Global Analysis of a Multi-scale HIV/AIDS Model with Different Treatment Strategies

Peipei Hu[1], Fereshteh Nazari[2], Okuneye Kamaldeen[2], Baojun Song[3]
[1]Shanghai University, [2]Arizona State University, [3]Monticlair State University

Abstract: In this study, mathematical models are developed to explore how viral load variability caused by treatment can influence the prevalence of HIV. Density-independent and dependent treatment strategies are considered. If the density-independent treatment is employed, a global forward bifurcation alone can entirely determine the dynamical behavior of the model. If we introduce the density-dependent treatment, model behaviors tend to be rather complex. In this case, backward bifurcations are possible. Thus, the outcomes are also a function of initial data. For both kinds of models, it is shown that HIV treatments may increase the basic control number, thus, increasing the spread of HIV infections. Using HIV/AIDS mortality data of China, we estimate a part of our parameters. The model results support the conclusion that the HIV/AIDS mortality of China will continue increasing if there in no change in the control strategy.

1 Introduction

AIDS is caused by human immunodeficiency virus (HIV), which is one of the chronic infectious diseases seriously affect human health. There are more than 25 million people died of AIDS annually, 33.4 million new infected world-wide. Over the past 20 years, the spread of AIDS in China appears increasing very fast, as can be seen in Figure1. It was estimated that accumulated HIV infections in China was 780 000; and there were 48000 new infections in 2011[17].

Currently, there is no cure for HIV infection. In 2013, 12.9 million people living with HIV were receiving antiretroviral therapy (ART) globally, of which 11.7 million were receiving ART in low- and middle-income countries. While treatment gives people with HIV infection a chance for a healthy and prolong life, However, treatment with anti-retroviral (ARV) drugs can effectively control the virus. It negatively affects the control of transmission dynamics of the HIV. This is because treating HIV infected individuals leads to a longer lifetime and as a result creates more chance of transmitting the virus. On the other hand, treatment can decrease the infectiousness of the HIV infected individual. Our interesting question is to assess the HIV treatment strategy in the population level and individual level.

A set of mathematical models have been used to link the immunological and epidemiological aspects of HIV in the between- and within-host interaction levels [4, 7]. Beginning with Sasaki and Iwasa [8], researchers started to conceptually link within-host processes to

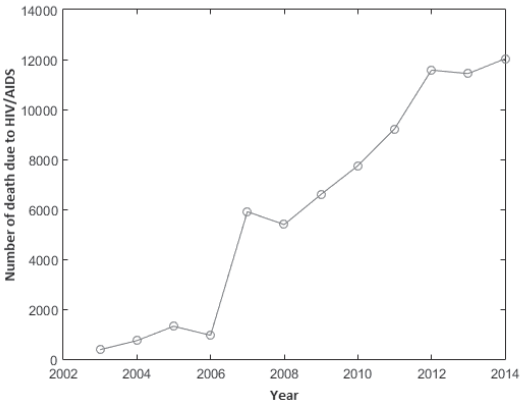

Figure 1: Annual Mortaility of AIDS in China

between-host processes. The studies of acute infections by Antia [9, 10], and Ganusov [5] which included various biological aspects such as a host-immune response, host heterogeneity, and a threshold mortality function. In 2002, Gilchrist and Sasaki [6] nested a within-host model within a susceptible-infected- recovery (SIR) epidemic model.

In this study, we try to explore the effects of variable viral load in two groups of treated and untreated individuals on the transmission dynamics of HIV at between-host level. Under, a mathematical model to couple the between-host and the within-host model is formulated in Section 2. A rigorous qualitative analyses of the model under three different assumptions for treatment function is provided in Section 3. A study about the parameters of within-host model has impact on the between-host model is provided in section 4. In Section 5 we discuss about the existence of backward bifurcation and finally, in Section 6 numerical simulations as well as parameter estimation is carried out.

2 Model Formulation

2.1 A micro-model for HIV

We modify the model from [16] to construct our model for HIV infection within a host (with/without treatment). The the total number of targeted T-cells at time τ is $T_i(\tau)$ number of the infected T-cells is $T_i^*(\tau)$, and number of the free human immunodeficiency virus (virions) is $V_i(\tau)$, where i=1 is for without treatment and i=2 is for with treatment. A healthy T-cell (T) becomes infected as a result of the free virions attack according to the law of mass-action with a rate $\alpha p V_i$. π and d are the birth rate and natural death rate of the susceptible healthy T-cells, respectively. Infected T-cells decreases due to the either natural death or the virus infection induced cell death at the rates d and d_i. Infected target cells (T_i^*) produce free virions at rate nqd_i where q is accounting for the effects of pro-tease inhibitors for the virus. n is number of free virus produced by lysing a T cell. Therefore, $p = q = 1$ means that there is no treatment (marked as (T_1, T_1^*, V_1)) and $p < 1,\ q < 1$ means that there is treatment (marked as (T_2, I_2^*, V_2)). Free virions are further cleared at a rate

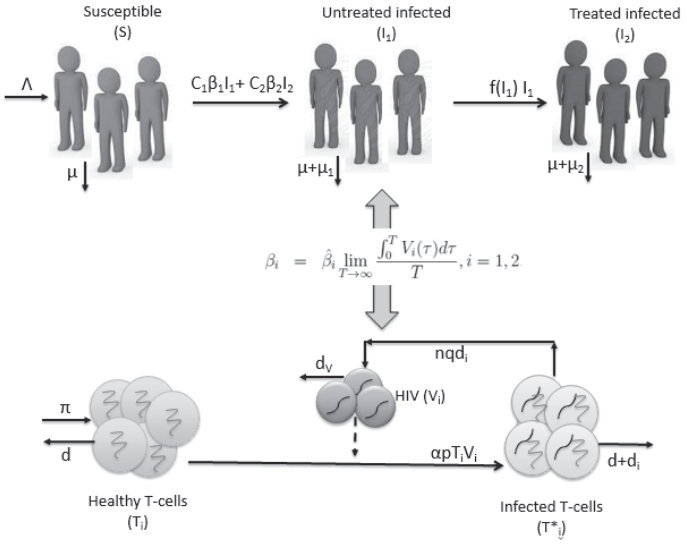

Figure 2: Flow Chart

d_v by the immune system. Thus, the within-host model with/without treatment is given by the following system of differential equations.

$$\begin{cases} \dfrac{dT_i(\tau)}{d\tau} &= \pi - \alpha p V_i T_i - dT_i, \\ \dfrac{dT_i^*(\tau)}{d\tau} &= \alpha p V_i T_i - (d+d_i)T_i^*, \\ \dfrac{dV_i(\tau)}{d\tau} &= nqd_i T_i^* - d_V V_i, \\ i &= 1, 2. \end{cases} \tag{2.1}$$

2.2 A Macro-model for HIV with density-dependent/independent treatment strategy

The HIV between-host model to be considered here is formulated by dividing the total sexually active population (in particular, in China) at time t into compartments of susceptible, $S(t)$, infected without treatment, I_1 and infected with treatment, I_2. The population of susceptible individuals (S) is increased by the recruitment of new sexually active individuals into the current population of susceptible individuals at a rate Λ. It is further decreased by infection, following effective contacts with infected individuals, I_1 and I_2, at rates of $c_1\beta_1 I_1$ and $c_2\beta_2 I_2$, respectively. Here, β_i, for i=1,2 denote the transmission probability of infected individuals without and with treatment, respectively. c_1 and c_2 are accounting for the number of effective contacts per year. The population is also decreased by natural death at a rate μ. The population of infected individuals without treatment is decreased due to the either natural death or disease-induced death at rates μ and μ_1. It is further decreased due to the

treatment at a rate $f(I_1)$, where, $f(I_1)$ is variable based on the number of infections varies. If the size of the infected individuals is small then it is reasonable to assume that each infected individual has a higher chance of receiving treatment. As a result from [13], we suppose that $f(I_1)$ is a linear function of the number of infected individuals so that $f(I_1) = \gamma I_1$ which is referred as *density-independent treatment strategy*. If the pool of infected individuals is large enough then limited health infrastructure and budgets prevent us from providing treatment for all infected individuals. Hence, we consider the reduction in *per-capita* treatment rate so that $f(I_1) = \frac{A}{B+I_1}$ which is referred as *density-dependent treatment strategy*, we also consider another density-dependent treatment strategies: $f(I_1) = \alpha_1 + \alpha_2 e^{-\gamma I_1}$. Similarly, the population of the infected individuals with treatment is decreased due to the either natural death or disease-induced death at rates μ and μ_1. Thus, the between-host model is given by the following system of differential equations:

$$\begin{cases} \frac{dS(t)}{dt} &= \Lambda - c_1\beta_1 SI_1 - c_2\beta_2 SI_2 - \mu S, \\ \frac{dI_1(t)}{dt} &= c_1\beta_1 SI_1 + c_2\beta_2 SI_2 - (\mu + \mu_1)I_1 - f(I_1)I_1, \\ \frac{dI_2(t)}{dt} &= f(I_1)I_1 - (\mu + \mu_2)I_2. \end{cases} \tag{2.2}$$

Since the within-host interactions are happening in the different time scale (τ) than the between-host level interactions (t), the following function make a link between them as the Figure 2.

$$\beta_i = \hat{\beta}_i \lim_{T\to\infty} \frac{\int_0^T V_i(\tau)d\tau}{T}, \quad i = 1, 2.$$

The variables and parameters are tabulated in Table 2.

3 Analysis of the Coupled-Model with Density-independent Treatment

3.1 Basic analysis

In this section we consider the density-independent treatment strategy, that is, $f(I_1) = \gamma$. So, the between-host model (2.2) can be rewritten as the following

$$\begin{cases} \frac{dS(t)}{dt} &= \Lambda - c_1\beta_1 SI_1 - c_2\beta_2 SI_2 - \mu S, \\ \frac{dI_1(t)}{dt} &= c_1\beta_1 SI_1 + c_2\beta_2 SI_2 - (\mu + \mu_1)I_1 - \gamma I_1, \\ \frac{dI_2(t)}{dt} &= \gamma I_1 - (\mu + \mu_2)I_2. \end{cases} \tag{3.1}$$

It is easy to show that the trajectories starting in Ω will stay for forward time, where

$$\Omega = \{(S, I_1, I_2) \in \mathbb{R}_3^+ : S + I_1 + I_2 \leq \Lambda/\mu\}. \tag{3.2}$$

Now, let us show Ω is positive invariant. The rate of change of the total populations ($N = S + I_1 + I_2$) is given by

$$\frac{dN}{dt} = \Lambda - \mu N.$$

Hence, it follows for comparison theorem [18] that

$$N(t) \leq N(0)e^{-\mu t} + \frac{\Lambda}{\mu}[1 - e^{-\mu t}].$$

All parameters of the model are non-negative, with the death rates μ, μ_1, μ_2, recruitment terms Λ and transmission coefficients β_1, β_2 together with the contact rates c_1 and c_2 positive. Furthermore, each of the total sub-populations (is assumed to be positive for $t = 0$. Since Ω is positively invariant and it is sufficient to study the model in Ω. The disease-free equilibrium (DFE) of the model (3.1), obtained by the setting the right-hand side of the equations in the model to zero, is given by (3.1)

$$E_0 = (\Lambda/\mu, 0, 0). \tag{3.3}$$

Using the next generation operator method, the matrices $\mathcal{F}$ (of the new infection terms) and $\mathcal{V}$ (of the transition terms) associated with the model (3.1) are given, respectively, by

$$\mathcal{F} = \begin{pmatrix} S\beta_1 c_1 & S\beta_2 c_2 \\ 0 & 0 \end{pmatrix},$$

$$\mathcal{V} = \begin{pmatrix} \mu + \mu_1 + \gamma & 0 \\ -\gamma & \mu + \mu_2 \end{pmatrix}.$$

Thus, *the basic control number* of the model (3.1), defined by $\mathcal{R}_c = \rho(\mathcal{F}\mathcal{V}^{-1})$ (where ρ is the spectral radius of the next generation matrix $\mathcal{F}\mathcal{V}^{-1}$), is given by

$$\mathcal{R}_c = \rho(\mathcal{F}\mathcal{V}^{-1}) = \frac{\Lambda}{\mu}\left(\frac{c_1\beta_1}{\mu + \mu_1 + \gamma} + \frac{c_2\beta_2}{\mu + \mu_2}\frac{\gamma}{\mu + \mu_1 + \gamma}\right) \tag{3.4}$$

Theorem 3.1. *The DFE, E_0, of the model (3.1) is locally asymptotically stable (LAS) if $\mathcal{R}_c < 1$, and unstable if $\mathcal{R}_c > 1$.*

If there is no treatment, that is, $\gamma = 0$, then *the basic reproduction number* is

$$\mathcal{R}_0 = \frac{\Lambda}{\mu}\left(\frac{c_1\beta_1}{\mu + \mu_1}\right).$$

Thus,

$$\begin{aligned} \mathcal{R}_c - \mathcal{R}_0 &= \frac{\Lambda}{\mu}\left(\frac{c_1\beta_1}{\mu + \mu_1 + \gamma} + \frac{c_2\beta_2}{\mu + \mu_2}\frac{\gamma}{\mu + \mu_1 + \gamma} - \frac{c_1\beta_1}{\mu + \mu_1}\right) \\ &= \frac{\Lambda}{\mu}\frac{\gamma}{\mu + \mu_1 + \gamma}\left(\frac{c_2\beta_2}{\mu + \mu_2} - \frac{c_1\beta_1}{\mu + \mu_1}\right). \end{aligned}$$

If $\frac{c_2\beta_2}{\mu_2} > \frac{c_1\beta_1}{\mu_1}$, then $\mathcal{R}_c > \mathcal{R}_0$. It is shown that HIV treatments may increase the basic control number and the incidence of HIV if $\frac{c_2\beta_2}{\mu_2} > \frac{c_1\beta_1}{\mu_1}$.
Following, the possible existence of an endemic equilibrium of the density-independent treatment model (3.1) when the infected components are non-zero is explored. Let,

$$E_1 = (\hat{S}, \hat{I}_1, \hat{I}_2) \tag{3.5}$$

be an arbitrary endemic equilibrium of the model (3.1), where $\hat{S}$, $\hat{I}_1$ and $\hat{I}_2$ are obtained from setting the right-hand side of the equations in the model (3.1) to zero, given by

$$\hat{S} = \frac{(\mu+\mu_2)(\mu_1+\mu+\gamma)}{c_1\beta_1(\mu+\mu_2)+c_2\beta_2\gamma}, \quad \hat{I}_1 = \mathcal{R}_c - 1, \quad \hat{I}_2 = \frac{\gamma(\mathcal{R}_c-1)}{\mu+\mu_2}.$$

Thus, endemic equilibrium E_1 exists whenever $\mathcal{R}_c > 1$.

3.2 Asymptotic stability of equilibria

3.2.1 Global stability of the infection-free equilibrium E_0

Following theorem guarantees global asymptotic stability of the infection-free equilibrium E_0 of density-independent treatment model 3.1.

Theorem 3.2. *The disease-free equilibrium E_0 of density-independent treatment model* (3.1) *is globally asymptotically stable in Ω whenever $\mathcal{R}_c < 1$ and unstable whenever $\mathcal{R}_c > 1$.*

Proof. Consider the following global Lyapunov function

$$V(S, I_1, I_2) = I_1 + \frac{\mu+\mu_1+\gamma}{\gamma}\left[1 - \frac{\Lambda}{\mu}\left(\frac{c_1\beta_1}{\mu+\mu_1+\gamma}\right)\right] I_2. \tag{3.6}$$

For $\frac{\Lambda}{\mu}\left(\frac{c_1\beta_1}{\mu+\mu_1+\gamma}\right) < R_c < 1$, so that $V \geq 0$.
The derivatives of $V(S, I_1, I_2)$ along the positive solution of equation (3.1) is

$$\begin{aligned} \dot{V}(S, I_1, I_2) &= c_1\beta_1 S I_1 + c_2\beta_2 S I_2 - (\mu+\mu_1+\gamma) I_1 \\ &+ \frac{\mu+\mu_1+\gamma}{\gamma}\left[1 - \frac{\Lambda}{\mu}\left(\frac{c_1\beta_1}{\mu+\mu_1+\gamma}\right)\right][\gamma I_1 - (\mu+\mu_2) I_2]. \end{aligned} \tag{3.7}$$

Since $S < \frac{\Lambda}{\mu}$, simplifying equation (3.7), we get

$$\begin{aligned} \dot{V} &< \left[c_2\beta_2\frac{\Lambda}{\mu} - \frac{(\mu+\mu_2)}{\gamma}(\mu+\mu_1+\gamma)(1 - \frac{\Lambda}{\mu}\frac{c_1\beta_1}{\mu+\mu_1+\gamma})\right] I_2 \\ &= \frac{\mu+\mu_2}{\gamma}(\mu+\mu_1+\gamma)\left[\frac{\Lambda}{\mu}\frac{c_2\beta_2\gamma}{(\mu+\mu_2)(\mu+\mu_1+\gamma)} + \frac{\Lambda}{\mu}\frac{c_1\beta_1}{(\mu+\mu_1+\gamma)} - 1\right] \\ &= \frac{\mu+\mu_2}{\gamma}(\mu+\mu_1+\gamma)[\mathcal{R}_c - 1] I_2. \end{aligned}$$

Since $S, I_1, I_2 > 0$, then if $\mathcal{R}_c < 1$, $\dot{V}(S, I_1, I_2) < 0$. Thus, all solution trajectories in Ω approach the infection free equilibrium E_0. □

3.2.2 Local stability of the endemic equilibrium E_1

Theorem 3.3. *If $\mathcal{R}_c > 1$, then the endemic equilibrium $\mathcal{E}_1$ is locally asymptotically stable in Ω.*

Proof. The Jacobian matrix of the system (3.1) at (3.3) is

$$\mathcal{J} = \begin{bmatrix} -\frac{\Lambda}{\hat{S}} & -c_1\beta_1\hat{S} & -c_2\beta_2\hat{S} \\ \frac{\Lambda}{\hat{S}} - \mu & c_1\beta_1\hat{S} - \gamma - \mu - \mu_1 & c_2\beta_2\hat{S} \\ 0 & \gamma & -\mu - \mu_2 \end{bmatrix},$$

Hence, it follows from Routh Hurwitz criterion of polynomial of degree 3:
let $\omega_1 = -|J|,\ \omega_2 = -Trace(J)$ and $\omega_3 = \begin{bmatrix} j_{11} & j_{12} \\ j_{21} & j_{22} \end{bmatrix} + \begin{bmatrix} j_{22} & j_{23} \\ j_{32} & j_{33} \end{bmatrix} + \begin{bmatrix} j_{11} & j_{13} \\ j_{31} & j_{33} \end{bmatrix}$.
Since,

$$\begin{aligned}
\omega_1 &= \left(\frac{\Lambda}{\hat{S}} - \mu\right)\hat{S}(\mu+\mu_2)(\mu_1+\mu+\gamma) > 0 \text{ since } \frac{\Lambda}{\hat{S}} > \mu, \\
\omega_2 &= \frac{\Lambda}{\hat{S}} + \gamma + 2\mu + \mu_1 + \mu_2 - c_1\beta_1\hat{S} > 0 \text{ since } \gamma + \mu + \mu_1 > c_1\beta_1\hat{S} \text{ from model (3.1)}, \\
\omega_3 &= \frac{\Lambda}{\hat{S}}(\gamma + 2\mu + \mu_1 + \mu_2) + \frac{\Lambda}{\hat{S}}(\mu+\mu_2) + (\frac{\Lambda}{\hat{S}} - \mu)c_1\beta_1\hat{S} > 0,
\end{aligned}$$

and

$$\begin{aligned}
\omega_2\omega_3 &= \left(\frac{\Lambda}{\hat{S}} + \gamma + 2\mu + \mu_1 + \mu_2 - c_1\beta_1\hat{S}\right)\left(\frac{\Lambda}{\hat{S}}(\gamma + 2\mu + \mu_1 + \mu_2) - c_1\beta_1\hat{S}\right) \\
&> \left(\frac{\Lambda}{\hat{S}} - \mu\right)\hat{S}(\mu+\mu_2)(\mu_1+\mu+\gamma) = \omega_1,
\end{aligned}$$

we deduce that the three roots of the characteristics polynomial of (3.8) are negative. □

3.2.3 Global stability of the endemic equilibrium E_1

The following theorem shows global asymptotic stability of the endemic equilibrium E_1 of of the model (3.1).

Theorem 3.4. *The endemic equilibrium E_1 of the density-independent treatment model* (3.1) *is globally asymptotically stable in Ω whenever $\mathcal{R}_c > 1$.*

Proof. Let consider the following global Lyapunov function for $E_1 = (\bar{S}, \bar{I}_1, \bar{I}_2)$,

$$V_2(S, I_1, I_2) = (S - \bar{S}) - \bar{S}\ln\frac{S}{\bar{S}} + (I_1 - \bar{I}_1) - \bar{I}_1\ln\frac{I_1}{\bar{I}_1} + \mathcal{A}\left[(I_2 - \bar{I}_2) - \bar{I}_2\ln\frac{I_2}{\bar{I}_2}\right]. \quad (3.8)$$

Assume $\mathcal{A} = \dfrac{\alpha_2\bar{S}}{\mu+\mu_2}$, then computing the derivative of V along the trajectories of the system

given by (3.1), we obtain

$$\begin{aligned}\frac{dV}{dt} &= (\Lambda - c_1\beta_1 SI_1 - c_2\beta_2 SI_2 - \mu S) - \frac{\bar{S}}{S}(\Lambda - c_1\beta_1 SI_1 - c_2\beta_2 SI_2 - \mu S)\\ &+ (c_1\beta_1 SI_1 + c_2\beta_2 SI_2 - (\mu + \mu_1 - \gamma)I_1)\\ &- \frac{\bar{I}_1}{I_1}[c_1\beta_1 SI_1 + c_2\beta_2 SI_2 - (\mu + \mu_1 - \gamma)I_1]\\ &+ \frac{\alpha_2\bar{S}}{\mu + \mu_2}\left[(\gamma I_1 - (\mu + \mu_2)I_2) - \frac{\bar{I}_2}{I_2}(\gamma I_1 - (\mu + \mu_2)I_2)\right]. \end{aligned} \tag{3.9}$$

We have,

$$\begin{gathered}\Lambda = c_1\beta_1\bar{S}\bar{I}_1 + c_2\beta_2\bar{S}\bar{I}_2 + \mu\bar{S}\\ (\mu + \mu_1 + \gamma) = c_1\beta_1\bar{S} + c_2\beta_2\bar{S}\frac{\bar{I}_2}{\bar{I}_1}\\ \mu + \mu_2 = \frac{\gamma\bar{I}_1}{\bar{I}_2}\end{gathered}$$

Thus,

$$\begin{aligned}\frac{dV}{dt} &= c_1\beta_1\bar{S}\bar{I}_1 + c_2\beta_2\bar{S}\bar{I}_2 + \mu\bar{S} - \mu S\\ &- \frac{\bar{S}}{S}[c_1\beta_1\bar{S}\bar{I}_1 + c_2\beta_2\bar{S}\bar{I}_2 + \mu\bar{S} - c_1\beta_1 SI_1 - c_2\beta_2 SI_2 - \mu S]\\ &- \left(c_1\beta_1\bar{S} + c_2\beta_2\bar{S}\frac{\bar{I}_2}{\bar{I}_1}\right)I_1 - \frac{\bar{I}_1}{I_1}\left[c_1\beta_1 SI_1 + c_2\beta_2 SI_2 - (c_1\beta_1\bar{S} + c_2\beta_2\bar{S}\frac{\bar{I}_2}{\bar{I}_1})I_1\right]\\ &+ \frac{\alpha_2\bar{S}}{\mu + \mu_2}\left[(\gamma I_1 - (\mu + \mu_2)I_2) - \frac{\bar{I}_2}{I_2}(\gamma I_1 - (\mu + \mu_2)I_2)\right]\\ &= \mu\bar{S}\left(2 - \frac{\bar{S}}{S} - \frac{S}{\bar{S}}\right) + c_2\beta_2\bar{S}\bar{I}_2\left(3 - \frac{\bar{S}}{S} - \frac{I_1\bar{I}_2}{\bar{I}_1 I_2} - \frac{S\bar{I}_1 I_2}{\bar{S}I_1\bar{I}_2}\right)\\ &+ c_1\beta_1\bar{S}\bar{I}_1\left(2 - \frac{\bar{S}}{S} - \frac{S}{\bar{S}}\right). \end{aligned} \tag{3.10}$$

Applying the inequality of arithmetic and geometric means, for non-negative real numbers $a_1, a_2, ...a_n$, $\frac{a_1+a_2+...+a_n}{n} \geq (a_1a_2...a_n)^{\frac{1}{n}}$, we obtain

$$2 \leq \frac{\bar{S}}{S} + \frac{S}{\bar{S}} \text{ and } 3 \leq \frac{\bar{S}}{S} + \frac{I_1\bar{I}_2}{\bar{I}_1 I_2} + \frac{S\bar{I}_1 I_2}{\bar{S}I_1\bar{I}_2}.$$

Hence, each item of (3.10) is negative, and as a result $\frac{dV}{dt} \leq 0$. That is, the endemic equilibrium E_1 is globally asymptotically stable whenever it comes to exist. This completes the proof. □

4 Micro Parameters Influence Basic Control Number

To show the influence of the within-host model to between-host model, we consider the dynamic of within-host model, according to[16],

the disease free equilibrium and endemic equilibrium of within-host model without treatment is given following

$$(\hat{T}_1, \hat{T}_1^*, \hat{V}_1) = (\frac{\pi}{d}, 0, 0), \quad (\tilde{T}_1, \tilde{T}_1^*, \tilde{V}_1) = \left(\frac{dv(d+d_1)}{\alpha n d_1}, \frac{R_{0,1}-1}{r d_1 \alpha (d+d_1)}, \frac{R_{0,1}-1}{\alpha d v (d+d_1)} \right),$$

where basic reproduction number

$$R_{0,1} = \frac{\alpha n d_1 \pi}{d d v (d+d_1)}.$$

the disease free equilibrium and endemic equilibrium of within-host model with treatment is given following

$$(\hat{T}_2, \hat{T}_2^*, \hat{V}_2) = (\frac{\pi}{d}, 0, 0), \ (\tilde{T}_2, \tilde{T}_2^*, \tilde{V}_2) = (\frac{dv(d+d_2)}{\alpha p q n d_2}, \frac{R_{0,2}-1}{n d_2 \alpha p (d+d_2)}, \frac{R_{0,2}-1}{\alpha p d v (d+d_2)})$$

where basic reproduction number

$$R_{0,2} = \frac{\alpha n d_2 \pi p q}{d d v (d+d_2)}.$$

If $V \to V^*$, then the linkage function can be expressed by

$$\beta(V) = \hat{\beta} \lim_{T \to \infty} \frac{\int_0^T V(\tau) d\tau}{T} = \hat{\beta} V^*.$$

Using the basic control number in section (3.1), we can obtain the following result

(1) If $R_{0,1} < 1$ *and* $R_{0,2} < 1$, then

$$R_c = 0.$$

(2) If $R_{0,1} > 1$ *and* $R_{0,2} < 1$, then

$$R_c = \frac{\Lambda}{\mu} \left[\frac{c_1 \hat{\beta} \frac{R_{0,1}-1}{\alpha d v (d+d_1)}}{\mu + \mu_1 + \gamma} \right].$$

(3) If $R_{0,1} > 1$ *and* $R_{0,2} > 1$, then

$$\begin{aligned} R_c &= \frac{\Lambda}{\mu} \left[\frac{c_1 \hat{\beta} \frac{R_{0,1}-1}{\alpha d v (d+d_1)}}{\mu + \mu_1 + \gamma} + \frac{c_2 \hat{\beta} \frac{R_{0,2}-1}{\alpha p d v (d+d_2)}}{\mu + \mu_2} \frac{\gamma}{\mu + \mu_1 + \gamma} \right] \\ &= \frac{\Lambda}{\mu} \left[\frac{c_1 \hat{\beta} \frac{R_{0,1}-1}{\alpha d v (d+d_1)}}{\mu + \mu_1 + \gamma} \right] + \frac{\Lambda}{\mu} \left[\frac{c_2 \hat{\beta}}{\mu + \mu_2} \frac{\gamma}{\mu + \mu_1 + \gamma} \left(\frac{n q d_2 \pi}{d d v^2 (d+d_2)^2} - \frac{1}{\alpha p d_v (d+d_2)} \right) \right]. \end{aligned}$$

Thus, the basic reproduction number of the within-host model can determine the dynamics of the between-host model, and the parameter of within-host model can also influence the between-host model. p and q are parameters of treatment, the smaller value of p, q, the better effect of treatment, the smaller of basic control number.

5 Analysis of the Model with Density-dependent Treatment

In this section, we considered the non-linear treatment strategy given by $f(I_1) = \dfrac{A}{B + I_1}$. Thus, system (2.2) becomes:

$$\begin{cases} \dfrac{dS(t)}{dt} &= \Lambda - c_1\beta_1 SI_1 - c_2\beta_2 SI_2 - \mu S, \\ \dfrac{dI_1(t)}{dt} &= c_1\beta_1 SI_1 + c_2\beta_2 SI_2 - (\mu + \mu_1)I_1 - \frac{AI_1}{B+I_1}, \\ \dfrac{dI_2(t)}{dt} &= \frac{AI_1}{B+I_1} - (\mu + \mu_2)I_2. \end{cases} \tag{5.1}$$

5.1 Disease free equilibrium *(DFE)*

5.1.1 Local stability

The model (5.1) has an DFE, obtained by setting the right hand side of equations in (5.1) to zero, given by

$$\mathcal{E}_0^1 = (S^*, I_1^*, I_2^*) = (\Lambda/\mu, 0, 0).$$

Similarly as in section 3, the local stability is obtained using the next generation matrix. We thus obtain the basic control number (of the model (5.1)) as

$$\mathcal{R}_c^1 = \frac{\Lambda}{\mu}\left[\frac{c_1\beta_1}{\mu + \mu_1 + \frac{A}{B}} + \frac{c_2\beta_2}{\mu + \mu_2}\frac{\frac{A}{B}}{\mu + \mu_1 + \frac{A}{B}}\right].$$

Hence, $\mathcal{E}_0^1$ is locally asymptotically stable in Ω whenever $\mathcal{R}_c^1 < 1$.

5.2 Existence of backward bifurcation

In this section, we investigate the existence of backward bifurcation using the theorem [11]. The epidemiological consequence of the backward bifurcation phenomenon in disease transmission models is that having the associated reproduction number of the model less than unity, while necessary, is no longer sufficient for effective disease control. In a backward bifurcation situation, effective community-wide control of the disease (when $\mathcal{R}_c < 1$) is dependent on the initial size of the sub-population of the model. Thus, backward bifurcation makes effective disease control difficult. It is instructive, therefore, to explore the possibility of backward bifurcation in the model (5.1).
We use the following Theorem to study the backward bifurcation

Theorem 5.1. *[11] Consider a system of ordinary differential equations*

$$\frac{dx}{dt} = f(x, \phi), f : R^n \times R \to R^n and\ f \in\ C^2(R^n \times R), \tag{5.2}$$

with a parameter ϕ, Assumed that:

1. *0 is an equilibrium of the system,* $f(0,\phi) \equiv 0$ *for all* ϕ*; and*

2. *Zero is a simple eigenvalue of* $A = D_x f(0,0) = (\frac{\partial f_i}{\partial x_i}(0,0))$ *and all other eigenvalues of* A *have negative real parts*

Let $W = [w_1, w_2, ...w_n]^T$ *and* $V = [v_1, v_2, ..., v_n]$ *be a right and a left eigenvector matrix A, respectively, associated to eigenvalues zero and* $f_k(x,\phi)$ *be the kth com-ponent of* $f(x,\phi)$*. Then the local dynamics of system around the equilibrium point 0 is totally determined by the signs of a and b below:*

$$\begin{aligned} a &= \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ b &= \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \end{aligned}$$

Particularly, if $a > 0$ *and* $b > 0$*, then a backward bifurcation accurs at* $\phi = 0$ *for system* (5.2)*.*

We use c_1 as the bifurcation parameter and apply Theorem (5.1) to model (5.1) to determine the bifurcation at $R_c = 1$. the left and right eigenvectors of the Jacobian matrix evaluated at the infection-free equilibrium and at $\mathcal{R}_0 = 1$ are as follows:

$$W = [-\frac{\Lambda}{\mu^2}(\frac{B}{A}c_1\beta_1(\mu+\mu_2) + c_2\beta_2), \frac{B(\mu+\mu_2)}{A}, 1]^T, V = [0,1,0].$$

Hence,

$$\begin{aligned} a &= 2\frac{(\mu+\mu_2)^2}{A} - \frac{2\Lambda}{\mu^2}\left(\frac{B}{A}c_1\beta_1(\mu+\mu_2) + c_2\beta_2\right)(c_1\beta_1 + c_2\beta_2), \\ b &= \frac{\Lambda}{\mu}\frac{B(\mu+\mu_2)}{A}\beta_1 \end{aligned}$$

Since b is always positive, it follows that the bifurcation type depends on the sign of a. It can be shown that a is positive whenever the following inequality holds:

$$\mu^2(\mu+\mu_2)^2 > \Lambda(B_1c_1\beta_1(\mu+\mu_2) + Ac_2\beta_2)(c_1\beta_1 + c_2\beta_2). \tag{5.3}$$

From Theorem (5.1), the model (5.1) undergoes a backward bifurcation at $\mathcal{R}_c = 1$ whenever the inequality (5.3) holds. We state the following results:

Theorem 5.2. *Suppose the inequality* (5.3) *holds. Then at* $\mathcal{R}_c^1 = 1$*, the model* (5.1) *has a backward bifurcation.*

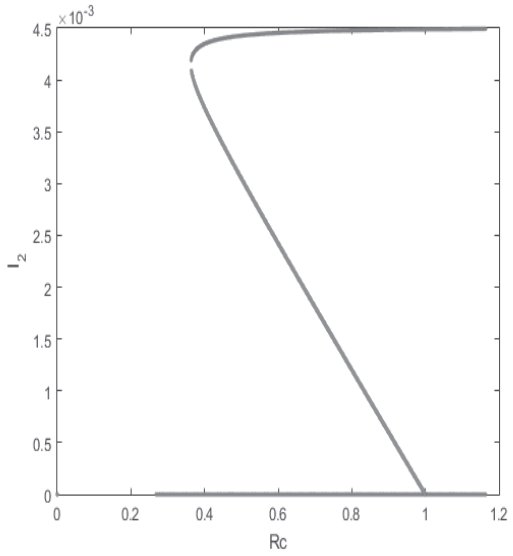

Figure 3: Backward bifurcation of parameter values set $\Lambda = 1,\ \mu = 1/30,\ \mu_1 = 1/12,\ \mu_2 = 100,\ \beta_1 = 2.5,\ \beta_2 = 9.8,\ A = 0.5,\ B = 0.5,\ c_2 = 0.5$. Blue represent stable equilibrium, red represent unstable.

5.3 Analysis of the model with different density-dependent treatment strategies

We considered the non-linear treatment strategy given by $f(I_1) = \alpha_1 + \alpha_2 e^{-\gamma I_1}$. Thus, system (2.2) becomes:

$$\begin{cases} \dfrac{dS(t)}{dt} &= \Lambda - c_1\beta_1 SI_1 - c_2\beta_2 SI_2 - \mu S, \\ \dfrac{dI_1(t)}{dt} &= c_1\beta_1 SI_1 + c_2\beta_2 SI_2 - (\mu + \mu_1)I_1 - (\alpha_1 + \alpha_2 e^{-\gamma I_1})I_1, \\ \dfrac{dI_2(t)}{dt} &= (\alpha_1 + \alpha_2 e^{-\gamma I_1})I_1 - (\mu + \mu_2)I_2. \end{cases} \tag{5.4}$$

The basic control number of model (5.4) is given by:

$$\mathcal{R}_c^* = \frac{\Lambda}{\mu}\left[\frac{c_1\beta_1}{\mu + \mu_1 + (\alpha_1 + \alpha_2)} + \frac{c_2\beta_2}{\mu + \mu_2}\frac{\alpha_1 + \alpha_2}{(\mu + \mu_2 + \alpha_1 + \alpha_2)}\right].$$

so that $\mathcal{E}_0^2$ is locally-asymptotically stable in Ω whenever $\mathcal{R}_c^* < 1$.
Similarly, the left and right eigenvectors of the another density-dependent treatment is given by :

$$W = \left[\frac{\Lambda}{\mu_1^2}\left[c_1\beta_1(\frac{\mu + \mu_1}{\alpha_1 + \alpha_2}) + \gamma\right], \frac{\mu + \mu_2}{\alpha_1 + \alpha_2}, 1\right]^T, V = [0, 1, 0].$$

Hence, the bifurcation coefficients is given as:

$$\begin{aligned} a &= 2\alpha_1\gamma\left(\frac{\mu+\mu_2}{\alpha_1+\alpha_2}\right)^2 - \frac{2\Lambda}{\mu^2}\left[c_1\beta_1(\frac{\mu+\mu_1}{\alpha_1+\alpha_2}) + c_2\beta_2\right]^2 \\ b &= \beta_1\frac{\Lambda}{\mu}\frac{\mu+\mu_2}{\alpha_1+\alpha_2}. \end{aligned}$$

Clearly, b is always positive. It can be shown that a is positive whenever the following inequality holds:

$$\alpha_1\gamma\mu^2(\mu+\mu_2)^2 > \Lambda\left[c_1\beta_1(\mu+\mu_1) + c_2\beta_2(\alpha_1+\alpha_2)\right]^2 \tag{5.5}$$

Theorem 5.3. *Suppose the inequality* (5.5) *holds or* $a > 0$. *Then at* $\mathcal{R}_c^* = 1$, *the model* (5.4) *has a backward bifurcation.*

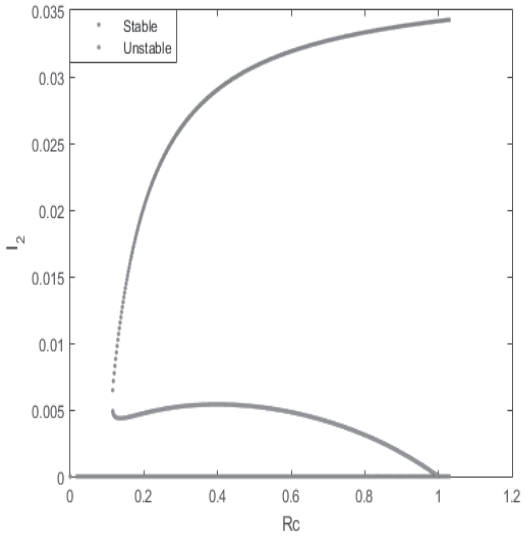

Figure 4: Backward bifurcation of the parameter values set $\Lambda = 1$, $\mu = 1/30$, $\mu_1 = 1/12$, $\mu_2 = 20$, $\beta_1 = 1.5$, $\beta_2 = 0.5$, $\gamma = 20$, $\alpha_1 = 4.8113, \alpha_2 = 0.3539, c_2 = 0.01$. Blue represent stable equilibrium, red represent unstable.

6 Parameter Estimation and Prediction

The adjusted natural death rate is 0.0213 according to[14], with the available data for the mortality data from 2008 to 2014 in China [12], we use Markov chain Monte Carlo (MCMC)

method to estimate the other parameter, which are tabulated in (1). Figure 5 shows that the model solution fits the data and the model estimate HIV/AIDS mortality of China will continue increasing if there is no change in the control strategy. Using the estimated parameter values in Table (1) and the formula [13],we are able to estimate the average prolong lifespan in China.The estimated 3.4036 years.That means the ART treatment can prolong infectious lifespan.

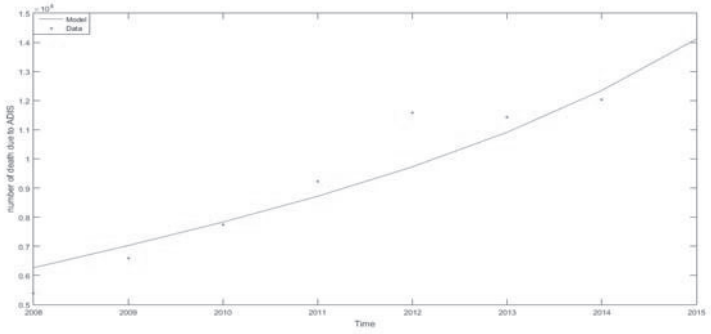

Figure 5: Data Fitting

Table 1: Estimated Parameters

Parameter	Λ	$c_1\beta_1$	$c_2\beta_2$	μ_1	μ_2	γ
Estimated value	113425.3	4.7319×10^{-7}	1.6087×10^{-8}	0.2052	0.1066	0.3181

7 Sensitivity Analysis

To assess the impact of the sensitivity of each parameter of the model (3.1) on the numerical simulation results generated, a global sensitivity analysis is carried out using Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficients (PRCC) on the basic control number $\mathcal{R}_c$ of model (3.1). Figure (6) shows $c_1, c_2, \beta_1, \beta_2$ has positive correlation to $\mathcal{R}_c$, the other parameter has negative correlation to $\mathcal{R}_c$, and the parameter c_1, β_1 and γ are the key parameters that influence $\mathcal{R}_c$ and the total number of infected individuals.

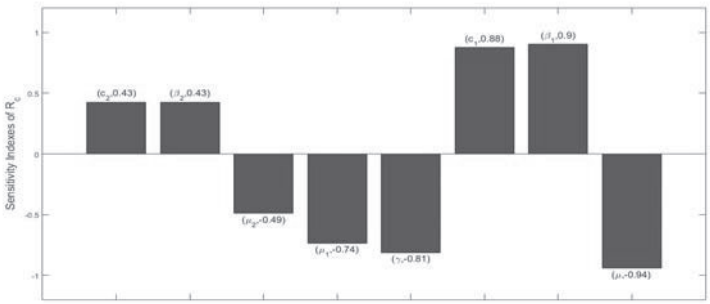

Figure 6: Sensitivity Analysis of $\mathcal{R}_c$

8 Conclusion and Discussion

In this study, we use a new deterministic mathematical model to explore how viral load variability caused by treatment can influence the prevalence of HIV in a population. We proposed two treatment strategies, density-independent/ dependent treatment. Some of the main theoretical and epidemiological findings of this study are summarized below

(1) The disease-free equilibrium of model (3.1) is globally asymptotically stable whenever the associated basic control number $\mathcal{R}_c$ is less than unity.

(2) The endemic equilibrium of model (3.1) is globally asymptotically stable whenever the associated basic control number $\mathcal{R}_c$ is bigger than unity.

(3) Under some circumstance, HIV treatments may increase the incidence of HIV.

(4) Density-dependent treatments lead to bi-stability. Thus, we do not know the outcome if we only know information on R_c. Actually, we have shown that initial values are critical to the outcomes.

(5) Micro parameters influence basic control number which can be expressed explicitly.

(6) Parameter estimation and prediction shows the following.

   (a) The average life time of HIV patients after treatment is increased by 3.4036 years.

   (b) According to the present treatment policy, if we do not make some change, the HIV/AIDS mortality of China will continue increasing.

(7) Sensitivity analysis of the model (3.1) to variability in each parameter show that

   (a) The parameter c_1, β_1 and γ are the key parameters that influence $\mathcal{R}_c$ and the total number of infected individuals.

   (b) Sensitivity analysis of model (5.4) and model (5.1) is same as model (3.1).

9 Acknowledgments

We would like to thank Dr. Carlos Castillo-Chavez, Executive Director of the Mathematical and Theoretical Biology Institute (MTBI), for giving us this opportunity to participate in this research program. We would also like to thank Summer Director Dr. Anuj Mubayi for his efforts in planning and executing the day-to-day activities of MTBI. This research was conducted in MTBI at the Simon A. Levin Mathematical, Computational and Modeling Sciences Center (SAL MCMSC) at Arizona State University (ASU). This project has been partially supported by grants from the National Science Foundation (DMS 1263374), the National Security Agency (H98230-15-1-0021), the Office of the President of ASU, and the Office of the Provost at ASU. We thank Professor Leon Arriola for his help. We thank Preston Swan and Ciera Duran for their logistic support for the program.

Symbol	Description
Variables	
S	Susceptible individuals
I_1	Untreated-infected individuals
I_2	Treated-infected individuals
T_1	Healthy targeted T-cells without treatment
T_2	Healthy targeted T-cells with treatment
T_1^*	Infected T-cells without treatment
T_2^*	Infected T-cells with treatment
V_1	Virions without treatment
V_2	Virions with treatment
Parameters	
Λ	Recruit rate
β_1	Infection rate (without treatment)
β_2	Infection rate (with treatment)
μ_1	Disease death rate of untreated people
μ_2	Disease death rate of treated people
γ	Treatment rate
π	Rate of supply of T cells from precursors
d	Nature death rate of T-cell
α	Infection rate of virus
d_i	Disease death rate of infected cells
n	No. of free virus produced by lysing a T cell
p	Treatment efficiency
q	Treatment efficiency

Table 2: Description of variables and parameters of the treatment models given by (2.1) and (2.2).

Parameter	Units	Values	References
π	$mm^{-3}day^{-1}$	20	[1]
d	day^{-1}	0.02	[3]
α	$mm^{-3}day^{-1}$	0.0002	[3]
d_i	day^{-1}	0.24	[3]
p	–	0.3	[15]
q	–	0.3	[15]

Table 3: Parameter values

References

[1] Blower, S. M., Hayley B. Gershengorn, and R. M. Grant. A tale of two futures: HIV and antiretroviral therapy in San Francisco. *Science* 287.5453 (2000): 650–654.

[2] Anderson, R. M., Mathematical studies of parasitic infection and immunity, *Science* 264 (5167)(1994): 1884–1886.

[3] Lou Jie, J.H. Wu, Li Chen, Y. Ruan, Y. Shao, A sex-role-preference model for HIV transmission among men who have sex with men in China, *BMC Public Health* 9(Suppl 1)(2009): S10.

[4] Feng, Z., Velasco-Hernandez, J., Tapia-Santos, B., Leite, M. C. A. A model for coupling within-host and between-host dynamics in an infectious disease. *Nonlinear Dynamics*,68(2012): 401–411.

[5] Ganusov, V. V., C. T. Bergstrom, R. Antia, Within-host population dynamics and the evolution of micro parasites in a heterogeneous host population,*Evolution* 56(2)(2002): 213–223.

[6] Gilchrist, M. A., A. Sasaki, Modeling host parasite co-evolution: a nested approach based on mechanistic models, *Journal of Theoretical Biology* 218(2002): 289–308.

[7] Coombs, D., Gilchrist, M.A., Ball, C.L., Evaluating the importance of within- and between-host selection pressures on the evolution of chronic pathogens. *Theoretical population biology*, 72(2007): 576–591.

[8] Sasaki, A., Iwasa, Y., Optimal growth schedule of pathogens within a host: switching between lyric and latent cycles. *Theoretical population biology* 39(1991): 201–239.

[9] Antia, R., Levin, B.R., May, R.M., Within-host population dynamics and the evolution and maintenance of parasite virulence. *The American Naturalist*, 144(1994): 457–472.

[10] Antia, R., Lipsitch, M., Mathematical models of parasite responses to host immune defenses. *Parasitology*, 115(1997): S155–S167.

[11] Castillo-Chavez, C and B. Song, Dynamical models of tuberculosis and their applications, *Mathematical Bio sciences and Engineering*, 1 (2004): 361–404.

[12] http://www.chinacdc.cn/en/

[13] Song baojun, Wen Du, Jie Lou, Different types of backward bifurcation due to density-dependent treatments, *Mathematical Biosciences and Engineering*, December(2013): 1651-1668.

[14] Lou Jie, Hongna Zhou, Dong Liang, Zhen Jin, and Baojun Song, The coupled within- and between-host dynamics in the evolution of HIV/AIDS in China.*Journal of Applied Analysis and Computation* 5. no. 4 (2015): 731–750.

[15] Perelson, Alan S. Modeling the interaction of the immune system with HIV. In Mathematical and Statistical Approaches to AIDS Epidemiology, *Springer Berlin Heidelberg*, (1989): 350–370.

[16] Nowak, Martin A., and Charles RM Bangham. Population dynamics of immune responses to persistent viruses.*Science* 272.5258 (1996): 74–79.

[17] The Ministry of Health of the People's Republic of China, China's AIDS Epidemic is Estimated in 2011, 18(1)(2012):1-5

[18] Lakshmikantham, V. and Leela, S.Differential and Integral Inequalities: Theory and Applications. *Academic Press, New York*.