1. Supplementary Discussion
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1. SUPPLEMENTARY DISCUSSION. Alternative therapies using viruses.

The hunter-virus therapeutic approach can be compared with alternative strategies using viruses for controlling HIV replication such as the defective interfering viruses (DIVs) and conditional replicating anti-HIV gene therapy viruses (Morris et al., 2004). These viruses are incapable of replicating by themselves but can compete with HIV during replication and also alter HIV functions. Similar to hunter viruses, they only replicate in a host cell co-infected with HIV. In general, the outcome of DIVs as antiviral agents has been limited (Huang & Baltimore, 1970; Roux et al., 1991). One proposed anti-HIV gene therapy uses the viral vector ability for expressing ‘ribozymes’ from infected cells (Mautino & Morgan, 2002). Ribozymes can cleave and destroy specific mRNAs, such as highly conserved HIV-1 RNA coding for the viral envelope, causing partial or complete blockage of HIV-1 production from a cell. This viral vector also competes for encapsidation of viral RNA, causing further inhibition of HIV.

The use of DIVs and gene therapy viruses to treat viral infections has been studied theoretically (Bangham & Kirkwood, 1990; Lund et al., 1997; Madsen et al., 1997; Nelson & Perelson, 1995; Szathmary, 1993; Weinberger et al., 2003). Two studies stand out by involving different therapeutic strategies and analyzing the dynamics using parameterized models. One by Nelson & Perelson (1995) modeled a HIV-derived DIV carrying interfering genes (i.e. ribozymes) that obstructs HIV replication by slowing the assembly of HIV-1 and producing HIV with reduced infectivity. Results indicate that the efficiency of this strategy depends on the
expected infectivity and proliferation for the DIV relative to HIV; and for realistic parameter values the study concluded that DIV survival in peripheral blood is improbable. Thus, for a highly-optimistic set of parameter values (including DIV proliferation 50 times those of HIV—an optimistic value because the DIV is HIV-derived) the model stabilizes with a CD4 cell population of about 60% the normal value; moderately optimistic values (involving DIV proliferation 10 times those of HIV) predict a recovery to 45% of the normal level.

Similarly, Weinberg et al. (2003) modeled a conditionally replicating virus (crHIV) for anti-HIV-1 gene therapy that reduces HIV production from infected cells. It differs from the previous model in the type of cells pursued by the therapeutic viruses: the DIV (Nelson & Perelson, 1995) targets HIV-infected cells (through an engineered envelope), while the crHIV targets uninfected cells. Both were HIV-derived. Thus, the crHIV-infected cells remain on hold until an eventual HIV infection, after which the cells produce numerous crHIV and few HIV virions. The efficiency of a crHIV was described in terms of HIV replication inhibition $D$, and production of crHIV relative to HIV from a double-infected cell $P^2$. Results show that a very potent inhibition ($D \leq 0.1$) causes crHIV to die out and HIV to rebound, suggesting a threshold value for HIV inhibition that provides enough packing material in the cell for both types of virions. The HIV ‘setpoint’ depended on the relative production of crHIV ($P^2$). Thus for a high relative replication ($P^2 = 10,000; D=0.4$), a HAART-like HIV level is reached; but if it is lower ($P^2 = 50; D = 0.2$), the HIV reduction is about 10 fold. This lower value for crHIV replication is equivalent to the DIV highly optimistic values set from Nelson & Perelson (1995), indicating that these viruses require a large proliferation for having impact on HIV population. Additionally, this particular therapy generates a substantial crHIV population that would be evenly distributed as free virions and within crHIV-infected cells (over a thousand virions per mm$^3$ for median parameters values).

2.1. SUPPLEMENTARY METHODS. Model Construction. This section describes the rationale used to represent the infection system in a model.

HIV-1 may infect several types of cells but preferentially replicates in activated CD4$^+$ T lymphocytes (Haase, 1999; Hellerstein et al., 2003; Pierson et al., 2000). This main cell target exhibits a cycling pattern between resting and CD4 cell activated stages. Cells generally persist in a resting state until encountering the relevant antigen and then becoming activated. Activated
cells proliferate while helping the immune response; then cells die or revert to a resting condition. A typical healthy individual has about 1000 cells mm$^{-3}$ CD4 cells in peripheral blood, with an estimated 3\% activated and the remainder in resting stage (Hunt et al., 2008). Thus, the model assumes that CD4 cells routinely undergo some activation, deactivation and replication, though the balance among these processes shifts from healthy to an HIV-infected condition. In particular, resting cells $x'$ grow due to a constant influx of cells into the modeled system (peripheral blood) at rate $\lambda$, cell deactivation $rx$, and cell proliferation $[p/(1 + x'/x_{\text{mean}})]x'$. This proliferation describes the regular mitotic division of resting CD4 cells without an immune activation (Macallam et al., 2004; McLean & Michie, 1995). The saturation function for proliferation enhances cell replication at low cell density. Functions describing the gain and loss of resting and activated cells per unit time from each cell stage are depicted in Fig. 1. The model predicts the healthy steady state of CD4 cells.

The model assumes that HIV causes CD4 cell death through the killing of activated infected cells (Haase, 1999), and indirectly by inducing a generalized immune activation (i.e. HIV increases activation, cell division and activation–induced cell death (Grossman et al., 2002)), and enhanced apoptosis (i.e. HIV-mediated mechanisms that induce death of uninfected CD4 either activated or resting (Gougeon, 2003)). Thus, apoptosis of uninfected cells can be triggered by HIV-1 through the activation-induced cell death (AICD) that results from repeated antigenic stimulation in activated cells (Ahr et al., 2004); or as a result of HIV proteins (i.e. gp120 envelope protein) that prime uninfected nonspecific (resting and activated) CD4 cells for apoptosis (Ahr et al., 2004; Gougeon, 2003); or by other HIV-mediated mechanisms (Badley et al., 2000). The model implemented those indirect mechanisms by assuming that cell activation, activated cell expansion, and apoptosis of uninfected resting and activated cells were dependent on HIV load. It assumed that activated cells have greater susceptibility to undergo apoptosis than resting cells. Notice that HIV may infect resting cells but generally it does not replicate in these cells (Pierson et al., 2000). However, a small flux of HIV $v_F$ was assumed for representing a small number of viral particles released from infected cells that are not explicitly represented in the model (Perelson et al., 1997). On the other hand, HIV-infected cells do not replicate because HIV arrests the cell cycle (Jowett et al., 1995).

Viral evasion from the immune system was considered a secondary force for driving infection progression and not included in this study. This was based on the observations that
most HIV-1 mutants are expected at primary infection (Coffin, 1995); other lentiviruses with similar capability of mutating do not develop diseases (Fauci & Desrosiers, 1997); and viral escape may eventually happen but at a latter stage of the infection (Goulder et al., 1997). The model considers a cytotoxic T lymphocyte (CTL) response of killing infected cells as the primary immune strategy for fighting HIV infection (Koup et al., 1994; McMichael & Rowland-Jones, 2001; Schmitz et al., 1999). The CTL response is described by the number of HIV-specific CD8+ T effector cells \( l \), which consists of a single dominant cell clone. The model assumes these cells \( l \) proliferate as a function of activated CD4 cell abundance \( x \) and HIV load \( v \) (McMichael & Rowland-Jones, 2001; Wodarz & Jansen, 2001); and with a logistic growth \( (1 – \frac{l}{l_{\text{max}}}) \), where \( l_{\text{max}} \) is the maximum number of cells per mm\(^3\). CTL proliferation depended on free virus instead of the more conventional infected cells because viral load varied more over time than number of infected cells. For the simulations, CTL proliferation started when HIV load was over 10 vir mm\(^{-3}\). It corresponds to a delay observed in SIV and SHIV for triggering the response, due perhaps to a threshold level of antigen (Davenport et al., 2004).

The model assumes that hunter virus specifically infects HIV-infected cells and reproduces through a rapid cytopathic infection that kills the cell. The released hunter viruses are competent to sustain the therapeutic infection (Fig. 1).

2.2. SUPPLEMENTARY METHODS. Basic Reproductive Ratio Equation.

The basic reproductive ratio \( R_0^w \) (Nowak & May, 2000) describes the number of secondary infections produced by a single infection, and when this ratio is larger than one (\( R_0^w > 1 \)), the hunter virus can invade the HIV infection. \( R_0^w \) is defined as the product of two quantities: (1) the ‘net production of hunter viruses’, \( c/(b+il) \), this is the rate of hunter viruses produced per double-infected cell \( z \), \( c \), during its mean life, \( 1/(b+il) \); and (2) the ‘net number of infections’, \( ay/q \), this is the infection rate of HIV-infected cell per hunter virus, \( ay \), during the hunter virus life time, \( 1/q \). Thus, multiplying the net production of hunter viruses by the net number of infections, results in the number of secondary infections \( R_0^w = \frac{ay}{q} \frac{c}{(b+il)} \) (see symbols in table 1).
2.3. SUPPLEMENTARY PARAMETER VALUE TABLE. Table S1 provides range of parameter values and rationale for selecting default parameter values indicated in Table 1.

Values vary due to individual variation, lab techniques and mathematical models used to fit the data. Some parameter values were adjusted per numbers of cells or viruses consistent with the definitions in the equations. Notice that death rate of a cell (or a virus) is estimated from average life span \( t_{ls} = 1/j \) or from half-life \( t_{\frac{1}{2}} = \ln 2/j \). Half-life is the time when half of the cell population (or virus) has disappeared.

**Table S1.** Estimation of default parameter values.

| Parameter | Default value d\(^{-1}\) | References |
|-----------|--------------------------|------------|
| \( \lambda \) | Production rate of resting cell | 1 cell mm\(^3\) | Cells from thymus: \( \lambda = 1 \) cell mm\(^3\) d\(^{-1}\) (Di Mascio et al., 2006); \( \lambda = 0.26 \) cell mm\(^3\) d\(^{-1}\) (Kaufmann et al., 2001) |
| \( p \) | Replication rate of resting cell | 0.0045 | Naïve \( p = 0.0039 \) d\(^{-1}\), memory \( p = 0.027 \) d\(^{-1}\) (Kaufmann et al., 2001) |
| \( p^o \) | Proliferation rate of activated cell | 0.02 | \( p^o = 0.057 \) d\(^{-1}\) overestimation in HIV absence that assumes only activated cells proliferate (Ribeiro et al., 2002) |
| \( p^o n^o \) | Proliferation rate of activated cell due to infection | 0.007 vir\(^{-1}\) mm\(^3\) | Based on total CD4 proliferation 0.136 d\(^{-1}\), overestimation in HIV presence that assumes only activated cells replicate (Ribeiro et al., 2002) |
| \( d \) | Death rate of resting cell | 0.003 | \( d = 0.006 \) d\(^{-1}\), half-life naïve 114 d (Kaufmann et al., 2001); \( d = 0.033 \) d\(^{-1}\), half-life memory 21d (Kaufmann et al., 2001); half-life naïve 4–12 mo, memory 1–2 mo (Richman, 2000); \( d = 0.0014 \) d\(^{-1}\), life-span 2 yr (Michie et al., 1992) |
| \( d^o \) | Death rate of activated cell | 0.03 | \( d^o = 0.01 \) d\(^{-1}\) (Stafford et al., 2000); \( d^o = 0.03 \) d\(^{-1}\) (Kaufmann et al., 2001) |
| \( a \) | Death rate of HIV infected cell | 0.33 | \( a = 0.33–0.49 \) d\(^{-1}\) (Perelson et al., 1996; Phillips, 1996; Stafford et al., 2000); \( a = 0.53 \) d\(^{-1}\), life-span 1.9 d (Klenerman et al., 1996); \( a = 0.5–1 \) (Davenport et al., 2004) |
| \( b \) | Death rate of double-infected cell | 2 | Based on virus release within 8 h of infection before lysis (Schnell et al., 1977) |
| \( m \) | Activation rate | 0.0011 | \( m = 0.002 \) d\(^{-1}\) in HIV absence (Kaufmann et al., 2001) |
| \( m n \) | Activation rate due to infection | \( 4.4 \times 10^{-5} \) vir\(^{-1}\) mm\(^3\) | Based on total cell activation in HIV presence: 0.005 d\(^{-1}\) (Kaufmann et al., 2001); 0.0036 d\(^{-1}\) (Phillips, 1996) |
| \( r \) | Deactivation rate | 0.026 | \( r = 0.026 \) d\(^{-1}\) same in HIV presence or absence (Kaufmann et al., 2001) |
| Parameter | Description | Value | Notes |
|-----------|-------------|-------|-------|
| \( \beta \) | HIV infection rate | 0.004 \( \text{vir}^{-1} \text{mm}^3 \) | \( \beta = 0.00027 \text{vir}^{-1} \text{mm}^3 \text{d}^{-1} \) (Phillips, 1996); \( \beta = 0.0035 \) (Murray et al., 1998); \( \beta = 0.00065 \) (Stafford et al., 2000); upper bound \( \beta = 0.007 \) (Layne et al., 1989) |
| \( \alpha \) | Hunter virus infection rate | 0.02 \( \text{vir}^{-1} \text{mm}^3 \) | Assumed larger than HIV infection rate \( \beta \) and similar to CTL killing rate \( i \) |
| \( \theta \) | Apoptotic rate of resting cell | 0.00044 \( \text{vir}^{-1} \text{mm}^3 \) | Assumed 10 fold lower than \( \beta \). HIV proteins in contact with CD4 cell induce apoptosis (Ahr et al., 2004; Finkel et al., 1995) |
| \( \theta^\circ \) | Apoptotic rate of activated cell | 0.005 \( \text{vir}^{-1} \text{mm}^3 \) | Assumed larger than \( \beta \). Repeated antigen stimulation on activated cell induces death (Alimonti et al., 2003) |
| \( k \) | HIV-1 production rate by single infected cell | 50 \( \text{vir cell}^{-1} \) | \( k = v_1 a_1 \), \( a_1 = 150 \), is total number of infectious HIV produced by a cell: \( v_1 \sim 140 \) (Dimitrov et al., 1993), \( v_1 = 180 \) (Haase, 1999) |
| \( k_i \) | HIV-1 production rate by double infected cell | 5 \( \text{vir cell}^{-1} \) | Assumed \( k_i = 0 \) but can be a fraction of a single-infected cell production (\( k_i = 0.1 k \)) since hunter virus stops cellular machinery in few hours (Schnell et al., 1977) |
| \( c \) | Hunter virus production rate | 1,800 \( \text{vir cell}^{-1} \) | \( c = w_1 b \). \( w_1 \) is total number of infectious hunter viruses produced by a double-infected cell. In vitro \( \sim 3,333 \) particles are released and a fraction is infectious (Schnell et al., 1977). Assumed \( w_1 = 900 \) |
| \( u \) | HIV removal rate | 3 | Based on life span of \( \frac{1}{4} \) day, \( u = 3 \text{d}^{-1} \) (Perelson et al., 1996; Phillips, 1996; Stafford et al., 2000); \( u = 9-36 \text{d}^{-1} \) (Markowitz et al., 2003; Ramratnam et al., 1999); \( u = 3.6-21 \text{d}^{-1} \) (Wu et al., 2005); 0.35 \( \text{d}^{-1} \) (Dixit & Perelson, 2005) † |
| \( q \) | Hunter virus removal rate | 2 | Assumed lower than \( u \) since hunter virus envelope has human cell receptors |
| \( g \) | CTL proliferation rate | 0.00038 \( \text{vir}^{-1} \text{mm}^3 \text{cell}^{-1} \text{mm}^3 \) | Based on \( g' = 0.054 \text{d}^{-1} \) (Kaufmann et al., 2001); \( g' = 0.94 \text{d}^{-1} \) (Davenport et al., 2004) and adjusting units |
| \( h \) | CTL death rate | 0.025 | \( h = 0.015 \text{d}^{-1} \), half-life 45 d (Ogg et al., 1999). |
| \( i \) | CTL killing rate | 0.02 \( \text{cell}^{-1} \text{mm}^3 \) | \( i = 0.02 \text{cell}^{-1} \text{mm}^3 \text{d}^{-1} \) (Mandl et al., 2007); \( i = 0.1-0.2 \text{d}^{-1} \) (Asquith, 2006); \( i = 1 \text{d}^{-1} \) (Klenerman et al., 1996); \( i = 1 \text{cell}^{-1} \text{mm}^3 \text{d}^{-1} \) (Altes et al., 2002) |
| \( v_F \) | Virus flux rate | 0.84 \( \text{vir mm}^{-3} \) | 1–7% of HIV load is released from long-life infected cells, macrophages and other reservoirs (Perelson et al., 1997) |
| \( l_{\text{max}} \) | Maximum CTL density | 500 \( \text{cell mm}^{-3} \) | At acute infection, up to 80–90% of CD8 cells are activated and a fraction is HIV specific (Appay et al., 2002); after seroconversion to advance infection 1.6–18% of total CD8 are HIV specific (Betts et al., 2001). At acute infection CD8 peaks around 1,500 \( \text{cell mm}^{-3} \) (Lindback et al., 2000), and it was assumed \( \frac{1}{5} \) is CTL maximum value.
x'_{\text{mean}}$  Average resting cell density  970 cell mm$^{-3}$  CD4 cell density in healthy human blood is 1,000 cell mm$^{-3}$ (Ramratnam et al., 1999). Assumed 970 resting and 30 activated (2.2 % of CD4 cells with markers HLA-DR and CD38, Hunt et al., 2008). Assumed resting cells have density dependent regulation

†Some conflicting experimental estimates may differ in magnitude, i.e. HIV virion clearance and production rates. However, large estimates of HIV virion clearance tend to cancel a large estimate of viral production rate, with little effect on the therapy efficiency in recovery of CD4 cells.

2.4. SUPPLEMENTARY METHODS. Sensitivity Analysis

To evaluate sensitivity of the model to parameter magnitudes, we conducted a stochastic hypercube sampling analysis (LHS) by drawing parameter values for individual runs from appropriate statistical distributions (Marino et al, 2008). The relevant range of magnitudes for each parameter was identified from the published literature when possible. For each model parameter, available data were used to parameterize a lognormal probability distribution. Means and standard deviations of these distributions were chosen so that about 95 % of 100 log–normally distributed random values fit within the observed range for each parameter. If simulations performed poorly (convergence errors in the numerical integrations of the differential equations) due to extreme parameter values, the ranges from which the distributions were established were instead based on a parameter range factor (see below).

In the absence of published studies or in the presence of convergence problems with the model, ranges were chosen to be as large as possible, consistent with stable model behavior. For each parameter, ranges were obtained as the interval $p/f$ to $p\times f$, where $p$ is the default parameter value and $f$ is the parameter range factor. Three parameter range factors were tried ($f = 1.05, 1.1$ and $1.15$; the largest of these consistent with stable simulations was used in each case), from which the means and standard deviations of the log-normal probability distributions were chosen as above. Means and 95 % confidence intervals of the resulting distributions are shown in table S2. The model was numerically simulated 100 times for HIV infection, and for each of these the number of resting CD4 cells was determined at 64 time points over the disease progression. For
each time point, median CD4 count and inter-quartile range (IQR) was obtained and plotted in figure S1.

The LSH on the therapeutic infection sampled all the parameters values in Table S2 within ranges centered at default values. Since the therapy was assumed to start when CD4 counts reached 300 cells mm\(^{-3}\), it started at a different time in each run of the sampling. If CD4 cell counts do not approach the therapy threshold, therapy was not initiated. In each individual simulation, if CD4 counts at day 3000 were higher than at the start of therapy it was considered a rebound. In this respect, 86 % of the simulations gained resting CD4 cells. The ‘mean’ CD4 resting cell count at day 3000 was 46 % the total healthy level (95 % CI for the mean, 44–47 %). This CI for the mean was estimated as mean \(\pm 1.96 \times \frac{\sigma}{\sqrt{n}}\), where \(\sigma\) is the standard deviation (\(\sigma = 14\ %\)) and \(n\) the number of simulations (\(n = 500\)). The 95 % CI for the data was 19–72 %. An intermediate recovery (300–400 cells mm\(^{-3}\)) was observed in 20 % of the simulations. The mean percentage of the HIV observed after 10 days of therapy was 7.6 % (95 % CI for the mean, 6.9–8.2 %) taking as 100 % the HIV counts right before therapy.

**Table S2.** Estimation of confidence interval for parameter values for a stochastic sampling.

| Parameter                                      | Default value d\(^{-1}\) | Range from table S1 (observations) | Mean (95 % CI for sampling)                        |
|------------------------------------------------|---------------------------|-----------------------------------|--------------------------------------------------|
| \(\lambda\) Production rate of resting cell   | 1 cell mm\(^{-3}\)       | 0.26 – 1, (2)                     | 0.549, (0.35, 0.86) \(\dagger\) [0.95, 1.05] \(\dagger\) |
| \(p\) Replication rate of resting cell         | 0.0045                    | 0.0039 – 0.027, (3)               | 0.0045, (0.0043, 0.0047) \(\dagger\)            |
| \(p^o\) Proliferation rate of activated cell    | 0.02                      | 0.02 – 0.057, (2)                 | 0.021, (0.02, 0.021) \(\dagger\) [0.02, 0.0219 0.021] |
| \(p^o \cdot n^o\) Proliferation rate of activated cell due to infection | 0.007 vir\(^{-1}\) mm\(^{-3}\) | unknown                           | 0.007, (0.0067, 0.0073)                          |
| \(d\) Death rate of resting cell                | 0.003                     | 0.0014 – 0.033, (4)               | 0.003, (0.002, 0.006) \(\dagger\)              |
| \(d^o\) Death rate of activated cell            | 0.03                      | 0.01 – 0.03, (2)                  | 0.017, (0.01, 0.03) [0.03, 0.028, 0.031]         |
| \(a\) Death rate of HIV infected cell           | 0.33                      | 0.33 – 1, (5)                     | 0.41, (0.36, 0.46) \(\dagger\) [0.33, 0.31, 0.35] |
| Parameter | Description | Value | Ranges |
|-----------|-------------|-------|--------|
| $m$ | Activation rate | 0.0011 | 0.0011 – 0.002, (2) |
| | | | [0.0011, (0.0011, 0.0012)]† |
| $mn$ | Activation rate due to infection | $4.4 \times 10^{-5}$ vir mm$^{-3}$ | $(3.8 – 9.2) \times 10^{-5}$, (2) |
| | | | [4.4, (3.9, 5.5)]$\times 10^{-5}$ † |
| $r$ | Deactivation rate | 0.026 | unknown |
| | | | 0.026, (0.025, 0.028) |
| $\beta$ | HIV infection rate | 0.004 vir$^{-1}$ mm$^{-3}$ | 0.00027 – 0.007, (5) |
| | | | 0.004, (0.0039, 0.0044) † |
| $\theta$ | Apoptotic rate of resting cell | 0.00044 vir$^{-1}$ mm$^{-3}$ | unknown |
| | | | 0.00044, (0.00042, 0.00049) |
| $\theta^\circ$ | Apoptotic rate of activated cell | 0.005 vir$^{-1}$ mm$^{-3}$ | unknown |
| | | | 0.005, (0.0048, 0.0052) |
| $k$ | HIV-1 production rate by single infected cell | 50 vir cell$^{-1}$ | 46 – 59, (3) |
| | | | 52.1, (46, 59) |
| | | | [50, (47, 53)] |
| $u$ | HIV removal rate | 3 | 0.35 – 36, (6) |
| | | | 3, (2.8, 3.2) † |
| $g$ | CTL proliferation rate | 0.00038 vir$^{-1}$ mm$^{-3}$ cell$^{-1}$ | 0.00002-0.00041, (3) |
| | | | 0.00037, (0.00036, 0.00039) † |
| | | | [0.00038, (0.00036, 0.00040)] |
| $h$ | CTL death rate | 0.025 | 0.015 – 0.025, (2) |
| | | | 0.02, (0.017, 0.024) † |
| | | | [0.025, (0.024, 0.027)] |
| $i$ | CTL killing rate | 0.02 cell$^{-1}$ mm$^{-3}$ | 0.1 – 1, (4) |
| | | | 0.02, (0.018, 0.022) † |
| $v_F$ | Virus flux rate | 0.84 vir mm$^{-3}$ | 0.12 – 0.84, (2) |
| | | | 0.84, (0.7, 0.96) |
| $l_{max}$ | Maximum CTL density | 500 cell mm$^{-3}$ | unknown |
| | | | 498, (459, 539) |
| | | | [500, (476, 525)] |
| $b$ | Death rate of double-infected cell | 2 | unknown |
| | | | 2, (1.904, 2.100) |
| $\alpha$ | Hunter virus infection rate | 0.02 vir$^{-1}$ mm$^{-3}$ | unknown |
| | | | 0.02, (0.019, 0.021) |
| $c$ | Hunter virus production rate by infected cell | 1800 vir cell$^{-1}$ | unknown |
| | | | 1800, (1714, 1890) |
| $q$ | Hunter virus death rate | 2 | unknown |
| | | | 2, (1.904, 2.100) |
| $i'$ | CTL killing rate of double-infected cells | 2 cell$^{-1}$ mm$^{-3}$ | unknown |
| | | | 2, (0.018, 0.022) |

† Wider ranges result in convergence errors during numerical integration of the differential equations.

‡ For LHS on therapeutic infection with means at default values and ranges estimated such as in’ unknown’. These confidence intervals applied to HIV infection produced similar results as in Fig. S1.
Figure S1. Variation in the progression of HIV infection from a stochastic sampling of the parameters values (Table S2). Median CD4 resting cell counts and inter-quartile range are indicated over time. A) HIV infection progression over 8 years. B) HIV infection progression during the first 200 days. Interrupted lines describe resting CD4 cell counts for a default simulation.

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