Mathematical Considerations

To facilitate analysis of the rate equations governing the kinetics of a viral infectivity assay (Eqs. 2–5) in the main text), we introduce non-dimensional variables $i \equiv I/V_0$, $v \equiv V/V_0$, $f \equiv F/NV$, $c \equiv C/NV$, and $g \equiv (F+C)/NV = f+c$. We also introduce non-dimensional time $t = (k_s + k_n)T$ and the non-dimensional parameters $\sigma \equiv k_s/(k_s + k_n)$, $\lambda \equiv k_\ell L/(k_s + k_n)$, $\gamma \equiv k_r/(k_s + k_n)$, and $\beta \equiv k_f B/k_r$. Then Eqs. 2–5 become

$$\frac{di}{dt} = N\lambda f v, \tag{1'}$$

$$\frac{dv}{dt} = -(N\lambda f + 1 - \sigma)v, \tag{2'}$$

$$\frac{df}{dt} = -\gamma(\beta f - c) - \sigma f - \lambda f(1-f), \tag{3'}$$

and

$$\frac{dc}{dt} = \gamma(\beta f - c) - \sigma c + \lambda f c. \tag{4'}$$

Because $\gamma \equiv k_r/(k_s+k_n)$ is on the order of 10^4 for physically relevant parameters, perturbation expansions in γ^{-1} of the form $f = f_0 + \gamma^{-1}f_1 + \gamma^{-2}f_2 + \cdots$ and $c = c_0 + \gamma^{-1}c_1 + \gamma^{-2}c_2 + \ldots$ lead to solutions of Eqs. 1'-4'. The zeroth-order truncation, $f = f_0$ and $c = c_0$, is equivalent to the usual quasi-steady-state approximation, $k_f BF \approx k_r C$, which holds for time scales longer than the *gp*120-sCD4 equilibration time. That approximation gives $c \approx \beta g/(1+\beta)$ and $f \approx g/(1+\beta)$.

Adding Eqs. 3' and 4' and applying the steady-state approximation yield

$$\frac{dg}{dt} = -\sigma g - \lambda(1+\beta)^{-1}g(1-g), \tag{5'}$$

lymphocytes by mitogens significantly increases the rate at which they are infected by HIV. Therefore, it is conceivable that stimulation with PHA significantly increased the probability of target-cell infection i_∞ and the number of secondary virions V_n. Therefore, additional experiments to determine the branching number of both resting and stimulated lymphocytes are needed.

Since the branching number, $NV_n k_\ell L/(k_s + k_n)$, is proportional to target-cell concentration, we can extrapolate from the conditions of Deen et al. ($L \approx 10^6$ cells cm^{-3} and $B_{min} > 10$ μg cm^{-3}) to the conditions in human blood ($L \approx 10^6$ cells cm^{-3}) and human lymph nodes ($L \approx 10^8$ cells cm^{-3}). Such extrapolation indicates a minimum therapeutic concentration of $\approx$ 1000 µg cm^{-3} of sCD4 to treat established infections in vivo (a very high concentration). Even more pessimistically, we note that target-cell infection by direct cell-to-cell contact is probably less easily blocked than infection by free virus in the fluid medium. Experiments examining this situation are also required.

The predictions about therapeutic use of sCD4 hold if the only effect of sCD4

which is a form of the Bernoulli equation and can be solved by separation of variables.

Substituting g(t) into Eq. 2' gives an expression for $v(t)$. Next, substituting $g(t)$ and $v(t)$ into Eq. 1′ gives an expression for $i(t)$. As $t \to \infty$, $i(t)$ can be approximated by

$$i_\infty \approx e^{-(1-\sigma)t_p} \frac{\zeta N}{N-1} e^{-\zeta/\delta} \sum_{j=0}^{\infty} \frac{(\zeta/\delta)^j}{(1+\delta j)j!}, \tag{6'}$$

where $\zeta \equiv [\exp(-\sigma t_p)](N-1)\lambda/(\lambda+1+\beta)$ and $\delta \equiv [\lambda+\sigma(1+\beta)]/(\lambda+1+\beta)$. Equation 6' is related to the incomplete gamma function, and the approximation that yields it relies on the fact that $N \gg 1$. Notice that $\zeta \leq N-1$ and $\delta \leq 1$.

The parameter ζ is a measure of the degree to which assay conditions promote target cell infection. Expressing ζ in dimensional variables gives

$$\zeta \equiv e^{-(k_s+k_n)T_p} \frac{(N-1)k_\ell L}{k_\ell L + (1+K_{assoc}B)(k_s+k_n)}. \tag{7'}$$

Target-cell infection is less probable as $\zeta \to 0$, that is, as $T_p \to \infty$, $L \to 0$, $B \to \infty$, or $(k_s+k_n) \to \infty$. Conversely, target-cell infection is more probable as $\zeta \to N-1$, that is, as $T_p \to 0$, $L \to \infty$, $B \to 0$, or $(k_s+k_n) \to 0$. Expansions of Eq. 6′ for each of those limits lead to the expressions

$$I_\infty \approx \frac{NV_0 k_\ell L e^{-(k_s+k_n)T_p}}{k_\ell L + (1+BK_{assoc})(k_s+k_n)} \left(1 - \frac{\zeta}{1+\delta} + \cdots\right) \text{ as } \zeta \to 0 \tag{8'}$$

and

$$I_\infty \approx \frac{V_0 N e^{-k_n T_p}}{N-1} \left[1 - \frac{1-\delta}{\zeta} + \cdots\right] \text{ as } \zeta \to N-1. \tag{9'}$$

For both limiting cases δ appears only in the higher-order terms. Note that experimentally I_∞ corresponds to the number of infected cells at $T \approx 10^5$ seconds.

As explained in the main text, Eqs. 7' and 8' are useful for the design and analysis of experiments to measure the parameters K_{assoc}, k_s, k_n, k_ℓ, and NV_0. Figure 5 in the main text shows some characteristics of the transition from the regime of Eq. 8′ (small ζ) to the regime of Eq. 9′ (large ζ). ■

is to block free virus from infecting target cells. Siliciano et al. and Lanzavecchia et al. have suggested that sCD4 may also act to protect $CD4^+$ lymphocytes from indirect or autoimmune effects induced by *gp* 120. If that is the case, then much lower concentrations of sCD4 may be of therapeutic use.

The branching number can also be used to estimate the immune response that an anti -*gp* 120 vaccine must induce to protect against HIV infection. In that instance K_{assoc} is the equilibrium constant for association of *gp120* and neutralizing antibody (Ig), and B_{min} is the minimum concentration of Ig required to extinguish the spread of infection. Assuming that neutralizing Ig has a K_{assoc} identical to that of sCD4 (a rather high-affinity Ig) and a molecular weight of about 150,000 and that $V_n i_\infty \approx 300$ yields $B_{min} \approx 0.03$ mg cm^{-3} for blood. For lymph nodes we calculate that a concentration of about 3 mg cm^{-3} will be required to prevent growth of infection. Normally, the total concentration of all the hundreds of thousands of antibodies in serum is ≈ 20 mg cm^{-3}. Thus an anti-*gp*120 vaccine must induce and maintain an extremely high concentration of antibody.