Post-treatment control of HIV infection

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Edited by Charles S. Peskin, New York University, Manhattan, NY, and approved March 13, 2015 (received for review October 8, 2014)

Antiretroviral therapy (ART) for HIV is not a cure. However, recent studies suggest that ART, initiated early during primary infection, may induce post-treatment control (PTC) of HIV infection with HIV RNA maintained at <50 copies per mL. We investigate the hypothesis that ART initiated early during primary infection permits PTC by limiting the size of the latent reservoir, which, if small enough at treatment termination, may allow the adaptive immune response to prevent viral rebound (VR) and control infection. We use a mathematical model of within host HIV dynamics to capture interactions among target cells, productively infected cells, latently infected cells, virus, and cytotoxic T lymphocytes (CTLs). Analysis of our model reveals a range in CTL response strengths where a patient may show either VR or PTC, depending on the size of the latent reservoir at treatment termination. Below this range, patients will always rebound, whereas above this range, patients are predicted to behave like elite controllers. Using data on latent reservoir sizes in patients treated during primary infection, we also predict population-level VR times for noncontrollers consistent with observations.

HIV latency | immune exhaustion | HIV viral rebound | mathematical modeling

In the VISCONTI study, 14 patients, who initiated combination antiretroviral therapy (ART) within 3 mo of their estimated date of infection and remained on durable treatment for 1–8 y were able to control HIV infection after treatment cessation (1, 2). These "post-treatment controllers" (PTCs) have maintained their plasma HIV RNA levels to <50 copies per mL, with the exception of a few viral blips between 4 and 9 y; also, their CD4 T-cell counts increased during ART from a median of 502 cells/mm^3 to a median of 927 cells/mm^3 and they have maintained a nearly normal CD4 T-cell count following treatment discontinuation (median 827 cells/mm^3). There have also been other reports of PTCs (3, 4).

In the SPARTAC study (5) of 165 patients who initiated short-term ART within 6 mo of seroconversion and reached plasma viral loads <400 copies per mL at the time of stopping ART, four maintained viral loads <400 copies per mL for 164–202 wk after treatment cessation, supporting observations of post-treatment control, albeit at a low frequency. Additionally, the study found that longer-term treatment, ≥12 wk compared with treatment for <12 wk, was associated with a higher probability of control (5).

Some individuals have the ability to control HIV in the absence of treatment. Elite controllers (ECs) or suppressors were first identified in 2005 (6); these individuals naturally control HIV infection, maintaining undetectable viral loads (<50 copies per mL) (7, 8). ECs have since been the focus of study because understanding how they control infection may lead to advances in treatments and vaccines (7, 9). From these investigations, several key clinical characteristics of ECs have been uncovered. For example, ECs tend to have protective HLA alleles and maintain a measurably stronger cytotoxic T lymphocyte (CTL) response than noncontrollers (7, 8, 10).

The PTCs reported in ref. 1 do not appear to be ECs because they typically lacked protective HLA class I alleles—specifically, HLA-B*27 and B*57—that are generally overrepresented in ECs, as well as the strong HIV-specific immune responses found in most ECs (10). Further, ECs form only a fraction of a percent of the population (11, 12), far less than the 5–15% of study patients found to be PTCs (1, 2).

The existence of a latent reservoir is one of the major hurdles in eradicating HIV infection (13). Latently infected cells are unaffected by ART, undergo homeostatic proliferation (14), and their population is established early after infection (15–17). Typical measurements of the reservoir size in chronically HIV-infected patients are in the range of 0.6–40 per 10^6 CD4$^+$ cells (18). However, measurements differ depending on the patient cohort studied and the assay used (19), with estimates ranging from as low as 0.03–3 per 10^6 resting CD4$^+$ cells (20) to as high as 55 ± 108 per 10^6 CD4$^+$ cells (21). Further, a recent study examining noninduced HIV proviruses suggested that the size of the replication-competent latent reservoir may be up to 60 times larger than previously thought (22). Despite its relatively small size, the reservoir is long-lived; patients on treatment show a decaying reservoir with a half-life estimated to be between 6 and 44 mo, with an estimated time to complete eradication of up to 70 y (20, 23). The activation of latently infected cells may be responsible for persistent viremia and viral blips seen in patients on ART (24–26).

In the VISCONTI study (1), treatment was initiated during primary infection, potentially limiting the seeding of the latent reservoir (16, 27). Intriguingly, comparisons of integrated DNA in resting CD4$^+$ cells between PTCs and ECs suggest that both sets harbor similar latent reservoirs in size and composition (1).

In the VISCONTI study (1), 12 of the 14 PTCs had symptomatic primary infection. Further, during primary infection [median 1.6 (range 1.1–2.1) mo after estimated exposure], they exhibited high viral loads (median 5.0 log HIV-1 RNA copies per mL), low CD4$^+$ T-cell counts (median 502 cells/mm^3) and the median Fiebig stage was V, suggesting that many of the subjects were near set-point viremia (28, 29). After ART was

Significance

Recent reports suggest that antiretroviral therapy (ART) initiated early after HIV infection increases the likelihood of post-treatment control (PTC) in which plasma virus remains undetectable after treatment cessation. However, only a small fraction of patients treated early attain PTC. We develop a mathematical model of HIV infection that provides insight into these phenomena, suggesting that treatments restricting or reducing the latent reservoir size may allow immune responses to control infection posttreatment. Our model makes predictions about immune response strengths and latent reservoir sizes needed for a patient taken off treatment to exhibit PTC that may help guide future studies.

Author contributions: J.M.C. and A.S.P. designed research, performed research, and wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1419162112/-/DCSupplemental.

discontinued, these 14 subjects all maintained HIV RNA <50 copies per mL for a median of 89 mo. Thus, this study suggests that during HIV infection, some individuals may have two off-treatment set-points, one high, e.g., 10^3 to 10^5 copies per mL, as typically seen in untreated HIV-infected subjects, and one low, e.g., the "controlled" viral load set-point below 50 copies per mL seen in the PTCs.

Why some patients are able to control HIV after treatment cessation is uncertain. Treatment during primary infection is known to reduce latent reservoir sizes (16, 27) and delay viral rebound upon cessation of treatment (5). A number of factors may play a role, including the size of the latent reservoir (1, 2, 30), the rate at which latently infected cells become activated, and the strength of the host immune response (7). Our modeling hypothesis combines these factors: latently infected cells activate to yield virus-producing cells, promoting further viral replication. If the rate of generation of new productively infected cells is small, the adaptive immune response mounted by post-treatment controllers may be sufficiently strong to control infection. We explore this hypothesis using a mathematical model, a variant of the standard viral dynamic model of HIV infection and treatment (31–33), which incorporates the dynamics of the latent reservoir and explicit CTL effector cell dynamics (34, 35). We show that in certain parameter regimes, our model predicts viral rebound and reestablishment of chronic HIV infection after therapy is stopped (Fig. 1*A*). However, our model also predicts post-treatment control if the latent reservoir is sufficiently small and if the strength of the cell-mediated response is above a threshold value (Fig. 1*B*). Last, our model predicts, with very strong CTL responses, behavior similar to that seen in ECs.

Methods

Model of Post-treatment HIV Viral Dynamics. Our model, shown schematically in *SI Appendix*, Fig. S1, is given by the following equations:

$$\begin{aligned}\frac{dT}{dt}&=\lambda-dT-(1-\varepsilon)\beta VT\\ \frac{dL}{dt}&=\alpha_L(1-\varepsilon)\beta VT+(\rho-a-d_L)L\\ \frac{dI}{dt}&=(1-\alpha_L)(1-\varepsilon)\beta VT-\delta I+aL-mEI\\ \frac{dV}{dt}&=pI-cV\\ \frac{dE}{dt}&=\lambda_E+b_E\frac{I}{K_B+I}E-d_E\frac{I}{K_D+I}E-\mu E,\end{aligned}\qquad [1]$$

where T represent target cells, I productively infected cells, L latently infected cells, E effector cells, and V virus. Target cells are created at rate λ, die at rate d per cell, and become infected with infectivity rate constant β. Productively infected cells produce virus at rate p per cell and die at rate δ per cell by viral cytopathic effects. Virions are cleared at rate c. We assume that upon infection a fraction of cells, α_L, become latently infected. They may then be activated to become productively infected at rate a or die at rate δ_L. These cells may also proliferate at rate ρ (14).

Following the approach in ref. 34, based on the model developed in ref. 35, we assume effector cells, E, kill productively infected cells, I, at rate mEI, where m is the CTL killing rate constant. We associate a high killing rate with a strong immune response. Effector cells are assumed to be produced at rate λ_E and to be lost at rate μ. Effector cells proliferate in an infected cell density-dependent manner with maximum rate b_E, where the proliferation term is $b_E(I/(K_B+I))E$. High viral loads (and therefore high infected cell densities) may induce some immune impairment, e.g., immune exhaustion (36, 37). Allowing for the rate of this impairment to saturate, we model the loss of functional effector cells by the term $d_E(I/(K_D+I))E$, where K_D is chosen larger than K_B.

We also include in the model treatment with reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). As shown in ref. 38, the combined effect of both drug classes can be represented by the overall treatment effectiveness, ε, where $0 \le \varepsilon \le 1$, and $\varepsilon = 1$ is 100% effective therapy. When treatment is stopped, drug efficacy $\varepsilon = 0$.

Alternative versions of this model that incorporate logistic growth of target cells, logistic growth of latently infected cells to better mimic homeostatic proliferation, and a more complex model of CTL exhaustion due to Johnson et al. (39) are presented in *SI Appendix* and are shown to give rise to similar behavior as model Eq. **1**.

Parameters. Baseline model parameters are summarized in *SI Appendix*, Table S1. Where possible, we used published estimates. Parameters describing the dynamics of target cells T, productively infected cells I, and virus V are discussed in *SI Appendix*.

The parameters characterizing the dynamics of the latent reservoir remain unclear. As in previous modeling work, we assume that the fraction of infections that result in latency $\alpha_L = 10^{-6}$ and the death rate of these cells is $d_L = 0.004$ d^{-1} (38). The results in Archin et al. (40) suggest that $\beta\alpha_L$, where β is the mass-action infection rate constant, is of the order of 10^{-14} mL per cell per d, and our values of β (41, 42) and α_L (*SI Appendix*, Table S1) are consistent with this estimate. Latently infected cells are isolated from resting CD4$^+$ T memory cells, whose lifespan has been estimated to be ~6 mo (43, 44), consistent with our choice of d_L. We further assume that the latent cell activation rate a is 10^{-3} d^{-1}, indicating that, if there are 10^6 latently infected cells body-wide, 1,000 will activate every day. Also, with these parameter choices, the fraction of latently infected cells that activate before they die, $a/(a+d_L)$, is 0.2. Though this number is not known precisely, it most likely is a generous overestimate because T cells generally need to encounter their cognate antigen to become activated. In treated patients, the latent reservoir generally decays; estimates give an average reservoir half-life of 44 mo (20) but vary widely, from as low as 6 mo (23) to as high as 58 mo (20). We take the half-life $t_{1/2} = 44$ mo and use it to set the latently infected cell proliferation rate ρ, $\rho = a + d_L - \ln(2)/t_{1/2} \approx 0.0045$ d^{-1}, as in ref. 24, assuming that the contribution of new infections while on treatment is negligible (45).

The latent reservoir size at treatment cessation, L_0, is an important control parameter. Measurements of latent reservoir sizes vary widely (1, 22, 40), likely due to interpatient variability (15) and inherent stochasticity (46–48), so we would anticipate variation in L_0. We take L_0 in the range 10^{-1} to 10^2 per 10^6 CD4$^+$ T cells, consistent with published ranges (21, 40).

We choose a maximum effector cell proliferation rate, $b_E = 1$ d^{-1} consistent with the estimates in Davenport et al. (49) and a maximum rate of exhaustion of effector cells, $d_E = 2$ d^{-1} (close to the value used in ref. 39), that is greater than b_E so that the effector population can be effectively reduced by exhaustion. We use the effector cell killing rate m as a second control parameter indicating the strength of the immune response. The death rate of productively infected cells, $mE + \delta$, is of order 1 d^{-1} but can be as large as 1.4 d^{-1} (50). Thus, mE must be of order 1 d^{-1}. For our baseline parameters (*SI Appendix*, Table S1), the HIV-specific effector cell concentrations are also of order 1 cell/mL. Thus, we vary the parameter m between 0 and 1 mL per cell per d to modulate the effector cell killing rate mE.

Model Analysis. Using numerical simulation, we investigated the viral dynamics after treatment cessation. Our modeling predictions depend on the size of the latent reservoir, L_0, at the moment of treatment cessation. At the end of treatment, patients may have different latent reservoir sizes L_0, which can depend on patient-specific parameters but also on the initiation time of therapy. We also require corresponding values, at the time of treatment cessation, for target cells T, infected cells I, virus V, and effector cells E. Assuming therapy is effective, the cell and viral concentrations T, I, E, and V all reach dynamical equilibrium with the latent reservoir size, L, after a short

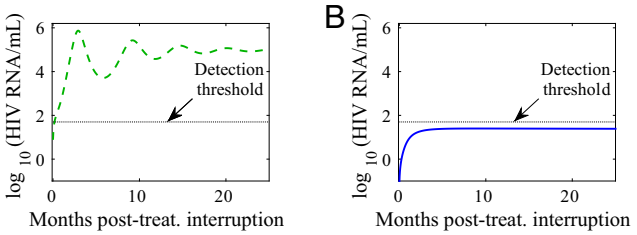

Fig. 1. Model predictions on viral load dynamics after treatment interruption depending on the initial latent reservoir size, L_0. (*A*) Viral rebound for $L_0 = 100$ per 10^6 CD4$^+$ cells. (*B*) Post-treatment control for $L_0 = 1$ per 10^6 CD4$^+$ cells. Other parameters as in *SI Appendix*, Table S1, and the detection threshold, marked by the dashed line, is set to 50 copies per mL.

transient (*SI Appendix*, Fig. S2). Because the transient is less than 6 mo, and the median treatment duration for PTCs in ref. 1 was 36.5 mo, we take for T, I, E, and V at the end of treatment their values in quasi-equilibrium with a prespecified latent reservoir size, L_0. We obtain these quasi-equilibrium values numerically (*SI Appendix*, Fig. S2).

Results

Post-treatment Control and Latent Reservoir Size. We begin by examining viral dynamics at treatment interruption, using baseline parameters in *SI Appendix*, Table S1, assuming different post-treatment latent reservoir sizes, L_0.

For latent reservoir sizes in the upper part of the measured ranges, our model predicts VR, with dynamics reminiscent of primary infection dynamics. An example is given in Fig. 1*A* assuming that at treatment cessation the latent reservoir size $L_0 = 100$ per 10^6 $CD4^+$ cells. However, for much smaller values of L_0, we find that the predicted viral load increases slightly at treatment cessation but remains low and below the level of detection (Fig. 1*B*), which we interpret as PTC. For other values of L_0 at treatment cessation, simulations show that the VL can remain low, below the level of detection, for long periods of time before rebounding (*SI Appendix*, Fig. S3); these are not to be confused with PTC for which the VL is stably maintained below 50 copies per mL. Fig. 1*B* shows PTC viral dynamics after treatment cessation assuming $L_0 = 1$ per 10^6 $CD4^+$ cells. Thus, our model with a fixed set of parameters, except for L_0, which is allowed to vary, predicts the existence of distinct viral set-points in a single patient after treatment cessation, with the set-point achieved after treatment cessation depending, in part, on the latent reservoir size L_0.

Post-treatment Control and the Strength of the Immune Response. We hypothesize that patients who exhibit post-treatment control generate an adaptive immune response that is sufficiently strong to control infection after treatment interruption if the rate of generation of new productively infected cells, aL, is sufficiently small. If the value of the latent cell activation rate, a, is fixed, as it is here, it is sufficient for L_0 to be small.

This hypothesis suggests a relationship among the latent reservoir size, the strength of the HIV-specific adaptive immune response, and post-treatment control, which we now explore. Our model assumes the immune response is cell mediated, but humoral and innate immune responses may also play a role as discussed later.

Fig. 2*A* shows the predicted viral load set-points in absence of treatment, as $t \to \infty$, using the baseline parameters in *SI Appendix*, Table S1, as a function of the CTL killing rate, m. Solid lines indicate achievable, stable set-points, marked as VR or PTC. The dashed line indicates unstable steady states at which the system cannot remain, and which are of no physiological relevance. Mathematically, solid and dashed lines are the linearly stable and unstable fixed points, respectively, of Eq. **1**, which were calculated analytically (see *SI Appendix* for details). We mark three regimes in the CTL response parameter m, regimes I–III, and interpret this set-point diagram in the different regimes as follows:

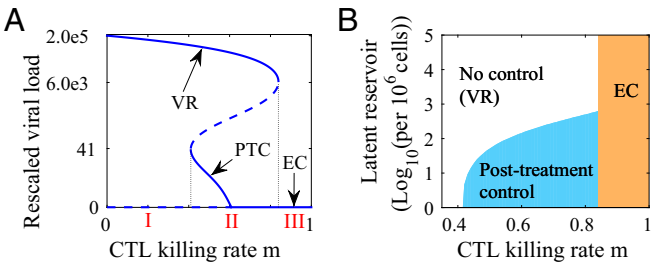

Fig. 2. Bifurcation diagrams indicating parameter regimes with post-treatment control. (*A*) Steady-state viral load as a function of the CTL killing rate m; solid lines indicate linearly stable viral set points. In regime I, only VR is possible, whereas in regime II, both PTC and VR are possible. Regime III corresponds to EC, with viral loads predicted to decay to zero over long times. Note that the curve is the projection of the steady states in 6 dimensions, T, L, I, V, and E as a function of m, onto the V–m plane. (*B*) Post-treatment control, viral rebound, or elite control depending on the latent reservoir size at treatment termination, L_0, and the CTL killing rate, m. Note that the threshold in L_0 for PTC increases with the CTL killing rate m.

Noncontrollers. For CTL responses in regime I, the only possible set-point is a VR set-point. We would therefore expect, upon cessation of treatment, reestablishment of chronic HIV infection for patients in this regime, regardless of the latent reservoir size, L_0.

Elite controllers. For the strongest CTL responses, i.e., those in regime III, our model predicts a zero viral load set-point. That is, as $t \to \infty$, the viral load would go to zero. However, at all finite times, virus would be present, likely due to some residual viral replication and latent cell activation/ensuing virus production, but at very low values; this is consistent with the phenomenon of elite control. ECs are capable of spontaneously controlling HIV infection with viral loads below detection without treatment (7). Studies show that these individuals have stronger-than-average HIV-specific CTL responses (7, 10), which is consistent with a high CTL killing rate, m.

Post-treatment controllers. In the middle regime II, the VR and PTC viral set-points are bistable—i.e., the system of equations (1) possesses two off-treatment set-points (positive steady states), both of which can be stable. Therefore, in this regime VR may occur, but so may PTC, with either a low, finite viral set-point or, as in the case of EC, a zero viral set-point. CTL responses may be sufficiently strong to control HIV infection, depending on the disease state at treatment cessation. The disease state is not simply characterized by viral load but by all of the variables in the model, and the set-point diagram in Fig. 2*A* should only be used as a guide. For example, a patient with CTL responses in this PTC range, whose viral load is lower than the PTC set-point at treatment termination, may nonetheless experience VR if their latent reservoir size is large.

The disease state can be characterized by the latent reservoir size at treatment cessation, L_0, because in our model, while on treatment, the cell populations T, I, and E, and the viral population, V, are all in dynamical equilibrium with the latent reservoir size, L. Fig. 2*B* shows regions of VR, PTC, and EC as a function of the latent reservoir size at treatment cessation, L_0, and the CTL killing rate m. Mathematically speaking, these regions are the basins of attraction of the VR, PTC, and EC fixed points and all initial conditions, calculated as described above, lie in one of these regions. If at treatment interruption latent reservoir sizes and CTL strengths are in the blue region marked PTC, the CTL response is sufficiently strong to prevent ensuing VR. As m increases, the maximum latent reservoir size that permits post-treatment control also increases, following the curve separating the blue (post-treatment control) and white (viral rebound) regions in Fig. 2*B*.

Slow Viral Rebound in Non-PTCs. In non-PTC patients, viral rebound upon cessation of treatment may not be immediate, and may be delayed by months or years (1). The cause of delayed rebound can be attributed to a number of sources; e.g., in the long term, viral mutation and CTL escape are increasingly likely. However, the delay may also simply be associated with slow underlying viral dynamics (51). Figure 7 in ref. 1 shows a survival curve of times until viral rebound in a cohort of 70 patients, treated within 6 mo of estimated HIV-1 infection, who continued treatment for at least 1 y and interrupted therapy while their HIV RNA was <50 copies per mL. Loss of control (VR) was

defined as two sequential viral load measurements >50 copies per mL, with a median time between measurements of 3 mo, or one viral load measurement >50 copies per mL followed by resumption of ART.

Our model predicts that after treatment interruption there will some delay before viral load detection, and that the length of this delay is associated with the latent reservoir size at treatment termination (*SI Appendix*, Fig. S3). An AIDS Clinical Trials Group study, ACTG A5345, will test this hypothesis. The length of the delay is also associated with CTL strength m. As m approaches the boundary between no control and post-treatment control in Fig. 2, for a given latent reservoir size at treatment termination, the delay before viral load detection gets large (*SI Appendix*, Fig. S3). In fact, the delay can be years, as observed in the Mississippi baby (52, 53). Assuming no external causes (e.g., CTL escape) are the source of VR, we can use our model to predict times to VR (see *SI Appendix* for details). These predictions can be used to address the clinically pertinent question of how long viral load must remain undetectable before we can say with some measure of confidence that it is evidence of post-treatment control. Our model-predicted rebound times will correspond to the time that viral load calculated from Eq. **1** crosses the detection threshold of 50 copies per mL, $T_{\mathrm{det}}(L_0, m)$, and should therefore precede the observed viral rebound times in ref. 1 as the patients were sampled infrequently and presumably rebounded before they were sampled (Fig. 3).

Discussion

ART has been shown to improve both the quality and length of life (54, 55). The VISCONTI study (1), as well as others (3, 4), report that patients treated shortly after HIV exposure, in some cases, may be able to control infection after treatment cessation. PTC of infection corresponds to functional cure, sustained remission that does not require therapy. Why only a small fraction of treated patients exhibit PTC is unknown and is the focus of our investigation.

The 14 PTCs reported in ref. 1 initiated treatment early during primary infection. Here we explored the hypothesis that potent early treatment not only drove viral loads below the limit of detection but also interrupted the formation of the latent reservoir, so that upon cessation of ART, the adaptive immune response was then able to control infection. To investigate this hypothesis, we created a mathematical model of viral dynamics encompassing both effector cell and latent reservoir dynamics, extending previously published models (24, 34, 35, 56). Though HIV-specific antibody responses may also play a role in PTC, here we focused on cell-mediated responses, including the possibility of immune exhaustion.

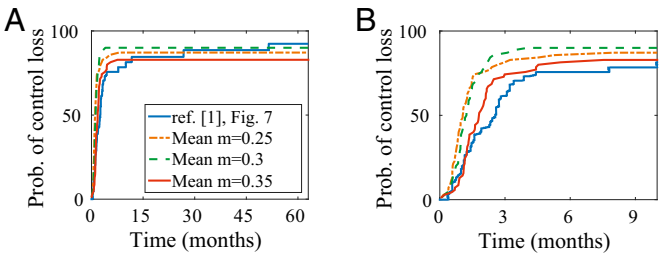

Fig. 3. Time to viral load detection in the case of viral rebound, and chronic infection reestablishment. The legend indicates mean CTL strength m of an assumed population-level beta distribution (*SI Appendix*) for each curve. (*A*) Probability of control loss calculated from 70 simulated patients with latent reservoir size and CTL killing rate sampled from distributions in *SI Appendix*, Fig. S4 compared with the probability of control loss from ref. 1. (*B*) Probability of control loss as in *A*, zoomed in to first 10 mo. Other parameters as in *SI Appendix*, Table S1.

Our model predicts that for a very strong effector cell response (m near 1; regime III in Fig. 2*A*), HIV infection will always be controlled; this corresponds to the case of ECs, individuals who can spontaneously control HIV infection. PTCs do not share clinical characteristics with ECs (1). For individuals who mount a very weak effector cell response, our model predicts viral rebound will occur after therapy is interrupted. However, in our model, there is a midrange in effector cell strength, m (regime II in Fig. 2*A*), where both high and low viral load set-points are potentially attainable in the absence of therapy. Which set-point is attained depends on the latent reservoir size at treatment termination, L_0, and the CTL strength, m (Fig. 2*B*). Just having a very low latent reservoir size is insufficient to guarantee PTC, consistent with the observations reported by Chun et al. (57). That a single HIV-infected individual can have two distinct set-points in the absence of therapy is biologically indicated as well. Before treatment, the median viral load of the 14 PTCs was 10^5 copies per mL, and they had a median Fiebig stage of V, consistent with some of the PTCs being at a high viral load set-point (28). Because the PTCs did not have characteristics of ECs, the PTCs who began therapy at an earlier Fiebig stage and those in Fiebig stage V and not yet at set-point would have been expected to attain a viral load set-point above 50 copies per mL if therapy were not initiated. After treatment cessation, the PTCs had viral loads that remained <50 copies per mL for a median of 89 mo, consistent with being at a low viral set-point.

Our model of effector cell dynamics, which underlies the possibility of an individual having two distinct viral load set-points, is relatively simple and based on prior work (34, 35). A number of more complex models that incorporate additional immune system features, such as the role $CD4^+$ T cells as both helper cells and target cells, precursor and effector $CD8^+$ cells, as well as more explicit models of immune impairment have also been shown to exhibit coexistence of two stable viral set-points (58–60). However, none of these models incorporate latently infected cells or ART and hence are not suitable for predicting PTC.

Although our modeling was focused on explaining PTC, we also used our model to make predictions about the time to VR, in the case that PTC is not achieved. Using data on the latent reservoir size from patients treated within 45 d of inferred infection (40), we predict VR times qualitatively similar to those reported in ref. 1: most rebounds are within the first 6 mo (Fig. 3). Smaller latent reservoir sizes increase the predicted rebound times (*SI Appendix*, Fig. S3), consistent with observations in ref. 5. These consistencies with experimental data suggest that our model with the assumed parameter values is capturing not only the qualitative phenomenon of PTC, but also some of the quantitative features of failure to obtain PTC.

Our modeling prediction of VR delay associated with a small latent reservoir size is consistent with the delayed viral rebound observed in the Mississippi Baby (52). Within 30 h of birth, that HIV^+ infant was prescribed combination ART. Although treatment was suspended after 18 mo, levels of plasma HIV-1 RNA, proviral DNA in peripheral-blood mononuclear cells, and HIV-1 antibodies, as assessed by means of clinical assays, had remained undetectable in the child for ~27 mo before viral rebound (52, 53). Although the child was infected in utero, it is likely that, at the time of treatment, the child's latent reservoir was small, because the largest contributor to the reservoir are memory cells (14), and the memory response only develops after birth. The two HIV-1–infected "Boston patients" (61) also experienced delayed rebound, by 12 wk and 8 mo, following cessation of ART after allogenic hematopoietic stem cell transplants for the treatment of lymphoma; their latent reservoirs were also likely very small, because HIV-1 DNA and RNA were not detectable in peripheral blood mononuclear cells, $CD4^+$ T cells, and plasma up to 21 and 42 mo after transplantation in the two patients (62). Although our predictions are consistent with these observations,

there are alternative hypotheses, including CTL escape, rebound arising from dynamics associated with the developing or recovering immune responses, or stochastic latent cell activation without immune control (51).

Though our model, as well as that of Hill et al. (51), predicts delays in viral rebound, the models are different. Our model is deterministic and focuses on the potentially large number of latent cell activations that can occur at treatment cessation (1,000 per day assumed in a patient with 10^6 latently infected cells), and their interaction with an immune response that may lead to PTC. The model of Hill et al. (51) focuses on the activation of latently infected cells after a latency reducing regime is applied. Because the number of remaining latently infected cells is assumed to be small, the Hill model is stochastic and focuses on determining the waiting time until a latently cell is activated and triggers a sustained chain of infection in the absence of an immune response.

As a mechanism for control of HIV infection, we focused on the cytolytic role of HIV-specific effector cells, presumably $CD8^+$ T cells, although NK cells are also cytolytic effectors and therefore could be considered to be included in our model. $CD4^+$ and $CD8^+$ T cells, as well as NK cells, have significant noncytolytic functions that have not been included in our model. Our model also did not consider HIV-specific antibody responses (63, 64) that could affect the details of the viral dynamic model in a number of ways (65). Whether these features of immune responses play a role in PTC is unknown. However, our model has shown that including a simple effector cell response that can become exhausted is sufficient to recapitulate many of the features seen in PTC and has allowed us to make predictions about the conditions necessary to achieve PTC and the time to VR when PTC is not attained.

In formulating our model, we assumed that latently infected cell activation drives ongoing viremia in patients on ART. Investigation of decay kinetics of the latent reservoir in patients on ART, over long times, revealed an average reservoir half-life of 44 mo (20). We took this 44-mo half-life as the underlying decay rate for the latent reservoir, motivating our choice of the latently infected cell proliferation rate, ρ. However, this parameter as well as all of the baseline parameters that we choose presumably vary among individual patients and affect quantitative predictions. Thus, the precise values of the immune response strengths, m, and the latent reservoir sizes, L_0, that generate PTC in Fig. 2*B* should not be interpreted too literally. More significantly, the effector cell response strength m is not well characterized biologically; this is a key knowledge gap for the model and also the field. Last, we made the simplifying assumption that the latent reservoir represents a homogeneous population of cells, whereas in reality, the reservoir is composed of multiple T-cell types, including naive, central memory, effector memory, transitional memory, and terminally differentiated cells (14). Each cell type carries with it its own characteristics—e.g., decay rates. Because PTCs in ref. 1 were treated early in primary infection, interfering with the seeding of the reservoir, it is possible the composition of their latent reservoirs in terms of these cell types differs from patients who were not treated during acute infection. Differing latent reservoir compositions may contribute to viral rebound and post-treatment control of HIV in a way not foreseen in our model. To investigate such effects, further characterization of cell subsets in PTCs will be needed. Key to such an investigation are the activation rates a, which control the rate of influx of productively infected cells, aL_0, at treatment cessation. For this present study, in absence of an estimate, we fixed a at 10^{-3} d^{-1} A smaller a, however, would yield a slower influx of new virus-producing cells, and therefore like small values of L_0, enhances the probability of post-treatment control.

However simple, our model gives realistic viral dynamics and supports our hypothesis that a small latent reservoir is necessary, but not sufficient, for post-treatment control. Our model offers a number of testable predictions: (*i*) There is a range of typical effector cell responses where PTC cannot be attained, no matter how small the viral reservoir. This regime describes most patients, because PTCs comprise 5–15% of the population (1) and elite controllers comprise <1% of the population (11, 12). (*ii*) For individuals with responses in this regime, boosting their immune responses before termination of treatment may enhance the probability of post-treatment control. Such a boost may be achievable via therapeutic vaccination (66, 67) (*SI Appendix*, Fig. S5). (*iii*) Conversely, if immune responses are compromised or weakened, i.e., if the CTL killing rate, m, is decreased, a post-treatment controller may revert to regime I and experience viral rebound. Thus, our model predicts that care should be taken when prescribing immune suppressants, e.g., corticosteroids, aimed at treating unrelated conditions, to post-treatment controllers. (*iv*) There is a regime of very strong effector cell responses where control is always attained, even in the absence of therapy. This regime corresponds to the phenomena of elite control. (*v*) Between these two regimes, PTC is predicted to be possible. (*vi*) Importantly, in the regime where PTC is possible, the effector cell response strength of PTCs is not distinguishable from those of viral rebounders. Thus, while having protective HLA alleles and strong HIV-specific immune responses characterize ECs, they do not characterize PTCs. (*vii*) More significantly, even for CTL strengths sufficient for PTC, a small latent reservoir size is necessary. If the latent reservoir is too large or activated too rapidly, the resulting cell infections after ART is stopped may not be controlled, resulting in viral rebound. (*viii*) The maximum reservoir size that would permit PTC is predicted to increase with CTL strength. (*ix*) Even if PTC is not achievable, a diminished latent reservoir can delay viral rebound upon cessation of treatment. (*x*) Strategies aimed at reducing the latent reservoir size, either through ART initiated early during primary infection (1, 27) or through the use of latency-reversing agents, such as histone deacetylase inhibitors (68, 69), DNA methylase inhibitors (70), disulfiram (71), auranofin (30), and activators of protein kinase C or toll-like receptors (72) may enhance the odds that patients attain post-treatment control of HIV infection (*SI Appendix*, Fig. S5). If ART is initiated too early, adequate immune responses may not develop. Thus, the use of latency reversing agents may be a preferred strategy and their combination with therapeutic vaccination should also be considered (*SI Appendix*, Fig. S5).

Understanding the biological basis of post-treatment control will be greatly enhanced by modeling efforts combined with prospective clinical trials, including more robust data collection on relevant effector responses, latent reservoir sizes, and rates of latency reactivation.

ACKNOWLEDGMENTS. We thank Rustom Antia, Rob J. de Boer, John Mellors, George Shaw, Jonathan Li, and Laurent Hocqueloux for comments and discussions that helped improve this manuscript. This work was performed under the auspices of US Department of Energy Contract DE-AC52-06NA25396 and supported by National Institutes of Health Grants R01-AI028433, R01-OD011095, and UM1-AI100645.

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