Supporting Text

CD4 Down-Modulation Timescale. Three HIV genes, namely, *nef*, *env*, and *vpu*, are responsible for down-modulation of surface CD4 receptors via independent pathways. Together, the products of these genes rid the surface of an infected cell of nearly all CD4 molecules (1). Of the three genes, *nef* has been shown to have the predominant down-modulating influence (1). Piguet *et al.* (2) have recently measured the fraction of surface CD4 receptors internalized, $i(t)$, by *nef* and the fraction of internalized receptors recycled back to the surface, $r(t)$, as a function of time, t, on transfected 293T cells. Assuming that infection aborts (or significantly inhibits) the continued presentation of CD4 receptors on the cell surface, as suggested by $r(t) < 10\%$ (2), it follows that the fraction of CD4 molecules expressed on the surface at time t, $x(t) \approx 1 - i(t)$, where the infection rate $k = k_0 x(t)$, with k_0 the infection rate in the absence of CD4 down-modulation (see Eq. **4** in the main text). Letting $x(t) = \exp(-t/t_d)$, where $t = 0$ marks the onset of *nef* expression in an infected cell, which is approximately the infection event because *nef* is expressed early in the HIV life cycle, we fit the $i(t)$ data of Piguet *et al.* (2) and find $t_d \approx 40$ min or 0.028 day (Fig 6).

Other experiments suggest, however, that CD4 down-modulation may be significantly slower. For instance, in Jurkat cells, CD4 down-modulation was not observed for up to 12–16 h after infection with wild-type viruses (3). Similarly, 3 days after infection, only 92% of CD4 molecules were down-modulated on average in PBMC (1). We therefore investigate the effect of CD4 down-modulation on multiple infections by varying t_d over two orders of magnitude from 0.028 to 2.8 days (see main text).

Scaling Regimes. We derive three sets of conditions that give rise to the power law scaling, $T_i^* \sim \left(T_1^*\right)^i$, and describe how these conditions relate to the various scaling regimes in Figs. 4 and 5.

At short times following the onset of infection, the number of infected cells, T^*, is sufficiently small that changes in V and T may be neglected. Let this regime hold for $t <$

t_s. Further, if $t_s < t_d$, infected cells continue to express nearly normal levels of CD4 in this regime. The evolution of multiply infected cell subpopulations may then be written as

$$\frac{dT_1^*}{dt} = k_0 V_0 T_0 - k_0 V_0 T_1^* - \delta T_1^* \approx k_0 V_0 T_0 - \delta T_1^* \quad \textbf{[1]}$$

and

$$\frac{dT_i^*}{dt} = k_0 V_0 T_{i-1}^* - k_0 V_0 T_i^* - \delta T_i^* \approx k_0 V_0 T_{i-1}^* - \delta T_i^* \quad \textbf{[2]}$$

where the latter approximations are based on the assumptions that $T_1^* << T_0$ and $T_i^* << T_{i-1}^*$. Solving Eq. **1** with the initial condition that $T_1^*(0) = 0$, we get

$$T_1^*(t) = \frac{k_0 V_0 T_0}{\delta}\left(1 - e^{-\delta t}\right) \quad \textbf{[3]}$$

which when δt is small, i.e., $t << 1/\delta$, becomes

$$T_1^*(t) = k_0 V_0 T_0 t \quad \textbf{[4]}$$

Substituting Eq. **3** in Eq. **2** for $i = 2$, it can be shown that

$$T_2^*(t) = \frac{\left[T_1^*(t)\right]^2}{T_0}\frac{\left(1 - e^{-\delta t} - \delta t e^{-\delta t}\right)}{\left(1 - e^{-\delta t}\right)^2} \quad \textbf{[5]}$$

which when δt is small becomes

$$T_2^*(t) = \frac{\left[T_1^*(t)\right]^2}{T_0} \sim \left[T_1^*(t)\right]^2 \quad \textbf{[6]}$$

It can be shown similarly that $T_3^* \sim \left(T_1^*\right)^3$, and so on. Thus, for small times, $t < \min(t_s, t_d, 1/\delta)$, the power law scaling, $T_i^* \sim \left(T_1^*\right)^i$, is obtained.

We next consider larger times where T^* is sufficiently large that viral production and clearance are rapid compared with the rate of evolution of T^*. Let this happen for times $t > t_{eq}$. Then, the pseudo-steady-state solution of Eq. **8** in the main text along with the approximation $\sum_i T_i^* = T^* \approx T_1^*$, since $T_i^* << T_{i-1}^*$, yields,

$$V \approx \frac{\delta N T_1^*}{c} . \textbf{[7]}$$

If $t_d < t_{eq}$, infected cells will have begun to down-modulate CD4 so that k changes with time for these cells. Let us assume that t_d is small compared with the timescale over which T^* varies. This holds, for instance, for the parameter values used in Fig. 4*a*. Then, after the first infection of a cell, a narrow time window exists during which the cell can be infected again. During this window, V may be assumed to remain constant. The average number of additional infections a cell first infected at time t undergoes is then given by

$$\nu = \int_t^\infty k_0 e^{-(x-t)/t_d} V(x) dx \approx k_0 V(t) \int_t^\infty e^{-(x-t)/t_d} dx = k_0 V(t) t_d . \textbf{[8]}$$

Because infections may be assumed to be independent processes following Poisson statistics, the probability that the cell undergoes $(i - 1)$ additional infections, i.e., it is totally infected i times, is

$$P(i) = \frac{e^{-\nu} \nu^{i-1}}{(i-1)!} \approx \frac{\nu^{i-1}}{(i-1)!} \textbf{[9]}$$

where $n! = n(n-1).2.1$, and the latter approximation arises from the assumption that t_d is small so that $\nu = k_0 V t_d \rightarrow 0$. In a small time interval Δt ($>t_d$) near t, if ΔT^* is the number of cells infected, the fraction of these cells that are infected i times is $\Delta T^* P(i)$. If the number of cells infected before time t_{eq} that survive at time t is assumed to be small, then considering all intervals Δt from t_{eq} to t, it follows that $T_i^* \propto T^* P(i)$. Therefore, combining Eqs. **7**–**9**, we get

$$T_i^* \propto \frac{T^*}{(i-1)!}\left(\frac{k_0 t_d \delta N}{c}\right)^{i-1}\left(T_1^*\right)^{i-1} \quad \textbf{[10]}$$

and recognizing that $T^* \approx T_1^*$, the desired scaling,

$$T_i^* \propto G(i)\left(T_1^*\right)^i \sim \left(T_1^*\right)^i, \quad \textbf{[11]}$$

emerges, where $G(i) = [(k_0 t_{d\delta} N/c)^{i-1}]/(i-1)!$.

This same scaling emerges in yet another limit where t_d is large compared with the timescale over which T^* varies. Then, we may use the approximation $k = k_0$ and rewrite Eq. **2** as

$$\frac{dT_i^*}{dt} = k_0 V T_{i-1}^* - k_0 V T_i^* - \delta T_i^* \text{ for } i>1 \quad \textbf{[12]}$$

and

$$\frac{dT_1^*}{dt} = k_0 V T - k_0 V T_1^* - \delta T_1^* \quad \textbf{[13]}$$

which for $T_i^* << T_{i-1}^*$ and $T_1^* << T$ simplifies to

$$\frac{dT_i^*}{dt} \approx k_0 V T_{i-1}^* - \delta T_i^* \text{ for } i > 1 \textbf{ [14]}$$

and

$$\frac{dT_1^*}{dt} = k_0 V T - \delta T_1^* \textbf{ [15]}$$

Substituting the pseudo-steady-state approximation, Eq. **7**, in Eqs. **14** and **15**, we get

$$\frac{dT_i^*}{dt} \approx k_0 \frac{\delta N T_1^*}{c} T_{i-1}^* = K T_1^* T_{i-1}^* - \delta T_i^* \text{ for } i>1 \textbf{ [16]}$$

and

$$\frac{dT_1^*}{dt} = (KT - \delta) T_1^* \textbf{ [17]}$$

where $K = k_0 \delta N/c$ is a constant. Assuming T to vary slowly, Eq. **17** can be solved to give

$$T_1^*(t) = T_1^*(0) e^{-(KT-\delta)t} \textbf{ [18]}$$

where $T_1^*(0)$ is the value of T_1^* at $t \approx t_{eq}$ when the pseudo-steady-state approximation (Eq. **7**) first applies and is thus nonzero. Substituting Eq. **18** in Eq. **16** for $i = 2$ yields

$$\frac{dT_2^*}{dt} = K\left[T_1^*(0) e^{-(KT-\delta)t}\right]^2 - \delta T_2^* \textbf{ [19]}$$

solving which with the initial condition $T_2^*(0) \approx 0$ gives

$$T_2^*(t) = \frac{K}{(2KT-\delta)}\left[T_1^*(t)\right]^2\left(1-e^{-(2KT-\delta)t}\right)$$ **[20]**

which for $t >> 1/(2KT - \delta)$ yields,

$$T_2^*(t) = \frac{K}{(2KT-\delta)}\left[T_1^*(t)\right]^2 \sim \left[T_1^*(t)\right]^2 .$$ **[21]**

In summary, the power law scaling, $T_i^* \approx \left(T_1^*\right)^i$, arises according to our model in the following three cases: (*i*) At small times after the onset of infection, $t < \min(t_s, t_d, 1/\delta)$, where t_s is the timescale over which V and T vary, t_d is the timescale for CD4 down-modulation, and $1/\delta$ is the average lifetime of infected cells; (*ii*) at large times, $t > t_{eq}$, when T^* is sufficiently large that V is in pseudo-steady-state with T^*, i.e., $V \approx N\delta T^*/c$, and when CD4 down-modulation is rapid, $t >> t_d$; and (*iii*) at large times, $t > t_{eq}$, and when CD4 down-modulation is slow, $t << t_d$. Below, we show how these parameter regimes relate to the scaling regimes in Figs. 4 and 5.

In Fig. 4a, t_d (= 0.028 days) is so small that no short time scaling is observed. When T_1^* increases to $\approx 2 \times 10^5$, i.e., at $t \approx$ 1–1.5 days, the pseudo-state approximation, $V \approx N\delta T^*/c$, holds. Note that the curves for V and T^* are parallel around $t \approx 1.5$ days in Fig. 2*a*. Because $t_d << t$, case (*ii*) above applies and the power law scaling is observed. In Fig. 4*b*, t_d = 0.28 day, and $V \approx V_0$ for times larger than t_d after the onset of infection (Fig. 2*a*). Also, $1/\delta >> t_d$. Thus, case (*i*) applies, and a short time scaling is observed up to $T_1^* \approx$ 3-4 $\times 10^4$, which corresponds to $t \approx 0.3$ days. For $t > t_d$, the scaling temporarily vanishes. However, when $\approx 2 \times 10^5 < T_1^* < 10^6$, case (*ii*) applies and the scaling reemerges. In Fig. 4*c*, t_d (= 2.8 days) is large. Of the three times, t_s, t_d, and $1/\delta$, the shortest is $1/\delta \approx 0.7$ day. Thus, the short-term scaling [case (*i*)] is observed until $t \approx 0.7$ days. By the end of the short-term scaling regime, however, V is nearly in pseudo-equilibrium with T^* and case (*iii*) applies, since $t_d >> t$. Thus, with minor deviations during the transition from cases (*i*)

to (*iii*), a single scaling regime that spans the entire first phase of T^* is observed in Fig. 4*c*.

We present in Fig. 5*a* the time evolution of T_i^* and present in Fig. 5*b* the corresponding parametric plots of $T_i^*(t)$ vs. $T_1^*(t)$, for $k_0 = 2 \times 10^{-10}$ day^{-1}, $t_d = 0.28$ day, and $V_0 = 10^8$. The corresponding evolution of T, V, and T^* are presented in Fig. 2*c*. The lower value of k_0 compared with Fig. 2*a* implies that infection proceeds at a slower rate. Thus, in Fig. 2*c*, T^* remains small, which in turn postpones the rise in V and the subsequent fall of T. The dynamics, however, is qualitatively similar to that in Fig. 2*a*. The same scaling regimes are observed as in Fig. 4*b* ($t_d = 0.28$ day), except that the second scaling regime appears delayed. Short time scaling is observed for $T_1^* < 4\text{–}5 \times 10^3$, which corresponds in Fig. 5*a* to $t \approx 0.3$ day. Note in Fig. 2*c* that $V \approx V_0$ and $T \approx T_0$ for much longer times than 0.3 day. Thus, this short-term scaling may be attributed to case (*i*) above. The second scaling regime occurs in the range $2 \times 10^6 < T_1^* < 10^7$, which corresponds to the time interval 5 days $< t <$ 6.5 days in Fig. 5*a*. Note in Fig. 2*c* that this is precisely the time interval during which T^* evolves parallel to V indicating that the pseudo-steady-state approximation holds. Scaling as described by case (*ii*) above thus applies. Note that the lower infection rate in Fig. 2*c* compared with Fig. 2*a* postpones the attainment of the pseudo-steady state in Fig. 2*c*. Accordingly, the second scaling regime is postponed in Fig. 5*b* compared with Fig. 4*b*. However, the small time scaling is limited by CD4 down-modulation, which is chosen to have the same timescale, in both cases. In accordance, the short-time scaling occurs for the same times in Figs. 4*b* and 5*b*.

In Fig. 5*c*, we present the time evolution of T_i^*, and in Fig. 5*d* the corresponding parametric plots of $T_i^*(t)$ vs. $T_1^*(t)$, for $k_0 = 2 \times 10^{-10}$ day^{-1}, $t_d = 0.28$ day, and $V_0 = 10^{10}$. The evolution of T, V, and T^* for these parameters is shown in Fig. 2*d*. The two orders of magnitude higher V_0 dramatically shortens the first phase of evolution of T^* to $t \approx 0.8$ days. However, the lower infectivity allows target cells to proliferate, and the evolution follows predator-prey dynamics. In Fig. 5*d*, we find that a short time power law scaling

of T_i^* is observed for $T_1^* < 3–4 \times 10^5$, which from Fig. 5*c* corresponds to $t \approx 0.3$ day, again corresponding to the CD4 down-modulation time, since $V \approx V_0$ and $T \approx T_0$ during these times. However, no further scaling regimes are observed as the first phase of T^* evolution ends immediately thereafter. For higher values of k_0 or V_0, the first phase is further short-lived and the power law scaling is difficult to observe (data not shown).

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3. Lama, J. (2003) *Curr. HIV Res.* **1,** 167–184.