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

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
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:

\[
\begin{align*}
\frac{dx}{dt} &= \frac{bxy}{(x+y+c)(v+\eta)} - \beta xv \\
\frac{dy}{dt} &= \beta xv - ay \\
\frac{dS}{dt} &= \lambda - d_S S - \beta_m Sv \\
\frac{dI}{dt} &= \beta_m Sv - a_I I \\
\frac{dv}{dt} &= ky + k_o I - uv
\end{align*}
\]

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_S, and become infected upon contact with virus at a rate β_m. Infected non-specific cells die with a rate a_I. Virus is produced by specific and non-specific infected cells with a rate k and k_o, 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 \( R_0 = \frac{\beta_m k_o}{d_S a_I u} \). 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:

\[
S^* = \frac{u a_m}{\beta_m k_o}, \quad I^* = \frac{\lambda}{\beta_m a_m}, \quad v^* = \frac{\beta_m k_o d_S a_I}{u}, \quad x^* = 0, \quad y^* = 0
\]

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 \((\beta v^s + c)(v + \eta))/((\beta v^s + d - v^s)) > 0\), 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, \(v^s\), 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

\[
\frac{dx_1}{dt} = \frac{r v x_1 (\gamma + \eta + \mu)}{(x_1 + y_1 + \gamma + \mu)} dx_1 - bx_1 v
\]

\[
\frac{dy_1}{dt} = bx_1 v - ay_1
\]

\[
\frac{dx_2}{dt} = \frac{\beta v x_2 (\gamma + \eta + \mu)}{(x_2 + y_2 + \gamma + \mu)} dx_2 - bx_2 v
\]

\[
\frac{dy_2}{dt} = bx_2 v - ay_2
\]

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: \(\beta = 0.01\); \(d = 0.5\); \(a = 1\); \(r = 2\); \(c = 10\); \(\eta = 10\); \(\gamma = 1\); \(k = 1\); \(u = 1\); \(\beta_{ns} = 0.2\); \(\lambda = 0.12\); \(d_{ns} = 0.1\); \(a_{ns} = 0.2\); \(k_{ns} = 1\). S(0) = 0/\(d_{ns}\); I(0) = 0; y(0) = 0. (a) x(0) = 1; v(0) = 1 and (b) x(0) = 100; v(0) = 100.
Outcomes of model (2) assuming the presence of two virus-specific helper cell responses that are regulated independently. (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, \( \beta \), and the death rate of infected cells, \( \alpha \). 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

\[
\begin{align*}
\frac{dx_1}{dt} &= r_2 x_1 (y + \eta) - \beta x_2 v x_1 \\
\frac{dy_1}{dt} &= \beta x_2 v - \alpha y_1 \\
\frac{ds}{dt} &= \lambda - \alpha n s - \beta m s v \\
\frac{dl}{dt} &= \beta m s v - \alpha n y \\
\frac{dv}{dt} &= k (y_1 + y_2) + k_m I - u v
\end{align*}
\]
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 specific helper cells 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; Kastenmüller 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:

\[
\frac{dx_1}{dt} = \frac{r_1 x_1 (\gamma + \eta)}{(x_1 + y_1 + x_2 + y_2 + c)(v + \eta)} - dx_1 - \beta x_1 v
\]
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
Ahmed, 2001; Thomsen et al., 1998; van Stipdonk et al., 2001,
rate of the infected cells. (b) Dependence on the rate of CTL proliferation,
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,  

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$</td>
<td>0.015 day$^{-1}$ vol$^{-1}$</td>
</tr>
<tr>
<td>$d$</td>
<td>0.1 day$^{-1}$</td>
</tr>
<tr>
<td>$a$</td>
<td>0.45 day$^{-1}$</td>
</tr>
<tr>
<td>$r_1$</td>
<td>0.5 day$^{-1}$</td>
</tr>
<tr>
<td>$r_2$</td>
<td>0.05 day$^{-1}$</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>10 vol$^{-1}$</td>
</tr>
<tr>
<td>$\eta$</td>
<td>10 vol$^{-1}$</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>1 day$^{-1}$</td>
</tr>
<tr>
<td>$k$</td>
<td>3.33 day$^{-1}$</td>
</tr>
<tr>
<td>$w$</td>
<td>0.0002 day$^{-1}$ vol$^{-1}$</td>
</tr>
<tr>
<td>$b$</td>
<td>0.01 day$^{-1}$</td>
</tr>
<tr>
<td>$p$</td>
<td>0.0003 day$^{-1}$ vol$^{-1}$</td>
</tr>
<tr>
<td>$q$</td>
<td>0.001 vol$^{-1}$</td>
</tr>
</tbody>
</table>

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 life-span 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; Kastenmüller 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 uncertainty 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