

A Translational Pharmacology Approach to Predicting Outcomes of Pre-exposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine

Cottrell ML, Yang KH, Prince HM, Sykes C, White N, Malone S, Dellon ES, Madanick RD, Shaheen NJ, Hudgens MG, Wulff J, Patterson KB, Nelson JA, Kashuba AD

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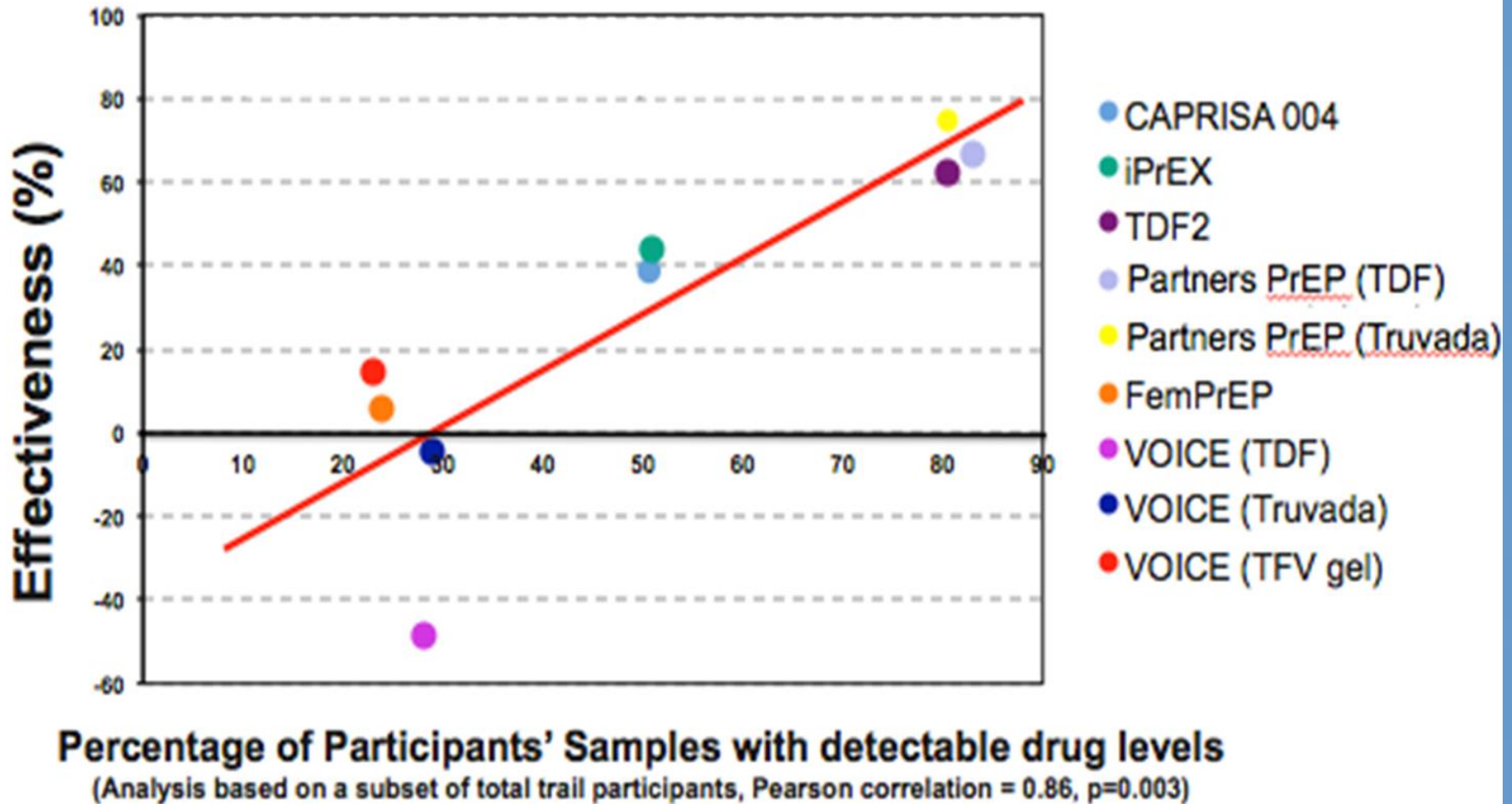


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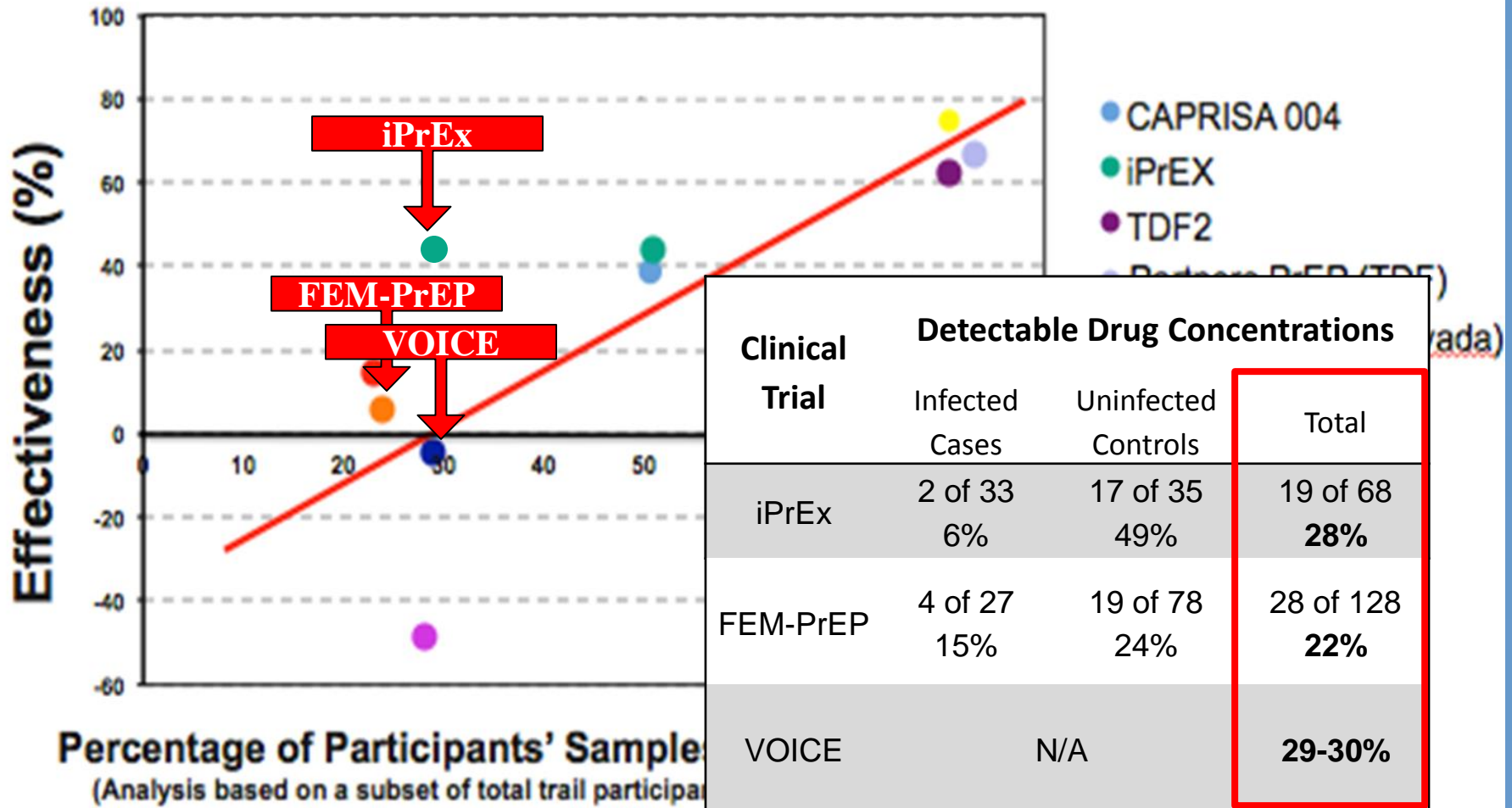
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Adherence Correlates with Clinical Trial Results



SS Abdool Karim, personal communication

Adherence Correlates with Clinical Trial Results

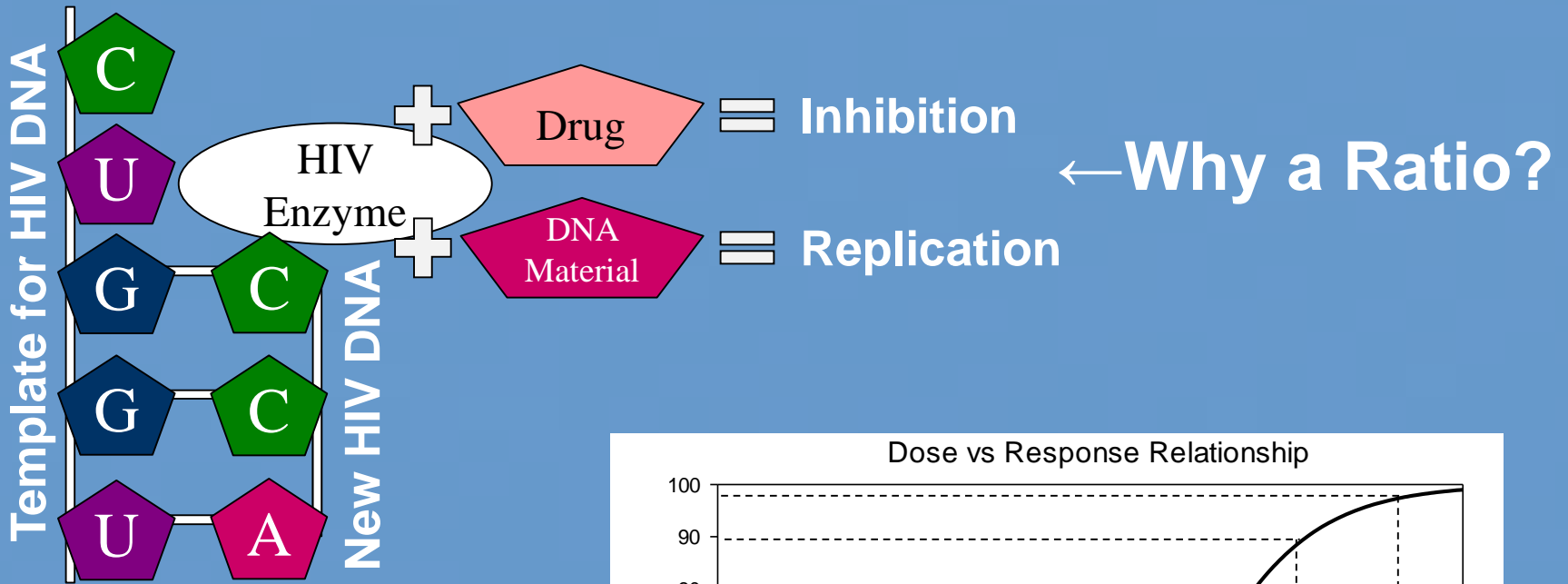


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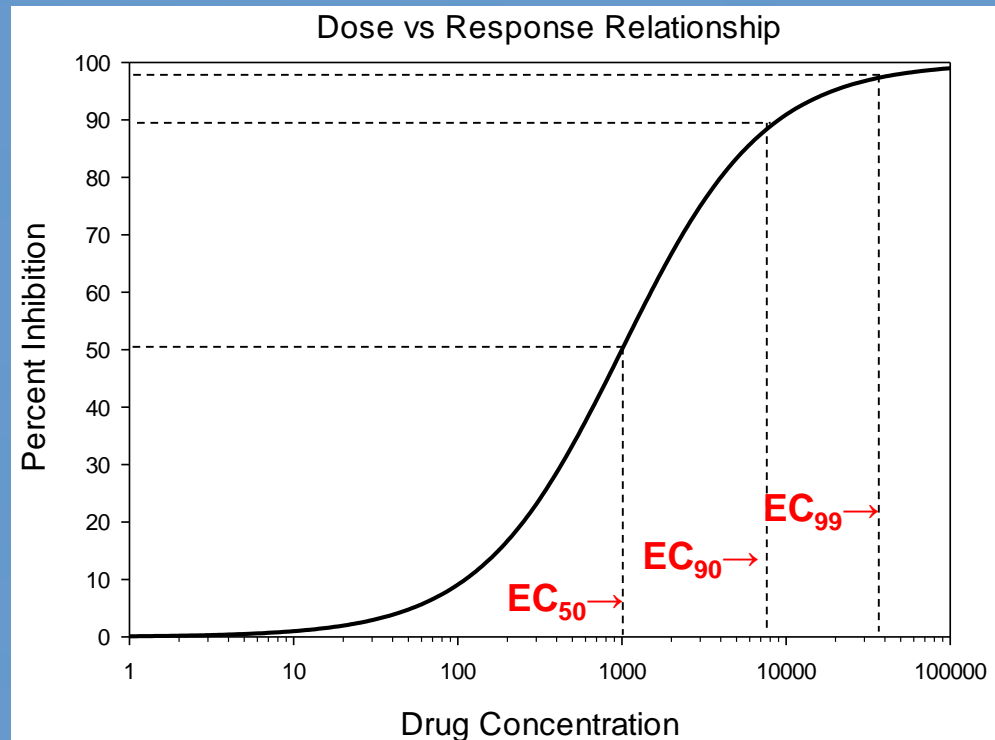
Study Approach

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 \pm FTC for HIV PrEP

Selecting a Target



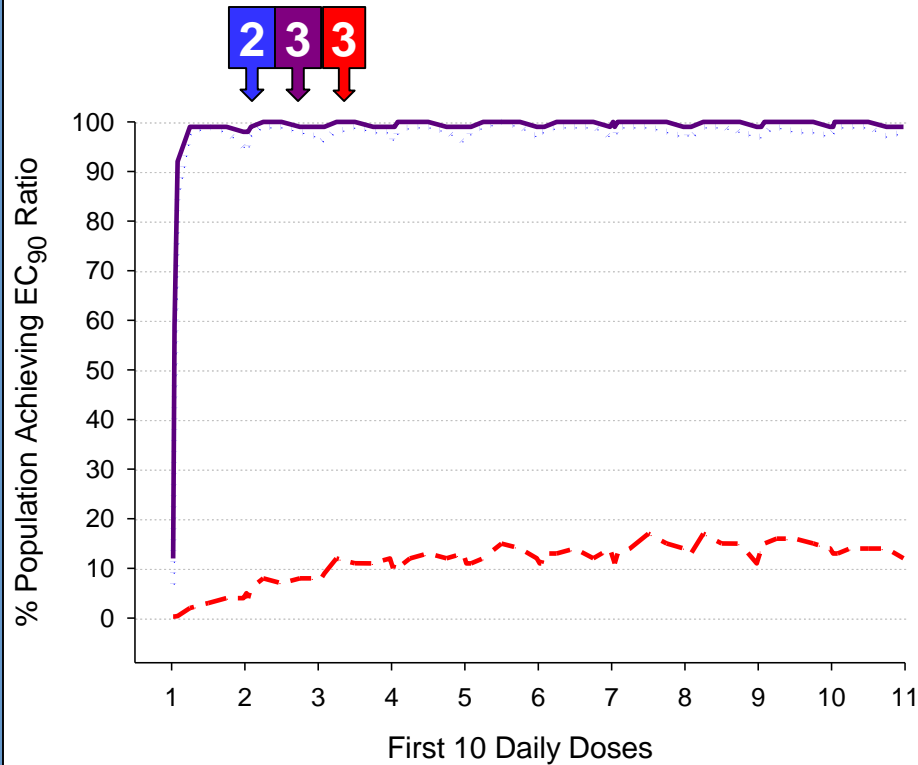
Why EC90? →



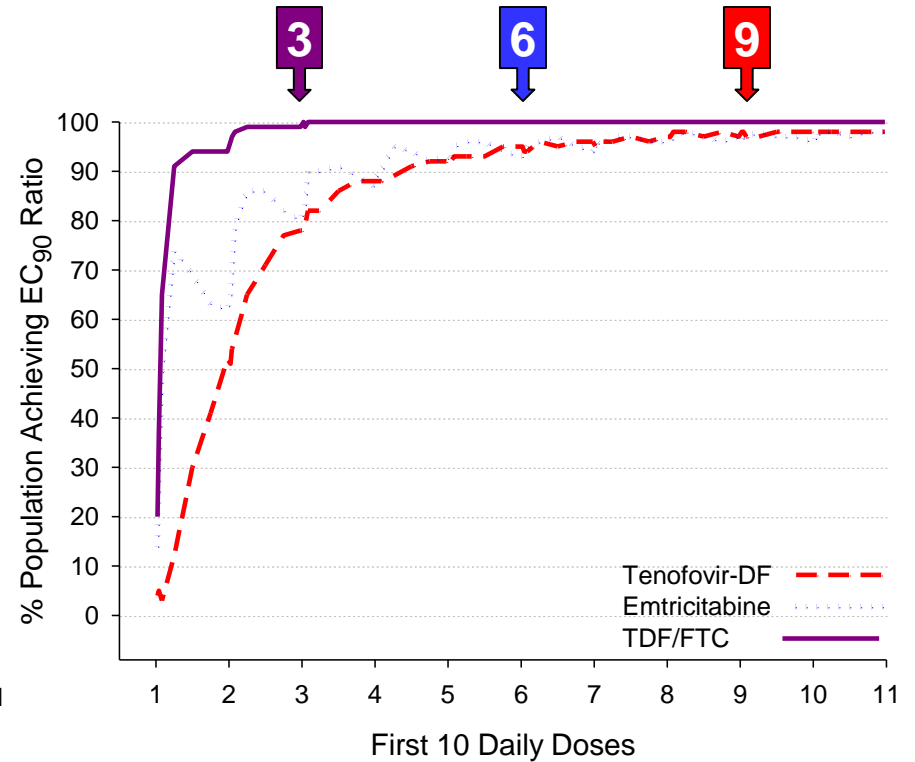
Predicting Efficacy

First 10 Daily Doses

Lower FGT Tissue



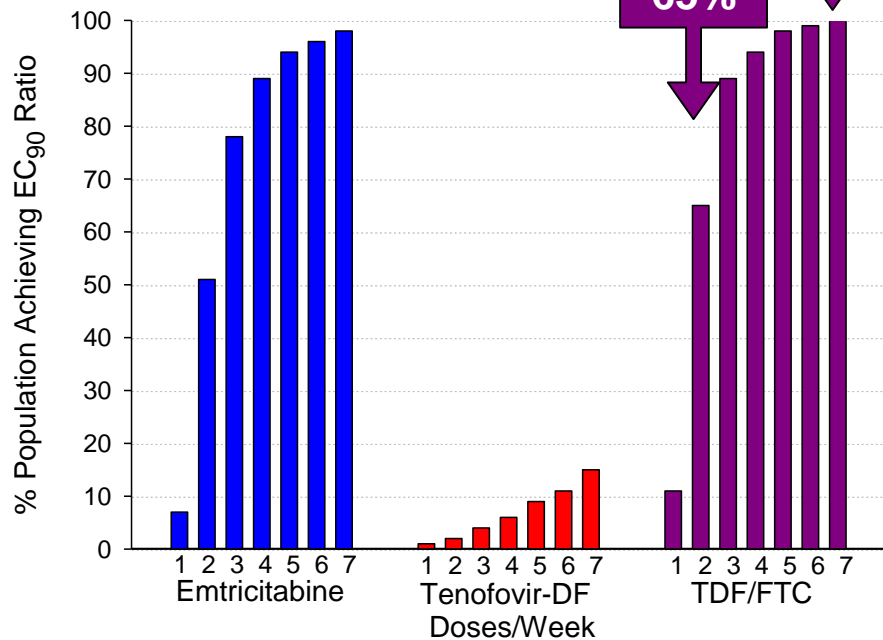
Rectal Tissue



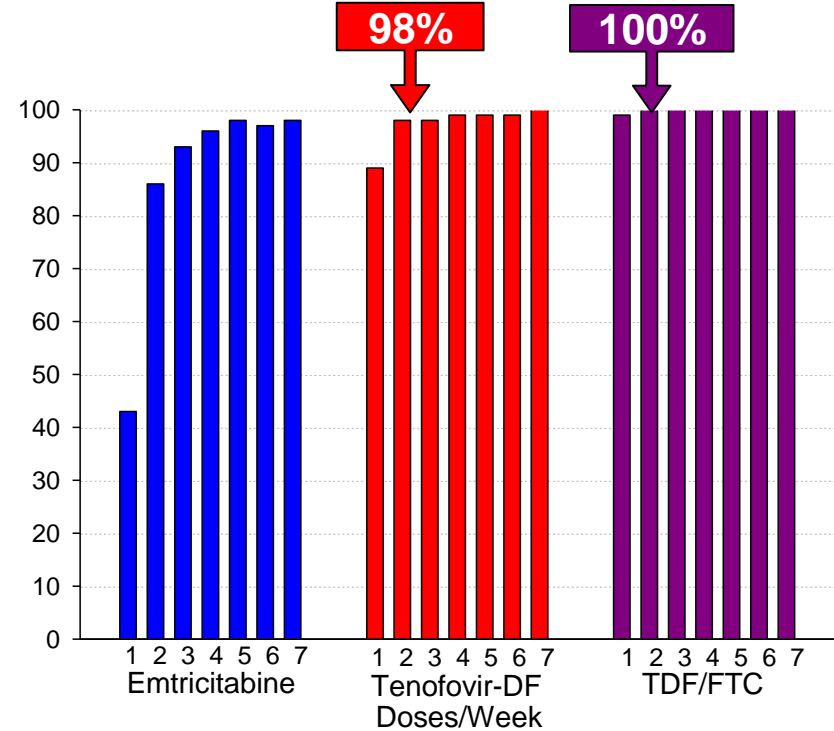
Predicting Efficacy

Reduced Frequency Dosing

Lower FGT Tissue



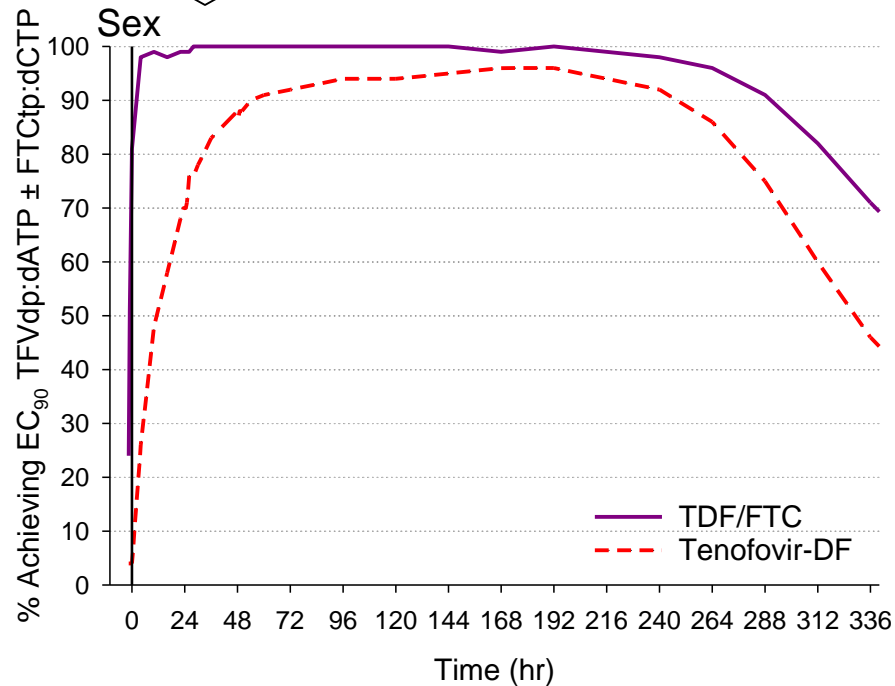
Rectal Tissue



Predicting Efficacy On Demand PrEP

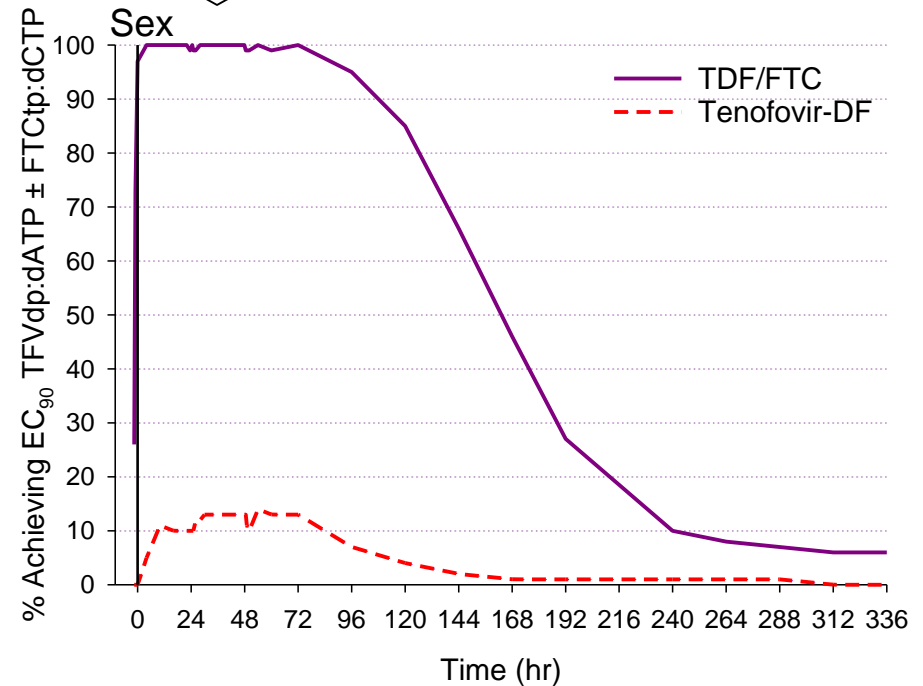
Rectal Tissue

Take #2 Tabs 2-24hrs
before sex
Take #1 Tab 24hrs later
Take #1 Tab 48hrs later



Lower FGT Tissue

Take #2 Tabs 2-24hrs
before sex
Take #1 Tab 24hrs later
Take #1 Tab 48hrs later



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. 100% of population achieves our efficacy target with daily versus 100% in lower GI tract and 65% in FGT with twice weekly Truvada[®]
4. Our model reasonably correlated with clinical trial results