Modeling and analysis of a periodic delays spatial diffusion HIV model with three-stage infection process

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Abstract Considering the antiviral drugs can act on the fusion, reverse transcription, and budding stages of HIV infected cells, in this paper, we formulate a two periodic delays heterogeneous space diffusion HIV model with three-stage infection process to study the effects of periodic antiviral treatment and spatial heterogeneity on HIV infection process. We first study the well-posedness of the full system incorporates the ultimate boundedness, the global existence of the solution and the existence of strong global attractor for $\omega$-periodic semiflow for the model. We derive the basic reproduction number $R_0$, which is defined as the spectral radius of the next generation operator. We further prove that $R_0$ is a threshold for the elimination and persistence of HIV infection by comparison principle and persistence theory for nonautonomous system, i.e., the HIV infection will be eliminated when $R_0 < 1$ and will persist when $R_0 > 1$. In the spatial homogeneous case, we obtain the explicit expression of $R_0$ and show the global attractivity of the positive steady state by using the fluctuation method. Some numerical simulations are conducted to illustrate the theoretical results and our works suggest that both spatial heterogeneity and periodic delays caused by periodic antiviral therapy have a remarkable impact on the progression of HIV infection and should not be overlooked in clinical treatment process. Keywords HIV model · Spatial diffusion · Periodic delays · Threshold dynamics · Numerical simulation

1 Introduction

HIV (Human Immunodeficiency Virus) is a viral infection that affects the immune system, gradually leading to a weakened defense mechanism against various infections and diseases. It is primarily transmitted through sexual contact, blood transfusion, needle sharing, and from an infected mother to her child during pregnancy, childbirth, or breastfeeding[1]. Upon entering the body, HIV targets and destroys a specific type of white blood cells called CD4 T lymphocytes, which play a crucial role in coordinating the immune response. As the virus replicates, the CD4 cell count declines, resulting in a weakened immune system. This progressive immune system deterioration leads to a condition known as AIDS (Acquired Immunodeficiency Syndrome), characterized by severe vulnerability to infections and certain types of cancers. One of the reasons HIV is a challenging infection to combat is its ability to evade the immune system and integrate its genetic material into the DNA of the infected cells[2].
This integration makes it difficult for the body’s immune system to recognize and eliminate the virus effectively. Additionally, HIV has a high mutation rate, resulting in different strains of the virus with varying characteristics and response to treatments. Although there is currently no cure for HIV, significant advancements have been made in the development of antiretroviral therapy (ART)\(^3\). ART involves a combination of medications that can suppress viral replication, allowing the immune system to recover and function more effectively. Early diagnosis and initiation of ART have been instrumental in improving the quality of life for people living with HIV and reducing the risk of transmitting the virus to others. Prevention remains a critical aspect of combating HIV infection. Strategies such as practicing safe sex, using sterile needles for injections, ensuring blood and organ donation screening, and providing antiretroviral prophylaxis to pregnant women can significantly reduce the transmission of HIV\(^4\). Public awareness campaigns, education, and access to testing and treatment services are essential in controlling the spread of the virus and supporting individuals affected by HIV.

HIV undergoes several critical processes within the host cells to replicate and spread throughout the body. These processes include cell fusion, reverse transcription, and budding (see Figure 1). Cell Fusion: HIV primarily infects CD4 T lymphocytes and macrophages, which play essential roles in the immune response. The first step in the HIV replication cycle is the process of cell fusion\(^5\). The virus binds to specific receptors on the surface of the target cell, primarily the CD4 receptor and a co-receptor called CCR5 or CXCR4. This binding triggers a conformational change in the viral envelope glycoprotein (gp120), allowing it to interact with the host cell membrane\(^6\). Upon binding, the viral envelope fuses with the host cell membrane, resulting in the release of the viral core into the cytoplasm of the host cell. This fusion process allows the viral genetic material to enter the host cell, initiating the subsequent steps of the replication cycle. Reverse Transcription: Once inside the host cell, the viral core contains two identical copies of the single-stranded RNA genome, along with several enzymes, including reverse transcriptase. Reverse transcription is the process by which the viral RNA genome is converted into double-stranded DNA\(^7\). Reverse transcriptase synthesizes a complementary DNA strand using the viral RNA as a template. This process involves the synthesis of a complementary DNA strand (cDNA) from the viral RNA genome, followed by degradation of the RNA template and synthesis of the second DNA strand to generate a double-stranded DNA molecule. The newly synthesized viral DNA, known as the proviral DNA, is then transported into the nucleus of the host cell, where it integrates into the host cell’s chromosomal DNA with the help of another viral enzyme called integrase\(^8\). Integration allows the viral genetic material to become a permanent part of the host cell’s genome. During budding, the viral structural proteins, such as Gag and Gag-Pol, are synthesized and transported to the host cell’s plasma membrane. These structural proteins assemble at the inner surface of the plasma membrane, encapsulating the viral RNA and enzymes, forming a new viral particle called a virion. As the assembly process progresses, the host cell’s plasma membrane wraps around the viral particle, acquiring its envelope from the cell membrane. This budding process eventually leads to the release of the mature virion from the host cell, allowing it to infect new target cells and continue the cycle of replication\(^9\). A number of researchers have studied the HIV infection process through modeling and analysis. We mainly introduce some classic research work here. Wang and Li\(^10\) formulated a mathematical model that describes HIV infection of CD4+ T cells and studied the global dynamics of the system. Perelson and Ribeiro\(^11\) reviewed the developments in HIV modeling, emphasizing quantitative findings about HIV biology uncovered by studying acute infection. Considering the impact of latent infected cell on the process of HIV infection, Rong and Perelson\(^12\) established a compartment model to study HIV persistence, the latent reservoir and viral blips. To investigate the influence of time delay on the HIV infection, Culshaw and Ruan\(^13\)
formulated a time-delayed HIV infection model to study the threshold dynamical behaviors of the system. Wu and Zhao\cite{14} investigated the dynamics of a two infection routes and two viral strains HIV infection model. Guo et al\cite{15} developed and analyzed a mathematical HIV infection model that includes sequential cell-free virus infection and cell-to-cell transmission.

Antiviral therapy is also an important research topic in the field of HIV dynamics modeling. Hosseoni and Ganham formulated a multi-scale HIV infection model to study APOBEC3G-Based anti-retroviral therapy\cite{16}. Suryawanshi and Hoffmann\cite{17} presented a multi-scale mathematical modeling framework to study antiviral therapeutic opportunities in targeting HIV-accessory proteins. Rong and Perelson\cite{18} developed a mathematical model that considers latently infected cell activation in response to stochastic antigenic stimulation to study viral blips and latent reservoir persistence in HIV-infected patients on potent therapy. Considering the age since infection and spatial factors, Wu and Zhao\cite{19} formulated an age-structured HIV/AIDS epidemic model with HAART\textsuperscript{(highly active antiretroviral therapy)} and spatial diffusion and studied the threshold dynamics of HIV transmission. It is worth mentioning that Wang et al\cite{20} formulated and investigated the global dynamics of a spatial diffusion HIV model with 2-LTR and periodic therapy. In the paper, they assumed the drug efficacy function is periodic, which is characterized by a quick rise to a maximum soon after drug intake. Afterwards, Wu et al\cite{21} investigated the evolution dynamics of a time delays heterogeneity spatial diffusion HIV latent infection model with periodic therapies and two strains. However, the above research works just consider the constant time delay, few time-dependent periodic delays spatial heterogeneity diffusion models are formulated to investigate the infection process of HIV within the host. In fact, on the one hand, antiviral drugs can act on the three stages of HIV infected cells: fusion, reverse transcription, and budding. On the other hand, HIV infected individuals periodically consume antiviral drugs to prevent the fusion of the HIV virus with cells in the body, reverse transcription of the virus, and virus budding. Due to the periodicity of antiviral drug efficacy, it is inevitable that the time delay in these three processes is time dependent, that is, the periodic function of time (more details are discussed in Sect.2). To the best of our knowledge, thus far, the global dynamics of a periodic delay reaction-diffusion disease model have only been explored by Zhao et al.\cite{22, 23}. Building upon the insights from their work, the objective of this paper is to investigate the threshold dynamics of an HIV latent infection model in a heterogeneous environment, specifically focusing on the challenges associated with periodic nonlocal infection and periodic delays, which are relevant to HIV periodic antiviral therapy.

We organize the paper as follows. In Sect.2 and Sect.3, we formulate the model and study its well-posedness, respectively. In Sect.4, we derive the basic reproduction number $R$ by the definition of the next generation operator. We first prove the threshold dynamics for the full system in terms of $R_0$, and then show the corresponding spatial homogeneity diffusion system with constant time delays admits a globally attractive positive equilibrium in Sect.5. In Sect.6, we conduct some numerical simulations to verify the theoretical results and discuss the impact of some key factors on HIV infection process. The paper concludes with a brief summary in Sect.7.
Figure 1. The flowchart of the three stages (fusion, reverse transcription, budding) of HIV infection within-host.

2 Model simulation

According to the literature [24], the process of HIV infection can be mainly divided into three stages: the first stage is that the adsorption has been reverse transcribed; The second stage is integration and transcription; In the third stage, core particle assembly and budding (see Figure 1). In clinical treatment, antiviral therapy can directly address every step of virus replication and infection, thereby interrupting the replication and spread of the virus. Due to the periodicity of antiviral treatment, we can assume that all parameters of the model are continuous function with a time period of 12h [25].

In order to finely characterize the infection process of HIV within-host, we first characterize the reverse transcription process. Let $p$ be the completion of reverse transcription, and the time-dependent growth rate of reverse transcription process is $c_1(t)$. We assume that the reverse transcription completion degree $p = p_{I_1} = 0$ when susceptible cells $T(x, t)$ turns into infected cells at the beginning, parameter $P_I$ represents the reverse transcription completion degree of the infected cells that have no ability to proliferate $I_1(x, t)$ into latent infected cells $L(x, t)$ and infected cells that have the ability to proliferate $I(x, t)$. Let $\omega_1(p, x, t)$ be the density distribution of the infected cells with the reverse transcription completion degree $p$ at location $x$ and time $t$. Record $Q_1(x, t) = c_1(t)\omega_1(p, x, t)$ as the density distribution of newly infected cells that have completed the reverse transcription process and successfully integrated viral RNA into cell DNA. Furthermore, consider $J_1(\omega_1, x, t)$ as the flux, indicating the movement of hosts with infection development level $p$, in the direction of increasing $p$, at a specific location $x$ and time $t$. Similar to [26], we have the following

$$\frac{\partial \omega_1(p, x, t)}{\partial t} = D_{I_1} \Delta \omega_1(p, x, t) - \frac{\partial J_1(p, x, t)}{\partial p} - \mu_{I_1}(x, t)\omega_1(p, x, t),$$

where $D_{I_1}$ and $\mu_{I_1}$ represent the diffusion coefficient and natural death rate of $I_1(x, t)$. Since $J_1(p, x, t) =$
\(c_1(t)\omega_1(p, x, t)\), we have
\[
\frac{\partial\omega_1(p, x, t)}{\partial t} = D_{I_1} \Delta \omega_1(p, x, t) - \frac{\partial [c_1(t)\omega_1(p, x, t)]}{\partial p} - \mu_{I_1}(x, t)\omega_1(p, x, t),
\tag{2.1}
\]

From the standpoint of biological views, we assume that the boundary condition of system (2.1) is \(\omega_1(0, x, t) = \beta(x, t)S(x, t)V_1(x, t)/c_1(t)\), where \(\beta(x, t)\) is the infection rate of infectious free virus \(V_1(x, t)\). Now, we set \(\eta_I := h_I(t) := p_I + \int_0^t c_1(s)ds\), and define \(\hat{\omega}_1(p, x, \eta_I) = \omega_1(p, x, h_I^{-1}(\eta_I))\), \(\hat{\mu}_{I_1}(x, \eta_I) = \mu_{I_1}(x, h_I^{-1}(\eta_I))\), \(\hat{c}_1(\eta_I) = c_1(h_I^{-1}(\eta_I))\), where \(h_I^{-1}(\eta_I)\) is the inverse function of \(h_I(t)\). Then, we have
\[
\frac{\partial \hat{\omega}_1(p, x, \eta_I)}{\partial \eta_I} = \frac{D_{I_1}}{\hat{c}_1(\eta_I)} \Delta \hat{\omega}_1(p, x, \eta_I) - \frac{\partial \hat{\omega}_1(p, x, \eta_I)}{\partial p} - \frac{\hat{\mu}_{I_1}(x, \eta_I)}{\hat{c}_1(\eta_I)} \hat{\omega}_1(p, x, \eta_I).
\]

Set \(w(x, s) = \hat{\omega}_1(x, s + p - \eta_I, s)\), then we obtain
\[
\frac{\partial w(x, s)}{\partial s} = \frac{D_{I_1}}{\hat{c}_1(\eta_I)} \Delta w(x, s) - \frac{\hat{\mu}_{I_1}(x, \eta_I)}{\hat{c}_1(\eta_I)} w(x, s).
\]

Note that \(\eta_I - (p - p_I) \leq \eta_I\), one has
\[
w(x, \eta_I) = \int_\Omega G_{I_1}(h_I^{-1}(\eta_I), h_I^{-1}(x, y, \eta_I - p + p_I))w(y, \eta_I - p + p_I)dy,
\]
where \(G_{I_1}(x, y, t, t_0)\) is the Green function with respect to \(\frac{\partial u}{\partial n} = \Delta u - \mu_{I_1}(\cdot, t)u\) subjects to no-flux boundary condition in the bounded domain \(\Omega\). Furthermore, we have
\[
\hat{\omega}_1(x, p, \eta_I) = \int_\Omega G_{I_1}(h_I^{-1}(\eta_I), h_I^{-1}(x, y, \eta_I - p + p_I))\hat{\omega}_1(y, p_I, \eta_I - p + p_I)dy.
\]

We define \(\tau_1(p, t)\) as the time it takes for an infected cell to progress from reverse transcription completion level \(p_I\) to reverse transcription completion level \(p\) at time \(t\). It follows from \(dp/dt = c_1(t)\) that
\[
p - p_I = \int_t^{t - \tau_1(p, t)} c_1(s)ds, h_I(t - \tau_1(p, t)) = p_I + \int_0^t c_1(s)ds - \int_{t - \tau_1(p, t)}^t c_1(s)ds = h_I(t) - (p - p_I).
\]

Set \(s = h_I(r)\), then we can obtain that
\[
\int_{\eta_I - (p - p_I)}^{\eta_I} \frac{\hat{\mu}_{I_1}(s)}{c_1(s)} ds = \int_{t - \tau_1(p, t)}^t \mu_{I_1}(s)ds.
\]

It follows that
\[
\omega_1(p, x, t) = \hat{\omega}_1(p, x, h_I(t)) = \int_\Omega G_{I_1}(x, y, t, t - \tau_1(p, t))\omega_1(y, 0, t - \tau_1(p, t))dy
\]
\[
= \int_\Omega G_{I_1}(x, y, t, t - \tau_1(p, t))\frac{\beta(y, t - \tau_1(p, t))S(y, t - \tau_1(p, t))V_1(y, t - \tau_1(p, t))}{c_1(t - \tau_1(p, t))}dy.
\]

Define \(\tau_1(t)\tau_1(p, t)\), then we have \(p_I = \int_{t - \tau_1(p, t)}^t c_1(s)ds\) and \(1 - \tau_1(t) = c_1(t)/c_1(t - \tau_1(t))\). Subsequently, we have
\[
Q_1(x, t) = c_1(t)\omega_1(p_I, x, t) = (1 - \tau_1(t)) \int_\Omega G_{I_1}(x, y, t, t - \tau_1(t))\beta(y, t - \tau_1(t))S(y, t - \tau_1(t))V_1(y, t - \tau_1(t))dy.
\tag{2.2}
\]
Similarly, we denote $q$ as the budding level of free virus produced by the infected cells with proliferate ability, and the time-dependent growth rate of budding progress is denoted as $c_2(t)$. Assuming that the budding completion rate $q = d_{I_2} = 0$ when transitioning from $I(x, t)$ to $I_2(x, t)$ at the beginning, and $q = q_v$ when budding infectious free virus $V_1(x, t)$ and no-infectious virus $V_2(x, t)$ from $I_2(x, t)$. Set $\omega_2(q, x, t)$ be the density distribution of infected cells whose budding completion is $q$ at time $t$. Record $Q_2(x, t) = c_2(t)\omega_2(q_v, x, t)$ as the distribution of infected cells that have completed the budding process and successfully released free viruses. Hence, we have

\[
Q_2(x, t) = (1 - \tau_2^2(t))\epsilon(t - \tau_2(t))K \int_{\Omega} G_{I_2}(x, y, t, t - \tau_2(t))I(y, t - \tau_2(t))dy,
\] (2.3)

where $G_{I_2}(x, y, t, t_0)$ represents the Green function with respect to $\frac{\partial u}{\partial \nu} = D_{I_2}\Delta u - \mu_{I_2}(\cdot, t)u$ with respect to no-flux boundary condition. Parameter $K$ represents the burst size of $I(x, t)$ and $\epsilon(t)$ represents the apoptosis rate of $I(x, t)$, time-delayed $\tau_2(t)$ is the time it takes the infected cells $I(x, t)$ to complete the budding process, it satisfies with $q_v = \int_{t - \tau_2(q_v, t)}^{t} c_2(s)ds$ and $1 - \tau_2^2(t) = c_2(t)/c_2(t - \tau_2(t)) > 0$.

Combined (2.2) with (2.3), we have the following periodic delays reaction-diffusion HIV infection model with space heterogeneity

\[
\begin{align*}
\frac{\partial S(x, t)}{\partial t} &= D_S\Delta S(x, t) + \Lambda(x, t) - \beta(x, t)S(x, t)V_1(x, t) - \mu_S(x, t)S(x, t), \\
\frac{\partial I_1(x, t)}{\partial t} &= D_{I_1}\Delta I_1(x, t) + \beta(x, t)S(x, t)V_1(x, t) - \mu_{I_1}(x, t)I_1(x, t) - B_1(x, t), \\
\frac{\partial L(x, t)}{\partial t} &= D_L\Delta L(x, t) - (\delta(x, t) + \mu_L(x, t))L(x, t) + \eta(x, t)B_1(x, t), \\
\frac{\partial I(x, t)}{\partial t} &= D_I\Delta I(x, t) - (\epsilon(x, t) + \mu_I(x, t))I(x, t) + \delta(x, t)L(x, t) + (1 - \eta(x, t))B_1(x, t), \\
\frac{\partial I_2(x, t)}{\partial t} &= D_{I_2}\Delta I_2(x, t) - \mu_{I_2}(x, t)I_2(x, t) + \epsilon(x, t)I(x, t) - B_2(x, t), \\
\frac{\partial V_1(x, t)}{\partial t} &= D_{V_1}\Delta V_1(x, t) - c(x, t)V_1(x, t) + (1 - \gamma(x, t))B_2(x, t), \\
\frac{\partial V_2(x, t)}{\partial t} &= D_{V_2}\Delta V_2(x, t) - d(x, t)V_2(x, t) + \gamma(x, t)B_2(x, t), \\
\frac{\partial S(x, t)}{\partial \nu} = \frac{\partial I_1(x, t)}{\partial \nu} = \frac{\partial L(x, t)}{\partial \nu} = \frac{\partial I(x, t)}{\partial \nu} = \frac{\partial I_2(x, t)}{\partial \nu} = \frac{\partial V_1(x, t)}{\partial \nu} = \frac{\partial V_2(x, t)}{\partial \nu} = 0, \quad x \in \partial \Omega,
\end{align*}
\] (2.4)

where $B_1(x, t) = (1 - \tau_1^2(t)) \int_{\Omega} G_{I_1}(x, y, t - \tau_1(t))\beta(y, t - \tau_1(t))S(y, t - \tau_1(t))V_1(y, t - \tau_1(t))dy$, $B_2(x, t) = (1 - \tau_2^2(t))K \int_{\Omega} G_{I_2}(x, y, t - \tau_2(t))\epsilon(y, t - \tau_2(t))I(y, t - \tau_2(t))dy$. Since $I_1(x, t), I_2(x, t)$ and $V_2(x, t)$ of system (2.4) are decoupled from the other equations. In addition, we denote $(w_1(x, t), w_2(x, t), w_3(x, t), w_4(x, t)) = (S(x, t), L(x, t), I(x, t), V_1(x, t))$ for the sake of simplicity. it suffices to investigate the following system:
\[
\begin{aligned}
\frac{\partial w_1(x,t)}{\partial t} &= D_S \Delta w_1(x,t) + \Lambda(x,t) - \beta(x,t)w_1(x,t)w_4(x,t) - \mu_S(x,t)w_1(x,t), \\
\frac{\partial w_2(x,t)}{\partial t} &= D_L \Delta w_2(x,t) - (\delta(x,t) + \mu_L(x,t))w_2(x,t) \\
&\quad + \eta(x,t)(1 - \tau_1(t)) \int_{\Omega} G_{I_1}(x,y,t)\beta(y,t - \tau_1(t))w_1(y,t - \tau_1(t))w_4(y,t - \tau_1(t))dy, \\
\frac{\partial w_3(x,t)}{\partial t} &= D_I \Delta w_3(x,t) - (\epsilon(x,t) + \mu_I(x,t))w_3(x,t) + \delta(x,t)w_2(x,t) \\
&\quad + (1 - \eta(x,t))(1 - \tau_1(t)) \int_{\Omega} G_{I_1}(x,y,t)\beta(y,t - \tau_1(t))w_1(y,t - \tau_1(t))w_4(y,t - \tau_1(t))dy, \\
\frac{\partial w_4(x,t)}{\partial t} &= D_{V_1} \Delta w_4(x,t) - c(x,t)w_4(x,t) \\
&\quad + (1 - \gamma(x,t))(1 - \tau_2(t))K \int_{\Omega} G_{I_2}(x,y,t)\epsilon(y,t - \tau_2(t))w_3(y,t - \tau_2(t))dy, \\
\frac{\partial w_1(x,t)}{\partial \nu} &= \frac{\partial w_2(x,t)}{\partial \nu} = \frac{\partial w_3(x,t)}{\partial \nu} = \frac{\partial w_4(x,t)}{\partial \nu} = 0, x \in \partial \Omega,
\end{aligned}
\]
(2.5)

3 The well-posedness of system (2.5)

In this section, we are devoted to studying the well-posedness of system (2.5). For this purpose, we give the following assumption

**Assumption 3.1.** For system (2.5), we assume

1. The diffusion coefficients \(D_S, D_L, D_I, D_{V_1}\) are all positive constants;
2. Function \(\Lambda(x,t), \mu_1(x,t), \mu_S(x,t), \mu_L(x,t), c(x,t), \epsilon(x,t), \beta(x,t), \gamma(x,t)\) and \(\eta(x,t)\) are all Hölder continuous and positive on \(\bar{\Omega} \times \mathbb{R}\), and \(\omega\)-periodic in \(t\), where \(\omega = 24 h\), and hence \(\tau_1(t)\) (\(j = 1, 2\)) are both \(\omega\)-periodic functions with respect to time \(t\).

Now, we define \(\mathbb{M} := C(\mathbb{R}^4, \bar{\Omega})\), which is a Banach space equipped the norm \(\|\cdot\|_{\mathbb{M}}\). We set \(\bar{T} = \max t \in [0, \omega] \|\tau_1(t), \tau_2(t)\|\) and introduce \(\mathfrak{M} := C([-\bar{T}, 0], \mathbb{M})\) equipped with the norm \(\|\psi\| = \max_{\theta \in [-\bar{T}, 0]} \|\psi(\theta)\|_{\mathbb{M}}\), where \(\psi \in \mathfrak{M}\). Clearly, \(\mathfrak{M}\) is a Banach space. We define the positive cones of the spaces \(\mathbb{M}\) and \(\mathfrak{M}\) as \(\mathbb{M}^+ := (\mathbb{R}^4_+, \bar{\Omega})\) and \(\mathfrak{M}^+ := C([-\bar{T}, 0], \mathbb{M}^+)\), respectively. Thus, both \((\mathbb{M}, \mathbb{M}^+)\) and \((\mathfrak{M}, \mathfrak{M}^+)\) are ordered spaces. For a function \(w : [-\bar{T}, \xi] \to \mathbb{M}\) with \(\xi > 0\), we set \(w_t \in \mathfrak{M}\) as \(w_\theta(x) = (w_1(\theta), w_2(\theta), w_3(\theta), w_4(\theta))\) for all \(\theta \in [-\bar{T}, 0]\) and \(t \in [0, \xi]\). Let \(\mathbb{Q} := C(\mathbb{R}, \bar{\Omega})\), \(\mathbb{Q}^+ := C(\mathbb{R}^+, \bar{\Omega})\), and \(\mathcal{T}(s,t) := \text{diag}T_1(s,t), T_2(s,t), T_3(s,t), T_4(s,t) : \mathbb{Q} \to \mathbb{Q}\) be the evolution operator associated with \(\frac{\partial w}{\partial t} = D \Delta w - \mu(x,t)w = A(t)w\) subject to the No-flux boundary condition. Here, \(D = \text{diag}D_S, D_L, D_I, D_{V_1}, \mu(x,t) = (\mu_S(x,t), \mu_L(x,t) + \delta(x,t), \epsilon(x,t) + \mu_I(x,t), c(x,t))^T\), and \(A(t) = \text{diag}A_1(t), A_2(t), A_3(t), A_4(t)\). Given that \(\mu(x,t)\) is \(\omega\)-periodic in \(t\), according to Lemma 6.1 [27], we know that \(\mathcal{T}(s + \omega, t + \omega) = \mathcal{T}(s,t)\) for \((s,t) \in \mathbb{R}^2\) with \(t > s\). Furthermore, we establish that the operator \(\mathcal{T}(s,t)\) is strongly positive and compact. Define operator
\( \mathcal{F} = (\mathcal{F}_1, \mathcal{F}_2, \mathcal{F}_3, \mathcal{F}_4) : [0, \infty) \times \mathfrak{M} \to \mathbb{M} \) as follows:

\[
\mathcal{F}_1(t, \psi) := \Lambda(\cdot, t) - \beta(\cdot, t)\psi_4(\cdot, t),
\]

\[
\mathcal{F}_2(t, \psi) := \eta(x, t)(1 - \tau_1'(t)) \int_\Omega G_{I_1}(x, y, t - \tau_1(t)) \beta(y, t - \tau_1(t))\psi_1(y, -\tau_1(t))\psi_4(y, -\tau_1(t))dy,
\]

\[
\mathcal{F}_3(t, \psi) := (1 - \eta(x, t))(1 - \tau_1'(t)) \int_\Omega G_{I_1}(x, y, t - \tau_1(t)) \beta(y, t - \tau_1(t))\psi_1(y, -\tau_1(t))\psi_4(y, -\tau_1(t))dy,
\]

\[
\mathcal{F}_3(t, \psi) := (1 - \gamma(x, t))(1 - \tau_2'(t))\mathcal{K} \int_\Omega G_{I_2}(x, y, t - \tau_2(t))\epsilon(y, t - \tau_2(t))\psi_3(y, -\tau_2(t))dy,
\]

for \((x, t) \in \Omega \times [0, \infty), \psi = (\psi_1, \psi_2, \psi_3, \psi_4) \in \mathfrak{M}\). Then we can rewrite system (2.5) as the following abstract Cauchy problem

\[
\begin{align*}
dw dt &= \mathcal{A}(t)w + \mathcal{F}(w, t), t > 0, \\
w_0 &= \psi. \tag{3.6}
\end{align*}
\]

Based on Theorem 1[28], we can show that system (3.6) always admits a unique solution, \(w(\cdot, t, \psi), t \in [0, t_f)\) with \(w_0 = \psi, t_f \leq \infty\) for \(\psi \in \mathfrak{M}_+\). Based on the definition of \(\tau_j(t)(j = 1, 2)\), we have the compatibility conditions of \(I_1\) and \(I_2\) as follow:

\[
\begin{align*}
I_1(\cdot, 0) &= \int_{-\tau_1(0)}^{0} \mathcal{T}_{2}(s, 0)\beta(\cdot, s)S(\cdot, s)V_1(\cdot, s)ds, \\
I_2(\cdot, 0) &= \int_{-\tau_2(0)}^{0} \mathcal{T}_{5}(s, 0)\epsilon(\cdot, s)I(\cdot, s)ds. \tag{3.7}
\end{align*}
\]

Define the following space

\[
\mathcal{D} := \left\{ \phi \in C([-\tau, 0], C(\mathbb{R}^n_+, \Omega)) : \phi_2(\cdot, 0) = \int_{-\tau_1(0)}^{0} \mathcal{T}_{2}(s\theta)\beta(\cdot, s)\phi_1(\cdot, s)\phi_6(\cdot, s)ds, \\
\phi_5(\cdot, 0) = \int_{-\tau_2(0)}^{0} \mathcal{T}_{5}(s, 0)\epsilon(\cdot, s)\phi_4(\cdot, s)ds \right\}
\]

It is obvious that system (2.4) admits a unique solution \(U(\cdot, t, \phi) = (S(\cdot, t), I_1(\cdot, t), L(\cdot, t), I(\cdot, t), I_2(\cdot, t), V_1(\cdot, t), V_2(\cdot, t))\) with initial condition \(U_0 = \phi\) for all \(\phi \in \mathcal{D}\). Based on Corollary 4 [28], we can verified that \(U(\cdot, t, \phi) \geq 0\) on the maximal existence interval. According to (3.7), we have that

\[
\begin{align*}
I_1(\cdot, t) &= \int_{t-\tau_1(t)}^{t} \mathcal{T}_{2}(s, t)\beta(\cdot, s)S(\cdot, s)V_1(\cdot, s)ds, \\
I_2(\cdot, t) &= \int_{t-\tau_2(t)}^{t} \mathcal{T}_{5}(s, t)\epsilon(\cdot, s)I(\cdot, s)ds,
\end{align*}
\]

and hence we know that \(I_j(\cdot, t) \geq 0(j = 1, 2)\) for \(t \in [0, t_f]\). To prove the ultimate boundedness of the solution of system (2.5), we set \(N(t) = \int_{\Omega}(K(S(x, t) + I_1(x, t) + L(x, t) + I(x, t) + I_2(x, t)) + V_1(x, t) + V_2(x, t))dx\), then it follows from system (2.5) that

\[
\frac{dN(t)}{dt} \leq K \int_{\Omega} A(x, t)dx - \mu N(t) \leq \bar{K} \mu \Omega - \mu N(t).
\]
We have that $N(t) \leq \frac{\lambda K |\Omega|}{\mu} := \mathcal{N}$ for $t > t_1 > 0$ by using the comparison principle, where $f = \max_{(x,t) \in \mathbb{P} \times [0,\omega]} f(x,t), \bar{f} = \min_{(x,t) \in \mathbb{P} \times [0,\omega]} f(x,t)$. Hence, from the third equation of system (2.5), we have $\partial L(x,t)/\partial t \leq D_L \Delta L(x,t) + \eta \beta N^2 - (\delta + \mu_L) L(x,t)$, which leads to $L(x,t) \leq \frac{\eta \beta N^2}{(\delta + \mu_L)}$ for $t > t_2 > t_1 > 0$. This leads to $L(x,t)$ is ultimately bounded. Similarly, we can prove that the ultimate boundedness of $I_1, I_2, I_3, I_4$ and $S$. Thus, the comparison argument implies that the global existence and ultimate boundedness of the solutions of system (2.5) with initial condition in $\mathcal{S}$, and thus those of system (2.5) in $\mathcal{M}_+$ hold. Based on Lemma 2.6[29] together with Theorem 2.9 [30], we have the following theorem

**Theorem 3.2.** System (2.5) with $w_0 = \psi$ has a unique solution $\omega(\cdot,t \psi)$ on $[0, +\infty)$ for any $\psi \in \mathcal{M}_+$. Furthermore, system (2.5) generates a $\omega-$periodic semiflow $\mathcal{H}(t) : w_1(t) : \mathcal{M}_+ \to \mathcal{M}_+$ for $t \geq 0$, and $\mathcal{H}(t)$ admits a strong global attractor in $\mathcal{M}_+$.

### 4 The basic reproduction number of system (2.5)

We are mainly arm to deriving the functional expression of the basic reproduction number of system (2.5) by applying the method mentioned in [22].

Let $\mathbb{X} := C(\mathbb{R}^3, \mathbb{P}), \mathbb{X}_+ := C(\mathbb{R}^3, \mathbb{P})$ and Banach space $C_\omega(\mathbb{R}, \mathbb{X})$ equipped with the norm $||\phi||_{C_\omega(\mathbb{R}, \mathbb{X})} := \max_{\theta \in [0,\omega]} ||\phi(\theta)||_{\mathbb{X}}, \phi \in C_\omega(\mathbb{R}, \mathbb{X})$. From [26, Lemma 2.1], we have

**Lemma 4.1.** [26, Lemma 2.1] System

\[
\begin{aligned}
\frac{\partial S(x,t)}{\partial t} &= D_S \Delta S(x,t) + \Delta(x,t) - \mu_S(x,t) S(x,t), t > 0, x \in \mathbb{P}, \\
\frac{\partial S(x,t)}{\partial \nu} &= 0, t > 0, x \in \partial \mathbb{P},
\end{aligned}
\]

always admits a globally attractive positive $\omega-$periodic solution $S^*(x,t)$.

Hence, we know that system (2.5) admits an infection-free $\omega-$periodic steady state $E_0(x,t) = (S^*(x,t), 0, 0, 0)$. Linearizing system (2.5) at $E_0(x,t)$ and considering the equation for infection compartments, we have

\[
\begin{aligned}
\frac{\partial u_1(x,t)}{\partial t} &= D_L \Delta u_1(x,t) + \eta(x,t)(1 - \tau'_1(t)) \int_{\Omega} G_{I_1}(x, y, t - \tau_1(t)) \beta(y, t - \tau_1(t)) S^*(y, t - \tau_1(t)) dy - (\delta(x,t) + \mu_L(x,t)) u_1(x,t), \\
\frac{\partial u_2(x,t)}{\partial t} &= D_I \Delta u_2(x,t) + (1 - \eta(x,t))(1 - \tau'_1(t)) \int_{\Omega} G_{I_2}(x, y, t - \tau_1(t)) \beta(y, t - \tau_1(t)) S^*(y, t - \tau_1(t)) dy - (\epsilon(x,t) + \mu_I(x,t)) u_2(x,t), \\
\frac{\partial u_3(x,t)}{\partial t} &= D_{I_3} \Delta u_3(x,t) + (1 - \gamma(x,t))(1 - \tau'_2(t)) \mathcal{K} \int_{\Omega} G_{I_3}(x, y, t - \tau_2(t)) u_2(y, t - \tau_2(t)) dy - c(x,t) u_3(x,t), \\
\frac{\partial u_1(x,t)}{\partial \nu} &= \frac{\partial u_2(x,t)}{\partial \nu} = \frac{\partial u_3(x,t)}{\partial \nu} = 0, x \in \partial \mathbb{P},
\end{aligned}
\]

(4.9)
where \((u_1, u_2, u_3) = (w_2, w_3, w_4)\). Let \(X : C([-\tau, 0], X), X_+ : C([-\tau, 0], X_+)\). Define \(L(t) : X \to X\) by

\[
L = \begin{pmatrix}
\psi_1 & 0 & 0 \\
\psi_2 & 0 & 0 \\
\psi_3 & 0 & 0
\end{pmatrix}
\begin{pmatrix}
\eta(\cdot, t)(1 - \tau'_1(t)) \int_\Omega G_{t, t}(\cdot, y, t, t - \tau_1(t)) \beta(y, t - \tau_1(t)) \psi_1(y, t - \tau_1(t)) \\
(1 - \eta(\cdot, t))(1 - \tau'_1(t)) \int_\Omega G_{t, t}(\cdot, y, t, t - \tau_1(t)) \beta(y, t - \tau_1(t)) \psi_1(y, t - \tau_1(t)) \\
\psi_4(y, t - \tau_1(t))dy
\end{pmatrix},
\]

for \(t \in \mathbb{R}, (\psi_1, \psi_2, \psi_3) \in X\) and \(-V(t)u = D_u - W(t)u, D_u = \text{diag}(D_L, D_I, D_{V_1})\) and

\[
[\mathcal{W}(t)](x) = \begin{pmatrix}
\delta(x, t) + \mu_I(x, t) & 0 & 0 \\
-\delta(x, t) & \mu_I(x, t) + \epsilon(x, t) & 0 \\
0 & 0 & -(1 - \gamma(x, t))(1 - \tau'_2(t)) \int_\Omega G_{t, t}(\cdot, y, t, t - \tau_2(t)) \epsilon(y, t - \tau_2(t))dy & c(x, t)
\end{pmatrix}.
\]

Let \(\Psi(s, t) = \text{diag}(\mathcal{T}_2(\cdot, t), \mathcal{T}_3(\cdot, t), \mathcal{T}_4(\cdot, t)), t \geq s\) be the evolution operators subject to the system \(du/dt = -V(t)u\), where \(\mathcal{T}_k(k = 2, 3, 4)\) are defined in Sect. 2. Since \(\Psi(s, t)\) is a positive operator, it follows that \(\Psi(s, t)X_+ \subset X_+, t > s\). Based on Theorem 3.12 [31], we know that \(-V(t)\) is resolvent positive. Hence, for \(L(t)\) and \(W(t)\), we have the following lemma.

**Lemma 4.2.** For operators \(L(t)\) and \(W(t)\), we have

1. The positive of \(L(t) : X \to X\) holds for \(L(t)X_+ \subset X_+\),
2. \(-V(t)\) is resolvent positive.

Hence, the cumulative number of infectious cells at time \(t\) resulting from all the previously active viruses up to time \(t\) can be described as follows:

\[
\int_0^{+\infty} \Psi(t, t - f)L(t - f)u_{t-f}df = \int_0^{+\infty} \Psi(t - f, t)L(t - f)u(t - f + \cdot)df.
\]

In the next, we define

\[
[\mathcal{S}u](t) := \int_0^\infty \Psi(t - s, t)L(t - s)u(t - s + \cdot)ds, t \in \mathbb{R}, u \in C_\omega(\mathbb{R}, X),
\]

\[
[\mathcal{E}u](t) := L(t)\int_0^\infty \Psi(t - s + \cdot, t + \cdot)u(t - s + \cdot)ds, t \in \mathbb{R}, u \in C_\omega(\mathbb{R}, X).
\]

Let \(E, F\) be two bounded linear operators on \(C_\omega(\mathbb{R}, X)\) as follows

\[
[Eu](t) = \int_0^\infty \Psi(t - f, t)u(t - f)df, [Fu](t) = L(t)u, t \in \mathbb{R}, u \in C_\omega(\mathbb{R}, X).
\]

Then we have \(\mathcal{S} = E \circ F\) and \(\mathcal{S} = F \circ E\), it leads to \(\mathcal{S}\) and \(\mathcal{S}\) have the same spectral radius. Based on the definition of the next generation operator, we have the basic reproduction number of system (2.5) as follows

\[
R_0 := r(\mathcal{S}) = r(\mathcal{E}), \text{ where } r(\cdot) \text{ is the spectral radius.}
\]

We set \(\mathcal{P}(t) : \mathcal{P}(t)\phi = u_t(\phi)\) be the solution map of system (4.9) on \(X\), where \(u_t(\phi)(\theta) = u(t + \theta, \phi) = (w_2(t + \theta, \phi), w_3(t + \theta, \phi), w_4(t + \theta, \phi)), t \geq 0, \theta \in [-\tau, 0]\) and \(u_t(\phi)\) with \(u(\theta = \phi(\theta), \theta \in [-\tau, 0]\) is the unique solution of system (4.9). Hence, it is obvious that \(\mathcal{P}(\omega)\) is the Poincaré map with respect to system (4.9). Let \(r(\mathcal{P}(\omega))\) be the spectral radius of \(\mathcal{P}(\omega)\). From Theorem 3.7[32], one has
Lemma 4.3. \( r(P(\omega)) \) has the same sign as \( R_0 - 1 \).

Define phase space and its positive cone as follow

\[
\begin{align*}
\mathbb{H} &:= C([-\tau_1(0), 0], \mathbb{Q}) \times C([-\tau_1(0), 0], \mathbb{Q}) \times C([-\tau_2(0), 0], \mathbb{Q}), \\
\mathbb{H}_+ &:= C([-\tau_1(0), 0], \mathbb{Q}_+) \times C([-\tau_1(0), 0], \mathbb{Q}_+) \times C([-\tau_2(0), 0], \mathbb{Q}_+). 
\end{align*}
\]

For ordered Banach space \((\mathbb{H}, \mathbb{H}_+)\) and function \( v : [-\tau_1(0), +\infty) \times [-\tau_1(0), +\infty) \times [-\tau_2(0), +\infty) \to \mathbb{R} \), we define \( v_t \in \mathbb{H} \) by \( v_t(\theta) = (v_1(t + \theta_1), v_2(t + \theta_1), v_3(\theta_2)), \theta := (\theta_1, \theta_1, \theta_2) \in [-\tau_1(0), 0] \times [-\tau_1(0), 0] \times [-\tau_2(0), 0], t \geq 0 \). We set \( \hat{\tau} = \min{\tau_1, \tau_2} \), where \( \tau_j = \min_{t \in [0,\omega]} \tau_j(t), j = 1, 2 \). It follows that \(-\tau_1(0) = 0 = \tau_2(0) \leq t - \tau_1(t) \leq \hat{\tau}_j \tau_1(\hat{\tau}) \leq \hat{\tau} - \hat{\tau} = 0 \). By the method of steps as shown in Lemma 3.2[26], we have the following result

Lemma 4.4. If \( \varphi \in \mathbb{H}_+ \), then system (4.9) with initial values \( v_0 = \varphi \) has a unique non-negative solution \( v(\cdot, t, \varphi) \) on \([0, +\infty)\).

In fact, Theorem 3.2 and Lemma 4.4 show that for \( \varphi \in \mathbb{H}_+ \) and \( \psi \in X_+ \) with \( \psi_1(\cdot, \theta_1) = \varphi_1(\cdot, \theta_1), \psi_2(\cdot, \theta_1) = \varphi_2(\cdot, \theta_1), \theta_1 \in [-\tau_1(0), 0] \) and \( \psi_3(\cdot, \theta_3) = \varphi_3(\cdot, \theta_3), \theta_3 \in [-\tau_2(0), 0] \), then we can verify that \( u(\cdot, t, \varphi) = v(\cdot, t, \psi), t \geq 0 \). Here \( u(\cdot, t, \psi) \) and \( v(\cdot, t, \varphi) \) are respectively the solutions of system (4.9) with initial values \( u_0 = \varphi \) and \( v_0 = \psi \). Now, we give the results of the eventually positiveness of the periodic semiflow \( P(t) : P\varphi = v_t(\phi) \) of system (4.9) for any \( \phi \in \mathbb{H} \).

Lemma 4.5. If \( \varphi \in \mathbb{H}_+ \) with \( \varphi \neq 0 \), then the solution \( v(\cdot, t, \varphi) \) of system (4.9) with \( v_0 = \varphi \) meets with \( v_k(\cdot, t) > 0 \) for \( t > 2\hat{\tau}(k = 1, 2, 3) \) and therefore \( P(t)\varphi \geq 0 \) for \( t > 3\hat{\tau} \).

Proof. From Lemma 4.4 we know that \( v_k(t) \geq 0, t \geq 0 \) on each interval \([m\hat{\tau}, (m + 1)\hat{\tau}], m \in \mathbb{N} \). Now, we choose a large enough constant \( A > \max\{\hat{\mu}_L + \delta, \hat{\mu}_T + \epsilon, \hat{\epsilon}\} \) such that \( h_1(\cdot, t, v_1) := -(\mu_L(\cdot, t) + \delta(\cdot, t))v_1 + Av_1, h_2(\cdot, t, v_2) := -\mu_L(\cdot, t) + \epsilon(\cdot, t))v_2 + Av_2, h_3(\cdot, v_3) := -c(\cdot, t)v_3 + Av_3 \) are increasing in \( v_k(k = 1, 2, 3) \), respectively. Then it follows that \( v_k(k = 1, 2, 3) \) satisfy the following system

\[
\begin{align*}
\begin{cases}
\frac{\partial v_1(x, t)}{\partial t} &= D_L\Delta v_1(x, t) + \eta(x, t)(1 - \tau_1(t)) \int_\Omega G_{I_1}(x, y, t, t - \tau_1(t))\beta(y, t - \tau_1(t))S^*(y, t - \tau_1(t)) dy - Av_1(x, t) + h_1(x, t, v_1), \\
\frac{\partial v_2(x, t)}{\partial t} &= D_L\Delta v_2(x, t) + (1 - \eta(x, t))(1 - \tau_1(t)) \int_\Omega G_{I_1}(x, y, t, t - \tau_1(t))\beta(y, t - \tau_1(t))S^*(y, t - \tau_1(t)) dy - Av_1(x, t) + h_1(x, t, v_1), \\
\frac{\partial v_3(x, t)}{\partial t} &= D_L\Delta v_3(x, t) + \delta(x, t)v_1(x, t) - Av_2(x, t) + h_2(x, t, v_2), \\
\frac{\partial v_4(x, t)}{\partial t} &= D_L\Delta v_4(x, t) + (1 - \gamma(x, t))(1 - \tau_2(t))K \int_\Omega G_{I_2}(x, y, t, t - \tau_2(t))v_2(y, t - \tau_2(t)) dy - Av_3(x, t) + h_3(x, t, v_3), \\
\frac{\partial v_5(x, t)}{\partial t} &= D_L\Delta v_5(x, t) + (1 - \gamma(x, t))(1 - \tau_2(t)) \int_\Omega G_{I_2}(x, y, t, t - \tau_2(t))v_2(y, t - \tau_2(t)) dy - Av_3(x, t) + h_3(x, t, v_3), \\
\end{cases}
\end{align*}
\]

\[\frac{\partial v_i(x, t)}{\partial v} = \frac{\partial v_i(x, t)}{\partial v} = 0, x \in \partial \Omega,\]
Therefore, for given $\phi \in \mathbb{H}_+$, one has

$$
\begin{aligned}
v_1(t, \phi) = & \tilde{T}_2(0, t)\phi_1(0) + \int_0^t \tilde{T}_2(s, t)h_1(\cdot, s, v_1(\cdot, s))ds + \int_0^t \tilde{T}_2(s, t)\eta(y, s)(1 - \tau'_1(s)) \\
& \cdot \int_\Omega G_1(\cdot, y, s, s - \tau_1(s)) \cdot \beta(y, s - \tau_1(s))S^*(y, s - \tau_1(s))v_3(s, y, s - \tau_1(s))dyds,
\end{aligned}
$$

$$
\begin{aligned}
v_2(t, \phi) = & \tilde{T}_3(0, t)\phi_2(0) + \int_0^t \tilde{T}_3(s, t)h_2(\cdot, s, v_2(\cdot, s))ds + \int_0^t \tilde{T}_3(s, t)(1 - \eta(y, s))(1 - \tau'_1(s)) \\
& \cdot \int_\Omega G_1(\cdot, y, s, s - \tau_1(s)) \cdot \beta(y, s - \tau_1(s))S^*(y, s - \tau_1(s))v_3(s, y, s - \tau_1(s))dyds \\
& + \int_0^t \tilde{T}_3(s, t)\delta(x, s)v_1(x, s)ds,
\end{aligned}
$$

$$
\begin{aligned}
v_3(t, \phi) = & \tilde{T}_4(0, t)\phi_3(0) + \int_0^t \tilde{T}_4(s, t)h_3(\cdot, s, v_3(\cdot, s))ds + \int_0^t \tilde{T}_4(s, t)(1 - \gamma(y, s))(1 - \tau'_2(s)) \\
& \cdot \int_\Omega G_{I2}(\cdot, y, s, s - \tau_1(s))\epsilon(s - \tau_2(s))v_2(s, y, s - \tau_2(s))dyds,
\end{aligned}
$$

where $\tilde{T}_2(s, t), \tilde{T}_3(s, t), \tilde{T}_4(s, t) : \mathbb{Q} \rightarrow \mathbb{Q}$ are the evolution operator with respect to $\partial w_k/\partial t = D_kw_k - Aw_k(k = 2, 3, 4)$ subject to the no-flux boundary condition. Since $c_i = \tau_i(t)(i = 1, 2)$ are the increasing function with respect to $t \in \mathbb{R}$, then we have that $[-\tau_i(0), 0] \subset c_i([0, \hat{\tau}])$. In a general context, we suppose that $\varphi_3 > 0$, then from Lemma 4.4, it follows that there admits an $(x_0, \theta_3) \in \Omega \times [-\tau_1(0), 0]$ such that $v_3(x_0, \theta_3) > 0$. From the first equation of Eq. (4.10), we have $v_1(\cdot, t, \varphi) > 0$ for $t > \hat{\tau}$. Note that $s - \tau_1(s) > \hat{\tau}$ for $s > 2\hat{\tau}$, then we can obtain that $v_2(\cdot, t, \varphi) > 0$ for $t > 2\hat{\tau}$, and it follows from the last equation of Eq. (4.10) that $v_3(\cdot, t, \varphi) > 0$ for $t > 2\hat{\tau}$. Hence, the strongly positive of $\mathcal{P}(t)$ holds for $t > 3\hat{\tau}$. The proof is finished.}

Based on the conclusions in [22, Lemma 3.8] and [33, Lemma 5], we have

**Lemma 4.6.** For Poincaré maps $\tilde{\mathcal{P}}(\omega) : X \rightarrow X$ and $\mathcal{P}(\omega) : \mathbb{H} \rightarrow \mathbb{H}$, $\tilde{\mathcal{P}}(\omega)$ and $\mathcal{P}(\omega)$ have the same spectral radius, i.e., $r(\tilde{\mathcal{P}}(\omega)) = r(\mathcal{P}(\omega))$. Moreover, $\mathcal{R}_0$ has the same sign $\text{asr}(\mathcal{P}(\omega)) - 1$.

**Lemma 4.7.** There admits a positive $\omega$-periodic function $\upsilon^*(x, t)$ such that $e^{\rho t}\upsilon^*(x, t)$ satisfies system (4.9), where $\rho = \frac{\ln r(\mathcal{P}(\omega))}{\omega}$.

## 5 Threshold dynamics of system (2.5)

In this section, we first present a threshold dynamics of system (2.5) in term of $\mathcal{R}_0$, and then show the only positive constant steady state in spatial homogeneous case is globally attractive. To this end, we define the following two Banach spaces

$$
\begin{aligned}
\mathbb{Y} = [C([-\tau_1(0), 0], \mathbb{Q})]^3 \times [C([-\tau_2(0), 0], \mathbb{Q})], \\
\mathbb{Y}_+ = [C([-\tau_1(0), 0], \mathbb{Q}_+)]^3 \times [C([-\tau_2(0), 0], \mathbb{Q}_+)].
\end{aligned}
$$

Similar to the proof of lemma 3.2 [26], we can obtain that for any $\varphi \in \mathbb{X}_+, \psi \in \mathbb{Y}_+$ with $\psi_j(\cdot, \hat{\theta}_j) = \varphi_j(\cdot, \hat{\theta}_j), \forall \hat{\theta}_1, \hat{\theta}_2, \hat{\theta}_3 \in [-\tau_1(0), 0], \hat{\theta}_4 \in [-\tau_2(0), 0]$, where $\hat{\theta} := (\hat{\theta}_1, \hat{\theta}_2, \hat{\theta}_3, \hat{\theta}_4)$, it follows that $w(\cdot, t, \varphi) =$
$z(\cdot, t, \psi), t \geq 0$, where $w(\cdot, t, \varphi)$ with $w_0 = \varphi$ and $z(\cdot, t, \psi)$ with $z_0 = \psi$ are both solutions of system (2.5). Based on the Lemma 4.1 [26], we have that the $\omega$-periodic semiflow $\mathcal{L}(t)\psi = w(t, \psi), t \geq 0$ of system (2.5) on space $\mathbb{Y}_+$ satisfies: (1) $\mathcal{L}(0) = I$; (2) $\mathcal{L}(t + \omega) = \mathcal{L}(\omega) \circ \mathcal{L}(t), t \geq 0$; (3) $\mathcal{L}(\psi)$ is continuous in $(\psi, t) \in \mathbb{Y}_+ \times (0, \infty)$. Furthermore, $\mathcal{L}(t)$ has a global attractor in $\mathbb{Y}_+$. From system (2.5), it is easy to obtain that $w_m(x, t, \phi)(m = 2, 3, 4)$ satisfy

$$\frac{\partial w_2(x, t)}{\partial t} \geq D_L \Delta w_2(x, t) - (\delta + \mu_L)w_2(x, t),$$

$$\frac{\partial w_3(x, t)}{\partial t} \geq D_I \Delta w_3(x, t) - (\hat{\epsilon} + \hat{\mu}_I)w_3(x, t),$$

$$\frac{\partial w_4(x, t)}{\partial t} \geq D_{V_1} \Delta w_4(x, t) - \hat{c}w_4(x, t),$$

$$\frac{\partial w_m(x, t)}{\partial \nu} = 0, x \in \partial \Omega, t > 0$$

for $\forall \phi \in \mathbb{Y}_+$. If there admits a $t^* > 0$ such that $w_m(\cdot, t^*, \phi) \neq 0$ for some $m \in \{2, 3, 4\}$, then we get $w_m(x, t, \phi) > 0$ for all $t > t^*, x \in \overline{\Omega}$ by applying the parabolic maximum principle. Since the uniform boundedness of system (2.5), we have the $V_1(x, t)$ equation admits a positive constant $A_1$ such that $V_1(x, t, \phi) < A_1$ for any $t > 0, x \in \overline{\Omega}$. Thus, we obtain $S(x, t, \phi) = v_1(x, t, \phi_1) > 0$, where $v_1(x, t, \phi_1)$ satisfies the linear system as follows:

$$\begin{cases}
\frac{\partial v_1(x, t)}{\partial t} = D_S \Delta v_1(x, t) + \Lambda(x) - (\beta(x, t)A_1 + \mu_S(x, t))v_1(x, t), \\
\frac{\partial v_1(x, t)}{\partial \nu} = 0, v_1(x, 0) = \phi_1(x, 0), x \in \partial \Omega.
\end{cases}$$

(5.11)

Hence, we further obtain $\liminf_{t \to \infty} S(x, t, \phi) \geq \hat{a} := \min_{(x, t) \in \mathbb{Y}_+ \times [0, \omega]} v_1^\ast(x, t)$, where $v_1^\ast(x, t)$ is the globally attractive positive periodic solution of system (5.11). Above all, we have the following result

**Lemma 5.1.** For the solution of system (2.5) with $w_0 = \phi \in \mathbb{Y}_+, w(x, t, \phi)$. If there admits some $t^* > 0$ such that $w_m(\cdot, t^*, \phi) \neq 0$ for some $m \in \{2, 3, 4\}$, then $w_m(x, t, \phi) > 0$ for all $t > t^*, x \in \overline{\Omega}$ and there exists a initial value independent constant $\hat{a} > 0$ such that $\liminf_{t \to \infty} S(x, t, \phi) \geq \hat{a}$ uniformly for $x \in \overline{\Omega}$.

**Theorem 5.2.** For system (2.5), we have

1. The infection-free $\omega$-periodic solution $E_0(x, t) = (w_1^\ast(x, t), 0, 0, 0)$ is globally attractive when $R_0 < 1$, where $w_1^\ast(x, t) = S^\ast(x, t)$ in system (4.8).

2. The system admits at least one positive $\omega$-periodic solution $E^+(x, t) = (w_1^+(x, t), w_2^+(x, t), w_3^+(x, t), w_4^+(x, t))$ when $R_0 > 1$. Moreover, there admits a $\xi > 0$ such that for all $\phi \in \mathbb{Y}_+$ with $\phi_m(\cdot, 0) \neq 0(m = 2, 3, 4)$,

$$\liminf_{t \to \infty} \min_{x \in \overline{\Omega}} w_j(x, t, \phi) \geq \xi, j = 1, 2, 3, 4.$$

**Proof.** For statement (1), we can obtain that $r(\mathcal{P}(\omega)) < 1$ and $\mu = \frac{\ln r(\mathcal{P}(\omega))}{\omega} < 0$ from Lemmas 4.6
and 4.7. Then we consider the following system with positive constant $\zeta$

\[
\begin{align*}
\frac{\partial v_1^\zeta(x, t)}{\partial t} &= D_L \Delta v_1^\zeta(x, t) + \eta(x, t)(1 - \tau_1^t) \int_\Omega G_1(x, y, t, t - \tau_1(t))\beta(y, t - \tau_1(t))(S^*(y, t - \tau_1(t)) + \zeta) \\
&\quad \cdot v_3^\zeta(y, t - \tau_1(t))dy - (\delta(x, t) + \mu_L(x, t))v_1^\zeta(x, t), \\
\frac{\partial v_2^\zeta(x, t)}{\partial t} &= D_I \Delta v_2^\zeta(x, t) + (1 - \eta(x, t))(1 - \tau_1^t) \int_\Omega G_1(x, y, t, t - \tau_1(t))\beta(y, t - \tau_1(t))(S^*(y, t - \tau_1(t)) + \zeta) \\
&\quad \cdot v_3^\zeta(y, t - \tau_1(t))dy + \delta(x, t)v_1^\zeta(x, t) - (\epsilon(x, t) + \mu_I(x, t))v_2^\zeta(x, t), \\
\frac{\partial v_3^\zeta(x, t)}{\partial t} &= D_I \Delta v_3^\zeta(x, t) + (1 - \gamma(x, t))(1 - \tau_2^t)K \int_\Omega G_{I_2}(x, y, t, t - \tau_2(t))v_2^\zeta(y, t - \tau_2(t))dy \\
&\quad - c(x, t)v_3^\zeta(x, t), \\
\frac{\partial v_1^\zeta(x, t)}{\partial \nu} &= \frac{\partial v_2^\zeta(x, t)}{\partial \nu} = \frac{\partial v_3^\zeta(x, t)}{\partial \nu} = 0, x \in \partial \Omega.
\end{align*}
\]

We set $v^\zeta(x, t, \varphi) = (v_1^\zeta(x, t, \varphi), v_2^\zeta(x, t, \varphi), v_3^\zeta(x, t, \varphi))$ be the unique solution of system (5.12) with $v_0^\zeta(\varphi)(x, \theta) = (\varphi_1(x, \theta_1), \varphi_2(x, \theta_1), \varphi_3(x, \theta_2))$ for $\theta := (\theta_1, \theta_2) \in [-\tau_1(0), 0] \times [-\tau_2(0), 0], x \in \overline{\Omega}, \varphi \in \mathbb{H}$ and $v_0^\zeta(\varphi)(x, \theta) = (v_1^\zeta(x, t + \theta_1, \varphi), v_2^\zeta(x, t + \theta_1, \varphi), v_3^\zeta(x, t + \theta_2, \varphi))$ for all $x \in \overline{\Omega}$ and $t \geq 0$. Define $P_\zeta(\omega) : \mathbb{H} \to \mathbb{H}, P_\zeta(\omega)\varphi = v_0^\zeta(\varphi), \varphi \in \mathbb{H}$, as the Poincaré map of system (5.12). It is easy to obtain that $\lim_{\zeta \to 0} r(P_\zeta(\omega)) = r(P(\omega)) < 1$. Based on lemma 4.7, we know that there admits a $v^\ast(x, t) = e^{-\mu_\zeta^\ast}v_2^\zeta(x, t)$, where $\mu_\zeta = \ln r(P_\zeta(\omega)) < 0$. For this $\zeta > 0$, since $S^*(x, t)$ in global attractive, hence, applying the comparison principle, we can obtain that there admits a large enough integer $m_1 > 0$ such that $m_1 \omega > \hat{\tau}$ and $w_1(x, t) \leq S^*(x, t) + \zeta, x \in \overline{\Omega}, t \geq m_1 \omega - \hat{\tau}$. Therefore, we can further obtain that

\[
\begin{align*}
\frac{\partial w_2(x, t)}{\partial t} &\leq D_L \Delta w_2(x, t) + \eta(x, t)(1 - \tau_1^t) \int_\Omega G_1(x, y, t, t - \tau_1(t))\beta(y, t - \tau_1(t))(S^*(y, t - \tau_1(t)) + \zeta) \\
&\quad \cdot w_4(y, t - \tau_1(t))dy - (\delta(x, t) + \mu_L(x, t))w_2(x, t), t \geq m_1 \omega, \\
\frac{\partial w_3(x, t)}{\partial t} &\leq D_I \Delta w_3(x, t) + (1 - \eta(x, t))(1 - \tau_1^t) \int_\Omega G_1(x, y, t, t - \tau_1(t))\beta(y, t - \tau_1(t))(S^*(y, t - \tau_1(t)) + \zeta) \\
&\quad \cdot w_3(y, t - \tau_1(t))dy + \delta(x, t)w_2(x, t) - (\epsilon(x, t) + \mu_I(x, t))w_3(x, t), t \geq m_1 \omega, \\
\frac{\partial w_4(x, t)}{\partial t} &\leq D_I \Delta w_4(x, t) + (1 - \gamma(x, t))(1 - \tau_2^t)K \int_\Omega G_{I_2}(x, y, t, t - \tau_2(t))w_3(y, t - \tau_2(t))dy \\
&\quad - c(x, t)w_4(x, t), t \geq m_1 \omega, \\
\frac{\partial w_2(x, t)}{\partial \nu} = \frac{\partial w_3(x, t)}{\partial \nu} = \frac{\partial w_4(x, t)}{\partial \nu} = 0, x \in \partial \Omega.
\end{align*}
\]

Hence, we can verify that there admit some $n_1 > 0$ such that $(w_2(x, t, \varphi), w_3(x, t, \varphi), w_4(x, t, \varphi)) \leq n_1 v^\zeta(x, t), t \in [m_1 \omega - \hat{\tau}, m_1 \omega], x \in \overline{\Omega}, \varphi \in \mathbb{Y}_L$. Applying the result of Proposition 1[26], we have $(w_2(x, t, \varphi), w_3(x, t, \varphi), w_4(x, t, \varphi)) \leq n_1 v^{\ast}v^\zeta(x, t), t \geq m_1 \omega, x \in \overline{\Omega}$. Then we have

$$
\lim_{t \to \infty} (w_2(x, t, \varphi), w_3(x, t, \varphi), w_4(x, t, \varphi)) = (0, 0, 0) \text{ uniformly for } x \in \overline{\Omega}.
$$

In the next, we show that $\lim_{t \to \infty} w_1(x, t, \varphi) = S^*(x, t)$ by applying the definition of internally chain transitive sets[34]. Since $w_1(x, t, \varphi)$ is the solution of a nonautonomous system which is asymp-
totic to system (4.8), we can verify that system (4.8) generates a solution semiflow $\hat{\mathcal{P}}(t), t \geq 0$ on $C([-\bar{\tau}(0), 0], \mathbb{Q}_+).$ Then $\hat{\mathcal{P}}$ is Poincaré map of system (4.8) and its has a global attractor in $C([-\bar{\tau}(0), 0], \mathbb{Q}_+).$ We rearrange $\omega$-periodic semiflow $\mathcal{L}(t)$ as $\mathcal{L}(t)\varphi = (w_1(t + \zeta_1, \varphi), w_2(t + \zeta_2, \varphi), w_3(t + \zeta_3, \varphi), w_4(t + \zeta_4, \varphi))$ for $(\zeta_1, \zeta_2, \zeta_3, \zeta_4) \in [-\tau_1(0), 0] \times [-\tau_1(0), 0] \times [-\tau_1(0), 0] \times [-\tau_2(0), 0], t \geq 0$. It follows from $\lim_{t \to \infty} w_m(x, t, \varphi) = 0, m = 2, 3, 4$ that $\mathcal{J} = \mathcal{J} \times \{0\} \times \{0\}$, where $0(t, \theta_1) = 0, \theta_1 \in [-\tau_1(0), 0], 0(t, \theta_2) = 0, \theta_2 \in [-\tau_2(0), 0]$. Based on the property of operator $\mathcal{L}(t)$, we know that $0 \notin J, 0 \notin J$. Hence, we can obtain $J$ is an internally chain transitive set for $\hat{\mathcal{P}}(w)$ from lemma 1.2.1[34], this leads to that $J$ is an internally transitive chain set for $\hat{\mathcal{P}}(\omega)$. Define $w_0^0 \in C([-\bar{\tau}(0), 0], \mathbb{Q}_+)$ by $w_0^0(t, \theta) = w_0^0(t, \theta), \theta \in [-\bar{\tau}(0), 0]$. Considering the global attractivity of $\mathcal{J} \neq \{0\} \times \{0\}$ and $w_0^0$ in $C([-\bar{\tau}(0), 0], \mathbb{Q}_+) \setminus \{0\} \times \{0\}$, we have that $\mathcal{J} \cap W^s(w_0^0) \neq \emptyset$, where $W^s(w_0^0)$ is the stable set of $w_0^0$. Hence, by Theorem 1.2.1[34], we have

$$
\lim_{t \to \infty} ||(w_1(t, \varphi), w_2(t, \varphi), w_3(t, \varphi), w_4(t, \varphi)) - (w_1^0(t), 0, 0, 0)|| = 0.
$$

This proof of statement (1) is finished.

Now, we prove that statement (2). In this case, we know $R > 1, r(\mathcal{P}(\omega)) > 1$ and $\mu = \frac{\ln r(\mathcal{P}(\omega))}{\omega} > 0$. To complete the proof, we first introduce some denotations which will be used in later. We set

$$
\mathcal{A}_0 := \{ \varphi \in \mathbb{Y}_+ : \varphi_2(\cdot, 0) \neq 0, \varphi_3(\cdot, 0) \neq 0, \text{and } \varphi_4(\cdot, 0) \neq 0 \},
$$

$$
\partial \mathcal{A}_0 := \mathbb{Y} \setminus \mathcal{A}_0 = \{ \varphi \in \mathbb{Y}_+ : \varphi_2(\cdot, 0) \equiv 0 \text{ or } \varphi_3(\cdot, 0) \equiv 0 \text{ or } \varphi_4(\cdot, 0) \equiv 0 \},
$$

$$
M_0 := \{ \varphi \in \partial \mathcal{A}_0 : \mathcal{L}^n(\omega)(\varphi) \in \partial \mathcal{A}_0, \forall n \in \mathbb{N} \},
$$

$$
\omega(\varphi) := \text{the omega limit set of the positive orbit } \gamma^+ = \{ \mathcal{L}^n(\omega)(\varphi) : \forall n \in \mathbb{N} \}.
$$

We divide the proof into three steps.

**Step 1.** $\omega(\varphi) = E, E = (w_0^0, 0, 0, \bar{0}), \varphi \in M_0$. Obviously, $\mathcal{L}^n(\omega)(\varphi) \in \partial \mathcal{A}_0$ for $\varphi \in M_0, n \in \mathbb{N}$. For any $n \in \mathbb{N}$, if $w_m(\cdot, nw, \varphi) \equiv 0 (m = 2, 3, 4)$, then we have $w_m(\cdot, t, \varphi) \equiv 0$ for $t \geq 0$. Otherwise, it leads to a contradictions with lemma 5.1. Suppose that $w_4(\cdot, t, \varphi) \equiv 0$ for $t \geq 0$, then we have $w_4(\cdot, t, \varphi) = w_0^0(\cdot, t)$ uniformly for $\varphi \in \overline{\mathbb{Y}}$ from the first equation of system (2.5). From the $w_2$ equation in system (2.5), we obtain that $\partial w_2(x, t, \varphi)/\partial t \leq D_L \Delta w_2(x, t, \varphi) - (\bar{\xi} + \rho_2) w_2(x, t, \varphi)$, which leads to $\lim_{t \to \infty} w_2(x, t, \varphi) = 0$ uniformly for $x \in \overline{\mathbb{Y}}$. Thus, we can further have that $\partial w_3(x, t, \varphi)/\partial t \leq D_L \Delta w_3(x, t, \varphi) - (\xi + \rho_2) w_3(x, t, \varphi)$ and $\partial w_4(x, t, \varphi)/\partial t \leq D_L \Delta w_4(x, t, \varphi) - \omega w_4(x, t, \varphi)$. Subsequently, we can verify that $\lim_{t \to \infty} w_3(x, t, \varphi), w_4(x, t, \varphi) = (0, 0)$ uniformly for $x \in \overline{\mathbb{Y}}$. If $w_4(\cdot, t, \varphi) \equiv 0$ for some $t_4 \geq 0$, then $w_4(\cdot, t, \varphi) > 0$ for $t \geq t_4$ from Lemma 5.1. Hence, we have $w_2(\cdot, t, \varphi) \equiv 0$ or $w_3(\cdot, t, \varphi) \equiv 0$ for $t \geq t_4$. In a general context, we suppose $w_2(\cdot, t, \varphi) \equiv 0$, then $\lim_{t \to \infty} w_4(\cdot, t, \varphi) \equiv 0$ uniformly for $x \in \overline{\mathbb{Y}}$ from the $w_2$ equation in system (2.5). It further follows from $w_3$ equation in system (2.5) that $\lim_{t \to \infty} w_3(\cdot, t, \varphi) \equiv 0$ uniformly for $x \in \overline{\mathbb{Y}}$. Thus, $w_1(\cdot, t, \varphi)$ satisfies $\lim_{t \to \infty} w_1(x, t, \varphi) = w_1^0(x, t), x \in \overline{\mathbb{Y}}$. Above all, we have $E = \omega(\varphi)$ for all $\varphi \in M_0$.

**Step 2.** $\limsup_{n \to \infty} ||\mathcal{L}^n(\omega) - E|| \geq \xi^*$ for small enough number $\xi^* > 0$ and $\varphi \in \mathcal{A}_0$. Consider the
following system

\[
\begin{align*}
\frac{\partial v^\xi_1(x,t)}{\partial t} &= D_L \Delta v^\xi_1(x,t) + \eta(x,t)(1-\tau_1'(t)) \int_\Omega G_{I_1}(x,y,t,t-\tau_1(t))\beta(y,t-\tau_1(t))(S^*(y,t-\tau_1(t)) - \xi) \\
& \quad \cdot v^\xi_2(y,t-\tau_1(t))dy - (\delta(x,t) + \mu_L(x,t))v^\xi_1(x,t), \\
\frac{\partial v^\xi_2(x,t)}{\partial t} &= D_I \Delta v^\xi_2(x,t) + (1-\eta(x,t))(1-\tau_1'(t)) \int_\Omega G_{I_1}(x,y,t,t-\tau_1(t))\beta(y,t-\tau_1(t))(S^*(y,t-\tau_1(t)) - \xi) \\
& \quad \cdot v^\xi_3(y,t-\tau_1(t))dy + \delta(x,t)v^\xi_2(x,t) - (\epsilon(x,t) + \mu_I(x,t))v^\xi_3(x,t), \\
\frac{\partial v^\xi_3(x,t)}{\partial t} &= D_{V_1} \Delta v^\xi_3(x,t) + (1-\gamma(x,t))(1-\tau_2'(t))K \int_\Omega G_{I_2}(x,y,t,t-\tau_2(t))v^\xi_2(y,t-\tau_2(t))dy \\
& \quad - c(x,t)v^\xi_3(x,t), \\
\frac{\partial v^\xi_1(x,t)}{\partial \nu} &= \frac{\partial v^\xi_2(x,t)}{\partial \nu} = \frac{\partial v^\xi_3(x,t)}{\partial \nu} = 0, \quad x \in \partial \Omega.
\end{align*}
\]

(5.14)

We set \( v^\xi(x,t,\varphi) = (v^\xi_1(x,t,\varphi), v^\xi_2(x,t,\varphi), v^\xi_3(x,t,\varphi)) \) be the unique solution of system (5.14) with initial value \( v^\xi_0(\varphi)(x,\theta) = (\varphi_1(x,\theta_1), \varphi_2(x,\theta_1), \varphi_3(x,\theta_1)) \) for \( \theta := (\theta_1, \theta_2) \in [-\tau_1(0),0] \times [-\tau_2(0),0], x \in \Omega, \varphi \in \mathbb{H} \) and \( v^\xi_0(\varphi)(x,\theta) = (v^\xi_1(x,t+\theta_1,\varphi), v^\xi_2(x,t+\theta_1,\varphi), v^\xi_3(x,t+\theta_2,\varphi)) \) for all \( x \in \Omega \) and \( t \geq 0 \). Define \( \mathcal{P}_\xi(\omega) : \mathbb{H} \to \mathbb{H}, \mathcal{P}_\xi(\omega)\varphi = v^\xi_0(\varphi), \varphi \in \mathbb{H} \), as the Poincaré map of system (5.14). Thus, we can choose a small enough number \( \xi > 0 \) such that \( \xi < \eta_{\min_{(x,t)}} w^\xi_1(x,t), r(\mathcal{P}_\xi(\omega)) > 1. \) For this \( \xi > 0 \), there admits a \( \xi^* > 0 \) such that \( ||\varphi - E|| \leq \xi^* \), then we obtain \( ||\mathcal{L}(t)\varphi - \mathcal{L}E|| \leq \xi, t \in [0,\omega] \). In the next, suppose that \( \limsup ||\mathcal{L}^n(\omega)(\varphi) - E|| \leq \xi^* \) for some \( \varphi_0 \in \mathcal{A}_0 \). Then \( ||\mathcal{L}^n(\omega)(\varphi_0) - E|| < \xi^* \) for \( n \geq m_2 \). Setting \( t = t_0 + n\omega \) with \( t_0 \in [0,\omega) \) and \( n = [t/\omega] \) for all \( t \geq m_2\omega \), one has

\[
||\mathcal{L}(t)\varphi_0 - \mathcal{L}(t)E|| = ||\mathcal{L}(t_0)(\mathcal{L}^n(\omega)(\varphi_0)) - \mathcal{L}(t_0)E|| < \xi.
\]

Based on lemma 5.1, we have \( 0 < w^\nu_m(x,t,\varphi) < \xi, w^\nu_1(x,t,\varphi) \geq w^\nu_1(x_0,t_0) - \xi, m = 2, 3, 4 \) for \( t \geq m_2\omega - \tau \). Thus, we can further obtain that

\[
\begin{align*}
\frac{\partial w_2(x,t)}{\partial t} \geq & D_L \Delta w_2(x,t) + \eta(x,t)(1-\tau_1'(t)) \int_\Omega G_{I_1}(x,y,t,\tau_1(t))\beta(y,t-\tau_1(t))(S^*(y,t-\tau_1(t)) - \xi) \\
& \quad \cdot w_3(y,t-\tau_1(t))dy - (\delta(x,t) + \mu_L(x,t))w_2(x,t), t \geq m_2\omega, \\
\frac{\partial w_3(x,t)}{\partial t} \geq & D_I \Delta w_3(x,t) + (1-\eta(x,t))(1-\tau_1'(t)) \int_\Omega G_{I_1}(x,y,t,\tau_1(t))\beta(y,t-\tau_1(t))(S^*(y,t-\tau_1(t)) - \xi) \\
& \quad \cdot w_3(y,t-\tau_1(t))dy + \delta(x,t)w_3(x,t) - (\epsilon(x,t) + \mu_I(x,t))w_3(x,t), t \geq m_2\omega, \\
\frac{\partial w_4(x,t)}{\partial t} \geq & D_{V_1} \Delta w_4(x,t) + (1-\gamma(x,t))(1-\tau_2'(t))K \int_\Omega G_{I_2}(x,y,t,\tau_2(t))w_3(y,t-\tau_2(t))dy \\
& \quad - c(x,t)w_4(x,t), t \geq m_2\omega, \\
\frac{\partial w_2(x,t)}{\partial \nu} = & \frac{\partial w_3(x,t)}{\partial \nu} = \frac{\partial w_4(x,t)}{\partial \nu} = 0, x \in \partial \Omega.
\end{align*}
\]

(5.15)

for \( \varphi_0 \in \mathcal{A}_0 \). Then there exists an \( m_3 > 0 \) such that \( (w_2(x,t,\varphi_0), w_3(x,t,\varphi_0), w_4(x,t,\varphi_0)) \geq m_3e^{\kappa't^\nu}v^\nu_5(x,t) \) for \( x \in \overset{\circ}{\Omega} \) and \( t \in [m_3\omega - \tau, m_3\omega] \), where \( e^{\kappa't^\nu}v^\nu_5(x,t) \) is a solution of system (5.14) with
\[ \mu_\xi = \ln r(\mathcal{P}_\xi(\omega))/\omega. \]
Hence, we have 
\[ (w_2(x, t, \varphi_0), w_3(x, t, \varphi_0), w_4(x, t, \varphi_0)) \geq m_3 e^{\mu_\xi t} v_*^\sigma(x, t) \rightarrow +\infty \]
as \( t \rightarrow +\infty \) due to \( \mu_\xi > 0 \), which leads to a contradiction with the ultimate boundedness of system (2.5). Above all, we know that \( E \) is an isolated invariant set for \( \mathcal{L}(\omega) \) in \( \mathbb{Y}_+ \) and \( W^s(E) \cap \mathcal{A}_0 = \emptyset \).

Based on Theorem 3.7 [30] and Theorem 1.3.1 [34], we know that \( \mathcal{L}(\omega) \) has a global attractor \( \mathcal{B}_0 \) in \( \mathcal{A}_0 \) and it is uniformly persistent associated with \( (\mathcal{A}_0, \partial \mathcal{A}_0) \), i.e., there admits a small enough number \( \delta > 0 \) such that
\[ \liminf_{n \rightarrow +\infty} d(\mathcal{L}^n(\varphi), \partial \mathcal{A}_0) \geq \sigma, \varphi \in \mathcal{B}_0. \quad (5.16) \]

It follows that \( \varphi_m(\cdot, 0) > 0, \varphi \in \mathcal{B}_0 \) and \( \mathcal{B}_0 = \mathcal{L}(\omega) \mathcal{B}_0 \). Set \( \mathcal{D}_0 := \bigcup_{t \in [0, \omega]} \mathcal{L}(t) \mathcal{B}_0 \), then we obtain that \( \lim_{t \rightarrow +\infty} d(\mathcal{L}(t)\varphi, \mathcal{D}_0) = 0, \mathcal{D}_0 \subset \mathcal{A}_0 \) for any \( \varphi \in \mathcal{A}_0 \). Set \( q : \mathbb{Y}_+ \rightarrow \mathbb{R}_+ \) be the continuous function \( q(\varphi) = \min \{ \min_{x \in \Omega} \varphi_2(x, 0), \min_{x \in \Omega} \varphi_3(x, 0), \min_{x \in \Omega} \varphi_4(x, 0) \}, \forall \varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4) \in \mathbb{Y}_+ \). Since the compactness of \( \mathcal{D}_0 \), it follows that
\[ \liminf_{t \rightarrow +\infty} q(\mathcal{L}(t)\varphi) = \liminf_{t \rightarrow +\infty} \min \{ \min_{x \in \Omega} w_2(x, t, \varphi), \min_{x \in \Omega} w_3(x, t, \varphi), \min_{x \in \Omega} w_4(x, t, \varphi) \} \geq \xi^* \]
for some enough number \( \xi^* > 0 \) and any \( \varphi \in \mathcal{A}_0 \). Based on lemma 5.1, it further leads to
\[ \liminf_{t \rightarrow +\infty} \min_{x \in \Omega} w_i(x, t, \varphi) \geq \xi \]
for any \( \varphi \in \mathcal{A}_0, \xi \in (0, \xi^*), i = 1, 2, 3, 4 \).

**Step 3.** To complete the proof, it suffices to show the existence of a positive periodic steady state of system (2.5). In fact, we know that the solution map \( \widetilde{\mathcal{L}}(t) : \mathcal{M} \rightarrow \mathcal{M} \) of system (2.5) is an \( \alpha \)-contraction subject to an equivalent norm on \( \mathcal{M} \) from Theorem 3.5.1 [34]. Set \( \mathcal{B}_0 := \{ \varphi \in \mathcal{M}_+: \varphi_2(\cdot, 0) \neq 0, \varphi_3(\cdot, 0) \neq 0, \varphi_4(\cdot, 0) \neq 0 \} \). \( \partial \mathcal{B}_0 := \{ \varphi \in \mathcal{M}_+: \varphi_2(\cdot, 0) = 0 \) or \( \varphi_3(\cdot, 0) = 0 \) or \( \varphi_4(\cdot, 0) = 0 \} \). Obviously, \( \widetilde{\mathcal{L}}(\omega) \) is \( \varphi \)-uniformly persistent with \( g(\varphi) = d(\varphi, \partial \mathcal{B}_0) \) for \( \varphi \in \mathcal{B}_0 \). Based on Theorem 4.5 [30], we know that system (2.5) admits an \( \omega \)-periodic solution \( (u_1^\omega(\cdot, t), u_2^\omega(\cdot, t), u_3^\omega(\cdot, t), u_4^\omega(\cdot, t)) \) with \( u_i^\omega \in \mathcal{B}_0 \). Let \( \omega_i(\cdot, \omega_i) = u_i^\omega(\cdot, \omega_i) \), where \( (\omega_1, \omega_2, \omega_3, \omega_4) \in [-\tau_1(0), 0]^3 \times [-\tau_2(0), 0] \). Since the uniqueness of solution and lemma 5.1, it follows that \( (w_1^\omega(\cdot, t), w_2^\omega(\cdot, t), w_3^\omega(\cdot, t), w_4^\omega(\cdot, t)) \) is a strictly positive periodic solution of system (2.5).

In the spatial homogeneous case, we assume the model parameters and time delays \( \tau_i(t)(k = 1, 2) \) are all positive constants, then system (2.5) reduces to the time-delayed spatial diffusion system as follows:

\[
\begin{align*}
\frac{\partial w_1}{\partial t} &= D_S \Delta w_1 + \Lambda - \beta w_1w_4 - \mu_S w_1, \\
\frac{\partial w_2}{\partial t} &= D_L \Delta w_2 + \eta \beta e^{-\mu_L \tau_1} \int_{-\tau_1} G(x, y, D_I, \tau_1) w_1(y, t - \tau_1) w_4(y, t - \tau_1) dy - (\delta + \mu_L) w_2, \\
\frac{\partial w_3}{\partial t} &= D_I \Delta w_3 + (1 - \eta) \beta e^{-\mu_L \tau_1} \int_{-\tau_1} G(x, y, D_I, \tau_1) w_1(y, t - \tau_1) w_4(y, t - \tau_1) dy - (\epsilon + \mu_I) w_3 + \delta w_2, \\
\frac{\partial w_4}{\partial t} &= D_V \Delta w_4 + (1 - \gamma) K e^{-\mu_L \tau_2} \int_{-\tau_2} G(x, y, D_V, \tau_2) w_3(y, t - \tau_2) dy - c w_4, \\
\frac{\partial w_i}{\partial \nu} &= 0, x \in \partial \Omega, \quad i = 1, 2, 3, 4.
\end{align*}
\]

where \( G(x, y, t) \) is the Green function with respect to \( \partial w/\partial t = \Delta w \) with no-flux condition. The basic reproduction number \( R_0 \) of system (5.17) given by
\[ R_0 = r(FV^{-1}), \]
where matrices $F$ and $V$ are given by

$$F = \begin{pmatrix} 0 & 0 & \eta e^{-\mu_1 \tau_1} \Lambda / \mu_S \\ 0 & 0 & (1 - \eta) e^{-\mu_1 \tau_1} \Lambda / \mu_S \\ 0 & 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} \delta + \mu_L & 0 & 0 \\ -\delta & \mu_I + \epsilon & 0 \\ 0 & -(1 - \gamma) e^K e^{-\mu_2 \tau_2} c \end{pmatrix}.$$ 

After some calculations, we can have that $R_0$ of system (5.17) is

$$R_0 = \frac{\Lambda e^{-\mu_1 \tau_1} e^{-\mu_2 \tau_2} \beta e(1 - \gamma) K}{\mu_S (\epsilon + \mu_I) c} \left( \frac{\eta \delta}{\delta + \mu_L} + (1 - \eta) \right).$$

**Theorem 5.3.** Set $w(\cdot, t, \varphi)$ be the solution of system (5.17) with initial condition $w_0 = \varphi \in \mathbb{H}_+$, one has

1. The infection-free equilibrium $E_0 = (\Lambda / \mu_S, 0, 0, 0)$ is globally attractive when $R_0 < 1$.
2. When $R_0 > 1$, the system (5.17) has a unique globally attractive positive equilibrium $w^* = (w^*_1, w^*_2, w^*_3, w^*_4)$ for $\forall \varphi \in \mathbb{H}_+$ with $\varphi_m(\cdot, 0) \equiv 0$, $m = 2, 3, 4$.

**Proof.** It is obvious that the following set

$$\mathcal{D} = \{ w_i \in \mathbb{H}_+, w_i(x, \tau_0) \leq \Lambda / \mu \, (i = 1, 2, 3, 4), \tau_0 \in [-\tau, 0], x \in \overline{\Omega} \},$$

where $\mu = \min \{ \mu_S, \delta + \mu_L, \epsilon + \mu_I, c \}$ is positively invariant for operator $\hat{\mathcal{L}}(t)$. Therefore, we only investigate the dynamical behaviors of system (5.17) on $\mathcal{D}$. We can directly have that statement (1).

In the next part, we are devoting to showing statement (2). It is easy to obtain that if $R_0 > 1$, then system (5.17) has a unique positive equilibrium $E^* = (w^*_1, w^*_2, w^*_3, w^*_4)$ satisfies

$$\Lambda - \beta w^*_1 w^*_4 - \mu_S w^*_1 = 0, \quad e^{-\mu_1 \tau_1} \beta w^*_1 w^*_4 - (\delta + \mu_L) w^*_2 = 0,$$

$$e^{-\mu_1 \tau_1} (1 - \eta) \beta w^*_1 w^*_4 + \delta w^*_2 - (\epsilon + \mu_I) w^*_3 = 0, \quad e^{-\mu_2 \tau_2} K (1 - \gamma) e w^*_3 - c w^*_4 = 0.$$

After some calculations, one has

$$w^*_1 = \frac{\Lambda}{\mu_S (R_0 - 1)}, \quad w^*_4 = \frac{\mu_S}{\beta (R_0 - 1)}, \quad w^*_2 = \frac{e^{-\mu_1 \tau_1} \beta w^*_1 w^*_4}{\delta + \mu_L}, \quad w^*_3 = \frac{\epsilon \mu_S (R_0 - 1)}{\beta e^{-\mu_2 \tau_2} (1 - \gamma) K}.$$

Now, we show the global attractivity of $w^*$ of system (5.17) by using the fluctuation method mentioned in [35]. To this end, we set $w^*_i(x) := \limsup_{t \to \infty} w_i(x, t), w_i(x) := \liminf_{t \to \infty} w_i(x, t), \forall x \in \overline{\Omega}$. Since system (5.17) is uniformly persistent, it follows that there admits an $\bar{\xi} > 0$ such that $w^*_i \geq w_i \geq \bar{\xi}, i = 1, 2, 3, 4, x \in \overline{\Omega}$. Applying Fatou’s lemma and the method mentioned in Theorem 7.1[36], we have

$$0 \leq \Lambda - \beta W_{1, \infty} W_{4, \infty} - \mu_S W_{1, \infty}, \quad \Lambda - \beta W_{1, \infty} W_{4, \infty} - \mu_S W_{1, \infty} \leq 0,$$

$$0 \leq e^{-\mu_1 \tau_1} \eta \beta W_{1, \infty} W_{4, \infty} - (\delta + \mu_L) W_{2, \infty} \leq 0,$$

$$0 \leq (1 - \eta) \beta e^{-\mu_1 \tau_1} W_{1, \infty} W_{4, \infty} + \delta W_{2, \infty} - (\epsilon + \mu_I) W_{3, \infty} \leq 0,$$

$$e^{-\mu_2 \tau_2} (1 - \gamma) K e W_{3, \infty} - c W_{4, \infty} \geq 0,$$

where $W_i^\infty = \sup_{x \in \overline{\Omega}} w_i(x), \forall i = 1, 2, 3, 4$. Substituting

$$W_{1, \infty} \leq \frac{\Lambda}{\mu_S + \beta W_{4, \infty}}, \quad W_{1, \infty} \leq \frac{\Lambda}{\mu_S + \beta W_{4, \infty}},$$

$$W_{2, \infty} \leq \frac{e^{-\mu_1 \tau_1} \eta \beta W_{1, \infty} W_{4, \infty}}{\delta + \mu_L}, \quad W_{2, \infty} \leq \frac{e^{-\mu_1 \tau_1} \eta \beta W_{1, \infty} W_{4, \infty}}{\delta + \mu_L}.$$
into the above inequalities yields

\[
(1 - \eta) e^{-\mu t_1} \beta \frac{W_{4,0}^\infty A}{\mu_S + \beta W_{4,0}^\infty} + \frac{\delta}{\delta + \mu_L} \frac{\Lambda \eta \beta e^{-\mu t_1} W_{4,0}^\infty}{\mu_S + \beta W_{4,0}^\infty} - \frac{c}{(\epsilon + \mu_L) e^{-\mu t_2}} \frac{W_{4,0}^\infty}{(1 - \gamma) K_{\epsilon}} \geq 0,
\]

\[
(1 - \eta) e^{-\mu t_1} \beta \frac{W_{4,0}^\infty A}{\mu_S + \beta W_{4,0}^\infty} + \frac{\delta}{\delta + \mu_L} \frac{\Lambda \eta \beta e^{-\mu t_1} W_{4,0}^\infty}{\mu_S + \beta W_{4,0}^\infty} - \frac{c}{(\epsilon + \mu_L) e^{-\mu t_2}} \frac{W_{4,0}^\infty}{(1 - \gamma) K_{\epsilon}} \leq 0.
\]

Then, we have \( (1 + \mu_L) e^{-\mu t_2} (1 - \gamma) K_{\epsilon} (W_{4,0} - W_{4,0}^\infty) (R_0 - 1) \geq 0 \), which implies that \( W_{4,0} \geq W_{4,0}^\infty \), it then follows that \( W_{4,0} = W_{4}^\infty \). Moreover, we can obtain \( W_{1,0} = W_{1}^\infty, W_{2,0} = W_{2}^\infty, W_{3,0} = W_{3}^\infty \). This then yields

\[
\lim_{t \to \infty} w(x, t, \varphi) = (W_{1}^\infty, W_{2}^\infty, W_{3}^\infty, W_{4}^\infty), \quad x \in \Omega.
\]

(5.18)

It needs to show (5.18) uniformly holds for \( x \in \Omega \). For \( \forall \psi \in \omega(\varphi) \), there admits a sequence \( t_m \to \infty \) such that \( \mathcal{L}(t_m) \varphi \to \psi \) \( (m \to \infty) \) in \( \mathcal{H} \), so we have \( \lim_{t \to \infty} w(x, t_m + \tau_0, \varphi) = \psi(x, \tau_0) \) uniformly for \( (x, \tau_0) \in \Omega \times [-\tau, 0] \). It follows from (5.18) that \( \psi(x, \tau_0) = (W_{1}^\infty, W_{2}^\infty, W_{3}^\infty, W_{4}^\infty) \), which leads to \( \omega(\varphi) = \{(W_{1}^\infty, W_{2}^\infty, W_{3}^\infty, W_{4}^\infty)\} \), it further follows that \( (W_{1}^\infty, W_{2}^\infty, W_{3}^\infty, W_{4}^\infty) \) is the unique globally attractive positive equilibrium of system (5.17) from \( \omega(\varphi) \) is invariant for \( \mathcal{L}(t) \), and hence \( (W_{1}^\infty, W_{2}^\infty, W_{3}^\infty, W_{4}^\infty) = w^* \). This completes the proof. \( \square \)

6 Numerical simulations

In this section, we conduct some numerical simulations to illustrate the influence of the periodic incubation periods due to the periodic drug treatment and the spatial heterogeneity on the infection process of HIV within the host. To this end, we first assume the bounded domain \( \Omega = (0, \pi) \) for simplicity. To describe the periodic of the HAART treatment, as similar arguments those in [21], we can assume some parameters in system (2.5) have the following form

\[
\beta(x, t) = \beta(x) P(t), \quad \delta(x, t) = \delta(x) \eta_{HI}(t), \quad \Lambda(x, t) = \Lambda(x), \quad \epsilon(x, t) = \epsilon(x) Q(t),
\]

\[
\eta(x, t) = \eta(x), \quad \mu_I(x, t) = \mu_I(x), \quad \mu_S(x, t) = \mu_S(x), \quad \mu_L(x, t) = \mu_L(x), \quad c(x, t) = c(x), \quad \gamma(x, t) = \gamma(x) \Pi(t),
\]

where \( P(t) = (1 - \eta_{HI}(t))(1 - \eta_{RT}(t))(1 - \eta_{R5}(t)) \), \( Q(t) = 1 - \eta_{PI}(t), \Pi(t) = 1 - \eta_{FI}(t) \). Here, the biological meaning of \( \eta_k, k = \{II, FI, RT, R5, PI, IFI\} \) can be found in Sect.2[21] for details. The values of \( \eta_k \) are choose as in [21]

\[
\eta_{PI}(t) = 0.9 - 0.1 \sin \left( \frac{\pi}{12} \right), \quad \eta_{RT}(t) = 0.79 - 0.15 \sin \left( \frac{\pi}{12} \right), \quad \eta_{II}(t) = 0.89 - 0.15 \sin \left( \frac{\pi}{12} \right),
\]

\[
\eta_{HI}(t) = 0.85 - 0.15 \sin \left( \frac{\pi}{12} \right), \quad \eta_{FI}(t) = 0.8 - 0.15 \sin \left( \frac{\pi}{12} \right), \quad \eta_{R5}(t) = 0.9 - 0.15 \sin \left( \frac{\pi}{12} \right),
\]

(6.19)

\[
\eta_{IFI}(t) = 0.85 - 0.15 \sin \left( \frac{\pi}{12} \right).
\]

Furthermore, from Sect.7[21], the values of model parameters in system (2.5) are listed in the following Table
Table 1. The values of some parameters in system (2.5)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Lambda(x)$</td>
<td>$1.25 \times 10^4$ cells ml$^{-1}$ day$^{-1}$</td>
<td>$c(x)$</td>
<td>23 day$^{-1}$</td>
</tr>
<tr>
<td>$\mu_S(x)$</td>
<td>0.0025 day$^{-1}$</td>
<td>$K$</td>
<td>1000 cells ml$^{-1}$ day$^{-1}$</td>
</tr>
<tr>
<td>$\eta(x)$</td>
<td>0.001 day$^{-1}$</td>
<td>$\gamma(x)$</td>
<td>0.02 day$^{-1}$</td>
</tr>
<tr>
<td>$\epsilon(x)$</td>
<td>0.01 day$^{-1}$</td>
<td>$D_S$</td>
<td>0.09648 mm$^2$ day$^{-1}$</td>
</tr>
<tr>
<td>$\delta(x)$</td>
<td>0.002 day$^{-1}$</td>
<td>$D_L$</td>
<td>0.03 mm$^2$ day$^{-1}$</td>
</tr>
<tr>
<td>$\mu_I(x)$</td>
<td>0.045 day$^{-1}$</td>
<td>$D_I$</td>
<td>0.05 mm$^2$ day$^{-1}$</td>
</tr>
<tr>
<td>$\mu_L$</td>
<td>0.0055 day$^{-1}$</td>
<td>$D_{Y_1}$</td>
<td>0.17 mm$^2$ day$^{-1}$</td>
</tr>
</tbody>
</table>

In addition, we choose $\beta(x) = 1.5 \times 10^{-5}(1 + 0.35 \sin 2x)$ and the periodic time delays $\tau_1(t), \tau_2(t)$ and the initial values of system (2.5) have the following form

$$\tau_1(t) = 1.5\eta_{H1}(t), \tau_2(t) = 1.5\eta_{P1}(t),$$

$$w_1(x, \theta) = 1870(1 + 0.05 \sin 2x), w_2(x, \theta) = 1000(1 + 0.05 \sin 2x),$$

$$w_3(x, \theta) = 1400(1 + 0.05 \sin 2x), w_4(x, \theta) = 500(1 + 0.05 \sin 2x), (x, \theta) \in [0, \pi] \times [-\hat{\tau}, 0].$$

6.1 The dynamical behaviors of system (2.5)

For the above set of model parameters, we can calculate the basic reproduction number numerically and have $R_0 = 2.533 > 1$ by using the method mentioned in [33], which implies that HIV infections will be persist within the host. In fact, in Fig.2, we can see that the solution surface of system (2.5) moves away the zero plane as time approaches infinity. This is in lines with Theorem 5.2 (2). When we choose $\beta(x) = 4.2 \times 10^{-6}(1 + 0.35 \sin 2x)$ and the other parameters values are the same as in Table 1, we can have $R_0 = 0.843 < 1$. In Fig.3, it is showed that the solution surface of system (2.5) approaches zero plane as time goes infinity. This indicates that the HIV infections will be eliminated within-host eventually, which is in lines with Theorem 5.2 (1).
Figure 2. The dynamical behaviors of system (2.5) when $\mathcal{R}_0 > 1$. Here $\beta(x) = 1.5 \times 10^{-5}(1 + 0.35 \sin 2x)$ and the other parameters values are the same as in Table 1.
The dynamical behaviors of system (2.5) when $R_0 < 1$. Here $\beta(x) = 4.2 \times 10^{-6} (1 + 0.35 \sin 2x)$ and the other parameters values are the same as in Table 1.

6.2 The impact of time delays and spatial heterogeneity on HIV infection process

In this subsection, we are devoted to investigate the impact of time delays $\tau_j(t)$ and spatial heterogeneity on HIV infection process. To this end, we first study the influence of time delays $\tau_j(t)$ and spatial heterogeneity on $R_0$. We set the space-averaged infection rate $\beta_0 := \frac{1}{|\Omega|} \int_\Omega \beta(x) dx \approx 0.0017$ and the time-averaged time-delayed $\tau_0^j := \frac{1}{\omega} \int_0^\omega \tau_j(t) dt, j = 1, 2$. Then we have $\tau_1^0 \approx 1.2632, \tau_2^0 \approx 1.3421$.

To investigate the influence of spatial heterogeneity on the progression of HIV infection, we depict in Figure 4 the impact of model parameters on the basic reproduction number $R_0$ under two scenarios: $\beta(x)$ and $\beta_0$. Specifically, as shown in Figure 4 (a), we can observe that the functional form of $\beta(x)$ has a significant effect on the value of $R_0$, indicating that the spatial factor cannot be ignored in influencing $R_0$. Furthermore, from Figures 4 (b), (d), (e) and (f), it can be seen that $R_0$ is a decreasing function of $c(x), \eta(x)$ and $\gamma(x)$, while from Figure 4 (c), it can be seen that $R_0$ is an increasing function of $\epsilon(x)$.

It is worth mentioning that a common phenomenon in Figures 4 (a)-(f) is that the value of $R_0$ under the $\beta(x)$ scenario is significantly larger than that under the $\beta_0$ scenario. This implies that ignoring the impact of spatial heterogeneity on $R_0$ would seriously underestimate the risk of HIV infection outbreaks within the host, which is clearly detrimental to the treatment of HIV-infected individuals.
and the control of HIV transmission among the population.

Similarly, in Figure 5, we demonstrate the influence of model parameters on the basic reproductive number $R_0$ under two scenarios: $\tau_j(t)$ and $\tau_j^0$, $j = 1, 2$. Likewise, from Figures 5 (a)-(f), we can observe that the value of $R_0$ under the $\tau_j(t)(j = 1, 2)$ scenarios is significantly larger than that under the $\tau_j^0$ scenario. This indicates that compared to the constant time delay model, the model considering time-dependent delays $\tau_j(t)$ caused by periodic antiviral therapy can more accurately reflect the impact of periodic antiviral treatment on the progression of HIV infection. Moreover, compared to the time-dependent delay $\tau_j(t)$ scenario, the constant time delay scenario significantly underestimates the value of $R_0$, which can lead to an underestimation of the possibility of HIV infection outbreaks within the host. This is highly unfavorable for HIV clinical treatment.

To visually demonstrate the impact of the two contrasting scenarios, $\beta(x)$ vs. $\beta_0$ and $\tau_j(t)$ vs. $\tau_j^0$, on the progression of HIV infection within the host, we present the three-dimensional and two-dimensional profile plots of the solutions to system (2.5) in Figures 6 and 7, respectively. In Figure 6, the red and green surfaces (curves) correspond to the solution dynamical behaviors under the $\beta(x)$ and $\beta_0$ scenarios, respectively. Particularly, in the two-dimensional plot, we can observe that the $\omega_1$ region is significantly larger than the $\Omega_2$ region. Therefore, compared to the $\beta(x)$ scenario, considering the infection rate as $\beta_0$ would lead to a substantial underestimation of the viral and cellular loads of HIV within the host. Similarly, in Figure 7, the pink and blue surfaces (curves) represent the dynamical evolution of the solutions to system (2.5) under the $\tau_j(t)$ and $\tau_j^0$ scenarios, respectively. It can be observed that under the time-dependent delay scenario, the viral and cellular loads of HIV are significantly higher compared to the constant times delay scenario. This is mainly because the constant time delay scenario overlooks the periodic rebound of the HIV-infected cells and viruses within the host caused by periodic antiviral therapy. In conclusion, both spatial heterogeneity represented by $\beta(x)$ and time delays induced by periodic antiviral therapy represented by $\tau_j(t)$ have a notable impact on the progression of HIV infection. Therefore, these two factors should not be overlooked in the modeling and clinical treatment process.
Figure 4. The impact of parameters on $R_0$ for cases $\beta(x)$ (the red color line) and $\beta_0$ (the blue color line). (a) $\beta(x) = 1.5 \times 10^{-5}(1 + k \sin(mx))$, the other parameters values are the same as in Table 1; (b) $c(x) = 20 + k$, the other parameters values are the same as in Table 1; (c)-(f): The impact of $\epsilon(x)$, $\eta(x)$, $\gamma(x)$ and $\mu_1(x)$ on $R_0$, respectively. The other parameters values are the same as in Table 1.
Figure 5. The impact of parameters on $R_0$ for cases $\tau_j(t)$ (the pink color line) and $\tau_j^0$ (the green color line). (a) $\beta(x) = 1.5 \times 10^{-5}(1 + k \sin(mx))$, the other parameters values are the same as in Table 1; (b) $c(x) = 20 + k$, the other parameters values are the same as in Table 1; (c)-(f): The impact of $\epsilon(x), \eta(x), \gamma(x)$ and $\mu_I(x)$ on $R_0$, respectively. The other parameters values are the same as in Table 1.
Figure 6. The dynamical behaviors of system (2.5) with $\beta(x) = 1.5 \times 10^{-5}(1 + 0.35\sin(2x))$(the green color solution surface) and $\beta_0$ (the red color solution surface) when $R_0 > 1$. The other parameters values are the same as in Table 1.
Figure 7. The dynamical behaviors of system (2.5) with $\tau_j(t)$ (the pink color solution surface) and $\tau_j^0$ (the blue color solution surface) when $R_0 > 1, j = 1, 2$. The other parameters values are the same as in Table 1 and $\beta(x) = 1.5 \times 10^{-5}(1 + 0.35 \sin(2x))$. 
7 Conclusion

As mentioned in Wang et al.\[20\] and Wu\[21\], joint effects of incubation periods, periodic antiviral therapy and heterogeneity spatial diffusion are worth studying in the investigation of HIV infection within the host. Considering the antiviral drugs can act on the fusion, reverse transcription and budding stages of HIV infected cells, in this paper, we present and analyze a periodic delays spatial diffusion HIV infection model with three-stage infection process.

In theoretical part, we first study the well-posedness of the full system incorporates the global existence of the solution for system (2.5). Moreover, the existence of strong global attractor for \(\omega\)-periodic semiflow is proved. Based on the theory mentioned in Liang et al.\[32\], as a key threshold parameter that measure the risk of HIV infection within the host, we derive the basic reproduction number \(R_0\), which is defined as the spectral radius of the next generation operator and can be calculated numerically. It is worth mentioning that two periodic delays are introduced in our model, which reflects the influences of periodic antiviral therapy on the prevention of HIV infection process. Inspired by Zhao\[34\], we ensure the linearized infectious compartments system generates an eventually strongly monotone periodic semiflow by defining a phase space. We further prove that \(R_0\) is a threshold for the elimination and persistence of HIV infection by comparison principle and persistence theory for nonautonomous system, i.e., the HIV infection will be eliminated when \(R_0 < 1\) and will persist when \(R_0 > 1\). In the spatial homogeneous case, we obtain the explicit expression of \(R_0\) and show the global attractivity of the positive equilibrium by using the fluctuation method.

In numerical simulation part, we display the dynamical behaviors of the solutions for system (2.5) associated with \(R_0 > 1\) (and \(R_0 < 1\)) (see Figures 2-3). To discuss the impacts of time delays \(\tau_j(t)\)\((j = 1, 2)\) and spatial heterogeneity on the HIV infection, we set the space-averaged infection rate \(\beta_0\) and time-averaged delays \(\tau_0^j\). In Figures 4-5, we display the impact of some model parameters on \(R_0\). In Figures 6-7, we discuss the capacity of infected cells and productive virus for \(\beta(x)(\beta_0)\) and \(\tau_j(t)(\tau_0^j)\) cases. Our simulation results suggest that both spatial heterogeneity and periodic delays caused by periodic antiviral therapy have a remarkable impact on the progression of HIV infection. However, there exists different antiviral therapy drug combination and HIV strains and their effects are worth investigating. Hence, it motivates us to introduce multi-strain into the model and discuss the effects of different antiviral drug treatment strategies. We leave it for further work.

Declarations

Ethical Approval

Not applicable for this study.

Conflict of interest

The authors declare that there is no competing interest.
Authors’ contributions

Peng Wu contributed to the conception of the study, contributed to manuscript preparation and performed the theoretical analyses, numerical simulations and wrote the manuscript.

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Availability of data and materials

Not applicable.

References


