

Mathematical Models of the Complete Course of HIV Infection and AIDS

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Mathematical models of HIV infection are important to our understanding of AIDS. However, most models do not predict both the decrease in CD4+ T cells and the increase in viral load seen over the course of infection. By including terms for continuous loss of CD4+ T cells and incorporating alteration in viral clearance and viral production, two new models have been created that accurately predict the dynamics of the disease. The first model is a clearance rate reduction model and is based on a 10% per year decrease in both viral clearance and CD4+ T cell levels. A macrophage reservoir model incorporating the observation that macrophage viral production increases up to 1000 fold in the presence of opportunistic infections that become increasingly common as disease progresses. Both viral clearance and macrophage reservoir models predict the expected decrease in T cell levels and rise in viral load observed at the onset of AIDS.

Keywords: AIDS; Mathematical modeling; HIV; Macrophage reservoir; Viral clearance

INTRODUCTION

For most people, infection with HIV is the start of a progressive illness that results in death due to the increasing occurrence of opportunistic infections. The ultimate cause is the progressive degradation of the immune system by the virus resulting in AIDS. Mathematical models have been important to the study of AIDS. However, most current models do not predict the increase in viral load seen during the onset of AIDS. In the absence of a comprehensive model, applying quantitative mathematical techniques to test various explanations for AIDS to accurately predict the full course of disease has been problematic. Through the development of new models we hope to help clarify how HIV causes AIDS and perhaps aid in its solution.

HIV infection is characterized by three major phases: a peak in viral load following initial infection, a quasi steady state or latent phase where viral load rises slowly and CD4+ T cell counts fall for up to 10 years, and finally a dramatic rise in virus and a loss of CD4+ T cells associated with the development of AIDS (Pantaleo *et al.*, 1993).

Recent models, such as those shown in Fig. 1, predict the early phases of disease but do not predict the decrease in CD4+ T cell counts and rise in peripheral virus seen in

AIDS (Kapadvanjwala and Sofer, 1989; Perelson and Nelson, 1999; Stafford *et al.*, 2000; Gumel *et al.*, 2001). Viral production is based exclusively on CD4+ T cells, and all rates are considered to remain constant. Thus, as T cell counts drop in these models, so must the viral load. The paradox of a high viral load in the absence of normal T cell levels has yet to be solved satisfactorily.

dos Santos and Coutinho (2001) have recently reported a lymph node lattice model that predicts all three phases of the disease. In this model, CD4+ T cells are redistributed to the lymph nodes where the entire course of infection is hypothesized to occur. However, studies indicate that lymph nodes deteriorate over the course of infection indicating a long-term loss of lymphocytes, which is incompatible with the model (Rosenberg *et al.*, 1994; Orenstein *et al.*, 1997; Maas *et al.*, 1998; Bouhdoud *et al.*, 2000). Additionally, calculations based on several studies indicate that a large portion of the virus may be in the peripheral blood. In a typical patient, 10^9 – 10^{10} virus particles are produced per day in the entire body (Ho *et al.*, 1995; Perelson *et al.*, 1996). Assuming that the entire viral production enters the 5000 ml of blood in an average person, the concentration of the virus would be 2×10^5 – 2×10^6 copies per ml (cpm). Given a half-life of virus in blood of 6 h (Perelson *et al.*, 1996), in a 24 h period 94.25% of the virus would have been cleared leaving

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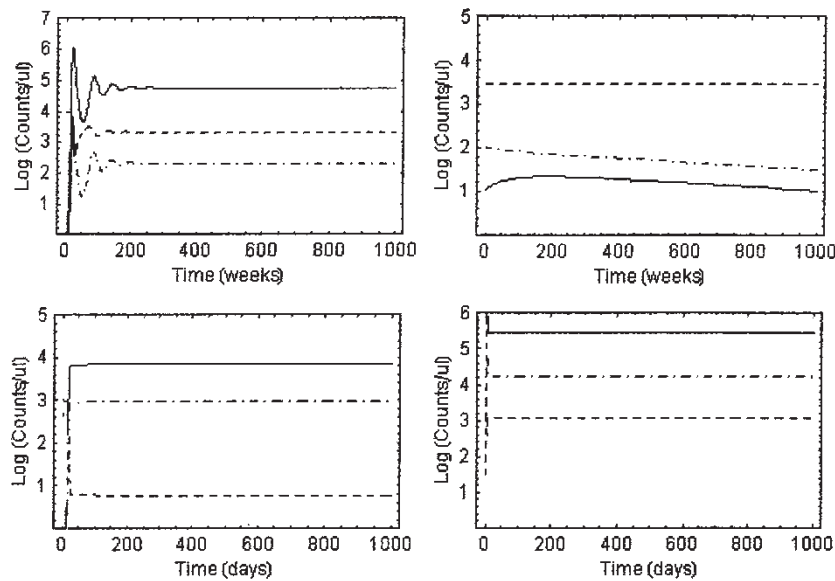


FIGURE 1 Recent mathematical models of AIDS. Clockwise from top left: Kapadvanjwala and Sofer, 1989; Perelson and Nelson, 1999; Stafford *et al.*, 2000; Gumel *et al.*, 2001. Virus (—), CD4 + T cells (---) and infected CD4 + T cells (— · —) Note: early dynamics are predicted, but not the fall of CD4 + T cells and rise in virus late in infection.

a final viral load of 13,500–135,000 cpm. Since these values are in good agreement with the typical viral loads reported for HIV patients in steady state measurements (Schacker *et al.*, 1996; Stafford *et al.*, 2000), it would seem that a large proportion of the virus produced each day actually enters the blood. Thus, any proposed model should account for both lymphatic and peripheral increases in viral load.

The dos Santos and Coutinho (2001) model represents just one explanation for the dynamics of an HIV infection. There are two further explanations which could account for high viral loads in the absence of normal CD4 + T cell counts. One of the hallmarks of AIDS is the inability of the body to efficiently clear infections of all kinds (Hansen *et al.*, 1985; Barr, 1992; Matsuo *et al.*, 2001). Thus, it is reasonable to hypothesize that as HIV infection progresses to AIDS, the immune system loses the ability to clear virus efficiently, resulting in a longer residence time for the virus population. We term this the viral clearance reduction hypothesis.

Another reasonable explanation is that there are other viral reservoirs that become larger or more active as T cells are lost and HIV infection progresses to AIDS. Although several cell types aside from CD4 + T cells can become productively infected, the prime candidate for such a reservoir seems to be HIV infected macrophages (Igarashi *et al.*, 2001). Infected macrophages are typically thought to account for less than 1% of the viral load early in infection. However, in the presence of opportunistic infections and other cellular factors, the viral production in these same cells can sharply increase (Kalter *et al.*, 1991; Orenstein *et al.*, 1997; Moriuchi *et al.*, 1998). Increased viral output coupled with the long life of macrophages (Perelson *et al.*, 1996) may account for

the increasing viral load seen in AIDS. We term this the macrophage reservoir model.

We address these issues using a simple target-cell-limited model with terms to account for a decreasing CD4 + T cell count, decreasing clearance rate, and release of virus from a macrophage reservoir. Although the hypotheses are formally independent, it should also be clear that a combination of the two is possible.

EQUATION PARAMETERS

Patient Data

Viral concentrations for the early phase of infection (up to day 500) were taken from 10 patients published by Stafford *et al.* (2000). Additional early phase data and viral concentrations from later in disease were obtained from cumulative patient data (Fauci *et al.*, 1996). These data were then used to compare predicted and observed viral load and CD4 + T cell counts.

The Equations

The equations below were taken from Stafford *et al.* (2000) and include activated CD4 + T cells (T), infected CD4 + T cells (T_i) in cells/ul, and virus concentration (V) in cpm

$$\begin{aligned} \frac{dT(t)}{dt} &= \lambda_T - d_T T - k_T TV, & T(0) &= T_0 \\ \frac{dT_i(t)}{dt} &= k_T TV - \delta_T T_i, & T_i(0) &= T_{i0} \\ \frac{dV(t)}{dt} &= \pi_T T_i - cV, & V(0) &= V_0 \end{aligned} \quad (1)$$

where $\lambda = dT_0$ is the rate of CD4 T cell production, k_T is the rate of infection of T cells, d_T is the death rate of normal T cells, δ_T is the death rate of productively infected cells, π_T is the rate of virus production (virions/cell/day) and c is the clearance rate constant for the virus.

Target-cell-limited models like this have been used in other studies as well (Nowak and Bangham, 1996; Bonhoeffer *et al.*, 1997). The Stafford model assumes that activated CD4+ T cells are the primary targets for the virus (Schnittman *et al.*, 1990). Activated CD4+ T cells represent approximately 1% of the total CD4+ T cell population (Sachsenberg *et al.*, 1998). Since there are an average of 1000 T cells/ul in normal blood (Perelson and Nelson, 1999), $T_0 = 10$ cells/ul. $T_{i0} = 0$ since initially no T cells are infected, and $V_0 = 1 \times 10^{-6} \text{ ml}^{-1}$ representing an arbitrarily small amount of virus present immediately after infection (Stafford *et al.*, 2000). The terms of the equations are summarized in Table I.

The Stafford model does not predict a change in T cell counts seen in the development of AIDS. In contrast HIV infected patients T cell counts drop steadily over the course of infection due to decreasing thymic function or a reduction in post-thymic CD4+ T cell proliferation (Douek *et al.*, 1998; Douek *et al.*, 2001). Based on patient data from Fauci *et al.* (1996), the rate of loss of CD4+ T cells was estimated at 10% per year after an initial drop of 40% in the first year (Fig. 2). The calculated 10% drop in CD4+ T cell matched the data very well. From this drop we derive the average loss of T cell production on any given day ($f = 0.00028t$). Thus the new production rate of activated T cells becomes $\lambda_t = (dT_0)(1 - f)$. Substituting

this new expression, λ_t , for λ_T now accurately reflects the gradual loss of T cells. As expected, this modification made to the model in terms of λ_t does not appreciably affect the predictions in the first year.

THEORY I. VIRUS CLEARANCE RATE REDUCTION MODEL

Modification of Clearance Rate Term

Research indicates that early in infection, CD4+ T cells account for more than 90% of the productively infected cells in the body (Haase, 1999). If CD4+ T cells remain the main source of virus throughout the course of infection, then the relationship between the immune system and the virus must change. It is possible that an HIV weakened immune system may lose the ability to clear virus efficiently, as it does with many types of pathogens (Hansen *et al.*, 1985; Barr, 1992; Matsuo *et al.*, 2001). Though some studies suggest that clearance rates do not change throughout infection (Ho *et al.*, 1995), there is a significant amount of variation in the measurements derived from different studies (Ho *et al.*, 1995; Mittler *et al.*, 1999; Ramratnam *et al.*, 1999). Thus, it is reasonable to hypothesize changes in viral clearance rates as we have done here. For the purpose of this model, we assume that the clearance rate of the virus, c , decays at the same rate as the activated T cell concentration. Thus, $c_t = c(1 - f)$. Figure 3 shows the kinetics of the entire course of infection when this term is added.

Model Kinetics

As shown in Fig. 3, the shape of the theoretical curve follows the patient data well. When viral clearance drops below some critical value, viral load actually increases even as T cells continue to decrease. At this point, any virus introduced into the system persists for a considerable period of time.

The only noticeable discrepancy is that the Fauci *et al.* (1996) data reach a steady state viral load approximately 10 times lower than the data presented in Stafford *et al.* (2000). This is likely due to increasingly sensitive viral quantification techniques, such as RT PCR, which have been improved over the past several years.

This model strongly suggests that small changes in viral clearance can account for large changes in peripheral viral load, a concept that to date has been largely ignored.

THEORY II. THE MACROPHAGE RESERVOIR MODEL

Recent data have supported the concept of infected macrophages as a second reservoir capable of sustaining high viral loads late in infection (Orenstein *et al.*, 1997; Igarashi *et al.*, 2001). In the presence of opportunistic

TABLE I Description of variables and constants

Terms	Description of variables and constants	Values (/ul)
λ_T	Rate of production of T cells	dT_0/day
λ_t	Rate of production of T cells with decay term (f)	$dT_0(1 - f)/\text{day}$
f	Decay of T cell production over course of infection (10%/year)	(0.00028t)
λ_M	Rate of production of macrophages	dM_0/day
d_T	Natural death rate of healthy T cells	0.01/day
d_M	Natural death rate of healthy macrophages	0.0037/day
k_T	Viral infection rate (CD4+ T cells)	0.00027/virus-day
k_M	Viral infection rate (macrophages)	0.00027/virus-day
δ_T	Death rate of infected T cells	0.39/day
δ_M	Death rate of infected macrophages	0.024/day
π_T	Viral production per T cell	850/day
π_M	Viral production per macrophage	$0.1 \times 10^3/\text{day}$
c	Clearance rate of the virus	3/day
c_t	Reducing clearance rate of virus over time	$c(1 - f)$
T	Uninfected activated CD4+ T cells	$T_0 = 10$
T_i	Infected CD4+ T cells	$T_{i0} = 10$
V	Virus produced by T cells	$V_0 = 10^{-6}$
M	Uninfected macrophages	$M_0 = 200$
M_i	Infected macrophages	$M_{i0} = 0$
V^*	Total virus from T cells and macrophages	$V_0^* = 10^{-6}$

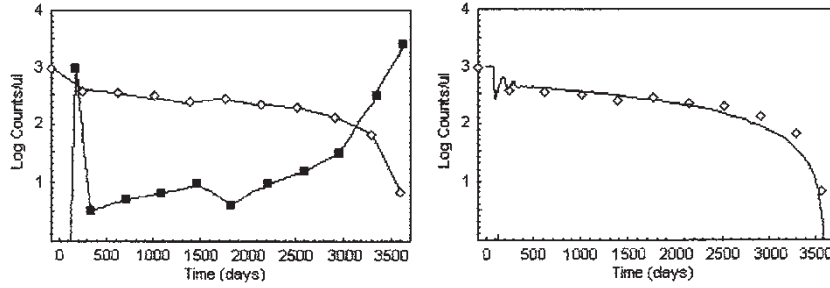


FIGURE 2 Patient data and predicted loss of CD4 + T cells. (left) Patient data for observed viral load (■) and loss of CD4+ T cells (◇) taken from Fauci *et al.* (1996). In the first year approximately 40% of the T cells are lost. (right) Comparison of predicted (—) and observed (◇) loss of CD4+ T cells in patients. Patient data follows a 10% a year decrease with $R^2 = 0.9099$ following the first year.

infections, which are strongly associated with AIDS, a sharp increase in viral production up to near 1000 fold has been reported (Moriuchi *et al.*, 1998; Kalter *et al.*, 1991). Orenstein *et al.* (1997) reported macrophage viral production that was too high to resolve by the techniques employed, indicating that increases in viral production may be higher still.

Using this information as a basis, equations that incorporate the concept of a macrophage second reservoir were derived and are presented below.

$$\begin{aligned} \frac{dT(t)}{dt} &= \lambda_T - d_T T - k_T TV^*, \quad T(0) = T_0 \\ \frac{dT_i(t)}{dt} &= k_T TV^* - \delta_T T_i, \quad T_i(0) = T_{i0} \\ \frac{dM(t)}{dt} &= \lambda_M - d_M M - k_M MV^*, \quad M(0) = M_0 \quad (2) \\ \frac{dM_i(t)}{dt} &= k_M MV^* - \delta_M M_i, \quad M_i(0) = M_{i0} \\ \frac{dV^*(t)}{dt} &= \pi_T T_i + \pi_M M_i - cV^*, \quad V^*(0) = V_0 \end{aligned}$$

These expressions include activated CD4+ T cells (T), infected CD4+ T cells (T_i), macrophage cells (M), infected macrophage cells (M_i), and combined T cell and macrophage viral load (V^*). In addition to coefficients

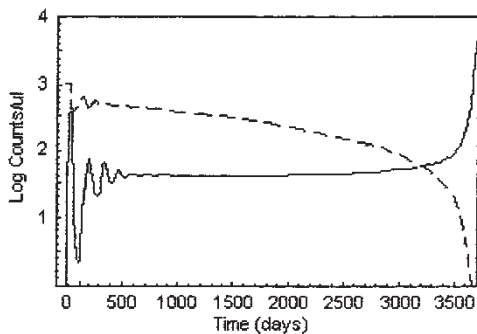


FIGURE 3 Clearance rate reduction model. Theoretical curves: viral load in copies/ul (—) and CD4 + T cell count in cells/ul, (---).

defined previously, λ_M is the production rate of macrophages, d_M is the death rate of health macrophages, δ_M the death rate of infected macrophages, k_M represents the infection rate of macrophages and π_M the production of virus by infected macrophages.

Parameter Estimations

Terms for the equations are also outlined in Table I above. For the purposes of calculation initial macrophage count, M_0 , is taken as 200 macrophages ul^{-1} and all macrophage cells are assumed capable of being infected. The term for the death rate of healthy macrophages, d_M , was derived from the assumption that the half-life of a tissue macrophage is 90 days. Although the exact half-life of a macrophage is not well defined, varying the half-life of macrophages from 45 days to 180 days did not have a significant effect on viral load and T cell counts (data not shown). Thus, the model is relatively insensitive to healthy macrophage lifetime.

Production of macrophages, $\lambda_M = d_M M_0$, is assumed to remain constant throughout infection. The half-life of infected macrophages, δ_M , has been estimated at 14.1 days (Perelson *et al.*, 1996; Finzi *et al.*, 1999; Zhang *et al.*, 1999). The virus infectivity constant for macrophages (k_M) is assumed to be comparable to the virus infectivity constant for CD4+ T cells (k_T) based on early infection dynamics (Wodarz *et al.*, 1999). Research has shown that k_M and k_T are widely variable depending on viral tropism as well as by the presence of cytokines and pathogenic infections (Kalter *et al.*, 1991; Lederman *et al.*, 1994; Verani *et al.*, 1997; Moriuchi *et al.*, 1998).

Production of virus by macrophages is low or undetectable in early infection and uses as T cell counts drop and opportunistic infections increase (Orenstein *et al.*, 1997). This can be modeled by the expression:

$$\pi_M = 0.1 + 1 \times 10^{(3f)}$$

In this formulation, macrophage viral production stimulated by opportunistic infections and other cellular components does not rise above 1000 times the original production in the time frame of the model, which

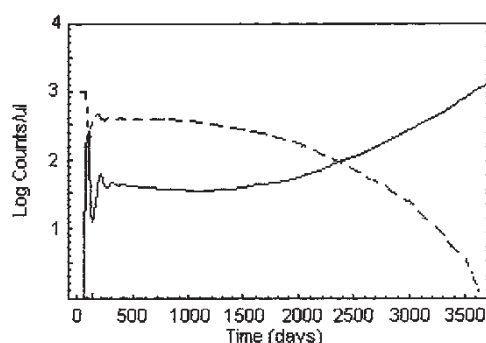


FIGURE 4 Macrophage reservoir model. Theoretical curves: Viral load in HIV copies/ul (—) and CD4 + T cell count in cells/ul, (---).

approaches the upper limit of macrophage virus production in the literature (Kalter *et al.*, 1991). Figure 4 shows patient data (left) against the predicted dynamics of the infection with the added macrophage reservoir (right).

Model Kinetics

The shape of the theoretical curve follows the pattern seen in the patient data reasonably well. However, as noted earlier, the steady state value of the Fauci *et al.* (1996) patient data is about 10 times lower than that of the patient data from Stafford *et al.* (2000). As well, predicted viral load does not rise as steeply as it does in the patient data near the end of infection. This may reflect a variation in measurement techniques or possibly higher macrophage viral production than has been previously measured.

DISCUSSION

Although the dynamics of an HIV infection are complex, we have devised two models that follow the patterns of viral expression and CD4+ T cell levels during the course of an entire infection. These models, as well as the model proposed by dos Santos and Coutinho (2001), rely on very different concepts. Aspects of all three models may be present in an actual infection.

In designing a model of AIDS, it is important to understand the dynamics of both host and viral systems. To be complete, a model of AIDS must include the hallmark decrease in CD4+ T cell counts and rise in viral load. Through the addition of a term derived from observed data (Fauci *et al.*, 1996), the kinetics of CD4+ T cell production during infection were successfully modeled. The model corresponds to an annual decrease of CD4+ T cells of 10% per year after an initial drop of about 40%.

The paradox of high viral load in the absence of normal CD4+ T cell values is central to the theories that purport to explain the onset of AIDS. In addition to the explanation proposed by dos Santos and Coutinho (2001), essentially two hypotheses remain. First, if it is assumed that CD4+ T cells remain the primary source of virus

throughout infection, then the kinetics of the T cell/virus relationship must change. A reasonable theory is that the virus is not cleared as efficiently as disease progresses. This was modeled by the addition of a term that decreases clearance rate, c , by the same rate as the decrease in CD4+ T cell production.

The effect of this term on the model shows marked sensitivity to changes in clearance rate. For example, doubling the viral clearance rate from $c = 3$ to $c = 6$ decreases steady state viral load approximately 3 fold and halving the clearance rate from $c = 3$ to $c = 1.5$ more than doubles it. Ho *et al.* (1995) suggest that clearance rate remains constant over the course of infection based on individual measurements that vary as much as 2.5 fold.

We have shown here that a 2 fold change in the viral clearance rate has a large effect on viral load. In addition, recent studies report clearance rate measurements as much as 10 times faster than those measured by Ho *et al.* (1995) (Ramratnam *et al.*, 1999). Thus, there is greater than 10 fold variation in measured clearance rates, adequate to account for the dramatic changes in viral load seen over the course of AIDS within the error of current measurements. Despite this, little attention is given in the literature to the effects of reduction in viral clearance rate.

The second hypothesis is that viral production must increase as T cell counts decrease. This requires the presence of a second viral reservoir capable of essentially replacing the waning CD4+ T cell reservoir. Many other types of cells are capable of becoming productively infected, but macrophages appear particularly important (Ho *et al.*, 1986; Nicholson *et al.*, 1986). Throughout the early phases of infection, macrophage viral production is low and CD4+ T cells are clearly the primary source of virus. However, studies have shown that in the presence of opportunistic infections, macrophage virus production increases greatly (Orenstein *et al.*, 1997). In the current model, macrophage viral production increases as a function of time paralleling the decrease in CD4+ T cell counts and the observed rise in the occurrence of opportunistic infections leading up to AIDS. The predicted rise in virus is not as sharp in the model as it is in the observed data, which may be due either to other important virus producing cell types or to greater macrophage viral production than has previously been reported.

Simple models that focus on the most important aspects of the HIV/host relationship are essential to the study of AIDS. Much research must be done to assess the quantitative importance of each of these models on the dynamics on HIV infection. However, the macrophage reservoir is well supported in the literature. These studies strongly suggest that infected macrophages are capable of producing the large amount of virus seen late in infection. This information may prove valuable in the treatment of HIV infected patients. For instance, it has been observed that reverse transcriptase inhibitors, such as PMBA, used in rhesus macaque SHIV research are not effective on

virally infected macrophages (Igarashi *et al.*, 2001). If it is found that macrophages account for much of the viral load in humans late in infection, this could have an effect on chosen methods of treatment depending on the stage of disease.

Similarly, although a definitive study on changes in viral clearance rate has not yet been performed, changes in the clearance rate can clearly account for the dynamics seen in AIDS. If it is discovered that decreasing viral clearance rates are common to HIV infection, then alternate methods of treatment may be sought, especially treatments that enhance the immune system or affect clearance rate.

SUMMARY

We have shown that a simple target-cell-limited model can be modified to include dynamics of the entire course of HIV infection and AIDS. Two models have been proposed here, and results concur with observed data and evidence in the literature. Though much research must be done to determine the complete dynamics of AIDS, simple models such as these may help to further the understanding of the pathogenesis of HIV.

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