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THE COUPLED WITHIN- AND BETWEEN-HOST DYNAMICS IN THE EVOLUTION OF HIV/AIDS IN CHINA*

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Abstract In this work, we develop and analyze mathematical models for the coupled within-host and between-host dynamics caricaturing the evolution of HIV/AIDS. The host population is divided into susceptible, the infected without receiving treatment and the infected receiving ART treatment in accordance with China's *Four-Free-One-Care Policy*. The within-host model is a typical ODE model adopted from literatures. The between-host model incorporates age-since-infection described by a system of integrodifferential equations. The two models are coupled via the viral load and number of CD4+ T cells of within the hosts. For the between-host model with an arbitrarily selected HIV infected individual, we focus on the analyses of the basic reproduction number $\mathcal{R}_0$ and the stabilities of equilibria. Through simulations we also find that the within-host dynamics does influence the between-host dynamics, and the nesting of within-host and between-host play a very important role in the HIV/AIDS evolution.

Keywords Within-host, between-host, nested model, HIV/AIDS.

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1. Introduction

Biological processes occur at several nested levels of organization. The importance of nested levels of biological organization is particularly apparent in the evolutionary epidemiology of infectious diseases. One of the major challenges in evolutionary biology is to understand the evolutionary causes and consequences of these levels of organization [19, 23]. Pathogens can have demographically significant effects at the level of the host population, as a result of their transmission among individuals [18, 19].

In the past decades, many mathematical models have described the immunological and epidemiological processes within their separate scales in diseases such as

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HIV, Hepatitis C and malaria. Viral and bacterial dynamic mathematical models have contributed immensely to our understanding of the within-host interaction of the pathogen with the host immune system [9, 15, 17], and these typically track the dynamics of the pathogen density as well as the state of host defense mechanisms (e.g. density of lymphocytes) over the course of an infection. Particularly, these models have been used to study rapidly mutating viruses such as HIV or hepatitis C, and to understand how the within-host dynamics affect antigenic evolution [6,9,15,17,20]. On the other hand, population-level (between-host) dynamics of many diseases have been studied by numerous articles and books [1, 13].

Recently, there have been several efforts directed toward nesting models (also called embedded models) of within-host dynamics into models of between-host dynamics when studying pathogen evolution. Nested models explicitly link dynamical processes that occur at different scales. The importance of linking mathematical immunology and mathematical epidemiology was recognized [5]. Beginning with Sasaki and Iwasa [24], researchers started to conceptually link within-host processes to between-host processes. The studies of acute infections by Antia et al. [2, 4], and Ganusov et al. [12] which included various biological aspects such as a host-immune response, host heterogeneity, and a threshold mortality function. In 2002, Gilchrist and Sasaki [10] nested a within-host model within a susceptible-infected-recovery (SIR) epidemic model. Using the similar dynamical approach, there has been considerable interest in linking within- and between-host levels of disease dynamics, such as in the study of HIV and HCV [7,18,19]. One important goal of the evolutionary epidemiology of infectious diseases is to understand how such nested processes affect the epidemiological and evolutionary dynamics of host-pathogen interactions.

One of our specific goals is to study the HIV evolutionary epidemiology in both individual and population levels in China. It has come to our attention that HIV infected patients in China are receiving free treatments (through "Four-Free-One-Care Policy" program) on combined antiretroviral therapy which includes mainly reverse transcriptase inhibitors (RTIs) provided by the government. One can read from the Manuals for National AIDS Antiviral Treatment for Free in China [25] that the treatments are based on current availability of antiviral drugs. Accordingly, we distinguish HIV infected patients by the number of CD4+ T cells whether it is greater than 350/ml or less than 350/ml, as this value is a criterion in Chinese guidelines for initiating antiretroviral therapy (ART). For the MSM (men who have sex with men) population, it is reasonable that a certain proportion of infected MSM whose CD4+ T cell less than 350/ml will receive ART treatment offered by the China's Four-Free-One-Care Policy.

In this paper, we develop a coupled within- (immunological) and between-host (epidemiological) dynamic model of HIV/AIDS. We first introduce an ordinary differential system of HIV dynamics within an infected host. We then consider an age-structured between-host HIV/AIDS model to describe the dynamics of host birth and death and the transmission of HIV/AIDS within the host population. We nest the within-host model within the epidemiological model by linking the dynamics of the within-host model to the additional host mortality, treatment rate, and transmission rate of the infection. The developed multi-scale model of HIV describes the joint affections of the immunological process and the SIA epidemiological process, which linked through age-since-infection and through the epidemiological parameters which depend on the within-host viral load and number of CD4+ T

cells. We theoretically analyze our mathematical models. Simulations further show the influence of the within-host dynamics on the between-host dynamics.

This paper is organized as follows. In Section 2 we build the two models. In Section 3 we carry out a series analyses, main focus on the derivation of the basic reproduction number $\mathcal{R}_0$ and the stabilities of disease-free steady state. In Section 4 we discuss the existence of endemic stationary steady state and its stability. Finally, Section 5 is devoted to elucidating the connection between within-host viral dynamics and the epidemiology of HIV through extensive simulations based on massive parameter estimations.

2. The coupled within- and between-host model of HIV

2.1. A within-host model of HIV

First, we introduce a simple within-host (immunological) model. The work in literature [21] examined a model for the interaction of HIV with CD4+ T cells that considers four populations: uninfected T cells, latently infected T cells, actively infected T cells, and free virus. From their model, some puzzling quantitative features of HIV infection were explained. Here, we adapt the model in [21] for our within-host model of HIV. The model reads

$$\begin{cases} \dfrac{dT(\tau)}{d\tau} = s - \mu_T T(\tau) + rT(\tau)\left(1 - \dfrac{T(\tau)+T^*(\tau)+T^{**}(\tau)}{T_{max}}\right) - k_1 T(\tau)V(\tau), \\ \dfrac{dT^*(\tau)}{d\tau} = k_1 T(\tau)V(\tau) - \mu_T T^*(\tau) - k_2 T^*(\tau), \\ \dfrac{dT^{**}(\tau)}{d\tau} = k_2 T^*(\tau) - \mu_b T^{**}(\tau), \\ \dfrac{dV(\tau)}{d\tau} = N\mu_b T^{**}(\tau) - k_1 T(\tau)V(\tau) - \mu_V V(\tau), \\ T(0) = T_0 > 0, T^*(0) = T_0^* \geq 0, T^{**}(0) = T_0^{**} \geq 0, V(0) = V_0 > 0. \end{cases} \tag{2.1}$$

In system (2.1), $T(\tau)$ is the concentration of uninfected T cell population along with the time τ changing; $T^*(\tau)$ is the concentration of latently infected T cell population; $T^{**}(\tau)$ is the concentration of actively infected T cell population size, and $V(\tau)$ is the concentration of HIV population. The biological meaning of each parameter can be found in Table 1. We do not give explanation here. System (2.1) exhibits two steady states, an uninfected state in which no virus is present and an endemically infected state, in which virus and infected T cells are present. Chose parameter N, the number of infectious virus produced per actively infected T cell, as the critical parameter and define

$$N_{crit} = \frac{(k_2 + \mu_T)(\mu_V + k_1 T_0)}{k_1 k_2 T_0},$$

where T_0 is the initial value of variable T. If $N < N_{crit}$, then the uninfected state is the only steady state in the nonnegative orthant, and this state is stable. For $N > N_{crit}$, the uninfected state is unstable and the endemically infected state can be either stable, or unstable and surrounded by a stable limit cycle. For details of more theory results one can find in literature [21].

Initial values $T(0)$, $T^*(0)$, $T^{**}(0)$, and $V(0)$ in the within-host model (2.1) are critical in the model since an infected individual is characterized by these initial values as we can see in the between-host models.

2.2. A between-host model of HIV

We now introduce an epidemiological model of HIV spread in population. We denote by $S(t)$ the number of susceptible human individuals, where t is the chronological time. We structure the infected individuals by age-since-infection τ . Let $i(t,\tau)$ be the density of individuals infected by HIV at time $t-\tau$ and $i_A(t,\tau)$ be the density of individuals who are infected by HIV at time $t-\tau$ and receive ART at time t. We suppose that susceptible hosts join the system (through birth or immigration) at a fixed rate of Λ individuals/time and die at a fixed rate of d per time. Infected individuals randomly contact susceptibles and new infections are generated at a transmission rate $\beta(\tau)$. We emphasize that the transmission rate changes with the age of the infection τ. After infected by HIV, some HIV positive individuals will receive ART therapy at rate $\gamma(\tau)$. Along to the "Four-Free-One-Care Policy" in China, it is reasonable to assume that the therapy rate is a function of the CD4+ T cells in HIV positive individual. Finally, infected individuals are subject to additional mortality due to the infection, at a time dependent rate $\alpha_I(\tau)$ and $\alpha_A(\tau)$ respectively.

The dynamics is thus described by the system of integrodifferential equations

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - dS(t) - \dfrac{S(t)}{N(t)} \displaystyle\int_0^\infty \beta(\tau)[i(t,\tau) + \varepsilon i_A(t,\tau)]d\tau, \\ \left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial \tau}\right) i(t,\tau) = -\gamma(\tau)i(t,\tau) - \alpha_I(\tau)i(t,\tau), \\ i(t,0) = \dfrac{S(t)}{N(t)} \displaystyle\int_0^\infty \beta(\tau)[i(t,\tau) + \varepsilon i_A(t,\tau)]d\tau, \\ \left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial \tau}\right) i_A(t,\tau) = \gamma(\tau)i(t,\tau) - \alpha_A(\tau)i_A(t,\tau), \\ i_A(t,0) = 0, \end{cases} \tag{2.2}$$

where $N(t) = S(t) + \displaystyle\int_0^\infty [i(t,\tau) + i_A(t,\tau)]d\tau$.

Here, we assume that all susceptible individuals have approximately the same equilibrium level of healthy CD4+ T cells.

2.3. Model linkage

It is reasonable to suppose that the viral load of the transmitting host should affect the rate at which it releases infectious inocula and, in turn, the probability of a successful transmission of an inoculum per host-host interaction. So here we suppose that the transmission rate of an infection should be an increasing function of viral load, i.e., the transmission coefficient of HIV $\beta(\tau)$ is dependent on the within-host viral load. We may assume that $\beta(\tau)$ is proportional to the Hill function of viral load $V(\tau)$ at a given age-since-infection τ:

$$\beta(\tau) = \beta_0 \rho(V(\tau)) = \beta_0 \left(\frac{V(\tau)}{V(\tau) + \Omega}\right). \tag{2.3}$$

Hill function has been used in describing the effect of immunization for long time [3, 14].

$\gamma(\tau)$ is the rate of treatment for HIV positive individuals. Along to the "Four-Free-One- Care Policy", it is reasonable to assume that

$$\gamma(\tau) = \begin{cases} \gamma_0 & \text{for} \quad T(\tau) + T^*(\tau) + T^{**}(\tau) \leq 350, \\ 0 & \text{for} \quad T(\tau) + T^*(\tau) + T^{**}(\tau) > 350. \end{cases} \tag{2.4}$$

Furthermore, the infected hosts die at a variable rate dependent on their viral load or the concentration of CD4+ T cells at $\alpha_I(\tau)$ and $\alpha_A(\tau)$ for HIV positive individuals and these who receive ART respectively. Here we assume them be the piecewise functions as follows:

$$\alpha_I(\tau) = \begin{cases} \alpha_{I0} & \text{for} \quad T(\tau) + T^*(\tau) + T^{**}(\tau) < 350, \\ d & \text{for} \quad T(\tau) + T^*(\tau) + T^{**}(\tau) \geq 350, \end{cases} \tag{2.5}$$

and

$$\alpha_A(\tau) = \begin{cases} \alpha_{A0} & \text{for} \quad T(\tau) + T^*(\tau) + T^{**}(\tau) < 350, \\ d & \text{for} \quad T(\tau) + T^*(\tau) + T^{**}(\tau) \geq 350. \end{cases} \tag{2.6}$$

Systems (2.1) and (2.2) are provided with the following initial conditions:

$$\begin{aligned} &T(0) = T_0, \quad T^*(0) = T_0^*, \qquad T^{**}(0) = T_0^{**}, \qquad V(0) = V_0, \\ &S(0) = S_0, \quad i(0,\tau) = i^0(\tau), \quad i_A(0,\tau) = i_A^0(\tau). \end{aligned} \tag{2.7}$$

In the next section we will compute explicit expressions for the equilibria of system (2.2) and will establish their local stability.

3. Analysis

A fundamental analysis to the adopted model (2.1) was done by Perelson et al. [21]. Treating the linkage function (2.3) as an input to model (2.2) and making use of the known results in [21], we can analyze model (2.2), thus dealing with a lower dimensional system. That is, when analyzing the between-host model (2.2) is a known function. However, the linkages $\beta(\tau), \gamma(\tau), \alpha_I(\tau), \alpha_A(\tau)$ are all associated with a specific set of HIV infected individuals identified by the same initial values T_0, T_0^*, T_0^{**} and V_0. i.e., we will analyze model (2.2) for an arbitrarily selected HIV infected individual.

We first here introduce the following three shortcuts and give their biological meanings.

(a) $\pi_1(\tau) = e^{-\int_0^\tau (\gamma(\sigma)+\alpha_I(\sigma))d\sigma}$ is the probability that an infected individual who receives ART survives up to age-since-infection τ.

(b) $\pi_2(\tau) = e^{-\int_0^\tau [\alpha_A(\sigma)]d\sigma}$ is the probability that an infected individual who does not receive ART survives up to age-since-infection τ.

(c) $\pi_3(\tau, u) = \frac{\pi_2(\tau)}{\pi_2(u)} = \frac{e^{-\int_0^\tau \alpha_A(\sigma)d\sigma}}{e^{-\int_0^u \alpha_A(\sigma)d\sigma}} = e^{-\int_u^\tau \alpha_A(\sigma)d\sigma}$ is the conditional probability that an infected individual who does not receive ART survives from u to τ of age-since-infection given that the individual has survived up to age-since-infection u.

3.1. The basic reproduction number

The disease-free steady state to system (2.2) is $\varepsilon_0 = (S_0^*, 0, 0)$ with $S_0^* = N_0^* = \frac{\Lambda}{d}$. We consider the local stability of the disease-free equilibrium; and in the process we can find the basic reproductive number. First, we derive the linearized equations about the disease-free equilibrium. To introduce the linearization at the disease-free steady state ε_0, we first make a shift $S(t) = S_0^* + x(t)$, $i(t,\tau) = z(t,\tau)$, $i_A(t,\tau) = z_A(t,\tau)$, and $N(t) = N_0^* + n(t)$. Then the linearized system of system (2.2) about the disease-free steady state ε_0 is:

$$\begin{cases} \dfrac{dx(t)}{dt} = -dx(t) - \dfrac{S_0^*}{N_0^*}\displaystyle\int_0^\infty \beta(\tau)[z(t,\tau) + \varepsilon z_A(t,\tau)]d\tau, \\ \left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial \tau}\right) z(t,\tau) = -\gamma(\tau)z(t,\tau) - \alpha_I(\tau)z(t,\tau), \\ z(t,0) = \dfrac{S_0^*}{N_0^*}\displaystyle\int_0^\infty \beta(\tau)[z(t,\tau) + \varepsilon z_A(t,\tau)]d\tau, \\ \left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial \tau}\right) z_A(t,\tau) = \gamma(\tau)z(t,\tau) - \alpha_A(\tau)z_A(t,\tau), \\ z_A(t,0) = 0. \end{cases} \tag{3.1}$$

To determine the stability of the trivial steady state of system (3.1), we look for solutions of the form $x(t) = xe^{\lambda t}$, $z(t,\tau) = z(\tau)e^{\lambda t}$ and $z_A(t,\tau) = z_A(\tau)e^{\lambda t}$. This gives us the following eigenvalue problem:

$$\begin{cases} \lambda x = -dx - \dfrac{S_0^*}{N_0^*}\displaystyle\int_0^\infty \beta(\tau)[z(\tau) + \varepsilon z_A(\tau)]d\tau, \\ \dfrac{dz(\tau)}{d\tau} = -[\lambda + \gamma(\tau) + \alpha_I(\tau)]z(\tau), \\ z(0) = \dfrac{S_0^*}{N_0^*}\displaystyle\int_0^\infty \beta(\tau)[z(\tau) + \varepsilon z_A(\tau)]d\tau, \\ \dfrac{dz_A(\tau)}{d\tau} = -[\lambda + \alpha_A(\tau)]z_A(\tau) + \gamma(\tau)z(\tau), \\ z_A(0) = 0. \end{cases} \tag{3.2}$$

The solution to the second differential equation in (3.2) is

$$z(\tau) = z(0)e^{-\lambda\tau}\pi_1(\tau). \tag{3.3}$$

Replacing $z(\tau)$ by equation (3.3) in the fourth differential equation in (3.2), we arrive at

$$\frac{dz_A(\tau)}{d\tau} = -[\lambda + \alpha_A(\tau)]z_A(\tau) + \gamma(\tau)z(0)e^{-\lambda\tau}\pi_1(\tau). \tag{3.4}$$

Solving (3.4) by the method of constant variation, we obtain that

$$z_A(\tau) = e^{-\lambda\tau}\pi_2(\tau)\left(\int_0^\tau \gamma(\tau)z(0)\frac{\pi_1(\tau)}{\pi_2(\tau)}d\tau + C_0\right),$$

with $z_A(0) = C_0 = 0$. Finally, we have a closed form for $z_A(\tau)$, given by

$$z_A(\tau) = e^{-\lambda\tau}\pi_2(\tau)\int_0^\tau \gamma(\tau)z(0)\frac{\pi_1(\tau)}{\pi_2(\tau)}d\tau. \tag{3.5}$$

Substituting (3.3) and (3.5) in the third equation in (3.2), we have

$$z(0) = \frac{S_0^*}{N_0^*} \int_0^\infty \beta(\tau)[z(0)e^{-\lambda\tau}\pi_1(\tau) + \varepsilon e^{-\lambda\tau}\pi_2(\tau) \int_0^\tau \gamma(\tau)z(0)\frac{\pi_1(\tau)}{\pi_2(\tau)}d\tau]d\tau.$$

Noticing that $\frac{S_0^*}{N_0^*} = 1$, we obtain the following characteristic equation:

$$G(\lambda) = 1,$$

where

$$G(\lambda) = \int_0^\infty \beta(\tau)[e^{-\lambda\tau}\pi_1(\tau) + \varepsilon e^{-\lambda\tau}\pi_2(\tau) \int_0^\tau \gamma(\tau)\frac{\pi_1(\tau)}{\pi_2(\tau)}d\tau]d\tau.$$

$G(0)$ is used to define the basic reproduction number of infected individuals. That is,

$$\mathcal{R}_0 = \int_0^\infty \beta(\tau)\left(\pi_1(\tau) + \varepsilon \int_0^\tau \gamma(u)\pi_1(u)\pi_3(\tau,u)du\right)d\tau. \tag{3.6}$$

3.2. The stability of disease-free steady state

We have the following theorem.

Theorem 3.1. *Consider model* (2.2)*. If* $\mathcal{R}_0 < 1$*, then the disease-free equilibrium* ε_0 *is locally asymptotically stable. Otherwise, it is unstable.*

Proof. Letting $A(\tau) = \beta(\tau)\pi_1(\tau)$ and $B(\tau) = \varepsilon\beta(\tau)\int_0^\tau \gamma(u)\pi_1(u)\pi_3(\tau,u)du$, we rewrite $G(\lambda)$ as

$$G(\lambda) = \int_0^\infty e^{-\lambda\tau}[A(\tau) + B(\tau)]d\tau.$$

Suppose $\mathcal{R}_0 < 1$. Assume that $\lambda = a + bi$ is a complex solution of $G(\lambda) = 1$ with $a \geq 0$. Then

$$\begin{aligned}
|G(\lambda)| =& \mid \int_0^\infty e^{-\lambda\tau}[A(\tau) + B(\tau)]d\tau \mid \\
\leq& \mid \int_0^\infty e^{-(a+bi)\tau}A(\tau)d\tau \mid + \mid \int_0^\infty e^{-(a+bi)\tau}B(\tau)d\tau \mid \\
=& \int_0^\infty \mid e^{-(a+bi)\tau} \mid A(\tau)d\tau + \int_0^\infty \mid e^{-(a+bi)\tau} \mid B(\tau)d\tau \\
=& \int_0^\infty e^{-a\tau}A(\tau)d\tau + \int_0^\infty e^{-a\tau}B(\tau)d\tau \\
=& G(a) \leq G(0) = \mathcal{R}_0 < 1.
\end{aligned}$$

Hence, the equation $G(\lambda) = 1$ has solutions with only negative real part and the disease-free equilibrium is locally asymptotically stable.

When $\mathcal{R}_0 > 1$, for fixed λ real, we have $G(0) = \mathcal{R}_0 > 1$. Furthermore,

$$\lim_{\lambda\to\infty} G(\lambda) = 0.$$

Hence, the equation $G(\lambda) = 1$ has a real positive root. Therefore, the disease-free equilibrium is unstable. □

4. The endemic stationary steady state and its stability

4.1. The existence of endemic stationary steady state

To find the endemic stationary steady state $\varepsilon^* = (S^*, i^*(\tau), i_A^*(\tau))$, we have to solve the following system:

$$\begin{cases} \Lambda - dS^* - \dfrac{S^*}{N^*}\displaystyle\int_0^\infty \beta(\tau)[i^*(\tau) + \varepsilon i_A^*(\tau)]d\tau = 0, \\ \dfrac{di^*(\tau)}{d\tau} = -\gamma(\tau)i^*(\tau) - \alpha_I(\tau)i^*(\tau), \\ i^*(0) = \dfrac{S^*}{N^*}\displaystyle\int_0^\infty \beta(\tau)[i^*(\tau) + \varepsilon i_A^*(\tau)]d\tau, \\ \dfrac{di_A^*(\tau)}{d\tau} = \gamma(\tau)i^*(\tau) - \alpha_A(\tau)i_A^*(\tau), \\ i_A^*(0) = 0. \end{cases} \tag{4.1}$$

Solving the second differential equation in system (4.1), we obtain

$$i^*(\tau) = i^*(0)\pi_1(\tau). \tag{4.2}$$

Replacing $i^*(\tau)$ in the fourth differential equation in (4.1) by (4.2), we obtain

$$\frac{di_A^*(\tau)}{d\tau} = -\alpha_A(\tau)i_A^*(\tau) + \gamma(\tau)i^*(0)\pi_1(\tau). \tag{4.3}$$

Solving (4.3) by the method of constant variation, we get

$$i_A^*(\tau) = \pi_2(\tau)\left(\int_0^\tau \gamma(\tau)i^*(0)\frac{\pi_1(\tau)}{\pi_2(\tau)}d\tau + C_0\right)$$

with $C_0 = i_A^*(0) = 0$.

So we have

$$i_A^*(\tau) = \pi_2(\tau)\int_0^\tau \gamma(\tau)i^*(0)\frac{\pi_1(\tau)}{\pi_2(\tau)}d\tau. \tag{4.4}$$

Substituting N^* by $S^* + \int_0^\infty i_1^*(\tau)d\tau + \int_0^\infty i_A^*(\tau)d\tau$ in the third equation in (4.1), we get

$$i^*(0) = \frac{S^*}{S^* + \int_0^\infty i_1^*(\tau)d\tau + \int_0^\infty i_A^*(\tau)d\tau}\int_0^\infty \beta(\tau)[i^*(\tau) + \varepsilon i_A^*(\tau)]d\tau,$$

which can be rewritten as:

$$\frac{\frac{S^*}{i^*(0)}}{\frac{S^*}{i^*(0)} + \int_0^\infty \frac{i^*(\tau)}{i^*(0)}d\tau + \int_0^\infty \frac{i_A^*(\tau)}{i^*(0)}d\tau}\int_0^\infty \beta(\tau)\left[\frac{i^*(\tau)}{i^*(0)} + \varepsilon\frac{i_A^*(\tau)}{i^*(0)}\right]d\tau = 1. \tag{4.5}$$

For simplicity, let

$$\int_0^\infty \frac{i^*(\tau)}{i^*(0)}d\tau = \rho_1, \qquad \int_0^\infty \frac{i_A^*(\tau)}{i^*(0)}d\tau = \rho_2.$$

It is easy to check that

$$\int_0^\infty \beta(\tau)\left[\frac{i^*(\tau)}{i^*(0)}+\varepsilon\frac{i_A^*(\tau)}{i^*(0)}\right]d\tau=\mathcal{R}_0.$$

Substituting above relations in equation (4.5), we can rewrite the equation (4.5) in the following form:

$$\frac{S^*\mathcal{R}_0}{S^*+(\rho_1+\rho_2)i^*(0)}=1. \tag{4.6}$$

Since

$$\Lambda-dS^*-i^*(0)=0 \tag{4.7}$$

and considering both (4.6) and(4.7), we get

$$\begin{aligned} S^*&=\frac{\Lambda(\rho_1+\rho_2)}{\mathcal{R}_0-1+d(\rho_1+\rho_2)},\\ i^*(0)&=\frac{\Lambda(\mathcal{R}_0-1)}{\mathcal{R}_0-1+d(\rho_1+\rho_2))}. \end{aligned} \tag{4.8}$$

Then from equations (4.2), (4.4) and (4.8) we get

$$i^*(\tau)=\frac{\Lambda(\mathcal{R}_0-1)}{\mathcal{R}_0-1+d(\rho_1+\rho_2))}\pi_1(\tau)$$

and

$$i_A^*(\tau)=\frac{\Lambda(\mathcal{R}_0-1)}{\mathcal{R}_0-1+d(\rho_1+\rho_2))}\pi_2(\tau)\int_0^\tau\gamma(\tau)\frac{\pi_1(\tau)}{\pi_2(\tau)}d\tau.$$

Therefore, there is a unique endemic equilibrium $\varepsilon^*=(S^*,i^*(\tau),i_A^*(\tau))$ when the basic reproduction number $\mathcal{R}_0>1$.

4.2. The stability of endemic stationary steady state

Now we consider the local stability of the endemic equilibrium ε^*. First we derive the linearized equations of ε^*. Let

$$\begin{aligned} &S(t)=S^*+x(t), && i(t,\tau)=z(t,\tau)+i^*(\tau),\\ &i_A(t,\tau)=z_A(t,\tau)+i_A^*(\tau), && N(t)=N^*+n(t). \end{aligned}$$

Then the linearized system at the endemic equilibrium ε^* is:

$$\begin{cases} \dfrac{dx(t)}{dt} = -dx(t) + \dfrac{S^*}{N^*}\dfrac{n(t)}{N^*}\displaystyle\int_0^\infty \beta(\tau)[i^*(\tau) + \varepsilon i_A^*(\tau)]d\tau \\ \qquad\qquad - \dfrac{S^*}{N^*}\displaystyle\int_0^\infty \beta(\tau)[z(t,\tau) + \varepsilon z_A(t,\tau)]d\tau \\ \qquad\qquad - \dfrac{x(t)}{N^*}\displaystyle\int_0^\infty \beta(\tau)[i^*(\tau) + \varepsilon i_A^*(\tau)]d\tau, \\ \left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial \tau}\right) z(t,\tau) = -\gamma(\tau)z(t,\tau) - \alpha_I(\tau)z(t,\tau), \\ z(t,0) = -\dfrac{S^*}{N^*}\dfrac{n(t)}{N^*}\displaystyle\int_0^\infty \beta(\tau)[i^*(\tau) + \varepsilon i_A^*(\tau)]d\tau \\ \qquad\qquad + \dfrac{S^*}{N^*}\displaystyle\int_0^\infty \beta(\tau)[z(t,\tau) + \varepsilon z_A(t,\tau)]d\tau \\ \qquad\qquad + \dfrac{x(t)}{N^*}\displaystyle\int_0^\infty \beta(\tau)[i^*(\tau) + \varepsilon i_A^*(\tau)]d\tau, \\ \left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial \tau}\right) z_A(t,\tau) = \gamma(\tau)z(t,\tau) - \alpha_A(\tau)z_A(t,\tau), \\ z_A(t,0) = 0. \end{cases}$$

We look for solutions of the form $x(t) = xe^{\lambda t}$, $z(t,\tau) = z(\tau)e^{\lambda t}$, $z_A(t,\tau) = z_A(\tau)e^{\lambda t}$, and $n(t) = ne^{\lambda t}$. Then we obtain the following eigenvalue problem:

$$\begin{cases} \lambda x = -dx + \dfrac{S^*}{N^*}\dfrac{n}{N^*}\displaystyle\int_0^\infty \beta(\tau)[i^*(\tau) + \varepsilon i_A^*(\tau)]d\tau \\ \qquad - \dfrac{S^*}{N^*}\displaystyle\int_0^\infty \beta(\tau)[z(\tau) + \varepsilon z_A(\tau)]d\tau \\ \qquad - \dfrac{x}{N^*}\displaystyle\int_0^\infty \beta(\tau)[i^*(\tau) + \varepsilon i_A^*(\tau)]d\tau, \\ \dfrac{dz(\tau)}{d\tau} = -[\lambda + \gamma(\tau) + \alpha_I(\tau)]z(\tau), \\ z(0) = -\dfrac{S^*}{N^*}\dfrac{n}{N^*}\displaystyle\int_0^\infty \beta(\tau)[i^*(\tau) + \varepsilon i_A^*(\tau)]d\tau \\ \qquad + \dfrac{S^*}{N^*}\displaystyle\int_0^\infty \beta(\tau)[z(\tau) + \varepsilon z_A(\tau)]d\tau \\ \qquad + \dfrac{x}{N^*}\displaystyle\int_0^\infty \beta(\tau)[i^*(\tau) + \varepsilon i_A^*(\tau)]d\tau, \\ \dfrac{dz_A(\tau)}{d\tau} = -[\lambda + \alpha_A(\tau)]z_A(\tau) + \gamma(\tau)z(\tau), \\ z_A(0) = 0. \end{cases} \tag{4.9}$$

Solving the second differential equation in (4.9), we obtain

$$z(\tau) = z(0)e^{-\lambda\tau}\pi_1(\tau). \tag{4.10}$$

Replacing $z(\tau)$ in the fourth differential equation in (4.9) by equation (4.10), we have

$$\frac{dz_A(\tau)}{d\tau} = -[\lambda + \alpha_A(\tau)]z_A(\tau) + \gamma(\tau)z(0)e^{-\lambda\tau}\pi_1(\tau). \tag{4.11}$$

Solving (4.11) by the method of constant variation, we obtain

$$z_A(\tau) = e^{-\lambda\tau}\pi_2(\tau)\left(\int_0^\tau \gamma(\tau)z(0)\frac{\pi_1(\tau)}{\pi_2(\tau)}d\tau + C_0\right)$$

with $z_A(0) = C_0 = 0$. So we have

$$z_A(\tau) = e^{-\lambda\tau}\pi_2(\tau)\int_0^\tau \gamma(\tau)z(0)\frac{\pi_1(\tau)}{\pi_2(\tau)}d\tau.$$

We adopt the following notations

$$\rho(\lambda) = \int_0^\infty [e^{-\lambda\tau}\pi_1(\tau) + e^{-\lambda\tau}\pi_2(\tau)\int_0^\tau \gamma(\tau)\frac{\pi_1(\tau)}{\pi_2(\tau)}d\tau]d\tau,$$
$$\mathcal{R}_0(\lambda) = \int_0^\infty \beta(\tau)[e^{-\lambda\tau}\pi_1(\tau) + \varepsilon e^{-\lambda\tau}\pi_2(\tau)\int_0^\tau \gamma(\tau)\frac{\pi_1(\tau)}{\pi_2(\tau)}d\tau]d\tau.$$

From the first and third equation in Equation (4.9), we obtain $\lambda x = -Z_1(0) - \mathrm{d}x$. Therefore,

$$x = -\frac{Z_1(0)}{\lambda + \mathrm{d}}. \tag{4.12}$$

Linearizing the equation for the total population size

$$N = S + \int_0^\infty i(t,\tau)\mathrm{d}\tau + \int_0^\infty i_A(t,\tau)\mathrm{d}\tau,$$

we obtain

$$n = x + \int_0^\infty z(\tau)\mathrm{d}\tau + \int_0^\infty z_A(\tau)\mathrm{d}\tau. \tag{4.13}$$

Substituting equations (4.12) and (4.13) in the first equation of system (4.9), and then cancelling $z_1(0)$ from both sides of the resulting equation, we obtain the following characteristic equation for $\lambda : H(\lambda) = 1$, where

$$H(\lambda) = -\frac{1}{\lambda + d}\cdot\frac{i^*(0)}{N^*}\cdot\mathcal{R}_0\cdot\left[1 - \frac{S^*}{N^*}\right] + \frac{S^*}{N^*}\mathcal{R}_0(\lambda) - \frac{S^*}{N^*}\cdot\rho(\lambda)\cdot\frac{i^*(0)}{N^*}\cdot\mathcal{R}_0. \tag{4.14}$$

Note that

$$\frac{S^*}{N^*} = \frac{1}{\mathcal{R}_0}, \qquad \frac{i^*(0)}{N^*} = \frac{\mathcal{R}_0 - 1}{\mathcal{R}_0(\rho_1 + \rho_2)}.$$

Substituting above relations in equation (4.14) we can rewrite the characteristic equation in the following form:

$$\frac{\mathcal{R}_0(\lambda)}{\mathcal{R}_0} = 1 + \frac{i^*(0)}{\lambda + d}\cdot\left[\frac{1}{S^*} - \frac{1}{N^*}\right] + \frac{\mathcal{R}_0 - 1}{\mathcal{R}_0(\rho_1 + \rho_2)}\cdot\rho(\lambda).$$

For λ with $\Re\lambda \geq 0$ we have

$$\left|\frac{\mathcal{R}_0(\lambda)}{\mathcal{R}_0}\right| \leq 1.$$

On the other hand, the following inequality holds since $\mathcal{R}_0 > 1$:

$$\left|1 + \frac{i^*(0)}{\lambda + d} \cdot \left[\frac{1}{S^*} - \frac{1}{N^*}\right] + \frac{\mathcal{R}_0 - 1}{\mathcal{R}_0(\rho_1 + \rho_2)} \cdot \rho(\lambda)\right| > 1.$$

Hence, for λ with $\Re\lambda \geq 0$, the characteristic equation $H(\lambda) = 1$ has only solutions with negative real parts. Thus, the equilibrium ε^* is locally asymptotically stable. This concludes the existence of stationary steady state. We collect this discussion in the following theorem

For the existence and stability of the endemic equilibrium, we have the following Theorem :

Theorem 4.1. *When $\mathcal{R}_0 > 1$, one unique endemic stationary steady state ε^* exists and it is locally asymptotically stable. When $\mathcal{R}_0 < 1$, there is not an endemic stationary steady state.*

5. Simulations

Using the data of men who have sex with men (MSM) in Beijing of 2010 as initial values, we present some simulations in this section. The observed HIV prevalence rates among MSM in Beijing is 7.8% in 2010 [16]. In order to set the initial conditions, we have to estimate the target population of MSM living in Beijing in 2010. The national census in 2010 [26] showed that the population data for Beijing is about 19 million. 51.6% of them are male and 82.7% of them were of 15 years to 65 years. We suppose 3% of males in Beijing in 2005 are MSM, of which 86% live in the city [26]. Also, we suppose that 20% of HIV infected MSM accepted ART in 2010. For simplicity, we suppose the initial values of i and i_A ($i^0(\tau)$ and $i_A^0(\tau)$) follow uniform distribution. But as a comparison, we will show that there is no big difference if $i^0(\tau)$ and $i_A^0(\tau)$ follow normal distribution. The relative infectiousness of ART MSM_+ to non-ART MSM_+ has several quite different values [11, 22]. ART can reduce HIV transmission from 60% [22] to 99% [11]. Here we choose $\varepsilon = 0.4$. For threshold constant of Hill function, we choose the highest concentration of HIV virus during the infection in *vivo* to be the value of Ω. A summary of the parameter values used in this paper is given in Table 1.

We, however, have to honestly say that choosing parameter values in vivo situation is very difficult. Many of the parameters in our model have not been measured. For those parameters, we borrow the similar ones from literature [21]. A list of the parameter values used in this paper is shown in Tables 1, 2 and 3. But nevertheless we believe that other sets of parameters can give similar outcomes.

To study the time course of the infection, we numerically integrate system (1) and (2). For the within-host system (1) we choose initial conditions of an uninfected individual; $T(0) = 1000, T^*(0) = T^{**}(0) = 0$, infected with free virus, $V(0) = V_0$. Here we consider the case of exposure to one infectious virion per milliliter, which corresponds to $V_0 = 10^{-3}$ mm^{-3} [21]. For parameter values in *vivo* in Table 1 and Table 2, the infected steady state is stable. In parameter regimes where the infected state is unstable, the system undergoes sustained oscillations around the infected state. The parameter regime of oscillations is necessarily different from that in Table 1 and Table 2. Table 3 gives the default parameters used in our study of oscillations. We study the influence of behaviors of the within-host system in

Table 1. Parameters of the within-host model and the between-host model

Paras	Description	Values
s	Rate of supply of T cells from precursors	$10/day/mm^3$
r	Rate of growth for the T cell population	0.03/day
T_{max}	Maximum T cell population level	$1500/mm^3$
μ_T	Death rate of uninfected and latently infected T cells	0.02/day
μ_b	Death rate of actively infected T cells	0.24/day
μ_V	Death rate of free virus	2.4/day
k_1	Rate constant for T cells becoming infected	2.4×10^{-5} $/day/mm^3$
k_2	Rate latently T cells convert to actively infected	3×10^{-2}/day
N	No. of free virus produced by lysing a T cell	1500
Λ	Recruitment rate into target population per year	4318/year
d	Natural removal rate of MSM- per year	0.0213/year
ε	The reduction of infectivity due to ART	0.4
β_0	Probability of transmission	0.27
α_{I0}	Death rate of infected MSM	0.1786/year
α_{A0}	Death rate of ART MSM	0.0893/year
γ_0	ART rate of MSM+	0.3
Ω	Threshold constant of Hill function	12560

Table 2. Parameters for polymodal curve

Paras	Description	Values
s	Rate of supply of T cells from precursors	$1/day/mm^3$
N	No. of free virus produced by lysing a T cell	1000
β_0	Probability of transmission	0.07
Ω	Threshold constant of Hill function	2500

Table 3. Parameters for oscillations

Paras	Description	Values
r	Rate of growth for the T cell population	12/day
μ_T	Death rate of uninfected and latently infected T cells	0.06/day
μ_V	Death rate of free virus	5/day
k_1	Rate constant for T cells becoming infected	$3.2/day/mm^3$
k_2	Rate latently T cells convert to actively infected	1.2×10^{-4}/day
N	No. of free virus produced by lysing a T cell	1200
β_0	Probability of transmission	34
Ω	Threshold constant of Hill function	32

these regimes to the between-host system by numerical integration, using Matlab R008b.

Three kinds of dynamics of the nested models are shown. In Figure 1, HIV infection dynamics in *vivo* (the left figure) and HIV prevalence among MSM (the

right figure). Parameters are given in Table 1. $\mathcal{R}_0 = 1.371$ under this situation. The left figure shows the free virus population and CD4+ T cells in *vivo* versus infection time and the right figure shows the HIV prevalence in MSM population versus time. The free virus population in *vivo* shows a single peak. Along with this trend in *vivo*, HIV prevalence among MSM population arrives a steady state in a simple way, regardless of $i^0(\tau)$ and $i_A^0(\tau)$ follow uniform distribution or follow normal distribution (the shape parameter $\sigma = 30$ and the location parameter $\mu = 5$ year). Since the dynamics has very small difference regardless of $i^0(\tau)$ and $i_A^0(\tau)$ follow uniform distribution or follow normal distribution, so in this section we suppose i and i_A follow uniform distribution for simplicity.

Figure 2 shows a multi-peak situation in *vivo*. Along with the oscillation of the dynamics in *vivo*, HIV prevalence in MSM population shocks rise to the steady state. Parameter values are chosen from Table 2 and the reproduction number $\mathcal{R}_0 = 1.429$ under this situation. As a special situation, figure 3 shows the osicillatory behavior in *vivo* (the left subfigure), which leads to a strong shocks of the HIV prevalence in MSM population (the right subfigure). But amplitudes of curves in MSM population increase first and then decrease along with time. $\mathcal{R}_0 = 1.428$ under this situation.

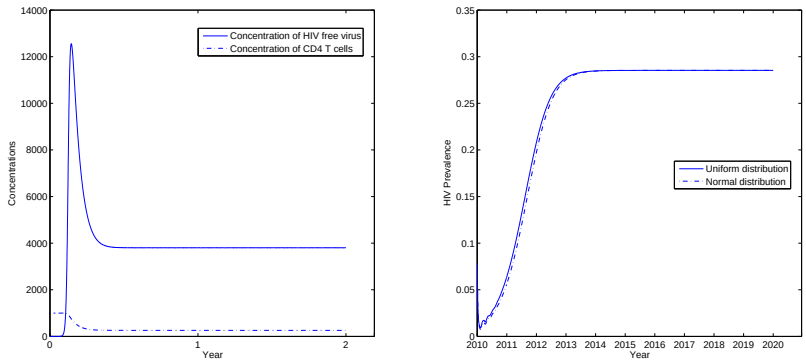

Figure 1. Dynamics of HIV infection in *vivo* (the left figure) and HIV prevalence in MSM (the right figure) under uniform distribution and normal distribution respectively. Parameters are given in Table 1.

To show more influence of the within-host dynamics to the between-host dynamics, we plot the relation of $\mathcal{R}_0$ (Figure 4) along with the parameters k_1 and N (the left-above figure), s and μ_v (the right-above figure); N and the initial value of virus V_0 (the left-bottom figure) ; β_0 (in *vitro*) and N (the right-bottom figure) respectively. It is obvious that parameters in *vivo* have directly effect to the reproduction number $\mathcal{R}_0$ in population level. From the left-above figure of Figure 4 we find that $\mathcal{R}_0$ increases along with the increase of k_1 (and N). On the other hand, the right-above figure of Figure 4 shows that $\mathcal{R}_0$ increases along with the increase of s and decreases along with the increase of μ_v and the initial value of HIV virus V_0 (the left-bottom figure). As a comparison, Figure 5 shows that the HIV prevalence increases with k_1 and the HIV initial values in *vivo*, V_0, respectively, which is consistent with the relations of reproduction number $\mathcal{R}_0$ and k_1 and V_0 respectively. In short words, the epidemiological reproduction number and the prevalence are sensitive to the within-host parameters.

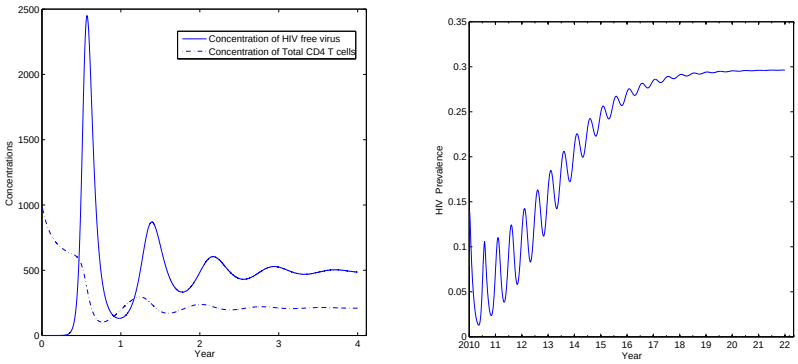

Figure 2. Dynamics of HIV infection in *vivo* (the left figure) and HIV prevalence in MSM (the right figure) shown by polymodal curve. Parameters are given in Table 2.

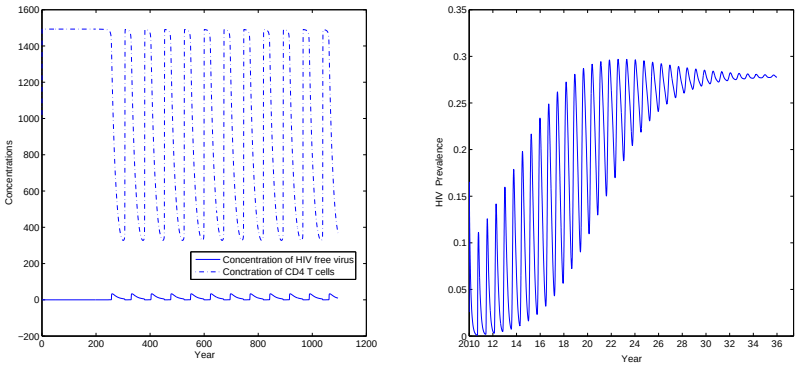

Figure 3. Dynamics of the systems with parameters set in the oscillatory region given in Table 3 (the left figure) and HIV prevalence in MSM population versus time (the right figure).

6. Discussion

Linking different scales of biological organization with nested models has recently paid more attention, focusing on nesting a model of within-host dynamics into a model of between-host epidemiological dynamics. In this paper, we developed a nested dynamical models in the evolution of HIV/AIDS in China. Our main objective is to evaluate whether or not the nesting of models has been important in developing our understanding of HIV/AIDS evolution. As we have seen, our answer is a qualified 'yes'. Plotting the epidemiological reproduction number against each within-host parameter reveals that the reproduction number is a monotone function of the parameter when the remaining parameters are fixed as in Table 1. Also, the dependence of the HIV prevalence on each immunological parameter is also monotone when the remaining parameters are fixed at values listed in Table 1. As shown in the right figure in Figure 1, there is no big difference in results when $i^0(\tau)$ and $i_A^0(\tau)$ follow uniform distribution or follow normal distribution. Also, we find

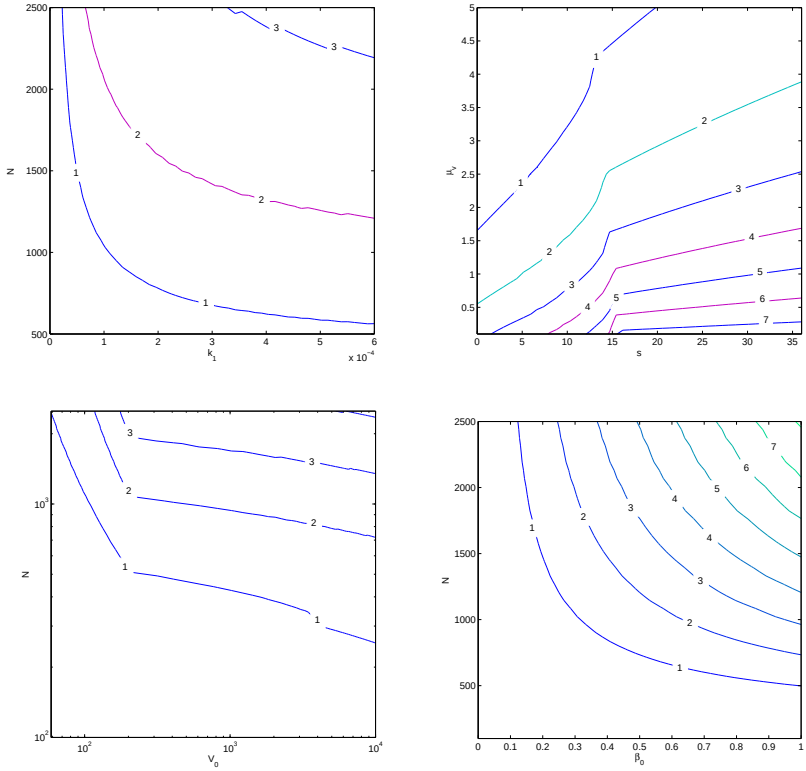

Figure 4. The relation of R_0 along with the parameters k_1 and N (the left-above figure); s and μ_v (the right-above figure); N and V_0 (the left-bottom figure) and β_0 (in *vitro*) and N (the right-bottom figure) change in *vivo* respectively. Other parameters are chosen in Table 1.

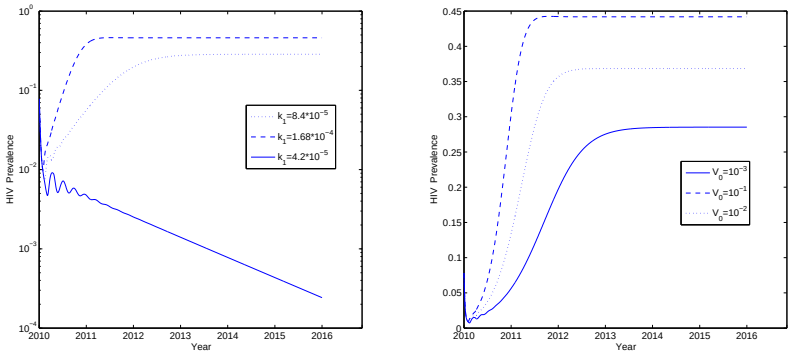

Figure 5. HIV prevalence vs. the infection rate of blood T cells k_1 and initial virus V_0 respectively. HIV prevalence increases with increased infection rate k_1 and viral load V_0.

without surprise that HIV total prevalence is increasing with increasing k_1, which is consistent with the relation of reproduction number $\mathcal{R}_0$ and k_1. On the contrary in literature [18], authors state that increasing infection rate in vivo decreases the HIV prevalence in vitro. It is also explained in [18] that this phenomenon,indeed, captured the trade-off between treatment in vivo and prevalence in HIV. But we do not observe this result in our model.

A model in which nesting is essential is one whereby there is reciprocal feedback between levels of organization. The nesting of models will be essential for studying the evolution of diseases in which the inoculum size affects the progression of the disease, because this will likely lead to a reciprocal feedback between within- and between-host dynamics. Unfortunately, our model consider only within-host dynamics influencing between-host processes but not vice versa. Until now, we have no a clear idea about how to consider the reciprocal feedback of HIV evolution.

Since the linkages are determined by a specific set of HIV infected individuals identified by T_0, T_0^*, T_0^{**} and V_0, functions $\beta(\tau)$, $\gamma(\tau)$, $\alpha_I(\tau)$, and $\alpha_A(\tau)$ vary as the initial values change.Consequently, (6.1) varies with T_0, T_0^*, T_0^{**} and V_0. When substituting the linkages into between-host model from the within-host model, we automatically consider the epidemiological behavior of $(T_0, T_0^*, T_0^{**}, V_0)$-type of HIV infected individuals. Therefore, (6.1) finds the basic reproductive number for these specific infected individuals, but it is not for a *typical* HIV infected individual because the initial values are not allowed to change. If these values can be varied, one has to find the *expected* value for $\mathcal{R}_0(T_0, T_0^*, T_0^{**}, V_0)$. Ideally, given that $F(T_0, T_0^*, T_0^{**}, V_0)$ is the joint probability distribution of T_0, T_0^*, T_0^{**}, and V_0, then the basic reproductive number is given by

$$\tilde{\mathcal{R}}_0 = \int_0^\infty \int_0^\infty \mathcal{R}_0(T_0, T_0^*, T_0^{**}, V_0) \mathrm{d}F(T_0, T_0^*, T_0^{**}, V_0).$$

Unfortunately, models (2.1) and (2.2) cannot access to any information about joint probability distribution $F(T_0, T_0^*, T_0^{**}, V_0)$. We, however, can avoid this difficulty by considering models (2.1) and (2.2) as a whole system, thus getting rid of the restrictions from the arbitrary fixed initial conditions. Using the common used approach, we will linearize the whole system about a disease-free steady state. That is, if one wants to get rid of the joint probability distribution of T_0, T_0^*, T_0^{**}, and V_0, one has to collectively linearize model (2.1) and (2.2) at a proper steady state. By virtue of dynamical behaviors of system (2.1), it is enough to deai with the following three interesting cases.

6.1. Virus have not established within hosts

If the virus does not establish within hosts, we linearize system (2.1-2.2) about the steady state $\left(\frac{s}{\mu_T}, 0, 0, 0, \frac{\Lambda}{d}, 0, 0\right)$. We pay a closed attention to that since $\beta(\tau)[i(t,\tau) + \varepsilon i_A(t,\tau)]$ are non-linear terms, they will be dropped in the linearized equations. Repeat the exact same computation in our derivation for $\mathcal{R}_0(T_0, T_0^*, T_0^{**}, V_0)$, we end up $\mathcal{R}_0(T_0, T_0^*, T_0^{**}, V_0) = 0$; and hence, $\mathcal{R}_0 = 0$. The biological meaning of this case is extremely trivial that the disease cannot establish in population level if virus cannot establish themselves within hosts.

6.2. Virus have established in an endemic equilibrium

Our work advances current research on $\mathcal{R}_0$ for the coupled within-host and between-host dynamical models by distinguishing a individual infection and the set of all infections.

If the virus within hosts has established in an endemic equilibrium $(T_\infty, T_\infty^*, T_\infty^{**}, V_\infty)$, we linearize system (2.1-2.2) about the steady state $\left(T_\infty, T_\infty^*, T_\infty^{**}, V_\infty, \frac{\Lambda}{d}, 0, 0\right)$.

In this case, the linkage becomes $\beta(\tau) = \frac{\beta_0 V_\infty}{V_\infty + \Omega}$. We linearize system (2.1-2.2) about the steady state $\left(T_\infty, T_\infty^*, T_\infty^{**}, V_\infty, \frac{\Lambda}{d}, 0, 0\right)$. Again, a completely similar manipulation to our computation for $\mathcal{R}_0$ in subsection 3.1 gives us the expression for the basic reproduction number, which is given by

$$\tilde{\mathcal{R}}_0 = \int_0^\infty \frac{\beta_0 V_\infty}{V_\infty + \Omega} \left(\pi_1(\tau) + \varepsilon \int_0^\tau \gamma(u)\pi_1(u)\pi_3(\tau, u)du \right) d\tau. \tag{6.1}$$

$\int_0^\infty \frac{\beta_0 V_\infty}{V_\infty + \Omega} \pi_1(\tau)d\tau$ is the expected secondary cases produced by a typical HIV infected individual who does not receive ART during the entire infection life. Similarly, $\int_0^\infty \frac{\beta_0 V_\infty}{V_\infty + \Omega} \varepsilon \int_0^\tau \gamma(u)\pi_1(u)\pi_3(\tau, u)du d\tau$ is the expected secondary cases produced by the typical HIV infected individual who does receive ART during the entire infection life. The sum of this two gives us the basic reproductive number for the coupled within-host and between host dynamical model (2.1-2.2).

Since CD4+ T cells and virus evolve much faster than HIV spreads between hosts, system (2.1) and system (2.2) have distinct time scales. Hence we can soundly assume that system (2.1) has already stabilized around the endemic steady state when studying the coupled dynamics. Then (6.1) is the proper the expression for the basic reproduction number. In this work, the basic reproduction number (6.1), if changes in the initial values $(T_0, T_0^*, T_0^{**}, V_0)$ are allowed, is a proper one.

Following the approach of next generation operator [8], if we set $\beta(\tau)$, $\gamma(\tau)$, $\alpha_I(\tau)$, $\alpha_A(\tau)$ all to be respective constants, formula (6.1) reduce to $\frac{\beta}{\gamma + \alpha_I} + \frac{\beta\gamma\varepsilon}{\alpha_A(\gamma + \alpha_I)}$. This is exactly the same R_0 for the reduced between-host model (without incorporating age-since-infection).

6.3. Virus have established in a sustainable oscillation

The third dynamical behavior of system (2.1) is the appearance of a stable periodic trajectory. For this case we are also be able to find the basic reproductive number for the coupled system (2.1) and (2.2). Let $(T_p(\tau), T_p^*(\tau), T_p^{**}(\tau), V_p(\tau))$ be the stable periodic solution to system (2.1). To find the basic reproduction number, we linearize system (2.1-2.2) about the stable periodic solution. Applying the same approach used in subsection 3.1 and setting $\beta(\tau) = \frac{\beta_0 V_p(\tau)}{V_p(\tau) + \Omega}$, we find the basic reproductive number is

$$\tilde{\mathcal{R}}_0 = \int_0^\infty \frac{\beta_0 V_p(\tau)}{V_p(\tau) + \Omega} \left(\pi_1(\tau) + \varepsilon \int_0^\tau \gamma(u)\pi_1(u)\pi_3(\tau, u)du \right) d\tau.$$

Acknowledgments

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