Target Cell Limited and Immune Control Models of HIV Infection: A Comparison

Rob J. De Boer
Alan S. Perelson

SFI WORKING PAPER: 1996-11-083

SFI Working Papers contain accounts of scientific work of the author(s) and do not necessarily represent the views of the Santa Fe Institute. We accept papers intended for publication in peer-reviewed journals or proceedings volumes, but not papers that have already appeared in print. Except for papers by our external faculty, papers must be based on work done at SFI, inspired by an invited visit to or collaboration at SFI, or funded by an SFI grant.

©NOTICE: This working paper is included by permission of the contributing author(s) as a means to ensure timely distribution of the scholarly and technical work on a non-commercial basis. Copyright and all rights therein are maintained by the author(s). It is understood that all persons copying this information will adhere to the terms and constraints invoked by each author's copyright. These works may be reposted only with the explicit permission of the copyright holder.

www.santafe.edu
Target cell limited and immune control models of HIV infection: a comparison

Rob J. De Boer\(^1\) and Alan S. Perelson\(^2\)

1. Theoretical Biology, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands, Email: rdb@alive.biol.ruu.nl

2. Theoretical Division, MS-K710, Los Alamos National Laboratory, Los Alamos, NM 87545, U.S.A., Email: asp@lanl.gov

Abstract

We develop various mathematical models of the clinical latency stage of HIV-1 infection assuming that HIV-1 infection is limited either by the availability of cells that HIV can infect or by a specific anti-HIV cellular immune response. The former models we call "target-cell-limited". Comparing the models by phase plane analysis we find that they all belong to the class of predator-prey models. In the target-cell-limited models the virus is a predator feeding upon target cell prey, while in the immune-control models the virus is a prey that is controlled by an immune response predator. Because both classes of models are of predator-prey type they behave similarly in most circumstances. We find that both types of model can account for the generic picture of disease progression in which the CD4 T cell count slowly decreases and the viral load slowly increases. Additionally, we find that both types of models can adequately describe the clinically observed changes in the plasma HIV-1 RNA loads in response to retroviral therapies.

Introduction

A typical HIV-1 infection has a long clinical latency phase (Coffin, 1995). Following an initial viremia, the viral load in peripheral blood declines rapidly and establishes a quasi-equilibrium level. The length of the clinical latency phase correlates negatively with the quasi-equilibrium level that is attained shortly after the initial viremia (Mellors et al.,
1996). During disease progression there is a slow increase in the viral load, and a slow decrease in the CD4⁺ T cell count in peripheral blood. Because of the slowness of disease progression, it had been thought that the processes of HIV-1 replication and the destruction of infected CD4⁺ cells would also have a slow time scale. This viewpoint has recently been contradicted by mathematical analysis of data obtained in patients treated with anti-viral drugs inhibiting either HIV-1 protease (Ho et al., 1995; Perelson et al., 1996) or HIV-1 reverse-transcriptase (RT) (Wei et al., 1995). Following such a therapeutic perturbation of the quasi-equilibrium, the HIV-1 RNA load and the CD4⁺ T cell count in the peripheral blood change drastically on a time scale of weeks. It was estimated that in patients with CD4 counts below 500, the average HIV-1 generation time is 2–3 days, leading to ~140 generations per year (Perelson et al., 1996), that CD4⁺ T cells are replenished at an average rate of about ten cells per µl per day (Ho et al., 1995; Wei et al., 1995), and that the average total HIV-1 production is about 10¹⁰ virions per day (Perelson et al., 1996). Clinical latency therefore appears to be a quasi-equilibrium in which fast HIV-1 replication and clearance, and CD4⁺ T cell loss and renewal remain in almost perfect balance. According to this view, disease progression involves a slow change of parameters that gradually moves the quasi-equilibrium to higher viral loads and lower CD4⁺ T cell counts.

The crucial question arising from this novel view is the nature of the processes setting the long-term balance between viral replication and clearance (Coffin, 1995). One obvious control process is the anti-viral immune response. HIV-1 infection elicits both humoral and cellular immune responses (Fauci, 1993; Weiss, 1993). CD8⁺ T lymphocytes, which suppress and/or kill virus infected cells, are thought to be the dominant defense mechanism, and it has been postulated that long term survival is associated with a good cellular immune response (Klein et al., 1995; Rinaldo et al., 1995, Shearer & Clerici, 1996, Nowak & Bangham, 1996, Levy et al., 1996; Wolinsky et al., 1996). Another significant control factor is the availability of “target” cells, i.e., cells that HIV is able to infect (Coffin, 1995; Phillips, 1996; De Boer & Boucher, 1996). The primary target of HIV-1 infection is an activated CD4⁺ T cell (Fauci, 1993; Weiss, 1993).

A variety of clinical data sets suggest that virus replication is limited by the availability of target cells. Suppressing the immune system with either cyclosporine (Andrieu et al., 1988; Schwarz et al., 1993; Weber & Galpin, 1995) or prednisolone (Andrieu et al., 1995;
Corey, 1995) can have beneficial effects because it decreases the CD4+ T cell count and sometimes (Weber & Galpin, 1995) decreases the viral load. Stimulating the immune system with IL-2 tends to increase the viral load (Kovacs et al., 1995). Immunization of HIV-1 infected patients with either influenza vaccine (Staprans et al., 1995; O’Brien et al., 1995), hepatitis B vaccine (Cheeseman et al., 1996), or tetanus toxoid (Stanley et al., 1996), which should activate T cells, tends to increase the viral load. A similar increase in HIV is seen during infection with pathogenic organisms (Goletti et al., 1996). Because the number of activated CD4+ T cells, i.e., target cells, decreases with immune suppression and increases with immune stimulation, these results suggest that the infection may be “target-cell-limited” during such post-treatment transients.

In this paper we perform a comparative study of target-cell-limited and immune-controlled models of HIV infection. To enable an objective comparison between models we set the unknown parameters such that the models all have a similar clinical latency equilibrium. This is the equivalence approach advocated by Irvine & Savageau (1985). Our main conclusion is that both target-cell limited and immune control models have similar behavior, and can account for the dynamics observed after drug perturbation experiments.

**Biological variables and parameters**

The models that we develop involve various cells types: non-infected quiescent T cells, $Q$, (non-infected) activated or cycling CD4+ cells, which we consider to be target cells $T$, productively infected T cells, $I$, cytotoxic effector T cells, $E$, and HIV-1 virus particles, $V$. Recent studies on the dynamics of HIV-1 turnover and the rate of CD4+ T cell recovery following the administration of antiretroviral drugs provide estimates for some of the parameters of the models. The maximum rate at which T cells self-renew, if it is assumed to occur solely by cell division, is about 0.1 day$^{-1}$ (Ho et al., 1995; Wei et al., 1995). This self-renewal rate decreases approximately linearly with the CD4 T cell count, suggesting that the growth rate is density dependent and is governed by a logistic-like growth function. The CD4 cell count in an uninfected individual is approximately 1000 CD4+ T cells per $\mu l$. Resting T cells are assumed to live about a thousand days (McLean & Michie, 1995). The average life time of a productively infected T cell is estimated to be two days (Ho et al., 1995; Wei et al., 1995; Perelson et al., 1996), and the average life time of virus particles is estimated to be eight hours (Perelson et al., 1996).
The clinical status of a patient is typically assessed by measuring CD4 T cells counts and viral loads in the blood. The typical patient that we consider has a CD4+ T cell count of say 200 cells per μl, and a viral load of approximately $10^5$ copies per ml of plasma. A major problem with current data is that it provides little information about the lymphoid compartment. Since only 2% of lymphocytes circulate in the blood (Westermann & Pabst, 1990), and the lymphoid tissue is a major reservoir of HIV-1 (Pantaleo et al., 1993; Embretson et al., 1993; Haase et al., 1996) we have an incomplete view of the disease process. The fraction of infected cells in the lymphoid tissue is much higher than that in the peripheral blood (Pantaleo et al., 1993; Embretson et al., 1993). For the parameter values established above, our models can only account for significant depletion of CD4+ T cells when we assume that at least 10% of target cells are productively infected (see below). Since such a fraction of productively infected cells is unrealistically high for peripheral blood, we assume the HIV-1 infection processes occur in the lymphoid tissue, and that the infected cells in our model reflects an average of blood and lymphoid tissue infection.

In our models virus particles, $V$, are produced by productively infected cells, $I$, at rate $p$ per cell, and are cleared at a per capita rate $c$, i.e.,

$$\frac{dV}{dt} = pI - cV,$$

(1)

where the clearance rate constant $c$ may involve binding of particles to CD4+ cells and clearance by antibodies. Because the dynamics of the viral particles are much faster than the dynamics of cells, (Perelson et al. (1996) estimated $c \geq 3 \text{ day}^{-1}$), we make a quasi steady state assumption for Eq (1), i.e.,

$$\overline{V} = (p/c)I,$$

(2)

where the overbar denotes a steady state quantity.
Target cell limitation

**Logistic model.** Recent data on the rate of recovery of CD4 T cells after antiretroviral therapy suggest that CD4 cell growth may be density dependent and follow a logistic-like growth equation (Ho et al., 1995). Thus, we model the population dynamics of target cells, $T$, and productively infected cells, $I$, as

$$\frac{dT}{dt} = \alpha_T T(1 - T_{tot}/T_{max}) - \beta TV, \quad \text{and} \quad \frac{dI}{dt} = \beta TV - \delta_I I,$$

where $V$ is described by Eq. (1) or (2). Here $\alpha_T = 0.1$ day$^{-1}$ is the maximum rate of T cell renewal, $T_{max} = 1000$ cells per $\mu$l is the non-infected equilibrium CD4 count, $\beta$ is an infection rate (cells per particle per day), and $\delta_I = 0.5$ day$^{-1}$ is the turnover rate of productively infected T cells. The total number of T cells, $T_{tot} = T + I$. The equilibrium of this model is at

$$\bar{T} = \frac{c\delta_I}{p\beta}, \quad \bar{V} = \frac{\alpha_T(p\beta T_{max} - c\delta_I)}{\beta(\alpha TC + p\beta T_{max})}, \quad \text{and} \quad \bar{I} = \frac{c\alpha_T(p\beta T_{max} - c\delta_I)}{p\beta(\alpha TC + p\beta T_{max})} = \frac{c\bar{V}}{p}. \quad (4a, b, c)$$

We set parameters such that this equilibrium corresponds to a CD4 T cell count of approximately 200 cells per $\mu$l and a viral load of $10^5$ copies per ml. Since we assume that most of the HIV-1 infected T cells are in the lymphoid tissue, the peripheral CD4 count is defined by the number of uninfected CD4$^+$ cells, $T$. Requiring $\bar{T} = 200$, we solve Eq. (4a) for $p\beta$, which is the only unknown parameter combination, to find $p\beta = (0.5 \times 3)/200 = 7.5 \times 10^{-3}$. Having estimated $p\beta$, we know all parameters in the equilibrium expression for the infected cells (Eq. 4c), and hence compute that $\bar{I} \approx 30$. Because $\bar{V} = (p/c)\bar{I}$ and we require $\bar{V} \approx 100$ particles per $\mu$l, we find that the production rate $p = 10$ particles per cell per day. Lastly, we obtain $\beta = 7.5 \times 10^{-4}$.

Thus, we see that our requirement of significant T cell depletion yields parameter estimates that imply a high fraction of productively infected cells (i.e., over 10%). In other words, in our model significant T cell depletion requires sufficiently high infection levels. Knowing the number of productively infected cells, and requiring a viral load of $10^5$ virions per ml, we obtained $p = 10$. Since the average lifetime of an infected cell is two days, this implies that an infected cell would produce 20 virus particles during its lifetime. This is 5-fold less than the recent estimate of Haase et al. (1996). Thus, our requirement of a realistic
clinical latency equilibrium with a CD4 cell count of 200 per μl and a viral load of 10^5 virions per ml, constraints the parameters β and p such that we have many infected cells and that p cannot be fitted to the data. Similar results pertain to the activated T cell model.

**Activated T cell model.** Activated T cells make better targets for HIV infection than quiescent cells (Bukrinsky et al., 1991). Thus, we propose a second target-cell-limited model in which we distinguish quiescent and activated T cells. This model was originally devised by Stilianakis et al. (1997), and is similar to the models of Essunger and Perelson (1994). In this model, we assume that quiescent T cells are activated at rate αQ, die at rate δQ, and appear by the proliferation of activated T cells at a maximum rate r. Activated CD4 cells, T, appear by activation of quiescent cells, they revert to quiescent stage at a rate r, and they are infected by virus at a rate β. Thus,

\[
\frac{dQ}{dt} = \frac{2rT}{1 + T_{tot}/T_{max}} - (\alpha Q + \delta Q)Q, \quad \text{and} \quad \frac{dT}{dt} = \alpha Q Q - rT - \beta TV, \quad (5a, b)
\]

where the \(2/(1+T_{tot}/T_{max})\) term defines a density dependent regulation of the proliferation rate. When \(T_{tot} = T_{max}\) proliferation stops, and activated T cells simply revert to the quiescent stage. For the infected T cells we copy Eq. (3b), i.e.,

\[
\frac{dI}{dt} = \beta TV - \delta I, \quad (6)
\]

and V is still given by Eq. (1).

The total number of T cells in this model is \(T_{tot} = Q + T + I\), and the CD4 cell count is \(Q + T\). The clinical latency equilibrium is at

\[
\bar{T} = \frac{c\delta I}{p\beta}, \quad \bar{V} = \frac{p\alpha Q Q}{c\delta I} - \frac{r}{\beta}, \quad \text{and} \quad \bar{I} = \frac{c}{p} \bar{V}, \quad (7a, b, c)
\]

The value of \(\bar{Q}\) can easily be computed; it is too complicated to warrant printing here.

For the life-span of quiescent human T cells we employ the empirical estimate of McLean and Mitchie (1995) and set \(\delta Q = 0.001 \text{ day}^{-1}\). By setting \(r = 1 \text{ day}^{-1}\) we assume that activated T cells revert quite rapidly to the quiescent stage. In the Appendix we derive that the maximum growth rate of the CD4 population is determined by the activation rate \(\alpha Q\) and that the CD4 cell count should remain below \(T_{max}\). Thus, setting \(T_{max} = 1100\) we
obtain a normal CD4 cell count of approximately 1000 CD4$^+$ T cells per $\mu$l. We employ $\alpha_Q$ and $\beta$ for setting the equilibrium CD4 count. All other parameters remain the same as those in the logistic model. Chosing $\alpha_Q = 0.13$ day$^{-1}$ and $\beta = 0.01$ we find, at equilibrium, $Q \approx 193$ cells per $\mu$l, $T \approx 15$ cells per $\mu$l, $I \approx 20$ cells per $\mu$l, and $V \approx 67$ particles per $\mu$l. This has the desired level of a CD4 count, $Q + T$, of approximately 200 cells per $\mu$l and a viral load of $6.7 \times 10^4$ per ml.

**Phase plane results.** Comparing the target-cell-limited models by phase plane analysis we point out their similarity and their relationship to predator-prey models. We reduce both models to two ODEs by making a quasi-steady state assumption for virus (Eq. 2), and a second quasi-steady state assumption for the target cell population, $T$, in the activated T cell model. Plotting the “prey” population $T$ (or $Q$) on the horizontal and the “predator” population $I$ on the vertical axis, we obtain two very similar phase planes (see Fig. 1). In the logistic model the location of the vertical predator nullcline determines the CD4 cell count of the latency equilibrium. We set the CD4 count to 200 by tuning the infection rate $\beta$. For these parameter values the equilibrium is a stable spiral point. The nullclines of the activated T cell model (Fig. 1b) resemble those of the logistic model, but the prey nullcline (heavy line) is slightly curved and the predator nullcline (light line) is slanted. The equilibrium remains a stable spiral point, but tends to be more stable than that of Fig. 1a.

**Disease progression.** For a typical patient, during the asymptomatic, clinical latency phase the CD4 cell count slowly decreases and the viral load slowly increases. The onset of AIDS is defined as reaching a CD4 count of 200 cells per $\mu$l or below. An aim of theoretical modeling is to find a disease progression parameter that decreases the CD4 count and increases the viral load. This is an interesting problem because one would expect the viral load to decrease with decreasing CD4 counts if the virus is target-cell-limited. If this were true, it would contradict the data, and would be an argument against a target cell limited model.

We can incorporate disease progression by assuming that the virus increases its infection rate $\beta$. This assumption has been the focus of a model developed by Schenzle (1994) and is in agreement with data suggesting that the virus quasispecies becomes more virulent during progression (Tersmette et al., 1989; Schellekens et al., 1992; Connor and Ho, 1994;
Perelson et al., submitted), but is at odds with other data suggesting that the virulence remains similar (Wolinsky et al., 1996). In the clinical latency equilibrium of the logistic model, Eq. (4), the CD4 count, \( T \), is an inverse function of the infection rate \( \beta \). The viral load is a complicated function of \( \beta \) however. When \( \beta \) is small, increasing \( \beta \) increases the viral load; when \( \beta \) is large it is the other way around (Fig. 2a).

In Fig. 2a we plot the equilibrium viral load and CD4 count as a function of \( \beta \) in the logistic model. Disease progression is interpreted as an increase of \( \beta \) in time. Observe that CD4 count, \( T \) (light line), is inversely related to \( \beta \), and that the viral load (dark line) first increases and then decreases. This decrease of the viral load is in disagreement with the data, but is natural in simple host-parasite models. For the current parameters the equilibrium is stable only for \( \beta < 0.0014 \); the model behavior is oscillatory otherwise (not shown).

Two other parameters that might change during disease progression are \( T_{\text{max}} \), the maximum T cell count, and \( \alpha_T \) or \( \alpha_Q \), the T cell self-renewal rates. A biological argument for decreasing \( T_{\text{max}} \) would be that during HIV-1 infection lymphoid tissues is destroyed, which could lower the maximum number of T cells that can be maintained. An argument for choosing \( \alpha_T \) or \( \alpha_Q \) as a progression parameter is that HIV-1 infection involves hyperactivation of the immune system (Fauci, 1993). Both \( \alpha_T \) and \( T_{\text{max}} \) are however absent from the equilibrium equation for uninfected T cell of the logistic model (Eq. 4a). Thus changing either of the two fails to decrease the CD4 cell count. This occurs because in the logistic model the CD4 count is set by parameters of the virus only (see Eq. 4a).

Interestingly, changing the T cell activation rate, \( \alpha_Q \), seems to be the best parameter for modeling progression in the activated T cell model. Increasing \( \alpha_Q \) decreases the number of quiescent T cells and hence causes the CD4 T cell count to go down and the viral load to go up (Fig. 2b). Moreover, recent data (Tse et al., unpublished data) suggest that as T cell counts falls a higher fraction of CD4 cells are activated. This demonstrates that target-cell-limited models can account for the observed clinical pattern of decreasing CD4 counts and increasing viral loads during disease progression. The equilibrium is stable over the full range of \( \alpha_Q \) values depicted in Fig. 2b. Modeling disease progression by increasing virus infectivity, i.e., \( \beta \), in the activated T cell model yields results that are similar to those of the logistic model (cf. Fig. 2a).
Conclusion. For modeling a target-cell-limited HIV infection the activated T cell model is superior to the logistic model. The activated T cell model can account for the typical picture of disease progression (Fig. 2b), whereas the logistic model cannot (Fig. 2a). Phase plane analysis shows that activated T cell model is a predator-prey model with a slanted predator nullcline, whereas the logistic model has a vertical nullcline. This tends to make the clinical latency equilibrium more stable in the activated T cell model.

Immune-control

Cytotoxic T cell (CTL) model. An alternative to target cell limitation of HIV replication is immune control. We define an immune-control model as one in which the high turnover rate of infected cells $\delta_T = 0.5 \text{ day}^{-1}$ is entirely due to their removal by CD8$^+$ CTLs. This clearly is extreme but it allows us to clearly distinguish immune control models from target cell limited models.

Naive CD8$^+$ T cells require activation and co-stimulation by antigen presenting cells (APCs) in the lymphoid compartment in order to become effector CTLs (Nonacs et al., 1992; Chen et al., 1992; Kundig et al., 1995). Since the presentation of HIV-1 peptides depends on the interaction of virus particles with APCs, we assume that the activation and proliferation of CTLs is a function of the viral load. At the effector stage, CTLs interact with productively infected cells, $I$. The turnover rates of CTLs can be estimated from data on other viral infections. Following the successful clearance of an LCMV infection, the CTL effector levels drop 95% in about three weeks (Ahmed & Gray, 1996). Thus, we calculate that the turnover of the CTLs should maximally be on the order of $\delta_E \simeq 0.2$ per day (i.e., $\ln(0.05)/21 = -0.14$).

In order to distinguish between target cell limitation and immune control, we need to assume in an immune-control model that virus replication is not limited by the target cell density. We thus assume that

$$\frac{dI}{dt} = \beta V - kIE. \tag{9}$$

Note $\beta$ now has units of day$^{-1}$ and that in essence a constant value of $T$ has been incorporated into $\beta$. We assume that $V$ is still given by Eq. (1).

It is possible to develop a class of models that are intermediate between target cell limita-
tion and immune control by assuming that the rate of target cell infection is a saturating function of the target cell density, $T$, i.e.,

$$\frac{dI}{dt} = \beta V \frac{T}{\theta + T} - kIE.$$  \hspace{1cm} (10)

For $\theta \gg T$, this reduces to the target cell limited model, whereas for $\theta \ll T$ one obtains the immune control model.

To make the model of Eq. (9) “equivalent” to the target cell limited models we require that at the latency equilibrium $\delta_l = kE = 0.5 \text{ day}^{-1}$, so that productively infected cells are lost at the observed rate of $0.5 \text{ day}^{-1}$. Solving Eq. (9) and using Eq. (2) we obtain $E = p\beta/(ck)$. Since $c = 3 \text{ day}^{-1}$, this allows us to compute the product of the infection rate and the production rate as $p\beta = ckE = 1.5 \text{ day}^{-1}$. Choosing for our earlier estimate of a production rate of $p = 10$ virions per productively infected cell per day we obtain $\beta = 0.15 \text{ day}^{-1}$.

Considering such a simple “pure” immune-control model however forces us to develop a relatively sophisticated model for the CTLs. Combining Eq. (9) with the simplest possible CTL model, i.e.,

$$\frac{dE}{dt} = \alpha_E EV - \delta_E E,$$ \hspace{1cm} (11)

yields a structurally non-robust model with perpendicular nullclines (see Fig. 3a). Solving Eq. (11), we obtain $V = \delta_E/\alpha_E$. Thus, the equilibrium viral load is independent of parameters describing viral replication! Nowak and Bangham (1996) in a different immune-control model also find that the equilibrium viral load is determined only by the immune-control parameters. Since we require $V = 100$ at equilibrium, and $\delta_E = 0.2 \text{ day}^{-1}$, we find that we must choose $\alpha_E = 0.002 \text{ day}^{-1}$. Further, because the equilibrium viral load no longer depends on the production rate $p$, we can fit any measured virion production rate by adjusting the infection rate $\beta$. This was not the case in the target cell limited models.

A valid criticism of this model is that in HIV infected individuals the viral load in the lymphoid tissue could be so high that Eq. (11) would predict unrealistically high rates of generation of effector cells. To rectify this, we can use an activation function that saturates, i.e.,

$$\frac{dE}{dt} = \frac{\alpha_E EV}{1 + vV} - \delta_E E.$$ \hspace{1cm} (12)
Now, CTL activation/proliferation has a maximal rate of $\alpha_E/\epsilon_V$. Solving Eq. (12) for the equilibrium value of $V$, we obtain $\overline{V} = \delta_E/(\alpha_E - \delta_E \epsilon_V)$. This still yields a non-robust perpendicular nullcline (see Fig. 3b). Assuming a maximum CTL proliferation rate of about one doubling per day, i.e., assuming $\alpha_E/\epsilon_V = 1$ day$^{-1}$, we obtain an equilibrium viral load of $\overline{V} = 100$ by setting $\alpha_E = \epsilon_V = 2.5 \times 10^{-3}$.

We can obtain a structurally robust immune-control model by employing the model of De Boer and Perelson (1995) that allows for competition between CTLs when interacting with antigen presenting cells. In this model,

$$\frac{dE}{dt} = \frac{\alpha_E EV}{1 + \epsilon_V V + \epsilon_E E} - \delta_E E. \tag{13}$$

The maximum per capita proliferation rate is still $\alpha_E/\epsilon_V = 1$, and $\epsilon_E$ defines the intensity of the competition. The equilibrium of this model, found by solving Eqs. (1), (10), and (13), is

$$\overline{E} = \frac{p\beta}{kc}, \quad \overline{V} = \frac{\delta_E (kc + \epsilon_E p\beta)}{kc(\alpha_E - \delta_E \epsilon_V)}, \quad \text{and} \quad \overline{I} = \frac{c}{p} \overline{V}. \tag{14}$$

Note that $\overline{V}$ now depends on immune control parameters such as $\delta_E$ and $k$. In this model the $I$-nullcline is slanted, making the model structurally stable, and the equilibrium stable (see Fig. 3c). Setting $\epsilon_E = 1$, $k = 1$, and requiring $\alpha_E/\epsilon_V = 1$ and $\overline{V} = 100$, we find $\alpha_E = \epsilon_V = 3.75 \times 10^{-3}$.

There are alternative ways to make the immune-control model structurally robust. For example, one could allow some target cell limitation, i.e., use Eq. (10) instead of (9), or one could include a source of naive cells from the thymus in the CTL equation. With a fully activated and proliferating CTL population such a source term should make a relatively small contribution to the population size. We prefer to use the model with competition, Eq. (13), because a small source term, or a small effect of target-cell-limitation, would only make the model marginally stable. Further, using Eq. (13) the steady state value of $V$ depends on immune system parameters, which is a desirable feature in an immune control model.

**Disease progression.** In immune-control models a natural method for modeling disease progressing is to decrease the activation/proliferation rate $\alpha_E$ of the CTLs. Such a decline could be due to the senescence of CTLs as recently observed via telomere shortening (Effros
et al., 1996; Wolthers et al., 1996), and/or to decreased T cell help due to progressive CD4+ T cell loss. Focusing on the structurally stable immune-control model, we see from Eq. (14) that decreasing $\alpha_E$ increases the equilibrium viral load without affecting the equilibrium level of the immune response, $E$. Since the equilibrium in the pure immune-control models is independent of the CD4 cell count, one can easily account for the typical picture of disease progression by independently assuming that the CD4 cell count decreases with increasing viral load.

**Conclusion.** Models of HIV infection that are purely immune-controlled also have the form of predator-prey models. The proliferation/activation function of the CTLs that we use in Eq. (14) is known in ecology as the Beddington (1975) “functional response”. Modeling disease progression in immune-control models can be done by reducing the immune responsiveness parameter $\alpha_E$.

**Anti-viral treatment**

The activated T cell model and the CTL model have similar phase planes and can both account for the typical scheme of disease progression. We now compare their behavior when HIV infection is treated by either a protease inhibitor or an RT inhibitor. An RT inhibitor is expected to reduce the infection rate $\beta$, whereas a protease inhibitor should reduce the production rate of infectious virions. A previous model of protease inhibitor action (Perelson et al., 1996) distinguished between infectious and non-infectious virions. One can simplify matter in two ways. First, if the number of infectious virions decreases this in turn will reduce the infection rate. Thus, one can model the action of protease inhibitors as a decrease in $\beta$. Second, one can assume that in the presence of a protease inhibitor the total virion production rate $p$ decreases. Note that in the CTL model the equilibrium viral load $\overline{V}$, and the equilibrium immune response level $E$, depend on the product $p\beta$ only (see Eq. 14). Thus, under this assumption, the effect of both forms of treatment should be identical. In the activated T cell model this symmetry is broken (see Eq. 7b), i.e., the effect of reducing $p$ differs from that of reducing $\beta$. Here we will study the effects of drugs changing either $\beta$ or $p$.

First consider treatment with an RT-inhibitor that brings about a two-fold reduction in the infection rate $\beta$. In Fig. 4 the light lines depict the pre-treatment situation (i.e., the
same nullclines as those in Fig. 1), and the heavy lines are the nullclines for this two-fold RT-inhibitor treatment. Recall that $\bar{I}$ and $\bar{V}$ are proportional, so that $\bar{I}$ is a measure of the viral load. We observe that if $\beta$ is a reduced a new equilibrium is attained, which in the activated T cell model is located at an almost two-fold higher CD4 count and a somewhat higher infected cell level and hence higher virus load (Fig. 4a). In the CTL model this treatment brings about an two-fold reduction of the immune response and a somewhat lower viral load (Fig. 4b). Thus, even in the absence of drug resistance, an RT-inhibitor treatment hardly influences the equilibrium viral load. Instead it increases CD4 count in the target-cell-limitation model, and decreases the immune response in the CTL model. Treatment with a drug that reduces $p$ has very similar effects (see below).

The heavy gray lines in Fig. 4 depict the trajectories corresponding to giving this two-fold RT-inhibitor treatment to a patient in the clinical latency equilibrium. Transiently the virus load is significantly reduced by such a treatment, but the virus rebounds and attains the new equilibrium. Recent clinical data have confirmed that the wild-type virus load declines and rebounds before drug resistance evolves (De Jong et al., 1996). Previous theoretical studies on target-cell-limitation models have predicted the decrease and rebound of wild-type virus by the typical oscillatory nature of predator-prey models (McLean et al., 1991; McLean & Nowak, 1992; Frost & McLean, 1994; McLean et al., 1995; De Jong et al., 1996; Stilianakis et al., 1997). Because the CTL model is also a predator-prey model, the same type of viral decline and rebound can be seen in immune-control models. Thus, the rebound in viral load can not be used as evidence in favor of a target cell limited model.

The trajectories in Fig. 4 do not allow one to compare the time courses of viral rebound between the two models and the clinical data. For the target cell limited models it has been well established that for current parameter values one obtains a good correspondence in the time course of the viral load between the model and the data (De Jong et al., 1996; De Boer & Boucher, 1996; Stilianakis et al., 1997). A similar good correspondence is also possible in the immune-control models (not shown). Because the viral load typically rebounds in about a month (De Jong et al., 1996), a good fit requires a fairly high turnover of the immune effector cells $E$ however. Because cytotoxic effector cells are known to be short-lived (Ahmed & Gray, 1996), immune-control can in principle account for a realistic time course of the viral load. Due to immune memory effects it could also be however that the decline of the immune response during anti-viral therapy is much slower. In this case,
target-cell-limitation is expected to be the dominant control process during the first weeks of treatment (De Boer et al., submitted).

It may seem paradoxical that an RT-inhibitor may increase the viral load in the activated T cell model (Fig. 4a). The same effect can also occur in the logistic model however. Eq. (4b) shows that the viral load is a complex function of the infection rate $\beta$: changing $\beta$ can either increase or decrease the viral load. Thus this paradoxical effect is normal for models assuming that the HIV infection is target-cell-limited. If $\beta$ is further decreased by treatment with an RT-inhibitor, the viral load will ultimately decrease and become zero (at a transcritical bifurcation point). For reason of simplification, our models have ignored the loss of virus particles by binding target cells. Incorporating this hardly changes the response of the viral load to changing $\beta$.

**Therapy and Drug Resistance**

Monotherapy with protease or RT-inhibitors generally results in the eventual development of drug resistance (Larder et al., 1989; Larder et al., 1991; Boucier et al., 1992; Wei et al., 1995; Lineberger et al., 1995). In the presence of antiretroviral treatment, the drug-sensitive wild type virus is ultimately outcompeted by drug-resistant variants having a higher infection rate $\beta$, or viral production rates $p$. Thus, in terms of our models, antiretroviral treatment and the development of drug resistance correspond to changes in either $\beta$ or $p$. Plotting the equilibrium viral load as a function of either $\beta$ or $p$ (Fig. 5), allows us to examine the effects of antiretroviral treatment in the presence of drug resistance. For example in Fig. 5b, starting at a virion production rate of $p = 10$ particles per cell per day, a drug treatment that decreases $p$ corresponds to moving leftwards. Note that a a drug effect that reduces $p$ up to a four-fold reduces the viral load only marginally. Further reduction of $p$ causes the virus to “suddenly” be eradicated. The subsequent development of drug resistance corresponds to moving rightwards, i.e., to increasing $p$. This will increase the viral load again. The light lines in Fig. 5 depict the response of the CD4 count, or the immune response, to changing $\beta$ or $p$ by treatment and resistance development.

In both models either form of antiretroviral treatment, and of resistance, hardly affects the equilibrium viral load until a (transcritical) bifurcation point is reached. In the target-cell-limitation model this is the critical treatment level that reduces $p$ or $\beta$ below the value needed to sustain the virus. In the immune-control model the bifurcation point is
where the bifurcation parameter equals zero. Reducing parameters to zero is not realistic however. Note that the immune response, $E$, declines linearly with $\beta$ or $p$. Hence at some point the effect of the immune response is so small that some form of target cell limitation should take over as a control mechanism.

The clinical data on the equilibrium viral load during treatment with RT-inhibitors suggest that after drug resistance develops the viral load is either similar to the pre-treatment level (De Jong et al., 1996), or is reduced 10-100 fold (Schuurman et al., 1995; Eron et al., 1995). The reduction of the equilibrium virus load by an RT-inhibitor treatment is difficult to explain with the models presented here: up to the bifurcation point changing $\beta$ has hardly any effect on the viral load because of the compensatory responses of the target cells or the immune response. A straightforward solution for this problem is to assume that the virus also kills uninfected cells (Bonhoeffer et al., submitted). Given the same assumption it is also possible to have significant T cell depletion with low fractions of productively infected cells, and higher values of the virion production rate $p$ in any of our models (not shown).

**Conclusion.** In both target-cell-limited and in immune-control situations an antiretroviral treatment with limited effects (e.g., due to drug resistance) has a negligible effect on the viral load. The effect of the treatment is largely reflected in the levels of either the target cells or the immune response. A treatment with a sufficiently strong impact eradicates the drug-sensitive virus when the virus is target-cell-limited, but first eradicates the immune response when the virus is immune-controlled. This makes sense from an ecological point of view because the predator should go extinct before the prey does.

**HIV Can be Viewed as Either a Predator or a Prey**

Obviously the target-cell-limited and the immune-control models can be combined. In such models, where the target cells form a prey species, the virus is a predator, and the immune response is a super-predator. Such a “food-chain” model can provide further insights in the control processes regulating the viral load (Nowak & Bangham, 1996; De Boer et al., submitted; Müller & De Boer, submitted). The simplest food-chain model employs Eq. (11) for $E$ the “super-predator” population (cf. Nowak & Bangham, 1996). By the solution of Eq. (11), $\bar{V} = \delta_E/\alpha_E$, one would conclude that the equilibrium viral load
is determined by the immune-control parameters $\delta_E$ and $\alpha_E$ only (Nowak & Bangham, 1996). Thus, in a food-chain model immune control would seem to dominate over target cell limitation.

Generally, this need not be true however. First, there is a non-robustness in this argument because adding yet another level to the food chain, i.e., a population regulating the CTL numbers, would make the virus target-cell-limited again. Adding a regulator population $R$, Eq. (11) changes into the system

$$\frac{dE}{dt} = \alpha_E EV - \delta_E E - k_R ER , \quad \text{with} \quad \frac{dR}{dt} = \alpha_R RE - \delta_R R$$  (15a, b)

where $k_R$ determines the magnitude of a possibly very small down-regulatory effect of $R$ on $E$. Solving Eq. (15) we obtain $\bar{E} = \delta_R / \alpha_R$ and $\bar{R} = (\alpha_E V - \delta_E) / k_R$. Observe that the effector level is independent of the magnitude $k_R$ of the down-regulatory effect. Furthermore, since Eq. (15) is required for determining $\bar{E}$ and $\bar{R}$, the equilibrium viral load $V$ has to be solved from the remaining equations of the model (e.g., Eq. (2) and (10)). Since these do not depend on the immune-control parameters $\alpha_E$ and $\delta_E$ the viral load has become target-cell-limited again. In theoretical ecology this is a well known result. For instance, in Lotka-Volterra type models, the effects of an enrichment of a food-chain system differ when the food chain has an even or odd length (Ginzburg and Akçakaya, 1992). This problem could well be an artifact of the over-simplified interaction terms that are used in these ecological models (and in the immune control model of Eq. (11)). A solution to this problem is to allow for a direct form of competition (Ginzburg and Akçakaya, 1992; Abrams, 1994), as we have in Eq. (13) and in De Boer and Perelson (1994, 1995).

Second, when the virus load is so high that the immune response can be considered to be at a maximal level, e.g., by saturation and competition (cf. Eq. 13), the HIV infection also becomes target cell limited. Indeed, allowing for competition amongst the CTLs (cf. Eq. 14) makes the viral load dependent on many more parameters (cf. Eq. 15) than those of the immune response. Third, we as argue elsewhere (De Boer et al., submitted) the time scale with which the CTL response declines following a perturbation of the clinical latency equilibrium by therapeutic intervention may be much slower that the time scale with which the target cell levels rise. This makes HIV transiently target cell limited.

**Conclusion.** In a food-chain model of an HIV infection where the immune response
is a top-predator it may seem likely that the immune-control dominates of the target-cell-limitation (Nowak & Bangham, 1996). In many situations this need not be correct however. The first effect of an antiretroviral treatment in a food-chain model is expected to be the eradication of the immune response, i.e., of the top-predator. This makes the HIV infection target-cell-limited, and as a consequence vulnerable to eradication by more intensive treatment.

**Discussion**

The available data do not allow us to distinguish between our simple target cell limited and immune control models. One approach is to concentrate on the more complicated “food-chain” or “combined” models that incorporate target cell limitation, virus, and immune control (Nowak and Bangham, 1996; De Boer et al. submitted; Müller and De Boer, submitted). We have seen above however that such models suffer from a non-robustness because adding another level to the food-chain, i.e., any population down-regulating the immune response, has a major impact on the results. Additionally, realistic models should allow for saturation (cf. Eq. 10 and/or competition, cf. Eq. 13) effects. It is well known in theoretical ecology that in food-chain models such effects easily lead to humped-shaped nullclines, Hopf-bifurcations, high amplitude oscillatory behavior and/or chaos. (Hastings and Powell, 1991). Thus, the behavior of such a model soon becomes too complex for addressing the simple questions of interest in HIV infection.

Elsewhere (Müller and De Boer, submitted), we study the differences between target cell limited and immune control models by concentrating on the variations in the viral load that both control mechanisms can account for. Individuals differ widely, i.e., orders of magnitude in their viral loads (Mellors et al., 1996). Immune control models seem to have little difficulty explaining this because (i) individuals are expected to differ widely in their immune responsiveness (e.g., because of MHC differences), and (ii) the viral load can be inversely proportional to the immune responsiveness parameter $\alpha_E$ (Nowak and Bangham, 1996). A problem with all current immune control models is that the turnover rate constant for productively infected cells, i.e., $\delta$ in the model of Perelson et al.(1996) or $kE$ in our model, shows very little variation amongst individuals (Ho et al., 1995; Wei et al., 1995; Perelson et al., 1996; Klererman et al., submitted). This poses a strong constraint on the variation in the viral load current immune controls can account for (Müller and
De Boer, submitted). We have taken this to suggest that the mechanism of immune control is largely non-cytotoxic (Müller and De Boer, submitted). Accounting for the wide variations in viral load in target cell limited models is also problematic because target cell availability is not expected to differ by orders of magnitude among different HIV infected individuals. Variation in T cell activation does allow for some variation in viral loads however (cf. Fig. 2b).

Although the available data do not allow us to conclude whether HIV infection is target cell limited or immune controlled, there is convincing evidence that target cell availability plays a role. Increasing target cell levels by IL-2 treatment (Kovacs et al., 1995) or by vaccination (Staprans et al., 1995; O'Brien et al., 1995; Cheeseman et al., 1996; Stanley et al., 1996) tends to increase the virus load. Because such therapeutic interventions are perturbations of the clinical latency equilibrium, the reported effects on the viral load could just reflect a transient impact of increased target-cell-availability. Thus, these data do not rule out the possibility that the equilibrium viral load is completely immune controlled (cf. De Boer et al., submitted). Similar ambiguities are to be expected in other experiments manipulating target cell numbers.

Another experimental approach would be to measure the effect of therapeutic perturbations of the clinical latency equilibrium on the specific anti-viral immune response. Recent data show that CD8 cell numbers, and several non-specific immune responsiveness parameters, increase when viral loads drop by antiretroviral treatment (Kelleher et al., 1996). If the same were true for the specific anti-viral immune response, we would argue that the immune response is limited by the HIV infection, instead of the other way around.

Acknowledgements

Portions of this work were performed under the auspices of the U.S. Department of Energy. This work was supported by the National Institutes of Health (RR06555) and the Santa Fe Institute Theoretical Immunology Program through a grant from the Joseph P. and Jeanne M. Sullivan Foundation. Our scientific collaboration was further supported by a grant from NATO (GRC960019).
Appendix

We further analyze the self-renewal in the activated T cell model by making a quasi-steady state assumption for the activated cells, in the absence of the virus. Setting $dT/dt = 0$ in Eq. (5b) we obtain

$$T = \frac{\alpha_Q}{r} Q,$$  \hspace{1cm} (A.1)

which shows that the fraction of activated cells is given by the ratio $\alpha_Q/r$.

Because $dT/dt = 0$ we may add Eq. (5b) to (5a). By substituting Eq. (A.1) into (5a) we obtain for the quiescent cells

$$\frac{dQ}{dt} = \frac{\alpha Q}{1 + \kappa Q} - \delta Q,$$  \hspace{1cm} (A.2)

where $\alpha = 2\alpha_Q$, $\delta = \delta_Q + \alpha_Q$ and $\kappa = (1 + \alpha_Q/r)/T_{max}$. The maximum per capita growth rate is $\alpha - \delta = \alpha_Q - \delta_Q$, which for our estimate $\delta_Q = 0.001$ is approximately equal to $\alpha_Q$.

This model is identical to an earlier model of ours (De Boer & Perelson, 1994), which was developed from realistic T cell activation schemes.

The non-trivial equilibrium of Eq. (A.2) is at

$$Q = \frac{\alpha - \delta}{\kappa \delta}.$$  \hspace{1cm} (A.3)

Because the CD4 cell count is $Q + T = Q(1+\alpha_Q/r)$, we obtain for the uninfected equilibrium CD4 cell count

$$\text{CD4} = \frac{\alpha_Q - \delta_Q}{\alpha_Q + \delta_Q} T_{max},$$  \hspace{1cm} (A.4)

which always remains below $T_{max}$.  

19
References


De Boer, R. J., Müller, V. & Boucher, C. A. B. The control of HIV infection: can anti-viral therapy be enhanced by target cell depletion? Submitted.


Kovacs, J. A., Baseler, M., Dewar, R. J., Vogel, S., Davey, R. T., Falloon, J., Polis, M. A.,


Müller, V. & De Boer, R. J. Mathematical models of HIV-1 infection incorporating a non-cytotoxic cellular immune control of the virus. Submitted.


**Figure legends**

Figure 1. Nullclines of the target-cell-limited models. Making quasi-steady state assumptions for the virus particles, and for target cells in the activated T cell model, both models become two-dimensional, and can be analyzed in a phase-plane. The heavy line is the nullcline of the prey species (T or Q) and the light line is the nullcline of the predator, I. Panel (a) depicts the logistic model for $\beta = 7.5 \times 10^{-4}$, $\alpha_T = 0.1 \text{ day}^{-1}$, and $T_{max} = 1000$ cells. Panel (b) depicts the activated T cell model for $\alpha_Q = 0.13$, $r = 1$, $\delta_Q = 0.001$, $\beta = 0.01$, and $T_{max} = 1100$. Invariant parameters: $p = 10 \text{ day}^{-1}$, $\delta_I = 0.5 \text{ day}^{-1}$, and $c = 3 \text{ day}^{-1}$.

Figure 2. Disease progression studied by continuing the clinical latency equilibrium as a function of a “progression” parameter. The light line is the CD4 count per $\mu l$ on a linear scale. For the logistic model (a) we pick the infection rate $\beta$ as the disease progression parameter. (It should be noted that the equilibrium is involved in a Hopf bifurcation around $\beta = 0.0014$, not shown.) For the activated T cell model we obtain realistic disease progression by picking the T cell activation rate $\alpha_Q$ as a progression parameter.

Figure 3. Nullclines of the three immune-control models. The heavy line is the nullcline of the prey species (i.e., I) and the light line is the nullcline of the predator, E. Parameters: (a) $\alpha_E = 0.002$, $\epsilon_V = \epsilon_E = 0$; (b) $\alpha_E = \epsilon_V = 2.5 \times 10^{-3}$, $\epsilon_E = 0$; (b) $\alpha_E = \epsilon_V = 3.75 \times 10^{-3}$, $\epsilon_E = 1$; Invariant parameters: $\delta_E = 0.2 \text{ day}^{-1}$, $p = 10 \text{ day}^{-1}$, $\delta_I = 0.5 \text{ day}^{-1}$, and $c = 3 \text{ day}^{-1}$.

Figure 4. A two-fold effective RT-inhibitor treatment. The light lines depict the nullclines of Fig. 1b and 3c, respectively. The effect of reducing $\beta$ two-fold in the activated T cell model (a) and in the immune control model of Fig. 3c (b) is depicted by the heavy nullclines. The gray lines depict trajectories corresponding to this anti-viral treatment. One observes that the viral load (as measured by the I variable) initially declines, and ultimately attains an equilibrium level that is similar to the pre-treatment level.

Figure 5. Protease and RT-inhibitor treatment. (a,b) the equilibrium viral load (dark line) and CD4 T cell count (light line) as a function of the infection rate, $\beta$, and the virion production rate, $p$, in the activated T cell model. (c,d) the equilibrium viral load (dark line) and the effector cell level, E (light line). One observes that the effects of drug therapy
and resistance are largely reflected in the CD4 T cell count (a,b) or in the immune response level (c,d); up to the bifurcation points the viral load hardly changes.
Fig. 3
Fig. 5