MODELING HIV-1 INFECTION AND IMMUNE RESPONSES
UNDER DRUGS OF ABUSE

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ABSTRACT

The frequent use of drugs of abuse among HIV infected individuals is a major concern. Drugs of abuse, such as opiates, have been widely associated with enhancing HIV replication, accelerating disease progression, and diminishing host-immune responses. Moreover, opiates such as morphine have also been associated with decreasing the viral mutation rate. The rapid replication of HIV may result in increased production of mutant viruses that can escape detection by the host’s immune system. This shows that the use of drugs of abuse can make it harder to effectively manage HIV infections. It is thus important to gain insights into the effects of drugs of abuse on HIV dynamics. This dissertation presents mathematical models that help investigate the effects of morphine-altered antibody responses on SIV dynamics, effects of morphine pharmacodynamics on HIV dynamics, and effects of morphine on HIV-infections with two viral species. Using our models, we show that in a subpopulation of SIV infected morphine addicted macaques, the presence of drugs of abuse may cause significantly diminished antibody responses, resulting in more severe infection with increased SIV infectivity, a decreased viral clearance rate, increased viral load,
and higher CD4+ T cell loss. We also show that the infection threshold, the viral load, and the CD4+ T cell count largely depend on morphine pharmacodynamic parameters. Magnitudes of the basic reproduction number, and the numerical simulations results of our two viral species model show that the wild type virus dominates both in the presence of morphine and in the absence of morphine. The presence of morphine generally results in higher proportion of wild-type virus than mutant virus thereby resulting into a higher total viral load. Results in this dissertation may be useful to develop HIV control strategies, such as antibody based vaccines, for drug abuse groups.
The faculty listed below, appointed by the Dean of the School of Graduate Studies, have examined a dissertation titled “Modeling HIV-1 Infection and Immune Responses Under Drugs of Abuse”, presented by Jones Mutune Mutua, candidate for the Doctor of Philosophy degree, and certify that in their opinion it is worthy of acceptance.

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DEDICATION

To my mother, my late father, and Prof. Mutuku Mutinga.
CHAPTER 1
INTRODUCTION

Human Immunodeficiency Virus (HIV) is a common infectious disease that has become a major public health challenge in the world. Worldwide over 33 million people currently live with the virus, while an estimated 1.8 million new infections and 1 million AIDS-related deaths occur annually [78, 83]. Furthermore, according to UNAIDS [83], 76.1 million individuals have become infected with HIV with 35 million AIDS-related deaths since the start of the epidemic.

HIV is mostly transmitted through sexual intercourse, contaminated blood mainly from sharing drug injection equipment such as syringes, and mother-to-child during pregnancy, childbirth, or breastfeeding. Once the virus (Figure 1) invades the human body, it can eventually progress to acquired Immunodeficiency Syndrome (AIDS) stage. HIV also attacks the immune system which is responsible for fighting infections in the body, hence making it weaker and vulnerable to opportunistic infections. The major challenge about HIV is that no effective cure for the virus currently exists. This fact has prompted the emergence of studies which look at ways to control the virus.
Among HIV-infected people, the frequency of use and dependence on drugs of abuse, such as opiates, is rapidly increasing with drug users constituting a large cohort within the HIV-infected population [21, 67]. The Centers for Disease Control and Prevention [10] estimated that in the US 28% of total AIDS cases and 33% of yearly new HIV cases were associated with the use of drugs of abuse. These statistics reflect that the use of drugs of abuse drastically exacerbates the public health burden. More importantly, drug users, once infected with HIV, are at a greater risk of suffering from higher viral load, rapid disease progression, and higher HIV-associated neurocognitive disorders (HAND) [28, 71, 92]. It is thus critical to understand how drugs of abuse affect the viral dynamics within HIV-infected individuals.

One of the effects of drugs of abuse that has been shown in laboratory experiments is the alteration of virus-specific antibody responses [38]. These experiments, utilizing simian immunodeficiency virus (SIV) infection in morphine addicted macaques, have provided useful insights of antibody responses in the presence of drugs of abuse. Virus-specific antibodies have the significant role of protecting individuals against a wide variety of viral infections. These antibodies are known to play a role in
controlling established HIV infection, and preventing new infections [44, 59]. These observations indicate that drugs of abuse can impact virus dynamics indirectly by altering antibody responses.

We note that these experimental studies [37, 38] have utilized constant morphine. However, drugs of abuse are often taken periodically and the concentration of drugs of abuse changes periodically over time. Thus, the periodic use of these drugs of abuse can result into periodic changes of virus-specific antibody concentrations in the body. Therefore, when devising antibody mediated controls, such as with vaccines, it is important to study how the alteration of antibody responses due to the presence of drugs of abuse can change various aspects of viral dynamics both in the constant morphine and periodic morphine cases.

Some previous studies provide key insights into the mechanisms that form the basis of multiple infections of cells by HIV [18, 34, 40]. In the center of these multiple infections are virions that have diverse genetic material and may become resistant to drug therapies, or may escape the host immune responses all together. This leads to significant barriers to the treatment of HIV by antiviral drugs or to the development of effective vaccines. The use of drugs of abuse could be attributed to the virions escaping the immune responses. Experimental studies [70, 80] have shown that morphine contributes to viral replication and evolution. However, the exact role morphine plays in virus dynamics with viral evolution remains unclear. It is thus important to understand the effects of morphine on the viral dynamics of HIV when multiple viral species, namely wild-type and mutant viruses, are present.

Mathematical modeling of virus dynamics has been useful in understanding
the interplay of viral dynamics and immune responses [9, 58, 63, 64]. However, limited study has been done relating to modeling of HIV dynamics and drugs of abuse [82, 88]. Our goal in this dissertation is to provide such mathematical models that offer insights on the effects of opiates, such as morphine, on viral dynamics of HIV.

In chapter 2, we provide some background of relevant mathematical modeling of HIV dynamics, and biological concepts for HIV such as the HIV life cycle and the immune system. We also present some techniques for theoretical analysis used in the dissertation.

In chapter 3, we develop viral dynamic models that incorporate virus-specific antibody responses to study the quantitative effects of morphine-altered antibody responses on SIV infection dynamics over the first 200 days post infection. The models are parameterized using viral load and virus-specific antibody data from morphine-added macaques infected with a mixture of SIV and SHIV (simian human immunodeficiency virus).

In chapter 4, we develop and analyze a model for HIV dynamics under periodic morphine intake. We conduct an analysis of the non-autonomous model system and establish the local and global properties of viral dynamics. Furthermore, we discuss how various aspects of pharmacodynamics of morphine affect the viral dynamics in HIV-infections.

In chapter 5, we develop and analyze a viral dynamics model with two viral species under morphine conditioning. We calculate the basic reproduction number for each virus strain and perform numerical simulations to examine the effects of morphine on the HIV-infection dynamics in wild-type and mutant virus.
In chapter 6, we present the conclusions and discussion of the dissertation.
HIV BACKGROUND AND LITERATURE REVIEW

HIV life cycle

An HIV virion requires a cell in order to replicate. The virus targets the helper T cells, specifically known as CD4+ T cells, which are vital in maintaining a fully functioning immune system which is responsible for fighting infections [84]. The CD4+ T cells contain proteins that can bind to foreign substances such as HIV. The virus starts its process of replication by binding itself to the receptors on the surface of the CD4+ T cell. The HIV envelope and membrane of the cell then join together allowing the HIV virion to enter the CD4+ T cell. Since HIV is a retrovirus and has two strands of RNA, a DNA copy of the RNA is made inside the cell through a process known as reverse transcription. The viral RNA is converted to DNA in the CD4+ T cell nucleus. Through the integration process, the converted viral DNA is carried to the nucleus of the cell and hidden into the DNA of the CD4+ T cell. At this stage, when the CD4+ T cell makes its proteins, it also makes new HIV proteins. Through the transcription process, the HIV strands separate and a new strand is created which gives instructions on making new HIV. As these new strands are made, each corresponds to a string of proteins. This process continues until the strand is translated to a virus particle which is able to make new protein. The new immature (noninfectious) virus particles then assemble on the surface of the cell after which they bud from the host CD4+ T cell and mature to become infectious utilizing protease
proteins [84]. A schematic diagram of the HIV life cycle is presented in Figure 2.

Figure 2. Schematic diagram of the HIV life cycle [94]

As this process of viral replication continues, the infected individual’s immune system weakens. The individuals then mainly go through acute and chronic HIV infections before reaching the AIDS stage, which is the final and most severe of the HIV infection stages [39, 84]. After the initial HIV infection, individuals experience symptoms which can be compared to those of a flu infection. At this stage of infection, the viral load is very high, then after a relatively short period of time the viral load declines to reach a set point where it can remain for many years. In an effort to control
the HIV replication process, HIV antiretroviral drugs have been developed. The major classes of these antiretroviral drugs include fusion inhibitors, reverse transcriptase inhibitors, integrase inhibitors, and protease inhibitors.

**Immune system**

The immune system is responsible for preventing the body against infections as well as removing existing infections. It comprises of cells, tissues, and molecules which work together to protect the body. There are two types of immunity: innate and adaptive. Innate immunity acts as the front line defense mechanism which protects the body from most common infections. Adaptive immunity, on the other hand, is an immune response that must recognize foreign materials in the body by using white blood cells commonly known as lymphocytes (T and B cells). The T cells help eliminate foreign materials that live inside the infected cell of an individual and also help the B cells to make antibodies. The B cells main activity is the production of antibodies which help to kill foreign invaders before they can infect an individual’s cell.

In addition to antibodies playing a major role in controlling HIV infections, the “killer” T cells, also known as cytotoxic T lymphocytes (CTLs), are also important HIV immune control T cells. The production of cytokines can limit viral reproduction, reduce the amount of receptors available on the target cells, and destroy infected cells directly [49]. As these CTLs are continuously generated, they exert pressure on the virus which can cause the virus to mutate to a form that can evade the CTLs [15, 68]. Maintaining a well functioning immune system is very important especially in the fight against HIV, since a dysfunctional one can lead to increased viral loads and/or
increased disease progression.

**Viral dynamics modeling**

Many studies on HIV dynamics modeling have been undertaken more than we can exhaustively review here. Thus in this dissertation, we present a brief summary of some articles which have focused on within-host HIV dynamics models relating to immune system, and drugs of abuse. We also highlight some experimental studies which provide information that has been, and can be, useful in developing new models.

We start by considering the simplest and earliest basic model of viral infection [32, 93]. This model incorporates the main classes of HIV infection which include uninfected target cells, $T$, infected cells, $I$, and free virus, $V$ (see Figure 3).

![Figure 3. Schematic diagram of the basic model of HIV infection.](image)

In this model, target cells are generated at a constant rate $\lambda$ and die at per capita rate $d$. Upon interaction with free virus, the target cells become infected at
a rate $\beta$. Infected cells die at a per capita rate $\delta$ and produce virus at a rate $p$ per infected cell. Virions are cleared at a per capita rate $c$. The model is described by the following set of ordinary differential equations:

\[
\frac{dT}{dt} = \lambda - \beta VT - dT,
\]

\[
\frac{dI}{dt} = \beta VT - \delta I, \tag{2.1}
\]

\[
\frac{dV}{dt} = pI - cV.
\]

This model was shown to be able to describe the kinetics of acute HIV infection [61, 64, 65, 75] and has led to the development of the field of study on viral dynamics [58, 63].

Tomaras et al. [81] extended the basic model (2.1) by considering the effects of antibodies in enhancing virion clearance, neutralizing virus, and the possibility of enhancing the rate of infected cell loss. This model provided a description of both the antibody timing and the viral load dynamics to determine salutary or detrimental effects of early antibody responses on control of plasma viremia. From this model, it was observed that the initial B-cell response to the transmitted or founder virus does not control initial virus levels during the first 40 days of virus infection. An important question about the effectiveness of these antibodies posed in the study was whether they could be protective if they are present before infection, or whether different types of antibodies would need to be used from the development of effective HIV-1 vaccines and induced prior to infection.

Ciupe [14] developed a mathematical model of multivalent antibody binding.
This model was used to determine the dynamical interactions between HIV and antibodies as well as to predict conditions under which pre-existing or HIV induced antibodies contribute to viral protection. The model results show that at the beginning of infection, the total virus largely consists of free virus, and just a few antibody-virion immune complexes. However, the results show that after about 1 year, less than 1% of the total virus is free and the remaining proportion is in the form of antibody-virion complexes.

Ciupe et al. [13] presented models which investigate poly-specific and strain-specific neutralizing antibodies following HIV infection. One of the models described antibody immune responses following continuous immunization, whereas the other described antibody responses following natural infection. The numerical results from these models present a situation where viruses are cleared in the presence of only poly-specific immune responses and persist when both strain-specific and poly-specific neutralizing antibodies are present.

Viral RNA can evolve rapidly and can often evade the activities of the host immune responses and adapt to varying environments [19, 33, 95]. Models have been developed that account for the evolution of virus during the course of infection. One of the best ways in which virus evolution has been described is by considering the dynamics of different virus strains with different traits. Ball et al. [5] developed a model that extended the basic model of viral dynamics (2.1) and examined the competition between virus strains within an infected host. The model results showed that the virus strains were dominant at the beginning and at the late stages of the infection.
Alizon and Boldin [3], inspired by Ball et al. [5], developed a model with multiple target cells. The model results show interesting properties in co-receptor switching including the initial dominance of virus strains that infect CCR5+ cells, a late switch in some HIV infections and an associated drop in the number of uninfected T-cells.

Other studies that have developed models that factor in mutation of virus include the work by Nowak and Bangham [56] that explored the relationship between immune responses, viral load and virus diversity. A model which captures the antigenic escape dynamics was developed by Wodarz and Nowak [20]. Their model specifically incorporated mutant virus and immune responses, which can include either B cells or T cells. This model assumes that each strain-specific response responds to only one strain.

**HIV infections and drugs of abuse**

Experimental studies have shown that drugs of abuse constitute to the alteration of virus-specific antibody responses. Here we present a few that have provided valuable insights on the effects of drugs of abuse on HIV infections. Kumar et al. [38] presented a study that involved an experiment carried out on six morphine-exposed and 3 control male Indian rhesus macaques that were intravenously inoculated with mixture of SIV viruses. They followed these animals for about 56 weeks to determine, among other things, the binding as well neutralizing antibody levels and cellular immune responses.

Rivera-Amill et al. [70] presented a review study that contributes to the understanding of how drugs of abuse might influence immune selective pressure to
variation in different SIV genes. Their work showed that viral evolution is altered in
the setting of drugs of abuse. However, one limitation of this study was that it could
not determine the direct impact of morphine on evolution.

Mathematical modeling of HIV under drugs of abuse is very limited. A most
recent model on HIV dynamics and drugs of abuse is provided by Vaidya et al. [87].
This model consists of two subpopulations of target cells (CD4+ T cells) categorized
based on the level of co-receptor expressions - one with lower susceptibility to infection
(i.e. lower infection rate) due to a low level of co-receptor expression, $T_l$, and another
with higher susceptibility (i.e. higher infection rate) due to a high level of co-receptor
expression, $T_h$. In addition, the model contains productively infected cells, $I$, and
free virus, $V$. The study assumes that target cells are generated at a constant rate
$\lambda$ and die at per capita rate $d$. Upon interaction with free virus, target cells, $T_l$
and $T_h$, become infected at rates $\beta_l$ and $\beta_h$, respectively. Infected cells die at a per
capita rate $\delta$ and produce virus at a rate $p$ per infected cell. Virions are cleared at
per capita rate $c$. Parameters $r$ and $q$ denote the transition rates from $T_l$ to $T_h$ and
from $T_h$ to $T_l$, respectively. The differential equations for this model are

$$\frac{dT_l}{dt} = \lambda + qT_h - dT_l - \beta_l VT_l$$

$$T_l(0) = T_{l0},$$

$$\frac{dT_h}{dt} = rT_l - dT_h - \beta_h VT_h - qT_h$$

$$T_h(0) = T_{h0},$$

$$\frac{dI}{dt} = \beta_l VT_l + \beta_h VT_h - \delta I$$

$$I(0) = I_0,$$  \hspace{1cm} (2.2)

$$\frac{dV}{dt} = pI - cV$$

$$V(0) = V_0.$$  

The model is validated by fitting it to the experimental viral load data [38], and key
parameters are estimated. This is the first model to have provided SIV viral dynamics parameter estimations in the presence of drugs of abuse. The model parameter estimations supported the experimental observation [8, 43, 47, 76, 77] that morphine promotes co-receptor expression in target cells, which can cause increased susceptibility of these cells to HIV/SIV infection. The study showed higher basic reproduction number ($R_0$) estimates in morphine-dependent animals than in control animals, indicating that morphine may induce additional obstacles for intervention strategies. The model, however, did not capture immune response effect in viral dynamics and the reason for this was because the model described the effects of morphine only for the first 3 months post-infection, when immune responses are largely absent.

A thesis study by Uhl [82], developed a novel mathematical model with two viral species (wild-type and mutant viruses) and cellular immune responses (CTLs) that incorporated immune escape and morphine effects. The model simulates the increase in viral load that results from the use of morphine by introducing terms that lower the mutation rate of the virus and host’s cellular immune response. The results from this study shows that the virus population switch, and wild-type dominance, occurs for sufficiently high morphine concentration. The results also show that reduced cellular immune response results in higher set point viral load.

**Data fitting**

In fitting the data to a model system of ordinary differential equations (ODEs), one can estimate some unknown parameters associated with the model. These ODEs are solved numerically using “ode15s” or “ode45” solvers in MATLAB. Together with these MATLAB solvers, the optimization functions “fminsearch” and “fmincon” are
also used. The most common data fitting method used is the least squares method. In this fitting method, the sum of the square residuals, i.e., the difference between the model predictions and the corresponding experimental data values, is minimized. The following formula is used for calculating the sum of the squared residuals:

$$ J = \frac{1}{M} \sum_{i=1}^{M} (y - y_i)^2 $$

(2.3)

where $M$ represents the total number of data points considered for fitting, and $y$ and $y_i$ represent the values predicted by the model and those given by the experimental data, respectively. Another form of least squares analysis method is known as non-linear least squares. This method is used to fit a set of $k$ observations with a model that is non-linear in $l$ unknown parameters ($k > l$). This fitting method is made easier by the use of the “lsqcurvefit” solver in MATLAB. For the best model parameter estimates obtained from the data fitting, a common practice is to find the confidence intervals (CI), which are computed from $n$ replicates, by bootstrapping the residuals [6, 24] obtained using the formula (2.3). One important aspect of the bootstrapping process is re-sampling with replacement. That means during this process, the randomly selected data samples can contain repeated data points.

Generally, in obtaining the confidence interval (CI) of model parameter estimations by bootstrapping method, the following steps are followed. (1) Choose a sample of $m$ data points. (2) Re-sample the $m$ data points over and over again, with replacement. (3) Run the simulation of the model and calculate the residual error between the simulated curve and the data at each data point. (4) Calculate the standard deviation of the error. This becomes the standard deviation for a normally
distributed random error term. (5) At each time point of the data, add a randomly chosen error from step 4 to the simulated curve at that point, and mark it as new data. (6) Repeat step 2 through 5 \( n \) times. (7) Run the model fitting simulations on each of the \( n \) bootstrapped data points, and calculate 95% confidence interval based off of the results of these simulations.

**Model comparison**

Akaike’s Information Criterion (AIC) provides a way to compare the quality of each model, relative to each of the other models being considered. Using the AIC computed values, a determination is made on which model most adequately describes reality among the examined ones. The best model is the one that has the lowest AIC values among all the other models. The following formula is used for calculating the AIC values [1]:

\[
AIC = M \log_e \left( \frac{J}{M} \right) + \frac{2M(N_p + 1)}{M - N_p - 2}
\]

(2.4)

where \( J \) is the sum of squared residuals, \( M \) is the number of data points used in data fitting, and \( N_p \) is the number of parameters estimated in the fitting.

**Comparison of two groups using the \( p \)-value**

A \( p \)-value is a number that lies between 0 and 1. This value helps us make a determination whether the results obtained in a study are statistically significant or not. A small \( p \)-value (usually \(< 0.05\)) indicates that the results being examined are statistically significant, whereas a large \( p \)-value (usually \(> 0.05\)) indicates that there is no statistical significance to the compared results. In MATLAB, one can
easily calculate the $p$-values using the t-test commands \([h, p] = \text{ttest2}(x, y)\) for two samples with equal means, and \([h, p] = \text{ttest2}(x, y, 'Vartype','unequal')\) for two samples of unequal variance. $p$ represents the $p$-value returned after running the command, and $x$ and $y$ represent the vectors of the samples being compared. If the command returns a value of $h = 0$, this indicates that ttest2 does not reject the null hypothesis at the default 5% significance level.

The basic reproduction number ($R_0$)

In the within-host modeling, the basic reproduction number, $R_0$, is defined as the average number of secondary infections occurring from a single infected cell among entirely uninfected cells [4, 16]. An important note about the $R_0$ is that it is a dimensionless number and not a rate, meaning it has no unit. In deriving the basic reproduction number, the next generation operator method [17, 89] is used. In this method, a model system described by a set of ordinary differential equations (ODEs) is considered. From these ODEs, two matrices of partial derivatives are created by differentiating every equation with respect to every variable. The first matrix, denoted by $F$, includes entries of the infectious terms that appear in each differential equation. The second matrix, denoted by $V$, includes entries that provide the average time spent between compartments. If an equation has neither infectious terms nor transfer terms, then the entries in the respective matrix are zeros. The product of $F$ and $V^{-1}$ gives the total new infections. The eigenvalues of the total new infections matrix (i.e., eigenvalues of $FV^{-1}$) are calculated. The basic reproduction number, therefore, is the largest of these eigenvalues. Mathematically, this can be summarized as follows:
From the ODEs, we introduce matrices $F = \left[ \frac{\partial F_i(x_0)}{\partial x_j} \right]$ and $V = \left[ \frac{\partial V_i(x_0)}{\partial x_j} \right]$ where $F_i$ represents the new infections, $V_i$ represents transfer of infection from one compartment to another, and $x_0$ represents the infection free equilibrium. The basic reproduction number, $R_0$, is the dominant eigenvalue of the matrix $FV^{-1}$. 
CHAPTER 3
MODELING HIV DYNAMICS IN MORPHINE-ALTERED ANTIBODY RESPONSES

In this chapter, using mathematical models that incorporate virus-specific antibody responses and experimental data from morphine-addicted macaques, we examine how morphine can alter virus-specific antibody responses affecting the dynamics of simian immunodeficiency virus infection in macaques. We show that morphine can significantly diminish virus-specific antibody responses in a sub-population of animals, hence resulting in reduced virus neutralization, reduced viral clearance, and an increased CD4+ T cell loss over the first 200 days post infection.

Introduction

The use of drugs of abuse such as opiates among HIV-infected people has been rapidly increasing. Drug abusers, once infected with HIV, suffer from higher viral load, rapid disease progression, and higher HIV-associated neurocognitive disorders (HAND) than non-drug users. Alteration of virus-specific antibody responses due to drugs of abuse may explain such infection complexity in drug abusers.

Experiments utilizing simian immunodeficiency virus (SIV) infection in morphine addicted macaques have provided useful understanding of antibody responses in the presence of drugs of abuse [38]. While morphine addicted animals show antibody responses of relatively smaller magnitude than control animals [38], whether these differences are significant in noticeably changing viral infection dynamics is not yet
understood. Experimental evidence and the recent modeling study [87] indicate that morphine use does not seem to significantly affect immune responses during the first 12 weeks post-infection. However, antibody responses and the effects of morphine on antibody levels become significantly pronounced over a longer period of time post-infection [38]. Moreover, careful consideration of the longer-term data obtained from individual SIV-infected animals indicate that about half of the morphine addicted animals studied exhibited rapid disease progression resulting in a very short lifespan [38]. This suggests that as far as the effects of morphine on long-term SIV infection is concerned, there are two different subpopulations of morphine-addicted animals, namely, a rapid-progressor morphine group and a slow-progressor morphine group as categorized in Kumar et al. [38]. Aligned with these different responses of animals to SIV infection under morphine conditioning, the rapid-progressor morphine group did not develop detectable antibody responses, whereas the slow-progressor morphine group and the control group did. Thus, there appears to be a complex relationship among morphine, antibody responses and virus dynamics that modeling may be able to reveal.

**Experiment and data**

Rhesus macaques used for the study were obtained from the Caribbean Research Primate Center and housed in the Animal Resource Center of the University of Puerto Rico, San Juan. The experimental protocol was approved by the Institutional Animal Care and Use Committee and the research was performed in accordance with the Guide for the Care and Use of Laboratory Animals [53].

The data used in this study was obtained from an experiment involving 12 male
rhesus macaques (*Macaca mulatta*)—six morphine-dependent and six control macaques [37, 38]. The animals were negative for simian T-cell leukemia virus type 1 and simian retrovirus. The morphine dependence was established by injecting intramuscularly increasing doses of morphine (1-5 mg/kg) over a 2-week period. All 12 animals were infected intravenously with mixture of viruses $SHIV_{KU-1B}, SHIV_{89-6P}$, and $SIV_{17E-Fr}$. These animals were monitored for a period of 28 weeks, and levels of circulating CD4$^+$ T cells, viral loads, and virus-specific antibody were measured at weeks 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 post-infection as described in [37]. The morphine-dependent animals were maintained on morphine throughout the study period.

**Model development**

The model developed in this chapter generalizes the viral dynamics model previously used to describe HIV infection in humans and SIV infection in macaques [41, 57, 62, 65, 75, 87]. In particular, we extend a previous SIV dynamics model (2.2) under morphine conditioning [87] by incorporating the effects of virus-specific antibody responses. The previous study [87] modeled the effects of morphine seen early in infection, i.e., within 3 months post infection, where immune responses were largely absent. Here we focus on modeling the effects of morphine for a longer period of time, during which virus-specific antibody responses become important. The schematic diagram of our model is presented in Figure 4.

As in Tomaras et al. [81], we consider three major possible effects of virus-specific antibodies: reduction in virus infectivity, i.e. virus neutralization, with efficacy $\epsilon_A$, enhanced virus clearance due to antibody binding to cell-free virus with
per capita rate $\sigma A(t)$, and antibody-dependent destruction of infected cells with per capita rate $\gamma A(t)$. Here, $A(t)$ represents the time course of virus-specific antibody levels. We model the efficacy of virus neutralization by antibody using the formula 

$$\epsilon_A = \frac{\eta A(t)}{1 + \eta A(t)},$$

whose value lies between 0 and 1 with $\epsilon_A = 0$ in the absence of antibodies (i.e., $A(t) = 0$) and $\epsilon_A = 1$ for extremely high antibody levels (i.e. $A(t) \to \infty$). 

$\eta$, $\sigma$ and $\gamma$ are constants introduced to represent the net effect of antibodies on the virus dynamics parameters governing viral infection, viral clearance and infected cell death. Note that $\eta = 0$, $\sigma = 0$ and $\gamma = 0$ represent the model corresponding to the absence of antibodies [81].

Virus-specific antibody data [38] show that following infection the virus-specific antibody level remains low, then gradually increases and finally saturates to a maximum level (see Figure 5). To capture this trend, we model the antibody response curve as $A(t) = \frac{at^n}{b^n + t^n}$, where $a$ represents the maximum antibody level, $b$ represents the time post-infection when the antibody level becomes half of the maximum and $n$ is a Hill coefficient.
Figure 4. Schematic diagram of the model. Uninfected CD4+ T cells: $T_i$ and $T_h$; infected cells: $I$; free virus: $V$; virus-specific antibody responses: $A$; target cells generation rate: $\lambda$; death rate of uninfected cells: $d$; infection rates: $\beta_l$ and $\beta_h$; infected cells death rate: $\delta$; virus production rate: $p$; clearance rate: $c$; transition rates: $r$ and $q$ from $T_i$ to $T_h$ and from $T_h$ to $T_i$, respectively; efficacy of virus neutralization: $\epsilon_A$; enhanced virus clearance rate: $\sigma_A(t)$; and destruction of infected cells rate: $\gamma_A(t)$.

The full model we study is described by the following set of equations:
\[ \frac{dT_l}{dt} = \lambda + qT_h - rT_l - (1 - \epsilon_A)\beta_l VT_l, \quad T_l(0) = T_{l0} \]

\[ \frac{dT_h}{dt} = rT_l - dT_h - qT_h - (1 - \epsilon_A)\beta_h VT_h, \quad T_h(0) = T_{h0} \]

\[ \frac{dI}{dt} = (1 - \epsilon_A)\beta_l VT_l + (1 - \epsilon_A)\beta_h VT_h - \delta I - \gamma A(t)I, \quad I(0) = I_0 \]  

(3.1)

\[ \frac{dV}{dt} = pI - cV - \sigma A(t)V, \quad V(0) = V_0. \]

where

\[ A(t) = \frac{at^n}{b^n + t^n} \]  

(3.2)

and

\[ \epsilon_A = \frac{\eta A(t)}{1 + \eta A(t)} \]  

(3.3)

**Parameter estimation**

As discussed in Vaidya et al. [87], we take \( T_{h0} = 40,980/ml, \ T_{l0} = T(0) - T_{h0} \) for the control group, and \( T_{h0} = 60,650/ml, \ T_{l0} = T(0) - T_{h0} \) for the morphine groups (both rapid-progressor and slow-progressor) as the initial populations of target cells, where \( T(0) \) is the total number of initial target cells per ml. According to the estimate of the number of target cells for SIV infection in macaques [85], we take 5% of the measured CD4 count as the value of \( T(0) \). As estimated in Mohri et al. [52] and Stafford et al. [75], we take 100 days as the average life span of uninfected target cells, i.e., \( d = 0.01 \) per day. Since the animals were initially uninfected, we set \( I_0 = 0 \) [85]. As estimated previously [87], we take the virus infectivity rates as \( \beta_l = 5.72 \times 10^{-10} \)
ml/day and $\beta_h = 5.72 \times 10^{-8} \text{ ml/day}$. Chen et al. [11] estimated the SIV burst size in vivo in rhesus macaques as approximately $5 \times 10^4$ virions per infected cell. Because productively infected cells live about 1 day [48], we take the viral production rate $p = 5 \times 10^4$ virions per day per infected cell. As estimated by Ramratnam et al. [66], the virion clearance rate during chronic infection in humans varies between 9.1 per day and 36 per day. Here we use the average $c = 23$ per day. However, we recognize that this rate might be higher in macaques [96].

Each macaque was infected intravenously with 2-ml inoculums containing $10^4 TCID_{50}$ of each of $SHIV_{KU-1B}$, $SHIV_{89-6P}$, and $SIV_{17E-Fr}$. The total of $3 \times 10^4 TCID_{50}$ of viruses comprises at least $3 \times 10^5$ SIV RNA copies [46]. A macaque, on average, weighs 1/10 of a human, which approximately gives 1.5 liters of extracellular water in a macaque. Assuming that the infused virions (RNA copies) are dispersed into the extracellular water, the initial viral load, $V_0$, can be estimated as $V_0 \approx 3 \times 10^5/1.5L \approx 200$ viral RNA copies/ml. Thus, we take $V_0 = 200$ copies/ml.

We estimate parameters $a$, $b$, and $n$ associated with antibody response curve, $A(t)$, from the virus-specific antibody data, using the nonlinear least-squares “lsqcurvefit” solver in MATLAB. The $A(t)$ curve is then used as a known function in the viral dynamics model. To estimate other key model parameter values, the system of ordinary differential equations (ODEs) is solved numerically using the “ode15s” solver in MATLAB. Using the nonlinear least squares regression formula (2.3), the predicted log_{10} viral load values are fitted to the corresponding log-transformed viral load data. For each best-fit parameter estimate, 95% confidence intervals (CI) are provided, which are computed from 500 replicates, by bootstrapping the residuals [6, 24]. Un-
less otherwise stated, a two-tailed test with two samples of unequal variance is used to test for significance of the estimated parameters in this chapter.

**Results**

Morphine-altered virus-specific antibodies

Using experimental data, we obtained the antibody response curve, $A(t)$, for each animal from the rapid-progressor morphine group, the slow-progressor morphine group, and the control group. The estimated values for $a$, $b$, and $n$ along with their median values are given in Table 1. The best-fit curves for each animal are shown in Figure 5. To highlight the distinction between the groups, we also plotted the curves for each group corresponding to median values of $a$, $b$, and $n$ (Figure 6). As mentioned earlier, the pattern of antibody response is that initially the antibody level remains relatively low, then gradually increases and later saturates. Our estimates show that the maximum antibody level, $a$, the time post-infection when the antibody level becomes half of the maximum, $b$, as well as the Hill coefficient, $n$, in the rapid-progressor morphine group are significantly lower ($p < 0.05$) than the control group (median $a = 1.5$ ng/ml, $b = 0.3$ days, $n = 1.99$ for the rapid-progressor morphine group versus the median $a = 2444$ ng/ml, $b = 119.9$ days, $n = 7.6$ for the control group) (Table 1, Figure 6).
Table 1. Estimated values for $a$, $b$, and $n$ for individual animals, and $p$-values used to test significance of the estimated values.

<table>
<thead>
<tr>
<th>Animal</th>
<th>$a$ (ng/ml)</th>
<th>$b$ (days)</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-progressor morphine group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/04L</td>
<td>1.50</td>
<td>0.30</td>
<td>1.99</td>
</tr>
<tr>
<td>1/28Q</td>
<td>1.50</td>
<td>0.30</td>
<td>1.99</td>
</tr>
<tr>
<td>1/42N</td>
<td>1.50</td>
<td>0.30</td>
<td>1.99</td>
</tr>
<tr>
<td>Median</td>
<td>1.50</td>
<td>0.30</td>
<td>1.99</td>
</tr>
<tr>
<td><strong>Slow-progressor morphine group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/52N</td>
<td>626</td>
<td>22</td>
<td>2.20</td>
</tr>
<tr>
<td>1/56L</td>
<td>557</td>
<td>109.3</td>
<td>6.99</td>
</tr>
<tr>
<td>1/02N</td>
<td>256</td>
<td>92.00</td>
<td>5.66</td>
</tr>
<tr>
<td>Median</td>
<td>557</td>
<td>109.3</td>
<td>5.66</td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/31P</td>
<td>3128</td>
<td>118.50</td>
<td>10.50</td>
</tr>
<tr>
<td>2/02P</td>
<td>2028</td>
<td>121.60</td>
<td>4.70</td>
</tr>
<tr>
<td>2/AC42</td>
<td>1359</td>
<td>127.90</td>
<td>13.20</td>
</tr>
<tr>
<td>MAC-1</td>
<td>2860</td>
<td>81.40</td>
<td>3.00</td>
</tr>
<tr>
<td>MAC-2</td>
<td>2026</td>
<td>56.90</td>
<td>11.00</td>
</tr>
<tr>
<td>MAC-3</td>
<td>3800</td>
<td>121.30</td>
<td>1.40</td>
</tr>
<tr>
<td>Median</td>
<td>2444</td>
<td>119.90</td>
<td>7.60</td>
</tr>
</tbody>
</table>

| **p-value**             |             |            |     |
| Rapid vs. Slow-progressor morphine group | 0.3511 | 0.0758    | 0.1739 |
| Slow-progressor morphine vs. control group | 0.9376 | 0.4678    | 0.3697 |
| Rapid-progressor morphine vs. control group | 0.0069 | 0.0003    | 0.0444 |
Figure 5. Fitted curves to virus-specific antibody levels from individual animals (the rapid-progressor morphine group: 1/04L, 1/28Q, 1/42N; the slow-progressor morphine group: 1/52N, 1/56L, 1/02N; the control group: 2/31P, 2/02P, 2/AC42, MAC-1, MAC-2, MAC-3).
Figure 6. Virus-specific antibody curve plotted using median values of $a$, $b$, and $n$.

When we compare the slow-progressor morphine group with the control group, we found that none of the antibody curve related parameters are significantly different (Table 1), showing that in the slow-progressor morphine group morphine has minimal effect on the measured antibody responses. However, we note that animal “1/52N” has an extremely high estimated value, $a = 6264$ ng/ml, while all other animals have a value of a less than 3800 ng/ml. Also, the set point CD4 count of this animal remains extremely high throughout the infection; its set point CD4 count is higher than 700 cells/$\mu L$, while the maximum set point CD4 count of all other animals in the morphine group is 39 cells/$\mu L$. Excluding animal 1/52N, the value of $a$ in the slow-progressor morphine group is significantly lower than that in the control group ($p < 0.05$).

Between the two morphine groups (rapid-progressor and slow-progressor), none
of the antibody curve related parameters are significantly different (Table 1). Again, excluding animal “1/52N”, and using two sample t-test with equal but unknown variances, all of \( a, b, \) and \( n \) become significantly different \( (p < 0.05) \) between the two groups of animals under morphine conditioning. While the effects of morphine on altering antibody responses can be quite variable among animals, the antibody responses can be severely hampered in some animals due to the presence of morphine.

**Viral dynamics model selection**

To identify the important model components representing the effect of morphine-altered antibody responses on explaining viral dynamics, we considered 7 other different variants of model (3.1) in which we leave out one or more hypothesized effects of virus-specific antibody on viral neutralization, enhanced virion clearance or antibody-mediated cellular loss and then compared them based on the Akaike’s Information Criterion (AIC) values of the best fit to the median viral load data for the first 28 weeks post-infection (Table 2). The antibody response curve \( A(t) \) presented earlier was used in each of these models. For a fair comparison of models, we made six parameters free in each case. The parameters fitted in each model are listed in Table 2. Model-2 that only incorporates the effect of antibodies on virus neutralization and enhanced virus clearance had the lowest AIC (Table 2). However, other models, e.g., models 4, 5 and 6 also had low values of AIC. We further examined in detail whether Model-2 was the best one by fitting individual animal data to the full model, i.e. model-1. In this case, we obtained extremely small values of \( \gamma \) (on the order of \( 10^{-9} \)) in most of the animals (Table 3), asserting that there is almost no effect of antibodies on infected cell killing. We also performed the fittings for \( A(t) \) using a spline curve
fit to the virus-specific antibody response in each animal and found that the fitting was not improved. In addition, the explicit formula for \( A(t) \) (equation (3.2)) allows clear comparison between the different groups. Therefore, we use \( A(t) \) given by equation (3.2) and model-2, which has the lowest AIC value, to provide further results on morphine-altered antibody responses.

Table 2. Fitted parameters, calculated Akaike’s Information Criterion (AIC) values and Sum of Squared Residuals (SSR) for model fits to median data for each model.

<table>
<thead>
<tr>
<th>Model</th>
<th>Fitted parameters</th>
<th>Rapid-progressor morphine group</th>
<th>Slow-progressor morphine group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SSR</td>
<td>AIC</td>
<td>SSR</td>
</tr>
<tr>
<td>Model-1 (Basic model)</td>
<td>( \eta, \gamma, \sigma, \lambda, r, q )</td>
<td>8.30</td>
<td>125.3</td>
<td>3.37</td>
</tr>
<tr>
<td>Model-2 (( \gamma = 0 ))</td>
<td>( \eta, \delta, \sigma, \lambda, r, q )</td>
<td>6.17</td>
<td>122.6</td>
<td>3.13</td>
</tr>
<tr>
<td>Model-3 (( \eta = 0 ))</td>
<td>( \beta_t, \gamma, \lambda, r, q )</td>
<td>8.28</td>
<td>125.3</td>
<td>3.36</td>
</tr>
<tr>
<td>Model-4 (( \sigma = 0 ))</td>
<td>( \eta, \gamma, c, \lambda, r, q )</td>
<td>7.46</td>
<td>124.3</td>
<td>3.27</td>
</tr>
<tr>
<td>Model-5 (( \gamma = \eta = 0 ))</td>
<td>( \beta_t, \delta, \sigma, \lambda, r, q )</td>
<td>8.37</td>
<td>125.3</td>
<td>3.19</td>
</tr>
<tr>
<td>Model-6 (( \gamma = \sigma = 0 ))</td>
<td>( \eta, \delta, c, \lambda, r, q )</td>
<td>8.08</td>
<td>125.0</td>
<td>3.38</td>
</tr>
<tr>
<td>Model-7 (( \sigma = \eta = 0 ))</td>
<td>( \beta_t, \gamma, c, \lambda, r, q )</td>
<td>8.18</td>
<td>125.1</td>
<td>3.26</td>
</tr>
<tr>
<td>Model-8 (( \sigma = \eta = \gamma = 0 ))</td>
<td>( \beta_t, \delta, c, \lambda, r, q )</td>
<td>8.09</td>
<td>125.0</td>
<td>3.69</td>
</tr>
</tbody>
</table>
Table 3. Model-1 estimated parameters for individual animals and their 95% confidence intervals in parentheses.

<table>
<thead>
<tr>
<th>Animal</th>
<th>$\lambda$ (cell ml$^{-1}$ day$^{-1}$)</th>
<th>$r$ (day$^{-1}$)</th>
<th>$q$ (day$^{-1}$)</th>
<th>$\gamma$ (ml ng$^{-1}$ day$^{-1}$)</th>
<th>$\sigma$ (ml ng$^{-1}$ day$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-progressor morphine group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/04L</td>
<td>3630 (3311-3995)</td>
<td>0.22 (0.08-0.40)</td>
<td>$1.2 \times 10^{-5}$ (5.4 x 10^{-5}, 3.4 x 10^{-4})</td>
<td>$1.2 \times 10^{-5}$ (1.2 x 10^{-6}, 3.7 x 10^{-5})</td>
<td>$1.0 \times 10^{-8}$ (4.7 x 10^{-10}, 3.7 x 10^{-8})</td>
</tr>
<tr>
<td>1/28Q</td>
<td>3630 (3400-3870)</td>
<td>0.21 (0.07-0.45)</td>
<td>$1.5 \times 10^{-5}$ (4.1 x 10^{-4}, 3.4 x 10^{-4})</td>
<td>$1.4 \times 10^{-5}$ (5.1 x 10^{-6}, 3.2 x 10^{-5})</td>
<td>$1.0 \times 10^{-8}$ (1.6 x 10^{-9}, 3.6 x 10^{-8})</td>
</tr>
<tr>
<td>1/42N</td>
<td>3630 (3307-4021)</td>
<td>0.25 (0.18-0.84)</td>
<td>$1.6 \times 10^{-5}$ (6.3 x 10^{-5}, 3.0 x 10^{-5})</td>
<td>$1.0 \times 10^{-5}$ (6.5 x 10^{-6}, 2.7 x 10^{-5})</td>
<td>$1.1 \times 10^{-8}$ (6.5 x 10^{-9}, 3.5 x 10^{-8})</td>
</tr>
<tr>
<td><strong>Slow-progressor morphine group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/52N</td>
<td>3629 (3628-3629)</td>
<td>0.29 (0.21-0.32)</td>
<td>$2.8 \times 10^{-4}$ (1.3 x 10^{-4}, 3.6 x 10^{-4})</td>
<td>$1.1 \times 10^{-5}$ (3.0 x 10^{-6}, 3.4 x 10^{-5})</td>
<td>$1.1 \times 10^{-3}$ (1.1 x 10^{-4}, 2.6 x 10^{-3})</td>
</tr>
<tr>
<td>1/56L</td>
<td>3630 (3580-3674)</td>
<td>0.22 (0.17-0.32)</td>
<td>$1.0 \times 10^{-4}$ (2.4 x 10^{-4}, 2.5 x 10^{-4})</td>
<td>$1.0 \times 10^{-9}$ (2.5 x 10^{-9}, 2.7 x 10^{-9})</td>
<td>$1.0 \times 10^{-4}$ (2.4 x 10^{-4}, 2.5 x 10^{-4})</td>
</tr>
<tr>
<td>1/02N</td>
<td>3630 (3629-3630)</td>
<td>0.21 (0.16-0.26)</td>
<td>$1.0 \times 10^{-4}$ (4.8 x 10^{-5}, 3.3 x 10^{-4})</td>
<td>$5.9 \times 10^{-4}$ (3.4 x 10^{-4}, 8.0 x 10^{-4})</td>
<td>$4.8 \times 10^{-3}$ (2.7 x 10^{-3}, 6.5 x 10^{-3})</td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/31P</td>
<td>3630 (3626-3633)</td>
<td>0.17 (0.13-0.20)</td>
<td>$1.3 \times 10^{-4}$ (7.9 x 10^{-5}, 1.8 x 10^{-4})</td>
<td>$1.0 \times 10^{-9}$ (1.1 x 10^{-10}, 2.4 x 10^{-9})</td>
<td>$1.0 \times 10^{-4}$ (3.1 x 10^{-6}, 2.2 x 10^{-4})</td>
</tr>
<tr>
<td>2/02P</td>
<td>3630 (3628-3630)</td>
<td>0.20 (0.13-0.22)</td>
<td>$2.0 \times 10^{-4}$ (1.2 x 10^{-5}, 2.0 x 10^{-4})</td>
<td>$9.8 \times 10^{-9}$ (4.6 x 10^{-9}, 1.6 x 10^{-8})</td>
<td>$2.0 \times 10^{-4}$ (7.4 x 10^{-6}, 2.0 x 10^{-4})</td>
</tr>
<tr>
<td>2/AC42</td>
<td>3630 (3613-3643)</td>
<td>0.20 (0.15-0.36)</td>
<td>$1.0 \times 10^{-4}$ (4.3 x 10^{-5}, 1.9 x 10^{-4})</td>
<td>$1.6 \times 10^{-4}$ (3.4 x 10^{-5}, 3.0 x 10^{-4})</td>
<td>$1.0 \times 10^{-4}$ (2.1 x 10^{-5}, 2.0 x 10^{-4})</td>
</tr>
<tr>
<td>MAC-1</td>
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<td>0.18 (0.13-0.30)</td>
<td>$1.0 \times 10^{-4}$ (1.5 x 10^{-5}, 2.8 x 10^{-5})</td>
<td>$1.0 \times 10^{-9}$ (2.9 x 10^{-10}, 2.7 x 10^{-9})</td>
<td>$1.0 \times 10^{-4}$ (5.2 x 10^{-6}, 3.5 x 10^{-7})</td>
</tr>
<tr>
<td>MAC-2</td>
<td>3630 (3629-3631)</td>
<td>0.14 (0.08-0.19)</td>
<td>$1.0 \times 10^{-4}$ (1.6 x 10^{-5}, 2.4 x 10^{-4})</td>
<td>$1.1 \times 10^{-9}$ (1.0 x 10^{-9}, 1.9 x 10^{-9})</td>
<td>$1.0 \times 10^{-4}$ (5.6 x 10^{-6}, 2.3 x 10^{-7})</td>
</tr>
<tr>
<td>MAC-3</td>
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<td>0.20 (0.20-0.42)</td>
<td>$1.0 \times 10^{-4}$ (7.8 x 10^{-6}, 3.5 x 10^{-4})</td>
<td>$1.0 \times 10^{-9}$ (2.3 x 10^{-10}, 2.8 x 10^{-9})</td>
<td>$1.0 \times 10^{-4}$ (9.3 x 10^{-6}, 3.7 x 10^{-4})</td>
</tr>
</tbody>
</table>
Variation of parameter estimates among animals in three groups

Using the antibody response curve $A(t)$ (Eq. 3.2) as a known function in model-2, we estimated the parameters by fitting the viral load data from the individual animals in the rapid-progressor morphine, the slow-progressor morphine and the control groups. These parameter estimates along with the 95% bootstrap confidence intervals of the estimated parameters are given in Table 4. The corresponding best-fits to the data from each animal and the median data of the three groups of animals are shown in Figure 7. Among the estimated parameters, we found that the scaling factor associated with the effect of virus-specific antibody responses on virus neutralization, $\eta$, and the transition rate from $T_h$ to $T_l$, $q$, are significantly different between the rapid-progressor and the slow-progressor morphine groups, and between the rapid-progressor morphine and the control groups ($p < 0.05$). This observation is consistent with results discussed in Vaidya et al. [87]. Similarly, as in the previous study [87], the estimated parameter values for the transition rate from $T_l$ to $T_h$, $r$, are higher in the morphine-dependent groups than in the control group. However, this difference was not statistically significant ($p > 0.05$). This could be because of the smaller number of animals in the two morphine groups, as the morphine treated animals were subdivided into two groups in this study and/or because of consideration of our model over a longer period of time during which virus-specific antibodies play important roles in virus dynamics (Figure 6). In addition, we did not observe any significant difference in the other estimated parameters ($p > 0.05$) among the groups. As shown by our median data best-fit curves (Figure 7), we observe a higher set-point viral load in the rapid-progressor and in the slow-progressor morphine groups than
in the control group (5.4 log_{10} in the rapid-progressor morphine group, 5.2 log_{10} in the slow-progressor morphine group, and 4.2 log_{10} in the control group). This observation is consistent with the experimental results in Kumar et al. [37].
Table 4. Model-2 estimated parameters for individual animals, fitted parameter values to median data and their 95% confidence intervals in parentheses, and the mean values of $\epsilon_A$ calculated over a period of 200 days post infection using

$$\epsilon_A = \frac{1}{200} \int_0^{200} \left( \frac{\eta A(t)}{1+\eta A(t)} \right) dt.$$ 

<table>
<thead>
<tr>
<th>Animal</th>
<th>$\lambda$ (cell ml$^{-1}$ day$^{-1}$)</th>
<th>$r$ (day$^{-1}$)</th>
<th>$q$ (day$^{-1}$)</th>
<th>$\delta$ (day$^{-1}$)</th>
<th>$\sigma$ (ml ng$^{-1}$ day$^{-1}$)</th>
<th>$\eta$ (ml ng$^{-1}$ day$^{-1}$)</th>
<th>mean value ($\epsilon_A$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/04L</td>
<td>3630 (3396-3901)</td>
<td>0.20 (0.14-0.28)</td>
<td>1.1 x 10$^{-4}$</td>
<td>0.56 (0.43-0.75)</td>
<td>2.8 x 10$^{-3}$ (6.8 x 10$^{-4}$ - 5.1 x 10$^{-3}$)</td>
<td>1.0 x 10$^{-4}$ (1.8 x 10$^{-6}$ - 1.9 x 10$^{-4}$)</td>
<td>1.5 x 10$^{-4}$</td>
</tr>
<tr>
<td>1/28Q</td>
<td>3773 (3322-4481)</td>
<td>0.24 (0.18-0.48)</td>
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<td>0.80 (0.68-0.94)</td>
<td>2.3 x 10$^{-3}$ (8.0 x 10$^{-5}$ - 3.0 x 10$^{-3}$)</td>
<td>1.1 x 10$^{-4}$ (1.9 x 10$^{-8}$ - 1.2 x 10$^{-4}$)</td>
<td>1.6 x 10$^{-4}$</td>
</tr>
<tr>
<td>1/42N</td>
<td>5000 (4688-5278)</td>
<td>0.40 (0.16-0.69)</td>
<td>1.2 x 10$^{-4}$</td>
<td>0.30 (0.26-0.53)</td>
<td>2.3 x 10$^{-3}$ (2.3 x 10$^{-4}$ - 4.6 x 10$^{-3}$)</td>
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<td>1.6 x 10$^{-4}$</td>
</tr>
<tr>
<td>Median data</td>
<td>3630 (3440-3835)</td>
<td>0.16 (0.06-0.34)</td>
<td>1.0 x 10$^{-2}$</td>
<td>0.31 (0.09-0.47)</td>
<td>1.1 x 10$^{-2}$ (7.4 x 10$^{-3}$ - 1.4 x 10$^{-2}$)</td>
<td>1.9 x 10$^{-6}$ (4.1 x 10$^{-7}$ - 3.3 x 10$^{-6}$)</td>
<td>2.8 x 10$^{-6}$</td>
</tr>
<tr>
<td>1/52N</td>
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<td>0.53 (0.44-0.63)</td>
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<td>1.0 x 10$^{-6}$ (1.3 x 10$^{-7}$ - 2.0 x 10$^{-6}$)</td>
<td>1.1 x 10$^{-3}$</td>
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<tr>
<td>1/56L</td>
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<td>0.41 (0.28-0.62)</td>
<td>0.18 (0.04-0.34)</td>
<td>0.32 (0.24-0.36)</td>
<td>2.3 x 10$^{-6}$ (1.5 x 10$^{-7}$ - 4.4 x 10$^{-6}$)</td>
<td>1.0 x 10$^{-6}$ (6.8 x 10$^{-8}$ - 1.8 x 10$^{-6}$)</td>
<td>2.4 x 10$^{-4}$</td>
</tr>
<tr>
<td>1/02N</td>
<td>3630 (3511-4757)</td>
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<td>0.10 (0.02-0.18)</td>
<td>0.75 (0.55-0.96)</td>
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<td>1.5 x 10$^{-4}$</td>
</tr>
<tr>
<td>Median data</td>
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<td>0.17 (0.11-0.22)</td>
<td>0.10 (0.02-0.21)</td>
<td>0.65 (0.42-0.68)</td>
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<td>1.0 x 10$^{-6}$ (3.3 x 10$^{-7}$ - 2.6 x 10$^{-6}$)</td>
<td>2.4 x 10$^{-4}$</td>
</tr>
<tr>
<td>2/31P</td>
<td>3629 (3591-3661)</td>
<td>0.31 (0.23-0.41)</td>
<td>0.68 (0.51-0.91)</td>
<td>0.31 (0.24-0.34)</td>
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<td>1.2 x 10$^{-3}$</td>
</tr>
<tr>
<td>2/02P</td>
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<td>0.20 (0.10-0.34)</td>
<td>0.66 (0.40-0.74)</td>
<td>2.3 x 10$^{-3}$ (7.1 x 10$^{-4}$ - 4.4 x 10$^{-3}$)</td>
<td>1.0 x 10$^{-4}$ (3.4 x 10$^{-5}$ - 2.0 x 10$^{-4}$)</td>
<td>6.6 x 10$^{-2}$</td>
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<tr>
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<td>3630 (3627-3632)</td>
<td>0.14 (0.11-0.18)</td>
<td>0.33 (0.14-0.46)</td>
<td>0.54 (0.46-0.61)</td>
<td>5.3×10⁻⁴ (2.8×10⁻⁴, 3.0×10⁻³)</td>
<td>4.9×10⁻⁵ (1.2×10⁻⁷, 1.9×10⁻⁶)</td>
<td>2.2×10⁻²</td>
</tr>
<tr>
<td>MAC-1</td>
<td></td>
<td>3630 (3115-3693)</td>
<td>0.13 (0.10-0.25)</td>
<td>0.18 (0.07-0.29)</td>
<td>0.38 (0.16-0.39)</td>
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<td>1.0×10⁻⁴ (1.4×10⁻⁵, 1.5×10⁻⁴)</td>
</tr>
<tr>
<td>MAC-2</td>
<td></td>
<td>3629 (3610-3647)</td>
<td>0.13 (0.10-0.16)</td>
<td>0.28 (0.12-0.45)</td>
<td>0.61 (0.40-0.82)</td>
<td>3.2×10⁻⁶ (7.1×10⁻⁷, 5.9×10⁻⁶)</td>
<td>1.0×10⁻⁷ (9.9×10⁻⁹, 2.0×10⁻⁶)</td>
</tr>
<tr>
<td>MAC-3</td>
<td></td>
<td>3630 (3574-3684)</td>
<td>0.16 (0.08-0.20)</td>
<td>0.24 (0.06-0.43)</td>
<td>0.40 (0.24-0.53)</td>
<td>2.3×10⁻⁶ (1.4×10⁻⁷, 4.6×10⁻⁶)</td>
<td>1.0×10⁻⁶ (5.9×10⁻⁸, 2.0×10⁻⁶)</td>
</tr>
<tr>
<td>Median data</td>
<td></td>
<td>3630 (3628-3631)</td>
<td>0.15 (0.12-0.19)</td>
<td>0.18 (0.07-0.31)</td>
<td>0.65 (0.41-0.81)</td>
<td>2.5×10⁻³ (1.1×10⁻³, 4.4×10⁻³)</td>
<td>1.1×10⁻⁶ (2.2×10⁻⁷, 2.7×10⁻⁶)</td>
</tr>
</tbody>
</table>
Effects of morphine-altered antibody responses on virus neutralization and enhanced viral clearance

As revealed by our data fitting procedure, the main effects of virus specific antibody responses are the neutralization of virus and enhancement of viral clearance.
To quantify these effects due to morphine, we computed the efficacy of virus-specific antibodies in reducing the infection rate, \( \epsilon_A \), and the rate of enhanced virus clearance, \( \sigma_A(t) \), for each group of animals. Our results at the end of the 200 day post infection period clearly show lower efficacy of antibody responses to reduce virus infection in the morphine-dependent groups (almost 100% lower in the rapid-progressor and 79% lower in the slow-progressor) when compared to \( \epsilon_A = 2.6 \times 10^{-3} \) of the control group (Figure 8). We also calculated the mean value of \( \epsilon_A \) (Table 4) over the time course of 200 days post infection and found that the mean antibody neutralization efficacy was lower in the morphine group (99.7% lower in the rapid-progressor and 76% lower in the slow-progressor) than the control group (\( \epsilon_A = 1.0 \times 10^{-3} \)). Similarly, we found that the rate of enhanced virus clearance for the 200 day post-infection period is lower in the rapid-progressor morphine group (almost 100% lower), and in the slow-progressor morphine group (69% lower) when compared to the control group (6.1 day\(^{-1}\)) (Figure 8). The mean value of \( \sigma_A(t) \) over the time course of 200 days post infection is 99.2% lower in the rapid-progressor morphine group, 65% lower in the slow-progressor morphine group when compared to the control group (2.4 day\(^{-1}\)). These results suggest that morphine can alter the antibody responses resulting in substantial effects on virus dynamics.
Figure 8. Predicted effects of morphine-altered virus-specific antibody responses on virus neutralization and enhanced virus clearance. The horizontal lines show the mean values of $\epsilon_A$ and $\sigma_A(t)$ for each group calculated over a period of 200 days post infection using $\epsilon_A = \frac{1}{200} \int_0^{200} \left( \frac{\eta_A(t)}{1 + \eta_A(t)} \right) dt$ and $\sigma_A(t) = \frac{1}{200} \int_0^{200} \sigma_A(t) dt$.

Effects of morphine-altered antibody response on CD4 count

Using our model, we predicted the dynamics of the count (Figure 9) and estimated the CD4 loss in the first 200 days post infection. The morphine group showed a lower CD4 count compared to the control group. At 200 days post-infection, we predict the CD4 count to be 70 cells/$\mu L$ for the rapid-progressor morphine group and 152 cells/$\mu L$ for the slow-progressor morphine group, while in the control group it is maintained at 185 cells/$\mu L$. With this prediction, we found a greater CD4 loss in the morphine-dependent groups (93% and 85% in the rapid-progressor and the slow-
progressor morphine groups, respectively) than the control group (82% loss) (Figure 9). We note that the CD4 data is more chaotic and not frequent enough to use for longer period fitting. However, we compared our results with the experimentally measured values of the CD4 count [37, 38], in which a loss of 99% at week 14 in the rapid-progressor morphine group, 97% loss at week 28 in the slow-progressor morphine group and 83% loss at week 28 of the control group were observed. This shows that our model predictions are qualitatively consistent with the experimentally measured values, but with a slight difference in magnitude.

Figure 9. Predicted effects of morphine-altered virus-specific antibody responses on CD4 count and CD4 loss.
Basic reproduction number \((R_0)\)

We examine how morphine conditioning affects the basic reproduction number, defined as the average number of secondary infections occurring from a single infected cell introduced into a population of entirely uninfected cells. It can be shown that if \(R_0 < 1\), infection is avoided and if \(R_0 > 1\), infection is established [89]. With \(A(t) = A(0)\), we can derive the basic reproduction number of our model using the next-generation method [89] outlined in chapter 2.

The model system 3.1 has exactly one infection-free equilibrium

\[
X_0 = \left( \begin{array}{c}
\frac{\lambda(d + q)}{d(d + r + q)}, \\
\frac{\lambda r}{d(d + r + q)}, \\
0, \\
0
\end{array} \right),
\]

and equations for the infected cell and virus compartments of the linearized system at \(X_0\) take the form

\[
\begin{align*}
\frac{dI}{dt} &= \frac{\lambda}{d(d + r + q)}(\beta_l(d + q) + \beta_h r)(1 - \epsilon A(0))V - \delta I, \\
\frac{dV}{dt} &= pI - cV - \sigma A(0)V.
\end{align*}
\]

We introduce the following two matrices:

\[
F = \begin{pmatrix}
0 & \frac{\lambda}{d(d + r + q)}(\beta_l(d + q) + \beta_h r)(1 - \epsilon A(0)) \\
0 & 0
\end{pmatrix}, \quad V = \begin{pmatrix}
\delta & 0 \\
-p & c + \sigma A(0)
\end{pmatrix}.
\]

These expressions give

\[
FV^{-1} = \begin{pmatrix}
\frac{\lambda p(\beta_l(d + q) + \beta_h r)(1 - \epsilon A(0))}{\delta d(d + r + q)(c + \sigma A(0))} & \frac{\lambda (\beta_l(d + q) + \beta_h r)(1 - \epsilon A(0))}{d(d + r + q)(c + \sigma A(0))} \\
0 & 0
\end{pmatrix},
\]

Then \(R_0\) corresponds to the dominant eigenvalue of \(FV^{-1}\), that is...
\[ R_0 = \frac{\lambda_p (\beta_l (d + q) + \beta_h r) (1 - \epsilon_A(0))}{\delta d (d + r + q) (c + \sigma A(0))}. \]

Using our parameter estimates in this formula, we obtained \( R_0^R = 6.48 \) (for the rapid-progressor morphine group), \( R_0^S = 2.12 \) (for the slow-progressor morphine group), and \( R_0^C = 1.55 \) (for the control group). Since \( R_0 > 1 \) in all three groups, infection is predicted to occur in all the groups consistent with the data. Morphine does not seem to have role in determining establishment of the infection. However, having a higher value of \( R_0 \) in the rapid-progressor morphine group indicates that the morphine may cause an extra obstacle that needs to be overcome in order to avoid infection by pre-exposure prophylaxis (PrEP). These estimated \( R_0 \) values indicate that the effectiveness of PrEP required to prevent infection is at least 85% in the rapid-progressor morphine group, while 53% effectiveness and 36% effectiveness are needed to prevent infection in the slow-progressor morphine group and the control group, respectively.
CHAPTER 4
EFFECTS OF MORPHINE PHARMACODYNAMICS ON HIV-INFECTION DYNAMICS

In this chapter, we develop a model to analyze the effects of periodic morphine intake. We consider two cases, namely, intravenous morphine (IVM), and slow-release oral morphine (SROM) and integrate several morphine pharmacodynamic parameters related to these cases into our HIV-infection dynamics model. We show how time-varying changes in morphine concentration and the time-varying HIV-specific antibody responses affects the viral infection threshold, viral load, and the CD4 count.

Introduction

In chapter 3, we developed a model incorporating the effects of morphine-altered virus specific antibody responses on viral dynamics. We obtained interesting results for constant morphine conditioning. These results provided the need to examine whether periodic morphine intake produces similar effects. It is possible that periodic morphine intake can result to time-varying antibody responses effects within HIV-infected individuals thereby causing periodic virus neutralization and periodic virus clearance. It is therefore important to examine what effects periodic morphine intake can have on HIV viral dynamics. To study these effects, we consider two cases of morphine intake: intravenous morphine (IVM) and slow-release oral morphine (SROM).
Model development

We develop a pharmacodynamic morphine effect model by incorporating time-varying efficacy ($\Omega_I(t)$) of virus-specific antibodies in the reduction of virus infectivity, and time-varying enhancement ($\Omega_c(t)$) of virus clearance due to antibody binding to cell-free virus. The schematic diagram of the model is presented in Figure 11. Here, $\Omega_I(t) = \eta A(t) \left(1 + \eta A(t)\right)$ and $\Omega_c(t) = \sigma A(t)$, where $A(t)$ represents the time-varying HIV-specific antibodies responses which depend on morphine concentration. We model the time-varying HIV-specific antibody responses using the formula $A(t) = \left(1 - \frac{M(t)^n}{M_h^n + M(t)^n}\right)$, where $M(t)$ is a function that represents morphine concentration at time $t$ (see Eq. 4.2 and 4.3), $M_h$ represents the time when morphine concentration becomes half, and $n$ is the Hill coefficient. The $A(t)$ is formulated in such a way that its value lies between 0 and 1 with $A(t) = 0$ for a very high morphine concentration (i.e., $M(t) \to \infty$) and $A(t) = 1$ (maximum) in the absence of morphine (i.e., $M(t) = 0$), consistent with the results in chapter 3 on the effect of morphine on antibody responses. An example of a graph describing the dynamics of antibody responses ($A(t)$) in morphine concentration is given in Figure 10 (a).

In our model, we assume that under periodic intake of morphine, time-varying parameters $\Omega_I(t)$, $\Omega_c(t)$ become periodic functions of period $\tau$, i.e., $\Omega_I(t) = \Omega_I(t + \tau)$ and $\Omega_c(t) = \Omega_c(t + \tau)$, respectively.

We describe the infection dynamics using the following set of equations:
\[ \frac{dT_i}{dt} = \lambda + qT_h - rT_i - (1 - \Omega_I(t))\beta_i VT_i, \quad T_i(0) = T_{i0} \]

\[ \frac{dT_h}{dt} = rT_i - dT_h - qT_h - (1 - \Omega_I(t))\beta_h VT_h, \quad T_h(0) = T_{h0} \]

\[ \frac{dI}{dt} = (1 - \Omega_I(t))\beta_I VT_i + (1 - \Omega_I(t))\beta_h VT_h - \delta I, \quad I(0) = I_0 \quad (4.1) \]

\[ \frac{dV}{dt} = pI - cV - \Omega_c(t)V, \quad V(0) = V_0 \]

Morphine concentration profile, \( M(t) \)

*Intravenous morphine (IVM).* In this case, morphine is directly injected into the blood stream. One reason why IVM may be preferred by drugs of abuse users is that its direct administration into the circulation provides a rapid effect [50]. A previous study on pharmacokinetics and pharmacodynamics of opioids [45] has shown that intravenous administration of drugs is best described by an exponential decay function. Thus, we consider a function of the form \( M(t) = a_0e^{-b_1t} \) to explain the dynamics of intravenous morphine for a period of single intake. Therefore for a periodic intake of IVM we model the morphine concentration as

\[ M(t) = a_0e^{-b_1(t-t_k)}, \quad t_k \leq t < t_{k+1} \quad k = 0, 1, 2, ... \quad (4.2) \]

where, \( \Delta t = t_{k+1} - t_k \) represents morphine intake time interval, \( a_0 \) represents the morphine dose, and \( b_1 \) denotes the decay rate. Note that \( t_{1/2} = \log(2)/b_1 \) (see Figure 10 (b) for a graph describing the \( M(t) \) dynamics for the IVM case).

*Slow-release oral morphine (SROM).* In this case, morphine is taken orally and can be used as a maintenance pharmacotherapy treatment for opioid-dependent individuals who respond poorly to other available maintenance treatments [26]. It
has also been reported that SROM may be associated with reduced opioid craving [7, 23, 27, 31, 36, 51, 90]. Moreover, the use of SROM among HIV-infected persons may present an additional safety advantage due to its lower risk with interactions with other drugs [74]. It is important to study the effects of SROM conditioning on HIV-infected persons. In using the SROM as a maintenance treatment, it is critical to strike the right balance between the need for the drug and its addictivity. In oral morphine intake, the concentration of morphine in the blood slowly increases and then decreases after it reaches a peak. This phenomena can approximately be captured using a function of the form

\[ M(t) = M_0 + a \sin(\tau t + b) \] (4.3)

where, \( M_0 \) represents the mean level of morphine, \( a \) denotes the amplitude, and \( b \) represents the phase shift in the function. (see Figure 10 (c) for a graph describing the \( M(t) \) dynamics for the SROM case).
Figure 10. (a) Morphine concentration \( M(t) \) vs antibody responses \( A(t) \) at time \( t \), and morphine concentration dynamics for (b) IVM case and (c) SROM case.
Figure 11. Schematic diagram of the pharmacodynamics of morphine model.
Table 5. Model (4.1) parameter values and their interpretations.

<table>
<thead>
<tr>
<th>Description</th>
<th>Parameter</th>
<th>Estimate</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproduction rate of T cells</td>
<td>$\lambda$</td>
<td>$3630 \text{ cells ml}^{-1} \text{ day}^{-1}$</td>
<td>[87]</td>
</tr>
<tr>
<td>Infection rate of $T_l$</td>
<td>$\beta_l$</td>
<td>$2.29 \times 10^{-9}$ day$^{-1}$</td>
<td>Estimate, [87]</td>
</tr>
<tr>
<td>Infection rate of $T_h$</td>
<td>$\beta_h$</td>
<td>$2.29 \times 10^{-7}$ day$^{-1}$</td>
<td>Estimate, [87]</td>
</tr>
<tr>
<td>Death rate of uninfected T cells</td>
<td>$d$</td>
<td>0.01 day$^{-1}$</td>
<td>[75, 52]</td>
</tr>
<tr>
<td>Death rate of infected T cells</td>
<td>$\delta$</td>
<td>0.65 day$^{-1}$</td>
<td>Estimate, [87]</td>
</tr>
<tr>
<td>Virion production rate</td>
<td>$p$</td>
<td>2500 day$^{-1}$</td>
<td>[87]</td>
</tr>
<tr>
<td>Virion clearance rate</td>
<td>$c$</td>
<td>23 day$^{-1}$</td>
<td>[66]</td>
</tr>
<tr>
<td>Transition rate from $T_l$ to $T_h$</td>
<td>$r$</td>
<td>0.15 day$^{-1}$</td>
<td>[87]</td>
</tr>
<tr>
<td>Transition rate from $T_h$ to $T_l$</td>
<td>$q$</td>
<td>0.18 day$^{-1}$</td>
<td>[87]</td>
</tr>
<tr>
<td>Net $A(t)$ effect scaling factor</td>
<td>$\eta$</td>
<td>0.8 ml ng$^{-1}$</td>
<td>Assumed</td>
</tr>
<tr>
<td>Net $A(t)$ effect scaling factor</td>
<td>$\sigma$</td>
<td>0.5 day$^{-1}$</td>
<td>Assumed</td>
</tr>
<tr>
<td>Time morphine concentration is half</td>
<td>$M_h$</td>
<td>50 days</td>
<td>Assumed</td>
</tr>
<tr>
<td>Hill’s coefficient</td>
<td>$n$</td>
<td>5</td>
<td>Assumed</td>
</tr>
<tr>
<td>Morphine dose</td>
<td>$a_0$</td>
<td>100 [0 – 200]</td>
<td>Varied</td>
</tr>
<tr>
<td>Morphine half life</td>
<td>$b_1$</td>
<td>4 [1 – 10] hours</td>
<td>Varied</td>
</tr>
<tr>
<td>Morphine mean level</td>
<td>$M_0$</td>
<td>100 [50 – 200]</td>
<td>Varied</td>
</tr>
<tr>
<td>Amplitude</td>
<td>$a$</td>
<td>50 [0 – 100]</td>
<td>Varied</td>
</tr>
<tr>
<td>Drug intake interval</td>
<td>$\Delta t$, $\tau$</td>
<td>8 [2 – 22] hours</td>
<td>Varied</td>
</tr>
</tbody>
</table>
**Viral infection threshold \( (R_i) \)**

Because of the periodic conditions described by our model (4.1), a more realistic measure for when an infection can die out or persist can best be described using an infection threshold, which is described in this section.

Using a similar approach to that of Wang and Zhao [91], Liu, Zhao and Zhou [42], Vaidya and Rong [88], and Vaidya and Wahl [86], we now derive the viral infection threshold, \( R_i \). We consider the model system 4.1 with \( \tau \)-periodic functions \( \Omega_I(t) \) and \( \Omega_c(t) \). The equations for the infected cells and virus compartments of the linearized system at the infection-free equilibrium, \( X_0 \), take the form

\[
\frac{dI}{dt} = -\delta I + \frac{\lambda}{d(d+r+q)} (\beta_I(d+q) + \beta_hr) (1 - \Omega_I(t))V, \quad (4.4)
\]

\[
\frac{dV}{dt} = pI - cV - \Omega_c(t)V.
\]

We consider

\[
F_\tau(t) = \begin{pmatrix}
0 & \frac{\lambda}{d(d+r+q)} (\beta_I(d+q) + \beta_hr) (1 - \Omega_I(t)) \\
0 & 0
\end{pmatrix}, \quad \mathcal{V}_\tau(t) = \begin{pmatrix}
\delta & 0 \\
-p & c + \Omega_c(t)
\end{pmatrix}.
\]

We assume that \( Y(t,s), \ t \geq s \) is the evolution operator of the linear \( \tau \)-periodic system

\[
\frac{dy}{dt} = -\mathcal{V}_\tau(t)y \quad (4.5)
\]

That is, for each \( s \in \mathbb{R} \), the \( 2 \times 2 \) matrix \( Y(t,s) \) satisfies

\[
\frac{d}{dt} Y(t,s) = -\mathcal{V}_\tau(t) Y(t,s) \quad \forall t \geq s, \ Y(s,s) = I,
\]

where \( I \) is the \( 2 \times 2 \) identity matrix. Then the monodromy matrix, \( \Phi_{-\mathcal{V}_\tau}(t) \) of (4.5), is equal to \( Y(t,0), \ t \geq 0 \).
Let \( \phi(s) \) be the initial distribution of virus particles. Then \( \mathcal{F}_r \phi(s) \) is the rate of new infected cells produced by the virus particles which were introduced at time \( s \). Given \( t \geq s \), then \( Y(t,s)\mathcal{F}_r \phi(s) \) provides the distribution of those virus particles which were newly produced by infected cells at time \( s \) and remain in the virus compartment at time \( t \).

Let \( C_\tau \) be the ordered Banach space of \( \tau \)-periodic functions from \( \mathbb{R} \) to \( \mathbb{R}^2 \) with the maximum norm \( \| \cdot \| \) and the positive cone \( C_\tau^+ := \{ \phi \in C_\tau : \phi(t) \geq 0 \ \forall t \in \mathbb{R} \} \). We now define a linear operator \( \mathcal{L} : C_\tau \to C_\tau \) by

\[
(\mathcal{L}\phi)(t) = \int_0^\infty Y(t,t-a)\mathcal{F}_r \phi(t-a) \ \forall t \in \mathbb{R}, \phi \in C_\tau
\]

Here, \( \int_0^\infty Y(t,t-a)\mathcal{F}_r \phi(t-a)da = \int_0^t Y(t,s)\mathcal{F}_r \phi(s)ds \) gives the distribution of accumulated new viruses at time \( t \) produced due to all those viruses \( \phi(s) \) at times before \( t \). Therefore, \( \mathcal{L} \) is the next infection operator [86, 91], and we define infection threshold as \( R_i = \rho(\mathcal{L}) \), the spectral radius of \( \mathcal{L} \).

As in Wang and Zhao [91] and Liu, Zhao and Zhou [42], we let \( W(t,\theta) \) be the monodromy matrix of the linear \( \tau \)-periodic system

\[
\frac{d\tau}{dt} = \left( -\mathcal{V}_\tau(t) + \frac{\mathcal{F}_\tau(t)}{\theta} \right) \tau, \ t \in \mathbb{R}, \quad (4.6)
\]

with parameter \( \theta \in (0, \infty) \). Since \( \mathcal{F}_\tau \) is non-negative and \( -\mathcal{V}_\tau(t) \) is co-operative, it follows that \( \lim_{\theta \to \infty} \rho(W(\tau,\theta)) < 1 \). and \( \rho(W(\tau,\theta)) \) is continuous and non increasing in \( \theta \in (0, \infty) \). Thus, as proved in Wang and Zhao [91], we have the following results.

**Lemma 4.1.** The following statements hold

(i) If \( \rho(W(\tau,\theta)) = 1 \) has a positive solution \( \theta_0 \), then \( \theta_0 \), is an eigenvalue of operator \( \mathcal{L} \), and hence \( R_i > 0 \).

(ii) If \( R_i > 0 \), then \( \theta = R_i \) is the unique solution of \( \rho(W(\tau,\theta)) = 1 \).
(iii) \( R_i = 0 \) if and only if \( \rho(W(\tau, \theta)) < 1 \) for all \( \theta > 0 \).

**THEOREM 4.2.** (see [91]). The infection-free equilibrium \( X_0 \) is locally asymptotically stable if \( R_i < 1 \), and unstable if \( R_i > 1 \).

**Global dynamics**

By deriving a condition for the global stability of \( X_0 \) in the following theorem, we establish that the condition for global eradication of the virus from the body is given by \( R_i < 1 \).

**THEOREM 4.3.** If \( R_i < 1 \), then the unique infection-free equilibrium,

\[
X_0 = \left( \frac{\lambda(d + q)}{d(d + r + q)}, \frac{\lambda r}{d(d + r + q)}, 0, 0 \right),
\]

is globally asymptotically stable.

**PROOF.** Let \( R_i < 1 \). Then Theorem 4.2, implies that \( X_0 \) is locally asymptotically stable, i.e., \( \rho(\Phi_{F - V}(\tau)) < 1 \). We can choose \( j_0 > 0 \) small enough giving \( \rho(\Phi_{G(j_0)}(\tau)) < 1 \), where

\[
G(j_0)(t) = \begin{pmatrix}
-\delta & \left( \frac{\lambda(d + q)}{d(d + r + q)} + j_0 \right) \beta_i (1 - \Omega_I(t)) + \left( \frac{\lambda r}{d(d + r + q)} + j_0 \right) \beta_h (1 - \Omega_I(t)) \\
p & -(c + \Omega_e(t))
\end{pmatrix}
\]

From the first and the second equations of system (4.1), we have \( \frac{dT_l}{dt} \leq \lambda + qT_h - (d + r)T_l \) and \( \frac{dT_h}{dt} \leq rT_l - (d + q)T_h \). This implies that \( T_l(t) \leq \hat{T}_l(t) \to \frac{\lambda(d + q)}{d(d + r + q)} \) as \( t \to \infty \) and \( T_h(t) \leq \hat{T}_h(t) \to \frac{\lambda r}{d(d + r + q)} \) as \( t \to \infty \). Therefore, for \( j_0 > 0 \), there exists \( t_{j_0} \) such that \( T_l(t) \leq \frac{\lambda(d + q)}{d(d + r + q)} + j_0, T_h(t) \leq \frac{\lambda r}{d(d + r + q)} + j_0 \forall t \geq t_{j_0} \). Then from the third and the fourth equations of system (4.1), we have
\[
\frac{dI}{dt} \leq -\delta I + \left( \frac{\lambda(d + q)}{d(d + r + q)} + j_0 \right) \beta_l(1 - \Omega_I(t))V + \left( \frac{\lambda r}{d(d + r + q)} + j_0 \right) \beta_h(1 - \Omega_I(t))V,
\]
\[
\frac{dV}{dt} = pI - cV - \Omega_c(t)V.
\]  
(4.7)

Now, consider the following comparison system

\[
\frac{\hat{d}I}{dt} = -\delta \hat{I} + \left( \frac{\lambda(d + q)}{d(d + r + q)} + j_0 \right) \beta_l(1 - \Omega_I(t))\hat{V} + \left( \frac{\lambda r}{d(d + r + q)} + j_0 \right) \beta_h(1 - \Omega_I(t))\hat{V},
\]
\[
\frac{d\hat{V}}{dt} = p\hat{I} - c\hat{V} - \Omega_c(t)\hat{V}.
\]  
(4.8)

According to Zhang and Zhao [97], there exists a positive, \( \tau \)-periodic function \((\bar{I}(t), \bar{V}(t)) \) such that \((\hat{I}(t), \hat{V}(t))^T = e^{\Theta t}(\bar{I}(t), \bar{V}(t))^T \) is a solution of system (4.8), where

\[
\Theta = \frac{1}{\tau} \ln(\rho(\Phi_{G(j_0)}(\tau))).
\]

Here, \( \rho(\Phi_{G(j_0)}(\tau)) < 1 \) \( \iff \) \( \Theta < 0 \), which implies \((\hat{I}(t), \hat{V}(t))^T \to (0,0)^T \) as \( t \to \infty \).

Therefore, the \((0,0)^T \) solution of system (4.8) is globally asymptotically stable.

For any non-negative initial value \((I(0), V(0))^T \) of system (4.7), we can choose a sufficiently large \( m > 0 \) satisfying \((I(0), V(0))^T \leq m(I(0), V(0))^T \). Clearly, \( m(\hat{I}(t), \hat{V}(t))^T = me^{\Theta t}(\hat{I}(t), \hat{V}(t))^T \) is also a solution of (4.8). Then applying the comparison principle [73], we get \((I(t), V(t))^T \leq m(\hat{I}(t), \hat{V}(t))^T \forall t > 0 \). Therefore we get \( I(t) \to 0 \) and \( V(t) \to 0 \) as \( t \to \infty \). Then, by the theory of asymptotically autonomous systems [79], we get \( T_l(t) \to \frac{\lambda(d+q)}{d(d+r+q)} \) and \( T_h(t) \to \frac{\lambda r}{d(d+r+q)} \) as \( t \to \infty \). Hence, \( R_i < 1 \) gives a condition for \( X_0 \) to be globally asymptotically stable.

\[\square\]

**Effects of morphine pharmacodynamics on HIV dynamics**

According to Lemma 4.1, the infection threshold \( (R_i) \) can be obtained by solving \( \rho(W(\tau, \theta)) = 1 \) for \( \theta \). Therefore, using our model (4.1), in the form of system (4.6), we
computed $R_i$ numerically to study how $R_i$ depends on the pharmacodynamic parameters $a_0$, $t_{1/2}$, $M_0$, and $a$. As seen in Figures 12 and 14, each of these parameters can affect $R_i$. Note that the range of these parameters considered do not make $R_i$ less than 1, thereby causing the infection to remain persistent. Furthermore, we used our model (4.1) to evaluate the influence of the pharmacodynamic parameters on the dynamics of viral load and CD4 count in both IVM and SROM cases.

Intravenous morphine (IVM) case

As seen in Figure 12, an increase in morphine dose and/or a half-life increases the infection threshold ($R_i$). In particular, a morphine dose greater than 50 (i.e., $a_0 > 50$) causes a faster increase in $R_i$ (Figure 12 (a)). Also, we observe that a decrease in morphine intake interval from 22 hours to 2 hours (Figure 12 (c)) increases the infection threshold from 3.59 to 6.07.

Figure 12. Viral infection threshold, $R_i$, as a function of (a) the morphine dose, $a_0$, (b) the half-life of morphine, $t_{1/2}$, and (c) the morphine intake interval.
The results we obtain from varying the pharmacodynamic parameters show that an increase in the morphine dose increases the viral load at the end of 200 days post infection from $-3.8 \log_{10}$ to $5.1 \log_{10}$ (Figure 13 (a)), with a more pronounced increase occurring for morphine doses between 50 and 125. Also, increasing the half-life of morphine increases the 200 days post infection viral load from $-3.9 \log_{10}$ to $5.1 \log_{10}$ (Figure 13 (b)).

From Figures 13 (c) and 13 (d), we observe that an increase in the morphine dose, as well as an increase in a half-life decreases the CD4 count from 354 to 256 cells/µL, and from 353 to 260 cells/µL, respectively.
Figure 13. Changes in viral load and CD4 count with varying morphine dose, $a_0$, and morphine half-life, $t_{1/2}$.

Slow-release oral morphine (SROM) case

Figures 14 (a) and 14 (b) show that an increase in the mean level of morphine and/or a decrease in the amplitude increases the infection ($R_i$). Specifically, we observe a faster increase in $R_i$ when the mean level is between 50 and 125 (i.e., $50 \leq M_0 \leq 125$),
then almost no change in $R_i$ when $M_0 > 125$ (Figure 14 (a)). Furthermore, we see a faster increase in $R_i$ when the amplitude decreases from 100 to 25 (Figure 14 (b)). Our results also show that decreasing morphine intake interval from 22 hours to 2 hours increases the infection threshold from 5.89 to 6.20 (Figure 14 (c)). However, we observe that the effect on $R_i$ remains almost constant for morphine intake interval greater than 8 hours (Figure 14 (c)).

Figure 14. Viral infection threshold, $R_i$, as a function of (a) the mean level of morphine, $M_0$, (b) the morphine amplitude, $a$, and (c) the morphine intake interval.

Figure 15 (a) shows that an increase in the mean level of morphine increases the 200 day post infection viral load from $5.14 \log_{10}$ to $5.27 \log_{10}$ whereas an increase in the amplitude decreases the viral load at the 200 day post infection from $5.26 \log_{10}$ to $5.01 \log_{10}$ (Figure 15 (b)). These results suggest that the SROM pharmacodynamic parameters play a minimal role in altering the viral load dynamics compared to the IVM case.

Our results on the effects of the SROM pharmacodynamic parameters on CD4 count
show that an increase in the mean level of morphine dose decreases the CD4 count from 340 to 246 cells/µL (Figure 15 (c)). On the other hand, an increase in the amplitude increases the CD4 count from 250 to 285 cells/µL (Figure 15 (d)).

Figure 15. Changes in viral load and CD4 count with varying mean level of morphine, \( M_0 \), and the morphine amplitude, \( a \).
CHAPTER 5
EFFECT OF MORPHINE ON HIV-INFECTION WITH TWO VIRAL SPECIES

In this chapter, we develop and analyze a mathematical model to evaluate the effects of morphine on the viral dynamics of HIV when two viral species, namely, the wild-type virus and the mutant virus, are present in an individual. We calculate the reproduction number ($R^B_0$) for each species both in the presence of morphine and in the absence of morphine. We also perform the sensitivity analysis to identify the parameters that largely affect $R^B_0$. Using our model, we perform numerical simulations to study the effects of the fitness cost of the mutant virus, and the effects of escape ratio on HIV dynamics under morphine conditioning.

Introduction

As HIV infects a new cell, the virus releases its high genetic material in the form of viral RNA and uses the reverse transcriptase protein to create a DNA copy of itself (Figure 2). The reverse transcription process is responsible for most mutations [5]. The production of mutant viruses can present a significant challenge to the control of HIV as they can evade detection by antibodies and other immune system components which play a significant role in controlling the progression of an infection. Multiple infections of a host cell poses a greater risk of increased mutation rate [5]. Experimental studies have shown that morphine can affect the viral mutation as well as the cellular immune responses [69, 70, 80] and previous studies have also suggested that viral escape might contribute to increased viral burden and disease progression [2, 25, 30, 60]. However, the understanding of the viral escape in the setting of drugs of abuse remains unclear. Therefore, it is important to understand the
interplay between the use of morphine, the immune responses, the viral escape, and the fitness cost on HIV dynamics in two viral species.

**Model development**

The ODE model we consider in this chapter further extends the model (3.1). Specifically, we include populations of wild-type viruses, $V_1$, and mutant viruses, $V_2$, in the model. Upon interaction with the viruses $V_1$ or $V_2$, the target cells, $T_l$ and $T_h$, become infected cells $I_1$ and $I_2$, respectively. The schematic diagram of the model is presented in Figure 16, and the model parameter values are given in Table 6.
The wild-type virions infect target cells $T_l$ and $T_h$ at rates $\beta_{l1}$ and $\beta_{h1}$, respectively. We let $\alpha$ represent the fitness cost of the mutant virus, a reduction in the mutant infection rate relative to the wild-type infection rate caused by mutation [29, 82]. Thus, we assume mutant virions infect the target cells $T_l$ and $T_h$ at rates $\beta_{l2} = (1 - \alpha)\beta_{l1}$ and $\beta_{h2} = (1 - \alpha)\beta_{h1}$, respectively. We assume mutation occurs within a cell infected with the wild-type virus (i.e., forward mutation) and denote the proportion of cells infected with the wild-type virus that become mutant [35] by $f$, where $0 < f < 1$. Previous studies utilizing SIV have shown that less mutation occurs in the presence of morphine [54, 80]. To capture this morphine effect on the mutation rate in our model, we take $f = \frac{k}{\mu + \gamma M}$. Here, $M$ represents the morphine concentration, and the parameters $k$, $\mu$, and $\gamma$ are introduced to model the lowered mutation rate caused by morphine [54, 55, 70, 82].

As in chapter 3, we take $\epsilon_A = \frac{\eta A(t)}{1 + \eta A(t)}$ (3.3) to model the efficacy of virus neutralization by antibodies with $A(t) = \frac{a t^n}{b^n + t^n}$ (3.2), where the values of $a$, $b$, and $n$ are provided in Table 1. Furthermore, antibodies enhance the clearance of the wild-type virus at a per capita rate $\sigma_1 A(t)$. Similarly, we denote enhanced clearance rate for the mutant virus by $\sigma_2 = \psi \sigma_1$, where $0 \leq \psi \leq 1$ represents the escape ratio, a reduction in the ability of antibodies to destroy mutant viruses. The proposed model we study in this chapter is therefore described by the following set of equations:
\[
\frac{dT_l}{dt} = \lambda + qT_h - dT_l - rT_l - \epsilon_A (\beta_l V_1 T_l - \beta_l V_2 T_l), \quad T_l(0) = T_{l0}
\]
\[
\frac{dT_h}{dt} = rT_l - dT_h - qT_h - \epsilon_A (\beta_h V_1 T_h - \beta_h V_2 T_h), \quad T_h(0) = T_{h0}
\]
\[
\frac{dI_1}{dt} = (1-f) (1-\epsilon_A) (\beta_l V_1 T_l + \beta_h V_1 T_h) - \delta_1 I_1, \quad I_1(0) = I_{10}
\]
\[
\frac{dI_2}{dt} = (1-\epsilon_A) (f \beta_l V_1 T_l + f \beta_h V_1 T_h + \beta_l V_2 T_l + \beta_h V_2 T_h) - \delta_2 I_2, \quad I_2(0) = I_{20}
\]
\[
\frac{dV_1}{dt} = p_1 I_1 - c_1 V_1 - \sigma_1 A(t) V_1, \quad V_1(0) = V_{10}
\]
\[
\frac{dV_2}{dt} = p_2 I_2 - c_2 V_2 - \sigma_2 A(t) V_2, \quad V_2(0) = V_{20}
\]

**Model analysis**

The basic reproduction number \( R^B_0 \)

We derive the basic reproduction number, \( R^B_0 \), for model (5.1) with \( A(t) = A(0) \).

The model system (5.1) has exactly one infection-free equilibrium

\[
X_0 = \left( \frac{\lambda(d+q)}{d(d+r+q)}, \frac{\lambda r}{d(d+r+q)}, 0, 0, 0, 0 \right),
\]

and the equations for the infectious and virus classes of the linearized system at \( X_0 \) take the form:

\[
\frac{dI_1}{dt} = \frac{\lambda(1-f)(1-\epsilon_A(0))}{d(d+r+q)} (\beta_l (d+q) + \beta_h r) V_1 - \delta_1 I_1,
\]
\[
\frac{dI_2}{dt} = \frac{\lambda(1-\epsilon_A(0))}{d(d+r+q)} [f (\beta_l (d+q) + \beta_h r) V_1 + (\beta_l (d+q) + \beta_h r) V_2] - \delta_2 I_2,
\]
\[
\frac{dV_1}{dt} = p_1 I_1 - c_1 V_1 - \sigma_1 A(0) V_1,
\]
\[
\frac{dV_2}{dt} = p_2 I_2 - c_2 V_2 - \sigma_2 A(0) V_2.
\]
We introduce the following two matrices:

\[
\mathcal{F}_B = \begin{pmatrix}
0 & 0 & \frac{\lambda(1-f)(1-\epsilon_A(0))}{d(d+r+q)} (\beta h_1 (d+q) + \beta h_1 r) & 0 \\
0 & 0 & \frac{\lambda(1-\epsilon_A(0))}{d(d+r+q)} (\beta h_1 (d+q) + \beta h_1 r) & \frac{\lambda(1-\epsilon_A(0))}{d(d+r+q)} (\beta h_2 (d+q) + \beta h_2 r) \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix},
\]

and

\[
\mathcal{V}_B = \begin{pmatrix}
\delta_1 & 0 & 0 & 0 \\
0 & \delta_2 & 0 & 0 \\
-p_1 & 0 & c_1 + \sigma A(0) & 0 \\
0 & -p_2 & 0 & c_2 + \sigma A(0)
\end{pmatrix}.
\]

These expressions give \( \mathcal{F}_B \mathcal{V}_B^{-1} \) as:

\[
\begin{pmatrix}
X_{2\times2} & Y_{2\times2} \\
0_{2\times2} & 0_{2\times2}
\end{pmatrix},
\]

where

\[
X = \begin{pmatrix}
\frac{\lambda p_1 (1-f)(1-\epsilon_A(0))}{d(d+r+q)(c_1 + \sigma A(0))} (\beta h_1 (d+q) + \beta h_1 r) & 0 \\
\frac{\lambda p_1 (1-\epsilon_A(0))}{d(d+r+q)(c_1 + \sigma A(0))} (\beta h_1 (d+q) + \beta h_1 r) & \frac{\lambda p_2 (1-\epsilon_A(0))}{d(d+r+q)(c_2 + \sigma A(0))} (\beta h_2 (d+q) + \beta h_2 r)
\end{pmatrix},
\]

\[
Y = \begin{pmatrix}
\frac{\lambda (1-f)(1-\epsilon_A(0))}{d(d+r+q)(c_1 + \sigma A(0))} (\beta h_1 (d+q) + \beta h_1 r) & 0 \\
\frac{\lambda (1-\epsilon_A(0))}{d(d+r+q)(c_1 + \sigma A(0))} (\beta h_1 (d+q) + \beta h_1 r) & \frac{\lambda (1-\epsilon_A(0))}{d(d+r+q)(c_2 + \sigma A(0))} (\beta h_2 (d+q) + \beta h_2 r)
\end{pmatrix}.
\]

Then \( R_0^B \) corresponds to the spectral radius of \( \mathcal{F}_B \mathcal{V}_B^{-1} \), that is

\[
R_0^B = \rho(\mathcal{F}_B \mathcal{V}_B^{-1}) = \max \{ R_0^1, R_0^2 \}
\]

where
\[
R_0^1 = \frac{\lambda p_1 (1 - f)(1 - \epsilon_A(0)) [\beta_{11}(d + q) + \beta_{11}r]}{\delta_1 d(d + r + q)(c_1 + \sigma_1 A(0))}, \quad \text{and}
\]
\[
R_0^2 = \frac{\lambda p_2 (1 - \epsilon_A(0)) [\beta_{22}(d + q) + \beta_{22}r]}{\delta_2 d(d + r + q)(c_2 + \sigma_2 A(0))}.
\]

**Theorem 5.1.** (See [89]) If \( R_0^B < 1 \), then the infection-free equilibrium is locally asymptotically stable and unstable if \( R_0^B > 1 \).

Using the basic reproduction number formula derived above and the parameter values in Table 6, we now calculate the basic reproduction number, \( R_0^B \). We obtained \( R_0^1 = 2.25 \) (for the wild-type virus) and \( R_0^2 = 2.22 \) (for the mutant virus) when we have very high \( (A(t) \approx 2444, \text{Figure 6}) \) virus-specific antibody responses (i.e., in absence of morphine) whereas when we have very low \( (A(t) \approx 0, \text{Figure 6}) \) virus-specific antibody responses (i.e., in presence of morphine), \( R_0^1 = 2.85 \) (for the wild-type virus) and \( R_0^2 = 2.28 \) (for the mutant virus). Therefore, \( R_0^B = \max \{ R_0^1, R_0^2 \} = 2.25 \) (in absence of morphine) and \( R_0^B = \max \{ R_0^1, R_0^2 \} = 2.85 \) (in presence of morphine). We note that this basic reproduction number estimate is consistent with previous estimates [87]. When compared to the estimates obtained in chapter 3, we observe a consistency in that in the presence of morphine we have higher estimate than in the absence of morphine.

**Sensitivity to \( R_0^B \)**

To identify important parameters that affect \( R_0^B \), we performed sensitivity analysis by calculating the sensitivity indices [12]. The sensitivity index of \( R_0^1 \) (for the wild-type virus) and \( R_0^2 \) (for the mutant virus) with respect to a parameter \( x \), is given by \( \frac{\partial R_0^1}{\partial x} \times \frac{x}{R_0^1} \) and \( \frac{\partial R_0^2}{\partial x} \times \frac{x}{R_0^2} \). The negative (or positive) sign of the sensitivity index indicates whether the wild-type or mutant reproduction number decreases (or increases) when the corresponding
parameter is increased. From the calculated sensitivity indices (Figures 17 and 18), we observe that the most sensitive parameters are $\lambda$, $p_1$, and $\delta_1$ (for wild-type) and $\lambda$, $p_2$, and $\delta_2$ (for mutant). We note that while Figures 17 and 18 suggest that $\lambda$, $p_1$, $\delta_1$, $p_2$, and $\delta_2$ have the largest impact on the basic reproduction number, the parameters $\beta_{h1}$, $c_1$, $\sigma_1$, $\beta_{h2}$, $c_2$, and $\sigma_2$ also have significant impact on $R_0^B$. Therefore, the effect of these parameters can not be entirely ignored while developing HIV control strategies. From our sensitivity analysis, we observed that neither $d$, $f$ nor $\epsilon_A$ seem to play a significant role in the reproduction number.

Figure 17. Sensitivity of parameters to $R_0^1$ (wild-type virus).
Figure 18. Sensitivity of parameters to $R_0^2$ (mutant virus).

Based on our sensitivity analysis we note that $p_1$, $\delta_1$, $p_2$, and $\delta_2$ are important for $R_0^B$. We now identify the regions in the space of these parameters where the wild-type or the mutant virus is dominant.
Figure 19. Contour plots showing how the basic reproduction number depends on $p_1$, the production rate of wild-type virus and $\delta_2$, the death rate of cells infected by the mutant virus, (a) in the presence of morphine and (b) in the absence of morphine.
Figure 20. Contour plots showing how the basic reproduction number depends on $p_2$, the production rate of mutant virus and $\delta_1$, the death rate of cells infected by the wild-type virus, (a) in the presence of morphine and (b) in the absence of morphine.

As shown in Figures 19 and 20, the $p_1\delta_2$ and $p_2\delta_1$-parameter spaces are divided by the curves $p_1 = f(\delta_2)$ and $p_2 = f(\delta_1)$, respectively. Above or below these curves either the wild-type virus or the mutant virus dominates. As shown in Figure 19, an increase in $\delta_2$ in the mutant virus dominating region and/or a decrease in the $p_1$ in wild-type virus dominating region decreases the value of $R^B_0$ eventually reaching the region where $R^B_0 < 1$. Similarly, in Figure 20, an increase in $\delta_1$ in the wild-type virus dominating region and/or a decrease in the $p_2$ in mutant virus dominating region decreases the value of $R^B_0$ eventually reaching the region where $R^B_0 < 1$.

In our study, we find that (in the presence of morphine) if $p_1 < 17500$ and $\delta_2 > 1.58$, or $p_2 < 21900$ and $\delta_1 > 1.97$, then $R^B_0 < 1$ (Figures 19 (a) and 20 (a)). On the other
hand, in the absence of morphine, we find that if \( p_1 < 22200 \) and \( \delta_2 > 1.53 \), or \( p_2 < 22500 \) and \( \delta_1 > 1.55 \), then \( R_0^B < 1 \) (Figures 19 (b) and 20 (b)).

Table 6. Model (5.1) parameter values and their interpretations.

<table>
<thead>
<tr>
<th>Description</th>
<th>Parameter</th>
<th>Estimate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproduction rate of T cells</td>
<td>( \lambda )</td>
<td>( 3510 \text{ ml}^{-1}\text{day}^{-1} )</td>
<td>[87]</td>
</tr>
<tr>
<td>Infection rate of T_1 by V_1</td>
<td>( \beta_{11} )</td>
<td>( 5.72 \times 10^{-10} \text{ day}^{-1} )</td>
<td>Estimate, [87]</td>
</tr>
<tr>
<td>Infection rate of T_1 by V_2</td>
<td>( \beta_{12} )</td>
<td>( 5.72 \times 10^{-10} \text{ day}^{-1} )</td>
<td>Estimate, [87]</td>
</tr>
<tr>
<td>Infection rate of T_2 by V_1</td>
<td>( \beta_{21} )</td>
<td>((1 - \alpha)\beta_{11} \text{ day}^{-1})</td>
<td>Calculated</td>
</tr>
<tr>
<td>Infection rate of T_2 by V_2</td>
<td>( \beta_{22} )</td>
<td>((1 - \alpha)\beta_{11} \text{ day}^{-1})</td>
<td>Calculated</td>
</tr>
<tr>
<td>Fitness cost</td>
<td>( \alpha )</td>
<td>0.2 [0-1]</td>
<td>Varied</td>
</tr>
<tr>
<td>Death rate of T cells</td>
<td>( d )</td>
<td>0.01 day^{-1}</td>
<td>[75, 52]</td>
</tr>
<tr>
<td>Death rate of I_1</td>
<td>( d_1 )</td>
<td>0.69 day^{-1}</td>
<td>[87]</td>
</tr>
<tr>
<td>Death rate of I_2</td>
<td>( d_2 )</td>
<td>0.69 day^{-1}</td>
<td>[87]</td>
</tr>
<tr>
<td>Production rate of V_1</td>
<td>( p_1 )</td>
<td>( 5 \times 10^4 \text{ day}^{-1} )</td>
<td>[11, 87]</td>
</tr>
<tr>
<td>Production rate of V_2</td>
<td>( p_2 )</td>
<td>( 5 \times 10^4 \text{ day}^{-1} )</td>
<td>[11, 87]</td>
</tr>
<tr>
<td>Clearance rate of V_1</td>
<td>( c_1 )</td>
<td>23 day^{-1}</td>
<td>[66]</td>
</tr>
<tr>
<td>Clearance rate of V_2</td>
<td>( c_2 )</td>
<td>23 day^{-1}</td>
<td>[66]</td>
</tr>
<tr>
<td>Transition rate from T_1 to T_2</td>
<td>( r )</td>
<td>0.16 day^{-1}</td>
<td>[87]</td>
</tr>
<tr>
<td>Transition rate from T_1 to T_2</td>
<td>( q )</td>
<td>0.24 day^{-1}</td>
<td>[87]</td>
</tr>
<tr>
<td>Net ( A(t) ) effect on infection</td>
<td>( \eta )</td>
<td>( 1.1 \times 10^{-5} \text{ ml ng}^{-1} )</td>
<td>Assumed</td>
</tr>
<tr>
<td>Net ( A(t) ) effect on clearance of V_1</td>
<td>( \sigma_1 )</td>
<td>( 2.5 \times 10^{-3} \text{ day}^{-1} )</td>
<td>Assumed</td>
</tr>
<tr>
<td>Net ( A(t) ) effect on clearance of V_2</td>
<td>( \sigma_2 )</td>
<td>( \psi\sigma_1 \text{ day}^{-1} )</td>
<td>Assumed</td>
</tr>
<tr>
<td>Escape ratio</td>
<td>( \psi )</td>
<td>0.1[0-1]</td>
<td>Varied</td>
</tr>
<tr>
<td>Morphine concentration</td>
<td>( M )</td>
<td>400 [0-400] ng ml^{-1}</td>
<td>Varied</td>
</tr>
<tr>
<td>Morphine parameters affecting mutation rate ( f )</td>
<td>( k )</td>
<td>( 3 \times 10^{-5} )</td>
<td>[82]</td>
</tr>
<tr>
<td>Morphine parameters affecting mutation rate ( f )</td>
<td>( \mu )</td>
<td>0.167</td>
<td>Assumed</td>
</tr>
<tr>
<td>Morphine parameters affecting mutation rate ( f )</td>
<td>( \gamma )</td>
<td>1</td>
<td>Assumed</td>
</tr>
<tr>
<td>Initial number of T cells</td>
<td>( T_{0,0} )</td>
<td>( T(0) - T_{0,0} )</td>
<td>[87]</td>
</tr>
<tr>
<td>Initial number of infected cells</td>
<td>( I_{0,0} )</td>
<td>40980</td>
<td>[87]</td>
</tr>
<tr>
<td>Initial number of Virus</td>
<td>( V_{1,0} )</td>
<td>200</td>
<td>[46, 85]</td>
</tr>
<tr>
<td>Initial number of Virus</td>
<td>( V_{2,0} )</td>
<td>40 [0-200]</td>
<td>Varied</td>
</tr>
</tbody>
</table>
Numerical simulation results

Using the parameter values presented in Table 6, we solved our model (5.1) over a period of 500 days and plotted the individual viral loads ($V_1$ and $V_2$), the total viral load ($V_1 + V_2$), the ratio of the wild-type and the mutant viral loads ($V_1/V_2$), and the percentage of the wild-type in the total viral load ($\%$ of $V_1 = \frac{V_1}{V_1 + V_2} \times 100$). We also plotted the CD4 count. For these plots, we varied the fitness cost ($\alpha$) from 0% to 100%, corresponding to 0 to 1 in the model. Similarly, the escape ratio was varied from 0 to 1.

Effect of fitness cost ($\alpha$)

We studied the effects of the fitness cost of the mutant virus on the HIV dynamics by varying the parameter $\alpha$ for the cases of the presence of morphine and the absence of morphine (Figure 21). Our results show no effect of the fitness cost on $V_1$, $V_1 + V_2$, and on the CD4 count in the presence of morphine, whereas in the absence of morphine, increasing the fitness cost results in an increase in the $V_1$ and in the CD4 count before leveling for a higher fitness cost (Figure 21). This may be attributed to a successful immune responses escape by the mutant virus for a lower fitness cost. Then as the immune responses conform to recognize the mutants, the virus mutation is suppressed thereby allowing more replication of the wild-type virus. Furthermore, our results show that in the presence and in the absence of morphine, increasing the fitness cost decreases the $V_2$, and increases the ratio $V_1/V_2$. From the results we see almost no difference on the percentage of $V_1$ in the presence and in the absence of morphine (Figure 21) for a higher fitness cost.
Figure 21. Effects of fitness cost ($\alpha$) on HIV dynamics.

Effect of escape ratio ($\psi$)

Here, we studied the effects of the escape ratio by varying the parameter $\psi$ for the presence of morphine and the absence of morphine cases (Figure 22). Our results show no effect of the escape ratio on the $V_1$, $V_1 + V_2$, and on the CD4 count in the presence and in the absence of morphine. However, we observe slightly higher viral load in $V_1$ and $V_1 + V_2$, and lower CD4 count in the presence of morphine (Figure 22) than in the absence of morphine. Also, we see that as the escape ratio increases, $V_2$ decreases with about $2.2 \log 10$ in the absence of morphine, whereas in the presence of morphine the $V_2$ remains constant at a higher value. Moreover, an increase in escape ratio results in a higher, but constant, $V_1/V_2$.
in the presence of morphine compared to in the absence of morphine which shows a gradual increase in $V_1/V_2$. Our results show almost no difference on the percentage of $V_1$ in the presence and in the absence of morphine (Figure 22).

Figure 22. Effects of escape ratio ($\psi$) on HIV dynamics.
HIV remains a major public health challenge and one of the highest causes of death worldwide, with a rapidly increasing dependency on drugs of abuse, such as opiates, in HIV-infected patients [28, 71, 92]. While drugs of abuse are known to affect the HIV specific antibody responses [38], how these alterations in antibody response impact within-host HIV dynamics is not well understood. Therefore, studying the effect of drugs of abuse on antibody responses and consequently on viral dynamics is of great importance. In this dissertation, the models we develop extend from a previous mathematical model of SIV dynamics under morphine conditioning [87].

The model we developed in chapter 3 incorporated the effects of morphine-altered antibody responses. A previous study that focused on viral dynamics for the first 3 months post infection [87] did not find any role of immune responses in virus dynamics, consistent with the low HIV-specific antibody levels during this period (Figure 6). However, we studied viral dynamics for a longer period of time (i.e., 200 days, Figure 7) and found that the effect of morphine-altered antibody responses becomes significant enough to alter long-term viral dynamics. Using our model and the data from SIV/SHIV infected rhesus macaques with and without morphine conditioning, we determined that the maximum antibody level \( a \), the time when the antibody level becomes half-maximal \( b \), and the Hill coefficient \( n \) (slope of the time-response curve) are significantly lower in the rapid-progressor morphine group than in the control group (Table 1, Figure 6).

Furthermore, excluding animal 1/52N, which has unusually high antibody levels and high CD4 count, and using a two sample t-test with equal but unknown variances,
these quantities also become significantly different between the rapid-progressor group and the slow-progressor group. While the precise mechanism by which morphine alters virus-specific antibody responses remains to be determined, our results show that morphine has a significant effect on altering antibody responses, with a tendency to decrease virus-specific antibody levels and to cause a delay in the time to reach half-maximal antibody responses. Using these trends of the antibody response, our models further identified that the long term (200 days post infection) viral dynamics is best described by a model that includes two immune response effects: reduction of the cell infection rate and an increase in the virus clearance rate (Table 2). Our models did not support the third effect considered, namely, antibody-dependent infected cell killing.

Using the best supported model, we quantified the effect of morphine-altered antibody responses on the virus infection rate and the virus clearance rate for 200 days post-infection (Figure 8). Our results show that the efficacy of antibody responses on reducing virus infection is significantly less in the morphine-dependent animals when compared to the control group (Figure 8). Similarly, morphine dependence leads to less enhanced virus clearance in the slow-progressor morphine group and in the rapid-progressor morphine group than the control group (Figure 8). A higher virus infection rate and/or a lower virus clearance rate in the morphine-dependent animals results in a higher viral load (Figure 7). The dynamics predicted by the model also shows that CD4 count decreases faster in the morphine-dependent groups than in the control group. Thus, there is a higher CD4 drop in the presence of morphine (Figure 9). Although this difference in CD4 drop was not statistically significant ($p > 0.05$), our results suggest that there are noticeable effects of morphine-altered virus-specific antibody responses on CD4 count and that morphine may exacerbate the disease progression.

We also computed the basic reproduction number, $R_0$, as 6.48, 2.12, and 1.55 for
the rapid-progressor morphine, the slow-progressor morphine, and the control groups, respectively, consistent with the observation that the infection got established in each group ($R_0 > 1$). The higher value of $R_0$ and the lower level of viral-specific antibody response in the rapid-progressor morphine group imply that morphine can make pre-infection intervention strategies, such as antibody-based vaccines and PrEP, less effective.

To understand the effects of periodic morphine intake, we developed a pharmacodynamic morphine model that incorporated time-varying efficacy of virus-specific antibodies in chapter 4. In the model, we considered two cases of morphine pharmacodynamics, namely, intravenous morphine (IVM) and slow release oral morphine (SROM). In intravenous morphine, the direct administration of morphine into the circulation provides a rapid effect [50]. On the other hand, slow-release oral morphine can be used as pharmacotherapy maintenance treatment for opioid-dependent individuals [7, 23, 26, 27, 31, 36, 51, 90]. Using our pharmacodynamic morphine model, along with functions that describe morphine dynamics for IVM and SROM cases, we formulate the infection threshold $R_i$, that provides a condition for global stability of infection free equilibrium. We predict that the infection dies out if $R_i < 1$ (Theorem 4.3). We determined that the HIV-infection dynamics largely depend on the pharmacodynamic parameters in both IVM and SROM cases.

In the IVM case, we sought to understand the effects of morphine dose ($a_0$) and the half-life ($t_{1/2}$) on the viral dynamics. Our results show that increasing the morphine dose, and the half-life increases the infection threshold (Figure 12) as well as the viral load (Figure 13). Similarly, increasing these pharmacodynamic parameters decreases the CD4 count (Figure 13).

For the SROM case, the pharmacodynamic parameters we considered to study the HIV-infection dynamics were the mean level of morphine ($M_0$) and the morphine amplitude ($a$). From our results we observe that increasing the mean level of morphine increases the
infection threshold and the viral load, and decreases the CD4 count. Furthermore, our results show that increasing the amplitude decreases the infection threshold (Figure 14), as well as the viral load (Figure 15). However, an increase in amplitude increases the CD4 count (Figure 15).

We also studied the influence of morphine intake interval on the infection threshold. We observed that the infection threshold in both IVM and SROM cases grows as the intake interval decreases (Figures 12 and 14). It is worth noting that, in both the IVM and SROM cases, the infection threshold is greater than one (i.e., $R_i > 1$), suggesting the infection remains persistent (Figures 12 and 14).

Experimental studies have shown that the use of drugs of abuse such as morphine can affect the mutation rate in macaques [70]. Our model of two viral species we developed in chapter 5 helps in understanding the interplay of morphine and immune responses escape, and the fitness cost on HIV dynamics. We derived the basic reproduction number for the viral dynamics model as $R^B_0 = \max\{R^1_0, R^2_0\}$, where $R^1_0$ and $R^2_0$ are the reproduction numbers for the wild-type virus and mutant virus, respectively. For our model, we computed $R^B_0 = 2.25$ (in the absence of morphine) and $R^B_0 = 2.85$ (in the presence of morphine). Using our model, we studied the effects of the fitness cost and the mutant escape ratio on various aspects of HIV dynamics (Figures 21 and 22). Our results suggest that the escape ratio plays no role in altering the dynamics of the wild-type virus. Furthermore, our study shows that whether or not morphine is present, the wild-type virus dominates.

We acknowledge the several limitations of our study. A limited data set has been used to estimate parameters in chapter 3. Therefore, some of the numerical estimates may not be certain. More data from experimental studies including morphine conditioning and immune responses are needed to obtain more precise parameter estimates and related results. We considered only antibody responses in our model. However, other immune
responses such as those involving CD8\(^+\) cells or NK cells might have some effects on the viral dynamics. Experimental studies involving periodic morphine conditioning could help more accurately estimate the pharmacodynamic parameters which we observed play an important role in HIV-infection dynamics.

Future goals stemming from this dissertation include the need to develop and analyze a model that incorporates a time-varying morphine concentration to study the HIV-infection dynamics in two viral species. Also, additional work is needed to conduct the analysis to establish that infection persists (i.e., global analysis for \( R_i > 1 \) case) for the morphine pharmacodynamics model discussed in chapter 4. Other areas which could be of interest include: development of a model that can help in understanding the effects of morphine on HIV-infection dynamics in multiple viral species, formulation of optimal control problems related to the models discussed in this study, as well as conducting a study that incorporates both the effects of virus-specific antibody responses and CTLs to understand the HIV dynamics under morphine conditioning.
REFERENCES


VITA

Jones Mutune Mutua was born in 1987 in Kibwezi, Kenya. He received a B.S. degree in Mathematics and a minor in Computer Science from the University of Eastern Africa, Baraton, Kenya in 2012. He received a M.S. degree in Mathematics and Statistics from the University of Missouri-Kansas City in 2014.