Supplementary material Text S1

Modeling the timing of anti-latency drug administration during HIV treatment

Additional details and explanations of modeling methods.

1. Model properties

We used a model of viral dynamics with productively and latently infected cells:

$$\begin{aligned} dT/dt &= \lambda - d_T T - \beta VT \\ dI/dt &= f\beta VT - \delta I + \alpha L \\ dL/dt &= (1-f)\beta VT - (\alpha+\omega)L \\ dV/dt &= pI - cV \end{aligned} \qquad \text{Eq.S1}$$

where the uninfected target (CD4+ T) cells (T) are replaced at a rate λ and die at the rate d_T. They are infected by free virus (V) according to the mass action law with infectivity β. A large fraction f becomes productively infected (I) and short-lived, producing virus at the rate p and dying at death rate δ. A small fraction ($1-f$) becomes latently infected (L) and does not produce virus. The latently infected cells are activated at a rate α, upon which they become productive and short-lived, and die at a rate ω. The model assumes that the activation rate of latently infected cells increases with viral load in an S-shaped manner

$$\alpha = 0.8\{0.5 + \arctan[3(\log V - \log 5\cdot 10^5)/\pi\} \qquad \text{Eq.S2}$$

while the death rate of latently infected cells is constant ($\omega = 2\times10^{-4}$).

In this model, the initial infection will spread if the basic reproductive ratio is

$$R_0 = f\frac{\lambda\beta p}{d_T\delta c} > 1, \qquad \text{Eq.S3}$$

i.e. the initial spread does not depend on the dynamics of the latent reservoir. The increase in the fraction of the latently infected cells $1-f$ in the range between 0 and 0.1 only proportionally increases the size of the latent reservoir without any other influence on the dynamics of the system.

It is hard to obtain a closed mathematical form for the steady states of the variables because of the highly nonlinear form of the dependence of α on V. Therefore we obtained the steady states for the viral load and latent reservoir numerically as the values after 500 simulated days. In the simulation, we

assumed that the death rate of productively infected cells δ and the clearance rate of the virus, at $\delta = 0.8$ day^{-1} and $c = 20$ day^{-1} respectively, do not vary much across individuals, and that the variation of the chronic viral load is mostly the result of the differences in infectivities β or rates of virus production by infected cells p. We assumed $f = 0.995$ in all simulations.

The steady-state size of the latent reservoir depends on R_0 differently if this change is effected by the change in infectivity or by the change in virus production rate (Figure S1).

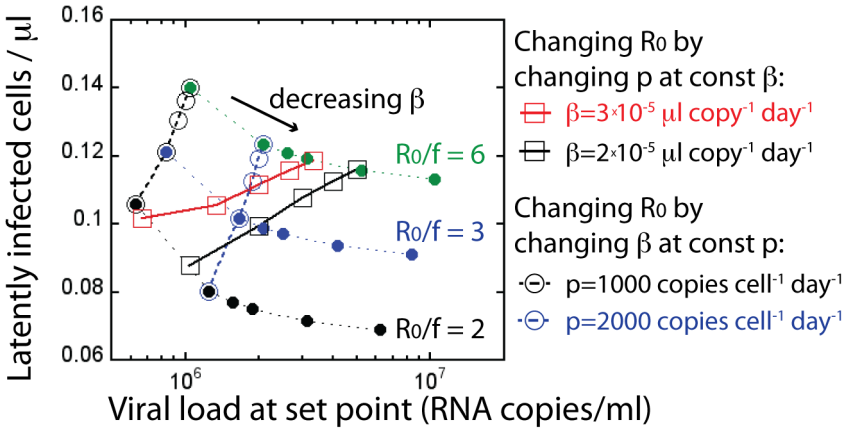

Figure S1. Effect of changing infectivity or virus production rate on the size of the latent reservoir at viral set point.

The size of the latent reservoir would increase with the increase of the set point viral load if the basic reproductive ratio R_0 increases solely because of the increased infectivity (open circles and dashed lines in Figure S1) or if it increases only because of the change in virus production rate (open squares and full lines). However, the latent reservoir would decrease with the increase of the set point viral load if infectivity decreases at constant R_0.

It is believed that viral production rates are the most variable, both across infected cells in an individual and as averages across individuals. This assumption has also been made in estimating the size of the latent reservoir in the ref. (1), where the variations in R_0 and in chronic viral load are assumed to be the result of only variations in viral production rates p across patients. With this assumption, our model (Eq.S1) also shows an increase of the viral reservoir with increasing chronic viral load, as found in ref. (1) (Figure S2, full lines at constant infectivity β).

2. Overall individual turnover rates

In reference (2), we determined the overall turnover rates of latently infected cells for individual SIV-infected rhesus macaques by comparing the patterns of immune escape in plasma and in resting infected cells. From the delay of escape in the resting cells we could infer an overall turnover rate for each monkey. We found that these "average" individual turnover rates positively correlated with individual set point viral loads.

In this paper we use a model in which the *instantaneous* activation rate of latently infected cells depends on *instantaneous* viral load in a similar way as the dependence of the overall activation rate on the chronic viral load from the previous study (2).

In order to see if the model Eq.S1-S2 would result in a similar relationship between the overall activation rate and the chronic viral load as found in (2), we simulated immune escape in 15 individuals using this model applied to the dynamics of escape, and then determined the overall activation rates and chronic viral loads for each individual.

The equations for the viral escape model were:

$$\begin{aligned} dT/dt &= \lambda - d_T T - \beta_W WT - \beta_E ET \\ dI_W/dt &= f\beta_W WT - \delta_W I_W + \alpha L_W \\ dI_E/dt &= f\beta_E WT - \delta_E I_E + \alpha L_E \\ dL_W/dt &= (1-f)\beta_W WT - (\alpha+\omega)L_W \\ dL_E/dt &= (1-f)\beta_E WT - (\alpha+\omega)L_E \\ dW/dt &= p_W I_W - cW \\ dE/dt &= p_E I_E - cE \end{aligned} \qquad \text{Eq.S4}$$

where W and E are the wild-type and escape mutant viral loads, and the subscripts W and E refer to wild-type and escape mutant respectively. The activation rate α depended on viral load as described in Eq.S3 in all individuals. We assumed $f = 0.0995$, $\omega = 2\times10^{-4}$ day^{-1} and $c = 20$ day^{-1} for all. In addition, we assumed that initially without immune response $\delta_{W0} = \delta_E = 0.8$ day^{-1}, but that after 10 days the immune response emerges, increasing δ_W to $\delta_{W0} + \Delta$, causing the escape mutant to overtake. The individuals varied in disease-free target cells frequencies (i.e. λ and d_T), in infectivities and virus production rates of wild type and escape mutant, and in the time during infection when the escape mutation occurs.

Following the experimental setup in (2), we "sampled" the wild type and escape mutant viral loads first weekly and later fortnightly and monthly (18 time points during 200 days of infection), and the fraction b_W of WT in the latently infected cells less frequently, at 9 time points. We then used the equations from (2):

$$\begin{aligned} d\Lambda/dt &= W + E - \bar{\alpha}\Lambda \\ db_W/dt &= W/\Lambda - b_W(W+E)/\Lambda \end{aligned} \qquad \text{Eq.S5}$$

to fit the overall activation rate $\bar{\alpha}$ for this individual. In Eq.S5, Λ is a dummy variable proportional to the total number of latently infected cells. The results are shown as red full circles in Figure S2 against the experimental results (black full circles) from (2).

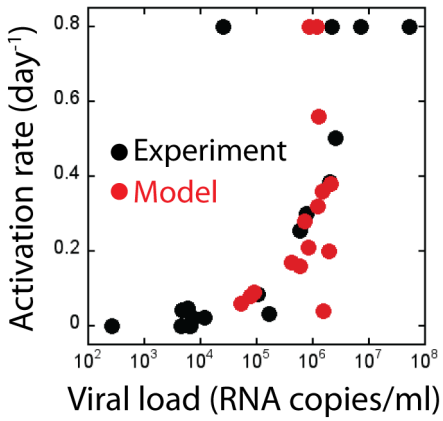

Figure S2. Dependence of the overall activation rate on the chronic viral load. Simulation results from the model Eq.S4 (red full circles) are compared to experimental results from the study (2).

These simulation results show that the dependence of activation rate of latently infected cells similar to Eq.S3 could cause the dependence of the overall activation rate on the chronic viral load observed in (2).

REFERENCES

1. **Archin NM**, **Vaidya NK**, **Kuruc JD**, **Liberty AL**, **Wiegand A**, **Kearney MF**, **Cohen MS**, **Coffin JM**, **Bosch RJ**, **Gay CL**, **Eron JJ**, **Margolis DM**, **Perelson AS**. 2012. Immediate antiviral therapy appears to restrict resting CD4+ cell HIV-1 infection without accelerating the decay of latent infection. Proc Natl Acad Sci USA **109**:9523–9528.
2. **Reece J**, **Petravic J**, **Balamurali M**, **Loh L**, **Gooneratne S**, **De Rose R**, **Kent SJ**, **Davenport MP**. 2012. An "escape clock" for estimating the turnover of SIV DNA in resting CD4+ T cells. PLoS Pathog **8**:e1002615.