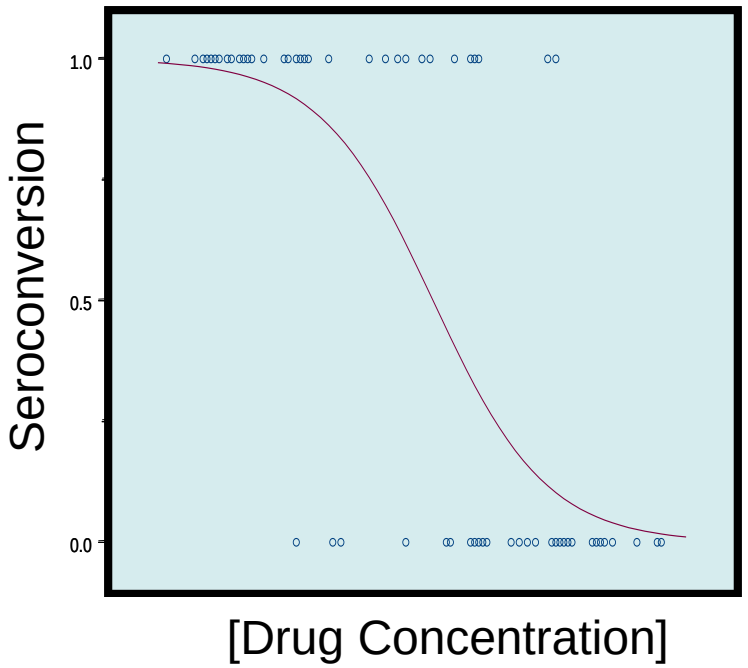
3-D Pharmacology

Where & when should PK sampling occur?

Pharmacokinetics (PK)

Pharmacodynamics (PD)





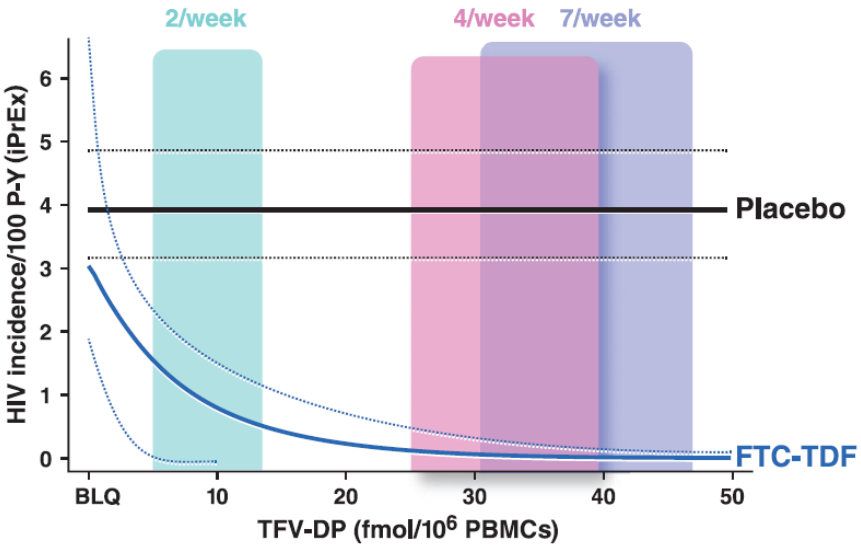
Pharmacokinetic – Pharmacodynamic Link

Doesn't have to be active drug @ site of action, it only has to be informative

Concentration-Response

What are target tissue concentrations?

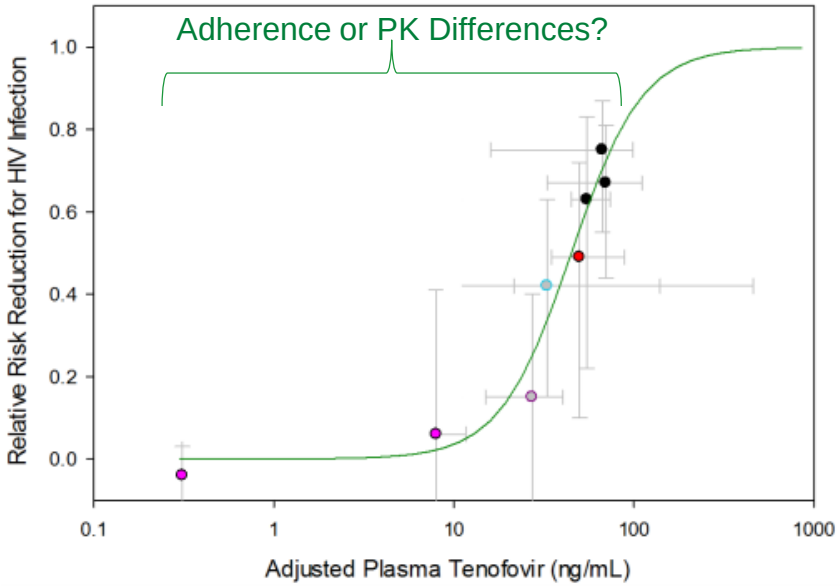
Within Study: iPrEx



Controlling for covariates
IC_{90} 16 fmol/10^6 PBMC

Anderson, *et al*., Sci Trans Med 2012

Among Studies



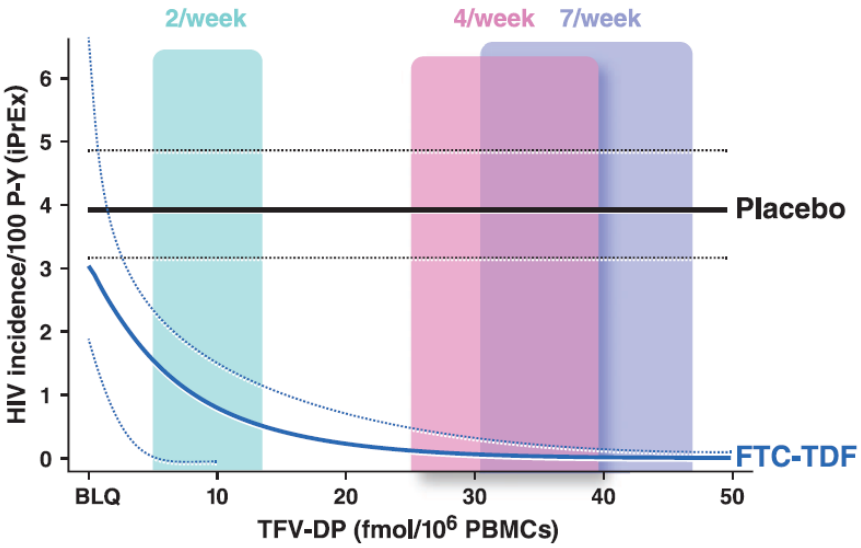
Parameter	Estimate	CV%
E_{max}	0.94	44
EC_{50}	43	44
EC_{90}	107	44
Gamma	2.4	56

Hendrix, Cell 2013

Concentration-Response

What are target tissue concentrations?

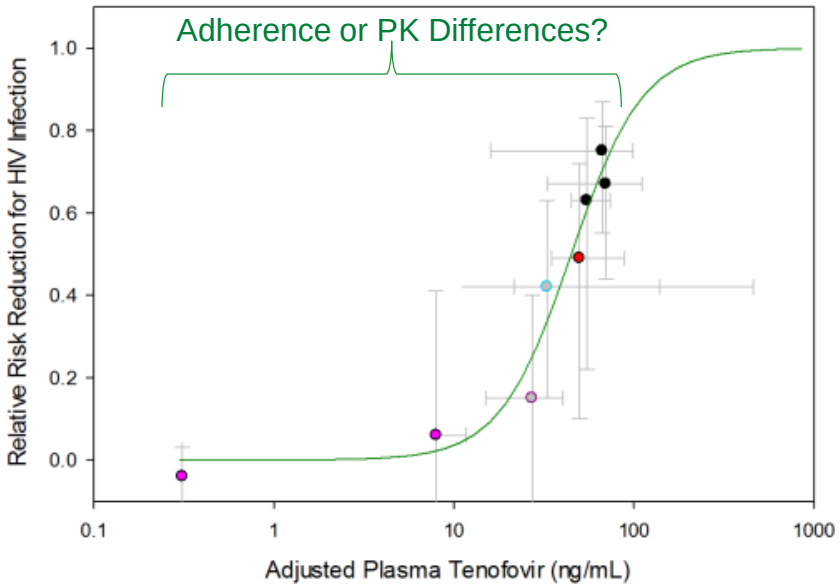
Within Study: iPrEx



***EC*$_{90}$** PBMC TFV-DP 16 fmol/10^6 cells =>
4 doses per week adherence =>
Css TFV-DP PBMC/MMC 4.4 oral 300mg TDF =>
Target *83 fmol/10^6 Colon MMC*

HPTN 066 (Hendrix, *et al*., ARHR 2015)

Among Studies

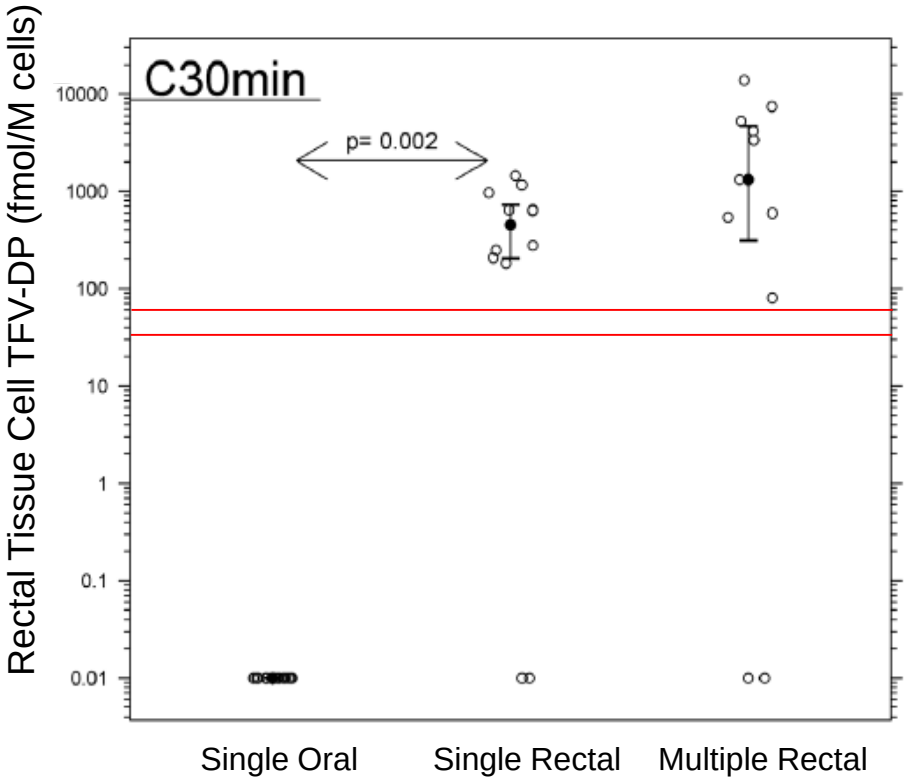


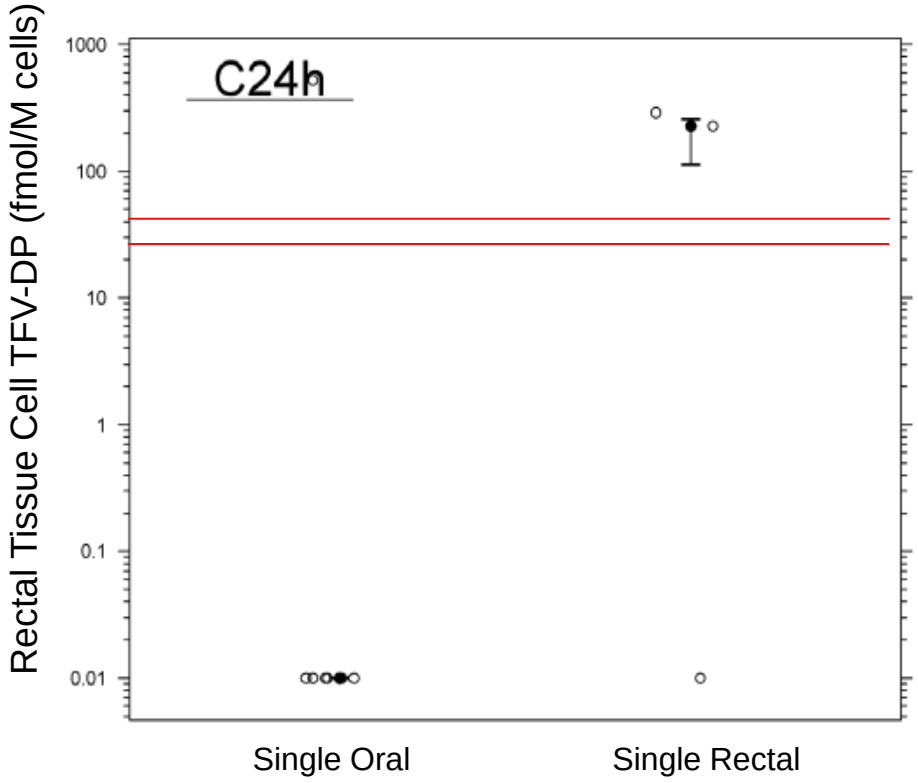
***EC*$_{90}$** Plasma TFV 107 ng/mL =>
Daily adherence =>
Css TFV 1% vaginal dose=>
Target *2,000 fmol/mg tissue homogenate*

MTN-001 (Hendrix, *et al*. PLOS One 2013)

RMP-02/MTN-006

How soon does protection occur?





RMP-02/MTN-006 Yang, et al. PLOS One 2014

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^{14}C-TDF Study

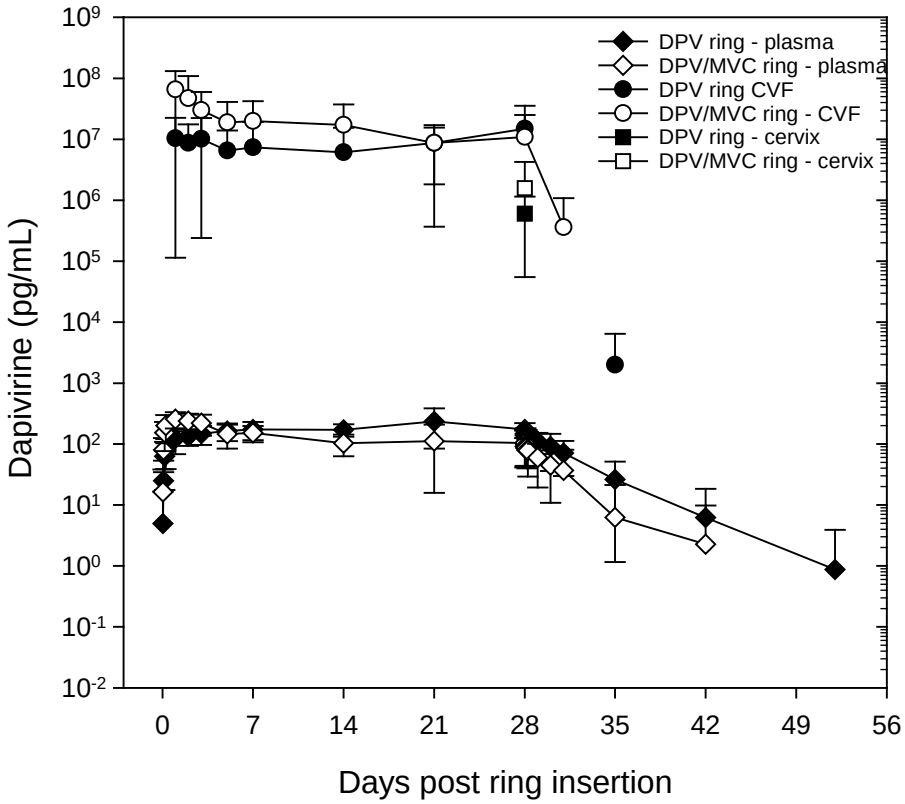
How long does protection last?

^{14}C-TDF Single Dose Study

Location	Moiety	Half-life*	
Plasma	TFV	69	(55, 77)
PBMC	TFV-DP	48	(38, 76)
Blood CD4+ Cells	TFV-DP	112	(100, 118)
VT	TFV	47	(38, 53)
VT	TFV-DP	53	(45, 68)
VT Total Cells	TFV-DP	66	(43, 202)
VT CD4+ Cells	TFV-DP	139	(121, 167)
CVL**	TFV	40	(38, 43)
CVL Cells	TFV-DP	-	
CT	TFV	31	(24, 36)
CT	TFV-DP	34	(21, 40)
CT Total Cells	TFV-DP	82	(43, 89)
CT CD4+ Cells	TFV-DP	60	(52, 72)
Colon Brush	TFV	20	(20, 21)

Louissaint, *et al*. ARHR 2013

MTN-013 Dapivirine Vaginal Ring Study

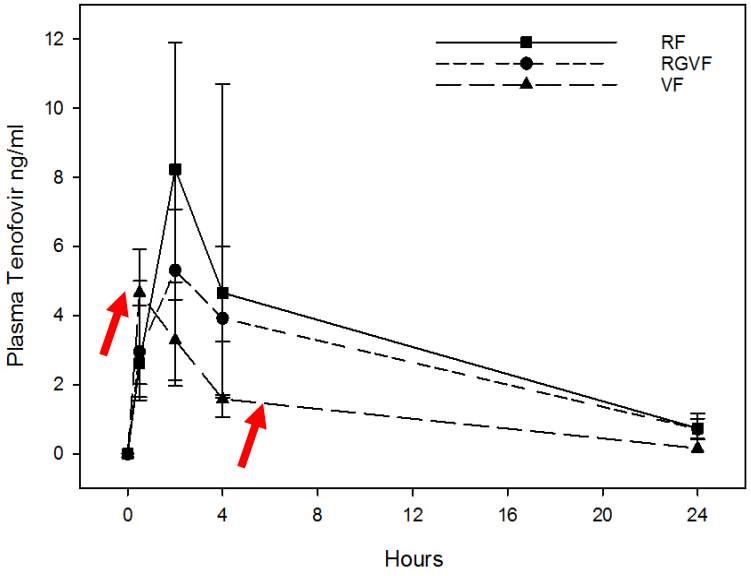


Chen, *et al*. JAIDS 2015

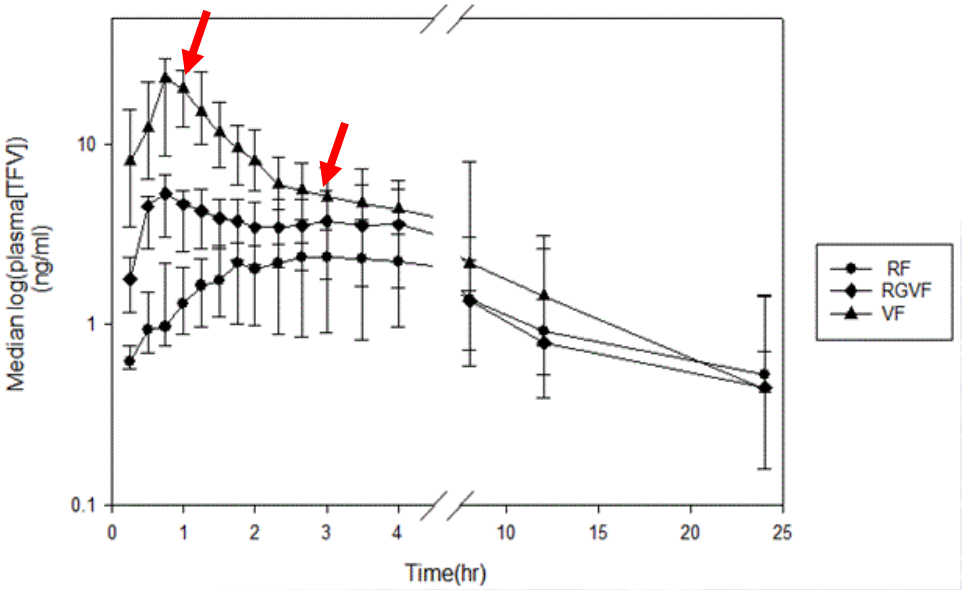
Sampling Frequency Impact

How to sample to estimate PK parameters?

CHARM 01



CHARM 02



PK	Units	RF TFV (CH02)	RGVF TFV (CH02)	VF TFV (CH02)	VF TFV (CH01)
C_{max}	ng/ml	4 (1, 5)	6 (5, 8)	23 (13, 31)	5 (3, 6)
AUC	ng*hr/ml	30 (15, 55)	39 (19, 57)	82 (49, 137)	36 (23, 57)

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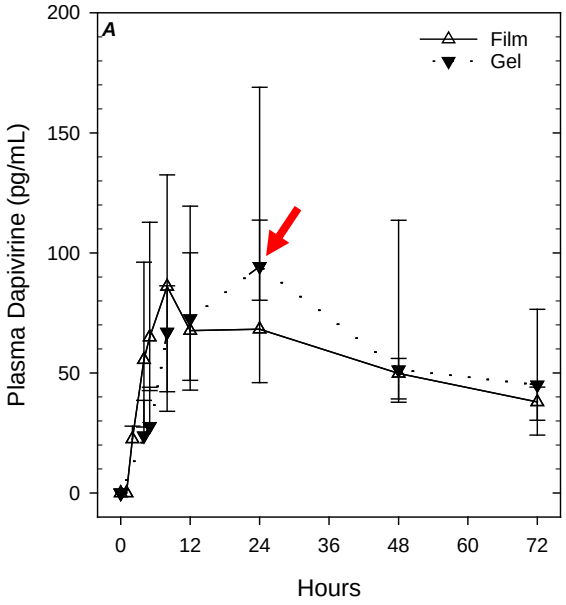
Sampling for PK-PD

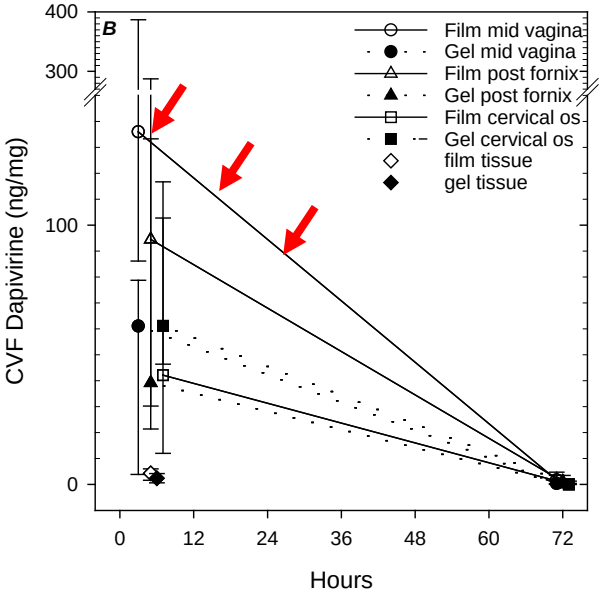
How to select sample times for PK-PD?

FAME 02b Single Dose DPV Gel v. Film Comparison

Plasma DPV (pg/mL)



CVF DPV (ng/mg)

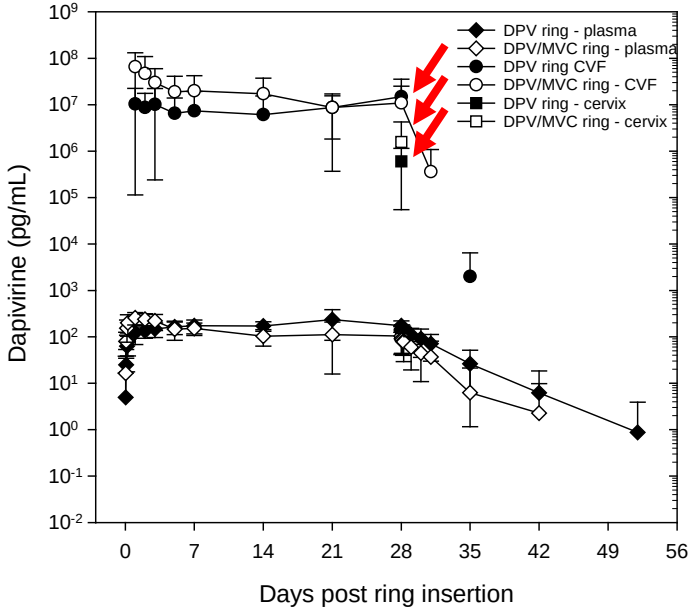


Plasma C_{max} relevant?

CVF & CT peak?

CVF & CT half-life?

MTN-013 DPV±MVC
28 day Vaginal Ring



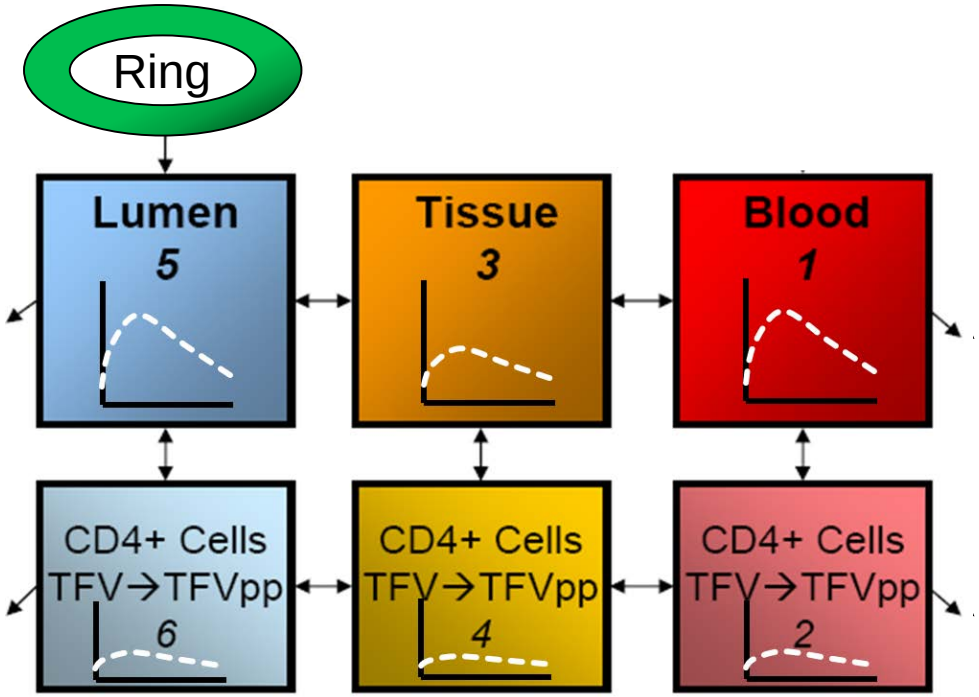
Plasma & CVF inform tissue

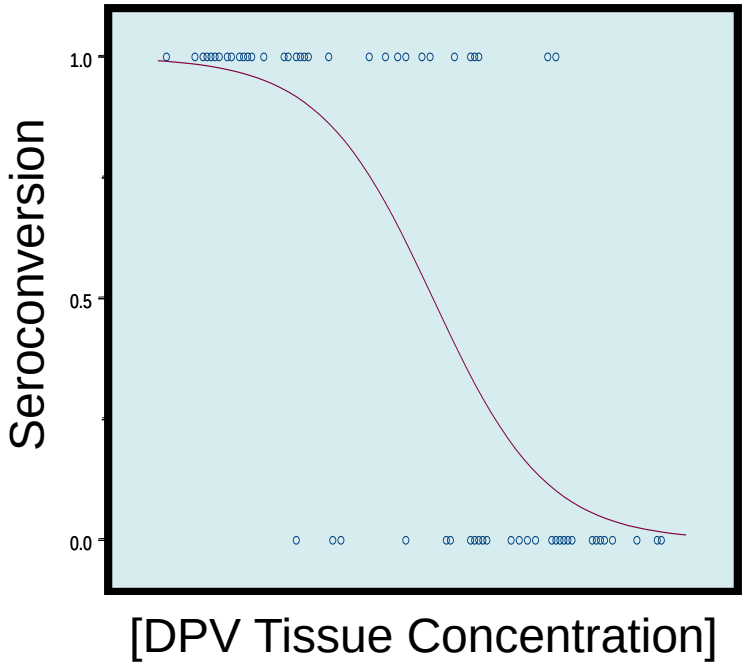
Estimating Unknowns

How to estimate [drug] without sampling?

Pharmacokinetics (PK)

Pharmacodynamics (PD)



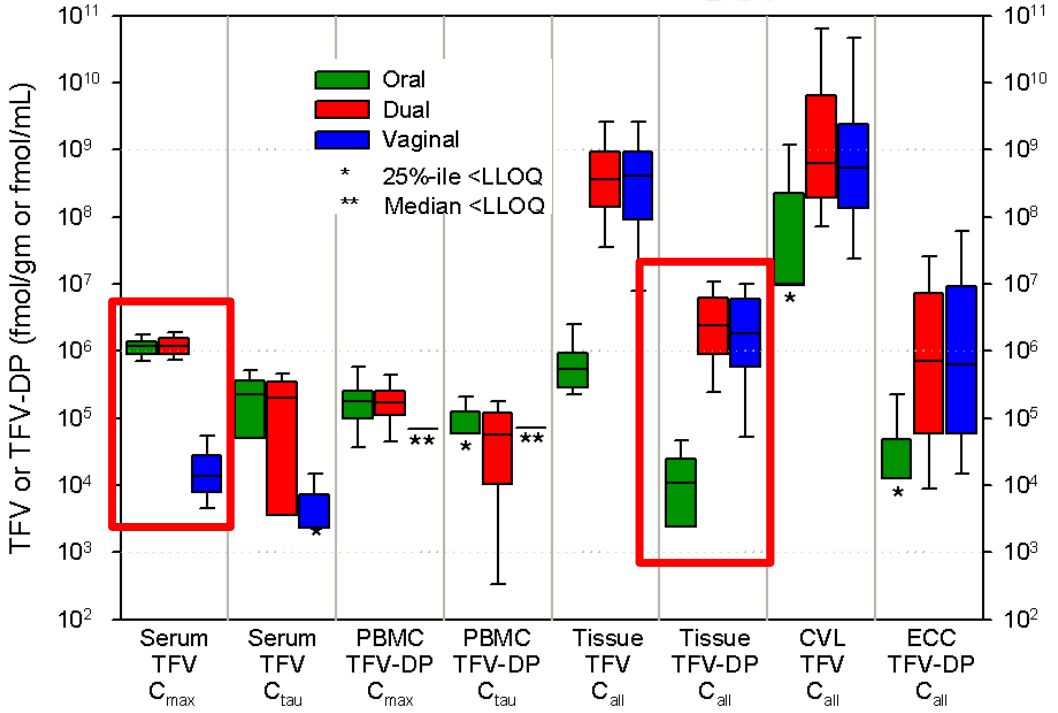


Pharmacokinetic – Pharmacodynamic Link

Doesn't have to be active drug @ site of action, it only has to be informative

MTN-001 PK Compartments
Describe or Predict?

- Tenofovir daily
- Oral, Vaginal, Dual
- Cross-over design
- 144 Women
- Africa, US
- 6-compartment PK

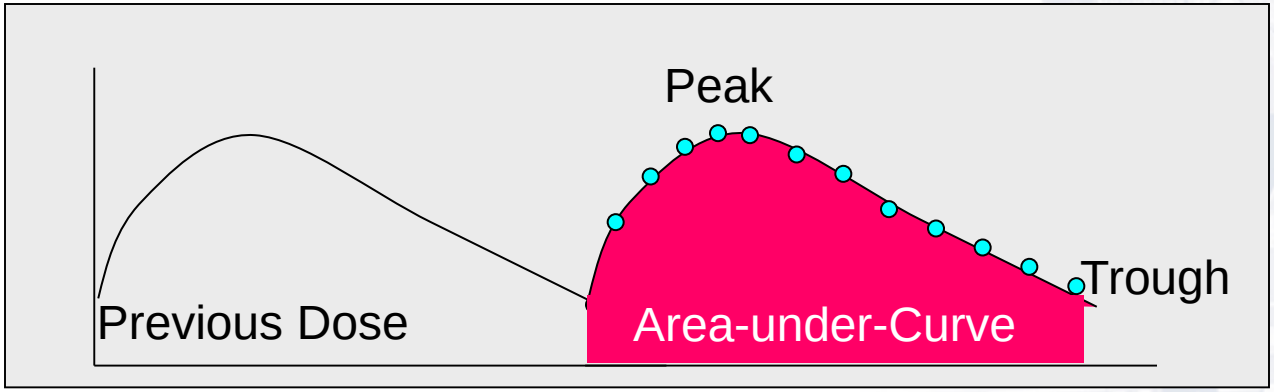


- *If tissue relevant: Expect vaginal >> oral efficacy*
- *If systemic relevant: Expect oral >> vaginal efficacy*
- *Vaginal tissue TFV-DP **Vaginal 130x > Oral** (topical tissue advantage)*
- *Serum TFV **Oral 56x >Vaginal** (serum doesn't reflect tissue)*
- *Rectal gel dosing shows similar trends*

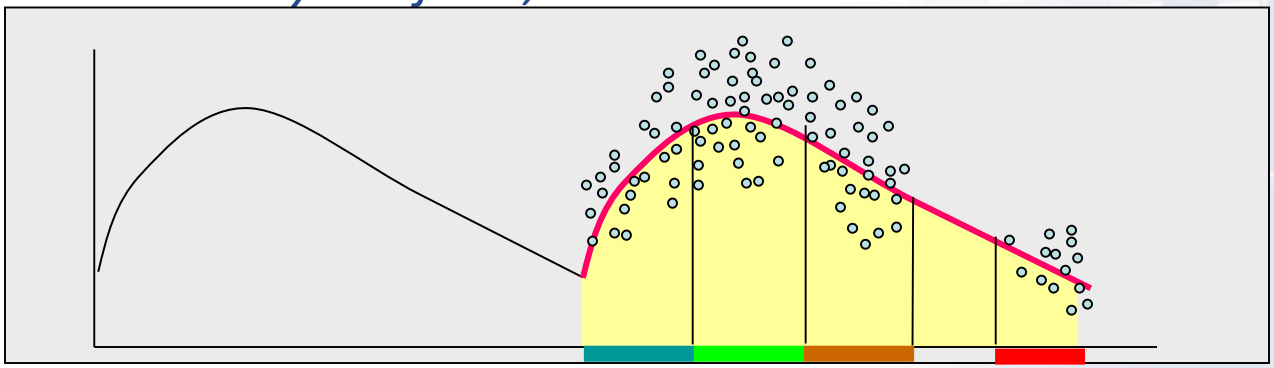
Hendrix, *et al. PLOS One 2013*

Sparse Sampling PK
PK Estimates w/o intensive sampling?

- Traditional Intensive PK Sampling
  - *Few Subjects, Many Times*



- Sparse Sampling (Population PK)
  - *Many Subjects, Few Times*



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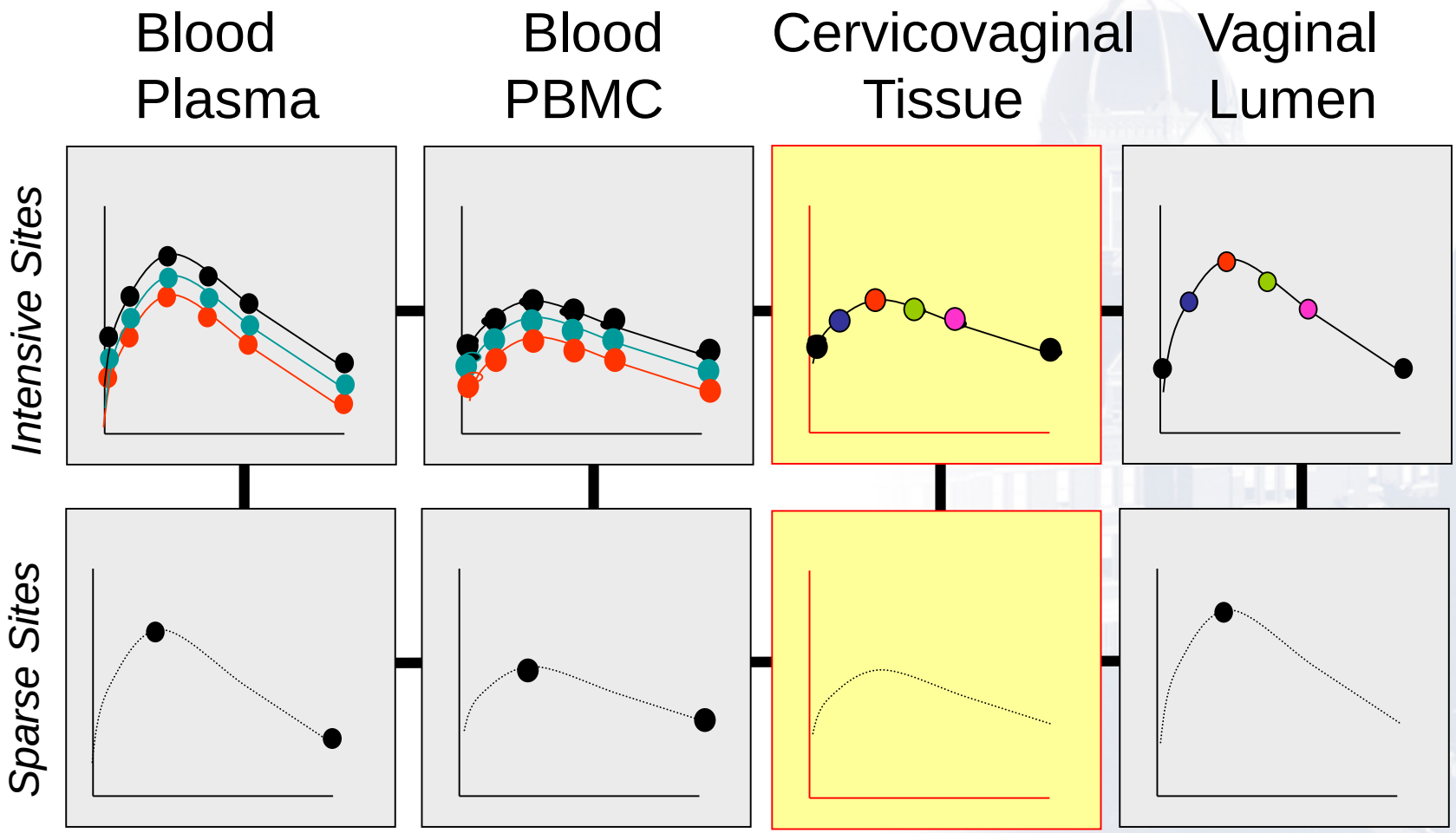
PK Model Building (MTN-001)

Maximizing data from mixed site capacity?



Initial estimates from HPTN 050

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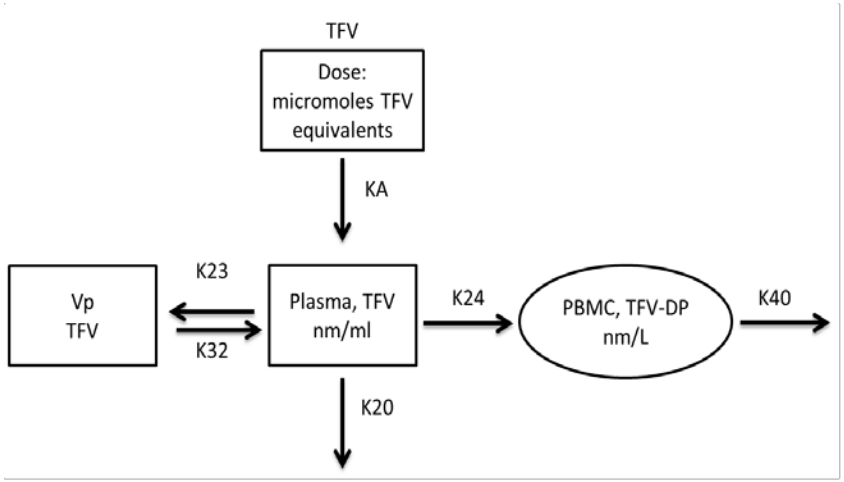
Population PK Modeling

How to describe individual PK within a pop'n?

- Sparsely sampling each subject
- Model PK parameters (CL, V_c, KA)



- Adjust for adherence
- Covariate effect on PK parameters
- Inter-subject & residual variability
- *Enables clinical trial simulation*

	Final Model	
Parameter	Value (%RSE)	Bootstrap Median (95%CI BSV, %CV) n = 2,000
Obj Func	2,575	
Condition #	179	
FI*	0.98 (0.015–4.17)	
KA (h^{-1})	9.79 (65.18)	10.21 (1.04–45.29)
V_c/F (L)	385.71 (14.84)	376.11 (28.5–475)
cov WT (kg) on V_c	−2.16 (34.52)	−1.78 (-3.37 to -0.16)
K23 (h^{-1})	0.631 (24.7)	0.680 (0.411–12.92)
K32 (h^{-1})	0.396 (23.24)	0.398 (0.238–0.848)
K20 (h^{-1})	0.13 (17.81)	0.14 (0.10–1.51)
K24 (h^{-1})	0.017 (72.48)	0.019 (0.009–0.537)
K40 (h^{-1})	0.013 (16.63)	0.014 (0.009–0.052)
Absorption lag (h)	0.5 (35.49)	0.5 (0.005–0.665)
BSV KA (%CV)	160.2 (169.1)	164.97 (1.60–271.83)
BSV V_c (%CV)	19.3 (45.1)	18.84 (0.19–29.11)
BSV K20 (%CV)	36.22 (33.99)	33.25 (12.09–51.68)
BSV K24 (%CV)	159.49 (69.95)	168.93 (57.51–616.05)
Proportional, TFV (%CV)	27.48 (5.24)	27.36 (22.95–31.71)
Proportional, TFV-DP (PBMC) (%CV)	31.18 (7.21)	30.89 (27.08–35.11)

Burns, *et al.*, J Clin Pharmacol 2015

Modelling v. Simulation

- Modelling objective & process
  - Estimating where you don't observe
  - Estimate parameters of explanatory or predictive value to your study question
  - Data to parameters, e.g., *C, t* → *CL, V, HL*
- Simulation objective & process
  - Dosing regimens you didn't study
  - Begin with parameters and generate data based on variety of experimental designs
  - Parameters to data, e.g., *CL, V, HL* → *C, t*

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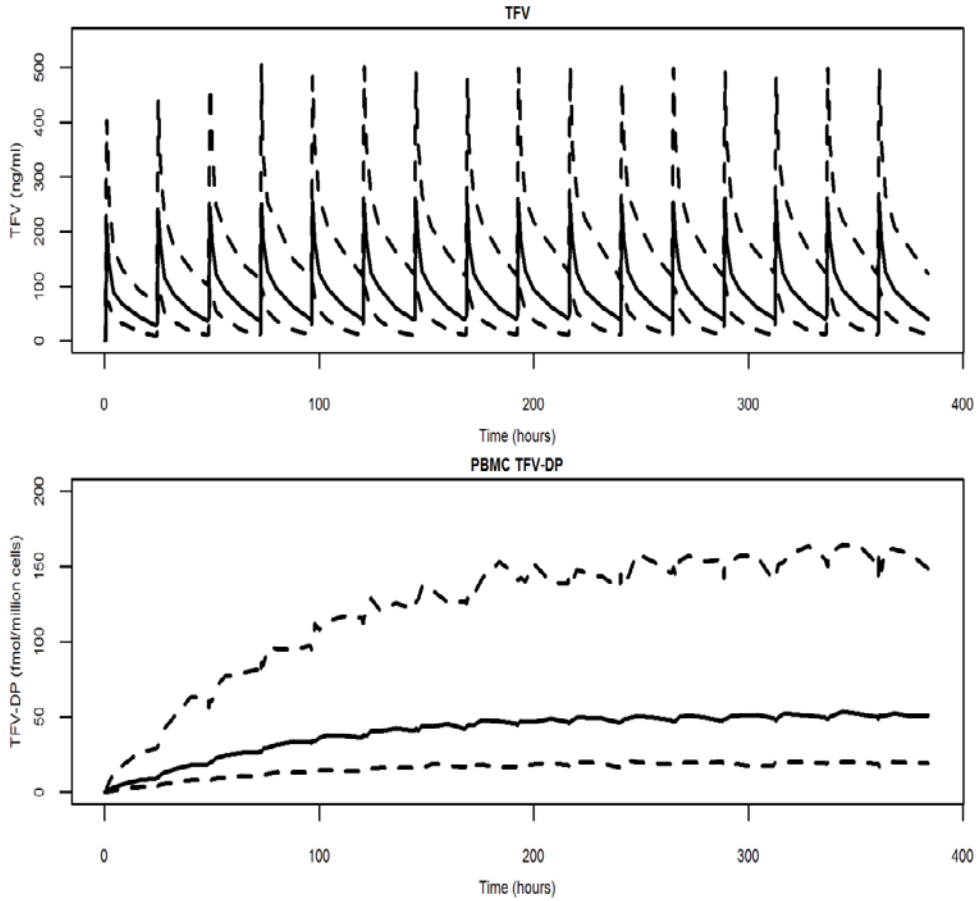
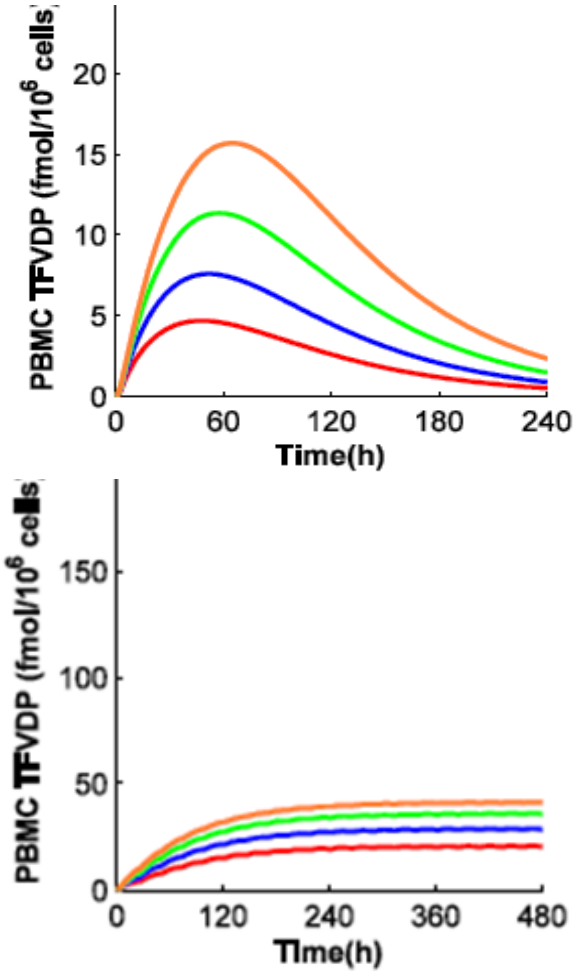
Adjusting for Adherence
Simulation concurs with DOT

Population PK Simulation



Mechanistic Model Simulation

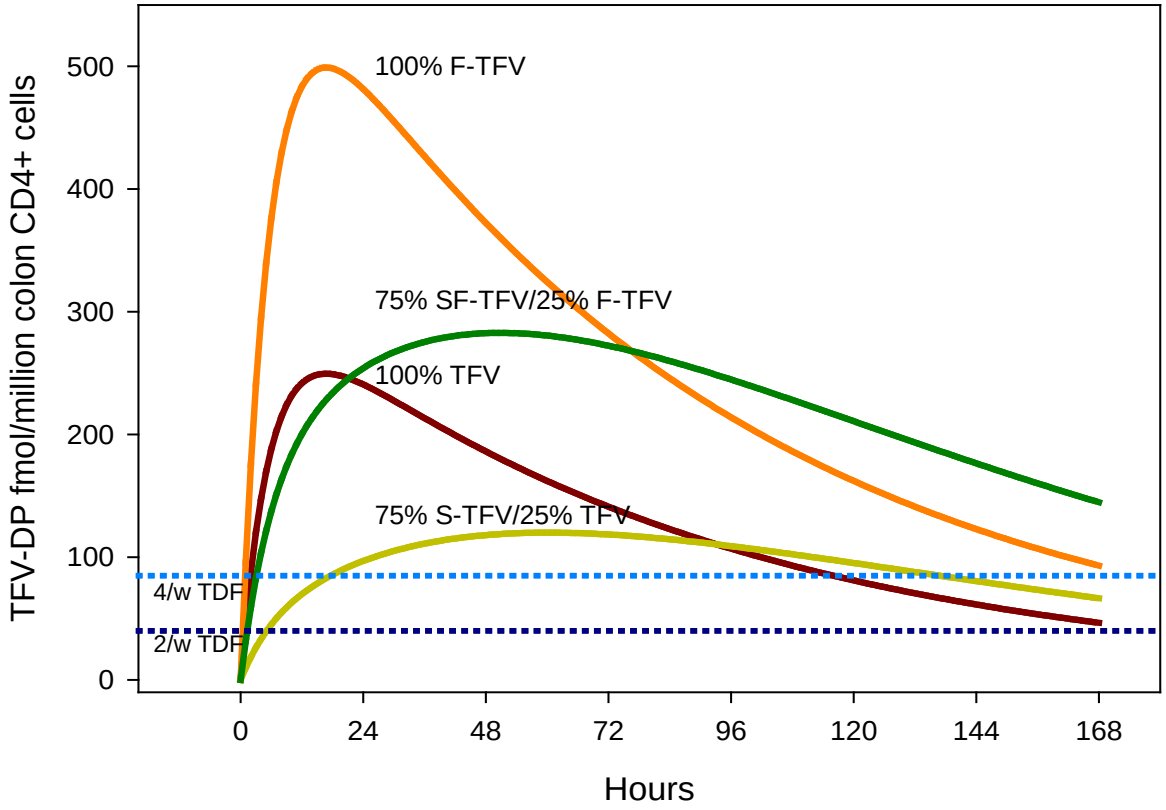


Burns, *et al.*, J Clin Pharmacol 2015

Madrasi, *et al.,* CPT Pharmacometrics Sys Pharmacol 2014

Applying PK Models to Simulate
How to optimize rectal formulations?

Single dose enhanced tenofovir enema for HIV prevention



TFV enema PK Enhancements

- Bioavailability (F)
  - TFV analogs
  - Hypotonic vehicle
- Sustained release (S)
  - Nanoparticle
  - Gelling agent

Reference Targets

- Colon CD4+ cell TFV-DP
- Bridging RCT-PK studies

Designing Microbicide RCT

Why perform 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 “test drive” on a computer
- Ask “What if?” questions

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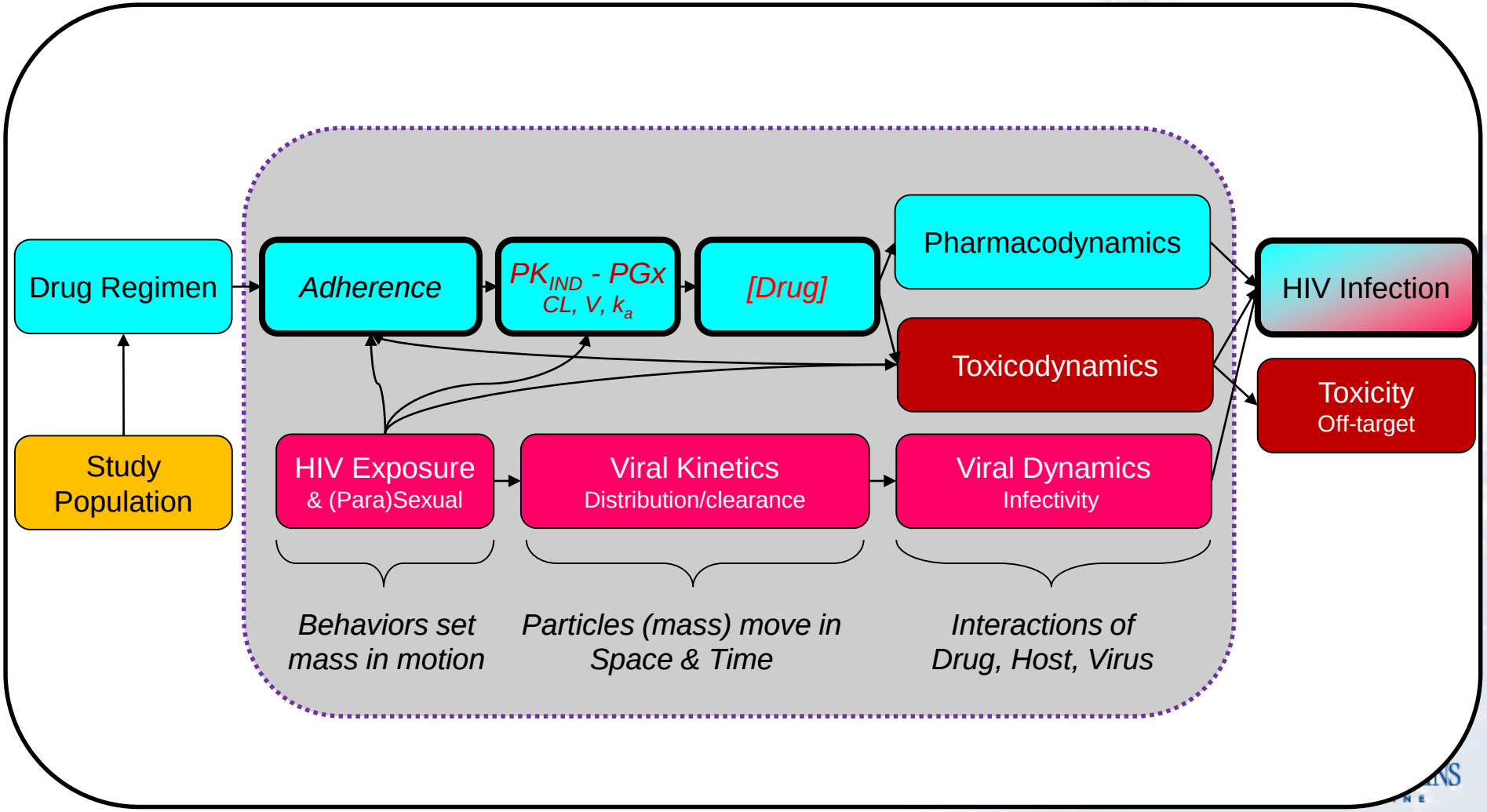
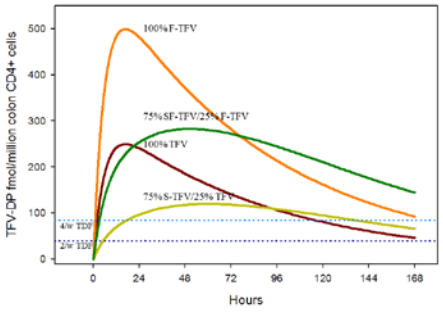
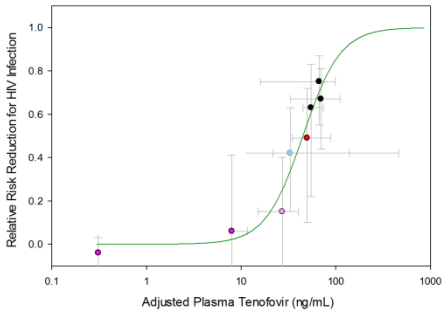
Designing Microbicide RCT

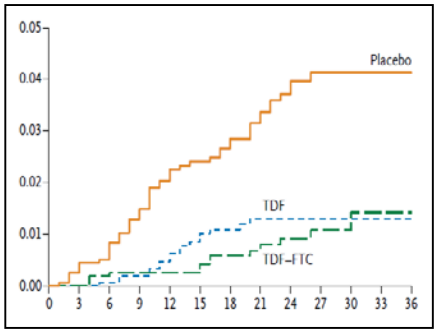
What data are needed for PrEP CTS?



Refining RCT Design
Clinical Trial Simulation







- Pharmacokinetic Model

$$C_e = \frac{D \cdot k_{1e}}{V_c \cdot (k_{e0} - k_e)} \left(e^{-k_e t} - e^{-k_{e_0} t}\right)$$

- Pharmacodynamic Model

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

- Infection Prevention Model

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

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Summary

What are PK design principles?

…sample throughout the dosing interval

…sample when PK parameter of interest is most influenced

…escalating doses to assess dose-proportionality

…sample to inform prescribing (how soon? how long?)

…single dose & steady-state

…multiple adjacent compartments simultaneously

…sparsely in many better than intensively in a few

…PK & PD simultaneously, range of concentrations & varied regimens (concentration-, time-dependent PK-PD)

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THANK YOU

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