SUPPLEMENTAL TEXT FOR
'Determinants of the efficacy of HIV latency reversing agents and implications for drug and treatment design'

Ruian Ke, Jessica M. Conway, David M. Margolis, and Alan S. Perelson

Analytical approximation to the model for latency reversal with an LRA

The ordinary differential equations (ODEs) describing latency reversal with an LRA (see the main text for the description of the model) are

$$\frac{dL}{dt} = (\rho - d)L - \eta L - \alpha L + \omega R$$

$$\frac{dA}{dt} = (\rho - \delta)A + \alpha L - \gamma A \qquad \text{(S1)}$$

$$\frac{dR}{dt} = (\rho - d)R + \gamma A - \omega R$$

This is a linear system of ODEs and thus can be solved analytically. However, the solution to the system involves solving a characteristic equation with a 3rd order polynomial, and thus it is difficult to understand intuitively. To derive an approximation that is understandable, such that intuition can be drawn upon, we make the simplifying assumption that the induced cells (A) go to the uninduced state (L) directly without going through the refractory state. Then, the ODEs become

$$\frac{dL}{dt} = (\rho - d)L - \eta L - \alpha L + \gamma A$$

$$\frac{dA}{dt} = (\rho - \delta)A + \alpha L - \gamma A \qquad \text{(S2)}$$

Solving the ODE system we find the solution for the total size of the reservoir ($L(t)+A(t)$) is

$$L(t) + A(t) = C_1\left[\frac{1}{2\alpha}(d + \eta - \alpha - \delta - \gamma - K)e^{\left[\rho - \frac{1}{2}(\alpha+\gamma+\delta+d+\eta-K)\right]t}\right] + C_2\left[\frac{1}{2\alpha}(d + \eta - \alpha - \delta - \gamma + K)e^{\left[\rho - \frac{1}{2}(\alpha+\gamma+\delta+d+\eta+K)\right]t}\right]$$

where $K = \sqrt{\alpha^2 + 2\alpha(\gamma + d + \eta - \delta) + (d + \eta - \delta - \gamma)^2}$, and C_1 and C_2 are constants that are determined by the initial conditions.

To further simplify this expression, we assume that the natural death rate $\eta$and natural activation rate α are negligible and thus set $\eta = 0$ and $\alpha = 0$. This is a good assumption because death or activation of latently infected cells occur infrequently and thus they do not contribute to the dynamics of the reservoir during the short time period of LRA exposure considered in this study. Note that, the value of the parameter ρ used in this study is also small, and can be neglected in theory. However, since we are interested in how the reservoir size depends on changes in ρ during therapeutic interventions, such as with a LRA or anti-proliferative drugs, we keep this parameter in the expression. The solution to the total reservoir size then becomes

$$L(t) + A(t) = C_1 \left[\frac{1}{2\alpha}(-\alpha - \delta - \gamma - K)e^{\left[\rho - \frac{1}{2}(\alpha+\gamma+\delta-K)\right]t}\right] + C_2 \left[\frac{1}{2\alpha}(-\alpha - \delta - \gamma + K)e^{\left[\rho - \frac{1}{2}(\alpha+\gamma+\delta+K)\right]t}\right]$$

where *K* becomes $K = \sqrt{(\alpha+\gamma+\delta)^2 - 4\alpha\delta}$.

Since $\rho - \frac{1}{2}(\alpha+\gamma+\delta-K) > \rho - \frac{1}{2}(\alpha+\gamma+\delta+K)$, the long-term dynamics are governed by the 1st term in the Eqn. above (with the highest exponent on the exponential, and thus we drop the 2nd term, and get

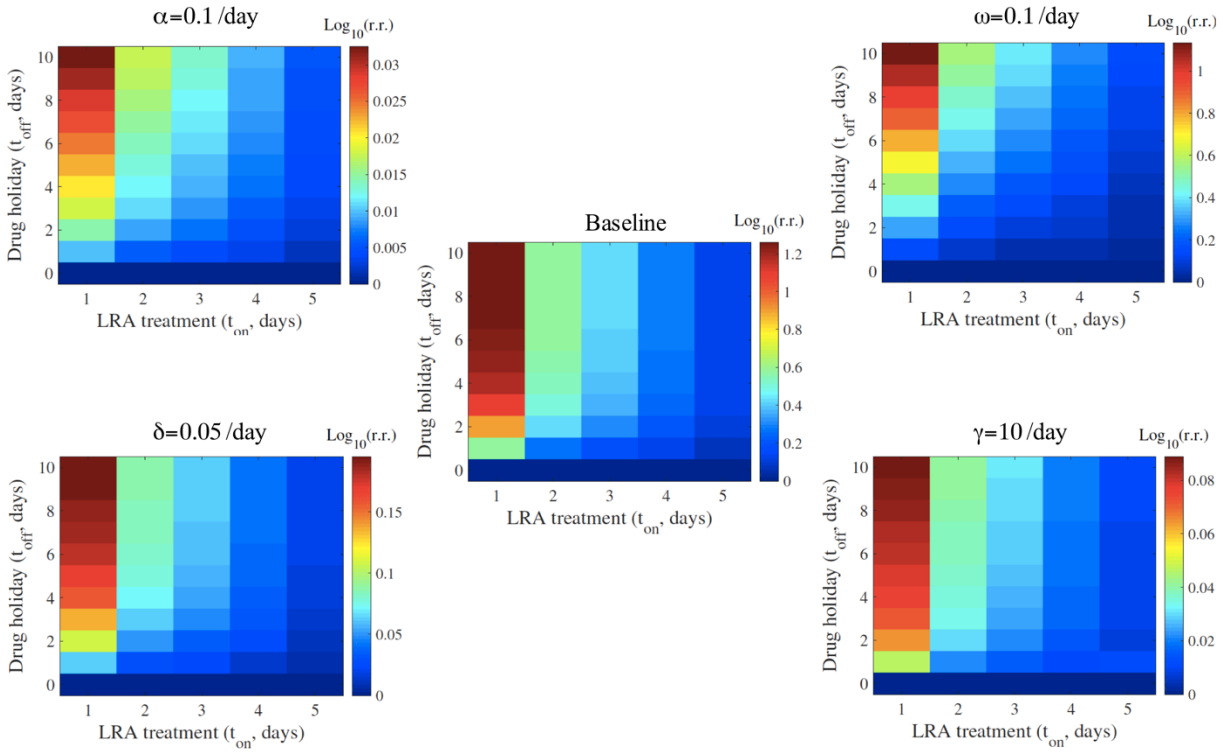
$$L(t) + A(t) \approx C_1 \left[\frac{1}{2\alpha}(-\alpha - \delta - \gamma - K)e^{\left[\rho - \frac{1}{2}(\alpha+\gamma+\delta-K)\right]t}\right]$$

Then the long-term reduction in the total reservoir size therefore can be expressed as

$$\frac{L(t) + A(t)}{L(0) + A(0)} \approx e^{\left[\rho - \frac{1}{2}\left(\alpha+\gamma+\delta-\sqrt{(\alpha+\gamma+\delta)^2-4\alpha\delta}\right)\right]t} \qquad \text{(S3)}$$

Let Ψ be the long-term exponential rate of reservoir decline, i.e. the negation of the exponent, so

$$\Psi = \frac{1}{2}\left(\alpha+\gamma+\delta-\sqrt{(\alpha+\gamma+\delta)^2-4\alpha\delta}\right) - \rho. \quad \text{(S4)}$$



Supplemental Figure 1. The dependence of the HIV reservoir reduction (r.r.) on different LRA pulsatile regimens and parameter combinations. The middle panel shows the dependence on the LRA regimens using baseline parameter values: α=1.8/day, δ=0.5/day, γ=1/day and ω=1/day. Other panels show the dependence when one of the baseline parameter value is altered. Note that the baseline value of δ here is chosen to be 0.5/day to highlight the benefits of pulsatile regimens; when δ=0.05/day (used as an alternative baseline in the main figures), the reservoir reduction is minimal. Overall, Model simulations suggest that when the period of vulnerability ($1/\gamma$) is the same on and off LRA, one LRA dose followed by a sufficiently long resting period before another LRA dose is the best strategy, although the benefits of such a pulsatile regimen heavily depends on parameter values as indicated in the different panels (note that the scales of the color-axis are different in different panels).