

# Target cell limited and immune control models of HIV infection: a comparison

Rob J. De Boer<sup>1</sup> and Alan S. Perelson<sup>2</sup>

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<sup>+</sup> 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<sup>+</sup> 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<sup>+</sup> 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  $\sim 140$  generations per year (Perelson *et al.*, 1996), that CD4<sup>+</sup> T cells are replenished at an average rate of about ten cells per  $\mu\text{l}$  per day (Ho *et al.*, 1995; Wei *et al.*, 1995), and that the average total HIV-1 production is about  $10^{10}$  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<sup>+</sup> 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<sup>+</sup> 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<sup>+</sup> 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<sup>+</sup> 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  $0.1 \text{ day}^{-1}$  (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  $\mu\text{l}$ . 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).