Does Pharmacology Support On Demand PrEP?

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Conflict of Interest

- UNC has received research funding from:
  - Gilead Sciences Inc
  - Merck Research Laboratories
  - GlaxoSmithKline
- Consultant
  - Merck Research Laboratories
  - Viiv Healthcare

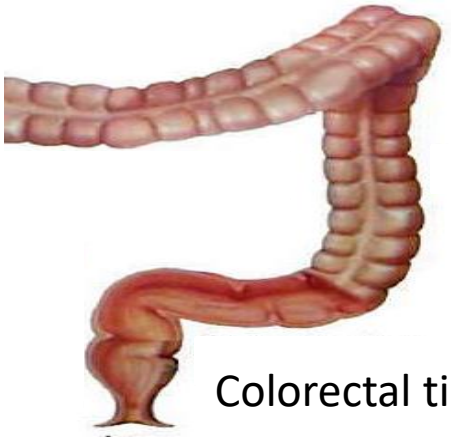
Pharmacology Goals for Event Driven Dosing

Prevent HIV infection by delivering.....

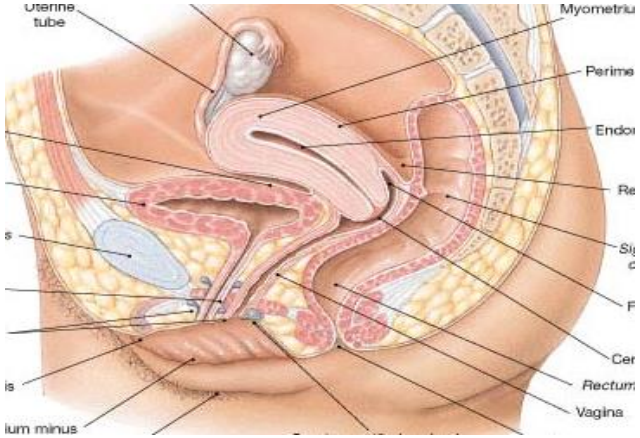
1. the right drug(s)
2. to the right biological site(s)
3. at the right concentration(s)
4. for the right length of time

The Right Site

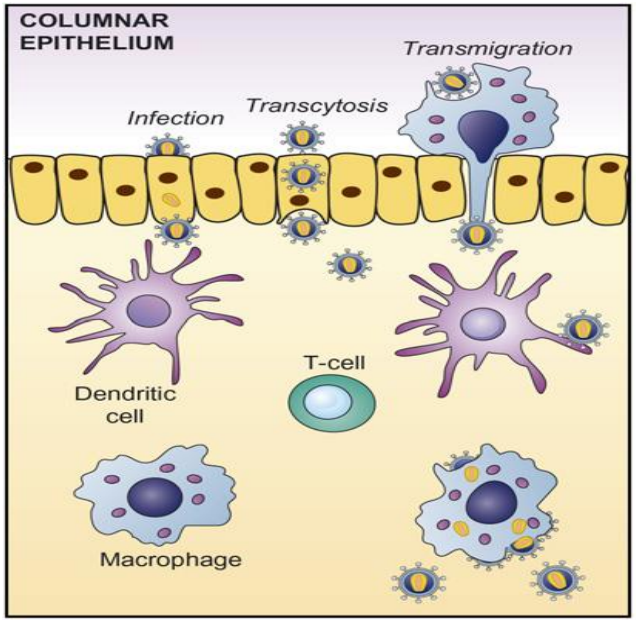
Mucosal Tissues

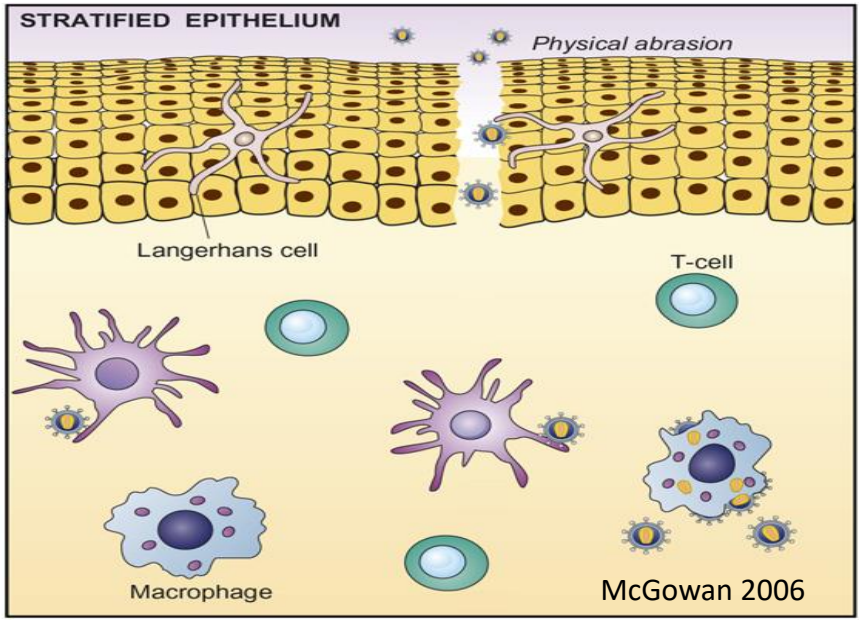


Colorectal tissue



Female Genital Tract Tissue

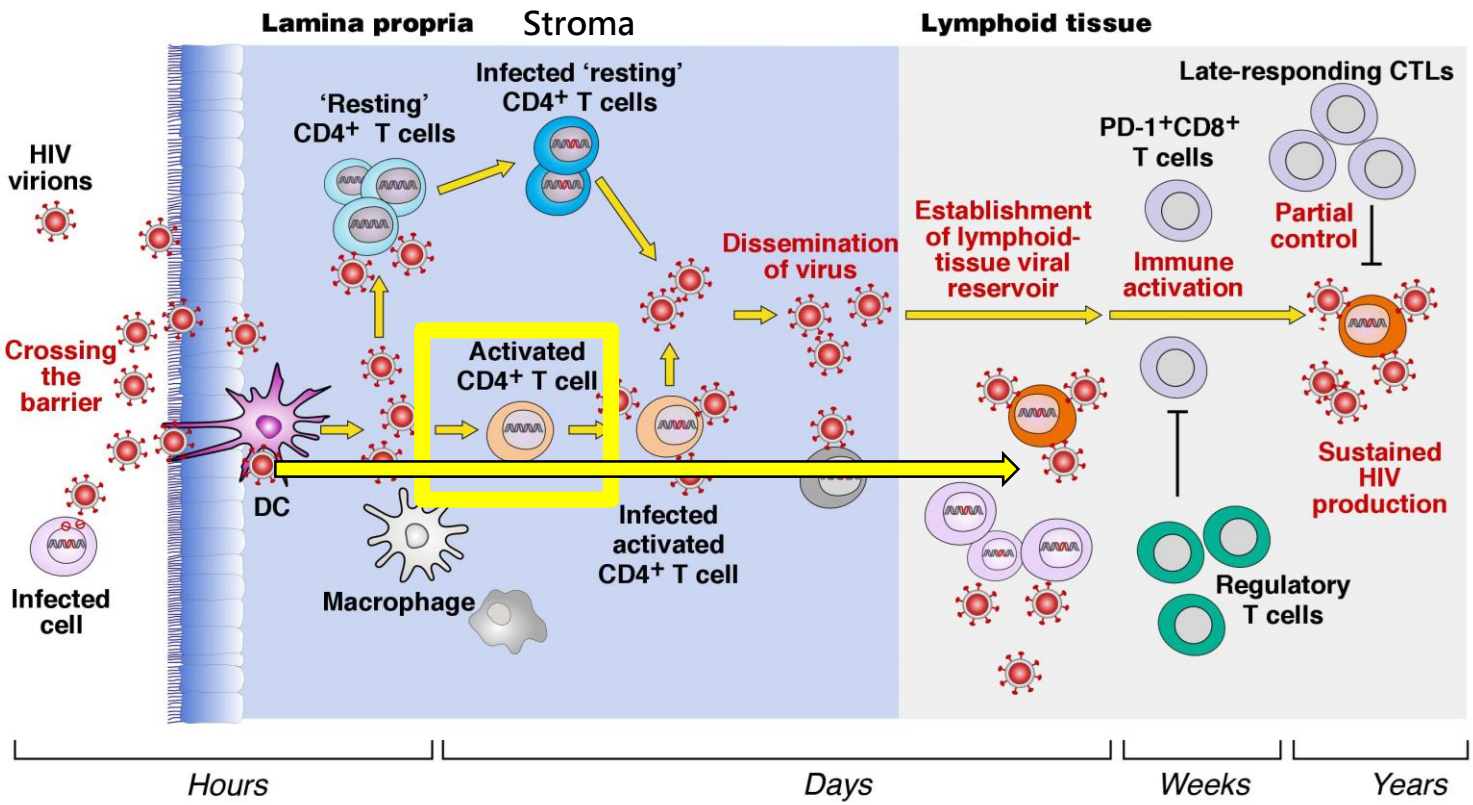




McGowan 2006

The Right Site

Early Events in HIV Infection



Adapted from: AT Haase, *Nature Rev Immunol* 5(10):783, 2005

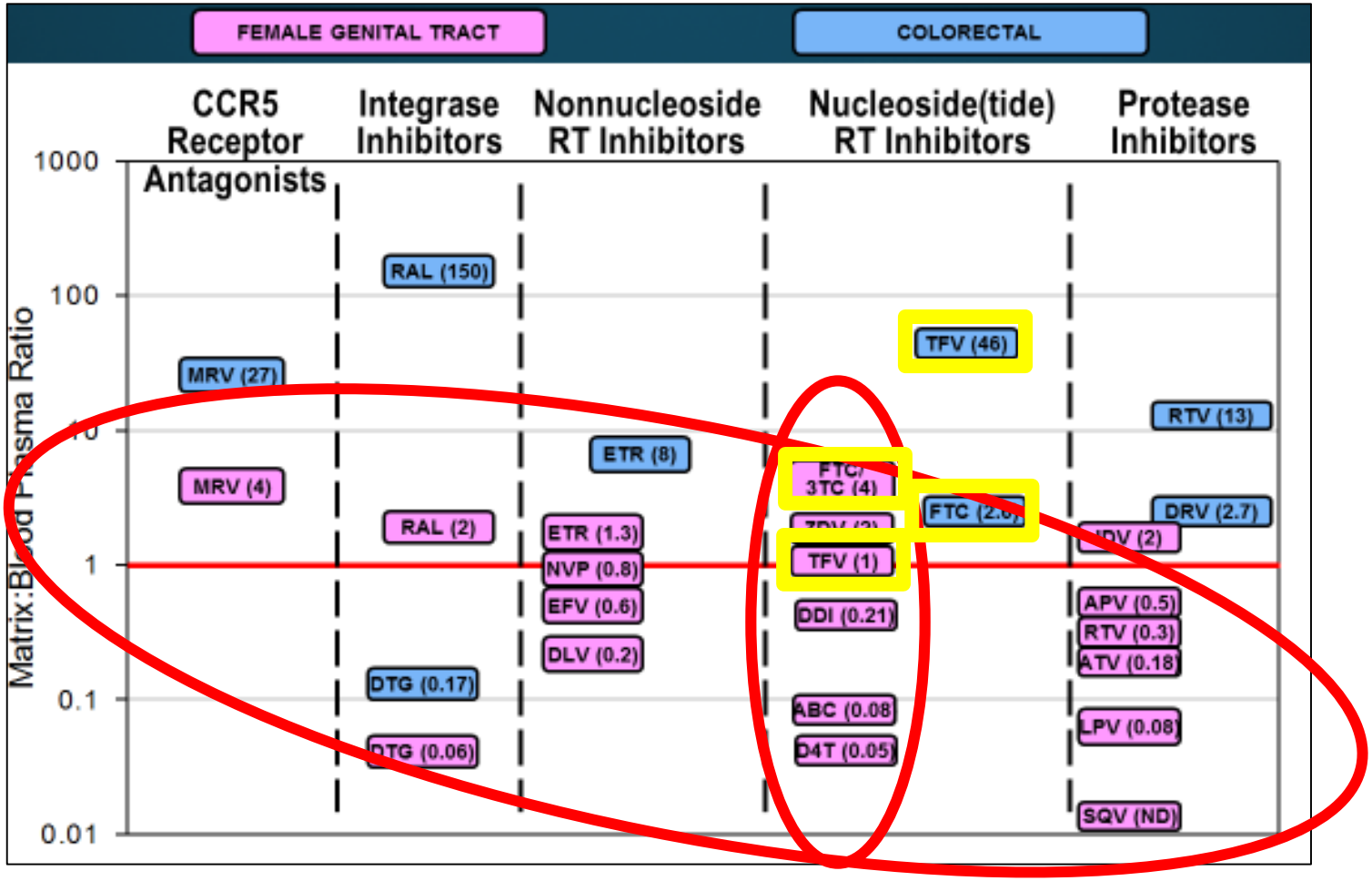
Fauci A. WAC 2010

Where should infection be aborted?

What is the ARV target conc'n needed to abort HIV infection?

The Right Site

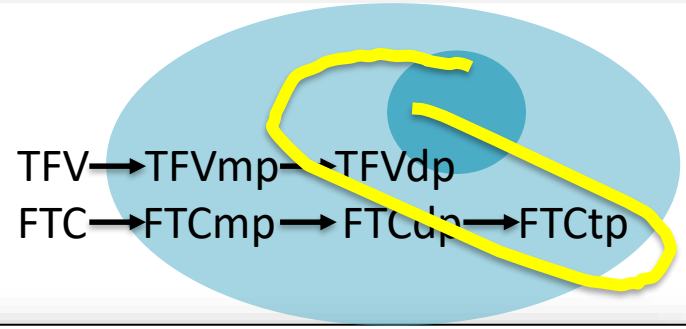
Oral ARV Dosing: FTG and Colorectal Concentration Relative to Blood

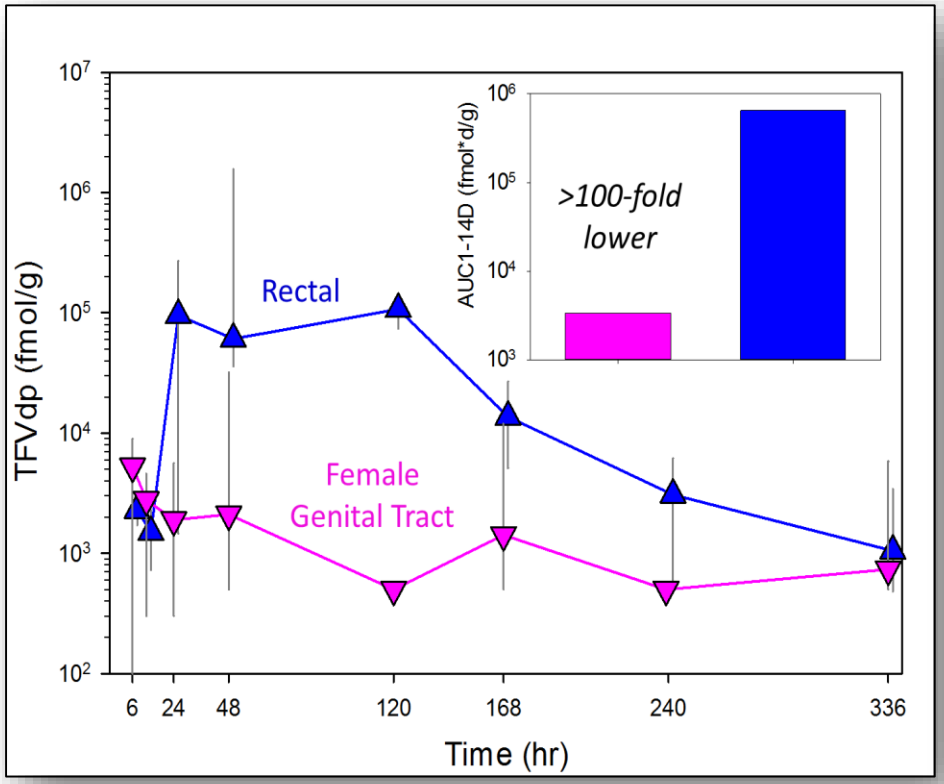


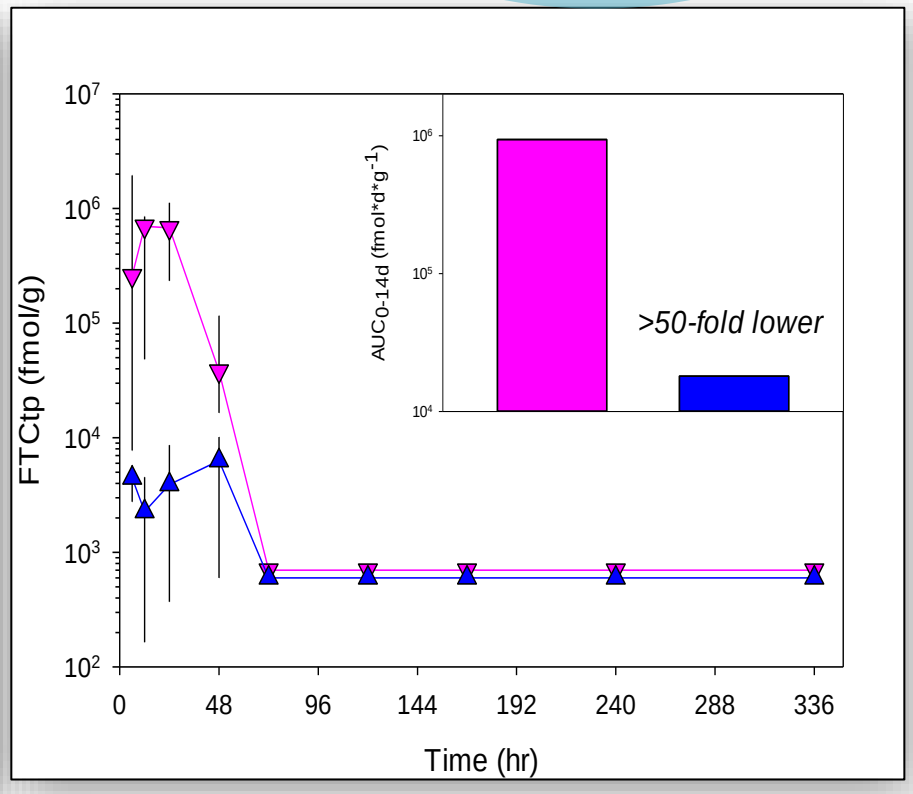
Thompson et al. J Acquir Immune Defic Syndr. 2013 Jul; 63(02): S240

The Right Concentration:

TFVdp and FTCtp In Mucosal Tissues





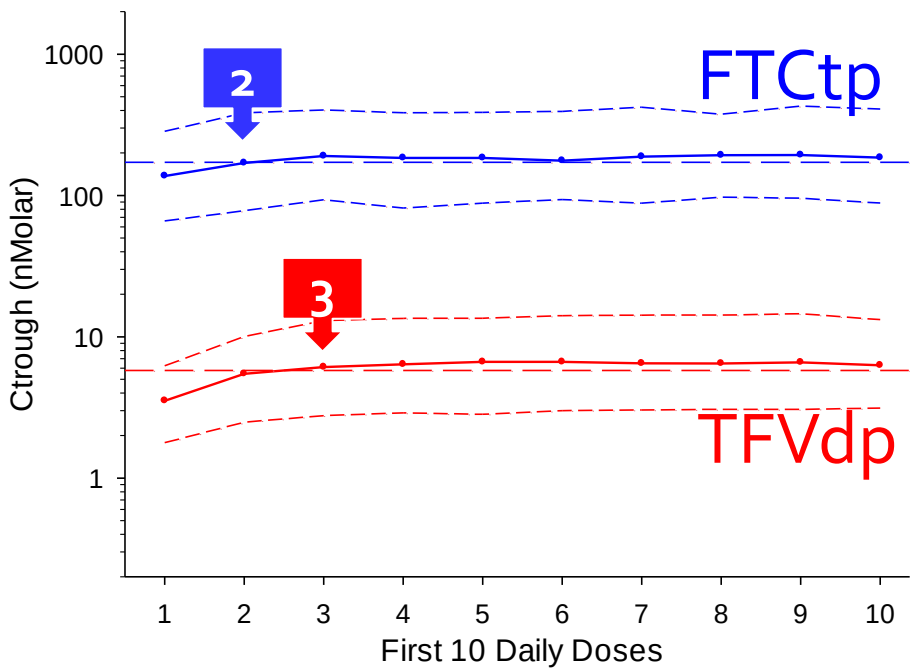


Sci Transl Med. 2011 Dec 7;3(112):112re4.

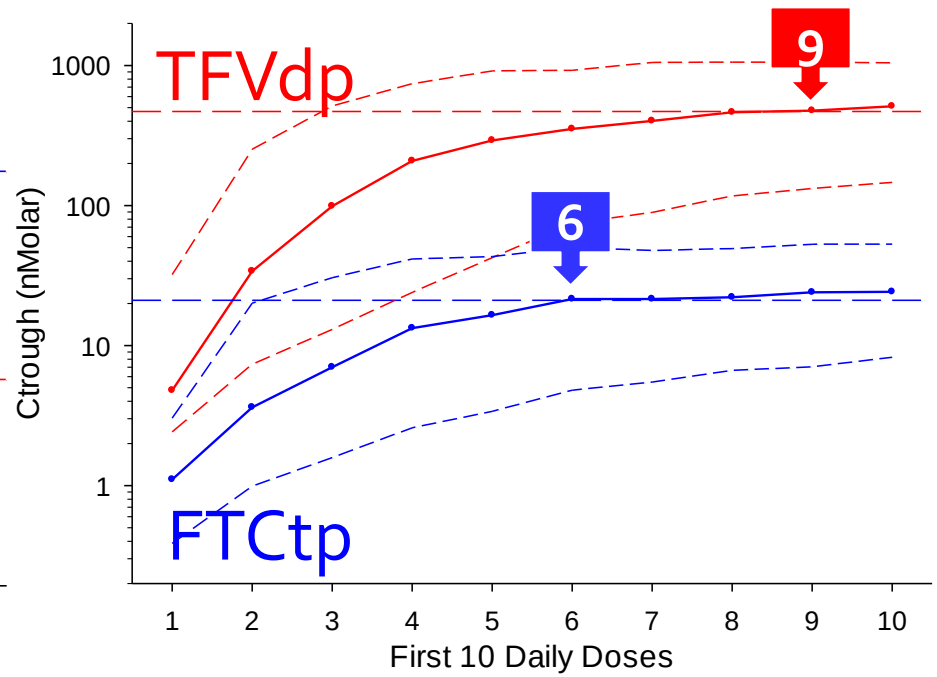
The Right Concentration

How Many Doses to Get to Steady-State Conditions?

Lower FGT Tissue



Rectal Tissue

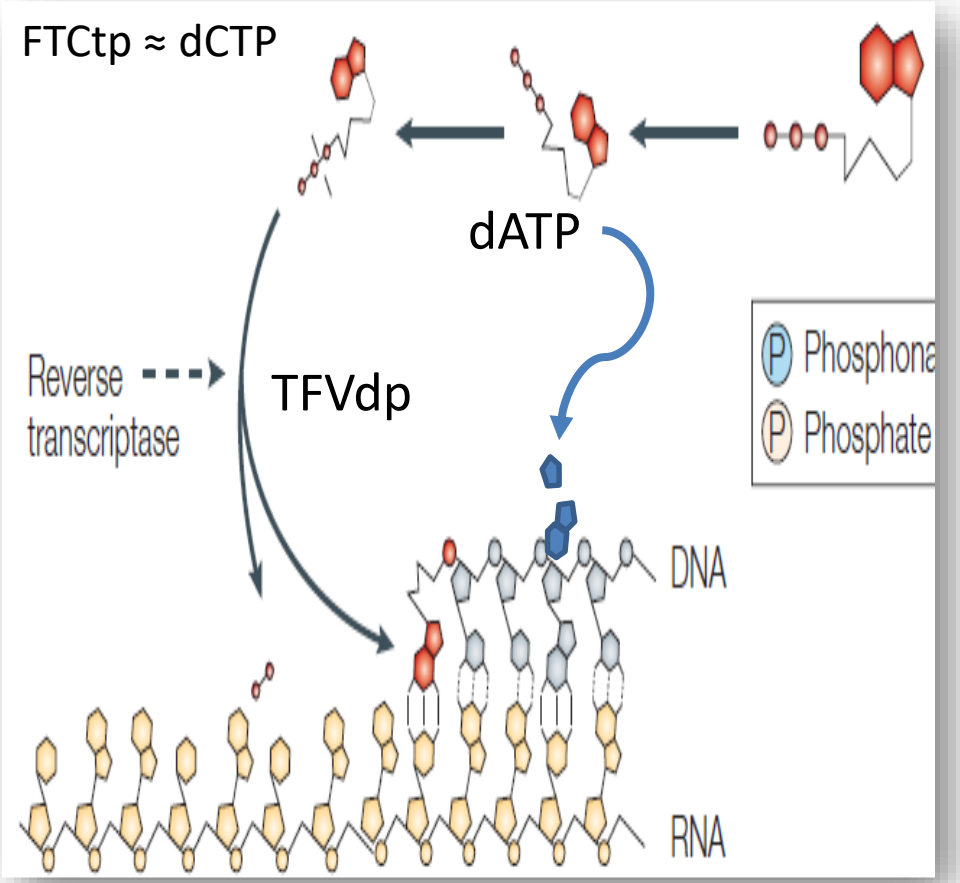


Cottrell et al J Infect Dis. 2016 Jul 1;214(1):55

Yang K. American Conference on Pharmacometrics 5, Abstract. Las Vegas NV October 12-15, 2014.

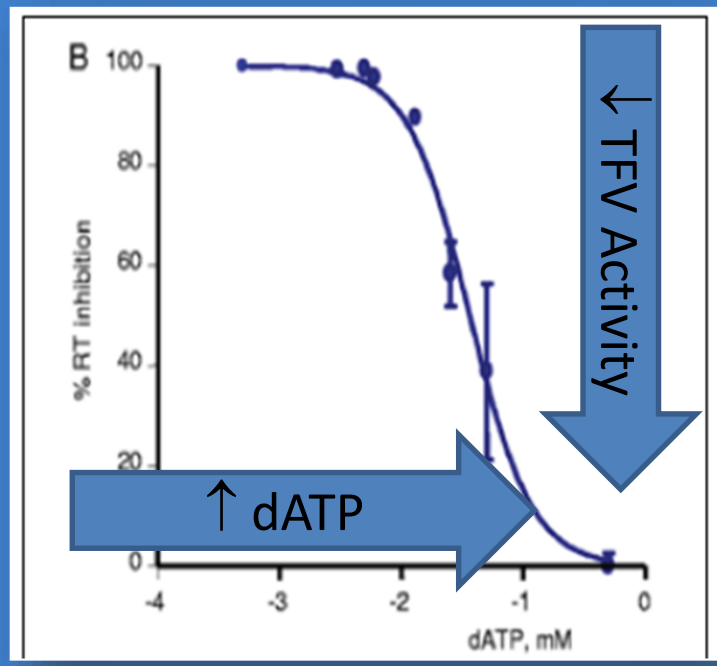
The Right Concentration:

More Than Just TFVdp and FTCtp For Efficacy In Mucosal Tissues



De Clerq Nature Reviews 2005

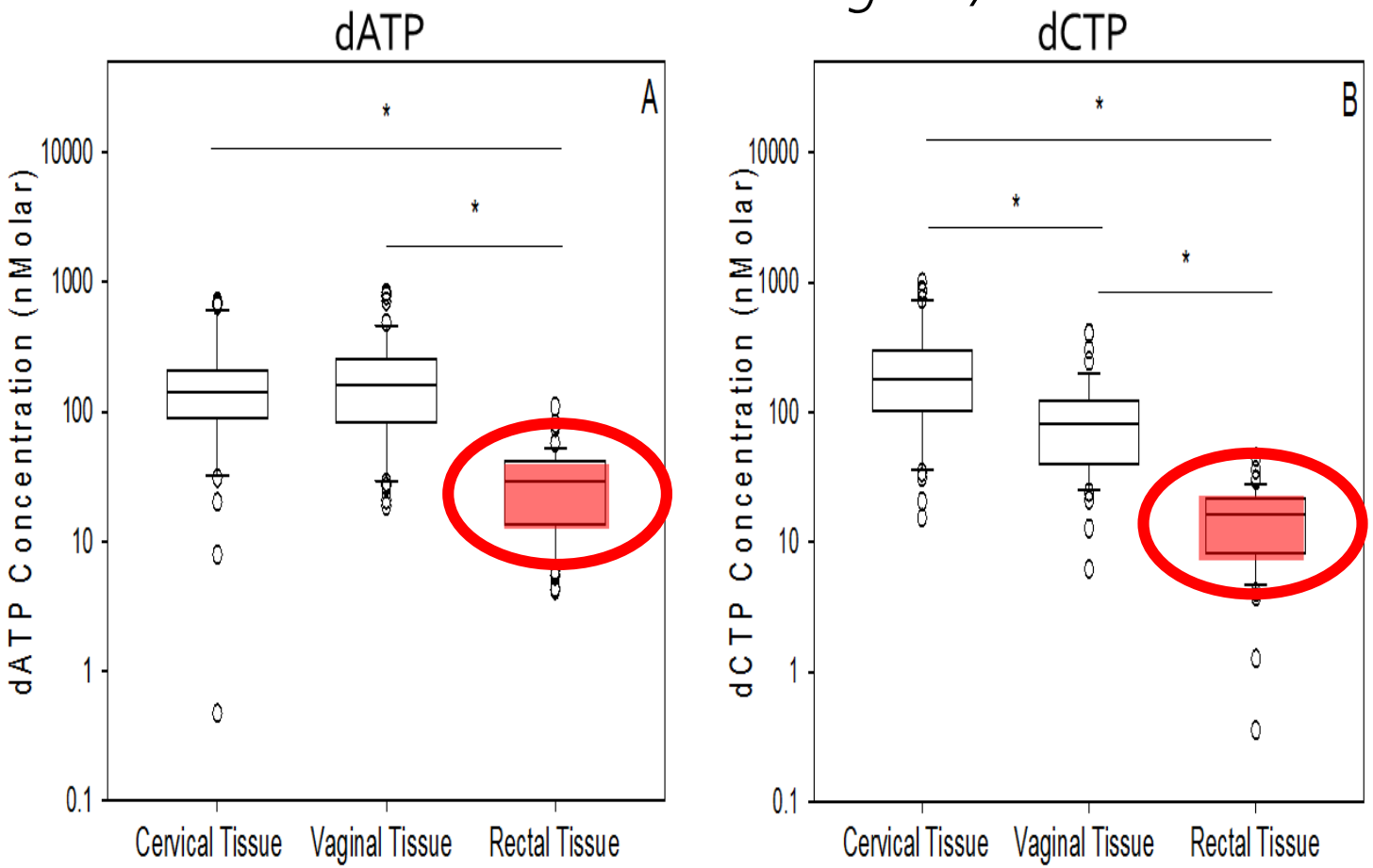
Reversion of TFVdp RT Inhibition With High dATP/TFVdp Ratios In Vitro



Garcia-Lerma et al J Virol 2011

The Right Concentration

Rectal Tissue dATP and dCTP <<< Vaginal/Cervical Tissue



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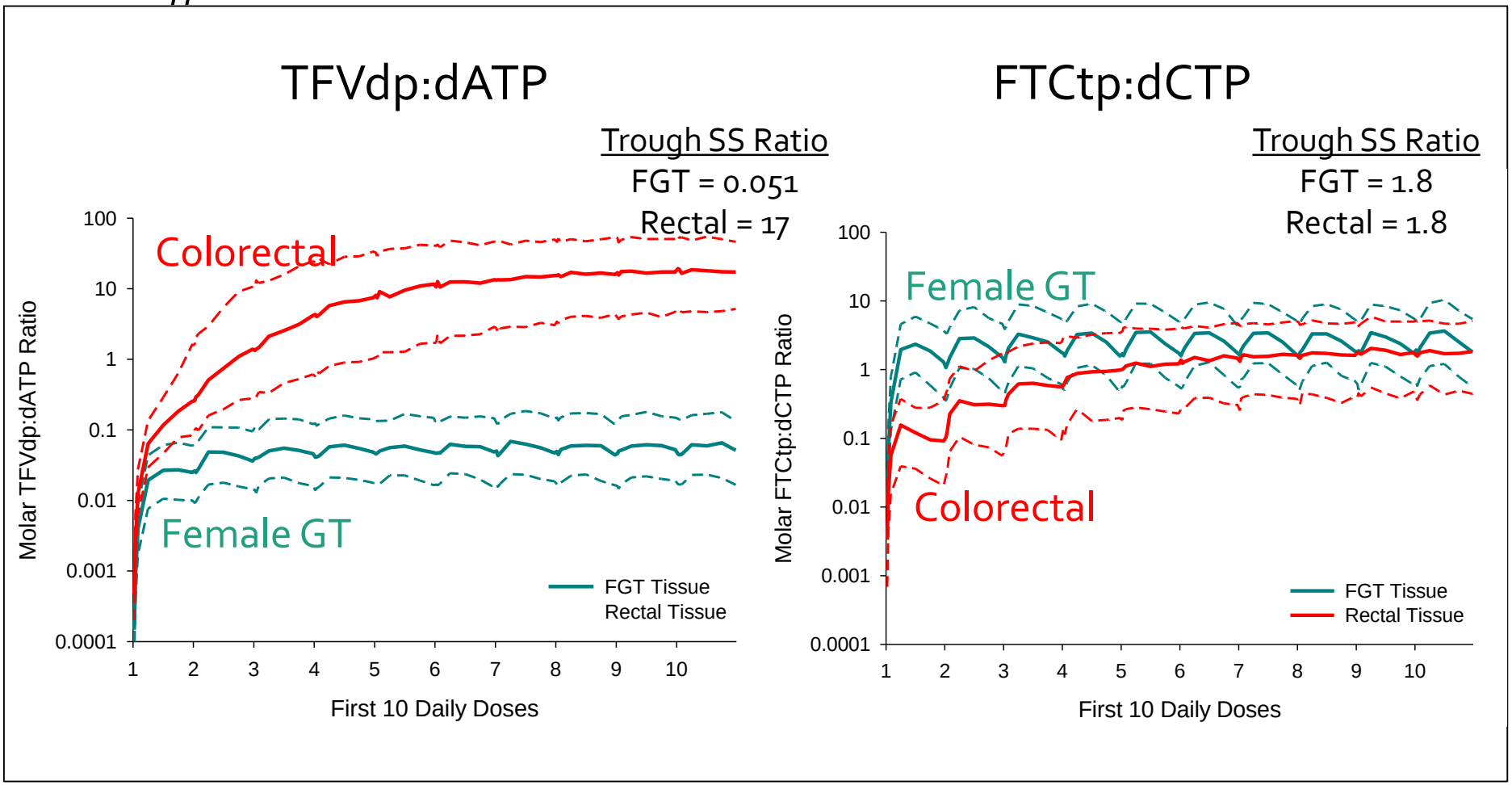
The Right Concentration

How Different are These Ratios in Mucosal Tissues?



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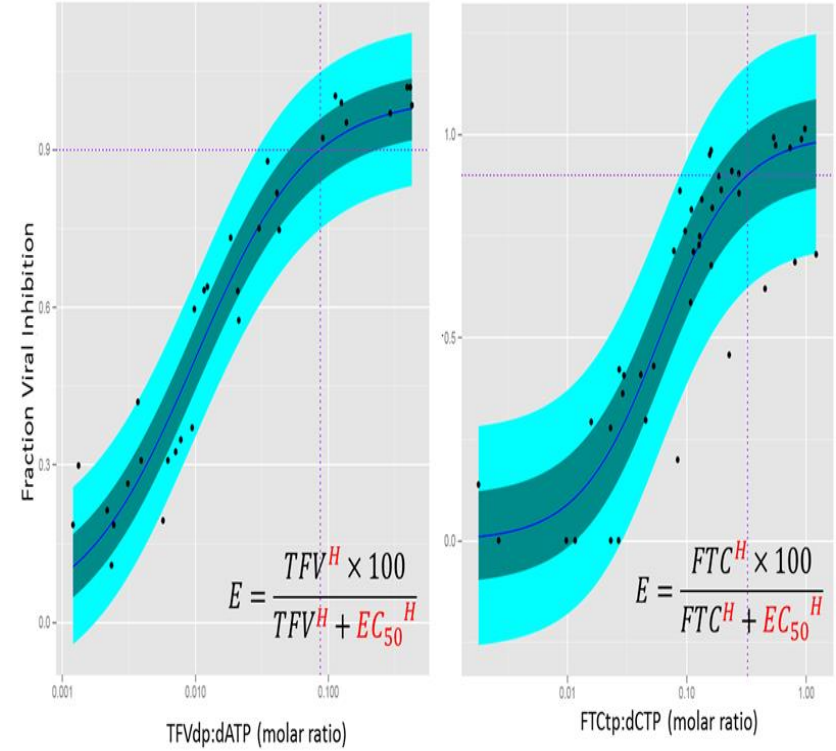
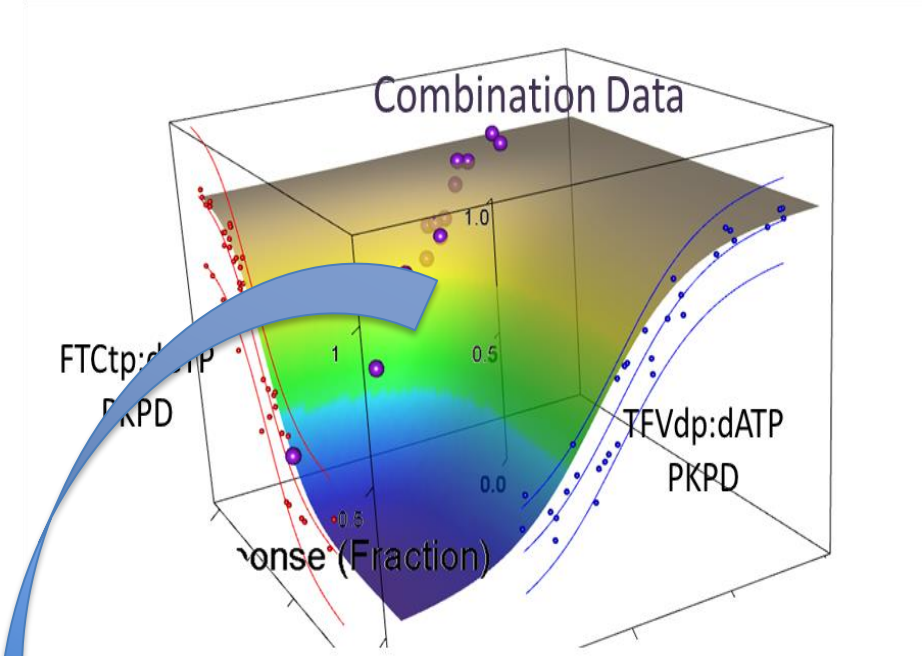
The Right Concentration

Choosing Pharmacologic Targets





- Ψ=0.632* (±0.074 SE), p<0.001
- Median-effects/Chou-Talalay shows combination index = 0.4-0.8

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

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

Target Ratios for Cellular Protection

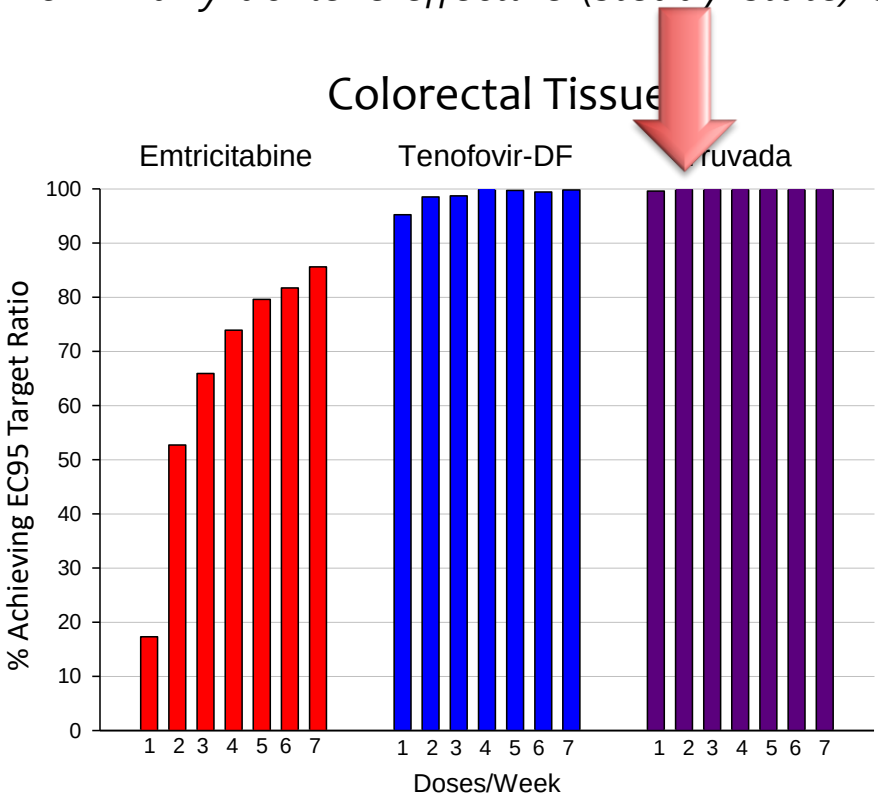
Evaluating Ψ:
- <1 = synergy
- 1 = Additivity
- >1=antagonism

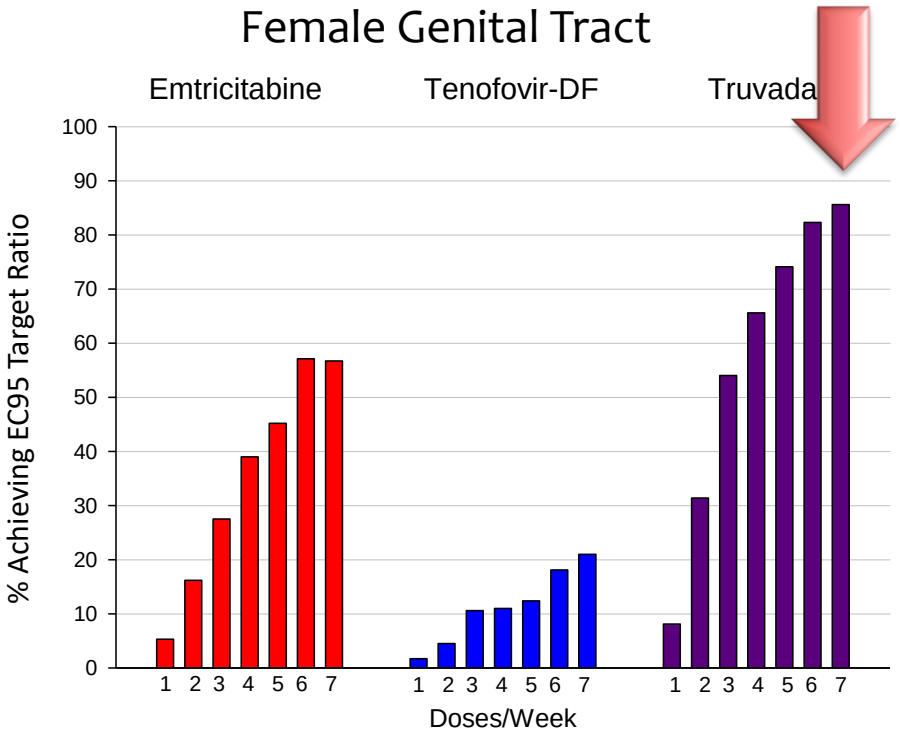
The Right Concentration

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

Estimating Efficacy With Various Doses/Week

How many achieve effective (steady-state) concentrations at the end of dosing interval?





iPrEx OLE= ↓ HIV incidence by 90% with 2 Truvada doses per week

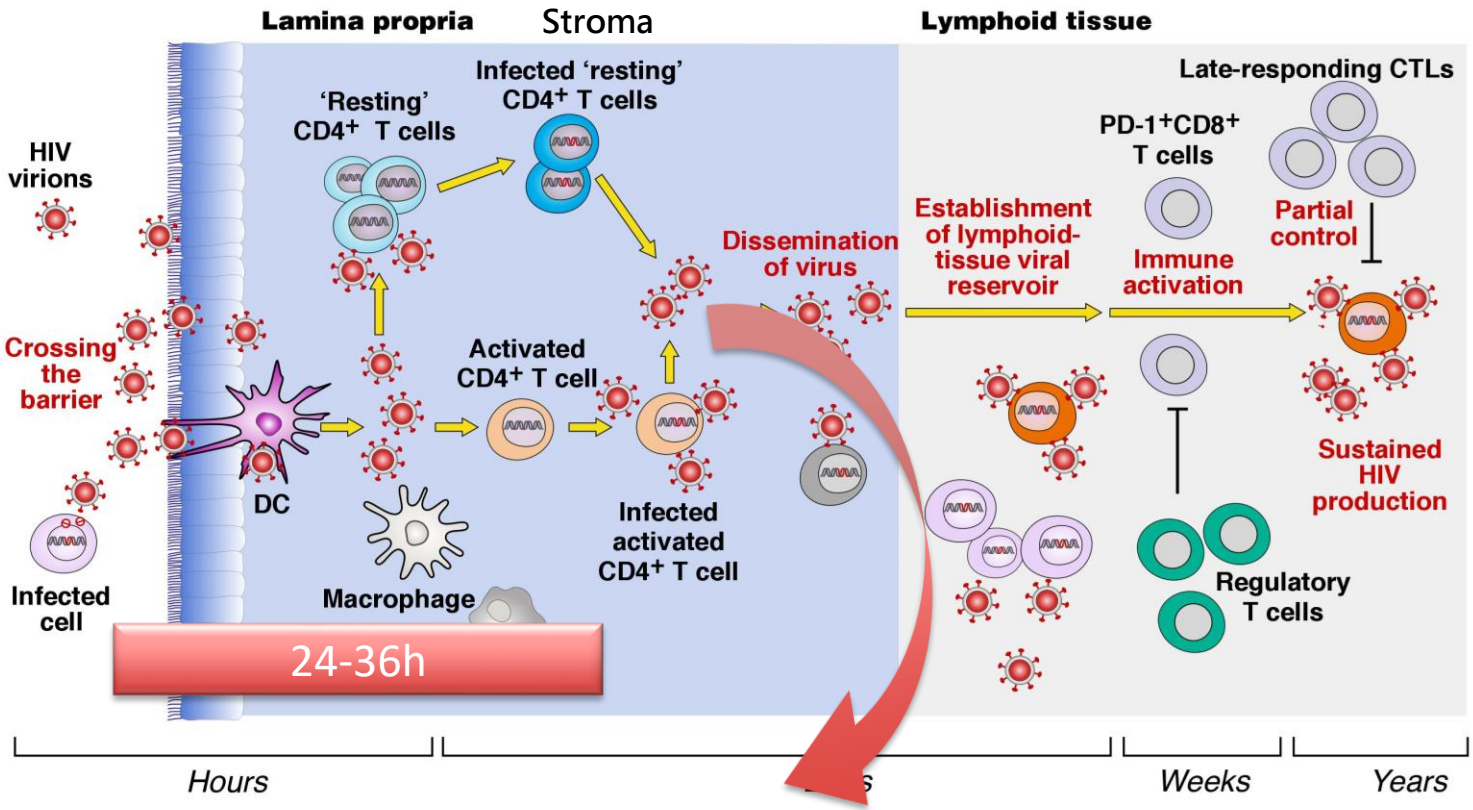
Anderson et al. Sci Transl Med Sep 12, 2012; 4(151): 151ra125.

Partners PrEP= ↓ HIV incidence by 90% with 7 Truvada doses per week

Donnell D et. al. JAIDS. 2014;66(3):340-348.;

The Right Time

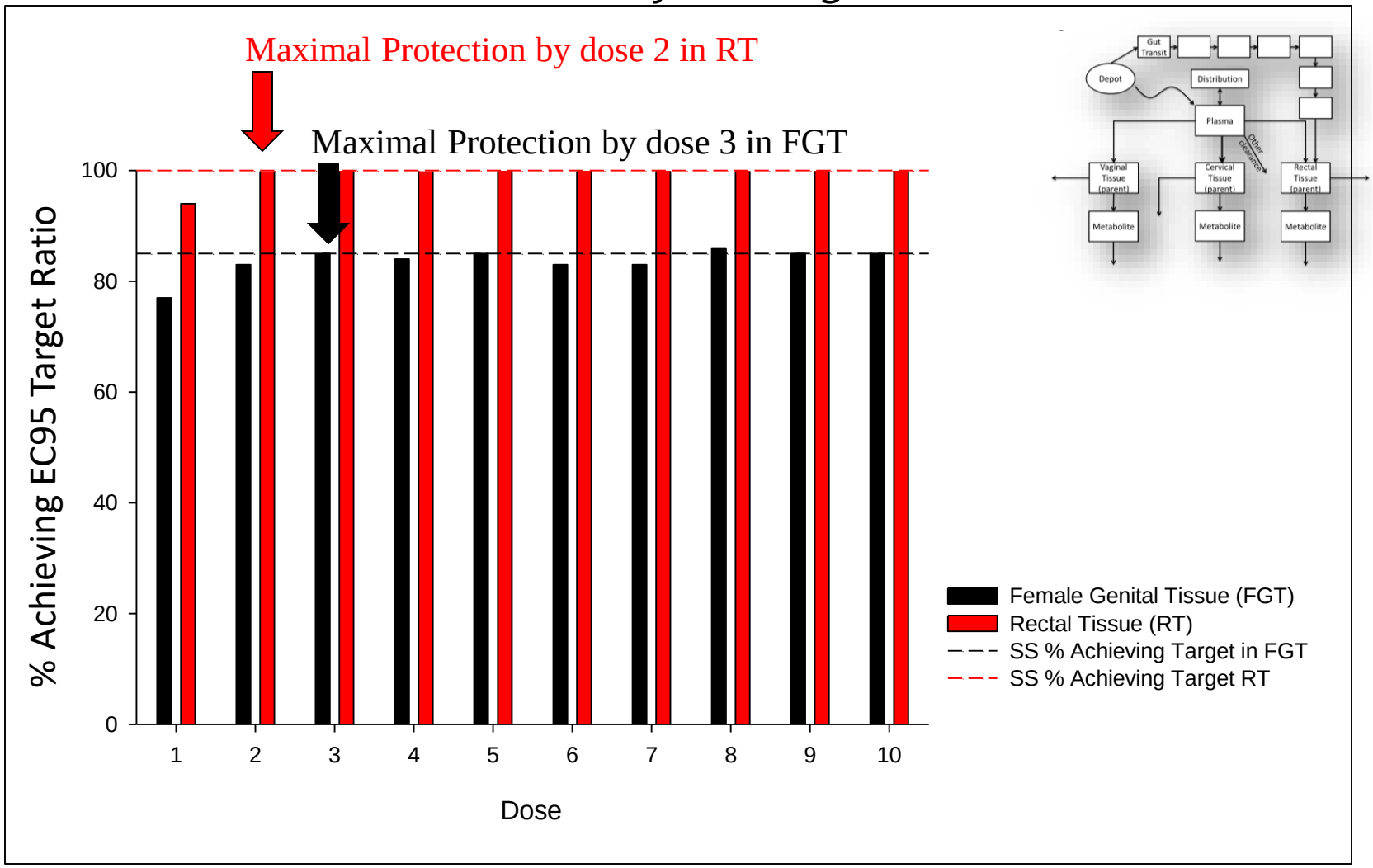
On Demand PrEP



replication-competent HIV may reside in cervical tissue cx up to 8d (Collins 2000)

The Right Concentration

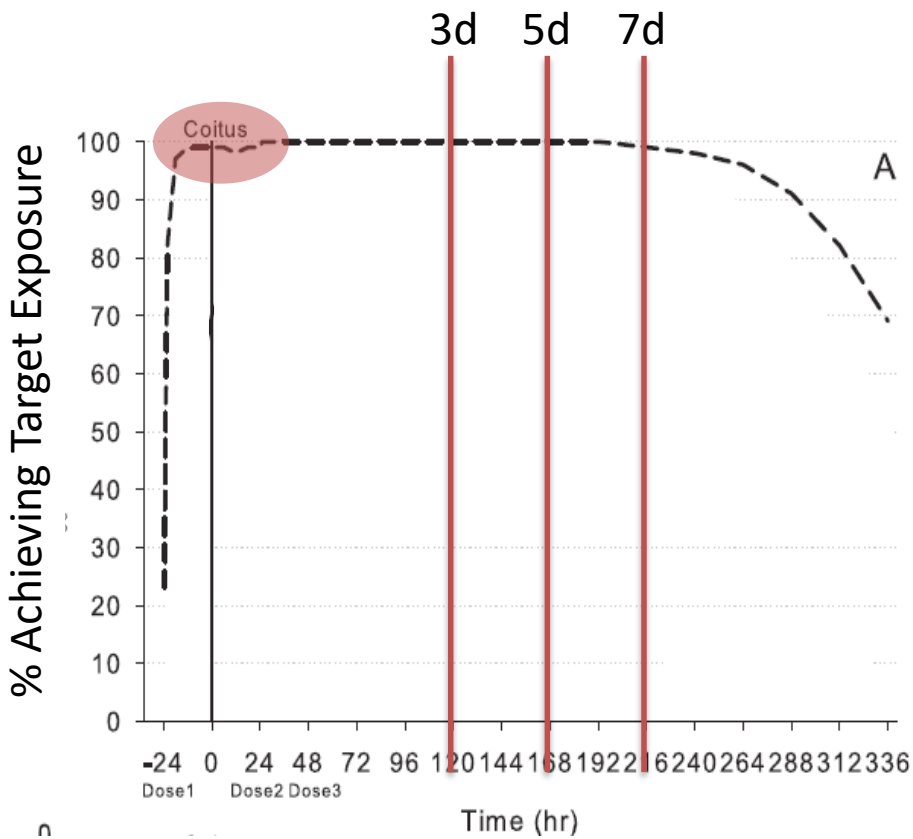
Time To Maximal Protection; Daily Dosing with Truvada®



The Right Time

Estimating Truvada Efficacy With Ipergay Dosing Strategy

Colorectal tissue



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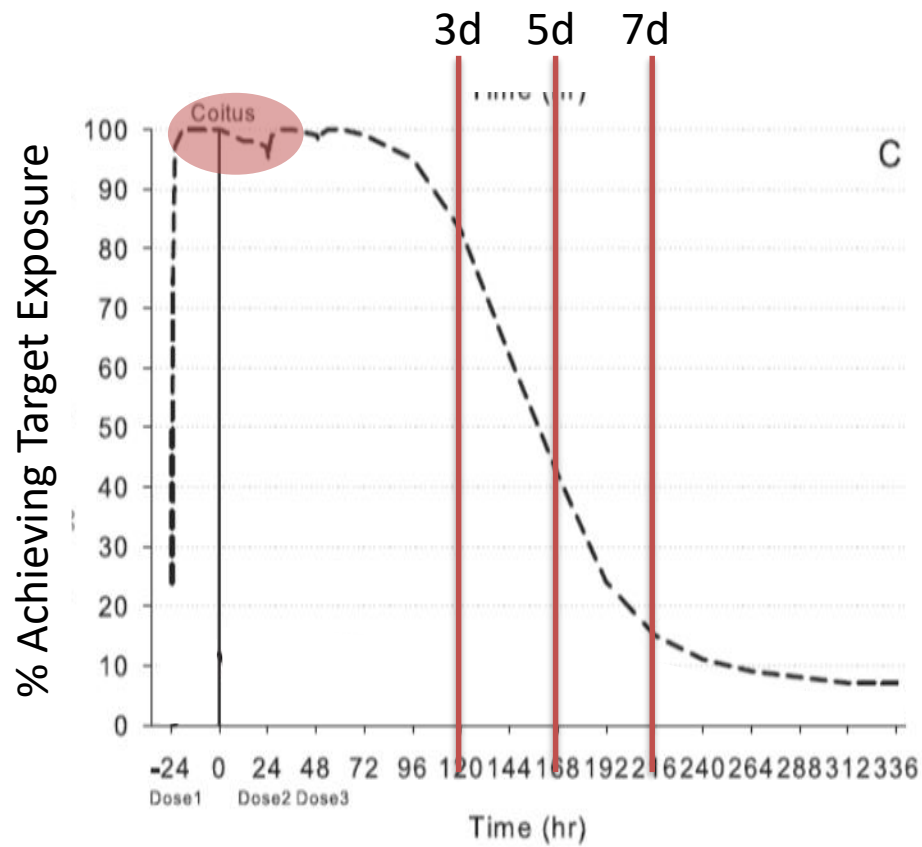

Does Pharmacology Support On Demand PrEP?

- Yes if…..
  - Drug/metabolite can quickly reach sites of infection *Right site*
    - mucosal tissues/regional lymph nodes
  - Drug/metabolite achieves potent concentrations *Right conc*
    - above IC50, IC95?
  - Drug/metabolite has long residence time to cover residual virus *Right time*
    - Otherwise may need to continue dosing

- Caveats
  - Can virus be trafficked to sites of low drug concentrations?
  - Do inflammatory processes overwhelm the activity of standard doses/dose frequencies?
  - Might other sources of pharmacologic variability exist (eg microbiome)?

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R01 AI096138

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T32 GM086330
K23 HD064814
R37 DK049381
R56 AI091547
K23 AI077355

GSK/Viiv
Gilead
Tibotec
Merck

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HIV CARE Collaboratory of AIDS Researchers for Eradication
UNIVERSITY OF NORTH CAROLINA CENTER FOR AIDS RESEARCH