J. Math. Biol. (2012) 64:495–512
DOI 10.1007/s00285-011-0422-8

Mathematical Biology

Evolutionary game theoretic strategy for optimal drug delivery to influence selection pressure in treatment of HIV-1

Yu Wu · Mingjun Zhang · Jing Wu · Xiaopeng Zhao · Lijin Xia

Received: 27 March 2010 / Revised: 6 March 2011 / Published online: 19 April 2011

Abstract Cytotoxic T-lymphocyte (CTL) escape mutation is associated with long-term behaviors of human immunodeficiency virus type 1 (HIV-1). Recent studies indicate heterogeneous behaviors of reversible and conservative mutants while the selection pressure changes. The purpose of this study is to optimize the selection pressure to minimize the long-term virus load. The results can be used to assist in delivery of highly loaded cognate peptide-pulsed dendritic cells (DC) into lymph nodes that could change the selection pressure. This mechanism may be employed for controlled drug delivery. A mathematical model is proposed in this paper to describe the evolutionary dynamics involving viruses and T cells. We formulate the optimization problem into the framework of evolutionary game theory, and solve for the optimal control of the selection pressure as a neighborhood invader strategy. The strategy dynamics can be obtained to evolve the immune system to the best controlled state. The study may shed light on optimal design of HIV-1 therapy based on optimization of adaptive CTL immune response.

Keywords HIV · Evolutionary game theory · Fitness · Selection pressure · Optimization

Mathematics Subject Classification (2000) 91A22 · 92D25 · 93C15

1 Introduction

Within-patient HIV (human immunodeficiency virus) evolution shows viral mutational escape from cytotoxic T-lymphocyte (CTL) recognition. Epitope-specific CTL

Y. Wu · M. Zhang (✉) · J. Wu · X. Zhao · L. Xia
Mechanical, Aerospace and Biomedical Engineering Department,
University of Tennessee, Knoxville, TN 37996, USA
e-mail: mjzhang@utk.edu

response plays a critical role in the control of HIV. Recent studies indicate that there are two types of CTL escape mutation, one is reversible, and the other is conservative (Leslie et al. 2004; Picado et al. 2006). The mutations are driven by strong selection pressure. The main difference between the two types of the CTL escape mutations is that, while the selection pressure disappears or is weakened, the reversible mutant will revert to a wild type virus, while the conservative one will be maintained. The reversible mutation usually carries a significant cost to viral replicative capacity, while the conservative one occurs at little or no cost to the virus. The cost here is associated with different degrees of constraint on viral replication. In our previous work (Wu et al. 2010), a mathematical model has been proposed to describe the population dynamics. The model shows different behavior of reversible and conservative mutants, which agrees well with the experimental observations (Leslie et al. 2004). In the prior model, the extent to selection pressure measurement will determine the degree to which escape mutations revert or are maintained. It is interesting to note that the virus load is not simply reversely proportional to the selection pressure. There is an optimal selection pressure under which the virus can be most effectively controlled (Wu et al. 2010).

In this paper, we propose an optimal control approach to minimize the steady virus load. The goal is to develop an optimal drug delivery strategy for HIV treatment. We formulate it as an optimization problem in the framework of evolutionary game theory, and thus solve for optimal control of selection pressure by evaluation of neighborhood invader strategy (NIS) (Apaloo et al. 2009). In the formulation, the selection pressure is regarded as a drug delivery strategy that can be controlled by delivering cognate peptide-pulsed dendritic cells (DCs) into lymph nodes. The fitness generating function, G function, is chosen to be the object function of the optimal control. By employing the strategy dynamics, an arbitrary given initial selection pressure will evolve to NIS, and the immune system will evolve to the optimal state. Thus, we can maximize the effectiveness of adaptive CTL immune response by controlling the selection pressure, which can be achieved by DC based therapy (Bousso and Robey 2003; Henrickson et al. 2008). Our previous work also demonstrated that the CTL immune response could be enhanced by recruitment of cognate antigen-pulsed DCs (Wu et al. 2010).

2 Model formulation

To describe the evolutionary dynamics of HIV virus and human leukocyte antigen (HLA) restricted CTL response, and understand the DCs based adaptive immunotherapy, we proposed a controlled population model as shown in (1), where V_i are free infectious virions in the extracellular environment, V_1 is the population of wild type virus with TW10 epitope, V_2 is the mutant with only T242N mutation, V_3 is the mutant with only G248A mutation and V_4 is the mutant with both T242N and G248A mutations, T_1 represents the population of uninfected helper T cells, T_2 is the helper T cells infected by HIV virus, and T_3 is the HLA restricted CTLs. Due to high possibility of coinfection and direct cell to cell virus transmission (Jung et al. 2002; Dang et al. 2004; Levy et al. 2004; Chen et al. 2005; Wodarz and Levy 2009; Jolly and Sattentau 2004; Sattentau 2008), multiple virions may coexist in one cell. Thus, we treat the helper T cells infected by all types of virus population V_i as one population

T_2 and T_3 is the collection of CTLs directed to arbitrary V_i. The differential equations to describe the controlled population model are as follows

$$\dot{V}_1 = Nd_2T_2 - dV_1 - (k_1 + k_2 - k_1k_2)Nd_2T_2 + k_3r_2Nd_2T_2 \tag{1a}$$
$$\dot{V}_2 = r_2Nd_2T_2 - dV_2 + k_1(1 - k_2)Nd_2T_2 - k_3r_2Nd_2T_2 \tag{1b}$$
$$\dot{V}_3 = r_3Nd_2T_2 - dV_3 + k_2(1 - k_1)Nd_2T_2 + k_3r_4Nd_2T_2 \tag{1c}$$
$$\dot{V}_4 = r_4Nd_2T_2 - dV_4 + k_1k_2Nd_2T_2 - k_3r_4Nd_2T_2 \tag{1d}$$
$$\dot{T}_1 = s_1 + rT_1 - r_1T_1(V_1 + r_2V_2 + r_3V_3 + r_4V_4) - d_1T_1 \tag{1e}$$
$$\dot{T}_2 = r_1T_1(V_1 + r_2V_2 + r_3V_3 + r_4V_4) - d_2T_2 - (k + u)k_{\max}T_2T_3 \tag{1f}$$
$$\dot{T}_3 = s_2 + c_1(k + u)T_3(V_1 + c_2V_2 + c_3V_3 + c_4V_4) - d_3T_3 \tag{1g}$$

where

$$k_1 = (k + u)^n$$
$$k_2 = a(k + u)^n$$
$$k_3 = 1 - (k + u)^n$$
$$N = \frac{N_0}{1 + r_2 + r_3 + r_4}$$

In the above equations, u is the control term for the adaptive immunity, which can be achieved by adaptive immunotherapy, such as injecting highly loaded cognate peptide-pulsed DCs into lymph nodes.

The normalized parameter $k \in [0, 1]$ is a quantification of the selection pressure, which is a representation of the strength of cell-mediated immunity and related to the CTLs' capability to recognize specific epitopes. Specifically, $k = 1$ corresponds to the maximum pressure, while $k = 0$ represents that epitopes will not be recognized by the CTLs at all. Only those $CD8^+$ T cells that bind to the peptide HLA complex with enough affinity will be primed and become CTLs. Recent studies indicated that CTL activation would not occur below an antigen dose threshold (Bousso and Robey 2003; Henrickson et al. 2008). Thus k is proportionally dependent on the affinity of TCR/peptide HLA binding and the dose of HLA class I alleles HLA-B57 and HLA-B5801.

After infection of the helper T cells, reverse transcription occurs during which the wild type virus can mutate with a probability of k_1 at Gag residue 242 from Thr to Asn, while TW10 can also mutate with a probability of k_2 at residue 248 from Gly to Ala. Thus, the probability with which wild type epitope TW10 mutate to mutant T242N at each proliferation cycle is $k_1(1 - k_2)$, and the probability for mutation from TW10 to T248A is $k_2(1 - k_1)$. Both mutation T242N and G248A occur with probability k_1k_2. Since the viral escape mutation is driven by selection pressure, the mutation rate should be dependent on selection pressure, though the relationships may vary in various situations. We assume that the mutation rate is linearly proportional to selection pressure ($n = 1$). The coefficient is normalized to 1 for T242N mutant, and the scale factor for G248A mutant is defined as a. The value of a can be estimated from experiment data (Leslie et al. 2004), which is approximately 0.5 based on experimental observations.

It is believed that the virus may restore viral fitness to some degree by reversion at the residue, which has a profound effect on viral fitness (Richman et al. 2003). A carefully designed experiment predicts that the mutant T242N undergoes reversion after transmission to HLA B57/5801-negative recipients, while the other G248A maintains stability (Leslie et al. 2004). Thus, we hypothesize that the probability of substitution of Asn by Thr at residue 242 is inversely proportional to the selection pressure. As a result, the probability can be assumed as $k_3 = 1 - (k + u)^n$.

Equation (1a) describes the evolution of wild type virus (TW10). When infected helper T cell T_2 bursts due to intracellular virus growth, the V_1 population is increased. There are on average $N = N_0/(1+r_2+r_3+r_4)$ free virion released to the extracellular environment by each dead T_2 cell, so the growth rate is Nd_2T_2. The probability with which wild type virus convert to mutants at each proliferation cycle is $k_1 + k_2 - k_1k_2$, while the mutant T242N will revert to wild type with probability k_3 at each cycle. The natural decay term $-dV_1$ accounts for loss of viral infectivity, viral death, and/or clearance from the body.

In Eq. (1b), the V_2 population increases at a rate of $r_2Nd_2T_2$, where r_2 is the ratio of the fitness of V_2 to that of V_1. Since the mutation at Gag residue 242 is associated with a significant fitness cost to the virus, we choose $r_2 = 0.1$. The V_2 population also arises due to CTL escape mutation from wild type at a rate $k_1(1 - k_2)Nd_2T_2$ and decreases due to reverse mutation to wild type at a rate of $-k_3r_2Nd_2T_2$.

The V_3 population increases at r_3 times the rate of V_1. Since G248A arises at little or no effect on viral fitness (Forshey et al. 2002; Picado et al. 2006), the parameter $r_3$that represents the ratio of the fitness of V_3 to the fitness of V_1 is chosen to be 0.7. The mutation Gly to Ala at residue 248 occurs with the probability $k_2(1 - k_1)$ at each proliferation cycle.

Equation (1d) describes similar growth and decay rate of V_4 population as that of V_2 and V_3. Since V_4 comes from double-point mutations of wild type V_1, the conversion probability is k_1k_2 due to positive selection. In the absence of selection pressure, T242N will revert while G248A is stable. Thus, a rate term $k_3r_4Nd_2T_2$ is subtracted from V_4 population and added to V_3.

Equation (1e) models the population dynamics of uninfected helper T cells. Uninfected helper T cells T_1 can arise from precursors at a constant rate s_1, and also grow from proliferation at a rate rT_1. The term $r_1T_1(V_1 + r_2V_2 + r_3V_3 + r_4V_4)$ models the rate at which free virus infects a helper T cell. Here r_1 is the infectivity of wild type virus V_1, describes the ability of wild type virus to enter, survive and multiply in $CD4^+$ T cells, and r_2, r_3, and r_4 are ratios of the infectivity of the mutants V_2, V_3, and V_4 to r_1, respectively, provided that the strength of infectivity is linearly proportional to the fitness (Goodenow et al. 2003). Here we assumed that after entry into host T cells, wild type virus and mutants have the same proliferation rates, so the virus fitness is linearly proportional to the entry efficiency. Wild type virus V_1 infects T_1 cells with a rate constant r_1 and causes them to become productively infected cells T_2, thus the mass action type of term $r_1T_1V_1$ is subtracted from Eq. (1e) and added to Eq. (1f). Similarly, mutants $V_i (i = 2, 3, 4)$ infect T_1 cells with rate constants $r_1r_i (i = 2, 3, 4)$. The last term $-d_1T_1$ is the death rate.

In Eq. (1f), infected helper T cell T_2 increases when members of the T_1 population infected by virus. The T_2 population allows virus to grow (uninhibited) inside them.

But after exceeding their carrying capacity for the virus, they burst and release their intracellular virus into the extracellular environment (Perelson and De Boer 1993; Day et al. 2009). In addition, an infected helper T cell may die via apoptosis or necrosis (Plymale et al. 1999), then a small percentage of intracellular virus are released. We integrated these considerations into a single decay rate $-d_2T_2$ and assume that there are on average N_0 free virus released to the extracellular environment by each dead T_2 cell. Infected helper T cells are also killed by epitope-specific CTLs T_3. Since the strength of cell-mediated immunity represents the selection pressure, we formulated it as a mass action type of term $(k+u)k_{\max}T_2T_3$, where $k \in [0, 1]$ is the normalized parameter for selection pressure, and $k_{\max}$ is the maximum cytotoxic killing rate, i.e. infected cells T_2 are killed at a per capita rate of $k_{\max}T_3$ when $k = 1$.

In Eq. (1g), epitope-specific CTLs T_3 are inducted from precursor at a constant rate $s_2.T_3$ may also be activated into proliferation and differentiation cycle, when they contact with the cognate peptide and HLA class I on antigen presenting cells (APC). Though T_3 is the group of CTLs directed to all kinds of epitopes, including wild type V_1 and mutants $V_i (i = 2, 3, 4)$, we can express the escape mechanism by introducing the recognition parameter $c_i (i = 2, 3, 4)$. c_1 is the rate at which a T_3 cell will proliferate due to recognition of a wild type TW10 epitope, and $c_i (i = 2, 3, 4)$ are the ratio of rates due to mutants $V_i (i = 2, 3, 4)$ to c_1, respectively. Since the selection pressure k is proportional to the affinity of TCR/peptide HLA binding and the dose of HLA-B57 and HLA-B5801, which are determinants for CTL priming, the proliferation rate should also proportional to k. Thus, we can define the rate term $c_1(k+u)T_3(V_1 + c_2V_2 + c_3V_3 + c_4V_4)$. The decay rate $-d_3T_3$ is added to account for the limited life-span.

3 Formulation as an optimal control problem

Let $\mathbf{x} = [V_1\ V_2\ V_3\ V_4\ T_1\ T_2\ T_3]^{\mathrm{T}}$, then system (1) can be converted as a nonlinear control problem

$$\dot{\mathbf{x}} = f(\mathbf{x}, k, u) \tag{2}$$

where $\mathbf{x}$ is the state vector, and each component indicates the population of species; u is the control variable, which is used to adjust the selection pressure. So a positive control will increase the selection pressure, while a negative one will make a down-regulation.

The major goal of HIV therapy is to suppress the virus growth and keep the virus under control for as long as possible. Long-term viral load is the major measurement criterion for the evaluation of effect of the therapy. Thus, we consider an object function as the total virus load

$$J(k, u) = \sum_{i=1}^{4} x_i(k, u) \tag{3}$$

where $x_i (i = 1, \ldots, 4)$ are the concentration of wild type HIV and the various mutants.

Based on the above discussion, the problem can be turned into as an optimal control problem. For a given initial selection pressure $k \in \Sigma$, $\Sigma = \{n \in \mathbb{R} | 0 \leq n \leq 1\}$, we will find an optimal control u_{opt} that minimize the object function in the steady state.

$$J_{\text{opt}}(k) \equiv \min_{u \in \Omega} J(k, u), \quad \Omega = \left\{ n \in \mathrm{R} | 0 \leq n + k \leq 1 \right\} \tag{4}$$

subject to

$$f(\mathbf{x}, k, u) = 0 \tag{5}$$

To obtain an optimal solution, we put the formulation into the framework of evolutionary game theory, which will facilitate the calculation to find the optimal control.

4 Evolutionary game theoretical analysis

Under the framework of evolutionary game theory, system (2) can be expressed as

$$\dot{\mathbf{x}} = \mathbf{G}(\mathbf{x}, k, u)\mathbf{x} \tag{6}$$

where $\mathbf{G}(\mathbf{x}, k, u) = diag(G_i(\mathbf{x}, k, u)), i = 1, \ldots, 7$, is the G function that is usually defined as the per capita growth rate, describing the capability of a species to survive. A species can be dominant if and only if it can maximize the G function of itself and minimize that of the other species. Here u is treated as a control strategy. To minimize the steady virus load, the optimal strategy must be chosen to be a neighborhood invader strategy (NIS), which is a strategy that can invade any population with a nearby strategy value, and results in a minimum principle (Apaloo et al. 2009). Thus, the solution of the optimal control problem is now equivalent to finding the NIS.

NIS minimum principle A strategy $u^* \in \Omega$ is said to be a neighborhood invader strategy for the equilibrium x_i^* if, when the species maintains at steady state $x_i = x_i^*$, for any perturbation to the strategy $\delta u \neq 0$ in a close neighborhood of u^*, $N(u^*)$,

$$G_i(k, u^* + \delta u, x_i^*, x_j) > 0 \tag{7}$$

In other words, u^* is an NIS for x_i^* if and only if u^* is the unique solution to the minimization problem

$$\min_{\delta u \in N(u^*)} G_i(k, u^* + \delta u, x_i^*, x_j)|_{i \neq j} = G_i(k, u^*, x_i^*, x_j^*)|_{i \neq j} = 0 \tag{8}$$

where $x_j^* (j \neq i)$ are steady states of the other species with strategy $u = u^*$.

As a key concept in the evolutionary game theory, the NIS landscape is a plot of the per capita growth rate, $G_i(k, u, \mathbf{x})$, as a function of a focal individual's strategy. A strategy is a NIS if individuals with this strategy are always better than others without using this strategy, and thus can invade (Traulsen et al. 2006). Thus, to minimize

the HIV-1 population, all other species must adopt the same NIS as the HIV-1 does, otherwise the HIV-1 will invade. The conditions for a strategy u to possess the ability of invasion and satisfy the NIS minimum principle include (Apaloo et al. 2009)

$$\mathbf{G}(k, u, \mathbf{x}^*)|_{u=u^*} = 0 \tag{9}$$

$$\mathbf{x}^* > 0 \tag{10}$$

$$\mathbf{Re}(\lambda_i) < 0 \tag{11}$$

$$\left.\frac{dG_i(k, u, \mathbf{x}^*)}{du}\right|_{u=u^*} = 0 \tag{12}$$

$$\left.\frac{d^2G_i(k, u, x_i^*, x_j)}{du^2}\right|_{u=u^*} > 0 \tag{13}$$

where λ_i are the eigenvalues of the Jacobian matrix evaluated at the steady state $\mathbf{x} = \mathbf{x}^*, u = u^*$. Conditions (9)–(11) ensure that $\mathbf{x}^*$ is an ecologically stable equilibrium (ESE) point with respect to the population dynamics, which may be determined in terms of k^* from Eq. (9). Equations (12) and (13) represent the first-order and second-order conditions for G_i to take on a minimum with respect to u at $u = u^*$, respectively. Equation (12) can be used to solve for u^* as a function of $\mathbf{x}^*$.

The strategy dynamics for minimizing G function can be described by the following differential equation

$$\dot{u} = -\sigma \frac{dG_i(k, u, \mathbf{x}^*)}{du} \tag{14}$$

where $\sigma > 0$ is the evolutionary 'speed' parameter related to the velocity of strategy dynamics, and is influenced by the specific therapy. As the strategy varies with time, the NIS landscape keeps on changing. The strategy dynamics (14) will allow the G function to "down valleys" of lower fitness. The evolution of strategy will not stop until reaching the bottom of the valley, where conditions (12) and (13) are satisfied. Thus, the equilibrium of (14) is the solution to optimization problem (8).

By using evolutionary game theory, the solution of optimization problem (4) can be obtained from problem (8) and the object function (3) is replaced by G function. To minimize the object function (3), the corresponding G function for the total HIV virus is

$$G_{\text{virus}}(k, u, \mathbf{x}) = \frac{\dot{x}_1 + \dot{x}_2 + \dot{x}_3 + \dot{x}_4}{x_1 + x_2 + x_3 + x_4} = \frac{d_2 x_6 N(1 + r_2 + r_3 + r_4)}{x_1 + x_2 + x_3 + x_4} - d \tag{15}$$

Thus, G_{virus} is abundance dependent. It is clear from (15) that for a given abundance of virus, G_{virus} is proportional to the density of infected helper T cells x_6, which suggests that the fitness of HIV is determined by x_6. This is reasonable since all HIV viruses arise from infected helper T cells. Once the infected helper T cells are minimized, the viruses are most effectively controlled. Thus, we consider the object function as the G function of x_6

$$G_6(k, u, \mathbf{x}) = \frac{r_1 x_5 (x_1 + r_2 x_2 + r_3 x_3 + r_4 x_4)}{x_6} - d_2 - (k + u) k_{\max} x_7 \qquad (16)$$

In the evolutionary context, the strategy dynamics will be solved to maximize the G function and achieve the NIS, which is based on the theory of Darwinian dynamics. Here the strategy is chosen to be the control u to selection pressure. The control could be applied by DCs based therapy, i.e., injection of DCs pulsed with HLA-restricted epitope into lymph nodes, and thus will vary the selection pressure by changing the overall avidity of the interactions between epitope-specific T cells and cognate antigen-bearing DCs (Bousso and Robey 2003; Henrickson et al. 2008).

The NIS landscape for a given initial selection pressure k can be obtained by the following two steps:

1. Calculate the steady state $\mathbf{x}^*$ at u by using condition (9), and the G function G_i at u;
2. Calculate the G function G_i with fixed x_i^* and perturbation of strategy by δu.

Once we have NIS landscape, we can integrate the strategy dynamics Eq. (14) numerically. The strategy is evolved from initial value $u_0 = 0$; The derivatives in Eq. (14) can be obtained from the slope of the NIS landscape at $u = u_0$. Then u will be updated to u_t following (14). The NIS landscape keeps on changing with updated u_t. The dynamics trends to steady state while the slope of NIS landscape at $u = u_t$ approaches zero, where condition (12) is satisfied. The strategy will then evolve to u^*, the solution of the optimization problem (8).

5 Results

As reported in Wu et al. (2010), the virus load is not simply reversely related to the selection pressure. There is an optimal value under which we can suppress the virus to a lowest level by adaptive CTL immune response. By using evolutionary game theory, we can get a clear picture to optimize the selection pressure.

5.1 Stability analysis

To ensure that $\mathbf{x}^*$ is an ESE point with respect to the population dynamics, conditions (9)–(11) must be satisfied. Following Eqs. (9) and (10), the ecological equilibrium can be determined. Then we evaluate the Jacobian matrix $\mathbf{J}$ at the ecological equilibrium. The seven eigenvalues of $\mathbf{J}$ can be determined by solving the characteristic equation $\det(\mathbf{J} - \lambda \mathbf{I}) = 0$. The ecological equilibrium is an ESE if and only if all the seven eigenvalues have negative real parts. By using this criterion, the parameter region for ESE can be determined numerically. The parameters used in simulation are chosen from the stable region. The definitions and values are given in Table 1.

Following the procedures outlined in Sect. 4, we can depict the NIS landscape for initial selection pressure k, and further to calculate the optimal control u^* by evolution of the strategy dynamics. The results are shown below.

Table 1 Variables and parameters

Symbol	Interpretation	Initial and default values	Comments
V_1	Free wild-type epitope TW10 in the extracellular environment	100 mm^{-3}	Estimated (Ho et al. 1995)
V_2	T242N	0	There were initially no mutants
V_3	G248A	0	There were initially no mutants
V_4	T242N & G248A	0	There were initially no mutants
T_1	Uninfected helper T cells in plasma	100 mm^{-3}	Estimated (Ho et al. 1995)
T_2	Infected helper T cells in plasma	0	There were initially no infected T cells
T_3	TW-10 specific CTLs in plasma	1 mm^{-3}	We set the initial time of our simulation at which the TW10-specific CTLs are just activated by APC and migrate out from the lymph nodes, and then begin to hunt for the antigen-positive somatic cells
s_1	Rate of supply of helper T cells from precursors	20 day^{-1} mm^{-3}	(Perelson and De Boer 1993; Perelson and Nelson 1999)
s_2	Rate of supply of CTLs from precursors	1 day^{-1} mm^{-3}	(Janeway et al. 2008)
r	Rate of proliferation for the helper T cell stimulated by normal environmental antigens	0.03 day^{-1}	(Perelson and De Boer 1993)
r_1	Rate for helper T cells becoming infected by wild-type TW10	0.005 mm^3 day^{-1} (variable)	Estimated (Perelson and De Boer 1993)
r_2	Ratio of the rate for helper T cells becoming infected by T242N to r_1	0.1	T242N escape mutation arises at a cost to viral replicative capacity (Leslie et al. 2004)
r_3	Ratio of the rate for helper T cells becoming infected by G248A to r_1	0.7	G248A mutation in B clade infections occurs at little or no cost to viral replicative capacity (Leslie et al. 2004; Picado et al. 2006)
r_4	Ratio of the rate for helper T cells becoming infected by T242N&G248A to r_1	0.1	T242N escape mutation comes at a cost to viral replicative capacity (Leslie et al. 2004)

Table 1 continued

Symbol	Interpretation	Initial and default values	Comments
N_0	Virus burst size, average number of free virus produced by lysing a helper T cell	1000	(Merrill 1987; Layne et al. 1989)
d	Death rate of virus	2.4 day^{-1}	(Perelson and De Boer 1993)
d_1	Death rate of uninfected helper T cells	0.02 day^{-1}	(Perelson and De Boer 1993)
d_2	Death rate of infected helper T cells	0.24 day^{-1}	(Perelson and De Boer 1993)
d_3	Death rate of CTLs	0.03 day^{-1} variable	Estimated (Perelson and De Boer 1993)
c_1	Maximum rate of proliferation for the CTLs stimulated by TW10	0.0001 mm^3 day^{-1} variable	Estimated (Luzyanina et al. 2001)
c_2	The ratio of proliferation rate for CTLs stimulated by TW10 to that stimulated by T242N mutant	0.01	T242N mutation causes substantial loss of recognition (Leslie et al. 2004)
c_3	The ratio of proliferation rate for CTLs stimulated by TW10 to that stimulated by G248A mutant	0.2	G248A mutation alone brings about a partial loss of recognition of the epitope (Leslie et al. 2004)
c_4	The ratio of proliferation rate for CTLs stimulated by TW10 to that stimulated by T242N&G248A mutant	0.001	The combination of the T242N and G248A mutations completely abrogates recognition at low peptide concentration (Leslie et al. 2004)
k_{max}	Maximum rate for TW10 be killed by CTLs	0.01 mm^3 day^{-1} variable	Estimated (Wick and Self 2004)
k	Coefficient of selection pressure	0–1	Normalized
u	The control to the selection pressure		
k_1	The probability of mutation at T242	k^n	The probability of mutation is proportional to the selection pressure
k_2	The probability of mutation at G248	ak^n	
a	The ratio of mutation probability of residue 248 to that of residue 242	0.5	The mutation probability of T242 is higher than that of G248
n		1	In this paper, the mutation probability is assumed to be linearly proportional to the selection pressure

5.2 The NIS landscape

The NIS landscape shows the variation of the G-function with the strategy. While the strategy dynamics always drive species towards lower points in the landscape, the

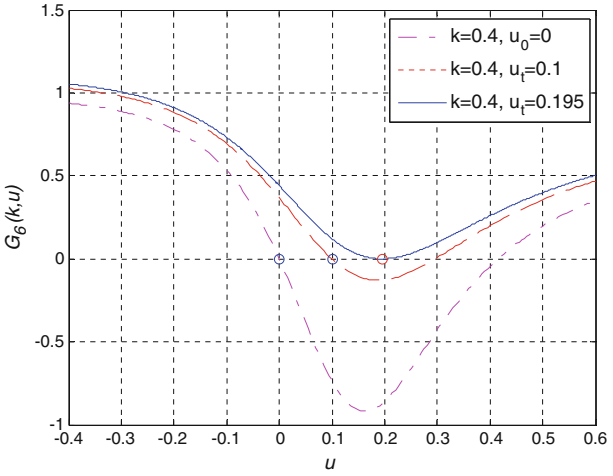

Fig. 1 The NIS landscape for selection pressure $k = 0.4$. The *three circles* represent the ESEs, $G_6(k, u) = 0$, located at $u_0 = 0$, $u_t = 0.1$, and $u_t = 0.195$, respectively. However, only $u_t = 0.195$ satisfies condition (12) and is NIS. For the rest two ESEs, any positive perturbation of the strategy δu will result in $G_6(k, u_t + \delta u) < 0$, thus will decrease the x_6 steady population. Using strategy dynamics, the ESEs roll down along the slope, while the valleys keep on shifting over time. The motion will not stop until the ESE reaches the bottom of the valley, and stay there as NIS. Any perturbation to NIS will result in invading of virus population

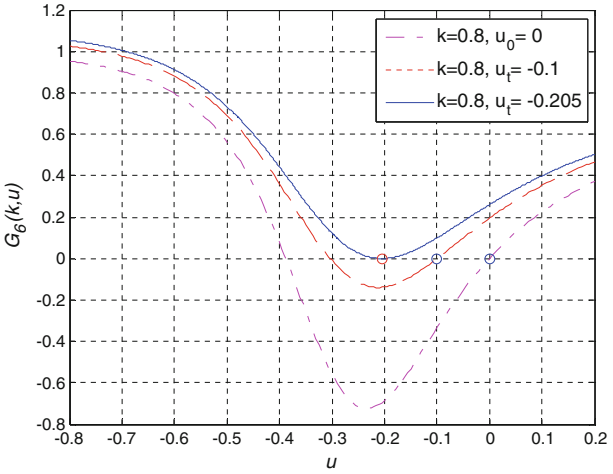

Fig. 2 The NIS landscape for selection pressure $k = 0.8$. The *three circles* show the ESEs, $G_6(k, u) = 0$, located at $u_0 = 0$, $u_t = -0.1$, and $u_t = -0.205$, respectively. However, only $u_t = -0.205$ satisfies condition (12) and is NIS. For the other ESEs, any negative perturbation of the strategy δu will result in $G_6(k, u_t + \delta u) < 0$, thus will decrease the x_6 steady population. So, x_6 cannot invade unless the NIS $u_t = -0.205$ is adopted

landscape will keep on shifting, causing valleys and peaks to appear and disappear in the landscape until the system reaches an equilibrium. The NIS landscape for initial selection pressure $k = 0.4$ and 0.8 are plotted in Figs. 1 and 2, respectively. The valleys are steep at first, and then the slope decrease as the strategy u evolves over time.

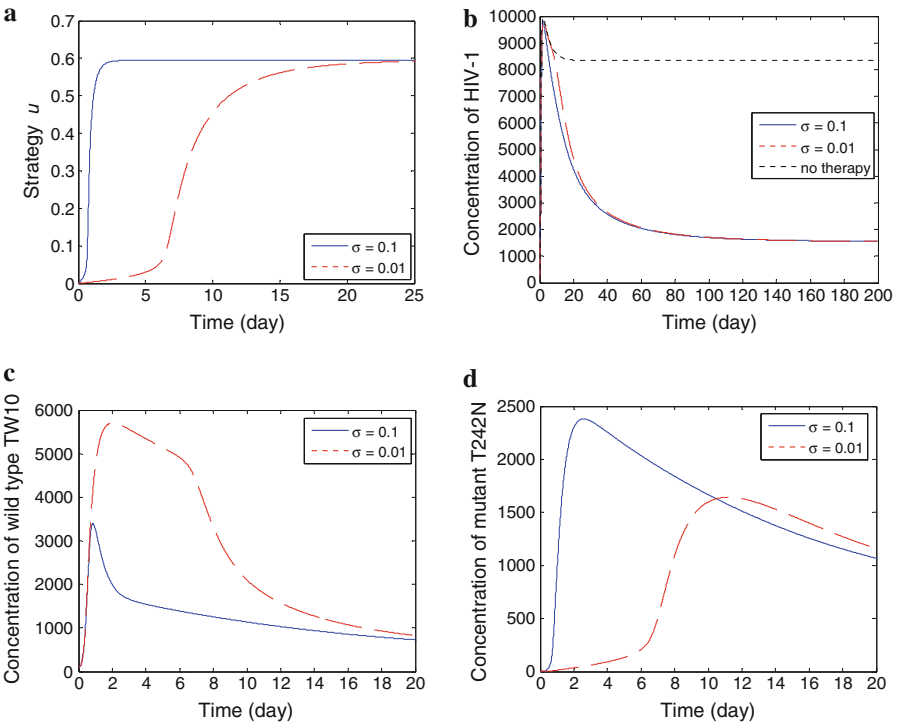

Fig. 3 The evolution of optimal strategy dynamics and concomitant virus dynamics with selection pressure $k = 0$. The strategy dynamics is very fast with parameter $\sigma = 0.1$, and relatively slow with $\sigma = 0.01$. It approaches the optimal value $u_{\text{opt}} = 0.595$ in just 2 days with $\sigma = 0.1$. For $\sigma = 0.01$, strategy evolves to NIS in three successive stages: slow increasing during the first 6 days are followed by a second phase of fast approaching, which makes a transition into a third phase of slow progressing in the neighborhood of NIS. The effects of therapy are compared in **b**. The total HIV-1 load can be effectively compressed to less than 1559, while the steady load will exceed 8000 without therapy, suggesting a significant effect. **d** shows that the wild-type TW10 virus is sensitive to selection pressure. A high dose and fast therapy will significantly decrease the wild-type virus load and stimulate the CTL escape mutation

The ESEs, marked as circles in the figures, are rolling down from mountainside to the bottom of the valley. The ESE will be a NIS equilibrium $(\mathbf{x}^*, u^*)$ once it arrives at the bottom of the valley, where the slope of the curve equals zero. Thus, any perturbation to the NIS strategy will lead to an increase in viral fitness.

5.3 Dynamics for the optimal strategy

The strategy dynamics (14) are designed to drive arbitrary initial strategy towards the NIS. The derivative in (14) can be obtained from the slope at corresponding ESE in the NIS landscape. Thus, the evolutionary 'speed' is proportional to the gradient at ESE, and will slow down in the neighborhood of NIS. Figures 3, 4, 5 and 6 demonstrate the evolution of optimal strategy dynamics and concomitant virus dynamics with different strength of selection pressure.

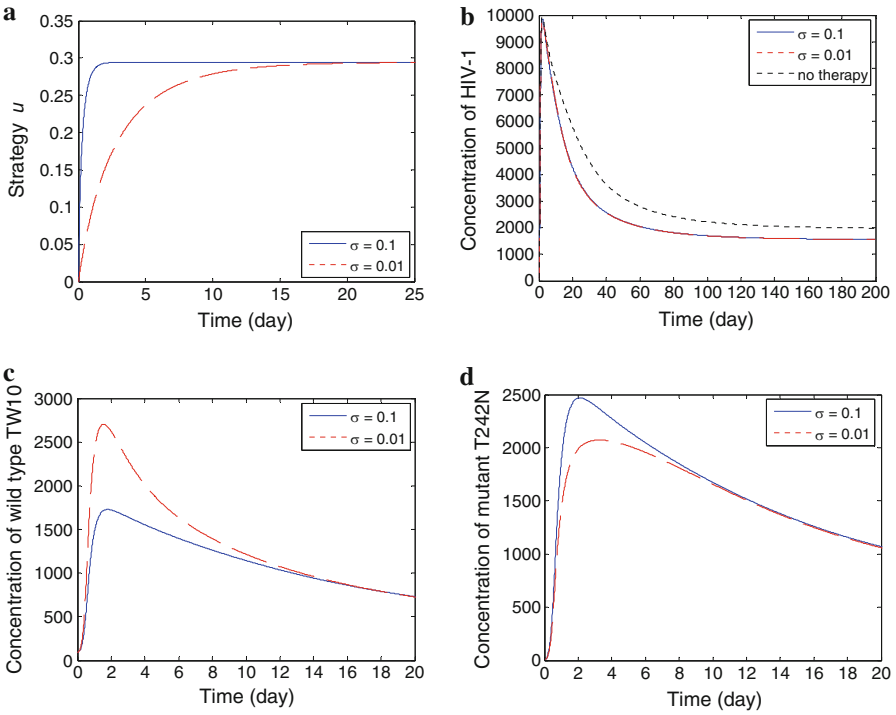

Fig. 4 The evolution of optimal strategy dynamics and concomitant virus dynamics with selection pressure $k = 0.3$. The strategy dynamics is very fast with parameter $\sigma = 0.1$, and relatively slow with $\sigma = 0.01$. It approaches the optimal value $u_{\text{opt}} = 0.295$ in just 2 days with $\sigma = 0.1$. Strategy evolves to NIS very fast in the initial phase and then slows down as the NIS is approached from below. The total HIV-1 load can be effectively compressed to less than 1559

The optimal strategy is local-state-dependent, that is, the strategy is calculated locally at parameter profile and equilibrium $\mathbf{x}^*$. Although we calibrate the model with literature data, the model parameters can easily be changed to patient-specific clinical parameters as needed. To demonstrate the influence of inter-patient heterogeneity to optimal strategy, we studied how the optimal strategy dynamics changes when the parameter profiles are changed. The strategy dynamics (14) is substituted by specific parameter settings

$$\dot{u} = -\sigma \frac{dG_i(k, u, \mathbf{x}^*, r_i', c_i')}{du} \tag{17}$$

where r_i' and c_i' are the current parameter settings.

Figure 7a–h shows the evolution of optimal strategy dynamics with different parameter profiles. There is a concomitant shift of optimal strategy as parameter profiles change. Obviously the impact of individual parameter to optimal strategy is heterogeneous. To better capture the strategy dynamics, one should pay special attention to those parameters with most significant impact factors.

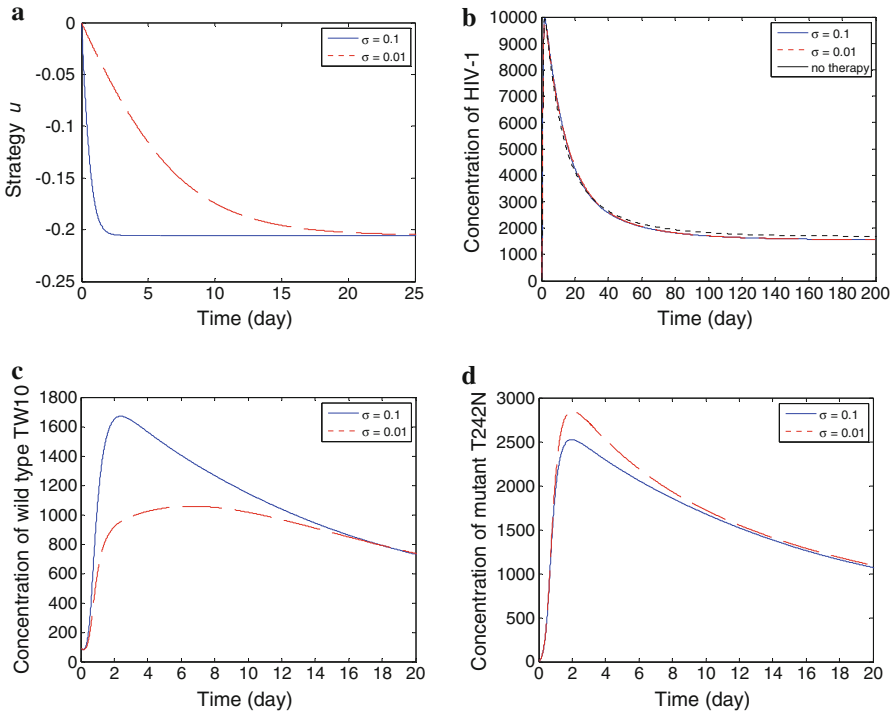

Fig. 5 The evolution of optimal strategy dynamics and concomitant virus dynamics with selection pressure $k = 0.8$. The strategy dynamics is very fast with parameter $\sigma = 0.1$, and relatively slow with $\sigma = 0.01$. It approaches the optimal value $u_{\text{opt}} = -0.205$ in just 2 days with $\sigma = 0.1$. The rate of evolution slows down as the strategy approaching the NIS. Then effect of therapy is not very significant because the initial selection pressure $k = 0.8$ supply a good condition for adaptive CTL immune response

The current model demonstrates the heterogeneous dynamics of reversible and conservative mutants while selection pressure changes over time. By employing the evolutionary game theory, the strategy dynamics for selection pressure can be determined. Thus, the selection pressure can be optimized for long-term HIV control. We anticipate that in conjunction with experimental observations, these results could be useful in DCs based immunotherapy for HIV treatment.

6 Discussions and conclusions

The escape mutation under selection pressure can protect HIV-1 against being detected by CTL adaptive immune response. The behaviors of mutants show diverse relationship with the selection pressure. Recent studies indicated that there were two distinct mutants, one is reversible, and the other is conservative. Although both mutants arise from the wild type HIV-1 pushed by strong selection pressure, they show different characteristics in the absence of selection pressure. The reversible mutant reverts to wild type, while the conservative one maintains. Since the adaptive immune response

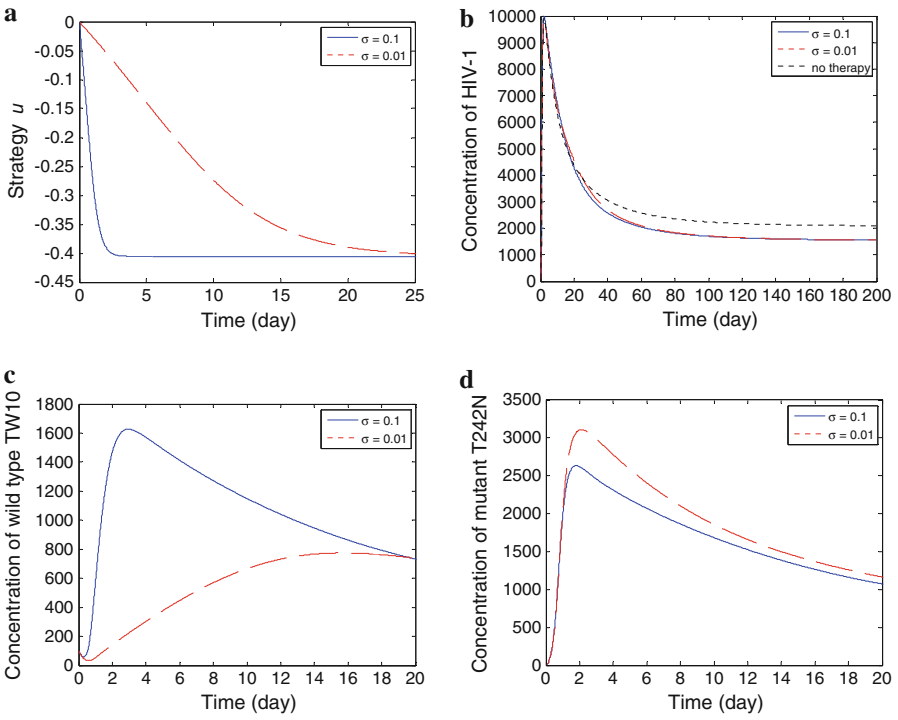

Fig. 6 The evolution of optimal strategy dynamics and concomitant virus dynamics with selection pressure $k = 1$. The strategy dynamics is very fast with parameter $\sigma = 0.1$ and relatively slow with $\sigma = 0.01$. It approaches the optimal value $u_{\text{opt}} = -0.405$ in just 2 days with $\sigma = 0.1$. The total HIV-1 load can be effectively compressed to less than 1559

exerts a major influence on selection pressure, an optimized adaptive CTLs immune response can facilitate HIV control.

This paper has proposed a mathematical model to describe the dynamics of wild type HIV-1 and mutants under adaptive CTLs immune response. The model suggests that an intermediate strength of the CTLs response can minimize overall virus load. To quantify the adaptive CTLs immune response that most effectively suppresses the virus, we further converted the model into an optimal control problem by introducing a control term to selection pressure. To solve for the optimal control, and to find the evolutionary strategy to achieve the optimal value, we have formulated the control problem in the framework of evolutionary game theory. Thus, the object function is equivalent to the G function, the optimal control corresponds to the NIS and the evolutionary strategy could be the strategy dynamics. By using the NIS minimum principle, we can obtain the NIS landscape, and then solve for the strategy dynamics. So we can maximize the effectiveness of adaptive CTLs immune response by controlling the selection pressure following the strategy dynamics.

The CTLs immune response can be regulated by employing DCs based adaptive immunotherapy. Since antigen specific CTLs are mostly primed by cognate antigen

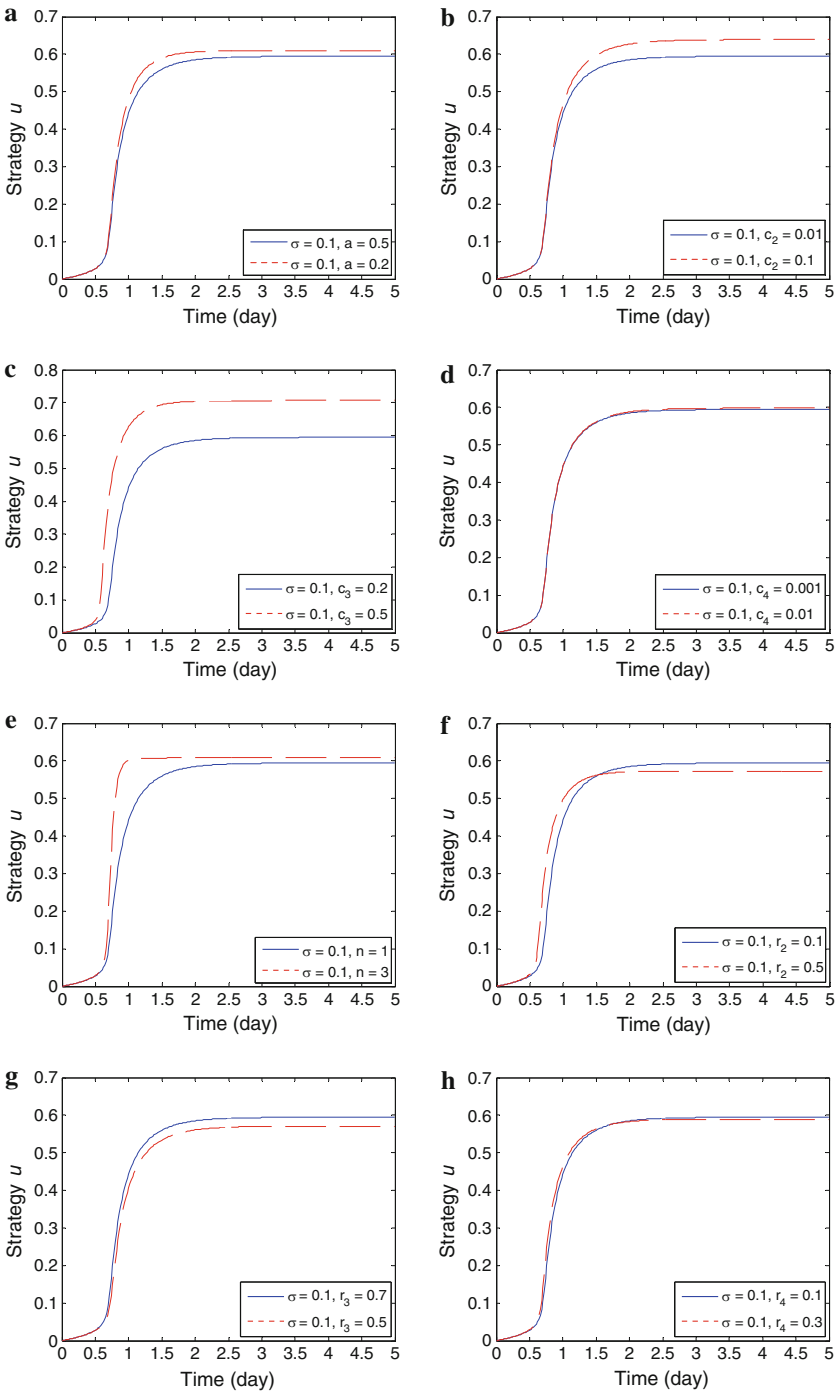

Fig. 7 The variation of optimal strategy dynamics with varying parameter profiles. Parameters c_2 and c_3 show significant influences on optimal strategy, while the impact of parameters c_4 and r_4 are trivial

loaded DCs in lymph nodes (Stoll et al. 2002; Bousso and Robey 2003; Mempel et al. 2004; Skokos 2007; Henrickson et al. 2008), DC-based immune therapy, injection of inactivated peptide/antigen-pulsed DC vaccines, could be a promising strategy for regulating cell-mediated immunity. The use of DCs as adjuvant cells has been tested experimentally and clinically (Lu et al. 2004; Pedersen and Ronchese 2007; Routy and Nicolette 2010). We previously demonstrated that CTL immune response could be regulated by modulating the overall avidity of the interactions between antigen-specific CTLs and cognate antigen-bearing DCs, and could be achieved by adjustment of the dose of vaccine, or the density of complexes of cognate pMHC per DC (Wu et al. 2010).

The proposed mathematical model, as well as the evolutionary game theory applied, provides a tool to understand the evolutionary dynamics of CTL escape mutants and an effective way to determine the optimal antigen-specific CTL immune strength. This model, once trained with clinical data and accomplished with parameter fitting, will facilitate DC based therapy design and enable individualized treatment.

References

Apaloo J, Brown JS, Vincent TL (2009) Evolutionary game theory: ESS, convergence stability and NIS. Evol Ecol Res 11:489–515

Bousso P, Robey E. (2003) Dynamics of CD8+ T cell priming by dendritic cells in intact lymph nodes. Nat Immunol 4:579–585

Chen J, Dang Q, Unutmaz D, Pathak VK, Maldarelli F, Powell D, Hu WS (2005) Mechanisms of non-random human immunodeficiency virus type 1 infection and double infection: preference in virus entry is important but is not the sole factor. J Virol 79:4140–4149

Dang Q, Chen J, Unutmaz D, Coffin JM, Pathak VK, Powell D, KewalRamani VN, Maldarelli F, Hu WS (2004) Nonrandom HIV-1 infection and double infection via direct and cell-mediated pathways. Proc Natl Acad Sci USA 101:632–637

Day J, Friedman A, Schlesinger LS (2009) Modeling the immune rheostat of macrophages in the lung in response to infection. PNAS 106:11246–11251

Forshey BM, von Schwedler U, Sundquist WI, Aiken C (2002) Formation of a human immunodeficiency virus type 1 core of optimal stability is crucial for viral replication. J Virol 76:5667–5677

Goodenow MM, Rose SL, Tuttle DL, Sleasman JW (2003) HIV-1 fitness and macrophages. J Leukocyte Biol 74:657–666

Henrickson SE et al (2008) T cell sensing of antigen dose governs interactive behavior with dendritic cells and sets a threshold for T cell activation. Nat Immunol 9:282–291

Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M (1995) Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 373:123–126

Janeway C, Murphy KP, Travers P, Walport M (2008) Immuno biology, chap 10, 7th edn. Garland Science, New York

Jolly C, Sattentau QJ (2004) Retroviralspread by induction of virological synapses. Traffic 5:643–650

Jung A, Maier R, Vartanian JP, Bocharov G, Jung V, Fischer U, Meese E, Wain-Hobson S, Meyerhans A (2002) Multiply infected spleen cells in HIV patients. Nature 418:144

Layne SP, Spouse JL, Dembo M (1989) Quantifying the infectivity of HIV. Proc Natl Acad Sci USA 86:4644–4648

Leslie AJ et al (2004) HIV evalution CTL escape mutation and reversion after transmission. Nat Med 10(3):282–289

Levy DN, Aldrovandi GM, Kutsch O, Shaw GM (2004) Dynamics of HIV-1 recombination in its natural target cells. Proc Natl Acad Sci USA 101:4204–4209

Lu W, Arraes LC, Ferreira WT, Andrieu JM (2004) Therapeutic dendritic-cell vaccine for chronic HIV-1 infection. Nat Med 10:1359–1365

Luzyanina T, Engelborghs K, Ehl S, Klenerman P, Bocharov G (2001) Low level viral persistence after infection with LCMV: a quantitative insight through numerical bifurcation analysis. Math Biosci 173:1–23

Mempel TR, Henrickson SE, von Andrian UH (2004) T-cell priming by dendritic cells in lymph nodes occurs in three distinct phases. Nature 427:154–159

Merrill S (1987) AIDS: background and the dynamics of the decline of immunocompetence. In: Perelson AS (ed) Theoretical immunology, part 2. Addison-Wesley, Redwood City, pp 59–75

Pedersen AE, Ronchese F (2007) CTLA-4 blockade during dendritic cell based booster vaccination influences dendritic cell survival and CTL expansion. J Immune Based Ther Vaccines 5:9

Perelson AS, De Boer R (1993) Dynamics of HIV infection of CD4+ T cells. Math Biosci 114:81–125

Perelson AS, Nelson PW (1999) Mathematical analysis of HIV-1: dynamics in vivo. SIAM Rev 41:3–44

Picado JM et al (2006) Fitness cost of escape mutation in p24 Gag in association with control of human immunodeficiency virus type 1. J Virol 80(7):3617–3623

Plymale DR, Tang DS, Comardelle AM, Fermin CD, Lewis DE, Garry RF (1999) Both necrosis and apoptosis contribute to HIV-1-induced killing of CD4 cells. AIDS 13:1827–1839

Richman DD, Wrin T, Little SJ, Petropoulos CJ (2003) Rapid evolution of the neutralizing antibody response to HIV type 1 infection. Proc Natl Acad Sci USA 100:4144–4149

Routy JP, Nicolette C (2010) Arcelis (TM) AGS-004 dendritic cell-based immunotherapy for HIV infection. Immunotherapy 2:467–476

Sattentau Q (2008) Avoiding the void: cell-to-cell spread of human viruses. Nat Rev Microbiol 6:815–826

Skokos D et al (2007) Peptide-MHC potency governs dynamic interactions between T cells and dendritic cells in lymph nodes. Nat Immunol 8:835–844

Stoll S, Delon J, Brotz TM, Germain RN (2002) Dynamic imaging of T cell-dendritic cell interactions in lymph nodes. Science 296:1873–1876

Traulsen A, Pacheco JM, Imhof LA (2006) Stochasticity and evolutionary stability. Phys Rev E 74:021905

Wick D, Self SG (2004) On simulating strongly interacting, stochastic population models. II. Multiple compartments. Math Biosci 190:127–143

Wodarz D, Levy D (2009) Multiple HIV-1 infection of cells and the evolutionary dynamics of cytotoxic T lymphocyte escape mutants. Evolution 63:2326–2339

Wu Y, Xia LJ, Zhang MJ, Zhao XP (2010) Immunodominance analysis through interactions of CD8+ T cells and DCs in lymph nodes. Math Biosci 225:53–58