

Pharmacokinetics and Pharmacodynamics of the Reverse Transcriptase Inhibitor Tenofovir & Prophylactic Efficacy against HIV-1 Infection



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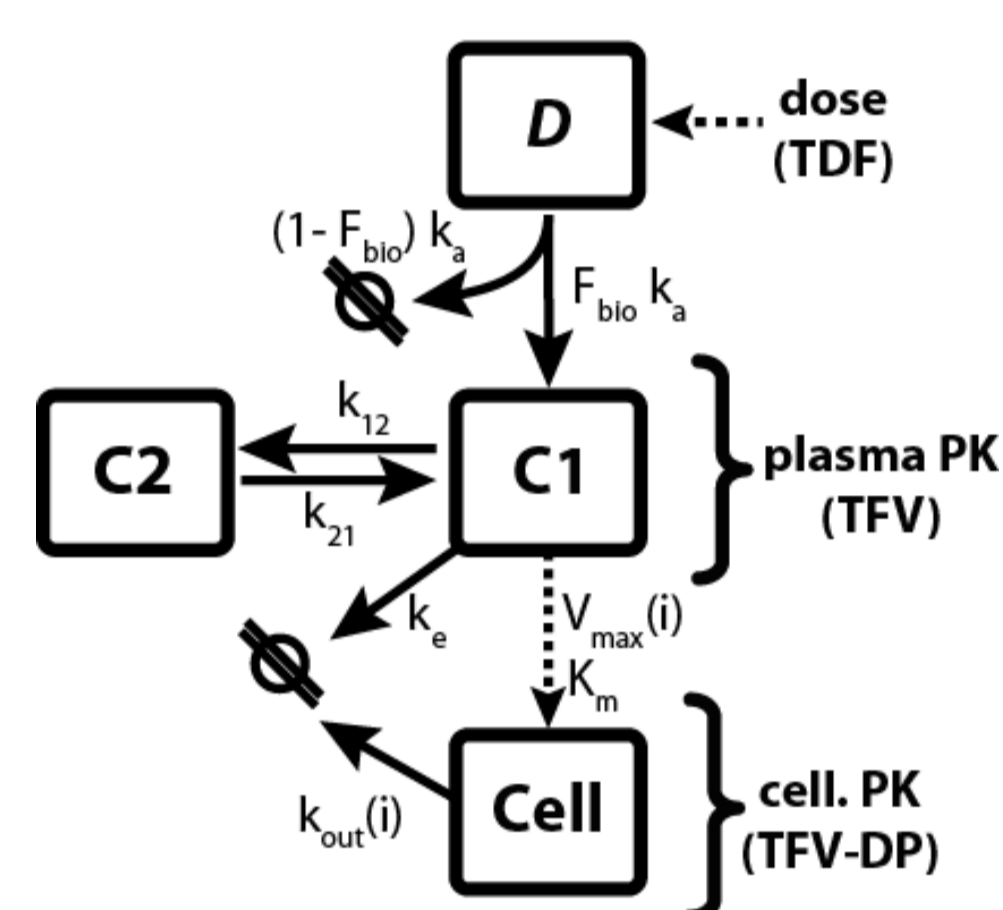
Background and Objectives

After almost 30 years since the discovery of HIV-1 as the causal agent of AIDS the epidemic is still not controlled. The spread of HIV-1 could be halted, if effective vaccines were available. Unfortunately, after years of research this goal seems elusive. In order to further prevent sexual HIV-1 transmission, the use antiviral drugs was suggested (nominated as the breakthrough of the year 2011 [1]).

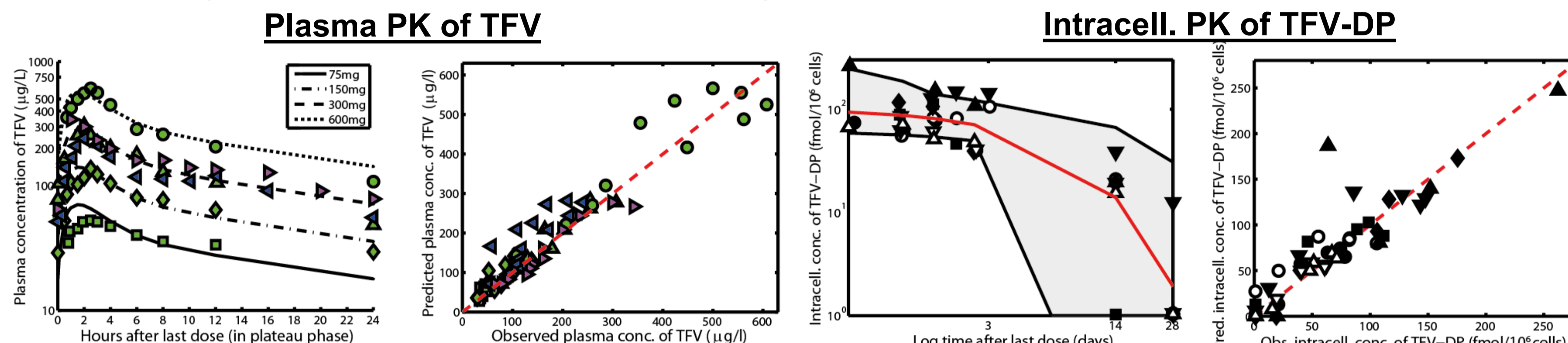
Pre-exposure prophylaxis (PrEP) aims to protect healthy individuals at high risk (e.g. sero-negative partners in sero-discordant couples) from acquiring HIV-1 infection. The administered antivirals decrease the infectivity of the transmitted virus, which subsequently decreases the likelihood of (irreversible) infection of the individual at risk. The pro-drug tenofovir-disoproxil-fumarate (TDF) is a key component in all currently tested regimens. Truvada (TDF + emtricitabine) was just recently approved by the FDA for use as PrEP [2]. The aim of this study is to assess the pharmacokinetics and pharmacodynamics of the prodrug tenofovir-disoproxil-fumarate (TDF), to probe the efficacy of different prophylactic strategies and to assess the sensitivity towards the number of transmitted viruses, timing of TDF administration and adherence. In view of the recent approval this may raise awareness, encourage experimental assessment and help to avoid the misuse of TDF-based PrEP, which carry the risk of drug resistance selection and HIV-1 spread through risk compensation.

[1] Cohen J. Science (2011) 334(6063): p. 1628; [2] Cohen J. Science (2012) 336(6083): p. 792

Pharmacokinetics



TDF is administered orally. After first pass of TDF through the liver, tenofovir (TFV) is formed. TFV is also the predominant circulating form [3,4]. After uptake into HIV target cells, TFV can become sequentially phosphorylated to form tenofovir diphosphate (TFV-DP), the active form, which is an analog of endogenous dATP. TFV-DP subsequently competes with dATP for incorporation into nascent viral DNA during HIV-1 reverse transcription (RT), where it prevents further DNA polymerization during RT, once it becomes incorporated [5]. TFV-DP thus prevents the production of pro-viral DNA, which is required for stable host cell infection and viral replication..

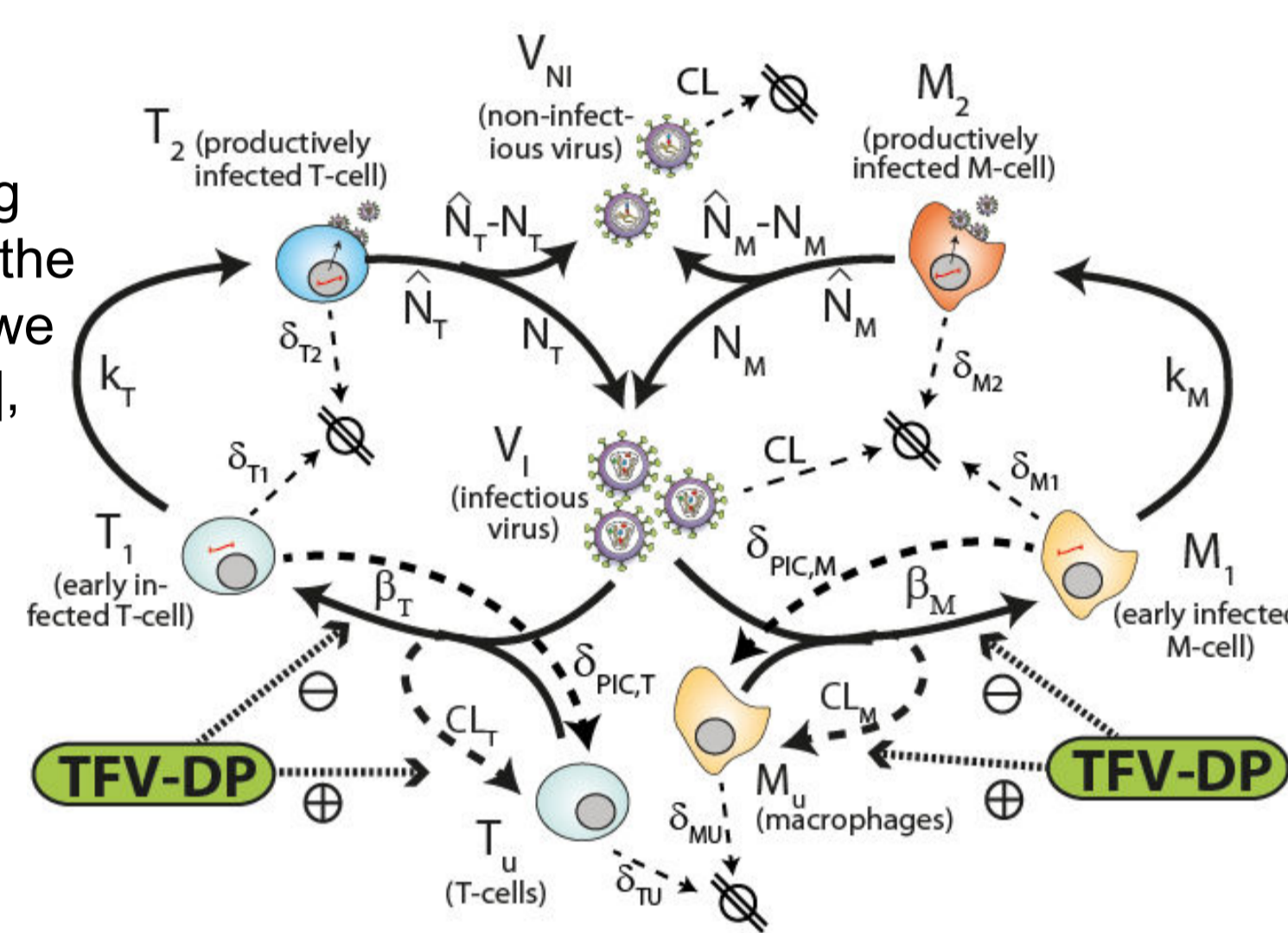


[3] Naesens L. et al. Antimicrob Agents Chemother (1996) 49(1): p. 22-28; [4] Kearney BP. et al. Clin Pharmacokinet (2004) 43(9): p. 595-612; [5] von Kleist M. et al. PLoS Comput. Biol. (2012) 8: e1002359; [6] Droste J. et al. Antimicrob Agents Chemother (2005) 49(2): p. 680-4; [7] Barditch-Crovo. et al. Antimicrob Agents Chemother 45(10): p. 2733-39; [8] Chittick G. et al. Antimicrob Agents Chemother 50(4): p. 1304-10; [9] Hawkins T. et al. J Acquir Immune Defi Syndr 39(4): p. 406-11

Antiviral Efficacy

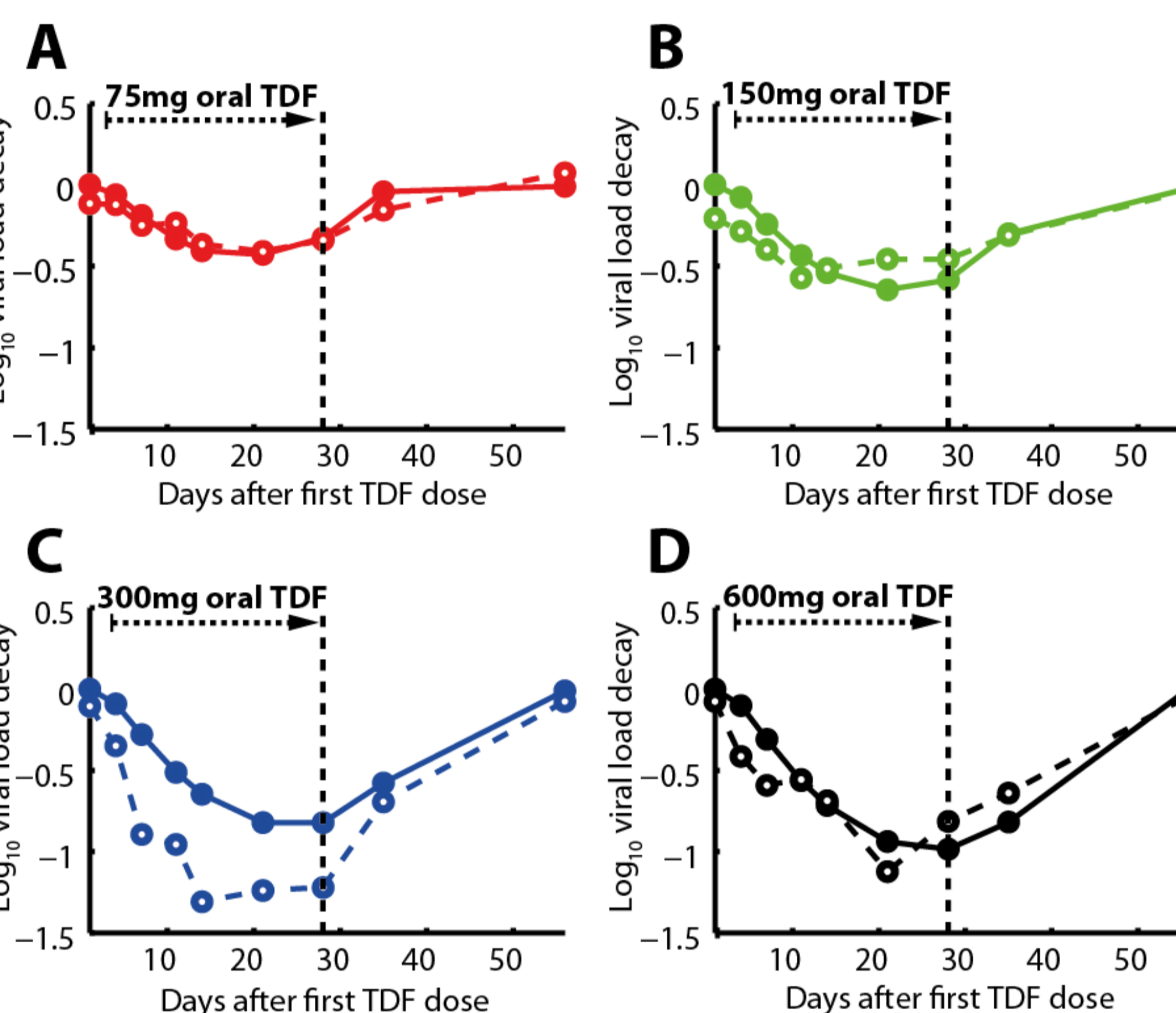
In order to predict (i) viral load kinetics following TDF treatment in HIV-infected patients and (ii) the infection probability for uninfected individuals, we adopted the virus dynamics model from [10,11], which is depicted on the right.

$$\begin{aligned} \frac{d}{dt} T_U &= \lambda_T + \delta_{PIC,T} \cdot T_1 - \delta_T \cdot T_U - \beta_T(t) \cdot V_1 \cdot T_U \\ \frac{d}{dt} M_U &= \lambda_M + \delta_{PIC,M} \cdot M_1 - \delta_M \cdot M_U - \beta_M(t) \cdot V_1 \cdot M_U \\ \frac{d}{dt} T_1 &= \beta_T(t) \cdot V_1 \cdot T_U - (\delta_{T_1} + \delta_{PIC,T} + k_T) \cdot T_1 \\ \frac{d}{dt} M_1 &= \beta_M(t) \cdot V_1 \cdot M_U - (\delta_{M_1} + \delta_{PIC,M} + k_M) \cdot M_1 \\ \frac{d}{dt} T_2 &= k_T \cdot T_1 - \delta_{T_2} \cdot T_2 \\ \frac{d}{dt} M_2 &= k_M \cdot M_1 - \delta_{M_2} \cdot M_2 \\ \frac{d}{dt} V_1 &= N_M \cdot M_2 + N_T \cdot T_2 \\ &\quad - V_1 \cdot [CL + (CL_T(t) + \beta_T(t)) \cdot T_U + (CL_M(t) + \beta_M(t)) \cdot M_U] \\ \frac{d}{dt} V_{NI} &= [(\hat{N}_T - N_T)T_2 + (\hat{N}_M - N_M)M_2] - CL \cdot V_{NI} \end{aligned}$$



PK-PD Coupling

$$\begin{aligned} \beta_{T/M}(t) &= \beta_{T/M}(\phi) \cdot (1 - \eta(t)) \\ CL_{T/M}(t) &= \left(\frac{1}{P_{rev}} - (1 - \eta(t)) \right) \cdot \beta_{T/M}(\phi) \\ 1 - \eta(t) &= \frac{IC_{50}}{IC_{50} + C_{cell}(t)} \end{aligned}$$



For predicting viral load kinetics in infected individuals, we used the deterministic infected (drug-free) fix-point of the model as a starting condition and then monitored viral dynamics following 28 days monotherapy with 75- 150-, 300- and 600mg oral TDF. Median predicted viral decay is represented by the solid lines. Measured median viral decay data was taken from [7] (dashed lines).

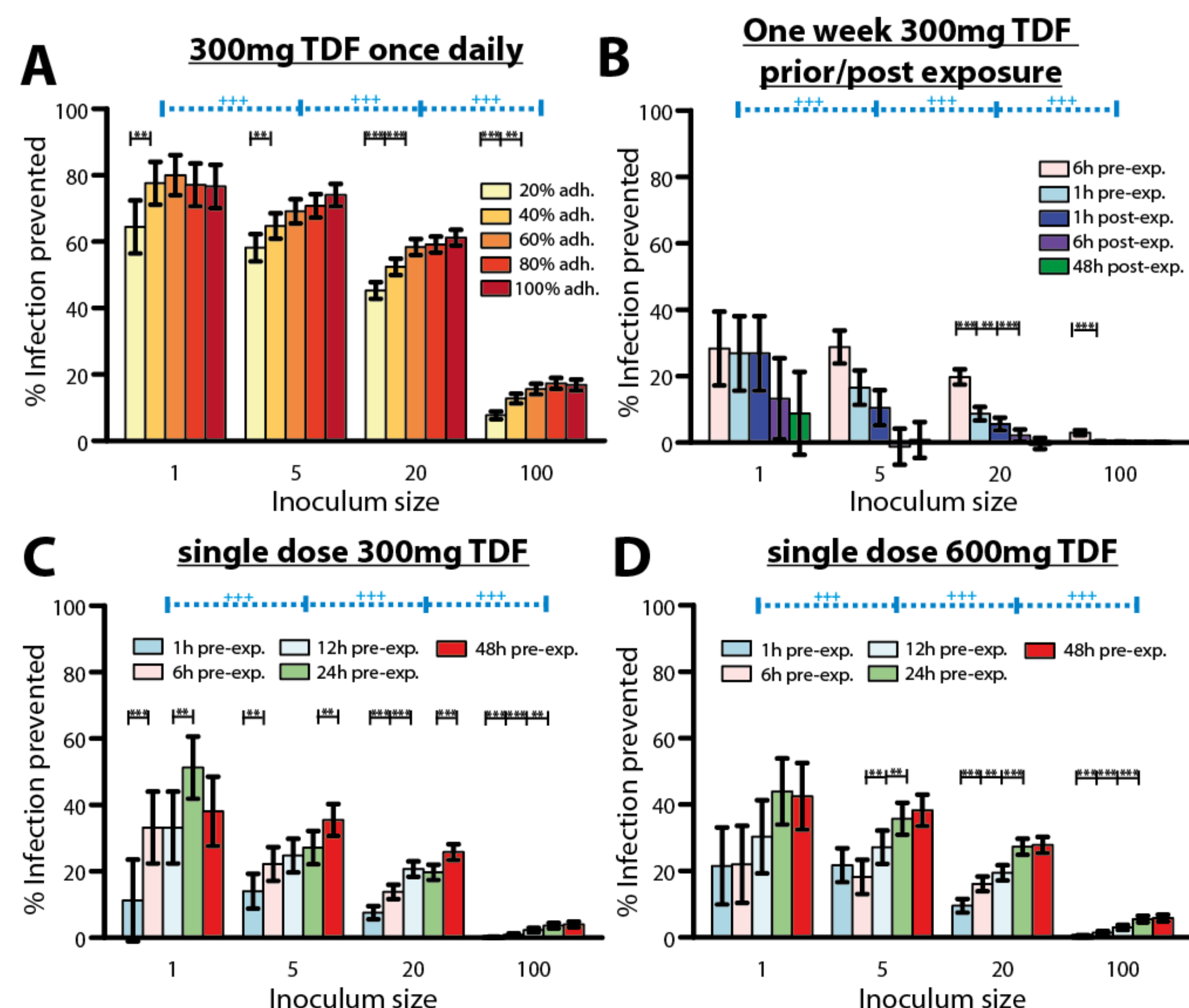
[10] von Kleist M. et al. Plos One, 2011: e18204; [11] von Kleist M. et al. Plos Comp Biol, 2010: e1000720

Prophylactic Efficacy

For assessing the infection probability, we used the uninfected fix-point of the model as starting condition and inoculated the respective number of infectious viruses V_0 to simulate viral challenges. Infection (and thus transmission) denotes an intrinsically stochastic process. To fully regard intrinsic stochasticity, we choose a hybrid stochastic-deterministic simulation approach, see e.g. [10]. In the simulations, infection was irreversible by the time that the predicted number of viruses exceeded 1 million particles (because the system behaves deterministically and approaches its infection fix-point). Therefore, we recorded an infection event during our simulations, whenever the viral population crossed this threshold in a previously uninfected 'virtual patient' at risk. The percentage infections prevented, when TDF is taken prophylactically was then calculated using the following formula:

$$\% \text{ infections prevented} = 100 \cdot \left(1 - \frac{P(\text{inf.} | V_0, S)}{P(\text{inf.} | V_0, \emptyset)} \right)$$

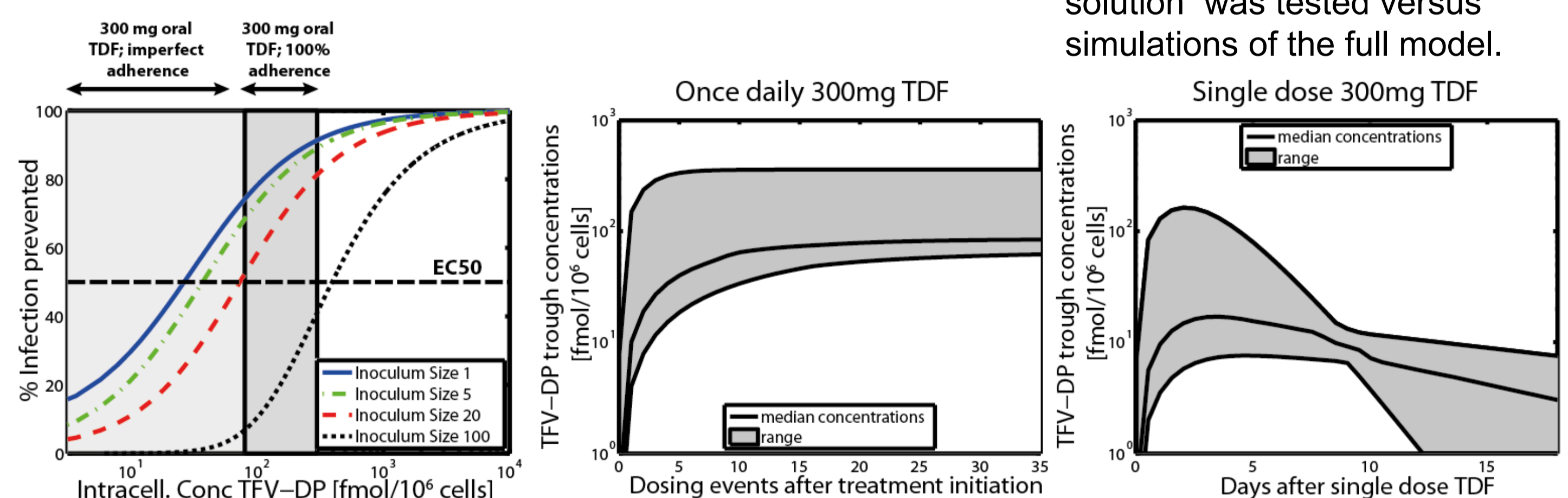
where $P(\text{inf.} | V_0, \emptyset)$ is the probability of infection in the absence of drugs \emptyset , when $V_0 \in \{1, 5, 20, 100\}$ infectious viruses come into contact with a cellular environment that facilitates their reproduction within the susceptible individual.



Concentration-response and analytical solution

$$\begin{aligned} P_0 &= \underbrace{P(\emptyset | V_0(\tau=1) = n)}_{\text{clearance during first repl. cycle}} + \underbrace{\sum_{\tau=2}^{\infty} \sum_{i=1}^{\infty} P(\emptyset | V_0(\tau) = i) \cdot P(V_0(\tau) = i)}_{\text{clearance during subsequent repl. cycles}} \\ P(\emptyset | V_0(\tau=1) = n) &\gg \sum_{\tau=2}^{\infty} \sum_{i=1}^{\infty} P(\emptyset | V_0(\tau) = i) \cdot P(V_0(\tau) = i) \\ P_0 &= P(\emptyset | V_0 = n) + \epsilon \\ \Rightarrow P_0 &\approx P(\emptyset | V_0 = n) \\ P_0 &\approx P(\emptyset | V_0 = 1)^n \\ P(\text{inf} | V_0 = n) &\approx 1 - P(\emptyset | V_0 = n) = 1 - (P(\emptyset | V_0 = 1))^n \end{aligned}$$

The process of infection was interpreted as a branching process. Under the assumption that (i) the virus is much more likely to be cleared in the first round of replication (before amplification) and that (ii) infectious challenges are independent, a very simple analytical solution for the infection probability could be derived. The solution was tested versus simulations of the full model.



Conclusions

The prophylactic efficacy of TDF is limited by a slow accumulation of the active anabolite (TFV-DP) and variable TFV-DP half life. TDF is most efficacious when only few viral particles reach a cellular environment that facilitates their reproduction (denoted as inoculum size). The majority of infections (~80%) however is believed to be caused by a single founder virus [12]. Once daily 300mg oral could yield up to ~80% protection if at least 40% of the pills were ingested and few viruses are inoculated. Single dose (event-driven) PrEP was inefficient ≤10% when administered shortly before virus exposure (it could yield up to 50% protection when given 24h before exposure), due to the slow accumulation of TFV-DP. Efficacy could not be increased with increasing dosage or prolonged administration. Other drugs, which may accumulate more rapidly could be better suited for event-driven PrEP. Daily TDF PrEP is insensitive to poor adherence, if more than 40% of pills are ingested. Clinical trials, however, indicate that the willingness to take PrEP may be lower than the "pharmacologic forgiveness" of the drug in some patients [13]. In view of the recent approval of Truvada for PrEP, further research is warranted to assess the long-term consequences of PrEP use outside of clinical trials, in particular with regard to "sporadic" or "event driven" use of PrEP.

[12] Keele BF. PNAS 105(21), 2008: 7552-7; [13] van Damme L. 19th CROI, abstract 32LB