



Systems Pharmacology pipeline to assess NRTIs for repurposing in pre-exposure prophylaxis against HIV-1 infection



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Introduction

While HIV-1 cannot be cured, current efforts focus on developing pharmaco-intervention strategies to halt the epidemic. Two strategies have been proposed: (i) Treatment-as-prevention (TasP) denotes the immediate treatment initiation in an infected individual. This decreases the patients' virus load and thereby markedly reduces the infectivity of this potential transmitter. However, onwards transmission may preferentially occur early after infection [1], when the transmitter is unaware of his infection, arguing that TasP may only prevent a small fraction of transmissions in practice. (ii) Pre-exposure prophylaxis (PrEP) aims to protect uninfected individuals at risk from acquiring the disease. Here, an uninfected individual takes anti-viral drugs, which decreases the probability of infection in the case of viral exposure. Our objective was to use a predictive PK-coupled MMOA model for nucleoside reverse transcriptase inhibitors (NRTIs) [2,3] to explore the potential of NRTIs alone and in combination for repurposing in the context of PrEP. We focussed on lamivudine (3TC), emtricitabine (FTC) and tenofovir (TDF). We elucidate the mechanisms of prevention at various physiological scales and assess pharmacological limitations and opportunities in various prophylactic scenarios.

Methods

Module I (Target-site PK)

We previously developed PK models for TDF, FTC and 3TC, which link oral prodrug application with the kinetics of the intracellular active anabolite [3].

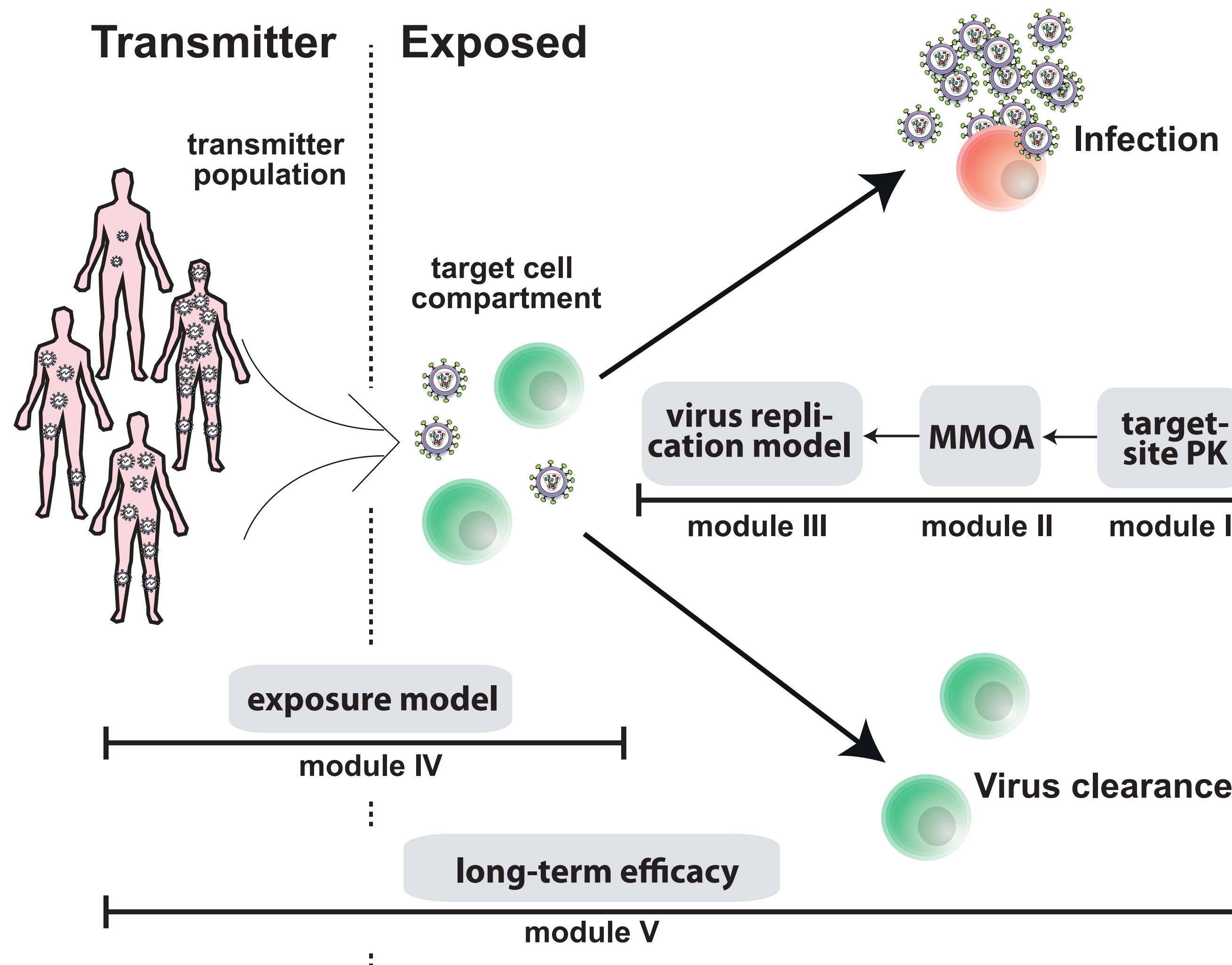
Module II (MMOA)

We utilized a previously developed [4] and validated [3] molecular mechanism of action (MMOA) model for NRTIs, which explicitly considers reverse transcriptase-mediated polymerization of nascent viral DNA. The MMOA model takes *in vitro* measurable micro-kinetic parameters as input (binding affinity, maximum catalytic rate, excision efficacy) and can be used to compute the IC₅₀ with respect to preventing cell infection.

Module III (Virus replication)

The viral replication model [2] consisted of infectious and uninfected virus and two major classes of HIV-1 target cells in various stages of infection. To quantify the infection probability, we derived (1) a **chemical master equation** (CME) and (2) a **branching process**, based on the viral dynamics model. The CME is particularly suitable to quantify the effect of NRTIs, when the latter changes on the time-scale of interest, whereas the branching process is sufficient if the change is marginal. Assuming statistical independence, the probability of infection given n transmitted viruses is related to the probability of infection given a single virus according to:

$$P(\text{inf}|V_0 = n) = 1 - (1 - P(\text{inf}|V_0 = 1))^n$$



Module IV (exposure model)

The probability of infecting the exposed individual is influenced by the number of transmitted viruses. Further, the number of transmitted viruses *per coitus* depends on the viral load of the transmitter.

The probability of transmitting n viruses to an uninfected partner when the infected partner has viral load k is modelled as a binomial process:

$$P(V_0 = n|VL = k) = \binom{\|k^m\|}{n} \cdot r^n \cdot (1-r)^{(\|k\|^m - n)}$$

where m is an exponent of the viral load and r is the success probability.

Module V (long-term efficacy)

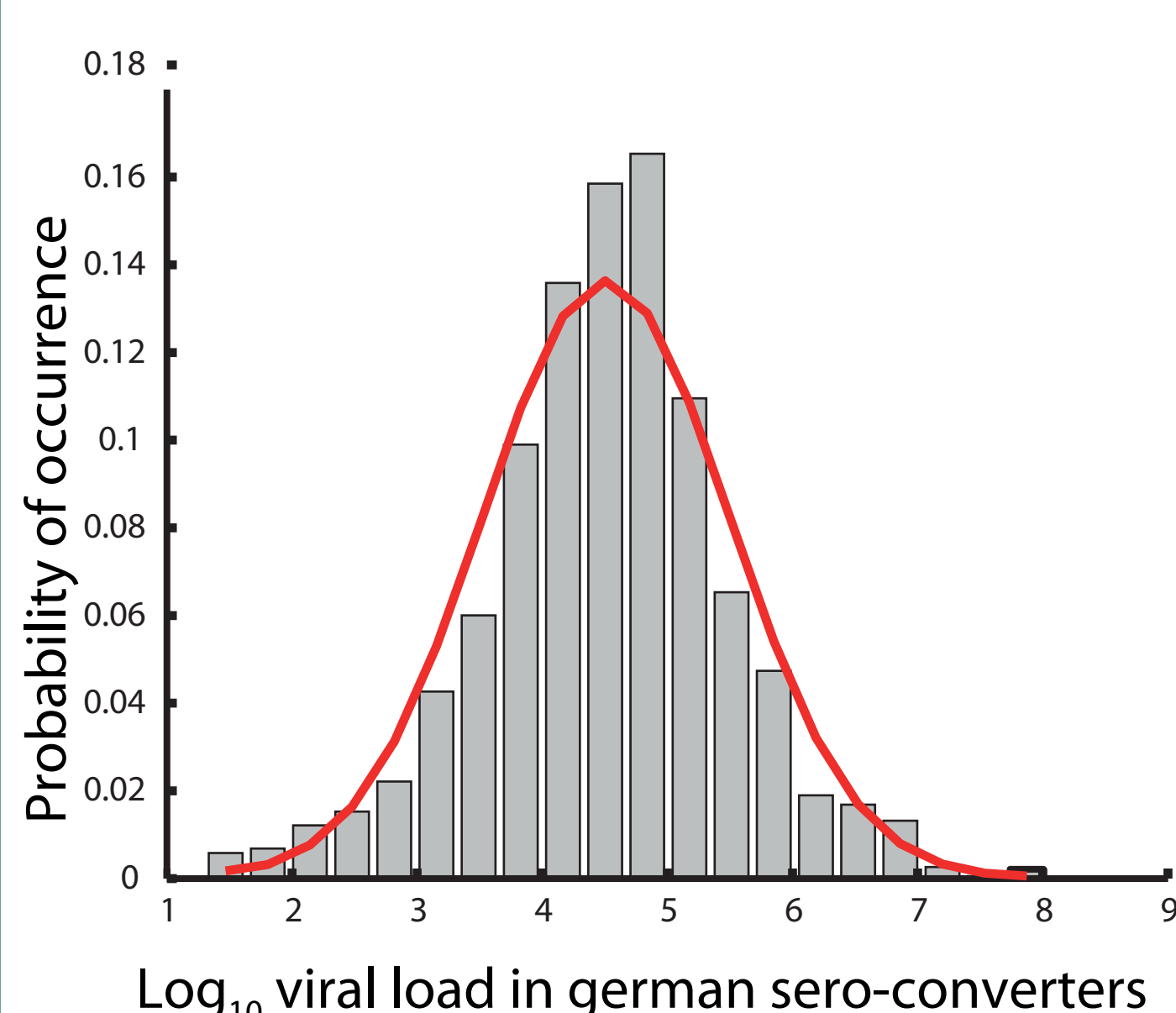
Sexual behaviour and risk compensation can affect the outcome of a PrEP-trial, because an uninfected person at risk may repeatedly be exposed to virus. The efficacy of a PrEP intervention in a clinical trial of duration T (ω_T) can be written as:

$$1 - \omega_T = \frac{1 - (1 - \bar{P}_0(\text{inf}) \cdot (1 - \psi))^{T \cdot N_S}}{1 - (1 - \bar{P}_0(\text{inf}))^{T \cdot N_0}}$$

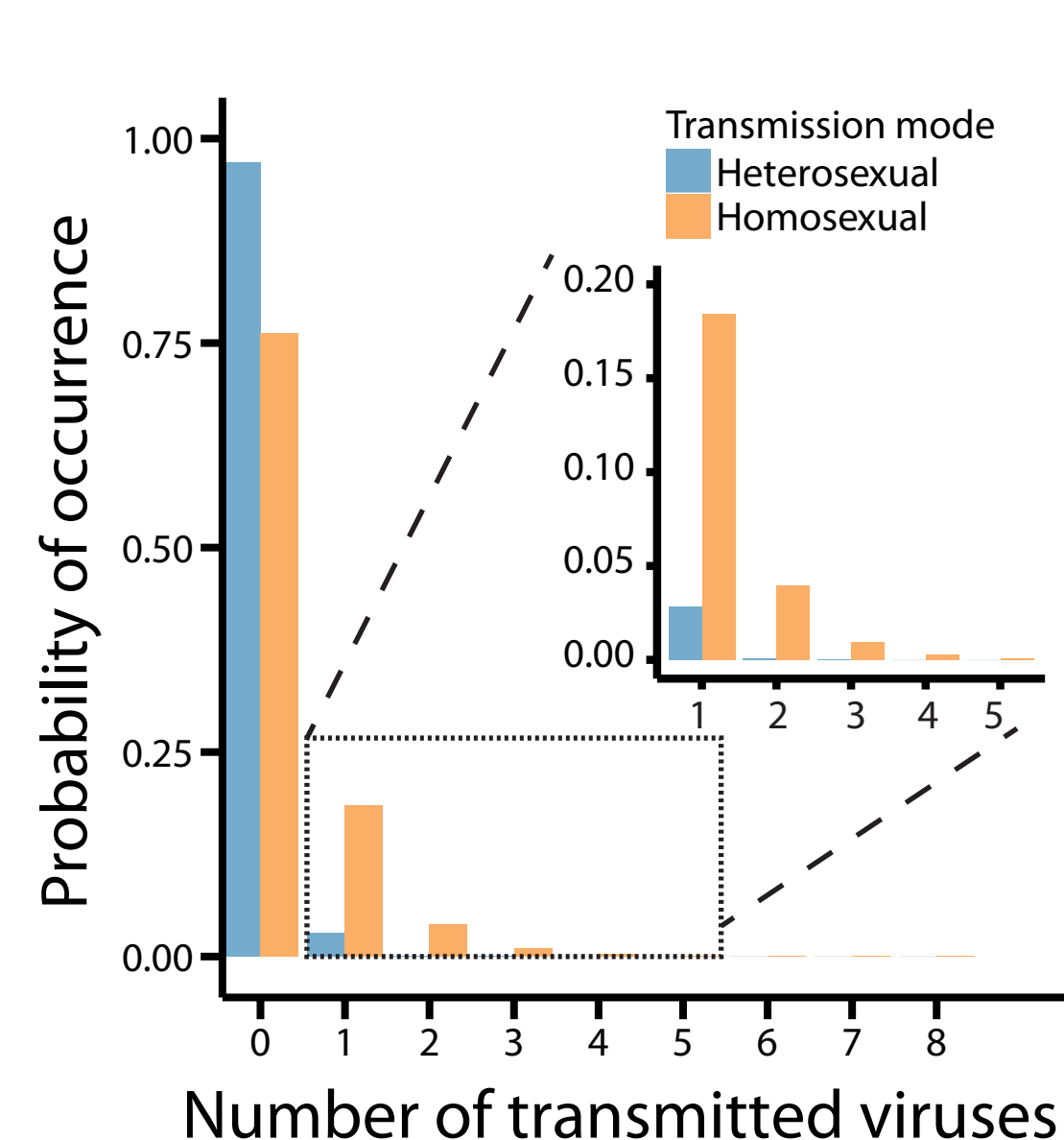
where ψ is the efficacy of a PrEP strategy *per coitus* and $P_0(\text{inf})$ is the *per coitus* probability of infection without PrEP. N_S and N_0 are the average number of risky sex acts per month in the treatment- and placebo arms. T is the trial duration in months.

Results

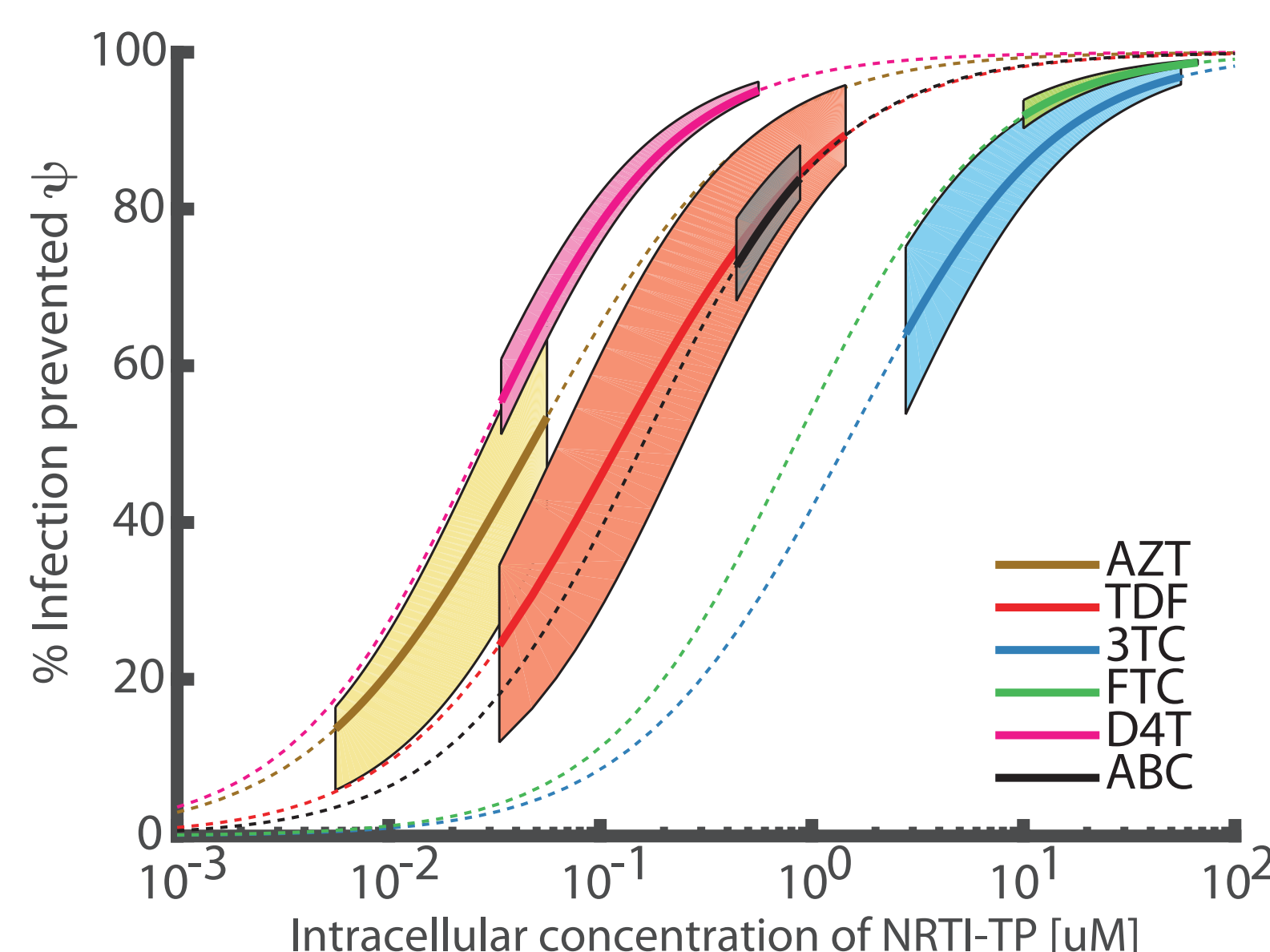
Viral load distribution



Transmitted virus distribution

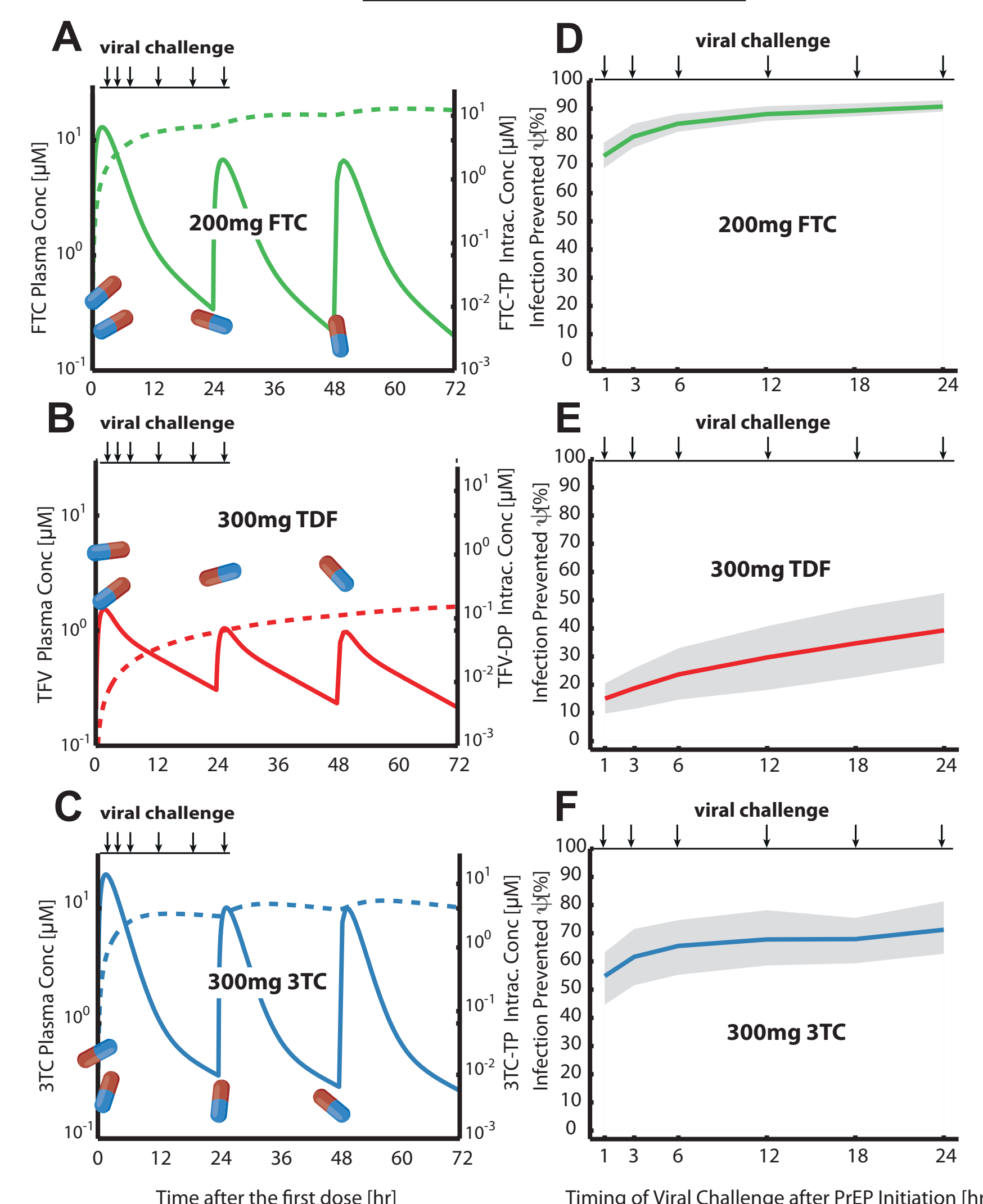


Once daily PrEP



The figure above shows the reduction in infection *per coitus* during **once daily PrEP** with different NRTIs. The lines represent the mean reduction, whereas the shaded regions denote its 25-75th percentile for clinically relevant concentration ranges. The branching process approach was used for this computation.

PrEP on demand



The figure shows PK profiles and the reduction in infection *per coitus* for **PrEP on demand**. The computation was performed using the **CME** approach.

Clinical Efficacy of PrEP

Efficacy estimates from PrEP trials can be confounded by factors like trial duration, risk compensation, sexual behaviour and mode of transmission, complicating a direct comparison. The mean PrEP-efficacy *per coitus* on the other hand is directly comparable between trials. It is computed from a trial result according to:

$$(1 - \psi) = \frac{1 - \sqrt[T \cdot N_S]{(1 - \bar{P}_0(\text{inf}))^{N_0 \cdot T} + \omega_T - \omega_T \cdot (1 - \bar{P}_0(\text{inf}))^{N_0 \cdot T}}}{\bar{P}_0(\text{inf})}$$

Conclusion

Our framework allowed to benchmark all currently approved NRTIs with respect to PrEP efficacy. Our predictions indicated that FTC and 3TC are superior to TDF, in contrast to current beliefs [4], and in particular with respect to 'PrEP on demand'. However, TDF does have advantages over 3TC and FTC in preventing transmission of drug resistant viruses and with respect to poor adherence (not shown on poster), favouring the combination of either TDF+FTC or TDF+3TC. Our pipeline revealed a dependency between reported efficacy endpoints in PrEP trials and the trial follow-up durations. This may explain contradicting reports with regard to PrEP efficacy.

In summary, we present the first approach to mechanistically model PrEP efficacy by integrating viral loads within the donor population and mode of- and timing of viral challenge with respect to PK-PD in the exposed individual. The framework can inform epidemiologic models and can be extended to other drug classes and also be used to explore TasP efficacy with- and without PrEP.

References

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