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; Boughdoud 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 $2 \times 10^5 - 2 \times 10^6$ 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...
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; Gumel et al., 2001), 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 ($Ti$) in cells/ul, and virus concentration ($V$) in cpm

$$\frac{dT(t)}{dt} = \lambda_T - d_T T - k_{TV} T,$$  
$$T(0) = T_0$$

$$\frac{dT_i(t)}{dt} = k_{TV} V - \delta_T T_i,$$  
$$T_i(0) = T_{i0}$$

(1)

$$\frac{dV(t)}{dt} = \pi_T T_i - e V,$$  
$$V(0) = V_0$$
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, \( \delta_T \) is the death rate of productively infected cells, \( \pi_T \) 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. \( T_0 = 0 \) since initially no T cells are infected, and \( V_0 = 1 \times 10^{-6} \) 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). Since there are an average of 1000 T cells/ul in normal blood (Perelson and Nelson, 1999), \( T_0 = 10 \) cells/ul. \( T_0 = 0 \) since initially no T cells are infected, and \( V_0 = 1 \times 10^{-6} \) 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.

### TABLE I Description of variables and constants

<table>
<thead>
<tr>
<th>Terms</th>
<th>Description of variables and constants</th>
<th>Values (ul)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \lambda_T )</td>
<td>Rate of production of T cells</td>
<td>( dT_0/day )</td>
</tr>
<tr>
<td>( \lambda_c )</td>
<td>Rate of production of T cells with decay term (f)</td>
<td>( dT_0(1 - f)/day )</td>
</tr>
<tr>
<td>f</td>
<td>Decay of T cell production</td>
<td>0.00028/t</td>
</tr>
<tr>
<td>( \lambda_M )</td>
<td>Rate of production of macrophages</td>
<td>( dM_0/day )</td>
</tr>
<tr>
<td>( \delta_T )</td>
<td>Natural death rate of healthy T cells</td>
<td>0.01/day</td>
</tr>
<tr>
<td>( \delta_M )</td>
<td>Natural death rate of healthy macrophages</td>
<td>0.0037/day</td>
</tr>
<tr>
<td>( k_T )</td>
<td>Viral infection rate (CD4+ T cells)</td>
<td>0.00027/virus-day</td>
</tr>
<tr>
<td>( k_M )</td>
<td>Viral infection rate (macrophages)</td>
<td>0.00027/virus-day</td>
</tr>
<tr>
<td>( \pi_T )</td>
<td>Death rate of infected T cells</td>
<td>0.39/day</td>
</tr>
<tr>
<td>( \pi_M )</td>
<td>Death rate of infected macrophages</td>
<td>0.024/day</td>
</tr>
<tr>
<td>c</td>
<td>Clearance rate of the virus</td>
<td>3/day</td>
</tr>
<tr>
<td>( c_i )</td>
<td>Reducing clearance rate of virus</td>
<td>( c(1 - f) )</td>
</tr>
<tr>
<td>T</td>
<td>Uninfected activated CD4+ T cells</td>
<td>( T_0 = 10 )</td>
</tr>
<tr>
<td>( T_I )</td>
<td>Infected CD4+ T cells</td>
<td>( T_0 = 10 )</td>
</tr>
<tr>
<td>V</td>
<td>Virus produced by T cells</td>
<td>( V_0 = 10^{-6} )</td>
</tr>
<tr>
<td>M</td>
<td>Uninfected macrophages</td>
<td>( M_0 = 200 )</td>
</tr>
<tr>
<td>Mi</td>
<td>Infected macrophages</td>
<td>( M_i = 0 )</td>
</tr>
<tr>
<td>V*</td>
<td>Total virus from T cells and macrophages</td>
<td>( V_0 = 10^{-6} )</td>
</tr>
</tbody>
</table>

The Stafford model incorporates an arbitrarily small amount of virus introduced into the system which 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
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.

\[
\frac{dT(t)}{dt} = \lambda_T - d_T T - k_T TV^*, \quad T(0) = T_0
\]

\[
\frac{dTi(t)}{dt} = k_T TV^* - \delta_T T, \quad Ti(0) = Ti_0
\]

\[
\frac{dM(t)}{dt} = \lambda_M - d_M M - k_M MV^*, \quad M(0) = M_0
\]

\[
\frac{dMi(t)}{dt} = k_M MV^* - \delta_M M, \quad Mi(0) = Mi_0
\]

\[
\frac{dV^*(t)}{dt} = \pi_T Ti + \pi_M Mi - cV^*, \quad V^*(0) = V_0
\]

These expressions include activated CD4+ T cells (T), infected CD4+ T cells (Ti), macrophage cells (M), infected macrophage cells (Mi), and combined T cell and macrophage viral load (V*). In addition to coefficients defined previously, \(\lambda_M\) is the production rate of macrophages, \(d_M\) is the death rate of healthy macrophages, \(\delta_M\) the death rate of infected macrophages, \(k_M\) represents the infection rate of macrophages and \(\pi_M\) 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, \(\delta_M\), 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:

\[
\pi_M = 0.1 + 1 \times 10^{36}
\]

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
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 then 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 additional 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 P MBA, 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.

**References**


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