The dual role of DCs in the immune response to HIV-1 infection

Supplementary Material:

Equation Justification and Parameter Estimation

Equation 1 describes the population of resting $CD4^+$ T-cells in an LN (T_4). S_4 represents the homeostatic source of naïve $CD4^+$ T-cells (i.e. $CD45RA^+/CD62L^+$) flowing into the LN from the periphery, independent of infection. The value of this is calculated as $\mu_4 T_4$ at time 0, to meet the assumption of homeostasis in the absence of infection. Because investigators have observed an increase in flux of lymphocytes through the LN after immunization (Hay & Hobbs, 1977), and HIV-1 patients often present lymphadenopathy during acute infection (Cooper et al., 1985), $\phi_4(D_M+D_L)/(D_M+D_L)+f_{10}$ represents the increased influx of resting $CD4^+$ T-cells due to production of chemokines by mature and licensed DCs (Foley et al., 2005; Izmailova et al., 2003; Reinhart, 2003), the upregulation of homing receptors due to non-productive contact with DC-associated virus in the periphery (Cloyd et al., 2001; Kirschner et al., 2000), and LN-homing central memory cells (Sallusto et al., 1999). ϕ_4 (the maximum rate of additional $CD4^+$ influx) is estimated to be on the same order of magnitude as S_4. The terms $r_{DM}D_M T_4$ and $r_{DL}D_L T_4$ represent the removal of cells from this resting $CD4^+$ population as they are activated by mature and licensed DCs, respectively. r_{DM} and r_{DL} are estimated to be on the order of 10^{-8} based on the observed rate of contact between DCs and T-cells *in situ* (Miller et al., 2004). It has been found that the majority of cells killed during HIV-1 infection are not productively infected (Jekle et al., 2003). To this end, $k_{ab}\left(\frac{1}{\frac{T_C}{c_5}+1}\right)VT_4$ represents removal of cells from this population through abortive infection-induced apoptosis and bystander killing effects. k_{ab} is estimated so as to make

this term greater than the productive rates of infection. $\mu_4 T_4$ represents the rate of removal of resting $CD4^+$ T-cells from the LN through the combined effects of exit to efferent lymph and cell death. Lymphocytes exit an average 1g LN at a rate of 7.2×10^8 / day (Hall & Morris, 1965; Hay & Hobbs, 1977) which, given our initial conditions, corresponds to a half-life of approximately 0.45 days. This is faster than turnover due to apoptosis and other cell death (McCune et al., 2000).

Equation 2 describes the population of activated helper T-cells (T_H). The terms $(1-b_M)\, r_{DM} D_M T_4$ and $(1-b_L) r_{DL} D_L T_4$ represent the fraction of $CD4^+$ T-cells that are activated by antigen-presenting mature and licensed DCs, respectively, but are not infected by DC-associated virus during priming. Once T-cells receive antigenic and co-stimulatory signals from DCs, they undergo clonal expansion. $p_H T_H$ represents this proliferation of helper T-cells upon activation. p_H is estimated to be 0.5–0.7 per day, which corresponds to a doubling time of 1–1.4 days (Hedfors & Brinchmann, 2003; Kaur et al., 2000). $k_V\left(\frac{1}{\frac{T_C}{c_1}+1}\right) V T_H$ represents infection of helper T-cells by virus, resulting in transfer of cells from this population to the infected population. Mature and licensed DCs have been found to be infected with HIV-1 and to bind HIV-1 on the cell surface protein DC-SIGN. During DC–T-cell interaction, there is a co-localization of virus, CD4 receptor and HIV-1 co-receptors, allowing DCs to facilitate infection of T-cells (Lekkerkerker et al., 2006). The terms $k_{DM}\left(\frac{1}{\frac{T_C}{c_2}+1}\right) D_M T_H$ and $k_{DL}\left(\frac{1}{\frac{T_C}{c_3}+1}\right) D_L T_H$ represent infection of helper T-cells by this DC-associated virus, transferring these cells from this population to the infected population. All infection terms in this model account for the ability of CTLs to inhibit infection through secretion of chemokines, such as CCL3 (MIP-1α), CCL4 (MIP-1β)

and CCL5 (RANTES), which compete with HIV-1 for co-receptor binding (Geiben-Lynn, 2002). $\mu_H T_H$ represents the rate of removal of helper T-cells from the LN via exit to efferent lymphatics and apoptosis. Though activation makes T-cells more susceptible to apoptosis (Green et al., 2003) and alters expression of cell adhesion molecules (Janeway, 2005) that likely alters the transit rate of helper T-cells though the LN, we assume helper T-cells flow though the LN with a half-life similar to that of resting cells.

Equation 3 describes the dynamics of productively infected $CD4^+$ T-cells (I). The terms $b_M r_{DM} D_M T_4$ and $b_L r_{DL} D_L T_4$, the complements to the similar terms in equation 2, describe resting $CD4^+$ T-cells that are activated and concurrently infected by DCs during antigen presentation. The parameters b_M and b_L determine what fraction are infected during activation. Since approximately 2% of total-body activated helper T-cells are infected during chronic HIV-1 infection (Haase, 1999), this is an upper band used to estimate these parameters. The terms $k_V(\frac{1}{\frac{T_C}{c_1}+1})VT_H$, $k_{DM}(\frac{1}{\frac{T_C}{c_2}+1})D_M T_H$, and $k_{DL}(\frac{1}{\frac{T_C}{c_3}+1})D_L T_H$ represent the infection of activated T-helper cells, as described in equation 2. It has been observed that resting $CD4^+$ T-cells can be productively infected *in vivo*, however, these cells are less commonly infected compared with activated infected cells (Eckstein et al., 2001; Ostrowski et al., 1999). This phenomenon is thought to particularly occur in the milieu of lymphoid tissue (Eckstein et al., 2001; Unutmaz et al., 1999). The term $\alpha k_{ab}(\frac{1}{\frac{T_C}{c_5}+1})VT_4$ represents the case where resting $CD4^+$ T-cells become productively infected. To account of the incomplete permissiveness of resting cells, this term is scaled by the fraction α, which is estimated to make this infection term 10% of the activated helper T-cell infection term, as is observed in a histoculture infection model

(Eckstein et al., 2001). The term $\mu_I I$ represents removal of infected T-cells from the LN. Though infection alters the behavior of these cells, we assume that infected T-cells flow through the LN with a half-life on the same order of magnitude as that of resting cells. The term $\kappa_I T_C I$ represents the ability of CTLs to kill infected cells through perforin/granzyme and FAS/FAS ligand mechanisms (Janeway, 2005). κ_I is estimated such that each CTL kills approximately one infected cell per day at a steady state (Wick et al., 2005).

In equation 4, the production of virus (V) is represented by $N(\frac{1}{\frac{T_C}{c_4}+1})\mu_I I$. The parameter N represents the 'burst size', or average number of infectious virions produced during the lifetime of an infected cell, estimated to be 100–1000 (Haase et al., 1996; Levy et al., 1996). In the case of the upper estimate of 1000, N is estimated based on in vitro infection, which would not include inhibitory effects of CTLs. Since parameter μ_I determines the length of an infected cell lifetime, the product $\mu_I N$ determines virus production per infected cell per time (Perelson et al., 1993). This production is down regulated by the action of CTLs producing CAF and α-defensins (Geiben-Lynn, 2002; Levy, 2003). $\mu_V V$ represents the loss of virus, as HIV-1 particles are labile, cleared by the innate immune responses, and flow out of the LN in efferent lymph. However, infectious virus is protectively sequestered on follicular dendritic cells for up to 9 months (Smith et al., 2001). Based on experiments measuring the decline in follicular dendritic cell-associated viral RNA after initiation of antiretroviral therapy, μ_V is estimated to correspond to a virion half-life of 1.7 days (Cavert et al., 1997). As lymphoid tissue is the major site of HIV-1 production, with viral concentration two orders of magnitude greater than in plasma (Haase, 1999), we consider free virus that enters the LN from the blood to

be negligible.

Equation 5 describes the population of resting $CD8^+$ T-cells (T_8). S_8 represents the source of naïve $CD8^+$ T-cells entering the LN from the periphery. The value of S_8 is calculated as $\mu_8 * T_8$ at time 0, to meet the assumption of homeostasis in the absence of infection. As it has been shown that continuous recruitment of naïve $CD8^+$ T-cells is important during chronic infections (Vezys et al., 2006), $\phi_8(D_M+D_L)/(D_M+D_L)+f_{11}$ represents the increased influx of resting $CD8^+$ T-cells due to production of chemokines by DCs (Foley et al., 2005; Izmailova et al., 2003; Reinhart, 2003). ϕ_8 is estimated to be on the same order of magnitude as S_8 (Cooper et al., 1985; Hay & Hobbs, 1977). Because DCs cross-present exogenous antigens on MHC class I molecules, DCs can present antigen to $CD8^+$ T-cells. The term $r_{8L}D_LT_8$ represents the activation of resting $CD8^+$ T-cells by antigen-presenting mature DCs. Some investigators have reported that $CD8^+$ cells require more or different co-stimulatory signals to become fully activated CTLs (Whitmire & Ahmed, 2000). DCs have been shown to upregulate co-stimulatory molecules that promote CTL formation, such as CD86 (Ridge et al., 1998) and 4-1BBL (Bukczynski et al., 2005; Futagawa et al., 2002), upon CD40–CD40L interaction with helper T-cells. Thus we define 'licensed DCs' as having interacted with helper T-cells to become competent to prime $CD8^+$ T-cells. We estimate r_{8L} to be on the same order of magnitude as the $CD4^+$ priming parameters r_{DM} and r_{DL}. The term μ_8T_8 represents the rate of removal of resting $CD8^+$ T-cells from the LN. The half-life of these cells is estimated to be on the same order of magnitude as that of $CD4^+$ T-cells.

In equation 6, CTLs that become activated (T_C) proliferate, as represented by the term p_CT_C. The value of p_C is estimated to be similar to that of $CD4^+$ helper T-cells

(Hedfors & Brinchmann, 2003; Kaur et al., 2000). $\mu_C T_C$ represents the death and out-flow of CTLs from the LN. The half-life of these cells is estimated to be on the same order of magnitude as that of $CD4^+$ T-cells.

Equation 7 describes the population of LN-resident immature DCs (D_I). There is evidence that there are resident immature DCs in the LN, and that immature DCs migrate from the periphery to the LN without having encountered antigen (Lutz & Schuler, 2002). We include a homeostatic immigration term to account for this (S_{DI}). In this model, mature DCs are defined as having encountered HIV-1 antigen. Thus the term $\delta D_I V$ represents the maturation of DCs that have encountered antigen from virus particles within the LN, the term $\varepsilon D_I I$ represents the maturation of DCs that have encountered antigenic HIV-1 protein from infected cells within the LN, and the term $\gamma D_I(D_M+D_L)$ represents maturation due to antigen secreted from already matured and licensed DCs within the LN (Carbone et al., 2004). $\mu_{DI} D_I$ represents the removal of immature DCs from the LN. We estimate the half-life of these cells to be approximately 30 days (Kamath et al., 2002; Ruedl et al., 2000).

Equation 8 describes mature DCs (D_M). The prototypical behavior of DCs is that, after encountering antigen in the periphery, they mature and travel to the LN (Barratt-Boyes et al., 1997; Janeway, 2005). Therefore, the term $\phi_{DM}\beta V/(\beta V + f_{13})$ represents this migration of mature DCs from the periphery. We assume this migration rate is a function of the amount of virus in the periphery, which is proportional by β to the amount of virus in the LN. This rate would also be dependent on the population of immature DCs in the periphery, but we assume this is a constant due to homeostasis, and include this level within the parameter ϕ_{DM}. We estimate β is 1%, based on the ratio of virus in the

plasma to virus in lymphoid tissue (Haase, 1999). In this model, licensed DCs (D_L) are defined as mature DCs that have interacted with helper T-cells, causing upregulation of co-stimulatory molecules. The term $\lambda D_M T_H$ represents this transfer of cells from the mature to the licensed pool. $\mu_{DM} D_M$ represents the deactivation or death of mature DCs. Mature DCs are estimated to live 2–3 days (Lanzavecchia & Sallusto, 2001; Ruedl et al., 2000), which corresponds to a half-life of 1.4–2.1 days. Because mature DCs present antigen on MHC-I, they are susceptible to being killed by CTLs (Ronchese & Hermans, 2001; Yang et al., 2006), though some findings suggest that DCs might be partially protected from CTL killing while in the LN (Yang et al., 2006). The term $\kappa_M T_C D_M$ represents the ability of CTLs to kill mature DCs through perforin/granzyme and FAS/FAS ligand mechanisms (Ronchese & Hermans, 2001; Yang et al., 2006).

In equation 9, the term $\mu_{DL} D_L$ represents the deactivation of licensed DCs, with an estimated half-life similar to that of mature DCs (Lanzavecchia & Sallusto, 2001; Ruedl et al., 2000). Because licensed DCs also present antigen on MHC-I, they are also susceptible to being killed by CTLs, represented by the term $\kappa_L T_C D_L$ (Ronchese & Hermans, 2001; Yang et al., 2006).

Supplementary Sensitivity Analysis Results

We analysed parameters related to $CD4^+$ T-cells and virus during chronic state infection by LHS/PRC (Supplementary Table S2). Two parameters, the average number of virions produced per infected cell lifetime (N) and the death rate of infected cells (μ_I), which determines the average length of a cell lifetime both determined the rate of virus production. Increasing either of these parameters (μ_I, N) increased viral load. We also find that infection of active T-helper cells by free virus (k_V), has a significant positive

correlation with viral load. Destruction rate of virions (μ_V), has a significant negative correlation with viral load. Thus, our model suggests that any mechanism that reduces the destruction of virions, such as a defect in clearance by phagocytes or protective sequestration of virus, should increase viral load. Finally, we find that the parameter controlling the rate of abortive infection/bystander killing of resting $CD4^+$ T-cells (k_{ab}) has a significant negative correlation with viral load. Although abortive infection and bystander killing is implicated in the loss of $CD4^+$ T-cells in progressive HIV-1 disease, we find that this mechanism has a net effect of decreasing viral load by removing host cells that might have otherwise had a chance of becoming productively infected.

Next, we analysed parameters related to $CD8^+$ T-cells during chronic state infection (Supplementary Table S3). As expected, since $CD8^+$ T-cells are precursors to antiviral effector CTLs, many $CD8^+$ T-cell related parameters are significantly correlated with viral load. The parameters that control recruitment of additional $CD8^+$ T-cells (ϕ_8, f_{11}) are significantly correlated with viral load: increasing ϕ_8 or decreasing f_{11} allows greater $CD8^+$ T-cell recruitment, decreasing viral load. The parameter that controls the rate of proliferation of primed CTLs (p_C) has a significant negative correlation with viral load. In contrast, mechanisms that remove $CD8^+$ T-cells (μ_8, μ_C) increase viral load. The importance of these parameters highlight the idea that controlled migration of cells through lymphoid tissue is critical during HIV-1 infection (Vezys et al., 2006).

The model also predicts that parameters involved in CTL effector functions are significantly correlated with viral load. Parameters that control non-lytic anti-viral functions of CTLs are significant. Specifically, CTL-produced anti-viral factors inhibiting infection of T-helpers by mature DC-associated virus (c_2), and inhibiting viral

production by infected cells (c_4) each correlate with viral load. Because these parameters appear in the denominator of the equations (see Supplementary Data), increasing these parameters decreases the strength of the CTL non-lytic viral inhibition. Thus, these parameters are positively correlated with viral load. The lytic killing of infected cells and licensed DCs (κ_I and κ_L, respectively) also correlate with viral load. By killing infected cells, CTLs decrease viral load. CTL killing of DCs is hypothesized to serve as a negative feedback, to shutdown an immune response that has successfully run its course (Ronchese & Hermans, 2001). While this might be advantageous to prevent excess tissue damage once an acute pathogen is cleared, our result shows that this dampening of immune response during a chronic HIV-1 infection leads to an increase in viral load.

Model equations:

$$\frac{dT_4}{dt} = S_4 + \frac{\phi_4(D_M + D_L)}{(D_M + D_L) + f_{10}} - r_{DM}D_M T_4 - r_{DL}D_L T_4 - k_{ab}(\frac{1}{(\frac{T_C}{c_5}) + 1})VT_4 - \mu_4 T_4 \quad (1)$$

$$\frac{dT_H}{dt} = (1 - b_M)r_{DM}D_M T_4 + (1 - b_L)r_{DL}D_L T_4 + p_H T_H - k_V(\frac{1}{(\frac{T_C}{c_1}) + 1})VT_H - k_{DM}(\frac{1}{(\frac{T_C}{c_2}) + 1})D_M T_H - k_{DL}(\frac{1}{(\frac{T_C}{c_3}) + 1})D_L T_H - \mu_H T_H \quad (2)$$

$$\frac{dI}{dt} = b_M r_{DM}D_M T_4 + b_L r_{DL}D_L T_4 + k_V(\frac{1}{(\frac{T_C}{c_1}) + 1})VT_H + k_{DM}(\frac{1}{(\frac{T_C}{c_2}) + 1})D_M T_H + k_{DL}(\frac{1}{(\frac{T_C}{c_3}) + 1})D_L T_H + \alpha k_{ab}(\frac{1}{(\frac{T_C}{c_5}) + 1})VT_4 - \mu_I I - \kappa_I T_C I \quad (3)$$

$$\frac{dV}{dt} = N(\frac{1}{(\frac{T_C}{c_4}) + 1})\mu_I I - \mu_V V \quad (4)$$

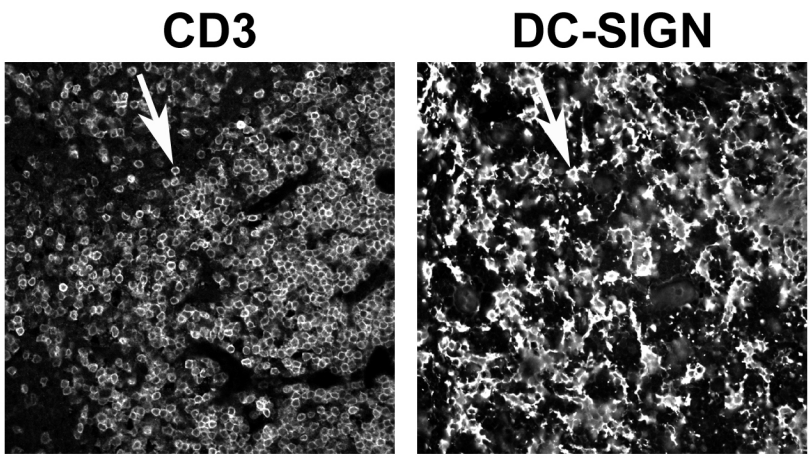
$$\frac{dT_8}{dt} = S_8 + \frac{\phi_8(D_M + D_L)}{(D_M + D_L) + f_{11}} - r_{8L}D_L T_8 - \mu_8 T_8 \quad (5)$$

$$\frac{dT_C}{dt} = r_{8L}D_L T_8 + p_C T_C - \mu_C T_C \quad (6)$$

$$\frac{dD_I}{dt} = S_{DI} - \gamma D_I(D_M + D_L) - \delta D_I V - \epsilon D_I I - \mu_{DI}D_I \quad (7)$$

$$\frac{dD_M}{dt} = \frac{\phi_{DM}\beta V}{\beta V + f_{13}} + \gamma D_I(D_M + D_L) + \delta D_I V + \epsilon D_I I - \lambda D_M T_H - \mu_{DM}D_M - \kappa_M T_C D_M \quad (8)$$

$$\frac{dD_L}{dt} = \lambda D_M T_H - \mu_{DL}D_L - \kappa_L T_C D_L \quad (9)$$



Supplementary Fig. S1. Sections (14 μm) of macaque LN tissues were stained with monoclonal antibodies specific for either CD3 or DC-SIGN. Laser scanning confocal fluorescence microscopy was performed to visualize the stained cells and an example of each staining is shown. The arrows mark example individual cells in LN paracortex. CD3 staining provides a halo pattern for each T cell, whereas DC-SIGN staining provided a much more cytoplasmic and dendritic pattern.

Supplementary Table S1. *Summary* model parameters and initial conditions*

Parameter Definition	Symbol	Estimated Value	Sampling Range
Variables			
Number of Resting $CD4^+$ T-cells	T_4		
Number of Active T-helper cells	T_H		
Number of Infected cells	I		
Number of Virions	V		
Number of Resting $CD8^+$ T-cells	T_8		
Number of Active CTLs	T_C		
Number of Immature DCs	D_I		
Number of Mature DCs	D_M		
Number of Licensed DCs	D_L		
Initial Conditions			
Initial population of naïve $CD4^+$	T_40	$3.5x10^8$ cells	
Initial population of naïve $CD8^+$	T_80	$1.2x10^8$ cells	
Initial population of imm. DC	D_I0	$1.2x10^8$ cells	
Source and Recruitment			
Homeostatic source of naïve $CD4^+$	S_4	$T_40 \cdot \mu_4$ cells/day	
Homeostatic source of naïve $CD8^+$	S_8	$T_80 \cdot \mu_8$ cells/day	
Homeostatic source of imm. DC	S_{DI}	$D_I0 \cdot \mu_{DI}$ cells/day	
Max. recruitment rate of naïve $CD4^+$ by DC	ϕ_4	$3x10^8$ cells/day	$1x10^7$ - $1x10^9$
Michaelis–Menten constant of DC effect on naïve $CD4^+$ recruitment	f_{10}	$5x10^7$ cells	$1x10^6$ - $1x10^8$
Max. recruitment rate of naïve $CD8^+$ by DC	ϕ_8	$3x10^8$ cells/day	$1x10^7$ - $1x10^9$
Michaelis–Menten constant of DC effect on naïve $CD8^+$ recruitment	f_{11}	$5x10^7$ cells	$1x10^6$ - $1x10^8$
Max. immigration rate of mat. DC due antigen	ϕ_{DM}	$2x10^8$ cells/day	$1x10^7$ - $1x10^9$
Michaelis–Menten constant of antigen effect on mat. DC immigration	f_{13}	$5x10^6$ virus	$1x10^5$ - $1x10^7$
Death/Exit to Efferent Lymph			
Death/Exit rate of naïve $CD4^+$	μ_4	1.55 /day	1 - 2
Death/Exit rate of T-helper	μ_H	1.55 /day	1 - 2
Death/Exit rate of infected cells	μ_I	1.55 /day	1 - 2
Destruction rate of virus particles	μ_V	0.4 /day	0.2 - 0.8
Death/Exit rate of naïve $CD8^+$	μ_8	1.55 /day	1 - 2
Death/Exit rate of CTL	μ_C	1.55 /day	1 - 2
Death rate of imm. DC	μ_{DI}	0.025 /day	0.01 - 0.04
Death rate of mat. DC	μ_{DM}	0.49 /day	0.3 - 0.7
Death rate of lic. DC	μ_{DL}	0.49 /day	0.3 - 0.7
Proliferation / Clonal Expansion			
Proliferation rate of T-helper	p_H	0.6 /day	0.4 - 0.8
Proliferation rate of CTL	p_C	0.6 /day	0.4 - 0.8
Priming			
Priming rate of naïve $CD4^+$ by mat. DC	r_{DM}	$8x10^{-8}$ cells/DC·day	$1x10^{-9}$ - $1x10^{-7}$
Priming rate of naïve $CD4^+$ by lic. DC	r_{DL}	$8x10^{-8}$ cells/DC·day	$1x10^{-9}$ - $1x10^{-7}$
Priming rate of naïve $CD8^+$ by lic. DC	r_{8L}	$1x10^{-6}$ cells/DC·day	$1x10^{-7}$ - $1x10^{-5}$
Infection			
Abortive infection and bystander effects of naïve $CD4^+$	k_{ab}	$6x10^{-9}$ cells/V·day	$1x10^{-10}$ - $1x10^{-8}$

Fraction of abortive infections that become productive	α	0.01	0.0005 - 0.02
Infection rate of T-helper by virus	k_V	$9x10^{-8}$ cells/V·day	$1x10^{-8}$ - $1x10^{-6}$
Infection rate of T-helper by mat. DC-associated virus	k_{DM}	$7x10^{-4}$ cells/DC·day	$1x10^{-5}$ - $1x10^{-3}$
Infection rate of T-helper by lic. DC-associated virus	k_{DL}	$7x10^{-4}$ cells/DC·day	$1x10^{-5}$ - $1x10^{-3}$
Fraction of naïve $CD4^+$ infected during priming by mat. DC	b_M	0.01	0.005 - 0.02
Fraction of naïve $CD4^+$ infected during priming by lic. DC	b_L	0.01	0.005 - 0.02
Virus Properties			
Average number of virus produced by an infected cell	N	300 virus/ inf.cell·day	100-1000
Ratio of virions in periphery to virions in LN	β	0.01	0.005 - 0.02
CTL Effector Functions			
Inhibition of virus infection by CTL	c_1	$1x10^8$ cells	$1x10^7$ - $1x10^9$
Inhibition of mat. DC-associated virus infection by CTL	c_2	$1x10^8$ cells	$1x10^7$ - $1x10^9$
Inhibition of lic. DC-associated virus infection by CTL	c_3	$1x10^8$ cells	$1x10^7$ - $1x10^9$
Inhibition of infected cell virus production by CTL	c_4	$1x10^8$ cells	$1x10^7$ - $1x10^9$
Inhibition of abortive infection/bystander effects by CTL	c_5	$1x10^8$ cells	$1x10^7$ - $1x10^9$
Killing rate of infected cells by CTL	κ_I	$2x10^{-6}$ cells/CTL·day	$1x10^{-7}$ - $1x10^{-5}$
Killing rate of mat. DC by CTL	κ_M	7×10^{-8} cells/CTL·day	$1x10^{-9}$ - $1x10^{-7}$
Killing rate of lic. DC by CTL	κ_L	8×10^{-8} cells/CTL·day	$1x10^{-9}$ - $1x10^{-7}$
DC Maturation and Licensing			
Maturation rate of DC due to virus antigen	δ	5×10^{-11} cells/V·day	$1x10^{-12}$ - $1x10^{-10}$
Maturation rate of DC due to infected cell antigen	γ	7×10^{-9} cells/I·day	$1x10^{-9}$ - $1x10^{-7}$
Maturation rate of DC due to antigen from other DCs	ε	1×10^{-8} cells/DC·day	$1x10^{-10}$ - $1x10^{-8}$
Licensing rate of mat. DCs by T-helper	λ	4×10^{-6} cells/Th·day	$1x10^{-7}$ - $1x10^{-5}$

*see Supplementary Material for complete parameter estimation with references

Supplementary Table S2. *Sensitivity of $CD4^+$ T-cell and virus parameters during chronic state*

Parameter Definition	Symbol	LHS/PRC correlation coefficient
Max. recruitment rate of naïve $CD4^+$ by DC	ϕ_4	0.407
Michaelis–Menten constant of DC effect on naïve $CD4^+$ recruitment	f_{10}	-0.123
Death/Exit to Efferent Lymph		
Death/Exit rate of naïve $CD4^+$	μ_4	-0.133
Death/Exit rate of T-helper	μ_H	0.031
Death/Exit rate of infected cells	μ_I	0.882*
Destruction rate of virus particles	μ_V	-0.960*
Proliferation/Clonal Expansion		
Proliferation rate of T-helper	p_H	-0.046
Infection		
Abortive infection and bystander effects of naïve $CD4^+$	k_{ab}	-0.531*
Fraction of abortive infections that become productive	α	0.025
Infection rate of T-helper by virus	k_V	0.086*

Virus Properties		
Average number of virus produced by an infected cell	N	0.869*

* = statistically significant correlation ($P < 9.1 \times 10^{-4}$)

Supplementary Table S3. *Sensitivity of CD8$^+$ T-cell parameters during chronic state*

Parameter Definition	Symbol	LHS/PRC correlation coefficient
Max. recruitment rate of naïve CD8$^+$ by DC	ϕ_8	-0.668*
Michaelis–Menten constant of DC effect on naïve CD8$^+$ recruitment	f_{11}	0.181*
Death/Exit to Efferent Lymph		
Death/Exit rate of naïve CD8$^+$	μ_8	0.329*
Death/Exit rate of CTL	μ_C	0.673*
Proliferation/Clonal Expansion		
Proliferation rate of CTL	p_C	-0.384*
CTL Effector Functions		
Inhibition of virus infection by CTL	c_1	0.092
Inhibition of mat. DC-associated virus infection by CTL	c_2	0.570*
Inhibition of lic. DC-associated virus infection by CTL	c_3	0.098
Inhibition of infected cell virus production by CTL	c_4	0.685*
Inhibition of abortive infection/bystander effects by CTL	c_5	-0.106
Killing rate of infected cells by CTL	κ_I	-0.962*
Killing rate of mat. DC by CTL	κ_M	-0.017
Killing rate of lic. DC by CTL	κ_L	0.731*

* = statistically significant correlation ($P < 7.7 \times 10^{-4}$)

Supplementary Table S4. *Sensitivity of DC parameters during chronic state*

Parameter Definition	Symbol	LHS/PRC correlation coefficient
Max. immigration rate of mat. DC due antigen	ϕ_{DM}	-0.143*
Michaelis–Menten constant of antigen effect on mat. DC immigration	f_{13}	0.014
Death/Exit to Efferent Lymph		
Death rate of imm. DC	μ_{DI}	0.038
Death rate of mat. DC	μ_{DM}	0.080
Death rate of lic. DC	μ_{DL}	0.158
Priming		
Priming rate of naïve CD4$^+$ by mat. DC	r_{DM}	0.263*
Priming rate of naïve CD4$^+$ by lic. DC	r_{DL}	0.042
Priming rate of naïve CD8$^+$ by lic. DC	r_{8L}	-0.952*
Infection		
Infection rate of T-helper by mat. DC-associated virus	k_{DM}	0.928*
Infection rate of T-helper by lic. DC-associated virus	k_{DL}	0.188
Fraction of naïve CD4$^+$ infected during priming by mat. DC	b_M	-0.052
Fraction of naïve CD4$^+$ infected during priming by lic. DC	b_L	0.037
Virus Properties		
Ratio of virions in periphery to virions in LN	β	-0.065
DC Maturation and Licensing		
Maturation rate of DC due to virus antigen	δ	0.113
Maturation rate of DC due to infected cell antigen	γ	0.081
Maturation rate of DC due to antigen from other DCs	ε	-0.014
Licensing rate of mat. DCs by T-helper	λ	-0.946*

* = statistically significant correlation ($P < 5.9 \times 10^{-4}$)

Supplementary Table S5. *Global sensitivity analysis identifies parameters that can cause progression to AIDS-like state*

Parameter Definition	Symbol	LHS/PRC correlation coefficient	eFAST index
Max. recruitment rate of naïve $CD4^+$ by DC	ϕ_4	0.112	0.039**
Michaelis–Menten constant of DC effect on naïve $CD4^+$ recruitment	f_{10}	-0.036	0.005
Max. recruitment rate of naïve $CD8^+$ by DC	ϕ_8	-0.377*	0.053**
Michaelis–Menten constant of DC effect on naïve $CD8^+$ recruitment	f_{11}	0.020	0.005
Max. immigration rate of mat. DC due antigen	ϕ_{DM}	0.023	0.137**
Michaelis–Menten constant of antigen effect on mat. DC immigration	f_{13}	0.031	0.004
Death/Exit to Efferent Lymph			
Death/Exit rate of naïve $CD4^+$	μ_4	0.068	0.003
Death/Exit rate of T-helper	μ_H	0.041	0.008
Death/Exit rate of infected cells	μ_I	0.207*	0.018
Destruction rate of virus particles	μ_V	-0.446*	0.139**
Death/Exit rate of naïve $CD8^+$	μ_8	0.243*	0.019
Death/Exit rate of CTL	μ_C	0.322*	0.028
Death rate of imm. DC	μ_{DI}	0.068	0.002
Death rate of mat. DC	μ_{DM}	0.004	0.008
Death rate of lic. DC	μ_{DL}	0.036	0.003
Proliferation/Clonal Expansion			
Proliferation rate of T-helper	p_H	0.005	0.003
Proliferation rate of CTL	p_C	-0.157*	0.007
Priming			
Priming rate of naïve $CD4^+$ by mat. DC	r_{DM}	0.266*	0.069**
Priming rate of naïve $CD4^+$ by lic. DC	r_{DL}	0.024	0.002
Priming rate of naïve $CD8^+$ by lic. DC	r_{8L}	-0.776*	0.556**
Infection			
Abortive infection and bystander effects of naïve $CD4^+$	k_{ab}	-0.261*	0.167**
Fraction of abortive infections that become productive	α	0.080	0.006
Infection rate of T-helper by virus	k_V	0.242*	0.014
Infection rate of T-helper by mat. DC-associated virus	k_{DM}	0.608*	0.159
Infection rate of T-helper by lic. DC-associated virus	k_{DL}	0.038	0.003
Fraction of naïve $CD4^+$ infected during priming by mat. DC	b_M	0.043	0.003
Fraction of naïve $CD4^+$ infected during priming by lic. DC	b_L	0.005	0.006
Virus Properties			
Average number of virus produced by an infected cell	N	0.291*	0.180**
Ratio of virions in periphery to virions in LN	β	0.028	0.002
CTL Effector Functions			
Inhibition of virus infection by CTL	c_1	0.034	0.003
Inhibition of mat. DC-associated virus infection by CTL	c_2	0.147*	0.011
Inhibition of lic. DC-associated virus infection by CTL	c_3	0.019	0.002
Inhibition of infected cell virus production by CTL	c_4	0.345*	0.017
Inhibition of abortive infection/bystander effects by CTL	c_5	-0.060	0.006
Killing rate of infected cells by CTL	κ_I	-0.826*	0.370**
Killing rate of mat. DC by CTL	κ_M	-0.022	0.012
Killing rate of lic. DC by CTL	κ_L	0.344*	0.020

DC Maturation and Licensing

Maturation rate of DC due to virus antigen	δ	0.033	0.006
Maturation rate of DC due to infected cell antigen	γ	-0.023	0.004
Maturation rate of DC due to antigen from other DCs	ε	-0.005	0.007
Licensing rate of mat. DCs by T-helper	λ	-0.746*	0.271**

* = significant correlation by LHS/PRC ($P < 2.4 \times 10^{-4}$)

** = significant total-order sensitivity index by eFAST ($P < 0.01$)

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