Advances in Difference Equations
a SpringerOpen Journal

RESEARCH Open Access

The global dynamics in a wild-type and drug-resistant HIV infection model with saturated incidence

Wei Chen[1], Nafeisha Tuerxun[1] and Zhidong Teng[1*]

*Correspondence:
zhidong_teng@sina.com;
zhidong1960@163.com
[1]College of Mathematics and Systems Science, Xinjiang University, Urumqi, People's Republic of China

Abstract

In this paper we investigate the global dynamics in an HIV virus infection model with saturated incidence. The model includes two viral strains, one is wild-type (i.e. drug sensitive) and another is drug-resistant. The wild-type strain can mutate and become drug-resistant during the process of reverse transcription. The nonnegativity and boundedness of solutions are established. The basic reproduction numbers of two strains and the existence of equilibria are also obtained. The threshold criteria on the local and global stability of equilibria and the uniform persistence of the model are established by using the linearization method, constructing suitable Lyapunov functions and the theory of persistence in dynamical systems. Moreover, the mathematical analysis and numerical examples show that model may have a positive equilibrium which is globally asymptotically stable.

Keywords: HIV virus infection model; Wild-type and drug-resistant virus; Saturated incidence; Basic reproduction number; Stability and persistence

1 Introduction

It is well known that mathematical models that describe the dynamical behaviors of virus infection play an important role in understanding the mechanism of the diffusion of virus. There has been much interest in mathematical modeling of viral dynamics within-host. So, the research of virus dynamics with specific immune response, which can control the virus propagation, has drawn significant attention [1–6]. A few years ago, Perelson et al. in [7] constructed a model that has been widely adopted to model the plasma viral load in HIV infected patients as follows:

$$\begin{cases} \frac{dT(t)}{dt} = \lambda - dT - kVT, \\ \frac{dT_s(t)}{dt} = kVT - \delta T_s, \\ \frac{dV(t)}{dt} = N\delta T_s - cV. \end{cases}$$

Treating HIV-infected patients with a combination of several antiretroviral drugs usually contributes to a substantial decline in viral load and an increase in CD_4^+ T cells. Nevertheless, there is a reasonable chance that drug-resistant variants of HIV preexist even

before the initiation of therapy due to a single mutation, or a number of mutation combinations can result in drug resistance by Ribeiro and Bonhoeffer in 2000 (see [8, 9]). In order to study the mechanism of the emergence of drug resistance during the treatment of HIV-infected patients, a dynamical model including wild-type and drug-resistant strains was proposed by Rong et al. in [9] as follows:

$$\begin{cases} \frac{\mathrm{d}T(t)}{\mathrm{d}t} = \lambda - dT - k_s V_s T - k_r V_r T, \\ \frac{\mathrm{d}T_s(t)}{\mathrm{d}t} = (1-u)k_s V_s T - \delta T_s, \\ \frac{\mathrm{d}V_s(t)}{\mathrm{d}t} = N_s \delta T_s - cV_s, \\ \frac{\mathrm{d}T_r(t)}{\mathrm{d}t} = uk_s V_s T + k_r V_r T - \delta T_r, \\ \frac{\mathrm{d}V_r(t)}{\mathrm{d}t} = N_r \delta T_r - cV_r. \end{cases} \tag{1}$$

Usually the rate of infection in most HIV-1 models is assumed to be bilinear in the virus and the uninfected cells. However, the actual incidence rate is probably not linear over the entire range of virus and the uninfected cells. Thus, it is reasonable to assume that the infection rate of HIV-1 is given by the Beddington–DeAngelis functional response [10], which was introduced by Beddington [11] and DeAngelis et al. [12]. For a specific nonlinear incidence rate, we consider the following HIV-1 infection model with saturated incidence:

$$\begin{cases} \frac{\mathrm{d}T(t)}{\mathrm{d}t} = \lambda - dT - \frac{k_s V_s T}{1+\omega_1 V_s} - \frac{k_r V_r T}{1+\alpha_1 V_r}, \\ \frac{\mathrm{d}T_s(t)}{\mathrm{d}t} = (1-u)\frac{k_s V_s T}{1+\omega_1 V_s} - \delta T_s, \\ \frac{\mathrm{d}V_s(t)}{\mathrm{d}t} = N_s \delta T_s - cV_s, \\ \frac{\mathrm{d}T_r(t)}{\mathrm{d}t} = u\frac{k_s V_s T}{1+\omega_1 V_s} + \frac{k_r V_r T}{1+\alpha_1 V_r} - \delta T_r, \\ \frac{\mathrm{d}V_r(t)}{\mathrm{d}t} = N_r \delta T_r - cV_r. \end{cases} \tag{2}$$

The biological significance of variables and parameters in model (2) is given in Table 1.

In model (2), the parameter u $(0 < u < 1)$ is the conversion fraction at which cells infected by the wild-type mutate and become drug-resistant during the process of reverse transcription of viral RNA into proviral DNA (SR conversion, for short). It should be noted that the backward mutation from drug-resistant to wild-type strain is neglected since the wild-type virus dominates the population before the initiation of therapy (see [13, 14]).

Table 1 Biological significance of variables and parameters

Variable/Parameter	Description
$T(t)$	concentrations of uninfected target cells at time t
$T_s(t)$	concentrations of cells productively infected by wild-type virus at time t
$T_r(t)$	concentrations of cells productively infected by drug-resistant virus at time t
$V_s(t)$	concentrations of wild-type virus at time t
$V_r(t)$	concentrations of drug-resistant virus at time t
λ	recruitment rate of uninfected cells
d	death rate of uninfected cells
k_s	infection rate of target cells by wild-type virus
k_r	infection rate of target cells by drug-resistant virus
δ	death rate of infected cells
N_s	burst size of wild-type strain
N_r	burst size of drug-resistant strain
c	clearance rate of free virus

And the terms $\frac{k_s V_s T}{1+\omega_1 V_s}$ and $\frac{k_r V_r T}{1+\alpha_1 V_r}$ express the saturated incidence for virus V_s and V_r, where ω_1 and α_1 are the nonnegative constants. When $\omega_1 = 0$ or $\alpha_1 = 0$, the corresponding incidence degrades into bilinear incidence for V_s or V_r.

In [9], we see that model (1) with bilinear incidence is investigated. The authors only obtained the existence and local stability of the infection-free equilibrium, the equilibrium with only wild-type virus, drug-resistant virus, and the coexistence equilibrium (see Proposition 1 and Proposition 2 in [9]). We all know that in many realistic infectious diseases the nonlinear incidence rates play very important roles, and the global dynamics of the model, including the global asymptotic stability of equilibria, the uniform persistence, etc., also needs to be investigated in detail. In [5, 15], we see that the global dynamics for virus infection models with nonlinear incidence rates is discussed. Therefore, in this paper we carry out the research for a wild-type and drug-resistant HIV infection model with saturated incidence. We establish a series of threshold criteria for the local and global asymptotic stability of infection-free, drug-resistant strain infection equilibria, and the uniform persistence of HIV infection.

The organization of this paper is as follows. In Sect. 2, the nonnegativity and boundedness of solutions are established, and then the basic reproduction numbers of two strains and the existence of equilibria are obtained. In Sect. 3, the main theorems on the local and global stability of equilibria of model (2) are stated and proved. In Sect. 4, the uniform persistence of model (2) is also investigated. In Sect. 5, some numerical examples are given to illustrate our main results. In the last section, a brief conclusion is presented.

2 Preliminaries

For any integer $n > 0$, denote $R_+^n = \{(x_1, x_2, \dots, x_n) \in R^n : x_i \geq 0, i = 1, 2, \dots, n\}$. The initial condition for model (2) is given by

$$\big(T(0), T_s(0), V_s(0), T_r(0), V_r(0)\big) = (T_0, T_{s0}, V_{s0}, T_{r0}, V_{r0}) \in R_+^5. \tag{3}$$

Firstly, on the positivity and boundedness of solutions for model (2), we have the following result.

Theorem 1 *The solution* $(T(t), T_s(t), V_s(t), T_r(t), V_r(t))$ *of model* (2) *with initial condition* (3) *is defined for all* $t \in [0, \infty)$ *and is nonnegative and ultimately bounded.*

Proof On the nonnegativity of solutions, by the continuity of solutions with respect to initial values, we only need to prove that, for any positive initial value $(T_0, T_{s0}, V_{s0}, T_{r0}, V_{r0})$, the solution $(T(t), T_s(t), V_s(t), T_r(t), V_r(t))$ with initial condition (3) is also positive for any $t > 0$ in the definition interval. From the first equation of model (2), we have

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} > -\left(d + \frac{k_s V_s}{1 + \omega_1 V_s} + \frac{k_r V_r}{1 + \alpha_1 V_r}\right) T(t).$$

Hence, as $T_0 > 0$, we directly have $T(t) > 0$ for any $t > 0$ in the definition interval.

Define $m(t) = \min\{T_s(t), V_s(t), T_r(t), V_r(t)\}$. Obviously, $m(0) = \min\{T(0), T_s(0), V_s(0), T_r(0), V_r(0)\} > 0$. By the continuity of solutions there exists $\delta > 0$ such that $m(t) > 0$, when $t \in [0, \delta)$. We only need to prove $m(t) > 0$ for all $t \geq 0$ in the definition interval. Suppose that

there exists $t^* > 0$ such that $m(t^*) = 0$ and $m(t) > 0$ for all $t \in [0, t^*)$. Then there exist the following cases: (1) $m(t^*) = T_s(t^*)$, (2) $m(t^*) = V_s(t^*)$, (3) $m(t^*) = T_r(t^*)$, and (4) $m(t^*) = V_r(t^*)$.

For case (1), according to $m(t) > 0$ for all $t \in [0, t^*)$, from the second equation of model (2), we know $\frac{dT_s(t)}{dt} > -\delta T_s$. Thus, $T_s(t) > T_s(0)e^{-\delta t}$ for any $t \in [0, t^*)$. Taking $t \to t^*$, then $0 = T_s(t^*) \geq T_s(0)e^{-\delta t^*} > 0$, which leads to a contradiction. Similarly, we can get the contradiction for cases (2), (3) and (4). Therefore, $(T(t), T_s(t), V_s(t), T_r(t), V_r(t))$ is positive for all $t \geq 0$ in the definition interval.

Define a Lyapunov function

$$W(t) = T(t) + T_s(t) + \frac{1}{2N_s}V_s(t) + T_r(t) + \frac{1}{2N_r}V_r(t).$$

We have

$$\frac{dW(t)}{dt} = \lambda - dT - \frac{1}{2}\delta T_s - \frac{c}{2N_s}V_s - \frac{1}{2}\delta T_r - \frac{c}{2N_r}V_r \leq \lambda - nW(t),$$

where $n = \min\{d, \frac{\delta}{2}, c\}$. Since solution $U(t)$ of the comparison equation

$$\frac{dU(t)}{dt} = \lambda - nU(t)$$

with initial condition $U(0) = U_0 \geq 0$ is defined for all $t \in [0, \infty)$ and satisfies $\lim_{t\to\infty} U(t) = \frac{\lambda}{n}$, by the comparison principle, we directly have that $W(t)$ is bounded, and hence solution $(T(t), T_s(t), V_s(t), T_r(t), V_r(t))$ is also bounded. Thus, $(T(t), T_s(t), V_s(t), T_r(t), V_r(t))$ can be defined for all $t \in [0, \infty)$. Furthermore, since $W(t) \leq U(t)$ as $W(0) \leq U(0)$, we obtain that $\limsup_{t\to\infty} W(t) \leq \lim_{t\to\infty} U(t) = \frac{\lambda}{n}$. This implies that the solution $(T(t), T_s(t), V_s(t), T_r(t), V_r(t))$ is also ultimately bounded. This completes the proof. □

Following the concept of the basic reproductive number for an epidemic disease presented in [16], we define the wild-type strain infection reproduction number R_s and the drug-resistant strain infection reproduction number R_r as follows:

$$R_s = \frac{k_s N_s \lambda}{dc}, \qquad R_r = \frac{k_r N_r \lambda}{dc}.$$

The fraction $\frac{1}{c}$ gives the average life-span of a virus for strain i ($i = r, s$). $\frac{\lambda}{d}$ is the steady-state target cell density at the beginning of the strain i infection process (i.e. near the infection-free steady state). $k_i N_i$ gives the magnitude of virus particles produced by one strain i infectious (virus-producing) cell during its average survival time. Multiplying these quantities together gives the expected number of newly infected cells produced by a single newly for strain i infected cell, that is, R_i.

Now, we discuss the equilibrium of model (2). The equilibrium can be given from the following equations:

$$\begin{cases} \lambda - dT - \frac{k_s V_s T}{1+\omega_1 V_s} - \frac{k_r V_r T}{1+\alpha_1 V_r} = 0, \\ (1-u)\frac{k_s V_s T}{1+\omega_1 V_s} - \delta T_s = 0, \\ N_s \delta T_s - cV_s = 0, \\ u\frac{k_s V_s T}{1+\omega_1 V_s} + \frac{k_r V_r T}{1+\alpha_1 V_r} - \delta T_r = 0, \\ N_r \delta T_r - cV_r = 0. \end{cases} \tag{4}$$

Obviously, model (2) always has a unique infection-free equilibrium $E_0 = (\frac{\lambda}{d}, 0, 0, 0, 0)$. When $T_s > 0$ and $T_r = 0$, from (4) we directly have $V_r = 0$ and $V_s T = 0$, and then $T_s = 0$, which leads to a contradiction. When $T_s = 0$ and $T_r > 0$, from (4) we can obtain that if $R_r > 1$, then model (2) has a unique boundary equilibrium $E_r = (T_1, 0, 0, T_{r1}, V_{r1})$ with

$$T_1 = \frac{\lambda(k_r + d\alpha_1 R_r)}{dR_r(k_r + d\alpha_1)}, \qquad T_{r1} = \frac{dc(R_r - 1)}{N_r\delta(k_r + d\alpha_1)}, \qquad V_{r1} = \frac{d(R_r - 1)}{k_r + d\alpha_1},$$

and if $R_r \leq 1$, then E_r does not exist. When $T_s > 0$ and $T_r > 0$, from (4) we can obtain that

$$T_r = \frac{\lambda}{\delta} - T_s - \frac{\lambda(1 + \omega_1 \frac{\delta}{c} N_s T_s)}{\delta(1-u)R_s} := T_r(T_s) \tag{5}$$

and

$$T_s = \frac{\frac{\lambda}{\delta}((1-u)R_s - 1) + (((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r - R_r)T_r}{R_s + \omega_1 \frac{\lambda}{c} N_s + ((R_s + \omega_1 \frac{\lambda}{c} N_s)\alpha_1 \frac{\delta}{c} N_r + \omega_1 \frac{\delta}{c} N_s R_r)T_r} := T_s(T_r). \tag{6}$$

Clearly, functions $T_r(T_s)$ and $T_s(T_r)$ are decreasing in $T_s \geq 0$ and $T_r \geq 0$, respectively. We have

$$T_r(0) = \frac{\lambda}{\delta R_s(1-u)}\big((1-u)R_s - 1\big), \qquad T_r(+\infty) = -\infty,$$

$$T_s(0) = \frac{\frac{\lambda}{\delta}((1-u)R_s - 1)}{R_s + \omega_1 \frac{\lambda}{c} N_s}, \qquad T_s(+\infty) = \frac{((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r - R_r}{(R_s + \omega_1 \frac{\lambda}{c} N_s)\alpha_1 \frac{\delta}{c} N_r + \omega_1 \frac{\delta}{c} N_s R_r}.$$

Furthermore, from $T_r(T_s) = 0$ and $T_s(T_r) = 0$, we obtain

$$T_s^* = \frac{\lambda((1-u)R_s - 1)}{\delta(1-u)R_s + \lambda\omega_1 \frac{\delta}{c} N_s}, \qquad T_r^* = \frac{\frac{\lambda}{\delta}((1-u)R_s - 1)}{R_r - ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r}.$$

It is easy to verify that $T_s(0) < T_s^*$ when $(1-u)R_s > 1$. From $T_r(0) < T_r^*$ we let

$$R_r = (1-u)R_s + \big((1-u)R_s - 1\big)\alpha_1 \frac{\lambda}{c} N_r := R_{ru}(R_s).$$

This shows that curves $T_r(T_s)$ and $T_s(T_r)$ have a unique intersection point (T_{sc}, T_{rc}) in the positive quadrant, which means $E_c = (T_c, T_{sc}, V_{sc}, T_{rc}, V_{rc})$ is the unique positive equilibrium of model (2). Thus, we finally have the following results.

Theorem 2

(i) *Model* (2) *always has a unique infection-free equilibrium* E_0;

(ii) *If* $R_r > \max\{1, (1-u)R_s + ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r\}$, *then model* (2) *only has equilibria* E_0 *and* E_r;

(iii) *If* $(1-u)R_s > 1 \geq R_r$, *then model* (2) *only has equilibria* E_0 *and* E_c;

(iv) *If* $(1-u)R_s + ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r > R_r > 1$, *then model* (2) *has three equilibria* E_0, E_r, *and* E_c.

The existence of equilibria for model (2) is also intuitively expressed in Fig. 1. From Theorem 2 and Fig. 1, we can find that the saturated coefficient ω_1 of wild-type virus V_s

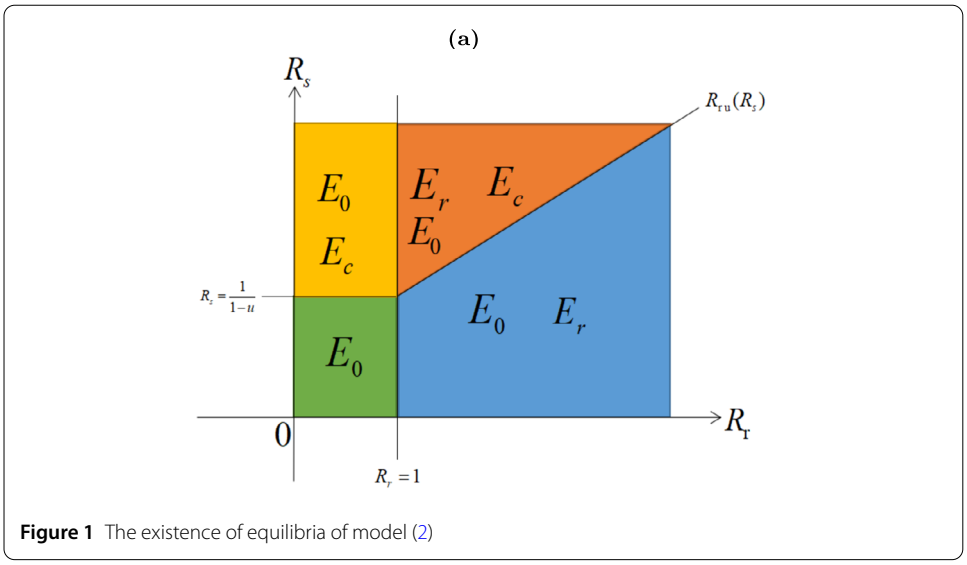

Figure 1 The existence of equilibria of model (2)

has no effect on Fig. 1. Along with the decreasing of saturated coefficient α_1, the orange region will shrink, and it finally becomes the region $\{(R_s, R_r) : (1-u)R_s > R_r > 1\}$ as $\alpha_1 \to 0$. On the contrary, along with the increasing of saturated coefficient α_1, the orange region will enlarge, and it finally becomes the region $\{(R_s, R_r) : (1-u)R_s > 1, R_r > 1\}$ as $\alpha_1 \to +\infty$.

3 Stability of equilibrium

Let $E = (T, T_s, V_s, T_r, V_r)$ be any equilibrium of model (2). By calculating, we get that the Jacobian matrix at equilibria E is

$$J(E) = \begin{pmatrix} -d - \frac{k_s V_s}{1+\omega_1 V_s} - \frac{k_r V_r}{1+\alpha_1 V_r} & 0 & -\frac{k_s T}{(1+\omega_1 V_s)^2} & 0 & -\frac{k_r T}{(1+\alpha_1 V_r)^2} \\ (1-u)\frac{k_s V_s}{1+\omega_1 V_s} & -\delta & (1-u)\frac{k_s T}{(1+\omega_1 V_s)^2} & 0 & 0 \\ 0 & N_s\delta & -c & 0 & 0 \\ u\frac{k_s V_s}{1+\omega_1 V_s} + \frac{k_r V_r}{1+\alpha_1 V_r} & 0 & u\frac{k_s T}{(1+\omega_1 V_s)^2} & -\delta & \frac{k_r T}{(1+\alpha_1 V_r)^2} \\ 0 & 0 & 0 & N_r\delta & -c \end{pmatrix}. \tag{7}$$

Firstly, for the stability of equilibrium E_0, we have the following results.

Theorem 3

(a) *If* $(1-u)R_s < 1$ *and* $R_r < 1$, *then infection-free equilibrium* E_0 *is locally asymptotically stable*.

(b) *If* $R_s \le 1$ *and* $R_r \le 1$, *then* E_0 *is globally asymptotically stable*.

(c) *If* $(1-u)R_s > 1$ *or* $R_r > 1$, *then* E_0 *is unstable*.

Proof At equilibrium E_0, from (7) the characteristic equation of $J(E_0)$ is

$$f(X) = (X+d)\big(X^2 + (\delta+c)X + \delta c\big(1-(1-u)R_s\big)\big)\big(X^2 + (\delta+c)X + \delta c(1-R_r)\big) = 0. \tag{8}$$

One root of (8) is $X_1 = -d < 0$. When $(1-u)R_s < 1$ and $R_r < 1$, by the Routh–Hurwitz criterion, all roots of the equations

$$X^2 + (\delta+c)X + \delta c\big(1-(1-u)R_s\big) = 0 \tag{9}$$

and

$$X^2 + (\delta + c)X + \delta c(1 - R_r) = 0 \tag{10}$$

have negative real parts, respectively. This implies that E_0 is locally asymptotically stable. When $(1-u)R_s > 1$ or $R_r > 1$, we easily see that equation (9) or (10) has at least a root with positive real part. This implies that E_0 is unstable.

For the global stability of E_0, we define Lyapunov function $L_1(t)$ as follows:

$$L_1(t) = T_0\left(\frac{T}{T_0} - \ln\frac{T}{T_0} - 1\right) + T_s + \frac{1}{N_s}V_s + T_r + \frac{1}{N_r}V_r.$$

We have

$$\begin{aligned}\frac{\mathrm{d}L_1(t)}{\mathrm{d}t} &= \left(1 - \frac{T_0}{T}\right)\left(\lambda - dT - \frac{k_s V_s T}{1+\omega_1 V_s} - \frac{k_r V_r T}{1+\alpha_1 V_r}\right) + \left((1-u)\frac{k_s V_s T}{1+\omega_1 V_s} - \delta T_s\right)\\ &\quad + \left(u\frac{k_s V_s T}{1+\omega_1 V_s} + \frac{k_r V_r T}{1+\alpha_1 V_r} - \delta T_r\right) + \frac{1}{N_r}(N_r\delta T_r - cV_r) + \frac{1}{N_s}(N_s\delta T_s - cV_s)\\ &= dT_0\left(2 - \frac{T}{T_0} - \frac{T_0}{T}\right) + \frac{c(R_s-1)}{(1+\omega_1 V_s)N_s}V_s - \frac{c\omega_1 V_s^2}{(1+\omega_1 V_s)N_s}\\ &\quad + \frac{c(R_r-1)}{(1+\alpha_1 V_r)N_r}V_r - \frac{c\alpha_1 V_r^2}{(1+\alpha_1 V_r)N_r}.\end{aligned}$$

When $R_s \le 1$ and $R_r \le 1$, then $\frac{\mathrm{d}L_1(t)}{\mathrm{d}t} \le 0$ and the set $M = \{(T, T_s, V_s, T_r, V_r) : \frac{\mathrm{d}L_1(t)}{\mathrm{d}t} = 0\} \subset \{(T, T_s, V_s, T_r, V_r) : T = T_0, T_s \ge 0, V_s \ge 0, T_r \ge 0, V_r \ge 0\}$.

For any solution trajectory $\{(T(t), T_s(t), V_s(t), T_r(t), V_r(t)) : t \ge 0\} \subset M$, we have $T(t) \equiv T_0$. From the first equation of model (4), we obtain $\frac{k_s V_s(t) T_0}{1+\omega_1 V_s(t)} + \frac{k_r V_r(t) T_0}{1+\alpha_1 V_r(t)} \equiv 0$, which implies $V_s(t) = V_r(t) \equiv 0$. From the third and fifth equations of model (4), we also get $N_s\delta T_s(t) - cV_s(t) = 0$ and $N_r\delta T_r(t) - cV_r(t) = 0$, which further imply $T_s(t) = T_r(t) \equiv 0$. Hence, $(T(t), T_s(t), V_s(t), T_r(t), V_r(t)) \equiv E_0$. From LaSalle's invariance principle [17], E_0 is globally asymptotically stable. This completes the proof. □

Remark 1 In Theorem 3, we only obtained the global asymptotic stability of E_0 under $R_s \le 1$ and $R_r \le 1$. Therefore, based on conclusion (a) of Theorem 3, an interesting open problem is whether we can establish the global asymptotic stability of E_0 when $(1-u)R_s \le 1$ and $R_r \le 1$.

Next, about the stability of equilibrium E_r, we have the following results.

Theorem 4

(a) *If* $R_r > \max\{1, (1-u)R_s + ((1-u)R_s - 1)\alpha_1\frac{\lambda}{c}N_r\}$, *then equilibrium* E_r *is locally asymptotically stable.*
(b) *If* $R_r > 1$ *and* $R_r < (1-u)R_s + ((1-u)R_s - 1)\alpha_1\frac{\lambda}{c}N_r$, *then* E_r *is unstable.*
(c) *If* $R_r > \max\{1, R_s + \alpha_1\frac{\lambda}{c}N_r(R_s - 1)\}$, *then* E_r *is globally asymptotically stable.*

Proof At equilibrium E_r, from (7) the characteristic equation of $J(E_r)$ is

$$f(X) = \left(X^2 + a_1X + a_0\right)\left(X^3 + b_2X^2 + b_1X + b_0\right) = 0, \tag{11}$$

where

$$a_1 = \delta + c, \qquad a_0 = \delta c \frac{k_r(R_r - (1-u)R_s - ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r)}{R_r(k_r + d\alpha_1)},$$

$$b_2 = d + c + \delta + \frac{dk_r(R_r - 1)}{k_r + d\alpha_1}, \qquad b_1 = d(\delta + c) + \frac{\delta c\alpha_1 + k_r(\delta + c)}{k_r + d\alpha_1 R_r} d(R_r - 1),$$

$$b_0 = \frac{k_r + d\alpha_1}{k_r + d\alpha_1 R_r} d\delta c(R_r - 1).$$

When $R_r > \max\{1, (1-u)R_s + ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r\}$, we have $a_i > 0$ and $b_i > 0$ for $i = 0, 1, 2$. Since

$$\begin{aligned} b_1 b_2 - b_0 = {} & \left(d(\delta + c) + \frac{d\delta k_r(R_r - 1)}{k_r + d\alpha_1 R_r}\right)\left(d + c + \delta + \frac{dk_r(R_r - 1)}{k_r + d\alpha_1 R_r}\right) \\ & + \frac{dck_r(R_r - 1)}{k_r + d\alpha_1 R_r}\left(d + c + \frac{dk_r(R_r - 1)}{k_r + d\alpha_1 R_r}\right) \\ & + \frac{d\delta c\alpha_1(R_r - 1)}{k_r + d\alpha_1 R_r}\left(\delta + c + \frac{dk_r(R_r - 1)}{k_r + d\alpha_1 R_r}\right) > 0. \end{aligned}$$

According to the Routh–Hurwitz criterion, all roots of equation (11) have negative real parts. Therefore, E_r is locally asymptotically stable. When $R_r > 1$ and $R_r < (1-u)R_s + ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r$, the equation $X^2 + a_1 X + a_0 = 0$ has at least a positive real part root. This implies that E_r is unstable.

To obtain the global stability of E_r, we define Lyapunov function $L_2(t)$ as follows:

$$\begin{aligned} L_2(t) = {} & T_1\left(\frac{T}{T_1} - \ln\frac{T}{T_1} - 1\right) + T_s + \frac{1}{N_s} V_s + T_{r1}\left(\frac{T_r}{T_{r1}} - \ln\frac{T_r}{T_{r1}} - 1\right) \\ & + \frac{1}{N_r} V_{r1}\left(\frac{V_r}{V_{r1}} - \ln\frac{V_r}{V_{r1}} - 1\right). \end{aligned}$$

We have

$$\begin{aligned} \frac{\mathrm{d}L_2(t)}{\mathrm{d}t} = {} & \left(1 - \frac{T_1}{T}\right)\left(\lambda - dT - \frac{k_s V_s T}{1 + \omega_1 V_s} - \frac{k_r V_r T}{1 + \alpha_1 V_r}\right) + \left((1-u)\frac{k_s V_s T}{1 + \omega_1 V_s} - \delta T_s\right) \\ & + \frac{1}{N_s}(N_s \delta T_s - cV_s) + \left(1 - \frac{T_{r1}}{T_r}\right)\left(u\frac{k_s V_s T}{1 + \omega_1 V_s} + \frac{k_r V_r T}{1 + \alpha_1 V_r} - \delta T_r\right) \\ & + \frac{1}{N_r}\left(1 - \frac{V_{r1}}{V_r}\right)(N_r \delta T_r - cV_r) \\ = {} & dT_1\left(2 - \frac{T}{T_1} - \frac{T_1}{T}\right) + \frac{k_r V_{r1} T_1}{1 + \alpha_1 V_{r1}}\left(4 - \frac{T_1}{T} - \frac{T_r V_{r1}}{T_{r1} V_r} - \frac{T_{r1} V_r T}{T_r V_{r1} T_1}\frac{1 + \alpha_1 V_{r1}}{1 + \alpha_1 V_r}\right. \\ & \left. - \frac{1 + \alpha_1 V_r}{1 + \alpha_1 V_{r1}}\right) - \frac{k_r V_{r1} T_1}{1 + \alpha_1 V_{r1}} \frac{\alpha_1 (V_r - V_{r1})^2}{(1 + \alpha_1 V_{r1}) V_{r1} (1 + \alpha_1 V_r)} \\ & - \frac{ck_r(R_r - R_s - \alpha_1 \frac{\lambda}{c} N_r(R_s - 1))}{R_r(k_r + d\alpha_1)(1 + \omega_1 V_s) N_s} V_s - u\frac{k_s V_s T}{1 + \omega_1 V_s}\frac{T_{r1}}{T_r} - \frac{c\omega_1}{(1 + \omega_1 V_s) N_s} V_s^2. \end{aligned}$$

Obviously, when $R_r > \max\{1, R_s + \alpha_1 \frac{\lambda}{c} N_r(R_s - 1)\}$, we have $\frac{\mathrm{d}L_2(t)}{\mathrm{d}t} \le 0$ and the set $M = \{(T, T_s, V_s, T_r, V_r) : \frac{\mathrm{d}L_2(t)}{\mathrm{d}t} = 0\} \subseteq \{(T, T_s, V_s, T_r, V_r) : T = T_1, T_s \ge 0, V_s \ge 0, T_r = T_{r1}, V_r =$

$V_{r1}\}$. From $T(t) \equiv T_1$, $T_r(t) \equiv T_{r1}$ and $V_r(t) \equiv V_{r1}$, we have $\lambda - dT_1 - \frac{k_s V_s(t) T_1}{1+\omega_1 V_s(t)} - \frac{k_r V_{r1} T_1}{1+\alpha_1 V_{r1}} \equiv 0$, which implies $V_s(t) \equiv 0$. From the third equation of model (4), we get $N_s \delta T_s(t) - c V_s(t) \equiv 0$, which implies $T_s(t) \equiv 0$. Hence, $(T(t), T_s(t), V_s(t), T_r(t), V_r(t)) \equiv E_r$. Thus, LaSalle's invariance principle implies that E_r is globally asymptotically stable. This completes the proof. □

Remark 2 In Theorem 4, we only obtained the global asymptotic stability of E_r when $R_r > \max\{1, R_s + \alpha_1 \frac{\lambda}{c} N_r (R_s - 1)\}$. Therefore, combining conclusion (a) of Theorem 4 an interesting open problem is whether we can establish the global asymptotic stability of E_r when $R_r > \max\{1, (1-u)R_s + ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r\}$.

Remark 3 It is regretful that we here do not establish the corresponding criteria on the local and global stability for positive equilibrium E_c of model (2). The reasons are that the analysis of the characteristic equation of $J(E_c)$ is very complex, and the construction of a suitable Lyapunov function is also very difficult. However, in the next section we can establish the uniform persistence of model (2) when positive equilibrium E_c exists.

4 Uniform persistence

Theorem 5 *If* $(1-u)R_s > 1 \geq R_r$ *or* $(1-u)R_s + ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r > R_r > 1$, *then model* (2) *is uniformly persistent. That is, there exists a positive constant* δ *such that, for any positive solution* $(T(t), T_s(t), V_s(t), T_r(t), V_r(t))$ *of model* (2),

$$\liminf_{t\to\infty} T(t) \geq \delta, \qquad \liminf_{t\to\infty} T_s(t) \geq \delta, \qquad \liminf_{t\to\infty} V_s(t) \geq \delta,$$

$$\liminf_{t\to\infty} T_r(t) \geq \delta, \qquad \liminf_{t\to\infty} V_r(t) \geq \delta.$$

Proof For any $x_0 = (T_0, T_{s0}, V_{s0}, T_{r0}, V_{r0}) \in R^5_+$, let $u(t, x_0) = (T(t, x_0), T_s(t, x_0), V_s(t, x_0), T_r(t, x_0), V_r(t, x_0))$ be the solution of model (2) with the initial condition $u(0, x_0) = x_0$. From the proof of Theorem 1, we have $\limsup_{t\to\infty} u(t, x_0) \leq \frac{\lambda}{n}$, where $n = \min\{d, \frac{\delta}{2}, c\}$. Hence, for any constant $\epsilon > 0$, there is $T_0 > 0$, when $t \geq T_0$ we get $u(t, x_0) < \frac{\lambda}{n} + \epsilon$. Then, from the first equation of model (2), we have

$$\frac{\mathrm{d}T(t, x_0)}{\mathrm{d}t} \geq \lambda - dT - k_s V_s T - k_r V_r T \geq \lambda - \left(d + (k_s + k_r)\left(\frac{\lambda}{n} + \epsilon\right)\right) T(t, x_0).$$

From the comparison theorem and the arbitrariness of ϵ, we have

$$\liminf_{t\to\infty} T(t, x_0) \geq \frac{\lambda}{d + (k_s + k_r)\frac{\lambda}{n}}.$$

This shows that $T(t, x_0)$ is uniformly persistent.

Define

$$X = \left\{x = (T, T_s, V_s, T_r, V_r) \in R^5_+ : T \geq 0, T_s > 0, V_s > 0, T_r > 0, V_r > 0\right\}.$$

The boundary of X is

$$\partial X = \left\{(T, T_s, V_s, T_r, V_r) \in R^5_+ : T \geq 0, T_s = 0 \text{ or } V_s = 0 \text{ or } T_r = 0 \text{ or } V_r = 0\right\}.$$

Denote

$$M_\partial = \left\{x_0 \in R_+^5 : u(t,x_0) \in \partial X, \forall t \geq 0\right\}.$$

Let $\omega(x_0)$ be the ω-limit set of solution $u(t,x_0)$. Then we consider the following two cases.

Case (1): $(1-u)R_s > 1 \geq R_r$. From Theorem 2, model (2) has only two equilibria E_0 and E_c. Let $M_0 = \{E_0\}$. It is clear that $M_0 \subset \bigcup_{x_0 \in M_\partial} \omega(x_0)$. For any $x_0 \in M_\partial$, let $x_0 = (T_0, T_{s0}, V_{s0}, T_{r0}, V_{r0})$. Due to $u(t,x_0) \in \partial X$ for all $t \geq 0$, we have $T_s(t,x_0) \equiv 0$ or $V_s(t,x_0) \equiv 0$ or $T_r(t,x_0) \equiv 0$ or $V_r(t,x_0) \equiv 0$. If $T_s(t,x_0) \equiv 0$, then from the second equation of model (2), we have $V_s(t,x_0) \equiv 0$. Thus, model (2) degenerates into the following form:

$$\begin{cases} \frac{\mathrm{d}T(t,x_0)}{\mathrm{d}t} = \lambda - dT(t,x_0) - \frac{k_r V_r(t,x_0) T(t,x_0)}{1+\alpha_1 V_r(t,x_0)}, \\ \frac{\mathrm{d}T_r(t,x_0)}{\mathrm{d}t} = \frac{k_r V_r(t,x_0) T(t,x_0)}{1+\alpha_1 V_r(t,x_0)} - \delta T_r(t,x_0), \\ \frac{\mathrm{d}V_r(t,x_0)}{\mathrm{d}t} = N_r \delta T_r(t,x_0) - cV_r(t,x_0). \end{cases} \tag{12}$$

If $T_{r0} + V_{r0} = 0$, then from system (12) we can obtain $T_r(t,x_0) \equiv V_r(t,x_0) \equiv 0$. Thus, model (2) can further degenerate into

$$\frac{\mathrm{d}T(t,x_0)}{\mathrm{d}t} = \lambda - dT(t,x_0).$$

It follows that $\lim_{t\to\infty} T(t,x_0) = \frac{\lambda}{d} = T_0$. This shows that $\omega(x_0) = E_0 \subset M_0$.

If $T_{r0} + V_{r0} > 0$, without loss of generality, we assume $T_{r0} > 0$ and $V_{r0} \geq 0$. From the second equation of system (12), we can obtain $T_r(t,x_0) \geq T_{r0}e^{-\delta t} > 0$ for all $t \geq 0$, and then, from the third equation of (12), we further obtain $V_r(t,x_0) > V_{r0}e^{-ct} \geq 0$ for all $t > 0$. Choose a Lyapunov function as follows:

$$U_0(t) = T_0\left(\frac{T}{T_0} - \ln\frac{T}{T_0} - 1\right) + T_r + \frac{1}{N_r}V_r.$$

We obtain

$$\frac{\mathrm{d}U_0(t)}{\mathrm{d}t} = dT_0\left(2 - \frac{T_0}{T} - \frac{T}{T_0}\right) + \frac{c}{N_r}(R_r - 1)V_r - \frac{c\alpha_1 V_r^2}{(1+\alpha_1 V_r)N_r} \leq 0$$

and $\{(T,T_r,V_r) : \frac{\mathrm{d}U_0(t)}{\mathrm{d}t} = 0\} \subset \{(T,T_r,V_r) : T = T_0\}$. If $T(t,x_0) \equiv T_0$, then from the first equation of system (12), we have $V_r(t,x_0) \equiv 0$; further, from the third equation of system (12), we have $T_r(t,x_0) \equiv 0$. Thus, LaSalle's invariance principle [17] implies that $(T(t,x_0), T_r(t,x_0), V_r(t,x_0)) \to (T_0,0,0)$ when $t \to \infty$. This shows that $\omega(x_0) = E_0 \subset M_0$.

If $V_s(t,x_0) \equiv 0$, from the third equation of model (2), we have $T_s(t,x_0) \equiv 0$. Similar to the above argument, we also get $\omega(x_0) = E_0 \subset M_0$.

If $T_r(t,x_0) \equiv 0$, from the fourth equation of model (2), we have $V_s(t,x_0) \equiv 0$ and $V_r(t,x_0) \equiv 0$. Then, from the third equation of model (2), we have $T_s(t,x_0) \equiv 0$. Thus, model (2) degenerates into

$$\frac{\mathrm{d}T(t,x_0)}{\mathrm{d}t} = \lambda - dT(t,x_0).$$

It follows that $\lim_{t\to\infty} T(t,x_0) = T_0$. This shows that $\omega(x_0) = E_0 \subset M_0$.

If $V_r(t,x_0) \equiv 0$, from the fifth equation of model (2), we get $T_r(t,x_0) \equiv 0$. Similar to the above argument, we also get $\omega(x_0) = E_0 \subset M_0$.

Finally, we have $M_0 = \bigcup_{x_0 \in M_\partial} \omega(x_0)$. Furthermore, it is clear that M_0 is isolated invariant and non-cycle in ∂X.

Now, we prove that $W^s(E_0) \cap X = \emptyset$, where $W^s(E_0)$ is the stable set of E_0. Suppose that there is an $x_0 \in X$ such that $\lim_{t\to\infty} u(t,x_0) = E_0$, then we have $\lim_{t\to\infty} T(t,x_0) = T_0$. Hence, for any constant $\epsilon > 0$, there is $T^* > 0$ such that $T(t,x_0) \geq T_0 - \epsilon$ and $V_s(t,x_0) < \epsilon$ for any $t \geq T^*$. Define the function

$$U_1(t) = T_s(t,x_0) + \frac{1}{N_s} V_s(t,x_0).$$

We have $\lim_{t\to\infty} U_1(t,x_0) = 0$. When $t \geq T^*$, we have

$$\begin{aligned}\frac{\mathrm{d}U_1(t)}{\mathrm{d}t} &= (1-u)\frac{k_s V_s(t,x_0) T(t,x_0)}{1+\omega_1 V_s(t,x_0)} - \delta T_s(t,x_0) + \frac{1}{N_s}\big(N_s \delta T_s(t,x_0) - c V_s(t,x_0)\big) \\ &\geq \left((1-u)\frac{k_s(T_0-\epsilon)}{1+\omega_1\epsilon} - \frac{c}{N_s}\right) V_s(t,x_0).\end{aligned}$$

Due to $(1-u)R_s > 1$, we choose enough small $\epsilon > 0$ such that $(1-u)\frac{k_s(T_0-\epsilon)}{1+\omega_1\epsilon} - \frac{c}{N_s} > 0$. Thus, $U_1(t)$ is increasing for $t \geq T^*$. Hence, we know that $U_1(t)$ does not tend to zero as $t \to \infty$, which leads to a contradiction. This shows that $W^s(E_0) \cap X = \emptyset$. According to the theory of persistence in dynamical systems (see [18]), there is a constant $\delta > 0$ such that, for any $x_0 \in X$, one has

$$\begin{aligned}&\liminf_{t\to\infty} T_s(t,x_0) \geq \delta, \qquad \liminf_{t\to\infty} V_s(t,x_0) \geq \delta, \qquad \liminf_{t\to\infty} T_r(t,x_0) \geq \delta, \\ &\liminf_{t\to\infty} V_r(t,x_0) \geq \delta.\end{aligned}$$

This shows that model (2) is uniformly persistent.

Case (2): $(1-u)R_s + ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r > R_r > 1$. From Theorem 2, model (2) has three equilibria E_0, E_r, and E_c. Denote $M_0 = \{E_0, E_r\}$. It is clear that $M_0 \subset \bigcup_{x_0 \in M_\partial} \omega(x_0)$. For any $x_0 \in M_\partial$, let $x_0 = (T_0, T_{s0}, V_{s0}, T_{r0}, V_{r0})$. Due to $u(t,x_0) \in \partial X$ for all $t \geq 0$, we have $T_s(t,x_0) \equiv 0$ or $V_s(t,x_0) \equiv 0$ or $T_r(t,x_0) \equiv 0$ or $V_r(t,x_0) \equiv 0$. If $T_s(t,x_0) \equiv 0$, then, similar to the above argument, model (2) degenerates into system (12).

If $T_{r0} + V_{r0} = 0$, from a similar argument as in case (1), we can obtain $\omega(x_0) = E_0 \subset M_0$.

If $T_{r0} + V_{r0} > 0$, then we also can obtain $T_r(t,x_0) > 0$ and $V_r(t,x_0) > 0$ for all $t > 0$. Choose the Lyapunov function

$$U_2(t) = T_1\left(\frac{T}{T_1} - \ln\frac{T}{T_1} - 1\right) + T_{r1}\left(\frac{T_r}{T_{r1}} - \ln\frac{T_r}{T_{r1}} - 1\right) + \frac{1}{N_r} V_{r1}\left(\frac{V_r}{V_{r1}} - \ln\frac{V_r}{V_{r1}} - 1\right).$$

Then we have

$$\begin{aligned}\frac{\mathrm{d}U_2(t)}{\mathrm{d}t} &= dT_1\left(2 - \frac{T_1}{T} - \frac{T}{T_1}\right) + \frac{k_r V_{r1} T_1}{1+\alpha_1 V_{r1}}\left(4 - \frac{T_1}{T} - \frac{T_r V_{r1}}{T_{r1} V_r} - \frac{T_{r1} V_r T}{T_r V_{r1} T_1}\frac{1+\alpha_1 V_{r1}}{1+\alpha_1 V_r}\right. \\ &\quad \left. - \frac{1+\alpha_1 V_r}{1+\alpha_1 V_{r1}}\right) - \frac{k_r V_{r1} T_1}{1+\alpha_1 V_{r1}} \frac{\alpha_1 (V_r - V_{r1})^2}{(1+\alpha_1 V_{r1}) V_{r1} (1+\alpha_1 V_r)} \leq 0\end{aligned}$$

and the set $\{(T, T_r, V_r) : \frac{dU_2(t)}{dt} = 0\} = \{(T_1, T_{r1}, V_{r1})\}$. Hence, LaSalle's invariance principle [17] implies that $(T(t,x_0), T_r(t,x_0), V_r(t,x_0)) \to (T_1, T_{r1}, V_{r1})$ as $t \to \infty$. This shows that $\omega(x_0) = E_r \subset M_0$.

If $V_s(t,x_0) \equiv 0$ or $T_r(t,x_0) \equiv 0$ or $V_r(t,x_0) \equiv 0$, then, following a similar argument as in case (1), we can also obtain $\omega(x_0) = E_0$ or $\omega(x_0) = E_r$, and hence $\omega(x_0) \subset M_0$.

Finally, we have $M_0 = \bigcup_{x_0 \in M_\partial} \omega(x_0)$. Furthermore, it is clear that E_0 and E_r are isolated invariant and M_0 is non-cycle in ∂X.

Now, we prove that $W^s(E_0) \cap X = \emptyset$ and $W^s(E_r) \cap X = \emptyset$. Similar to the above argument in case (1) we can get $W^s(E_0) \cap X = \emptyset$. Suppose that there is $x_0 \in X$ such that $\lim_{t\to\infty} u(t,x_0) = E_r$, then we have $\lim_{t\to\infty} T(t,x_0) = T_1$. Hence, for any constant $\epsilon > 0$, there is $T^* > 0$ such that $T(t,x_0) \geq T_1 - \epsilon$ and $V_s(t,x_0) < \epsilon$ for any $t \geq T^*$. Define the function

$$U_3(t) = T_s(t,x_0) + \frac{1}{N_s} V_s(t,x_0).$$

We have $\lim_{t\to\infty} U_3(t,x_0) = 0$. When $t \geq T^*$, we have

$$\begin{aligned}\frac{dU_3(t)}{dt} &= (1-u)\frac{k_s V_s(t,x_0) T(t,x_0)}{1+\omega_1 V_s(t,x_0)} - \delta T_s(t,x_0) + \frac{1}{N_s}\big(N_s \delta T_s(t,x_0) - c V_s(t,x_0)\big) \\ &\geq \left((1-u)\frac{k_s(T_1-\epsilon)}{1+\omega_1\epsilon} - \frac{c}{N_s}\right) V_s(t,x_0).\end{aligned}$$

Due to $(1-u)R_s + ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r > R_r > 1$, we choose enough small $\epsilon > 0$ such that $(1-u)\frac{k_s(T_1-\epsilon)}{1+\omega_1\epsilon} - \frac{c}{N_s} > 0$. Then $U_3(t)$ is increasing for $t \geq T^*$. Thus, we know that $U_3(t)$ does not tend to zero, which leads to a contradiction. Hence, $W^s(E_r) \cap X = \emptyset$. According to the theory of persistence in dynamical systems (see [18]), there is a constant $\delta > 0$ such that, for any $x_0 \in X$, one has

$$\liminf_{t\to\infty} T_s(t,x_0) \geq \delta, \qquad \liminf_{t\to\infty} V_s(t,x_0) \geq \delta, \qquad \liminf_{t\to\infty} T_r(t,x_0) \geq \delta,$$

$$\liminf_{t\to\infty} V_r(t,x_0) \geq \delta.$$

This shows that model (2) is also uniformly persistent. This completes the proof. □

Remark 4 An interesting open problem is whether the positive equilibrium E_c is also globally asymptotically stable when the conditions in Theorem 5 are satisfied.

5 Numerical examples

In this section, we provide the numerical examples to illustrate the global asymptotic stability of the equilibria for model (2), and Examples 1 and 2 can further verify Remarks 1 and 2, respectively.

Example 1 In model (2), we take the parameters $\lambda = 10^5$, $d = 0.1$, $k_s = 1.0 \times 10^{-8}$, $k_r = 1.0 \times 10^{-8}$, $u = 0.6$, $\delta = 1$, $N_s = 2000$, $N_r = 900$, $c = 11$, $\omega_1 = 10^{-5}$, and $\alpha_1 = 10^{-4}$. By calculating, we have $R_s \approx 1.8182 > 1$, $(1-u)R_s \approx 0.7273 < 1$, and $R_r \approx 0.8182 < 1$. Furthermore, we also have the infection-free equilibrium $E_0 = (10^6, 0, 0, 0, 0)$. We give three different groups of initial values in Table 2.

The numerical simulations given in Fig. 2 illustrate that equilibrium E_0 may be globally asymptotically stable. This shows that the open problem given in Remark 1 may be right.

Table 2 Initial values of model (2)

	T_0	T_{s0}	V_{s0}	T_{r0}	V_{r0}
1	10^5	10^2	10^3	10^4	10^2
2	8×10^4	4×10^3	5×10^4	10^2	10^3
3	9×10^5	10^4	7×10^5	6×10^2	7×10^2

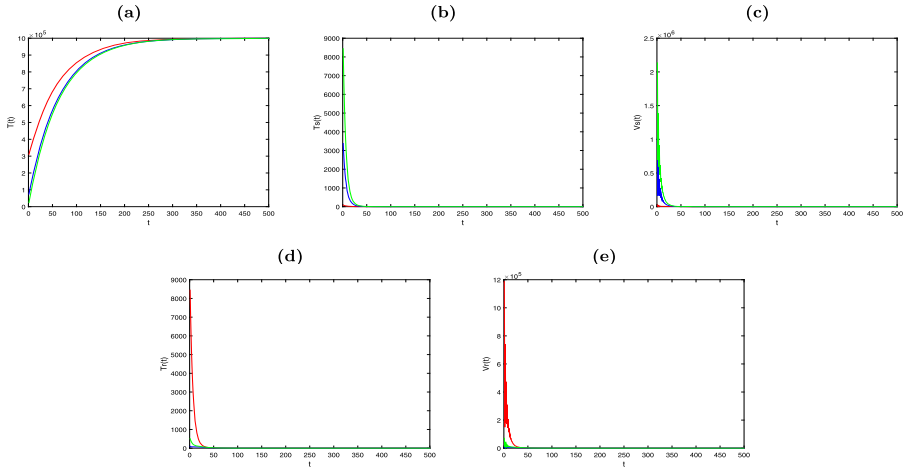

Figure 2 (**a**) Dynamical behaviors of uninfected target cells; (**b**) Dynamical behaviors of infected cells infected by wild-type virus; (**c**) Dynamical behaviors of drug-resistant virus; (**d**) Dynamical behaviors of infected cells infected by wild-type virus; (**e**) Dynamical behaviors of drug-resistant virus

Table 3 Initial values of model (2)

	T_0	T_{s0}	V_{s0}	T_{r0}	V_{r0}
1	10^6	9×10^3	10^7	10^5	10^5
2	8×10^4	4×10^5	5×10^6	10^3	3×10^3
3	9×10^5	3×10^2	6×10^5	5×10^4	6×10^4

Example 2 In model (2), we take the parameters $\lambda = 10^5$, $d = 0.005$, $k_s = 1.2 \times 10^{-9}$, $k_r = 1.0 \times 10^{-8}$, $u = 0.6$, $\delta = 1$, $N_s = 2000$, $N_r = 250$, $c = 10$, $\omega_1 = 10^{-3}$, and $\alpha_1 = 10^{-7}$. By calculating, we have $R_r = 5$, $(1-u)R_s + ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r = 2.15$ and $R_s + (R_s - 1)\alpha_1 \frac{\lambda}{c} N_r = 5.75$. Hence, $\max\{1, (1-u)R_s + ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r\} < R_r < R_s + (R_s - 1)\alpha_1 \frac{\lambda}{c} N_r$. Furthermore, we also have the boundary equilibrium $E_r = (4.76 \times 10^6, 0, 0, 7.62 \times 10^4, 1.90 \times 10^6)$. We give three different groups of initial values in Table 3.

The numerical simulations given in Fig. 3 illustrate that equilibrium E_r may be globally asymptotically stable. This shows that the open problem given in Remark 2 may be right.

Example 3 In model (2), we take the parameters $\lambda = 10^5$, $d = 0.005$, $k_s = 1.2 \times 10^{-9}$, $k_r = 4.0 \times 10^{-10}$, $u = 3 \times 10^{-5}$, $\delta = 1$, $N_s = 2000$, $N_r = 1000$, $c = 10$, $\omega_1 = 10^{-8}$, and $\alpha_1 = 10^{-2}$. By calculating, we have $(1-u)R_s \approx 4.80$, $R_r = 0.8$, and $(1-u)R_s > 1 \geq R_r$, and model (2) has a coexistence equilibrium $E_c \approx (4.80 \times 10^6, 1.6 \times 10^6, 1.520 \times 10^7, 2.416, 241.577)$. We give three different groups of initial values in Table 4.

The numerical simulations given in Fig. 4 illustrate that equilibrium E_c may be globally asymptotically stable. This shows that the open problem given in Remark 4 may be right.

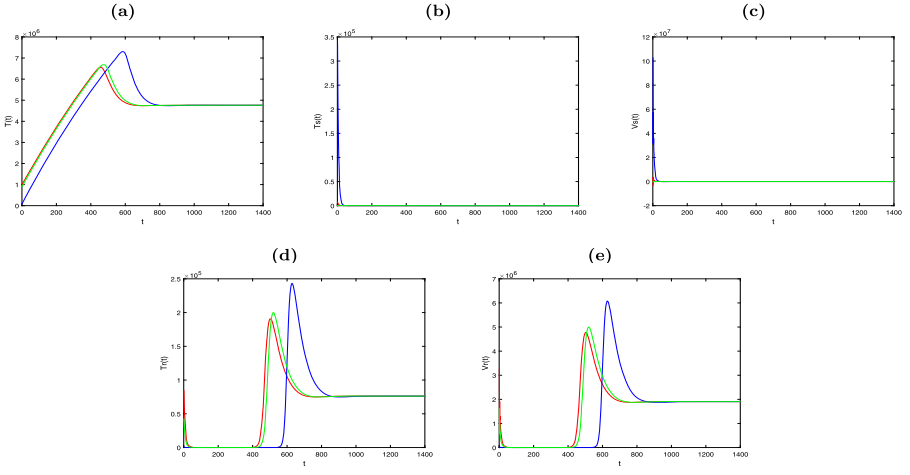

Figure 3 (**a**) Dynamical behaviors of uninfected target cells; (**b**) Dynamical behaviors of infected cells infected by wild-type virus; (**c**) Dynamical behaviors of drug-resistant virus; (**d**) Dynamical behaviors of infected cells infected by wild-type virus; (**e**) Dynamical behaviors of drug-resistant virus

Table 4 Initial values of model (2)

	T_0	T_{s0}	V_{s0}	T_{r0}	V_{r0}
1	10^6	10^3	10^{-6}	10^{-2}	10
2	9×10^3	7×10^3	5×10^{-3}	40	10^2
3	9×10^6	10^4	9×10^{-1}	10^{-1}	9×10^2

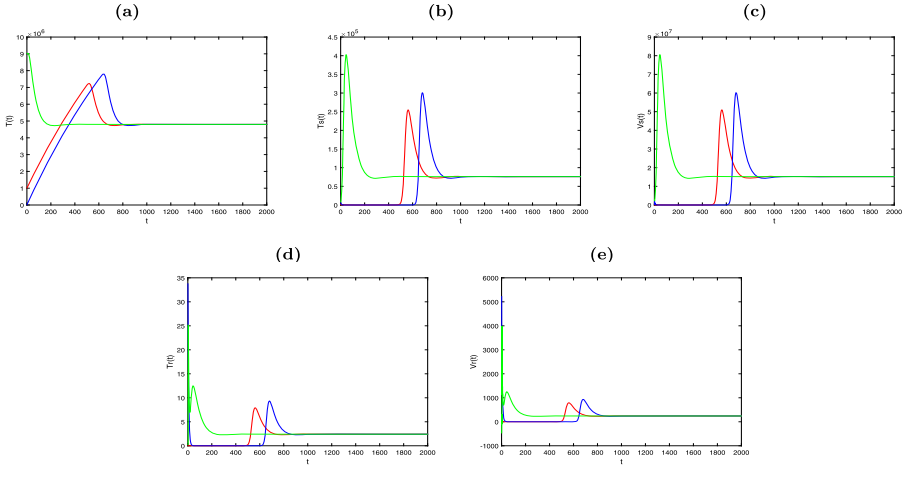

Figure 4 (**a**) Dynamical behaviors of uninfected target cells; (**b**) Dynamical behaviors of infected cells infected by wild-type virus; (**c**) Dynamical behaviors of drug-resistant virus; (**d**) Dynamical behaviors of infected cells infected by wild-type virus; (**e**) Dynamical behaviors of drug-resistant virus

Example 4 In model (2), we take the parameters $\lambda = 10^5$, $d = 0.005$, $k_s = 1.2 \times 10^{-8}$, $k_r = 1.0 \times 10^{-8}$, $u = 3 \times 10^{-5}$, $\delta = 1$, $N_s = 2000$, $N_r = 1000$, $c = 10$, $\omega_1 = 10^{-8}$, and $\alpha_1 = 10^{-8}$. By calculating, we have $(1-u)R_s + ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r \approx 52.798$, $R_r = 20$, and $(1-u)R_s + ((1-u)R_s - 1)\alpha_1 \frac{\lambda}{c} N_r > R_r > 1$, and model (2) has a coexistence equilibrium

Table 5 Initial values of model (2)

	T_0	T_{s0}	V_{s0}	T_{r0}	V_{r0}
1	10^5	10^3	10^{-4}	10^{-3}	100
2	8×10^4	4×10^3	5×10^7	10	10
3	9×10^5	10^2	10	5	9×10^2

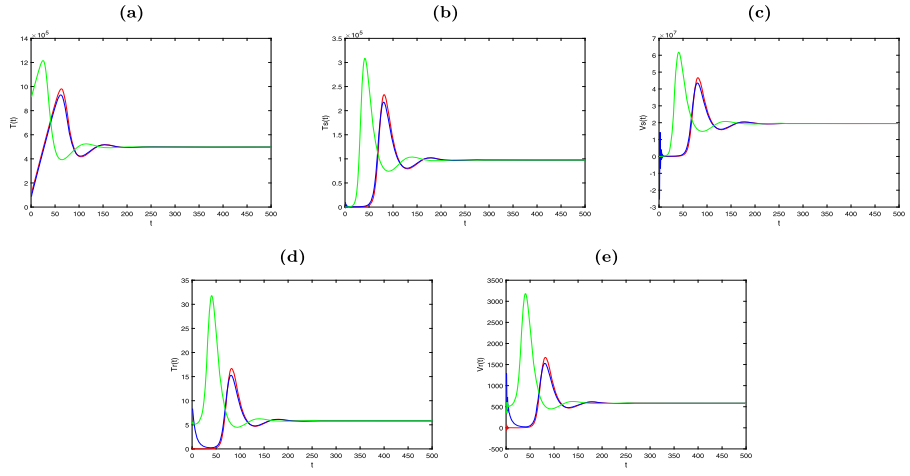

Figure 5 (**a**) Dynamical behaviors of uninfected target cells; (**b**) Dynamical behaviors of infected cells infected by wild-type virus; (**c**) Dynamical behaviors of drug-resistant virus; (**d**) Dynamical behaviors of infected cells infected by wild-type virus; (**e**) Dynamical behaviors of drug-resistant virus

$E_c \approx (4.979 \times 10^5, 9.750 \times 10^4, 1.950 \times 10^7, 5.826, 582.635)$. We give three different groups of initial values in Table 5.

The numerical simulations given in Fig. 5 illustrate that equilibrium E_c may be globally asymptotically stable. This shows that the open problem given in Remark 4 may be right.

6 Conclusion

In this paper, we study the global dynamics for a two-strain HIV infection model with saturated incidence which includes wild-type (i.e. drug sensitive) and drug-resistant strains. The wild-type strain can mutate and become drug-resistant during the process of reverse transcription. The main results are presented in Theorems 1–5. Concretely, the nonnegativity and boundedness of solutions are obtained in Theorem 1; the existence of wild-type strain-free equilibrium and coexistence equilibrium is also obtained in Theorem 2; Theorems 3 and 4 show the sufficient and necessary threshold conditions for the local and global asymptotic stability of infection-free and wild-type strain-free equilibria; and the uniform persistence of HIV infection model is established in Theorem 5.

There are some problems waiting for further investigation. Firstly, Remarks 1 and 2 consider an interesting open problem is whether we can establish the global asymptotic stability of equilibria under the appropriate conditions. And it is meaningful to study more complex models (see [19]), for example, a two-strain infection model with delayed saturation incidence (see [20]) and general nonlinear incidence (see [15, 21]), etc. Furthermore, it is more reasonable to consider the dynamical behaviors of a virus infection model with spatial diffusion and age-dependence (see [22–25]). We will leave these problems for future investigation.

Acknowledgements
We would like to thank the anonymous referees for their helpful comments and the editor for his constructive suggestions, which greatly improved the presentation of this paper.

Funding
This research is supported by the Natural Science Foundation of China (Grant No. 11771373, 11861065) and the Natural Science Foundation of Xinjiang Province of China (Grant No. 2016D03022).

Availability of data and materials
Data sharing is not applicable to this article as no data sets were generated or analysed during the current study.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
All authors contributed equally to this work. All authors read and approved the final manuscript.

Publisher's Note

Received: 13 September 2019 Accepted: 6 January 2020 Published online: 14 January 2020

References

1. Rong, L., Gilchrist, M.A., Feng, Z.: Modeling within-host HIV-1 dynamics and the the evolution of drug resistance: trade-offs between viral enzyme function and drug susceptibility. J. Theor. Biol. **247**, 804–818 (2007)
2. Feng, Z., Velasco-Hernandez, J., Tapia-Santons, B.: A mathematical model for coupling within-host and between-host dynamics in an environmentally-driven infectious disease. Math. Biosci. **241**, 49–55 (2013)
3. Feng, Z., Velasco-Hernandez, J., Tapia-Santons, B.: A model for coupling within-host and between-host dynamics in an infectious disease. Nonlinear Dyn. **68**, 401–411 (2012)
4. Bonhoeffer, S., Nowak, M.A.: Pre-existence and emergence of drug resistance in HIV-1 infection. Proc. R. Soc. Lond. B **264**, 631–637 (1997)
5. Huang, G., Ma, W., Takeuchi, Y.: Global analysis for delay virus dynamics model with Beddington–DeAngelis functional response. Appl. Math. Lett. **24**, 1199–1203 (2011)
6. Cen, X., Feng, Z., Zhao, Y.: Coupled within-host and between-host dynamics and evolution of virulence. Math. Biosci. **270**, 204–212 (2015)
7. Perelson, A.S., Neumann, A.U., Markowitz, M., et al.: HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. Science **271**, 1582–1586 (1996)
8. Ribeiro, R.M., Bonhoeffer, S.: Production of resistant HIV mutants during antiretroviral therapy. Proc. Natl. Acad. Sci. **97**, 7681–7686 (2000)
9. Rong, L., Feng, Z., Perelson, A.S.: Emergence of HIV-1 drug resistance during antiretroviral treatment. Bull. Math. Biol. **69**, 2027–2060 (2007)
10. Huang, G., Ma, W., Takeuchi, Y.: Global properties for virus dynamics model with Beddington–DeAngelis functional response. Appl. Math. Lett. **22**, 1690–1693 (2009)
11. Beddington, J.R.: Mutual interference between parasites or predators and its effect on searching efficiency. J. Anim. Ecol. **44**, 331–340 (1975)
12. DeAngelis, D.L., Goldstein, R.A., O'Neill, R.V.: A model for trophic interaction. Ecology **56**, 881–892 (1975)
13. Bonhoeffer, S., May, R.M., Shaw, G.M.: Virus dynamics and drug therapy. Proc. Natl. Acad. Sci. **94**, 6971–6976 (1997)
14. Shiri, T., Garira, W., Musekwa, S.D.: A two-strain HIV-1 mathematical model to assess the effects of chemotherapy on disease parameters. Math. Biosci. Eng. **2**, 811–832 (2005)
15. Miao, H., Teng, Z., Li, Z.: Global stability of delayed viral infection models with nonlinear antibody and CTL immune responses and general incidence rate. Comput. Math. Methods Med. (2016). https://doi.org/10.1155/2016/3903726
16. Van den Driessche, P., Watmough, J.: Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Biosci. **180**, 29–48 (2002)
17. Kuang, Y.: Delay Differential Equations with Application in Population Dynamics. Academic Press, Boston (1993)
18. Butler, G., Freedman, H.I., Waltman, P.: Uniformly persistent systems. Proc. Am. Math. Soc. **96**, 425–430 (1986)
19. Ngina, P., Mbogo, R.W., Luboobi, L.S.: HIV drug resistance: insights from mathematical modelling. Appl. Math. Model. **75**, 141–161 (2019)
20. Kaddar, A.: On the dynamics of a delayed SIR epidemic model with a modified saturated incidence rate. Electron. J. Differ. Equ. **2009**, 133 (2009)
21. Elaiw, A.M., Raezah, A.A., Hattaf, K.: Stability of HIV-1 infection with saturated virus-target and infected-target incidences and CTL immune response. Int. J. Biomath. (2017). https://doi.org/10.1142/S179352451750070X
22. Duan, X., Yin, J., Li, X.: Competitive exclusion in a multi-strain virus model with spatial diffusion and age of infection. J. Math. Anal. Appl. **459**, 717–742 (2018)
23. Yang, Y., Ruan, S., Xiao, D.: Global stability of an age-structured virus dynamics model with Beddington–DeAngelis infection function. Math. Biosci. Eng. **12**, 859–877 (2015)
24. Shen, M., Xiao, Y., Rong, L.: Global stability of an infection-age structured HIV-1 model linking within-host and between-host dynamics. Math. Biosci. **263**, 37–50 (2015)
25. Wang, J., Zhang, R., Kuniya, T.: Mathematical analysis for an age-structured HIV infection model with saturation infection rate. Electron. J. Differ. Equ. **2015**, 33 (2015)