Journal of Theoretical Biology 304 (2012) 143–151

Contents lists available at SciVerse ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Infection of HIV-specific CD4 T helper cells and the clonal composition of the response

Sarah M. Roy, Dominik Wodarz *

Department of Ecology and Evolutionary Biology, 321 Steinhaus Hall, University of California, Irvine, CA 92697, USA

ARTICLE INFO

Article history:
Received 12 October 2011
Received in revised form
13 March 2012
Accepted 14 March 2012
Available online 30 March 2012

Keywords:
Helper T cells
Mathematical models
Virus dynamics
Apparent competition

ABSTRACT

A hallmark of human immunodeficiency virus is its ability to infect CD4+ T helper cells, thus impairing helper cell responses and consequently effector responses whose maintenance depends on help (such as killer T cells and B cells). In particular, the virus has been shown to infect HIV-specific helper cells preferentially. Using mathematical models, we investigate the consequence of this assumption for the basic dynamics between HIV and its target cells, assuming the existence of two independently regulated helper cell clones, directed against different epitopes of the virus. In contrast to previous studies, we examine a relatively simple scenario, only concentrating on the interactions between the virus and its target cells, not taking into account any helper-dependent effector responses. Further, there is no direct competition for space or antigenic stimulation in the model. Yet, a set of interesting outcomes is observed that provide further insights into factors that shape helper cell responses. Despite the absence of competition, a stronger helper cell clone can still exclude a weaker one because the two clones are infected by the same pathogen, an ecological concept called "apparent competition". Moreover, we also observe "facilitation": if one of the helper cell clones is too weak to become established in isolation, the presence of a stronger clone can provide enhanced antigenic stimulation, thus allowing the weaker clone to persist. The dependencies of these outcomes on parameters is explored. Factors that reduce viral infectivity and increase the death rate of infected cells promote coexistence, which is in agreement with the observation that stronger immunity correlates with broader helper cell responses. The basic model is extended to explicitly take into account helper-dependent CTL responses and direct competition. This study sheds further light onto the factors that can influence the clonal composition of HIV-specific helper cell responses, which has implications for the overall pattern of disease progression.

1. Introduction

Human immunodeficiency virus-1 (HIV-1) infection typically progresses through three phases: the acute phase in which extensive initial virus growth is observed that is eventually down-regulated; the chronic or asymptomatic phase during which virus load remains relatively low and the patient appears healthy; and the AIDS phase during which virus load rises sharply and destroys the CD4 T helper cell population to a degree at which the immune system effectively ceases to function. The dynamics between HIV-1 replication and immune responses has been subject to much research, both experimentally and mathematically (Douek et al., 2003; Nowak and May, 2000; Perelson, 2002; Simon and Ho, 2003). This has provided many insights not only into patterns of disease progression but also into aspects of therapy. A characteristic that sets HIV infection apart from many other viral infections is the ability of the virus to impair not only the immune system as a whole, but also HIV-specific immune responses in particular (Kalams and Walker, 1998; Rosenberg and Walker, 1998; Rosenberg et al., 1997, 2000). Moreover, the ability of HIV to evolve rapidly in vivo (Ho et al., 1995; Mansky and Temin, 1995; Nowak, 1990; Wei et al., 1995) allows the virus to escape immune responses that are mounted by the patient (Goulder and Walker, 1999; Goulder et al., 1997, 2001; Klenerman et al., 2000; McMichael and Phillips, 1997; Phillips et al., 1991; Price et al., 1997). These aspects significantly contribute to the inability of the immune response to control the infection in the long term, eventually leading to uncontrolled viral replication and the development of AIDS.

HIV-1 infects a variety of cell types, including CD4+ helper T cells, macrophages, and dendritic cells, all of which play central roles in the establishment of immune effector responses, such as cytotoxic T lymphocyte (CTL) and B cell responses. Infection of these cells is the basis for virus-induced immune impairment, the dynamics of which has been analyzed in detail mathematically

* Corresponding author: Tel.: +1 949 824 2531; fax: +1 949 824 2181.
E-mail address: dwodarz@uci.edu (D. Wodarz).

0022-5193/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jtbi.2012.03.015

and experimentally (El-Far et al., 2008; Kalams and Walker, 1998; Komarova et al., 2003; Korthals Altes et al., 2003; Lifson et al., 2000; McLean and Kirkwood, 1990; Moir et al., 2011; Rosenberg and Walker, 1998; Rosenberg et al., 1997, 1999, 2000; Wodarz and Nowak, 1999; Wodarz and Jansen, 2001; Wodarz and Hamer, 2007; Wodarz et al., 2000). Experiments have shown that HIV-specific helper cell infection not only occurs, but occurs preferentially over infection of T cells with other specificities (Douek et al., 2002, 2003). This makes intuitive sense because HIV-specific T cells are likely to be abundant in anatomical areas that contain HIV-infected cells, allowing transmission to occur not only via free virus, but also from cell to cell through virological synapses (Hubner et al., 2009).

This study extends previous work and examines the dynamics of virus replication in HIV-specific helper T cell responses assuming the existence of two helper cell clones rather than one. We examine the consequences of HIV-specific helper cell infection for the dynamics and the clonal composition of the helper cell response in the simplest setting, assuming no competition between the helper cell clones and the absence of helper-dependent effector responses. Interestingly, the model suggests that even in this simple setting, relatively complex dynamics are observed that can shape the early composition of the HIV-specific T helper cell response and that can therefore have lasting consequences for progression of the disease (Lifson et al., 1997). The effect of competition between helper cell clones and the presence of helper-dependent effector responses are subsequently studied in extensions of the basic model.

2. Basic dynamics of HIV-specific helper cell infection

We discuss a basic model that describes HIV dynamics in HIV-specific CD4+ T helper cells, assuming only a single helper cell population. This will form the basis for a more complex model that takes into account two helper cell clones, directed against different epitopes of the virus. Besides the specific helper cells, the model also takes into account an alternative target cell population, which can include non-specific helper cells as well as macrophages and dendritic cells. We denote uninfected and infected non-specific target cells by S and I, respectively. Uninfected and infected specific helper cells are denoted by x and y, respectively. The free virus population is denoted by v. The model is given by the following set of ordinary differential equations that describe the average time course of the infection:

$$\begin{aligned}
\frac{dx}{dt} &= \frac{rxv(\gamma+\epsilon)(\gamma+\eta)}{(x+y+\epsilon)(v+\eta)} - dx - \beta xv \\
\frac{dy}{dt} &= \beta xv - ay \\
\frac{dS}{dt} &= \lambda - d_{ns}S - \beta_{ns}Sv \\
\frac{dI}{dt} &= \beta_{ns}Sv - a_{ns}I \\
\frac{dv}{dt} &= ky + k_{ns}I - uv
\end{aligned} \tag{1}$$

The HIV specific helper cells proliferate upon contact with virus with a rate r. While at relatively low virus load, the T cell proliferation rate is proportional to the amount of virus, v, this dependency saturates at higher virus loads. Further, the T cell proliferation term saturates as the overall number of specific T cells $(x+y)$ grows, implying a regulatory mechanism that prevents unbounded growth of the immune response. The degree of saturation is given by the parameters ε and η. They also appear in the numerator of the expression such that large values of ε and η do not reduce the proliferation term and require rescaling of r. Upon contact with virus, the specific helper cells become infected with a rate β, and infected helper cells die with a rate a. Non-specific target cells are produced with a rate λ, die with a rate d_{ns}, and become infected upon contact with virus at a rate β_{ns}. Infected non-specific cells die with a rate a_{ns}. Virus is produced by specific and non-specific infected cells with a rate k and k_{ns}, respectively. Finally, free virus decays with a rate u. In this notation, the subscript "ns" stands for non-specific.

Note that the model is phenomenological in nature, describing complex biological processes with relatively simple terms. As mentioned above, the non-specific target cell population contains a group of cells consisting of T cells, dendritic cells and macrophages. In the equations, they are assumed to be produced with a constant rate λ. This might be a correct assumption in general, but T cells are also likely to undergo cell divisions, which is not captured in the model. Hence, the rate λ should be considered to be a general input term and it is difficult to relate it to a particular process, the kinetics of which could be measured. On the other hand, the equation for the specific T cells ignores a constant production term assuming that significant increases in this population are driven mainly by antigen-induced cell division, as has been done in previous immune response models (Antia et al., 2005; Nowak and May, 2000; Wodarz, 2006). A production term can significantly impact the dynamics if the number of immune cells is very low, further explored in Fig. 2.

This model is very similar to previous work that incorporated HIV-specific helper cells into mathematical models of HIV infection (Wodarz and Hamer, 2007). Specifically, their model only differed in the term that describes the proliferation of HIV-specific T cells, which was still antigen-driven, but limited through logistic growth. This was altered in the current study to include the more realistic assumption of saturated T cell proliferation. The paper by Wodarz and Hamer (2007) also considered antigen-driven expansion of infected HIV-specific helper cells. This was not included in the current model because its relevance is unclear given the relative short life-span of infected cells. Additionally, including this assumptions leads to biologically dubious outcomes, such as 100% prevalence of the virus in the T helper cell population (Wodarz and Hamer, 2007).

Model properties are summarized as follows. Because of the strong similarity of this model and its properties to the one analyzed in Wodarz and Hamer (2007), this section is designed to be more of an overview than a full analysis. For details, the reader is referred to Wodarz and Hamer (2007). The outcomes of the model include failure to establish a virus infection; successful infection in the absence of a specific helper cell response; and establishment of infection in the presence of specific helper cells. It is useful to define the basic reproductive ratio of the virus (Nowak and May, 2000) in the non-specific target cells only, given by $R_0 = \lambda\beta_{ns}k_{ns}/d_{ns}a_{ns}u$. If $R_0 > 1$, then the virus can establish an infection in the non-specific target cells alone and can therefore persist. If the T cell response does not become established, the system converges to the following equilibrium:

$$S^* = \frac{ua_{ns}}{\beta_{ns}k_{ns}}, \quad I^* = \frac{\lambda\beta_{ns}k_{ns} - d_{ns}a_{ns}u}{\beta_{ns}k_{ns}a_{ns}}, \quad v^* \frac{\lambda\beta_{ns}k_{ns} - d_{ns}a_{ns}u}{\beta_{ns}a_{ns}u},$$
$$x^* = 0, \quad y^* = 0.$$

On the other hand if the helper cell response does become established the system converges to a different steady state at which all populations are greater than zero. This is given by the solution of a fourth degree polynomial and is thus not written out here.

Whether the specific T cell response is established can depend both on model parameters and on the initial conditions. Since the model does not include a production term for specific helper cells, the initial number of helper cells must be greater than zero for

this population to expand in response to antigenic stimulation. If this is the case, the specific T cell response always becomes established if $((r\nu^*(\gamma+\epsilon)(\gamma+\eta))/(\epsilon(\nu^*+\eta)))-\beta_{ns}\nu^*-d>0$, i.e. if the rate of antigen-induced proliferation is greater than the combination of the natural death rate and virus-induced impairment of the response. This condition is not fulfilled if the amount of stimulating virus, ν^*, either lies below a threshold or above a threshold. If virus load is too low, it is insufficient to stimulate the response. If it is too high, the degree of immune impairment outweighs the degree of antigenic stimulation. This balance between immune stimulation in immune impairment has been described before (e.g. Wodarz et al., 2000; Younes et al., 2007). If the inequality does not hold, the specific helper cell response may or may not become established depending on the initial conditions (Fig. 1). A high initial virus load and a high initial number of specific helper cells can promote establishment of the helper cell response. It generates more infected cells, which in turn can provide higher levels of stimulation, thus leading to positive feedback. This dependence on initial conditions does, however, not occur in the entire parameter region in which the above inequality is not fulfilled. If the rate of helper cell expansion is too weak relative to the rate of loss, then the only outcome is failure of the response. This was determined by numerical simulations, and an analytic condition could not be obtained. This is explored more extensively in the study by Wodarz and Hamer (2007).

Now assume that the basic reproductive ratio of the virus in the non-specific cells alone is less than one ($R_0<1$), i.e. an infection cannot be established in the non-specific cells alone. We observe the same dependence of outcome on initial conditions as before, i.e. a high initial virus load and a high initial helper cell population can lead to the establishment of the infection. In this case, the helper cell response obviously is established, and the virus is present in both specific and non-specific target cells. Again, if the rate of helper cell expansion is too weak relative to the rate of loss, then the infection can never be established.

We note that the cases in which the establishment of the specific helper cell response depends on the initial conditions (beyond the trivial requirement that $x_0>0$) are not likely to be biologically realistic. It requires that the majority of virus replication occurs in specific helper cells rather than in non-specific target cells. In reality, however, infected specific helper cells make up about 1–10% of all infected cells in the blood (Douek et al., 2002), and the non-specific helper cells are thought to act in part as reservoirs that contribute to the maintenance of the virus in the host. Because the described dynamics are a property of the model, however, they are still important to discuss, and Fig. 1 does not rely on any measured parameters and is shown for illustrative purposes only.

While these insights are conceptually not novel (Wodarz and Hamer, 2007), this model provides the foundation for incorporating two specific helper cell clones in which the virus can replicate, described in the following section.

3. Infection dynamics in two helper cell clones

Here, we add a second helper cell clone to the model, directed against a different viral epitope. We denote clone 1 by subscript 1, and clone two by subscript 2. It is assumed that the two clones only differ in their proliferation rates, r_1 and r_2. The equations thus become

$$\frac{dx_1}{dt}=\frac{r_1x_1\nu(\gamma+\epsilon)(\gamma+\eta)}{(x_1+y_1+\epsilon)(\nu+\eta)}-dx_1-\beta x_1\nu$$

$$\frac{dy_1}{dt}=\beta x_1\nu-ay_1$$

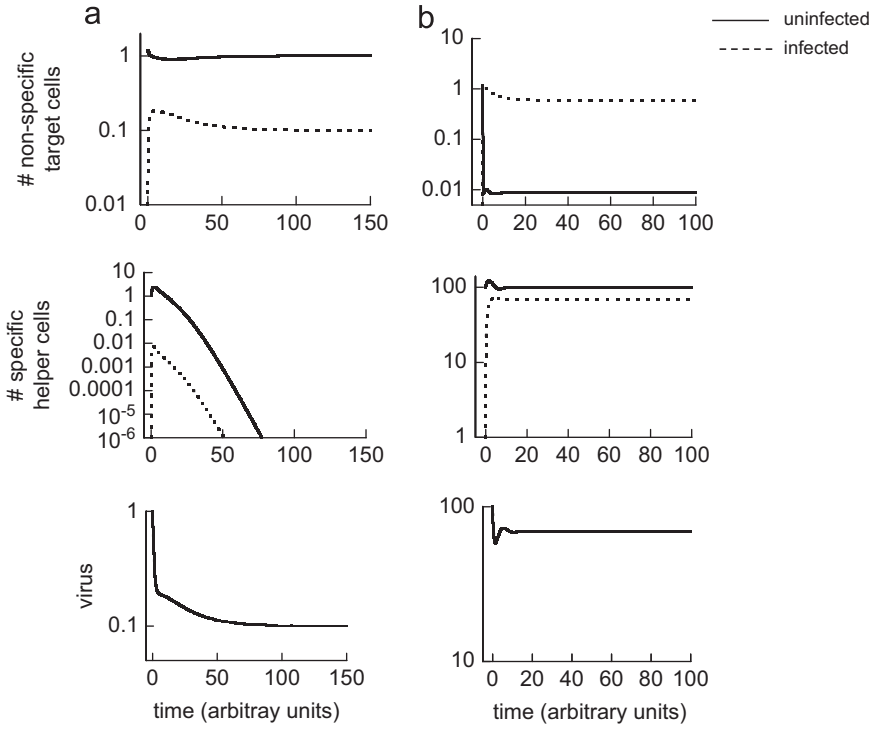

Fig. 1. Properties of model (1) assuming a single helper cell clone, demonstrating the dependence of the outcome on initial conditions. (a) Simulations are started with a low initial virus load and a low initial number of virus-specific helper cells, leading to the extinction of the specific helper cell response. (b) Simulations are started with a high initial virus load and a high initial number of virus-specific helper cells, leading to the persistence of the specific helper cell response. Note, this we consider this outcome biologically unrealistic because it requires most infected cells to be specific helper cells. Nevertheless, it is explored for completeness and parameters are chosen arbitrarily for illustrative purposes: $\beta=0.01$; $d=0.5$; $a=1$; $r=2$; $\varepsilon=10$; $\eta=10$; $\gamma=1$; $k=1$; $u=1$; $\beta_{ns}=0.2$; $\lambda=0.12$; $d_{ns}=0.1$; $a_{ns}=0.2$ $k_{ns}=1$. $S(0)=\lambda/d_{ns}$; $I(0)=0$; $y(0)=0$. (a) $x(0)=1$; $\nu(0)=1$ and (b) $x(0)=100$; $\nu(0)=100$.

$$\frac{dx_2}{dt} = \frac{r_2 x_2 v(\gamma+\epsilon)(\gamma+\eta)}{(x_2+y_2+\epsilon)(v+\eta)} - dx_2 - \beta x_2 v$$
$$\frac{dy_2}{dt} = \beta x_2 v - a y_2$$
$$\frac{dS}{dt} = \lambda - d_{ns} S - \beta_{ns} S v$$
$$\frac{dI}{dt} = \beta_{ns} S v - a_{ns} y$$
$$\frac{dv}{dt} = k(y_1+y_2) + k_{ns} I - uv \quad (2)$$

In this section, it is assumed that the two immune cell clones are not in any type of direct competition with each other. The rate of helper cell proliferation only saturates with the number of helper cells belonging to the same clone, and not all specific helper cells in the system. The two clones are therefore regulated independently. The clones also do not compete through immune-mediated suppression of virus load because our model does not include helper-induced effector responses. (In many models that include effector responses, one effector clone can suppress virus load to levels that are too low to stimulate other clones, leading to competitive exclusion.) The reason for this assumption is that we seek to examine the effects of specific helper cell infection in the absence of further complicating factors. The impact of direct competition and effector responses will be explored below.

The model properties were studied largely by numerical simulations. It will be assumed that the basic reproductive ratio of the virus in the non-specific target cells alone is greater than one, ensuring the establishment of a successful infection in this system. Furthermore, we assume that each helper cell clone in isolation can become established without dependence on initial population sizes (except zero), the conditions for which were discussed in the last section. Under these assumptions, two outcomes are observed (Fig. 2): (i) both helper cell clones become established. (ii) One of the helper cell clones becomes established, while the other one goes extinct. The persisting clone is the stronger one, i.e. its net rate of expansion is faster. This exclusion occurs in the absence of any competitive interactions. The reason is that the two helper cell clones are infected by a common virus population. This leads to the phenomenon of "apparent competition" (Holt, 1977), in which the stronger helper cell clone produces an amount of virus that is too high for the weaker clone to survive.

To make sure that these dynamics are not at odds with established quantitative parameters of HIV infection, the simulation in Fig. 2 was run taking into account the two most established parameter measurements (Perelson et al., 1996): an average infected cell life span of 2.2 days, and an average life-span of plasma virions of 0.3 days. The rest of the parameters, while largely uncertain, were selected such that the percentage of infected specific helper cells lies within the observed range of 1–10% (Douek et al., 2002) (Fig. 2). Because the non-specific target cell population encompasses several different cell types, some of which can be characterized by a relatively long life-span when infected, an overall life-span of 5 days was assigned to this population. This is necessarily arbitrary, but aims to capture the existence of both shorter lived infected T cells and the longer lived infected antigen-presenting cells in this population.

Fig. 3a shows how the outcome depends both on the rate of helper cell infection, β, and the death rate of infected cells, a. The base-line parameter values for this plot are taken from Fig. 2 and are thus within biologically realistic ranges. A lower rate of helper cell infection and a higher death rate of infected cells promotes coexistence of both responses rather than exclusion. If these two parameters are influenced by immune effector responses of any kind, it can be interpreted to mean that stronger virus

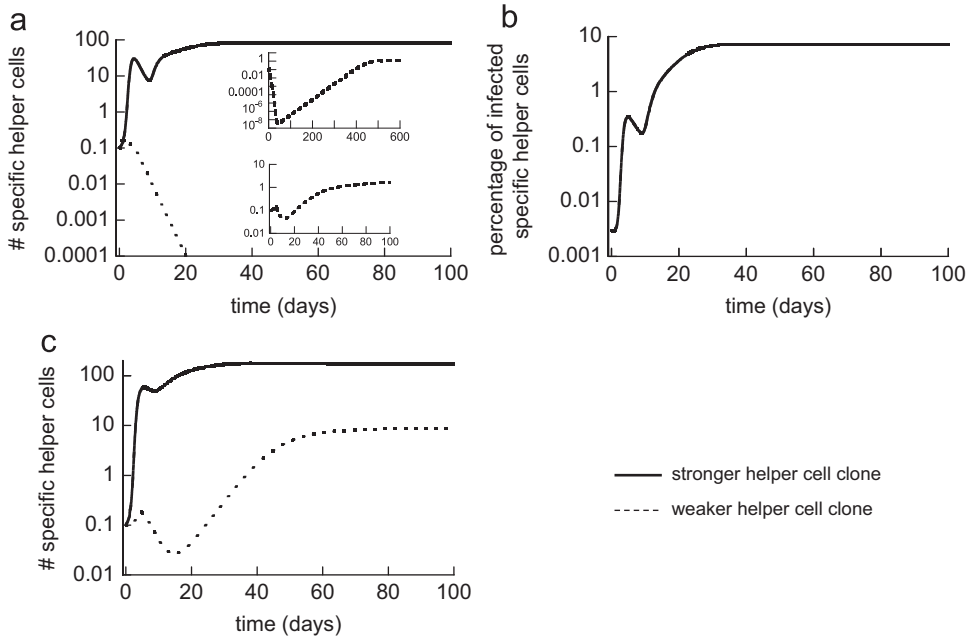

Fig. 2. Outcomes of model (2) assuming the presence of two virus-specific helper cell responses that are regulated independently. (a) Only one clone, the stronger one, persists. The other clone goes extinct, although it would persist in isolation (see inset). In the inset, two graphs are given. The upper graph plots the weaker helper cell response using a model without a production term for specific helper cells. Initial virus replication severely impairs the helper cell response before it settles at a steady state. The drop of this population to such low levels is likely to be unrealistic because at these low numbers, a production term can significantly influence the dynamics. In reality, the helper cell population cannot fall much below the naïve base-line levels. The lower graph displays the same simulation with a constant production term $\xi=0.01$ day^{-1} vol^{-1}. (b) This graph shows the percentage of infected specific helper cells among all infected cells, corresponding to the simulation presented in part (a). (c) In this simulation, both helper cell clones coexist. For all cases, simulations can be performed for different tissue compartments or blood. In each case, the appropriate unit volume (vol) should be chosen to measure cell/viral densities. Parameters were chosen as follows. (a) $\beta=0.015$ day^{-1} vol; $d=0.1$ day^{-1}; $a=0.45$ day^{-1}; $r_1=0.5$ day^{-1}; $r_2=0.05$ day^{-1}; $\varepsilon=10$ vol^{-1}; $\eta=10$ vol^{-1}; $\gamma=1$ vol^{-1}; $k=1$ day^{-1}; $u=3.33$ day^{-1}; $\beta_{ns}=0.01$ day^{-1} vol; $\lambda=100$ day^{-1} vol^{-1}; $d_{ns}=0.01$ day^{-1}; $a_{ns}=0.2$ day^{-1}; $k_{ns}=0.1$ day^{-1}. $S(0)=\lambda/d_{ns}$; $I(0)=0.1$; $x_1(0)=0.1$; $y_1(0)=0$; $x_2(0)=0.1$; $y_2(0)=0$; $v(0)=1$. (b) Same, except $\beta=0.005$ day^{-1} vol.

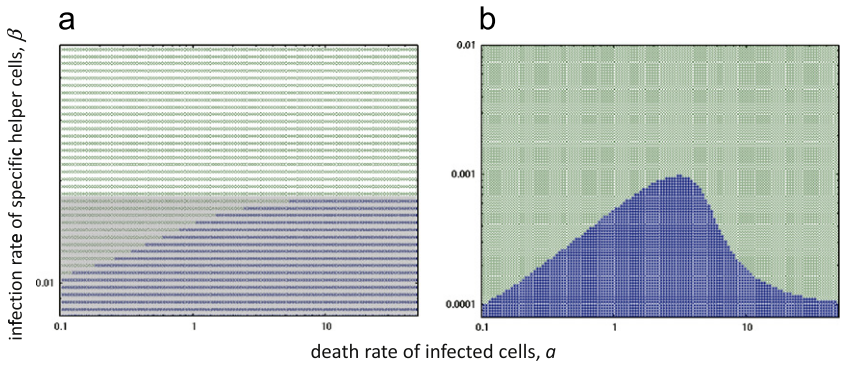

Fig. 3. Outcomes of model (2) depending on the death rate of infected cells, a, and the infection rate of specific helper cells, β. Blue indicates coexistence and green indicates persistence of only the stronger clone. (a) The shaded area indicates the parameter region in which the weaker clone persists in isolation. A lower death rate of infected cells and a higher infection rate of specific helper cells promotes exclusion through apparent competition. When the infection rate of specific helper cells lies above a threshold (above the shaded area), then the weaker helper cell clone never persists, even in isolation. If the infection rate of specific helper cells crosses another threshold, both helper cell populations go extinct (not shown). (b) In contrast to part (a), this plot assumes that the weaker helper cell clone cannot persist in isolation in the parameter region under consideration. In this case, a stronger helper cell clone can facilitate the maintenance of the weaker clone. This occurs for intermediate death rate of infected specific helper cells. If the infection rate of specific helper cells becomes too large this is not possible anymore because the net expansion rate of the weaker helper cell clone becomes too small. If the infection rate of specific helper cells is increased further, both helper cell clones go extinct (not shown). Base-line parameters were chosen as follows. (a) $d=0.1\ \text{day}^{-1}$; $r_1=0.5\ \text{day}^{-1}$; $r_2=0.05\ \text{day}^{-1}$; $\varepsilon=10\ \text{vol}^{-1}$; $\eta=10\ \text{vol}^{-1}$; $\gamma=1\ \text{vol}^{-1}$; $k=1\ \text{day}^{-1}$; $u=3.33\ \text{day}^{-1}$; $\beta_{ns}=0.01\ \text{day}^{-1}\ \text{vol}$; $\lambda=100\ \text{day}^{-1}\ \text{vol}^{-1}$; $d_{ns}=0.01\ \text{day}^{-1}$; $a_{ns}=0.2\ \text{day}^{-1}$; $k_{ns}=0.1\ \text{day}^{-1}$. (b) Same, except $r_1=8\ \text{day}^{-1}$; $r_2=0.014\ \text{day}^{-1}$. Initial conditions were as follows. Upon introduction of the weaker clone, the system was at the equilibrium describing persistence of the stronger clone alone (given this equilibrium was stable, as determined numerically). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

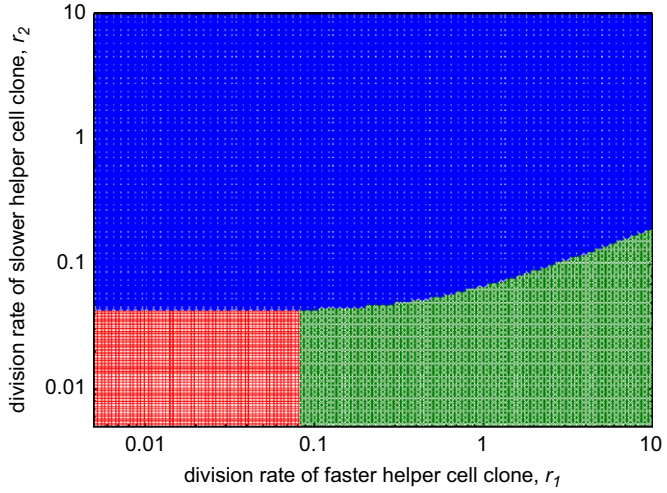

Fig. 4. Outcomes of model (2) depending on the antigen-induced growth rate of the stronger (r_1) and the weaker (r_2) helper cell clone. Blue indicates coexistence; green indicates persistence of only the stronger clone; red indicates extinction of both clones. Base-line parameters were chosen as follows. $\beta=0.015\ \text{day}^{-1}\ \text{vol}$; $d=0.1\ \text{day}^{-1}$; $a=0.45\ \text{day}^{-1}$; $\varepsilon=10\ \text{vol}^{-1}$; $\eta=10\ \text{vol}^{-1}$; $\gamma=1\ \text{vol}^{-1}$; $k=1\ \text{day}^{-1}$; $u=3.33\ \text{day}^{-1}$; $\beta_{ns}=0.01\ \text{day}^{-1}\ \text{vol}$; $\lambda=100\ \text{day}^{-1}\ \text{vol}^{-1}$; $d_{ns}=0.01\ \text{day}^{-1}$; $a_{ns}=0.2\ \text{day}^{-1}$; $k_{ns}=0.1\ \text{day}^{-1}$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

suppression leads to coexistence of the helper cell clones, while less efficient virus suppression leads to the exclusion outcome. The region in which exclusion of one clone is observed varies, depending on the uncertain parameter values. In particular, the relative rates of antigen driven T cell proliferation, r_1 and r_2, play an important role, which is shown in Fig. 4. If the proliferation rate of the weaker clone, r_2, lies above a threshold relative to the value of r_1, coexistence is observed, otherwise, exclusion occurs. The higher the value of r_1, the higher the value of r_2 needs to be to ensure coexistence. Other parameters can also affect the outcomes, although some of them are biologically difficult to interpret, such as the saturation terms used in the model.

So far, we have assumed that each individual helper cell clone can establish a response in isolation. Now, we assume that only one of the helper cell clones can establish a response in isolation, and that the other one is too weak to persist. In this case, we observe a parameter region in which the presence of the stronger clone enables the weaker clone to persist as well, leading to coexistence (Fig. 3b, again using the base-line parameters from Fig. 2). The presence of the stronger clone allows additional infection to occur, and this boosts virus load to sufficient levels to also successfully stimulate the weaker clone. Hence, in this scenario, a cooperative effect occurs. This is observed for intermediate rates of infected cell death. If the death rate of infected cells is too high, not enough virus is produced by the stronger clone to maintain the weaker clone. If the death rate of infected cells is sufficiently low, too much virus is produced by the stronger clone, such that the degree of impairment outweighs the degree of stimulation of the weaker clone. Similarly, the degree of immune impairment is too strong for the weaker clone to persist if the infection rate of specific helper cells lies above a threshold. On the other hand, if the infection rate of helper cells lies below a threshold, then the weaker clone can already persist alone without the need for the stronger clone because the degree of immune impairment is relatively weak. In general, to observe this behavior, the weaker clone must be unable to persist in isolation, and the stronger clone must provide sufficient virus for antigenic stimulation, but not too much virus to avoid significant impairment.

4. Effect of direct competition

So far we have assumed that each clone is regulated separately, i.e. that they do not directly compete in any way. This was done because the occurrence of competition among immune cell clones is controversial (Fryer et al., 2009; Kastenmuller et al., 2007) and we aimed to show that even in the absence of competition, similar outcomes can be observed through indirect effects. Here, we include direct competition into the model and explore the outcomes. The model is now given by the following set of ordinary differential equations:

$$\frac{dx_1}{dt}=\frac{r_1x_1v(\gamma+\epsilon)(\gamma+\eta)}{(x_1+y_1+x_2+y_2+\epsilon)(v+\eta)}-dx_1-\beta x_1v$$

$$\frac{dy_1}{dt} = \beta x_1 v - a y_1$$
$$\frac{dx_2}{dt} = \frac{r_2 x_2 v(\gamma+\epsilon)(\gamma+\eta)}{(x_1+y_1+x_2+y_2+\epsilon)(v+\eta)} - d x_2 - \beta x_2 v$$
$$\frac{dy_2}{dt} = \beta x_2 v - a y_2$$
$$\frac{dS}{dt} = \lambda - d_{ns} S - \beta_{ns} S v$$
$$\frac{dI}{dt} = \beta_{ns} S v - a_{ns} y$$
$$\frac{dv}{dt} = k(y_1+y_2) + k_{ns} I - u v \quad (3)$$

Direct competition is expressed in the saturation term of helper cell proliferation. In the previous model, proliferation of a particular clone only saturated when the number of cells belonging to that clone rose to higher levels. In the current model, saturation is determined by the total number of specific helper cells, belonging to either clone ($x_1+y_1+x_2+y_2$). In contrast to the previous model (2), this formulation is characterized only by one outcome: persistence of one specific helper cell clone and extinction of the other. The clone with the larger net rate of expansion persists. This is not surprising because the two clones are in direct competition with each other with no degree of niche separation.

5. Effector responses

So far, we have considered the dynamics of virus infection in specific helper cells in the absence of any effector responses, such as cytotoxic T lymphocyte (CTL) or B cell responses, although the helper cell responses promote the development of the effector responses, which in turn can suppress the virus population. The reason for this omission is that we wanted to see how the basic dynamics between HIV and the specific helper cells can influence the clonal composition of the helper cell response without adding further components to the model with uncertain biological assumptions. It is thought that a broad helper cell response promotes better virus control, presumably through the induction of effector responses. The nature of the relationship between the breadth of the helper cell response and the quality and breadth of the CTL response, however, remain unknown, and conflicting experimental data have been reported (Chouquet et al., 2002; Feeney et al., 2004; Karlsson et al., 2007; Rolland et al., 2008). In this section, we aim to show that indirect interactions can still shape the clonality of the helper cell response if a helper-dependent effector response is added to the model. As an example, we consider CTL, denoted by C. Modifying model (2) leads to the following equations:

$$\frac{dx_1}{dt} = \frac{r_1 x_1 v(\gamma+\epsilon)(\gamma+\eta)}{(x_1+y_1+\epsilon)(v+\eta)} - d x_1 - \beta x_1 v$$
$$\frac{dy_1}{dt} = \beta x_1 v - a y_1 - p y_1 C$$
$$\frac{dx_2}{dt} = \frac{r_2 x_2 v(\gamma+\epsilon)(\gamma+\eta)}{(x_2+y_2+\epsilon)(v+\eta)} - d x_2 - \beta x_2 v$$
$$\frac{dy_2}{dt} = \beta x_2 v - a y_2 - p y_2 C$$
$$\frac{dS}{dt} = \lambda - d_{ns} S - \beta_{ns} S v$$
$$\frac{dI}{dt} = \beta_{ns} S v - a_{ns} y - pIC$$
$$\frac{dv}{dt} = k(y_1+y_2) + k_{ns} I - u v$$
$$\frac{dC}{dt} = \frac{g(x_1+x_2)(y_1+y_2+I)}{qC+1} - bC \quad (4)$$

The rate of CTL expansion depends both on the presence of uninfected specific helper cells (x_1+x_2) and the presence of infected cells (y_1+y_2+I). Infected helper cells are assumed to be compromised. Both helper cell clones can promote CTL expansion. Helper cells are thought to activate CTL indirectly via the activation of professional antigen presenting cells. Hence, a helper cell clone of a given specificity need not just promote one specific CTL clone, but can promote the rise of different CTL responses. In the absence of stimulation, the CTL die with a rate b. This is a phenomenological model and could be formulated in a number of different ways with a number of different assumptions. Some models of CTL dynamics assume the rate of expansion to be proportional to the number of CTL, which leads to a stronger expansion term and significantly less stable dynamics. For the current context, we have kept the model to a simple form, assuming that upon interaction with antigen and helper cells, the specific CTL population rises, presumably through an induced proliferation program, and acquires effector activity. Due to the phenomenological nature of the model, details of the CTL differentiation pathway have not been taken into account. The CTL are assumed to have both lytic and non-lytic activity. They lyse infected cells with a rate p and they inhibit the rate of virus production by infected cells with a rate q.

In this model, exclusion of one helper cell clone via indirect interactions is still observed. We thus explored the dependence of the model outcome on CTL parameters. Fig. 5 shows how the outcome depends on the strength of the lytic and non-lytic effector mechanisms and the rate of CTL expansion and death. The simulations are again based on the available parameter estimates used thus far. Increasing the rate of lytic or non-lytic effector activity (i.e. increasing the values of p and q, Fig. 5a) leads to a reduction in the amount of virus and the number of infected cells. If these rates of effector activity lie below a threshold, then apparent competition can lead to the exclusion of the weaker helper cell clone. The square in the graph indicates a sample parameter combination where we checked for biological realism. The infected specific helper cells make up about 8% of the total infected cell population, consistent with observed ranges (Douek et al., 2002). In addition, CTL-mediated lysis contributes between 9% and 18% of total infected cell death, depending on the cell type under consideration, an order of magnitude that is consistent with previously obtained parameter estimate ranges (Asquith et al., 2006). Once the rate of effector activity crosses a threshold, exclusion does not occur anymore and the two helper cell clones coexist. This result is directly analogous to the result in Fig. 3a, where a reduction in the viral replication kinetics and an increase in the death rate of infected cells (parameters that are essentially altered by non-lytic and lytic CTL effector mechanisms, respectively) promoted coexistence rather than exclusion. Finally, if the rates of CTL-mediated effector activities are higher and lie above a threshold, the weaker helper cell clone again goes extinct and only the stronger clone persists. However, the mechanism is not apparent competition in this case. Strong immunity suppresses virus load (arising from all cell types) to levels that are simply too low to stimulate the weaker clone. If the rate of CTL-mediated effector activity was increased further, virus load would become too low to even stimulate the stronger helper cell clone, which, however, is not shown in Fig. 5a. As shown in Fig. 5b, similar trends are observed for the parameters that describe the rate of CTL proliferation, g, and the rate of CTL death, b. The higher the value of g and the lower the value of b, the stronger the degree of virus suppression and the lower virus load becomes. Lower degrees of virus suppression lead to exclusion of the weaker helper cell clone through apparent competition. Increasing the degree of virus suppression leads to coexistence, and a further increase in the degree of virus suppression results in levels of

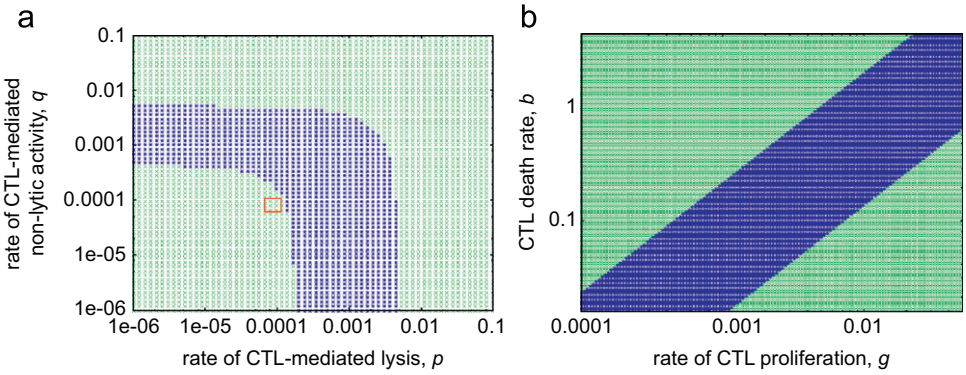

Fig. 5. Outcomes of model (4) depending on CTL parameters. Blue indicates coexistence; green indicates persistence of only the stronger clone. (a) Dependence on the rate of lytic, p, and non-lytic, q, effector activity. The red square indicates a parameter regime where apparent competition leads to the exclusion of the weaker helper cell clone. In this region, the specific infected helper cells make up about 8% of the total infected cell population, and CTL-mediated lysis contributes between 9% and 18% to the death rate of the infected cells. (b) Dependence on the rate of CTL proliferation, g, and the death rate of CTL, b. Base-line parameters were chosen as follows. $\beta=0.015$ day^{-1} vol; $d=0.1$ day^{-1}; $a=0.45$ day^{-1}; $r_1=0.5$ day^{-1}; $r_2=0.05$ day^{-1}; $\varepsilon=10$ vol^{-1}; $\eta=10$ vol^{-1}; $\gamma=1$ vol^{-1}; $k=1$ day^{-1}; $u=3.33$ day^{-1}; $\beta_{ns}=0.01$ day^{-1} vol; $\lambda=100$ day^{-1} vol^{-1}; $d_{ns}=0.01$ day^{-1}; $a_{ns}=0.2$ day^{-1}; $k_{ns}=0.1$ day^{-1}; $g=0.0002$ day^{-1} vol; $b=0.01$ day^{-1}; $p=0.0003$ day^{-1} vol; $q=0.001$ vol. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

virus load that are too low to stimulate the weaker helper cell clone.

6. Discussion and conclusion

We have investigated the basic dynamics of HIV replication in two helper T cell clones that are specific to HIV. This extends previous work that examined HIV dynamics in a single population of specific helper T cells (Wodarz and Hamer, 2007). It is complementary to another study (Korthals Altes et al., 2003) that also examined HIV dynamics in the presence of polyclonal helper cell responses, but assumed the existence of effector responses that remove the virus population and are directly driven by the specific helper cells. They showed an array of interesting and complex behavior, including multiple steady states that are simultaneously stable. In contrast, our model considers a much simpler scenario. The main model did not take into account helper-dependent effector responses and excluded the possibility for any competition among the helper cell clones. Nevertheless, complex dynamics were observed that included both negative and positive interactions between the helper cell clones through a shared pathogen. On the one hand, a stronger helper cell clone can exclude a weaker one through apparent competition, maintaining an amount of virus that is too high for the weaker clone to persist. On the other hand, a stronger clone can facilitate the establishment of a weaker clone by increasing the amount of antigenic stimulation to levels that are sufficient to ensure expansion of the weaker clone.

Our model set-up is likely to apply best to the initial phase of HIV infection due to the absence of helper-driven effector responses. Effector responses only arise some weeks post infection. In addition, while the exact role of help for effector cells is still debated, there is evidence that acute CTL responses develop without the need for help and that help plays a bigger role in the long-term maintenance of CTL (Borrow et al., 1996; Kaech and Ahmed, 2001; Thomsen et al., 1998; van Stipdonk et al., 2001, 2003). If the dynamics described in this paper apply in the early phases of the infection, this could set the stage for the remaining disease process (Lifson et al., 1997), which is likely to be influenced by the breadth of the remaining HIV-specific helper cells (Rosenberg et al., 1997). According to the model, innate or helper-independent responses that influence the death rate of infected cells and the infection rate of the virus could play a crucial role in this respect. Both a high rate of cell killing and a low infection rate promote coexistence of the different helper cell clones, consistent with the notion that stronger virus suppression leads to broader immune responses (Harrer et al., 1996; Rosenberg et al., 2000). Note that we have shown through an extension of the model that the generation of helper-dependent CTL responses does not alter our main conclusions about the role of indirect interactions for determining the clonal composition of the helper cell response, so in principle, our arguments could be valid in the longer term as well. Stronger CTL-mediated reduction of viral replication kinetics and a higher CTL-mediated death rate of infected cells is predicted to promote coexistence rather than exclusion and thus a broader response. However, it is premature to speculate about the longer term dynamics because the relationship between the nature of the helper cell response, the nature of the CTL response, and the quality of virus control remain too uncertain at this stage.

Exclusion of weaker immune cell clones by stronger ones has been explored with mathematical models in the context of cytotoxic T lymphocyte (CTL) responses. Competition for antigenic stimulation has been a major mechanism by which exclusion, and thus a narrow immune response, was explained (Nowak, 1996; Nowak et al., 1995a, 1995b). In such models, coexistence between different CTL clones is difficult to achieve and has been accounted for by various mechanisms. It can occur through the evolution of antigenic escape mutants that trigger immune responses directed against new epitopes (Nowak, 1996; Nowak et al., 1995a, 1995b). Alternatively, persistence of multiple CTL clones can occur in a non-equilibrium situation in which the lifespan of CTL precursors is sufficiently long such that extinction does not occur within a realistic time frame (Wodarz and Nowak, 2000). Finally, the complex dynamics between polyclonal helper cell responses and helper-driven CTL mentioned above can allow for the persistence of broad responses (Korthals Altes et al., 2003). The difficulty in achieving coexistence of immune cell clones in the context of direct competition is further reflected in our model extension in which both helper cell clones can negatively impact the expansion of either clone. Survival of only one helper cell clone was the only possible outcome under this assumption. The notion that direct competition shapes the dynamics of immune responses remains controversial (Fryer et al., 2009; Kastenmuller et al., 2007). According to our model, however, exclusion can be observed among different HIV-specific helper cell clones even in the absence of any competition, simply as a consequence of the fact that they are infected and killed by the same virus population. This certainly can be a reasonable assumption to make, since

a substantial amount of mixing of cells and viruses occurs in the blood, and even within lymph nodes. In contrast to direct competition, coexistence of the helper cell clones can readily occur.

Obviously, in vivo more than two helper cell clones can arise. The principles explored here, however, would still hold, albeit in a more complex setting. Depending on the exact expansion rates of the different helper cell clones, preliminary simulations (not shown) indicate that all responses can coexist, that one response leads to the exclusion of all others under consideration, or that some of the clones persist while others go extinct. This has not been explored further because consideration of two helper cell clones is sufficient to describe the main results of this study and because further exploration would only make sense once some of the notions explored here have been shown to be relevant in experimental systems.

It is encouraging that the dynamics described here are observed for parameter combinations that are based on empirically measured values for the life-span of infected cells and the decay rate of free virus, and occur in regimes where the percentage of infected specific helper cells lies within measured bounds. On the other hand, a number of uncertainties prevent more quantitatively exact approaches. First, other parameters in our model are unknown. In addition the same biological processes can be described mathematically in a variety of ways, which in turn could potentially influence results. Related to this, our uncertainly about the exact processes that occur during helper cell activation, and the consequently phenomenological nature of the model, provides further difficulties for parameterizing the equations and for providing quantitatively exact predictions. Finally, our model (like most models) does not take into account all aspects of HIV biology that may influence details of the dynamics and the interpretation of parameters. For example, while our model assumes virus spread through cell-free virions, recent evidence indicates that direct cell-to-cell transmission might be as important (Hubner et al., 2009). Moreover, it has to be noted that different micro-environments for HIV replication can be spatially separated. Distinct quasi-species compositions have been observed in different anatomical areas of an HIV-infected patient, and this presents a spatially complex scenario that has not been taken into account in our model (Sala et al., 1994). Such spatial considerations could potentially alter our results, which merits further investigation. Nevertheless, our modeling approach is very valuable because it highlights the key assumptions that lead to the observed dynamics and provides new insights into factors that can determine the clonal composition of helper cell responses, which might have important implications for the overall process of disease progression. A first step towards empirically testing the model predictions would be in vitro experiments that mimic the assumptions of the model and where the individual cell populations can be easily tracked over time, allowing model fitting to the data. The dynamics occurring in vivo are characterized by complications, such as spatially distinct locations where virus replication takes place, which also renders the measurement of the appropriate populations difficult. More theoretical work will be required to analyze such more complex situations and to guide specific experiments.

References

Antia, R., Ganusov, V.V., Ahmed, R., 2005. The role of models in understanding CD8+ T-cell memory. Nat. Rev. Immunol. 5, 101–111.

Asquith, B., Edwards, C.T., Lipsitch, M., McLean, A.R., 2006. Inefficient cytotoxic T lymphocyte-mediated killing of HIV-1-infected cells in vivo. PLoS Biol. 4, e90.

Borrow, P., Tishon, A., Lee, S., Xu, J., Grewal, I.S., Oldstone, M.B., Flavell, R.A., 1996. CD40L-deficient mice show deficits in antiviral immunity and have an impaired memory CD8+ CTL response. J. Exp. Med. 183, 2129–2142.

Chouquet, C., Autran, B., Gomard, E., Bouley, J.M., Calvez, V., Katlama, C., Costagliola, D., Riviere, Y., 2002. Correlation between breadth of memory HIV-specific cytotoxic T cells, viral load and disease progression in HIV infection. AIDS 16, 2399–2407.

Douek, D.C., Picker, L.J., Koup, R.A., 2003. T cell dynamics in HIV-1 infection. Annu. Rev. Immunol. 21, 265–304.

Douek, D.C., Brenchley, J.M., Betts, M.R., Ambrozak, D.R., Hill, B.J., Okamoto, Y., Casazza, J.P., Kuruppu, J., Kunstman, K., Wolinsky, S., Grossman, Z., Dybul, M., Oxenius, A., Price, D.A., Connors, M., Koup, R.A., 2002. HIV preferentially infects HIV-specific CD4+ T cells. Nature 417, 95–98.

El-Far, M., Halwani, R., Said, E., Trautmann, L., Doroudchi, M., Janbazian, L., Fonseca, S., van Grevenynghe, J., Yassine-Diab, B., Sekaly, R.P., Haddad, E.K., 2008. T-cell exhaustion in HIV infection. Curr. HIV/AIDS Rep. 5, 13–19.

Feeney, M.E., Tang, Y., Roosevelt, K.A., Leslie, A.J., McIntosh, K., Karthas, N., Walker, B.D., Goulder, P.J., 2004. Immune escape precedes breakthrough human immunodeficiency virus type 1 viremia and broadening of the cytotoxic T-lymphocyte response in an HLA-B27-positive long-term-nonprogressing child. J. Virol. 78, 8927–8930.

Fryer, H.R., Scherer, A., Oxenius, A., Phillips, R., McLean, A.R., 2009. No evidence for competition between cytotoxic T-lymphocyte responses in HIV-1 infection. Proc. Biol. Sci. 276, 4389–4397.

Goulder, P.J., Walker, B.D., 1999. The great escape—AIDS viruses and immune control. Nat. Med. 5, 1233–1235.

Goulder, P.J., Phillips, R.E., Colbert, R.A., McAdam, S., Ogg, G., Nowak, M.A., Giangrande, P., Luzzi, G., Morgan, B., Edwards, A., McMichael, A.J., Rowland-Jones, S., 1997. Late escape from an immunodominant cytotoxic T-lymphocyte response associated with progression to AIDS. Nat. Med. 3, 212–217.

Goulder, P.J., Brander, C., Tang, Y., Tremblay, C., Colbert, R.A., Addo, M.M., Rosenberg, E.S., Nguyen, T., Allen, R., Trocha, A., Altfeld, M., He, S., Bunce, M., Funkhouser, R., Pelton, S.I., Burchett, S.K., McIntosh, K., Korber, B.T., Walker, B.D., 2001. Evolution and transmission of stable CTL escape mutations in HIV infection. Nature 412, 334–338.

Harrer, T., Harrer, E., Kalams, S.A., Elbeik, T., Staprans, S.I., Feinberg, M.B., Cao, Y., Ho, D.D., Yilma, T., Caliendo, A.M., Johnson, R.P., Buchbinder, S.P., Walker, B.D., 1996. Strong cytotoxic T cell and weak neutralizing antibody responses in a subset of persons with stable nonprogressing HIV type 1 infection. AIDS Res. Hum. Retroviruses 12, 585–592.

Ho, D.D., Neumann, A.U., Perelson, A.S., Chen, W., Leonard, J.M., Markowitz, M., 1995. Rapid turnover of plasma virions and Cd4 lymphocytes in Hiv-1 infection. Nature 373, 123–126.

Holt, R.D., 1977. Predation, apparent competition and the structure of prey communities. Theor. Popul. Biol. 12, 197–229.

Hubner, W., McNerney, G.P., Chen, P., Dale, B.M., Gordon, R.E., Chuang, F.Y., Li, X.D., Asmuth, D.M., Huser, T., Chen, B.K., 2009. Quantitative 3D video microscopy of HIV transfer across T cell virological synapses. Science 323, 1743–1747.

Kaech, S.M., Ahmed, R., 2001. Memory CD8+ T cell differentiation: initial antigen encounter triggers a developmental program in naive cells. Nat. Immunol. 2, 415–422.

Kalams, S.A., Walker, B.D., 1998. The critical need for CD4 help in maintaining effective cytotoxic T lymphocyte responses. J. Exp. Med. 188, 2199–2204.

Karlsson, A.C., Iversen, A.K., Chapman, J.M., de Oliviera, T., Spotts, G., McMichael, A.J., Davenport, M.P., Hecht, F.M., Nixon, D.F., 2007. Sequential broadening of CTL responses in early HIV-1 infection is associated with viral escape. PLoS One 2, e225.

Kastenmuller, W., Gasteiger, G., Gronau, J.H., Baier, R., Ljapoci, R., Busch, D.H., Drexler, I., 2007. Cross-competition of CD8+ T cells shapes the immunodominance hierarchy during boost vaccination. J. Exp. Med. 204, 2187–2198.

Klenerman, P., Lechner, F., Kantzanou, M., Ciurea, A., Hengartner, H., Zinkernagel, R., 2000. Viral escape and the failure of cellular immune responses. Science 289, 2003.

Komarova, N.L., Barnes, E., Klenerman, P., Wodarz, D., 2003. Boosting immunity by antiviral drug therapy: a simple relationship among timing, efficacy, and success. Proc. Natl. Acad. Sci. USA 100, 1855–1860.

Korthals Altes, H., Ribeiro, R.M., de Boer, R.J., 2003. The race between initial T-helper expansion and virus growth upon HIV infection influences polyclonality of the response and viral set-point. Proc. Biol. Sci. 270, 1349–1358.

Lifson, J.D., Nowak, M.A., Goldstein, S., Rossio, J.L., Kinter, A., Vasquez, G., Wiltrout, T.A., Brown, C., Schneider, D., Wahl, L., Lloyd, A.L., Williams, J., Elkins, W.R., Fauci, A.S., Hirsch, V.M., 1997. The extent of early viral replication is a critical determinant of the natural history of simian immunodeficiency virus infection. J. Virol. 71, 9508–9514.

Lifson, J.D., Rossio, J.L., Arnaout, R., Li, L., Parks, T.L., Schneider, D.K., Kiser, R.F., Coalter, V.J., Walsh, G., Imming, R.J., Fisher, B., Flynn, B.M., Bischofberger, N., Piatak Jr., M., Hirsch, V.M., Nowak, M.A., Wodarz, D., 2000. Containment of simian immunodeficiency virus infection: cellular immune responses and protection from rechallenge following transient postinoculation antiretroviral treatment. J. Virol. 74, 2584–2593.

Mansky, L.M., Temin, H.M., 1995. Lower in vivo mutation rate of human immunodeficiency virus type 1 than that predicted from the fidelity of purified reverse transcriptase. J. Virol. 69, 5087–5094.

McLean, A.R., Kirkwood, T.B.L., 1990. A model of human-immunodeficiency-virus infection in T-helper cell clones. J. Theor. Biol. 147, 177–203.

McMichael, A.J., Phillips, R.E., 1997. Escape of human immunodeficiency virus from immune control. Annu. Rev. Immunol. 15, 271–296.

Moir, S., Chun, T.W., Fauci, A.S., 2011. Pathogenic mechanisms of HIV disease. Annu. Rev. Pathol. 6, 223–248.

Nowak, M., 1990. HIV mutation-rate. Nature 347. 522–522.
Nowak, M.A., 1996. Immune-responses against multiple epitopes—a theory for immunodominance and antigenic variation. Semin. Virol. 7, 83–92.
Nowak, M.A., May, R.M., 2000. Virus Dynamics. Mathematical Principles of Immunology and Virology. Oxford University Press.
Nowak, M.A., May, R.M., Sigmund, K., 1995a. Immune-responses against multiple epitopes. J. Theor. Biol. 175, 325–353.
Nowak, M.A., May, R.M., Phillips, R.E., Rowlandjones, S., Lalloo, D.G., McAdam, S., Klenerman, P., Koppe, B., Sigmund, K., Bangham, C.R.M., McMichael, A.J., 1995b. Antigenic oscillations and shifting immunodominance in Hiv-1 infections. Nature 375, 606–611.
Perelson, A.S., 2002. Modelling viral and immune system dynamics. Nat. Rev. Immunol. 2, 28–36.
Perelson, A.S., Neumann, A.U., Markowitz, M., Leonard, J.M., Ho, D.D., 1996. Hiv-1 dynamics in-vivo—virion clearance rate, infected cell life-span, and viral generation time. Science 271, 1582–1586.
Phillips, R.E., Rowland-Jones, S., Nixon, D.F., Gotch, F.M., Edwards, J.P., Ogunlesi, A.O., Elvin, J.G., Rothbard, J.A., Bangham, C.R., Rizza, C.R., et al., 1991. Human immunodeficiency virus genetic variation that can escape cytotoxic T cell recognition. Nature 354, 453–459.
Price, D.A., Goulder, P.J., Klenerman, P., Sewell, A.K., Easterbrook, P.J., Troop, M., Bangham, C.R., Phillips, R.E., 1997. Positive selection of HIV-1 cytotoxic T lymphocyte escape variants during primary infection. Proc. Natl. Acad. Sci. USA 94, 1890–1895.
Rolland, M., Heckerman, D., Deng, W., Rousseau, C.M., Coovadia, H., Bishop, K., Goulder, P.J., Walker, B.D., Brander, C., Mullins, J.I., 2008. Broad and Gag-biased HIV-1 epitope repertoires are associated with lower viral loads. PLoS One 3, e1424.
Rosenberg, E.S., Walker, B.D., 1998. HIV type 1-specific helper T cells: a critical host defense. AIDS Res. Hum. Retroviruses 14 (Suppl. 2), S143–S147.
Rosenberg, E.S., LaRosa, L., Flynn, T., Robbins, G., Walker, B.D., 1999. Characterization of HIV-1-specific T-helper cells in acute and chronic infection. Immunol. Lett. 66, 89–93.
Rosenberg, E.S., Billingsley, J.M., Caliendo, A.M., Boswell, S.L., Sax, P.E., Kalams, S.A., Walker, B.D., 1997. Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia. Science 278, 1447–1450.
Rosenberg, E.S., Altfeld, M., Poon, S.H., Phillips, M.N., Wilkes, B.M., Eldridge, R.L., Robbins, G.K., D'Aquila, R.T., Goulder, P.J., Walker, B.D., 2000. Immune control of HIV-1 after early treatment of acute infection. Nature 407, 523–526.
Sala, M., Zambruno, G., Vartanian, J.P., Marconi, A., Bertazzoni, U., Wain-Hobson, S., 1994. Spatial discontinuities in human immunodeficiency virus type 1 quasispecies derived from epidermal Langerhans cells of a patient with AIDS and evidence for double infection. J. Virol. 68, 5280–5283.
Simon, V., Ho, D.D., 2003. HIV-1 dynamics in vivo: implications for therapy. Nat. Rev. Microbiol. 1, 181–190.
Thomsen, A.R., Nansen, A., Christensen, J.P., Andreasen, S.O., Marker, O., 1998. CD40 ligand is pivotal to efficient control of virus replication in mice infected with lymphocytic choriomeningitis virus. J. Immunol. 161, 4583–4590.
van Stipdonk, M.J., Lemmens, E.E., Schoenberger, S.P., 2001. Naive CTLs require a single brief period of antigenic stimulation for clonal expansion and differentiation. Nat. Immunol. 2, 423–429.
van Stipdonk, M.J., Hardenberg, G., Bijker, M.S., Lemmens, E.E., Droin, N.M., Green, D.R., Schoenberger, S.P., 2003. Dynamic programming of CD8+ T lymphocyte responses. Nat. Immunol. 4, 361–365.
Wei, X.P., Ghosh, S.K., Taylor, M.E., Johnson, V.A., Emini, E.A., Deutsch, P., Lifson, J.D., Bonhoeffer, S., Nowak, M.A., Hahn, B.H., Saag, M.S., Shaw, G.M., 1995. Viral dynamics in human-immunodeficiency-virus type-1 infection. Nature 373, 117–122.
Wodarz, D., 2006. Killer Cell Dynamics: Mathematical and Computational Approaches to Immunology. Springer, New York.
Wodarz, D., Nowak, M.A., 1999. Specific therapy regimes could lead to long-term control of HIV. Proc. Natl. Acad. Sci. USA 96, 14464–14469.
Wodarz, D., Nowak, M.A., 2000. CD8 memory, immunodominance and antigenic escape. Eur. J. Immunol. 30, 2704–2712.
Wodarz, D., Jansen, V.A.A., 2001. The role of T cell help for anti-viral CTL responses. J. Theor. Biol. 211, 419–432.
Wodarz, D., Hamer, D.H., 2007. Infection dynamics in HIV-specific CD4 T cells: does a CD4 T cell boost benefit the host or the virus? Math. Biosci. 209, 14–29.
Wodarz, D., Arnaout, R.A., Nowak, M.A., Lifson, J.D., 2000. Transient antiretroviral treatment during acute simian immunodeficiency virus infection facilitates long-term control of the virus. Philos. Trans. R. Soc. London B Biol. Sci. 355, 1021–1029.
Younes, S.A., Trautmann, L., Yassine-Diab, B., Kalfayan, L.H., Kernaleguen, A.E., Cameron, T.O., Boulassel, R., Stern, L.J., Routy, J.P., Grossman, Z., Dumont, A.R., Sekaly, R.P., 2007. The duration of exposure to HIV modulates the breadth and the magnitude of HIV-specific memory CD4+ T cells. J. Immunol. 178, 788–797.