Chapter 3

HIV/AIDS Models

$\mathbf{M}$ ATHEMATICAL models that describe the host-pathogen interaction between the immune system and HIV should be able to explain the initial high rise in plasma viral load, its decline and settling to levels that are much lower than the peak viral load. The subsequent dramatic increase in the viral load during the later stage of the infection and timing of this increase should also be explained.

Many models explaining different aspects of the HIV infection have been developed. Most are deterministic single compartment models and are based on balancing population dynamics of the virus, the uninfected and actively infected target CD4$^+$ T cells in plasma [7, 71, 75, 77, 80, 84, 85]. These single compartment models can be expanded to explicitly model the immune response to the virus [70, 73, 76, 77, 87] or take into consideration other target cells that are co-circulating in plasma with the CD4$^+$ T cells [74, 78, 81, 85]. Models that include intracellular delays between cell infection and virus production [72, 82, 83], as well as stochastic models that take into account the random variations in HIV dynamics are also available [86]. The co-existence of both wild type and mutant virus strains has also been modelled [79]. Multi-compartmental models that show virus production by cells in other body compartments like tissue, as well as the trafficking of virus particles between compartments [71] have also been developed.

3.1   The Latently Infected Cell Model

Eradication of Human Immunodeficiency Virus - HIV infection does not seem possible with currently available antiretroviral drugs. "This is due primarily to the establishment of a pool of latently infected CD4$^+$ T cells during the very earliest stages of acute HIV infection that persists with an extremely long half-life, even with prolonged suppression of the plasma viral load using Highly Active Anti-Retroviral Therapy - HAART" [39, 40].

The 4 dimensional model presented below by equations (3.1)-(3.4) and schematically
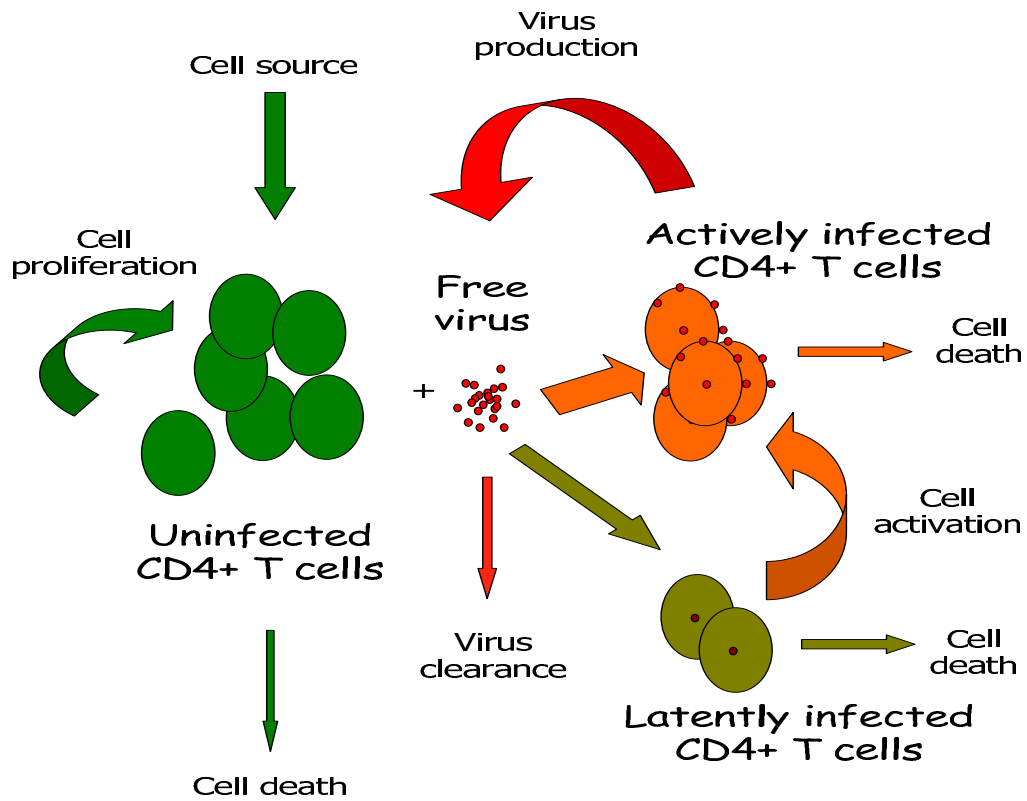
Figure 3.1: A schematic illustration of the interaction between the virus and target cells. Diagram is an expansion of that presented by [84].

illustrated in figure 3.1, has been presented in for example, [71, 77, 84, 85]. This so called latently infected cell model is single compartment and shows the interaction between the virus and the CD4$^+$ T cells in plasma. The model takes note of the fact that not all CD4$^+$ T cells actively produce virus upon infection. This is reflected by dividing the infected cell pool into latently and actively infected cells.

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T TV \tag{3.1}$$

$$\frac{dT_l}{dt} = q_l \beta_T TV - kT_l - \delta_l T_l \tag{3.2}$$

$$\frac{dT_a}{dt} = q_a \beta_T TV + kT_l - \delta_a T_a \tag{3.3}$$

$$\frac{dV}{dt} = r_T T_a - cV \tag{3.4}$$

State variables T, T_l, T_a and V are the plasma concentrations of the uninfected CD4$^+$ T cells, the latently infected CD4$^+$ T cells, the actively infected CD4$^+$ T cells and the

free virus particles, respectively. Equation (3.1) describes the population dynamics of the uninfected CD4$^+$ T cells. It shows that they are produced from a source at a rate s_T, die with a rate constant d_T and $\phi(T)$ is the proliferation rate term.

Most authors assume that the source term s_T is constant. However, since HIV may be able to infect cells in the thymus and bone marrow and thus lead to a reduced production of new immunocompetent T cells, some authors believe that s_T is a decreasing function of the viral load. An expression for s_T is given by [160] as

$$s_T(V) = s_T e^{-\theta V} \qquad (3.5)$$

Another form for the source rate term is given by [46, 99] as

$$s_T(V) = \theta s_T/(\theta + V) \qquad (3.6)$$

A slightly different form is given by [7] as

$$s_T(V) = \theta_1 s_T + \theta_2 s_T/(B_s + V) \qquad (3.7)$$

For the proliferation rate term, there are suggestions that the proliferation rate is density dependent with the rate of proliferation slowing as the T cell count gets high [90]. The most common form for proliferation is taken as the following logistic function [46, 50, 78, 85, 99]:

$$\phi(T) = pT(1 - \frac{T + T_l + T_a}{T_m}) \qquad (3.8)$$

with p as the proliferation rate constant and T_m is the T cell population density at which proliferation shuts off. Given that the infected cells make a small fraction of the total CD4$^+$ T cell count, especially when antiretroviral drugs are used [26, 161], it is common to simply express the proliferation term as

$$\phi(T) = pT(1 - \frac{T}{T_m}) \qquad (3.9)$$

A different form for the proliferation rate term has been suggested as [77]

$$\phi(T) = pT\frac{V}{C + V} \qquad (3.10)$$

where C is referred to as the half saturation constant of the proliferation process. Some authors incorporate the proliferation effect into the constant d_T, while others suggest that these terms depend on other variables of the system to best fit the clinical data.

Uninfected CD4$^+$ T cells are infected by the virus at a rate that is proportional to the product of their abundance and the amount of free virus particles. The proportionality

constant β_T is an indication of the effectiveness of the infection process and includes the rate at which virus particles find uninfected cells and the rate of virus entry.

Equations (3.2) and (3.3) describe the population dynamics of the latently and actively infected $CD4^+$ T cells, respectively. Parameters q_l and q_a are the probabilities that upon infection, a $CD4^+$ T cell will become latent or actively produce virus. Latently infected cells do not produce virus until they are activated, and k is the activation rate constant. The infected cells have respective death rate constants of δ_l and δ_a.

Initially, it was assumed that once infected, the $CD4^+$ T cell will actively produce virus and equation (3.11) is commonly used to describe the infected cell dynamics.

$$\frac{dT^*}{dt} = \beta_T TV - \delta T^* \tag{3.11}$$

where T^* represents the plasma concentration of all the infected $CD4^+$ T cells. The distinction in pools of infected $CD4^+$ T cells came about when Perelson *et al* observed that, after the rapid first phase of decay during the initial 1-2 weeks of antiretroviral therapy, plasma virus levels declined at a considerably slower rate [162]. This, and subsequent slower rates of viral decay were attributed to the turnover of a longer lived virus reservoir of infected cell population, which was determined to have a half-life of 1-4 weeks. This meant that on average, it would take between $\frac{1}{2}$ and 3 years of perfectly effective antiretroviral therapy to eradicate the virus [163].

Equation (3.4) similarly describes the population dynamics of the free virus particles and it can be seen that an actively infected $CD4^+$ T cell produces virus particles with a rate constant r_T and c is the death rate constant at which virus particles are cleared from plasma.

Not all virus particles are infectious. Some virus particles have defective proviral RNA, and as such, are not capable of infecting cells. But generally, V in equation (3.4) describes the population dynamics of the free infectious virus particles. Some authors however, make a distinction in pools of free virus particles as reflected in equations (3.12) - (3.16)

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T T V_i \tag{3.12}$$

$$\frac{dT_l}{dt} = q_l \beta_T T V_i - k T_l - \delta_l T_l \tag{3.13}$$

$$\frac{dT_a}{dt} = q_a \beta_T T V_i + k T_l - \delta_a T_a \tag{3.14}$$

$$\frac{dV_i}{dt} = f_i r_T T_a - c V_i \tag{3.15}$$

$$\frac{dV_n}{dt} = (1 - f_i) r_T T_a - c V_n \tag{3.16}$$

where V_i and V_n are the infectious and noninfectious virus particles, respectively. Infectious virus particles make a fraction f_i of the total virus pool, and it is assumed that both virus particle types are cleared from plasma with the same rate constant c.

3.2   Time Delay Models

Other models take into consideration the fact that there is a time delay between when a cell gets infected by the virus to when it starts to actively produce virus particles. Equation (3.19) is an upgrade of equation (3.3) and a slight variation of that presented by [72].

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T T V \tag{3.17}$$

$$\frac{dT_l}{dt} = q_l \beta_T T V - k T_l - \delta_l T_l \tag{3.18}$$

$$\frac{dT_a}{dt} = q_a \beta_T T(t - \tau) V(t - \tau) + k T_l - \delta_a T_a \tag{3.19}$$

$$\frac{dV_i}{dt} = r_T T_a - c V \tag{3.20}$$

τ is the time delay between cell infection and virus production.

Another variation of the delayed model is as presented by [83] for the actively infected CD4$^+$ T cells.

$$\frac{dT_a}{dt} = q_a \beta_T T_0 \int_0^\infty f(\tau) V(t - \tau) e^{-m\tau} d\tau + k T_l - \delta_a T_a \tag{3.21}$$

where $e^{-m\tau}$ represents cells that die before actively producing virus. This model assumes a constant target CD4$^+$ T cell population T_0 and $f(\tau)$ is the delay distribution function. This time delay concept is usually only applied to CD4$^+$ T cells. However, the concept could be extendable to other cells such as macrophages.

3.3   Immune Response Models

The latently infected cell model (3.1)-(3.4) that was presented in section 3.1 does not explicitly model the immune response to the virus. Instead the effects of the said immune response are incorporated into relevant parameters. In particular, the rates at which CD8$^+$ T cells kill infected cells and antibodies kill the virus are incorporated into the death rate constants δ_l and δ_a of the infected cells, and the clearance rate constant c of the virus. Parameters δ_l, δ_a and c therefore, "collectively reflect the immune system's *defensive* strength against HIV infection" [80]. Similarly, parameters β_T, and r_T "collectively reflect HIVs *offensive* strength"[80] against the immune system.

   The immune response to the virus can be explicitly modelled as illustrated by equations (3.22) - (3.26). The said immune response specifically focuses on the CD8$^+$ cytotoxic T lymphocytes - CTL. The rationale behind this model is that HIV infects immune cells which are needed in the expansion of a CTL response against infections. As a result, the ability of these cells to deliver help is compromised. This model is a variation of the one presented in [87].

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T T T^* \tag{3.22}$$

$$\frac{dT^*}{dt} = \beta_T T T^* - \delta T^* - b_I I T^* - b_E E T^* \tag{3.23}$$

$$\frac{dI}{dt} = \rho_I I T^* - \delta_I I \tag{3.24}$$

$$\frac{dP}{dt} = \rho_P T T^* P - k_E T^* P - \delta_P P \tag{3.25}$$

$$\frac{dE}{dt} = k_E T^* P - \delta_E E \tag{3.26}$$

State variables I, P and E represent the helper-independent CTL response (CTL$_i$), the helper-dependent CTL precursor response (CTL$_p$) and the helper-dependent CTL effector response (CTL$_e$), respectively. The help referred to is the uninfected CD4$^+$ T cells, whose responsibility it is to coordinate the immune response. The CTL$_i$ proliferates with a rate constant ρ_I, while the CTL$_p$ proliferates with a rate constant ρ_P and differentiates to CTL$_e$ in the presence of infected cells, with a rate constant k_E. Parameters δ_I, δ_P, δ_E are the respective death rate constants. The free virus particle dynamics are not explicitly modelled, as the assumption is that the said viral load correlates with the infected CD4$^+$ T cells, T^*.

   Some authors explicitly model the virus but only model the effector CTL$_e$ response to the virus [70]

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T TV \tag{3.27}$$

$$\frac{dT^*}{dt} = \beta_T TV - \delta T^* - b_E E T^* \tag{3.28}$$

$$\frac{dV}{dt} = r_T T^* - cV \tag{3.29}$$

$$\frac{dE}{dt} = \rho T^* - \delta_E E \tag{3.30}$$

where effectors are shown as being generated with a rate constant ρ, in the presence of infected cells. A version of the immune response model presented by [73] does not differentiate between the types of CTL responses and is given by equations (3.31)-(3.33).

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T TV \tag{3.31}$$

$$\frac{dT_8}{dt} = s_{T_8} + p_{T_8} T_8 V - d_{T_8} T_8 \tag{3.32}$$

$$\frac{dV}{dt} = r_T TV - b_v T_8 V \tag{3.33}$$

where T_8 represents the CD8$^+$ T cells.

3.4   The Chronically Infected Cell Model

As pointed out in section 3.1, it has been observed from individuals on antiretroviral therapy that there are several distinct phases in the decay characteristics of the viral load [162]. There is a first initial rapid decline which has been associated with the clearance rate of the virus particles in plasma. The next phase, referred to as the first observable phase, has been attributed to the decay or decline of the actively infected cells. The later phase, the second observable phase, could however, be attributed to a variety of reasons: It could be due to the decline or decay of the latently infected cells or there could be a subset of the actively infected cells that has a much slower death rate.

This subset of actively infected cells is believed to produce smaller amounts of virus particles over a longer period of time, and these cells are referred to as chronically infected. Equations (3.34)-(3.37) are a representation of the chronically infected cell model and similar to that as presented by [71, 162].

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T TV \tag{3.34}$$

$$\frac{dT^*}{dt} = (1-q)\beta_T TV - \delta T^* \tag{3.35}$$

$$\frac{dC^*}{dt} = q\beta_T TV - \mu C^* \tag{3.36}$$

$$\frac{dV}{dt} = r_T T^* + r_C C^* - cV \tag{3.37}$$

where variable C^* is the plasma concentration of the chronically infected CD4$^+$ T cells. Chronically infected cells make a fraction q of the actively infected cell pool. These cells produce virus with a rate constant r_C and they die with a rate constant μ.

3.5   The Extended Model

It is apparent that there are other cells in the body besides CD4$^+$ T cells that are as susceptible to the virus. The release of the virus from these cells and other infected compartments has been shown to affect the virus kinetics in plasma [113]. So while the chronically infected cell model fits the patient data, it is not the only reasonable biological model. The second observable phase of viral decay could also be linked to virus released from infected macrophages [162]. Macrophages live longer than the CD4$^+$ T cells and are chronic virus producers. An upgrade of the latently infected model is the single compartment 6 dimensional (6D) model given by equations (3.38)-(3.43), and models the target cells co-circulating in plasma [85].

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T TV \tag{3.38}$$

$$\frac{dT_l}{dt} = q_l\beta_T TV - kT_l - \delta_l T_l \tag{3.39}$$

$$\frac{dT_a}{dt} = q_a\beta_T TV + kT_l - \delta_a T_a \tag{3.40}$$

$$\frac{dM}{dt} = s_M - d_M M - \beta_M MV \tag{3.41}$$

$$\frac{dM^*}{dt} = q_M\beta_M MV - \mu M^* \tag{3.42}$$

$$\frac{dV}{dt} = r_T T_a + r_M M^* - cV \tag{3.43}$$

State variables M and M^* are the uninfected and infected macrophages respectively. Equation (3.41) shows that uninfected macrophages die with a rate constant d_M and are differently infected by the virus at a rate that is also proportional to their abundance.

Parameter β_M is an indication of the efficiency of the infection process, while q_M is the probability of successful infection (3.42). Infected macrophages die with a rate constant μ, and an infected macrophage cell produces virus with a rate constant r_M, as illustrated by equation (3.43). The model assumes that virus particles produced by infected CD4$^+$ T cells and macrophages are cleared from plasma with the same rate constant c. However, there are suggestions that virus produced from different cells are cleared at different rates [164].

Macrophages also reside in tissue (another compartment), and the extended model can therefore also reflect the release and trafficking of virus between tissue and plasma compartments, as given by equations (3.44)-(3.50) [71].

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T T V_T \tag{3.44}$$

$$\frac{dT_l}{dt} = q_l \beta_T T V_T - k T_l - \delta_l T_l \tag{3.45}$$

$$\frac{dT_a}{dt} = q_a \beta_T T V_T + k T_l - \delta_a T_a \tag{3.46}$$

$$\frac{dM}{dt} = s_M - d_M M - \beta_M M V_M \tag{3.47}$$

$$\frac{dM^*}{dt} = q_M \beta_M M V_M - \mu M^* \tag{3.48}$$

$$\frac{dV_T}{dt} = r_T T_a - c V_T + D_T(V_M - V_T) \tag{3.49}$$

$$\frac{dV_M}{dt} = r_M M^* - c V_M + D_M(V_T - V_M) \tag{3.50}$$

where V_T and V_M are the virus particles that are produced by CD4$^+$ T cells in plasma and by macrophages in tissue, respectively. Constants D_T and D_M represent the difference in virus concentrations between the two compartments, i.e., plasma and tissue.

3.6   The External Virus Source Model

There are many other models that have been developed besides the ones described above in sections 3.1 to 3.5 because there are additional reservoirs of virus. A quantitative image analysis technique was used to reveal that there is viral burden in lymphoid tissue [165], particularly on the surface of follicular dendritic cells (FDC). The source underlying the second phase kinetics might therefore also be the release of virus trapped in follicular dendritic cells (FDC).

Equation (3.51) is a variation of equation (3.43). The equation shows virus released from other sources such as macrophages and FDCs, expressed as $v_x(V)$, as an external

virus source. An external source in this context, is any virus releasing or producing cell or compartment, other than $CD4^+$ T cells in plasma.

$$\frac{dV}{dt} = r_T T_a + v_x(V) - cV \tag{3.51}$$

where $v_x(V)$ is the external virus production rate. The simplest expression for the external source term would be a constant function:

$$v_x(V) = r_{ex} \tag{3.52}$$

or be plasma virus population dependent [77]:

$$v_x(V) = \frac{g_V V}{b + V} \tag{3.53}$$

where g_V is called the process growth rate and b is referred to as the half saturation constant. The later version is more applicable since most of the virus thought to be trapped and released from FDCs varies with the amount of virus that is freely circulating in plasma. This external virus source concept can be extended as given by equation (3.54):

$$\frac{dV}{dt} = r_T T_a + r_M M^* + v_x(V) - cV \tag{3.54}$$

An external source in this case (3.54), would be any virus releasing or producing cell or compartment, other than $CD4^+$ T cells and macrophages.

Some authors explicitly model virus dynamics in follicular dendritic cells as illustrated by the following model [71]:

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T TV \tag{3.55}$$

$$\frac{dT^*}{dt} = q\beta_T TV - \delta T^* \tag{3.56}$$

$$\frac{dV}{dt} = r_T T^* - (c + b)V + uV_b \tag{3.57}$$

$$\frac{dV_b}{dt} = bV - uV_b - c_b V_b \tag{3.58}$$

where V_b represents virus particles that are trapped or bound to FDC. Parameter b is the rate constant at which free virus particles bind to FDC, and these bound virus particles unbind or dissociate from FDC with a rate constant u.

3.7   The Composite Long Lived Cell Model

Continued follow up of persons who have remained on HAART for extended periods of time has provided strong evidence for the existence of a possible reservoir in long-lived CD4+ memory T lymphocytes, a third phase of HIV decay observed during HAART. The kinetics of decay are extremely slow, and the half-life of the memory cell reservoir has been estimated at between 6 and 44 months. As a consequence, the predicted time for effective therapy required to fully eradicate the virus from the body ranges from 9 to 72 years. This suggested that a true virologic cure is unattainable using the conventional antiretroviral drugs. Table 3.1 is a summary of these important findings. Most of the figures can be found in [166] or have been deduced from [166] by [67].

Table 3.1: Virus reservoir and life span.

Infected cell	Size	Half-life	Eradication
Active CD4	3×10^7	1 day	25 days
FDC	$3 \times 10^8 - 10^{11}$	$1 - 4$ wks	$0.5 - 2.8$ yrs
Macrophage	n.a	$1 - 4$ wks	n.a
Memory CD4	$10^5 - 10^6$	$6 - 44$ mon	$9 - 72$ yrs

<div align="center">[67]</div>

A composite model for the virus and all target cell dynamics can be presented to include the following sources of virus:

- Short lived actively infected CD4+ T cells (T_a, T^*).
- Latently infected CD4+ T cells (T_l)
- Chronically infected CD4+ T cells (C^*).
- Infected macrophages (M^*).
- Long lived memory CD4+ T cells (L^*)
- Follicular dendritic cells (FDC).

The composite model will be complex to analyse and can still be further extended to include the immune response to the virus and inter-compartmental trafficking of virus particles.

Given the foregoing, the resulting expression describing the virus dynamics, when taking the virus sources itemized above into consideration would be:

$$\frac{dV}{dt} = r_T T_a + r_C C^* + r_M M^* + r_L L^* + uV_b - (c + b)V \tag{3.59}$$

3.8   Stochastic Models

Many biological processes are known to have random variations and the HIV infection is stochastic by nature [86]. The argument being put forth in favour of stochastic models is that since stochastic models take into account the random nature of the HIV infection, they give a more realistic scenario of the HIV dynamics when compared to deterministic models. Also, the use of stochastic models paves the way to access the random variations in many of the risk variables with respect to the future course of the infection.

Equations (3.60)-(3.63) are a stochastic model of the HIV infection dynamics and are a slight variation of that presented in [86].

$$\Delta T(t) = s_T \Delta t + p(t)T(t)\Delta t - d_T T(t)\Delta t - \beta_T T(t)V(t)\Delta t + \varepsilon_1(t)\Delta t \quad (3.60)$$

$$\Delta T_l(t) = q_l \beta_T T(t)V(t)\Delta t - kT_l(t)\Delta t - \delta_l T_l(t)\Delta t + \varepsilon_2(t)\Delta t \quad (3.61)$$

$$\Delta T_a(t) = q_a \beta_T T(t)V(t)\Delta t + kT_l(t)\Delta t - \delta_a T_a(t)\Delta t + \varepsilon_3(t)\Delta t \quad (3.62)$$

$$\Delta V(t) = r_T(t)T_a(t)\Delta t - cV(t)\Delta t + \varepsilon_4(t)\Delta t \quad (3.63)$$

where $\varepsilon_i(t)$, $i = 1, 2, 3, 4$ are the random noises.

3.9   Models Adopted in this Thesis

The latently infected cell model (3.1)-(3.4) and the co-circulating target cell extended model (3.38)-(3.43) are the models that are adopted in this thesis and will be discussed below. However, the concepts that will be presented in the following chapters are not model specific, in that they can be extended or applied to any other model.

A summary of all the parameters in the latently infected and extended models is presented in table 3.2.

3.9.1   Validity: Limitations and Adequacy of Models

None of the models presented in the preceding sections can completely exhibit all that is observed clinically and account for the full course of the infection as previously illustrated by figure 2.3 in section 2.1.3. The main reason for the models' limitation is lack of a good understanding of the immunology of the human body against HIV. Biological systems tend to exhibit multi-compartmental interactions that are usually not well understood and as a result, can not be accurately modelled mathematically. The accuracy of the models though, is increasing with new medical discoveries.

Table 3.2: Parameters in the latently infected and extended models.

Parameter and description		L	E
s_T	Source rate for CD4$^+$ T cells	$\star$	$\star$
p	Proliferation rate for CD4$^+$ T cells	$\star$	$\star$
T_m	Proliferation shut down CD4$^+$ T cell count	$\star$	$\star$
d_T	Death rate for uninfected CD4$^+$ T cells	$\star$	$\star$
β_T	Infection rate for CD4$^+$ T cells by virus	$\star$	$\star$
δ_l	Death rate for latently infected CD4$^+$ T cells	$\star$	$\star$
δ_a	Death rate for actively infected CD4$^+$ T cells	$\star$	$\star$
q_l	Fraction of infected CD4$^+$ T cells that becomes latent	$\star$	$\star$
q_a	Fraction of infected CD4$^+$ T cells that becomes active	$\star$	$\star$
k	Activation rate for latently infected CD4$^+$ T cells	$\star$	$\star$
s_M	Source rate for macrophages		$\star$
d_M	Death rate for uninfected macrophages		$\star$
β_M	Infection rate for macrophages by virus		$\star$
q_M	Probability of successful infection of macrophage by virus		$\star$
μ	Death rate for infected macrophages		$\star$
r_T	Virus particle production rate per infected CD4$^+$ T cell	$\star$	$\star$
r_M	Virus particle production rate per infected macrophage		$\star$
c	Death rate for virus particle	$\star$	$\star$
η_{rt}	Efficacy of all RTIs in regimen	$\star$	$\star$
η_{pi}	Efficacy of all PIs in regimen	$\star$	$\star$
α_{rt}	Differential RTI penetration into macrophages		$\star$
α_{pi}	Differential PI penetration into macrophages		$\star$
η_{ps}	Efficacy of all proliferation suppressors in regimen	$\star$	$\star$
η_{da}	Efficacy of all cell death accelerators in regimen	$\star$	$\star$
Total: Number of parameters		**12**	**18**

$*$indicates the applicable parameter.

L: Latently infected cell model. **E**: Extended model.

All parameters except s_T and s_M are rate constants.

A point to consider is that these models do not take into account other extenuating environmental, social and welfare factors that may affect the progression of the infection. Organ health, for example, the extent to which the immune system is repairable as the infection progresses is another issue that these models do not take into consideration. Most of these models however, do adequately explain the interaction of the virus and the immune system up to the clinical latency stage.

In an attempt to account for the later or advanced stage of the infection, some model parameters are assumed to change as the infection progresses [75, 80, 167, 168]. These assumptions, though not clinically validated, do give a virus and target cell profile that complies with clinical observations. Other suggestions are that the prolonged production and destruction of the immune cells ultimately results in an immune collapse.

The models adopted for this thesis are single compartment, do not include intracellular delays, neither do they explicitly model the immune response to the virus. The reasons for adopting these models are that:

1. The latently infected cell model adequately models the virus and target cell dynamics. Its simplicity lends its self to provide analytical insights more readily, which can then be extended to other models.

2. The extended model is useful because it can simulate persistent virus replication under potent HAART that leads to the maintenance of a low steady state viral load [71].

3. It is currently difficult to get viral load measurements from tissue or any other compartment besides plasma, except in experimental settings. This thesis will therefore not consider the compartmental models.

4. The immune response to the virus can not be measurably quantified. Instead the effects of the said immune response are incorporated into relevant parameters. In particular, the rates at which CD8 T cells kill infected cells and virus are incorporated into the death rate constants δ_l and δ_a of the infected cells, and the clearance rate constant c of the virus. Parameters δ_l, δ_a and c therefore, "collectively reflect the immune system's *defensive* strength against HIV infection" [80]. Similarly, parameters β_T, and r_T "collectively reflect HIVs *offensive* strength"[80] against the immune system. This thesis will therefore not consider models that explicitly show the immune response to the virus.

5. The effect of intracellular delays in virus production from infection can be lumped into the production and clearance rate parameters of the virus. After the initial infection period, the delay effect loses its significance as all it does is shift the

virus curve to the left by the time delay. Furthermore, this delay is in the order of minutes, and when compared with the long asymptomatic period of several years, the delay is of no consequence.

3.9.2   Parameter Estimates

Generally, the rates of lymphocyte turnover during health and disease are poorly characterized. This limits our understanding of diseases like HIV-infection that lead to increased rates of cellular turnover and ultimately to deterioration of the immune system. HIV-1 infection is known to increase the turnover rates of CD4$^+$ and CD8$^+$ T cells and to deplete the populations of naïve CD4$^+$ T cells, naïve CD8$^+$ T cells, and memory CD4$^+$ T cells [116]. Current estimates for the turnover rates of CD4$^+$ T cells vary between 1 and 2% in normal individuals to $1-10\%$ in HIV- 1 infected patients [116].

Various clinical studies have been carried out in order to obtain estimates for the model parameters. However, most of the studies focus on obtaining estimates for c, δ_a, β_T and r_T. There are inter-individual variations in parameter estimates within a study. Furthermore, there are variations in estimates for a particular parameter between studies. Generally, parameters β_T and r_T have the widest variation, while parameters c and δ_a are known to have the least variations. Not much effort however, has been made to determine variations in macrophage cell related parameters. However, one could intuitively expect β_M and r_M to have a wider variation when compared to μ. Values for parameter estimates that were used in this thesis are presented in Appendix A.

Figure 3.2 shows how the plasma concentrations of the uninfected CD4$^+$ T cells (T), all infected CD4$^+$ T cells (T*), uninfected macrophages (M), infected macrophages (M*), and free virus particles (V), vary with time from initial infection to the asymptomatic stage. The initial decline of the uninfected cells and the increase in viral load are very rapid. All variables however, do eventually settle in damped oscillations to their respective infected steady state values.

3.10   Model Parameters Affected by Therapy

Therapy generally entails the use of reverse transcriptase and protease inhibitors (replication cycle based therapy) as well as proliferation suppressors and cell death accelerators (immune based therapy). As a control input, the model parameters that are affected by these drugs have been identified in for example [85, 169].

Reverse transcriptase inhibitors do not directly prevent cell infection. Rather, these antiretroviral agents reduce virus replication by reducing the probabilities q_l, q_a and q_M
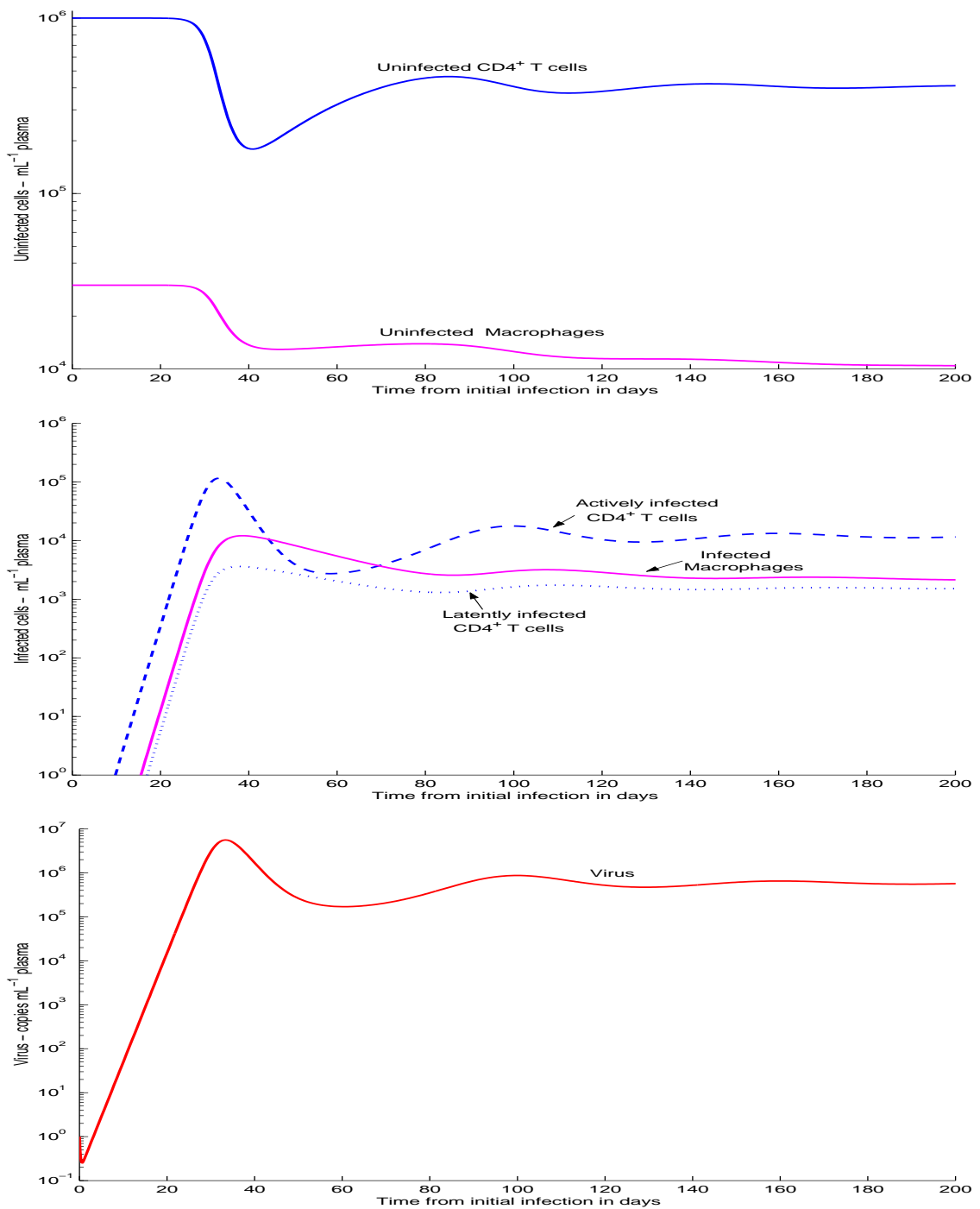
Figure 3.2: Simulated plasma concentrations for T, T_a, T_l, M, M^* and V. Parameters are as in Table A.4.

Table 3.3: Model parameters affected by therapy

Inhibitor/Drug	Parameters Affected	Efficacy
Reverse transcriptase inhibitors	q_l, q_a, q_M	η_{rt}, $\alpha_{rt}\eta_{rt}$
Protease inhibitors	r_T, r_M	η_{pi}, $\alpha_{pi}\eta_{pi}$
T cell proliferation suppressors	p	η_{ps}
Infected T Cell death rate accelerators	δ_l, δ_a	η_{da}
Induced CD4$^+$ T cell death (apoptosis)	d_T	η_{ap}

of successful cell infection. η_{rt}: $0 \leq \eta_{rt} < 1$ is the combined efficacy of all the reverse transcriptase inhibitors used. Perfect inhibition occurs when $\eta_{rt} = 1$ and there is no inhibition when $\eta_{rt} = 0$. Differential reverse transcriptase inhibitor penetration into target CD4$^+$ T cells and macrophages is reflected by parameter α_{rt}, where $0 \leq \alpha_{rt} \leq 1$. Most authours present β_T and β_M as the parameters affected by reverse transcriptase inhibitors for simplicity.

Protease inhibitors reduce the rates r_T and r_M at which infectious virus particles are produced. This leads to the production of mostly noninfectious virus particles. η_{pi}: $0 \leq \eta_{pi} < 1$ is the combined efficacy of all the protease inhibitors used. Similarly, perfect inhibition occurs when all virus particles that are produced are noninfectious. That is, when $\eta_{pi} = 1$ and there is no inhibition when $\eta_{pi} = 0$. In practice however, perfect inhibition does not seem attainable with any class of replication cycle based antiretroviral agents. Differential protease inhibitor penetration into target CD4$^+$ T cells and macrophages is reflected by parameter α_{pi}, where $0 \leq \alpha_{pi} \leq 1$.

Immune based therapies only affect host cell parameters. Cell proliferation suppressors reduce parameter p, and η_{ps}: $0 \leq \eta_{ps} < 1$ is the combined efficacy of all the proliferation suppressors used.

Infected CD4$^+$ T cell death rate accelerators would increase parameters δ_l and δ_a. η_{da}: $\eta_{da} \geq 1$ is the combined efficacy of all the cell death accelerating therapies used.

Therapies that induce CD4$^+$ T cell death (apoptosis) would increase parameter d_T, and η_{ap}: $\eta_{ap} \geq 1$ is the combined efficacy of all the apoptosis inducing drugs used.

Table 3.3 presents a summary of which model parameters are affected by the various types of drugs used to treat HIV infection.

3.11   Chapter Summary

Many models explaining different aspects of the HIV infection have been developed. Most of these are deterministic single compartment models. Though most of the models can not account for the full infection progression, they do however, adequately explain the interaction of the virus and the immune system up to the clinical latency stage. The following is a summary of virus and target cell dynamics that have been, and have yet to be modelled.

Modelled Dynamics:

1. Interaction between CD4$^+$ T cells and the virus in plasma
2. Inclusion of macrophages and other long lived target cells of the HIV. These macrophages or long lived cells could be in plasma with the CD4$^+$ T cells (co-circulating target cell model) and/or in tissue (compartmental model)
3. Trapping and release of virus from follicular dendritic cells
4. Release of virus from other unspecified external sources
5. Virus mutations: Resistance
6. Time delay from initial infection to release of virus from infected cell
7. Infection progression from initial virus inoculation to AIDS
8. Immune response to the virus:
    (a) Inclusion of CD8$^+$ (killer, Effector) T cells dynamics in plasma
    (b) Inclusion of Memory T cell dynamics in plasma
9. Stochastic or Random variations in virus dynamics

Un-modelled Dynamics:

1. Environmental and social factors that influence infection progression.
2. Organ health. For example, the extent to which the immune system is repairable
3. Other clinically observed phenomena

Model parameters that are affected by therapy have been identified, and studies have been conducted in order to obtain estimates for the model parameters. However, most of the studies focus on obtaining estimates for c, δ_a, β_T and r_T. There are inter-individual variations in parameter estimates within a study, as there are also variations in estimates for a particular parameter between studies. Generally, parameters β_T and r_T have the widest variation, while parameters c and δ_a are known to have the least variations. Not much effort however, has been made to determine variations in macrophage cell related parameters.