

A model for the immune system response to HIV: AZT treatment studies¹

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Denise E. Kirschner²
Department of Mathematics
Texas A & M University
College Station, Texas 77843-3368
w:409-845-7955, FAX:409-845-6028
e-mail:dek@math.tamu.edu

Alan S. Perelson
Theoretical Division
Los Alamos National Laboratory
Los Alamos, New Mexico 87545
w:505-667-6829, FAX:505-665-3493
e-mail: asp@receptor.lanl.gov

Abstract

We use mathematical models to describe the interaction of the immune system with the human immunodeficiency virus (HIV). Our model includes T-lymphocytes and macrophages, cells which can be infected with the virus. Using our model we compare the efficacy of AZT treatments given at different stages of disease progression in order to predict when treatment should be initiated.

Key words: Model, ordinary differential equations, immunology, macrophages, HIV, AZT chemotherapy

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²Also in: Department of Medicine, Division of Infectious Diseases, Vanderbilt University School of Medicine.

18.1 Introduction

Over the past decade, a number of mathematical models have been developed to describe the interaction of the immune system with the human immunodeficiency virus (HIV). For example, Merrill (1989), Nowak *et al.* (1990), Nowak and May (1990, 1991, 1992), McLean (1988, 1990), McLean and Nowak (1991), Anderson and May (1989), Nelson and Perelson (1992), and Harnevo (1993). Different phenomena are explained by the different models, but none of the models exhibit all of what is observed clinically. This is partly due to the fact that much about this disease's mechanics is still unknown. However, many of the major features can be simulated with even the simplest of models.

Perelson (1989) presented a simple model for the interactions of HIV in the immune system. Perelson *et al.* (1993) extended these previous results and rigorously established some of the model's behavior seen in simulations. The model exhibited many of the characteristics of AIDS seen clinically: the long latency period, low levels of free virus in the body, and the depletion of $CD4^+$ T4 cells. The effects of AZT were studied in a preliminary way. Here, we extend that model by including macrophages and monocytes, cells that are thought to be reservoirs for HIV (Peluso *et al.*, 1985). We also do a more complete study of AZT treatment, and compare therapy strategies particularly with regard to the timing of the initiation of AZT treatment.

Zidovudine (AZT) is presently one of the FDA approved drugs used in the treatment of HIV infected individuals. Three others also approved are in the dideoxynucleoside family. These drugs all work as inhibitors of reverse transcriptase. HIV is an RNA virus. When HIV infects a cell, its RNA is transcribed into DNA (a unique feature of a retrovirus). AZT interferes with this process—halting cellular infection and spread of the virus.

There is much available data on AZT treatment (*e.g.* McLeod *et al.*, 1992; Hirsch, 1990). Many laboratories and clinics are keeping close accounts of patient treatment courses with respect to effectiveness and results. Of interest here is the fact that there are conflicting results as to whether treatment at the early stage of disease (defined as $CD4^+$ T cell counts between 200–500/mm³ of blood) (Fischl, 1990; Graham, 1992) or later stage (below 200/mm³) (Hamilton, 1992; Cox, 1990) is better. Other questions regarding chemotherapy are whether the dosage should be large (defined as 800–1500 mg/day) or small (defined to be less than 700 mg/day) (Cooper, 1991), and what should be the duration of treatment (Volberding, 1990). Further questions involve the possibility of combined chemotherapy treatments, drug side effects, chemotherapy scheduling, and drug resistance. This paper deals specifically with the question of treatment stage, given a fixed time frame of two years for treatment, based on resistance and side effect developments.

18.2 Presentation of simple model

In order to generate a realistic model of infection by HIV, we need to take into consideration a number of features of the life history of the virus. HIV is a retrovirus. When it infects a $CD4^+$ T cell ($CD4^+$ T4 cell), the enzyme reverse transcriptase which it produces, makes a DNA copy of its genome. This DNA copy is then integrated into the DNA of the infected cell. The viral DNA, called the provirus,

will be duplicated with the cell's DNA every time the cell divides. Thus a cell, once infected, remains infected for life. Within a T cell the provirus can remain latent, giving no sign of its presence for months or years (Ho *et al.*, 1987).

Stimulation of the T cell by antigen can lead to the production of new virus particles that bud from the surface of the infected cell. The budding can take place very rapidly, leading to the lysis of the host cell (this seems to be the case in CD4⁺ T4 cell infection), or it can take place slowly and spare the host cell, as seen in macrophages and monocytes.

Perelson (1989) and Perelson *et al.* (1993) modeled these events by considering cells that are uninfected, cells that are latently infected, i.e., that contain the virus but are not producing it, cells that are actively infected, i.e., that are producing virus, and the population of free viral particles. They described the dynamics of these populations by the system of ordinary differential equations that we give below.

Let T denote the concentration of uninfected CD4⁺ T4 cells, and let T^* and T^{**} denote the concentrations of latently infected and actively infected CD4⁺ T4 cells. The concentration of free infectious virus particles is V . Definitions and numerical information for the parameters can be found in Table 18.1. We assume that the dynamics of the various populations are:

$$\frac{dT}{dt} = s - \mu_T T + rT \left(1 - \frac{T + T^* + T^{**}}{T_{max}}\right) - k_1 VT, \quad (1)$$

$$\frac{dT^*}{dt} = k_1 VT - \mu_T T^* - k_2 T^*, \quad (2)$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**}. \quad (3)$$

$$\frac{dV}{dt} = N\mu_b T^{**} - k_1 VT - \mu_V V \quad (4)$$

In (1), s is a source term and represents the rate of generation of new (presumably uninfected) CD4⁺ T4 cells. T cells have a finite life-span and die with rate μ_T per cell. In (2), latently infected T cells are also assumed to have the same natural death-rate, μ_T , although other factors can augment the natural death rate (*i.e.* we assume that although the cell is a host to virion, it is unaffected by their presence). In (1), r represents the growth rate of T cells.

The other terms in (1) and (2) deal with the effects of HIV. The term $k_1 VT$ models the rate that free virus V infects CD4⁺ T4 cells. Once a T cell has been infected, it becomes a latently infected or T^* cell: thus this term is subtracted from (1) and added to (2).

Equation (3) models the actively infected CD4⁺ T4 population. At rate $k_2 T^*$, latently infected cells become actively infected. Actively infected cells produce virus and die at rate μ_b . Equation (4) models the free virus population. We assume that when an actively infected CD4⁺ T4 cell becomes stimulated through exposure to antigen, replication of the virus is initiated and N viruses are produced before the host cell dies. Free virus is lost by binding to uninfected CD4⁺ T4 cells at rate $k_1 VT$. Infected cells tend to lose their CD4, and hence binding to infected cells is neglected. The next term, $-\mu_V V$, accounts for viral loss of infectivity and/or removal from the body.

In the absence of virus, the T cell population has the steady state value

$$T_0 = \frac{T_{max}}{2} \left[1 - \frac{\mu_T}{r} + \sqrt{\left(1 - \frac{\mu_T}{r}\right)^2 + \frac{4s}{rT_{max}}} \right].$$

Thus reasonable initial conditions for this system of equations are $T(0) = T_0$, $T^*(0) = 0$, $T^{**}(0) = 0$, and $V(0) = V_0$ for infection by free virus, or $T(0) = T_0$, $T^*(0) = T_0^*$, $T^{**}(0) = T_0^{**}$, $V(0) = V_0$ for infection by both infected cells and virus.

This system has two steady states. The first, when no virus is present (the *uninfected steady state*), occurs when $T = T_0$, $T^* = 0$, $T^{**} = 0$ and $V = 0$. The second (the *endemically infected steady state*) has each of the cell populations at positive values. We showed, in Perelson *et al.* (1993), that if the parameter N was below a critical value, N_{crit} , the uninfected steady state is stable and the infected steady state is unstable. At $N = N_{crit}$, the stability is exchanged through a transcritical bifurcation and the infected steady state becomes locally stable. For $N > N_{crit}$, we could not show global stability because other bifurcations can occur. For example, stability can be lost for the infected steady state giving rise to stable limit cycles. We believe this only occurs for parameter values that lie outside of the biologically possible ranges.

In Perelson *et al.* (1993) AZT treatment was studied with this simple model. The model showed that if the number of virion produced per CD4⁺ T4 cell is forced below N_{crit} through AZT treatment, then the immune system can recover to state where the uninfected state is stable. Otherwise, infection still ensues.

18.3 Presentation of an extended model

We now extend this simple model by including the macrophage/monocyte (mac/mono) cell population. According to Meltzer *et al.* (1990), there are approximately 6000/mm³ white blood cells in a healthy human. No more than 5% of these are in the mac/mono population. Approximately 10% of these cells are CD4⁺ (Pauza, 1988), hence an initial condition for uninfected macrophages would be $M(0) = 30/\text{mm}^3$. The reasons for including the macrophage/monocyte cell populations are many. HIV is cytopathic in CD4⁺ T4 helper cells; however, macrophages/monocytes survive once infected, and slowly bud new virus particles. They, therefore, play a role as a viral source referred to as a reservoir. Also of importance is the fact that infected macrophages appear to be able to infect CD4⁺ T4 cells through presentation of antigen. We assume this happens at a rate of 1×10^{-6} per day (MMWR, 1989; Unanue *et al.*, 1968). Macrophages have a long life span, so we take the death rates to be 5×10^{-3} per day (Delemarre *et al.*, 1990).

Modifying equations (1)-(4) to include the macrophage terms, we have the following model describing the interactions of HIV in the immune system:

$$\frac{dT}{dt} = s - \mu_T T + rT \left[1 - \frac{T + T^* + T^{**}}{T_{max}} \right] - [k_1 V + k_3 M^*] T, \quad (5)$$

$$\frac{dT^*}{dt} = (k_1 V T + k_3 M^* T) - \mu_T T^* - k_2 T^*, \quad (6)$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**}, \quad (7)$$

$$\frac{dV}{dt} = N\mu_b T^{**} + \Pi_M M^* - \mu_V V - k_1 VT, \quad (8)$$

$$\frac{dM}{dt} = \mu_M (E_M - M) - k_4 VM, \quad (9)$$

$$\frac{dM^*}{dt} = k_4 VM - \mu_{M^*} M^*$$

Specific explanations of all terms in this model come directly from the simple model, except for the added macrophage terms. Here, in Equation (5), we have a further loss term due to infected macrophages infecting CD4⁺ T4 cells. In equation (6), this effect is represented as a gain term for the infected population. In equation (8), we have a new source term for viral production from infected macrophages. Here, we point out the differences between N , which is a non-dimensional scaler representing the number of virus produced during the lifetime of an actively infected CD4⁺ T4 cell, and Π_M which is a rate of viral production per unit time in macrophages. However, both represent a production of new virion particles at some level. For the two new equations, (9) and (10), we represent the birth/death of macrophages as an equilibrium where we think of $\mu_M \cdot E_M$ as the "source" for macrophages above some equilibrium, and μ_M as a natural death rate. This is followed by a mass action infection term which is carried to the last equation as a source; and finally a loss term due to natural death. Notice, we have assumed that there is no latently infected macrophage population since the virus seems to always replicate once inside them. We also assume that macrophages produce virus at a slow constant rate, sparing the host cell, so there is only natural death, not death by bursting like that for infected CD4⁺ T4 cells.

18.4 Analysis of extended model

To begin the analysis of the larger system, we will first seek equilibrium solutions. Setting the left hand sides of (6),(7),(9), and (10) to zero yields

$$T^* = \frac{k_1 VT + k_3 M^* T}{\mu_{T^*} + k_2}, \quad (11)$$

$$T^{**} = \frac{k_2}{\mu_{T^*} + k_2} \left(\frac{k_1 VT + k_3 M^* T}{\mu_{T^*} + k_2} \right)$$

$$M = \frac{\mu_M E_M}{k_4 V + \mu_M},$$

$$M^* = \frac{k_4 V}{\mu_{M^*}} \left(\frac{\mu_M E_M}{k_4 V + \mu_M} \right)$$

Substituting (12) and (14) into (8) we find

$$\frac{dV}{dt} = N\mu_b \frac{k_2}{\mu_{T^*}} \left(\frac{k_1 VT + k_3 M^* T}{\mu_{T^*} + k_2} \right) + \Pi_M \frac{k_4 V}{\mu_{M^*}} \left(\frac{\mu_M E_M}{k_4 V + \mu_M} \right) - \mu_V V - k_1 VT \quad (15)$$

The equation $\frac{dV}{dt} = 0$ has two possible solutions, $\bar{V} = 0$ and

$$\bar{T} = \frac{\mu_V - \Pi_M \frac{k_4 V}{\mu_{M^*}} \left(\frac{\mu_M E_M}{k_4 V + \mu_M} \right)}{\left[\frac{N \mu_b k_2 k_1}{\mu_T} - k_1 + \frac{N \mu_b k_2}{\mu_T} \left(\frac{k_3 k_4}{\mu_T} \frac{\mu_M E_M}{k_4 V + \mu_M} \right) \right]}$$

If $V = 0$, then from (11), (12), and (14) $T^* = T^{**} = M^* = 0$. Substituting into Equation (11) and (13), we again find there exists one steady state in which the virus is totally absent, with the steady state values for $\bar{T} = T_0$ as before and a steady state for the macrophage population being $\bar{M} = E_M$. For the other case, arising from the second solution, (15), we again, have an endemically infected steady state. In this state we have the following values: ((12) comes from $\frac{dT}{dt} = 0$)

$$\bar{T} = \frac{\mu_V \mu_T \mu_{M^*} (k_4 \bar{V} + \mu_M) - \Pi_M k_4 \mu_T \mu_M E_M}{\mu_{M^*} (N \mu_b k_2 [k_1 k_4 + k_1 \mu_M + \mu_M E_M] - \mu_T k_1 (k_4 \bar{V} + \mu_M))},$$

$$\bar{T}^* = \frac{k_1 \bar{V} \bar{T} + k_3 \frac{k_4 \bar{V}}{\mu_{M^*}} \left(\frac{\mu_M E_M}{k_4 \bar{V} + \mu_M} \right)}{\mu_{T^*}},$$

$$\bar{T}^{**} = \frac{k_2}{\mu_{T^*}} \frac{k_1 \bar{V} \bar{T} + k_3 \frac{k_4 \bar{V}}{\mu_{M^*}} \left(\frac{\mu_M E_M}{k_4 \bar{V} + \mu_M} \right)}{\mu_{T^*}}. \quad (19)$$

$$\bar{M} = \frac{\mu_M E_M}{k_4 \bar{V} + \mu_M}. \quad (20)$$

$$\bar{M}^* = \frac{k_4 \bar{V}}{\mu_{M^*}} \left(\frac{\mu_M E_M}{k_4 \bar{V} + \mu_M} \right), \quad (21)$$

$$\bar{V} = \frac{s - \mu_T \bar{T} + r \bar{T} \left[1 - \frac{T_{TOT}}{T_{max}} \right] - k_3 \bar{M}^* \bar{T}}{k_1 \bar{T}}. \quad (22)$$

These steady states are in implicit form. To express them explicitly we must solve (22), the equation for \bar{V} . Substituting the expressions for \bar{T} and \bar{M}^* into (22), we get a fifth order polynomial in \bar{V} of the form $a\bar{V}^5 + b\bar{V}^4 + c\bar{V}^3 + d\bar{V}^2 + e\bar{V} + f$. We wish to apply Descartes rule of signs to this polynomial to determine the number of positive roots. It is easy to show $\hat{a} > 0$, $\hat{b} < 0$ and $\hat{f} < 0$, as they are all composed of terms of the same sign. However, the signs of the remaining coefficients could not be determined analytically. Checking the signs using the values given in Table 18.1, we find that all the remaining signs are negative. This would indicate that there is only one sign change in the quintic polynomial, hence only one positive root. Interesting additional analysis would investigate the possibility of multi-feasible steady states through parameter changes. We will refer to the one positive steady state value as \bar{V} , and continue to write the steady states in implicit form.

The Jacobian matrix for the system (5)–(10) is given by: $\bar{A} =$

$$\begin{pmatrix} \bar{a} & -\frac{r\bar{T}}{T_{max}} & -\frac{r\bar{T}}{T_{max}} & -k_1\bar{T} & 0 & -k_3\bar{T} \\ k_1V + k_3M^* & -\mu_T - k_2 & 0 & k_1\bar{T} & 0 & k_3\bar{T} \\ 0 & k_2 & -\mu_b & 0 & 0 & 0 \\ -k_1V & 0 & N\mu_b & -\mu_V - k_1\bar{T} & 0 & \Pi_M \\ 0 & 0 & 0 & -k_4\bar{M} & -\mu_M - k_4V & 0 \\ 0 & 0 & 0 & k_4\bar{M} & k_4\bar{V} & -\mu_M^* \end{pmatrix}$$

with

$$\bar{a} = s - \mu_T - k_1\bar{V} + k_3\bar{M}^* + r\left[1 - \frac{(2\bar{T} + \bar{T}^* + \bar{T}^{**})}{T_{max}}\right].$$

It can be easily shown that in both the uninfected and infected steady states with parameter values from Table 18.1, the value of \bar{a} is negative.

For the uninfected steady state to be asymptotically stable we require that after an introduction of a small amount of virus, $dV/dt < 0$. Setting $T = \bar{T}$ and $V = \bar{V}$ for the uninfected steady state values and examining (15), we find a restriction on N such that $dV/dt < 0$, if and only if

$$N < \bar{N}_{crit} \equiv \frac{\mu_T \cdot (\mu_T + k_2) [\mu_V \mu_M + k_1 \bar{T} \mu_M - \Pi_M k_4 \cdot \mu_M E_M]}{\bar{T} \mu_b k_2 [k_1 \mu_M + k_3 \cdot k_4 E_M]}.$$

This condition is equivalent to a condition on Π_M , namely,

$$\Pi_M < \frac{-N \bar{T} \mu_T k_2 [k_1 \mu_M + k_3 k_4 E_M] + \mu_T \cdot (\mu_T + k_2) [\mu_V \mu_M + k_1 \bar{T} \mu_M]}{k_4 \mu_M E_M}.$$

Typical values for the parameters of N_{crit} yield a range of $N_{crit} \in [1, 420]$. Notice the dependence of N_{crit} on Π_M . This dependence is one of the key features which separates the simple model from the macrophage model. In the previous model without macrophages, with the parameters given in Table 18.1, $N_{crit} = 774$. Thus, including macrophages as another source of virus production decreases N_{crit} to the point where N will almost always be greater than N_{crit} . Thus, HIV infections which would have died out in the absence of macrophages, are now able to persist if macrophages can be infected. Because the dynamics of the infection are governed by the parameters N and now Π_M , we expect there to be some interactive component, depending on both. Figure 18.1 shows a two parameter bifurcation diagram for the stability of the steady states. The region in the lower triangular portion of the graph is where the uninfected steady state is locally stable, and the upper region is where the endemically infected steady state is locally stable.

At $N = N_{crit}$, the uninfected and infected steady states merge, and, only for values of $N > N_{crit}$, is the endemically infected steady state in the positive orthant. This situation is similar to the results in the simple model (Perelson *et al.*, 1993). Also, there are parameters such that with $N > N_{crit}$, stability of the endemically infected state may be lost, and limit cycles may appear through a Hopf bifurcation.

18.5 AZT and other drug treatments

There have been a few models examining the affects of AZT on the immune system once infected with HIV. For example, McLean and Nowak (1992) have presented a

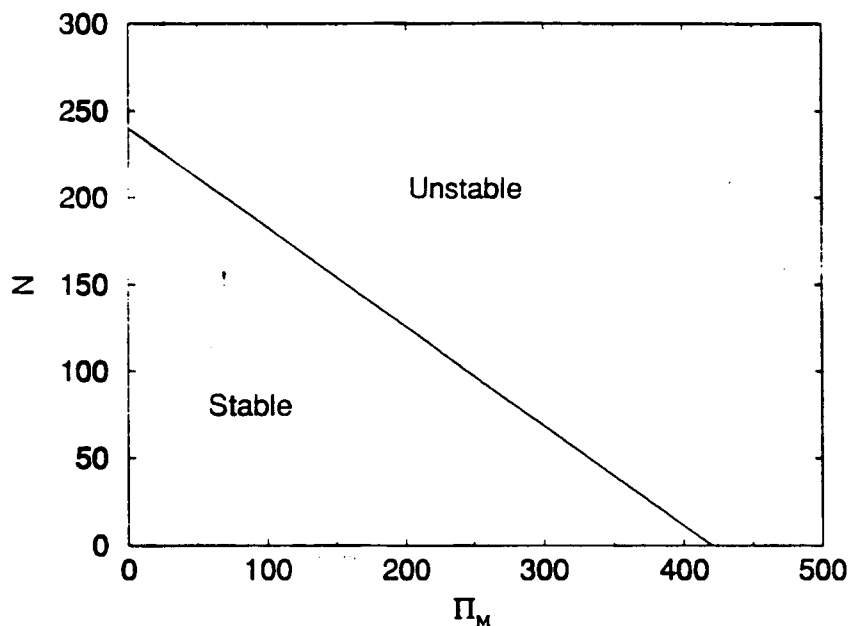


Figure 18.1: Graph of the two-parameter bifurcation between N and Π_M . The area below the line is the stable region for the uninfected steady state. The dependence of stability on both N and Π_M is expected as the production of virions depends significantly on both.

model dealing with the complication of the onset of AZT-resistant strains of HIV during treatment. Agur (1989) and Cojocaru and Agur (1992) have examined the effects of chemotherapy on normal, uninfected cells through cell cycle drug protocols.

This paper deals specifically with estimating an efficacious therapy regime to insure benefits to the patient. We base this 'benefit' solely on an increase or retention of the $CD4^+$ T cell count.

There is much clinical evidence to support the use of AZT in HIV infected individuals. Aside from the possibility of prolonging life in an HIV positive individual, it may make them less infectious to their sexual partners (Anderson *et al.*, (1993). Controversy exist, however, among clinicians as to who should be treated, when they should be treated and with what dose. Some studies have shown that treatment intervention of patients with $CD4^+$ T4 cell counts between 200 mm^{-3} and 100 mm^{-3} is the best possible approach (Fischl, 1990), and yet others argue treatment at the early stages of the disease with individuals who have little or no symptoms and higher than 200 mm^{-3} $CD4^+$ T4 cell count is the best therapy (Graham, 1992). The Concorde study was devoted entirely to this issue of early versus late treatment. The results of which seem to indicate that there may be no benefit from early treatment. A problem arising from the use of AZT is the multiple and sometimes harmful side effects, as well as the ineffectiveness of AZT after a certain time due to the capability of the virus to mutate and become resistant to AZT treatment. To mimic these effects, we only consider treatments that last two years, the typical time until resistance is observed (McLeod *et al.*, 1992).

We introduce the affect of a drug that reduces viral replication by multiplying the parameters N and Π_M by the scalar step function

$$z(t) = \left\{ \begin{array}{l} 1 \text{ outside the treatment period} \\ P \text{ during the time of AZT treatment.} \end{array} \right\}$$

The parameters, $N \cdot z(t)$ and $\Pi_M \cdot z(t)$ represent new virion production. Drugs such as AZT reduces virion production in a dose dependent manner. Therefore, P is proportional to the dose of the drug. (Another interpretation for the proportion P is that efficacy of the drug may differ from patient to patient: therefore, P could also represent the varying effectiveness of the drug in halting viral reproduction.)

18.6 Numerical results

In Perelson *et al.* (1993), we studied the behavior of the simple T cell model extensively. We used a combination of bifurcation theory and direct numerical solutions to characterize the dynamical behavior of the model under a biologically realistic range of parameter values. We found results which best represented the clinical data (*e.g* Conner *et al.*, 1993), were obtained when we allowed the source of CD4⁺ T4 cells, s , to be a monotonically decreasing function depending on the viral concentration, V . This models the possibility for infection of T cell precursors. In order to use the most realistic dynamic models of HIV infection in our studies of AZT treatment, we also take

$$s = s(V) = s\theta/(\theta + V) \text{ with } \theta \text{ a scaling parameter.} \quad (23)$$

in the numerical studies reported below.

18.6.1 Models without AZT

Numerical calculations of the simple and extended systems yield the numerical solution curves seen in Figures 18.2 and 18.3. If we compare the results, we see that in the T cell only model (Figure 18.2), the depletion occurs over a period of approximately two years, whereas in the macrophage model (Figure 18.3), the depletion occurs over a four to five year period. In the T cell model, the level of infection, as measured by free virus, V , or by infected cells, T^* and T^{**} , is much lower than in the macrophage model. Thus by acting as a reservoir the macrophages allow the occurrence of a much greater level of infection with, consequently, greater T cell depletion.

18.6.2 Effects of AZT

Using the extended model, which gave us realistic looking T cell depletion dynamics (*c.f.* Conner *et al.* 1993), we examine in Figure 18.4 the effects of a drug which reduces the number of infectious virions produced by infected CD4⁺ T4 cells and macrophages by (a) 25%, (b) 50%, and (c) 90%. For simplicity of presentation we only report effects on the concentrations of uninfected T cells. In both Figures 18.4b and 18.4c, this reduction of N changes the dynamics of the system in such a way

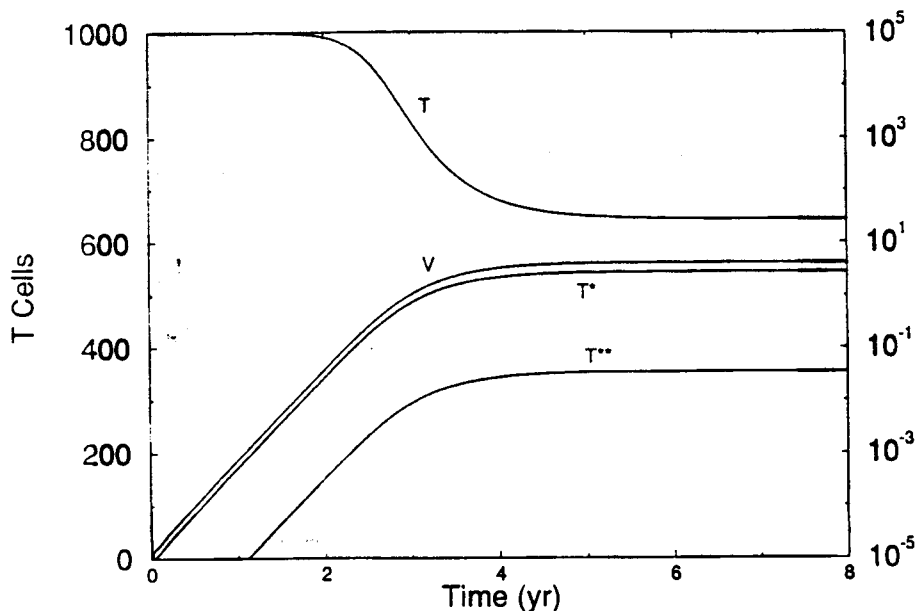


Figure 18.2: Graph of the system of Equations (1–4) with the parameter values given in Table 18.1 (Shown are dependent variable populations T , T^* , T^{**} , and V).

that T , rather than continuing to decline, begins to recover. The decline in N switches the stability of the steady states because N is now less than N_{crit} . If we were able to administer drug treatment for an unlimited amount of time, with no side effects, then, theoretically, we could suppress infection indefinitely. We also varied treatment protocol by beginning treatment at different starting points of disease progression, which is marked by numbers of CD4⁺ T4 cells. We began treatment just after the CD4⁺ T4 cell depletion begins, i.e. at 2 years, and after the CD4⁺ T4 cell count had fallen below 200, i.e. after 4 years. If we examine the graphs in Figure 18.4, we see the CD4⁺ T4 cell numbers are most affected by the treatment which is given at early stage of infection. The period of CD4⁺ T4 cell counts which are high is longest in this region, indicating that greater benefit to the immune system is achieved. This early treatment benefit is only now realized, and has been suggested as a more optimal treatment strategy (Temin and Bolognesi, 1993); however, this does not directly agree with the Concorde study.

18.7 Discussion

Two models have been presented here, both of which display features of HIV and AIDS effects to the human immune system. This suggests that even models as simple as these may have great value in attaining an understanding of AIDS and HIV's role in *in vivo* infection.

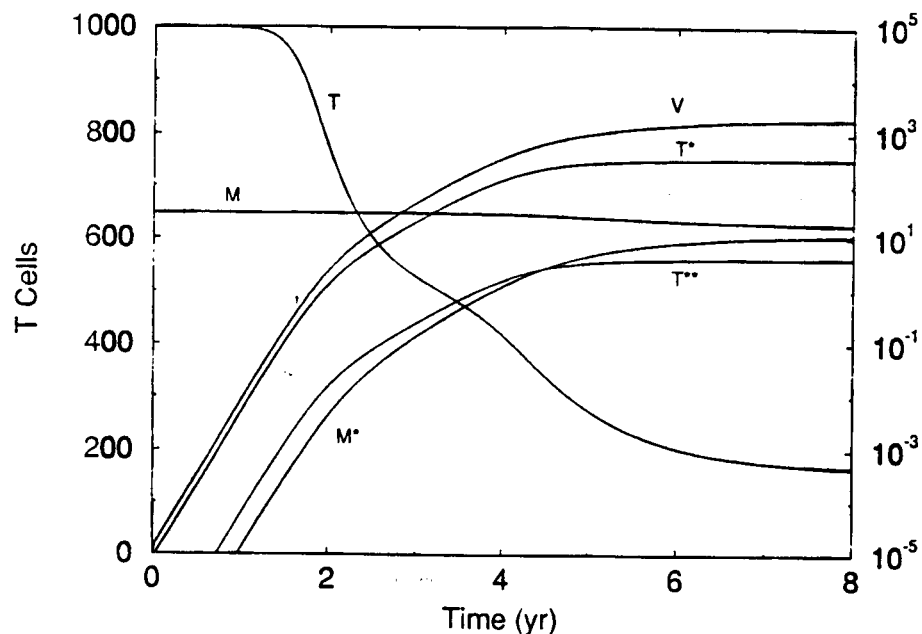


Figure 18.3: Graph of the system of Equations (5-10) with the parameter values given in Table 18.1 (Shown are dependent variable populations T , T^* , T^{**} , V , M , and M^*). Notice that the CD4⁺ T4 cell depletion occurs more slowly than in Figure 18.2.

One of the interesting predictions of the extended model, as with that of the simple model is that N , the number of virion produced per actively infected CD4⁺ T4 cell, needs to be above some critical level for HIV infection to persist and be fatal. There is evidence of different types of virion, referred to as 'rapid/high' and 'slow/low' (Fenyo *et al.*, 1988; Nara *et al.*, 1990). Rapid/high viruses grow rapidly in T cells and produce high numbers of new virus, whereas slow/low grow poorly in T cells. Slow/low virus, however, may grow well in macrophages, thus our two models can describe the survival of each of these populations separately.

The extended model served to reveal much beyond that of the simple model. First, the model exhibited slower depletion of CD4⁺ T4 cells as seen in many clinical cases. Second, the model lead to substantially greater depletion of T cells, even down to levels below 200 as seen in patients. Third, the critical virion production number was on the order of a ten times less than that of the simple model, implying persistence of infection in the presence of very few virions (although the initial inoculation may be large or small). And, lastly, using the extended model we were able compare the effectiveness of different treatment protocols for administering AZT, given that a patient can only receive benefit from the drug for a period of two years.

Our analysis of the simple model in Perelson *et al.* (1993) and our work here on the extended model reveal that if the effects of a drug force N below N_{crit} , then CD4⁺ T4 cell depletion can be halted. Introducing AZT at the beginning of the CD4⁺ T4 cell depletion, when T cell counts are still high, seems to be the

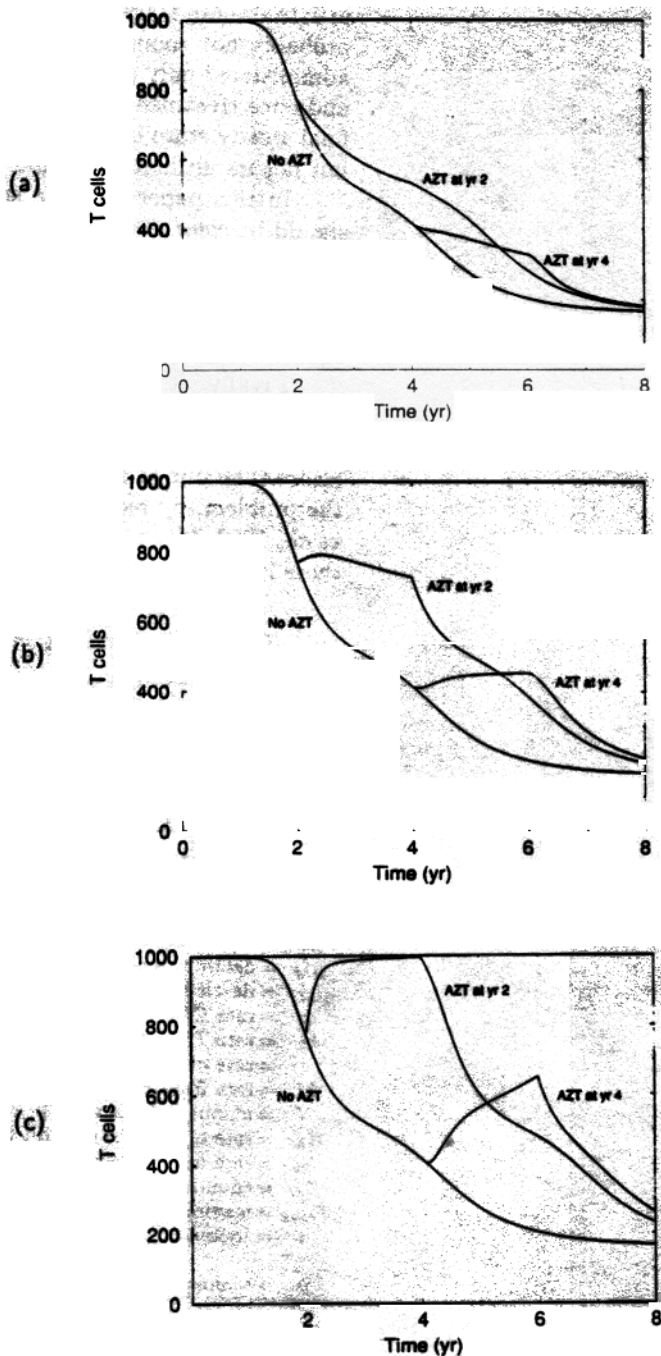


Figure 18.4: Numerical results of AZT treatment for equations (5)-(10). The reduction in number of virion produced by $CD4^+$ T4 cells and macrophages is (a) 25%, (b) 50%, (c) 90%. The different graphs represent T cell concentrations with no treatment, treatment after 2 years,

most beneficial. Given in the early stages of disease, the drug increases the time until profound T cell depletion occurs, and hence it should increase the time before opportunistic infections become a problem. This can be seen in Figure 18.4. Given in late disease stage the drug causes a minor improvement in T cell numbers but probably not enough of a recovery to be protective. However, since treatment is administered only during a two year regime, in both cases the recovery is transient and once treatment is stopped T cell numbers continue their decline and the same final steady state is reached. Thus, treatment changes the dynamics of the disease but not its ultimate outcome.

In this paper we have spoken extensively about AZT treatment, however it should be clear that the results apply to any treatment that can reduce viral replication rates. In fact, AZT being a reverse transcription inhibitor rather than a direct viral replication inhibitor only indirectly affects viral load. Kirschner and Webb (1994), however, have proposed a different model using partial differential equations and have more mechanistically modeled the effects of AZT treatment.

Finally, it is worrisome that early treatment of HIV infection with drug chemotherapy may, and usually has, lead to resistance later on. This, of course, will reduce the time frame therapy can be administered. New research with 'cocktails' (more than one at a time) of drug chemotherapy have shown promise in addressing the problem, by reducing the chance of mutation for resistance (Chow and Hirsch *et al.*, 1993; Meng *et al.*, 1992). New work by Kirschner and Webb (1995) explores these issues.

Table 18.1: Compilation of dependent variables, parameters and constants.

Dependent Variables	Initial Values
T = Uninfected CD4 ⁺ T4 cell population	1000 mm ⁻³
T^* = Latently infected CD4 ⁺ T4 cell population	0.0
T^{**} = Actively infected CD4 ⁺ T4 cell population	0.0
V = Infectious HIV population	1.0×10^{-3} mm ⁻³
M = CD4 ⁺ macrophage/monocyte population	30 mm ⁻³
M^* = Infected macrophage/monocyte population	0.0
Parameters and Constants	Values
μ_T = death rate of uninfected CD4 ⁺ T4 cell population	0.02 d ⁻¹
μ_{T^*} = death rate of latently infected CD4 ⁺ T4 cell	0.02 d ⁻¹
μ_b = death rate of actively infected CD4 ⁺ T4 cell	0.24 d ⁻¹
μ_V = death rate of free virus	2.4 d ⁻¹
μ_M = death rate of uninfected mac/mono population	5×10^{-3} d ⁻¹
μ_{M^*} = death rate of infected mac/mono population	5×10^{-3} d ⁻¹
k_1 = rate CD4 ⁺ T4 cells becomes infected by free	2.4×10^{-5} mm ³ d ⁻¹
k_2 = rate T^* cells convert to actively infected	3×10^{-3} d ⁻¹
r = rate of growth for the CD4 ⁺ T4 cell population	0.03 d ⁻¹
k_4 = rate free virus infects mac/mono cells	10^{-6} d ⁻¹
N = number of free virus produced by T^{**} cells	1200
Π_M = rate of free virus production by infected macrophages	300 d ⁻¹
k_3 = rate infected mac/mono infects CD4 ⁺ T4 cells (cell to cell)	10^{-6} d ⁻¹
E_M = equilibrium number for mac/mono population	30 mm ⁻³
T_{max} = maximum CD4 ⁺ T4 cell population level	1.5×10^3 mm ⁻³
s = source term for uninfected CD4 ⁺ T4 cells	
if source is not constant, see eqn.(23)	10 d ⁻¹ mm ⁻³
θ = scaling parameter for $s(V)$	1

References

- Agur, Z. (1989). A new method for reducing cytotoxicity of the anti-AIDS drug AZT. *Biomedical Modeling and Simulation*, ed. D.S. Levine., J.C. Baltzer AG, Scientific Publishing Co. **IMACS**, pp. 59–61.
- Anderson, D.J. *et al.* (1992). Effects of disease stage and AZT therapy on the detection of HIV-1 in semen. *Journal of the American Medical Association*. **267**, 20:2769–2774.
- Anderson, R.M. and May, R.M. (1989). Complex dynamical behavior in the interaction between HIV and the immune system. *Cell to Cell Signalling: From Experiments to Theoretical Models*. A. Goldbeter, ed. Academic Press, New York. pp. 335–349.
- Chow, Y. K. and Hirsch, M. S. *et al.* (1993). Use of evolutionary limitations of HIV-1 multidrug resistance to optimize therapy, *Nature*, **361**:650–655.
- Cojocaru, L. and Agur, Z. (1993). New mathematical methods for evaluating toxicity of anti-cancer drugs and AZT. Preprint.
- Concorde Coordinating Committee 1994. NRC/ANRS randomized double-blind controlled trial of immediate and deferred AZT in symptom-free HIV infection. *The Lancet*, **343**:871–81.
- Conner, R.I. *et al.* (1993). Increased viral burden and cytopathicity correlate temporally with CD4+ T-Lymphocyte decline and clinical progression in HIV-1 infected individuals. *Virology* April **67**:1772–1777.
- Cooper, D.A. *et al.* (1991). The efficacy and safety of AZT with or without acyclovir in the treatment of patients with AIDS related complex. *AIDS* **5**:933–943.
- Cox, H.P., *et al.* (1990). Outcomes of treatment with AZT of patients with AIDS and symptomatic HIV infection. *Nurse Practitioner* **15**:36–43.
- Delemarre, F.G.A., *et al.* (1990). Repopulation of macrophages in popliteal lymph nodes of mice after liposome-mediated depletion. *J. Leukocyte Biology* **47**:251–257.
- Fenyo, E.M., *et al.* (1988). Distinct replicative and cytopathic characteristics of HIV isolates. *Journal of Virology* **62**:4414–4419.
- Fischl, M.A., *et al.* (1990). The safety and efficacy of AZT in the treatment of subjects with mildly symptomatic HIV type 1. *Annals of Internal Medicine* **112**:727–737.
- Gendelman, H.E., Orenstein, *et al.* (1989). The macrophage in the persistence and pathogenesis of HIV infection. *AIDS* **3**:475–495.
- Graham, M.H., *et al.* (1992). The effects on survival of early treatment of HIV infection. *New England Journal of Medicine* **326**:1037–1042.
- Hamilton, J.D., *et al.* (1992). A controlled trial of early vs. late treatment with AZT in symptomatic HIV infection. *New England Journal of Medicine* **326**:437–443.

- Harnevo, L.E. (1993). Simple Models for interactions of the HIV and the immune system: can we point to a specific threshold for the onset of AIDS? (to appear) *Proceedings of the World Congress for Non-linear Analysts*.
- Hirsch, M.S., (1990). Chemotherapy of HIV infections: Current practice and future prospects. *Journal of Infectious Diseases* **161**:845-857.
- Ho, D.D., Pomerantz, R.J., and Kaplan, J.C. (1987). Pathogenesis of infection with human immunodeficiency virus. *N. Engl. J. Med.* **317**:278.
- Johnston, R.B. (1988). Monocytes and Macrophages. *Medical Intelligence* **346**:747-752.
- Kirschner, D. and Webb, G.F. (1994). A Model for the Treatment Strategy in the Chemotherapy of AIDS, (submitted to) *Journal of AIDS*, November 1994.
- Kerschner, D. and Webb, G.F. (1995). A Model for Resistance in the Chemotherapy of AIDS. (in preparation).
- McLeod, G.X., et al. (1992). Zidovudine: 5 years later. *Annals of Internal Medicine* **117**:487-501.
- McLean, A. (1988). HIV infection from an ecological viewpoint. *Theoretical Immunology, Part Two*, A.S. Perelson, ed., pp. 77-84.
- McLean, A., Nowak, M. (1991). Interactions between HIV and other pathogens. *Journal of Theoretical Biology* **155**:69-86.
- McLean, A., Nowak, M. (1992). Competition between AZT sensitive and AZT resistant strains of HIV. *AIDS* **6**:71-79.
- Meltzer, M.S., Skillman, D.R., et al. (1990). Macrophages and the human immunodeficiency virus *Immunology Today* **11**, 6:217-223.
- Meng, T.C. et al. (1992). Combination Therapy with AZT and DDC in patients with advanced HIV infection, *Annals of Internal Medicine*, **116**, 1:13-19.
- Merrill, S. (1989). Modeling the interaction of HIV with cells of the immune response. In *Mathematical and Statistical Approaches to AIDS Epidemiology*, C. Castillo-Chavez, ed., Lect. Notes in Biomath., Springer-Verlag, New York, **83**:371-385.
- MMWR (1989). Prevention and control of influenza: Recommendations of the Immunization Practices Committee, **38**:297-298, 303-11.
- Nara, P.L., et al. (1990). Emergence of viruses resistant to neutralization by V3-specific antibodies in experimental HIV type 1 IIIB infection of chimpanzees. *Journal of Virology* **64**:3779-3791.
- Nelson, G.W. and Perelson, A.S. (1992). A mechanism of immune escape by slow-replicating HIV strains. *Journal of Acquired Immune Deficiency Syndromes* **5**:82-93.
- Nowak, M.A., May, R.M., and Anderson, R.M. (1990). The evolutionary dynamics of HIV-1 quasispecies and the development of immunodeficiency disease. *AIDS* **4**:1095-1103.
- Nowak, M.A. and May, R.M. (1991). Mathematical biology of HIV infections: Antigenic variation and diversity threshold. *Math. Biosciences* **106**:1-21.

- Nowak, M.A. and May, R.M. (1992). Coexistence and competition in HIV infection. *Journal of Theoretical Biology* **159**: 329–342.
- Pauza, D.(1988). HIV persistence in monocytes leads to pathogenesis and AIDS. *Cellular Immunology* **112**:1–11.
- Peluso, R., *et al.*, (1985). A trojan horse mechanism for the spread of Visna in monocytes. *Virology* **147**:231–236.
- Perelson, A.S. (1989). Modeling the interaction of the immune system with HIV, *Mathematical and Statistical Approaches to AIDS Epidemiology*, C. Castillo-Chavez, ed., Lect. Notes in Biomath., Springer-Verlag, New York, **83**:350–370.
- Perelson A., Kirschner, D., DeBoer, R. (1993). The dynamics of HIV infection of CD4⁺ T cells. *Mathematical Biosciences* **114**:81–125.
- Temin, H.M. and Bolognesi, D.P. (1993). Where has HIV been hiding? *Nature*, **362**:292–293.
- Unanue E.R. *et al.* (1968). The immune response of mice to antigen in macrophages. *Immunology* **127**:287–96.
- Volberding, P.A., *et al.* (1990). AZT in asymptomatic HIV infection. *New England Journal of Medicine* **322**:940–949.