S2 Supplementary Text

Probability of Infection

In the sequel, we will derive an approximate analytical solution for computing the probability of HIV-1 infection $P_{\text{inf}}$ based on the mathematical model used in the main manuscript. The analytical approximation will be compared with simulation results.

From probability conservation, it follows that

$$P_{\text{inf}} = 1 - P_{\emptyset} \tag{S1}$$

where $P_{\emptyset}$ is the probability that the infection is prevented (virus extinction). The process of virus extinction can be viewed as a branching process, where the virus may be entirely cleared during each consecutive replication cycle $\tau = 1, \infty$.

$$P_{\emptyset} = P(\emptyset | V_0(\tau = 1) = n) + \sum_{\tau = 2}^{\infty} \sum_{i = 1}^{\infty} P(\emptyset | V_0(\tau = i)) \cdot P(V_0(\tau = i)) \cdot P(V_0(\tau = i)) \cdot P(V_0(\tau = i)). \tag{S2}$$

where $P(V_0(\tau = i))$ denotes the probability to have $i = 1, \infty$ infectious viruses at the beginning of the $\tau$th infection cycle, and $P(\emptyset | V_0(\tau = i))$ denotes the conditional probability that the infection becomes cleared during the $\tau$th infection cycle when the number of infectious virus was $i$ at the beginning of the $\tau$th infection cycle. In our case, we want to know the infection probability for specific inoculum sizes at $\tau = 1$. From eq. (S2) it follows that

$$P(\emptyset | V_0(\tau = 1) = n) \leq P_{\emptyset}. \tag{S3}$$

For ease of notation we have replaced $V_0(\tau = 1)$ by $V_0$. Under the reasonable assumption that virus challenges are independent events, we may further write

$$P_{\emptyset} \approx P(\emptyset | V_0 = 1)^n \tag{S4}$$

It now follows from eq. (S1), (S3) & (S4) that the infection (proliferation) probability in the context of $n$ inoculated viral particles is computed according to

$$P(\text{inf} | V_0 = n) \approx 1 - P(\emptyset | V_0 = n) = 1 - (P(\emptyset | V_0 = 1))^n \tag{S5}$$

Therefore, an analytical expression for the probability of non-infection (virus clearance) within the first round of replication with inoculum size one $P(\emptyset | V_0 = 1)$ needs to be derived in order to compute the infection probability with an arbitrary inoculum size $i$ analytically (see below for derivation). The % infections prevented can then be computed using eq. (11) (main article) by considering the two scenarios of drug presence and -absence.
Analytical Solution for the Probability of non-Infection

As previously described, we are seeking an analytical expression for the probability of virus clearance during the first replication cycle in the case when one virus particle was inoculated \( P(\emptyset|V_0 = 1) \). The viral replication cycle can be interpreted as a branching process, see Fig. S1 (left panel), where the infection may be prevented during each stage \{V_0, T_1, T_2, M_1\} \rightarrow \emptyset before the production of viral progeny. We may thus write:

\[
P(\emptyset|V_0 = 1) = P(V_0 \rightarrow \emptyset) + P(V_0 \rightarrow T_1 \rightarrow \emptyset) + P(V_0 \rightarrow M_1 \rightarrow \emptyset) + P(V_0 \rightarrow T_1 \rightarrow T_2 \rightarrow \emptyset) + P(V_0 \rightarrow M_1 \rightarrow M_2 \rightarrow \emptyset),
\]

where \( P(V_0 \rightarrow \emptyset) \) denotes the probability that free virus becomes entirely cleared before infecting cells and e.g. \( P(V_0 \rightarrow T_1 \rightarrow T_2 \rightarrow \emptyset) \) denotes the joint probability of extinction in the late infected T-cell compartment \( (T_2 \rightarrow \emptyset) \) before the production of viral progeny and after successful infection and integration into T-cells \( (V_0 \rightarrow T_1 \rightarrow T_2) \). The joint probabilities of extinction in infectious compartments \( T_1, T_2, M_1 \) and \( M_2 \) can be computed from the conditional probabilities of extinction:

\[
egin{align*}
P(V_0 \rightarrow T_1 \rightarrow \emptyset) &= P(T_1 \rightarrow \emptyset|V_0 \rightarrow T_1) \cdot P(V_0 \rightarrow T_1) \\
P(V_0 \rightarrow M_1 \rightarrow \emptyset) &= P(M_1 \rightarrow \emptyset|V_0 \rightarrow M_1) \cdot P(V_0 \rightarrow M_1) \tag{S6} \\
P(V_0 \rightarrow T_1 \rightarrow T_2 \rightarrow \emptyset) &= P(T_2 \rightarrow \emptyset|T_1 \rightarrow T_2) \cdot P(T_1 \rightarrow T_2|V_0 \rightarrow T_1) \cdot P(V_0 \rightarrow T_1) \\
P(V_0 \rightarrow M_1 \rightarrow M_2 \rightarrow \emptyset) &= P(M_2 \rightarrow \emptyset|M_1 \rightarrow M_2) \cdot P(M_1 \rightarrow M_2|V_0 \rightarrow M_1) \cdot P(V_0 \rightarrow M_1),
\end{align*}
\]

which are related to the reaction rates of the utilized model (see Fig. 1B and Table 2, main manuscript) via:

\[
egin{align*}
P(V_0 \rightarrow \emptyset) &= \frac{cl_v}{\beta_T(t) \cdot T_U + \beta_M(t) \cdot M_U + cl_v} \\
P(V_0 \rightarrow T_1) &= \frac{\beta_T(t) \cdot T_U}{\beta_T(t) \cdot T_U + \beta_M(t) \cdot M_U + cl_v} \\
P(V_0 \rightarrow M_1) &= \frac{\beta_M(t) \cdot M_U}{\beta_T(t) \cdot T_U + \beta_M(t) \cdot M_U + cl_v} \\
P(T_1 \rightarrow \emptyset|V_0 \rightarrow T_1) &= \frac{\delta_{T_1} + \delta_{PIC,T}}{\delta_{T_1} + \delta_{PIC,T} + k_T} \\
P(M_1 \rightarrow \emptyset|V_0 \rightarrow M_1) &= \frac{\delta_{M_1} + \delta_{PIC,M}}{\delta_{M_1} + \delta_{PIC,M} + k_M} \\
P(T_1 \rightarrow T_2|V_0 \rightarrow T_1) &= \frac{k_T}{\delta_{T_1} + \delta_{PIC,T} + k_T} \\
P(M_1 \rightarrow M_2|V_0 \rightarrow M_1) &= \frac{k_M}{\delta_{M_1} + \delta_{PIC,M} + k_M} \\
P(T_2 \rightarrow \emptyset|T_1 \rightarrow T_2) &= \frac{\delta_{T_2}}{\delta_{T_2} + N_T} \\
P(M_2 \rightarrow \emptyset|M_1 \rightarrow M_2) &= \frac{\delta_{M_2}}{\delta_{M_2} + N_M},
\end{align*}
\]

\[\]
with parameter $c_V = CL + T_U \cdot CL_T(t) + M_U \cdot CL_M(t)$. All parameters are exemplified in the main manuscript and parameter values can be derived from Table 2 (main manuscript). Before the onset of infection, parameters $T_U$ and $M_U$ may be approximated by $\lambda_T/\delta_T$ and $\lambda_M/\delta_M$ respectively.

Note, that the parameters $\beta_T(t), \beta_M(t), CL_T(t)$ and $CL_M(t)$ are affected by the intracellular concentrations of TFV-DP via eqs. (8)-(10) in the main manuscript. This allows us to assess the % infections prevented for arbitrary intracellular TFV-DP concentrations and arbitrary virus inoculum sizes via eqs. (S5), (S6)-(S8) in conjunction with eq. (11) (main article), which is shown in Fig. 6 (main article).

A comparison between the predicted % infections prevented resulting from this approximation and simulated % infections prevented using the entire model is shown in Fig. S1 (right panel) herein. As can be seen, the analytical solution (on the x-axis) may in some cases slightly underpredict the % infections prevented because it only considers the first round of replication (see eq. (S3)) as compared to the simulation of the full model. This potential error is, however, very minor and therefore we believe that the approximate analytical solution is reasonable to assess the % infections prevented in the context of our model.

References