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# Stability in a Multi-Stage HIV Infection Model with General Incidence Rate

Ruiwen Yang[1], Xiaofei Wei[1] and Jiemei Li[1,†]

**Abstract** In this paper, we propose a multi-stage HIV infection model with general incidence rate to describe the influence of raltegravir intensification on viral dynamics. The basic reproduction number $R_0$ is established. The infection-free equilibrium $E_0$ is locally asymptotically stable if $R_0 < 1$. The infection equilibrium $E^*$ is locally asymptotically stable if $R_0 > 1$.

**Keywords** Multi-stage models, Lyapunov, incidence, stability

**MSC(2010)** 34D20, 92C37.

## 1. Introduction

AIDS, caused by the human immunodeficiency virus (HIV), is a contagious disease that damages the immune system and can lead to severe illness and even death. In the field of AIDS treatment, the application of mathematical models has become a crucial area. Over the past few decades, many scholars have made remarkable contributions by developing different types of HIV mathematical models to better understand the development and treatment of AIDS.

In 1996, Nowak [1] proposed the earliest host-virus dynamic model

$$\begin{cases} \dfrac{dT}{dt} = s - \beta VT - dT, \\ \dfrac{dI}{dt} = \beta VT - \delta I, \\ \dfrac{dV}{dt} = N\delta I - cV, \end{cases} \tag{1.1}$$

which described the dynamic behavior and diffusion process of HIV in the human body based on differential equations.

In 2002, Callaway [2] proposed an efficient antiretroviral therapy model, which considered the impact of HIV treatment drugs on the model. Reverse Transcriptase Inhibitors (RT) can interfere with the transcription process of HIV virus, while Protease Inhibitors (PI) can disrupt HIV's ability to generate infectious viral particles, thus allowing infected cells to produce two types of viruses: one type contains infectious virus particles $V_I$,while the other type is a non-infectious virus $V_{NI}$.

In 2012, Dimitra [3] added two compartments to the existing model: one for infected cells without integrated DNA ($I_1$),and another for infected cells unable to

†the corresponding author.
Email address:yangruiwen2620@163.com(R.Yang),xiaofei288199@126.com(X.Wei), lijiemei81@126.com(J.Li)
[1]Department of Mathematics, Lanzhou Jiaotong University, Lanzhou, Gansu 730070, China

produce virus due to Raltegravir ($I_2$),providing a more accurate description of the role and effects of Raltegravir in the treatment of HIV, where a and b are the rates of 2-LTR circle formation and integration into DNA. References [4] studies the $(n+2)$dimensional nonlinear HIV dynamic model, which characterizes the interacting T cells of the HIV particle, susceptible $CD4^+T$ cells, and $n-$stages of infected $CD4^+T$ cells. References [5] investigated a randomized, multistage model to evaluate the effects of intensive therapy with the integrase inhibitor raltegravir on viral load and 2-LTR dynamics in HIV-suppressive therapy patients.

In 2017, Wang Xia [6] has established an infectious disease model with multiple infection stages and efficient antiretroviral therapy as follows:

$$\begin{cases} \dfrac{dT}{dt} = s - (1-\varepsilon_{RT})\beta V_I T - dT, \\ \dfrac{dI_1}{dt} = (1-\varepsilon_{RT})\beta V_I T - d_1 I_1 - (1-\varepsilon_{II})k_1 I_1 - k_2 I_1, \\ \dfrac{dI_2}{dt} = (1-p)(1-\varepsilon_{II})k_1 I_1 - \delta I_2 + aL, \\ \dfrac{dI_3}{dt} = k_2 I_1 - d_3 I_3, \\ \dfrac{dL}{dt} = p(1-\varepsilon_{II})k_1 I_1 - d_L L - aL, \\ \dfrac{dV_I}{dt} = (1-\varepsilon_{PI})N\delta I_2 - cV_I, \\ \dfrac{dV_{NI}}{dt} = \varepsilon_{PI} N\delta I_2 - cV_{NI}. \end{cases} \tag{1.2}$$

Detailed biological considerations of the parameters of the model (1.2) can be found in Table 1.

This model can better simulate the infection process of HIV, including multiple stages such as acute infection, chronic infection, and immune failure, and the impact of antiretroviral therapy in this model is also considered.

In 2012, Hattaf [7] proposed a general form of incidence function $f(x,y,v)v$, where $f \in C^1([0,+\infty),\mathbb{R}^3_+,\mathbb{R}_+)$ and satisfies

(i) $f(0,y,v)v = 0$, for all $y \geq 0$ and $v \geq 0$;

(ii) $\dfrac{\partial f(x,y,v)}{\partial x} > 0$, for all $x > 0$, $y \geq 0$ and $v \geq 0$;

(iii) $\dfrac{\partial f(x,y,v)}{\partial y} \leq 0$ *and* $\dfrac{\partial f(x,y,v)}{\partial v} \leq 0$, for all $x > 0$, $y \geq 0$ and $v \geq 0$.

The incidence rate can accurately describe the transmission and infection process of HIV, thus better support the research on disease treatment.References [8] employed the aforementioned general incidence rate to investigate a delayed virus infection model with Gaussian white noise disturbances.

References [9] considered the HIV model with general incidence rate, CTL immune response and intracellular delay. References [10] proposed a random HIV infection model with logical target cell growth, general nonlinear incidence rate, CTL immune response and parameter perturbation. Zhai [11] reduced the infection rate of susceptible persons by generating protection awareness on them through education and publicity, and proposed a new HIV/AIDS extinction threshold $\lambda_0$,

**Table 1.** Summary of model parameters

| Para. | Description |
|---|---|
| T | The counts of uninfected cells |
| $I_1$ | The counts of infected cells that have finished the process of reverse transcription |
| $I_2$ | The counts of infected cells which can produce virus |
| $I_3$ | The counts of infected cells that fail the DNA integration |
| $L$ | The counts of latently infected cells ($L$) |
| $V_{NI}$ | Non-infectious viral particles owing to efficacy of protease inhibitors |
| $V_I$ | Infectious viral particles |
| $s$ | Generation rate of uninfected cells |
| $d$ | Death rate of uninfected cells |
| $\beta$ | A rate at which the virus infects uninfected cells |
| $d_1$ | Death rate of cells in the $I_1$ class |
| $k_1$ | A Rate at which $I_1$ cells move to $I_2$ |
| $k_2$ | Rate at which $I_1$ cells move to $I_3$ |
| $p$ | A small fraction of infected cells become latently infected |
| $\delta$ | Death rate of infected cells in the $I_2$ class |
| $d_3$ | Death rate of infected cells in the $I_3$ class |
| $d_L$ | Death rate of $L$ |
| $a$ | A rate of productively infected cells |
| $N\delta$ | Generation rate of virus release form an infected cell per unit time |
| $c$ | Viral clearance rate |
| $\varepsilon_{RT}$ | Drug efficacy of reverse transcriptase inhibitor |
| $\varepsilon_{II}$ | Drug efficacy of integrase inhibitor |
| $\varepsilon_{PI}$ | Drug efficacy of protease inhibitor |

when $\lambda_0 < 1$, HIV/AIDS would be extinct, and when $\lambda_0 > 1$, the model experienced a stable distribution. Xu [12] studied the quantum stability of stochastic nonlinear time-delay systems under the action of multiple periodic pulses, defined the global weak stochastic exponential stability, and discussed the double effects caused by multiple periodic pulses. Wang [13] discussed the stability and stabilization of discrete semi-Markov jump linear time-delay systems, gave the probabilistic structure of Lyapunov-Krasovskill functional and semi-Markov switching signals, and determined the sufficient conditions for system stability.

In recent years, scholars have considered various practical factors and proposed different forms of incidence rates, such as bilinear incidence, standard incidence and general incidence rate [14]. Therefore, this paper adopts general incidence rate to describe HIV dynamics under drug treatment, which is more general and can be adjusted and modified according to specific situations. The introduction of general incidence rate can reduce the complexity of the computation in the model.

The general incidence rate was used to describe the dynamics of HIV under drug therapy. In the second section, the non-negative and boundedness of the model solution, the limiting behavior of the solution and the basic regeneration number are studied. In section 3, the global stability of the infection-free equilibrium point is studied. In section 4, the global stability of infection equilibrium point is studied.

## 2. Analysis of the model

Based on the above literature, the following dynamic model of HIV was studied in this paper

$$\begin{cases} \dfrac{dT}{dt} = s - (1-\varepsilon_{RT}) f(T(t), V_I(t)) V_I(t) - dT, \\ \dfrac{dI_1}{dt} = (1-\varepsilon_{RT}) f(T(t), V_I(t)) V_I(t) - d_1 I_1 - (1-\varepsilon_{II}) k_1 I_1 - k_2 I_1, \\ \dfrac{dI_2}{dt} = (1-p)(1-\varepsilon_{II}) k_1 I_1 - \delta I_2 + aL, \\ \dfrac{dI_3}{dt} = k_2 I_1 - d_3 I_3, \\ \dfrac{dL}{dt} = p(1-\varepsilon_{II}) k_1 I_1 - d_L L - aL, \\ \dfrac{dV_I}{dt} = (1-\varepsilon_{PI}) N\delta I_2 - cV_I, \\ \dfrac{dV_{NI}}{dt} = \varepsilon_{PI} N\delta I_2 - cV_{NI}. \end{cases} \tag{2.1}$$

Because variables $I_3$ and $V_{NI}$ are decoupled from the other equations in model (2.1), it is sufficient to analyze the dynamical behavior of the solutions of the fol-

lowing subsystem

$$\begin{cases} \dfrac{dT(t)}{dt} = s - (1-\varepsilon_{RT})f(T(t),V_I(t))V_I(t) - \mu_1 T(t), \\ \dfrac{dI_1(t)}{dt} = (1-\varepsilon_{RT})f(T(t),V_I(t))V_I(t) - d_1 I_1(t) - (1-\varepsilon_{II})k_1 I_1(t) - k_2 I_1(t), \\ \dfrac{dI_2(t)}{dt} = (1-p)(1-\varepsilon_{II})k_1 I_1(t) - \delta I_2(t) + aL(t), \\ \dfrac{dL(t)}{dt} = p(1-\varepsilon_{II})k_1 I_1(t) - d_L L(t) - aL(t), \\ \dfrac{dV_I(t)}{dt} = (1-\varepsilon_{PI})N\delta I_2(t) - cV_I(t). \end{cases} \tag{2.2}$$

The initial conditions for model (2.2) is given as follows:

$$\begin{aligned} &T(0) = T_0 > 0, \quad I_1(0) = I_{10} > 0, \quad I_2(0) = I_{20} > 0, \\ &L(0) = L_0 > 0, \quad V_I(0) = V_{I0} > 0. \end{aligned} \tag{2.3}$$

we assume that the incidence rate is the general incidence function $f(T,V_I)V_I$, where $f \in C(R_+^2, R_+)$ satisfy the following conditions:

(H1) $f(T,V_I)V_I \geq 0$, for $T \geq 0$ and $V_I \geq 0$; $f(T,V_I) = 0$ if and only if $T = 0$;

(H2) $\dfrac{\partial f(T,V_I)}{\partial T} \geq 0$, for $T \geq 0$ and $V_I \geq 0$;

(H3) $\dfrac{\partial f(T,V_I)}{\partial V_I} \leq 0$, for $T \geq 0$ and $V_I \geq 0$;

(H4) $\dfrac{\partial (f(T,V_I)V_I)}{\partial V_I} > 0$, for $T > 0$ and $V_I \geq 0$.

## 2.1. The non-negativity and boundedness of the solution

**Theorem 2.1.** *Each component of the solution to model (2.2), subject to condition (2.3), remains non-negative and bounded for all* $t \in [0, +\infty)$.

**Proof.** By theorems [15,16], we can prove that $T(t)$, $I_1(t)$, $I_2(t)$, $L(t)$, $V_I(t)$ are all non-negative for $t \geq 0$ and there exists a unique solution for model (2.2). For $t \geq 0$, we define

$$M(t) = T(t) + I_1(t) + I_2(t) + L(t) + \frac{1}{2(1-\varepsilon_{PI})N} V_I(t).$$

Due to the solution, for $t \geq 0$, we have

$$\begin{aligned} M'(t) &= s - \mu_1 T(t) - (d_1 + k_2) I_1(t) - \frac{\delta}{2} I_2(t) - d_L L(t) - \frac{c}{2(1-\varepsilon_{PI})N} V_I(t) \\ &\leq s - \zeta M(t), \end{aligned}$$

where $\zeta = \min\left\{\mu_1,\ d_1 + k_2,\ \dfrac{\delta}{2},\ d_L,\ c\right\}$. Hence, we get

$$\limsup_{t \to +\infty} M(t) \leq \frac{s}{\zeta},$$

thus, it implies that $T(t)$, $I_1(t)$, $I_2(t)$, $L(t)$, $V_I(t)$ is ultimately bounded. Then the proof is completed. □

## 2.2. Limiting behavior

**Theorem 2.2.** *Let $X$ be a solution of system (2.2). If $X(0) \in \mathbb{R}^5_+$ then the limit of $X(t)$ exists when $t \to +\infty$.*

**Proof.** Add the first four items of the system

$$s = \frac{\mathrm{d}T(t)}{\mathrm{d}t} + \mu_1 T(t) + \frac{\mathrm{d}I_1(t)}{\mathrm{d}t} + (d_1 + k_2)I_1(t) + \frac{\mathrm{d}I_2(t)}{\mathrm{d}t} + \delta I_2(t) + \frac{\mathrm{d}L(t)}{\mathrm{d}t} + d_L L(t).$$

Multiply both sides of the equation by $e^{\mu_1 t}$

$$\begin{aligned} se^{\mu_1 t} =& \frac{\mathrm{d}T(t)}{\mathrm{d}t}e^{\mu_1 t} + \mu_1 T(t)e^{\mu_1 t} + \frac{\mathrm{d}I_1(t)}{\mathrm{d}t}e^{\mu_1 t} + (d_1 + k_2)I_1(t)e^{\mu_1 t} + \frac{\mathrm{d}I_2(t)}{\mathrm{d}t}e^{\mu_1 t} \\ &+ \delta I_2(t)e^{\mu_1 t} + \frac{\mathrm{d}L(t)}{\mathrm{d}t}e^{\mu_1 t} + d_L L(t)e^{\mu_1 t}. \end{aligned}$$

Integrating from 0 to $t$ on both sides of the equation simultaneously,we obtain

$$\begin{aligned} \int_0^t se^{\mu_1 x}\mathrm{d}x =& \int_0^t \big(\frac{\mathrm{d}T(x)}{\mathrm{d}x}e^{\mu_1 x} + \mu_1 T(x)e^{\mu_1 x}\big)\mathrm{d}x \\ &+ \int_0^t \big(\frac{\mathrm{d}I_1(x)}{\mathrm{d}x}e^{\mu_1 x} + (d_1 + k_2)I_1(x)e^{\mu_1 x}\big)\mathrm{d}x \\ &+ \int_0^t \big(\frac{\mathrm{d}I_2(x)}{\mathrm{d}x}e^{\mu_1 x} + \delta I_2(x)e^{\mu_1 x}\big)\mathrm{d}x \\ &+ \int_0^t \big(\frac{\mathrm{d}L(x)}{\mathrm{d}x}e^{\mu_1 x} + d_L L(x)e^{\mu_1 x}\big)\mathrm{d}x, \end{aligned}$$

then,

$$\begin{aligned} \int_0^t se^{\mu_1 x}\mathrm{d}x =& \int_0^t \frac{\mathrm{d}T(x)e^{\mu_1 x}}{\mathrm{d}x}\mathrm{d}x + \int_0^t e^{(\mu_1 - (d_1+k_2))x}\frac{\mathrm{d}I_1(x)e^{(d_1+k_2)x}}{\mathrm{d}x}\mathrm{d}x \\ &+ \int_0^t e^{(\mu_1-\delta)x}\frac{\mathrm{d}I_2(x)e^{\delta x}}{\mathrm{d}x}\mathrm{d}x + \int_0^t e^{(\mu_1 - d_L)x}\frac{\mathrm{d}L(x)e^{d_L x}}{\mathrm{d}x}\mathrm{d}x. \end{aligned}$$

Hence,

$$\begin{aligned} \frac{s}{\mu_1}(e^{\mu_1 t} - 1) =& T(t)e^{\mu_1 t} + I_1(t)e^{\mu_1 t} + I_2(t)e^{\mu_1 t} + L(t)e^{\mu_1 t} - T_0 - I_{10} - I_{20} - L_0 \\ &- (\mu_1 - (d_1 + k_2))\int_0^t I_1(x)e^{\mu_1 x}\mathrm{d}x - (\mu_1 - \delta)\int_0^t I_2(x)e^{\mu_1 x}\mathrm{d}x \\ &- (\mu_1 - d_L)\int_0^t L(x)e^{\mu_1 x}\mathrm{d}x. \end{aligned}$$

Multiply both sides of the equation by $e^{-\mu_1 t}$

$$\begin{aligned} &\frac{s}{\mu_1}(1 - e^{-\mu_1 t}) \\ =& T(t) + I_1(t) + I_2(t) + L(t) - (T_0 + I_{10} + I_{20} + L_0)e^{-\mu_1 t} \\ &- (\mu_1 - (d_1 + k_2))\int_0^t I_1(x)e^{(x-t)\mu_1}\mathrm{d}x - (\mu_1 - \delta)\int_0^t I_2(x)e^{(x-t)\mu_1}\mathrm{d}x \\ &- (\mu_1 - d_L)\int_0^t L(x)e^{(x-t)\mu_1}\mathrm{d}x. \end{aligned} \tag{2.4}$$

From (2.4)and according to Lemma 3.3 in [17], we have

$$\frac{s}{\mu_1} \geq \limsup_{t\to+\infty} T(t) + \frac{d_1+k_2}{\mu_1} \limsup_{t\to+\infty} I_1(t) + \frac{\delta}{\mu_1} \limsup_{t\to+\infty} I_2(t) + \frac{d_L}{\mu_1} \limsup_{t\to+\infty} L(t),$$
$$\frac{s}{\mu_1} \leq \liminf_{t\to+\infty} T(t) + \frac{d_1+k_2}{\mu_1} \liminf_{t\to+\infty} I_1(t) + \frac{\delta}{\mu_1} \liminf_{t\to+\infty} I_2(t) + \frac{d_L}{\mu_1} \liminf_{t\to+\infty} L(t).$$

Subtracting two formulas yields

$$\begin{aligned} 0 \geq & \limsup_{t\to+\infty} T(t) - \liminf_{t\to+\infty} T(t) + \frac{d_1+k_2}{\mu_1}(\limsup_{t\to+\infty} I_1(t) - \liminf_{t\to+\infty} I_1(t)) \\ & + \frac{\delta}{\mu_1}(\limsup_{t\to+\infty} I_2(t) - \liminf_{t\to+\infty} I_2(t)) + \frac{d_L}{\mu_1}(\limsup_{t\to+\infty} L(t) - \liminf_{t\to+\infty} L(t)), \end{aligned}$$

then,

$$\begin{aligned} &\limsup_{t\to+\infty} T(t) = \liminf_{t\to+\infty} T(t), \limsup_{t\to+\infty} I_1(t) = \liminf_{t\to+\infty} I_1(t), \\ &\limsup_{t\to+\infty} I_2(t) = \liminf_{t\to+\infty} I_2(t), \limsup_{t\to+\infty} L(t) = \liminf_{t\to+\infty} L(t). \end{aligned} \tag{2.5}$$

Hence, the limit of $T(t), I_1(t), I_2(t), L_t$ exists when $t \to +\infty$.

Adding system(2.2), we get

$$V_I(t) = V_{I0}e^{-ct} + (1-\varepsilon_{PI})N\delta \int_0^t I_2(x)e^{(x-t)c}\,\mathrm{d}x,$$

then,

$$\begin{aligned} &\limsup_{t\to+\infty} V_I(t) \leq \frac{(1-\varepsilon_{PI}N\delta)}{c} \limsup_{t\to+\infty} I_2(t), \\ &\liminf_{t\to+\infty} V_I(t) \geq \frac{(1-\varepsilon_{PI}N\delta)}{c} \liminf_{t\to+\infty} I_2(t). \end{aligned} \tag{2.6}$$

From (2.5) and (2.6), we get

$$\limsup_{t\to+\infty} V_I(t) - \liminf_{t\to+\infty} V_I(t) \leq 0,$$

thus,

$$\limsup_{t\to+\infty} V_I(t) = \liminf_{t\to+\infty} V_I(t).$$

Hence, the limit of $V_I(t)$ exists when $t \to +\infty$. □

## 2.3. Basic reproduction number and equilibria

Using the method of reproducing matrices [18], considering the parts of infection and virus generation, the following matrix is defined

$$\mathbb{F} = \begin{pmatrix} 0\ 0\ 0 & (1-\varepsilon_{RT})f(s/\mu_1, 0) \\ 0\ 0\ 0 & 0 \\ 0\ 0\ 0 & 0 \\ 0\ 0\ 0 & 0 \end{pmatrix},$$

and

$$\mathbb{V} = \begin{pmatrix} D & 0 & 0 & 0 \\ -(1-p)(1-\varepsilon_{II})k_1 & \delta & -a & 0 \\ -p(1-\varepsilon_{II})k_1 & 0 & d & 0 \\ 0 & -(1-\varepsilon_{PI})N\delta & 0 & c \end{pmatrix},$$

in which

$$D = d_1 + (1-\varepsilon_{II})k_1 + k_2,\ d = d_L + a.$$

Because $\mathbb{F}$ is a non-negative matrix and $\mathbb{V}$ is a non-singular $M$-matrix, calculate the basic regeneration number

$$R_0 = \rho(\mathbb{F}\mathbb{V}^{-1}) = \frac{(1-\varepsilon_{RT})f(s/\mu_1, 0)(1-\varepsilon_{PI})N(1-\varepsilon_{II})k_1(ap+(1-p)d)}{Dcd}.$$

**Theorem 2.3.** *There is only one infection-free equilibrium $E_0 = (\bar{T},\ 0,\ 0,\ 0,\ 0)$ for model (2.2) if $R_0 < 1$ and an infection equilibrium $E^* = (T^*,\ I_1^*,\ I_2^*,\ L^*,\ V_I^*)$ if $R_0 > 1$, where $\bar{T} = s/\mu_1$.*

**Proof.** If $I_1 = 0,\ I_2 = 0,\ L = 0,\ V_I = 0$, then model (2.2) has only one infection-free equilibrium $E_0 = (\bar{T},\ 0,\ 0,\ 0,\ 0)$.

If $I_1 \neq 0,\ I_2 \neq 0,\ L \neq 0,\ V_I \neq 0$, one gets equations as follows:

$$\begin{aligned}
&(1-\varepsilon_{RT})f\left(T, \frac{(1-\varepsilon_{PI})N(1-\varepsilon_{II})k_1(s-\mu_1 T)(ap+(1-p)d)}{Dcd}\right) \\
&- \frac{Dcd}{(1-\varepsilon_{PI})N(1-\varepsilon_{II})k_1(ap+(1-p)d)} = 0, \\
&I_1 = \frac{s-\mu_1 T}{D}, \\
&I_2 = \frac{(1-\varepsilon_{II})k_1(s-\mu_1 T)(ap+(1-p)d)}{\delta Dd}, \\
&L = \frac{p(1-\varepsilon_{II})k_1(s-\mu_1 T)}{Dd}, \\
&V_I = \frac{(1-\varepsilon_{PI})N(1-\varepsilon_{II})k_1(s-\mu_1 T)(ap+(1-p)d)}{Dcd}.
\end{aligned}$$

Since $V_I > 0$, it means that $T < s/\mu_1$. Thus, the equation is defined on the interval $(0,\ s/\mu_1)$ by

$$\begin{aligned}
F(x) =&(1-\varepsilon_{RT})f\left(T, \frac{(1-\varepsilon_{PI})N(1-\varepsilon_{II})k_1(s-\mu_1 T)(ap+(1-p)d)}{Dcd}\right) \\
&- \frac{Dcd}{(1-\varepsilon_{PI})N(1-\varepsilon_{II})k_1(ap+(1-p)d)},
\end{aligned}$$

and we can obtain by conditions (H2) and (H3) that

$$F'(x) = \frac{\partial f}{\partial x} + \frac{\partial f}{\partial v}\left(\frac{-\mu_1(1-\varepsilon_{PI})N(1-\varepsilon_{II})k_1}{Dcd}\right).$$

Since $F(x)$ is strictly monotonically increasing with respect to $x$, one gets

$$\begin{aligned} F(0) &= -s, \\ F(\frac{s}{\mu_1}) &= f(\frac{s}{\mu_1}, 0) - \frac{Dcd}{(1-\varepsilon_{PI})N(1-\varepsilon_{II})k_1(ap+(1-p)d)} \\ &= \frac{Dcd}{(1-\varepsilon_{PI})N(1-\varepsilon_{II})k_1(ap+(1-p)d)}(R_0-1). \end{aligned}$$

If $R_0 < 1$, then there exists a $T^* \in (0,\ s/\mu_1)$ such that $F(x^*) = 0$. Thus, $T^*,\ I_1^*,\ I_2^*,\ L^*,$ and $V_I^*$ can be computed. □

We use the method of Lyapunov functionals to illustrate the global stability of the equilibria of model (2.2). Moreover, we assume that the following conditons hold:

(H5) $T - T_0 - \int_{T_0}^{T} \frac{f(T_0,0)}{f(\tau,0)} d\tau \to +\infty$, as $T \to +\infty$ or $T \to 0^+$;

(H6) $T - T^* - \int_{T^*}^{T} \frac{f(T^*,V_I^*)}{f(\tau,V_I^*)} d\tau \to +\infty$, as $T \to +\infty$ or $T \to 0^+$.

# 3. The global stability of the infection-free equilibrium

**Theorem 3.1.** *Suppose that the following conditions are satisfied*

$$Dcd + Dc\delta + Dd\delta + cd\delta > (1-p)(1-\varepsilon_{II})k_1(1-\varepsilon_{PI})N\delta.$$

*Then the infection-free equilibrium $E_0$ of model (2.2) is locally asymptotically stable if $R_0 < 1$; $E_0$ is unstable if $R_0 > 1$.*

**Proof.** The Jacobian matrix of model (2.2) at $E_0$ is given by

$$J_0 = \begin{pmatrix} -\mu_1 & 0 & 0 & 0 & -(1-\varepsilon_{RT})f(s/\mu_1,0) \\ 0 & -D & 0 & 0 & (1-\varepsilon_{RT})f(s/\mu_1,0) \\ 0 & (1-p)(1-\varepsilon_{II})k_1 & -\delta & a & 0 \\ 0 & p(1-\varepsilon_{II})k_1 & 0 & -d & 0 \\ 0 & 0 & (1-\varepsilon_{PI})N\delta & 0 & -c \end{pmatrix}.$$

It is easy to see that it has an eigenvalue $\lambda = -\mu_1 < 0$, and other eigenvalues are given by eigenvalues of the matrix

$$J_0 = \begin{pmatrix} D & 0 & 0 & (1-\varepsilon_{RT})f(s/\mu_1,0) \\ (1-p)(1-\varepsilon_{II})k_1 & -\delta & a & 0 \\ p(1-\varepsilon_{II})k_1 & 0 & -d & 0 \\ 0 & (1-\varepsilon_{PI})N\delta & 0 & -c \end{pmatrix},$$

to be exact, the roots of characteristic equation

$$\lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4 = 0,$$

where

$$b_1 = D + c + d + \delta > 0,$$
$$b_2 = D\,(c + d + \delta) + c\,(d + \delta) + d\delta > 0,$$
$$b_3 = Dcd + Dc\delta + Dd\delta + cd\delta - (1 - \varepsilon_{RT}) f(s/\mu_1, 0)(1 - p)(1 - \varepsilon_{II}) k_1 (1 - \varepsilon_{PI}) N\delta,$$
$$b_4 = Dcd\delta(1 - R_0).$$

From hypotheses and $R_0 < 1$, we have $b_i > 0, i = 1, 2, 3, 4$. Thus, $E_0$ is locally asymptotically stable if $R_0 < 1$ by the Routh-Hurwitz criterion. Denote

$$\begin{aligned} y(\xi) =& \xi^4 + (D + c + d + \delta)\xi^3 + (Dc + Dd + D\delta + cd + c\delta + d\delta)\xi^2 + \big(Dcd + Dc\delta \\ &+ Dd\delta + cd\delta - (1 - p)(1 - \varepsilon_{II}) k_1 (1 - \varepsilon_{PI}) N\delta f(T, V_I)\big)\xi + Dcd\delta(1 - R_0). \end{aligned} \tag{3.1}$$

From hypotheses and $R_0 > 1$, one gets

$$y(0) = Dcd\delta(1 - R_0) < 0, \quad \lim_{\xi \to +\infty} y(\xi) = +\infty.$$

Thus, (3.1) has at least one positive eigenvalue. Hence, $E_0$ is unstable if $R_0 > 1$. □

**Theorem 3.2.** *Assume that (H1)-(H6) hold. If $R_0 < 1$, then the infection-free equilibrium $E_0$ of (2.2) is globally stable.*

**Proof.** Let $(T(t),\ I_1(t),\ I_2(t),\ L(t),\ V_I(t))$ be a solution of (2.2) with the initial condition, we define a Lyapunov functional:

$$\begin{aligned} V_0 =& T - T_0 - \int_{T_0}^{T} \frac{f(T_0, 0)}{f(\tau, 0)} d\tau + I_1 + \frac{Dd}{(1 - \varepsilon_{II}) k_1 [ap + (1 - p)d]} I_2 \\ &+ \frac{Da}{(1 - \varepsilon_{II}) k_1 [ap + (1 - p)d]} L + \frac{Dd}{(1 - \varepsilon_{PI}) N (1 - \varepsilon_{II}) k_1 [ap + (1 - p)d]} V_I, \end{aligned}$$

where $s = \mu_1 T_0$. By (H1)-(H6), We know that $V_0$ is positively defined with respect to $E_0$. By calculating the time derivative of $V_0$ along the solutions of model (2.2), one gets

$$\begin{aligned} \dot{V}_0 =& \left(1 - \frac{f(T_0, 0)}{f(T, 0)}\right) \dot{T} + \dot{I}_1 + \frac{Dd}{(1 - \varepsilon_{II}) k_1 [ap + (1 - p)d]} \dot{I}_2 \\ &+ \frac{Da}{(1 - \varepsilon_{II}) k_1 [ap + (1 - p)d]} \dot{L} + \frac{Dd}{(1 - \varepsilon_{PI}) N (1 - \varepsilon_{II}) k_1 [ap + (1 - p)d]} \dot{V}_I \\ =& \mu_1 \left(1 - \frac{f(T_0, 0)}{f(T, 0)}\right) (T_0 - T) + (1 - \varepsilon RT) f(T, V_I) V_I \frac{f(T_0, 0)}{f(T, 0)} - D I_1 \\ &+ \frac{Dd(1 - p)}{ap + (1 - p)d} I_1 + \frac{Dap}{ap + (1 - p)d} I_1 - \frac{Dcd}{(1 - \varepsilon PI) N (1 - \varepsilon_{II}) k_1 [ap + (1 - p)d]} \\ =& - \frac{Dcd}{(1 - \varepsilon PI) N (1 - \varepsilon_{II}) k_1 [ap + (1 - p)d]} \left(1 - \frac{f(T, V_I)}{f(T, 0)} R_0\right) \\ & \mu_1 \left(1 - \frac{f(T_0, 0)}{f(T, 0)}\right) (T_0 - T). \end{aligned}$$

By (H1)-(H3) and $R_0 < 1$, one gets

$$\mu_1 \left(1 - \frac{f(T_0, 0)}{f(T, 0)}\right) (T_0 - T) \le 0, \quad \left(1 - \frac{f(T, V_I)}{f(T, 0)} R_0\right) \ge 0.$$

Hence, $\dot{V}_0 \leq 0$ if $R_0 < 1$.

Moreover, for $t \geq 0$, $\dot{V}_0 = 0$ means that $T(t) = T_0$, $I_1(t) = 0$, $I_2(t) = 0$, $L(t) = 0$, $V_I(t) = 0$. Thus, let $E_0$ be the largest compact invariant set in $\Gamma = \left\{(T_0,\ 0,\ 0,\ 0,\ 0) \in C | \dot{V}_0 = 0\right\}$. Since any solution of model is bounded, it follows from LaSalle invariance principle [15, 16] that $E_0$ is globally stable if $R_0 < 1$. □

## 4. The global stability of the infection equilibrium

**Theorem 4.1.** *Assume that (H1)-(H6) hold. If $R_0 > 1$, then the infection equilibrium $E^*$ of (2.2) is globally asymptotically stable.*

**Proof.** By the following Lyapunov function,

$$\begin{aligned} V =& \frac{\left(\frac{ap}{d_L + a} + 1 - p\right)(1 - \varepsilon_{II})k_1}{D}\left(T - T^* - \int_{T^*}^{T} \frac{f(T^*, V_I^*)}{f(\tau, V_I^*)} d\tau\right) \\ &+ \frac{\left(\frac{ap}{d_L + a} + 1 - p\right)(1 - \varepsilon_{II})k_1}{D}\left(I_1 - I_1^* - I_1^* \ln \frac{I_1}{I_1^*}\right) + \left(I_2 - I_2^* - I_2^* \ln \frac{I_2}{I_2^*}\right) \\ &+ \frac{a}{d_L + a}\left(L - L^* - L^* \ln \frac{L}{L^*}\right) + \frac{1}{N(1 - \varepsilon_{PI})}\left(V_I - V_I^* - V_I^* \ln \frac{V_I}{V_I^*}\right). \end{aligned}$$

$V$ is positive difinite with respect to $E^*$ and the time derivative of $V$ along the solutions of system (2.2) is

$$\begin{aligned} \dot{V} =& \frac{\left(\frac{ap}{d_L + a} + 1 - p\right)(1 - \varepsilon_{II})k_1}{D}\left(1 - \frac{f(T^*, V_I^*)}{f(T, V_I^*)}\right)\dot{T} \\ &+ \frac{\left(\frac{ap}{d_L + a} + 1 - p\right)(1 - \varepsilon_{II})k_1}{D}\left(1 - \frac{I_1^*}{I_1}\right)\dot{I}_1 + \left(1 - \frac{I_2^*}{I_2}\right)\dot{I}_2 \\ &+ \frac{a}{d_L + a}\left(1 - \frac{L^*}{L}\right)\dot{L} + \frac{1}{N(1 - \varepsilon_{PI})}\left(1 - \frac{V_I^*}{V_I}\right)\dot{V}_I. \end{aligned}$$

Noting that $s = (1 - \varepsilon_{RT})f(T^*, V_I^*)V_I^* + \mu_1 T^*$, $(1 - \varepsilon_{RT})f(T^*, V_I^*)V_I^* = DI_1^*$,and

$\delta I_2^* = (1-f)(1-\varepsilon_{II})k_1 I_1^* + aL^*$, we obtain that

$$\begin{aligned}
\dot{V} =& \frac{\left(\frac{ap}{d_L+a}+1-p\right)(1-\varepsilon_{II})k_1}{D}\left(1-\frac{f(T^*,V_I^*)}{f(T,V_I^*)}\right)\\
&\big((1-\varepsilon_{RT})(f(T^*,V_I^*)V_I^* - f(T,V_I)V_I + \mu_1(T^*-T)\big)\\
&+\frac{\left(\frac{ap}{d_L+a}+1-p\right)(1-\varepsilon_{II})k_1}{D}\left(1-\frac{I_1^*}{I_1}\right)\left(DI_1^*\frac{f(T,V_I)V_I}{f(T^*,V_I^*)} - DI_1\right)\\
&+\left(1-\frac{I_2^*}{I_2}\right)\left((1-p)(1-\varepsilon_{II})k_1 I_1 - \left(\frac{(1-p)(1-\varepsilon_{II})k_1 I_1^*}{I_2^*}+\frac{aL^*}{I_2^*}\right)I_2\right)\\
&+\left(1-\frac{I_2^*}{I_2}\right)aL(t) + \frac{a}{d_L+a}\left(1-\frac{L^*}{L}\right)(p(1-\varepsilon_{II})k_1 I_1 - dL)\\
&+\frac{1}{N(1-\varepsilon_{PI})}\left(1-\frac{V_I^*}{V_I}\right)((1-\varepsilon_{PI})N\delta I_2 - cV_I)\\
=&\frac{\mu_1\left(\frac{ap}{d_L+a}+1-p\right)(1-\varepsilon_{II})k_1}{D}\left(1-\frac{f(T^*,V_I^*)}{f(T,V_I^*)}\right)(T^*-T)\\
&+(1-p)(1-\varepsilon_{II})k_1 I_1^*\Bigg(5-\frac{f(T^*,V_I^*)}{f(T,V_I^*)}-\frac{I_1^* f(T,V_I)V_I}{I_1 f(T^*,V_I^*)V_I^*}-\frac{I_1 I_2^*}{I_1^* I_2}-\frac{I_2 V_I^*}{I_2^* V_I}\\
&-\frac{f(T,V_I^*)}{f(T,V_I)}\Bigg)+(1-p)(1-\varepsilon_{II})k_1 I_1^*\left(-1+\frac{f(T,V_I)V_I}{f(T,V_I^*)V_I^*}-\frac{V_I}{V_I^*}+\frac{f(T,V_I^*)}{f(T,V_I)}\right)\\
&+aL^*\left(6-\frac{f(T^*,V_I^*)}{f(T,V_I^*)}-\frac{I_1^* f(T,V_I)V_I}{I_1 f(T^*,V_I^*)V_I^*}-\frac{L^* I_I}{L I_1^*}-\frac{L I_2^*}{L^* I_2}-\frac{I_2 V_I}{I_2^* V_I^*}-\frac{f(T,V_I^*)}{f(T,V_I)}\right)\\
&+aL^*\left(-1+\frac{f(T,V_I)V_I}{f(T,V_I^*)V_I^*}-\frac{V_I}{V_I^*}+\frac{f(T,V_I^*)}{f(T,V_I)}\right).
\end{aligned}$$

Since the arithmetic mean is greater than or equal to the geometric means,

$$\begin{aligned}
&5-\frac{f(T^*,V_I^*)}{f(T,V_I^*)}-\frac{I_1^* f(T,V_I)V_I}{I_1 f(T^*,V_I^*)V_I^*}-\frac{I_1 I_2^*}{I_1^* I_2}-\frac{I_2 V_I^*}{I_2^* V_I}-\frac{f(T,V_I^*)}{f(T,V_I)}\le 0,\\
&6-\frac{f(T^*,V_I^*)}{f(T,V_I^*)}-\frac{I_1^* f(T,V_I)V_I}{I_1 f(T^*,V_I^*)V_I^*}-\frac{L^* I_I}{L I_1^*}-\frac{L I_2^*}{L^* I_2}-\frac{I_2 V_I}{I_2^* V_I^*}-\frac{f(T,V_I^*)}{f(T,V_I)}\le 0.
\end{aligned}$$

By hypotheses (H3)-(H4), one gets

$$\begin{aligned}
&-1+\frac{f(T,V_I)V_I}{f(T,V_I^*)V_I^*}-\frac{V_I}{V_I^*}+\frac{f(T,V_I^*)}{f(T,V_I)}\\
&=\frac{f(T,V_I)-f(T,V_I^*)}{f(T,V_I^*)}\frac{f(T,V_I)V_I-f(T,V_I^*)V_I^*}{f(T,V_I)V_I^*}\\
&\le 0.
\end{aligned}$$

Hence, $\dot{V}\le 0$ if $R_0>1$. Similarly, we can obtain that $E^*$ is globally attractive when $R_0>1$. □

## 5. Discussions and conclusions

In this paper, we develop a model with general incidence rate to describe the influence of raltegravir intensification on viral dynamics. We prove the existence of the limit of the solution and show that the infection-free equilibrium $E_0$ is asymptotically globally stable if $R_0 < 1$. The infection equilibrium $E^*$ is locally asymptotically stable if $R_0 > 1$.

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