MODELING THE EFFECTS OF DRUGS OF ABUSE ON HIV INFECTIONS WITH TWO VIRAL SPECIES

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Abstract

Injection drug use is one of the greatest risk factors associated with contracting human immunodeficiency virus (HIV), and drug abusers infected with HIV suffer from a higher viral load and rapid parthenogenesis. Replication of HIV may result in a large number of mutant viruses that can escape recognition of the host's immune response. Experimental results have shown that the presence of morphine can decrease the viral mutation rate and cellular immune responses. In this study, we present a mathematical model to determine if the decrease in mutation and cellular immune response in the presence of morphine can account for the increased viral load. We consider two viral species: a wild-type and a mutant. Our model shows that the morphine-altered mutation rate and cellular immune response allows the wild-type virus to out compete the mutant, resulting in a higher set point viral load. We also compute the basic reproduction number corresponding to each species and show that the dominant species is determined by a threshold morphine concentration, with the mutant dominating below the threshold and the wild-type dominating above. Furthermore, we performed stability analysis on the infection free and mutant only equilibria of the system and carried out numerical simulations to study the effects of morphine conditioning on viral load and selection of viral species reflect the increased viral load associated with morphine use.

1 Introduction

Human immunodeficiency virus (HIV) is a significant health concern around the world, with 36.9 infected people worldwide in 2018 [1]. HIV is a blood borne pathogen and one of the most common forms of transmission is by sharing needles used for injecting drugs of abuse, such as opioids, between infected and non-infected persons. Drugs of abuse have been shown to have adverse effects on the progression of HIV infections, including a higher

set point viral load and decreased amounts of CD4+ T cells [2]. Studies involving rhesus macaques and simian and human-simian immunodeficiency virus (SIV and HSIV) have shown that morphine may cause a faster progression to AIDS and pathogenesis in infected animals, and other studies of HIV have also demonstrated that a quicker progression to AIDS may be associated with opiate use [3]. It is therefore important to investigate the mechanisms by which morphine affects the progression of HIV infections and viral burden.

Cytotoxic T-lymphocytes (CTLs) are an important component of the human immune system for combating viral infections, including HIV, by limiting viral reproduction and the infection of hosts' target cells. In the acute stage of the infection the host's immune system responds by creating a large amount of virus specific CTLs. The CTLs perform actions to inhibit viral growth, for example by destroying infected cells directly. After the infection has progressed and the CTL immune response has been reduced it is possible for viruses to revert back to the original level (NEED REF). Therefore the production of CTLs plays a significant role in the progression of an infection [4]. Also, HIV possesses a high genetic variability which may result in the production of escape mutants that can avoid detection by CTLs [5]. The high number of CTLs puts pressure on the virus to quickly mutate to a form that can evade the CTLs. This pressure, combined with the quick replication speed of HIV, may result in a large number of mutant viruses being produced [13, 14]. The production of mutant viruses can be a significant barrier to the treatment of HIV by antiviral drugs or to the development of an effective vaccine [5].

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2 Methods

2.1 Mathematical Model

Our model is a variant of a standard HIV dynamics model that has been extended to include terms for morphine effects, viral evolution, and cellular immune response by the host [6, 22], and focuses on the long-term viral dynamics, morphine effects on mutation, and make-up of the viral load. Following Vaidya et al., we include two populations of CD4+ target cells based on CCR5 co-receptor expression- a population with lower susceptibility to infection, T_l, and a population with higher susceptibility to infection, T_h, due to lower and higher levels of co-receptor expression, respectively [2, 16]. Viral mutation is represented by including two viral species- a wild-type virus, V_w, that initiates the infection and a mutant virus, V_m, that is produced via mutation from the wild-type (CITE MUTATION). We assume free viral particles infect target cells to produce corresponding infected cell populations I_w and I_m. Due to mutation, a fraction ϵ of target cells infected by wild-type virus become mutant infected cells and the remainder, $(1-\epsilon)$, become wild-type infected cells [21]. Cellular immune responses are represented by a population of CTLs, denoted C,

which act by directly killing infected cells (CITE).

The wild-type and mutant viral populations are differentiated in two ways: a fitness cost of mutation and a mutant rate of escape from immune responses. The fitness cost of mutation is denoted F, where $0 \leqslant F \leqslant 1$, and is a reduction in the ability of the mutant virus to infect target cells compared to the wild-type virus, e.g., a value of $F = 0.2$ corresponds to a mutant virus that is 80% as effective at infecting target cells as the wild-type virus. We assume mutant virus will not have a higher infection rate than the wild-type, which would correspond to a negative value of F [28]. The mutant escape ratio, $B > 0$, is a reduction in the ability of the host's cellular immune response to kill cells infected by the mutant virus compared to cells infected by the wild-type virus. However, due to responses by epitope-specific CTLs there is some recognition of mutant infected cells by the host's immune responses (CITE 20,29?).

Target cells are recruited to the T_l population at constant rate λ and that target cells transition from T_l to T_h at rate r and from T_h to T_l at rate q [23]. Both populations of target cells die at per capita rate δ_T [6, 22]. Target cells in the T_l population are infected by the wild-type virus at rate β_l and by the mutant virus at rate $(1-F)\beta_l$. Similarly, T_h cells are infected at rates β_h and $(1-F)\beta_h$ by the wild-type and mutant viruses, respectively.

Both species of virus are produced by their corresponding infected cell population at rate p per cell and are cleared at rate δ_V [21]. Wild-type infected cells I_w are recruited from T_l and T_h at rates $(1-\epsilon)\beta_l$ and $(1-\epsilon)\beta_h$, respectively, and are killed by CTLs at rate b. Note that mutant infected cells I_m are recruited both by mutation from wild-type infected cells and by infection of target cells by mutant virus, at rates $\epsilon\beta_l$ and $\epsilon\beta_h$ for mutation and $(1-F)\beta_l$ and $(1-F)\beta_h$ for infection from corresponding target cell populations. CTLs kill I_m cells at rate $\frac{b}{1+B}$, where the base CTL killing rate b has been reduced in proportion to the mutant escape ratio $1+B$. Both classes of infected cells die at per capita rate δ_I. CTLs are produced at constant rate ω, die at rate δ_C, and are also produced at rate α in proportion to the total number of infected cells, $I_w + I_m$ [21].

We include the effects of morphine through three mechanisms: the increase in the T_h population due to increased co-receptor expression, the decrease in viral evolution, and the decrease in CTL production (CITE THESE?). To model the increase in T_h, we make the transition parameters r and q morphine dependent, i.e., $r = r(M)$ and $q = q(M)$, where M is the concentration of morphine, where $r(M)$ is an increasing function of morphine and $q(M)$ is a decreasing function of morphine. This will result in more target cells belonging to T_h over time, where they are more susceptible to infection [23]. We model $r(M)$ and $q(M)$ using an E_{max} model of the form

$$r(M) = r_c + (r_m - r_c)\eta_r(M)$$
$$q(M) = q_m + (q_c - q_m)\eta_q(M)$$

where

$$\eta_r(M) = \frac{M^n}{M_h^n + M^n}$$
$$\eta_q(M) = 1 - \eta_r(M),$$

where r_c and r_m are the minimum and maximum values of $r(M)$, q_c and q_m are the minimum and maximum values of $q(M)$, n is the Hill's coefficient for the E_{max} model, and M_h is the value of M that gives $r(M)$ and $q(M)$ the value half-way between their respective minimums and maximums. The decrease in viral evolution due to morphine is modeled as $\frac{\epsilon}{\mu+\eta M}$, where μ, η are parameters related to the effect of morphine on mutation. Similarly, we model the decrease in CTL production by introducing parameters γ, ξ and modeling the morphine dependent CTL production rate as $\frac{\alpha}{\gamma+\xi M}$. Finally, we assume the base CTL production rate, ω, decreases exponentially with morphine with decay rate ψ, giving $\omega e^{-\psi M}$. For simplicity we will sometimes write $\hat{\epsilon} = \frac{\epsilon}{\mu+\eta M}, \hat{\alpha} = \frac{\alpha}{\gamma+\xi M}$, and $\hat{\omega} = \omega e^{-\psi M}$.

The full model is given by the following seven-dimensional system of ODE's:

$$\frac{dT_l}{dt} = \lambda + q(M)T_h - r(M)T_l - \beta_l V_w T_l - (1-F)\beta_l V_m T_l - \delta_T T_l$$
$$\frac{dT_h}{dt} = r(M)T_l - q(M)T_h - \beta_h V_w T_h - (1-F)\beta_h V_m T_h - \delta_T T_h$$
$$\frac{dV_w}{dt} = pI_w - \delta_V V_w$$
$$\frac{dV_m}{dt} = pI_m - \delta_V V_m$$
$$\frac{dI_w}{dt} = (1 - \frac{\epsilon}{\mu+\eta M})(\beta_l V_w T_l + \beta_h V_w T_h) - bI_w C - \delta_I I_w$$
$$\frac{dI_m}{dt} = \frac{\epsilon}{\mu+\eta M}(\beta_l V_w T_l + \beta_h V_w T_h) + (1-F)(\beta_l V_m T_l + \beta_h V_m T_h) - \frac{b}{1+B} I_m C - \delta_I I_m$$
$$\frac{dC}{dt} = \omega + \frac{\alpha}{\gamma+\xi M}(I_w + I_m)C - \delta_C C.$$

2.2 Parameter Estimation

Where possible, estimates for parameter values are taken from previously published studies (GET REFS HERE). Following Vaidya et al., we assume 10^6 target cells per ml of blood, about $40980/ml$ belonging to the T_h population and the remaining $10^6 - 40980/ml$ to the T_l population. Since there are initially no infected cells, we take $I_w, I_m = 0$. In the experiment by Kumar et al. [2], rhesus macaques were infected intravenously with 2-ml inoculum containing a cocktail of three SIV viruses. The cocktail contained 10^5 HIV RNA copies of each of the three viruses, and assuming a macaque contains approximately 1.5 liters of extracellular water we can estimate $V_0 = \frac{3\times10^5}{1.5L} \approx 200$ viral RNA copies/ml [23], which we assume to belong entirely to the V_w population. Estimates for $\lambda, \beta_l, \beta_h, r_c, r_m, q_m, q_c$, and δ_I were taken from Vaidya et al., where their values were obtained by fitting the model to experimental data. In particular, they estimated β_h as approximately two orders of magnitude higher than β_l [23].

Based on modeling work by Stafford et al., we take $\delta_T = 1/100 = 0.01$, which corresponds to a target cell life span of 100 days [32]. Ramratnam et al. give an estimated range of HIV viral clearance between 9.1 and 36 virions per day, so we use their average value of 23 virions per day as our value for δ_V [31]. Mansky and Temin determined the *in vivo* mutation rate of HIV-1 to be 3.4×10^{-5} mutations per base pair per generation, so we take the mutation rate $\epsilon = 3 \times 10^{-5}$ [33]. We assume only forward mutation takes place, i.e., target cells infected by mutant virions will not revert to the wild-type infected class.

Following Konrad et al.[21], we take the CTL death rate $\delta_C \approx 10^{-1}$.

We use the estimate for the CTL production rate $\alpha = 6.7 \times 10^{-5}$ as in De Boer and Perelson [21, 35] (CHECK THESE).

We will vary the parameters γ and ξ that account for the effect of morphine on *alpha* will vary.

Previous modeling work by Ganusov gives a range of the CTL killing rate, b, between 0.01 and 0.4 [28] and the escape ratio B will be varied.

We will vary the fitness cost of mutation, F, between 0 and 1, and the mutant escape ratio, B, between 0 and 50.

The estimated parameters and their descriptions are summarized in Table 1:

Table 1: Parameter Values

Parameter	Value	Description	Reference
λ	3690 $mlday^{-1}$	Production rate of T_l cells	[23]
r_c	0.16 day^{-1}	Minimum value of r	[23]
r_m	0.52 day^{-1}	Maximum value of r	[23]
q_c	1.23×10^{-6} day^{-1}	Minimum value of q	[23]
q_m	0.25 day^{-1}	Maximum value of q	[23]
M_h	100	Half morphine value for $r(M), q(M)$	[25]
n	8	Hill's coefficient of morphine response	–
β_l	$10^{-9} ml\ day^{-1}$	Wild- type infection rate of T_l cells	[23]
β_h	$10^{-7} ml\ day^{-1}$	Wild -type infection rate of T_h cells	[23]
F	$0-1$	Fitness cost of mutation	–
p	2500 day^{-1}	Production rate of virus	???
b	0.25 $ml\ day^{-1}$	CTL killing rate of wild-type	[28]
B	$0-50$	Mutant escape ratio	–
α	6.7×10^{-5} $ml\ day^{-1}$	CTL proliferation rate	[35]
γ	1	Morphine effect on α	–
ξ	1	Morphine effect on α	–
ω	50 $mlday^{-1}$	CTL production rate	–
ψ	0.1	CTL prduction decay rate	–
ϵ	3×10^{-5}	Mutation rate	[33]
μ	1	Morphine effect on ϵ	–
η	1	Morphine morphine effect on ϵ	–
δ_T	0.01 day^{-1}	Target cell death rate	[32]
δ_V	23 day^{-1}	Virus clearance rate	[31]
δ_I	0.3 day^{-1}	Infected cell death rate	[23]
δ_C	0.63 day^{-1}	CTL death rate	[21]
M	$0-300$???	Concentration of morphine	[25]

3 Results

3.1 Basic Reproduction Number

The basic reproduction number, denoted R_0, is an important quantity in the study of viral dynamics and is defined as the average number of secondary infected cells resulting from a single initial infected cell when target cells are not limited [24]. The stability of the infection free equilibrium (IFE) can be described by the basic reproduction number, with the IFE being locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$ [24]. Since our model

contains two viral species, the basic reproduction number is obtained, as we show below, as a combination of the quantities R_0^w and R_0^m, corresponding to the wild-type and mutant viruses, respectively.

The IFE is the steady-state solution of the model in which all infected populations are zero. For our model, we compute the IFE as $(T_l^*, T_h^*, 0, 0, 0, 0, C^*)$, where

$$\begin{aligned} T_l^* &= \frac{\lambda(q(M)+\delta_T)}{\delta_T(q(M)+r(M)+\delta_T)}, \\ T_h^* &= \frac{\lambda r(M)}{\delta_T(q(M)+r(M)+\delta_T)}, \\ C^* &= \frac{\hat{\omega}}{\delta_C}. \end{aligned}$$

We now use the next generation operator method [36] to obtain an expression for the basic reproduction number of the model. The next-generation matrix is obtained from the infected subsystem of the model, i.e., the equations of the system that contain viruses and infected cells [36]. For our model, the infected subsystem is given by

$$\begin{aligned} \frac{dV_w}{dt} &= pI_w - \delta_V V_w \\ \frac{dV_m}{dt} &= pI_m - \delta_V V_m \\ \frac{dI_w}{dt} &= (1-\hat{\epsilon})(\beta_l V_w T_l + \beta_h V_w T_h) - bI_w C - \delta_I I_w \\ \frac{dI_m}{dt} &= \hat{\epsilon}(\beta_l V_w T_l + \beta_h V_w T_h) + (\hat{\beta}_l V_m T_l + \hat{\beta}_h V_m T_h) - \frac{b}{1+B} I_m C - \delta_I I_m. \end{aligned}$$

Next, we linearize the infected subsystem about the IFE and decompose it into $\mathcal{F} - \mathcal{V}$, where $\mathcal{F}$ is the infection part of the system, which describes newly infected components, and $\mathcal{V}$ is the transition part, which describes transitions of cells and viruses in and out of compartments. $\mathcal{F}$ and $\mathcal{V}$ for our model are given by

$$\mathcal{F} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ (1-\hat{\epsilon})(\beta_l T_l^* + \beta_h T_h^*) & 0 & 0 & 0 \\ \hat{\epsilon}(\beta_l T_l^* + \beta_h T_h^*) & (\hat{\beta}_l T_l^* + \hat{\beta}_h T_h^*) & 0 & 0 \end{bmatrix}$$

and

$$\mathcal{V} = \begin{bmatrix} \delta_V & 0 & -p & 0 \\ 0 & \delta_V & 0 & -p \\ 0 & 0 & \delta_I + bC^* & 0 \\ 0 & 0 & 0 & \delta_I + \frac{b}{1+B}C^* \end{bmatrix}.$$

The next generation operator is $\mathcal{F}\mathcal{V}^{-1}$ and its specral radius $\sigma(\mathcal{F}\mathcal{V}^{-1})$ is the basic reproduction number of the system. The basic reproduction number of our model is thus obtained as $R_0 = \sigma(\mathcal{F}\mathcal{V}^{-1}) = \max\{R_0^w, R_0^m\}$, where

$$R_0^w = \frac{(1-\hat{\epsilon})(\beta_h T_h^* + \beta_l T_l^*)p}{\delta_V(bC^* + \delta_I)}$$
$$R_0^m = \frac{(1-F)(\beta_h T_h^* + \beta_l T_l^*)(1+B)p}{\delta_V(\delta_I B + bC^* + \delta_I)}.$$

Note that since $\hat{\epsilon}, T_l^*, T_h^*$, and C^* are morphine dependent, R_0^w and R_0^m are also morphine dependent. Also note that if $R_0^w, R_0^m < 1$ the infection will die out while if either $R_0^w > 1$ or $R_0^m > 1$ the infection will persist [24]. Using the parameter values in Table 1 and $F = 0.2, B = 30, M = 0$ we compute $R_0^w = 0.078$ and $R_0^m = R_0 = 1.32$, indicating the mutant is the dominant viral population when no morphine is present. However, increasing the amount of morphine past a threshold value, M_{thresh} results in a population switch and the wild-type becoming the dominant population (Figure 1). We can determine the value of M_{thresh} by solving $R_0^w(M) = R_0^m(M)$ for M- if $M < M_{thresh}$ the mutant will dominate and if $M > M_{thresh}$ the wild-type will dominate.

Figure 1: Computed values of R_0^w and R_0^m as M. A population switch occurs at approximately $M = 100$.

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