What is the Time to Protection in Women taking Oral TDF/FTC?

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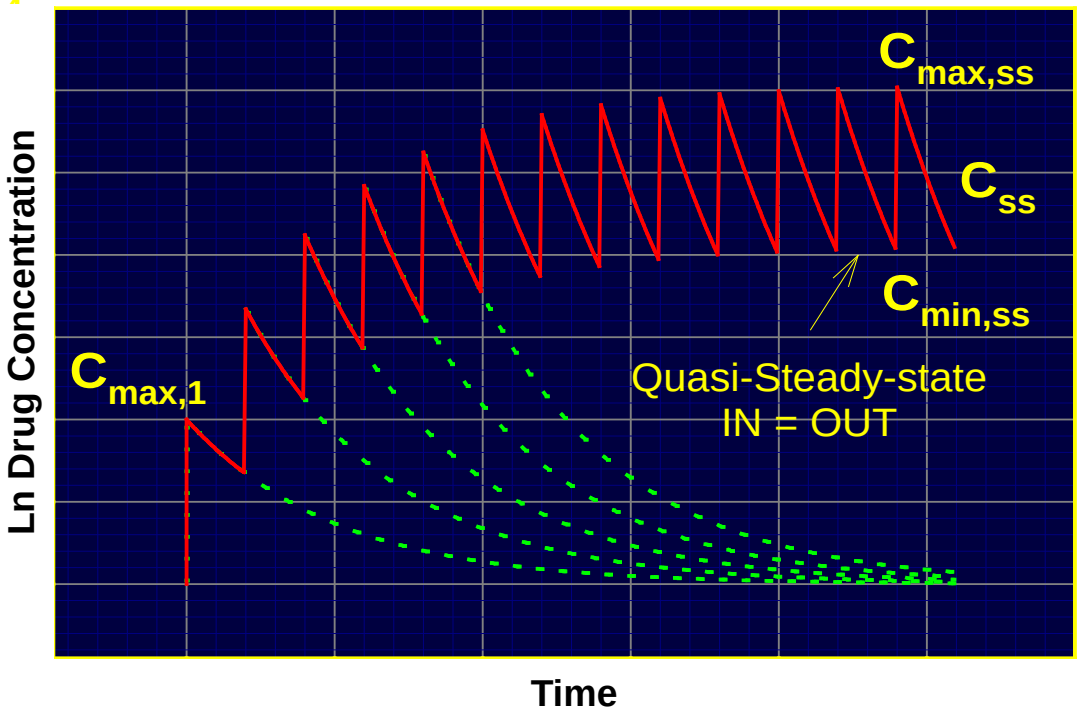
Background

- No study directly assessed time to clinical protection
- Rational assumptions & models required

- Time to *Protection* ≠ Time to *Steady-state*
- Anatomic compartment pharmacokinetics varies
- Protective doses vary with anatomic HIV risk
- Site of PrEP action not settled

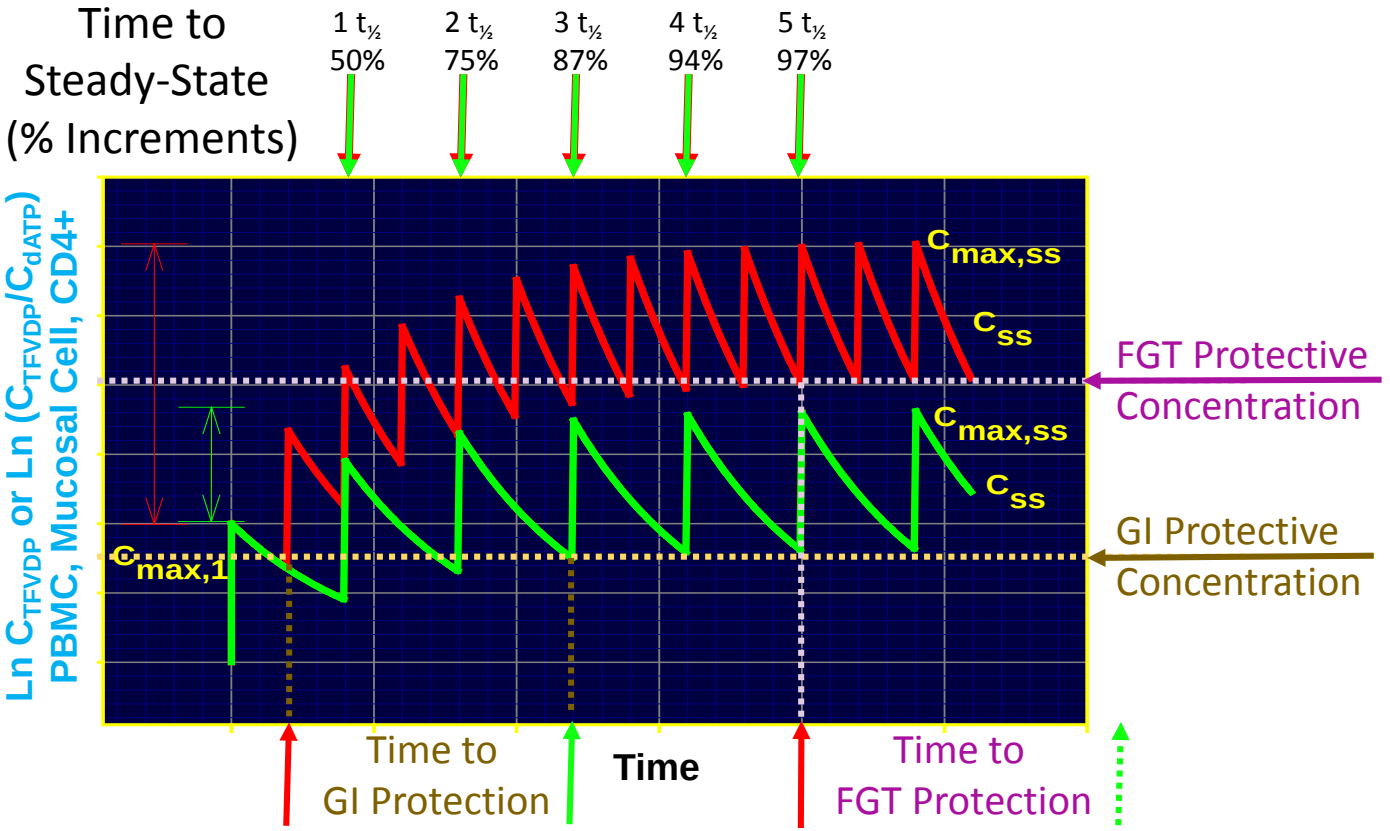
- 3 Investigator Perspectives

Concentration – Time Principles



- Repeat dosing gradually raises peaks (C_{max}) & troughs (C_{min})
- *Steady-state* occurs when peaks and troughs no longer change
- *Time to Steady-state* varies w/ half-life ($t_{1/2}$), independent of dose
- *Time to Protection* determined by dose, frequency, PK

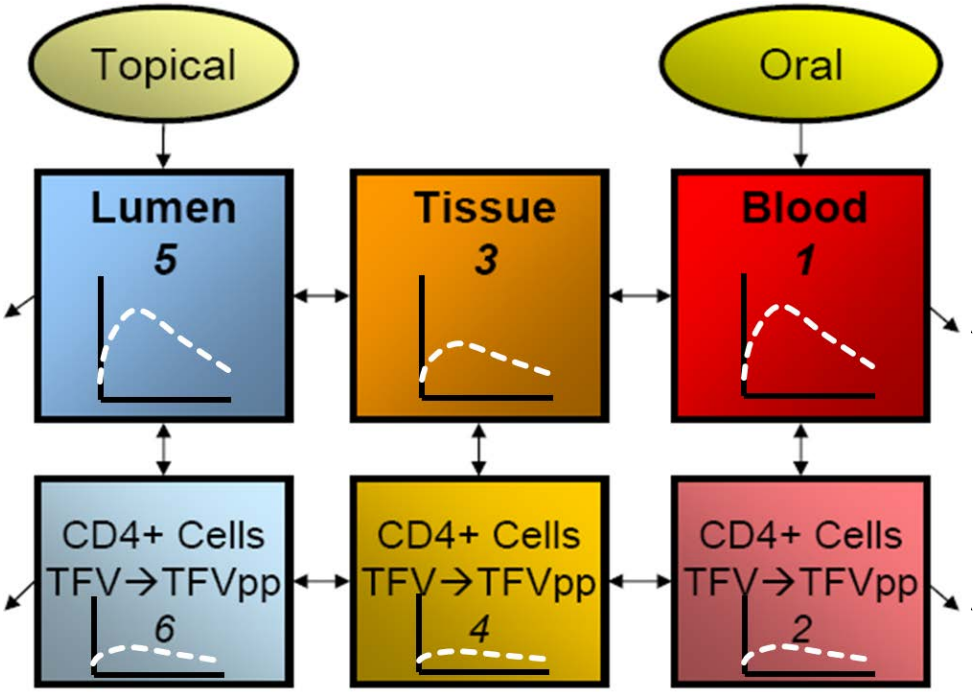
Compare 2 Regimens, 2 Infection Sites



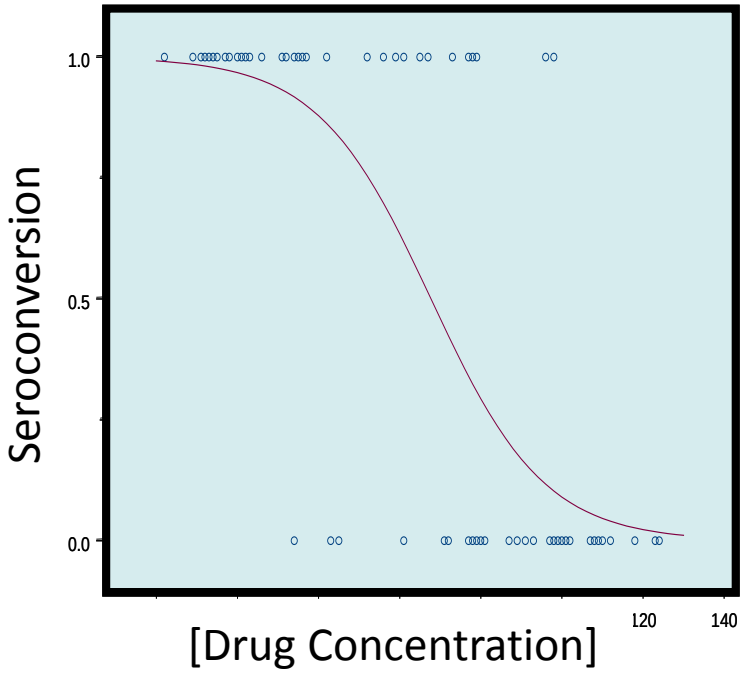
- *More frequent dosing, higher concentration, same time to Steady-state*
- *Time to Steady-State* may *(FGT)* or may not *(GI)* equal *Time to Protection*
- *Time to Protection* varies with risk site & regimen
- (Ignore numbers, order of time and direction of magnitude very roughly true)

Linking Effect & Target Concentration

Pharmacokinetics (PK)
Attaining the Target



Pharmacodynamics (PD)
Defining the Target

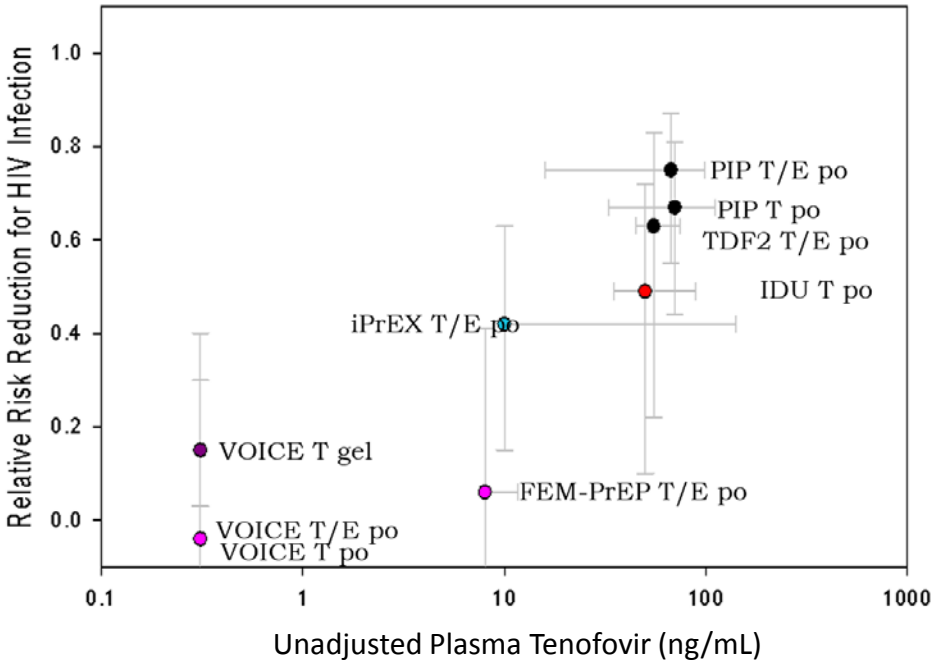


Pharmacokinetic – Pharmacodynamic Link

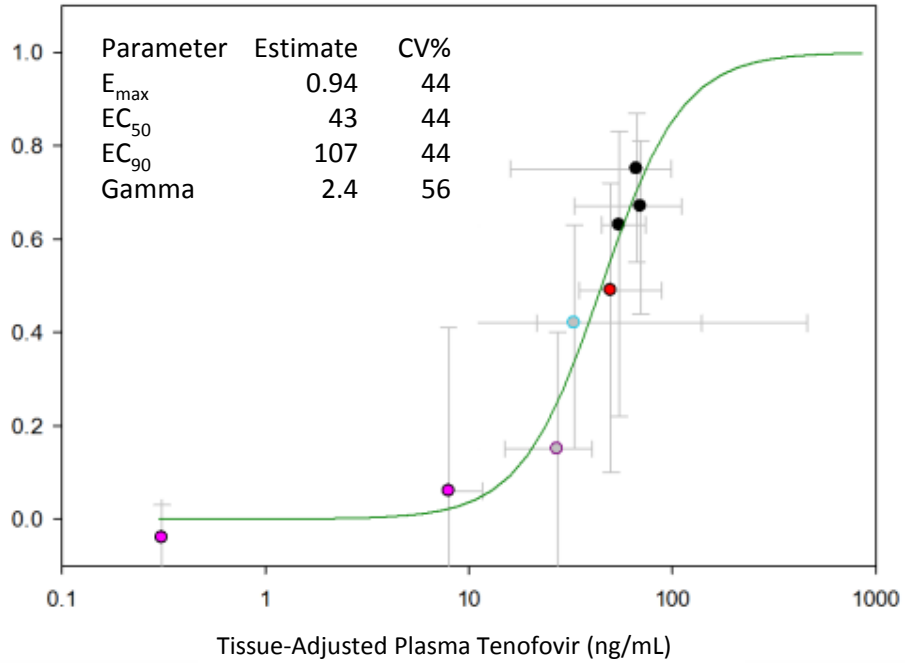
Doesn't have to be active drug @ site of action, it only has to be informative

Site of Action?

Unadjusted



Tissue-Adjusted

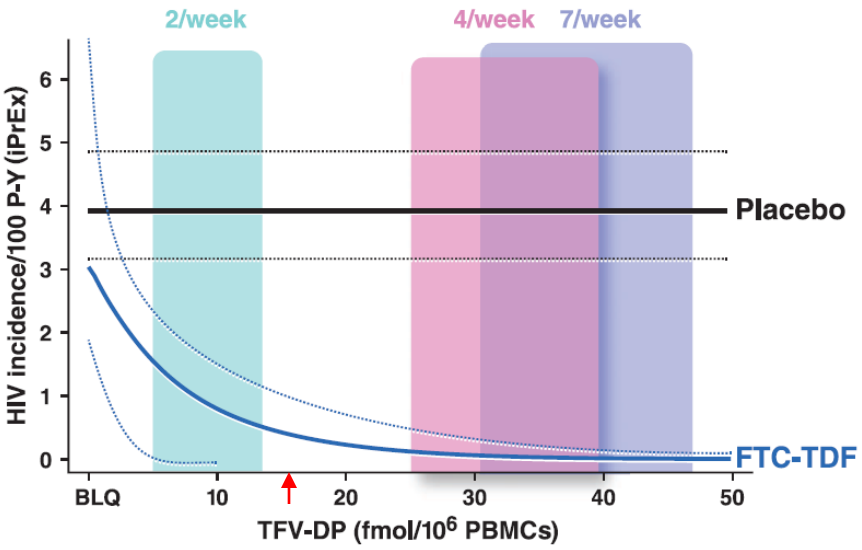


- When evaluating both oral & topical dosing, …
- Plasma concentration doesn't explain variation well.
- Tissue PK & susceptibility corrections explains far more variation.

Hendrix, Cell 2013

Protective Concentration Targets?

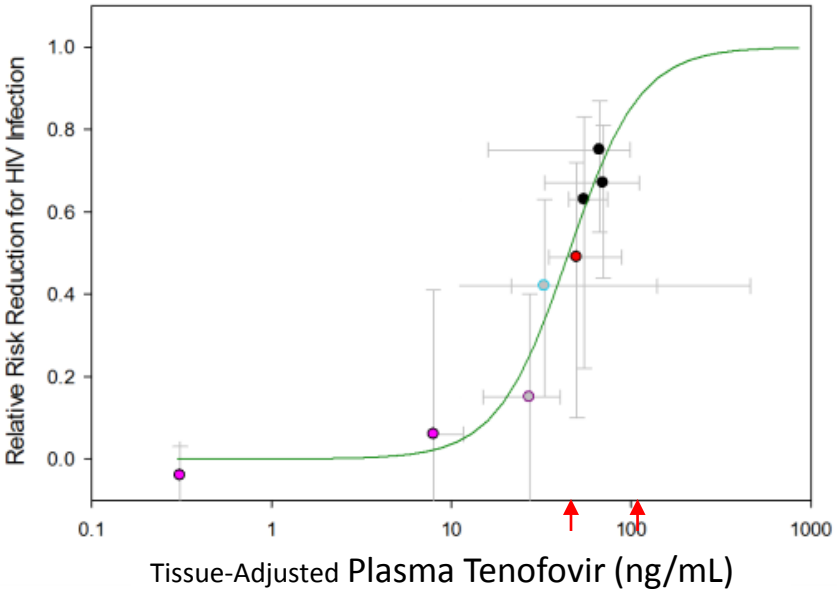
Within Study: iPrEx



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

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

Among Studies

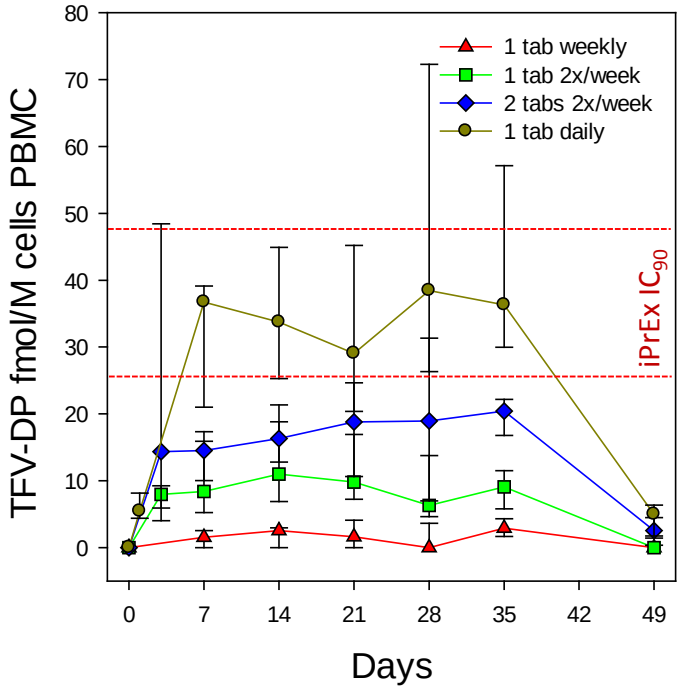


Parameter	Estimate	CV%
E_{max}	0.94	44
EC_{50}	43	44
EC_{90}	107	44
Gamma	2.4	56

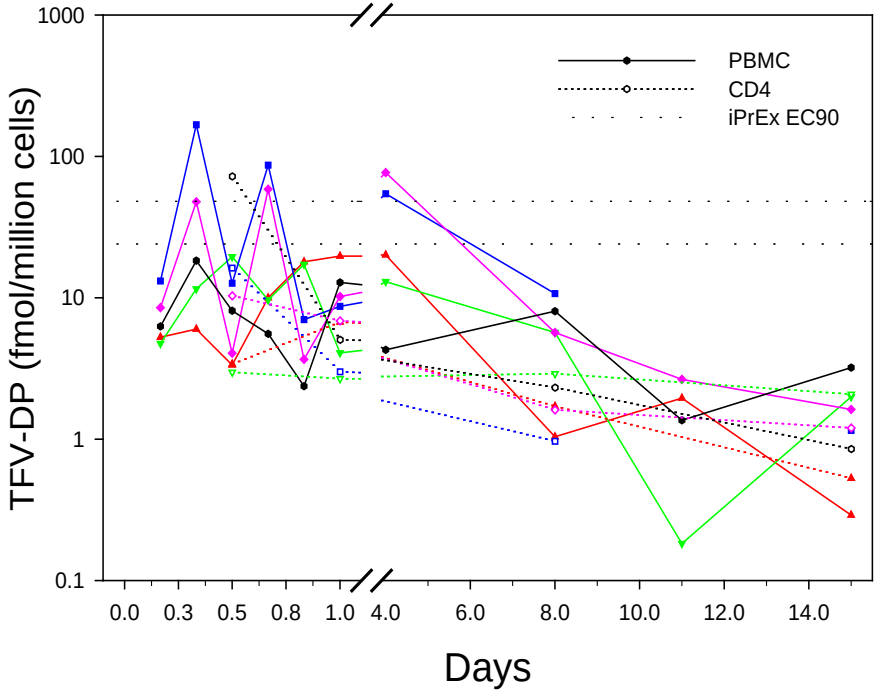
Hendrix, *Cell* 2013

Time to Protection?

Multiple Dose/Regimen (HPTN 066)



Single Dose (^{14}C-TDF Study)

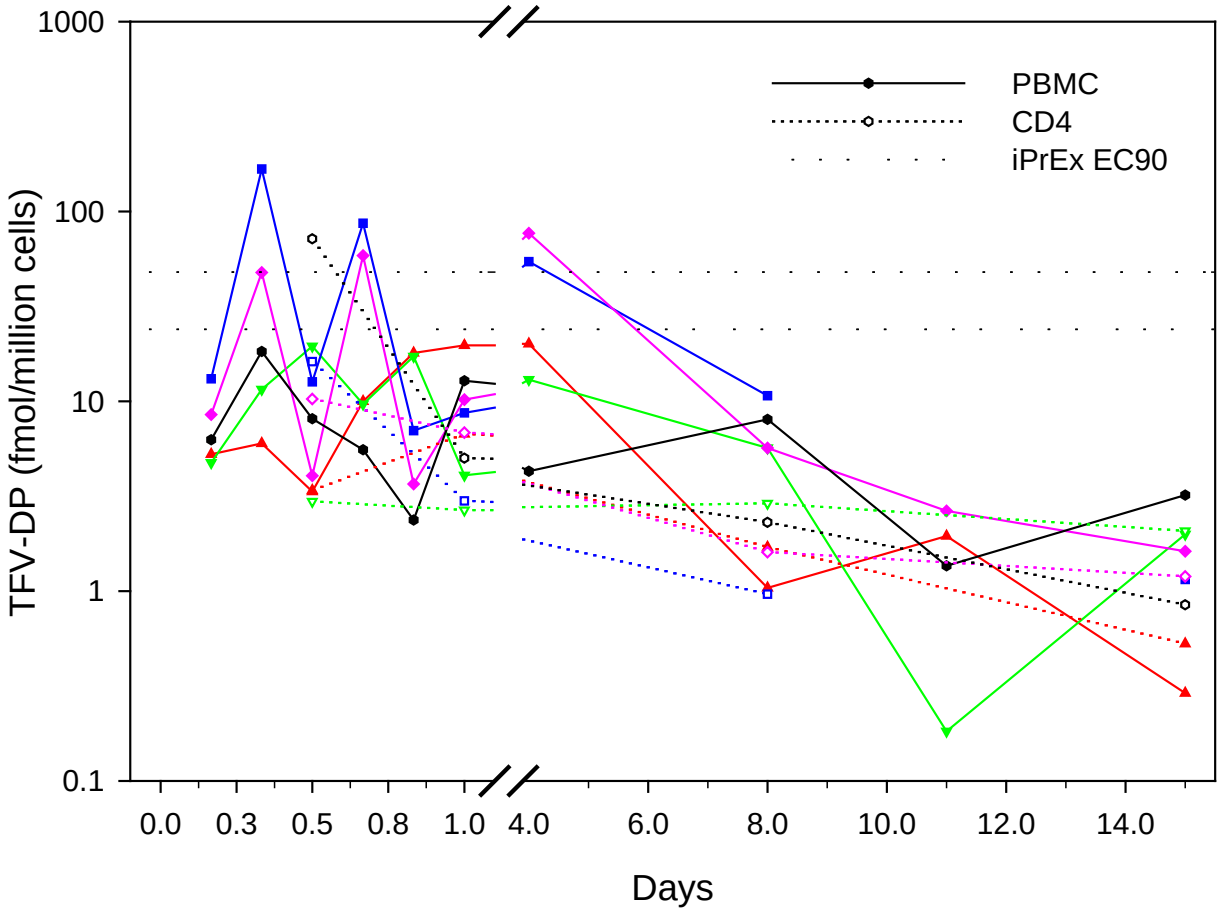


- Daily dosing consistently in iPrEx target range, but only after one week
  - Empiric data, not modeled data; only possible results are integer weeks
- Most subjects TFV-DP < iPrEx EC_{90} with single or double dose
- iPrEx EC_{90} likely not be relevant for vaginal protection
- PBMC data may not be relevant for colon & cervicovaginal tissue

Hendrix ARHR 2015; Louissaint *ARHR* 2013; Anderson *Sci Transl Med* 2012

Cell type specific PK?

- 6 healthy women
- Single oral dose
  - TDF
  - ^{14}C-TDF microdose
- Sample
  - Blood plasma, PBMC q4 x 24h
  - rectum, vagina, luminal fluid, blood D1, 8, 15
- Assays
  - TFV
  - TFV-DP



Louissaint, *et al*. ARHR 2013; Anderson, *et al*. Sci Transl Med 2012

Anatomic PK Variation?

Matrix	CD4+ Cells		Unfractionated Cells	
	$t_{1/2}$ (hrs)	T_{ss} 90% (days)	$t_{1/2}$ (hrs)	T_{ss} 90% (days)
PBMC	112 (100, 118)	16.3 (14.6, 17.2)	48 (38, 76)	7.0 (5.5, 11.1)
Colon	60 (52, 72)	8.8 (7.6, 10.5)	82 (43, 89)	12.0 (6.3, 13.0)
FGT	139 (121, 167)	20.3 (17.6, 24.4)	66 (43, 202)	9.6 (6.3, 29.5)

	RT:VT TFV Homogenate	RT:VT TFV-DP Homogenate	RT:VT TFV-DP CD4 Cells
24 hrs	33.8 (6.8, 37.8)	123.7 (8.4, 155.4)	19.20 (9.60, 28.8)

- CD4+ TFV-DP $t_{1/2}$ & T_{ss} FGT > PBMC > Colon
- CD4+ TFV-DP $t_{1/2}$ & T_{ss} > Unfract. cells for PBMC & FGT; colon similar
- 1.3 – 2.1 $\log_{10}$ RT>VT TFV-DP CD4+ & tissue homogenate, respectively
- TFV, TFV-DP homog. Rectal/Vaginal ratios c/w Patterson

Louissaint, *et al*. *AIDS Res Hum Retrovir* 2013; Patterson, *et al*. *STM* 2011

Summary

- FGT protection requires 6-7 doses per week
- ∴ Time to Protection must nearly equal T_{ss} (Steady-state)

- CD4+ cell most relevant cell even if site uncertain
- CD4+ TFV-DP $t_{1/2}$
  - FGT 139 hrs
  - PBMC 112 hrs
  - Colon 60 hrs

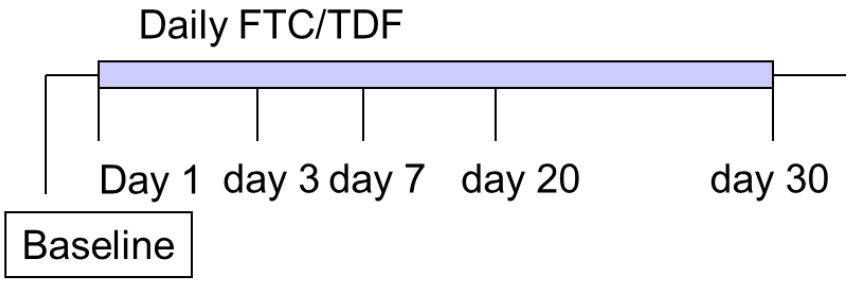
- ∴ Time to Protection
  - FGT 20 days
  - PBMC 16 days
  - Colon 9 days

Peter Anderson
University of Colorado

Cell-Prep: intracellular TFV-DP and FTC-TP

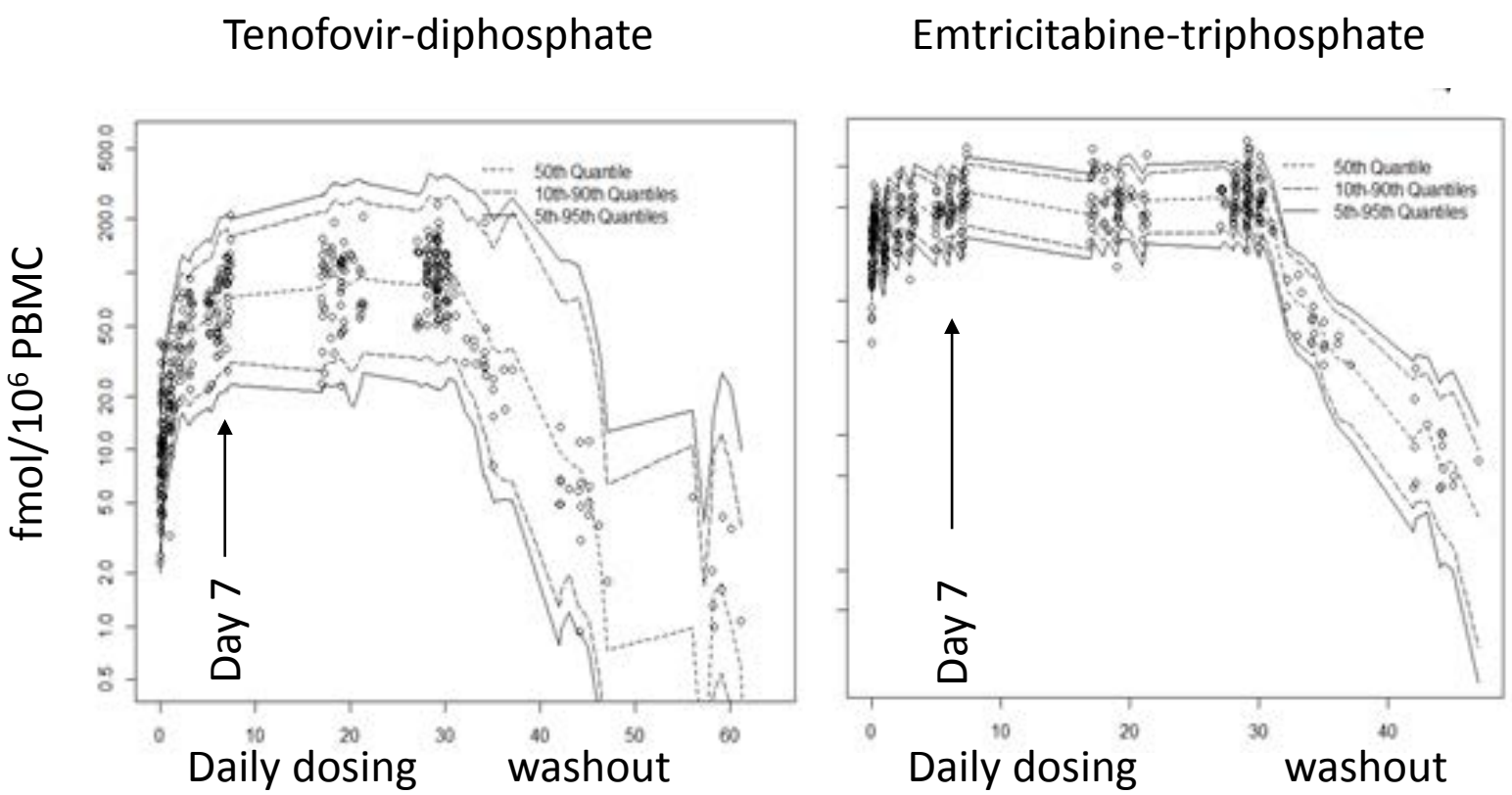
- Goal: Determine accumulation kinetics in PBMC, rectal mononuclear cells, cervical brush cells.

40 volunteers (13 female)



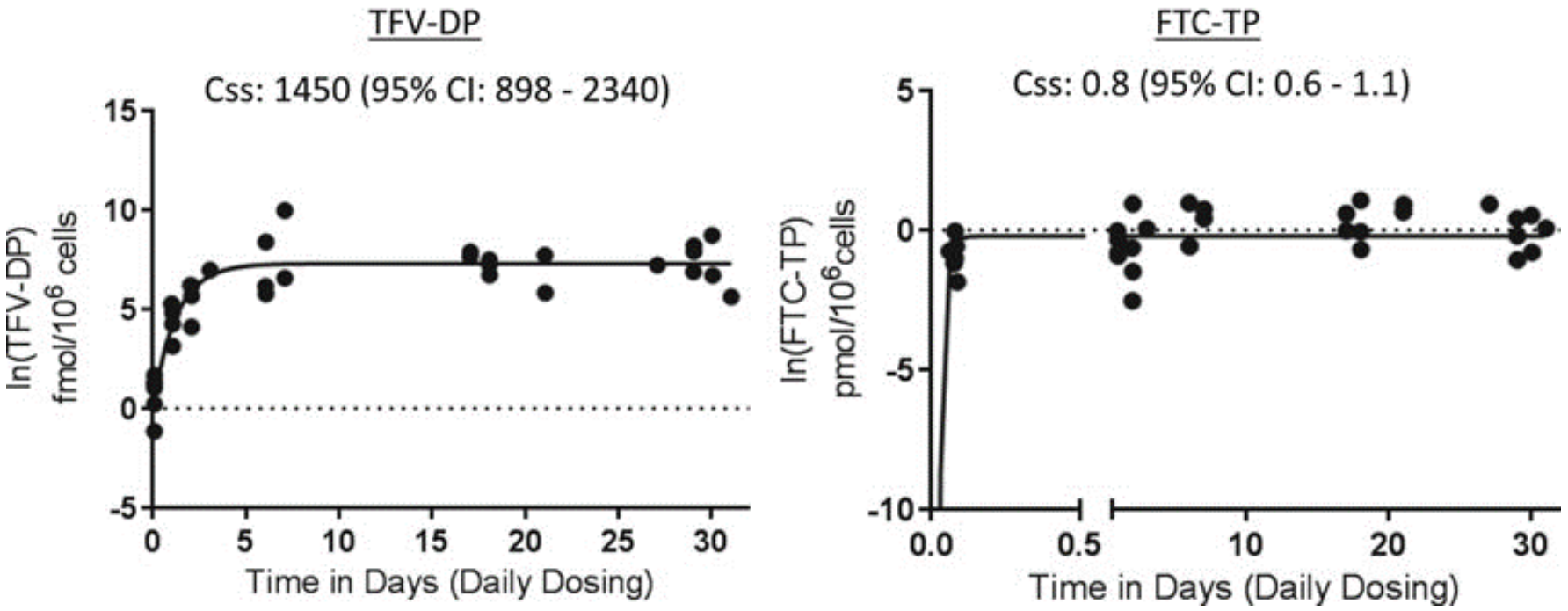
- Multiple PBMC at each visit
- One visit with one rectal sample
- One visit with one cervical sample

PBMC ~SS 7 days



Chen. PLoS ONE 11(11): e0165505. doi:10.1371/journal.

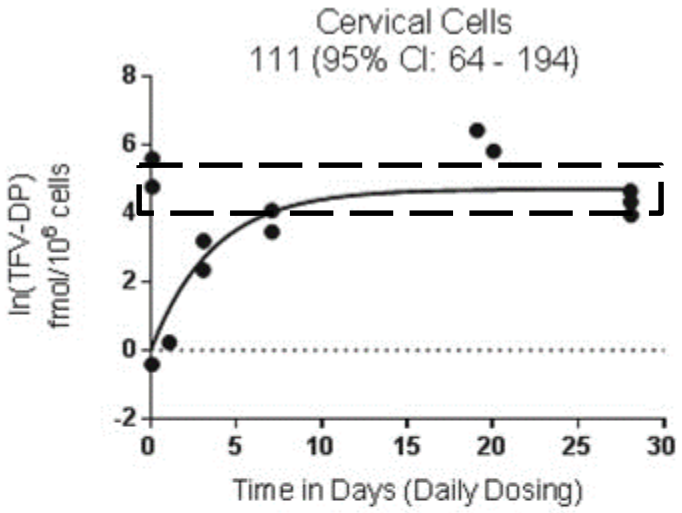
Rectal mononuclear cells

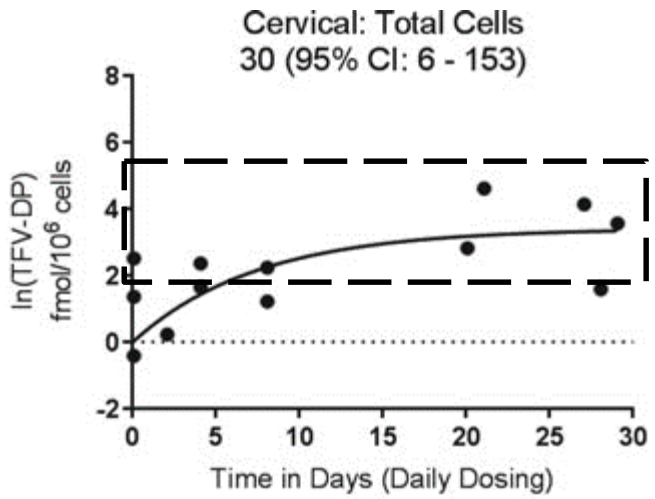


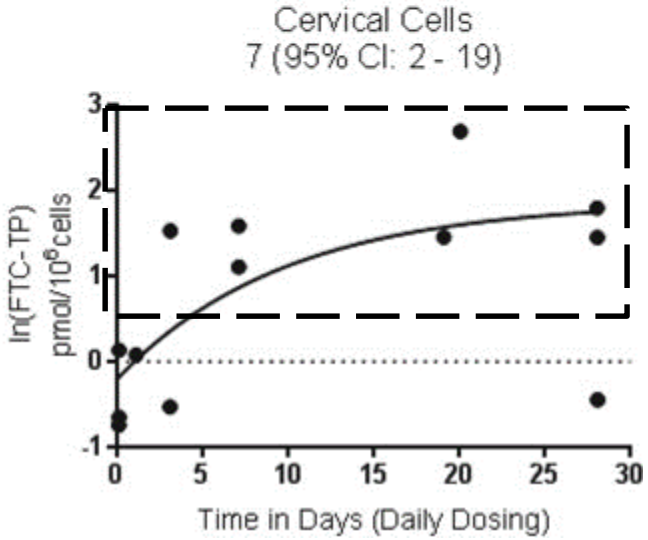
Seifert. ARHR. 2016 Oct/Nov;32(10-11):981-991.

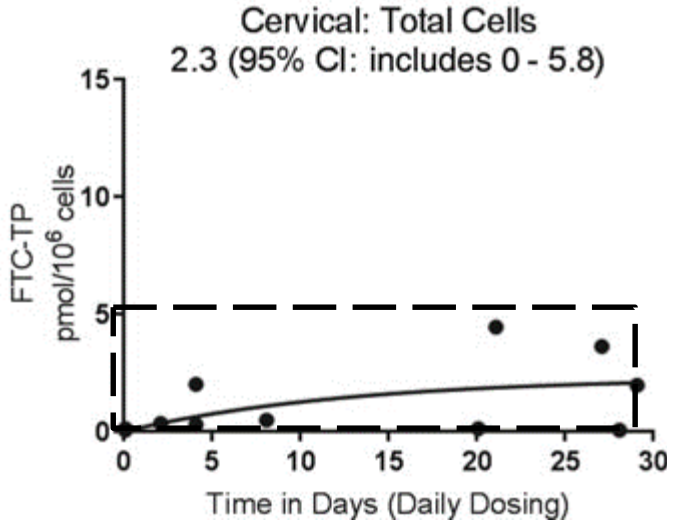
Cervical brush cells, viable and total

- N=13

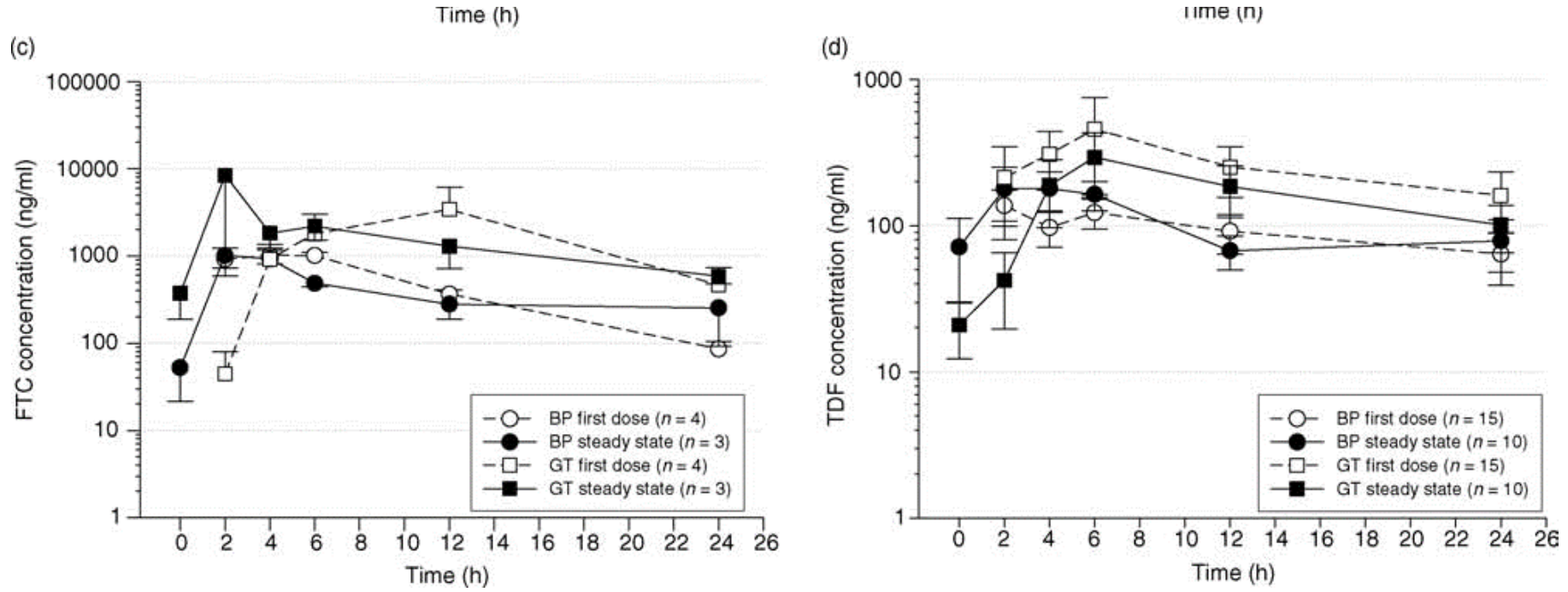








Dumond/Kashuba: First dose vs SS



Dumond. AIDS. 2007 Sep 12;21(14):1899-907.

Summary

- PBMC SS ~ day 7
- Rectal cells SS ~ day 5-7
- Cervical cells less conclusive. Under powered. Epithelial cells with low viability. Concentrations from days 1-7 overlapped with SS predictions.

Discussion points

- Parent TFV/FTC appears rapidly in CVF. Despite limited data in cervical epithelial cells, concentrations within first week overlapped with SS. Systemic drug reached SS at ~7 days.

- Relevance of male genital tract? We have no data in male genital tract tissue (eg foreskin)…possible PK similarities to female genital tract? Its relevant that we see high efficacy in MSM, presumably including insertive exposures.

- Relevance of PEP/animal models? Drug started within 36 hours after vaginal exposure effective in macaques (HIV-2). Event-driven oral dosing effective for vaginal exposures in macaques (SHIV).

PMID: 23226529, 25202923, 11000253

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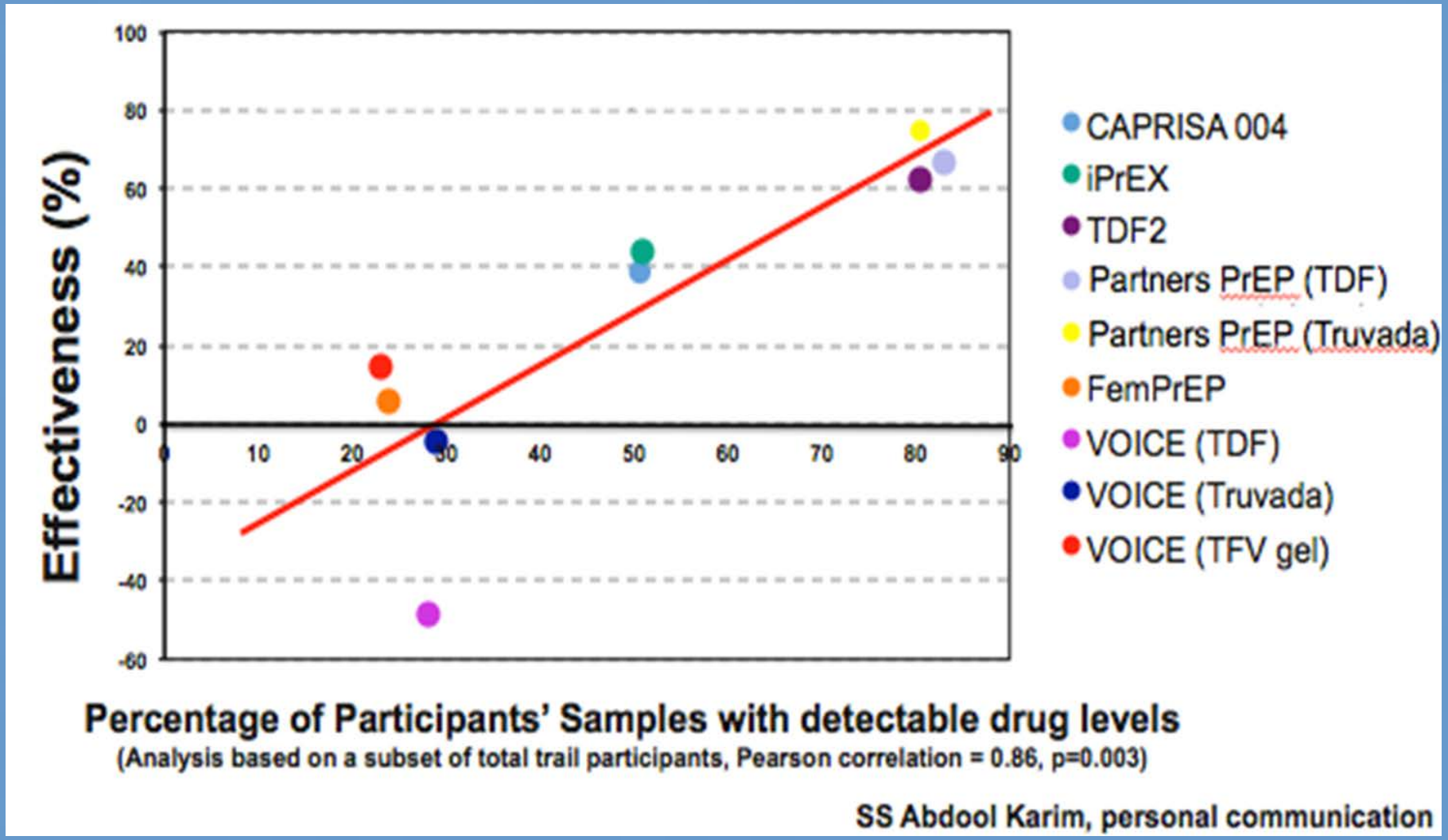
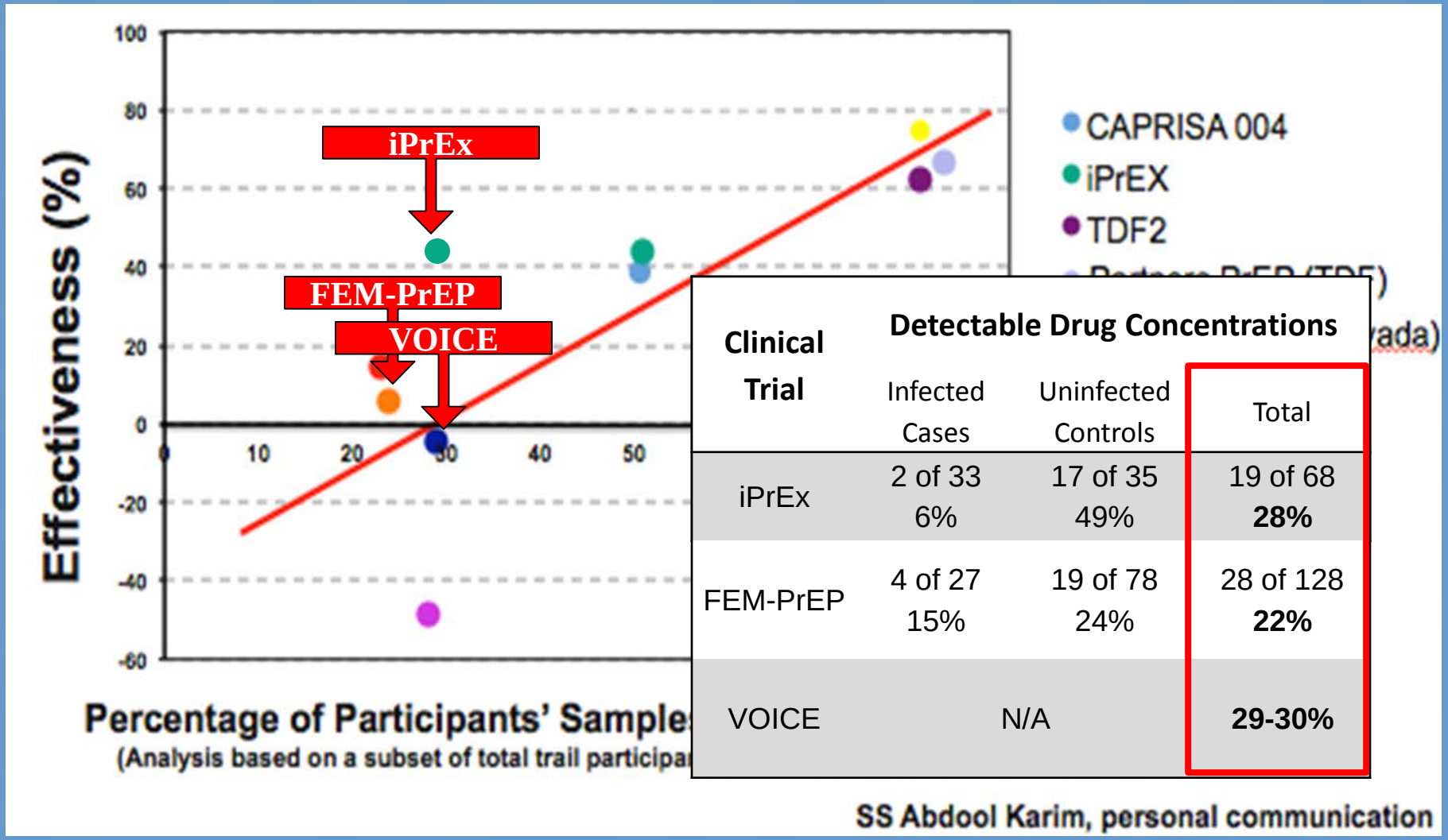
UNC Chapel Hill

Adherence Correlates with Clinical Trial Results



Adapted from Landovitz R. *PrEP for HIV Prevention: What We Know and What We Still Need to Know for Implementation*. CROI 2015.

Adherence Correlates with Clinical Trial Results



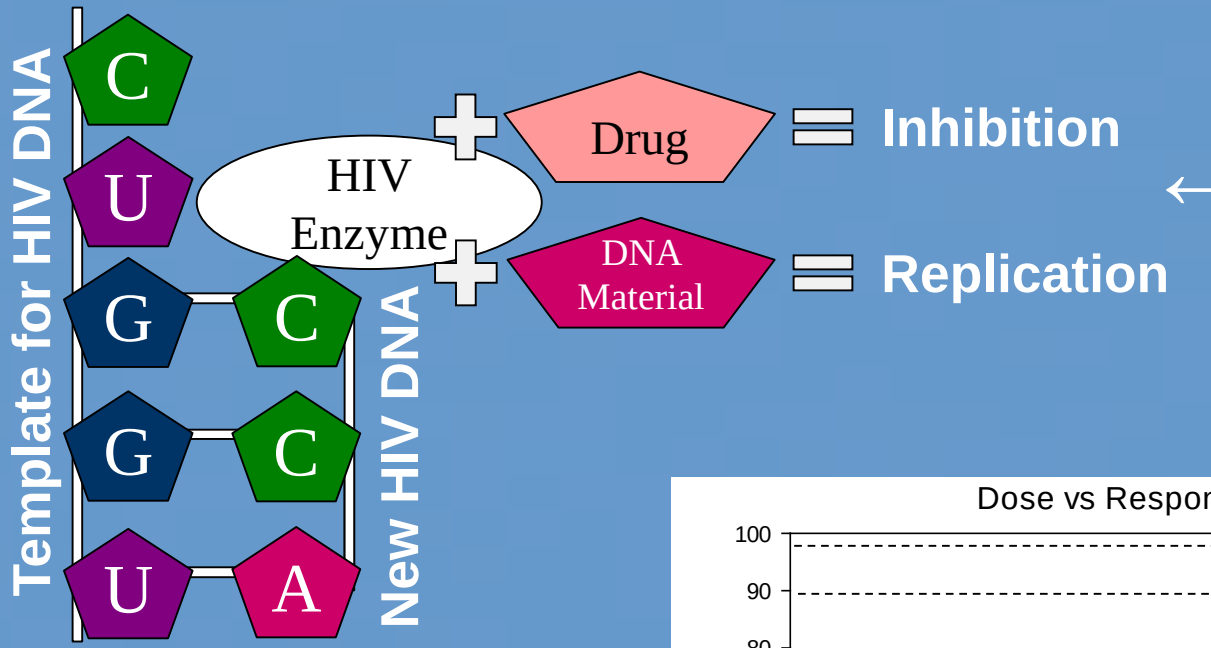
Clinical Trial	Detectable Drug Concentrations		
	Infected Cases	Uninfected Controls	Total
iPrEx	2 of 33 6%	17 of 35 49%	19 of 68 **28%**
FEM-PrEP	4 of 27 15%	19 of 78 24%	28 of 128 **22%**
VOICE	N/A		**29-30%**

Adapted from Landovitz R. *PrEP for HIV Prevention: What We Know and What We Still Need to Know for Implementation*. CROI 2015.

Approach to Predicting PrEP Efficacy

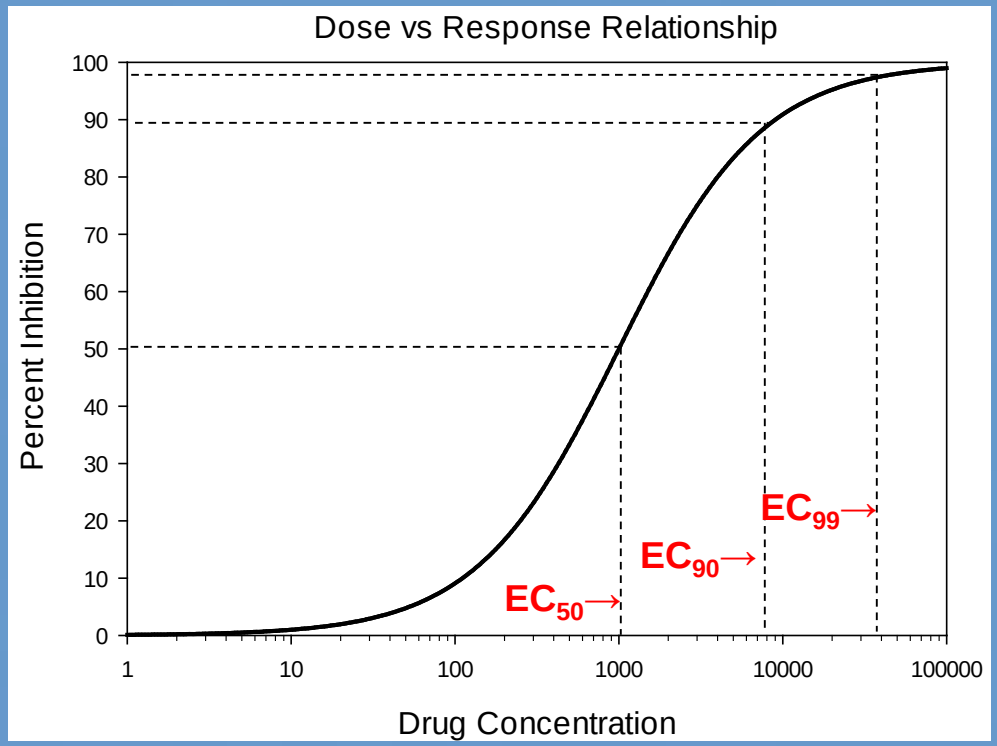
1. Determine drug concentrations in HIV susceptible tissues of healthy volunteers
2. Build mathematical model to predict drug concentrations in these tissues
3. Determine efficacy target to protect human cells from HIV infection
4. Predict the percent of the population that would achieve efficacy target if taking daily or intermittent TDF±FTC for HIV PrEP

Selecting an Efficacy Target

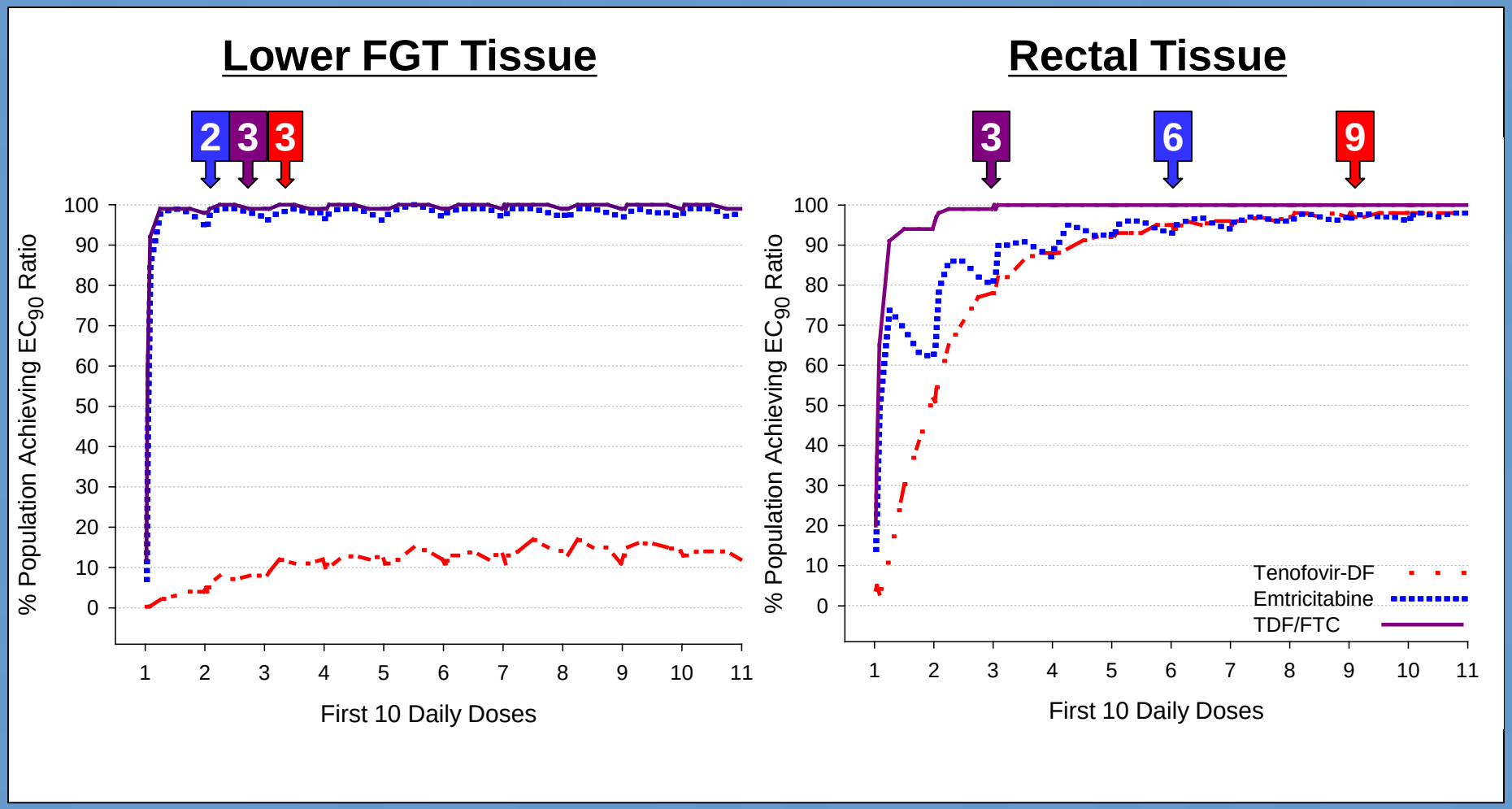


←Why a Ratio?

Why EC90?→



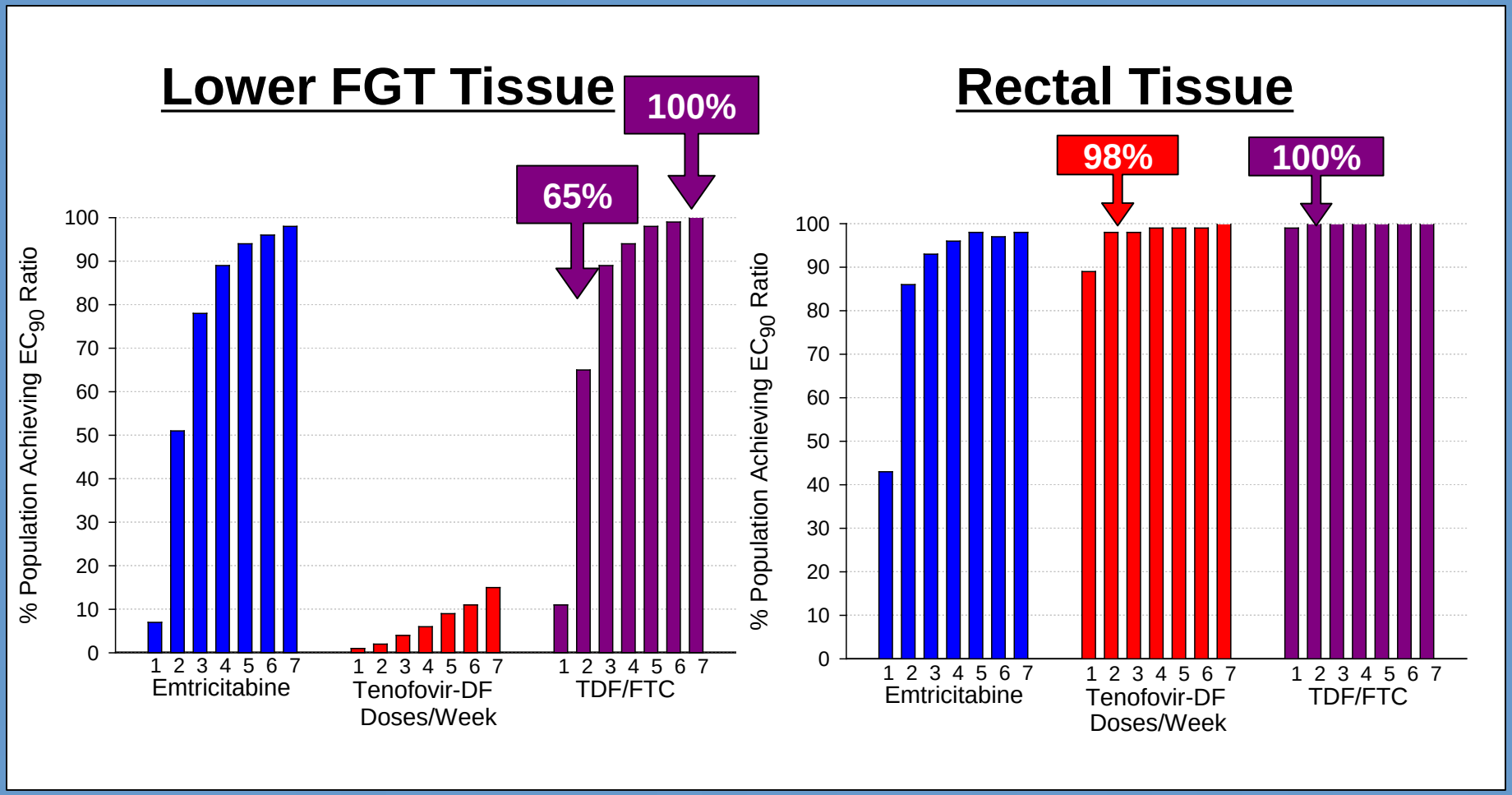
Predicting Efficacy in the Population
First 10 Daily Doses



Cottrell ML et al. *J Infect Dis*. 2016 Jul 1;214(1):55-64.

Predicting Efficacy in the Population

Reduced Frequency Dosing



Cottrell ML et al. *J Infect Dis*. 2016 Jul 1;214(1):55-64.

Study Conclusions

1. TDF active metabolite exposure in lower GI tract was greater than in FGT tissues
2. Mathematical modeling predicted drug concentrations in mucosal tissues
3. The maximal proportion of the population achieved our efficacy target by the 3rd dose of Truvada® PrEP
4. 100% of the population achieved our efficacy target with daily versus 100% in lower GI tract and 65% in FGT with twice weekly Truvada®
5. Our model reasonably correlated with clinical trial results

Discussion