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Threshold virus dynamics with impulsive antiretroviral drug effects

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Abstract The purposes of this paper are twofold: to develop a rigorous approach to analyze the threshold behaviors of nonlinear virus dynamics models with impulsive drug effects and to examine the feasibility of virus clearance following the *Manuals of National AIDS Free Antiviral Treatment in China*. An impulsive system of differential equations is developed to describe the within-host virus dynamics of both wild-type and drug-resistant strains when a combination of antiretroviral drugs is used to induce instantaneous drug effects at a sequence of dosing times equally spaced while drug concentrations decay exponentially after the dosing time. Threshold parameters are derived using the basic reproduction number of periodic epidemic models, and are used to depict virus clearance/persistence scenarios using the theory of asymptotic periodic systems and the persistence theory of discrete dynamical systems. Numerical simulations using model systems parametrized in terms of the antiretroviral therapy recommended in the aforementioned *Manuals* illustrate the theoretical threshold virus dynamics, and examine conditions under which the impulsive antiretroviral therapy leads to treatment success. In particular, our results show that only the drug-resistant strain can dominate (the *first-line treatment program* guided by the *Manuals*) or both strains may be rapidly eliminated (the *second-line treatment program*), thus the work indicates the importance of implementing the *second-line treatment program* as soon as possible.

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1 Introduction

Current antiretroviral HIV/AIDS therapy involves the simultaneous administration of two or more antiviral drugs, typically chosen from two major classes: reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) (Smith and Wahl 2005; Wahl and Nowak 2000). RTIs block the translation of viral RNA into DNA for incorporation into the host genome, thus preventing the infection of new cells. In contrast, PIs interfere with essential steps of protein cleavage in new virions, thus preventing infected cells from producing infectious viral particles (Janeway et al. 2001).

The *Manuals of National AIDS Free Antiviral Treatment in China* (http://www.chinaids.org.cn/n16/n1657/n32880.files/n32881.pdf) recommends the treatment should be based on antiviral drugs currently available in the country. The *first-line treatment* program includes three antiviral drugs: two kinds of Nucleoside reverse transcriptase inhibitors (NRTIs) and one Non-nucleoside reverse transcriptase inhibitors (NNRTs). Protease inhibitors, just in the beginning stages of production, are not expected to be put into widespread use and are expected to be incorporated into *the second-line treatment* program only after the appearance of drug resistance to the first-line drugs (http://www.chinaids.org.cn/n16/n1657/n32880.files/n32881.pdf). It is important to develop appropriate mathematical models to evaluate if therapies under either the first-line or the second-line program can lead to treatment success.

One challenge for such an evaluation arises due to the emergence of drug resistance. As a result of high mutation and replication rates as well as the host selection pressures, human immuno-deficiency virus type-1 (HIV-1) diversifies during the course of infection (Fisher et al. 1988). Strains that are resistant to one or several antiviral drugs have increased in frequency and patients can become infected with resistant virus, contributing to ineffective antiretroviral therapies. Insights into HIV dynamics in vivo have been obtained from mathematical modeling (see e.g., Nowak and May 2000; Perelson and Nelson 1999). Competition models have been formulated in the context of the dynamics of virus-host interactions over the last two decades (Berry and Nowak 1994; Frost and McLean 1994; Korthals Altes and Jansen 2000; McLean and Nowak 1992; Rong et al. 2007; Smith and Wahl 2004, 2005; Wahl and Nowak 2000). These models have embedded the knowledge on the possible dynamics of HIV-1 infection into relatively complex systems of non-linear differential equations, and have been successfully used to investigate the implications of different hypotheses for HIV dynamics through numerical simulations and some analytic studies. Relevant to our study here are the works (Smith and Wahl 2004, 2005), where impulsive differential equations are used to model the temporal evolution of drug concentrations during HIV-1 therapy using both RTIs and PIs. These works classify different regimes under the assumption of negligible, intermediate or high drug efficacy, and conclude that decreasing the interval between doses is more effective than increasing the dose

to control viral load. Relevant to our study here is also the work (Lou et al. 2009) where two therapy strategies (the *drugs perfect adherence strategy* and the *drugs therapy breaks strategy*) are modeled and simulated for the post exposure prophylaxis to HIV-1 exposure.

Our primary goal of this study is to investigate emergence of drug resistance during the course of different treatment programs in the setting guided by the aforementioned *Manuals*. A system of ordinary differential equations is employed to describe the virus dynamics, while the antiviral drug effects are characterized as nonlinear functions of drug concentrations in plasma. Assuming that the drug effects are instantaneous at dosing time and drug concentrations decay exponentially after the dosing time, we obtain impulsive differential equations (Lakshmikantham et al. 1989) to account for the time-varying drug concentrations in plasma. Since the time-courses of drug concentrations is dynamic, the antiviral effects are time-varying, which makes the model a non-autonomous system. Such a system is asymptotically periodic once the dose time interval is fixed, and thus the well-developed theory of periodic epidemic systems and the persistence theory of discrete dynamical systems are natural candidates of technical tools, which we will utilize to develop a systematic approach to qualitatively analyze the dynamical behaviors of such a complex impulsive differential system.

In mathematical epidemiology, periodic models are always formulated to account for impacts of seasonal environmental drivers on host-pathogen interactions, such as seasonal changes in host social behavior and contact rates, variation in encounters with infection stages, annual pulses of host births and deaths, changes in host immune defense systems and periodic vaccinations (Altizer et al. 2006; Grassly and Fraser 2006). Some general theoretical tools are developed to analyze these resultant periodic models, see Hess (1991) and Zhao (2003) for examples. Two popular techniques to address the disease dynamics in a periodic environment are the basic reproduction ratio derivation and persistence analysis. The basic reproduction ratio is defined as the expected number of secondary infections arising from a single individual during his or her entire infectious period, in a population of susceptibles (Anderson and May 1991; Diekmann and Heesterbeek 2000). This ratio may be derived by using the survival function method or the next generation method (Heffernan et al. 2005). For an autonomous ordinary differential system, the next generation matrix (Diekmann et al. 2010; van den Driessche and Watmough 2002) is an easy way to proceed. Recent developed theories in the literature (Bacaër and Guernaoui 2006; Bacaër 2007; Wang and Zhao 2008) can be adapted to define the basic reproduction ratio for periodic models in different scenarios, such as influenza pandemic (Bacaër and Ait Dads 2011), malaria (Lou and Zhao 2010), tuberculosis (Liu et al. 2010), hantavirus infection (Wesley et al. 2010) and so on. The persistence theory addresses the long-term survival of the pathogen in a system, and is developed mathematically for autonomous systems (for example Freedman and Moson 1990; Thieme 1993) and nonautonomous systems (see for example Magal and Zhao 2005; Thieme 1999, 2000). A recent monograph (Smith and Thieme 2011) by Smith and Thieme serves as a great review for the mathematical theory of persistence. This theory usually implies that the disease remains endemic when the basic reproduction ratio is greater than unity, see (Liu et al. 2010; Lou and Zhao 2010; Nakata and Kuniya 2010; Samanta 2010; Zhang and Teng 2007) for its applications to nonautonomous epidemic systems. Our study seems to be the first

attempt in applying the persistence theory of periodic epidemic systems to addressing the threshold virus dynamics with impulsive antiretroviral drug effects.

The rest of this paper is organized as follows. The next section presents the mathematical model and derives antiviral effects corresponding to the first-line and the second-line treatment programs in China. The basic reproduction numbers and mathematical analysis are established in Sects. 3 and 4 for both cases where drug treatment is either absent or used. Designed numerical simulations based on calculated effects of different drug combinations are illustrated in Sect. 5. A discussion section on the implications of the results completes the paper.

2 Model formulation

2.1 The model

Our model is a modified version of the virus dynamics model in Bonhoeffer et al. (1997), McLean and Nowak (1992) and Perelson et al. (1996) with specific consideration of the current HIV/AIDS treatment programs guided by the *Manuals of National AIDS Free Antiviral Treatment in China*.

We study the temporal dynamics of both the wild-type (i.e., drug sensitive) strain (V_w), and the drug-resistant strain (V_r). We assume that, during the course of wild-type viral replication, virus variants that are resistant to the drug arise at a certain rate, and we ignore mutations from the drug-resistant strain back to the wild-type (Wodarz and Lloyd 2004). We will consider the case where drugs may lose their intended effect to some degree for the drug-resistant strain.

Let T denote the number of the susceptible cells, I_w and I_r be numbers of the cells infected with the drug-sensitive virus and cells infected with the drug-resistant virus, V_w and V_r represent the respective concentrations of wild and drug-resistant virus. The virus dynamics is described by the following system of ordinary differential equations:

$$\begin{cases} \dfrac{dT(t)}{dt} = \lambda - \mu T(t) - \beta_w H_{rt}^w(t) T(t) V_w(t) - \beta_r H_{rt}^r(t) T(t) V_r(t), \\ \dfrac{dI_w(t)}{dt} = q\beta_w H_{rt}^w(t) T(t) V_w(t) - \alpha_w I_w(t), \\ \dfrac{dI_r(t)}{dt} = (1-q)\beta_w H_{rt}^w(t) T(t) V_w(t) + \beta_r H_{rt}^r(t) T(t) V_r(t) - \alpha_r I_r(t), \\ \dfrac{dV_w(t)}{dt} = p n_w H_p^w(t) \alpha_w I_w(t) - \mu_w V_w(t), \\ \dfrac{dV_r(t)}{dt} = (1-p) n_w H_p^w(t) \alpha_w I_w(t) + n_r H_p^r(t) \alpha_r I_r(t) - \mu_r V_r(t). \end{cases} \tag{1}$$

This model assumes that the susceptible cells are produced at a constant rate λ from a pool of precursor cells, and die at the constant rate μ. Susceptible cells become infected at rates $\beta_w H_{rt}^w(t) T(t) V_w(t)$ and $\beta_r H_{rt}^r(t) T(t) V_r(t)$ by sensitive and resistant virus respectively, where β_w and β_r characterize the infectivity of drug-sensitive and drug-resistant virus strains, $H_{rt}^w(t)$ and $H_{rt}^r(t)$ describe the effects of reverse transcriptase inhibitors on the wild-type and drug-resistant strains. We assume that $\beta_w > \beta_r$, so

the wild-type virus is more infectious than the drug-resistant strain in the absence of the drug (Wahl and Nowak 2000). We assume that during the course of wild-type viral-cell infection, virus variants that are resistant to the drug arise with probability $(1-q)$. In this model, α_w and α_r denote the death rates of the two different kinds of the infected cells respectively. Virions V_w and V_r are assumed to be cleared at rates μ_w and μ_r by the immune system, but are also assumed to be generated by the two types of the infected cells at rates $n_w\alpha_w$ and $n_r\alpha_r$, respectively, with $n_w\alpha_w \geq n_r\alpha_r$, i.e., the drug-sensitive virus is assumed to have higher replication rate (Korthals Altes and Jansen 2000). We further assume that drug-resistant variants arise with probability $(1-p)$ during the course of wild-type viral replication. The effects of protease inhibitors for wild-type and drug-resistant strains are characterized by $H_p^w(t)$ and $H_p^r(t)$, respectively.

2.2 The general functions for drug-effects

Recall that drug effects are described by the time-varying parameters $H_{rt}^w(t)$, $H_p^w(t)$, $H_{rt}^r(t)$ and $H_p^r(t)$. The subscript "rt" indicates reverse transcriptase inhibitors which block the translation of viral RNA into DNA for incorporation into the host genome, thus preventing the infection of new cells. In contrast, the subscript "p" denotes protease inhibitors which interfere with essential steps of protein cleavage in new virions, thus preventing infected cells from producing infectious viral particles (Janeway et al. 2001). As noted earlier, the superscripts "w" and "r" reflect the wild-type virus and drug-resistant virus, respectively.

We now describe these time varying parameters. Assuming that drugs are taken at time t_k and the effects of drugs are instantaneous. Therefore, we follow Smith and Wahl (2005) and describe the evolution of drug concentration by impulsive differential equations. At the dosing time $t = t_k$, the drug concentration for a specific drug is

$$D(t_k^+) = D(t_k^-) + D^i, \tag{2}$$

where D^i is the drug dosage used. Under the Chinese HIV/AIDS treatment program, the drug D can be Zidovudine (AZT), Lamivudine (3TC), Nevirapine (NVP) or ritonavir (RTV). For $t \neq t_k$, the drug concentration is governed by

$$\frac{dD(t)}{dt} = -gD(t), \quad t \neq t_k, \tag{3}$$

where g is the rate at which the drug D is cleared.

In this paper, we suppose that the drugs are taken every τ period and no dose is missed, reflecting regular dosing periods. Therefore, $t_{k+1} - t_k = \tau$ for any $k \geq 1$. In this case, we can see that

$$D(t_k^+) = \sum_{j=1}^{k} e^{-g(j-1)\tau} D^i = D^i \frac{1-e^{-gk\tau}}{1-e^{-g\tau}}.$$

Hence, $\lim_{k\to\infty} D(t_k^+) = D^i/(1-e^{-g\tau})$ and the drug concentration is asymptotic to the following $\tau-$periodic function:

$$\widetilde{D}(t) = e^{-gt(mod\ \tau)} \frac{D^i}{1 - e^{-g\tau}},$$

where $t(mod\ \tau)$ gives the modulus after division (t/τ).

We now describe the anti-viral effect coefficients ($H^w_{rt}(t)$, $H^w_p(t)$, $H^r_{rt}(t)$ and $H^r_p(t)$) corresponding to two different treatment programs in China.

2.2.1 First-line treatment program

According to the Manuals of National AIDS Free Antiviral Treatment in China (http://www.chinaids.org.cn/n16/n1657/n32880.files/n32881.pdf), the main first-line program for adults and adolescents living with AIDS (except for women who take nevirapine to prevent mother to child transmission) consists of:

$$AZT + 3TC + NVP,\ twice\ a\ day.$$

Therefore, we have

$$H^w_{rt}(t) = H^{AZT}_{rtw}(t) H^{3TC}_{rtw}(t) H^{NVP}_{rtw}(t)$$

and

$$H^r_{rt}(t) = H^{AZT}_{rtr}(t) H^{3TC}_{rtr}(t) H^{NVP}_{rtr}(t),$$

where $H^{AZT}_{rtw}(t)$, $H^{3TC}_{rtw}(t)$, $H^{NVP}_{rtw}(t)$, $H^{AZT}_{rtr}(t)$, $H^{3TC}_{rtr}(t)$ and $H^{NVP}_{rtr}(t)$ are the time-courses of the antiviral effect for the respective drug. Following Wahl and Nowak (2000), we suppose that antiviral effects of drugs can be described by the following Hill functions:

$$\begin{aligned}
H^{AZT}_{rtw}(t) &= \frac{(\Theta^w_{AZT})^{m_{AZT}}}{(\Theta^w_{AZT})^{m_{AZT}} + (D_{AZT}(t))^{m_{AZT}}},\\
H^{AZT}_{rtr}(t) &= \frac{(\Theta^r_{AZT})^{m_{AZT}}}{(\Theta^r_{AZT})^{m_{AZT}} + (D_{AZT}(t))^{m_{AZT}}},\\
H^{3TC}_{rtw}(t) &= \frac{(\Theta^w_{3TC})^{m_{3TC}}}{(\Theta^w_{3TC})^{m_{3TC}} + (D_{3TC}(t))^{m_{3TC}}},\\
H^{3TC}_{rtr}(t) &= \frac{(\Theta^r_{3TC})^{m_{3TC}}}{(\Theta^r_{3TC})^{m_{3TC}} + (D_{3TC}(t))^{m_{3TC}}},\\
H^{NVP}_{rtw}(t) &= \frac{(\Theta^w_{NVP})^{m_{NVP}}}{(\Theta^w_{NVP})^{m_{NVP}} + (D_{NVP}(t))^{m_{NVP}}},\\
H^{NVP}_{rtr}(t) &= \frac{(\Theta^r_{NVP})^{m_{NVP}}}{(\Theta^r_{NVP})^{m_{NVP}} + (D_{NVP}(t))^{m_{NVP}}},
\end{aligned}$$

where $D_{AZT}(t)$, $D_{3TC}(t)$ and $D_{NVP}(t)$ are the drug concentrations of the three drugs in plasma. Θ^w_{AZT}, Θ^w_{3TC} and Θ^w_{NVP} are the corresponding drug concentration which inhibits drug-sensitive viral replication by 50%, and Θ^r_{AZT}, Θ^r_{3TC} and Θ^r_{NVP} are the

corresponding drug concentration which inhibits drug-resistant viral replication by 50%. Parameter m with a suitable subindex for the specific drug is the slope parameter which is mathematically analogous to the Hill coefficient, a measure of cooperativity in the binding of multiple ligands to linked binding sites (Shen et al. 2008).

Note that $H_p^w(t) = H_p^r(t) \equiv 1$ in the first-line treatment program since protease inhibitors are not included. We remark also that when only one drug is taken, the concentration of other drugs is zero and the anti-viral effects can be computed in a similar way.

2.2.2 Second-line treatment program

One of the recommended second-line treatment programs for adults and adolescents living with AIDS is

$$TDF + 3TC + PI/RTV, \ once\ a\ day,$$

where TDF is the abbreviation of tenofovir disoproxil fumarate and PI/RTV is a protease inhibitor plus ritonavir. This program is recommended for patients without taking drug resistance testing. In areas where drug resistance testing is feasible, the combination of drugs should be changed based on the test results.

For the aforementioned second-line program, we will use the following anti-viral effects:

$$\begin{aligned} H_{rt}^w(t) &= H_{rtw}^{TDF}(t)H_{rtw}^{3TC}(t), \quad H_{rt}^r(t) = H_{rtr}^{TDF}(t)H_{rtr}^{3TC}(t), \\ H_p^w(t) &= H_{pw}^{RTV}(t), \quad H_p^r(t) = H_{pr}^{RTV}(t), \end{aligned}$$

where

$$\begin{aligned} H_{pw}^{RTV}(t) &= \frac{(\Theta_{RTV}^w)^{m_{RTV}}}{(\Theta_{RTV}^w)^{m_{RTV}} + (D_{RTV}(t))^{m_{RTV}}}, \\ H_{pr}^{RTV}(t) &= \frac{(\Theta_{RTV}^r)^{m_{RTV}}}{(\Theta_{RTV}^r)^{m_{RTV}} + (D_{RTV}(t))^{m_{RTV}}}, \end{aligned}$$

with terms self-explained, similar to what we used for the first-line treatment program.

3 Viral dynamics in the absence of treatment

In the absence of drugs, $H_{rt}^w(t) = H_{rt}^r(t) = H_p^w(t) = H_p^r(t) \equiv 1$ and system (1) reduces to an autonomous differential system, i.e., model coefficients are constant. The system has an infection free equilibrium, $E_0 = (\lambda/\mu, 0, 0, 0, 0)$, where two viral strains are absent. Following the "next-generation matrix" method (see Diekmann et al. 1990; van den Driessche and Watmough 2002), we obtain the basic reproduction number $\mathcal{R}_0 = \max\{\mathcal{R}_0^w, \mathcal{R}_0^r\}$ with $\mathcal{R}_0^w = pqn_w\lambda\beta_w/(\mu\mu_w)$ and $\mathcal{R}_0^r = n_r\lambda\beta_r/(\mu\mu_r)$. The numbers $\mathcal{R}_0^w$ and $\mathcal{R}_0^r$ are the basic reproduction numbers of the wild-type strain and drug-resistant strain, respectively. In the next two subsections, we briefly discuss how these reproduction numbers predict the viral dynamics.

3.1 Equilibria

System (1) has three possible equilibria: (i). the disease-free equilibrium $E_0 = (\lambda/\mu,\ 0,\ 0,\ 0,\ 0)$, which always exists; (ii). The drug-resistance equilibrium

$$E_r = \left(\frac{\mu_r}{n_r\beta_r},\ 0,\ \frac{\lambda n_r\beta_r - \mu\mu_r}{n_r\alpha_r\beta_r},\ 0,\ \frac{\lambda n_r\beta_r - \mu\mu_r}{\beta_r\mu_r}\right),$$

which exists if and only if $\mathcal{R}_0^r > 1$; and (iii). the coexistence equilibrium $E^* = (T^*, I_w^*, I_r^*, V_w^*, V_r^*)$ with $I_w^* > 0$ and $V_w^* > 0$, which exists if and only if $\mathcal{R}_0^w > 1$ and $\mathcal{R}_0^w > \mathcal{R}_0^r$. The coexistence equilibrium $(T^*, I_w^*, I_r^*, V_w^*, V_r^*)$, if exists, is given by

$$\begin{aligned}
T^* &= \frac{\mu_w}{n_w pq\beta_w},\\
I_w^* &= \frac{(n_w pq\beta_w\lambda - \mu\mu_w)(n_w pq\beta_w\mu_r - n_r\beta_r\mu_w)}{n_w pq\alpha_w\beta_w\Omega},\\
I_r^* &= \frac{(n_w pq\beta_w\lambda - \mu\mu_w)[(1-p)\beta_r\mu_w + p(1-q)\beta_w\mu_r]}{pq\alpha_r\beta_w\Omega},\\
V_w^* &= \frac{(n_w pq\beta_w\lambda - \mu\mu_w)(n_w pq\beta_w\mu_r - n_r\beta_r\mu_w)}{q\mu_w\beta_w\Omega},\\
V_r^* &= \frac{(n_w pq\beta_w\lambda - \mu\mu_w)[n_r(1-q) + n_w(1-p)q]}{q\Omega},
\end{aligned}$$

where

$$\Omega = n_w(1-p)\mu_w\beta_r + (n_w p\beta_w\mu_r - n_r\beta_r\mu_w).$$

Note that when there is no mutation (i.e., $p = 1$ and $q = 1$), the coexistence-equilibrium reduces to the drug-sensitive equilibrium

$$E_s = \left(\frac{\mu_w}{n_w\beta_w}, \frac{n_w\lambda\beta_w - \mu\mu_w}{n_w\alpha_w\beta_w}, 0, \frac{n_w\lambda\beta_w - \mu\mu_w}{\beta_w\mu_w}, 0\right).$$

3.2 The stability of equilibria

Simple calculations show that E_0 is locally stable if $\mathcal{R}_0 < 1$. On the other hand, if $\mathcal{R}_0^r > 1$, then E_r exists and E_0 is unstable. The Jacobian matrix of system (1) at E_r is

$$J_{E_r} = \begin{bmatrix}
-\mathcal{A} & 0 & 0 & -\mathcal{B} & -\frac{\mu_r}{n_r}\\
0 & -\alpha_w & 0 & q\mathcal{B} & 0\\
\mathcal{A} - d & 0 & -\alpha_r & (1-q)\mathcal{B} & \frac{\mu_r}{n_r}\\
0 & \mathcal{C} & 0 & -\mu_w & 0\\
0 & \mathcal{D} & n_r\alpha_r & 0 & -\mu_r
\end{bmatrix},$$

where

$$\mathcal{A} = \frac{\lambda n_r \beta_r}{\mu_r}, \quad \mathcal{B} = \frac{\beta_w \mu_r}{n_r \beta_r}, \quad \mathcal{C} = p n_w \alpha_w \quad \text{and} \quad \mathcal{D} = (1-p) n_w \alpha_w.$$

Hence, we have the characteristic polynomial for E_r given by

$$[q\mathcal{B}\mathcal{C} - (\omega + \alpha_w)(\omega + \mu_w)][\omega^3 - \mu\alpha_r\mu_r + \mathcal{A}(\omega + \alpha_r)(\omega + \mu_r) + \omega^2(\alpha_r + \mu_r)] = 0.$$

It is easy to see that roots of $q\mathcal{B}\mathcal{C} - (\omega + \alpha_w)(\omega + \mu_w) = 0$ are

$$\omega_1 = \frac{1}{2}\left(-\alpha_w - \mu_w - \sqrt{\frac{n_r\beta_r(\alpha_w - \mu_w)^2 + 4pqn_w\alpha_w\beta_w\mu_r}{n_r\beta_r}}\right),$$
$$\omega_2 = \frac{1}{2}\left(-\alpha_w - \mu_w + \sqrt{\frac{n_r\beta_r(\alpha_w - \mu_w)^2 + 4pqn_w\alpha_w\beta_w\mu_r}{n_r\beta_r}}\right).$$

Moreover, the equation

$$\omega^3 - \mu\alpha_r\mu_r + \mathcal{A}(\omega + \alpha_r)(\omega + \mu_r) + \omega^2(\alpha_r + \mu_r) = 0 \tag{4}$$

can be rewritten as

$$\omega^3 + (\mathcal{A} + \alpha_r + \mu_r)\omega^2 + \mathcal{A}(\alpha_r + \mu_r)\omega + (\mathcal{A} - \mu)\alpha_r\mu_r = 0.$$

Since $(\mathcal{A} - \mu)\alpha_r\mu_r = \alpha_r(n_r\beta_r\lambda - d\mu_r) > 0$ when $\mathcal{R}_0 > 1$ and

$$(\mathcal{A} + \alpha_r + \mu_r)[\mathcal{A}(\alpha_r + \mu_r)] - [(\mathcal{A} - \mu)\alpha_r\mu_r]$$
$$= \frac{d\alpha_r\mu_r^3 + n_r^2\beta_r^2\lambda^2(\alpha_r + \mu_r) + n_r\beta_r\lambda\mu_r(\alpha_r^2 + \alpha_r\mu_r + \mu_r^2)}{\mu_r^2} > 0,$$

we deduce that three roots of (4) are negative.

We also note that $\omega < 0$ if and only if $\mathcal{R}_0^w < \mathcal{R}_0^r$. Therefore we obtain, in the absence of drug treatment, the following

Theorem 1 *If $\mathcal{R}_0 < 1$, then the disease free equilibrium E_0 is locally stable: neither the drug-resistance equilibrium E_r nor the coexistence equilibrium E^* exists. If $\mathcal{R}_0 > 1$, then E_r exists and E_0 is unstable; furthermore, when $\mathcal{R}_0^w < \mathcal{R}_0^r$, E_r is locally stable and E^* does not exist; while $\mathcal{R}_0^w > \mathcal{R}_0^r$, E_r is unstable and E^* exists.*

The Jacobian matrix of system (1) at the coexistence equilibrium E^* (if exists) is given by

$$J_{E^*} = \begin{bmatrix} -\mu - \beta_w V_w^* - \beta_r V_r^* & 0 & 0 & -\beta_w T^* & -\beta_r T^* \\ q\beta_w V_w^* & -\alpha_w & 0 & q\beta_w T^* & 0 \\ (1-q)\beta_w V_w^* + \beta_r V_r^* & 0 & -\alpha_r & (1-q)\beta_w T^* & \beta_r T^* \\ 0 & n_w p\alpha_w & 0 & -\mu_w & 0 \\ 0 & n_w(1-p)\alpha_w & n_r\alpha_r & 0 & -\mu_r \end{bmatrix}.$$

Since the diagonal elements of the matrix J_{E^*} are all negative, a simple argument using Geršgorin theorem (Usmani 1987) shows that it is stable if it is diagonally dominant in rows. On the other hand, the sum of elements in each row is given respectively by

$$\begin{aligned} g_1 &= -\frac{n_w pq\beta_w \lambda}{\mu_w} - \frac{(\beta_w + \beta_r)\mu_w}{n_w pq\beta_w}, \\ g_2 &= \frac{\mathcal{K}_1 - \mathcal{K}_2}{n_w p\mu_w \Omega}, \\ g_3 &= \frac{\mathcal{K}_3 - \mathcal{K}_4}{n_w pq\beta_w \mu_w \Omega}, \\ g_4 &= n_w p\alpha_w - \mu_w, \\ g_5 &= n_w(1-p)\alpha_w + n_r\alpha_r - \mu_r, \end{aligned}$$

where

$$\begin{aligned} \mathcal{K}_1 &= n_w^3 p^3 q^2 \beta_w^2 \lambda\mu_r + n_w\mu_w^2(\beta_r(n_r p(\mu + \alpha_w) + (1-p)\mu_w) + p\beta_w\mu_r), \\ \mathcal{K}_2 &= n_r\beta_r\mu_w^3 + n_w^2 p\mu_w(n_r pq\beta_w\beta_r\lambda + (1-p)\alpha_w\beta_r\mu_w + p(\mu q + \alpha_w)\beta_w\mu_r), \\ \mathcal{K}_3 &= n_w^3 p^2 q^2 \beta_w^2 \lambda[(1-p)\beta_r\mu_w + p(1-q)\beta_w\mu_r] \\ &\quad + n_w\mu_w^2[n_r pq\alpha_r\beta_w\beta_r + ((1-q)\beta_w + \beta_r)((1-p)\beta_r\mu_w + p\beta_w\mu_r)], \\ \mathcal{K}_4 &= n_r\beta_r[\beta_w(1-q) + \beta_r]\mu_w^3 \\ &\quad + n_w^2 pq\beta_w\mu_w[(1-p)(\mu + \alpha_r)\beta_r\mu_w + p(\mu(1-q) + \alpha_r)\beta_w\mu_r]. \end{aligned}$$

Obviously $g_1 < 0$. Let

$$\mathcal{M} := \max\{\mathcal{K}_1 - \mathcal{K}_2, \mathcal{K}_3 - \mathcal{K}_4, n_w p\alpha_w - \mu_w, n_w(1-p)\alpha_w + n_r\alpha_r - \mu_r\}.$$

Since $\Omega > 0$, we conclude that the endemic equilibrium E^*, if exists, is locally stable if $\mathcal{M} < 0$.

It would be nice to show that E^* is asymptotically stable (if exists) without the condition $\mathcal{M} < 0$. However, our focus in this paper is the virus dynamics of model system (1) with certain treatments. As shall be shown, the model system with treatment will be a non-autonomous system for which the analogue of E^* is a periodic solution, and determining the stability of such a periodic solution is quite difficult although co-existence of two strains will be obtained using the persistence theory of discrete dynamical systems.

4 Dynamics with treatment

In the presence of drug treatment, the system has time-varying coefficients (anti-viral effects). These coefficients are asymptotically periodic. In particular, $D(t)$ is asymptotic to the following τ-periodic function

$$\tilde{D}(t) = e^{-gt(mod\ \tau)}\frac{D^i}{1-e^{-g\tau}}$$

in the sense that $\lim_{t\to\infty}(D(t)-\tilde{D}(t))=0$. Therefore, the model (1) with treatment is asymptotic to the following periodic system:

$$\begin{aligned}
\frac{dT(t)}{dt} &= \lambda - \mu T(t) - \beta_w \widetilde{H_{rt}^w}(t)T(t)V_w(t) - \beta_r \widetilde{H_{rt}^r}(t)T(t)V_r(t),\\
\frac{dI_w(t)}{dt} &= q\beta_w \widetilde{H_{rt}^w}(t)T(t)V_w(t) - \alpha_w I_w(t),\\
\frac{dI_r(t)}{dt} &= (1-q)\beta_w \widetilde{H_{rt}^w}(t)T(t)V_w(t) + \beta_r \widetilde{H_{rt}^r}(t)T(t)V_r(t) - \alpha_r I_r(t),\\
\frac{dV_w(t)}{dt} &= pn_w \widetilde{H_p^w}(t)\alpha_w I_w(t) - \mu_w V_w(t),\\
\frac{dV_r(t)}{dt} &= (1-p)n_w \widetilde{H_p^w}(t)\alpha_w I_w(t) + n_r \widetilde{H_p^r}(t)\alpha_r I_r(t) - \mu_r V_r(t),
\end{aligned} \tag{5}$$

with τ-periodic functions $\widetilde{H_i^w}(t)$ and $\widetilde{H_i^r}(t)$ for $i = rt, p$. This model still has an infection free state $(\lambda/\mu, 0, 0, 0, 0)$, and the so-called basic reproduction number introduced in Bacaër and Guernaoui (2006) and Wang and Zhao (2008) can be calculated and the persistence theory of non-autonomous semiflows (Zhao 2003) can be applied to show this reproduction number provides the critical parameter for the virus being extinct or persist.

4.1 The basic reproduction number

The linearization of system (5) at the infection free state $(\lambda/\mu, 0, 0, 0, 0)$ without the equation for susceptible cells, which is decoupled, is

$$\begin{aligned}
\frac{dI_w(t)}{dt} &= q\beta_w \frac{\lambda}{\mu}\widetilde{H_{rt}^w}(t)V_w(t) - \alpha_w I_w(t),\\
\frac{dV_w(t)}{dt} &= pn_w \widetilde{H_p^w}(t)\alpha_w I_w(t) - \mu_w V_w(t),\\
\frac{dI_r(t)}{dt} &= (1-q)\frac{\lambda}{\mu}\beta_w \widetilde{H_{rt}^w}(t)V_w(t) + \beta_r \frac{\lambda}{\mu}\widetilde{H_{rt}^r}(t)V_r(t) - \alpha_r I_r(t),\\
\frac{dV_r(t)}{dt} &= (1-p)n_w \widetilde{H_p^w}(t)\alpha_w I_w(t) + n_r \widetilde{H_p^r}(t)\alpha_r I_r(t) - \mu_r V_r(t).
\end{aligned} \tag{6}$$

To calculate the basic reproduction number, we denote

$$F(t) = \begin{pmatrix} 0 & q\beta_w \widetilde{H^w_{rt}}(t)\frac{\lambda}{\mu} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & (1-q)\beta_w \widetilde{H^w_{rt}}(t)\frac{\lambda}{\mu} & 0 & \beta_r \widetilde{H^r_{rt}}(t)\frac{\lambda}{\mu} \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

and

$$J(t) = \begin{pmatrix} \alpha_w & 0 & 0 & 0 \\ -pn_w \widetilde{H^w_p}(t)\alpha_w & \mu_w & 0 & 0 \\ 0 & 0 & \alpha_r & 0 \\ -(1-p)n_w \widetilde{H^w_p}(t)\alpha_w & 0 & -n_r \widetilde{H^r_p}(t)\alpha_r & \mu_r \end{pmatrix}.$$

So equations (6) can be rewritten as

$$\frac{dx(t)}{dt} = (F(t) - J(t))x(t).$$

Let $\Phi_A(\tau)$ and $\rho(\Phi_A(\tau))$ be the monodromy matrix of the linear τ-periodic system $z'(t) = A(t)z(t)$ and the spectral radius of $\Phi_A(\tau)$, respectively. Assume $Y(t, s)$, $t \geq s$, is the evolution operator of the linear periodic system $y'(t) = -J(t)y(t)$. That is, for each $s \in \mathbb{R}$, the 4×4 matrix $Y(t, s)$ satisfies

$$\frac{d}{dt}Y(t, s) = -J(t)Y(t, s) \quad \forall t \geq s, \quad Y(s, s) = I,$$

where I is the 4×4 identity matrix.

Let C_τ be the Banach space of τ-periodic functions from $\mathbb{R}$ to $\mathbb{R}^4$, equipped with the maximum norm. Suppose $\phi \in C_\tau$ is the initial distribution of infectious cells and the virus. Using the framework (Wang and Zhao 2008), we define the next infection operator $L : C_\tau \to C_\tau$ by

$$(L\phi)(t) = \int_0^\infty Y(t, t-a)F(t-a)\phi(t-a)da \quad \forall t \in \mathbb{R}, \quad \phi \in C_\tau.$$

The basic reproduction number is then defined as the spectral radius of the next infection operator, that is $\widetilde{\mathcal{R}_0} := \rho(L)$, the spectral radius of L. We will use the following result (Wang and Zhao 2008, Theorem 2.2) and we refer to Wang and Zhao (2008) for early versions of this result and relevant references:

Lemma 1 *The following statements are valid:*

(i). $\widetilde{\mathcal{R}_0} = 1$ *if and only if* $\rho(\Phi_{F-J}(\tau)) = 1$;
(ii). $\widetilde{\mathcal{R}_0} > 1$ *if and only if* $\rho(\Phi_{F-J}(\tau)) > 1$;
(iii). $\widetilde{\mathcal{R}_0} < 1$ *if and only if* $\rho(\Phi_{F-J}(\tau)) < 1$;

(iv). *The infection free state* $(\lambda/\mu, 0, 0, 0, 0)$ *is locally asymptotically stable* (*unstable*) *if* $\widetilde{\mathcal{R}_0} < 1$ (*resp.* $\widetilde{\mathcal{R}_0} > 1$).

Similarly, if we denote

$$F_w(t) = \begin{pmatrix} 0 & q\beta_w \widetilde{H_{rt}^w}(t)\frac{\lambda}{\mu} \\ 0 & 0 \end{pmatrix}, \quad J_w(t) = \begin{pmatrix} \alpha_w & 0 \\ -pn_w \widetilde{H_p^w}(t)\alpha_w & \mu_w \end{pmatrix},$$

we can define the basic reproduction number for the drug-sensitive virus $\widetilde{\mathcal{R}_0^w} := \rho(L_w)$, the spectral radius of the operator L_w, by

$$(L_w\phi)(t) = \int_0^\infty Y_w(t, t-a)F_w(t-a)\phi(t-a)da, \quad \forall t \in \mathbb{R},$$

where $Y_w(t, s)$, $t \geq s$, is the evolution operator of the linear periodic system $y'(t) = -J_w(t)y(t)$. Moreover, if we set

$$F_r(t) = \begin{pmatrix} 0 & \beta_r \widetilde{H_{rt}^r}(t)\frac{\lambda}{\mu} \\ 0 & 0 \end{pmatrix}, \quad J_r(t) = \begin{pmatrix} \alpha_r & 0 \\ -n_r \widetilde{H_p^r}(t)\alpha_r & \mu_r \end{pmatrix},$$

we can then define the basic reproduction number for the drug-resistant virus $\widetilde{\mathcal{R}_0^r} := \rho(L_r)$, the spectral radius of the operator L_r. This is given by

$$(L_r\phi)(t) = \int_0^\infty Y_r(t, t-a)F_r(t-a)\phi(t-a)da \quad \forall t \in \mathbb{R},$$

where $Y_r(t, s)$, $t \geq s$, is the evolution operator of the linear periodic system $y'(t) = -J_r(t)y(t)$.

Notice that

$$F(t) - J(t) = \left(\begin{array}{cc|c} \multicolumn{2}{c|}{F_w(t) - J_w(t)} & \begin{matrix} 0 & 0 \\ 0 & 0 \end{matrix} \\ \hline 0 & (1-q)\beta_w \widetilde{H_{rt}^w}(t)\frac{\lambda}{\mu} & \\ (1-p)n_w \widetilde{H_p^w}(t)\alpha_w & 0 & F_r(t) - J_r(t) \end{array}\right).$$

According to Theorem 1, $\widetilde{\mathcal{R}_0} > 1$ if and only if $\widetilde{\mathcal{R}_0^w} > 1$ or $\widetilde{\mathcal{R}_0^r} > 1$, and $\widetilde{\mathcal{R}_0} < 1$ if and only if $\widetilde{\mathcal{R}_0^w} < 1$ and $\widetilde{\mathcal{R}_0^r} < 1$. We can also further observe that $\widetilde{\mathcal{R}_0} = \max\{\widetilde{\mathcal{R}_0^w}, \widetilde{\mathcal{R}_0^r}\}$ from the computation algorithm (Wang and Zhao 2008, Theorem 2.1).

4.2 Treatment success

The following result indicates that a properly designed drug therapy can decrease the basic reproduction number to below the unity and clear out the virus. This is consistent

with findings of other modeling studies such as Perelson et al. (1997a), which suggest that the level of virus can be reduced to one clinically undetectable.

Theorem 2 *If the basic reproduction number* $\widetilde{\mathcal{R}_0} < 1$, *the infection free state* $(\lambda/\mu, 0, 0, 0, 0)$ *of system* (5) *is globally asymptotically stable.*

Proof By Lemma 1, we know that if $\widetilde{\mathcal{R}_0} < 1$, then the infection free state $(\lambda/\mu, 0, 0, 0, 0)$ is locally asymptotically stable. It is sufficient to prove that it is also globally attractive in this case. Since $\widetilde{\mathcal{R}_0} < 1$, we obtain $\rho(\Phi_{F-J}(\tau)) < 1$. Hence we can choose a small number $\delta > 0$ such that $\rho(\Phi_{G(\delta)}(\tau)) < 1$, where

$$G(\delta)(t) = \begin{pmatrix} -\alpha_w & q\beta_w \widetilde{H_{rt}^w}(t)(\frac{\lambda}{\mu}+\delta) & 0 & \delta \\ pn_w \widetilde{H_p^w}(t)\alpha_w & -\mu_w & 0 & 0 \\ 0 & (1-q)\beta_w \widetilde{H_{rt}^w}(t)(\frac{\lambda}{\mu}+\delta) & -\alpha_r & \beta_r \widetilde{H_{rt}^r}(t)(\frac{\lambda}{\mu}+\delta) \\ (1-p)n_w \widetilde{H_p^w}(t)\alpha_w & 0 & n_r \widetilde{H_p^r}(t)\alpha_r & -\mu_r \end{pmatrix}.$$

Since there exists some N_1 such that $T(t) \le \lambda/\mu + \delta$ for all $t \ge N_1\tau$, the following comparison holds for $t \ge N_1\tau$:

$$\begin{aligned}
\frac{dI_w(t)}{dt} &\le q\beta_w \widetilde{H_{rt}^w}(t)(\lambda/\mu+\delta)V_w(t) + \delta V_r(t) - \alpha_w I_w(t), \\
\frac{dV_w(t)}{dt} &= pn_w \widetilde{H_p^w}(t)\alpha_w I_w(t) - \mu_w V_w(t), \\
\frac{dI_r(t)}{dt} &\le (1-q)\beta_w \widetilde{H_{rt}^w}(t)(\lambda/\mu+\delta)V_w(t) + \beta_r \widetilde{H_{rt}^r}(t)(\lambda/\mu+\delta)V_r(t) - \alpha_r I_r(t), \\
\frac{dV_r(t)}{dt} &= (1-p)n_w \widetilde{H_p^w}(t)\alpha_w I_w(t) + n_r \widetilde{H_p^r}(t)\alpha_r I_r(t) - \mu_r V_r(t).
\end{aligned}$$

It then follows from Zhang and Zhao (2007a, Lemma 2.1) that there exists a positive τ-periodic function $h(t)$ such that $e^{\frac{1}{\tau} ln(\rho(\Phi_{G(\delta)}(\tau)))t} h(t)$ is a solution of the the following system

$$\begin{aligned}
\frac{dI_w(t)}{dt} &= q\beta_w \widetilde{H_{rt}^w}(t)(\lambda/\mu+\delta)V_w(t) + \delta V_r(t) - \alpha_w I_w(t), \\
\frac{dV_w(t)}{dt} &= pn_w \widetilde{H_p^w}(t)\alpha_w I_w(t) - \mu_w V_w(t), \\
\frac{dI_r(t)}{dt} &= (1-q)\beta_w \widetilde{H_{rt}^w}(t)(\lambda/\mu+\delta)V_w(t) + \beta_r \widetilde{H_{rt}^r}(t)(\lambda/\mu+\delta)V_r(t) - \alpha_r I_r(t), \\
\frac{dV_r(t)}{dt} &= (1-p)n_w \widetilde{H_p^w}(t)\alpha_w I_w(t) + n_r \widetilde{H_p^r}(t)\alpha_r I_r(t) - \mu_r V_r(t).
\end{aligned}$$

Since $\rho(\Phi_{G(\delta)}(\tau)) < 1$, we have $e^{\frac{1}{\tau} ln(\rho(\Phi_{G(\delta)}(\tau)))t} h(t) \to 0$ as $t \to \infty$. For any nonnegative initial value x^0, there is a sufficiently large M such that

$$(I_w(N_1\tau, x^0), V_w(N_1\tau, x^0), I_r(N_1\tau, x^0), V_r(N_1\tau, x^0)) \le Mh(0).$$

Since equations for infectious cells and the virus can be controlled by the comparison system, applying the comparison principle (see, e.g., Smith and Waltman 1995, Theorem B. 1), we obtain that

$$(I_w(t,x^0), V_w(t,x^0), I_r(t,x^0), V_r(t,x^0)) \le Me^{\frac{1}{\tau}ln(\rho(\Phi_{G(\delta)}(\tau)))(t-N_1\tau)}h(t)$$

holds for all $t \ge N_1\tau$. Therefore,

$$\lim_{t\to\infty}(I_w(t,x^0), V_w(t,x^0), I_r(t,x^0), V_r(t,x^0)) = 0,\ \forall x^0 \in \mathbb{R}^5_+.$$

By the theory of asymptotically autonomous semiflows (see Thieme 1992, Corollary 4.3), we have $T(t,x^0) \to \lambda/d$ as $t \to \infty$. Thus, the infection free equilibrium is globally attractive.

Using similar arguments, we can show that when the basic reproduction number for drug sensitive virus $\widetilde{\mathcal{R}_0^w} < 1$, then $\lim_{t\to\infty}(I_w(t), V_w(t)) = 0$. That is, the numbers of cells infected with wild-type virus and the wild-type strain will be eventually very small. In this case, the wild-type virus is suppressed by the treatment program.

4.3 Treatment failure

We now show at least the drug-resistant virus remains persistent under a treatment program which is not sufficiently efficient to reduce the basic reproduction number to below unity. We start with the case where the reproduction number for the drug-resistant virus exceeds unity.

Theorem 3 *If the basic reproduction number for the drug-resistant virus* $\widetilde{\mathcal{R}_0^r} > 1$, *then there exists an* $\epsilon > 0$ *such that every solution* $(T(t,x^0), I_w(t,x^0), I_r(t,x^0), V_w(t,x^0), V_r(t,x^0))$ *of system* (5) *with initial value* $x^0 = (T^0, I_w^0, I_r^0, V_w^0, V_r^0)$ *so that* $x_i^0 > 0$ *for some* $i \in \{2,3,4,5\}$ *satisfies*

$$\liminf_{t\to\infty} I_r(t,x^0) > \epsilon \text{ and } \liminf_{t\to\infty} V_r(t,x^0) > \epsilon,$$

and system (5) *admits at least one nontrivial periodic solution.*

Proof Let $P : \mathbb{R}^5_+ \to \mathbb{R}^5_+$ be the Poincaré map associated with system (5), that is

$$P(x^0) = (T(\tau,x^0), I_w(\tau,x^0), I_r(\tau,x^0), V_w(\tau,x^0), V_r(\tau,x^0)),\ \forall x^0 \in \mathbb{R}^5_+.$$

Define $X = \mathbb{R}^5_+$, $X_0 = \{x \in \mathbb{R}^5_+ : x_i > 0, i = 3,5\}$ and $\partial X_0 := X \backslash X_0 = \{x \in \mathbb{R}^5_+ : x_3 = 0 \text{ or } x_5 = 0\}$. Clearly, ∂X_0 is relatively closed in X. We first prove that P is uniformly persistent with respect to $(X_0, \partial X_0)$. It is easy to see that both X and X_0 are positively invariant, and system (5) is point dissipative. Set $M_\partial = \{x \in \mathbb{R}^5_+ : P^m(x) \in \partial X_0, \forall m > 0\}$. Then $M_\partial = \{(x_1,0,0,0,0) \in \mathbb{R}^+_5 : x_1 \ge 0\}$. Since $\widetilde{\mathcal{R}_0^r} > 1$, we have $\rho(\Phi_{F_r - J_r}(\tau)) > 1$. Hence, there exists a small $\delta_1 > 0$ such that

$\rho(\Phi_{F_r(\delta_1)-J_r}(\tau)) > 1$, where $F_r(\delta_1)$ is generated by replacing λ/d with $\lambda/d - \delta_1$ in the matrix $F_r(t)$. Since

$$\lim_{x^0 \to (\frac{\lambda}{d},0,0,0,0)} (T(t,x^0), I_w(t,x^0), I_r(t,x^0), V_w(t,x^0), V_r(t,x^0)) = \left(\frac{\lambda}{\mu}, 0, 0, 0, 0\right)$$

uniformly for $t \in [0, \tau]$, there exists $\delta_2 > 0$ such that

$$\|(T(t,y^0), I_w(t,y^0), I_r(t,y^0), V_w(t,y^0), V_r(t,y^0)) - \left(\frac{\lambda}{\mu}, 0, 0, 0, 0\right)\| \le \delta_1,$$

$\forall t \in [0, \tau]$, $\|y^0 - (\lambda/\mu, 0, 0, 0, 0)\| \le \delta_2$. We now claim that $\{(\lambda/\mu, 0, 0, 0, 0)\}$ is a uniform weak repeller for X_0. Namely,

Claim $\limsup_{n\to\infty} \|P^n(x^0) - (\lambda/\mu, 0, 0, 0, 0)\| \ge \frac{\delta_2}{2}$, *for all* $x^0 \in X_0$. *Suppose, by contraction, that* $\limsup_{n\to\infty} \|P^n(y^0) - (\lambda/\mu, 0, 0, 0, 0)\| \le \frac{\delta_2}{2}$ *for some* $y^0 \in X_0$. *Then there exists a* $N_2 > 0$ *such that*

$$\|(T(t,y^0), I_w(t,y^0), I_r(t,y^0), V_w(t,y^0), V_r(t,y^0)) - (\lambda/\mu, 0, 0, 0, 0)\| \le \delta_1$$

for all $t \ge N_2\tau$. *In this case, the following inequalities hold for* $t \ge N_2\tau$:

$$\begin{aligned}
\frac{dI_r(t)}{dt} &\ge \beta_r \widetilde{H^r_{rt}}(t)(\lambda/\mu - \delta_1)V_r(t) - \alpha_r I_r(t),\\
\frac{dV_r(t)}{dt} &\ge n_r \widetilde{H^r_p}(t)\alpha_r I_r(t) - \mu_r V_r(t).
\end{aligned}$$

For the comparison system

$$\begin{aligned}
\frac{dI_r(t)}{dt} &= \beta_r \widetilde{H^r_{rt}}(t)(\lambda/\mu - \delta_1)V_r(t) - \alpha_r I_r(t),\\
\frac{dV_r(t)}{dt} &= n_r \widetilde{H^r_p}(t)\alpha_r I_r(t) - \mu_r V_r(t),
\end{aligned} \tag{7}$$

since $\rho(\Phi_{F_r(\delta_1)-J_r}(\tau)) > 1$, it then follows from Zhang and Zhao (2007a, Lemma 2.1) that there exists a positive τ-periodic function $\tilde{h}(t)$ such that $e^{\frac{1}{\tau} ln(\rho(\Phi_{F_r(\delta_1)-J_r}(\tau)))t}\tilde{h}(t)$ is a solution of system (7). Since $\rho(\Phi_{F_r(\delta_1)-J_r}(\tau)) > 1$, $e^{\frac{1}{\tau} ln(\rho(\Phi_{F_r(\delta_1)-J_r}(\tau)))t}\tilde{h}(t) \to \infty$ as $t \to \infty$. For any nonnegative initial value y^0 with $y^0_3 > 0$ or $y^0_5 > 0$, there is a sufficiently small $\widetilde{M}$ such that $(I_r(N_2\tau, y^0), V_r(N_2\tau, y^0)) \ge \widetilde{M}\tilde{h}(0)$. Applying the comparison principle (see, e.g., Smith and Waltman 1995, Theorem B. 1), we have

$$(I_r(t,y^0), V_r(t,y^0)) \ge \widetilde{M} e^{\frac{1}{\tau} ln(\rho(\Phi_{F_r(\delta)-J_r}(\tau)))(t-N_2\tau)}\tilde{h}(t), \ \forall t \ge N_2\tau.$$

Therefore, $I_r(t, y^0) \to \infty$ and $V_r(t, y^0) \to \infty$ as $t \to \infty$. Thus we get a contradiction to the boundedness of solutions, and this proves the claim.

Note that every orbit in M_∂ approaches to $\{(\lambda/\mu, 0, 0, 0, 0)\}$, and $\{(\lambda/\mu, 0, 0, 0, 0)\}$ is acyclic in M_∂. It follows from Zhao (2003, Theorem 1.3.1) that P is uniformly persistent with respect to $(X_0, \partial X_0)$. Hence the solutions of system (5) are uniformly persistent with respect to $(X_0, \partial X_0)$ by Zhao (2003, Theorem 3.1.1). If $x_i^0 > 0$ for some $i \in \{2, 3, 4, 5\}$, we then easily see that $I_r(t, x^0) > 0$ and $V_r(t, x^0) > 0, \forall t > 0$. Hence, there exists an $\epsilon > 0$ such that any solution $x(t, x^0)$ of system (5) with initial value $x^0 \in \{x \in \mathbb{R}^5_+ : x_i \neq 0 \text{ for some i} \in \{2, 3, 4, 5\}\}$ satisfies $\liminf_{t\to\infty} I_r(t, x^0) > \epsilon$ and $\liminf_{t\to\infty} V_r(t, x^0) > \epsilon$. Furthermore, Zhao (2003, Theorem 1.3.6) implies that P has a fixed point $x^* \in X_0$. Thus, $(T(t, x^*), I_w(t, x^*), I_r(t, x^*), V_w(t, x^*), V_r(t, x^*))$, the solution through x^*, is a nontrivial periodic solution with $I_r(t, x^*) > 0$ and $V_r(t, x^*) > 0$.

The proof of Theorem 3 also shows that if the basic reproduction number for the drug-resistant virus $\widetilde{\mathcal{R}_0^r} > 1$, then there exists a drug-resistance periodic orbit in the form of $\widetilde{E}_r(t) = (T(t), 0, I_r(t), 0, V_r(t))$.

Notice that when the basic reproduction number for the wild-type virus is less than one, the wild-type strain is suppressed. However, this is not the case when the basic reproduction number of the drug-resistant virus is less than one. Our next result shows that $\widetilde{\mathcal{R}_0^w} > 1$ implies the persistence of both wide-type and drug-resistance strains regardless of the size for $\widetilde{\mathcal{R}_0^r}$.

Theorem 4 *If the basic reproduction number for the wild-type virus $\widetilde{\mathcal{R}_0^w} > 1$ and that for the drug-resistant virus $\widetilde{\mathcal{R}_0^r} < 1$, then there exists an $\eta > 0$ such that every solution $(T(t, x^0), I_w(t, x^0), I_r(t, x^0), V_w(t, x^0), V_r(t, x^0))$ of system (5) with initial value $x^0 = (T^0, I_w^0, I_r^0, V_w^0, V_r^0)$ and $x_i^0 > 0$ for $i = 2, 4$ satisfies*

$$\liminf_{t\to\infty} (I_w(t, x^0), I_r(t, x^0), V_w(t, x^0), V_r(t, x^0)) > (\eta, \eta, \eta, \eta),$$

and system (5) admits at least one positive periodic solution.

Proof Let $P : \mathbb{R}^5_+ \to \mathbb{R}^5_+$ be the Poincaré map associated with system (5), that is

$$P(x^0) = (T(\tau, x^0), I_w(\tau, x^0), I_r(\tau, x^0), V_w(\tau, x^0), V_r(\tau, x^0)), \ \forall x^0 \in \mathbb{R}^5_+.$$

Define $X = \mathbb{R}^5_+, U_0 = \{x \in \mathbb{R}^5_+ : x_i > 0, i = 2, 4\}$ and $\partial U_0 := X \backslash U_0 = \{x \in \mathbb{R}^5_+ : x_2 = 0 \text{ or } x_4 = 0\}$. Set $\widetilde{M}_\partial = \{x \in \mathbb{R}^5_+ : P^m(x) \in \partial U_0, \forall m > 0\}$. We claim that $\widetilde{M}_\partial = \{(x_1, 0, x_3, 0, x_5) \in \mathbb{R}^+_5 : x_i \geq 0, i = 1, 3, 5\}$. In fact, if $x^0 \in X$ and $x_i^0 > 0$ for $i = 2$ or $i = 4$, we have $I_w(t, x^0) > 0$ and $V_w(t, x^0) > 0$ for any $t > 0$. Thus $(T(t, x^0), I_w(t, x^0), I_r(t, x^0), V_w(t, x^0), V_r(t, x^0)) \notin U_0$ for any $t > 0$, and $\widetilde{M}_\partial = \{(x_1, 0, x_3, 0, x_5) \in \mathbb{R}^+_5 : x_i \geq 0, i = 1, 3, 5\}$. Hence, the solution through $y^0 \in \widetilde{M}_\partial$ satisfies the following system

$$\begin{aligned}
\frac{d\widetilde{T}(t)}{dt} &= \lambda - \mu\widetilde{T}(t) - \beta_r \widetilde{H_{rt}^r}(t)\widetilde{T}(t)\widetilde{V}_r(t), \\
\frac{d\widetilde{I}_r(t)}{dt} &= \beta_r \widetilde{H_{rt}^r}(t)\widetilde{T}(t)\widetilde{V}_r(t) - \alpha_r \widetilde{I}_r(t),
\end{aligned}$$

$$\frac{d\widetilde{V}_r(t)}{dt} = n_r \widetilde{H}_p^r(t)\alpha_r \widetilde{I}_r(t) - \mu_r \widetilde{V}_r(t). \tag{8}$$

Since $\widetilde{\mathcal{R}}_0^r < 1$, by the same argument as that of Theorem 2, we conclude that

$$(\widetilde{T}(t, y^0), \widetilde{I}_r(t, y^0), \widetilde{V}_r(t, y^0)) \to (\lambda/\mu, 0, 0)$$

as $t \to \infty$, where $(\widetilde{T}(t, y^0), \widetilde{I}_r(t, y^0), \widetilde{V}_r(t, y^0))$ is the solution of system (8) through y^0. Hence, every orbit in $\widetilde{M}_\partial$ approaches $\{(\lambda/\mu, 0, 0, 0, 0)\}$. Using similar arguments to that in the proof of Theorem 3, we can see that there exists an $\eta_1 > 0$ such that any solution $(T(t, x^0), I_w(t, x^0), I_r(t, x^0), V_w(t, x^0), V_r(t, x^0))$ of system (5) with initial value $x^0 \in \{x \in \mathbb{R}^5_+ : x_r \neq 0 \text{ or } x_4 \neq 0\}$ satisfies

$$\liminf_{t\to\infty} I_w(t, x^0) > \eta_1 \quad \text{and} \quad \liminf_{t\to\infty} V_w(t, x^0) > \eta_1.$$

Furthermore, Zhao (2003, Theorem 1.3.6) implies that P has a fixed point $\tilde{x}^* \in X_0$. Thus, the solution through $\tilde{x}^*$ is a positive periodic solution. If $\liminf_{t\to\infty} I_w(t, x^0) > \eta_1$ and $\liminf_{t\to\infty} V_w(t, x^0) > \eta_1$, using a comparison principle, we can show that there exists an $\eta_2 > 0$ such that $\liminf_{t\to\infty} I_r(t, x^0) > \eta_2$ and $\liminf_{t\to\infty} V_r(t, x^0) > \eta_2, \forall x^0 \in U_0$. Choosing $\eta = \min\{\eta_1, \eta_2\}$, we get the result.

If the basic reproduction number for wild-type virus $\widetilde{\mathcal{R}_0^w} > 1$ and that for the drug-resistant virus $\widetilde{\mathcal{R}_0^r} < 1$, there is a coexistence periodic orbit in the form of $\widetilde{E}^*(t) = (T^*(t), I_w^*(t), I_r^*(t), V_w^*(t), V_r^*(t))$.

4.4 Asymptotic periodicity

The original model is asymptotically periodic and convergent to the periodic system (5). So what we have obtained for system (5) remains true for model (1) using the theory of asymptotically periodic systems, see Zhang and Zhao (2007b) and Zhao (2003). In particular, using Zhao (2003, Lemma 1.2.2 and Theorem 1.2.1) and as discussed in Zhang and Zhao (2007b, Sect. 5), we obtain the following

Theorem 5 *The following statements hold for the model* (1)*:*

(i). *If the basic reproduction number* $\widetilde{\mathcal{R}_0} < 1$*, the infection free state* $(\lambda/\mu, 0, 0, 0, 0)$ *is globally attractive;*

(ii). *If the basic reproduction number for the wild-type virus* $\widetilde{\mathcal{R}_0^w} < 1$*, then* $\lim_{t\to\infty}(I_w(t), V_w(t)) = 0$*;*

(iii). *If the basic reproduction number for the wild-type virus* $\widetilde{\mathcal{R}_0^w} > 1$ *and that for the drug-resistant virus* $\widetilde{\mathcal{R}_0^r} < 1$*, then there exists an* $\eta > 0$ *such that* $\liminf_{t\to\infty}(I_w(t), I_r(t), V_w(t), V_r(t)) > (\eta, \eta, \eta, \eta)$ *for any initial value* x^0 *with* $x_i^0 > 0$ *for* $i = 2, 4$*;*

(iv). *If the basic reproduction number for the drug-resistant virus* $\widetilde{\mathcal{R}_0^r} > 1$*, then there exists an* $\epsilon > 0$ *such that* $\liminf_{t\to\infty} I_r(t) > \epsilon$ and $\liminf_{t\to\infty} V_r(t) > \epsilon$ *for any initial value* x^0 *with* $x_i^0 > 0$ *for some* $i \in \{2, 3, 4, 5\}$.

Note that if the drug-sensitive virus under a therapy exists, the drug-resistant virus will remain persistent (case (iii)). However, the drug-resistant strain can also persist if the sensitive strain is cleared through treatment (case (iv) with $\widetilde{\mathcal{R}_0^r} > 1$ and $\widetilde{\mathcal{R}_0^w} < 1$).

5 Numerical simulations

In this section, we present some numerical simulations to illustrate likely scenarios in a patient according to the free-treatment policy currently being implemented in China. We suppose perfect adherence, and drugs are taken at a fixed interval τ. Currently, three different combinations for the first-line and the second-line treatment programs are used:

(C1) Only a single of the three aforementioned drugs is used;
(C2) Two of the three aforementioned drugs are used;
(C3) Triple drugs are used.

To conduct numerical simulations, we use parameters close to the reality as much as possible. We first estimate relevant model parameters of antiviral effects.

5.1 Pharmacokinetics

We first estimate the value of parameter g, the clearance rate for a specific drug being used or is expected to be accessible in the near future in China. For the first-line treatment program, we fix the dosing interval $\tau = 0.5$ day so the drugs are taken twice a day. As an example, we estimate the value of g^{3TC}, the rate at which drug Heptodin (i.e. Lamivadin, 3TC) is cleared in vivo. Heptodin may be a good drug for gastrointestinal absorption: under normal circumstances, adult bioavailability after oral administration of Lamivudine is 80–85%. After oral administration, the average peak time (T_{max}) to arrive the maximum plasma concentration (C_{max}^{SS}) is about 1 hour. The valley peak concentration at steady state is $C_{max}^{SS} = 1.1$–$1.5\ \mu$g/ml and the trough value is $C_{trough}^{SS} = 0.015$–$0.020\ \mu$g/ml. The drug concentration $D(t)$ therefore eventually satisfies

$$\frac{D^{3TC}e^{-g^{3TC}\tau}}{1-e^{-g^{3TC}\tau}} \le D(t) \le \frac{D^{3TC}}{1-e^{-g^{3TC}\tau}},$$

which has $\frac{D^{3TC}}{1-\bar{r}}$ and $\frac{D^{3TC}\bar{r}}{1-\bar{r}}$ as maximal and minimal values, where D^{3TC} is the dosage of drug 3TC and $\bar{r} = e^{-g^{3TC}\tau}$. Choosing $\frac{D^{3TC}}{1-\bar{r}} = 1.25$ and $\frac{D^{3TC}\bar{r}}{1-\bar{r}} = 0.0175$, we get $\bar{r} = e^{-g^{3TC}\tau} = \frac{0.0175}{1.25}$, which implies that $g^{3TC} \approx 4.27$ and $D^{3TC} \approx 1.23$. In our simulations, we choose $g^{3TC} = 4$ and $D^{3TC} = 1.5$ respectively (Table 1). Similarly, we can estimate parameter values for other drugs, as shown in Table 1.

Given these parameters, we can describe the time-courses of drug concentrations in plasma and the antiviral effects (we use $1 - H_i^j$ to denote the effects of drugs on reducing infection or/and transition, with $i \in \{rt, p\}$ and $j \in \{w, r\}$), as shown in

Table 1 Parameters of pharmacokinetics

Parameters	Meanings	Value	Reference
Θ^w_{3TC}	Concentration of drug 3TC which inhibits drug-sensitive viral replication by 50%	0.0197 μg/ml	Wahl and Nowak (2000)
Θ^r_{3TC}	Concentration of drug 3TC which inhibits drug-resistant viral replication by 50%	200 × 0.0197 μg/ml	Wahl and Nowak (2000)
Θ^w_{AZT}	Concentration of drug AZT which inhibits drug-sensitive viral replication by 50%	0.0234 μg/ml	Wahl and Nowak (2000)
Θ^r_{AZT}	Concentration of drug AZT which inhibits drug-resistant viral replication by 50%	100 × 0.0234 μg/ml	Wahl and Nowak (2000)
Θ^w_{NVP}	Concentration of drug NVP which inhibits drug-sensitive viral replication by 50%	0.012 μg/ml	http://www.yp900.com/Drug-220179-A90218782025C48E09BA0436CF30D0.htm
Θ^r_{NVP}	Concentration of drug NVP which inhibits drug-resistant viral replication by 50%	5 × 0.012 μg/ml	http://www.yp900.com/Drug-220179-A90218782025C48E09BA0436CF30D0.htm
Θ^w_{RTV}	Concentration of drug RTV which inhibits drug-sensitive viral replication by 50%	0.0159 μg/ml	Wahl and Nowak (2000)
Θ^r_{RTV}	Concentration of drug RTV which inhibits drug-resistant viral replication by 50%	10 × 0.0159 μg/ml	Wahl and Nowak (2000)
Θ^w_{TDF}	Concentration of drug TDF which inhibits drug-resistant viral replication by 50%	0.04 μg/ml	http://www.giead.com/pdf/truvada_pi.pdf
Θ^r_{TDF}	Concentration of drug TDF which inhibits drug-resistant viral replication by 50%	3 × 0.04 μg/ml	http://www.gilead.com/pdf/truvada_pi.pdf
g^{3TC}	Rate at which drug 3TC is cleared in vivo	4 day^{-1}	http://www.gzbaozhilin.com/Html/livergall/liver/1260.html
g^{AZT}	Rate at which drug AZT is cleared in vivo	16 day^{-1}	http://baike.baidu.com/view/2260123.htm
g^{NVP}	Rate at which drug NVP is cleared in vivo	10 day^{-1}	http://www.yp900.com/Drug-220179-A90218782025C48E09BA0436CF30D0.htm
g^{TDF}	Rate at which drug TDF is cleared in vivo	1.5 day^{-1}	http://www.gilead.com/pdf/truvada_pi.pdf
g^{RTV}	Rate at which drug RTV is cleared in vivo	2 day^{-1}	Dai and Zhu (2005)
D^{3TC}	dosage of drug 3TC	1.5 μM	http://www.gzbaozhilin.com/Html/livergall/liver/1260.html
D^{AZT}	Dosage of drug AZT	2 μM	http://baike.baidu.com/view/2260123.htm
D^{NVP}	Dosage of drug NVP	2 μM	http://www.yp900.com/Drug-220179-A90218782025C48E09BA0436CF30D0.htm
D^{TDF}	Dosage of drug TDF	0.2 μM	http://www.gilead.com/pdf/truvada_ pi.pdf
D^{RTV}	Dosage of drug RTV	5 μM	Dai and Zhu (2005)
m_{3TC}	Slope parameter of 3TC	1.15	Shen et al. (2008)
m_{AZT}	Slope parameter of AZT	0.85	Shen et al. (2008)
m_{NVP}	Slope parameter of NVP	1.55	Shen et al. (2008)

Table 1 continued

Parameters	Meanings	Value	Reference
m_{TDF}	Slope parameter of TDF	0.97	Shen et al. (2008)
m_{RTV}	Slope parameter of RTV	2.5	Estimated
τ_1	Dosing interval of the first-line drugs	0.5 day	
τ_2	Dosing interval of the second-line drugs	1 day	

D^i and g^i are calculated from the literature mentioned

Fig. 1. Figure 1a gives an example of the time-course of a single-drug concentration (lamivudine, 3TC) in plasma, Fig. 1b plots the time courses of anti-viral effects on both drug-sensitive and drug-resistant strains after a patient takes the drug (3TC). This illustrates that the anti-viral effect of the drug is a periodic function with the period $\tau = 0.5$ day. Figure 1c shows dose effect responses of Lamivudine (3TC) to the drug sensitive strain, partially resistant strain and highly resistant virus. We observe that the anti-viral effect can reduce the virus to the near zero level with a rather low dose of 3TC for the drug-sensitive virus, implying that the drug can completely inhibit the sensitive-strain infection. However, for the highly resistant virus, this effect is insignificant even with a very high dose of 3TC ($1 - H \leq 0.5$ when the drug concentration reaches 10 μM).

5.2 Simulations

According to the *Manuals of National AIDS Free Antiviral Treatment in China* (http://www.chinaids.org.cn/n16/n1657/n32880.files/n32881.pdf), a patient starts to receive the treatment when the $CD4^+$ T cells is about 300 mm^{-3}. We thus suppose $T(0) = 300\ mm^{-3}$. Other initial values and model parameters in our simulations are shown in Tables 1, 2 and 3.

We now present some explanations for parameter values listed in Table 3. The recruitment rate of $CD4^+$ cells, λ, was chosen as 10 in Perelson et al. (1993) and 36 in Perelson (1989). Here, we suppose $\lambda = 20$. The parameter β_w can have values ranging from 2.4×10^{-5} to 2.4 (Kirschner and Webb 1997) and different literatures supported different values. Here we set $\beta_w = 2 \times 10^{-4}$. For β_r, we choose a smaller value than that of β_w since drug-resistant strains normally have a lower infection rate compared with the drug-sensitive strain. The value of n_w varies in different studies, being 10 in Kirschner and Webb (1997), 210 in Smith and Wahl (2005) and ranging from 500 to 5000 in Perelson et al. (1993). For illustration, we set $n_w = 150$. We also suppose $n_r = 120$, so that the drug-resistant strain can reproduce smaller numbers of free virus. For α_w and α_r, they were chosen as 0.5 and 0.2 in Wahl and Nowak (2000) and Wodarz and Lloyd (2004) respectively. Here we suppose $\alpha_w = \alpha_r = 0.24$.

Using our formulas for the two basic reproduction numbers in the absence of treatment, we obtain that $\mathcal{R}_0^w = 9.98$ and $\mathcal{R}_0^r = 6$. Hence the basic reproduction number $\mathcal{R}_0 = 9.98$. Since $\mathcal{R}_0^w > \mathcal{R}_0^r$, both of the drug-sensitive virus and drug-resistant virus will persist according to Theorem 1.

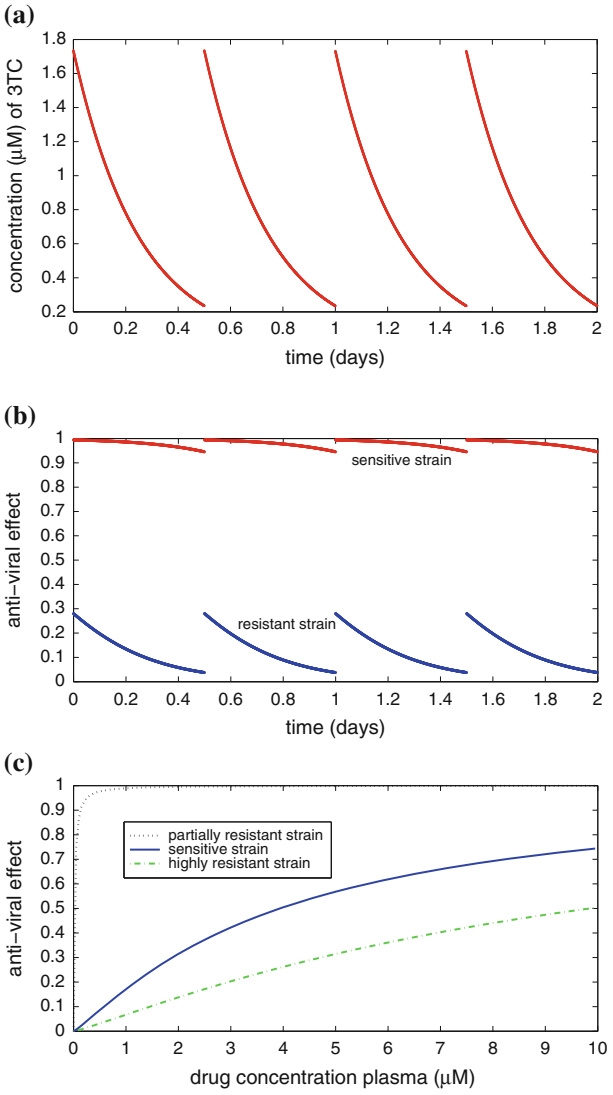

Fig. 1 Time-courses of drug concentration, antiviral efficacy and dose effect. We take lamivudine (3TC) as an example, with $g^{3TC} = 4$/day and $D^{3TC} = 1.5$ μM. **a** The drug concentration time-course in plasma. **b** The time-course of the drug efficacy on reducing infection for both drug-sensitive and drug-resistant strains. **c** Dose effects of Lamivudine (3TC) for the drug-sensitive and drug-resistant (partially/highly) viral strains. Parameter values can be found in Tables 1 and 3. The parameter Θ^{w}_{3TC} for the drug-sensitive virus is 0.0197 μM; Θ^{r}_{3TC} is 200 times (for partially resistant strains) or 500 times (for highly resistant strains) greater (that is 3.94 or 9.85 μM), respectively

Figure 2 compares the time course of infection in the absence of therapy with the time course of infection with a single-drug treatment (3TC). In the absence of therapy, the drug-sensitive strain dominates (solid lines). However, this is changed with a single-drug treatment (3TC). In comparison with the situation without a drug therapy, the proportion of infected cells decreases substantially with a single-drug treatment

Table 2 Variables and initial values

Variable	Meaning	Initial value
T	Concentration of uninfected $CD4^+$ T-cells	300 mm^{-3}
I_w	Concentration of $CD4^+$ T-cells infected by drug-sensitive virus	1 mm^{-3}
I_r	Concentration of $CD4^+$ T-cells infected by the drug-resistant virus	0.001 mm^{-3}
V_w	Concentration of the free drug-sensitive virus	1,000 mm^{-3}
V_r	Concentration of the free drug-resistant virus	0.001 mm^{-3}

(from 50 to 20%, the lower right corner sub-figure). Moreover, the drug (3TC)-treatment decreases $\widetilde{\mathcal{R}_0^w} = 0.22 < 1$, implying that the drug-sensitive virus will be cleared (Theorem 5). Note however that, in this case, $\widetilde{\mathcal{R}_0^r} = 5.24$ remains greater than unity, indicating that the drug-resistant strain is persistent.

Figure 3 plots the time courses of infection using different combinations of drugs under the first-line drugs program, focusing on the comparison between the single-drug treatment (3TC) and the triple-drug treatment (3TC, AZT and NVP). Although the basic reproduction number remains greater than unity for the triple-drug treatment (see Table 4), the drug-resistant strain emerges and becomes dominant with a low viral load after a long time lag. The triple-drug treatment greatly reduces the population of infected cells (solid lines): the immune system builds (the upper-left corner sub-figure), and the proportion of infected cells decreases to 7% (in comparison with 28% under the single-drug treatment).

Numerical calculations of the basic reproduction number using its definition in terms of the spectral radius of monodromy operators are possible. Figure 4 plots the relationship between dose intervals and the basic reproduction number, while fixing the daily dose. Using the parameters specified, the basic reduction number can be reduced to less than the unity once the dose interval is reduced to 8 hours. These calculations can also facilitate the optimal combinations of drugs and their dosages under the first-line program. For example, Fig. 5 illustrates how the basic reproduction number changes as a function of the dosages of three drugs in the triple-drug treatment program.

Next, we evaluate the efficientiveness of the second-line treatment program in China (3TC, TDF and RNV). Figure 6 reports the time courses of infection under a therapy guided by the second-line program. Compared with the first-line triple-drug treatment program (3TC, AZT and NVP, solid lines in Fig. 6), the second-line triple-drug treatment seems to be highly effective. Although the first-line treatment can reduce the basic reproduction number significantly (from 9.98 to 1.7), it fails to reduce it below unity. However, the second-line treatment can bring this number to below unity (from 9.98 to 0.01, see Table 4). As a result, both of the drug-sensitive and drug-resistant strains are cleared out: this is confirmed theoretically (Theorem 5) and numerically (Fig. 6). In this case, the immune system rebuilds.

Table 4 summarizes our calculation of the reproduction numbers for different treatment therapies. We note that the first-line treatment program can reduce the basic reproduction number greatly, but this program alone can not bring the basic reproduction number to below unity. So it fails to clear all of the virus and at least the drug-resistant strain presents (Theorem 5). On the other hand, the second-line treatment program

Table 3 Immune parameters

Parameter	Meaning	Value	Reference
λ	Source rate of susceptible $CD4^+$ T cells	20 mm^{-3} day^{-1}	Perelson et al. (1993), Perelson (1989)
μ	Natural death rate of T-cell	0.02 day^{-1}	Kirschner (1996)
β_w	Rate of drug-sensitive HIV virus infect healthy T-cells	0.0002 mm^{-3} day^{-1}	Kirschner and Webb (1997)
β_r	Rate of the drug-resistant HIV virus infect healthy T-cells	0.00015 mm^{-3} day^{-1}	Estimated
n_w	Number of free virus produced by lysing a drug-sensitive T-cell	150	Smith and Wahl (2005)
n_r	Number of free virus produced by lysing a drug-resistant T-cell	120	Estimated
q	Probability of drug-sensitive T cells that are infected arising from infection	0.999	Coffin (1995), Kirschner and Webb (1997)
p	Probability of drug-sensitive virus variants produced by infected T cells	0.999	Estimated
α_w	Death rate of drug-sensitive infected cells	0.24 day^{-1}	Wahl and Nowak (2000), Wodarz and Lloyd (2004)
α_r	Death rate of drug-resistant infected cells	0.24 day^{-1}	Wahl and Nowak (2000), Wodarz and Lloyd (2004)
μ_w	Death rate of the free drug-sensitive HIV virus	3 day^{-1}	Smith and Wahl (2005)
μ_r	Death rate of the free drug-resistant HIV virus	3 day^{-1}	Smith and Wahl (2005)

may reduce the basic reproduction number to below unity, thus can reduce the level of virus for both the wild-type and drug-resistant strains to a clinically undetectable level.

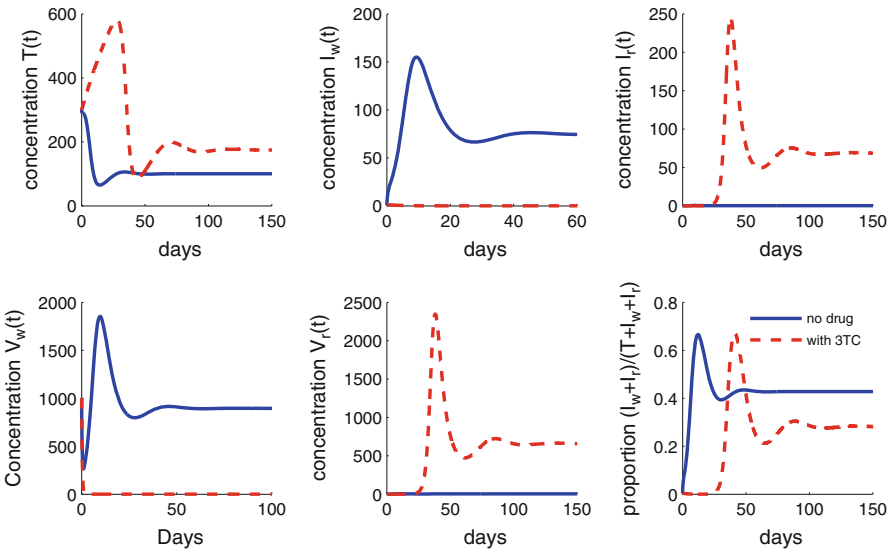

Fig. 2 Simulated time courses of infection in the absence of therapy and with the single-drug treatment (3TC) respectively. Parameter values are shown in Tables 1 and 3. In the absence of treatment, we have $\mathcal{R}_0^w = 9.98, \mathcal{R}_0^r = 6$ and so $\mathcal{R}_0 = 9.98 > 1$, the drug-sensitive virus dominates (*solid lines*). With a single-drug treatment (3TC) for patients, the reproduction numbers become $\widetilde{\mathcal{R}_0^w} = 0.22$ and $\widetilde{\mathcal{R}_0^r} = 5.24$: the drug-resistant strain dominates

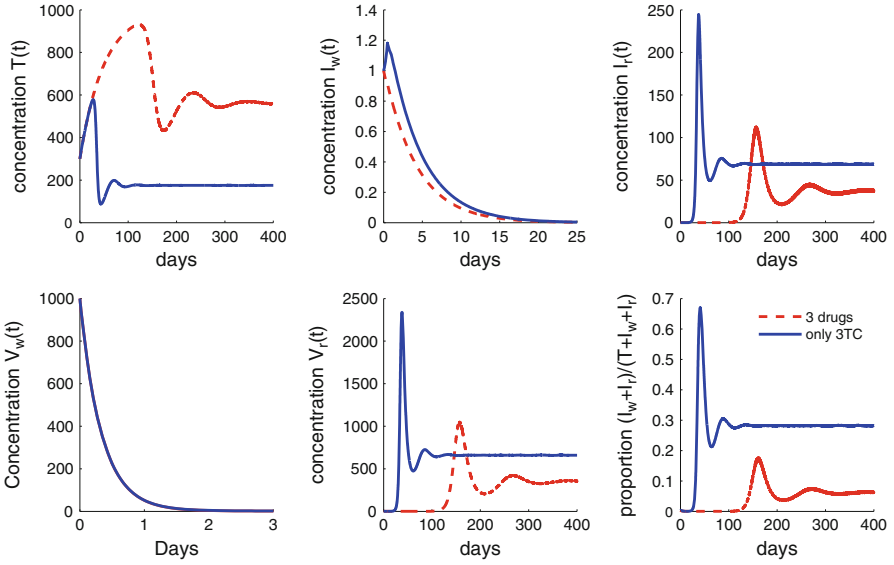

Fig. 3 Simulated time courses of infection using the first-line drugs: a comparison between the single-drug treatment (3TC) and the triple-drug treatment (3TC, AZT and NVP). Initial conditions are shown in Table 2. Parameter values are shown in Tables 1 and 3

Table 4 Reproduction numbers for each therapy

Treatment program	$\widetilde{\mathcal{R}_0^w}$	$\widetilde{\mathcal{R}_0^r}$	$\widetilde{\mathcal{R}_0}$
No drug	9.98	6	9.98
3TC	0.22	5.24	5.24
AZT	4.44	5.44	5.44
NVP	0.76	1.84	1.84
3TC & AZT	0.14	4.8	4.8
First-line	0.03	1.7	1.7
Second-line	5×10^{-6}	0.01	0.01

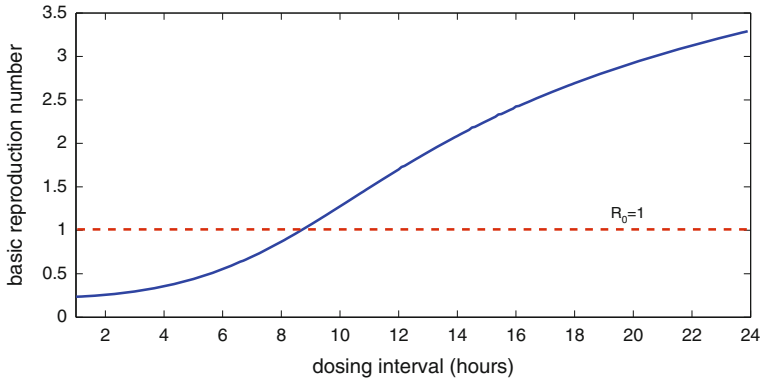

Fig. 4 The relationship between the basic reproduction number and the dose interval. The daily dosage is fixed at 3TC = 3 μM, AZT = 4 μM and NVP = 4 μM

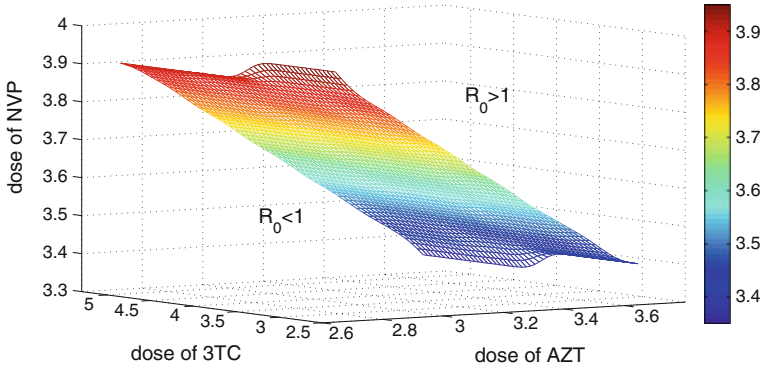

Fig. 5 The relationship among the basic reproduction number and the dosages of three drugs used, the dose interval is 0.5 days for each drug

6 Discussion

In this paper, we have considered a two-strain mathematical model to study the possible outcomes of the China's free AIDS-treatment policy with the two treatment

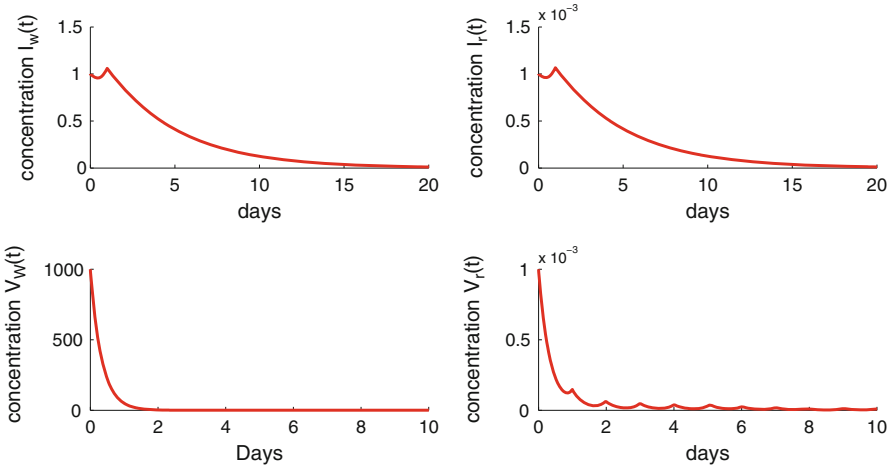

Fig. 6 Simulated time courses of infection under the second-line drugs (3TC, TDF and RNV). Initial conditions are shown in Table 2. Parameter values are shown in Tables 1 and 3

programs in China. Impulsive differential equations have been used to model the drug concentrations in plasma, and hence the full model is a non-autonomous ordinary differential system. We have developed a rigorous analysis of the model via the use of the theories of asymptotic periodic systems and persistence of discrete dynamical systems, and such an analysis naturally yields biologically important and qualitatively insightful quantities, the so-called basic reproduction numbers for both the wild-type and drug resistant strains. We have shown that these quantities completely determine the eventual outcomes of virus concentrations in a patient. In particular, a scenario of virus elimination has been provided via this model (see Theorem 5 (i) and Fig. 6). Early work on impulsive differential equations has been largely based on numerical simulations, but our study here clearly confirms the feasibility of analytical investigation of such models and a wide range of within-host virus dynamics models and population-level epidemiological models subject to interventions implemented in a sequence of discrete times

For the current therapies guided by the *Manuals of National AIDS Free Antiviral Treatment in China* (http://www.chinaids.org.cn/n16/n1657/n32880.files/n32881.pdf), our mathematical and numerical results show that the drug-resistant virus dominates (the *first-line treatment program*) or both the strains can be rapidly "cleared out" (the *second-line treatment program*). As such, both treatment programs will have positive effect in altering the virus dynamics, but the *second-line program* is much desirable in order to clear out the drug-resistant virus.

We should remark that our model assumed that the change of drug concentration is nearly instantaneous, i.e., the time-to-peak is negligible compared to the timescale of the interest (days). In reality, several drugs can be slowly absorbed after oral medication and reach peak plasma concentration after some delays. How to incorporate these delays in our model and analysis remains an interesting question. Note also that we assumed that the drugs are taken and absorbed in a prefect-adherence way,

clearly just an ideal condition. Finally, we note that latently infected cells or long-lived infected cells are not incorporated in our model (Perelson et al. 1997b). All of these assumptions make our results overestimating the viral effects of treatment programs.

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