HIV and Its Impact on the Infant Immune System

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Abstract

Many models have been developed which illustrate the interaction between the HIV virus and an adult's immune system. However, limited work has attempted to explain the interaction between HIV and an infant's immune system. In this study, we introduce a model that considers the dynamics between $CD4^+$ T cells, $CD8^+$ T cells, and the HIV virus. Analysis of the model gives rise to a threshold parameter, N_{crit}, which is the critical number of new viruses produced by an actively infected $CD4^+$ T cell. Numerical simulations are carried out, and sensitivity analysis is performed on N_{crit} to illustrate the differences between the progression of HIV in infants as compared to that in adults.

Keywords: HIV, immunology, $CD8^+$, $CD4^+$.

1 Introduction

Since the Human Immunodeficiency Virus was discovered in 1983, there have been about 60 million people infected worldwide, and over 4 million children have been infected under the age of 15. In 2003, there were about 5 million newly infected individuals, of which 700,000 were children under the age of 15. There are an estimated 40,000 new HIV infections per year [4], and women consist of 47% of the HIV positive adults [5]. HIV continues to be a threat to the world population, in part because of its harmful effect on the immune system.

The immune system is our body's defense against pathogens (bacteria or viruses), which constantly invade the human body. Some components of the immune system are the bone marrow, thymus, and red and white

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blood cells. The bone marrow produces leukocytes (red blood cells) and lymphocytes (white blood cells). Then the immature lymphocytes move to the thymus, which is the central organ in the immune system, and mature into T-cells [6]. There are three types of T-cells that mature in the thymus, T helper cells ($CD4^+$), T cytotoxic cells ($CD8^+$), and T suppressor cells [6]. The $CD4^+$ T cells stimulate other cells to produce antibodies that bind to a specific antigen in order to immobilize it, thereby assisting in infection prevention [3]. Pathogens escaping detection by antibodies can enter and infect different cells in the body. The surface of the infected cell changes causing the T helper cells to signal the T cytotoxic cells which then regulate the destruction of infected cells [3]. The T cytotoxic cells kill infected cells, preventing them from producing more pathogens. Finally, T suppressor cells signal the immune system to stop its attack against the pathogens. In the case of HIV infection the communication between T helper cells and T cytotoxic cells is disrupted, thus weakening the body's response to invaders. The virus attacks $CD4^+$ T cells, which are depleted by the ongoing battle to defeat HIV. This leads to the Acquired Immune Deficiency Syndrome (AIDS) [1].

The HIV virus can bind to $CD4^+$ T cells because of properties specific to those cells (see Figure 1). Interaction of the virus with $CD4^+$ T cells allows the uncoating and the entry of the nucleocapsid into the cell. The nucleocapsid of the virus contains the viral genome. HIV then uses reverse trancriptase to copy the two single strands of RNA into double-stranded DNA. This viral DNA then integrates into the DNA of the host cell, forever changing the properties of the particular cell. The virus remains inactive until the host cell is activated. Once the host cell is activated, the cell starts to reproduce copies of the viral RNA. New viral proteins assemble at the cell membrane and bud off to create new viruses. The process of budding off kills the host cell [1]. In other words, this process creates more virus particles, and at the same time destroys host cells of the immune system. Once the $CD8^+$ T cells are aware of the infection, they begin destroying actively infected cells. After a certain period of time, the $CD4^+$ T cell count starts to decline, leaving the immune system in a state of disorder. When $CD4^+$ T cells fall below a certain level, the immune system cannot recognize other pathogens entering the body, and opportunistic diseases normally end up defeating the immune system.

Although HIV is more prevalent in young adults, infants can also contract the virus from the infected mother. HIV is transmitted from a mother to her child in three different ways: during pregnancy (5% of total cases), childbirth (15% of total cases), and breastfeeding (10% of total cases)(ref). Overall, 25% of HIV- infected pregnant females pass on the disease to their infant. Studies have shown that children who were infected during pregnancy are more likely

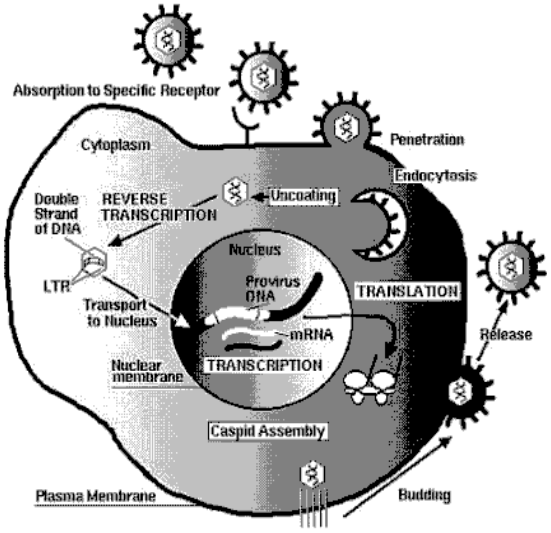

Figure 1: Life Cycle of the HIV virus

to progress faster to AIDS than children who were infected during childbirth and breastfeeding. Women are the fastest growing population of new HIV cases thus making more newborns vulnerable to the disease. However, the progression of HIV in infants has not been the focus for mathematical models.

There are numerous mathematical models which study the behavior of the HIV virus at a cellular level in an adult's immune system. These models ([11, 13]) focus on the interaction of HIV and the immune system in adults Both models use a deterministic approach to help understand how HIV progresses in the human body.

In our model, we compare the invasion of HIV in an adult's immune system to an infant's immune system. In order to gain insight into the difference between systems, we rely on numerical simulations and analysis of the threshold parameter.

2 The Model

There are numerous features of the HIV life cycle, and its interaction with $CD4^+$ and $CD8^+$ T cells we wish to account for in our model. To model these events, we consider $CD8^+$ T cells, uninfected $CD4^+$ T cells, latently infected $CD4^+$ cells, actively infected $CD4^+$ T cells, and the free HIV virus particles. One should note that we are using a deterministic model, which does not account for the very early stages of infection. The dynamics of the early stages of the disease can be captured more accurately through the use of a stochastic model.

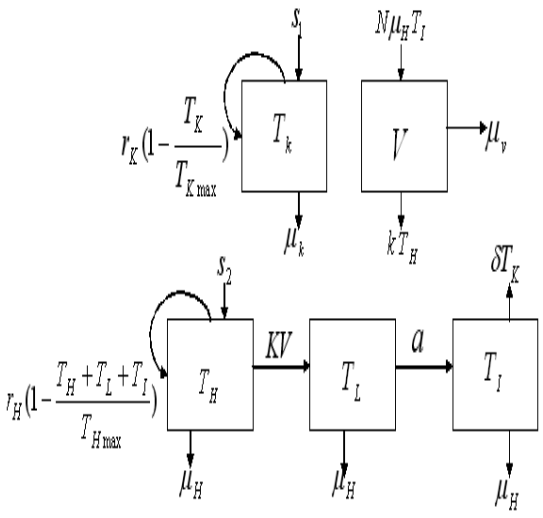

Figure 2: The Model

Let T_K denote the concentration of CD8$^+$ T cells, T_H denote the concentration of uninfected CD4$^+$ T cells, T_L denote the concentration of latently infected CD4$^+$ T cells, T_I denote the concentration of actively infected CD4$^+$ T cells, and V denote the concentration of free infectious virus particles. We have derived the following system of nonlinear ODE's to describe the dynamics of our model.

$$\dot{T}_K = s_1 - \mu_K T_K + r_K T_K\Big(1 - \frac{T_K}{T_{Kmax}}\Big) \quad (1)$$

$$\dot{T}_H = s_2 - \mu_H T_H - kVT_H + r_H T_H\Big(1 - \frac{T_H + T_L + T_I}{T_{Hmax}}\Big) \quad (2)$$

$$\dot{T}_L = kVT_H - \mu_H T_L - aT_L \quad (3)$$

$$\dot{T}_I = aT_L - \mu_I T_I - \delta T_I T_K \quad (4)$$

$$\dot{V} = N\mu_H T_I - kVT_H - \mu_V V \quad (5)$$

In equations (1) and (2), s_1 and s_2 are source terms and represent the rate of generation of new CD8$^+$ and CD4$^+$ T cells respectively, from precursors in the thymus.

Furthermore, other terms in equations (2) and (3) deal with the dynamics of HIV. For instance, the term kVT_H is the rate at which free virus infects CD4$^+$ T cells. When a T cell is infected, it becomes latently infected, meaning the T cell is not actively producing more virus particles or harming other

Variables and Parameters	Description
T_H	Uninfected $CD4^+$ T cells
T_K	Uninfected $CD8^+$ T cells
T_L	Latently infected $CD4^+$ T cells
T_I	Actively infected $CD4^+$ T cells
V	Free virus
s_1	Number of $CD8^+$ T cells supplied by the thymus
s_2	Number of $CD4^+$ T cells supplied by the thymus
r_K	Replication rate of $CD8^+$ T cells
r_H	Replication rate of $CD4^+$ T cells
T_{Kmax}	Maximum number of $CD8^+$ T cells
T_{Hmax}	Maximum number of $CD4^+$ T cells
μ_K	Natural death rate of $CD8^+$ T cells
μ_H	Natural death rate of $CD4^+$ T cells
μ_V	Natural death rate of virus cells
k	Rate at which $CD4^+$ T cells become latently infected
a	Rate at which latently infected $CD4^+$ T cells become actively infected
N	Average number of free virus produced by the death $CD4^+$ T cells
δ	Rate at which $CD8^+$ T cells kill the actively infected $CD4^+$ T cells

Table 1: Variables and Parameters.

cells. Therefore, kVT_H is subtracted from equation (2) because equation (2) corresponds to the dynamics of the $CD4^+$ T cells, and added to (3), which describes the behavior of the latently infected T cells. Equation (4) models the actively infected T cells. This considers the term aT_L which is the rate that latently infected cells are becoming actively infected. On the other hand, δ is the rate at which $CD8^+$ T cells kill actively infected $CD4^+$ T cells. Equation (5) models the free infectious virus population. An actively infected $CD4^+$ T cell produces an average of N virus particles when it dies from infection. In the absence of virus, the T-cell population has the steady state value T_0. Initial conditions for this system of equations are $T_K(0) = T_{K0}$, $T_H(0) = T_{H0}$, $T_L(0) = 0$, $T_I(0) = 0$, and $V(0) = V_0$ for virus free infection.

Also, it is known that there is a bound on the total number of T cells in the body. The logistic type terms in (1) and (2) 'shut off' the growth of T cells as the maximum population level is approached. We assume the rate at which $CD8^+$ and $CD4^+$ T cells replicate is larger than their death rate, meaning $r_K > \mu_K$, and $r_H > \mu_H$. We also assume that every cell that becomes infected must be latently infected before becoming actively infected. The last assumption is the death, the replication, and the infection rates of the cells whether they are $CD8^+$ or $CD4^+$ T cells are the same in the infant population and in the adult population. The definitions of parameters and

Variables and Parameters	Infants	Adults	Units
T_H	1500	1200	mm^{-3}
T_K	600	600	mm$^-3$
T_L	0	0	mm^{-3}
T_I	0	0	mm^{-3}
V	0	0	mm^{-3}
s_1	0.05	0.02	$\text{day}^{-1}\text{mm}^{-1}$
s_2	0.03	0.01	$\text{day}^{-1}\text{mm}^{-1}$
r_K	0.228	0.228	day^{-1}
r_H	0.456	0.456	day^{-1}
T_{Kmax}	1200	800	mm^{-3}
T_{Hmax}	2000	1600	mm^{-3}
μ_K	0.03	0.03	day^{-1}
μ_H	0.01	0.01	day^{-1}
μ_V	0.05	0.05	day^{-1}
k	0.0095	0.0095	mm^3
a	0.06	0.06	mm^3
N	100	500	Varies
δ	0.000095	0.000095	mm^3

Table 2: Default Parameter and Initial Conditions

values are given in Table 1.

First, we wish to remark that our model is well posed in the sense that the populations do not become negative, and the populations are bounded. Also, the nonnegative orthant is positively invariant, that is, any trajectory that starts in the nonnegative orthant remains there for all time. This result states that on each hyperbolic plane bounding the nonnegative orthant the vector fields point into $\mathbb{R}^5_+ = \{x \in \mathbb{R}^5 | x \geq 0\}$. For our model we have:

$$\begin{aligned}
\frac{dT_K}{dt}\Big|_{T_K=0} &= s_1 \geq 0 \\
\frac{dT_H}{dt}\Big|_{T_H=0} &= s_2 \geq 0 \\
\frac{dT_L}{dt}\Big|_{T_L=0} &= kV^*T_H^* \geq 0 \\
\frac{dT_I}{dt}\Big|_{T_I=0} &= aT_L^* \geq 0 \\
\frac{dV}{dt}\Big|_{V=0} &= N\mu_h T_I^* \geq 0
\end{aligned}$$

Within the nonegative orthant, there exists two steady states. One when there is no virus present, a *virus free* steady state, and another with a constant level of virus, an *endemically infected* steady state.

The *virus free* steady state occurs at $V^* = T_L^* = T_I^* = 0$ and

$$T_K^* = \frac{1}{2}\Big(1 - \frac{\mu_k}{r_k}\Big)T_{kmax}\left[1 + \sqrt{1 + 4\frac{s_1 r_k}{(r_k - \mu_k)^2 T_{kmax}}}\right] \tag{6}$$

$$T_H^* = \frac{1}{2}\Big(1 - \frac{\mu_h}{r_h}\Big)T_{hmax}\left[1 + \sqrt{1 + 4\frac{s_2 r_h}{(r_h - \mu_h)^2 T_{hmax}}}\right] \tag{7}$$

If $V \neq 0$ then we have an *endemically infected* steady state with the following coordinates:

$$T_K^* = \frac{\theta_1 + \sqrt{\theta_1^2 + 4 s_1 p_1}}{2 p_1} \tag{8}$$

$$T_H^* = \frac{\mu_v \psi \pi}{k\eta} \tag{9}$$

$$T_L^* = \frac{\mu_v \pi V^*}{\eta} \tag{10}$$

$$T_I^* = \frac{a \mu_v V^*}{\eta} \tag{11}$$

$$V^* = \frac{s_2 (k\eta)^2 + \mu_v \psi \pi [\theta_2 k\eta - p_2 \psi \pi \mu_v]}{k \mu_v \psi \pi [k\eta + (\pi + a)\mu_v]} \tag{12}$$

with

$$\begin{aligned} \theta_{1,2} &= r_{k,h} - \mu_{k,h} \\ p_{1,2} &= \frac{r_{k,h}}{T_{kmax,hmax}} \\ \psi &= a + \mu_h \\ \pi &= \mu_h + \delta T_K^* \\ \rho &= \mu_v + k T_H^* \\ \eta &= a \mu_h (N - \xi) \end{aligned}$$

and where

$$\xi = \frac{\psi \pi}{a \mu_h}$$

2.1 Stability of Virus Free Steady State

Linearizing our system around the virus free steady state gives the following Jacobian matrix

$$J(VF) = \begin{pmatrix} \theta_1 - 2p_1T_K^* & 0 & 0 & 0 & 0 \\ 0 & \theta_2 - 2p_2T_H^* & -p_2T_H^* & -p_2T_H^* & -kT_H^* \\ 0 & 0 & -\psi & 0 & kT_H^* \\ 0 & 0 & a & -\pi & 0 \\ 0 & 0 & 0 & N\mu_H & -\rho \end{pmatrix}$$

where the analysis only relies on the fact that $T_K^*, T_H^* > 0$. It follows that the virus free steady state is asymptotically stable if and only if all of the eigenvalues of J have negative real part. The eigenvalues are determined with the characteristic equation $p(\lambda) = det(\lambda\mathbf{I} - \mathbf{A}) = \mathbf{0}$. For J we have

$$p(\lambda) = (\lambda + d_1)(\lambda + d_2)(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3) = 0 \tag{13}$$

The first two solutions are

$$\lambda_1 = -d_1 = -\sqrt{(r_K - \mu_K)^2 + 4\frac{4s_1r_K}{T_{Kmax}}} < 0$$

and

$$\lambda_2 = -d_2 = -\sqrt{(r_H - \mu_H)^2 + 4\frac{4s_2r_H}{T_{Hmax}}} < 0$$

It is clear that λ_1 and λ_2 have negative real part. Finally, we are left to verify that

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 \tag{14}$$

has roots whose real portion is negative, where

$$a_1 = 2\mu_H + a + \mu_V + \delta T_K^* + kT_H^* \tag{15}$$

$$a_2 = T_K^*\delta(\mu_H + KT_H^* + a + \mu_V) + \mu_H(a + 2\mu_V + 2KT_H^* + \mu_H) + akT_H^* + a\mu_V \tag{16}$$

$$a_3 = \frac{(a + \mu_H)(\mu_V + kT_H^*)(\mu_H + \delta T_K^*)}{a\mu_H kT_H^*} - N \tag{17}$$

To verify that the real parts of the roots of (14) are negative, we use the Routh-Hurwitz criteria. which states that if (18)-(20) hold then (14) has

roots with negative real parts.

$$\begin{aligned} a_1 &> 0 \quad (18) \\ a_3 &> 0 \quad (19) \\ a_1 a_2 &> a_3 \quad (20) \end{aligned}$$

Clearly, (18) holds since all of the parameters are positive. Also, it is easily shown that (20) holds, but the resulting equation is long (see appendix). Hence, we are left to verify (19), which holds when

$$N < \frac{(a+\mu_H)(\mu_V + kT_H^*)(\mu_H + \delta T_K^*)}{a\mu_H k T_H^*} = N_{crit} \quad (21)$$

Thus, the virus free steady state is locally asymptotically stable when $N < N_{crit}$.

2.2 Global Stability of Virus Free Steady State

The above analysis only deals with the local stability of the virus free steady state. When $N < Ncrit$ there exists only one steady state in the nonnegative orthant and, through the method of Lyapunov, we will show that this steady state is globally stable. To do this, we construct a scalar function $L(t)$, such that

$$\begin{aligned} L(x^*) &= 0 \\ \frac{dL}{dt} &< 0 \end{aligned}$$

and for $x \neq x^*$

$$L(x) > 0$$

where x^* is the equilibrium in question.

Let us consider the following function, which we will see is a Lyapunov function

$$L(t) = T_L + NT_I + V \quad (22)$$

Observe, in the nonnegative orthant $L(t) \geq 0$

By substituting equations (3) and (4) into $L(t)$ we obtain,

$$\frac{dL}{dt} = T_L[a(N-1) - \mu_H] - N\delta T_I T_K - \mu_V V \quad (23)$$

we can clearly see that if the term in brackets is negative, then $\frac{dL}{dt}$ will be negative definite.

Thus, when

$$N < \frac{\mu_H}{a} + 1$$

$\frac{dL}{dt} < 0$. Furthermore, as t$\rightarrow \infty$, $L(t) \rightarrow 0$, T_L, T_I and V all approach 0. Hence, the solution is globally stable.

2.3 Existence and Stability of Endemically Infected Steady State

At $N = Ncrit$, the virus free steady state and the infected steady state coincide. Furthermore, there is a transcritical bifurcation at $N = Ncrit$, and the infected state emerges when $N > N_{crit}$ as a new steady state in $\mathbb{R}^5_+$. When $N < Ncrit$ the infected steady state does not lie in $\mathbb{R}^5_+$ and hence does not make sense biologically. Thus, it is only necessary to analyze the stability of the infected steady state for

$$N > N_{crit} > \xi$$

Linearizing our system around the infected steady state gives the following Jacobian Matrix, where the first row is zeros except for the one of the eigenvalues

$$J(EI) = \begin{pmatrix} -\beta & -p_2 T_H^* & -p_2 T_H^* & -kT_H^* \\ kV^* & -\psi & 0 & kT_H^* \\ 0 & a & -\alpha & 0 \\ -kV^* & 0 & N\mu_h & -\rho \end{pmatrix} \tag{24}$$

where

$$\begin{aligned} \beta &= \phi_2 + r_h\Big(1 - \frac{T_H^* + T_L^* + T_I^*}{T_{Hmax}}\Big) \\ \rho &= \mu_v + kT_H^* \end{aligned}$$

and $T_K^*, T_H^*, T_L^*, T_I^*$ and V^* are given in (8)-(12).

Once more, we wish to determine the eigenvalues of (24). Examining the characteristic polynomial $det(\mathbf{A} - \lambda\mathbf{I})$, we find it has the form:

$$p(\lambda) = (\lambda + d_1)(\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4)$$

where the first root is

$$\lambda_1 = -d_1 = -\sqrt{(r_K - \mu_K)^2 + 4\frac{s_1 r_K}{T_{Kmax}}} < 0$$

whose real part is clearly negative. For

$$(\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4) \tag{25}$$

we have

$$a_1 = \rho + \psi + \beta + \alpha \tag{26}$$

$$a_2 = KV^*T_H^*(p_2 - K) + \psi(a + \rho + \beta) + \alpha(\beta + \rho) \tag{27}$$

$$\begin{aligned} a_3 = KVp_2T_H^*(\alpha + \rho + a - T_H^*K) - K^2V^*T_H^*(\alpha + \psi) - \\ KT_H^*(aN\mu_h + KV^*\alpha + KV^*\psi) + \beta\rho(\alpha + \psi) + \psi\alpha\rho \end{aligned} \tag{28}$$

$$\begin{aligned} a_4 = KVT_H^*(ap_2\rho + KaN\mu_H - p_2T_H^*k\psi\alpha - ap_2T_H^*K) + \\ KT_H^*(V^*p_2\alpha\rho - \beta\mu_H aN) + \beta\psi\alpha\rho \end{aligned} \tag{29}$$

To establish the stability of the infected steady state it is necessary to verify that all of the roots of (25) have negative real part. To this end, we use the Routh-Hurwitz criteria, which in this case states that if

$$a_1 > 0 \tag{30}$$

$$a_2 > 0 \tag{31}$$

$$a_1a_2 > a_3 > 0 \tag{32}$$

$$\frac{a_1a_2a_3 - a_3^2}{a_1^2} > a_4 > 0 \tag{33}$$

hold then the real parts of the roots are negative. Analyzing the coefficients, it is clear that (30) holds. For $N > N_{crit}$, $a_4 > 0$. However, we are still left to verify (31)-(33). For certain parameter regimes all the conditions are met and the infected steady state is stable. On the other hand, there are certain parameter regimes where the infected steady state is unstable (Table 5).

2.4 Sensitivity Analysis

Next, a local sensitivity analysis is performed on the parameters relevant to the critical number of viruses produced by each dying CD4$^+$ T cell, that is, a, $\mu_{h,k}$, μ_v, k, δ, $r_{h,k}$, and $T_{hmax,kmax}$. The parameter with the sensitivity index of the greatest magnitude is the most effective in increasing N_{crit} when parameters are varied locally, where the sensitivity index is given by

$$S = \frac{\lambda}{N_{crit}} \frac{\partial N_{crit}}{\partial \lambda}$$

where λ represents a parameter. For our model we take into consideration two critical values for N, one calculated for infants and one calculated for

Parameter	*Sensitivity Index*
δ	0.9900
$T_K max$	0.9898
μ_V	0.9267
K	-0.9267

Table 3: Parameters with Greatest Sensitivity Index(Infants)

Parameter	*Sensitivity Index*
μ_K	-1.0908
μ_V	0.98864
K	-0.98864
δ	0.95162

Table 4: Parameters with Greatest Sensitivity Index (Adults)

adults. In other words, we calculate one N_{crit} using the parameters used for infants and another using the parameter values for adults (Table 2) From this we obtain the sensitivity indices contained in Table 3 and 4
For infants the greatest sensitivity index is obtained by the parameter δ. In biological terms, this implies that by increasing the rate at which $CD8^+$ T cells kill off the infected $CD4^+$ T cells, N_{crit} will increase most efficiently compared to changes in other parameters. In adults, increasing the death rate of the virus μ_v most effectively increases N_{crit} compared to the other parameters [10] [22].

3 Numerical Simulations

Numerical simulations were carried out to gain a better understanding of the dynamics of our system and to verify the results from our analysis. Also, simulations were used to differentiate between dynamics of HIV in an adult's immune system and an infant's immune system.

The parameters for the first simulation are chosen to model an HIV infected infant with $N < N_{crit}$. The virus-free equilibrium is reached in about 3500 days ($\sim$10 years) after infection (Figure 3). A $CD4^+$ T cell count of almost 1996 is reached after 20 days of infection, while a $CD8^+$ T cell count of 1042 is reached after 30 days of infection. The viral count rapidly declines to 0 free virions after only 20 days, but the latently and actively infected $CD4^+$ T cells take over 3000 days to clear out of the body.

The second simulation parameter values are for an infected infant with

Parameters	*Values*
s_1	0.03
s_2	0.01
r_K	0.228
r_H	0.456
T_{Kmax}	1200
T_{Hmax}	2000
μ_K	0.03
μ_H	0.001
μ_V	2.4
k	0.0095
a	0.006
N	500
δ	9.5×10^{-5}
T_K^*	1042.3
T_H^*	1995.6
N_{crit}	131.4547

Table 5: Parameters for Unstable Infected Steady State

$N > N_{crit}$. The stable endemic equilibrium is obtained about 550 days ($\sim$1.5 years) after infection (Figure 4). After an initial rise in the amount of $CD4^+$ T cells, they steadily decline to their steady state of about 150 cells. The $CD8^+$ T cells increase and stabilize to 1042 cells after approximately 50 days. There is a dramatic increase in the number of latently infected cells and free virus. After 500 days of infection ($\sim$1.4 years), latently infected cells, actively infected cells, and free virus reach their steady state, which we calculated beforehand.

The third simulation uses parameter values that model an infected adult with $N > N_{crit}$. It takes 1800 days ($\sim$5 years) after infection for the stable endemic equilibrium to be obtained (Figure 5). This result agrees with literature that states that HIV progresses faster into AIDS in infants than in adults.

The parameter values for the final simulation model an infected infant with $N > N_{crit}$. These parameters values result in oscillations, meaning the endemic equilibrium is unstable (Figure 6). Both uninfected $CD4^+$ T cells and $CD8^+$ T cells have an initial increase. After about 100 days of infection, the $CD4^+$ T cell count starts to decrease before oscillating. Surprisingly, the virus count stays very low although the $CD4^+$ T cell count drops almost to zero before oscillations occur. The latently infected cells increase dramatically before oscillations take place.

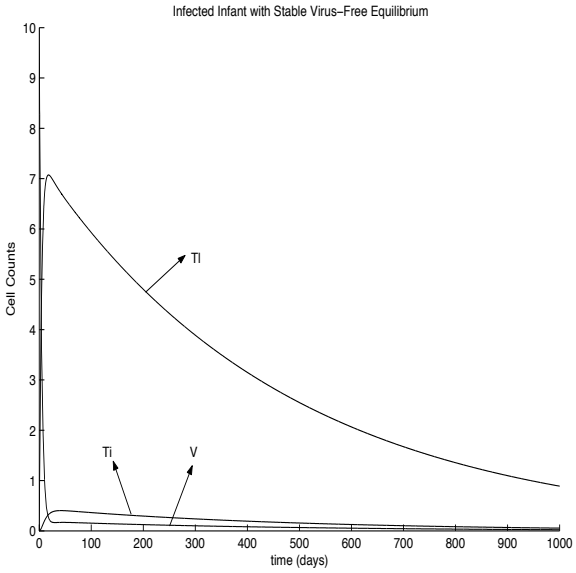

Figure 3: Virus Free Equilibrium for Infants

4 Discussion

Beginning with an understanding of the T cell dynamics in a healthy person, we have developed a model to describe the dynamics of T helper cells in a person infected with HIV including immune response, whether they be adult or infant. Although our model is quite simple, in the sense that it does not take into account for activated immune response, it does demonstrate that HIV can cause depletion of $CD4^+$ T cells. Numerical simulations with our model demonstrate that the loss of $CD4^+$ T cells can take place on a time scale of years, as is characteristic of $CD4^+$ T cells dynamics in a person affected with HIV.

An important result of our paper is the determination of N, which is the average number of free virus produced by each dying $CD4^+$ T cell, as a threshold parameter. When $N < N_{crit}$ it follows that the virus free steady state is locally asymptotically stale. When $N > N_{crit}$ the endemic equilibrium comes into existence, and is stable in certain parameter regimes, in others it is unstable (Figure 6). Also, for $N < \frac{\mu_h}{a} + 1$ the virus free steady state is globally stable.

The main focus of our paper was to compare and contrast the impact of HIV on an infants immune system with that of adults. From our model, it can be seen that the depletion of $CD4^+$ T cells in an infant occurs much more rapidly in infants compared to adults, which is consistent with our current knowledge of HIV. Sensitivity analysis was carried out on N_{crit} using parameters for adults, as well as for infants. The results of this indicate which parameter is most effective in increasing N_{crit}. This result is important as

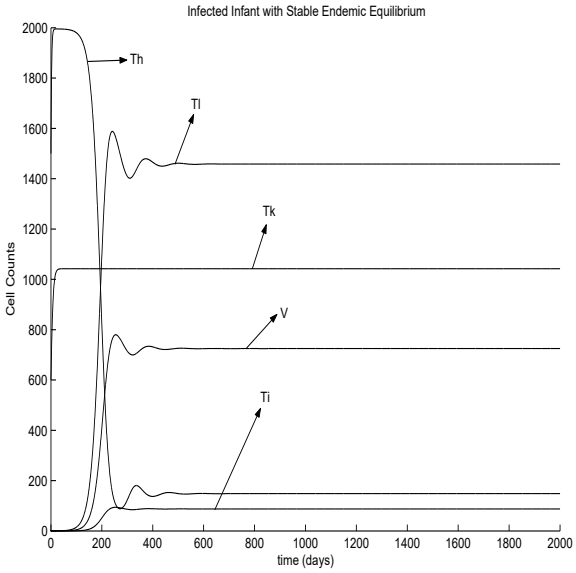

Figure 4: Stable Endemic for Infants

well. Increasing the value of N_{crit} allows the virus to reproduce more effectively, while still maintaining $N < N_{crit}$, meaning the virus will die out (the virus free steady state will be locally asymptotically stable).

In the case of adults, the parameter with the greatest sensitivity index is μ_k, which is the death rate of the CD8$^+$ T cells. For children, the parameter with the greatest sensitivity index is δ the rate at which the CD8$^+$ T cells kill off the actively infected CD4$^+$ T cells. Biologically, this implies that if one were treating an adult infected with HIV one would prescribe a drug or treatment that decreases the death rate of the CD8$^+$ T cells. However, if one were treating an infant infected with HIV one would prescribe a drug or treatment that increases the ability of CD8$^+$ T cells to kill of actively infected CD4$^+$ T cells. From our model, we can better understand why the progression of HIV to AIDS occurs more rapidly in infants than in adults. The way to combat this progression in children is to target and increase the rate at which the CD8$^+$ T cells kill of the HIV virus.

5 Future Work

The way we captured the effects of HIV on an infant's immune system was by finding parameter values specific for infants and using that in our numerical simulations. However, our long-term goal is to develop an age structured model which would be a more accurate tool to measure the differences between an HIV infected adult and an HIV infected infant. We would also incorporate an active immune response, meaning we would include a term

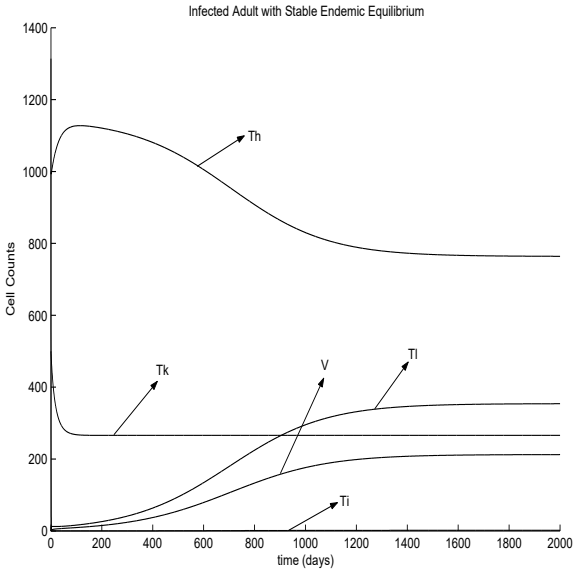

Figure 5: Stable Endemic for Adults

for $CD8^+$ T cells that would stimulate them to grow depending on how much virus is present.

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References

[1] Janeway, C.A., Travers, P., Walport, M., Shlomchik, M., *Immuno Biology 5*, 693, Garland Publishing, New York 2001.

[2] Greenberg, L., *AIDS: How It Works In the Body*, 35, Franklin Watts, New York 1992.

[3] *Immune Response - Overview*, The University of Arizona, July 15, 2004, http://www.biology.arizona.edu/immunology/tutorials/AIDS/response.html.

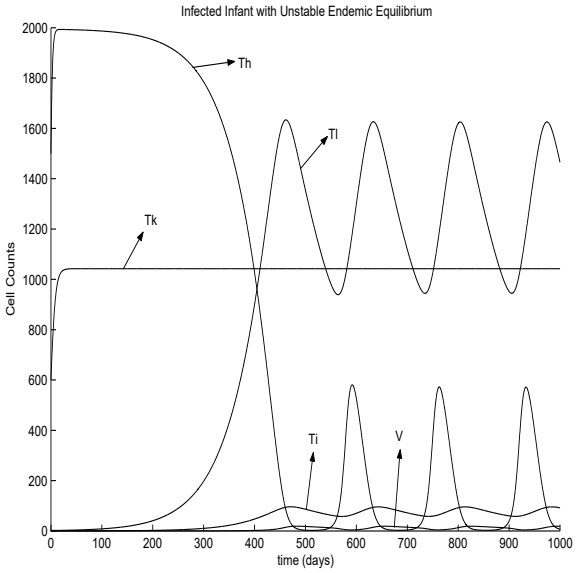

Figure 6: Unstable Endemic Equilibrium for Infants

[4] Pavia, A.T., *Primary Care of Infants and Children with HIV*, HIV InSite Base Chapter, July 16, 2004, http://hivinsite.ucsf.edu/InSite.jsp?page=home-00-00doc=kb-03-01-14.

[5] *HIV Impacts*, The University of Arizona, July 15, 2004, http://www.biology.arizona.edu/immunology/tutorials/AIDS/impacts.html.

[6] *Your Immune System*, Wellness Directory of Minnesota, July 16, 2004, http://www.mnwelldir.org/docs/immune1.htm.

[7] Linnemeyer, P.A., *The Immune System-An Overview*, Seattle Treatment Education Project, July 15, 2004, http://www.thebody.com/step/immune.html.

[8] *Immunology and HIV: Immune system's response to HIV*, The University of Arizona, July 15, 2004, http:/www.biology.arizona.edu/immunology/tutorials/AIDS/HIVimmune.html.

[9] Brauer, F., Castillo-Chávez, C., *Mathematical Models in Population Biology and Epidemiology*, Texts in Applied Mathematics, **40**, Springer-Verlag, New York 2001.

[10] Caswell, H. *Matrix Population Models: Construction, Analysis, and Interpretations.* Sinauer, 2001. Ch 9.

[11] Alan S. Perelson, Denise Kirschner, and Rob De Boer. *Dynamics of HIV Infection of CD4$^+$ T cells*. Mathematical Biosciences, 114:81-125 (1993) July 1993.

[12] Andrew J. McMichael, and Sarah L. Rowland-Jones. *Cellular Immune Responses to HIV*. Nature 410:980-987, April 2001.

[13] Denise Kirschner. *Using Mathematics to Understanding HIV Immune Dynamics*. Notices of the AMS 43(2):191-202, February 1996.

[14] World Health Organization: HIV/AIDS in Asia and the Pacific Region 2001. *Mother-to-Infant Transmission of HIV* World Health Organization Annex 2, 2001.

Data taken from the following:

[15] Norman J. Waecker, David P.Ascher, Merlin L. Robb, Richard Moriarty, Marvin Krober, William J. Rickman, Cliff A. Butzin, Gerald W. Fischer, and the Military Pediatric HIV Consortium. *Age-Adjusted CD4$^+$ Lymphocyte Parameters in Healthy Children at Risk for Infection with the Human Immunodeficiency Virus*. Clinical Infectious Diseases 17:123-5, July 1993.

[16] Ping Ye and Denise E, Kirschner. *Reevaluation of T cell Receptor Excision Circles as a Measure of Human Recent Thymic Emigrants*. The Journal of Immunology 169:4968-4979, March 2002.

[17] Lynne M. Mofenson, James Korelitz, William A. Meyer III, James Bethel, Kenneth Rich,, Savita Pahwa, John Moye, Jr., Robert Nugent, and Jennifer Read. *The Relationship between Serum Human Immunodeficiency Virus Type I (HIV-1) RNA Level, CD4 Lymphocyte Percent, and Long-Term Mortality Risk in HIV-1- Infected Children*. The Journal of Infectious Diseases 175:1029-1038, January 1997.

[18] William T. Shearer, Thomas C. Quinn, Philip LaRussa, Judy F. Lew, Lynne Mofenson, Susan Almy, Kenneth Rick, Edward Handelsman, Clemente Diaz, Marcello Pagano, Vincent Smeriglio, and Leslie A. Kalish. *Viral Load and Disease Progression in Infants Infected with Human Immunodeficiency Virus Type I*. New England Journal of Medicine 336: 1337-1342, May 1997.

[19] Andre J. Nahmias, W. Scott Clark, Athena P. Kourtis, Francis K. Lee, George Cotsonis, Christian Ibegbu, Donald Thea, Paul Palumbo, Peter Vink, R. J. Simonds, Steven R. Nesheim. *Thymic Dysfunction and Time of Infection Predict Mortality in Human Immunodefienciency Virus-Infected Infants*. The Journal of Infectious Diseases 178: 680-685, September 1998.

[20] Johan K. Sandberg, Noam M. Fast, Kimberly A. Jordan, Scott N. Furlan, Jason D. Barbour, Glenn Fennelly, Joanna Dobroszycki, Hans M. L. Spiegel, Andrew Wiznia, Michael G. Rosenberg, and Douglas F. Nixon. *HIV-Specific $CD8^+$ T Cell Function in Children with Vertically Acquired HIV-1 Infection Is Critically Influenced by Age and the State of the $CD4^+$ T Cell Compartment*. The Journal of Immunology 170: 4403-4410, February 2003.

[21] Seema H. Bajaria, Glenn Webb, Miles Cloyd, and Denise Kirschner. *Dynamics of Nave and Memory $CD4^+$ T Lymphocytes in HIV-1 Disease Progression*. Journal of Acquired Immune Deficiency Syndrome 30:41-58, January 2002.

[22] Leon Arriola *Forward Sensitivity Analysis: Adjoint and Non-Adjoint Problems*

[23] Paul Krogstad, Christel H. Uittenbogaart, Ruth Dickover, Yvonne J. Bryson, Susan Plaeger, and Alan Garfinkel. *Primary HIV Infection of Infants: The Effects of Somatic Growth on Lymphocyte and Virus Dynamics*. Clinical Immunology 92(1): 25-33, 1999.

[24] Barton F. Haynes, and Laura P. Hale. *The Human Thymus: A Chimeric Organ Comprised of Central and Peripheral Lymphoid Components*. Immunologic Research 18(2):61-78, 1998.

[25] Paediatric European Network for Treatment of AIDS (PENTA). *HIV-1 Viral Load and CD4 Cell Count in Untreated Children with Vertically Acquired Asymptotic or Mild Disease*. AIDS 12(4): F1-F8, 1998.

[26] K. Renee Fister, Suzanne Lenhart, and Joseph S. McNally. *Optimizing Chemotherapy in an HIV Model*. Electronic Journal of Differential Equations 32:1-12, December 1998.

[27] H.R. Hegde and S.M. Robbins. *Anergy and Human Immunodeficiency Virus Infection*. Medical Hypotheses 56(3): 376-380, 2001.